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Cancer as a form of life: Musings of the cancer and evolution symposium☆

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ABSTRACT

Advanced cancer is one of the major problems in oncology as currently, despite the recent technological and scientific advancements, the mortality of metastatic disease remains very high at 70–90%. The field of oncology is in urgent need of novel ideas in order to improve quality of life and prognosis of cancer patients. The Cancer and Evolution Symposium organized online October 14–16, 2020 brought together a group of specialists from different fields that presented innovative strategies for better understanding, preventing, diagnosing, and treating cancer. Today's SoC, the main reasons behind the high incidence and mortality of advanced cancer are, on one hand, the paucity of funding and efort directed to cancer prevention and early detection, and, on the other hand, the lack of understanding of the cancer process itself. I argue that besides being a disease, cancer is also a form of life, and, this frame of reference may provide a fresh look on this complex process. Here, I provide a different angle to several contemporary cancer theories discussing them from the perspective of "cancer *Bios* of Life" (i.e. biotic) point of view. The perspectives and the several "leaps" introduced here, by no means exclusive or comprehensive, are just a shortcut that will hopefully encourage the readers to further explore the contemporary oncology theoretical landscape.

Introduction The purpose of the Cancer and Evolution Symposium organized online between October 14–16, 2020 was to take a fresh look at cancer related problems and to investigate through a multidisciplinary approach new models and innovative diagnostic and therapeutic modalities in order to improve the quality and duration of life for cancer patients.

Advanced cancer represents one of the major problems in oncology as now, despite the recent technological and scientific breakthroughs, the mortality of metastatic disease is still as high as 70–90%. In the American Cancer Society 2020 statistics, the cancer death rate declined by 29%, from 1991 to 2020, including a 2.2% drop from 2016 to 2017, the largest single-year drop in cancer mortality ever reported (ACS website).

On the other hand, as Dr. Azra Raza pointed out in the opening session of the symposium, cancer mortality did not improve since 1990, when the government began keeping records of cancer patients. In fact, it is sobering to note that in the United States in 1930 cancer deaths were 110,694 in a population of 123 million compared with approximately 608,570 cancer deaths in a population of approximately 328.2 million in 2020, which means that cancer mortality has significantly increased in the last 90 years (Siegel et al., 2020). 80% of cancers occur after the age of 55 (Jemal, 2006; De Gregori, 2018; Wenger et al., 2020; ACS website) and this fact can only be partially explained by a parallel increase in the average life span of US population from approximately 59 years in 1930 to more than 78 years in 2020.

1. Early diagnosis

The first speaker, Azra Raza, the author of the "The First Cell: And the Human Costs of Pursuing Cancer to the Last", a deeply moving exploration of cancer from multiple perspectives, (Raza, 2019), proposed the use of new technologies like circulating tumor DNA (ctDNA) (Fisher et al., 2013), circulating tumor cells (CTCs) and DNA methylation, to detect cancers at an early stage. She also suggested that an earlier stage detection will lead to improvement of cancer survival. For some cancer types, like lung cancer, for example, this proposal is clinically relevant and, another speaker, Bonnie Anderson, Founder, Chairman & CEO of Verocyte, Inc., announced the introduction in 2021 of a nasal swab test using an

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RNA-whole transcriptome sequencing platform for early characterization of lung cancer nodules found on low-dose CT scans done for lung cancer screening in smokers. The introduction of this platform may improve the detection performance of the low-dose CT scans as demonstrated recently by Tammemägi et al. (2019). It is important to note though, that in one study, only 1.5% of the lung nodules detected through the yearly screening program were malignant (Kaminetzky et al., 2017). Also, the behavior of some cancers, like breast or prostate, for example, may be heterogeneous. Some of these tumors may have a benign behavior for cancers, neither invading locally, nor metastasizing and, consequently, the global, indiscriminately screening programs for breast and prostate cancers, may lead to over treatment of some patients without demonstrated survival improvements (Barratt et al., 2005; Wegwarth and Gigerenzer, 2013; Welch et al., 2016). What is clearly needed is the implementation of biomarkers that are able to detect early tumors with an aggressive potential. Recently, for example, the results of a large clinical study demonstrated that using MyProstateScore provided exceptional sensitivity and negative predictive value for ruling out aggressive prostate cancers, and may reduce the need for invasive testing in men referred for diagnostic prostate biopsy (Loeb et al., 2015). MyProstateScore test uses a multivariable model of serum prostate specific antigen, urinary prostate cancer antigen 3 and urinary TMPRSS2:ERG gene fusion presence.

2. Cancer prevention

The best way to address cancer is, of course, to prevent its initiation in the first place. Several personal life style changes can decrease cancer incidence and recurrence including exercise, dietary changes, weight reduction and smoking cessation. According to American Cancer Society, in the United State, smoking cessation alone can prevent 480,000 yearly cancer deaths (ACS website).

A futuristic perspective of cancer prevention was introduced by George Church who presented several applications of multiplexed eukaryotic gene editing (Church, 2015; Isaacs et al., 2011). His lab successfully replaced all known UAG stop codons in an *Escherichia coli* strain MG1655 with synonymous UAA codons (Lajoie et al., 2013). The synthetic bacteria exhibited increased resistance to T7 bacteriophage, demonstrating that new genetic codes could enable increased viral resistance. More recently, he demonstrated the strength of genomic editing by removing from the pig genome all porcine endogenous retroviruses (PERVs) (Niu et al., 2017a). These experiments lead to the intriguing idea that, in the near future, the human genome can be also edited and made viral infection resistant, thus preventing the development of virus induced cancers (HPV induced cervical and head and neck cancers, for example).

3. Understanding cancer as a form of life

The March 28, 2014 cover of Newsweek magazine read "you can't cure what you can't understand" alluding to the fact that the main reason behind our failure to find a cure for cancer is our lack of deep understanding of the cancer process.

The Cancer and Evolution symposium was mainly an effort in bringing forth several ideas that may be implemented in the near future and improve cancer prognostic by adopting novel, more efficient paradigms.

A suggestive analogy between the Cambrian explosion of new life forms and cancer macroevolution, made by Kenneth Pienta, James Shapiro and Henry Heng, and, the idea that cancer is a form of life, was the leitmotif of several symposium presentations. Denis Noble's model of purposeful randomness, Henry Heng's genome chaos theory, Kenneth Pienta's and JinSong Liu's introductions to the polyploid cell cycle concept, Charles Swanton work on clonal diversity and chromosomal complexity, James Shapiro and Perry Marshall investigations of cellular cognition, and Mark Levin's bioelectricity experiments were only some of the Symposium's highlights.

As Harold Varmus pointed out in his 1989 Nobel Banquet speech (Nobel Prize speech, 1989), cancer cells are a "distorted version of our normal selves". Properties that have been classically associated with cancer (i.e. the Warburg effect or genetic instability) are also present in different types of normal cells. Aerobic glycolysis is not only related to cancer but seems to also be the "hallmark of rapid proliferation" and the preferred metabolic program of normal cells when robust transient responses are needed (Vander Heiden et al., 2009). The hypermutator phenotype associated with cancer is also present in normal B and T lymphocytes. As opposed to cancer where it seems to represent a random phenomenon (please see for a discussion, Loeb et al., 2008), in normal lymphocytes it is highly regulated. Immunoglobulin genes are assembled during early B cell development and their variable (V) regions are further modified by somatic hypermutation occurring in germinal centers in mature B lymphocytes stimulated by antigen (Stavnezer, 1996), with the important distinction that in B cells these mutations are targeted only to the V region, beginning ~150 to 200 bp downstream of the promoter, and extend ~1.5-kb further downstream (Storb, 1996; Kinoshita et al., 2004; Liu et al., 2008). Also, like cancer cells, stem cells are immortal (Pepper, 2008). With one notable exception, all of the cancer hallmarks introduced by Hanahan and Weinberg, initially in 2000 and, then in 2011 (Hanahan and Weinberg, 2000; Hanahan and Weinberg, 2011), may be also present in different types of normal cells or non-cancerous conditions (i.e. infections, benign tumors) (Gatenby, 2009). The ten hallmarks are: self sufficiency in growth signals, insensitivity to growth inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, genetic instability and mutation, sustained angiogenesis, tissue invasion and metastasis, tumor promoting inflammation, deregulated energetics, and avoidance of immune destruction. The notable exception-chromosomal instability (CIN)-present in many solid tumors, is also present in several congenital CIN syndromes in which the patients affected are predisposed to cancer but only a minority of them develop cancer during their lives (Rajagopalan et al., 2003). Also, the presence of aneuploidy, another cancer hallmark, has been demonstrated in samples of normal liver, brain, and skin (Knouse et al., 2014).

Reversely, the hallmarks of life, introduced by Walker and Davies in 2012, may apply to cancer (Walker and Davies, 2012). Two of the hallmarks of life (globe, organization and top down causation) that, at the first glance, seem not to be shared by cancer, have been also associated to cancer in recent reviews (Paul, 2020a; Green, 2021). Macroscopically, experimental data accumulated over more than a decade, supports the concept of a cancer system formed by several geographically separated cancer tissues (the primary tumor, the local and the distant metastasis), co-dependent with the host body systems (Paul, 2020). Top-down causation is "a relation between system variables operating at different scales" (Green, 2021), and, in his paper, Green presents examples of interventions on higher-scale factors (tissue stiffness) that influence the behavior of lower-scale variables (gene expression and cellular behaviors) (for a discussion on this topic, see also the paper by Paul and Komarova in this issue).

What type of form of life is cancer anyway? I will briefly examine different cancer-like forms candidates, -or bionts as called here, -some of them discussed in the symposium-, others briefly alluded or not discussed at all. In order to present a broader view of the contemporary oncology theoretical landscape, I systematized

the various cancer theories into three large categories and, each in several sub-categories. The speakers presented data supporting more than one theory and my classification is by no means exclusive or comprehensive. They rather represent a shorthand that may encourage readers to explore them further. For a critical discussion of current cancer theories, please see also Henry Heng's book "Debating cancer The Paradox in Cancer Research" (Heng, 2008).

4. Three perspectives

To classify the biotics presented below, first I divided them in two broad categories according to two perspectives familiar to the physics community: the substantivalist approach, focused mostly on material entities and structures, and, the relationist approach, focused on the relationships between them. This dichotomy that became popular since the Newton-Leibnitz debate on the nature of space-time (Dooley, 2012), is highly significant also for Biology as has been pointed out by Denis Noble (2013). The substantivalist approach can be further sub-divided in two separate branches: a spatial perspective kindred to anatomy and a temporal perspective related to embryology and evolution. Relationist perspectives are physiology oriented and often use the explanatory tools of systems theory and networks dynamics.

