Progress With a Purpose: Eliminating Suffering and Death Due to Cancer

November 17, 2006
By Andrew C. Von Eschenbach, MD [1]

Cancer is the second leading cause of death in the United States, with more than 500,000 men, women, and children succumbing to the disease each year. The idea, then, that we can eliminate the suffering and death due to cancer in the United States by the year 2015 may appear impractical, if not irrational and impossible. It seems inconceivable that in the first part of the 21st century every patient could survive cancer. Doubt can be attributed to awareness of the biologic complexity of cancer and seeing the pace of clinical progress through the prism of the 20th century.

However, in 2002, when setting the goal of eliminating the suffering and death due to cancer, the National Cancer Institute (NCI) envisioned a future in cancer research and care that would be radically different from the past, and be the fruition of the cancer enterprise made possible by the National Cancer Act of 1971. Because of progress thus far, there are more than 10 million cancer survivors today, and two out of every three people diagnosed with cancer will be alive 5 years following diagnosis. Because of prospects for future progress, it is within our grasp to prevent more cancers from occurring, to detect others earlier and eliminate them more effectively and safely, and to modulate the behavior of other cancers, so that patients will be able to live with, and not die from, the disease.

For those willing to embrace the possibility of such a future, the question remains: How can such a goal be accomplished, and how can it be achieved in such a short time? This paper will describe the rationale for the goal and present a way forward that, with proper leadership and resources, will lead to this lifesaving objective. To achieve a clear vision of this path, one must scrutinize the past and acquire a new vantage point from which to see the future. It requires us to no longer consider cancer as an event clouded in mystery, but as a process with defined and knowable mechanisms that operate in a distinct manner over time, resulting in ample opportunities and sufficient time for intervention (Figure 1). It requires us to consider the pace and trajectory of future progress, not as an extrapolation of past experience, but as a new reality born of a metamorphosis in medical science and technology.
The pathway to preempting the outcome of the cancer process is not a defined roadmap; rather, it is a way forward, with sequential steps and parallel paths toward a defined goal. Inherent in the way forward is the assumption that paths will, at times, converge and technology will accelerate the speed of progress, so that over the next decade, passing milestones on the journey will be astounding compared with past progress. The key to seeing what is possible is to view the journey from the perspective of the evolution in scientific discovery. That is, the perspective of a metamorphosis from a macroscopic and microscopic view of cancer to a molecular one.

Macroscopic and Microscopic Traditions of the Past
The history of the quest to conquer cancer has been nested in a model of health and health care that has addressed disease from a phenotypic perspective. Our knowledge of cancer is derived from our observation of the manifestations of the disease. For thousands of years, this phenotypic perspective dominated the practice of medicine based on what we could learn using our five senses. Medical education focused on creating a sound foundation of physical diagnosis through observation, auscultation, percussion, and palpation. What we could feel and see defined the taxonomy of disease. Cancers were named for the organ in which they originated.

Approximately 100 years ago, we moved from this macroscopic view to a microscopic perspective. A revolutionary change of seeing cancer cells under a microscope refined our characterization of cancer and allowed us to infer more about its behavior, but again, an inference derived from what we could see or observe of cell size and shape. Certainly this was significant progress; and when our vision was further sharpened by x-ray techniques and laboratory studies, our ability to observe phenotypic expression of disease was dramatically enhanced. But in fact, the fundamental paradigm remained unchanged, and detection and diagnosis were completely discontinuous with therapeutic intervention.

Observing the anatomic and morphologic expression of cancer provided no insight into what the ideal intervention would be, and treatment required a separate and empiric set of strategies based on ablation or eradication of the phenotypic expression of the disease. Throughout most of the 20th century, our efforts at tumor ablation by surgery, radiation, and chemotherapy were largely empiric; progress was measured by expanding the limits of ablation and reducing the morbidity and mortality associated with therapy. But progress did occur.
At the beginning of the 20th century, cancer was a uniformly fatal disease. By the end of the 20th century, there were examples of enormous advances in some cancers, such as childhood leukemia and testicular cancer with chemotherapy, and dramatic improvements in the results of surgery and radiation therapy in early prostate and breast cancer. But in therapeutic strategies that required an understanding of mechanisms, such as immunotherapy, results were disappointing. Many cancers did not respond to chemotherapy regimens that were dramatically effective in other cancers, with no apparent explanation. The most significant benefit seemed to emanate from the major impact of a prevention strategy that was based on an observation of tobacco’s mechanistic causation of lung cancer.

