Cancer: Beyond Speciation

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A good account of the nature of cancer should provide not only a description of its consistent features, but also how they arise, how they are maintained, why conventional chemotherapy succeeds, and fails, and where to look for better targets. Cancer was once regarded as enigmatic and inexplicable; more recently, the “mutation theory,” based on random alterations in a relatively small set of proto-oncogenes and tumor suppressor genes, has enjoyed widespread acceptance.

The “mutation theory,” however, is noticeable for its failure to explain the basis of differential chemosensitivity, for providing a paucity of targets, especially druggable ones, and for justifying the development of targeted therapies with, in general, disappointingly abbreviated clinical benefit. Furthermore, this theory has mistakenly predicted a widespread commonality of consistent genetic abnormalities across the range of cancers, whereas the opposite, that is, roiling macrogenomic instability, is generally the rule. In contrast, concerning what actually is consistent, that is, the suite of metabolic derangements common to virtually all, especially aggressive, cancers, the “Mutation Theory” has nothing to say.

Other hypotheses merit serious consideration “aneuploidy theories” posit whole-genome instability and imbalance as causally responsible for the propagation of the tumor. Another approach, that is, “derepression atavism,” suggests cancer results from the release of an ancient survival program, characterized by the emergence of remarkably primitive features such as unicellularity, fermentation, and immortality; existential goals are served by heuristic genomic instability coupled with host-to-tumor biomass interconversion, mediated by the Warburg effect, a major component of the program.

Carcinogenesis is here seen as a process of de-speciation; however, genomic nonrestabilization raises issues as to where on the tree of life cancers belong, as a genuinely alternative modus vivendi. Philosophical considerations aside, genomic instability offers the prospect of subtle new therapies based on loss of information rather than gain; and the consistent, specific, and broad-spectrum perfidy of the Warburg effect highlights a supplemental target of the highest priority. © 2011 Elsevier Inc.
I. INTRODUCTION

A. Limitations of Heterogeneity and the "Many Disease" Model

The “many disease” view of cancer has, over time, successfully negotiated the transition from opinion to truism. This journey, as with all such journeys, has been rewarded by the removal of any obligation to exercise critical scrutiny, and so the “many disease” view has passed into conventional wisdom.

For is it not obvious that cancers involving different organs, different demographics, even different types of animals, with a wide range of distinctive etiologies, often specific treatments, and radically different outcomes, must surely be different diseases? And isn’t this, in turn, now well supported by a panoply of unique molecular aberrations?

Well, these are facts and cannot be disputed. We should acknowledge the heterogeneity so minutely described and documented; we are even prepared to extend the concept, for example, to a group of patients with the same “type” and stage of cancer (e.g., “advanced non-small-cell lung cancer”) who seem, for no obvious reason, to behave very differently from one another, whether treated or not. We also do not hesitate to invoke “clonal heterogeneity” within a given patient’s cancer, as the automatic explanation for any change in tumor behavior: a sudden growth spurt or the development of drug resistance, for example.

But to accept the fact of heterogeneity, whatever its boundless utility across the multiple levels of the nosological hierarchy, does not mandate that we necessarily accept the whole conceptual package. In particular, heterogeneity is more of a description of, than an explanation for, the spectrum of cancer. Heterogeneity, even though it might in some superficial way, “explain” differential drug sensitivity, is not in itself an explanation of cancer; rather, it is the heterogeneity itself that requires explanation. At the very least, we should try to interrogate what has now become the dominant paradigm in clinical oncology, not only to extract what is there that is genuinely useful, but also to appreciate the limits of the concept, and, in the hope that deeper understanding might lead to therapeutic solutions, to obtain direction as to where else we need to search for better treatments.

B. The Modern Cancer Research Enterprise: A “Ship of Fools?”

In the clinic today, even in well-resourced facilities, and with patients not restricted by financial considerations, it should be thoroughly understood how bad the state of affairs is, in most cases of advanced common
cancers. For example, in many aerodigestive cancers, we are flailing around with technologies from the 1960s (cisplatin), 1950s (fluorouracil), 19th century (radiation) and early 20th century (surgery); more recent innovations (e.g., taxanes, biologicals) are a decade or more old, and epitomizing the law of diminishing returns, tend to add disproportionately more to the cost than the efficacy. These and similar cancers, once metastatic, remain stubbornly incurable and survival increments over best supportive care (BSC) alone tally scarcely a year or two, on average. These modest clinical achievements, although worthwhile and even sometimes impressive, are meant to be constantly improved by the flow of knowledge from basic and applied research; however, in practice, this happens infrequently, despite the deluge of information, and the enormous dedication of thousands of people.

That such a vast and costly enterprise as modern cancer research should generate such meager returns on investment is cause for concern, and should prompt a question: as a society, do we really understand what we are dealing with, and if not, do we understand that we do not understand?

This essay represents an attempt to come to grips with these issues.

II. HOW TO “UNDERSTAND” CANCER

A. Characteristics Shared by all Cancers

All cancers, whatever their differences, are characterized by a number of common phenotypic features, without which they could not be grouped into a single categoric type. These features include progressive biomass accumulation of clonally derived cells, which arise within a pre-existing multicellular organism, but from inception, constitute tissue superfluous to adaptive requirements. Other definitions are possible (Vincent, 1987) but broadly similar. Cancers are a subtype of neoplasm, which is what is strictly being defined here, with the added proviso that all cancers manifest “invasiveness” in addition to superfluous cellular proliferation. Hanahan and Weinberg (Hanahan and Weinberg, 2000) identified six core traits that characterize cancer, that is, self-sufficiency in growth signals, insensitivity to antigrowth signals, apoptosis evasion, tissue invasion and metastasis, sustained angiogenesis, and limitless replicative potential. It is possible to consider expanding this “core” list to include the Warburg effect (WE), immortality, immune tolerance induction, autonomy, and “stemness”; but one at least which should be mentioned as “missing in action” from the original Hanahan–Weinberg is genetic instability; the recent update by Hanahan and Weinberg acknowledges “genome
instability and mutation” as an “enabling characteristic” (Hanahan and Weinberg, 2011).

From this line of thinking, which so far has been very mainstream, we can draw at least two conclusions. Firstly, if all cancers are characterized by a core of certain invariant features, then this is what we should be trying to understand, and so there is a sense in which the “many diseases” paradigm is misleading; and secondly, the constituent cells are clearly “transformed” in some heritable way, and therefore have to have evolved out of normality.

These two conclusions are neither contradictory, nor without mutual relevance. Taking them together, we can come to two further conclusions: parsimony would seem to suggest that a single or at least a limited set of molecular alterations underlies this common core of phenotypic characteristics, and might be common to all cancers; and furthermore, what is common to all cancers has to be understood as an evolutionary phenomenon.

Note that the “single or at least a limited set of molecular alterations” does not necessarily imply in a concrete way that these changes are all exactly the same in each cancer cell (although some may be), but that the command and control structure in every cancer cell is affected in a manner that results in the same sort of functional abnormality. In other words, there may or may not be identical molecular abnormalities, but there always has to be at least one conceptually similar type of abnormality in cellular control mechanisms. To date, this shared type of abnormality is generally accepted to exist, and to be represented by a broadly similar set of aberrations affecting control of the cell cycle; so far these have proven difficult to “drug.” I will argue here that additional, higher order commonalities characterize all cancer cells, which might prove superior targets.

B. Therapeutic Implications

From a therapeutic perspective, it would of course be an enormous advantage for there to be a limited or identical set of molecular abnormalities at which to target cancer drugs, across a range of cancers. Drugs, however subtle or indirect their mechanisms of action, are obliged to interact in a very concrete way with molecular targets, and the prospect of every cancer having a uniquely different set of molecular targets is actually a formidable, even insurmountable challenge to the prospects of ever developing curative therapy. Yet this is what the “many diseases” model of cancer seems to allow, and even imply, as does any naïve interpretation of “heterogeneity.”

The “many diseases” model of oncogenesis is popular today not least because it matches so well the vogue for “personalized medicine,” which
is sweeping the cancer community as well as the broader health care industry. Personalized cancer medicine involves not just the patient-specific features that always mandated individualized care (e.g., co-morbidities, performance status, age, patient’s wishes, etc.) but also the opportunity to use drugs that work in some patients but not others. These agents, moreover, should preferably be selected on measurable parameters in the tumor, that is, biomarkers, and most especially those that actually “drive” the cancer such as hormone receptor over-expression, growth factor receptor amplification/mutation, or other accessible oncogenic changes; in other words, the use of the so-called biologically targeted drugs. Successful drugs of this type would include tamoxifen for estrogen-receptor positive breast cancer; trastuzumab for HER2-positive breast cancer; imatinib for BCR-ABL transformed chronic myeloid leukemia (CML); sorafenib in renal and hepatocellular cancer; and gefitinib/erlotinib, two epidermal growth factor receptor tyrosine kinase inhibitors (e.g., EGFR-TKIs) for EGFR-mutated adenocarcinoma of the lung.

C. Personalized? Hardly

These therapies are not truly personalized in an individual sense, but apply (or not) to quite large subgroups of patients. In lung adenocarcinoma, for example, about 60% of never or light ex-smokers in East Asia are EGFR-mutated, and respond well to an EGFR-TKI (Mok et al., 2009). Nonetheless, their total lack of efficacy in the remaining 40% of marker-negative patients mandates a sorting process that can be enacted in every patient of this nonsmoking profile. Just as it is, today, unthinkable to manage any breast cancer patient without the knowledge of the ER, PR, and HER2 status, it will soon be unthinkable to manage advanced non-small-cell lung cancer (A-NSCLC) adenocarcinoma (the commonest subtype) without EGFR mutational analysis. Within a few years, most of the oncogenic drivers of never-smoking lung adenocarcinomas will be routinely measured and even druggable, for example β-RAF, HER2, ALK translocations, etc. In this march of progress, never-smoking lung cancer (actually 25% of all lung cancer) (Parkin et al., 2005) may be seen as a leading paradigm for other cancers in whom the druggable drivers (if indeed there are any) currently remain obscure.

Therefore, these trends do not exemplify personalized cancer medicine in the strict sense of the term; rather, they represent “subgroup cancer medicine,” a term that does not have quite the same cachet. Nonetheless, there is a central problem with most of these targeted drugs; in patients with advanced disease, their beneficial effects are temporary (Table I) and acquired resistance is almost inevitable. For example, in EGFR-mt+ A-NSCLC, EGFR-TKI are able to control the disease for around 9–10.5 months (gefitinib) or perhaps a bit longer with erlotinib (12–14
Table 1  Duration of Benefit

Some inhibitory treatments directed against oncogenic drivers in advanced cancers

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Genes</th>
<th>Disease</th>
<th>Median duration of benefit</th>
<th>Parameter</th>
<th>Cure?</th>
<th>References</th>
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<tbody>
<tr>
<td>EGFR-TKI</td>
<td>EGFR-Mt+</td>
<td>Adenocarcinaoma of the lung</td>
<td>9.5–14 m</td>
<td>PFS</td>
<td>No</td>
<td>Mok et al. ibid 2009;</td>
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<td>Rosell et al., ibid 2009;</td>
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<td>Paz-Ares et al., ibid 2010</td>
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<tr>
<td>Crizotinib</td>
<td>EML4-ALK</td>
<td>Adenocarcinaoma of the lung</td>
<td>&gt;6 m</td>
<td>PFS</td>
<td>No</td>
<td>Kwak et al., 2010</td>
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<tr>
<td>Sorafenib</td>
<td>Downstream of ras</td>
<td>Renal cell; hepatocellular</td>
<td>5.5 m</td>
<td>PFS</td>
<td>No</td>
<td>Kim et al., 2011;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>carcinoma</td>
<td>2.6 m</td>
<td>PFS</td>
<td></td>
<td>Arranz et al., 2011</td>
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<tr>
<td>Imatinib</td>
<td>Bcr-abl</td>
<td>CML</td>
<td>&gt;5 yr</td>
<td>PFS</td>
<td>No</td>
<td>Maybe</td>
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<tr>
<td>Trastuzumab</td>
<td>Her-2</td>
<td>Breast cancer</td>
<td>±3.6 m</td>
<td>PFS</td>
<td>No</td>
<td>Druker et al., 2002</td>
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<td>Bevacizumab</td>
<td>VEGF</td>
<td>E.g., colorectal cancer</td>
<td>4.7 m</td>
<td>Incremental OS</td>
<td>No</td>
<td>Vogel et al., 2002</td>
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<tr>
<td>Imatinib</td>
<td>C-kit</td>
<td>GIST</td>
<td>18–20 m</td>
<td>PFS</td>
<td>No</td>
<td>Hurwitz et al., 2004</td>
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<td>ARQ-197</td>
<td>C-MET</td>
<td>Adenocarcinoma lung</td>
<td>4.3 m</td>
<td>PFS</td>
<td>No</td>
<td>Blanke et al., 2008</td>
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<tr>
<td>Afatanib</td>
<td>T790Mt of EGFR</td>
<td>Adenocarcinoma lung</td>
<td>3.3 m</td>
<td>PFS</td>
<td>No</td>
<td>Schiller et al., 2010</td>
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<tr>
<td>Tamoxifen</td>
<td>Estrogen Receptor</td>
<td>Breast cancer</td>
<td>5–7 m</td>
<td>PFS</td>
<td>No</td>
<td>Miller et al., ibid 2010</td>
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<td>PLX-4032</td>
<td>β-Raf V600E</td>
<td>Melanoma</td>
<td>6–9 m (est)</td>
<td>PFS</td>
<td>No</td>
<td>Falkson and Falkson, 1996;</td>
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<td>Sullivan and Atkins, 2010</td>
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months) (Mok et al. ibid; Paz-Ares et al., 2010; Rosell et al., 2009; Zhou et al., 2010b). This is typical also of tamoxifen and other SERMs in ER+ breast cancer, for hormonal blocking agents in that disease (e.g., anastrazole, letrozole), in prostate cancer (with anti-androgens), in colorectal cancer initially responsive to anti-EGFR monoclonal antibodies (cetuximab, panitumumab), and renal cancer with respect to drugs like sunitinib, sorafenib, or everolimus. The only exceptions to this might (controversially) be imatinib in chronic phase CML or tamoxifen (or trastuzumab) in the adjuvant (post curative-intent surgical) settings, in which some patients may be nudged into cure via elimination of a small population of microscopic disease that surgery failed to eliminate. But, by-and-large, in the advanced setting, these drugs work for only a relatively short time; a 1 year period of good disease control, while very welcome in, say, a 47 year old with metastatic EGFR mt+ lung cancer, goes nowhere near indemnifying her against the loss of her life-years, since she will likely die about a year after failing EGFR-TKI, in the prime of her adult life.

Furthermore, these drugs do not work initially in everyone who is marker-positive, for reasons that are gradually being uncovered and which relate to genomic plasticity in the cancer cell. They work poorly or not at all in marker-negative patients; for instance, the most common subgroup of A-NSCLC is (ex)smoking adenocarcinoma, about 92% of whom are EGFR-wt, and which is typically lethal in approximately one year (Scagliotti et al., 2008). For these much more common patients who are not candidates for currently available targeted drugs, conventional chemotherapy is the default option and may provide some useful palliation and modest life extension that is typically measured in 6–18 months additional time. Conventional chemotherapy is, of course, commonly, but wrongly regarded as untargeted, but I shall return to this egregious misconception later.

Inevitably, drug resistance emerges sooner or later in nearly all patients with the advanced, common cancers, and most of the uncommon ones as well, whether they are candidates for highly targeted drugs or the so-called untargeted chemotherapy. It is also worth noting a paradox here that few if any advanced cancers have become curable as a direct result of modern biologically targeted drugs; and indeed the cures of aggressive, and otherwise lethal cancers wrought in the 1970s in respect of, say, lymphoma and germ cell cancers, were due to the actions of classical chemotherapeutic agents.

D. Resistance—You Can Count on It

Although there is persistent the hope that drug resistance might be reducible to a limited number of pharmacologically tractable mechanisms,
this has rarely proven possible. Drugs that “deal” with the T790M exon 20 mutations and C-MET amplification in EGFR mt+ lung cancers have emerged and appear to be modestly active (Miller et al., 2010; Schiller et al., 2010;) but attempts to deal with the drug extrusion pumps like p-glycoprotein (ABC B1), described over 30 years ago (Hall et al., 2009), have proven almost uniformly unsuccessful (McHugh and Callaghan, 2008) despite in vitro work that appeared to guarantee that p-gp inhibition was not only possible, but should work in patients with this form of “pleiotropic” drug resistance, and which led to major investment in drug development and failed clinical trials.