5. The spatial perspective

5.1. Cancer as an abnormal growth

The oncobiotic The Latin term "oncos" means "swelling, growth" and was introduced by Galen in the second century to refer to tumors and cancer in general. Even though the phenomenon of metastasis has been known for several centuries (Weiss, 1989), until recently, cancer treatment has been focused mainly on growth inhibition.

For a long time, growth has been considered the main cancer characteristic. As recent as in 2000, in the frequently cited hallmarks of cancer article, Hanahan and Weinberg described cancer as composed of cells with "defects in regulatory circuits that govern normal cell proliferation and homeostasis" (Hanahan and Weinberg, 2000). The tumoricentric view is not wrong, per se: some cancers kill patients by excessive tumor growth and, if we could better control cancer growth with minimum side effects, cancer might become a chronic disease, like diabetes. Unfortunately, with few notable exceptions, in most cancer cases, there are no drugs that can control cancer growth for a prolonged period. Metastatic disease is considered incurable mainly because, although systemic treatments may prolong the life of some patients, most of them will succumb due to a combination of uncontrolled cancer growth and cancer induced systemic complications.

Chemotherapy agents are drugs that have been designed to stop or to slow down the growth of cancer cells. On March 15, 1949, Mechlorethamine has been the first FDA approved chemical agent for the treatment of cancer, and for 43 years, until Interleukin-2 FDA approval in 1992, various classes of chemotherapy agents have been the only therapeutic options available for cancer treatment.

Chemotherapy benefits should not be dismissed. Chemotherapy cures the majority of advanced pediatric cancers, and, in addition, it also cures the majority of testicular cancers in men and choriocarcinomas in women, and also improves the quality of life and survival of many cancer patients. Anecdotally, there are also several reports of various types of metastatic cancers considered incurable, cured by standard chemotherapy (see, for example, Bardia et al., 2014; Paul et al., 2004). Why are these cancer types so responsive to chemotherapy? In general, we do not know the answer, but in testicular cancer, for example, it has been shown by a group from Cornell University that cancer stem cells that are usually resistant to chemotherapy, are more sensitive than the other cells in testicular tumors (Pierpont et al., 2017).

The main issue with chemotherapy agents given either alone or in combinations though, is that, except for the tumor types cited above, they do not work as well for the majority of cancers and their use in metastatic disease is considered palliative, and not curative. Also, unfortunately, as it is becoming more and more apparent, sometimes they may accelerate cancer progression (for a recent review see Middleton and al., 2018).

5.2. Cancer as an accumulation of random genetic alterations. The emperor of all theories

The current dominant paradigm in oncology, popularized by books like "The emperor of all maladies" considers cancer a disease due to random genetic alterations. In this paradigm, cancer-driving mutations or translocations are thought to disrupt cellular activities by modifying the function of one of three broad classes of genes: oncogenes, which activate neoplastic activity; tumor-suppressor genes, which decrease cell's ability to inhibit abnormal cell proliferation, and stability genes, which affect cell's damage repair mechanisms (Kinzler and Vogelstein, 1997; Vogelstein and Kinzler, 2004). It has been speculated that a first causal alteration in one of these classes of genes may lead to the initiation of tumorigenesis; subsequent causal mutational events are needed in order to drive tumor progression by providing a selective advantage to cancer cells through positive selection (Bozic et al., 2010; Nowell, 1976; Vogelstein and Kinzler, 2004; Wood et al., 2007).

Mutations got most of researchers' attention because such genetic alterations are considered permanent in the cell' life as opposed to epigenetic transformations considered mostly transitory. The consequence of these mutations is thought to be the rewiring of key intra-cellular signaling pathways, and also the fact that cancer cells become "addicted" to the (hyper) activity of a mutated protein belonging to a particular pathway. The term "oncogene addiction" has been initially introduced by Bernard Weinstein in 2000 and subsequently and, in 2002, a slightly modified definition was proposed by the same author (Weinstein, 2002, 2000). The "oncogene addiction" concept postulates that some tumors rely on "one single dominant oncogene for growth and survival, so that inhibition of this specific oncogene is sufficient to halt the neoplastic phenotype" (Luo et al., 2009). Cancer cells are seen as dependent or "addicted" to oncogenes that were initially acquired during multi step tumorigenesis and remain critical to the ongoing proliferation and viability of these cells long after they have progressed to a fully neoplastic state (Weinstein and Joe, 2008). A classic example are the VHL gene alterations in renal cell carcinoma (Del Bigio et al., 2012). In the last two decades or so, the concept of "oncogene addiction" has been extended to the idea of a "signaling pathway addiction" and cancer has been viewed as a „signaling pathway disease" (Sever and Brugge, 2015).

The genes responsible for this "bizarre circuitry" present inside the cancer cells (Vogelstein et al., 2013) are called "driver" genes in order to point to their relevance for the cancer process (they are the "drivers" of the cancer process) as opposed to "passenger" genes which are also genes mutated in the cancer cells but are considered to lack oncologic pathophysiologic relevance. The protein products of the "driver" genes confer growth advantage to the cells harboring them and, therefore, have been positively selected during the cancer evolution.

At the genetic level, each individual cancer has a unique make-up harboring idiosyncratic genetic „driver" alterations. Vogelstein et al. (2013) described an ingenious "20/20 rule" to detect the

„driver" genes. Their proposal was to identify a "driver" gene based on the pattern of the mutations rather than on the frequency of mutations of a specific gene in a certain tumor. To be classified as a "driver" oncogene, their requirement was that >20% of the recorded mutations in a specific gene are at recurrent positions and are missense. To be classified as a "driver" tumor suppressor gene, a similar requirement that >20% of the recorded mutations in the gene are inactivating was imposed (Vogelstein et al., 2013).

The term "biological targeted therapy" or simply „targeted therapy" refers to a new generation of cancer drugs designed to interfere with a specific molecular target (typically a protein) that has been proven to represent a "driver" of the oncologic process and has a critical role in tumor growth or cancer progression. Thus, the oncogene „addiction" described initially by Weinstein represents a rationale for molecular targeting in cancer therapy (Weinstein and Joe, 2006).

Since Paul Ehrlich and his "magic bullet" idea (Strebhardt, 2009), identifying unique cancer features that can be targeted with minor side effects on normal cells has been a relentless pursuit. The development of a plethora of targeted agents (Druker et al., 2001) and, in fact, the whole new field of precision medicine is based on the paradigm of cancer as an oncogene-addiction caused by driver genes alterations.

The first member of the new class of cancer targeted molecular agents was introduced by Brian J. Druker in 1996 (Druker et al., 1996), who used STI571, a small-molecule inhibitor, currently known as imatinib mesylate (Gleevec), for the treatment of chronic myelogenous leukemia (CML). Trastuzumab (Herceptin), a chimeric antibody directed against the epidermal growth factor receptor 2 (EGFR2) present on the surface of breast cancer cells, was the first targeted agent approved in 1998. Since the approval of trastuzumab there are multiple agents approved for different indications in solid tumors and hematological malignancies with variable efficacies. Imatinib mesylate has been one of the most successful of the targeted molecular agents and has been approved since 2001 for the treatment of chronic myeloid leukemia (CML). The long-term follow-up data of imatinib showed an impressive overall survival rate with 80–90% of the patients taking this drug being alive at 10 years (Kantarjian et al., 2012).

This favorable prognosis should not make us extrapolate positive results of this level of magnitude to other tumor types, and especially to solid tumors. In contrast to the idiosyncratic etiology of CML that is driven by only one „driver" mutation, solid tumors are much more complex than CML, and numerous „driver" mutations have been described in each solid tumor type. The average number of "driver" mutations present in a particular tumor, varies among cancer types with chromophobe kidney cancer having the fewest (2 genes) and endometrial carcinoma having the most (55 genes) (Kandoth et al., 2013).

In solid tumors, the presence of only one "driver" mutation that can be targeted is rare, and, in general, solid tumors are much more difficult to treat than CML. The presence of several "driver" mutations per cancer cell genome and redundant or alternate pathways in the tumor cells makes the majority of solid tumors resistant either de-novo or after a variable course of treatment and it quickly became clear that the benefit of these "smart agents" that target epidermal or vascular growth factors and tyrosine kinases is restricted to only a subgroup of patients, for example, those with adenocarcinoma of the lung harboring certain mutations or translocations.

Moreover, genetic heterogeneity is present not only among cancers from different patients but also, inside a tumor itself. Cancer cells are not only different from normal cells, but it turns out that there is also large heterogeneity present among the cancer cells themselves. Wang and al. sequenced the genomes of individual cells from two types of breast cancer and did not find any two individual cells that were genetically identical (Wang et al., 2014). A single tumor may contain clones with differently mutated genes and, the primary tumor and the metastatic tumors, may also be genetically different. Additionally, individual metastasis may harbor different mutations (Shlush et al., 2014; Yachida et al., 2010).

The genetic mutations paradigm received a lot of media and public attention and led to the new concept of personalized oncology and, more recently, to its improved version, precision oncology. Unfortunately, in solid tumors, most genomics-driven targeted therapies (chemotherapy, tyrosine kinase inhibitors, antibodies, genetic therapy using modified viral vectors), and, in general, cancer cells directed therapies (CAR-T cells treatments, adaptive immunotherapies) are associated with partial responses mostly due to genetic, epigenetic, spatial and temporal tumor heterogeneity. Heterogeneity is only one of the many mechanisms of cancer resistance. Other mechanisms such as multi-drug resistance, poor penetration of the drug due to mechanical constraints, enhanced DNA-repair, and target gene amplification (Vasan et al., 2019) have been classically described as being responsible for treatment failure in individual cases. More recently, chromosomal instability has been described as a mechanism to circumvent oncogene addiction and is associated with therapeutic resistance in many cancer types (Bakhoum et al., 2018).

The emperor is naked. Genetic mutations alone are not sufficient to explain cancer initiation. As shown in several recent publications, same type of mutations present in cancer are also present in normal tissues (Martincorena et al., 2015, 2018; Lee-Six et al., 2019; Yokoyama et al., 2019; Moore et al., 2020). At the conference, Robert Weinberg, one of the champions of the random genetic theory, acknowledged that the mechanism responsible for the metastatic process is most likely epigenetic.

