A vision for the National Cancer Program in the United States

Andrew C. von Eschenbach

Abstract | The intersection of two noble endeavors — the scientists’ quest to understand life itself and the physicians’ dedication to relieve suffering and prolong life — came into sharp focus in 1971 with the United States National Cancer Act. This focus has led to an exponential expansion of our understanding of cancer at the genetic, molecular and cellular levels, and concomitant advances in our ability to disrupt the disease process through prevention, early detection and successful treatment. At the National Cancer Institute we are committed to capitalize on these achievements. A new era is now within our grasp, a time when no one suffers or dies as a result of cancer.

In the United States, we have committed our national will and resources to conquering cancer — a commitment defined with the passage of the National Cancer Act in 1971. The hoped-for ‘cure’ for this complex set of diseases has proven far more elusive than anticipated, yet cancer research has yielded increasingly significant advances in terms of disease outcome. There are now over 10 million cancer survivors in the United States, compared with 3 million in 1971. Death rates from the four most common cancers — lung, breast, prostate and colorectal — continue to decline. In the past 10 years, we have experienced a 10% decline in mortality from cancer. Our progress foreshadows even greater opportunities, because beneath the statistics lies an explosion in our understanding of cancer as a disease process.

We need to evaluate success not only in terms of a mortality end point, but also in terms of illuminating new directions and pathways in understanding cancer as a disease process. The recognized limitations of combination chemotherapy in some major cancers — despite the old paradigm of mortality as the end point. But if we continue to nurture the investment in infrastructure and intellectual capital that we committed to in the United States over three decades ago, our scientific quest for knowledge will ensure that we will eventually see a time when cancers can become manageable, chronic diseases. Moreover, we have an opportunity to further build on this momentum in scientific understanding and undertake initiatives that will yield results at an exponential rate.

Our evolving understanding of cancer as a disease process — including the genetic, molecular and cellular mechanisms — is now providing targets for prevention, detection, elimination and control interventions. This growing knowledge of mechanisms in the cancer cell is paralleled by an expansion of our knowledge of the complex interaction of the cancer cell with its microenvironment and the host. The emergence of powerful technologies is helping to speed up the process of synthesis and integration of our knowledge. Not only will we understand the parts of the puzzle — the oncogenes, tumour-suppressor genes, cytokines, transduction pathways and so on — but we will understand the process of cancer as a disease. Today, the outcomes of cancer research have the power to transform the vision of the National Cancer Act of 1971 into an ambitious but achievable goal: the elimination of the suffering and death due to cancer by 2015.

At the turn of the twentieth century, the likelihood of an individual surviving cancer was zero. Today, two out of three people diagnosed with cancer will be alive 5 years after diagnosis. We can improve that result to three survivors out of every four individuals diagnosed if we just put into widespread practice what we already know to be effective. Based on extrapolation of an exponential growth in our knowledge of cancer, the advent of extraordinary enabling technologies such as bioinformatics and nanotechnology, as well as the strengths of our existing intellectual capital and resources such as the National Cancer Institute (NCI)-sponsored Cancer Centers and clinical trials networks, it is not unrealistic to envision closing the gap in 11 years.

How can we seize the day? In an article in Cell entitled ‘The hallmarks of cancer’, Hanahan and Weinberg describe the transformation of a normal human cell into its malignant counterpart as a small number of molecular, biochemical and cellular traits of ‘acquired capabilities’. They suggest that there are six alterations that drive carcinogenesis: evading apoptosis, self-sufficiency in growth signals, insensitivity to antigrowth signals, tissue invasion and metastasis, limitless replicative potential, and sustained angiogenesis. The implication of this model is that cancer is a defined set of processes controlled by a complex set of mechanisms. Although these acquired capabilities are independent mechanisms, the outcome of the process requires them to be interdependent. Therefore, the process of cancer is vulnerable to a strategy of interventions capable of pre-empting the process.

Pre-emption involves the integration of one or more targeted, mechanistic-based interventions that can prevent the process from developing, and/or detect and predict early disease, thereby allowing elimination and modulation of the virulence of the process. The success of pre-emption depends on our continuing the Discovery, Development and Delivery paradigm at the NCI (Box 1). In the future, we will have annual physical exams that will evaluate the environmental, genetic and lifestyle factors that determine an individuals’ susceptibility and resistance to cancer. Serum proteomic patterns will detect early cancer; changes in gene expression and cell physiology will herald clinically overt disease; and molecular profiles of tumour will determine recipes for targeted therapies. Discovery — the cornerstone of the 2015 goal — will enable us to develop interventions that move from empiricism to rational mechanistic-based interventions that deliver the right treatment, to the right patient, at the right time, for the right reason, with predictable desired outcomes, and with molecular diagnostics that enable real-time confirmation of biological impact. Discovery, Development and Delivery form the construct for progress. Within each of these stages are opportunities for prevention, detection, elimination and modulation of cancer, and they all must be integrated into a seamless continuous process.

