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Taking a broader view of things: towards a transdisciplinary approach to cancer

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Abstract

Cancer is widely considered an abnormality that emerges from within the body and which must be destroyed and defeated. But we still do not know precisely how and why cancer starts, and while a 'magic bullet' cure has failed to materialise, those adopting a more pragmatic stance are increasingly arguing that if we cannot eradicate all cancer cells, we should look instead towards a 'stalemate' and find ways of managing cancer as a chronic disease. This article seeks to extend the reach of research in this field by taking a broader view and working towards a transdisciplinary approach in order to better understand cancer. First, we draw attention to obstacles that hinder progress in formulating new perspectives on cancer. Second, we ask why the genocentric approach to cancer remains dominant. One explanation is the legacy of Cartesian thinking. Third, we consider new ways of conceptualizing cancer so that it is not only a scientific object but also an object of life that has a framed existence within the body as part of a wider process of biological evolution. We draw on two key examples which highlight the importance of adopting a transdisciplinary approach: multi-drug resistance and cancer genomics.

Keywords: cancer, transdisciplinary approach, sociology, philosophy, science, multi-drug resistance, cancer genomics

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1. Introduction

Over the past century, much cancer research has been justified by the hope of eradicating cancer through the means of finding a magic bullet cure. However, while cancer has become a highly competitive research field that brings together the brightest minds and is well funded, very little has been achieved so far in terms of eradication. Moreover, many cutting-edge cancer scientists argue that containment (and management) and not eradication is a more feasible strategy. Furthermore, early detection (via accurate imaging or biomarker discovery) followed by surgery remains the most expedient way to limit the development of cancer. By way of comparison, it took only a few decades to contain AIDS using drugs via a good understanding of the viral disease whereas after almost a century of research, cancer is still not properly controlled.

While each day specific kinases or genes are identified as being potential 'causes' of cancer, we are still far from understanding the disease completely. In order to make further gains in understanding, we make the case for a transdisciplinary approach. What might this entail? Steinmetz's (2007) work provides some useful clues. He argues that whereas interdisciplinarity is a condition in which disciplines retain their distinct borders and identities, transdisciplinarity provides 'a situation in which the borders of disciplines are eroded and new intermediate spaces or fields emerge' (Steinmetz, 2007: 55). While academic expertise is constrained by the logic of fields and their institutionally-enforced rules (Bourdieu, 1993) (as is discussed below) insights can nevertheless

be gained through encounters with other disciplines in intermediate spaces that are created beyond these fields and all parties in such relationships can be transformed as part of this process (Steinmetz, 2007).

Steinmetz (2007: 58) argues that in many instances, the barriers to transdisciplinarity are self-imposed or the result of hysteresis in the disciplinary habitus which leads scholars to adopt modes of practices that accord with earlier conditions of the field (Steinmetz, 2007: 58). However, he urges sociologists to 'shed long-standing disciplinary prejudices about topics like science, the humanities, theory, and the ideographic versus the nomographic, and to enter into open-ended and deterritorialised encounters with various intellectual others' (Steinmetz, 2007: 58).

Steinmetz's call for transdisciplinarity is primarily aimed at sociologists but here we utilise its insights to facilitate our research project: the authors of this article include a sociologist, a geneticist and a physicist/applied mathematician. Inspired by Steinmetz, this article seeks to pave the way for a transdisciplinary space where it is possible to bring together insights from a number of disciplines. In order to do so, we draw attention to field-specific obstacles that hinder progress in formulating new perspectives on cancer. Second, we ask why the genocentric approach to cancer remains dominant. One explanation put forward is the legacy of Cartesian thinking, which separates the scientist (or analyst) from the object of analysis as well as the cell from the organism.

Third, in drawing on a range of perspectives and insights, we consider new ways of conceptualizing cancer so that it is not only a scientific object but also an object of life that has a framed existence within the body as part of a wider process of biological evolution.

In arguing for a transdisciplinary approach to cancer, we draw on two key examples which highlight the importance of adopting this approach: multi-drug resistance and cancer genomics.