Furthermore, some undoubted drivers (e.g., mutated K-RAS), after 3 decades of intensive research, remain stubbornly undruggable (Young et al., 2009). K-RAS is certainly associated with, and may actually cause, relative or absolute drug resistance to the EGFR-TKIs in lung cancer (Mao et al., 2010), and to the anti-EGFR moAbs in colorectal cancer (Linardou et al., 2008). K-RAS mutations, furthermore, may be associated with lack of benefit to adjuvant chemotherapy with cisplatin/vinorelbine in resected NSCLC (Butts et al., 2010); however, data from other trials in A-NSCLC with chemotherapy does not necessarily substantiate K-RAS as a factor particularly associated with chemotherapy resistance, and the author has personally documented a dramatic response to pemetrexed single agent in a proven case of K-RAS mutant lung adenocarcinoma in an ex-smoker. Nevertheless mutant K-RAS is a prominent oncogenic driver and yet remains undruggable (McCormick, 2010).

Likewise, multiple other resistance mechanisms have been well described, but remain largely beyond the reach of modern ingenuity. Drugs like bevacizumab seem to exercise modest benefits not necessarily by cutting off blood supply, but paradoxically, by improving blood flow into tumors and hence drug delivery (Cao, 2010; Jain, 2005; Willett et al., 2007). Generally, the literature is full of optimistic early results, and dashed hopes thereafter; the recent relatively disappointing results in advanced breast cancer with a PARP-inhibitor may be a case in point (Sanofi Aventis, 2011).

In summary, drug resistance, especially “acquired” resistance after a period of responsiveness, is indeed further evidence of the fact of heterogeneity in cancer, and of the underlying genomic plasticity and clonal evolution. It is proof that cancer is not only an evolutionary phenomenon in its emergence (carcinogenesis), but that further evolution occurs after the initial transformation, and which is characterized by heritable variation (“descent with modification”), the grist to the mill of natural (and unnatural) selection. The specter of most concern however, is that both oncogenic drivers and drug-resistance mechanisms, at least those that might be druggable, could be highly variable patient-to-patient and even within the same patient’s cancer. This nihilistic perception is driven by, or
at least highly congruent with the standard evolutionary interpretation of cancer (*vide infra*), which relies heavily on serial random mutations.

However else cancer is understood (and there is no monopoly on this) it is inescapably true that a full understanding requires a clear appreciation of its evolutionary origins and character. This is not new, of course, but it is nevertheless appropriate to describe what the conventional wisdom has to say about this before advancing an alternative (or at least complementary) hypothesis, as an antidote to the naïve, or the therapeutic nihilism that the conventional wisdom might seem to encourage. This complementary hypothesis is, it should be immediately stated, is one that is also supportive of, reliant upon and consistent with Darwinian principles.

III. “CONVENTIONAL WISDOM”: THE DARWINIAN VIEW OF CANCER

A. Evolutionary Principles

Darwin, Wallace and Herbert Spencer, heavily influenced by Malthus, advanced several ideas to account for the development of biological diversity on earth (Table II). These ideas form the core of what became known as Darwinism.

Although initially controversial, the elegance of these ideas, their explanatory power, and the enormous and painstaking evidence collected by Darwin and others gradually led to their acceptance, not only in mainstream biology, but also in common parlance. However, the mechanism(s) by which evolution operated were entirely unknown, until the re-discovery of Mendelian genetics and its reconciliation with Darwinism in the decade 1936–1947: the “Modern (evolutionary) Synthesis” (brought about by Huxley (Huxley, 1942), Fisher (Fisher, 1930); Dhobzansky

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<th>Table II</th>
<th>Key Ideas of “Darwinism”</th>
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<td>1.</td>
<td>Common descent</td>
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<td>2.</td>
<td>Variation within populations</td>
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<td>3.</td>
<td>Descent with modification</td>
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<td>4.</td>
<td>Overpopulation</td>
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<td>5.</td>
<td>The struggle for existence (competition)</td>
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<td>6.</td>
<td>Natural selection</td>
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<td>7.</td>
<td>Survival of the fittest</td>
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(Dobzhansky, 1937); Mayr (Mayr, 1942); Simpson (Simpson, 1944); Haldane (Haldane, 1924–1934), Wright (Larson, 2004), and others.

Recent developments in molecular biology have only served to confirm both Darwinian evolution and the modern synthesis. Dawkins is associated with the “selfish gene” concept, which implies that gene preservation and transmission is an evolutionary priority (Dawkins, 1976). Nonetheless, surprisingly large areas of controversy remain, such as the precise mechanisms of speciation; the extent to which saltationism (“large jump” evolution, as opposed to gradualism) has contributed to, and continues to contribute to evolution; the role of epigenetic imprinting; the reasons for the evolution of sexual as opposed to asexual reproduction; and the precise grounding of the tree of life. Some of these controversies remain relevant to the evolution of cancer; in particular, the disputes around the primacy of the gene, as well as gradualism versus saltationism, should be noted.

Saltationism involves evolutionary change by large jumps in which intermediate forms do not, and never did, exist. This sort of evolution was named the “hopeful monster” hypothesis by the geneticist Richard Goldschmidt, who supported it as a kind of instantaneous speciation involving “…a complete change of the primary pattern or reaction system into a new one” (Goldschmidt R, 1940). By contrast, Darwin himself favored gradualism, encapsulated in the quote “Natura non facit saltum,” (i.e., nature does not make large jumps). Although it is currently difficult to obtain a true consensus statement about this, it seems that modern biologists generally favor gradualism while admitting occasional saltation-type exceptions, most notoriously the appearance of life itself, and the development of the eukaryotes. The “discovery” of sexual reproduction and the appearance of multicellular organisms are also candidate examples of saltationism. Furthermore, just how rapidly new species can evolve is also a matter of contention, although most seem to suggest that speciation usually occurs by reproductive isolation (“allopatric speciation”), coupled with a gradualistic series of small mutations and, perhaps, genetic drift. The prudent position for nonspecialists seems to be agnosticism on this issue.

The consistent message of the conventional wisdom is that however evolution proceeds, whether slowly or rapidly, it proceeds mainly, if not exclusively, by the action of serial mutations, which are themselves utterly random and stochastic. It is often said that “selection (in evolution) has no eyes for the future” (Williams, 1966), by which is meant that the accumulation of damage in DNA does not proceed according to any pattern, and that the phenotypic consequences are solely the result of the cumulative effect of these mutations interacting with each other and the unmutated DNA, resulting in a system that is complex, largely unpredictable and indeed truly chaotic in a mathematical sense.
B. Evolution of Cancer: The “Standard Model”

The standard model of carcinogenesis states that serial, random unrepaired mutations in regions of DNA, central to the command and control of the cell cycle, produce, in surviving cells, a condition of perpetual clonal expansion insensitive to growth-inhibitory signals. Further mutations accumulate randomly, disrupting not only cell number homeostasis but also positional homeostasis, such that invasion, a crucial hallmark of malignant as opposed to benign neoplasia, then occurs. Variants that are “more aggressive” are simply selected out because they have a “fitness” advantage, that is, an advantage in growth and proliferation, and succeed in not only expanding at the expense of the normal body, but also at the expense of less aggressive clones of erstwhile sibling cancer cells. This concept, incidentally, is pure Malthus, who believed that over time, population growth rate would come to approximate that of the most fertile group (Malthus, 2000).

In the version explicated by Greaves (Greaves, 2007), this paradigm is imposed upon normal stem cells, which are then unable to exit the cell cycle, via the usual pathways of apoptosis, senescence, post-mitotic differentiation, or return to quiescence, because each of these pathways has been disabled by a mutation. Thus the normally constrained program of clonal expansion is unleashed for no particular reason, except the occasional failure of DNA repair mechanisms, which then permit rare cells to serially and progressively escape the various bottlenecks imposed by multicellular existence to prevent just this exigency. In this view, serial, rare, but random hits on key DNA control machinery progressively free occasional cells to compete successfully in harsher and harsher environments, in which only the most robust and aggressive are able to survive and proliferate. In this cascade, the mechanisms underlying genetic stability are eventually themselves affected, leading to “genetic diversity” and, inevitably, drug resistance, on a purely random basis. Because these mutational events are undirected, and need to be multiple in order to fully transform the cell, this process usually takes decades. Notwithstanding this, cancer is made possible in the first place by the “lack of perfection” in evolutionary engineering, which is required to provide some plasticity in DNA to allow embryonic sculpting and indeed evolution itself.

In short, the conventional view might be summarized as saying that everything of importance in a cancer cell is due to a random mutation, and the variants so produced are simply selected based on relative proliferative advantage, itself a hereditary trait.

This description combines Darwinian mechanisms of random variation, differential fitness, and natural selection, with the action of initiating exogenous mutagens, working with various promoting factors, acting in the context of cellular hierarchies, and resulting in the unrestricted and
inappropriate depression of normally well-controlled programs of cell renewal and migration. Critically, in this view, there is absolutely no purpose to this, and although all cancers are meant to exhibit causative lesions in the same pathways, the exact position of these lesions is random; furthermore, they exist with multiple other relevant and irrelevant mutations, which at a level of detail are unique to each cancer, and to some extent to each cancer cell. Therefore although a naive version of the standard model would have only the same, very few genes always implicated in every patients across the range of cancers, a more sophisticated understanding requires only the same type of genetic aberration, with much irrelevant variation in the detailed minutiae.

Some versions acknowledge higher levels of genetic instability than can adequately be accounted for purely by random mutations, and indicate that DNA stabilization mechanisms might themselves have suffered disablement via the same random mutations, and having failed to fix themselves up, then contribute to DNA hyperinstability, with the net result that variant form production is increased. Nonetheless, most of this “secondary” variation is perceived, in the standard model, to be “genetic noise” (Heng, 2010 ibid).

The question, of course, is how much of this variation is cause and how much is effect, in terms of driving the malignant phenotype and/or drug resistance—and exactly how much has to be “targeted” therapeutically to regress the tumor, given that causality-reversal is conventionally considered a therapeutic strategy worthy of pursuit. Irrespective, these observations, on the fluidity of the cancer genome, and which seem now to be multiply confirmed, pose the gravest problems for the current simplistic “targeted” paradigm of therapy, as it struggles to seek validation in common cancers like those of the smoker’s lung, the breast, the pancreas, etc.

C. Problems with the Standard Model

As others have realized (Israël, 1996; Heng, 2010 ibid), the standard model has done little to help in the clinic, except to predict that drug-resistant forms will emerge as an adaptation to the particular stress of anticancer therapies, and may already have emerged (“by chance”) even before the start of therapy. However, we knew this already from experience. The standard model does not tell us which targets exist, which to attack, or how to do it. These shortcomings, per se, do not mean that the standard model is necessarily all wrong; inevitably, however, we are encouraged to look elsewhere for a more helpful theoretical framework. Nonetheless, while one purpose of this chapter is to critique the standard model, it is also important to recognize, but not to overfocus on, the “straw man,” or naive version of the standard model (Table III).
\begin{table}[h]
\centering
\begin{tabular}{l|p{6cm}|p{6cm}|p{6cm}|p{6cm}}
\hline
\textbf{Table III} & Models of Carcinogenesis: Criteria \\
\hline
 & (Standard model, basic) & (Standard model, advanced) & Genomic or karyotypic theory & Programatic: de-repression atavism ("the animal within") \\
 & "straw man" & "mutation theory" & (Heng–Duesberg causality) & \\
\hline
\textbf{Mutation} & Series of random mutations & Series of random mutations & Both cause and consequence, but more the latter & Carcinogens represent a survival threat via mutation \\
\textbf{Pathogenesis} & Dependency on a few consistent changes in a few consistent genes; causal consistency & Ongene/antioncogene dependence, continuously; aneuploidy just "noise"; causal consistency & Oncogenes initiate but later redundant or even absent, and not required; unstable aneuploidy the driver, takes over; causal inconsistency & Mutations dysregulate cell cycle, and trigger an ancient survival program, the Warburg effect, as the enabler; agnostic as to causal consistency \\
\textbf{Natural selection} & Irrelevant & Operative & Operative & Operative \\
\textbf{Common phenotypic traits} & Determined by a small set of genetic mutations & Stem cell self-renewal program de-repressed; WE not implicated, under emphasized; other traits explained by convergent evolution & Not emphasized & Re-emergent animal phylogenation; reprimtitivization; adaptive resilience; Warburg metabolism; genomic scrambling \\
\textbf{Genetic instability} & Not envisaged & Acknowledged; due to secondary mutations; not central, but allows further evolution in aggressivity and resistance & Causally fundamental, the real driver & Key component of survival program; purpose is discovery of better-adapted genome \\
\hline
\end{tabular}
\end{table}
<table>
<thead>
<tr>
<th>Heterogeneity</th>
<th>De-emphasized; only due to maturation hierarchy, persistent tissue-of-origin features</th>
<th>Acknowledged; accepts role of serial but random mutations, usually causing resistance</th>
<th>Emphasized, due to whole genome instability; unavoidable</th>
<th>Emphasized as central purpose; due to endogenous mutagen and “toleratort” function of the program</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priority</td>
<td>Gene-centric</td>
<td>Gene-centric; genetic instability an emergent epiphenomenon, but not central</td>
<td>Genes less important, genomic mayhem more important</td>
<td>Gene propagation deprioritized; priority now is “any cost cellular survival” via genomic novelty-seeking</td>
</tr>
<tr>
<td>Targets</td>
<td>A few, common genetic aberrations across a whole range of cancers</td>
<td>Constant continuing drivers exist, just need to be found and inhibited; confounded by secondary genetic noise</td>
<td>No or few constant drivers exist</td>
<td>Drivers and markers exist, but vulnerable to reshuffling; the WE, however, never rescrambled</td>
</tr>
<tr>
<td>Purpose</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Strongly purposed—“for survival”; explains phenotype</td>
</tr>
<tr>
<td>Solution</td>
<td>Inhibition of a few common drivers-naive</td>
<td>Individualized driver inhibition; either naïve or nihilistic</td>
<td>None suggested yet; nihilistic?</td>
<td>Overwhelming firepower via “absence” targeted therapies; combined with inhibition of WE, or of mutator phenotype</td>
</tr>
</tbody>
</table>
The standard model, however sophisticated, represents a “train wreck” perspective: everything is due to random accidental damage, nothing has purpose, every cancer is different, in the sense that individual DNA lesions are inconsistent, and the only known commonality is that at some level, at least, the cell cycle is stuck in the “go” position; more shadowy derangements are inferred to be present to account for invasion; and within the multiplicity of mutational abnormalities, the drivers are to be found, comprising an unknown (and perhaps unknowable) ensemble of (by definition) activated oncogenes and inactivated tumor suppressor genes. Except perhaps in childhood cancers, the path to carcinogenesis is gradualistic, and proceeds over decades. The minimum essential genetic lesions required to be targeted for therapy are unknown but discoverable in principle. Conscious of the need to explain ongoing post-transformational evolution, the model involves random damage to DNA homeostatic mechanism themselves, to explain clonal evolutionary exigencies like acquired drug resistance, as well as the emergence of much nonconsequential and noise-like variation; however, this DNA instability is not felt to be central to the malignant phenotype per se.

The key aspect of this model is that phenotypic variants can only, and do, appear entirely at random; if they are advantageous, they are selected and enrich the tumor thereafter. Those that are advantageous survive; those that survive must have been advantageous. In this view, the fact that all cancer cells, in all people, at all times, come to exhibit this nearly identical set of core traits has to be seen as a fantastically coincident type of convergent evolution, although this is not often acknowledged; rather, emphasis is placed on the proximate drivers that are known or believed to exist, in different embodiments, in different cancers, and different patients.

