

The University of Texas M. D. Anderson Cancer Center
Tobacco Funds - Programs and Budget
FY 2000-2001 Biennial

The University of Texas M. D. Anderson Cancer Center is pleased to present estimated budgets for projects which will be funded from the tobacco settlement funds generously appropriated for the 2000-2001 biennium. As these projects develop, funds may be shifted to meet unanticipated needs, and we understand that unspent funds initially budgeted for FY '00 will be carried forward to FY '01. We hope that future support from the state will enable us to continue and even expand these research and outreach initiatives. They represent a comprehensive and aggressive attack on tobacco-related cancer.

LUNG AND ORAL CANCER

Overview: Tobacco-related cancers of the oral cavity and lungs are a major health problem in Texas and throughout the United States today. The cure rate is only 14% for lung cancer, and less than 50% for oral cancer. Despite major efforts, these rates have not changed significantly in the last twenty years, but we have hope for change based on many exciting new laboratory findings. In one area, basic research has led to exciting new discoveries in the field of molecular and genetic epidemiology. This research may lead to a better understanding of why one smoker develops cancer and another doesn't. It may even help us predict which individuals are at highest risk and, therefore, candidates for novel prevention strategies.

***Purpose:** This program is designed to develop new "targeted" therapies through a better understanding of the biology of carcinogenesis. Currently, cancer patients who receive chemotherapy suffer many side effects because the treatment affects normal tissue and cancer cells alike. New basic research findings are beginning to allow us to detect the subtle molecular differences between cancer cells and healthy cells. By focusing on these differences, we hope to create targeted therapies that will affect cancer cells but not normal tissue. This will allow us to "tailor" cancer treatment, delivering more effective therapy with fewer side effects.*

The implementation of "Novel Targeted Approaches to Lung and Oral Cancers" will help us to:

- Increase our understanding of the biologic processes involved in lung and oral cancer development to enable the design of innovative methods of treating and preventing lung and oral cancer.
- Discover and develop novel agents aimed at specific molecular targets to interfere in the formation and spread of cancer without harming healthy tissue.
- Expand and improve our existing infrastructure to allow us to carry out state-of-the-art translational research in the treatment and prevention of lung and oral cancer.

1. Novel Agents for Lung and Oral Cancer Chemoprevention and Therapy This project will seek to develop novel agents through research using cells in culture and animal models. We will evaluate novel synthetic retinoids, novel triterpenoids, cyclooxygenase inhibitors, phenyl acetate, phenyl butyrate, tributyrin, and antiestrogens as single agents and in combination. Agents will be evaluated in cell culture systems to examine inhibition of cell proliferation, induction of differentiation, or induction of cell death both singly and in combination. Researchers will evaluate the most effective agents *in vivo* using systemic and localized (e.g., inhalation of liposomal aerosolized agents) delivery.

2. Molecular Diagnostics of Oral Cancer This program will establish a gene expression platform to characterize the most consistent alterations in oral cancers; verify these alterations and prepare them for analysis as arrays on microchips to define profiles for early detection and therapy assessment; and, establish a robust infrastructure and instrumentation for procurement, analysis, and informatics.

3. Protein Markers for Lung Cancer Detection and Risk Assessment High-throughput technologies will be used to identify potential markers of lung cancer development. We will establish differential protein or peptide profiles in the serum of lung cancer patients and normal controls using the novel SELDI ProteinChip™ technology; identify proteins that are expressed differentially in bronchial and oral epithelial cells from lung cancer patients and

“healthy” smokers; and then use these protein profiles to identify potential markers for the early detection of lung cancer.

4. Biomarker Modulation for Chemoprevention Trial Biomarkers for cancer risk will be identified and their modulation monitored during therapy. We will elucidate mechanisms of genetic instability, regulation of clonal outgrowth, and the consequences of upstream genetic and epigenetic changes. Biomarkers of cancer risk from specimens of normal, premalignant, and cancer tissue, will be identified and findings integrated into clinical research programs. Biomarker modulation and reversal of premalignant lesions will be correlated with chemopreventive treatment.