2. Questioning cancer research

Questioning cancer research does not mean undermining the hard work that has been done but highlighting potentially new therapeutic strategies. Nor does it mean that that we should cease to gain knowledge, through close empirical observation, in order to better understand how chemicals acting on tumours impact on them mechanistically. However, trying to understand cancer differently, i.e. defining it both as a scientific and social object, will put us in a stronger position to create new options regarding its treatment. There is significant entanglement between the evolution of scientific research on cancer (e.g. the discovery of faulty intracellular pathways or genes), and how scientists think about cancer, in part due to the way stakeholders (such as national research councils or charities) fund research, including their overriding aim to foster 'innovation' or 'innovative thinking' and thus engender competition among research institutions who seek to strengthen their position in various league tables. For these reasons it becomes difficult to revisit past ideas about cancer, engage with a range of disciplines, or consider epistemological issues in relation to obvious scientific paradoxes (such as multi drug resistance – see below). There is a sense, then, that in 'playing the game', the intellectual curiosity that might lead to genuine innovation is blocked and instead, researchers are compelled to 'innovate' within the pre-determined frameworks set in place by various funding bodies. Undoubtedly, advances in molecular biology and the genomic analysis of cancer have produced an incredible volume of data, but if research goals are restricted to those that accord with current technologies or the mainstream concepts of the day, that which has been done or thought before is often cast aside and so new insights gained through research may remain restricted in scope. For example, how can scientists be sure that they are able to deliver new concepts or break dogma with funding lasting between 3 to 5 years if the grant is deemed successful merely because it has managed to muster the approval of all the gatekeepers? Peer review processes in research provide a vital means of quality control and also, more significantly, of refining and nurturing, through feedback, new ideas and innovations. But research funding application processes often restrict innovation by encouraging researchers to anticipate what the gatekeepers are expecting. Furthermore, they are incredibly time consuming and writing applications takes up precious research time. For example, a recent study on the time spent preparing grant proposals in Australia estimated that preparing a new proposal took an average of 34 days per proposal (Herbert et al., 2013). The total estimated cost of the 3727 applications received by the National Health and Medical Research Council was estimated to be in the region of $66 million Australian dollars and 550 working years of researchers' time while the success rate for this particular call was 21 per cent (Herbert et al., 2013). These figures did not include the costs in time and money for

the peer reviewers. Aside from the time spent applying for funding, in addressing all the requirements of a funding call, researchers are often directed towards formally rational modes of action: their presentation of ideas follows a calculable, instrumental logic rather than one inspired by intellectual curiosity (Weber, 1968[1922]); they become cogs in the machine of university income generation. This procedural logic obstructs the kind of sustained curiosity that might, admittedly, lead to a research 'dead end' but which might, in more favourable circumstances – with dedication to vocation and serendipity – lead to genuine innovation. Such innovation might at best be intimated within the formally rational confines of a funding proposal, where the project's scope needs to be defined instrumentally in advance of conducting the research. In the field of science, the best proposals do not necessarily equate to the best ideas and the stakes here are very high: the type of research that gets done has an indirect role in mitigating (or not) the enormous death toll related to cancer (one out of eight deaths worldwide); yet very few argue this point apart from perhaps medics who, on a daily basis, witness the limitations of new drugs/'magic bullets'/innovations. The pharmaceutical industry's approach, which is predominantly rooted in a 'market logic' and preferring the 'business case', is restricted in its ability to innovate or think with a broader view, because of the constant pressure to promote a high and quick return on investment (to top different league tables e.g. FTSE). The 'logic of profit' leaves little incentive to launch new research programmes that draw on insights from a range of disciplines but which do not offer an immediate return on investment. The biotech model is predicated on the expectation of significant returns from cancer drugs (Macilwain, 2015).

The field of science itself also presents numerous constraints to innovation. Scientists are, according to Bourdieu (2004), the scientific field 'made flesh': through their training and experience they come to embody the presuppositions and state of play of the field. Through the training that presupposes entry to the field, they gain 'a practical sense of the problems to be dealt with' and 'the appropriate ways of dealing with them' (Bourdieu, 2004: 38). They also come to learn, implicitly, what is the 'right way to do science'. This leads to orthodoxies in the various sub-fields of scientific research, and these orthodoxies are defended by those occupying dominant positions in the field. Their dominance, which is threatened by the presence of newcomers who seek to impose an alternative (or heterodox) vision of science, is nevertheless enabled by possession of scientific capital, which is 'a particular kind of symbolic capital, a capital based in knowledge and recognition. It is a power which functions as a form of credit, presupposing the trust or belief of those who undergo it because they are disposed (by their training and the very fact of their belonging to the field) to give credit, belief)' (Bourdieu, 2004: 34). In cancer research, then, it is no surprise that there is a degree of 'group think' around the ways in which science should deal with the problem of cancer. As Gatenby (2012) points out, this is currently manifested in the belief that cancer is a disease of the genes, and there is a doxic belief that the generation of huge data sets and ever finer-grained molecular analysis will somehow lead to a solution for the problem of cancer. However, 'in the absence of a true understanding of cancer's evolution and ecology, we have failed to recognise the limits of these data' (Gatenby, 2012: S55). It seems increasingly unrealistic to be able to eradicate the heterogeneous, adaptive populations that are found in most cancers. As Gatenby (2009: 509) points out, '[o]ne centimeter cubed of cancer contains about 109 transformed cells and weighs about 1 gram, which means there are more cancer cells in 10 grams of tumour than there are people on Earth'. Hence the disappointment: the genocentric approach to cancer provides another instance of the limits of our ability to master reality through calculation and technical procedure (Weber, 1946[1918]). Cancer has become one of the *mythologies* (in Barthes's (1973) sense of the term) of our time. Drawing on ideological discourses of war and triumph, whether from real life (i.e. 'the war on terror') or from fictional, cinematic representations, cancer is considered an *abnormality* that emerges from within the body and which must be destroyed and defeated. But while a 'magic bullet' cure has failed to materialise, those adopting a more pragmatic stance are increasingly arguing that if we cannot eradicate all cancer cells, we should look instead to look towards a 'stalemate' and find ways of managing and living with cancer as a chronic disease (Gatenby, 2009), thus seeking to 'box-in the tumour cells with a discrete, focused strategy of containment' (Oronsky et at., 2015: 1). Many oncologists are coming round to the idea that therapeutic strategies that seek to control cancer might be more effective than those that seek to cure it, especially given that high doses of chemotherapy might often lead to tumours becoming unresponsive to further treatments (Gatenby, 2009). Moreover, the genocentric perspective on cancer has been challenged directly by those seeking to