The standard model does not generally mention or analyze the fact that cancer cell proliferation occurs in an asexual fashion; that somehow the cells escape Muller’s Ratchet (by which the disadvantageous mutations that occur in asexual organisms cannot be purged from the genome); that the autonomy observed implies that the cells have clearly ceased to be part of the multicellular animal, or that a highly characteristic, inevitable, and almost invariant metabolic program, the WE, suddenly appears as if by coincidence, in most and usually every aggressive cancer cell; and that very gross genomic changes occurring from cancer cell to cancer cell, and from one generation to the next, constitute a major departure from gradualist evolution, and threaten cozy assumptions about cause and effect. Nor does it note that occasionally—very occasionally, but categorically—descendant cancer cells can escape the dying host and be transmitted to a new host, as a whole cell, where they may successfully set up shop, and repeat the process over and over again, like any competent parasite (Murchison, 2008; Welsh, 2011).
As will be discussed by another contributor (Heng, 2009; Heng et al., 2006, 2010), a major failing of the standard model, even the more sophisticated version which accommodates hypermutation, relates to its inability to account for the sheer amount of mutational heterogeneity between patients, within the same patient, and even from one generation to the next in a particular tumor cell lineage. Heng’s viewpoint is that observations from the cancer genome sequencing project have failed to confirm that there is a universal pattern of genetic alterations shared among most cancers, revealing rather the opposite: genetic heterogeneity is much greater than expected, and the commonality much less.

This is regarded (by some, at least) as a threat to the gene-centric concept of cancer evolution, as contained in the standard model; and which should lead to alternative conceptualizations that account for the major consistent genetic finding, that is, macro-evolutionary instability, clearly evident at the genomic, and karyotypic level. In this latter viewpoint, cancer results as a combination of the more important macro-evolutionary rearrangements, evident karyotypically, and less important micro-evolutionary level (genetic and epigenetic) alterations that fine-tune adaptation. This viewpoint is unquestionably not only chaotic (sensu stricto), but especially saltationist, incompatible with organismal integrity, and a challenge to the standard model; primarily because the latter in no way envisages this large-scale whole genomic instability, cannot explain how this level of instability is compatible with ongoing cellular life, and requires that certain types of gene be consistently mutated in every cancer, by chance, but which is (apparently) not actually the case to the extent it should be.

It might, however, be argued that at least some sort of disablement of senescent, quiescent, apoptotic, or differentiation pathways is consistently found, and probably is necessary, and since massive genomic instability is most unlikely to reconstitute these normal exit strategies, that the standard model is not wholly incompatible with the “genome theory” of cancer elaborated by Heng et al. (ibid 2010). Also, it is wrong to suggest that at least some common drives (e.g., K-RAS in pancreatic cancer, and some lung and colorectal cancers) do not occasionally occur.

Nonetheless, what Heng et al. raise is that the precise mechanism of disablement is not necessarily constant from case to case or, more important, generation to generation within the same cancer and this hypervariability was never envisaged by the standard model, in which the malignant phenotype is seen as mediated by the continuing presence of particular genes, albeit with some potential for additional mutations to drive a more aggressive evolution. The reason that this is so serious is that drug treatments are going to fail inevitably sooner or later to the extent that driver functionality of any particular target becomes no longer necessary, or even disappears entirely, to be replaced by something else, and not just because
the target molecule itself might mutate further. What this teaches is that targeting extant drivers is unlikely to have more than a temporary benefit (and actually, this is almost always confirmed in the clinic, see Table I); I will suggest later that, as an alternative strategy, what might be better targeted, perhaps, is the absence of something.

One philosophical concern with the standard model is that it does not attribute biological purpose to the cancer cell. This does not mean that it would have been designed with the future “in mind”; I am categorically not making an argument for intelligent design, just that the machinery of the cancer cell, and the phenotypic traits that result, could actually have a biological function. This would be just like any normal cell, constructed to fulfill a biological role, based not necessarily on the idea that the future is known but that it is at least overwhelmingly likely at any given time, to be very similar to the past.

In this respect, we should note the less famous quote by Dobzhansky (in the same essay in which he more famously said that nothing makes sense except in the light of evolution). He said: “The enterprise of biology rests chiefly on two patterns of explanation. One is the organism-the-machine theory. The other is the theory of evolution...these explanations are complementary, without being either deducible from, or reducible to each other” (Dobzhansky, 1964). In other words, there are two ways to understand anything in biology (or indeed anything that is naturally or artificially constructed): firstly, to strip it down into its component parts, itemize them, see how they fit together, etc.; and secondly, to understand what the whole structure is for. What it does, how it does it, and above all, why it does it; in other words, what is it for.

So dare we ask, what is the cancer cell for? Many would object to this question as invalid. Must it necessarily be for something? For some purpose? Why can’t it just be a train wreck? After all, train wrecks exist, and they are not “for” anything but can only be understood as a failure to achieve the original objective. Engineering is not perfect, and so accidents happen; why should biological engineering be any better? The obvious production of occasionally nonviable offspring is a clear proof, if it were needed, that biological engineering (i.e., “natural” history) is far from perfect and, for reasons of parsimony and efficiency, needs only to be “good enough.” Surely, it could be argued that cancer must be like this, that is, a systems failure occasioned by the unattainably high price of, and lack of, necessity, for perfection. This view is not unreasonable, and a very much part of the standard model.

It may also be right. But we are entitled to at least ask the Dobzhansky question “could the cancer cell be for something”? “And if so, what”? The standard model (at least the recent version) maintains that the target cell of transformation could be the normal stem cell; in a variety of tissues (see the paper by A. Pietras in this volume) normal stem cells possess a program of
self-renewal. This program, in multicellular organisms, is normally constrained by a complex hierarchy of controls. Furthermore, this program is retained from the premetazoan era, that is, from the unicellular organisms that evolved into metazoa, and is clearly evident in unicellular organisms today. Mutations causing cancer disable one or more of the control systems regulating the cell cycle. As a result, the unrestrained cell cycle is unleashed. The transformed cell comes to behave as if it were a unicellular organism, since these same controls (now disabled) not only restrain the cycle, but tether the cell to the requirements of the organism as a whole. So, although the resulting cancer cell does not have a purpose, or function, per se, it manifests a program unbridled (self-renewal), which at one point in evolutionary history, certainly did have a purpose, and in the intact metazoan host, has a purpose but only to the extent it is harnessed to the needs of the entire organism.

Certainly, this particular interpretation of the standard model, while uncommon, is reasonable. But I shall try to push beyond this to see if other explanations are tenable. In particular, I will first look at an interesting paradigm, which I will call “Heng–Duesberg causality” in honor of its proponents; and then also my own perspective that carcinogenesis, and subsequent material events of clonal evolution, constitutes bona fide episodes of speciation, and even beyond that, a novel form of life itself. I shall now explain these theories, at the same time attempting to explore implications for therapy.

IV. ALTERNATIVE INTERPRETATIONS OF CANCER

A. Source Documentation

These deliberations are based on essays written by this author, one published (Vincent, 2010) and another in press (Vincent, Bio Essays in press 2011). I will also draw on a third essay (Vincent, in preparation). These essays deal with unorthodox conceptualizations of the malignant condition, and the therapeutic implications of these views. They are not offered as revealed facts, and even less as conventional wisdom, or indeed any kind of wisdom; but as alternative conjectures that are consistent with the known facts, with the general thrust of evolutionary theory, and which, in turn, have implications for those interested in therapy. However, I will first review some important precedent views, by two other sets of authors, which are somewhat consistent with, or bear upon, my own thoughts. Because these authors’ views on the maintenance of the malignant phenotype substantially overlap, I will group them together.
B. Heng–Duesberg Causality

In fact, most of the conjectures that I entertain are not new. The concepts of cancer as a novel species has been raised by several authors as an analogy (Pearson, 1981; Vineis, 2003) and even as a matter of fact (Duesberg and Rasnick, 2000; Huxley, 1956). Duesberg and Rasnick make the argument (for speciation) based on karyotypic alterations, which are often gross and in fact (within parameters) continuously unstable. Recently published (Klein et al., 2010) is a compelling set of data illustrating that initiating oncogenes may even, in certain cases, not be necessary for the subsequent maintenance of the malignant phenotype, and these authors further provide a review of the industrial-scale karyotypic diversity and phenotypic heterogeneity found even in tumors arising in the same target cell and initiated by the same oncogene. This is very similar content to the previously mentioned writings of Heng et al. (ibid 2010), for whom the malignant phenotype is maintained by whole-genome instability and not specific oncogenes. Both sets of authors contrast their positions with the “mutation theory” (i.e., standard model) of cancer, which predicts a continuing requirement for the initiating oncogene, in order for the cancer to be maintained, and which together with a relatively stable set of cooperating genetic alterations is meant to produce, in each cancer, a relatively constant phenotype (Lewin, 1997). Somewhat similar to the “genome theory” of Heng et al., Duesberg’s group proposes the “karyotypic theory,” which can perhaps be summarized, to quote and paraphrase (Duesberg et al., 2003; Fabarius, ibid 2003):

- The degree of malignancy is proportional to the degree of aneuploidy.
- Copy numbers of a given chromosome are often not the same in all cells of a given cancer as a result of the inherent instability of aneuploidy.
- Acquisition of drug resistance correlates with a specific karyotype.
- Oncogene-independent transformation occurs; that is, the initiating transgenic oncogene may later be dispensable, functioning as a carcinogen rather than a cancer gene.
- Carcinogens (including artificially activated oncogenes) initiate carcinogenesis by inducing random aneuploidy.
- Individual karyotypes maintain cancers, much as they maintain species.
- Aneuploidy destabilizes the karyotype by unbalancing teams of balance-sensitive mitosis genes; aneuploidy is inherently unstable.
- The resulting instability catalyzes the evolution of new cancer-specific karyotypes, much like species-specific karyotypes (emphasis added); and these cancer-specific karyotypes can function as “additional oncogenes.”
- Clonal karyotypes (as opposed to the initiating oncogene) determine the phenotype of cancers, that is, maintain the (existence of) the cancers, as well as their specific characteristics.
Transgenes function as carcinogens, catalyzing independent evolution of new cancers.

Duesberg and coworkers thus believe that “carcinogenesis is a form of speciation,” and that the appearance of new cancer-specific karyotypes is “much like species-specific karyotypes.” Furthermore, and tellingly, “carcinogenesis is proposed to be much like phylogenesis,” a theme to picked up below in connection with Huxley.

C. Speciation Criteria: Gene Flow versus Trait

As to the mechanisms underlying this genomic reshuffling and unstable aneuploidy, solutions have been suggested by Gisselsson and others (Gisselsson et al., 2001; Gisselsson, 2011a,b), involving telomere dysfunction, defects in the spindle assembly checkpoint, merotelic attachments, segregation errors, and perhaps a combination of mechanisms such as multiplier mitosis and/or incomplete cytokinesis, with some sister chromatid nondisjunction. The issue here is not so much the mechanism(s) by which continuous genomic instability is produced, but the consequences; however, if it is to be part of some program, then it must be explained how the mechanism is consistent with this, and whether it offers any prospects for genomic restabilization.

It may appear to a “nonspecialist” that speciation is always associated with karyotypic differences, but this is not quite true. Rather, what is key is the cessation of gene flow, which may be brought about opportunistically (e.g., by isolation of subpopulations, for various reasons). Gene flow is, of course, a concept that applies best to sexual species, or those asexual ones that employ horizontal gene transfer (HGT); cancer cells are asexual organisms, and HGT is not well documented among them. The conventional model of speciation indicates that it is caused by incompatible alleles, which have become alternatively fixed, in two previously isolated populations; this is known as the BDM model (after Bateson, Dobzhansky, and Muller) (Gavrilets, 2003). Chromosomal rearrangements are a relative and sometimes absolute barrier to successful recombination, or contribute to gamete nonviability by imbalance, and/or segregation problems in gametogenesis.

However, cancer cells are asexual and appear not to share genes by HGT. Therefore, each one is a genetic island, and to extend the metaphor, each lineage, an archipelago. Therefore since gene flow does not occur, except via lineage descent, karyotypic differences, which strongly imply speciation in sexual species, may matter less in the speciation discussion in respect of cancer cells versus their original host, or versus each other, in the same cancer lineage.

Consequently, while I do believe that karyotypic variation supports the idea of cancer as a different species from the originating host, and
additional, clonally ordered karyotypic distinction post carcinogenesis supports the existence of subsequent rounds of speciation, there is an element of analogy in this, and so I chose to pursue the idea of cancer as species from a trait perspective, taking a cue from Julian Huxley, who focused on autonomy as a central phenotypic characteristic. “Once the neoplastic process has crossed the threshold of autonomy” he said, “the resultant tumor can be logically regarded as a new biologic species” (Huxley, ibid 1956), and even “... as constituting a special organic phylum or major taxonomic group ....” I shall return to this concept of “phylogenation,” while noting here that Huxley was using it, I think, in a metaphorical sense to indicate the existence of a vast chasm between the originating host and its descendent cancer cell population, in that they are no longer a constituent part of the same individual; at the very least, it is legitimate to describe carcinogenesis as an act of “individuation.” While this is not necessarily pathological (childbirth, gamete release, and budding might all be normal examples), in the case of cancer the descendent cells are not only autonomous but also destructive of the original host, and their cells are now in unequivocal competition. While intraspecific competition is not uncommon, for good reasons it tends to be limited, whereas interspecific competition (at least in the same niche, as is the case here) is much more likely to be destructive, and fully transformed cancer cells are indeed always destructive of their host. As to whether they constitute “… a special organic phylum ...” is arguably true since, although cancers in different victims are more closely related to their originating hosts than to each other, they are better conceived as unicellular organisms, or at most a loose and facultative colony, and most categorically not any more a multicellular animal, or part of a multicellular animal. This might, because of a striking resemblance among all cancer cells, constitute a separate “special organic phylum,” in some literal sense. Or, going beyond even this, as I will later elaborate, cancer cells may constitute an entirely different form of life.

D. The Animal Within: Trait-Inferred Speciation

“The animal within” (Vincent, ibid 2010) illustrated various definitions of species (a strangely inflammatory topic) and concluded that although speciation in asexual organisms constituted a particular problem in definition, certain of the definitions did embrace the concept satisfactorily. In particular, the “cohesion species concept” (CSC) of Templeton (Templeton, 1989), together with the “evolutionary species concept (ESC) of Simpson (Simpson, 1961), proved most useful. The latter posits a lineage-relatedness series, evolving separately, with “its own unitary evolutionary role and tendencies.” The CSC describes forces of genetic cohesion, which in asexual species would tend to be genetic drift with natural selection, to ensure genetic similarity. One can readily see how a
population of asexual organisms, for example, bacteria, occupying a uniform ecological niche, and relatively isolated, could retain a large measure of genetic identity simply because of the convergent forces of natural selection. This does not, of course, necessarily imply genetic or genomic stagnation, as long as the entire population evolves more-or-less in concert, and the uniform application of the same forces of selection to the whole population might keep interindividual variation generally below a certain critical threshold, even in the absence of any HGT.

Nonetheless, it is probably worth re-examining the true extent of cohesion that actually exists in a population of cancer cells, either in culture, *in vivo*, or in the original patient. What appears to be the case is that although large scale differences can and often do occur between cancer cells in the same cancer, and a cancer cell and its descendants, there are broad karyotypic parameters that tend to bound this variation within certain limits. On the other hand, when, for example, a particular drug is introduced, the karyotype adjusts with the evolution of a drug-resistant subline; and the same may be true of a cancer cell as it comes to occupy and adapt to a different niche such as a different metastatic site. Trait differences of sufficient materiality might well constitute further rounds of speciation (or subspeciation, depending on the degree of difference and its clinicopathologic significance). However, it is reasonable to ask whether the obvious genetic plasticity of cancer cells to some extent undermines the notion that they should have attained the status of a novel species, if “species” is to be understood as a “type,” and a “type” is to be invested with constancy, or consistency.

It does not, however, undermine the notion that cancer cells, whatever they are, are categorically different from the species of the original host animal (or human), and that at least a separational speciation event has taken place, and, with the emergence of unicellularity, possibly something more than “mere” speciation: the emergence of a holozoan opisthokont (animal-like) protist, with facultative colonial attributes, and which might be labeled with the title *dyskaryota*.

**V. CANCER AS SPECIATION: IMPLICATIONS FOR BIOLOGY AND THERAPY**

**A. Words and Definitions Need to Matter**

What, it might be asked, does it matter if we choose to label carcinogenesis as an act of speciation? After all, definitions can be arbitrarily changed; but this seems an empty exercise unless there are tangible gains in knowledge, efficiency, or cancer management. Let us now consider the implications for biology, and then therapy.
B. Biology

Does the issue of “cancer as species” tell us anything about speciation in general? It seems unlikely that speciation in sexual organisms, in which one expects a lineage to separate into two closely similar but stably distinct types following some geographic isolation, has much in common with carcinogenetic speciation, which requires not only a sudden, vast taxonomic leap but also genetic instability.