But along this journey of an empiric approach to a macroscopic and microscopic perspective of cancer, an important transformation occurred. With the signing of the National Cancer Act of 1971, the NCI obtained both the authorities and the appropriations to begin a focused and directed effort to "understand" cancer. It was the catalyst that was necessary to rapidly and radically accelerate the emergence of the new field of molecular biology. With the discovery of DNA by Watson and Crick in 1953 and the post-World War II explosion in science and technologies that followed our understanding of the nature of matter and energy, the world was poised to begin the exploration of life processes in the cell.

The most egregious disruption of the nominal processes of proliferation and differentiation—and the most readily available for study—was the cancer cell. Cancer led the revolution in molecular and cell biology in the last quarter of the 20th century, and in the last decade of the century, we crossed the threshold into the molecular era. This was now more than a transformation. It was a metamorphosis in which the future in oncology will be no more like the past than a butterfly is like a caterpillar.

The Genesis of the Metamorphosis

We have begun, perhaps for the first time, to comprehend the genetic and molecular mechanisms responsible for the cancer phenomenon that we had been observing for centuries. We can understand that genetic mutations give rise to our susceptibility to cancers, that molecular and cellular events regulate malignant transformation, growth, invasion, and metastatic spread of cancer. We have begun to understand how and why patients develop cancer as well as suffer and die because of its progression. This new knowledge is leading directly to new insights as to how we might eliminate that suffering and death—not just for some, but for everyone.

The diverse areas of cancer research have brought forth enormous amounts of detailed knowledge of the pathogenesis of cancer.[1] Understanding inherited mutations or the damage to DNA caused by environmental factors (such as chemicals and radiation) that reprogram a cell to become or be more susceptible to becoming a cancer, now are providing insights into preventing or controlling the malignant process. Furthermore, epigenetic alterations and cell-to-cell interactions are emerging as important elements in the regulation or modulation of this malignant cascade, and are opportunities for preemption (Figure 2). This elegant story is unfolding at an exponential rate and, as previously described in the report of Hanahan and Weinberg,[2] the six process characteristics of cancer present an array of targets that make cancer vulnerable to prevention, detection, elimination, or modulation interventions.
In 2006, the knowledge being generated by molecular biology and genetics is having an increasing impact on cancer prevention, detection, diagnosis, and treatment. Such impact is apparent in the development of new molecularly targeted therapies, which directly interact with the specific aberration in the cellular machinery that is responsible for the malignant phenotype. From a molecular perspective, the selection of these interventions no longer depends on an empirical trial-and-error approach. Rather, therapy selection is a rational process based not on phenotype but on the understanding of the mechanism.

A decade ago, it would have seemed inexplicable that cancers like chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GIST), which have a radically different appearance and behavior, would both respond to the same therapy. From a molecular perspective, however, they share a mechanistic defect driving malignant expression, and the drug imatinib mesylate (Gleevec) targets the same tyrosine kinase pathway in both tumor types. Hailed as a "medical breakthrough of targeted therapy," imatinib mesylate marked the approval of the first drug to turn off the signal of a protein that directly causes the malignant phenotype. The portfolio of such therapies is expanding, and the next generation of molecular therapies will be designed to target multiple proteins in multiple signaling pathways.

The tools of molecular science and technology are not only applied to the disease but also to our enhanced understanding of the biologic complexity of the person. Furthermore, these tools as diagnostics allow for visualization and monitoring of the biologic impact of interventions. The molecular approach will make it possible to define the right treatment for the right patient, delivered at the right time, to the right location, and get the right predictable outcome that we can see and measure in real time. The tools of molecular medicine that science, technology, and innovation have been providing will help us define new interventions. That will radically change our entire system, across the spectrum of discovery, development, and delivery. In delivering those interventions to the patients who need them, we will further understand the biology of diseases in individual people. Delivery, then, becomes a platform of discovery. And discovery will enable us to develop interventions that move from empiricism to rational mechanistic-based interventions.

First-generation targeted therapies (Table 1) have only been available in the clinic for a few years, but progress in developing and delivering this next generation of agents to the patient is accelerating.
Paradigm Shift in Cancer
The era of molecular oncology heralds an entirely new paradigm for cancer diagnosis and treatment. It is aptly described as a "strategic inflection," which is a point of change described in the book *Only the Paranoid Survive* by Andy Grove, one of the founders of Intel.[3] If understood and embraced, a strategic inflection point leads to exponential growth and progress.[3] We are now able to approach cancer in a fundamentally new paradigm, by capitalizing on the tremendous progress we've made and are making progress with a purpose.

