Cancer, the eighth leading cause of death in the 1900s in the US, has now surpassed heart disease as the primary cause of death in people under the age of 85 [Twombly, 2005]. In recent years, cancer has become the number one killer in the UK, France, Canada and China, just to name a few. The World Health Organization estimates that cancer accounted for 7.6 million deaths (approximately 13% of all deaths) in 2008, and will likely reach 13.1 million deaths by 2030 [WHO, 2014]. To put these numbers in perspective, about 41% of Americans will be diagnosed with cancer at some point in their lives, and 21% will die from it [Annual report of president’s cancer panel, 2008–2009]. These stunning statistics are a true challenge and are very disconcerting for most cancer researchers. Long before President Nixon declared the war on cancer in 1971, extreme efforts were being made by researchers to decipher the mechanisms of how cancer works in the hope of producing a cure. Along the way, the gene mutation theory of cancer was developed and many key cancer genes/pathways were identified. Today entire cancer genomes are sequenced in order to identify the genetic landscape of cancer. With this molecular knowledge and impressive technologies available, we not only can create cancer in petri dishes and in a variety of animal models, but can also cure them effectively in the laboratory setting. The decades’ long promise is that these basic research efforts would soon translate to clinical reality. “Win the war on cancer”, and “eliminate cancer in our generation” have become battle cries, not just in the cancer research community, but also by the nation at large.
Over 300 billion dollars have been spent (since 1971), scores of research papers have been published, countless “breakthroughs” have been announced in newspapers, TV networks and university press releases. Unfortunately we have only seen real success in very few types of cancer, which account for a very small portion of all cancer patients. The ultimate goal of achieving beneficial translational strategies at the clinical level is still largely unfulfilled. This raises the question “Why?”

1.1 The Progress

Cancer has been observed since antiquity with recorded cases as far back circa 2500 BC in ancient Egypt. Impressive scientific observations led to the linkage of environmental causes since the mid-1700s, including the association between tobacco snuff and nose cancer, and between soot and scrotal cancer in chimney sweeps. The transition between the 19th and 20th centuries saw rapid growth in research driven by newly established biological concepts and technologies such as re-discovered laws of genetics, chromosome theory, tumor transplantation and cell culture methods, the isolation of tumor viruses, and by applying earlier genetics concepts and developmental biology to the study of cancer [Bernard et al., 2008]. Among these seminal works, Theodor Boveri (1914), the father of chromosome theory, suggested that cancer was due to defects of chromosomes as chromosomes are the carriers of heritable information [Boveri, 1914; 2008].

The history of modern cancer research nicely mirrors the development of biological concepts and technologies. With the blossoming of biochemistry (1920 to 1950) and the subsequent arrival of molecular biology (since 1950), the research landscape drastically changed with the focus shifting to gene-centric theories and analyses (since 1970s). Currently, gene/epigenetic/pathway profiling coupled with various large scale genomics, proteomics and metabolomics approaches (since 2000) have generated yet another wave of excitement and huge amounts of data, again with the promise of understanding the mechanism of cancer once for all.

From a molecular medical point of view, cancer is a disease entity defined by uncontrolled cell proliferation with the ability to invade
normal tissue/organs (both adjacent and distal). The cancer research strategy seems straightforward: understand the molecular basis of the key hallmarks of cancer and then specifically target these key features, especially cell overgrowth and invasiveness. It is generally accepted that the cancer process, similar to some other diseases, can be dissected into a series of stepwise stages where the early stages of this process should provide specific targets for molecular diagnosis and treatment. This concept has been the rationale for molecular-based approaches that have dominated cancer research for over a half of a century.

Gene-based cancer research has been an exciting ride with one breakthrough after another [Mukherjee, 2010]. Along the way, a series of landmark molecular studies has promised to finally solve the mystery of cancer. Various types of cancer gene mutations were identified, and increased familial cancers were linked to specific gene alleles with impaired function. The identification and characterization of cancer genes and application of these molecular targets in disease diagnosis and treatment have dominated current cancer research. With various -omics technologies and increased computational power, we should now be entering the victory lap.