What about speciation in asexual organisms? It seems also unlikely that we have much to learn here either. Asexual speciation probably proceeds under similar conditions, that is, geographic isolation, or at least alternative niche occupancy, which, combined with mutation or at least genetic drift, and influenced by differential forces of natural selection, drives novel alleles to fixation, resulting in the eventual emergence of two different but genetically stable genomes. This does not appear to be a good description of carcinogenesis either, although it might be informative for subsequent rounds of clonal evolution in an already extant cancer.

What is distinctive about carcinogenetic speciation is:

1. the emergence of a unicellular, perhaps colonial organism from a multicellular organism
2. the emergence of an asexual organism from a sexual one
3. the emergence of a genomically (and genetically) highly unstable organism from a genetically highly stable one
4. the emergence of a novel type that, while de facto closely related by descent from its originating host, is grossly dissimilar to this host, and therefore unrelated by resemblance
5. the emergence of a novel type whose existence is not only competitive with its original host of origin, but is, under natural conditions, eventually incompatible with it
6. a process that occurs rapidly, much more rapidly than the other types of “usual” speciation
7. the process of carcinogenetic speciation is both temporally and morphologically nongradualistic, that is, is saltationist

This latter point, however, should be qualified: it is acknowledged that some cancers go through a premalignant phase, during which time they are partially transformed; the adenoma–carcinoma sequence in the colon is just one of several good examples. Yet the adenomas, already autonomous, unicellular, and superfluous with respect to growth, have already crossed the Rubicon; they are bona fide neoplasms, and, in my opinion, have already speciated. The bigger point, however, is that there are no intermediate body-forms—no “missing links”—between the metazoan host and the unicellular neoplastic colony; the process is essentially saltationist. The further progressions to frank malignancy are but additional
rounds of speciation, and may or may not themselves be more gradualistic. But the biggest jump is saltationist especially when viewed against the more usual evolutionary time frames.

What I feel is most distinctive about carcinogenetic speciation is the lack of capacity to permanently restabilize the genome in an alternative configuration, all the while (even perhaps by this means) avoiding Muller’s Ratchet (the invariant collection of adverse mutations, normally purged by sexual recombination, and which ultimately dooms most asexual organisms).

At the very least, however, the obvious taxonomic divergence of the cancer from its host of origin, whatever one actually calls it, stands as a stark lesson for those who continue to deny the natural evolvability of life.

C. Therapy

There are two major sources of therapeutic nihilism, when it comes to cancer:

1. The belief that cancer cells are too similar to normal cells for there ever to exist an exploitable therapeutic index (type I nihilism)
2. The belief that whatever molecular targets we attack in the cancer cell, resistant variants will usually evolve before eradication is possible (type II nihilism)

The juxtaposition of these two sentiments opens up something of a paradox. On the one hand, the taxonomic gulf between cancer and its host must be caused by something, and which (unless we are very much mistaken) must be reducible to a set of molecular alterations; even if we allow that the initiating molecular alterations may be different from those that ultimately maintain the malignant phenotype on an ongoing basis, there always have to be appreciable biomolecular differences between cancer and normal cells, and which should, therefore, be also regarded as potential targets.

On the other hand, the genomic/genetic instability, which somehow goes along with this, seems guaranteed to lead quite rapidly to the evolution of drug resistance. But if the material drivers of the cancer cell’s existence, as targets, are themselves also alterable, perhaps this outcome may be incompatible with the continuing existence of the cancer cell, and if it happened a lot, the tumor as a whole might “go out of business.” That this appears not to be the usual case supports the Heng–Duesberg model, and is a strike against the conventional mutation theory; at least it suggests that there are mechanisms to counter this, either compensatory hyperproliferation or driver invulnerability/redundancy. Almost certainly however, and which is of immense interest therapeutically, many cancer cells do become nonviable, slip silently out of existence, and are recycled by the tumor.
Insofar as a large taxonomic chasm opens up between cancer cells and their hosts of origin, then this has to be mediated by “a core set of molecular alterations that being both causal and distinctive, are potential targets” (Vincent, ibid 2010). Furthermore, “These fundamental changes have to exist and *ipso facto* must represent the ultimate targets for rational drug design”; that is, to the extent that “rational” means “based on causality reversal.”

As to the nature of these molecular alterations, they are hypothesized to at least include the same genes involved in the evolution of multicellularity, since the development of cancer and the evolution of metazoa might be intimately related, as “bidirectional traffic on the same two-way street” (Vincent, ibid 2010). It turns out that this prediction is to a substantial extent backed up by the involvement of the cadherins, Hedgehog, Wnt, Notch, and others representing genes common to both processes, either through their constructive exploitation (evolution of multicellularity from unicellular organisms) or their deregulation (development of cancer in a multicellular host) (Farnie and Clarke, 2007; Lai, 2004; Rokas, 2008; Rubin and de Sauvage, 2006; Stemmler, 2008).

This notion that the genes involved in either multicellular evolution or cancer should at least to some extent be the same, not just because of the empirical evidence but because these macro-evolutionary processes represent opposite ends of the same processional pathway, is suggested as a potential “big idea”; one implication is that any new gene found to be involved in either one of these processes should be closely scrutinized for also being involved in the other.

I have suggested here that not only can the certain existence of categoric differences between normal cells and cancer be inferred, but their nature can be profitably suspected by extrapolation from a process that could be the reverse of carcinogenesis, that is, the genesis of the metazoan. This is not least because the properties of cell adhesion, positionality, cell population control, and intercellular communication are central to both metazoan life, when they are functional, and when they are dysfunctional, to cancer.

Lurking behind this is the issue of causality. The logic seems unassailable: since the cancer cells, by definition, behave differently from their cells of origin, there must be some causative molecular lesion(s), which maintain this malignant phenotype. This is true even if we are talking about the alterations that maintain the abnormal behavior, rather than these that first initiated it, and which may or may not be different, or even no longer operative.

This concept of causality, so entrenched into occidental thought, inevitably draws one to the concept of the “driver” therapeutic target, as distinct from the “marker” target concept. Essentially, the former (“driver” concept) implies an anticancer effect from successfully
addressing and preventing the operation of the proximate cause ("causality-reversal"); the latter, the "marker" concept, does not depend on "causality-reversal" but derives efficacy from using some distinguishing feature, for example, as a simple "delivery box" or address, to direct and deposit an otherwise indiscriminately cytotoxic warhead to selectively kill the tumor cells; or to otherwise use this mark of distinction to enable selective cytotoxicity in a more indirect and abstract manner, as long as it does not involve causality-reversal.

For both driver- and marker-type targets, the molecular features may be exploitable either as a presence or as an absence. In the case of the driver, a "driver"-type target, as a "presence," would be exemplified by oncogenes such as the mutant EGFR, or the BCR-ABL fusion. Both of these are clearly responsible for an important causal role in, respectively, a subset of pulmonary adenocarcinoma, and CML; both are carcinogenic as early events, but more importantly seem to be necessarily required to maintain the malignant phenotype; and consequently, being druggable, engender extra-ordinary therapeutic effects when inhibited. In this, they exemplify the "driver-inhibitor" model, in which bona fide drivers (even when not as powerfully causal than these two classic "oncogene addiction" type situations) are therapeutic when inhibited. Likewise, for marker-type targets exploitable through their presence, they are features on or in the cancer cells (preferably all and only the cancer cells) to which a warhead (e.g., a toxin or radioisotope) can be directed by a homing device (e.g., a monoclonal antibody). In this situation, either the marker does not contribute in any way to causality of the malignant phenotype, or if it does, that is not the aspect of it that is exploited by a marker-directed targeted therapy, only its distinctiveness. In certain cases, for example, EGFR-wt amplified cancers treated with, say cetuximab, the driver and marker functionalities may both be exploited, or it may not be clear which is being exploited.

The "absence" situations, some of which may arise as an important prediction of the Heng–Duesberg model, constitute a somewhat more difficult opportunity. However, they are vital to confront because they almost certainly are numerically more common than the "presence" opportunities, especially in the case of the drivers. Driver-absences (which does not mean the absence of any drivers, but rather refers specifically to driver mutations characterized by loss-of-function, that is, associated with tumor suppressor gene abnormalities, rather than gain-of-function) are characterized by either the physical absence or the functional absence of a key cellular control system, for example, p53 itself or p53 functionality or some other defective brake on the cell cycle, which therefore fails in its normal function to halt the cell cycle. Marker-absences are characterized by features, in which the mark of distinction is the lack of a particular structure or function on the cancer cells, but which is present in or on normal cells. The absence may or may not drive the cancer in a causal
sense, but exploitation by a marker-type therapy would not attempt to rectify the defect, merely to exploit it for a kind of “negative targeting” (vide infra). In the case of the driver absence, by contrast, the therapeutic effect would be achieved by some strategy designed to restore functionality so that the malignant phenotype could no longer be enabled; for example, restoration of apoptosis, if some lack had disabled it. This is difficult, and clinically successful examples of this sort of strategy are hard to find. Fig. 1.

In the case of marker absences, the strategy would consist of targeting a protective agent to normal cells and then exposing all the cells to an otherwise nonspecifically cytotoxic agent; amifostine plus concomitant radiotherapy would be a good example, the amifostine being activated by the milieu of normal cells but not the milieu of cancer cells. Upon metabolism to the active derivative, free radicals generated by the radiotherapy are quenched but only in the normal cells, which are, therefore, protected (Citrin et al., 2010). Amifostine is an approved drug and may also protect against radiomimetic and other chemotherapy, like platinum-based, as well as radiation itself.

These various mechanisms, incidentally, illustrate what it is about therapies that qualify them as “targeted”; not, as is commonly thought, that they are directed to interact with known specific molecules, rather that they are capable of inducing a selectively cytotoxic effect. It is possible for tumor selectivity to exist, even though the mechanisms for this might not actually be known; for example, that the addition of folate/B12 to a regimen of pemetrexed rescues the normal tissue but not the cancer cells
is a fact without a readily available explanation. But the lack of a known mechanism has not prevented this strategy from incorporation into the gold standard chemotherapy regimen for nonsquamous non-small-cell lung cancer, and it remains an excellent example of targeting.

D. Speciation and the Target

While it seems inescapable that causative molecular lesions must exist as either or both initiating and/or maintenance factors for the properties that distinguish the malignant phenotype from its normal cell of origin, it is not to be concluded that these lesions are always known, druggable, or even knowable. In particular, it cannot currently be stated which lesion, or combination of lesions, must be “addressed” in order to effect a cure, although the standard model would seem to suggest otherwise. Furthermore, as mentioned above, it should be appreciated that druggable driver–inhibitor opportunities may be few and far between, as “low-hanging fruit,” and should not constitute the sole aspirational model of drug designers; and while not unknown, it remains insufficiently appreciated that “absence” opportunities (both driver and marker), and marker-presence opportunities exist, but (the former especially) will require a particularly nuanced approach if they are to be exploited successfully. Most importantly, as per Heng–Duesberg, the proximate causality that maintains the malignant phenotype may involve, at least in part, a dynamically inconstant genotype (Heng) or massive genetic imbalance (Duesberg); in either case, the carcinogenic mechanisms are not readily obvious, and might even require excursions into unfamiliar domains of abstract thought to elucidate and exploit.

If the Heng–Duesberg model of proximate causality is correct, that is, that initiating oncogenes are later superfluous, that a constant set of common mutations does not exist, and that the neoplasm is maintained as such by massive genetic imbalance and/or the very lack of constancy in the genome, then I would submit that the traditionally staid driver–inhibitor model of targeted drug design, at least for the purposes of cure or markedly prolonged survival, is doomed to failure, and for reasons that are entirely distinct from the classical resistance mechanisms described. If the common advanced cancers are curable, it will probably require an unorthodox and probably nonobvious approach directed to this phenomenon of fluid causality.

Accepting a vast taxonomic gulf between normal cells and their malignant offspring exists, and that molecular changes must occur to cause this in an ongoing proximate fashion (and therefore banal “type I” nihilism is indeed inappropriate), I also believe that easy exploitation of this truth for curative purposes is not possible; and that even the ready-made opportunities for survival extension and other short-term palliative goals
Type II nihilism, the inevitable emergence of resistant variants, will not be unfamiliar to anyone involved in the day-to-day systemic therapy of common cancers. With the possible exception of complete surgical extirpation, there is no drug or modality to which common types of cancer cells cannot or do not exhibit resistance, sooner or later. Although this may to some extent be due to lineage heterogeneity, and the existence of, and selection for, inherently more drug-resistant stem-like cells, most commentators believe that genetic plasticity is responsible for hard-core drug resistance. This is certainly consistent with the Heng–Duesberg model of gross genome-wide instability coupled with florid micro-evolutionary changeability. Without disagreeing, I will offer a certain perspective of the meaning and significance of this, which goes beyond not only speciation but the “hyperspeciation” implied by the acquisition of the unstable genome.

VI. BEYOND SPECIATION: THE NATURE OF CANCER

A. What Type of Life?

There is little doubt that carcinogenesis entails the opening up of some sort of taxonomic gap between the metazoan host and the cancer cell; indeed this is implicit in the well-named concept of “transformation.” Furthermore, while it is true that not all speciation events involve karyotypic changes, the vast majority do (Heng, 2009), and the converse that karyotypic changes imply speciation is also probably true. It is also true that the autonomy, unicellularity, and asexuality, which characterize cancer cells, as well as certain other traits, mark them off as something very different from their host of origin.

As noted, the default taxonomic process (“speciation”) is not without problems; chief among those is the failure of the cancer karyotype to stabilize, although to characterize it as 100% chaotic would also be an exaggeration (Lin et al., 2009). Rather, cancer cells within a lineage appear to exhibit what has been described as “instability within stability” (Gusev et al., 2001). Nonetheless, there is a growing consensus that cancers exhibit more genomic flexibility than any other type of eukaryotic normal cell, even though there are some recognizable parameters of stability.

Therefore, it is legitimate to ask what type of life is represented by a cancer? And is it valid to group them all together, given that they would almost always be more closely related to their originating hosts than to each other? Cancers here would be suggested to be a type, sharing certain
descriptive and perhaps explanatory features, that is, similarity, but not
the close lineage relatedness that is usually implied by a taxonomic sub-
grouping. Indeed, without this core group of shared traits and features, it
would not be possible to talk about cancers as a “type” at all. It is precisely
this shared suite of features that has to be explained and placed in evolu-
tionary context. And while cancer cells within a particular patient are
certainly in a close lineage relationship with one another, cancer cells in
different individuals are not, despite their having more in common with
each other than with the hosts of origin that actually derived them. This
might be a unique problem in taxonomy, which adds gravitas to the
question at the start of this paragraph—what type of life, indeed, is repre-
sented by cancer?

B. Speciation or Despeciation?

Part of the problem as usual is semantic. “Speciation” is a seductively
simple-appearing word, but in fact it coheres two separate processes:
firstly, the act or process of separating from an existing species; and
secondly, the establishment of a novel species. There is an implicit assump-
tion that the first automatically implies the second, even that it is not
possible to have the first without the second. Yet, while the first process
(which we can call de-speciation) always occurs in carcinogenesis, it may
be that the second (respeciation) does not often occur because of persistent
genomic instability.

In this representation, cancer cells exist in a sort of taxonomic limbo;
having departed their original, stable karyotype, they engage in continu-
ous, albeit partial, genomic reshuffling, without establishing the novel
stability that would signal that they have achieved “type” status, that is,
a new species. So what are they? Do we have the words or the concepts to
describe them, let alone explain them?

C. An Alternative Form of Life

I have previously suggested (Vincent, ibid in press 2011) the idea that
cancer cells are actually an alternative form of life, one that is latent, and
encrypted in all eukaryotic cells, and which emerges as a solution to
perceived existential threats, as a resilient survival machine. Rather than
just a series of random mutations, the universal traits exhibited by cancer
cells represent the re-emergence of an ancient survival program.

In this characterization, and because it promotes survival, ongoing
genomic instability in fact is the whole point, part and parcel of the
emergent program; and this is what poses the problem for the concept
of speciation, at least as simplistically conceived.
Thus, returning to Dhoebuzansky, the cancer cell can be said to be “for something”—that is crude survival, as a better alternative to extinction. One can strip down an organism into its components and characterize them, but unless one knows the function of the whole, and what biological ends it promotes, the parts can only represent a very incomplete picture of reality.