Based on the molecular perspective that is evolving, we are already envisioning a future in which health care will be *personalized, preemptive, and predictive*. And with the continuing integration of information technologies and strategies of communication, health care for the patient will become even more *participatory*. In this new reality of health care, we will define cancer as either a preventable, curable, or chronic disease, and no longer feared as uniformly lethal.

The new era in biomedicine is being accelerated by technology, thanks to rapid advances occurring in bioinformatics, nanotechnology, imaging, and biomarkers. Integrating these technologies not only into discovery, but also into the development and delivery of these interventions presents the opportunity to radically alter the outcome for patients threatened by cancer. NCI is supporting a number of important technology-directed programs to enhance the pace of progress in this new era. Molecular imaging technologies, such as fluorodeoxyglucose positron emission tomography (FDG-PET) monitoring modalities, are used in an expanding number of settings to assess therapeutic

---

**Table 1**

<table>
<thead>
<tr>
<th>Targeted Therapy</th>
<th>Type of Therapy</th>
<th>Cancer Type</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Monoclonal antibody, angiogenesis inhibitor</td>
<td>Colorectal cancer</td>
<td>2/26/04</td>
</tr>
<tr>
<td>Bortezomib (Velcade)</td>
<td>Proteasome inhibitor</td>
<td>Multiple myeloma</td>
<td>5/13/03</td>
</tr>
<tr>
<td>Cetuximab (Erbitux)</td>
<td>Monoclonal antibody, EGFR inhibitor</td>
<td>Colorectal cancer</td>
<td>2/12/04</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>EGFR inhibitor</td>
<td>NSCLC, pancreatic cancer</td>
<td>11/18/04</td>
</tr>
<tr>
<td>Gefitinib (Iressa)</td>
<td>Enzyme inhibitor</td>
<td>NSCLC</td>
<td>5/5/03</td>
</tr>
<tr>
<td>Ibritumomab (Zevalin)</td>
<td>Radiolabeled monoclonal antibody</td>
<td>NHL</td>
<td>2/19/02</td>
</tr>
<tr>
<td>Imatinib mesylate (Gleevec)</td>
<td>Enzyme inhibitor</td>
<td>CML, GIST</td>
<td>4/18/03</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Monoclonal antibody</td>
<td>NHL</td>
<td>11/26/97</td>
</tr>
<tr>
<td>Sorafenib (Nexavar)</td>
<td>Angiogenesis inhibitor, enzyme inhibitor</td>
<td>Kidney cancer</td>
<td>12/20/05</td>
</tr>
<tr>
<td>Sunitinib (Sutent)</td>
<td>Enzyme inhibitor</td>
<td>GIST, kidney cancer</td>
<td>1/26/06</td>
</tr>
<tr>
<td>Tositumomab (Bexxar)</td>
<td>Radiolabeled monoclonal antibody</td>
<td>Follicular lymphoma</td>
<td>6/27/03</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>Monoclonal antibody</td>
<td>Breast cancer</td>
<td>9/25/98</td>
</tr>
</tbody>
</table>

CML = chronic myelogenous leukemia; EGFR = epidermal growth factor receptor; FDA = US Food and Drug Administration; GIST = gastrointestinal stromal tumor; NHL = non-Hodgkin’s lymphoma; NSCLC = non-small-cell lung cancer.
efficacy within a few hours or days of administration of a molecularly targeted therapy. The Cancer Genetic Markers of Susceptibility (CGEMS) initiative[4] aims to identify and pinpoint common variations in genes that make people susceptible to cancer. Previous studies have identified single-gene mutations that cause or are linked to cancer. These studies will provide insights into potential mechanisms of cancer susceptibility, by mapping low-penetrance gene mutations most often involved in cancer risk. This type of study design is especially valuable for detecting the genetic origins of complex diseases.

The National Nanotechnology Initiative[6] intends for scientists to be able to create new classes of structural materials that are expected to bring about lighter, stronger, smarter, cheaper, cleaner, and more precise products. One such nanotechnology-based diagnostic platform is the bio-barcode assay. Tiny magnetic particles that contain recognition agents for a cancer marker are added to a blood sample. If the cancer marker is present, the magnetic particles are attracted. Gold nanoparticle probes with DNA strands (the bio-barcode strands) are captured and identified by a microarray assay.[7]

Equally important is the growing experience of clinicians and scientists working in close collaboration to create a seamless continuum. Here, relevant clinical disease observations in patients and populations are being investigated in the laboratory for underlying mechanisms, while discoveries in the lab are translated into strategies to halt, reverse, or prevent disease.