5.1.2. Cancer as an epigenetic disease. Cancer as a modified program

Besides genes, other cellular structures or mechanisms have been considered essential for cancer. An important theory in contemporary oncology, has been the epigenetic model that considers cancer an epigenetic disease (for a comprehensive review Jones and Baylin, 2007 and, more recent, Flavahan et al., 2016). Classically, epigenetic changes such as DNA methylation or histone phosphorylation, acetylation and methylation can inhibit or activate gene expression (Biswas and Rao, 2018). Over the last two decades it has been also shown that non-coding RNAs (i.e. miRNAs, piRNAs, endogenous siRNAs, and long non-coding RNAs) play an important role in epigenetic control (Wei et al., 2017) and they can contribute to all classical hallmarks of cancer (Esteller, 2008; Schmitt and Lowe, 2013). If cancer cells can switch back and forth between different phenotypes (Hanahan et al., 2000; Hanahan and Weinberg, 2000), cancer may represent a controllable cellular state that can be rerouted to a non-neoplastic phenotype (Pisa, 2020). Epigenetic treatments have a proven efficacy in the treatment of hematologic malignancies, but the promise of targeting epigenetic abnormalities has not been yet realized for solid tumors (Arrowsmith et al., 2012). A better understanding of epigenetic mechanisms is crucial because metastatic disease seems to be mainly an epigenetic phenomenon (see section 5.2).

5.1.3. Cancer as a metabolic disorder. The energobiont

Another popular cancer theory is considering cancer as a structural abnormality of mitochondria or, a mitochondrial malfunction disease, and cancer a metabolic disorder in which the metabolism has been re-routed to anaerobic glycolysis (Warburg, 1956; Seyfried, 2012; Seyfried et al., 2014). According to the

mitochondrial metabolic theory of cancer, the large genomic heterogeneity seen in tumor cells arises as a consequence, rather than as a cause, of mitochondria malfunction (Seyfried et al., 2017). Recent work supports an important role also of respiration-and, more broadly, mitochondrial metabolism-in cancer cells growth and the Warburg effect significance for human cancer has been put into perspective (Dellacasagrande and Daniel, 2020). On the other hand, given the importance of metabolism on multiple essential cancer cell characteristics (i.e. division, invasion, metastasis) and the need of advanced cancers for increased energy (Fouad et al., 2019a), cancer cells can be also seen as cells with a modified metabolism, or energobionts. Recently, cancer cells metabolism is coming more and more into focus especially because of its relevance for the metastatic process and novel therapeutic approaches have been described (Fouad et al., 2020; Gill et al., 2016). A targeted treatment approach using high glucose consumption of some tumors as a vulnerability has been recently proposed (Fouad et al., 2019b).

5.2. *Cancer as a stromal disease: The tissue connection*

5.2.1. *Cancer as a maladaptation to a transformed ecological niche. The cancer supporting tissue*

In both versions of their hallmarks paper, Hanahan and Weinberg include a large section on cancer microenvironment and describe cancer both as a genetic disease and a tissular disease. They state that "important new inroads will come from regarding tumors as complex tissues in which mutant cancer cells have conscripted and subverted normal cell types to serve as active collaborators in their neoplastic agenda" (Hanahan and Weinberg, 2000, 2011).

All previous theories described above were focused only on the cancer cells themselves. The significance of the cancer cells-host tissue interactions and, in general, the importance of the "soil" as opposed to the "seed" in cancer development, has been strongly supported by the work of Isaiah Fidler (Fidler and Poste, 1977; Fidler et al., 1988). The work of Mina Bissell (Bissell and Hall, 2013) and Robert Weinberg (Barcellos-Hoff and Weinberg, 2000) brought additional experimental evidence to the theory of cancer as caused by an abnormal microenvironment. The tissue organization field theory proposed by Carlos Sonnenschein and Ana Soto (Soto and Sonnenschein, 2011) also suggests that cancer appears as a failure of the stroma to keep cancer control individual cells. Recently, James DeGregori has been also bringing forth a similar theory of cancer as a maladaptation to an aging, transformed microenvironment (DeGregori, 2018).

Taking into consideration the tissue component of cancer opens the possibility of treating cancer indirectly i.e. treating the cancer stroma, the cancer vasculature, enhancing the immune response against cancer. Indeed, tissular-directed approaches, alone or in combination with other treatment modalities, have been demonstrated to be successful in different clinical setups.

5.2.2. *Cancer as a wanderer. The puzzle of metastasis*

The metastatic process is related to 70–90% of cancer deaths in solid tumors and, developing specific therapeutic approaches directed towards metastasis is of crucial importance.

In his presentation, Robert Weinberg, made the crucial observation that as opposed to the uncontrolled growth of malignant tumors which seems to be, the result of genetic mutations, metastasis appears to be mainly an epigenetic process. In the 2011 updated version of their original hallmarks article, Hanahan and Weinberg, have noted already that the ability of cancer cells to invade and metastasize may not require new genetic mutations in addition to those already present in the primary tumors (Hanahan and Weinberg, 2011). Also, the majority of the "metastatic genes" proposed by Massagué and collaborators more than a decade ago (Nguyen and Massagué, 2007; Chiang and Massagué, 2008) in their step by step model of metastasis are not mutated. In addition, Vogelstein et al. noted that despite considerable effort, specific genetic alterations that distinguish cancers that metastasize from cancers that do not metastasize have not been yet identified (Vogelstein et al., 2013). The immediate conclusion, drawn by the Vogelstein team, is that there are no specific metastasis genes (Vogelstein et al., 2013).

A second study described widespread epigenetic reprogramming during the evolution of distant metastasis of pancreatic cancer in the absence of metastasis-specific driver mutations (Makohon-Moore et al., 2017). Another recent study (Ngollo et al., 2017) found also that, in prostate cancer the master regulator genes of metastasis are genes involved in epigenetic regulation.

These observations suggest a different picture of the metastatic process. The plethora of genetic abnormalities present in established malignant tumors may not be the main driver of metastases. No genetic mutation or mutations have been unequivocally shown to be associated with progression from localized to metastatic disease (Gerlinger et al., 2012). Recently, therapies specifically directed towards physiologic mechanisms hyper activated in metastatic cancercells (i.e. NADPH pathway, STING pathway) have been described (Gill et al., 2016; Tsuda and Yoshimura, 2018).

One of the core oncology dogmas, popularly known as the "Vogelgram", postulates that cancer develops in a linear way, based on the progressive accumulation of genetic alterations in a series of sequential steps (Fearon and Vogelstein, 1990). On the other hand, if invasion and metastasis are different non-sequitor programs, and they are activated separately in various cancer types, this may explain the fact that cancers arising from different cell type in the same organs may have different propensity to grow locally, to invade the surrounding stroma and to metastasize (Fouad, 2019). As an example, follicular and anaplastic thyroid cancers although arising from the same organ, behave very differently and have a very different prognostic. Follicular cancer, in general, behaves like a benign tumor as opposed to anaplastic thyroid cancer that is one of the most aggressive tumors described (Ghuzlan et al., 2008). Also cancer types grouped under the same class may have dissimilar propensities to metastasize. For example, roughly half of the sarcomas metastasize while the other half do not (Savvides et al., 2011) which is expected as sarcomas are a heterogeneous group of tumors, and, recently, as many as sixty-two different types of sarcomas have been described (Koelsche et al., 2021). Also, a non-sequential activation of different cancer cell programs in tumors of different locations might explain why the initial stage presentation of different cancer types varies so much and would also solve the riddle of the behavior of carcinomas of unknown origin where the primary tumor is never found. It is conceivable that in metastasis of cancers of unknown origin the metastatic program is activated before the division and invasion programs (Fouad, 2020).

The presentation made by Scott Bonner discussed the role of exosomes in cancer. Exosomes have been involved in the communication between the primary tumor and remote metastatic sites (Whiteside, 2013) and, cancer cell derived exosomes contain several molecules (mRNAs, for example) that may be involved in different aspects of the metastatic process. Exosomes play a complex role in cancer-depending of their cargo, they may have cancer stimulating or cancer inhibiting properties (Bao et al., 2012; Xue et al., 2015).

A team from Weill Cornell coordinated by David Lyden, provided an explanation for Paget's "seed and soil" clinical observation (Paget, 1889) and demonstrated that the site of distant metastasis is specified by the nature of the proteins expressed on the surface of

exosomes and the exosomes cargo are non-random (Rodrigues et al., 2019; Rodrigues et al., 2018). In 2020, his team published a comprehensive analysis of protein exosomes in five cancer types (breast, colorectal, lung, pancreatic, mesothelioma) (Hoshino et al., 2020) and found, that in cancer patients, the circulating plasma exosome proteins are derived from four different sources, the tumor itself, the tumor environment, distant organs (i.e., liver) and the immune cells, these data supporting the "cancerized" organism model described before (Pucci, 2015, 2017a).

In the near future, treatment directed towards bone marrow derived cells, tumor exosomes, and other key factors involved in the metastatic process may represent new therapeutic avenues.

6. The temporal perspective

6.1. *Cancer as a temporal disease. The dimension*

If an organism is akin to a symphony in which cells, tissues and organs interact harmoniously, as described in "The music of life" (Noble, 2006), cancer can be viewed as a disharmonious process in dissonance with the rest of the organism. Life is a process sculpted by two complementary temporal forces: evolution and development and, in cancer, both these forces are at work.

Cancer cells are asynchronous with the tissue where they originate and with the rest of the organism. It has been known for several years that chemotherapy agents may lead to an accelerated tempo in cancer development (Lee et al., 2012) and, as demonstrated in a mouse model, may even sometime promote metastasis (Sriramkumar et al., 2018). Furthermore, it has become apparent that targeted agents (Oxnard et al., 2012) and immunotherapy (Saleh and Elkord, 2019) may lead to hyperprogression in certain clinical contexts (Sanchez-Bernardo et al., 2019).

6.1.1. *Cancer as evolution. Controlled demolitions/reconstructions and random progressions*

One of the main premises of the symposium was that the neo-Darwinian explanatory framework needs to be replaced by a broader view that integrates contemporary research data.

In his presentation that was an expanded version of a previously published lecture (Noble, 2017), Denis Noble proposed the idea that blind chance does not account for the origin of variation as claimed by the neo-Darwinian gene-centric model of evolution; as a matter of fact, by using different level processes, organisms have developed sophisticated mechanisms to resist potentially harmful effects of many random genetic variations, and the DNA copies itself with astonishing accuracy. He also proposed the striking idea that randomness is harnessed by organisms in order to generate function. This idea contradicts Schrödinger's definition of life as a process of generating phenotypic order from molecular-level order, and introduces a novel explanatory framework. In Noble's view, life is a process of generating order from disorder from higher levels down, by imposing constrains at the lower levels.

This implies that cancer, being also a form of life, can harness stochasticity too, and this idea has been further expanded in Henry Heng's presentation and is also amply described in his book (Heng, 2019).

The link between cancer and evolution has been made more than forty years ago by Peter Nowell, who suggested in a seminal paper (Nowell, 1976) a model for the evolution of tumor cell populations in terms of stepwise increase in genetic variation.

Cancer cell evolution through genetic mutations has been acknowledged as an important factor leading to therapy resistance in solid tumors. For example, it has been shown that after a period of an initial response (10–16 months), targeting single mutant clones in a heterogeneous tumor, –as is the case, for example, with the oral inhibitor use in EGFR mutated adenocarcinoma of the lung–, may lead to resistance through intra tumoral evolution (Gibbons et al., 2016).

If resistant clones are present before administration of therapy, treatments designed to kill maximum numbers of cancer cells remove the sensitive clones, and, in fact, promote more rapid growth of the resistant populations (Gatenby et al., 2009a,b). In this context, acquired resistance to targeted agents is inevitable and, future therapies need to address more effectively spatial and temporal tumor heterogeneity (Greaves et al., 2012; Gerlinger et al., 2012; Marusyk et al., 2012; Park et al., 2016; Wang et al., 2014).

Cancer is a robust system that has the ability to maintain stable functioning despite various perturbations. The essential robustness of cancer is maintained through heterogeneous redundancy i.e. the cancer tissue contains a heterogeneous distribution of genetically different cancer cells maintained by genetic instability (Kitano, 2004).

Genetic mutations responsible for intra and intertumoral heterogeneity have been described by Charles Swanton and his team in several seminal papers (see Gerlinger et al., 2012; Jamal-Hanjani et al., 2017; Wilkinson et al., 2020) and Swanton made popular the suggestive notions of "trunk" mutations present in the majority of cancer clones versus "branch" mutations present in cancer subclones only.

In her talk, Natalia Komarova presented several interesting mathematical simulations of cancer cells interactions demonstrating that the outcome of therapeutic interventions may dependent also on the size of the cancer cell population. John Townsend presented a novel mathematical method (Cannataro et al., 2018) for evaluating the relative impact of specific mutations in a particular cancer clone with practical importance in choosing the most efficient therapy.

Although there is a general agreement of evolution associated with cancer progression, it is still unclear whether the same type of evolution occurs in different tumor types (Davis et al., 2017).

A novel evolutionary theory that has informed the Cancer Cambrian analogy, the core paradigm of the Cancer and Evolution Symposium, was presented by Henry Heng. For a comprehensive description of the theory, I recommend his recent book "Genome Chaos: Rethinking Genetics, Evolution and Molecular Medicine" (Heng, 2019). Briefly, this theory states that, due to either external *environmental factors* like microorganismal infections, exposures to carcinogens and other stressors, or, *internal cellular factors* like tissue/organs constrains or chromosomal instability, genomic chaos appears in a cell. This leads to a rapid phase of discontinuous macroevolution, or punctuated evolution, associated with non-random chromosome shuffling in which the whole karyotype is reorganized, followed by a slower phase of continuous microevolution, or stepwise Darwinian clonal evolution, in which the karyotype as a whole has been fixed and is shared between cells and among generations. In the experiment used to support his theory, Heng used an in vitro immortalization model of Li Fraumeni fibroblast cells. In this model, Heng observed first many instances of clonal translocations, aneuploidies and several karyotypic patterns appearing for a short duration of time and then disappearing, until after approximately 64 passages all clonal translocations were faithfully passed through many passages (up to >300) (Heng et al., 2006).

Single nucleus genome sequencing of breast cancers samples (Navin et al., 2011) supports Henry Heng's model and demonstrates that aneuploid rearrangements occur early in tumor evolution and remain highly stable as the tumor masses clonally expands, while, in contrast, point mutations seem to evolve gradually, generating extensive clonal diversity. In support of the macroevolution idea,

Stephens et al. (2011), demonstrated using next-generation sequencing, the presence in 2–3% of cancers, across many subtypes, of massive chromosomal rearrangements nearly all occurring during a single cellular catastrophe, a phenomenon called by authors "chromothripsis".

Current literature suggests that advanced carcinomas follow a *branching evolution model* for point mutations, and a *punctuated evolution model* for chromosomal number alterations (Davis et al., 2017). It is important to note that in real life both models may be at work in different tumor types, and, in some cases, they may be operating concurrently (Zack et al., 2013).

An important corollary for the two-stage evolution theory proposed by Henry Heng are the results of a study conducted by the Tracer X group coordinated by Charles Swanton (Turajlic et al., 2018). This group analyzed different types of clonal evolution in 101 samples of renal cell carcinoma, and, described seven evolutionary subtypes. The key finding was that both clonal diversity and chromosomal complexity may be important prognostic factors, and, significantly, may be associated with survival benefit. Also, both micro and macro evolution, as well as non-genetic diversity, seem to influence clinical outcomes. Low clonal diversity, and high chromosome complex tumors were more likely to rapidly and widely progress, while clonally heterogeneous tumors with or without high chromosomal complexity, were more likely to have an attenuated progression pattern, often with solitary metastasis. The authors concluded that cytoreductive nephrectomy, metastasectomy, or deferral of systemic therapy may not be beneficial in the low clonal diversity/high chromosomal complexity cases.

In his talk, Henry Heng also presented an interesting theory about chromosomal architecture systemic inheritance, -a novel complementary code to the genetic code-, and suggested that most transitional events in cancer (cancer formation, metastasis, and drug resistance) are achieved through chromosome rearrangements that change the system's information (Xu et al., 2015). In a nutshell, as he stated in his book, "the entire set of chromosomes of a given species is a new genomic coding, which defines the network structure (how individual genes interact) and serves as a 'blue print of system inheritance" and, also, "the physical position of the gene (or the address of the gene in the nucleus) is important for network's dynamics" (Heng, 2016). Remarkably, a similar idea has been introduced by Richard Goldschmidt in the "Macroevolution" chapter of his 1940 book "The material basis of evolution". I include here the citation that may be relevant not only for Henry Heng's genome chaos and chromosomal code theories, but to the Cancer and Evolution Symposium as well. "A repatterning of a chromosome may have the exact same effect as an accumulation of mutations. And even more, a complete repatterning might produce a new chemical system which as such, i.e. as a unit, has a definite and completely divergent action upon development, an action which can be conceived of as surpassing the combined actions of numerous individual changes by establishing a completely new chemical system. Model: two different pictures produced with the same set of mosaic blocks, the new picture 'emerging' only when all blocks are in their place. It is certainly most remarkable that the new developments in genetics lead to the same conclusions which are derived as postulates from an unbiased analysis of evolutionary field. This encourages me to believe that the dead end reached by neo-Darwinian theory based upon the conception of classical genetics can now be passed successfully" (Goldschmidt, 1940).

A similar theory of genome system architecture has been also prior proposed in 2005 by James Shapiro. "From an organizational point of view, distant effects of repetitive element dosage tell us that the whole genome is a single integrated system, regulated both in *cis*- and *trans* by networks employing DNA repeats" (Shapiro, 2005). Subsequently, other authors (Lee et al., 2012), also suggested that chromosomal translocations are non-random events happening "in a spatially regulated, site-specific, and signal-driven manner, reflecting actions involved in transcriptional activation, epigenetic regulation, three dimensional nuclear architecture, and DNA damage repair". Another more recent study, supporting Henry Heng's theory (Bielski and Sieuwerts, 2016), showed that karyotypic complexities of primary tumors are conserved in metastases, and metastatic cells appear to be generated from primary tumor cells in one step. Getting back to Denis Noble's idea that "randomness may be harnessed to generate function", the macroevolution process may be an example of deterministic chaos (Shapiro, 2016) like a sort of controlled demolition/reconstruction.

In cancer cells, chromosomal instability (CIN) is responsible for both numeric, somatic copy-number alterations (SCNA) and structural chromosomal changes that in a tumor may be also present in different clones or subclones and account for tumor heterogeneity. A SCNA model of cancer evolution has been proposed in which there is an interplay between genetic instability and CIN both contributing to tumor progression and recurrence, metastasis and drug resistance (Sansregret and Swanton, 2017). Another related model focused on chromosomal arm aneuploidies (CAA) has recently been published (Shukla et al., 2020). In this model, solid cancers initially preferentially gain chromosome arms, whereas they preferentially lose chromosome arms later during cancer development.

Data presented at the conference by Charles Swanton demonstrated the widespread presence of aneuploidy in different tumor types. His team analyzed SCNA of 1421 samples from 394 tumors across 22 tumor types and showed that continuous chromosomal instability results in pervasive SCNA heterogeneity (Watkins et al., 2020). A prior large study (Taylor et al., 2018) that analyzed aneuploidy across 10,522 tissue samples spanning 33 cancer types from the Cancer Genome Atlas (TCGA) dataset, found that whole chromosome or chromosome arm imbalance, occurs in 88% of cancers. Some types of cancer were shown to have a higher aneuploidy than others: virtually all glioblastomas and testicular germ cell tumors have at least one aneuploidy event. In colon cancer, the majority of tumors (85%) are aneuploid, likely due to CIN, and a minority of them (15%) have microsatellite instability (MSI). In general, these two mechanisms are not present within the same tumor (Cardoso et al., 2020), but this rule is not universal (Bakhoum and Landau, 2021). This is an oversimplification as the aneuploidy tumors may be further subclassified into tumors with low copy number chromosomal alterations and tumors with high copy number chromosomal alterations, with different histopathology and gene expression profile (Bakhoum et al., 2018).

Despite findings of the above studies demonstrating an association between aneuploidy and cancer, the question whether aneuploidy is positively selected in cancer, is still open. In Swanton's study, the subclonal landscape of SCNAs appeared to be determined mainly by positive and negative selection, as opposed to neutral evolution, that seemed to play a minor role (Watkins et al., 2020). A recent in vivo study (Hanahan et al., 2020) performed in mice predisposed to intestinal cancer (ApcMin/+), showed that certain levels of CIN can have contrasting effects in distinct tissues. Moderate CIN causes a remarkable increase in adenoma burden throughout the entire intestinal tract, and especially in the distal colon, but, strikingly, a higher level of CIN although promoted adenoma formation in the distal colon, had no effect in the small intestine.

What is the significance of aneuploidy? In some cancer types, the presence of aneuploidy has been associated with poor prognosis. For example, in prostate cancer, 23% of patients whose tumors had five or more predicted chromosome-arm alterations had

5.3 times higher odds of developing lethal cancer compared to those with the same Gleason score and without predicted aneuploidy (Carter et al., 2019). On the other hand, a single-chromosome gain can both promote or suppress metastasis in colorectal cancer depending on the specific supernumerary chromosome number (Vasudevan et al., 2020).

As previously demonstrated by Swanton's team (Burrell et al., 2012), a high rate of chromosomal errors is likely related to CIN. It is however important to point out that the presence of aneuploidy per se in a cell does not also automatically imply the presence of CIN.

Is CIN a prognostic factor? The relationship between CIN and prognosis is non-linear as, on one hand, moderate CIN has been associated with adverse patient outcome (Sansregret and Swanton, 2017), and linked with both intrinsic and acquired drug resistance, but, at the same time, extreme CIN might be associated with improved patient outcome (Bakhoum and Compton, 2012).