D. Historical Perspective

The notion that the cancer cell is an atavistic throwback does not quite capture the viewpoint I am advancing here, in the sense that “throwbacks” are accidental rather than purposive; however, there is an element of this line of thinking that does inform what I am proposing, and it is reasonable to acknowledge it and record the contributors.

I am grateful here to Greaves (Greaves, 2000) who has traced this history. According to Greaves, both Sir Herbert Snow (Snow, 1893) and Morley Roberts (Roberts, 1926) “suggested that cancer cells were derived from cells that retain a memory for amoeba-like selfish behavior and that can still escape by losing allegiance to the community of cells within which they reside.”

The following concepts are here enumerated:

A. Normal cells, at least some of them, are able to re-express archaic behaviors and characteristics, and which therefore have not been eradicated but just contained by subsequent evolutionary developments.

B. One of these characteristics consists of autonomy, and cells achieve this by escaping from the bonds that normally cause their activities to be subsumed in the interests of the whole organism.

C. The metazoan animal is in fact a “community of cells,” which despite this fragmentation somehow is roped together by overarching coordinating forces, which can nonetheless occasionally be over-ridden.

Greaves then introduces Lucien Israël, a French oncologist, who, in a 1990s essay, seemed to extend or at least interpret this idea of atavism in the form of a re-emergent, ancient survival program (Israël, ibid 1996).

Israël begins by questioning the model in which “cancer is a blind process, because of random mutations appearing at any time in random order and selected for the unpredictable advantage that some offer . . .,” that is, the standard model that he here credits to Nowell (Nowell, 1976) and Cairns (Cairns, 1975). Israël points to an alternative formulation that cancer’s “formidable survival efficacy” can instead be considered a type of program (i.e., “combined and integrated genetic responses”), which results from environmental threats, whether these are mutagenic or not. The by-product of this program’s expression is drug resistance that may go
some way toward explaining the relatively poor results achieved by oncologists (still true in 2011 as it was in 1995).

Israël believes that this survival program is inherited from the archaic precursors of metazoa, that is, the unicellular eukaryotes, and before them, the prokaryotes. One prokaryote survival program he sees as a possible type of precursor is the SOS regulon (Witkin and Kogoma, 1984), a coordinated, multifaceted stress response, which includes, most crucially for our purposes, the induction of “error prone” DNA replication, and which has apparently permitted not only survival in the face of recurrent environmental catastrophes but also the fact of evolution. In Israël’s view, cancer cells are the result of a similar set of “responses to danger,” in which the ongoing display of a defense and survival program is a predominant motif.

He is, however, quick to acknowledge that no inducible system such as the SOS has been observed in animal cells to date. Nonetheless, mutational hotspots, that is, genetic loci which being more susceptible to mutation, might act as an “early warning” system, especially if contained in genes normally responsible for genome integrity like p53, and whose disablement would result in a pre-emptive or at least an early response to existential threats. Hints of this idea can be found in a 1990 publication by Israël in which broad-spectrum resistance, and other malignant traits such as autonomy, seem to appear at an accelerated rate not explicable in terms of random mutations (Israël, 1990).

Israël concludes with the opinion that the drug resistance so commonly featured by cancer cells is in fact similar to the survival attributes of unicellular cells, and which enabled their survival under stress. The key aspect of this hypothesis is that neither the phenotypic attributes of the cancer cells nor the genetic instability are the result purely of stochastic mutations, but of a de-repressed, ancient program of survival. This having been said, there is a role for random mutations in evoking this program and for classical Darwinian selection to operate via the usual methods.

In a later publication (Israël, 1998), these ideas were again elaborated, with the refinement that it was the specific function of the “antioncogene system” to restrain and control this program in healthy cells, but in a manner that would, under conditions of existential threat, permit its release, not as an accident but, so to speak, “intentionally.”

This notion of inducible error-prone DNA replication seems to provide a connection with the Heng-Duesberg vision of karyotypic and macrogenomic instability, as described above, not only as an explanation for the phenomenon but as a reason for it as well, that is, as a survival strategy via genomic reshuffling, as with prokaryotes and the SOS regulon. This seemed to neatly account for both the cause of the genetic instability and one of its major consequences, drug resistance.
VII. THE NATURE OF CANCER: A TRAIT-BASED INFERENTIAL APPROACH

A. Cancer—A Consistent Suite of Traits

Cancer consistently manifests a highly characteristic suite of traits, ranging from ceaseless proliferation, through insult resilience, to aerobic glycolysis and aneuploidy; the usual explanation for this, that is, serial, blind, and random mutations followed by selection, might more parsimoniously be replaced by, or at least supplemented with, a programmatic explanation. This program would prioritize the continuation of cellular life over the preservation of the individual, the original species (or any species), and even, heretically, over the gene.

These various traits can be grouped under three broad categories: phylogenation, reprimitivization, and adaptive resilience. In turn, these three form the pillars of an overarching goal, which is essentially cellular survival at any cost (Vincent BioEssays, in press 2011). This viewpoint sees the cancer cell as a re-emergent protozoan-type organism, in whom specialized functions have been jettisoned as a means to sheer survival. Furthermore, this protozoan has a potential existence in every eukaryotic cell, able to be called into actuality by some trigger such as a perceived threat to the life of the cell. Clinical cancer is thus seen as a competitive struggle between this reawakened Precambrian organism, and the residual normal metazoan body; and one in which the metazoan usually loses, for a very coherent and compelling set of reasons.

B. Phylogenation

The concept of phylogenation is traceable to Julian Huxley, who opined that autonomy, per se, conferred upon the cancer cell a considerable taxonomic distance from the originating host. Now, it is true that collectively, cancer cells in different patients are more closely related to their originating hosts than to each other, and this constitutes a barrier to the literal interpretation of Huxley’s words. However, it is at the same time true that a cancer is no longer the same individual as the originating animal, nor even a member of the same species, either phenotypically or genetically, irrespective of the lineage descent; and considering the gross phenotypic differences, especially the aspects of metazoan deconstruction (unicellularity and host destruction), autonomy (growth factor sufficiency and growth inhibitor insensitivity), niche finding (invasion and metastasis), speciation (chromosomal changes and distinct evolutionary destiny), and parasitism (nonsymbiosis, and occasional transmissibility + absence of host anticipatory alterations), it is arguable that each cancer in each patient represents a newly emergent phylum, in which the constituent
cancer cells sit in an entirely different locale in the tree of life from the metazoan host.

The fact that different cancers in different individuals are less related to each other than to their respective hosts does not gainsay the taxonomic gulf between each cancer and its own host, which is the main point. The similarity of each cancer between individuals might then be misconstrued as a case of convergent evolution, but this similarity is more a consequence of the similarity of the universally inherited, underlying (and now de-repressed) program than pure randomness and selection.

C. Reprimivitization

Allied to this concept of phylogenation is the next collective category, reprimivitization. This category groups the traits that appear truly atavistic (“recurrence in an organism of a trait or character typical of an ancestral form . . .”) (Merriam Webster). These include re-emergent unicellularity (autonomy and metazoan deconstruction), immortality (telomerase de-repression and apoptotic evasion), fermentation (the WE), asexual reproduction/abandonment of the soma (maturation block, “stemness,” and retreat into the germ line), abrogation of the self (gross genomic instability and debasement), and inhospitability tolerance (WE).

The WE is prominently displayed here, and it is Otto Warburg who must be credited for providing the ancient but empirical theory of atavism with a biochemical grounding. It was Warburg who noted that cancer cells preferentially use glycolysis to produce ATP (i.e., ferment) even when oxygen is present: the WE. Upon this most central and fundamental of insights, which describes a universal cancer attribute, is founded not only the entire PET scan industry but what some consider one of the best hopes for the development of truly targeted anticancer drugs.

What I am focused on here is not these practical benefits for human health, actual or potential, but the philosophical significance of the WE. Warburg, apart from noting the retreat into a primitive type of metabolism more appropriate for the early and preoxygenated earth’s atmosphere, believed that sophistication and complexity, in animals, absolutely required oxidative phosphorylation. Absent the latter, therefore, a retreat into primivitization was inevitable, although he admitted ignorance as to how and why exactly this should be the case.

Warburg went on to proclaim that this metabolic “defect” was fundamental to cancer, in a causative sense: “. . . the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar” (Warburg, 1989). This position became known as the Warburg Hypothesis. With the discovery of oncogenes and the rise of the molecular biology of the gene, and the gene-centric emphasis in evolution, Warburg’s Hypothesis was believed discredited and was neglected.
However, Warburg never discounted the role of genetic initiators, and nuanced statements about the precise mode of causality and aerobic glycolysis probably suffered in translation from the original German. The misjudgment of the Warburg Hypothesis, dating back to the middle decades of the twentieth century, was probably based on a linguistic misinterpretation of the distinction between originating and proximate causality, and may well have cost us five or six decades in the war on cancer. Warburg, however, probably did err in his opinion that respiration in cancer cells was necessarily defective (Koppenol et al., 2011); it does appear that some degree of intact respiration can and does coexist with the accelerated and anaerobic glycolysis, which is typical of cancer cells.

My sense, reviewing this material (Warburg, 1928, 1956, 1956), is that Warburg was simply pointing out what is patently true, which is the indispensability of his effect in the process of carcinogenesis and the maintenance of the malignant phenotype: “By a prime cause of the disease I mean one that is found in every case of the disease” (Warburg, 1989 ibid). Indeed, a large quantum of venture capital is betting he was right, and, as a target, that one or more key components in this type of metabolism holds the potential, not only to cripple the malignant phenotype, but to do this in a highly specific and nontoxic way—an opinion long shared by this author. I shall also discuss (vide infra) the emerging work that indicates that the WE is deeply implicated in resistance to systemic therapies, and radiation.

For our immediate purposes, however, we are interested in the pragmatic aspects of Warburg metabolism and its ancient origins on the hypoxic earth. The modern understanding of the WE is still evolving and, along with its key role in drug resistance, will be more fully described below; but it is enough to note here the near-universality of this phenomenon in cancer, and its relative consistency across all (especially aggressive) cancer cells as a “package,” argue strongly against its purely stochastic rediscovery in every new case of malignancy, as almost fantastically unlikely.

Unicellularity is another defining trait of cancer and has been one of the signatures that have evoked analogies with ameba, for instance. However, it might be questioned whether cancers, which usually grow as collections of cells, are truly unicellular. Certainly, they are no longer team members of the originating metazoan host, and unquestionably represent a breakdown in the original version of multicellularity—a repudiation, perhaps, and which may have been occasioned by a perception that membership in the metazoan team may be associated with too high a chance of death and extinction. In this respect, the increased incidence of cancer with age makes a certain sense if the cancer cell is seen as trying to escape the sinking ship.
But are cancers unicellular? If by that is meant are they necessarily obligated to adopt a solitary existence, the answer is no; they usually grow in colonies of their siblings and close relatives, the dynamics of which are characterized by a mixture of cooperation and competition (Axelrod et al., 2006).

Furthermore, cancers exhibit organoid lineage hierarchies that resemble those found in normal tissues, especially in relation to stem cells, which suggest that the forces underlying these organizational paradigms in normality might continue to function in cancer. On the other hand, cancer cells seem fully viable on their own, and some of them at least are competent to repopulate an entire tumor from a single cell. If this is what unicellularity means, then cancer cells, especially cancer “stem” cells, certainly embody that within their repertoire.

As perceptively, and provocatively, noted by E.O. Wilson, it is sometimes difficult to know what, in biology, constitutes an “individual” (Wilson, 1975). Is the cancer an “individual”? If yes, it must be a multicellular animal, albeit of a different kind. But I am rather inclined to think that the defining autonomy is not only with respect to the originating metazoan (now transformed into a cross between a food source, habitat, waste-removal service, and killing field), but also with respect to each other cancer cell. But as Wilson notes, “There may be more than one way for nature to constrict a multicellular organism.”

An example of cooperation, for instance, is the secretion of VEGF, which serves to stimulate angiogenesis, without which tumors would remain relatively fixed in position and small in size (approximately <2 mm). A single cancer cell would not likely be able to secrete enough VEGF to attract capillary ingrowth; the same principle applies to the cooperation required of tumor cells in the production of a sufficient supply of diffusible products to overcome host defenses (Axelrod, 2006 ibid). So some degree of cooperation may well be essential to their growth and spread. But at the same time, the genetic heterogeneity in cancer cells seems poorly coordinated, and they almost certainly have the capacity to evolve independently, and outcompete each other. Yet it is a matter of no small interest that the members of the expanding cancer mass seem to be themselves resistant to the external killing effect mediated by milieu acidification and which “dissolves away” the normal tissue to make room for the expanding cancer; on the interface with normal cells, this may perhaps be due in part to lactate/proton export by tumor cells (Mathupala et al., 2010). Probably the correct description is of basically unicellular organisms with facultative colonial attributes, and which allow them to most effectively “hunt in packs” as they set about dismantling the host.

A “colony,” according to Wilson, has to either be physically united, or differentiated “into reproductive or sterile casts,” or both. At what point a well-functioning colony becomes indistinguishable from a “super-
organism” is perhaps arbitrary. Suffice to say I can see advantages for cancer cells, as units of survival, to be capable of cooperation with each other, but ultimately capable of an independent existence, and, under duress, just as capable of ruthless competition with sibling cancer cells. And as the lineage hierarchy within cancers comprises self-renewing “clonogenic” stem-like cells, as well as nonclonogenic end-stage members, which can be crudely seen as “reproductive and sterile casts,” respectively, and also because metastatic foci are composed of cells in a sort of united physical continuity, one should not underestimate the colony as a form of social organization still intact in cancer cells. Nonetheless, this is a very different form of multicellularity than the one that characterized the now-transformed cell’s previous life in the metazoan team, and the colonial attributes of cancer cells in no way undermine the concept of reprimitivization, and in fact reinforce it.

The reprimitivization argument is further buttressed by the reappearance of asexual reproduction. Of course, the somatic cells in metazoan tissue also require replenishment from stem cells, which occurs by asexual clonal expansion. But the difference here is that this process is perforce interrupted intergenerationally by an episode of sexual reproduction, and which may serve, while purging the genome of extreme variants, to permit a cautious amount of genetic diversity, followed by rigidly conservative rounds of somatic cell renewal. In the case of cancer cells, there is no longer any cleansing sexual recombination, and in each cancer cell the forces of genetic conservation are substantially disabled. Hence the cancer cells, freed from the obligation, or the ability, to conserve their genomes, essentially must abrogate their own identity.

Likewise immortality, a feature that must characterize at least some unicellular organisms, is a typical and striking feature of cancer and easily construed as an emergent primitive trait.

Thus, from a mortal, complex, sexual, and oxygen-respiring multicellular organism is born this immortal, fermenting, colonial, asexual, and stripped-down organism, and it is difficult to conceive of this as anything other than a primitive type of animal, in search of the late Precambrian. Whether genetic instability was a characteristic of the preoxygenated world might be unanswerable; but the absence of an ozone layer might at least imply that the earth’s surface was a much more mutagenic environment than it is today, as might the first appearance of oxygen-free radicals.

**D. Adaptive Resilience**

The final organizing principle is *adaptive resilience*. Adaptive resilience results from the combined effects of the sheer number of cancer cells (the “demographic cushion”), coupled with genetic hypervariation (“mutator
phenotype’’). These attributes allow the tumor to overcome obstacles to its survival, including (but not limited to) therapeutic challenges like chemotherapy or radiation. The genetic variability performs the role of novelty-generation, which is then heuristically tested against the environmental vicissitudes. Of necessity, many of the genomic variants will be nonviable, a fact that is compensated by the unlimited cellular proliferation.

The population explosion is enabled not only by the ceaseless proliferation but by biomass expansion as well. Ceaseless proliferation arises from oncogene activation and tumor suppressor gene inactivation; whether these might sometimes be only initiators, or always required for the maintenance of the proliferation, is an open question (Klein et al., 2010). Biomass expansion is enabled by the WE (Koppenol et al., 2011; Shlomi et al., 2011; Vander Heiden et al., 2009) (comprising glucose siphoning, accelerated glycolysis, subversion of oxidative phosphorylation, provisioning of substrates like acetyl CoA and ribose, and apoptosis evasion). Also contributing to biomass expansion is host destruction (nutrient diversion, milieu acidification, metastasis, invasion, enzymatic digestion, and biomass interconversion) together with host enslavement (as evidenced by angiogenesis, induced autophagy, and immunosuppression).

The source of genetic hypervariation is believed by many to be an attribute known as the “mutator phenotype.” This attribute is not without controversy (Loeb, 2010), but most commentators seem now to accept the empirical reality of high and persistent levels of point mutation, altered gene expression and aneuploidy, which together provide the basis for both micro- and macro-evolution (Campbell et al., 2010; Duesberg and Li, 2003; Fabarius et al., 2003; Heng, 2006, ibid 2009; Klein et al., 2010 ibid; Negrini et al., 2010; Salk et al., 2010;). I propose the mutator phenotype to comprise a “generator” function (consisting of defective DNA repair, and a tunable endogenous mutator in the form of reactive oxygen species, or ROS) but also a “tolerator” function, consisting of apoptosis evasion (probably due to binding of hexokinase II to the mitochondrial VDAC), which is a feature of the WE. The “tolerator” can be inferred because normal cells would either apoptose or repair the gross genome alterations, and cancer cells seem to be relatively delinquent in the performance of both of these tasks. Likely the very common p53 disablement contributes to both defective DNA repair and apoptosis evasion.

Thus is constructed a machine in which the associated DNA instability is not just a pointless collection of errors, but in fact the principal means to the goal of cellular survival. The cancer cell is not primarily a “growth machine,” as Warburg had thought (Warburg ibid, 1989), but rather a survival machine. Why it should be constructed like this probably relates to the extreme measures required to endure an environment much more challenging than our own, that is, the Precambrian. The list of perils would
have included nutrient deprivation, food-chain collapse, acidification, climate extremes, volcanism, radiation, and, as the ambient oxygen levels began to rise, reactive oxygen and other chemical species.

The latter phenomenon is believed to be the reason for the successful endosymbiosis with the alpha-proteobacterial mitochondria, acting as an oxygen detoxification system and only secondarily as a source of ATP. The availability of these “tame mitochondria,” in addition to the archaic glycolytic pathway, provided these early eukaryotes with the means to “tune” metabolism by toggling between oxidative phosphorylation and glycolysis. The relative utilization of each pathway would influence the cellular economy in terms of glucose consumption, pH, lipid and nucleic acid precursor generation, ATP production, ROS generation, and, closely related to mitochondrial function, apoptotic threshold; all factors relating to the WE.

ROS, it turns out, are quite mutagenic for both mitochondrial and nuclear DNA. By altering ROS production (and quenching), the cell would have a way to endogenously alter its rate of mutation. The WE provides a pragmatic package for the cell to switch to a high ROS, high substrate provision economy, resulting in massive biomass production (to sustain the population explosion), and genetic chaos required to “test drive” new gene–environment pairings. At the same time, the elevated glucose consumption ensures just enough ATP to sustain this, while the lactic acid by-product is exported into the milieu to facilitate the digestion of surrounding tissues in the project of lebensraum creation.

Thus the WE, a term created to describe the narrow (but fundamental) observation of aerobic glycolysis, is actually a whole package of far-reaching changes, all of which contribute to the malignant phenotype in a variety of ways: invasion, biomass interconversion and expansion; persistent DNA reshuffling, with the attendant possibilities for evolution; the ability to tolerate inhospitable environments characterized by hypoxia and acidosis, and most important, from our perspective, insult resilience (including drug and radiation resistance), especially by means of apoptosis evasion, and the aforementioned DNA heuristics.

At the same time, however, something has to be given up: multicellularity. Multicellularity requires genetic continuity, and above all, predictability. Otherwise the cooperative entrainment of cellular fate, and investment in the organism as a whole (as a propagator of genetic similarity) is utterly undermined. This is why metazoan deconstruction is the inevitable accompaniment of malignancy.

Recently, investigators have begun to elucidate a direct relationship between aspects of the WE and therapeutic resistance. For example, lactate dehydrogenase (LDH), an important glycolytic enzyme, is vital in the WE as it is responsible for the interconversion of pyruvate and lactate as well as generating NAD+, an essential cofactor in upstream glycolysis. Breast cancer cells resistant to paclitaxel were shown to express elevated
levels of LDH-A, and downregulation of LDH-A by siRNA increased sensitivity to paclitaxel (Zhou et al., 2010). The combination of oxamate (an LDH inhibitor) with LDH-A downregulation substantially potentiated paclitaxel in these cells, involving increased apoptosis. Paclitaxel therapy, in fact, actually induces LDH mRNA, which in turn promotes resistance. The actual mechanism may involve activation of the pentose phosphate shunt pathway, greatly enabled by the WE, and which in turn generates reduced glutathione, which then prevents the oxidative activation of proapoptotic cytochrome C (Vaughn and Deshmukh, 2008). Zhao et al. have also shown that HER-2 overexpressing cells are associated with increased glycolytic activity, and that HER-2 downregulation likewise downregulates glycolysis (Zhao et al., 2009).

Another approach to selectivity, which exploits the WE at the same time as overcoming cisplatin resistance, is the synthesis of a molecule that results from the fusion of cisplatin and dichloroacetate (DCA). DCA inhibits pyruvate dehydrogenase kinase (PDK), a key WE enzyme. The release of DCA from the fusion drug induces mitochondrial release of cytochrome C and apoptosis-inducing-factor (AIF), promoting both DNA damage and selective restoration of apoptosis in the cancer cells, but not the normal cells. DCA, by inhibiting PDK, disinhibits pyruvate dehydrogenase (PDH), which is then free to shuttle the pyruvate-derived metabolite acetyl CoA into the mitochondria, thus forcing the previously glycolytic cell back toward mitochondrial oxidative phosphorylation. Since this process is functioning normally in nonmalignant cells, this is not toxic to them. In cancer cells, however, the mitochondrial membrane potential is hereby reduced, which then opens the mitochondrial transition pores, releasing cytochrome C and AIF, and lowering the barrier to apoptosis (Dhar and Lippard, 2009).

The relationship of the WE to resistance has also been reviewed by Sattler et al. (2010). They also highlight the elevated levels of free radical scavenging metabolites, induced by the WE, and which tend to frustrate the effects of therapies that work by the generation of free radicals. These authors therefore advance the notion that specific inhibitors of the WE should be explored in combination with “established cancer treatments,” a sentiment that I strongly believe should be extended to any kind of cancer treatment, established or not.

Viewing the WE as a program, however multifaceted, opens the door to the highly attractive prospect that, if it can be activated as a whole in the process of carcinogenesis, it might ipso facto be able to be switched off as a whole, in the process of therapy, instead of piecemeal. The recent discovery that STAT1 may be responsible for the regulation of glycolysis, the Krebs cycle and oxidative phosphorylation, in such a way that its knockdown potentiates radiation, perhaps by energy deprivation (Pitroda et al., 2009), is indicative of what might be possible.
The author has also advanced the WE as an exploitable target in the selective potentiation of natural product cytotoxics, extruded by resistance pumps like p-gp and MRP-1, by an experimental drug, tesmilifene; this drug only potentiates taxanes, vinca alkaloids, and anthracyclines in pump-positive (resistant) cells and not their pump-negative, sensitive parent cell lines. The mechanism is likely to involve the substantial ATP consumption by these pumps, when activated by the cytotoxics, a condition aggravated to the point of lethality in cancer cells, but not normally respiring noncancer cells, by tesmilifene (Reyno et al., 2004; Vincent, 2006).

These various examples are intended to provide a flavor of what might be possible with resistance reversal by inhibition, or exploitation, of the WE, and the favorable therapeutic ratio (i.e., selectivity) that might accompany it.

VIII. RESISTANCE TO THERAPY: THE LONG ARM OF THE PROTEROZOIC

A. Resistance Reversal—A Sorry Tale

A multitude of drug and radiation resistance mechanisms have been and continue to be described. Given this wealth of knowledge, it is surprising how rarely this has been translated successfully into clinical application. As an explanation, it is tempting to speculate that whenever a mechanism has been successfully addressed, another one, hydra-like, will take its place. Insofar as the cancer cell is seen as embodying the above model of pragmatic hypermutation, as something that is either its very raison d’etre, or close to it, it is unlikely that a piecemeal approach to resistance-reversal will result in anything other than temporary victories, and more often than not abject failure to solve the problem. Therapeutic resistance is indeed a hard problem—the hard problem of oncology—in the sense that apparent greater understanding seems not to lead to any solution.

B. What the Cancer Cell Is For

We should take this opportunity to emphasize here a paradox. I have, along with others (Bergstein, 2003; Campbell et al., ibid 2010; Heng, 2010; Israël, ibid 1996; Nicholson and Duesberg, 2009), taken the view that oncogenesis is not only initiated by random mutations but that oncogenesis results in massive genetic instability, including random mutations, while preserving, in a peculiar sort of privileged way, the core de-repressed program that is actually causative, in the proximate, mediating sense. Understanding that the cancer cell is actually for something allows one
to put this in perspective: the “purpose” of the genetic instability is heuristic experimentation with novelty, probably in response to some dissatisfaction with the status quo ante. Without this perspective, the cancer cell would simply be seen as a collection of blind, stochastic errors, hopefully with a small core of constant but strangely elusive changes that could act as targets, buried in a cacophony of genetic noise, whose only importance is to act as a source of epiphenomenal drug resistance, that is, the “standard model.”

C. Why Targeted Drugs Usually Fail

There are several reasons why targeted approaches usually fail, sooner or later (more likely the former). Firstly, the targets may not actually exist, or not exist any longer (Klein, ibid 2010). Alternatively, the cell may lose dependency on a particular target because of redundancies. Or the target itself may mutate, so it can no longer bind the drug, but can, and does still, drive the cancer cell. Finally, some of the driver targets that do actually exist, like \( K-RAS \), or defective tumor suppressor genes, are really hard to “drug.”

Reasons for the elusive nature of these much sought after “constant targets” might include the following:

1. The real cause is a preordained program, including Warburg metabolism, controlled by a physiological switch.
2. Several different alterations could result in the same (type of) defect, that is, the details differ but the downstream pathway perturbations are the same, as a “final common pathway,” but perhaps less easy to “drug.”
3. The chromosomal instability is what really “causes” the malignant phenotype, at least in the sense of maintaining it, even if not initiating it. In this model, the malignant phenotype is not maintained by a small coterie of aberrant genes; rather, the cancer is actually maintained by the continuous, genome-level disablement of control pathways, and, which therefore, never re-establish meaningful restraints on the cell cycle (even assuming that a novel equilibrium, allowing the emergence of stabilizing effectors anew, could actually be created if only there was enough time) (Ptashne, 2009).

These explanations are not mutually exclusive.

D. More Difficult to Kill

In this view of the cancer cell, drug resistance is rendered inevitable in respect not only of single-targeted drugs but also multifaceted agents like classical chemotherapy/radiation, because the fidelity of DNA repair/
DNA constancy is no longer required by the simplified cancer organism (having sacrificed differentiation, identity and metazoan loyalties), and which, not coincidentally, reduces the vulnerability of the organism to genetic insult. For example, a much larger proportion of the DNA, no longer required, could then act as a giant decoy. Furthermore, the prolific genetic novelty provides excellent prospects at finding multiple ways to circumvent the effects of any drug or drug combination. And for as long as the cancer cell is a reduced, simplified object, it will be difficult to kill, not because it is sophisticated but because it is not.

E. Precambrian Training

Although the stem-cell nature of cancer contributes to resistance, this alone is not sufficient. Normal stem cells strive to protect their genomic integrity; but life’s challenges were variable, unpredictable and highly lethal. Hence the need to have evolved a broad spectrum, rapid response defense mechanism, of which stochastic genomic reshuffling was a major feature, and to which everything else might, at least temporarily, be sacrificed. I am not saying that all unicellular organisms are necessarily tolerant of egregious DNA damage, but I am saying the only cells that can tolerate, and propagate, egregious DNA damage are unicellular organisms, asexual as well, and in cancer, the DNA instability is the whole point. In this respect, cancer stem cells are very different from normal stem cells.

Furthermore, since, as this theory maintains, the resilient phenotype evolved in the Precambrian to deal with a certain suite of perils, we should not be surprised to discover that therapies exploiting similar mechanisms of action as these perils might not be very successful (Table IV). For instance, radiotherapy mimics extraterrestrial radiation absent the ozone layer; alkylating agents and some other forms of chemotherapy are radiomimetic; both radiation and certain chemotherapies induce ROS; antimetabolites mimic nutrient deprivation; thermal treatments (cryosurgery, etc.)

<table>
<thead>
<tr>
<th>Ancient threat</th>
<th>Modern therapeutic equivalent</th>
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<tbody>
<tr>
<td>Extraterrestrial radiation unshielded by an ozone layer</td>
<td>Radiotherapy and radiomimetic chemotherapy, e.g., alkylator, platins</td>
</tr>
<tr>
<td>Reactive oxygen species and other reactive species</td>
<td>Radiotherapy, radiomimetic chemotherapy including anthracyclines</td>
</tr>
<tr>
<td>Food chain collapse, nutrient deprivation</td>
<td>Antimetabolites</td>
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<tr>
<td>Climate changes</td>
<td>Cryotherapy, radiofrequency ablation</td>
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<td>Interspecies competition via chemical warfare</td>
<td>Natural product’ cytotoxics</td>
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mimic climate extremes; natural product chemotherapies recapitulate interspecies chemical warfare; and vascular disruption mimics food-chain collapse and anoxia. Therefore resistance to these agents is probably wired in to the repertoire of all cells that survived this period in the earth’s history.

F. Lessons from Mass Extinctions

Are cancer cells killable? One approach to this all-important question is to look back to the mass extinctions on earth of which there have been five, along with many minor ones. The one unifying theme seems to have been the combination of a sudden shock, superimposed upon a chronic stress—so-called press-pulse (Arens and West, 2008; Yedid et al., 2009). I have previously suggested (Vincent, BioEssays in press 2011) that eradication of a cancer should in some ways be akin to a mass extinction event, except that the requirement for selectivity is also imposed. In any event, we may have chanced upon this empirically, for example, with 5FU + radiation, representing, respectively, chronic nutrient deprivation and “sudden shock.” These methods do seem to be at least relatively effective in killing large numbers of cancer cells, and any selectivity there might arise from the same defects in DNA repair, which paradoxically sooner or later enable resistance to emerge.

IX. IS THERE AN ANSWER?

A. The Problem Restated

Despite sporadic interest in induced differentiation as a treatment strategy, most would still back eradication of the cancer as the surest route to cure. This would generally entail the very ambitious engineering challenge of designing a therapy that would seek, find, and specifically eradicate all potentially clonogenic transformed cells, while at the same time keeping damage to normal cells, not necessarily at zero, but at least below the threshold of intolerability. This is not to suggest that cytostasis, or lesser degrees of debulking, are not helpful, just that if cure is the goal, there is likely only one final way to guarantee it; anything else is inevitably a temporary palliative, or at best results in a “chronic disease” outcome.

It is safe to say that the first major chemotherapeutic successes were constructed mostly on an empirical basis. The theory seemed to consist mainly of a sense that it would be rational to treat a proliferative disease with antiproliferative drugs, coupled with a realization that it was possible to combine agents with nonoverlapping toxicities, and in the hope that available resistance mechanisms could not deal simultaneously with
different classes of drug administered in combination. However, the reason these drugs should be selectively toxic for malignant but not normal cells was not only poorly understood (Harrap, 1978), but even poorly misunderstood, as being based on the incorrect notion of rapidity of cell division (i.e., cell cycle time), rather than the more important growth fraction. Since most traditional anticancer drugs are more toxic to proliferating cells, “rapid proliferation” might be a reasonable hypothesis, but it is the latter (growth fraction) rather than the former (cycle time) which actually determines “rapidity of proliferation” for the tumor as a whole. In fact, some normal cells have a much shorter cell-cycle transit time (e.g., 12–24 h for bone marrow precursor cells, vs. about 2–3 days for many cancer types) (Donovan et al., 2005).

It is not actually possible to make sweeping generalizations about the growth fractions of tumors compared to normal tissues; some tumors have relatively low growth fractions and some normal tissues quite high growth fractions (Elion, 1985), or vice versa. In fact, it is quite clear that these purely kinetic considerations are not enough to explain selectivity, and while they most certainly speak to part of it, there is much they do not account for. Cisplatin, for example, is not affected by the proliferative status of the cells, and the same is true of the nitrosureas and bleomycin (Boyer and Tannock, 2005), yet these drugs are much more active against selected types of cancer than normal cells.

Some additional factor is obviously required to explain such selectivity as occurs, and that factor may well be differential DNA repair (Evers et al., 2010), although supplemental hypotheses exist in respect of apoptotic threshold (Wilson et al., 2009). The three most curable solid cancers (germ cells tumors, lymphomas, and gestational choriocarcinomas) apparently share highly intact proapoptotic machinery, retained from their normal tissues of origin, and which was necessary there because genetic rearrangements occur physiologically in each of these tissues, and result in errors that regularly require removal. This was hypothesized to be the reason that chemotherapy is so effective in curing this limited range of malignancies (Savage et al., 2009). Treatment of these cancers, for example, advanced testicular cancer or Hodgkin’s disease, is characterized by massive debulking, and usually permanent eradication of the cancers; yet only transient (albeit significant) toxicity occurs in normal tissues that recover fully, or almost fully in many patients (Muggia, 2009). It is unlikely that a lower apoptotic threshold in the cancers versus normal tissues is solely responsible for this, and possible that DNA repair is more intact in the normal tissues than the tumors; however much of this remarkable phenomenon remains to be explained (di Pietro et al., 2005).

Although the idea of differential DNA repair capacity has proven durable in general, the inadequacies of the whole conceptual package became clear in proportion to the inadequacies of these initial drug combinations.
when applied to the common cancers like non-small-cell lung, stomach cancer, and colorectal cancer. Although transient regressions were sometimes apparent, especially in breast and small-cell lung cancer, the overwhelming majority of all these cancer cases was either utterly drug resistant de novo, or rapidly became highly resistant.

In particular, it was realized that, while the initiating “causes of cancer” were readily apparent, they were generally of the “hit and run” variety and did not help to understand the day-to-day inner workings of the cancer cell. Nonetheless, the blossoming discipline of molecular biology seemed to offer a pathway to a deeper understanding, fuelling the optimism that once the proximate causation and mediation of the malignant phenotype was revealed, druggable and specific targets would rapidly emerge, and cures would automatically follow.

Although an immense amount has been learned as a consequence of this “war on cancer,” in only a handful of cases has this led to really effective targeted treatments, based on fundamental causality, and then only in rather unusual types of cancer such as CML, and less successfully, EGFR mutated or ALK-activated non-small-cell lung cancer subgroups, in which the benefits appear temporary, as with hormonal therapies in some breast and nearly all prostate cancers. Other targeted therapies (especially rituximab, trastuzumab, cetuximab, and bevacizumab) have been moderately successful, but seem to function at the level of relatively specific tumor markers, or contributory causality, rather than fundamental causality.

The philosophy underlying these and other sorts of targeted drugs is often based on a number of premises, some of which may, to a greater or lesser extent, be incorrect:

1. All cancers have dominantly acting driver abnormalities, which can be identified, called oncogenes.
2. These oncogenes are “necessary” causes of the cancer (whether or not they are sufficient).
3. These oncogenes have to be present in a continuous fashion to drive the cancer.
4. Inhibiting these driver oncogenes is sufficient to regress the cancer and may lead to a cure.
5. Oncogene products are druggable.
6. Because they drive the cancer, in a causative sense, and because cancer is abnormal, these drivers themselves must be qualitatively abnormal, and therefore side effects will generally be minimized.
7. If we cannot find the targets, we are just not looking hard enough.

Permeating this set of propositions is the notion of causality; if only the proximate cause can be identified, it can be inhibited, and the tumor cells will respond in some desirable way. In future, it was thought that even the
critical mutational aberrations in the nuclear DNA itself will be identifi-
able, and amenable to manipulation.

These ideas reflect much of Aristotelian causality: the “material” cause
is the tumor cells, the cause of the illness, and which must therefore be
made to disappear; the “formal” cause is represented by the entrenched
abnormal blueprint in the tumor DNA, and which is felt to represent the
ultimate target for corrective manipulation; and the “efficient” cause is the
chain of events that mediate the malignant phenotype, among which
specific, inhibitable, and necessary drivers are supposed to reliably exist.
Only the final, Aristotelian “purposive” causal aspect is, apparently,
irrelevant.

Furthermore, in this paradigm, drug resistance is conjectured as based
on specific mechanisms that can be diagnosed and addressed; for example,
for BCR-ABL mutations leading to imatinib resistance, there can always
be a dasatinib, or nilotinib; and for EGFR-TKI resistance, for example,
based on the T790M mutation, there will always be drugs like afatinib;
each of these successor drugs being allegedly efficacious against the newly
mutated forms of the driver oncogene products.

B. What’s So Wrong with This?

Unfortunately, serious questions can be raised about all of the above
premises.

1. ALL CANCER HAVE . . . ONCOGENES

Just because some cancers have identifiable, mutated oncogenes, which
do exist as a “presence” in a dominantly acting fashion, it may not be true
that all cancers must necessarily have them, or necessarily retain them
(Klein et al., ibid 2010; Perez-Caro et al., 2009) even if they needed
initiating oncogenes. What we need here is much more factual informa-
tion, including information about “gene sets” or pathways, as well as
individual genes, before we can properly evaluate the contributions of
individual genes versus “whole genome” causality (Boca et al., 2010).

2. THESE ONCOGENES ARE “NECESSARY” . . .

The implication is that in order to halt or regress the cancer, it is
sufficient merely to inhibit the oncogene(s) in question; that is, it presup-
poses that if oncogenes exist, there must be a state of absolute dependence
on one or more of them; a condition known as “oncogene addiction.” In
the case of BCR-ABL-associated CML, this situation may apply at least in
many if not all patients. In EGFR mt+ cancers, massive tumor reductions
certainly occur with small molecule EGFR-TKI blockade, but those
patients are never cured, either because the target EGFR mutates to resis-
tance via nonbinding (the T790M mutation) or alternative pathway
availability (c-Met amplification) or for other reasons not yet understood (Choi et al., 2010; Sequist et al., 2011; Suda et al., 2010). A similar situation is unfolding in ALK+ lung cancers for drugs like crizotinib.

It is not the case that unambiguous oncogene addiction-type situations exist for most cancers. Although K-RAS mutations seem to drive about 60% of colorectal cancers, and most cancers of the pancreas, the impossibility of successfully drugging ras has precluded the acid test in human patients. And while oncogenes have been known about for decades, very few have been successfully drugged, and it is possible, even likely, that pathway redundancies and other problems will continue to frustrate these efforts.

Therefore, although exploitable oncogene addiction situations do exist, so far they have been few in number, and it remains at best an open question on the generalizability of this approach. For instance, it might be possible to at least initiate transformation of cells by the inactivation of tumor suppressor genes, but whether full transformation can proceed without any help from or reliance on oncogenes is an open question; but it might be the case, for example, in retinoblastoma of childhood (Little et al., 2011).

3. THESE ONCOGENES ARE PRESENT IN A CONTINUOUS MANNER, TO DRIVE THE CANCER

As noted, Klein et al. document experimental situations in which the oncogene is required but only for initiation of the cancer, and thereafter is not only redundant but is actually lost altogether. This supports at least the possibility of the Heng–Duesberg concept of causality in which it is the instability of, or imbalance in, the whole genome that continues to drive the cancer, and not the presence of any particular gene. And since most human cancers present well into their tumor life spans (i.e., at about 20–25 tumor doublings, out of the maximum of 40 beyond which the host capitulates), the opportunity to direct a targeted agent against a mutated oncogene might be long past in real-life situations, if oncogene transience is indeed a real phenomenon.

While it is only fair to point out that how often this initiation-loss sequence occurs in actual human cancer, and indeed the whole Heng–Duesberg model of causality, has not even begun to be critically assessed, it is not a surprise that given the known level of genomic plasticity, cause-and-effect relations can alter with ongoing tumor evolution. Therefore we can anticipate not only loss of absolute dependency on a particular oncoprotein but also even, sometimes, actual loss of that protein. Either way, a targeted drug directed against this particular oncogene product would soon cease to be efficacious, and may even, via selection, accelerate its own failure.
Therefore, although the notion of causality as a therapeutic lead is seductive, it is certainly true that causal relations in a complex system are themselves complex, not easily disentangled, and will, unavoidably, be naive in their initial formulations. Perhaps the generally rather modest benefits to date of “targeted therapies” (Table II) reflect this.

4. INHIBITING THESE ONCOGENES WILL REGRESS THE CANCER, AND LEAD TO A CURE

This follows logically from the second premise above, and therefore suffers from the same weaknesses. It of course also depends on the feasibility of successful inhibition, below some ill-defined threshold of activity. If oncogenes are more loosely defined, as contributing to the malignant phenotype, rather than being absolutely necessary on an ongoing basis, one can allow that temporary but worthwhile benefits might materialize. But to imagine that benefit is guaranteed presupposes that an oncogene addiction exists in at least most of the tumor cells; and to suppose that oncogene addiction will enable a cure (via inhibition) is to suppose that cancers have no strategies to circumvent the obstacle, a supposition that appears demonstrably false. Even with CML, once the tumor has evolved to the accelerated or blast phase, imatinib and other BCR-ABL tyrosine kinase inhibitors are less and less likely to be efficacious (Skorski, 2011).

5. ONCOGENE PRODUCTS ARE DRUGGABLE

Of course, they may be, and some have been. But as noted, mutated KRAS remains undrugged, despite decades of effort (McCormick, 2010). It might be necessary to resort to antisense technology, an avenue that is being actively explored, but with no guarantees of success, either. Furthermore, there are several well-described oncogenes, for example, Myc, for which specific inhibitors do not appear to be even near the clinic.

6. BECAUSE THEY DRIVE . . . THE DRIVERS THEMSELVES MUST BE QUALITATIVELY ABNORMAL . . .

This may sometimes be true, but often it is not. BCR-ABL is mutationally abnormal, as are the activating mutated forms of EGFR (e.g., del 19 and exon 21 point mutations). However, neither gefitinib nor erlotinib are specific for the mutated form, and also inhibit the normal protein, which in fact may actually be also required for efficacy, in addition to inhibition of the mutant protein. Not surprisingly, on-target side effects occur, as a result of EGFR-wt inhibition in normal tissues (rash and diarrhea), but interestingly, these are generally mild-moderate.

Of more concern are situations in which increased production of an unmutated product contributes to cancer growth, as with EGFR wt amplification in colorectal and many cases of non-small-cell and other cancers. In these cases, there is only a vague hope that the cancers are “more reliant” on these gene products than normal cells, so that their inhibition
will result in a proportionately greater effect on the cancer, thus enabling what is known as a “therapeutic index.” Whether or not this situation exists can only be discovered empirically, in the intact human being. The level of expression is not necessarily a guide here; for example, for ER expression in breast cancers, the higher the level, the greater the sensitivity to inhibition (Bonomi et al., ibid 1988), whereas for thymidylate synthase, the opposite is true (Inoue et al., 2005; Ozasa et al., 2010; Salonga et al., 2000).

Thus although it might be argued that at some level, qualitative differences might exist, or even might have to exist between tumor and normal cells, this does not always translate into qualitative differences at the level of the protein actors that are the immediate and concrete targets; rather, the qualitative differences may only be apparent at “formal cause” level, that is, the DNA, which for the time being remains undruggable.

Furthermore, if it is true that transformation may be brought about by gene dose effects only, that is, without actual mutation at the DNA level, then there may never be any qualitative differences to exploit at all, and the only opportunities for selectivity might exist, for example, because of an unusual degree of “reliance” of the cancer cell on the gene in question, or that the really vital normal tissues do not depend on these genes, for example, the ER or androgen receptor, and expression and dependency are confined to nonvital organs, such as the remaining breast tissue; or that cancers may depend on oncofetal proteins normally repressed in the adult (Mizejewski et al., 2010).

7. IF WE CANNOT FIND THE TARGETS, WE ARE JUST NOT LOOKING HARD ENOUGH

This might be true, since an average driver might only afford a tiny growth advantage to a cancer cell (Bozic et al., 2010), and it might in fact be almost impossible to discern this. This type of driver, however, is unlikely to be “necessary” in the sense that as a single target, it could ever be addressed therapeutically in such a way that the cancer cell would then cease to exist.

Furthermore, it has been recently estimated that among the many mutations in a cancer cell, only a small fraction are actually driver mutations (Bozic et al., ibid 2010; Carter et al., 2009). And, I would agree, at least to some extent with Heng et al. (ibid 2010) that the data suggest with respect to most detected mutations in cancers in which this has been looked at (e.g., cancer of the pancreas (Blackford et al., 2009)), very few of the mutations occur in more than one cancer sample. In this pancreas survey ~89% of mutations did not occur in >1 patient, and a further 10% were mutated in only “2, 3 or 4 tumor samples” out of 114. On the other hand, K-RAS was mutated in 99%, TP53 in 82%, TTN in about 7%, SMAD4 in about 12.8%, and CDKN2A in about 20%. 
From this, one might conclude that K-RAS mutation is probably a necessary, ongoing dominant driver (and p53 also required in most patients, but as a function-absence abnormality); and SMAD4, and CDKN2A (i.e., p16) would be of interest. Nonetheless, the vast majority of mutations appear to be unique and as such, it will prove to be very difficult to know if any particular one is or is not an important driver. And, needless to say, only the important drivers will be worth pursuing for drug design purposes, and with current technology and preferences, only dominantly acting “presence” abnormalities would be considered suitable for drug design efforts, which would rule out TP53, CDKN2A, and perhaps even K-RAS that is, although oncogenic as a single, dominant allele, actually locked in an enzymatically inactive configuration. Finally, gene activity can be affected by epigenetic mechanisms, as might also be the case with CDKN2A in pancreatic cancer (Lomberk, 2011), and which might well be missed in a sweep of the DNA; therefore purely mutational analysis might underestimate the common involvement of certain genes influenced by epigenetic mechanisms (e.g., DNA methylation/demethylation aberrations, altered micro RNA, etc.)

Therefore, while I agree that undiscovered drivers might exist, it is not easy to discover them, nor easy to drug them; all these factors explain why so few drugs emerge from so simple and attractive a concept as the “driver-inhibitor” model.

C. Why Is Traditional Chemotherapy Generally Not Curative?

Combination chemotherapy came of age in the 1970s, and its successes and failures are by now empirically very well documented. As noted above, much remains to be learned about why it is highly active in certain situations and highly inactive in others; differential DNA repair and variable apoptotic threshold are candidate explanations. It is perhaps easier to comprehend why tumor cells in general might be resistant: apoptotic pathways are partially disabled, DNA repair and/or tolerance of DNA damage might be “good enough,” stem cell properties confer specific resistance mechanisms like extrusion pumps, etc., parts of the genome might function as a decoy and, above all, the unstable genome is more likely to generate resistant variants, which are then selected to survive.

It is obviously true that the curable cancers lack the slew of general and specific resistance mechanisms, but why this should be the case is unknown. It is equally obvious that the less sensitive cancers are equipped with resistance mechanisms of various sorts, some of which are specific for certain drugs. However, the central question as to why these sensitive cancers lack resistance mechanisms, and the resistant ones do not, is not often asked or answered; the standard model would suggest “random
mutations” as the explanation, but the well-known general similarity of drug sensitivity in most members of a particular tumor type compared to members of a different type indicates otherwise; for example, small cell versus non-small-cell lung cancer.

As suggested (Vincent, ibid BioEssays, in press 2011; Israël, 1996 ibid), to the extent that modern therapies resemble ancient existential threats, the cancer cells, manifesting an equally ancient survival program, may be well trained to circumvent them. In fact, these similarities might be quite striking (Table IV).

The Heng–Duesberg model, or any other model identifying accelerated macroevolution as the central fact of cancer, would also account for the rapid emergence of resistant variants, as would “adaptive resilience” as an ancient trait.

There may be an interesting reciprocal relationship between prognosis and drug sensitivity, which is pertinent here. In a recent trial of adjuvant chemotherapy in resected non-small-cell lung cancer, comparing a cisplatin-based regimen to observation, patients with a high level of ERCC1 (and hence, presumably, more proficient DNA repair) had an inherently better prognosis (i.e., absent chemotherapy) but no added benefit from the addition of chemotherapy. Conversely, those with low levels of ERCC1, and therefore less proficient DNA repair, had an inherently worse prognosis (absent treatment), but the biggest benefit from the chemotherapy; in fact, the chemotherapy could turn the worst group into the best (Olaussen et al., 2006).

What this appears to be telling us is that (subject to confirmation) cancers with poor DNA repair are more likely to evolve aggressive subclones, likely via mutation; whereas those that are less mutagenically prone will pursue a somewhat more indolent or at least less aggressive course absent therapy, that is, a prognostic determinant. On the other hand, the former, with less efficient DNA repair, may be more easily killed by DNA-damaging agents, whereas the latter, with more efficient repair, will tend to be more refractory to the effects of the chemotherapy—a predictive determinant.

That less efficient DNA repair should lead to the evolution of more diverse subclones makes sense, and it is also to be expected that upon exposure to chemotherapy, more damage would remain unrepaired and therefore more cells would be “pushed over the edge” and succumb (Helleday, 2010). On the other hand, with more DNA instability and hence diversity, there might also be more chance for resistant forms to evolve and therefore this situation may represent a trade-off, with the potential to generate conflicting results.

Therefore, and surprisingly, to the extent that traditional chemotherapy does exercise selective cytotoxicity to cancer cells, and is therefore targeted, at least part of the selectivity involves exploiting a “marker
absence” type of mechanism: the (relative) absence, or at least diminished capacity for DNA repair, compared to normal cells. The final determinant of cellular fate after exposure to chemotherapy or radiation, however, involves a poorly measurable and opaque relationship between DNA damage and apoptotic threshold; intensive efforts to manipulate the latter have not, to date, proven successful (Gimenéz-Bonafé et al., 2009). There may be more to gain by enhancing DNA damage via manipulation of DNA repair mechanisms (O’Connor et al., 2007).

As regards traditional chemotherapy, however, it is worth emphasizing that differential sensitivity remains underexplored and underexplained, and the potential for trade-offs may cloud interpretation of the result, especially with trial designs that prevent the clear delineation of prognostic effects from predictive ones.

D. A Shift in Emphasis?

As noted above, there is little to suggest that more hope should be placed in the emergence of novel driver-inhibitor type drugs, especially if the ambition is to cure rather than to temporize. (One exception to this might be novel drugs to disable Warburg-type metabolism, since it is apparently, a near-universal accompaniment and mediator of malignancy, and also fairly specific to cancer as well.) On the other hand, repair of the cell transformed by a molecular-absence type of driver situation (which are more common) may be beyond the reach of current technology. So where do the answers lie? I believe a case can be made for more intensive efforts to develop marker (as distinct from driver) opportunities, especially marker-absence opportunities that are more consistent with reality under conditions of a rapidly evolving cancer genome (i.e., Heng–Duesberg causality, or adaptive resilience).

For greater clarity, I am suggesting that while it might be possible to define at least some of the causative molecular lesions, either as aberrant presences or aberrant absences, successful therapeutic exploitation of these “driver” discoveries will either prove much more difficult than expected, or yield in general much less enduring remissions than we might wish. An alternative approach consists in exploiting distinguishing “marker” features, irrespective of causality. Analogous to driver opportunities that are due either to a presence or an absence of some molecular functionality, cancer marker opportunities stem either from the presence of a distinguishing feature, on or in the cancer cells, or an absence of one compared to normal cells. Furthermore, such marker features (whether present or absent) can be exploited in a variety of ways. One method involves using a simple structural type of approach, for example, the marker as an address box to which to deliver a warhead (address present only on the cancer cell) or a cytoprotective device (address present on
normal cells but absent on the cancer cells). Alternatively, these marker features can be exploited in a functional way, as long as the function is not expected to act via a causality mechanism. For example, a marker “presence” opportunity could be used to catalyze the activation of a cytotoxic drug, just like the relatively higher levels of thymidine phosphorylase in the tumor cell are used to activate the prodrug capecitabine (Van Cutsem *et al.*, 2001) or the use of SPARC and the gp60 receptor to actively deliver nab-paclitaxel to the tumor milieu (Desai *et al.*, 2009; Gradishar, 2006). In a marker-absence example, the concept (if not the actual reality) of an oncolytic virus that is kept inactivated by intact p53 in normal cells but the absence of p53 allows the progression of the viral life cycle to the cytolytic stage only in the cancer cells (O’Shea *et al.*, 2004).

Another marker absence function example previously quoted is the activation of amifostine in a normal cellular milieu but not the cancer cell milieu. This is a “functional” example because the amifostine is not simply deposited in the normal milieu, but has to be actively changed from its prodrug form to the entity actually capable of quenching radiation effects, that is, WR-1065 (vander Vigh and Peters, 1994).

It is important to appreciate the nuance that molecular particularities can be exploited as markers, even if they are causal drivers, if the result is an anticancer effect that is not mediated by a causality-reversal mechanism; if the latter, then it should be categorized as a “driver-type” therapy.

Obviously, marker-presentation mechanisms are much easier to envisage: simply identify a distinguishing feature on or in the cancer cell, and use it to deposit or activate a cytotoxic mechanism, which will then selectively kill the tumor cells. This is a perfectly rational strategy, and several successful drugs are either approved, based on this mechanism (e.g., capecitabine), or in development (e.g., maytansine linked to a trastuzumab-like antibody) (Isakoff and Baselga, 2011). It is also true that most immunotherapy approaches involve a “marker-presentation” type of strategy whether humoral or cellular, and whether the cytolytic capability is artificial or some endogenous branch of the immune system (like ADCC).

The problem with marker-presentation opportunities is that they appear in fact to be infrequent. Although tumor-specific antigens may exist, it is hard to find a universal one, one that does not differ from patient to patient. It is very difficult to redesign a drug for each patient, and this in fact imposes a limit on “personalized” medicine. Candidate target markers in the tumor cells include any enzyme expressed at levels higher than the surrounding tissue; oncofetal antigens like αFP, repressed in normal cells; components of markedly upregulated signal transduction pathways, like EGFR, but used for delivery purpose or immune attack; or mutant macromolecules that can be used for delivery or catalysis purposes. Note that the difference between normal and cancer cells need not be absolute but merely relative, provided careful attention is paid to lethal threshold effects.
It is, however, my belief that the really major type of missed opportunity is provided by the marker-absence category. This is because of the nature of cancer genomic instability; while it is true that all sorts of markers might be gained as a “presence” in the cancer cell, whether as oncogenic drivers or simply bystander phenomena, they are rarely, given the random nature of this process, going to be universal cancer markers. Loss of genetic information, however, is likely to be at least as frequent if not more so, and will include consistent areas of the genome across different patients, especially if the chromosomal loss enables a “driver” function. While it is not yet possible to think about “restoring” the missing chromosomal function to each tumor cell, it may well be possible to exploit consistent absences of genetic information in every cancer cell, at least of that type of cancer.

For this, Heng–Duesberg causality and the adaptive resilience/mutator phenotype both imply constant, roiling genetic reshuffling in which part or whole chromosome losses are frequent. And it matters little if one does not accept the Heng–Duesberg model of causality (i.e., it is the karyo-genotype that maintains the cancer via a mixture of gene imbalance, instability, mutational fine-tuning, and “context”); all one has to do is accept the empiric facts of massive genetic loss, irrespective of whether one regards it as a cause, or a consequence of the cancer, or both. But it is readily apparent that random macro- and micro-evolutionary change, accelerated as it is, will produce more distinctive constancy in the form of loss than of gain; and that the losses are extremely unlikely to be reconstituted, as a resistance mechanism and this is what needs to be exploited.

E. Are “Marker-Absence” Strategies Feasible?

The answer depends on two important factors: the constancy of identifiable loss of genetic information in cancer and the ability to design efficacious and selectively cytotoxic drugs based on this principle.

Genetic information can be embodied, or expressed, at the DNA, RNA, or protein level. If homozygously absent at the DNA level, then automatically it will also be absent at the RNA and protein levels. More commonly, however, is a hemizygous loss often accompanied by a second hit (the “two hit” hypothesis) in the remaining allele, which prevents expression (e.g., promoter methylation), or which results in the expression of a loss-of-function, mutant mRNA (e.g., point mutated, frame shifted, or truncated), so that no protein, or no functional protein, is expressed. The fact that these homo- or hemi-zygously deleted sequences often involve tumor suppression genes, that is, are “absence-driver” situations is not particularly germane to the general marker approach, except to highlight areas of relatively predictable genetic loss.
The ideal situation is where a homozygous DNA deletion accompanies a known type of cancer in a relatively high proportion of cases. In lung cancer, for example, about 30% of cases exhibit an homozygous deletion in chromosome arm 9p (Sato et al., 2005; Zhao et al., 2005). Cox et al. surveyed 636 cancer cell lines (Cox et al., 2005), finding 281 homozygous deletions. They also note that homozygous deletions may arise in or near fragile sites, compounded perhaps by DNA repair defects, or simply be random events. They also note, incidentally, that hemizygous loss was often accompanied by duplication of the remaining allele, finding “several thousand.” For homozygous deletions, glioma and pancreatic cancer cell lines seemed particularly prone to develop them, whereas cervical cancer and hepatocellular cancer cell lines were less likely. Furthermore, homozygous deletions were particularly likely to cluster around known tumor suppressor genes, especially CDKN2A, PTEN, RB1, and LMAD4, and/or bordered on seven of nine fragile sites known and sequenced at the time (e.g., FRA3B). However, 178 deletions were not “directed” in these ways. In the minority of these cell lines where this could be determined, it was clearly established that these deletions were somatically acquired (i.e., in the cancer) and spared normal cells, which is of course crucial to the prospects for selectivity.

Short of the “homozygous loss” ideal, however, loss of heterozygosity (LOH) with associated failure to express the cognate mRNA, and protein, seem much more common, and may be suitable. For example, 31 primary ovarian cancers were surveyed, revealing >380 small regions of “copy gain or loss” (and incidentally, 27 homozygous deletions) (Gorringe et al., 2007).

Some of the hemizygous loss situations will represent tumor suppressor genes that require full inactivation in order to drive the cancer, and which might reasonably be expected to lack any gene expression. However, others represent haplo-insufficient situations (e.g., TP53 or PTEN), in which LOH might still be a driver, even if some reduced level of normal expression off the remaining normal allele occurs, since protein levels supported by both alleles may be required for normal functioning (Berger and Pandolfi, 2011).

A variety of methodologies to identify genetic losses have been described, the more sophisticated and recent of which seem capable of finer and finer resolution (Caren et al., 2008; Gorringe et al., ibid 2007; Rothenberg and Settleman, 2010). Furthermore, it is also clear that microRNA might be selectively reduced or deleted in cancer cells (Davidson et al., 2010).

As to how drugs could be designed to exploit cancer-specific loss of information, a variety of strategies were noted above, some of which rely, for activation, on a specific function in normal tissues, lacking in cancer, as with activation of the cytoprotectant amifostine that is said to occur
selectively in normal cells because of the presence of an alkaline phosphatase and a permissive pH, neither of which occur in the tumor cell milieu; and others on lack of function in the cancer cells, present in normal cells (e.g., the concept, if not the reality, of oncolytic virus cytotoxicity, which “activates” the cytolytic virus life cycle only in the cancer, in the permissive milieu of absent p53); yet others might rely on the marker’s mere presence in normal cells for the simple delivery of a protective agents (e.g., G-CSF binding to its receptor in the normal myeloid line, as partial protection from otherwise myelosuppressive chemotherapy). It is easy to see (perhaps easier to see than to do) the possibility of designing a shield, enabled in some way by the genetic information present in normal cells, but absent in the cancer cells, which would then lack the shield; and then to apply an otherwise unselective cytotoxic, against which only the normal cells would be protected.

In 2007 was described a method (Varshavsky, 2007), envisaging a “deletion-specific vector,” consisting of a ring of DNA encoding a cytotoxic protein, together with an inactivating enzyme package triggered by the presence of specific sequences present in normal cells, but not cancer cells. Described as “a brilliant idea” by Bert Vogelstein, of John Hopkins, “because it exploits the Achilles heel of cancer. Deletions are likely to be present in every cancer” (Goymer, 2008 ibid). Varshansky was awarded the $1 million Gotham prize for this achievement. I have good reason to know that other variations are possible, at least conceptually.

The key concept to appreciate, however, is that gain of function mutations might be variable, and unstable; but loss of genetic information is unlikely ever to be reconstituted and repaired by the cancer cell, no matter how unstable its genome. Therefore, the target will not disappear, removing one important source of resistance. Not to underestimate the cancer cell, however, I would also advocate the accompanying cytotoxic insult be massive, overwhelming, and sudden, in the spirit of “shock and awe.” This, of course, puts a high demand on the mechanism of selectivity, whether the cytoprotective capabilities of the constructed shield or however embodied, and which will not be so easy to engineer in practice. But I think this is the best and perhaps only route to cure of the common cancers, especially if it is combined, as I think it should be, with emerging approaches aimed at disabling the WE (Vander Heiden et al., 2010).

**X. WHAT FORM OF LIFE?**

This question is rarely asked and never answered, at least explicitly. It is, however, implicit in the various evolutionary theories of cancer. The basic evolutionary view (standard model) is that cancer is simply the result of a
series of random mutations, and that selection for fitness enables the exhibition of a remarkable convergence of traits; a refinement of this acknowledges that an endogenous program of stem-like self-renewal is unleashed in this process, as exit strategies are blocked (i.e., by random, disabling mutations).

A somewhat different perspective, but still compatible with Darwinian selection, is provided by the atavism theories, common to which are that some kind of a survival “memory” (i.e., a de-repressed, ancient program) is reactivated under duress, leading to what is quite literally a re-emergent organism, albeit genetically unstable; and that this is a more parsimonious explanation than convergent evolution, for the many consistent aspects of the malignant phenotype.

I have here provided a viewpoint very much within this tradition, but characterizing the re-emergent program as none other than the WE, whose multiple facets explain much of the character of the cancer cell, not the least of which is the genetic instability referred to in the Heng–Duesberg model of oncogenic causality.

Furthermore, important therapeutic consequences flow from this, namely that missing genetic information specific to the cancer cell can be exploited to create a shield in normal cells to an otherwise indiscriminate cytotoxic, that this method of selective toxicity will be difficult to avoid, thus lowering the probability of resistance, provided the cytotoxic assault is abrupt and overwhelming. The WE is itself also an important driver target, whose inhibition might, if successful, lead to conversion to a chronic disease, or even, with concomitant chemotherapy, such as the “marker-absence” concept quoted above, a cure.

The concept of speciation is not enough to describe the cancer cell, conveying perhaps only half the truth, and the easy half of that: the despeciation from the host. What makes cancers difficult to classify taxonomically, is their continually unstable genetic makeup, which violates their depiction as a concrete type; unless, risking casuistry, it is their very instability that is their type-characteristic. The tree of life, as we perceive it, is an ensemble of generally stabilized genomic vehicles, and which allows the conclusion that purpose is served, or even defined by the continuation of genetic, or genomic identity. Cancer cells are unlike any other living creature, which raises the issue of where they reside on the tree of life, and which brings me back to Dobzhansky’s question: what are they for?

The only conclusion that can be drawn is that, as engines of biomass interconversion and purposed genomic innovation, they are “for” survival; of the cell, or even the cytoplasm; and exist in this fashion because they are, or were, for whatever reason, ill-served by the genetic stability with which they were previously associated. In effect, the cytoplasm has fired the old genome and is actively looking for a new one.
There is no obvious reason why this approach to life should not have proven a superior alternative, under conditions of constant environmental hostility and change, than the genetic stability that ultimately produced our lineage; except perhaps its very success seems to depend on the availability of large, multicellular organisms that, as resource outlets and residencies, can be parasitically exploited. Absent the host, where would the cancer cell be? Are they well enough adapted for the scarcity they would encounter as free-living organisms? Could there ever be enough biomass creation to support the demographic cushion necessary for this sort of genomic roulette, absent a host? Will the genomic rescrambling slow down in the face of resource scarcity? Should we be looking for free-ranging, unicellular “dyskaryotes” in nature? We should at least retain an open mind on this, notwithstanding how far-fetched it appears.

Cancer cells probably need us, certainly more than we need them; and unless a method exists to restabilize their genome, once a good “fit” has been discovered, it is hard to see how this form of life could continue to exist independently. Perhaps there really is an “off switch,” perhaps this is the only conclusion that makes any sense, and perhaps we should be devoting more resources to looking for it.

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