The 'Critical Path' to Progress

The foundation has been created for the right patient and the right tumor to receive the right intervention for the right reason at the right location and at the right time with the right outcome monitored in real time. The next significant step is to remove any developmental barriers to bringing these innovative safe and effective interventions to the patient more rapidly.

The path from discovery to delivery has at its interface, the developmental process. The results of the extraordinary explosion in innovation occurring in biomedical research-making the molecular metamorphosis possible—fulfill their purpose only when they are translated into interventions and solutions that are applied to patients. By its role in overseeing the development process, the Food and Drug Administration (FDA) is positioned as the bridge between the products generated in the biomedical research enterprise and the delivery of those solutions in our health-care system.

Because of the rapid pace of scientific discovery, as well as policy and regulatory activity in the field of product development, it is imperative that the FDA find ways to accelerate and make seamless the discovery-development-delivery continuum. The FDA must be equipped to deal with the opportunities and challenges that present themselves in the 21st century. The bridge supporting development must use modern science and technology to streamline, accelerate, and assure the safety of the transition. To aid in the transformation, the FDA has established the Critical Path Initiative.[8] Critical Path is anchored in the discovery and delivery components of health care. The initiative is about ensuring that new scientific discoveries are having an optimal impact on patient care.

The FDA has already shown a long-standing commitment to the prompt consideration and, when appropriate, early approval of new therapies for cancer patients. With the passage of the Food and Drug Administration Modernization Act (FDAMA) of 1997, which amended the Food, Drug, and Cosmetic Act, Congress enhanced the FDA's mission in ways that recognized that the agency would be operating in a new era, characterized by increasing technologic, trade, and public health complexities. Among other things, the FDAMA codified many of the FDA's initiatives and existing programs designed to expedite drug development and expand access to unapproved therapies. All of these measures have been instrumental in shortening the time to marketing approval for cancer drugs and biologics.

Two regulatory mechanisms codified in the FDAMA have given the FDA the authority to approve treatments for serious or life-threatening conditions that address unmet medical needs: Accelerated Approval and Expanded Access. Although each comes with its own set of requirements, they are both designed to make promising products available as early in the drug evaluation process as possible. Since 1996, the FDA has approved over 80 new cancer-related medications or new uses for already-available drugs. Nearly half of these have been reviewed and marketed within 6 months of
their submission to the agency. For example, imatinib mesylate was approved in a record 2.4 months.

The Critical Path Initiative, therefore, set out to turn the course of medical product development into a certain and affordable process. It addresses many of the challenges that plague the process of evaluation and testing that drugs, biologics, and devices must negotiate on their way to becoming available to patients. As part of the initiative, the FDA recognizes that incorporation of new science and technology is needed. This includes collaborating with the National Institutes of Health (NIH). The NIH has established a "roadmap"[9] of initiatives intended to speed the movement of research discoveries from bench to bedside within this framework. Under an Interagency Agreement, the NCI and the FDA will share knowledge and resources to enhance the efficiency of clinical research and the scientific evaluation of new cancer medications. The result will be a more unified, integrated, and efficient approach to the technology development and approval process. The collaboration will help both the FDA and the NCI take full advantage of their combined knowledge base at a time when many new types of anticancer agents are in the pipeline.

Opportunities on the 'Critical Path'

Across a broad perspective of health care, the Critical Path seeks to improve the medical product development process by encouraging development of new tools and standards (Figure 3). The "Critical Path Opportunities List"[10] presents highly targeted research projects intended to improve product development, including better evaluation tools, harnessing bioinformatics, moving manufacturing into the 21st century, and developing products to address urgent public health needs and specific at-risk populations. Priority areas will be in biomarker development and qualification and the design and conduct of clinical trials. New imaging techniques hold vast potential for use as biomarkers for an array of purposes in product development: measuring treatment efficacy, patient stratification, and improved diagnosis. But the predictive capacity of most new imaging techniques has not been rigorously evaluated, despite promising preliminary data. A lack of standardization of imaging methods and evaluation techniques further complicates their use in product development. Data gained from the standardization and qualification processes will likely provide evidence for clinical use.