construct an alternative paradigm that proposes a theory of organisms and holds that that cancer is a tissue-based disease (Sonnenschein and Soto, 2016). Sonnenschein and Soto's (2016) argument thus counters the dominant somatic mutation theory (SMT) which holds that cancer is a cell-based disease. According to SMT, molecular changes in the founder cell render it unable to control its proliferation, thus leading to the formation of a tumour. This model assumes that cells are quiescent. In contrast, the tissue organization field theory (TOFT) promulgated by Sonnenschein and Soto (2016: 70) argues that the default state of all cells is 'proliferation with variation and motility'. They point out that the search to identify the cancer cell is futile because both cancer cells and normal cells 'share the same fundamental behavioural properties, namely, proliferation and motility' (Sonnenschein and Soto, 2011: 4334). While some genetic differences exist between normal and cancer cells, the vast amounts of data concerning the genomes of thousands of cancers has yet failed to demonstrate any qualitative difference between pre-metastatic and metastatic neoplastic cell. They argue, therefore, that 'the search for identification of a cancer cell should be abandoned' (Sonnenschein and Soto, 2011: 4334). In another model, it is argued that it is the disruption of local tissue signals that enables cancer formation as cells 'transiently develop a self-defined fitness function' and are thus governed by their own heritable properties (Gatenby and Brown, 2017). Chemical treatments such as proton pump inhibitors and pH-buffers have opened up possibilities for alleviating the side effects of cancer and inhibiting the growth of tumours (Spugnini et al., 2015; Fais et al., 2014; Harguindey et al., 2013). Other approaches have drawn on insights from social theory, philosophy and physical/mathematical biology in order to understand cancer in its evolutionary context, as a living entity perceived as anomalous rather than abnormal (Stewart and Rauch, 2016). What these perspectives have in common is not only a questioning of the orthodoxy in cancer research but more generally they gesture towards the limits of scientific and medical thinking especially in the case of cancer. It is our contention that Gatenby's pragmatic stance and research by the likes of Sonnenschein and Soto provides a welcome contrast to orthodox perspectives on cancer precisely because their organicist approaches enable us to understand cancer as part of a wider process of biological evolution. As Bourdieu observes, activity in every social field is characterised by struggle between heterodoxy and orthodoxy (Bourdieu, 1993), and it is time to explore some of the positions occupied by those challenging the dominant assumptions of the field (Bourdieu, 1993). But in doing so, we also draw attention to the limits of the dominant frameworks of science and medicine today.

3. Limits of knowledge acquisition in science, reductionism and determinism

Knowledge acquisition operates through a number of well characterised principles that are inherent to what science is at a given time, often based on the social expectations and related constraints applied to science. These principles include, for example: (a) formulating a hypothesis including designing an experiment and drawing inference from previous work/data; (b) selection of 'significant' data (statistically this is known as the p-value) and the clearing of those that are deemed not significant; (c) distinguishing and separating data, to associate or identify groups of data; (d) providing a hierarchical organisation of data (from the most important/significant data to the least); and (e) centralising these data as a function of theories present at a particular time. These anthropological operations have been applied, in different ways, across various scientific disciplines. The notion of truth is relative to the set of representations used in a given society, i.e. the set of beliefs. Moreover, as Kuhn famously pointed out, science does not evolve through a linear accumulation of facts of knowledge and so the notion of 'scientific progress' is undermined by the fact that most scientific discoveries occur as a result of a break with the 'normal science' of the day (Kuhn, 2012[1962]). As a result, in order to make sense of scientific theories, we need to understand how a society is organised, its system of beliefs and representations at a given time. For example, the notion of 'energy conservation' in physics did not come from the magical or spontaneous mathematical spatial integration of a force but from the birth of economic rationalization and the related social transformations and industrial revolutions that occurred between the eighteenth and nineteenth centuries. Terms like 'force', 'work' or 'power' invented then and used in physics and elsewhere have their origins in that social transformation that we term 'modernity'. However these very physical concepts that have served us so well for a time nevertheless contain their own limits that are visible today under the name of 'black matter', namely an elusive substance that is required in order for our understanding of the universe to be compatible with current scientific theory.