To meet our objectives, we must optimize research platforms and enable investigators to work at peak efficiency by nurturing innovation in investigator-initiated research and expanding access to resources, tools and technologies. The NCI has adopted strategic initiatives in bioinformatics, development of innovative cancer interventions, clinical trial implementation, elimination of cancer health disparities, early detection, prevention and prediction of cancer risk, molecular epidemiology, and integrative cancer biology. In each of these areas, we plan to increase and focus resources to integrate infrastructure and foster...
collaborations through networks and consortia. For example, the NCI is creating the Cancer Biomedical Informatics Grid (caBIG; see online links box), an international collaboration to facilitate and enable research teams to share data and pursue new collaborative efforts to accelerate the timeline of conversion of data from information to knowledge (FIG. 1).

This bioinformatics platform will be used to redefine how cancer research is conducted and how data are electronically managed, analysed and shared. This grid will help create and disseminate conversion standards, common tools and a common language. It is being piloted in 51 of the 61 NCI-designated Cancer Centers (FIG. 2).

The global biotechnology/pharmaceutical industry — an unparalleled enterprise — will need to cooperate and partner with academic institutions and government agencies to enable development of combinations of interventions that will substantially change cancer care. These partnerships will undoubtedly drive commercialization paradigms that are new for health, but quite common in other fields where holders of intellectual property and patents must collaborate to drive progress, as in the computer industry. This integration is crucial to accelerating progress against cancer as well as other diseases.

The cost of delivering health care to all in need remains a concern. However, there are already examples in cancer where new molecularly targeted interventions markedly reduce the cost—benefit of treatment. The ultimate success in the fight against cancer will be preventing the initiation of cancer or its progression to a lethal form.

**Progress towards our goal**

**Integrative biology.** Using integrative biology, we aim to understand the extensive remodelling that cells undergo in signalling and transcription networks in response to the biochemical consequences of the genetic lesions that occur during the development of cancer. These processes are not adequately recapitulated using traditional experimental techniques.

Although researchers have begun to develop descriptive mathematical models of cellular processes, models depend heavily on knowledge of enzyme kinetics. For cancer, this approach is too cumbersome because of the large size of the networks to be modelled and the lack of detailed kinetic information on the interactions involved. We need to integrate knowledge in a higher order to understand the complex, interactive, dynamic and spatial relationships of the networks and systems within cancer cells and between cancer cells and their environment. The tumour microenvironment, or stroma, can involve signalling that includes cell–cell binding, cell–extracellular matrix interactions, paracrine/autocrine cytokines, and angiogenesis, tumour proliferation and tumour invasion. The microenvironment can affect drug access, metabolism and resistance, and therefore might be important to developing therapeutic approaches.

This is a discovery process for which specific outcomes are difficult to predict. The molecular signature of a cancer cell provides the foundation, but we now must be able to move beyond the single molecule or pathway. These integrated networks have been determined in yeast as a precursor to studies of even more complex pathways in cancer (FIG. 3).

The NCI’s Integrative Cancer Biology Program (see online links box) is designed to build analytical programs to query existing databases, to integrate the data on gene transcription, protein patterns and post-transcriptional modifications, to establish their relationships to one another, and to facilitate interdisciplinary collaborations to build the predictive models against which to test hypotheses. The traditional course of therapy used to treat tumours is based on using sequential therapeutic regimens after drug resistance arises. Tumours survive because of complex molecular systems and

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**Box 1 | NCI’s Discovery, Development and Delivery continuum**

The National Cancer Institute (NCI) is facilitating a seamless process in the United States for integrating discovery activities, accelerating the development of new interventions and ensuring the delivery of new evidence-based interventions for all cancers and all people in need. The main objectives are shown below.