Directly targeting CIN, although extremely attractive as a therapeutic idea, is a complex issue. A plethora of replication stress response factors, helicases, nucleases and alternative polymerases that promote fork stability have been described, and both pre-mitotic (Burrell et al., 2013) and mitotic (Bakhoum et al., 2018) defects appear to be involved in different tumor types.

There are currently thirty-six studies listed on ClinicalTrials.gov targeting ATR, CHK1, and WEE1 kinases, and DNA-dependent protein kinases, which all seem to play a key role in CIN. There are also several dozens of therapeutic agents targeting more than twenty other proteins involved in the replication stress leading to CIN are in pre-clinical development (Saldivar et al., 2018).

How do cancer evolution theories inform therapeutic choices? It is significant that Charles Swanton who has been studied tumor evolution for more than a decade, suggested at the end of his talk that immunotherapies directed against neoantigens associated with truncal clonal mutations may represent, in the future, one of the most effective cancer treatments (Gonzalez-Angelozzi et al., 2017).

Also, Robert Gatenby presented an ingenious treatment approach, informed by both ecology and evolution, that has already proven its efficacy in prostate cancer treatment (West et al., 2020). The goal of this new treatment paradigm, called "adaptive therapy", is to maintain a controllable stable tumor burden by allowing a precisely controlled population of treatment-sensitive cells to survive. For more than a decade, Gatenby and collaborators from the Moffitt Cancer Center in Miami, Florida have been refining the adaptive treatment protocol (Gatenby et al., 2009a, b, 2011; Orlando et al., 2012; Enriquez-Navas et al., 2016) consisting in the continuous use of smaller than usual doses of therapeutic agents that would not completely eradicate sensitive cancer cells, thus preventing resistant clones from developing. The hope of this innovative protocol is to maintain some sort of competition between the treatment sensitive and treatment resistant cancer cells. Recently, Gatenby and his collaborators published a paper in which he included three new ideas for the implementation of multidrug adaptive therapy in which the frequency-dependent "cycles" of tumor evolution, the availability and selection of treatments and the velocity of evolution are all taken into consideration (West et al., 2020).

As an alternative to the Nixon's "war on cancer", the banner of this "game of clones"(Aktipis, 2020) eco-evo approach to cancer treatment championed by Gatenby and his collaborators would read: "Make peace with cancer, not war!"

A word of caution: prostate cancer in which the efficacy of the eco-evo therapy has been demonstrated is a relative indolent form of cancer. Most elderly men diagnosed with this condition die "with" prostate cancer and not "because of" prostate cancer. Developing similar approaches in other more aggressive forms of cancer, i.e. pancreatic or small cell lung cancer may be challenging.

The main critique of the cancer evolution theory is that it does not explain the emergence of the metastatic phenotype, which is a highly regulated process unlikely to be caused by purely stochastic genetic events and survival of the fittest mechanisms. Cells with metastatic potential are present from the beginning in the primary tumor, and do not appear to be selected by an evolutionary process (Lafave et al., 2020). Also, the development of cancer in the first place is difficult to be explained solely by evolution. As shown by DeGregori, the majority of cancers occurs in older people (DeGregori, 2018) and, tissue aging, and the decline of defense mechanisms may all be alternative explanations for cancer development.

6.1.3 Cancer as development gone astray. The malignant embryo

We have deciphered the genetic code, but genes are not the blueprints for a developmental program (Noble, 2018). As suggested in the symposium there may be also other codes that can play significant roles in development i.e. the bioelectrical code proposed by Michael Levin (Levin and Martyniuk, 2018), or the glycoprotein code alluded by Frank Lauksen in his presentation (Lauksen, 2018).

The idea that cancer represents an embryonal developmental program gone haywire has been around for more than four decades (Pierce, 1978; Arechiga, 1978). As described by Dongre and Weinberg, there are several genes that may play a role both in embryogenesis and cancer (Dongre and Weinberg, 2019). Also similar to the neural crest migration (Kalcutt et al., 2010), the metastatic process represents a transformed cellular program, that once activated leads to the development of disseminated tumors at distance from the original site. Metastases may be driven by the selection of factors such as TGF beta, HGF, tumor necrosis factor (TNF)-alpha, Wnt and PDGF by the surrounding tumor stroma, and, the activation of several master regulators of embryogenesis in the tumor cells, such as the transcription factors Twist, Snail, Slug, Zeb1 and Zeb2, regarded as the epithelial to mesenchymal transition (EMT) core regulators (Dongre and Weinberg, 2019; Lambert et al., 2017).

Between 1988 and 1993, Vladimir Vinnitsky introduced the "anerogerminative cell theory" that described tumorigenesis as a "dynamic self-organizing process that mimics a self organizing process of early embryo development" (Vinnitsky, 1988, 1993). He postulated "five stages of development of a malignant tumor from an anerogerminative cell:

> "Stage 1: reproduction of anerogerminative cells. (This stage mimics a cleavage-stage embryo.)
> Stage 2: aggregation of anerogerminative cells and formation of the tumor germ, which consist of anerogerminative cells only. (This stage mimics a morula-stage embryo.)
> Stage 3: the transformation of the tumor germ to a tumor spheroid with a heterogeneous cell population. (This stage mimics the avascular blastocyst-stage embryo.)
> Stage 4: vascularization of the tumor spheroid and its further growth as a vascularized tumor. (This stage mimics the post-implantation blastocyst-stage embryo.)
> Stage 5: disaggregation of anerogerminative cells and their metastatic spreading into body tissues. (This stage mimics primordial germ cell migration)." (Vasiliev, 2004).

The hypothesis of Jingsong Liu is that the formation of polyploid giant cancer cells may lead to de-repression of a repressed embryonic program in somatic cancer cells responsible for drug resistance and disease relapse. His team analyzed 38 post

chemotherapy tissue samples of human ovarian cancers and found an increase expression of embryonic stem cell markers (Silva et al., 2012a).

Development and cancer have several common features, but the analogy only holds up to a point. Cancer is not a clockwise, step by step, goal driven process, like embryonal development. Its behavior can be best described as a "deterministic chaos" (Calin et al., 2008; Sharma, 2016).

Neither the standard developmental theory nor the evolutionary biology approaches to cancer fully capture its complex causal dynamics, and different proposals to unify the two fields (EvoDevo or DevoEvo) have been made (Gao, 2016).

6.1.3. Cancer as desynchrony. The cells that never sleep

Biological rhythms are master regulators of both prokaryotic and eukaryotic organisms and the researchers that discovered the molecular mechanisms that control circadian rhythms received a Noble prize in 2017. The idea that internal and external periodic changes may be also important for cancer biology has been around for several decades and cancer chronotherapy lead in the past to some interesting results (Levi, 2001; Filipski and Levi, 2009). A recent paper proposed that malignant cells could exploit and/or manipulate the host biological rhythms and these features may be relevant in the context of both local invasion and metastatic disease (Cardone and Antonijevic et al., 2020).

6.1.4. Cancer as a new life form. The neobiont novel to the future

Is the human body the growth medium for a new form of life, a neobiont or a dyskaryota to use the term suggested by Mark Vincent (2010)? Given the variation of chromosomes number present in the majority of cancer types, can we legitimately label an individual cancer as a new species?

Chromosome number variation is frequently associated with cancer (Ried et al., 2012), and whole genome doubling (WGD) has been found in as many as 37% of cancer samples and might accelerate genome evolution (Dewhurst et al., 2014). The team of TracerX coordinated by Charles Swanton, suggested that WGD might help buffer deleterious effects, such as homozygous disruption of essential genes (Watkins et al., 2020). The TracerX team study reported an even higher incidence of clonal WGD (49%). On the other hand, no significant increase in ploidy was observed between matched primary tumor and metastatic samples in the cohort as a whole, or in any individual tumor type in this study, but an analysis of an independent series of 1024 metastatic samples revealed that 13 focal SCNAs were enriched in metastatic samples, including gains in chromosome 8q24.1 (encompassing MYC) in clear cell renal cell carcinoma and chromosome 11q13.3 (encompassing CCND1) in HER2/Neu + breast cancer (Priestley et al., 2019).

It is remarkable that after decades of research, the nature of the "first cell" that initiates the cancer process is still unknown. Robert Weinberg has been a proponent of the cancer stem cell (CSC) theory for many years (Weinberg and Weinberg, 2014). Recently, as shown by a group of researchers from Cleveland, the dichotomy between "stemness" versus "non-stemness", has been replaced by an understanding of stemness as an "emergent, contextual property of interactions with the microenvironment and other cell types, within both the cancer and normal hierarchy" (Brooks et al., 2019). In his presentation, Weinberg suggested that epithelial stem cells have a quasi-mesenchymal phenotype (Lovisa and Weinberg, 2017) and he speculated about the nature of the cell that is the "object" of selection during cancer progression, which, in his opinion, is unlikely to be a CSC. Plasticity is one of the key features of malignant cells that have the capacity to shift dynamically between a differentiated state, with limited tumorigenic potential, and an undifferentiated or CSC state, which is responsible for long term tumor growth, resistance and recurrence (da Silva Dias et al., 2018).

Three presentations by James Shapiro, Kenneth Pienta and Jiusong Liu pointed to another potential "first cell" candidate: the polyploid giant cancer cell (PGCC). Both Shapiro and Pienta mentioned the fact that the polyploid cells have been described for more than a century but their significance for oncology has not been noticed. Interestingly, polyploidization has been proposed to have occurred twice early in the early evolution of vertebrates and the resulting paleopolyploid state of the mammalian genome can explain the multiple paralogs of many genes (e.g., Hox gene cluster) (Dehal and Boore, 2005; Ohno, 2013). The observation that polyploid giant cells in higher eukaryotes are capable of continuously generating rapidly proliferating mononucleated cells was first reported in 1905 by Lataste et al. (1905). Also, reversal of the polyploid giant cells to diploid or quasi-diploid cells was first reported in 2000 by the team of Ekaterina Erenpreisa (Erenpreisa et al., 2000; Illidge et al., 2000). At the conference Kenneth Pienta presented additional contemporary evidence that tumorigenesis, metastasis, and therapy resistance may all have the same culprit: the PGCC (Amend et al., 2019). In the lab, tetraploidization arises when the DNA damage signal lasts for a considerable time period, a situation that can be created by incubating cells with different chemotherapy agents that lead to DNA damage. Several research teams including those of De Lange, Lin and Pienta have exposed tumor cells to chemotherapy agents in vitro confirming the phenomenon.