The entanglement of science and society raises significant questions with regard to objects of nature and what should be considered as 'science'. For example, when the American Medical Association classified obesity as a disease (in 2013), obesity was thus defined as something to be 'cured'. Missing from such diagnoses are the underpinning socio-economic conditions of poverty or social inequality that might exacerbate this phenomenon. Along similar lines, in 2008, soon after Gordon Brown (then leader of the Labour Party in the UK) decided to revoke the retirement age allowing elderly to work longer, the prestigious medical research council of UK decided to include aging as a research priority area. Aging is a natural process of life on which biological evolution relies, but it in this instance, it was also defined as an object of scientific research because of political and economic imperatives. We need to consider, then, the biological reality of the ageing body alongside the social construction of age as a category and the ways in which the latter serves political and economic interests. Thus the extent to which an object of nature (e.g. disease, planet and so on) is truly a scientific object has to be revealed with a clear understanding of the wider society including its system of representations. It is therefore not a surprise that in our modern society the terms 'health condition' and 'disease' are interchangeable even if the former refers more to a social context and the latter to a biological context. We can see from these examples that science and society are inseparable, and so sociological analysis of science is necessary in order to unpick the relationship. Constructivist approaches such as those deployed by Latour and Woolgar (1986) have highlighted the linguistic, political and rhetorical devises deployed by scientists in their presentation of 'facts'. Other significant research has examined the construction of the 'medical gaze' (Foucault, 1973), the sociology of diagnosis (Brown, 1990; Jutel, 2009) and the role of experts and the formulation of an 'expert gaze' that mediates diagnosis (Gross, 2009). Science is no single thing, and various divergent ideological representations of science have been deployed by scientists over the centuries in order to make claims for the value of scientific research, whether for the purposes of expansion of science's authority into other domains, the monopolization of resources or for the sake of guarding the autonomy of practitioners (Gieryn, 1983). Reflecting on these processes, researchers have thus drawn attention to the *boundary work* that is involved in demarcating science from non-science (Gieryn, 1983). Boundary work is defined as 'the constitution of an "independent and self-contained field of knowledge" as the basis upon which professions can build their authority and exclusivity; and the labour of division which goes into erecting and maintaining boundaries between the professions and various other groups' (Fournier, 2000: 69). When applied to science, this notion of a *labour of division* is more appropriate than the Durkheimian *division of labour* because it highlights the considerable work that goes into the construction, maintenance and policing of the boundaries between disciplines so that they appear to be natural and part of the order of things (Fournier, 2000). It is our contention that the links between science and society need to be questioned by scientists themselves and that, to some extent, scientists, within the bounds of their field, are relatively disconnected not only from wider society but also from their object of study. This disjunction and the related abstracted epistemological position assumed by scientists in the western world can be traced back to Descartes' *cogito est*, i.e. since the seventeenth century, whereby the 'thinker' (*ego cogitans*) and its object of study (*res extensa*) are disconnected as part of the process of dividing into many pieces any complex natural system (Descartes, 1998[1637]). This paradigm has enabled significant developments in science but nevertheless impedes the reflexivity that is necessary in order for scientists to consider their object of study and also to reflect on the suppositions that they bring to their research. While scientists detach themselves from their object of study, they might fail to consider the presuppositions that they bring to the field. Probing the scientists' own presuppositions thus consists of 'objectifying the subject of objectification' and thus dispossessing these subjects (the scientists) of the privileges they grant themselves (Bourdieu, 2000). The position we occupy in the scientific field, or more broadly in the social world defines in great part the presuppositions we hold in relation to the very same phenomena. Our training in a given field provides us with the competences necessary in order to succeed in that field. However, the knowledge and skills that we acquire in order to 'put on the blinkers' also sometimes restrict us from seeing the limits of our epistemological position and bringing to the fore the tacit assumptions we make. For example, while cancer biologists might believe that the immortalised cancer cell lines that they keep in their incubators are truly representative of cancer, a cancer patient would probably think differently. The aforementioned disjunction and atomisation do not allow a clear synthesis of what cancer is. It is therefore not surprising that in this context subjective 'norms' are defined: for cancer

science this means that experimental/scientific measures between the pieces of the jigsaw are formulated and mathematisation is used; these procedures follow Descartes in dividing difficulties by examining them in as many parts as possible, but in doing so, they remove the unity, diversity or identity of natural objects (Descartes, 1998). This reductionism, by removing the object from its environment, e.g. the cell from the organism, significantly reduces the possibility of understanding its essence or the very reason for its existence.

Classifying cancer, diabetes or aging as diseases (or similarly health conditions) or scientific objects throws them into the process of disjunction and renders it difficult to re-synthesise or consider them in relation to the organisms or societies from which they originate. Furthermore, as knowledge is viewed and treated as information, this process is exacerbated. A prevalent idea is that if we invest to a greater extent in molecular technology, and if we sequence entire cancer populations cell by cell, we will surely solve the problem of cancer. However, unless we consider the cell within the organism, or even as part of a wider process of evolution, this total belief in information can only take us so far. It convinces us that we simply need to utilise more technology and accumulate facts in order to arrive at solutions. As Georg Simmel (2004[1900]) pointed out, an intellectualised approach to knowledge has much in common with the attitude conveyed by the money economy: both knowledge and money are abstracted forms that reduce the qualitative expressions of life to their quantitative or formally measurable aspects. They come to represent the highest forms of abstraction, and just as money can buy anything (including, we mistakenly believe, happiness), so information systems are seen to be able to solve every problem we encounter, even if, of course, this is not the case. Paradoxically, this sense of certainty co-exists with increasing sense of uncertainty surrounding the risks associated with information, science and technology (Beck, 1992; Giddens, 1990). Today, Descartes' (1998: 16) vision for science of gaining certainty by casting aside 'the shifting earth and sand in order to find rock or clay' seems increasingly far-fetched. Anthony Giddens (1990: 39), reflecting on Popper's assertion that science is built on shifting sands, argues that in science, '*nothing* is certain, and nothing can be proved, even if scientific endeavor provides us with the most dependable information about the world to which we can aspire'. In addition, the reductionism and disjunction of complex systems imposed with view to reconstructing them it at a later time through the lens of determinism (i.e. mathematisation) has significant limitations, as we will see below. The deterministic notion of 'time' in scientific research is often skewed towards the past and future only, and fails to consider the dynamics of the present. This hinders our ability to consider the possibility of new perspectives or representations that we might be able to envisage in the intermediate spaces enabled by transdisciplinary enquiry.

Let us consider the limits of determinism. Once a natural object is deemed reducible, scientists take steps to atomise the object. A tumour can be atomised into cells, a cell into organelles, an organelle into molecules, and molecules into atoms. Whether or not a theory of cancer is true, it will rely on rebuilding, step by step, how these elements interact in (often) artificial environments. The experimental testing will therefore be based on a form of determinism that uses the notion of causality. The local link that exists between elementary bricks will be experimentally tested through the production of a cause and the measure of its effect; and the difference between the cause and its effect will be measured through the time difference between those events. Unsurprisingly, all mathematical equations aiming at modelling a system whatever its complexity will use 'differential equations' whereby time does not exist in full but forms an appendix to measure causal relations. Within the very writing of those equations there is a tendency to overlook the present and to consider only past-to-future relations. The mathematisation or experimental testing of any theory is radically skewed as it is based on anticipation and expectation, and so overlooks the possibilities inherent in the present. The extent to which reductionism (locality) and determinism (causality) allow us to understand a broader system is questionable and this is highlighted by Maurice Merleau-Ponty, who points out that '[le temps] nait de mon rapport avec les choses…Ce qui est passé ou futur pour moi est présent dans le monde' (Merleau-Ponty, 1945). The notion of the 'succession of events' commonly known as 'time' is needed because the world has been atomised by scientific thinking and the disjunctions that are created in order to verify hypotheses. Furthermore, this view on time frames the superiority of the thinker or scientist that is reflected in her or his ability to control nature. It means being in a position of controlling time through experimental testing. Here, the wider scope of evolutionary time, with its dynamic potential and movement, is overlooked and so we propose that it is time to turn our attention towards this evolutionary moment, by means of a transdisciplinary approach.

4. Multi drug resistance in cancer

To support this point of view regarding the conceptual limits of determinism within a narrow temporal frame, let us consider an empirical example: 'multi drug resistance' (MDR). This example utilises insights from different disciplinary perspectives. Multi drug resistance in cancer is a phenomenon that is observed in patients following a number of years of chemotherapy. It occurs when a tumour becomes resistant to the chemotherapy and a relapse is observed. It is intriguing to observe that once a tumour (or cancer cells) becomes resistant to one type of chemotherapy, it also becomes resistant to many other different chemotherapies to which the tumour has never been exposed - hence the notion of multi drug resistance. Initially, the assumption was made that a molecular event would be able to 'vacuum clean' (or efflux) chemotherapy drugs from cancer cells (Dano, 1973). This hypothesis clearly took off when P-glycoprotein (Pgp) was identified as the membrane protein over-expressed in multi drug resistant cancer cells that actively extruded chemotherapy drugs (Juliano and Ling, 1976). However, there was an inherent problem linked to the concept of molecular 'specificity'. This refers to where cause-effect relationships arise from molecular affinity and, for example, two biological molecules interact as a function of their biochemical affinity. Defined this way, affinity corresponds to the energy exchanged when molecules are bound to each other; a very high affinity is defined as specificity. It follows naturally that an efficient biochemical reaction relies on high affinity between biochemicals. Note that 'efficiency' is also defined as the time lapse for the biochemical reaction to occur, meaning that high affinity reactions will occur over a short period of time. The logic that emerges from this view is also known as the 'key-lock' model whereby there is a need to match molecules chemically with one another. In this context, efficiency (i.e. the speed of the reaction) and affinity are equivalent. However, the key-lock model is problematic when one molecule becomes promiscuous and interacts with many different partners with similar efficacies, which is exactly what is observed and experimentally measured in MDR. In this context two scenarios are possible: either the promiscuous molecule is very large and has many interaction points to connect its partners, or the key-lock model has limitations and so efficiency and specificity/affinity are not necessarily equivalent. In multi drug resistance, therefore, the problem that needed to be resolved was this: how can low affinity reactions also be efficient? The incoherence of the 'key-lock' model in multi drug resistance was noted by Paul Roepe (2000):