5. Molecular Imaging for Early Detection The quality of diagnostic imaging for detection of early lung cancer will be improved by: a) increasing the sensitivity and specificity of spiral CT diagnostic imaging technology; b) developing functional imaging to observe the characteristics of tumors and the effects of therapy; and, c) establishing a robust infrastructure to rapidly assess new molecular imaging techniques.

6. Predictive Markers and Modulation of Response to Radiation This program will identify biological markers to predict tumor response to radiotherapy by evaluating biomarkers including EGFR, COX-2, E-cadherin, β -catenin, Ki-67, p53, and microvascular density in tumor specimens from 973 patients. Assay results will be correlated with the clinical outcome of these patients to establish the predictive power of individual biomarkers; development of combined therapeutic strategies based on these predictive markers.

7. Oral Cancer Gene Discovery Define genes regulating oral cancer behavior and investigate their mechanism of action. Focusing on two recently discovered genes, NJAC and headpin, investigate gene product antibodies, stable transfectants expressing these genes, and analysis of tumor specimens for expression of these gene products. We will develop targeted delivery approaches for peptide delivery of chemotherapy in oral cancer, and investigate the use of tissue immunofluorescence for identification of premalignant and malignant lesions.

8. Identification and Analysis of Genetic Events in Lung Carcinogenesis This project will identify genes contributing to lung cancer and develop targeted treatment strategies through: a) analysis of tumor suppressor and apoptosis functions for 3p suppressor genes at 3p21.3; b) development of targeted vectors for selective delivery of pro-apoptotic genes to tumor cells *in vivo*; c) identification of critical downstream pathways related to the expression of these genes for possible use as genetic targets for prognosis, diagnosis, and treatment, and correlate these parameters with clinical profiles and outcomes.

9. Chemoprevention of Lung and Oral Cancer Development of novel chemopreventive strategies for oral and lung cancer will be enhanced by targeting chemoprevention for high risk cohorts identified through quantitative risk models. New agents, e.g., triterpenoids, COX-2 inhibitors, GTE, 4HPR, CD-437, cell cyclin inhibitors, FTI, etc., will be evaluated through Phase II biomarker-integrated chemoprevention trials. We will develop innovative local application of retinoids through aerosolized delivery.

10. Biostatistics for Translational Research

We will develop innovative statistical methods for the design and analysis of translational studies of lung and oral cancer; establish efficient and reliable procedures for measuring biomarkers, and develop new and effective graphic tools for displaying vast amounts of biomarker data obtained from high-throughput genomic and proteomic screenings. Quantitative risk assessment models will be developed to identify high-risk individuals.

11. Infrastructure Support – Clinical and Administrative The infrastructure for the conduct of translational research will be strengthened. Funds will be used to purchase new and replacement equipment and invest in important new technologies. Specialists (e.g., lung cancer research pathologist, etc.) whose expertise is necessary for the conduct of these projects will be recruited. Provide administrative support to project investigators as needed, and report program results on a timely basis.

FY 2000-2001 Biennial Budget for Lung and Oral Cancer Programs

	<u>FY '00</u>	<u>FY '01</u>
Faculty Salaries	\$1,000,000	\$1,000,000
Other Salaries	750,000	750,000
Equipment, Supplies, start-up costs	<u>600,000</u>	<u>1,000,000</u>
Total	\$2,350,000	\$2,750,000

PALLIATIVE AND REHABILITATIVE CARE

Overview: The majority of patients with lung cancer and a significant number of those with other tobacco related cancers will die of progressive disease. These patients will develop a number of devastating physical and psychosocial symptoms before death, including pain, cachexia/anorexia, dyspnea, and asthenia. One of the main barriers for appropriate care of these patients is the lack of research on the mechanisms, assessment and management of these major symptom complexes. Another major barrier is the limited education available to physicians and other health care professionals. In particular, there is evidence that minority patients and those in rural areas receive more limited care. A third major barrier of access to palliative care is the current structure of the health care system and the lack of seamless transition from tertiary cancer care institutions into the community.