**Discovery**

- Improve our understanding of the genetic, environmental and lifestyle factors that affect cancer risk.
- Define the interaction between cancer cells and their microenvironment.
- Determine how energy balance interacts with genetic and environmental factors in the cancer process.
- Discover imaging methods, molecular biosensor and imaging-based interventions.
- Identify molecular targets for detection, prediction of risk, treatment and prevention.
- Promote systems biology and integrated oncology.
- Understand the causes of tobacco use, addiction and tobacco-related cancers.
- Determine the fundamental causes of cancer-related health disparities.

**Development**

- Validate molecularly targeted drugs and biological agents for detection, treatment and prevention.
- Develop novel combinations of drugs and regimens that can pre-empt the malignant process.
- Develop imaging and molecular biosensors for use in early detection, diagnosis, and prediction of risk.
- Find strategies to address the clinical, behavioural and societal issues associated with cancer susceptibility.
- Find specific approaches to reduce cancer-related health disparities.

**Delivery**

- Disseminate novel and effective approaches for prevention, early detection, prediction of risk, and treatments to defined, at-risk populations with defined outcomes and measures.
- Deliver molecularly targeted and combination therapies in a context of extracting biological information regarding efficacy.
- Widely disseminate ways to eliminate cancer-promoting behaviours such as unhealthy lifestyles and tobacco use.
- Incorporate symptom management and palliative care into quality-care standards.
- Eliminate disparities in cancer incidence, mortality and access to care.
- Apply the knowledge and experience gained from application of interventions to inform future discovery and development objectives.

Details of the Discovery, Development and Delivery continuum can be found in REF. 32. The annual budget of the NCI is approximately US $4.7 billion.
Scientists at the NCI are using innovative diagnostics, early warning of relapse prevention, early detection, development of emerging technology with potential use in targeted interventions that shut down the primary, secondary or multiple redundant pathways of tumour progression. It requires collaborative research, interdisciplinary researchers, novel bioinformatics and enabling technologies applied in ways that have not yet been tried, but that will be a high priority for the future\(^2\). An understanding of the complex system of interactions between the cancer cell and its microenvironment and the roles of chemical carcinogens, and known and unknown infectious agents, might well lead to new interventions for a range of cancers.

**Enabling technologies.** Nanotechnology is an emerging technology with potential use in prevention, early detection, development of innovative diagnostics, early warning of relapse and design of effective and safe therapeutic modalities\(^3\). Scientists at the NCI are using nanotechnology in molecular profiling to examine chromosomal alterations and changes in protein levels following exposure to carcinogens. For example, using nanotechniques, scientists have found that a change in the levels of proteins, following alteration of their gene precursors by the process of methylation, is associated with the development of cancer. Researchers are developing carbon nanotubes, nanowires, microcantilevers and quantum dots through the NCI’s Innovative Molecular Analysis Technologies Program (BOX 2 and see online links box). These tiny molecular sensing tools can be used to characterize interactions between proteins, perform molecular classification of tumours, enable high-throughput screening and predict therapeutic efficacy.

Nanotechnology can provide prevention interventions, for instance, by providing multifunctional micro/nanocarrier delivery vehicles to enable the oral administration of cancer-preventing nutraceuticals. Similar technologies could be used for non-invasive administration of reagents through other routes, for example, the buccal mucosa. Some of these interventions are nearing investigation in clinical studies.

For detection, screening and monitoring, nanodevices could be engineered for injection and subsequent extraction of proteins from the systemic or local circulation. The nanoparticles can absorb and harvest proteins or low-mass fragments, and separate the specimen of interest based on mass, charge, conformation, affinity or other characteristics. Early diagnosis and early warning of relapse are two areas in which nanotechnology can make a significant impact on the pre-emption of cancer.

**Proteomics:** Following closely on the heels of completion of the sequencing of the human genome, proteomics has evolved into a research area with considerable potential, especially for the early detection and prediction of cancer\(^7\). Novel high-throughput reverse-phase protein arrays are now used to quantify and analyse changing patterns in hundreds to thousands of signalling proteins simultaneously. The surface-enhanced laser desorption and ionization (SELDI) technique enables the analysis and profiling of complex protein mixtures from sera and isolated cells. It is used to generate patterns of low-molecular-weight proteins and peptides of interest. We have already seen progress in the development of new diagnostic approaches that measure and analyse changes in protein patterns.