> MDR cells are resistant to, and/or exhibit decreased retention of, literally hundreds of different hydrophobic compounds that are structurally divergent (…). Membrane transporters, like soluble enzymes, are exquisitely substrate-specific … If transporters were not specific, the cell would eventually become a high entropy chaotic mess … [as there are] no structural molecular motifs common to all the many different agents to which MDR cells are resistant. (…) MDR protein [Pgp] is a very unusual enzyme with extraordinarily broad substrate recognition capabilities; that is, it violates the law of enzyme specificity.

indeed,

> controversy remains over how P-gp recognizes hundreds of different hydrophobic drugs and pumps them out of the cell…' (Gottesman et al., 2009).

Our understanding of multi drug resistance is limited if it is only the temporal (i.e. efficiency/affinity) and never the spatial dimensions of biochemical interaction that are considered. The reason for this can be found in how biochemists initiated their field of research known today as 'enzymology'. In the early 18th Century, to demonstrate the presence of reactions, it became necessary to extract and purify enzymes to measure biochemical reactions in an aqueous medium in glass vases. This meant that the notion of 'reaction' was necessarily temporal given the removal of the enzyme from its initial site in the body. This procedure, however, lost the crucial information regarding the spatial presence of the enzyme in the body. This is why today all kinetic equations that measure on a temporal scale the enzymes' reactivity refer only to concentrations of enzymes in glass vases. This is far too simplistic. Given that any biochemical reaction relies on biochemical collisions to occur, it is possible to demonstrate that if two biochemicals are in a confined space, the likelihood of a reaction (i.e. efficiency) can be high even if the affinity between biochemicals is low. This explains the divergence between affinity and efficiency and underscores the possibility of molecular promiscuity. Pgp is not enough to explain multi drug resistance and so spatial restriction/confinement together with Pgp must be considered (figure 1).

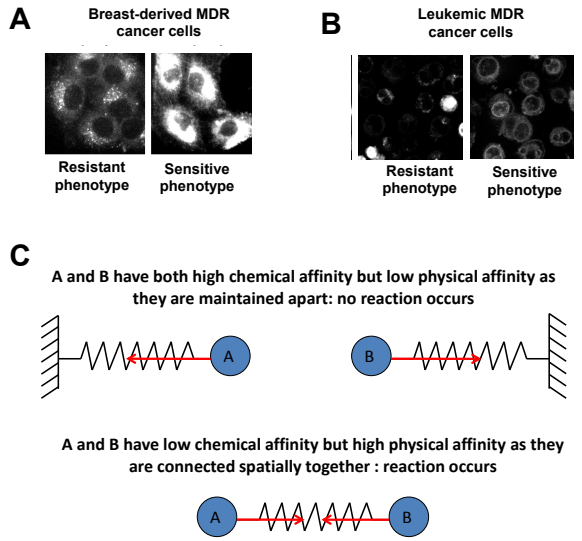

Figure 1. Representation of drug resistance in different cancer cells, i.e. in (A) breast derived cancer and (B) leukemic cells. Both cells were treated with anticancer agents (doxorubicin an anthracycline derivate) that are visible under specific conditions using adequate fluorescence techniques. Non-resistant cells accumulate high levels of doxorubicin whereas drug resistant cells accumulate less. This process can be reversed by changing the membrane (what we called 'confinement' in the text) with the possibility of either reversing or increasing drug resistance. (C) This is a representation of chemical vs. physical affinities. From a biochemical point of view, a reaction is only possible if two chemicals have affinity towards one another. However in a situation where the two chemicals are impeded in their opportunity to meet and react, the experimentalist will assume that the affinity is low. Alternatively, if two chemicals are encouraged to meet, even with low affinity, a reaction will occur. For an experimentalist, it may seem that the two chemicals have high chemical affinity whereas they have, in reality, very little affinity.

In recent years, it was demonstrated that it is the membrane that provides a confined space for high efficiency reactions to occur between a drug and Pgp whatever their affinity (Daniel et al., 2013). This example shows that the empirical testing of a theory needs to situate temporality within a spatial dimension in order to gain a stronger understanding of some of the paradoxes – such as MDR – that we encounter in scientific research where biochemical reactions do not follow an expected, deterministic or predictable pattern. Drawing on insights from physics, we see that chemical affinity can now be extended to incorporate a new 'physical affinity' that depends on spatial properties. In other words, the nature and properties of space need to be considered in biochemistry/biology.