Purpose: *The goal of this research program is to address these three major barriers to patient access to appropriate palliative care and rehabilitation. A number of specific research projects have been designed in order to address each of these major issues for the specific needs of patients with tobacco related cancers.*

1. Strategies for Rehabilitation in Patients with Advanced Tobacco Related Cancers

Patients with lung, esophageal, and head and neck cancers develop profound physical and mental fatigue. The traditional approach to this overwhelming fatigue has been to advise patients to decrease their level of activity in order to match their lack of energy, and to apply techniques for energy conservation. Recent evidence suggests that at least part of the lack of activity and sensation of fatigue in patients is due to de-conditioning, and some of the symptoms can be partially reversed by an approach based on increased activity, exercise and increasing aerobic capacity. This project will assess whether a personalized program of increased physical activity is capable of improving both subjective and objective measurements of fatigue in patients with advanced tobacco related cancers as compared to a more traditional and conservative approach, or a group receiving neither of these interventions. The main outcome of the study will be exercise, tolerance, fatigue, and other symptoms, such as pain or dyspnea, and quality of life.

2. Therapeutic Interventions for Cachexia in Tobacco Related Cancers

The traditional view of cancer cachexia considered this to be the result of increased energy consumption by the tumor and profound anorexia. An emerging view considers that cancer cachexia results from a profound metabolic imbalance related to the combination of tumor by-products and host cytokines. Our group has developed the methodology to assess both the objective and subjective effects of different interventions on cancer cachexia. This project will conduct randomized control trials to determine if these agents are capable of decreasing the metabolic abnormalities associated with malignancy, improving the nutritional status, and most importantly, improving appetite, energy and sensation of well-being in advanced tobacco related cancer.

3. The Assessment and Management of Dyspnea in Patients with Lung Cancer

Dyspnea is a frequent and devastating symptom in patients with advanced lung cancer. Unfortunately, limited research has been conducted on its mechanism and potential treatments. Cancer patients are not capable of tolerating these aggressive exercises (e.g., treadmill) used to test other populations, mostly due to other co-existing problems such as pain, asthenia, or cachexia. This project will seek to develop reliable bedside techniques that could be used for appropriate assessment of dyspnea. The main outcome of these trials will be subjective dyspnea as well as objective measurements of blood gases and respiratory effort.

4. The Impact of Telemedicine and Internet on the Delivery of Palliative Care and Professional Education for Patients in Rural Areas and Small Communities

The majority of patients with advanced cancer in small communities and rural areas have limited or no access to palliative cancer care. Their physicians and other health care professionals have limited training and are exposed to a small number of cancer deaths per year. In recent years, both telemedicine and the Internet have dramatically improved the access of these health care professionals to information and communications. This process is still time consuming and the quality of the information is not always reliable. This project will develop a patient-based training program for the delivery of palliative care in rural areas and small communities. This specially designed program, as well as a regular Internet based consultation program, will be made available to the rural physicians of patients discharged from UT MDACC. Randomized control trials will then assess the impact of the personalized mentoring program by UT MDACC faculty on the patterns of care received by patients in these rural areas and small communities. In addition, both the knowledge and practice patterns of physicians who receive this training will be assessed and compared to those who did not receive training.

5. The Development of Evidence-Based Practice Guidelines for the Delivery of Palliative Care in Tobacco Related Cancers

Evidence based practice guidelines are useful to insure appropriate delivery of surgical, medical and radiation oncology treatment for cancer patients, but such guidelines do not exist for the assessment and management of the main symptoms in end of life care. This project will focus on developing evidence based practice guidelines and to include them as part of an information program, and dissemination as a care path. The impact of such guidelines on patterns of physician prescription and assessment will be monitored as a main outcome of the evidence based guidelines.

6. Health Services Research and Access to Palliative Care Services for Patients in Different Regions of Texas

Cancer patients receive most of their care in the community as outpatients. However, their access to palliative cancer care in the community is limited. Less than ¼ of patients have access to hospice care for approximately one month before death. Access to palliative cancer care in hospitals is also limited. The purpose of this project is to study the patterns of care of patients who die of cancer in different regions of the State of Texas. Specific emphasis will focus on the access to health care resources, utilization, and place of death. Additionally, cost of care and level of health care coverage will also be assessed. This will allow for the establishment of plans for integrated community palliative care programs and will increase our knowledge of the health services utilization by advanced cancer patients.

7. Assessing the Symptoms of Tobacco-Related Cancers

Optimal management of cancer-related symptoms is dependent on frequent and accurate assessment and communication between patients and their health care providers. This project will test an interactive voice response telephone system that monitors patients' symptoms at their home, and notifies their health care team when symptom severity needs intervention. This new system has the potential of providing for early management of severe symptoms, possibly saving patients from additional hospitalization or unnecessary visits to emergency rooms. Lung cancer patients at both M. D. Anderson and the LBJ Hospital will participate.

8. The Development of Models for Pain and Other Symptoms in Advanced Cancer

Pain remains one of the most feared and poorly managed consequences of cancer. In addition, cancer treatment itself can cause severe pain, yet no models of cancer pain currently exist. Conventional pain models are based on the concept of “nociceptive” pain, due to tissue trauma or inflammation, or “neuropathic” pain, due to direct nerve damage. It is thought that cancer induces both types of pain, and possibly pain caused by unique mechanisms and mediators. Since new, more effective treatments are developed using experimental paradigms, it is imperative that suitable models of cancer pain exist. Using readily available resources, we plan to develop paradigms to test the following hypotheses: a) Cancer pain is produced by unique mechanisms distinct from neuropathic and nociceptive pain; b) These mechanisms can be modeled in an animal system; and, c) More effective analgesics for cancer-related pain can be developed using these models.

After behavioral characterization is completed, we will begin to define the signal transduction systems used to encode cancer pain and the effects of conventional analgesics on these systems. This will involve neuroanatomical and biochemical characterization of signals in relevant brain and spinal cord systems. These mediators include neuropeptides and their receptors (substance P, CGRP, endogenous opioids), second messengers (PKA, PKC), and signaling cascades (i.e., MAP kinases). Tumor-related factors (i.e., TNF- α) may also cause pain, so relevance of these signals will also be established.

FY 2000-2001 Biennial Budget for Palliative and Rehabilitative Care Programs		
	<u>FY '00</u>	<u>FY '01</u>
Faculty Salaries	\$ 242,100	\$ 242,100
Other Salaries	668,564	668,564
Equipment, Supplies, start-up costs		<u>196,320</u>
Total	\$ 910,664	\$1,106,984

CANCER PREVENTION: BEHAVIORAL SCIENCE

Overview: The strategic plan of the Division of Cancer Prevention includes specific goals to develop research on the genetic, psychobiological and psychosocial factors mediating nicotine dependence. To this end, the Division established the Tobacco Research and Treatment Program (TRTP) in 1994, within the Department of Behavioral Science. The mission of the Tobacco Research and Treatment Program is to conduct clinical research on the treatment, prevention and psychobiological mechanisms governing nicotine dependence, and to provide quality treatment for tobacco use cessation for our patients and members of the community.

1. Tobacco Research and Treatment Program (TRTP): Biobehavioral Research in Nicotine Dependence, Prevention and Cessation of Tobacco Use (Department of Behavioral Science).

Purpose: *The scope of the TRTP will be expanded to include additional faculty to carry out its mission and to provide substantive research support for the development of new treatments and prevention techniques for nicotine dependence. A primary goal of the TRTP program will be to support research aimed at the development of new behavioral and pharmacological treatments for nicotine dependence. The research will include:*

- The identification, evaluation and development of safe and effective pharmacotherapeutic treatments for nicotine addiction.
- The development, refinement, and pilot testing of behavioral interventions aimed at translating basic behavioral and cognitive research into novel behavioral therapies tailored to unique characteristics of the smoker.
- Evaluation of combined pharmacological and behavioral treatments, using integrated designs including tailoring interventions to specific psychological and genetic factors related to nicotine dependence.

- Studies focused on the dissemination of these treatments to community settings, including primary care sites, and studies which direct these interventions at special at-risk populations, such as minority smokers, pregnant women, and smokers with drug abuse and psychiatric comorbidities. This includes the translation of research-grade treatment materials such as manuals, videos, computer programs, etc., into products that can be used directly by smokers and health care providers in the clinical setting.

Purpose: The second goal of the TRTP is to support research aimed at the prevention of youth tobacco use and dependence. Research in this area may include:

- Investigations of pharmacological, physiological, and psychological characteristics of nicotine dependence in its early stages and especially during the transition between experimental and dependent use. This includes genetic susceptibility factors.
- Prevention programs aimed at youth sub-populations at high risk for tobacco use.
- Studies investigating the role of depression in smoking initiation, response to treatment, and relapse.
- Studies of factors that influence youth's responses to advertising, promotional, mass media, and warning messages aimed at discouraging tobacco use, including ethnicity, gender, and social class differences.
- Investigations of factors related to enhancing treatment participation among young smokers.

Purpose: The third objective will be to support studies of the basic biobehavioral mechanisms involved in the development of nicotine dependence. This includes the complex interplay of genetic, neurobiological, and cognitive factors and behavior-related to tobacco use. Research will include:

- Psychophysiological and genetic processes linking psychiatric morbidity (e.g., depression), personality and health behaviors with risk of tobacco use and dependence.
- Laboratory psychophysiology studies of mechanisms involved in the development of nicotine tolerance and its relation to dependence.
- Use of Ecological Momentary "Real-Time" Analysis or other related approaches in the examination of the relationship between basic biobehavioral factors and smoking behavior and relapse.
- Genetic determinants of individual differences in the reinforcing effect of nicotine alone or in connection with other drugs, such as alcohol.
- The development of new animal and/or human pharmacological models of smoking behavior that correlate with the human pattern of nicotine self-administration.
- A comparison of the neuroanatomical sites and neurochemical substrates in the addictive behavior of nicotine.
- Effects of nicotine on cognitive performance, affect, perception, vigilance, memory and motor skills.

To support these research objectives we propose the development of a Nicotine Dependence Treatment and Clinical Trials Core Research Facility, within the TRTP, and the recruitment of new faculty to carry out these mission specific objectives. The Nicotine Dependence Treatment and Clinical Trials Core Research Facility will be partially funded by current grants and new funds available from the tobacco settlement. Researchers are expected to obtain NIH and outside funding to support individual projects, using support available within the core to increase their competitiveness and scientific productivity.

2. Professional Education and Outreach On Tobacco Use Disorders The TRTP will also establish a program of professional education which includes the training of young scientists in behavioral treatments for tobacco use disorders and a physician/healthcare professional outreach education program to train providers in the prevention and cessation intervention delivery. The professional education program will include targeted recruitment of minority pre- and post-doctoral fellows, and the outreach program will focus on the delivery of service in rural and underserved areas in Texas. The two proposed programs are as follows:

A. Training Program in Tobacco Use Disorders The training program in Tobacco Use Disorders will include four post-doctoral fellows or Research Associate positions and four graduate student positions. Each research program within the TRTP will recruit and train 1-2 graduate students and postdoctoral fellows.

B. Tobacco Outreach Education Program (TOEP) The TOEP will be designed to provide health care professionals and educators located throughout the State of Texas with state-of-the-art approaches to tobacco use prevention and cessation. Within the framework of the TOEP, nationally and internationally recognized experts from U.T. M. D. Anderson and outside the institution will be involved in training of health care providers and educators on multiple aspects of tobacco control, which would include:

- Early prevention of tobacco use among youth.
- Smoking cessation approaches for young smokers.
- Theoretically sound behavioral approaches to smoking cessation.
- Pharmaceutical treatment of nicotine dependence.
- Smoking prevention and cessation programs among minority patients.

The TOEP will be developed in two major directions:

1) *Outreach Educational Events.* The outreach educational events will be organized throughout Texas to reach out to health professionals and educators working in remote communities with limited access to advanced postgraduate training. A series of training seminars on tobacco use prevention and cessation will be conducted in areas of Texas with high smoking rates and low penetration of cessation professional services. These areas will include East Texas, Central Texas, and South Texas, Lubbock, and other locations judged to be high impact and high need areas. We will solicit the consultation and support of several local and state professional agencies, including the Texas Medical Association, Texas Association of Family Practice Physicians, Physician Oncology Education Program, Nurse Oncology Education Program, Dental Oncology Education Program, Texas Association of School Counselors, Texas Affiliates of the American Cancer Society and American Heart Association, etc., in helping us to determine the areas of most need and arranging for continuing education credits for participating health professionals and educators.

2) *Videotaped Web-based and CD-ROM Training Materials.* A major goal of this program will be to videotape the TOEP lectures and seminars series. The tapes, along with all supporting material, will be duplicated and made available to all requesting health care providers and educators, in the above-mentioned communities and throughout the State of Texas. This will be provided as a service of M.D. Anderson Tobacco Research and Treatment Program. In addition, materials will also be made available for downloading on our webpage, and placed on CD-ROM with an interactive training guide. UT TV experts will be contracted to accomplish professional videotaping and duplicating the lectures, and a computer programmer with interactive and Web based applications experience will be hired.

FY 2000-2001 Biennial Budget for Cancer Prevention: Behavioral Science		
	<u>FY '00</u>	<u>FY '01</u>
Faculty Salaries	\$ 591,640	\$ 591,640
Other Salaries	935,040	935,040
Equipment, Supplies, start-up costs	<u>349,800</u>	<u>349,800</u>
Total	\$ <u>1,876,480</u>	\$ <u>1,876,480</u>

CANCER PREVENTION: EPIDEMIOLOGY

Overview: Funds will strengthen existing programs, build infrastructure, and create new programs to support our research goals. The unifying theme is the study of genetic susceptibility to nicotine addiction and to tobacco carcinogenesis. We outline two research projects, establishment of two core resources, and an educational program.

1. Expand Collaborative Research into Susceptibility to Tobacco Carcinogenesis and Addiction in Minorities

Purpose: Smoking is more prevalent in African Americans and lung cancer rates higher than whites and therefore, a major public health impact. We propose a joint research initiative with the Department of Pharmacy at Texas Southern University.

We will collaborate with Theodore Bates, Ph.D., Professor of Pharmaceutics and Dong Liang, Ph.D., Assistant Professor of Pharmaceutics of TSU. Their research interest is to study the mechanisms of drug absorption and disposition kinetics, pre-clinical and clinical pharmacokinetics, and novel drug delivery. Our dovetailing interest is to study genetic determinants of nicotine addiction. Findings will be translated to a study of nicotine pharmacokinetics and dopamine and serotonin receptor polymorphisms in minority smokers, and will also fund pilot studies at our institution relative to this area.

2. Create A Program in Nutritional Epidemiology

Purpose: Tobacco-related cancers are influenced at every stage in their natural history, from initiation and promotion through progression and metastasis, by nutritional factors that affect carcinogen metabolism, cell proliferation and differentiation, angiogenesis, DNA repair, and other processes. We propose:

A. To recruit expert faculty (nutritional epidemiologist, nutritional biochemist) to develop and apply biochemical markers to assess nutritional and metabolic status and to study gene-nutrient interactions related to tobacco-induced cancers.

B. To establish a core laboratory with state-of-the-art instrumentation and assays to support comprehensive nutrition-related testing, to be incorporated into our centralized lab (see #4, below).

3. Creation of a Center for Population Studies in Tobacco Research

Purpose: To facilitate population-based research in Texas, to enhance minority representation in research, and to encompass large, ethnically diverse, community-based research initiatives:

A. Enhancement of the Texas Cancer Registry: to create a system that would allow for rapid case ascertainment (less than 3 months post-diagnosis) of all cancers associated with tobacco use (lung, upper aerodigestive tract, esophagus, pancreas, colorectal, renal and bladder). This would increase minority representation in our studies.

B. Initiate Research in Minority Populations: to conduct a feasibility study to establish a unique Mexican American cohort that could include municipal workers - city, county, metropolitan transit workers, teachers (HISD), or of subscribers to minority-oriented magazines. We propose to recruit an epidemiologist with experience in cohort initiation and follow-up.

4. Centralized Processing, Storage and Genotyping Laboratory

Purpose: To develop an archiving laboratory for long term storage and tracking of samples utilizing state of the art technologies for epidemiologic research: 1) Individualized bar coding and tracking systems; 2) cryogenic repository of blood components and; 3) room temperature-based, automated storage system for acquiring a large DNA library.

A. To serve as a centralized "Genotyping Core" to support ongoing efforts to identify molecular biomarkers of individual risk from exposures to tobacco carcinogens and markers of nicotine addiction. These modifiers of risk include genotypes in carcinogen metabolism, DNA repair, stress responses, and immunity. Advances in the technologies allow high throughput, automated approaches for rapid, large-scale genotyping or cataloging, requiring highly skilled staff and the acquisition of certain front-end high cost equipment items. Though initially a high cost endeavor, this instrumentation will ultimately reduce the cost of our existing assays some 100 fold while conserving precious resources.

B. To expand molecular cytogenetic research into tobacco induced DNA damage.

5. Professional Education

Purpose: The Education Program will build upon our R25 Preventive Oncology Training Program, and will be designed to train future research investigators in any aspect of tobacco related cancer prevention.

Special emphasis will be placed on recruiting two postdoctoral and two graduate student positions from minority institutions in Texas. These trainees will participate in a cross-disciplinary curriculum that will include a tailored core curriculum including, for example: epidemiology, molecular genetics, behavioral science, cancer biology and statistics. The faculty mentors in the proposed program will be investigators at UTMDACC conducting peer-reviewed, externally funded, research projects, who supervise large laboratories and have extensive statistical/data management resources. A special arrangement with nearby Texas Southern University, Department of Pharmacy, will provide a unique opportunity for minority students.

FY 2000-2001 Biennial Budget for Cancer Prevention: Epidemiology Programs		
	<u>FY '00</u>	<u>FY '01</u>
Faculty Salaries	\$ 374,400	\$ 374,400
Other Salaries	513,520	513,520
Equipment, Supplies, start-up costs	<u>356,000</u>	<u>900,150</u>
Total	\$1,243,920	\$1,788,070

GENOMICS CORE

Overview: Genomics is the scientific discipline of in-depth, comprehensive evaluation of the genetic characteristics of cells. The revolution in molecular biology has led to the recognition that cancer is caused by accumulated alterations in the genes of cells. The behavior of cancer cells is determined by the sum total of all the accumulated abnormalities in genes. Cancer genomics has emerged as the result of new technology which makes possible the definition of a profile of mutations and altered expression of the genes in cancer cells as contrasted with normal cells. Genomics offers the promise of improving the understanding of an individual patient's cancer to direct treatment by correcting abnormalities or taking advantage of them as targets for drugs and other therapies. In addition, new knowledge gained through genomics will be applicable to improved tools for screening, diagnosis and prevention of cancer.

1. Cancer Genomics Core Laboratory Facility

Purpose: U.T. M. D. Anderson Cancer Center will establish a world-class core research resource for investigators to evaluate the genomics of tobacco-related and other cancers.

The Cancer Genomics Program includes laboratory investigators, specialized statisticians and informatics faculty to analyze effectively the extensive and comprehensive data generated by these types of laboratory studies. The Core Laboratory is the heart of the program. The Laboratory is planned to include instrumentation for two core technologies, microarrays and serial analysis of gene expression (SAGE), to aid both cancer gene profiling and discovery efforts. Two laboratory faculty skilled in genomics and support staff of three technicians will operate the laboratory. Four faculty members with expertise in informatics and three support data management personnel will address this crucial area. A laboratory administrator will provide support for the scientists. Support for training of two post-doctoral fellows and two students in the laboratory and in the associated informatics is planned.