Some of the early studies in this field were of ovarian cancer. When ovarian cancer is detected at an early stage, approximately 95% of patients survive for at least 5 years after undergoing conventional surgical and chemotherapeutic treatment. However, more than 80% of ovarian cancer cases are detected at highly metastatic stages, when the 5-year survival rate is less than 40%. Scientists at the NCI and the Food and Drug Administration (FDA) have entered into an unprecedented partnership to accelerate progress in this area. Focusing on the diagnosis of ovarian cancer, using proteomic spectra generated by high-resolution mass spectroscopy, researchers were able to develop a bioinformatics algorithm that segregated cancer from non-cancer. They report patterns that showed 100% sensitivity and 100% specificity in blinded validation tests (68/68 patients with cancer, including 18/18 patients with stage I disease and 43/43 apparently healthy individuals\(^8\)).

The same research team recently reported that prostate proteomic patterns correctly predicted 36 of 38 patients with prostate cancer, whereas 177 of 228 patients were correctly classified as having benign conditions. If validated in future studies, serum-proteomic-pattern diagnostics might be of value in deciding whether to perform a biopsy on a man with an increased level of prostate-specific antigen\(^6\). In addition, using a mouse model that recapitulates the full spectrum of human pancreatic intraepithelial neoplasias (PanINs), the investigators identified a
The promise of early detection is to find cancer while it is still localized and potentially curable. Tests that predict precursor lesions of in situ disease hold the greatest promise. With the advent of new technologies, including transcript analysis, genomic-based DNA methods and proteomics, the opportunities for identifying biomarkers for cancer are profound. A biomarker-discovery programme is in development at the NCI using mouse models to minimize environmental and genetic variation in peptide/protein measurements, to standardize biospecimen collections and to ensure reproducible peptide/protein preparations for unique gene and pathway identification. The genomic- and proteomic-based markers developed using this schema would be validated against patient specimens and, in concert with the Interagency Oncology Task Force, could then be used to generate a pipeline of new diagnostics. This programme could potentially set the standards for future methods of identification and validation of biomarkers for cancer and other diseases over the next few years.

Gene profiling. Development of microarray technology and its application to the field of integrative cancer biology will undoubtedly reveal which genes and proteins are either overexpressed or underexpressed in tumours. For example, investigators hypothesized that diffuse large B-cell lymphoma (DLBCL), the most common subtype of non-Hodgkin’s lymphoma, might include several molecularly distinct diseases and that the observed variability in clinical outcome is the result of underlying molecular heterogeneity. Two subtypes of DLBCL were identified using gene profiling with cDNA micorarrays customized to contain cDNA clones enriched with genes selectively expressed by lymphocytes to regulate cell function, known as the lymphochip. When correlated with clinical data, the two disease subtypes were found to follow different clinical courses.

These studies are among the first to establish the principle that gene-expression profiling and comprehensive genomic analysis of the array of signalling genes can be used to define cancer at the molecular level, thereby providing clinically relevant prognostic information that can be used to determine treatment regimens. This technology can also be expanded to detect the manifestations of genes amplified and deleted in tumours. Robotic-enabled sequencing and further validation of this technology will accelerate a comprehensive molecular classification of all cancers. This accomplishment will be of enormous clinical use, particularly when used to predict response to specific therapeutic interventions.

Although many methods could be used to deliver molecular diagnosis and prognosis to patients with lymphoma in the near future, one promising and cost-effective alternative is a custom-designed ‘diagnostic microarray’ that measures the expression of hundreds of key diagnostic and prognostic genes in a tumour biopsy sample. However, as new therapies are tested in clinical trials, it will be advantageous to perform whole-genome expression profiling on patient biopsy samples to create a molecular predictor of response to the new therapy. This approach constitutes ‘a molecular diagnosis cycle’ that will ensure that patients will receive optimal therapies based on the molecular features of their tumours.

Molecularly targeted therapies. The establishment of molecular-based markers confers the invaluable clinical advantage of identifying molecular pathways that can be selectively targeted for intervention. By way of example, the causative event leading to chronic myelogenous leukaemia (CML) has been identified as a chromosomal translocation that results in deregulation of the tyrosine kinase activity of the abnormal BCR-ABL chimeric protein. Understanding the biological mechanisms of CML not only provided the opportunity to screen for the translocation to identify affected individuals, but also identified a target for
Perspectives

...the cause of clinical resistance to imatinib and to identify a drug that can overcome that resistance. This demonstrates that today if we understand the mechanisms involved it will not take 10 years to discover drugs. Imatinib has also been shown to be effective against gastrointestinal stromal tumours in both adult and paediatric patients.

Results from early clinical trials with gefitinib — a small-molecule inhibitor of the epidermal growth factor receptor (EGFR) — indicated that it would be active against non-small-cell lung cancer (NSCLC), a disease that often has overexpression of EGFR and for which chemotherapy is not very effective. However, large randomized trials only showed responses in about 10% of patients with NSCLC. Investigators have recently found that the clinical response to gefitinib occurs in patients with NSCLC expressing mutations in EGFR. So, a drug that is seemingly a disappointment can be turned into a success when we apply it rationally using specific target identification, drug design and drug delivery. In the past, combination chemotherapy was based on the rationale of combating resistance to therapy. The strategy of targeted combination therapies is now based on exploiting susceptibility. The portfolio of 'targeted therapies' is already expanding, with FDA approval of bortezomib for relapsed and refractory multiple myeloma, and cetuximab and bevacizumab for advanced colorectal cancer (Table 1).

**Imaging.** In nearly all areas of cancer research, especially in the diagnosis of cancer and in real-time monitoring of the effectiveness of cancer therapies in vivo, imaging has a crucial role. The In vivo Cellular and Molecular Imaging Centers (ICMICs; see online links box) bring together experts from diverse scientific and technological backgrounds to conduct multidisciplinary research on cellular and molecular imaging in cancer. A broad array of imaging modalities such as high-energy-force magnetic resonance imaging (MRI), nuclear imaging prototypes, positron-emission tomography (PET), optical imaging and ultrasonography are being intensely developed. Researchers are using their expertise in MRI, PET and optical imaging to understand cancer vascularization, invasion and metastasis — knowledge that can be applied to monitoring therapeutic strategies in real time.

ICMIC researchers recently created a biosensor that slows down the activity of drugs that block ATP-binding pockets. Advanced high-throughput screening technologies of chemical libraries identified a lead compound for specific inhibitors to BCR–ABL kinase activity. Based on this screen, the drug imatinib was developed and has proven to be a highly effective therapy against CML with few debilitating side effects. It is now the standard therapy for newly diagnosed patients with early, chronic-phase disease and provides proof of principle that we are in the era of molecularly targeted therapies for cancer. A recent report identified specific mutations that led to resistance to imatinib in patients with CML, by keeping the target enzyme in an active state. Using technologies such as small-molecule screens, crystallography and imaging, a less selective inhibitor that could bind to these active targets was identified. The drug, BMS-354825, was effective against 14 of 15 imatinib-resistant CML mutations tested and is now in Phase I trials. This study used our understanding of the genetic, biochemical and structural characteristics of CML to identify...
Technologies supported through the Innovative Molecular Analysis Technologies Program have many applications, including those shown below.

- Detecting alterations and instabilities of genomic DNA.
- Measuring the expression of genes and gene products.
- Analysing and detecting gene and/or cellular products, including post-translational modifications and function of proteins.
- Identifying and characterizing infectious agents in cancer.
- Assaying the function of key signal-transduction networks involved in cancer.

nanoparticles with magnetic properties that ‘relax’ the activity of nearby molecules enough so that their activity can be captured by MRI or nuclear MRI. These sensors have also been shown to work well in a high-throughput assay format. Furthermore, these biosensors can be used to detect molecular targets of cancer with little or no toxicity and can be modified to be internalized by cells.

The NCI conducts comparative imaging studies to answer the question of screening modality effectiveness. These large-scale trials definitively evaluate technologies and outcomes in specific patient populations to establish standard-of-care guidance. The Digital Mammography Imaging Screening Trial (see online links box) is a large-scale effort to compare the diagnostic power of digital mammography with conventional, film-based mammography to detect breast cancer. The National Lung Screening Trial (see online links box) will determine whether lung cancer screening using low-dose spiral computed tomography in high-risk populations reduces mortality from this disease compared with standard X-ray screening.

Models of human cancer. In 1999, the NCI confronted the crucial need for well-designed, thoroughly characterized model systems to inform basic, clinical, epidemiological and translational cancer investigations by inaugurating the Mouse Models of Human Cancers Consortium (MMHCC; see online links box). The programme involves manipulation of the germline of laboratory mice, coupled with an unprecedented store of data on genetic alterations in human cancer and rapid acquisition of human and mouse genomic sequences (Box 3).

The MMHCC is based on an integrative, interdisciplinary systems approach to cancer research supported by bioinformatic underpinnings that integrate descriptive cancer model information with comparable human disease data. The Cancer Model Organisms Database, Cancer Images Database and Cancer Array Informatics database house the core descriptive data about all types of cancer models, not only mice. Because any researcher might submit data, this information store reflects the experience of the community of users who explore how well model systems inform human cancer therapy, prevention, early detection, imaging and population science. One resource implemented with the help of the MMHCC is the NCI Mouse Repository (see online links box), established to provide fully developed mouse cancer models and strains that are used to derive models, free of charge, to the worldwide scientific community. This service furnishes researchers with cancer-prone models that not only accurately mimic human cancers, but are supporting unprecedented discoveries about cancer.

Prevention. Advances in identifying key genetic, environmental, socioeconomic and behavioural determinants underlying the aetiology of cancer provide us with the opportunity to develop approaches to predict the risk of certain cancers and to prevent their occurrence. A strategic priority of the NCI is the prevention and early detection of cancer, and prediction of cancer risk. The NCI has created a new consortium of research centres to conduct early-phase cancer-prevention clinical trials. Six institutions will undertake studies to assess the cancer-preventive potential of new agents over the next 3 years15. The consortium members will design and conduct early-phase clinical trials, characterize the effects of agents on end points associated with cancer development and develop scientific insights into the mechanisms of cancer prevention using a network of institutions to conduct the studies. Cyclooxygenase (COX) inhibitors, statins, tea polyphenols and soy isoflavones are among the agents likely to be studied.

Prophylactic vaccines that stimulate the immune system to attack cancer-causing viruses and prevent viral infection given to healthy individuals are now in late stages of development. For example, human papilloma virus type 16 (HPV-16) infection is a causative factor of cervical neoplasia, so a prophylactic HPV-16 vaccine to prevent cervical neoplasia was tested in a double-blind study in which 2,392 young women were randomly assigned to receive placebo or HPV-16 virus-like-particle vaccine. The incidence of infection was 3.8 per 100 years at risk in the placebo group and 0 per 100 years in the vaccine group, showing the effectiveness of the vaccine19.

The field of chemoprevention is making enormous gains. Agents already in use include selective oestrogen–receptor modulators such as tamoxifen — to reduce the incidence of breast cancer in high-risk women — and other hormonal agents. Tamoxifen also works effectively for approximately 5 years in oestrogen-receptor-positive breast tumours to reduce the risk of recurrence. However, over longer periods of time, tamoxifen therapy loses its effectiveness. Based on our knowledge of other biochemical mechanisms to inhibit the oestrogen signalling pathway, another compound, letrozole, has been developed that acts to inhibit oestrogen synthesis and increase the disease-free survival rates in postmenopausal women following 5 years of tamoxifen therapy20. This example provides further evidence that we are beginning to manage cancer by the application of several pre-emptive interventions.

Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and COX2-selective inhibitors (COXIBs) such as celecoxib suppress the activity of COX2, an enzyme involved in arachidonic-acid metabolism, inflammation and cancer progression. Several NSAIDs and COXIBs have also been shown to have COX2-independent activities, such as suppression of the AKT signalling pathway, that might contribute to their anti-cancer effects21. NSAIDs have been associated with a reduction in the incidence and mortality of colorectal cancer. In an NCI-sponsored prevention trial, researchers reported that the COXIB celecoxib significantly reduced the number of colorectal polyps in patients with familial adenomatous polyposis, an inherited disorder that is associated with an almost 100% risk of colorectal cancer22. COX2 inhibitors are also in trials for other cancer types.

Cancer prevention through behaviour modification can be an extraordinarily powerful way to decrease cancer incidence and mortality; this is especially true because 30% of all cancer deaths are attributed to tobacco use23. Forty years after the first United States Surgeon General’s Report on Smoking and Health, tobacco use remains the nation’s leading cause of preventable premature death. An estimated 45.8 million American adults (22.5%) are current smokers; each year...
smoking causes one in five (440,000) deaths in America. Tobacco use is a global epidemic, and the burden of disease caused by tobacco is shifting to economically developing nations. Worldwide, lung cancer is the leading cause of death due to cancer, responsible for 25% of all cancer deaths. Preventing the young from initiating tobacco use remains a high priority, but we also know that helping those who smoke to quit would have an unparalleled impact in defeating the onset of cancer. As a result, the NCI and the United States Centers for Disease Control and Prevention are supporting a network of smoking-cessation helplines so that all smokers in the United States have free access to effective help to stop smoking. The continuing challenge to the medical, scientific and public-health communities is to formulate and implement evidence-based interventions to prevent cancer. The NCI is committed to eliminating the burden of tobacco addiction as a key component to reduce cancer suffering and death.

As we learn more about the molecular mechanisms of the aetiology and progression of cancer, we will be better able to guide and advise patients about individual lifestyle changes, including future pharmacological management.

**Genetic epidemiology:** NCI will further promote interdisciplinary collaboration through “cohort consortia.” For example, the Consortium of Cohorts is an international collaboration of 23 independently supported databases of population cohorts totalling 1.2 million individuals. These individuals are being followed for cancer incidence and mortality. The investigators involved have collected blood from most of the cohorts and buccal cells from some, along with extensive information on known or suspected cancer risk factors for the individuals. These consortia provide an integrative framework for nested case–control studies of specific cancers to systematically evaluate biomarkers of susceptibility and early-stage diagnosis. Nested case–control studies are studies that compare the cancer cases that develop in the cohort to a sample of individuals of similar age, race and gender who did not develop cancer. An example of such an effort is the Cohort Consortium for Breast and Prostate Cancer, which developed the hormone-related gene variants programme to identify genes that might influence susceptibility to hormone-related breast or prostate cancer and to develop ways to share data across genome and genotyping centres. In the case of prostate cancer, the findings will be applied to separate virulent from indolent disease so that early prostate ablation can be advised only when it is the appropriate treatment course.

NCI also supports the development of case–control consortia for epidemiologists studying less common cancers, such as the InterLymph Consortium studying the genetic basis for non-Hodgkin’s lymphoma, and another focusing on brain cancer. In addition, several scientists interested in familial cancer have formed an international family-based consortium to identify highly penetrant genes and environmental modifiers of inherited risk. Using case–control and familial studies, the convergence of epidemiological and molecular approaches has begun to yield important insights and opportunities that will lead to a fundamental understanding of the numerous phenomena involved in cancer causation, including the role of environmental and genetic factors.
A new cancer-research paradigm

The new research paradigm at the NCI hinges in large part, depend on the identification of risk. The future of cancer management will, enable scientists to quantify and predict the ability to pool data sets will better "strategic inflection" , which has the potential to change the world38. The world of cancer research will change with greater dependence and use of enabling technologies and the ever-increasing pace of discovery.

If we reflect on the momentum in RNA interference (RNAi) research, we get a glimpse into how rapid the acceleration of progress is. The crucial role that RNAi has in controlling endogenous and exogenous gene expression was first promoted only 6 years ago, with the characterization in Caenorhabditis elegans of a group of highly conserved pathways that require double-stranded RNA or a double-stranded RNA structure39. Studies of RNA-silencing that inhibits gene expression, depending on the nature of the RNA–RNA interaction, represent a paradigm for the link between basic research, technology development and clinical application39. The physiological roles of RNAi have been rapidly adopted and are now being applied on a whole-genome scale. Few new molecular biology techniques have advanced to realize practical application as rapidly as RNAi. In a recent review article by Duxbury and Whang41, the authors summarize the mechanisms underlying RNAi in mammalian cells and provide criteria for selection of suitable target-gene sequences, defining the structural characteristics of effective short interfering RNAs. Excitingly, RNAi is likely to have almost immediate clinical relevance in accelerating the process for identification and characterization of new drug targets and in the validation of drug-target interactions.

Increasing emphasis on the integration of data and information in an effort to understand the networks and systems of cancer will call for crucial improvement in collaborations and partnerships that are based on using common standards, methods of validation and communication in real time. There will be a greater need to expand interdisciplinary interaction between physical scientists and life scientists. The world will also change for patients — their diagnosis and prognosis will be more accurate and their treatments will no longer be based on statistical probability, but on molecular profiles and gene arrays.

We have a clear destination, an era in which the suffering and death due to cancer have been eliminated. And we have established a course for reaching this destination that depends on accelerating the progress of cancer research through the Discovery, Development and Delivery continuum of new effective means to disrupt the cancer process. This is a journey that will require our most advanced technology, an increased commitment of resources and innovative partnerships. But, most importantly, this is a journey we must make together.

Andrew C. von Eschenbach is at the National Cancer Institute, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892, USA.

e-mail: avonesch@mail.nih.gov
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A novel pancreatic mouse model40

Activation of Kras at physiological levels in progenitor cells of the mouse pancreas induces ductal lesions that recapitulate the full spectrum of human pancreatic intraepithelial neoplasias and, at low frequency, progress spontaneously to invasive and metastatic adenocarcinomas. The animals with early lesions also have an identifiable serum proteomic signature. A significant advance to overcoming the challenge of identifying interacting genes that contribute to human susceptibility to cancer involves the use of whole genome scans of interspecific Mus musculus/Mus spretus backcrosses. Other methods to define epistasis are very labour-intensive and time-consuming, and results from these strategies have been limited.