5. Cancer genomics

Let us consider a second example – cancer genomics – where we can also gain new insights by combining disciplinary perspectives to arrive at understanding that embraces complexity and extends beyond the sum of its parts. Developments in molecular techniques have greatly advanced the study and understanding of cancer. However, a deterministic approach is usually taken with separate studies addressing the genomics (DNA), epigenomics, transcriptomics (RNA) and proteomics (protein) aspects of cancer biology. Each component of the genetic and cellular machinery is thus 'atomised' as a separate entity and studied in isolation. Cancer genome sequencing has enabled the discovery of somatic (non-inherited) 'driver' changes in the DNA, which in the presence of causative or predisposing environmental factors lead to the initiation of cancer and confer a selective growth advantage to tumour cells. It is also the case that changes in the germline DNA (inherited) have been shown to stimulate tumour growth via different mechanisms (Carter et al., 2017). The currently accepted model of carcinogenesis is of early 'driver' mutations occurring in a small number of cells, and these mutations provide a selective growth advantage to normal cells allowing them to proliferate (Vogelstein et al., 2013). However, we still do not know how and why cancer starts in these cells, while at the same time, genomic instability and the process of genomic change are accelerated. The developing tumour consists of clonal colonies of cells, which continue to accrue genomic changes (giving rise to genetic heterogeneity) and which are subject to selection through the tumour microenvironment. The importance of tumour genetic heterogeneity has been recognised, and is an intense focus of study (Waclaw, et al., 2015). Heterogeneity is one of the main reasons for treatment failure, particularly for tumours that have metastasised. It has also led to the recognition that every patient has an individual genetic profile and treatment needs to be personalised. Population and evolutionary genetic methods have been used to analyse heterogeneity and reconstruct tumour evolution. However, since the outcome of evolution cannot be known in advance, predicting future outcomes still remains a difficult task. Alongside the genomic studies, epigenome studies, RNA sequencing (transcriptomics) and protein analysis (proteomics) have explored how the DNA message is translated into functional effects within the cell (Dawson 2017; Modelska et al. 2015). However, these studies are rarely performed together

meaning that there is no integrated analysis emerging from the separate disciplines. In spite of the large volume of work which exists, several important questions remain unanswered. It is still unknown how the seeds of cancer are germinated within a normal tissue, or how tumour cells can migrate and metastasise, i.e. how the physical/spatial environment is involved. Answering these questions needs application of a perspective that transgresses boundaries in order to arrive at new conclusions. For example, consideration of the three-dimensional structure of tumours and spatial constraints shows early promise in developing models which explain tumour growth and chemotherapy resistance (Waclaw, et al., 2015). Moreover, radically new ideas on the way cells self-select in response to environmental stress, through sampling of their genomic information (Almassalha et al., 2016), give clues to the way in which cancer is seeded.

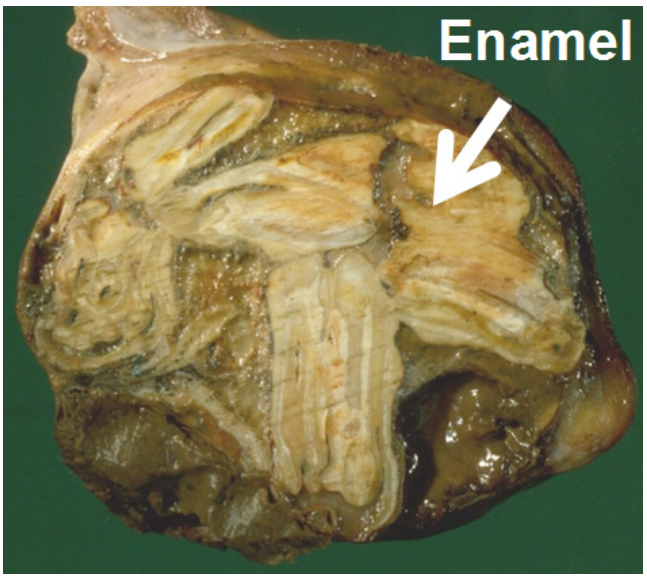

Figure 2. Section of equids testis with teratocarcinoma showing enamel (teeth) formation. This demonstrates how heterogeneous new tissues can develop in parallel with cancer. Teratocarcinoma can be found in every organ not only germinal organs (ovary or testis).

6. Thinking the unthinkable: cancer and evolution.

A transdisciplinary approach might take us even further in our bid to understand cancer. Cancer arises as a result of multiple factors, both environmental and genetic. However, in some instances, cancer is not an anarchic piece of tissue that has outgrown the limit of our body. It contains several layers of cells of different thicknesses that are organised in what looks like a well-defined and functional piece of tissue that can survive a hostile environment (figure 2). As evolution is, by definition, one of the most important hallmarks of biology as it allows life to be propelled forward, one could wonder whether cancer is not simply the result of biological evolution. In this context, while cancer might be thought of as a disease for scientists or a health condition for society, it may also be a natural and normal object of life. Evolution has a unique aspect in that it embraces contingency. Cause-effect and time (as understood only in relation to past-future relations) are meaningless in relation to evolution. This is because evolution cannot be understood in advance but only retrospectively and so we can consider that evolution is history in action. As a result, the link that exists between the past and the future discussed above is broken.