Several projects delineated in the Opportunities List are intended to stimulate innovation in trial design. Challenges do exist. Standardizing and automating clinical trials as much as possible could
dramatically improve the efficiency of clinical development, but may require new models of trial design and biostatistics. Many opportunities remain in this area. True to the idea of making progress along parallel paths with convergence points, the opportunities on the Critical Path converge with many NCI initiatives. For example, nanotechnologies will be used as biosensors and detection devices for molecular imaging and delivering drugs. Within the context of the NCI's Alliance for Nanotechnology in Cancer initiative, the FDA and the NCI are working together to create performance standards to ensure that safe nanoproducts reach the clinic expeditiously.

With regard to enhancing the development of therapeutics, the FDA has issued a new guidance for "exploratory" investigational new drug (IND) applications to conduct proof-of-concept or microdose human testing. This mechanism will allow safe testing of small doses of medications in order to understand fundamental mechanisms and biologic processes before going on to the traditional phases of clinical research, to better understand how biomarkers can be used to assess the impact of therapies, and to better match therapies to patients. The FDA, NCI, and the Centers for Medicare and Medicaid Services (CMS) are collaborating on the Oncology Biomarker Qualification Initiative (OBQI).[11] By collaborating, we can standardize the use of new technologies essential to refining the drug development process in order to develop personalized medicines. FDA and NCI are studying FDG-PET with the goal of bringing novel imaging probes and drug development together.

In all of these examples, the underlying purpose is to bring together the scientific, regulatory, and delivery expertise to improve the development of cancer therapies and the outcome for cancer patients. In 2003, the FDA and the NCI established the Interagency Oncology Task Force (IOTF), which encourages researchers and regulators to work together to accelerate drug development and the approval process. The IOTF's organizational structure consists of subcommittees that reflect the process of drug development. The activities of the task force include bioinformatics that will provide an infrastructure to make regulatory submissions more efficient, provide for electronic common technical documents, improve adverse event reporting, and standardize terminologies for research data sharing. The process subcommittee will identify and eliminate internal barriers that delay development in order to streamline processes. The OBQI subcommittees will define clinical endpoints for regulatory review and accelerate new imaging technologies. The chemoprevention group will facilitate the development of natural and synthetic agents and regimens designed to reduce the risk of cancer.

Conclusions
At the turn of the 20th century, the likelihood of surviving cancer was bleak. As we begin the 21st century, progress has been dramatic but the successes have been quite heterogeneous, with major advances in survival in some cancers like leukemia and testicular cancer, but with dismal failure in others like lung cancer and pancreatic cancer. To achieve the ultimate solution and eliminate all suffering and death, there is no single or prescribed path. It must be like the science that guides it—a process of exploration and innovation.

Just as scientific discovery cannot be prescribed, insights into preempting the cancer process cannot be predicted. Progress in cancer detection, diagnosis, and treatment is in a constant state of revolutionary evolution, and cancer care will morph from treatment to prevention. This is because advances in genomics, proteomics, and nanotechnology offer opportunities to detect cancer earlier when it is highly treatable, develop specifically targeted therapies, and open new doors for evidence-based prevention strategies. Integrated therapies will emerge that will be "solutions" to eliminate or modulate the cancer process. The essential importance of the molecular metamorphosis is that medicine will now morph to being more science than art.

Scientists have learned more about cancer in the last decade of the 20th century than has been learned in all the preceding centuries.[12] The information and knowledge of molecular biology and genetics emanating from science is illuminating a vision for eliminating the suffering and death due to cancer by 2015. The promise of the genetic and molecular age is an era of personalized, targeted prevention and therapeutic interventions. This vision is making it possible to understand this complex multifaceted series of events whose initiation and progression can be preempted on the pathway to a lethal phenotype. Instead of searching for treatment, the tools are now available to understand both the disease and the patient, and the intricate interactions between the two. From this understanding emerges the solution to the problem. The goal to eliminate the suffering and death due to cancer and to bring that about by 2015 is a call to action for the clinical oncology and research communities. The timeframe is ambitious, but the goal is achievable, and the effort and commitment are imperative because every step toward that goal is measured in lives saved.
Disclosures:
Dr. von Eschenbach was awarded the prestigious Janeway Award in conjunction with the 2006 meeting of the American Radium Society, held in Maui, Hawaii. This presentation of Dr. von Eschenbach's Janeway Lecture is adapted from the proceedings of that meeting.

References:

Source URL:

Links: