Cancer research in need of a scientific revolution: Using 'paradigm shift' as a method of investigation.

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Review

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Despite important human and financial resources and considerable accumulation of scientific publications, patents, and clinical trials, cancer research has been slow in achieving a therapeutic revolution similar to the one that occurred in the last century for infectious diseases. It has been proposed that science proceeds not only by accumulating data but also through paradigm shifts. Here, we propose to use the concept of 'paradigm shift' as a method of investigation when dominant paradigms fail to achieve their promises. The first step in using the 'paradigm shift' method in cancer research requires identifying its founding paradigms. In this review, two of these founding paradigms will be discussed: (i) the reification of cancer as a tumour mass and (ii) the translation of the concepts issued from infectious disease in cancer research. We show how these founding paradigms can generate biases that lead to over-diagnosis and over-treatment and also hamper the development of curative cancer therapies. We apply the 'paradigm shift' method to produce perspective reversals consistent with current experimental evidence. The 'paradigm shift' method enlightens the existence of a tumour physiologic–prophylactic–pathologic continuum. It integrates the target/anti-target concept and that cancer is also an extracellular disease. The 'paradigm shift' method has immediate implications for cancer prevention and therapy. It could be a general method of investigation for other diseases awaiting therapy.

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1. Introduction

But every time I read the papers, that old feeling comes on,
We're waist deep in the Big Muddy…'
–Pete Seeger (Waist deep in the Big Muddy)

Opening a paper on cancer research with the lyrics of a Pete Seeger's protest song, considered symbolic of the Vietnam war and the President Lyndon Johnson's policy of escalation (*http://en.wikipedia.org/wiki/Waist_Deep_in_the_Big_Muddy*), may seem inappropriate at first glance. However, viewing cancer research as a war on cancer is a common metaphor (Hanahan 2014). President Richard Nixon signed the National Cancer Act of 1971, beginning the 'War on Cancer'. Forty years later, we have observed an escalation in cancer research funding and therapy costs. Impressive advances in our understanding of the mechanisms of the disease have also occurred. This led to the discovery of Imatinib in 1996, for example, which proves the principle for targeted therapy in chronic myeloid leukaemia (Druker 2009). More than 15 years have passed and therapeutic breakthroughs due to targeted therapies remain an exception. The thousands of scientific publications indexed in bibliographic databases such as

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PubMed have not significantly changed the course of several solid tumours including brain, liver and pancreatic cancers (Berrino *et al.* 2007; De Angelis *et al.* 2014; Hanahan 2014). Bibliometric indexes are not therapeutic indexes, and current paradigms used in cancer research could be productive in terms of publications and patents while leading to therapeutic impasses.

In some ways, we are behaving like flying insects trying to escape from a closed room. Attracted by the outside light, insects continuously fly towards the glass of the window, while it would be counterintuitive to go through the darkness of the chimney flue. Science also progresses by reversing perspectives through the formulation of testable counterintuitive hypotheses. It is time for a scientific revolution in cancer research. This could be done by using the concept of 'paradigm shift' as a method of investigation

2. Epistemoligical considerations

It is in the mind of the researcher, in his intellectual approach itself that there are obstacles to the advancement of knowledge.

– Gaston Bachelard

Science does not only progress by accumulating data and analyses in established conceptual frameworks but also through paradigm shifts. A paradigm shift does not necessarily call into question the validity of experimental data. Changes in relationships between data may create paradigm shifts. The role of paradigm changes in the progress of science has long been discussed through the concepts of, for example, *epistemological obstacle* and *scientific revolution* (Kuhn 1962a, b; Bachelard 1938). For Bachelard, 'it is in the mind of the researcher, in his intellectual approach itself that there are obstacles to the advancement of knowledge' (Bachelard 1938). These obstacles are of course involuntary. Kuhn also discusses the importance of paradigm change through the concept of *scientific revolution* (Kuhn 1962a, b). He distinguishes *normal science* from *extraordinary science. Normal science* 'is directed to the articulation of those phenomena and theories that the paradigm already supplies' (Kuhn 1962b). It is a puzzle-solving process essential to the development of science. An example of *normal science* is the discovery of the elements that filled empty spaces in the periodic table (Kuhn 1962a). *Normal science* is exploitation of the paradigms created by *extraordinary science*. One limitation of *normal science* is that it tends to discover what it expects to discover. Hence, 'failure to solve part of the puzzle is likely to discredit first the scientist and not the theory' (Kuhn 1962b). In *normal science*, scientists put themselves in a state of voluntary servitude. In return, they are rewarded, for example, in the form of academic careers and grants. On the other hand, *extraordinary science* may be viewed as a catharsis-like process.

When a study fails to obtain its anticipated results and this anomaly persists, a crisis may occur. A possible way to resolve such a crisis is to adopt new perspectives through paradigm shifts. Transition from a Ptolemaic cosmology to a Copernican one, replacement of the Phlogiston theory by the Lavoisier's oxygen theory of combustion, or the Pasteur and Koch germ theory of diseases can be interpreted in term of s*cientific revolutions*. Importantly, in Kuhn's view 'every problem that normal science sees as a puzzle can be seen from another view as a counter-instance and thus a source of crisis'. Equally important is the reiteration of the importance and validity of the 'puzzle-solving' approach in the development of science. Although influential, the concept of 'scientific revolution' is not exclusive. For example, Popper's falsifiability, in which science proceeds by conjectures and refutations is another way to account for scientific progress. Serendipity may also explain some discoveries.

Now, let us consider the hypothesis that the difficulty of cancer research to achieve some of its therapeutic expectancies is interpretable as a of *crisis*, that this *crisis* could be solved using a paradigm shift, and that one of the *anomalies* or *epistemological obstacles* we have to deal with is the way we perceive the cancer cell itself.

3. Cancer as a scientific object and its 'space-time' framework

Objectivity is the founding postulate of science. Science is objective with regard to its method and its objects, but scientific inquiry is a human process. Archetypes, themata (Holton 1975), academism, and fashion (Kuhn 1962a, b; Bachelard 1938) operate in scientists' minds without their being aware of it. Such biases are not negative per se. They are intrinsic to the process of discovery. Some of them fuel creativity and have heuristic value. They also impact the social and cultural aspects of science. Nevertheless, unidentified biases may also hinder rather than advance scientific progress. This occurs when biases lead to a conceptual impasse. For a scientist, characterization and analysis of biases that belong to the paradigm he or she uses should be an integral part of the experimental procedure.

To achieve identification and analysis of the consequences of some of these biases in cancer research, we have chosen to consider cancer as a scientific object that emerged in the early 20th century in a 'space-time' framework. 'Oncology' comes from ancient Greek ' γκος' (onkos) meaning 'mass'. The reification of the disease of cancer as a tumour mass provides the 'space' part of our framework. The other part, 'time', is the late 19th century with Pasteur and Koch's germ theory of disease. These choices are not

exclusive. Other founding paradigms could be considered, such as the institution of cellular pathology by Virchow. More recently, the discovery of oncogenes and anti-oncogenes that defined cancer as a gene-driven disease according to the somatic mutation theory of carcinogenesis (Stehelin *et al.* 1976; Bishop 1983) could also be analysed for the possible biases they have introduced (Sonnenschein and Soto 2000; Soto and Sonnenschein 2014; Weinberg 2014). Significantly, methods and concepts of molecular genetics have deep foundations in microbiology.

4. The cancer cell: A legacy of microbiological medicine

> *One of the things a scientific community acquires with a paradigm is a criterion for choosing problems that, while the paradigm is taken for granted, can be assumed to have solutions.*
>
> *– Thomas Kuhn*

In the 'space-time' framework proposed to account for the emergence of cancer as a scientific object, the time we selected is the 19th century of Pasteur and Koch microbiology. We chose this period because microbiology and the germ theory of disease provided both the conceptual (Koch's postulates), the methodological (cell culture), and the therapeutic (cytotoxic drugs) grounds on which cancer cell research has been developed (Garcion *et al.* 2009). Historically, experimental cancer research focused on the isolation and culture of cancer cells as the causal agents of cancer, just as microbiologists focused at the same time on the isolation and culture of microbes as causal agents for infectious diseases. At this time, mammalian cell culture appeared 'to be no more difficult than the cultivation of many microbes… and [will be] of great value in the study of the problem of cancer' (Carrel and Burrows 1910). During the same period, another Nobel Prize recipient, Peyton Rous, viewed cell culture as 'a method whereby living tissue cells can be plated out in a culture medium just as bacteria' (Rous and Jones 1916). Likewise, in 1958, Eagle, in his presidential address at the 58th annual meeting of the Society of American Bacteriologists, noted, regarding nutritional cell culture requirements, 'at each step we fall back upon the prototype experiments of the microbiologist. But it is not only the techniques which are similar, but also the findings' (Eagle 1958). This commitment to microbiological paradigms focused cancer research on the characterization of cancer cells or cancer stem cells as microbe avatars. Implanting cultured cancer cells in animals to reproduce tumour growth is just the translation of one of the founding experiments of the germ theory of disease, i.e. the injection of microbes previously amplified in cultures into animals to reproduce infectious diseases (Garcion *et al.* 2009).

All these concerns do not question the interest of these approaches. The application of microbiological paradigms to cancer research led to the discovery of the oncogenic virus. Likewise, the importance of the cancer cell as a necessary causal agent in the development of the disease has been experimentally demonstrated. However, infectious disease and cancer can also be viewed as two *bio-logically* incommensurable diseases requiring alternative experimental and theoretical frameworks (Garcion *et al.* 2009). The cell culture method derived from microbiology has given the cancer cell cult status. The tendency of experimental cancer research to transform its purposes to make them fit into the experimental and conceptual frameworks of medical microbiology has not been sufficiently considered. One consequence of this dependence on microbiological paradigms is that cancer therapies, such as chemotherapy, focused on the destruction of cancer cells in the same way that antibiotics target bacteria, with the same consequences for the emergence of drug-resistant variants. Another consequence was underestimating for a long time other necessary causal agents such as non-tumourigenic cells and, as discussed below, the extracellular matrix (ECM) (Bissell and Radisky 2001).

5. Tumour: Symptom versus disease

The other component of the proposed 'space-time' framework is space. In the case of solid tumours, the cancer disease was primitively conceptualized in space as a *tumour mass*. This led to the clinical assumption that the tumour mass is the disease, with the consequence of legitimizing therapies focusing on tumour eradication. However, the alternative view of considering the tumour not as the disease but as a symptom of the disease has been given scant attention. This small paradigm shift radically changes views on what the disease is and what its therapy should be.

A symptom, once interpreted as a clinical sign by the physician, marks a disease, but it is not necessarily its causal factor. From a functional viewpoint, symptoms can also be interpreted as physiological means of fighting diseases (consider, for example, inflammation, fever, diarrhea, etc.). Suppressing symptoms can be viewed by patients and from a clinical standpoint as curing the disease. Arguing that suppressing symptoms suppresses the disease, however, is debatable. It is critical to discern from among the symptoms used to define a disease, the ones are the direct cause of the disease from those that are part of defence mechanisms. From a therapeutic standpoint, the former category of symptoms should be eradicated whereas the latter should be promoted. Cancer cells can be assigned to the first category. The situation might be somewhat different with the tumour, at least in the early phase.

Cancer, as a disease, is a process. During this process a physiological response developed as initially as a defence mechanism can be perceived as a causal symptom if it fails

to halt the progression of the disease or if its prophylactic function is perverted. The causal relationships between cancer as a disease and tumour as a symptom are deeply intertwined. Thus, it is difficult to imagine tumour formation as a defence mechanism whose dysfunction becomes a necessary causal factor in the course of the cancer process. When clinicians look at the disease progression, biologists should look at defence mechanisms for fighting the disease and enabling organism survival. Cancer cells are subjected to pressure selection and somatic evolution. However, cancer cells do not survive patients. Mutant cancer clones evolve on the timescale of the disease. That is the difference between organism-level and somatic cancer cell-level evolution. This is an additional difference between cancer and infectious diseases. Microbes are organisms that survive patient death because of their contagious nature. In cancer disease, the evolutionary process at the organism-level has to be viewed not as somatic mutations but as defence mechanisms against cancer cell proliferation and spreading. Accumulating evidence, presented below, suggests that one of these prophylactic mechanisms is the tumour itself.

6. The paradigm shift: Tumour function as prophylactic and cancer as a defect of tumour function – the tumour continuum

> *In learning a paradigm the scientist acquires theory, methods, and standards together, usually in an inextricable mixture. Therefore, when paradigms change, there are usually significant shifts in the criteria determining the legitimacy both of problems and of proposed solutions.*
>
> *– Thomas Kuhn*

In cancer, a defect in a physiological process does not necessarily suppress the function of the process but can generate a novel function involved in the progression of the disease (Nugue and Wion 2012). Let us consider the counterintuitive hypothesis that (i) tumour physiological function is a tissue defence mechanism against cancer cells and that (ii) defects in this physiological process result in the disease of cancer. If the physiological functions of the tumour are both to confine cancer cells in a location and to maintain them in a dormant state, just as stem cell niche controls stem cell homeostasis, then failure of this prophylactic function would result in cancer cell invasion and proliferation. These are precisely the hallmarks of cancer disease.

In this paradigm shift, tumour formation is viewed as the result of an evolutionary process whose initial aim is to stall the proliferation and the dissemination of cancer cells. In other words, cancer disease is the perversion of the tumour prophylactic potential into a pathologic process. A tumour is no longer an entity but a process. In the early stage of malignancies, tumour formation acts as a cancer-suppressing process. There is a continuum between prophylactic and pathologic tumours. Both clinical observations and experimental findings support this paradigm shift, as we will explore further in the following section.

7. The prophylactic potential of tumours: Clinical observations

The prophylactic tumour concept can account for a huge amount of observations reporting that some cancers can unexpectedly stop growing or even regress. Tumour maturation, cancer of unknown primary site, latent carcinoma and tumour dormancy are some examples.

7.1 *Tumour maturation*

The observation of tumour maturation is not new. It was already described 45 years ago as a rare reversal of the tumour process involved in the spontaneous regression of some cancers (Smithers 1969). This clinical observation could be reminiscent of the reversion of the cancer cell phenotype experimentally observed *in vivo* after implantation of teratocarcinoma cells in normal mouse blastocyst (Mintz and Illmensee 1975). Maturation process has also been observed following implantation of a transformed hepatic cell line in the liver (Coleman *et al.* 1993) and with carcinogenic mammary cells implanted in mammary glands (Booth *et al.* 2011). It is important to note that tumour maturation is usually interpreted as the reversal of the tumour process, not as the recovery of a tumour prophylactic function. This point is critical. It illustrates how the words used to describe a phenomenon (here, 'reversal' vs 'recovery') are embedded in the paradigm used and affect both experimental designs and interpretations. Viewing tumour maturation as a reversal or as a recovery can be considered as a vocabulary matter. This could be also a tipping point.

7.2 *Cancer of unknown primary site*

Cancer of unknown primary site (CUP) is a heterogeneous group of tumours that accounts for 3–5% of cancer (Morris *et al.* 2010). It is diagnosed when metastases are detected in the lack of detectable primary tumour using a standard diagnostic approach (Pavlidis and Pentheroudakis 2012). Although immunohistochemistry and transcriptomic profiling can now assign the tissue of origin, CUP is still considered a 'biological mystery' (Greco 2014). In the new paradigm proposed, CUP would result from partial failure of the prophylactic tumour function, which would have limited both cancer cell proliferation and dissemination. In CUP, the primary tumour would have been unable to avoid

the early spread of metastasizing cancer cells while being successful in limiting cancer cell proliferation locally in the primary site either through tumour maturation/regression or through the process of dormancy.

7.3 *Latent carcinoma*

Latent carcinoma, also viewed as 'cancer without disease' (Folkman and Kalluri 2004), was first described in the middle of the 20th century from a routine necropsy in the absence of clinically identified carcinoma (Andrews 1949; Franks 1954). These subclinical cancers meet the pathological definition of cancer, but they have not grown to cause symptoms (Welch and Passow 2014). For that reason, the term 'tumour without disease' might be preferred. This warrants the distinction between 'tumour' and 'cancer'. *Pathologic* tumours constitute cancer disease. *Prophylactic* tumours result in latent carcinoma. These seemingly implausible cancers have been a provocative but relatively marginal issue for a long time. This was in part due to the absence of an adequate corresponding theoretical framework able to explain them. The situation recently changed when it became apparent that (i) donor-related transmission of cancer can occur after transplantation of an apparent disease-free organ several years after the removal of a primary carcinoma in the donor (Strauss and Thomas 2010) and (ii) latent carcinoma commonly encountered for many cancers including prostatic, mammary and thyroid cancers lead to over-diagnosis and over-treatment (Esserman *et al.* 2014; Welch and Passow 2014). Indeed, current progress in biological sciences and technology now allow the detection of anomalies which are either silent for the patient or not readily observable in clinical examination. Strong arguments favour the role of tissue micro-environment in restraining cancer progression (Bissell and Hines 2011). Mechanisms involved in these processes are progressively revealed and are part of the concept of tumour dormancy, as detailed below.

7.4 *Tumour dormancy*

In 1954 the expression 'dormant cancer cell' was coined by Hadfield to describe cancer cells that are 'in a state of temporary mitotic arrest, no matter how long the period may be' (Hadfield 1954). Nowadays, the term tumour dormancy is used for delayed recurrence (>5 years) due to the long-term persistence following treatment of occult cancer cells or micro-metastases. It is commonly observed in many patients with breast, prostate, kidney cancers or melanoma. Tumour dormancy in the recurrence of cancer in patients already diagnosed for a primary cancer corresponds to metastasis dormancy. More than a century of clinical observations demonstrate that metastasis dormancy can be suppressed following surgical resection of the primary tumour (Demicheli *et al.* 2008) . Of course, this does not deny the utility of tumour resection, just as over-diagnosis, does not deny the importance of cancer screening. Nevertheless, it provides further evidence for the existence of a tumour prophylactic potential.

In its broad sense, tumour dormancy includes single cell and micro-metastases dormancy. The mechanisms involved in single cancer cell and micro-metatstasis dormancy are not identical. Single cell dormancy is usually considered as due to cell-cycle arrest. In contrast, micro-metastasis also includes a balance between proliferation and apoptosis (Holmgren *et al.* 1995). This is the point; in micro-metastasis or latent carcinoma dormancy, what is dormant is the disease, not the tissue or the cancer cell. Tumour dormancy is an active process. A cancer cell enters dormancy as a consequence of inhibitory signals. Paradoxically, such signals can be triggered by oncogenes in the process called oncongene-induced senescence (OIS) (Serrano *et al.* 1997; Collado and Serrano 2010). Other signals, such as BMP or neoangiogenesis blocking agents such as angiostatin, endostatin (O'Reilly *et al.* 1994; Gately *et al.* 1996; Nyberg *et al.* 2005) and thrombospondin-1 (Good *et al.* 1990; Naumov *et al.* 2006; Bissell and Hines 2011), are produced by tumour or cancer cells. The idea that the normal tissue micro-environment can act as a barrier to tumourigenesis is now widely accepted (Bissell and Hines 2011). The new paradigm we propose goes one step forward. It suggests that tumour formation is initially a defence mechanism against cancer cell spreading and proliferation. Cancer is the result of the failure of the tumour to fulfill its prophylactic function. In this model, latent carcinoma and micro-metastasis correspond to the time period during which the tumour exerts its physiological/prophylactic function of cancer cell containment. This reversal of perspective is important. Tumour growth is usually considered an active process and tumour dormancy is viewed as a passive one. For that reason, tumour dormancy is viewed as a failure of the tumour process. Associating growth with success, however, is a sociocultural bias, not a biological conclusion. In the proposed paradigm shift, in which the tumour protects the organism from cancer cell proliferation and dissemination, dormancy is the relevant successful active physiological process. For that reason, the term 'cancer dormancy' should be preferred to 'tumour dormancy'. How many experiments with rodents failing to develop experimental tumours were or still are discarded without further analysis, while they may be developing one of the most critical anti-cancer biological processes? We will never know. As Barber remarked, 'scientists are sometimes the agents, sometimes the objects, of resistance of their own discoveries' (Barber 1961).

Viewing tumour dormancy as an active physiological process offers the opportunity to understand the induction

of the dormant state and to reproduce it for therapeutic purposes. It provides also a conceptual framework for addressing over-diagnosis and over-treatement.

8. The prophylactic potential of tumour: Experimental evidences

Viewing tumours as evolutionary defence mechanisms of the organism against cancer cells should not be viewed as a provocative posture. The prophylactic potential of tumour is not only suggested by clinical observations, but is now supported by experimental and mechanistic evidences just waiting to be gathered in a unifying paradigm.

