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ORIGINAL ARTICLE

Why is it that despite signed capitulations, the war on cancer is still on?

Carlos Sonnenschein[a] *and Ana M. Soto* [a]

[a] *Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, Boston, MA USA*

Corresponding author: Ana M. Soto **ana.soto@tufts.edu**

Abstract

Almost half a century ago, under the concept of a War on Cancer, an all-out generously-funded worldwide scientific research effort was undertaken aimed at explaining cancer and eventually providing a cure for it. This massive effort was epistemologically based on a reductionist approach to the understanding of the biological sciences. In short, it adopted the premises of the somatic mutation theory of carcinogenesis (SMT) which was originally proposed in 1914 by Theodor Boveri and subsequently modified by its followers. In the last few years, a general unambiguous consensus by the originators and followers of this strategy has emerged that considered that this effort failed. Remarkably, however, the bulk of the active scientific community has ignored such a verdict and continues to work under the premises of the SMT and its variants. This Commentary documents the critical position of the "thought-leaders" and contrasts it with that of the bench-researchers at large who continue working on their respective experimental programs always consistent with the premises of the SMT, namely, that cancer is a cellular, subcellular and molecular disease. This curious and divergent attitude between cancer research leaders, on one side, and the bench-bound cancer researchers, on the other, should call the attention of all active participants who dedicated and still do dedicate their efforts to resolving the cancer puzzle and that of observers of the scientific scene. Patients, the practicing medical community and the public at large who ultimately funded such a massive undertaking deserve an explanation of a) why this well-meant scientific project failed, and b) whether there is a plausible alternative that may fare better than the unsuccessful one.

Keywords: Somatic Mutation Theory, Cancer Moonshot, Tissue Organization Field Theory, Cell Cycle, Development, Cell Proliferation

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Introduction

Though cancers have been known as a human disease since antiquity, their incidence increased significantly with the advent of the Industrial Revolution in Europe and North America in the 18th century. Ever since, cancers have assumed an increasing preeminence in the list of diseases responsible for human morbidity and mortality. This dubious privilege was in part due to the fact that infectious diseases and especially tuberculosis had begun to shed their dominance over most other human diseases with improved urban planning and the introduction of antibiotics in the 1940s and beyond. Instead, the increasing sources of pollutants due to the chemical revolution that followed War World II, the pervasive effects of Globalization and the carelessness with which the public health bureaucracy has dealt with these threats significantly contributed to making cancer a prominent culprit of human personal suffering and recently of worldwide governmental concern.

For over a century now, lay and scientific publications have considered cancers as a separate, discrete, unique entity within the broad field of biomedicine. A leading scientific publication validated in its pages

the strange, unique notion that "Cancer is at its core a microcosm of evolution" (Buchbinder and Flaherty 2016). Even in the non-fiction literature, probably as a marketing strategic approach, a 2010 literary best-seller has characterized cancer in its title as The Emperor of All Maladies (Mukherjee 2010). To our knowledge, neither researchers nor non-fiction writers have given a comparable characterization to diseases other than to cancer.

The response to the cancer threat

The perception that cancer was the centerpiece of most concerns in biomedicine and public health became crystalized in 1971 with the declaration of The War on Cancer by the then President of the United States of America, Richard M Nixon, who followed the recommendations of his scientific advisors and of both Chambers of the US Congress. Even though the War on Cancer originated in the USA, other countries having even a modest research capability agreed to support this metaphoric war effort.

The overt starting strategy to win the War had multiple targets, but the molecular explanation of the carcinogenesis process was its centerpiece. This rationale implied that the knowledge acquired from this massive investment would be eventually applied at the bedside and would have accumulated unprecedented knowledge in biology at large. Other aspects of this declaration, like cancer prevention, were given only limited representation in the strategy and consequently minor financial resources. Thus, the strategic plan to win the War centered in learning about cancer as a disease rather than in eliminating the easily identifiable environmental threats that by 1971 were already known to increase its incidence. Because of the present awareness of the gigantic direct and indirect costs of cancer to society, one wonders whether the short-term solution (laboratory bench research on cancer) was a wise decision when compared with the cost of changing societal behaviors. Given that the latter can no longer be ignored, and the acknowledged lack of success of the War on Cancer, the subject is now acquiring increased interest by government planners, the scientific community and the public at large (Sarewitz 2016;Belluz et al. 2016;Krugman 2015;Geman and Geman 2016).