The idea that "cancer is a somatic cell pregnancy" has been proposed several times in the history of oncology (Hart, 2007). At the conference, Jiusong Liu also presented a related theory in which he introduced the polyploid giant cancer cell cycle (PGCC) paradigm described prior in one of his articles (Liu, 2018). "During the initiation phase of the giant cell cycle, failed mitosis/cytokinesis activates endoreplication, by which cells can escape senescence/apoptosis. During the self-renewal phase, the polyploid cells grow autonomously and develop into compaction, morula- and blastocyst-like embryos and generate inner cell mass like stem cells. During the termination phase, polyploid growth ends and the inner cell-mass-like stem cells bud small embryonic-like stem cells. During the stability phase, these stem cells with acquired genetic/epigenetic mutations that arrested at different developmental hierarchies will gradually acquire competence in mitosis, achieve stable diploid karyotype and grow into tumors of different grades, including germ cell tumors." It is important to note that, in Liu's opinion, mutations are not necessary for the PGCC to form "mutations, per se, are not required for development of cancer as reprogramming can be achieved via activation of normal embryonic transcription factors. The genetic mutations, however, particularly in inherited cancers, like TP53 in Li Fraumeni syndrome, retinoblastoma genes in retinal cancer, or BRCA genes in familial breast cancer, can prime the somatic cells for dedifferentiation. Other mutations, such as KRAS or BRAF, may uncouple proliferation from differentiation and can lead to inhibition of stem cell maturation" (Liu, 2018).

The conversion from diploidy to polyploidy is part of normal mammalian development and differentiation occurs in at least three specialized cell types: chrophoblast (8N-64N), megakaryocytes (16 N–128 N) and hepatocytes (4N, 8N). A fourth type of polyploidization is seen in skeletal muscle and osteoclasts in which cell fusion generates polynucleated terminally differentiated cells. Polyploidy has also been observed sporadically under physiological conditions in lactating mammary gland, urothelium, mesothelium, and Purkinje neurons (Davoli and de Lange, 2011).

Three distinct causes of tetraploidization in cancer have been proposed: cell fusion, failure in cytokinesis or other steps in mitosis, and endoreduplication (Davoli and Lange, 2011). According to

Davoli and Lange, the role of polyploidy in cancer is to enhance robustness in the face of a mutator phenotype, buffering the consequences of chromosome losses, gene deletions, and inactivating mutations.

De Lange suggested that the explanation of polyploidy may reside in the loss of telomere function, early in tumorigenesis. In 2015, she proposed a theory that echoes the genome chaos theory of Henry Heng (De Lange, 2015), "A brief episode of high mutation rate followed by return to a more stable genome would avoid a potential mutational load that might hamper proliferation. In this regard, telomere dysfunction is different from other sources of genome instability, since it is reversible through the upregulation of telomerase. Upon acquisition of sufficient telomerase levels, this period of telomere-related scrambling will end, resulting in more stable, yet altered, genomes. The notion that tumors develop through a brief period of telomere dysfunction that generates extensive genetic diversity is borne out by data on genomic alterations during the development of breast cancer".

The existence of mechanisms that suppress multipolar mitoses raises the possibility of a novel therapeutic strategy for cancer: drugs that interfere with centrosome clustering mechanisms, could be lethal to tumor cells containing multiple centrosomes, but potentially spare normal cells. For example, HSET (also known as KIFC1) a kinesin protein, is nonessential for mitosis in normal cells, but is essential for the survival of cancer cells with extra centrosomes. Elevated HSET gene expression has been detected in numerous cancer types, including glioblastoma, lung, breast, colon and cervical cancers, in comparison to corresponding normal tissues (Pannu et al., 2015). Targeting it in vitro led to decreased cell viability of PGCCs by 90% (Kwon et al., 2008). Other centrosome declustering approaches have been suggested using for example griseofulvin, an antiparasitic drug (Quintyne et al., 2014).

In the future, polyploidy blocking and redirecting differentiation of PGCCs toward benign lineages may become promising therapeutic approaches for cancer. In addition, early embryo-like structures derived from PGCCs may represent a potential tumor vaccine (Salerno et al., 2018). Supporting this view induced pluripotent stem cells (IPSC) have been reported to elicit anti-tumor response in a mouse model. In a prophylactic setting, IPSC vaccines prevent tumor growth in syngeneic murine breast cancer, mesothelioma, and melanoma models.

Cancer cells behavior is similar in many respects to normal cells, like macrophages, for example. In fact, an intriguing hypothesis is that the metastatic cancer cells develop as result of fusion between cancer cells and macrophages (Pawelek and Ashkenas, 2010; Manjunath et al., 2020). The behavior of cancer cells is not unique and similar behaviors are present in other conditions, like tuberculosis (Richmond and Kaufman, 2007). The aggressive behavior of PGCCs that have been observed mainly in vitro experiments where cancer cells were exposed to chemotherapy agents is not supported by the natural evolution of most solid cancer tumors that develop over years. It is likely that, although conceptually attractive, the PGCC theory applies only to a limited number of cancer initiation scenarios, and, may be mostly relevant to the rapid cancer progression induced by therapeutic agents.

6.1.5. *Cancer as a return to an ancestral life form. The protobiont-travel to the past*

In 1978, Octavian Udriștoi, a Romanian physician published a book in which he proposed that the malignant transformation is due to the de repression of ancestral prokaryotic genes present in all multicellular organisms. He called them "anaerobic genes" because they appeared under the conditions of the primeval Earth atmosphere that was lacking oxygen. In a second edition of his book published in 1982, he included an English abstract of his theory in which he stated that "phenotypical expression of the cancerous cells is controlled by the ancestral genetic program".

Using similar arguments, in 2000, Rafael Sorkin, a physicist, published on line the idea that "cancer results from the breakdown of universal control mechanisms which developed in mutual association as part of the historical process that brought individual cells together into multi-cellular communities", and proposed to compare the genomes of uni-celled with multi celled organisms, in order to identify "potential sites for intervention aimed at restoring the damaged control mechanisms and arresting the cancer"(Sorkin, 2000).

More recently, in a series of publications, first independently and then together, Lineweaver, Davies and Vincent (Davies and Lineweaver, 2011; Vincent, 2010; Davies, Vincent and Lineweaver et al., 2014), proposed also an atavistic theory in which cancer is a reversal to a simpler, more robust primitive life form akin to a monocellular single-cell organism. Subsequently, Chen et al. suggested that cancer represents a loss-of-function-driven reverse evolution back to the unicellular "ground state" and that metastasis is driven by positive selection for general loss-of-function mutations of multicellularity-related genes (Chen et al., 2014).

At the conference, Paul Davies and Kimberly Bussey presented recent phylostratigraphy results (a technique that helps dating the evolutionary emergence of human genes through the tree of life history) from seven solid cancers, obtained from comparisons between the gene age and gene expression level in RNA sequencing data from TCGA (Domazet-Lošo, 2017; Trigos et al., 2017). Confirming their hypothesis, genes present in unicellular organisms were strongly upregulated, whereas genes of metazoan origin were primarily inactivated.

In the several publications cited above, Mark Vincent describes cancer as a "protozoan-like organism" that appears due to the reactivation in the genome of an "ancient de-repressed survival program". According to him, cancer represents sort of a regression to an "ancient and alternative organism, a living fossil, foreign to its host". In his opinion, clinical cancer is "a competitive struggle between a reawakened Precambrian organism, and the resistant, normal metazoan body". The core component of this "re-primitivization" process in which the cells return to an "ancient, de-repressed survival program" is in Mark Vincent's view the metabolic switch to aerobic glycolysis (the Warburg phenomenon).

We tested the idea of targeting the glucose avidity of cancer cells in a pilot study in which we administered increasing doses of 18F Fluoro-deoxyglucose (18F FDG) to cancer patients with different types of hypermetabolic tumors, and we obtained some interesting preliminary results (Vlad et al., 2020). Of course, like the majority of approaches using one treatment modality and targeting one cancer cell characteristic, in the long run, this approach may also lead to resistance, as cancer cells may use other metabolic substrates for their survival (glutamine, for example), and resistance may develop due to metabolic heterogeneity of various cancer clones.

Another proposal of Lineweaver, Davies and Vincent (Lineweaver et al., 2014) was to target cancer associated macrophages with a non-attenuated strain of Listeria monocytogenes. Although this idea to target cancer associated macrophages has not yet be proven effective, other alternative approaches using Listeria monocytogenes are in development (Wennerberg et al., 2019).

The protobiont theory has been criticized by Aurora Nedelcu who argued that cancer is "not a reversal to an ancestral-like single-celled life style and cancer cells in multicellular organisms should not be seen as analogous to regular single celled individuals in a unicellular species, but rather "cancer cells are analogous to single-celled opportunistic (cheater) mutants" (Nedelcu, 2017). She suggested also that "the loss of cooperative genes could have, besides the implicit benefits to the "selfish" mutants, additional negative

effects on other aspects of fitness at the cell level", like, for example, an enhanced sensitivity to stress or to environmental changes may be used for therapeutic purposes (Nedelcu, 2017).

6.1.6. *The evo-devo approach*

An interesting Evo Devo approach was recently proposed by James DeGregori in his book "Adaptive Oncogenesis". Starting from the observation that 80% of cancers occur after the age of 55, and recent data indicating the presence of mutations in various normal tissues from young individuals without cancer, DeGregori suggested a cell extrinsic origin of oncogenesis due to the physiologic decline of tissular control over cellular activity associated with aging. So basically, he brings forth the idea that cancer is an adaptation to a modified environment and he proposes therapeutic approaches directed to the microenvironment i.e. the oxygen levels or the pH of the environment, instead of the cancer cell itself (DeGregori, 2018; Vaupel et al., 2019; Swanton et al., 2017).

6.1.7. *The eco-devo approach. Integration spatial and temporal perspectives*

On the basis of a consensus conference of experts in the fields of cancer evolution and cancer ecology, a framework for classifying tumors was developed, leading to a 16 tumor types classification based on an *Evo-index* and an *Eco-index* (Maley et al., 2017). These indexes were computed using four components: the diversity of neoplastic cells (intra-tumoral heterogeneity) and changes over time in that diversity, (*Evo-index*), as well as the hazards to neoplastic cell survival and the resources available to neoplastic cells, (*Eco-index*). The hope of the authors was that these classifications would provide oncology clinicians with valuable information on how to choose more or less aggressive interventions based on the anticipated evolvability of those neoplasms, and would also be able to provide a framework for treatment efficacy based on repeated biopsies.

7. The relativistic perspective

7.1. *A systems biology look at cancer: The logobiont*

Logos in Greek means "word," "reason," or "plan" and cancer can also be seen on one hand as a communication disorder between cancer and different normal organism components either at the tissular or the organismic level, or as a disease following a different plan than the normal organism blue print. The importance of communication for understanding life, and, by extension, cancer, has been discussed in a series of papers by Guenther Witzany (Witzany, 2010, 2020; Baluška and Witzany, 2017). In his papers, Witzany presented elegant arguments to the fact that the equation 'life = physics + chemistry + information' is simply wrong. He proposed a different definition of life: "life is communicative interaction of three complementary levels of parallel cell communication, RNA communication, and virus communication" (Witzany, 2020). This communication "cannot be predicted or simulated by computing machines, because biocommunication does not function mechanistically and is not algorithm dependent" (Witzany, 2014). For Witzany biocommunication is the mysterious ingredient that would infuse life into cellular automata.