A recombination method for generating conditional knockout mutations37

A key limitation for generating effective mouse cancer models with tissue- or temporal-specific inactivation of a gene is the difficulty and time it takes to make a targeting vector. Now there is a newer and much simpler approach that uses homologous recombination in Escherichia coli to construct the often very elaborate targeting vectors. This novel mouse engineering strategy involves deriving strains with hypomorphic alleles of tumour suppressors. A hypomorphic series couples dose of Pten to a particular prostate progression stage; analysis of downstream targets can lead to improved definition of appropriate interventions for each disease stage.

A novel lung cancer mouse model33

The investigators developed a new model of lung adenocarcinoma in mice harbouring a conditionally activated allele of oncogenic Kras. This strategy is a significant advance over previous transgenic approaches for studying tumour initiation and progression, because it more closely mimics spontaneous activation of oncogenes and allows control of the timing, location and multiplicity of tumour initiation. In this case, the strategy also revealed that a new cell type contributes to lung adenocarcinoma development.

A genome-scanning method of interspecific backcross mice44

A significant advance to overcoming the challenge of identifying interacting genes that contribute to human susceptibility to cancer involves the use of whole genome scans of interspecific Mus musculus/Mus spretus backcrosses. Other methods to define epistasis are very labour-intensive and time-consuming, and results from these strategies have been limited.

A model of oncogenic RAS and AKT signalling35

One role for engineered cancer models is to generate novel approaches to therapy. Using retroviral gene transfer to coordinately activate RAS and AKT in gial progenitor cells, the authors verified that both are required for the development of gliomas, but not because of an effect on transcription; the pool of mRNA associated with polysomes (where protein synthesis occurs) is substantially and differentially altered, identifying translation regulation as a therapeutic target.

A PTEN mutant series36

This novel mouse engineering strategy involves deriving strains with hypomorphic alleles of tumour suppressors. A hypomorphic series couples dose of Pten to a particular prostate progression stage; analysis of downstream targets can lead to improved definition of appropriate interventions for each disease stage.

**Box 3 | Advances from the Mouse Models of Human Cancers Consortium**

The new research paradigm at the NCI hinges in large part, depend on the identification of risk. The future of cancer management will, enable scientists to quantify and predict the ability to pool data sets will better "strategic inflection" , which has the potential to change the world38. The world of cancer research will change with greater dependence and use of enabling technologies and the ever-increasing pace of discovery.

If we reflect on the momentum in RNA interference (RNAi) research, we get a glimpse into how rapid the acceleration of progress is. The crucial role that RNAi has in controlling endogenous and exogenous gene expression was first promoted only 6 years ago, with the characterization in Caenorhabditis elegans of a group of highly conserved pathways that require double-stranded RNA or a double-stranded RNA structure39. Studies of RNA-silencing that inhibits gene expression, depending on the nature of the RNA–RNA interaction, represent a paradigm for the link between basic research, technology development and clinical application39. The physiological roles of RNAi have been rapidly adopted and are now being applied on a whole-genome scale. Few new molecular biology techniques have advanced to realize practical application as rapidly as RNAi. In a recent review article by Duxbury and Whang41, the authors summarize the mechanisms underlying RNAi in mammalian cells and provide criteria for selection of suitable target-gene sequences, defining the structural characteristics of effective short interfering RNAs. Excitingly, RNAi is likely to have almost immediate clinical relevance in accelerating the process for identification and characterization of new drug targets and in the validation of drug-target interactions.

Increasing emphasis on the integration of data and information in an effort to understand the networks and systems of cancer will call for crucial improvement in collaborations and partnerships that are based on using common standards, methods of validation and communication in real time. There will be a greater need to expand interdisciplinary interaction between physical scientists and life scientists. The world will also change for patients — their diagnosis and prognosis will be more accurate and their treatments will no longer be based on statistical probability, but on molecular profiles and gene arrays.

We have a clear destination, an era in which the suffering and death due to cancer have been eliminated. And we have established a course for reaching this destination that depends on accelerating the progress of cancer research through the Discovery, Development and Delivery continuum of new effective means to disrupt the cancer process. This is a journey that will require our most advanced technology, an increased commitment of resources and innovative partnerships. But, most importantly, this is a journey we must make together.