This Commentary will center on some troubling features of the War on Cancer effort and its aftermath with special emphasis on epistemological aspects of the strategic plans adopted to fight it, the benefits and mistakes accrued from this effort and the lessons learned that may be applied to assure a brighter future to the management of research and clinical cancer in particular and to biology at large.

Recent accounts of Cancer as a disease

The overall strategy used to fight the War on Cancer was based on the notion that cancers were mostly lethal, cell-based, genetic, molecular and even vaguely articulated evolutionary diseases. The historical aspects of how the War was conceived has been dealt with in detail and we refer the reader to those sources (Sonnenschein and Soto 1999;Sonnenschein and Soto 2013;Heng 2016). In the last decade, a good number of those who actively and enthusiastically participated in initial and subsequent stages of the War on Cancer effort have unambiguously expressed the view that the War was being lost. As a result of these candid admissions a curious social situation has become obvious. It can be resumed as follows: despite the objective, documented capitulation on the part of the thought-leadership[1] who conceived and/or enthusiastically approved the original and subsequent strategies of the War on Cancer, the main effort in worldwide research laboratories continues to operate as if the War is either being won, or at least still being successfully fought. Evidence of this inconsistency can be witnessed by just perusing the Table of Contents of biomedical publications in the fields of basic and clinical cancer research, a sign that funds allocated to fight the War based on the premises adopted at its inception (see below) continue to be spent unabated.

The basic strategy of the War on Cancer

Briefly, the War on Cancer was and is still being fought under the tenets of the Somatic Mutation Theory of carcinogenesis (SMT). In its original version, this theory proposed that cancer was a cell-based disease and that the aberration responsible for the neoplasia that it eventually generated was centered in the chromatin of the nucleus of the original cancer cell (Boveri 1914;Nowell 1976;Cairns 1975;Mukherjee 2010;Sonnenschein and Soto 1999;Soto and Sonnenschein 2014). All along, it has been both explicitly and tacitly acknowledged that the default state of cells in multicellular organisms is

[1] The expression "thought-leaders" originated from an article written by Donald Hanahan (2014) in which he characterized a number of participants as such in a meeting held in Lugano Switzerland, at the end of 2012 where progress in cancer research and therapeutic outcomes were discussed.

quiescence, meaning that cells have to be stimulated in order to both proliferate and move, a notion that has been propagated for decades in cell biology textbooks at different educational levels (Lodish et al. 2008;Alberts et al. 2014;Weinberg 2014b).

On the occasion of being awarded the 2016 Lasker Prize, Bruce Alberts, the senior author of the textbook Molecular Biology of the Cell was evaluated by JL Goldstein, a Nobel Prize awardee, in the following terms "…A notable example of this latter accomplishment was his leadership role in teaming up with five other scientists to write the most influential textbook of its kind, Molecular Biology of the Cell. The first edition, which was published in 1984, is now in its 6th edition (appearing in 2015). This classic textbook has been translated into 11 languages (including Chinese) and has been devoured by tens of millions of students as well as established researchers, all of whom praise it for its clarity, the logic of its explanations, and its splendid illustrations. Even though the 2015 edition was assembled by seven authors, the material is integrated in such a way that it reads like the work of a single hand—undoubtedly the deft hand of Bruce Alberts" (Goldstein 2016).

Due to lacks of fit between its premises and the empirical data collected since its inception in 1914, the SMT became subject to a number of course-corrections. Just to name a few, these included intracellular abnormal metabolic components (Warburg 1956;Vander Heiden et al. 2009), failures in immunological surveillance (Burnet 1970), an attempt to make cancer an infectious disease which eventually generated the notions of oncogenes/suppressor genes (Bishop 2003), involving an assortment of cellular and acellular components of the tumor microenvironment (Bissell and Hines 2011;Kalluri 2016) and combinations of the above alternatives (Sonnenschein and Soto 1999;Soto and Sonnenschein 2014). Due to the lack of success in comprehensively explaining carcinogenesis, some of those add-ons were temporarily abandoned but years later they resurfaced with marginal modifications (Dang 2013;Wallace 2012). Notwithstanding, despite a generous multibillion dollar investment for over half a century on the SMT and its many variants, these theories remain empirically untested by their promoters (Soto and Sonnenschein 2011). Equally important, it is yet to be shown how those alleged causative mutations can be successfully manipulated in human patients in order to reverse the course of most cancers or substantially improve their diagnosis, prognosis and the quality of life of those patients (Prasad 2016;Prasad and Gale 2017;Tannock and Hickman 2016).