7.2. *Cancer as an escape artist. The immune synapse*

There is an ongoing dialogue between cancer and the immune system. Initially, according to the immune surveillance theory (Burnet, 1957; Thomas, 1959), the immune system recognizes newly arising tumor cells through the expression of tumor specific neo-antigens on tumor cells and eliminates them, keeping cancer under control. Subsequently, through the process of immunoediting described by Dunn and Schreiber (Dunn et al., 2002) some of the cancer cells may downregulate or lose some of the membrane antigens that allows them to be detected by the immune system and a neoplasm is formed (Vinay et al., 2015). Another mechanism that has been described in the last decades is the check point inhibition through which cancer cells send an "off" signal to the T cells, preventing the immune system from destroying the cancer (Pardoll and Topalian, 2018). The check-point molecules are part of the so called "immune synapse", a term originally used to describe the interaction between a T-cell and an antigen presenting cell (APC) (Norcross, 1984; Paul et al., 1986) and, subsequently, it was used to describe the interaction between immune cells and tumor cells (Wu et al., 2020). The release of checkpoints or "brakes" of immune activation that limit antitumor responses has resulted in extraordinary long-lasting tumor responses in patients with a large variety of cancers (Sharma and Allison, 2015) and hundreds of check-point inhibitors clinical trials are currently active. It is important to note that, fundamentally, these interventions are not directed to the cancer cell itself but are targeting the complex interactions of cancer cells with the immune system and can be considered novel forms of "communication therapy".

One of the reasons for the success of checkpoint inhibitors is related to the fact that immunotherapy is less plagued than targeted therapies by heterogeneity. In fact, check-point inhibition seems to work better in tumors with a higher number of mutations (but, interestingly, not in tumors with high aneuploidy scores) and, pembrolizumab, is the first tumor agnostic check-point inhibitor approved for any cancerous tumor that presents microsatellite instability (MSI) or has a high tumor mutation burden (TMB-H).

Recently, the 4 year survival of melanoma has increased to approximately 50% by using a combination of nivolumab and ipilimumab (Larkin et al., 2015) and the overall 5 year survival of non-small cell lung cancer using check point inhibitors has more than doubled compared to historical data (Gandhi et al., 2018; Garfinkels et al., 2019).

An inspiring presentation was delivered by Patrick Soon-Shiong who introduced the framework of his company, 'Quantum Oncotherapeutics' that addresses the dynamic nature of cancer evolution by using four modalities to induce immunogenic cell death, and, combines in an individualized approach low-dose chemotherapy, a tumor-specific adenovirus-vectored vaccine, interleukin-15-based immune enhancement and off the shelf high-affinity NK (haNK) cells.

7.3. *Cancer as a goal driven form of life. The telobiont (from "telos" in Greek, goal, purpose)*

Biological systems are a special category of systems that, as pointed out many times since Schrodinger's asked the famous "What is life?" question cannot be reduced to material (physical and chemical) or non-material (informational) characteristics.

James Shapiro and Perry Marshall have kindly shared with me their articles prior to publication. These articles present different perspectives on the idea that cognition is a fundamental property of all living cells (Shapiro, 2021; Marshall, 2021), as highlighted below.

The arguments of Shapiro is that all living cells have to adapt to their environment and this goal-driven behavior constitutes precisely cognition. In his paper, he contends that prokaryote cells are capable of cognition because "they can recognize available nutriments, discriminate between them, utilize them selectively and control their movements towards places where nutrients or energy sources are more available. Prokaryotes engage in chemical

communication that allows them to undertake certain complex multicellular activities, such as forming protective biofilms. They can undertake coordinated group migrations, discriminate and exclude unrelated competitors from kin (…). When subjected to DNA damage, they activate targeted response systems that serve to restore genome activity." (Shapiro, 2021). We can immediately see that all these behaviors may also apply to cancer cells.

Expanding the arguments of his book (Marshall, 2009), and following the same train of thought, Perry Marshall provides additional examples of cellular cognition including explicit references to cancer cells that are capable of self/non self-identification, able to resist different therapies and recruit blood vessels. He introduces the model of the cell as a "volational Turing machine" and suggests that the origin of life, information, cancer, evolution, artificial intelligence, and cognition can be all reduced to one problem: cognition (Marshall, 2021).

Attempting to define what distinguishes life from non-life, Sara Walker and Paul Davies stated that life forms exhibit "top down control of information over matter that instantiates it" (Walker and Davies, 2013). In their view, the origin of life is a reversal in the causal architecture in which "an abstract and non-physical systemic entity (algorithmic information) effectively becomes a causal agent capable of manipulating its material substrates" (Walker and Davies, 2013). But how did this reversal arise in the first place? How did the code appear in the first place from a material cause? This is a non-trivial problem, and Perry Marshall offered a generous prize to anyone who could solve it.

Why do cancer cells divide frantically, what is the purpose of their invasion into the surrounding tissues and migrating to distant sites, far away from their birth place? Is there any logic behind this behavior? An explanation offered by the protobiont theory is that in response to stressful conditions, cells reverse to a unicellular, atavistic life program, "safe mode" (Arturo, 2014) or, "ground state" (Chen et al., 2015), used for survival. Is cancer a maladaptive behavior suggested in response to stress? More than a decade ago, Susan Rosenberg suggested that the occurrence of random genetic mutations may be a tightly controlled, and, in a sense, "purposeful" response to stressful environments, and her team presented evidence of stress-induced mutagenesis programs (Rosenberg et al., 2000). Rosenberg's hypothesis was that stress-inducible mutagenesis mechanisms can "accelerate adaptive evolution in populations specifically when organisms are maladapted to their environments, i.e., when they are stressed, and then return genomes to low mutation rates in rare adapted mutants that thrive in the new environment and so are stressed no longer" (Galhardo et al., 2007). This hypothesis precedes Henry Heng's model of macro and micro evolution and fits both the tissue organization field and the adaptive mutagenesis theories briefly sketched above.

"Be fruitful and multiply" (Genesis 1:28). Since the first cell came forth on Earth, life has been religiously following this commandment and cancer cells make no exception. The goal of life is life itself. What do cancer cells want? The first answer that comes to mind is that cancer cells want to live, to expand and to spread their progeny all through the body. Similar to bacteria, the evolutionary goal seems to be to proliferate and pass on their genes (Aktipis, 2020) as opposed to cells in a multicellular organism who behave like members of a communist society for whom the goal is the well being of the entire organism. Athena Aktipis described five golden rules that cells in a cooperative society have to follow: don't over proliferate; do the tasks you're meant to do; don't take more resources than you need; clean after yourself; and die when you should (Aktipis, 2020). Cancer cells break down the rules imposed by the organism, dividing out of control, penetrating through the basal membranes, invading the surrounding tissue, and spreading to other organs. Athena Akti is characterized them as "cheaters" (Aktipis, 2020) and Kate Arney as "rebels" (Arney, 2014). This proclivity to anthropomorphize cancer proves that the tendency to think of cancer cells following a "goal" or having a "mind" of their own, is common among cancer researchers.

Why do cancer cells want to live forever? It appears that clonal and flexible cancer karyotypes simultaneously generate immortality and tumorigenicity independent of telomerase. With other words, immortality is a bonus that comes with genomic instability, and not an independent goal per se (Duesberg and McCormack, 2013).

Despite their extreme heterogeneity, it has been noted that the fact that "all cancer cells, in all people, at all times, come to exhibit a nearly identical set of core traits has to be seen as a fantastically coincident type of convergent evolution" (Vincent, 2012). Is the bottleneck phenotype of cancer cells a coincidence or a means to achieve their "goal"? Most likely, it is not a coincidence. The variety of genetic mutations and chromosomal alterations of cancer cells may function as signals for the activation of a small number of cellular programs (Hall, 2020) responsible for the "nearly identical set of core traits". As an example, recent evidence suggests that chromosomal instability (CIN) is a primary source of cytosolic double strength DNA (dsDNA), that, in turn, triggers the cGAS cGAMP-STING pathway activation (Bakhoum and Sakkouna, 2020). Importantly, the cGAS-cGAMP-STING pathway activation occurs independently of the type of genetic material present in the cytosol. Tumor cells cope with the presence of persistent inflammatory signaling arising from cGAS sensing of cytosolic dsDNA through silencing of downstream type I interferon signaling, at the same time selecting for NF-κB dependent activity to metastasize to distant organs (Bakhoum et al., 2018). Also, simultaneously, cancer cells inhibit the activity of the immune cells by selectively degrading extracellular cGAMP, an important immune stimulatory metabolite (Li et al., 2020).

Regardless of the cancer cells' goal (if there is one), sometimes they can be prompted to differentiate. As shown by Adam Telerman and Robert Amson, two researchers from Institut National Supérieur from Paris, France, tumor reversion is possible and "the reversion process involves a reprogramming mechanism using epigenetic and probably genetic tools that will supersede the changes in cancer by assembling and triggering alternative ways leading to the suppression of tumorigenicity" (Telerman and Amson, 2009).

7.4. Cancer as a systemic, multi-level process. The bobiobiont (from holos, "whole" Greek)

The systems biology framework introduced by Dennis Noble and the work of Michael Levin on bioelectricity may inspire the design of novel top down models and therapeutic avenues directed to the whole organism. An advantage of top-down models noticed by Michael Levin is "that they hold the promise to circumvent (…) the near impossibility of determining which low level components must be tweaked in order to achieve a desired systemic effect" (Pezzulo and Levin, 2015). The power of top-down approaches is a demonstration of Noble's biological relativity concept (Noble, 2013).

Since the landmark study published in 1947, in which Louis Langman and H.S. Burr demonstrated striking differences in voltage readings between women with cervical cancers and normal subjects (Langman and Burr, 1947), several studies have demonstrated the role of bioelectric signaling in cancer cell proliferation and tumor growth (reviewed by Levin in 2020). At the symposium, Michael Levin, one of the contemporary proponents of bioelectricity (Levin, 2014), presented some of his prior experiments that indicated the role of global tissular bioelectricity in regulating cancer cell metastasis (Payne et al., 2019). As a proof of

principle, Levin and his team demonstrated that the electrical state overrules the genetic state by inducing, in a tadpole model, metastatic melanoma behavior in the absence of genetic mutations, simply by disrupting the electrical communication between cells (Blackiston et al., 2011). In recent years, the idea of using electricity to treat cancer led to some interesting results. Tumor-treating Fields (TTFields) are low intensity, intermediate frequency, alternating electric fields delivered externally through noninvasive transducers placed locoregionally around the anatomic region of the tumor (Mun et al., 2018). TTF have been FDA approved for the treatment of brain cancer (Lacouture et al., 2020) and mesothelioma (Ceresoli et al., 2019). Another device using tumor-specific amplitude-modulated radiofrequency electromagnetic fields (AM RF EMF) has been also approved in Europe since 2018 for the treatment of liver cancer (Jordan et al., 2020). Prior proposals have been made to consider cancer a "channelopathy" (Prevarskaya et al., 2018) and the modulation of the bioelectricity of cancer cells using targeted agents directed to the membrane ion channels, as suggested by Levin, may represent a novel way of cancer treatment. Interestingly, both TTF and AM RF EMF treatments work by activating specific calcium channels, and result in increased levels of cytosolic Ca2+ (Jimenez et al., 2019). so, it is plausible that similar effects can be obtained by directly manipulating cancer cell membrane channels.

In a seminal article, Denis Noble described ten principles of systemic biology (Noble, 2007). Three of them (Biological functionality is multilevel; Transmission of information is not one way; There is no privileged level of causality) are illustrated in the figure below which represents a simplified version of the figure published in 2007 Noble's article. In the human body, there is an ongoing communication between the cancer cells, cancer tissues and the whole "cancerized" organism and these three levels are co-

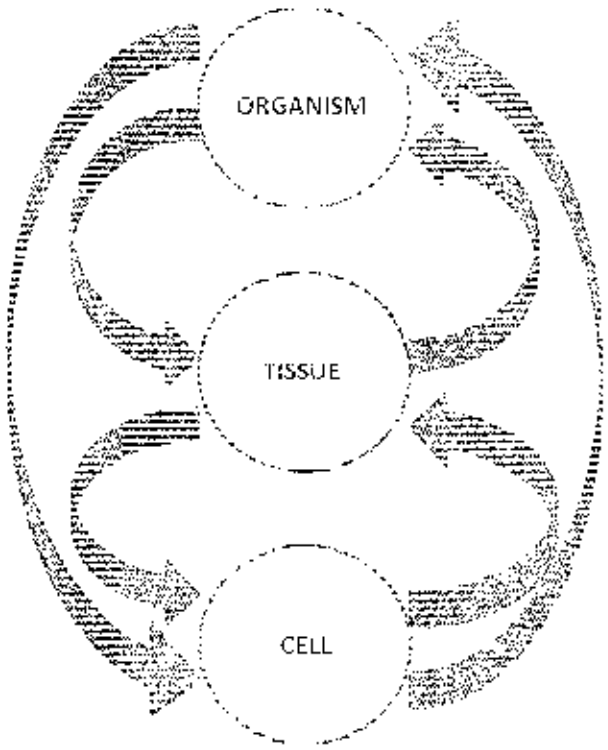

Fig. 1. Three co-dependent levels in cancer.

dependent (Fig. 1). Cancer is a multi level system in itself, a holobiont, that interacts with the organism, is influenced by it, and, at its turn, also influences the whole body (Paul, 2020). The term "holobiont" was introduced originally by Adolf Meyer-Abich in 1943 (Bordenstein et al., 2020), and was subsequently used by Lynn Margulis in an article from a book that she co-edited in 1991 (Margulis, 1991). The "holobiont" as used by Margulis, describes an integrated composite organism that contains besides the eukaryotic host other species (bacteria, fungi, viruses, etc). I use "holobiont" here in reference to cancer, using the original meaning coined by Meyer-Abich that defined the "holobiont" as a "specific biont within a strongly integrated whole, a "holobiome created through holobiosis, rather than as the whole itself" (Bordenstein et al., 2020).

Communication is crucial for the development and the functioning of the cancer holobiont. The pathologic cancer networks are formed through communication; in cancer, not only the stromal cells including fibroblasts and immune cells, but the entire organism is prompted to support cancer growth, invasion and metastasis (Paul, 2020a; Luo & Cho, 2019) through an "instigation" process previously described by Robert Weinberg and his team (Bierie et al., 2008). Networks, composed of various nodes and edges, may be described at different levels in cancer. In a cancer cell, nodes may represent protein/RNA molecules or DNA segments, where edges are their physical or signaling contacts. At the tissular levels, nodes can be the cancer cells and different stromal or immune cells and the edges, different molecules through which they communicate. At the level of the organism, nodes may represent the primary tumor, the metastatic sites, and the normal body organs, and, the edges, cellular, exosomal, metabolic or protein signals exchanged among them. In order to be able to disentangle such a complex multilayered network as cancer, novel targeted multi-scale approaches are needed that simultaneously target key elements of the cellular, tissular and systemic cancer networks. Top-down therapeutic approaches, targeting the tissular or the organismic level may be less affected by cancer genetic instability and heterogeneity than treatments targeting the cancer cells themselves and represent the "new wave" of cancer treatments (Paul, 2020; Paul and Kolokotrones, 2021). Taking into consideration the holobiont – a co-dependent system integrated into an organism, and, in continuous interaction with its systems , will allow us to develop therapeutic approaches that can indirectly target cancer by exploiting cancer's co-dependencies. As an example, treatment intervention combining diets that remove key amino acids from the food of cancer patients combined with classical oncologic therapies, are being developed (Gnanaolivu and Maddocks, 2021).

The holobiont model can be also applied to early cancer detection before it becomes clinically evident. As opposed to methods focused on detecting the presence of tumor related material (i.e. ctDNA, circulating tumor cells) in the blood or, malignant cells in tissue samples, early changes in the systemic metabolism reflecting the confrontation of the whole organism to cancer initiation can be developed. At the symposium Elizabeth O'Day, founder and CEO of Olaris Therapeutics, presented the advantages of using metabolomics for determining early treatment responses. She described metabolomics as a kind of fingerprint of the state of the organism integrating information about different variables including nutrition, genetic and epigenetic factors, age, lifestyle, environment, drugs, and disease. The potential of systemic metabolomics for detecting patients at risk for developing pancreatic cancer was demonstrated by Mayers et al, who reported that the increase of blood levels of branched amino acids (BCAA) is associated with a twofold increase in the risk of pancreatic cancer and may precede the clinical appearance of pancreatic cancer by 2–5 years (Mayers et al., 2016). These findings were substantiated by another large

prospective study done in Japan that found an association between increased plasma BCAA level and increased risk of pancreatic cancer more than 10 years before diagnostic (Kanazawa et al., 2018).

Also, the European Prospective Investigation into Cancer and Nutrition (EPIC) study, one of the largest cohort studies in the world, with more than half a million participants recruited from 10 European countries followed-up for almost 15 years, demonstrated the presence of plasma metabolomics changes long time before the actual diagnostic of cancer in several cancer types including, breast, lung, colorectal and prostate (Papadimitriou et al., 2018; Bao et al., 2013; Mayers et al., 2014; Papadimitriou et al., 2017).

In the same line of thought, Leroy Hood, co-founder of the Institute for Systems Biology and one of the advocates of personalized medicine, proposed a one million people longitudinal study that would collect different biomarkers data that could be subsequently used to develop testing platforms that would enable the diagnostic of cancer before its inception (Ye Kevin et al., 2020).

8. Cancer as an unknown life form. The cryptobiont (from "crypto" Greek. hidden, secret)

All theories presented above each with its own explanatory strengths, should not make us forget that a real comprehensive "theory of cancer" does not yet exist. Why? We started our investigation into the nature of cancer, and we described various "forms-of-life" i.e. "bionts". However, fundamentally, we do not know what life is, and, we cannot solve a mystery by introducing an even deeper one. Like the wise man in the old Buddhist parable about touching an elephant in a dark room and trying to determine its nature (Harrassers, 2021), each of the bionts described above may represent a piece of a complex puzzle that remains a work in progress.

Cancer is not a xenobiont, an alien life form. As Harold Varmus pointed out, cancer develops from the body's own normal cells, nevertheless, still now, with all technological advances, the precise causes, responsible for the inception of the malignant process in a particular organ, in a particular human being, are mostly unknown. As discussed above we don't even know if cancer starts from one cell, two cells or several cells!

Mark Vincent classified cancer treatments in two fundamental types: "*causality inhibition*" strategies, targeted towards the underlying causes, which currently, unfortunately, are still far from our current clinical treatment practices, and, "acausal" approaches that target specific cancer biomarkers or signatures (Vincent, 2017). At present, most of our current cancer treatments are "acausal" strategies directed to cancer itself, which is just an end result of a constellation of factors.

Cancer is still an enigma, a cryptobiont. Do we really need to solve this enigma to be able to treat cancer? Maybe not. Innovative and highly impactful therapeutic agents like penicillin or cisplatin were discovered by chance and significant breakthroughs into cancer treatment may come from serendipitous observations (see for example the story of the discovery of the CR/SR mouse, Cui et al., 2014; Lin, 2015).

9. Conclusion

The Cancer and Evolution Symposium demonstrated the power of transdisciplinary collaboration. The plethora of perspectives brought by the different experts speakers created a strong inspirational momentum prompting the organizers to initiate a series of conferences that will likely benefit in the future both the fields of cancer and evolution.

Cancer continues to be a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020 (WHO website). The therapeutic landscape of advanced and metastatic solid tumors, which are the main source of morbidity and mortality from cancer, currently consists of: chemotherapy, targeted agents (monoclonal antibodies and oral tyrosine kinase inhibitors), checkpoint inhibitors and various combinations of these agents. At this time, no treatment specifically targeting metastasis, cancer metabolism or epigenetic changes, polyploid giant cancer cells, chromosomal instability, genome chaos, or the cancer microbiont is available in current practice. Also, no treatment exploiting cancer evolution vulnerabilities under its neo Darwinian or other upgraded form presented at the Symposium, is currently approved.

The complexity of cancer mirrors the complexity of life itself. A deeper understanding of life's characteristics will, hopefully, also help us solve the cancer riddle and get us closer to curing advanced and metastatic cancer, or, maybe tame it into a chronic disease.

Biology is not physics and a theory of everything (TOE) may not exist in oncology. As data we gathered so far tells us that each cancer is unique and has a unique evolution. We may need to completely switch gears and, instead of looking for a global all-encompassing theory, direct our efforts at better personalizing cancer prevention and treatment strategies, and manage each patient individually, as a whole human being.

As a conclusion, it is important to remember the insightful and prescient observation of Peter Nowell, the father of the cancer evolution field: "Each patient's cancer may require individual specific therapy, and even this may be thwarted by emergence of a genetically variant subline resistant to the treatment". At present, the main reason of cancer treatment failures is due to our inability to fulfill the precision medicine promise of delivering the right treatment to the right patient, at the right time.

Author statement

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Declaration of competing interest

The author declare that they have no competing financial interests or personal relationships that could be perceived to have influenced the work reported in this paper.

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