8.1 *Protective function of the tumour mass against metastasis growth*

The first observation that could have suggested the prophylactic potential of tumours can be traced back to 1905 in the Ehrlich and Apolant's experiments of double inoculation (cited by Demicheli (Demicheli *et al.* 2008)). They observed that an experimental primary tumour delayed the growth of a secondary one (cited by Demicheli (Demicheli *et al.* 2008)). Their interpretation was that the already established tumour withdraws special nutritive substances required for the secondary tumour growth (Demicheli *et al.* 2008). A few years later, Marie and Clunet observed the capacity of tumour surgical resection to enhance cancer growth at metastasis sites, an observation later confirmed both experimentally and in some patients (Demicheli *et al.* 2008). One mechanistic explanation for the inhibition of metastasis growth by tumour mass was provided more than 80 years later. It was demonstrated that, in the experimental models of cancer used, the primary tumours produce and release angiostatin, an anti-angiogenic factor sufficient to induce micrometastasis dormancy (O'Reilly *et al.* 1994; Holmgren *et al.* 1995; Guba *et al.* 2001). The observed effect is a systemic prophylactic process. It originates in the primary tumour and provides one explanation for the existence of latent carcinoma and spontaneous tumour regression. Unfortunately, pro-angiogenic factors are also produced by primary tumour. Shifting the balance between pro- and anti-angiogenic factors in favour of angiogenesis is, in these experimental models, the condition for tumour growth and cancer disease.

These experiments unambiguously identify the production of circulating anti-angiogenic factors by the tumour. They illustrate one mechanism by which tumour can exert a prophylactic potential. This does not question the therapeutic importance of tumour removal that decreases metastasis incidence by suppressing the primary source of metastasing cells. Nevertheless, this also raises the possibility that a systemic global cancer dormancy state could be induced by a network of dormant prophylactic micro-tumours mutually controlling their dormant state. If this hypothesis turns to be correct, over-treating dormant tumours might have the adverse effect of disrupting the regulation of this cancer-suppressive network.

Other evidence that demonstrates the existence of mechanisms restraining local tumour progression and aggressiveness in the tumour have been recently produced. They concern the interactions between the tumour and its stroma (Bissell and Radisky 2001; Ozdemir *et al.* 2014; Rhim *et al.* 2014).

8.2 *Protective function of tumour stroma in cancer disease*

A tumour is made of cancer cells and stroma. Cellular components of tumour stroma include fibroblasts and cancer-associated fibroblasts, pericytes, smooth muscle cells and endothelial and immune/inflammatory cells. All these cells including cancer cells are embedded in a three-dimensional protein-rich extracellular matrix (ECM). In the current dominant paradigm, the tumour grows because stroma components provide the appropriate tumour micro-environment for this growth. A large amount of experiments and clinical data support this view (Joyce 2005; Tlsty and Coussens 2006; Arendt *et al.* 2010; Pietras and Ostman 2010). Hence, antagonizing stroma functions is considered a promising therapeutic strategy (Albini and Sporn 2007; Hiscox *et al.* 2011; Franco and Hayward 2012; Tchou and Conejo-Garcia 2012). Evidence that the tumour micro-environment restrains cancer progression exist (Bissell and Radisky 2001; Bissell and Hines 2011; Quail and Joyce 2013; Ozdemir *et al.* 2014; Rhim *et al.* 2014). The recent demonstration that attenuation of tumour stroma formation leads to a more aggressive phenotype in experimental models of pancreatic ductal adenocarcinoma (Ozdemir *et al.* 2014; Rhim *et al.* 2014) is in agreement with this. Tumour stroma is now viewed as a structure balancing between anti- and pro-carcinogenic functions (Bissell and Radisky 2001; Quail and Joyce 2013) .

9. Viewing cancer disease as an extracellular pathology: Cancer is also an ECM disease

The concept of a cell is, strictly speaking, only a morphological abstraction. Seen from a biological viewpoint, a cell cannot be considered by itself without taking its environment into account.

– Alfred Pischinger

The idea that the micro-environment is involved in cancer progression is not new. The 1889 Paget's seminal 'seed and soil' hypothesis pointed to the dependence of cancer cells (the seed) on their environment (the soil) in the metastasis

process. Dvorak's view that tumours are wounds that do not heal also considers the role of stroma in tumour growth (Dvorak 1986). The importance of considering cancer as a problem of tissue disorganization that necessarily implies micro-environment, and not exclusively as a cancer cell-based disease, has been extensively discussed by Smithers, Sonnenschein and Soto, and Bissel, among others (Smithers 1962; Bissell and Radisky 2001; Bissell and Hines 2011; Sonnenschein and Soto 2011). A huge amount of experimental and clinical data demonstrates the importance of the tumour stroma micro-environment in cancer disease (Mueller and Fusenig 2004; Joyce 2005; Bissell and Hines 2011; Quail and Joyce 2013). Targeting the tumour micro-environment is considered a complementary strategy to cancer cell cytotoxic therapies (Joyce 2005; Kenny *et al.* 2007; Ingber 2008; Allen and Louise Jones 2011).

Our conception of the role played by the micro-environment in cancer has been partially biased for a long time. Most initial studies focused on the supportive role of stroma in tumour growth but less on its cancer-suppressive functions. Even nowadays, 'reactive' tumour stroma is still largely considered as an 'activated' micro-environment made of 'activated' cells harboring 'activated' signalling pathways. Cancer associated fibroblasts are considered as 'activated' because they support cancer growth. In the reversed perspective where stroma controls tissue homeostasis, however, it is also the inhibition of the stroma cancer-suppressive potential that makes cancer disease. This bipolar function of stroma has been already discussed (Mueller and Fusenig 2004; Bissell and Hines 2011). It is consistent with the concept of the tumour prophylactic/pathologic continuum and provides one explanation for tumour dormancy.

As discussed above, one major component of cell stroma is ECM. Because ECM is a non-cellular component, considering ECM as a causative factor for cancer disease introduces an additional paradigm shift. Cancer is no longer viewed exclusively as a cell-centered disease but also as an extracellular pathology. As provocatively put by Smithers: 'should we analyse individual cars to understand a traffic jam?' (Smithers 1962). From a functional standpoint, ECM constitutes the dynamic scaffolding that gives physical support to cells. It is made of proteins, proteoglycans and polysaccharides. In addition, ECM meshwork also plays a critical role in controlling cell fate, notably during morphogenesis, tissue renewal, and repair in all tissues including stem cell niches (Watt and Huck 2013; Gattazzo *et al.* 2014). Mechanosensing and mechanotransduction are two of these processes by which cells sense ECM mechanical and physical cues through cell transmembrane adhesive proteins such as integrins, discoidin domain receptors and syndecan (DuFort *et al.* 2011; Schiller and Fässler 2013). These interactions activate many intracellular signal transduction pathways which control cell differentiation, proliferation and migration (DuFort *et al.* 2011; Hoffman *et al.* 2011).

Two other families of ECM proteins critically involved in controlling the flux of information between cells and ECM are matrix metalloproteinases (MMPs) and their endogeneous inhibitors called tissue inhibitors of metalloproteinase (TIMPs). MMPs are involved both in ECM turnover that remodels ECM scaffolding, and in the release of ECM-sequestered growth factors such as VEGF, bFGF and TGF-β. Importantly, MMPs have a dual effect as they also release anti-angiogenic factors such as endostatin and tumstatin from ECM and basement membrane components (Hamano et al. 2003; Heljasvaara *et al.* 2005; Martin and Matrisian 2007; Fukuda *et al.* 2011). The balance between MMP and TIMP activities is therefore essential for tissue homeostasis. Other matrix-associated proteins such as lysyloxydases or transglutaminase also play critical functions in modulating ECM structure (Kotsakis and Griffin 2007; Mayorca-Guiliani and Erler 2013).

These are only a few examples that show how ECM organization and composition control cell behavior and tissue homeostasis. Not surprisingly, during tumour progression, cancer associated fibroblasts, immune cells and cancer cells induce profound remodeling of tumour ECM that in turn influences the behavior of stromal cells. 'Cells make ECM, and ECM structures cell behavior' (Bissell *et al.* 1982). For that reason, cells and ECM should not be viewed as two distinct entities, but as components of a dynamic system, the tumour prophylactic–pathologic continuum. Any perturbation in ECM structure can alter tissue homeostasis and can lead to cancer cell proliferation and spreading, depending on the context. ECM remodeling is both a consequence and a causal cofactor in the development of cancer. Because it surrounds cancer cells, ECM can be viewed, at least etymologically speaking, as the circumstance ('circum'-around + 'stare'- to stand) of cancer. ECM is the 'circumstance' in which the cancer cell is embedded. It is 'circumstance' that makes tumour prophylactic, pathologic, or indeterminate, all these three states coexisting in the same tumour continuum.

10. Conclusions and perspectives: From paradigm shifts to cancer prevention and therapy

The therapeutic challenges posed by many cancers remain. Curing cancer is rare. Hence, the recurrent question is to what extent a scientific problem can be solved in the paradigm frameworks from which it originated. A possible way to tackle the problem is to use the 'paradigm shift' as a method of scientific inquiry. In the case of cancer research, this first requires identifying which paradigms grounded its emergence as a scientific object. Cancer research at end of the 19th and the beginning of the 20th centuries incorporated most of the conceptual, experimental and technological principles issued from microbiological medicine. The logical

implication of this 'microbiological framework' is that cancer appeared as an ersatz of infectious disease in which cancer cells are isolated and then conceptualized as organisms, i.e. microbe avatars. Application of the 'paradigm shift' principle as a method of investigation introduces several reversals of perspective, with implications in both cancer prevention and treatment.

A first paradigm shift views the tumour as a prophylactic–pathologic continuum. The fact that the tumour is embedded with prophylactic potential and that cancer is the reversal of this prophylactic potential into a pathologic one enlightens one challenge encountered by some targeted therapies. A prevision of the tumour prophylactic–pathologic continuum is that the same molecule or process viewed as a therapeutic target at the pathologic edge of the continuum could also behave as an anti-target at the prophylactic opposite end. For example, VEGF is a therapeutic target but is also anti-target since hypoxia can increase the tumour cancer stem cell pool and fuels metastasis (Loges *et al.* 2009; Conley *et al.* 2012; Nugue and Wion 2012). Some MMPs, initially considered as therapeutic targets for their role in EMC remodeling and cancer invasion are also viewed as anti-targets in regard to their ability to release anti-angiogenic and anti-inflammatory molecules (Dufour and Overall 2013). Likewise for the bipolar function of TGFβ: cancer-suppressive at one end of the continuum and involved in cancer progression at the other end (Ikushima and Miyazono 2010; Pickup *et al.* 2013; Principe *et al.* 2014). An additional example is provided by certain oncogenes that govern proliferation and senescent and apoptotic processes. Ras oncogene-induced senescence or Myc induced-apoptosis illustrate how oncogenes can be either targets or anti-targets, depending on the context (secondary lesions, micro-environment, etc.) (Lowe *et al.* 2004) . Indeed, the fact that a PubMed search with the keywords 'friend, foe, cancer' generates almost 200 entries is an indirect assessment of the relevance of the target/anti-target challenge in cancer therapy.

Another paradigm shift leads us to consider cancer as an extracellular pathology. As extensively discussed above, cancer disease was for a long time exclusively considered a cell disease at the expense of the role played by extra-cellular matrix. The role of ECM in cancer disease is nowadays acknowledged. Cancer can no longer be considered exclusively as a 'cellular pathology'. A systematic use of the 'paradigm shift' principle to question our dominant paradigms could have greatly accelerated the discovery that cancer is also an extracellular pathology, namely a disease of interactions, and the role played by the extracellular matrix in this process. A consequence of this paradigm shift is that identifying potential ECM-disrupting compounds in household and industrial products should be now a major public health concern. Also, it is important to note that a side-effect of almost all cancer therapies is to alter ECM mesh work and that, to date, none of cancer therapy has demonstrated any efficiency in repairing ECM structure and restoring its homeostasis function. These points must be integrated into future therapeutic protocols.

A third paradigm shift concerns cancer therapy. The search for targeted therapies ('magic bullets') aims to target special cells or specific cell functions. Application of the 'paradigm shift' method leads to a reversal of perspective in which cancer cells are no longer considered the target but the 'magic bullet' itself. This paradigm shift gave birth to the development of the cancer cell trap or tumour trap concepts, in which cancer cells are the 'bullets' that target a therapeutic trap where cancer cells are eliminated (van der Sanden *et al.* 2013; Jain *et al.* 2014). These are just a few examples illustrating the potential of the 'paradigm shift' as a method. Finally, the ultimate paradigm shift could come from a 2500 year old quote attributed to Sun Tzu: 'The supreme art of war is to subdue the enemy without fighting'. Rather than serving the cancer war machine, it is time to rethink the problem of cancer therapy in terms of *diplomacy*.

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