1.2 The Challenges

The development of various powerful molecular methodologies has further quickened the pace of discovery, bringing us ever closer to the goal of finding the entire set of key cancer genes, which has previously predicted to not exceed a handful. However the picture becomes more complex each year as we find more cancer genes than anticipated. Cancer genes now include oncogenes, tumor suppressor genes, cell death genes, expression regulating genes, DNA repair genes, cell cycle genes, caretaker genes, metabolic genes, chromosomal machinery genes, stress response genes, developmental genes, epigenetic regulation genes, tissue architecture genes, blood supply genes, mitochondria genes, and immunological genes just to name a few [Heng et al., 2009]. Many of them have multiple functions depending on the conditions [Horne et al., 2015a]. Furthermore, the same gene within different karyotypes can
display different or even conflicting functions. As pointed out by H. Harris, cancer research has become like the fashion world where there is a high level of excitement whenever a new molecular mechanism (such as a cluster of genes) is discovered, only to be replaced when the next gene cluster is uncovered [Harris, 2005]. This trend will for sure continue, as new fashions will certainly bring more gene clusters to the table.

Meanwhile, clinical implications of the identified gene mutations have been limited despite the very impressive lab data, excellent results in some animal models and noted success in familial cancers. For most solid tumors, early surgical removal results in the best patient outlook, but our large amount of accumulated molecular knowledge is of little help once metastasis occurs. Many chemo- and target-specific therapies initially reduce tumor size. However, this often does not translate into long term benefits, as many of these sky high expensive therapies prolong patients’ lives by only weeks or months at best and do not significantly improve the quality of life [Fojo and Grady, 2009; Mittral, 2007]. Therapeutic dosages of various drugs are typically designed to be just under the maximum dose tolerated by the general population, which in some cases has the disastrous effect of pushing these compromised patients over the edge.

This gap between molecular understanding (often based on exceptional models) and clinical implication is enormous and hard to cross. The majority of game-changing results from basic research have failed in the clinic, and the translational success is extremely low, giving people the impression that bridging the gap is like crossing the valley of death [Butler, 2008]. This serious situation deserves more attention and needs to be discussed within the cancer research community. Unfortunately, most researchers tend to play up the positive aspects of experimental progress and disqualify any discussion regarding the lack of translational relevance to clinical cases as “negative thinking”. In many researchers’ minds, cancer should be looked at as an issue of “half empty or half full”. As more genes are identified, it is simply a question of when the cup will be full.

Sadly, we have yet to reach the “half empty or half full” stage when it comes to the understanding of cancer. Current efforts have produced a
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A great deal of accumulated molecular data and associated inferences but in clinical terms, we have very little to show for these efforts. This strange situation undoubtedly questions the validity of the theoretical basis. Interestingly, the executive summary of the 2010–2011 annual report of the US President’s panel, titled “The future of cancer research: accelerating scientific innovation”, contained the following rare statement [Annual report of the president’s panel (2010–2011)]:

“America’s investment in cancer research has vastly expanded and deepened our understanding of the many diseases called cancer. Some of the genetic and environmental factors and biologic mechanisms that cause or contribute to cancer development, progression, and spread have been elucidated. This knowledge has led to the development of diverse interventions to reduce risk of cancer and more effectively treat some cancers, enabling many individuals to survive diseases that previously were almost universally fatal. Although notable, these achievements do not obscure the fact that cancer prevention and cure remain largely elusive…”

Despite the high praise for scientific achievements, this report undoubtedly underscores the gap between the impressive progress of molecular-based knowledge and clear lack of working achievements that effectively benefit most cancer patients. Beyond achieving a theoretical understanding of cancer, the ultimate goal is to benefit patients. Without real clinical success, no one can confidently claim that we are winning the war on cancer simply by accumulating molecular knowledge such as identifying and successfully targeting cancer genes or cancer specific pathways in the laboratory.

1.3 Hard Questions

Not all share this honest evaluation of our unexpectedly poor progress in the war on cancer, and few researchers have seriously considered this gap as a fundamental problem. The basic tenet of our scientific training leads us to respond to this lack of clinical progress with statements such as “As long as the research data are promising, the accumulated
knowledge will someday cure cancer” and “Science takes time to deliver in the clinic; the only way out is to keep digging.” Rather than question the theoretical concepts of current cancer research, many prefer to focus on the details surrounding specific techniques, particular experimental models or newer molecular targets. The belief is still the same: researchers have to find the key cause by collecting more data and applying more sophisticated analyses. If it is not a few key gene mutations, it must be a large number of drivers; if it is not caused by gene mutation, it must be epigenetic. If it is not DNA, it must be RNA. If it is not in the coding regions, then it must be in non-coding regions, and so on. Many focus on adding to the already overabundance of data leaving little time for researchers to critically read recent publications, synthesize one’s own data, or think outside of the (gene) box. The holy grail of cancer gene mutations might lie in the gene we have just discovered or perhaps one still in the freezer waiting to be isolated. And so it goes.

This situation has serious consequences for current cancer research. On the surface, “just do it” seems to reflect the positive attitude of the researchers. But when science runs out of new concepts, doing the same thing over and over again and expecting different results will only damage science. According to Einstein, it is insanity. Or at least, it is intellectual dishonesty.

The mindset that the long heralded gene-based answer was hiding in the genetic noise of cancer samples was certainly behind the cancer genome sequencing project officially launched in 2005 as the Cancer Genome Atlas (TCGA) project [Collins and Barker, 2007; Garber, 2005; Heng, 2007a]. If common gene mutations are the key for cancer, why not sequence them all directly from large numbers of cancer patients with different types of tumors? This unbiased and “big science” type of research should have ended a decade’s long effort to identify individual gene mutations once and for all and solve the issue of heterogeneity since large numbers of clinical samples would reveal the universally significant mutations and wash out less important “bystanders”. If no stone was left unturned, surely the Achilles’ heel of cancer would be identified. One powerful argument was that this approach would light up the entire genome (a metaphor similar to lighting up every single lamp
post to find a lost key). The question that no one dared to ask however was, “What if common gene mutations are not the key to cancer?”

Ten years later, after tens of thousands of samples have been sequenced, what has been found is not common cancer gene mutation patterns but rather an overwhelming level of genetic heterogeneity that occurs as both inter- and intra- tumor heterogeneity. This blows away the decades’ long belief that common cancer genes will be identified by comparing DNA sequencing between normal and cancer cells [Hayden, 2010a].

Like any political issue, results can be spun in many ways. The supporters of the cancer genome sequencing project tell people that the genome sequencing technologies have revealed the complexity of cancer. Major national newspapers have reported that genetic patterns have been found in the now decoded cancer genome. Instead of reporting the disappointing clinical findings, they insist that continued sequencing of the highly diverse gene mutations will result in personalized cancer diagnosis and treatment. Welcome to the era of sequencing everything!

Dissection of data from each genome sequencing publication is difficult due to the sheer volume of data. It requires persistence to critically analyze these reports and understand the real picture the reports paint. Many have only time and interest to read the often glowing title and abstract, making it hard to judge these more advanced technologies and the huge diversity of data they produce. Most papers do not provide a simple list of all the significant gene mutations detected and their clinical relevancy, but rather focus on the author’s choice of few mutations/pathways that make sense for storytelling.

A few have publically voiced their concerns of continuing to sequence yet more samples [Fox et al., 2009; Heng et al., 2011a; Nicholson, 2013; Strauss, 2013]. One such powerful voice is from a cancer guru, Bert Vogelstein, who proposed the model of stepwise progression of cancer based on genetic alterations, and led the first large scale cancer genome sequencing in a number of major cancer types. Vogelstein and others further stated that additional large-scale sequencing would not promote our understanding of the cancer landscape as hundreds of samples have already illustrated the overall complexity and, moreover, any such data would not change the big picture [Vogelstein et al., 2013].
Understandably, his view is at odds with sequence factory operators. Apparently, few — including the NCI (US National Cancer Institute) leadership — are really listening to him on this issue as the strategy of continuing to sequence is gaining popularity across the globe [Kaiser, 2010; Ledford, 2010]. His advice to stop sequencing more samples was not an easy one and should be very influential. Yet researchers who have followed his lead for decades now choose to ignore this valuable advice. Is it because people only believe what they want to believe? Why is it so difficult to critically evaluate the cancer genome sequencing project and its future? What is the potential harm of focusing on sequencing more samples? And is it the right time now to offer whole genome sequencing to less informed patients without understanding the true meaning of the large number of gene mutations and genome alterations?

1.4 New Paradigm

In the past several decades, numerous promising strategies have routinely come and gone in the cycle of hope/promise/disappointment that seems to be a key feature of cancer research. The prediction that cancer will soon be cured has been claimed so many times. For example, the targeted anti-angiogenesis therapy was hailed as the beginning of a new era in cancer therapy and led to a firm prediction by some leading molecular biologists that the NCI would soon close its doors. Unfortunately, angiogenesis inhibition was not the silver bullet and, like so many other promising ideas in cancer research, it did not improve patient outcomes [Hayden, 2009]. Yet not long ago, based on the promise of the human genome project, the leadership of the NCI declared that cancer would be cured by 2015. This obviously unrealistic goal was enthusiastically supported by many scholars and organizations including the American Association of Cancer Research. The 2015 deadline is now here with no cure in sight.

It seems that history has a pesky habit of repeating itself. It is easy to point out the limitations of some historical approaches and predictions, but difficult to use the lens of history to critically analyze our current strategies and promises, even though what we are doing today will be tomorrow’s history.
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Not surprisingly, the cancer genome sequencing project again offers the biggest promise to date. The moon shots project was launched in 2013 — based on the claimed and projected success of the cancer genome sequencing project to cure individual cancer patients using their genetic profiles — scheduled to be achieved within 10 years (now only 8 years left). But in reality, exactly because of the mind-boggling heterogeneity revealed by the cancer genome sequencing project, the goal of a cure has become more than ever elusive, which has surprisingly led some leading researchers to admit that the current approaches are not working and we do not even know how to interpret the massive amounts of data (Weinberg, 2014)!

There are many reasons why cancer research frequently repeats cycles of big-promise/huge-disappointment/confusion. In addition to the influence of various exciting technologies and impressive data generation capabilities, the increased pressure from patients and colleagues/funding agencies, and even personal gains of researchers all contribute. Those who make bold promises benefit from increased fame and funding but unfortunately are not held accountable when their key predictions do not meet their original promises. Furthermore, perhaps one most critical reason is the lack of critical thinking in the field and no vigorous debates directed towards the dominating cancer gene mutation theory, especially when it fails to explain many paradoxes as well as clinical reality.

Without the much needed debate, this serious scientific issue comes down to a subject of “he said, she said”. Whom do we believe? Of course, following the popular viewpoints becomes the safest strategy (but often not the most useful). The tradition of scientific debating is gradually lost, and different ideas are effectively suppressed, especially those that challenge the status quo.

To break up the tragic cycle and search for a new direction, we must discard false paradigms before committing any more resources and human effort to any other specific premise. We must critically analyze the rationale and the conceptual basis of current dominant beliefs in light of the –omics data and the gap between basic research and the clinic. Scientific logic and honesty must trump politics, personal gains, traditions and even arguing for the sake of arguing. We need to readdress the concepts on which these popular models are based, especially when
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the model has failed multiple times. The limitations of models in general should not be used as an excuse, as the main goal for cancer research is its clinical implications. In particular, we must realize the limitations of scientific inference, downplay the power of wishful thinking and hand waving, and pay more attention to some key paradoxes in the field.

Fortunately, many paradoxes in current cancer research can be solved by embracing a new evolutionary thinking that considers cancer as a genome alteration-mediated disease defined by a somatic cell evolutionary process, where system heterogeneity is the key. Specifically, addressing the following five types of questions have initiated the new conceptual framework of genome-based cancer evolutionary theory.

(1) The question of cancer heterogeneity: If cancer represents an evolutionary process, and the key factor for evolution selection is variation, what types of genetic and non-genetic heterogeneity matter the most for cancer evolution? Is it gene mutation? Is it epigene alteration or genome variation? Why is there so much heterogeneity at multiple genetic levels in the first place? What is the key contribution of this heterogeneity to normal cellular function and to cancer?

(2) The question of inheritance in cancer: Which genetic organization level defines the genetics of cancer cell: genes, epigenes or genomes? Why does gene-defined “parts inheritance” differ from genome-defined “system inheritance” or the blueprint? Is genetic inheritance precise or fuzzy?

(3) The question of the evolutionary mechanism of cancer: What is the dominant pattern of cancer evolution? Is it gene mutation mediated stepwise accumulation or punctuated genome re-organization? What is the genetic basis for different phases of somatic cell evolution? Is the mechanism of long-term population adaptation different from the population survival mechanism under high stress? Does cancer evolution follow Darwinian principles?

(4) The question of system constraint for cancer evolution: If the genome represents a level of constraint for genes, how can other cellular ecological constraints impact the genome? What are these factors that can contribute to the breakdown of system constraint and favor cancer
evolution? And what is the general mechanism to unify these diverse molecular mechanisms?

(5) The question of the knowledge gap between basic research and the clinic: Why is the knowledge gap between cancer gene mutation theory and clinical utility so wide? How do we apply the new genome theory to explain the mechanisms of rapid cancer evolution including drug resistance? What is the evolutionary role of outliers? Does this unique cancer evolutionary insight offer clinical implications for diagnosis and treatment? Why does fuzzy inheritance challenge the concept of precision medicine in cancer?

These issues will be debated throughout the book, which ultimately will lead to a sensitive yet profound question: Is the conceptual framework of the gene mutation theory still relevant in terms of guiding future cancer research? If the answer is “yes”, then we must define new technical strategies as clearly current gene mutation-based cancer research is heading in the wrong direction. (Increased gene-based knowledge can hardly apply to the clinic!) If, however, the answer is “no”, what new framework should be used and why (epigenetic-based, or genome-based, or tissue-based theories)? Since cancer genome sequencing has generated sufficient data, and more importantly, a high degree of confusion, the time is now to debate this issue. Such debate will impact the future of this field.

Obviously, addressing such questions is neither easy nor popular. According to Thomas Kuhn, when there are enough significant anomalies against a current paradigm, the scientific discipline will enter a state of crisis. Typical features of such a crisis include scientists on either side of the paradigmatic divide lacking the ability to understand the other's viewpoint or reasoning; the intensification of an intellectual “battle” between new ideas and the old paradigm; and a tremendous disinterest within the research community to provide a comprehensive scientific analysis to explain the inconsistencies despite the fact that the old paradigm is full of mistaken assumptions and failed predictions. Debate within current cancer research is needed to reveal these anomalies, an exercise that will undoubtedly result in the abandonment of the current paradigm and the search for a new one.
1.5 Outline

In the following chapters, we will try to debate issues in cancer research ranging from basic concepts to experimental designs/explanations. Each chapter will focus on the numerous paradoxes, common misconceptions and challenging issues related to a major topic. This discussion will be followed by hard and sometimes uncomfortable pertinent questions and critical analysis. We will debate key facts, key concepts and key interpretations of some well-known data or phenomena to examine seemingly important concepts based on artificially created constructs in order to expose any shaky logic and at the same time, explore highly significant developments that arise from what initially appear to be non-significant findings.

Our main goal is to introduce a new paradigm of genome theory as without it, the old paradigm will never be replaced no matter how outdated. During this debate, the key limitations of the current gene mutation theory of cancer will be critically reviewed (Chapter 2) followed by the brief description and commentary on over a dozen noted alternative theories of cancer (Chapter 3). To deliver this convincing message, the current status of the cancer genome sequencing project will be evaluated, which calls for a new framework (Chapter 4). Chapter 5 introduces the genome theory of cancer based on the discovery of two phases of cancer evolution, which are genome alteration-mediated macrocellular evolution and gene/epigene-mediated microcellular evolution. By redefining system inheritance, stochastic genome variation represents the driving force for cancer evolution that can unify diverse molecular pathways. Cancer population behavior will be further discussed in Chapter 6, leading to discussion regarding the recent discovery of a new form of inheritance termed fuzzy inheritance. The realization that genetic information is not as precise as we previously thought especially at the somatic cell level is highly significant; it not only provides the basis for understanding cancer heterogeneity, but also offers explanation for the missing heritability of common diseases, why most cancer gene mutations display low frequencies within the patient population and why it is challenging to target them. Chapter 7 will engage whether or not cancer should be considered as a new species as
well as the potential contribution of cancer evolutionary study to evolutionary theory in general. In Chapter 8, a number of important paradoxes will be discussed with application of the genome theory. Finally in the epilogue, some key messages of this book as well as future perspectives are briefly summarized.

To illustrate that a change in paradigm is long overdue, Kuhnian standards will be used to evaluate or grade current cancer research [Kuhn, 1962; Strohman, 1999]. This includes the incommensurability between believers and non-believers of the current paradigm, the lost confidence by some scientists within the field, encountering the increased opposition from the establishment also based on non-scientific reasons, and finally, the tremendous disinterest in trying to explain inconsistencies and provide a comprehensive scientific analysis seeking to answer these questions that might actually give direction to future research and technology.

In addition to re-evaluating some generally accepted concepts and famous case studies, we will also address the many paradoxes and untold stories associated with these individual success stories. New analyses and re-syntheses will provide a fresh and holistic picture of the current challenges in cancer research. We hope this new perspective will make you agree that there has been enough “business as usual” and it is now time for a real change.

It should be noted that the main goal of this book is not to provide a comprehensive coverage of current molecular cancer research or to systematically list many molecular details but rather to initiate much needed debate that hopefully leads to acceptance of a more realistic paradigm. To achieve this goal, we have raised hundreds of important questions that will effectively illustrate our points. With this open debate, we believe readers will appreciate this new perspective and will join in our search for a new direction, finally reaching the point of no return with regards to the gene-based approach. Please join us for this exciting, sometimes confusing and even painful, but ultimately an eye opening and game changing journey.