Evaluations of the War on Cancer strategies

Starting in the 1980s, evaluations of the data that was being collected under the War on Cancer program cautioned about the marginal impact of that massive investment (Bailar and Gornick 1997). However, it has been in the last ten years that the very thought-leaders who since 1971 enthusiastically promoted and/or embraced the SMT as the blueprint to vanish cancer began to openly acknowledge that such a strategy has failed.

In order to document the above referred consensus, samples of abridged quotations by those thought-leaders follow. In a wide ranging interview published online in the German magazine Der SPIEGEL over 6 years ago (July 29, 2010), J Craig Venter, a scientist-entrepreneur who was among the first to describe the content of the Human Genome, was asked about what were the medical benefits of the multibillion dollar Project, one of whose stated purposes was to identify those cancer cell mutations. Venter answered "Close to zero to put it precisely." Then, he added that "…this century will be remembered for how little, and not how much, happened in this field." Later, he was asked "Why is it taking so long for the results of genome research to be applied in medicine?" Venter answered: "Because we have, in truth, learned nothing from the genome other than probabilities. How does a 1 or 3 percent increased risk for something translate into the clinic? It is useless information." When he was later asked: Who is to blame for (those) false expectations? Venter answered "We were simply always looking at single genes because they were the only genes we had. When people lose their keys at night, they look under the lamp post. Why? Because that's where you can still see something." Then, when answering another question, perhaps sarcastically, Venter added "…Why did people think there were so many human genes? It's because they thought there was going to be one gene for each human trait. And if you want to cure greed, you change the greed gene, right? Or the envy gene, which is probably far more dangerous. But it turns out that we're pretty complex. If you want to find out why someone gets Alzheimer's or cancer, then it is not enough to look at one gene..." Again, Venter's views were already published in 2010.

Robert A Weinberg, an American Cancer Society professor at the Massachusetts Institute of Technology (MIT) and a widely recognized leader in the empirical field on cancer research aligned since the beginning of his four-decade long career with the SMT and its variants. Weinberg introduced the notion that a cancer cell was "a renegade cell. In 2014, Weinberg opined that "…

From the point of view of the reductionist hoping that a small number of molecular events (one base out of three billion!) might explain cancer, things went downhill from there (1982) for the next 30 years." Professor Weinberg concluded the analysis of his 40 years of battling the War on Cancer by asking "How will all this play out? I wouldn't pretend to know. It's a job, as one says on these occasions, for the next generation. Passing the buck like this is an enormously liberating experience, and so I'll keep on doing it!" (Weinberg 2014a).

Separately and almost simultaneously, Paul Davies, a theoretical physicist and principal investigator of the Center for the Convergence of Physical Sciences and Cancer Biology at Arizona State University at Tempe, in answer to the question "What scientific idea is ready for retirement?" posed by John Brockman, editor of Edge.org,[2] stated that "(C)ancer is one of the most intensively studied phenomena in biology, yet mortality rates from the disease are little changed in decades. Perhaps that's because we are thinking about the problem in the wrong way… A major impediment to progress is the deep entrenchment of a 50 year-old paradigm, the so-called somatic mutation theory."…"Unfortunately this theory, despite its simplicity and popular appeal, has only one successful prediction: that the administration of chemotherapeutic drugs is very likely to fail on account of the neoplasm's ability to rapidly evolve a resistant sub-population. Armed with the somatic mutation paradigm, the research community has become fixated on the promise of sequencing technology, which enables genetic and epigenetic changes in cells to be measured on a vast scale… Never has science offered a clearer example of a preoccupation with trees at the expense of the forest…" "The same genes that are active in cancer are also active in early embryogenesis (even in gametogenesis), and to some extent in wound-healing and tissue regeneration. These ancient genes are deeply-embedded and well-protected in our genomes. They run the core functionality of cells. Top of the functionality list is the ability to proliferate—the most fundamental modality of living organisms, with nearly 4 billion years of evolutionary refinement behind it. Cancer seems to be the default state of cells that are stressed or insulted in some way, such as by aging tissue architecture or carcinogenic chemicals, with tumors representing a reversion to an ancestral phenotype." He finally concluded that "In biology, few things are black or white. The somatic mutation paradigm is undeniably of some relevance to cancer, and sequencing data is certainly not useless. Indeed, it could prove a gold mine if only the research community comes to interpret that data in the right way. But the narrow focus of current cancer research is a serious obstacle to progress. Cancer will be understood properly only by positioning it within the great sweep of evolutionary history."

Also in 2014, Douglas Hanahan, the Director of the Swiss Institute for Experimental Cancer Research School of Life Sciences, at the Swiss Federal Institute of Technology Lausanne, Switzerland, reported that a consensus of cancer clinical and research thought-leaders who met at the World Oncology Forum, in Lugano, Switzerland, in late 2012, a question was asked: "… are we winning the War on Cancer, 40 years on? The conclusion was, in general, no. Despite the introduction of hundreds of new anticancer drugs, including advanced therapies (so-called magic bullets) aimed at particular weapons in the enemy's armamentarium, the consensus was that, for most forms of cancer, enduring disease-free responses are rare, and cures even rarer. Notable exceptions include some forms of leukaemia and of breast cancer, testicular cancer, and particular tumours— e.g., colorectal—amenable in early stages to total surgical resection." When offering alternative course-corrections to the SMT, Hanahan proposed to adopt an alternative approach, that he defined as 'holistic', to win the War on Cancer as follows: "The metaphorical war on cancer needs to adopt an analogous cancer battlespace plan, integrating knowledge about similar variables, including: a census of a cancer's variously specialized cells, the basis of their corruptions (e.g., genetic mutations, reprogrammed regulatory circuitry), their lines of communication, and the nature of their functional contributions to the war machine; the mechanistic composition of the armamentarium in a particular form of cancer that collectively supplies the hallmark capabilities necessary for tumour growth, invasion, and dissemination; the distinctive histological features of a cancer's assemblage in different tissue landscapes; and the characteristics and potential value of friendly forces that might be enlisted as part of tactical attacks throughout the many battlefields of disease." Next, Hanahan proposed "A refined battlespace-guided war on cancer" that encompasses a) prevention, b) "to take a world view of the enemy" and c) "the therapeutic war plan needs to be refined." (Hanahan 2014)

A comparable attitude was proposed by Harold Varmus, now a Senior Associate Member of the New York Genome Center, New York, NY, and the former director of both the U.S. National Institutes of Health

[2] https://www.edge.org/response-detail/25380

and later of the National Cancer Institute, who dealt with the shortcomings of the War on Cancer while being at the helm of the War effort acknowledged that "…Research has shown that cancers are intimately entwined with basic life processes—diseases of the genome, with perturbations of signaling pathways and essential cell functions. New diagnostic categories are based on genetic profiles, not just morphology." However, he acknowledged that "…Implausible goals that tarnished earlier campaigns, such as the elimination or cure of certain cancers by a certain date—the equivalent of a true moonshot—have been conspicuously absent." And "…fundamental problems in cancer biology (which he didn't identify) remain unsolved."[3]

Another sample of what thought-leaders are now thinking about the prospects of a successful end of the War on Cancer was reported in several lay publications by Eric Lander, another scientific entrepreneur, professor at the MIT, founder of the MIT-Harvard joint venture Broad Institute, and co-chair of the USA President's Council of Science and Technology, which has been promoting the Cancer Moonshot project. During a session at Spotlight Health, part of the 2016 Aspen Ideas Festival in Colorado, he was quoted as stating that cancer will eventually be tamed; however, "(I)t's not going to be all done in 10 years, but if we get it done in 40 years, I'm not going to be embarrassed," For this to happen, he suggested that "We should force the liberation of people's own medical records"[4]. The press release did not elaborate about who was he referring to when he said "We". Remarkably, James Watson, one of the main architects of the War on Cancer declaration, Nobel Prize co-winner with Francis Crick for their description of the structure of the DNA molecule, acknowledged that locating the genes that cause cancer has been "remarkably unhelpful" and the belief that sequencing one's DNA is going to extend one's life represents "a cruel illusion" (Apple 2016). Thus, altogether, regardless of the fine details of how the massive financial and human-power investment turned out to be unproductive when the cancer puzzle was to be solved, the target constituency of cancer patients, the cancer caring community and that of biologists at large, are obviously witnessing the capitulation by the original proponents and sustainers of the War on Cancer.

Of note, other than vague hints at the need to adopt undefined or "more-of-the-same" suggestions, to explain and eventually vanquish Cancer, no specific theoretical or empirical plausible alternative is being offered by the thought-leaders of the decades-old, well-funded War on Cancer (Joyner et al. 2016). [5]

What impact these admissions of failure are having on the cancer research community?

Notwithstanding all these widely disseminated, candid admissions of failure reported during the last decade, the SMT remains as the hegemonic theory among cancer researchers as demonstrated by the narrative of most recent publications that are exploring the subject (Martincorena and Campbell 2015;Gerlinger et al. 2012;Heng 2016). Introductory statements like "Cancer is a genetic disease caused by driver mutations of germline and somatic DNA" (Khan and Helman 2016), or "Tumors evolve from single cells." Or "Cancer arises from the clonal expansion of a single cell." (Davis and Navin 2016;Petljak and Alexandrov 2016;Nik-Zainal et al. 2016;Mertins et al. 2016;Tannock and Hickman 2016;Torres et al. 2016) or "Genetic mutations are a hallmark of cancer development, and more than 140 cancer driver genes have been described to date (1,2). Identification of all mutations in an actual tumor of a patient by whole-genome sequencing is rapidly emerging as the method of choice for precision diagnostics (3). However, detailed knowledge of the functional roles and relevance of most mutations arising during tumorigenesis are still lacking" (Gebler et al. 2016), are the rule in contemporaneous cancer research literature and even in Wikipedia, and, as referred to above, textbooks at all levels of education and non-fiction books.

The lack of correspondence between what can be certified as war capitulations (see above), on the one side, and the attitude of cancer researchers who continue exploring admittedly unproductive research strategies on the other, may lead impartial observers of the biological scene to conclude that this state of affairs resembles either a typical denial syndrome or a schizophrenic plot by various components of the cancer research enterprise. This unenviable situation in which the cancer research community at large is snarled becomes compounded by the fact that the SMT, as mentioned above, has never been rigorously tested. In this context, back in 1968, in a critical paper about the impact of theories in biology at large, the American geneticist Francisco Ayala suggested that

[3] https://meyercancer.weill.cornell.edu/news/2016-04-08/transformation-oncology

[4] https://www.statnews.com/2016/06/26/lander-cancer-cure-reality-check/

[5] As noted by an anonymous reviewer of this submission, "the articulation of defeat was typically in a tone of exhaustion, not of a eureka moment…"

"…science proposes explanatory hypotheses that must be testable, i.e. accessible to the possibility of rejection or falsification'' (Ayala 1968). Again, so far, such a test has been conducted neither by those who sided with the SMT before they realized its inadequacy nor by those who today still abide by it (Soto and Sonnenschein 2011). As pragmatic evidence for this assessment it could be considered noteworthy that two full years after the publication of the 2000 original, highly cited Hallmarks of Cancer review co-authored by Douglas Hanahan and Robert A. Weinberg in the journal CELL, their article was cited over 765 times and as of 2016, that review accumulated over 13,000 mostly approving references. An expanded view of the 2000 Hallmarks paper was published in 2011; after 2 years, it accumulated over 3,500 citations and as of 2016 it has been cited over 11,500 times (Hanahan and Weinberg 2011). In sharp contrast, the above-referred Professor Weinberg's 2014 critical assessment of the War on Cancer, published in the same legacy Journal, so far has accumulated about 45 citations.

Is moving the goal posts aimed at salvaging the War on Cancer or the SMT?

In contrast to the quotations of the cancer thought-leaders referred to above, researchers who are currently taking a less critical view of the acknowledged failures by the SMT and its consequences in the clinic favor the notion that further accumulation of quantitative research data under the same general paradigm will finally reconcile the tenets of the SMT with the hoped-for benefits to patients anticipated by the War on Cancer backers. For instance, some have concentrated their attention on searching for alternative loci where the ever alleged cancer gene mutations may be located , or epigenetic changes in histone genes (Lu et al. 2016;Torres et al. 2016), mitochondrial function (Wallace 2012), stromal components like fibroblasts (Kalluri 2016), etc. Results stemming from these alternative options have yet to compensate for the current admission of failure of the original SMT.

The alternative strategy that relies on poly-omics amounts to something akin to moving the goal posts whereby experimental and clinical data which used to be generated at the lab bench or the bedside will be enhanced or replaced by computational capabilities. The accumulation of computational generated data obtained always under the umbrella of the SMT is, in fact, incompatible with the premises of this theory. As an example, so called "cancer driver genes," considered a hallmark of specific cancers (Tokheim et al. 2016) have also been found in benign conditions and in premalignant lesions at frequencies higher than in the corresponding tumors (Kato et al. 2016). Also, empirical evidence documenting the present of somatic mutations in normal cells of normal tissues is mounting (Yadav et al. 2016). Summing up, both the War on Cancer Declaration and the recently proposed Cancer Moonshot project (Singer et al. 2016) share a common "greedy" reductionist approach that considers that mechanistic explanations of phenomena happening at higher levels of biological organization (tissues, organs, organism) will only be found at the level of molecules, more specifically, nucleic acid and protein molecules. The evaluation made above of the War on Cancer and of its main theoretical underpinning, i.e., the SMT, challenges their currency and, in turn, invites the proposition of alternative options to fulfill the original aims of benefiting cancer patients and explaining the pathogenesis of cancers.

An alternative view

Research expressly aimed at simultaneously testing the SMT and an alternative theory of carcinogenesis, i.e., the tissue organization field theory (TOFT) offers a different view of the carcinogenic process based on a novel epistemological approach in biology (Sonnenschein and Soto 1999). This theory has adopted the premises that a) cancer is a tissue-based disease ("development gone awry") (Soto and Sonnenschein 2011) and b) explicitly, proliferation with variation and motility is the default state of all cells (Soto et al. 2016). The data collected to simultaneously test the TOFT and the SMT were compatible with the TOFT and incompatible with the SMT (Maffini et al. 2004). Comparable conclusions could have been drawn by a number of reports aimed at explaining carcinogenesis published before and after the clearly stated claim that cancer is a tissue-based disease (Barcellos-Hoff and Ravani 2000;Bussard et al. 2010). Moreover, the other premise explicitly adopted by the TOFT that states that the default state of all cells is proliferation with variation and motility represents a truly paradigmatic change in biology at large (Soto et al. 2016).

Concluding remarks

The fields of cancer research and of biology at large are in the midst of a serious crisis. This crisis is due to the realization by a substantial segment of the scientific community that the research enterprise has reached a point where the epistemological bases of the current approaches are no longer providing real answers to very basic biological questions (Longo et al. 2012). The community is split between those who are in a state of denial before the challenges of resolving this situation and those who are at the so-called leadership positions who are at a total loss regarding integrating mountains of empirical data within an evolutionarily relevant theory. The current status of the science on carcinogenesis has reached this untenable position because for over a century it has pursued a reductionist strategy aimed at explaining biology at the level of molecules and under a misguided mechanistic approach (Sonnenschein and Soto 2016). The failure of this reductionist strategy is now becoming obvious to the public, researchers, and funding agencies and is widely chronicled in the scientific and lay press (Sarewitz 2016;Belluz et al. 2016;Geman and Geman 2016;Krugman 2015). Its remediation requires a radical epistemological reassessment and the adoption of an alternative organicist perspective (2016).

Finally, have we directly answered the Why question of the title? In an insightful paper, Sui Huang compared the war on cancer with the war on terror; he observed that while "the military has learned to learn from past failures", the cancer research community has yet to do it (Huang 2014). In addition to the arguments that we have made above, a comprehensive answer to that Why question will require an equally candid sociological analysis of the subject.

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