Cancer cannot be thought about in advance but needs to be simply contemplated in the present, in a manner analogous to a piece of art that resonates with our thoughts and triggers sensations that provide us with a proof of our own existence. Of course, with so many negative connotations, cancer is frightening as it reconnects us with nature: it demonstrates to us that the disjunction between human existence and nature (or the cell and the organism) is not a real one. It is, rather, the result of our own consciousness: 'je pense, j'existe', so Descartes thought. In this context Descartes' *cogito*, and related scientific theory or methods, is limited in its ability to conceptualise cancer.[1] As a result, it is important to change the current representations of cancer but to do so we need to try to think the unthinkable. While this may sound an impossible task, it is important to contemplate what biology and in particular evolution has to offer. There is a tendency to think about evolution often from the top, i.e. the extremity of the branches of an evolutionary tree. However, if we trace the opposite journey from the trunk to the branch, the trunk had to give rise to a bud. The bud may or may not have survived evolution and a branch from the bud may or may not have arisen to be fossilised. In any case the bud is the novelty, the thing that did not exist before and was thus devoid of representation. In other words, the bud is a monster, a novelty.

[1] In this article, there is not room to engage to a greater extent with the richness of Descartes' work. We merely draw attention to one key aspect of his legacy in scientific practice.

Thus if one thinks about the evolutionary tree from the trunk to the branches and if one believes in evolution, then by definition of evolution, the monster is a necessary entity. But there is more: a monster shows itself but cannot be spoken of because it appears for the first time and, consequently, is not yet recognised. The monster is a species that has yet to acquire a name and so it cannot yet be represented or thought about. In this context one could think of cancer as a sort of monstrous bud whose birth is on the tree of evolution, a kind of living piece of art invoking the present and challenging our perception of time. To get to grips with this complexity, we need to embrace intellectual transculturation and be 'open to freer interactions with outside knowledge formations' (Steinmetz, 2007: 52). We might therefore learn as much from perspectives in art or cinema as from Big Data because the above-mentioned monster cannot be spoken about or represented. As a consequence, Descartes' *cogito* might be replaced by: 'je pense, j'existe, mais qui suis-je vraiment?'

7.Conclusion: towards a transdisciplinary approach to cancer

Cancer is far more than a primary or continuous cancer cell line, but, regrettably, few bridges exist connecting science and other ways of thinking about cancer. A scientist might think about 'innovation' based on his/her cancer cells, but in doing so can lose sight of the fundamental fact that cells belong to organisms where they are constrained by cell to cell interactions as part of the whole organism. In contrast, the oncologist thinks about patients. The scientist and the oncologist are disconnected from one another, and both have different connections with society as a whole. Sociological analysis is perhaps best placed to account for the reasons behind the great faith that persists, among many cancer biologists, in a genocentric approach. Meanwhile, in the case of MDR in cancer, we have demonstrated that an understanding of temporal biochemical reactions can only take us so far if we neglect the spatial dimensions that are revealed to us by means of physical biology. These transdisciplinary insights extend beyond the sum of knowledge produced by each individual discipline. But transdisciplinary research is never going to be straightforward: it is likely to be disjunctive and messy if we are aware of the complexity and heterogeneity of knowledge production and also 'its hybrid nature, non-linearity, and reflexivity, transcending any academic disciplinary structure' (Lawrence, 2010: 127). Transdisciplinary approaches, if they are to be successful, rely on reflexivity, introspection, communication, collaboration and trust. This is especially important because the findings conveyed to us by colleagues in other disciplines might not be interpreted with the same clarity with which we perceive our own. Whilst in the case of interdisciplinarity we can return back to the fold of our disciplines having collaborated within zones of common interest, with transdisciplinarity, we have the opportunity to inhabit new spaces of intellectual collaboration where there are new rules and the disciplinary borders are fluid. The power relations in these new intermediate spaces are by no means utopian or egalitarian (why would they be?) and there is no obvious lingua franca. The problem remains, as for Weber (1946[1918]), that it is often difficult if not impossible to find bridges between the different value spheres of life. However, there is nevertheless an opportunity to create new forms of knowledge and greater insights into problems than could be produced by individual disciplines. Together, in a 'nonimperial encounter' in an intermediate space, as Steinmetz (2007) suggests, broader, more encompassing perspectives can be forged. Such are the challenges and rewards associated with adopting a transdisciplinary approach. If we take the example of cancer, we can wonder whether a single cell line in a dish is really representative of what cancer is all about.

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