FY 2000-2001 Biennial Budget Cancer Genomics Core Laboratory Facility

	<u>FY '00</u>	<u>FY '01</u>
Faculty Salaries	\$ 480,000	\$ 480,000
Other Salaries	370,000	370,000
Equipment, Supplies, start-up costs	<u>400,000</u>	<u>1,200,000</u>
Total	\$1,250,000	\$2,050,000

MOLECULAR MECHANISMS OF TOBACCO CARCINOGENESIS

Overview: Among the approximately 4000 components identified in tobacco smoke, at least 50 are known to be carcinogenic. The major chemical carcinogens include polycyclic aromatic hydrocarbons (PAH) such as benzo[a]pyrene (B[a]P), aromatic amines such as 4-aminobiphenyl, and nitrosamines such as 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK). In addition, tobacco smoke contains volatile compounds (e.g., benzene) and radioelements (e.g., polonium-210), and free radicals that may also play a role in its carcinogenicity. Many of the chemical carcinogens found in cigarette smoke require metabolic activation to reactive intermediates that bind covalently to DNA and form DNA adducts. These DNA adducts, if not repaired, can lead to mutations in oncogenes and tumor suppressor genes.

Despite our knowledge, there are considerable gaps in our understanding of the basic mechanisms of tobacco carcinogenesis. As noted above, tobacco smoke is a complex mixture of many carcinogens. It has been difficult to directly link specific tobacco carcinogens with specific tobacco cancers although work in animal model systems has provided evidence for a role of PAH and nitrosamines in lung cancer, aromatic amines in bladder cancer, and nitrosamines in pancreas and kidney cancer. An important component of the Program in Molecular Mechanisms of Tobacco Carcinogenesis will be to conduct studies examining the role of specific tobacco carcinogens in the etiology of specific tobacco-related cancers. Another area of research is the identification of new targets and agents for the prevention of tobacco cancers. Currently, the most promising chemopreventive agents for tobacco-related cancers appear to be retinoid derivatives (head and neck, lung, and bladder cancer). An important goal of this program will be to identify new agents and targets for chemoprevention of tobacco-related cancers.

***Purpose:** The overall goal of this research program is to study biochemical and molecular mechanisms underlying tobacco carcinogenesis. The specific aims of this program are as follows: i) to investigate molecular mechanisms underlying tobacco carcinogenesis in human tissues/cells and in animal model systems; ii) to further develop animal models for tobacco-related cancers; iii) to identify new agents and targets for the prevention and of tobacco-related cancers.*

1. Role of Specific Tobacco Carcinogen-Induced DNA Damage in Lung Cancer The overall goal of this research project is to determine the levels of DNA damage from several types of tobacco carcinogens in relation to lung cancer risk and to examine genetic factors that regulate the levels of this DNA damage.

2. Tobacco-Specific Nitrosamines and Risk of Pancreatic Cancer in Susceptible Individuals In this project, we will test the hypothesis that exposure to nitrosamine and alkylating agents in cigarette smoke increases the risk of pancreatic cancer in susceptible individuals.

3. Alterations in Gene Expression Induced by the Tobacco Carcinogen B[a]P and its Ultimate Carcinogenic Metabolite in Tracheal Epithelial Cells The goal of this project is to use a new technique called Rapid Analysis of Gene Expression (RAGE) to determine changes in gene expression in human bronchial epithelial cells treated with the tobacco carcinogen B[a]P or its carcinogenic metabolite BPDE.

4. Molecular Evolution of Gene Expression Patterns for Renal Cell Carcinoma Using combined technologies of laser capture microdissection and expression microarray analysis, this project will examine evolution of gene expression profiles from preneoplasia to frank malignancy in nitrosamine-induced RCC in the Eker rat.

5. Transgenic Model for Head and Neck Cancer This project proposes to further study and characterize several potential mouse models of head and neck cancer.

6. Mechanisms and Chemoprevention of Aromatic Amine-Induced Bladder Cancer in Mice The goal of this project is to determine the role that arachidonic acid metabolism plays in aromatic amine-induced bladder cancer.

7. Chemoprevention of PAH-Induced Carcinogenesis in Hamster Cheek Pouch by Targeted Approaches The goal of this project is to perform an integrated series of studies with EGF-receptor inhibitors, COX-2 inhibitors, and angiogenesis inhibitors with the ultimate goal of developing new chemopreventive strategies for tobacco-related head and neck cancers.

8. Chemopreventive Approaches to Esophageal Cancer The goal of this project is the development of effective chemopreventive measures including retinoids and non-steroidal inflammatory drugs for cancer of the esophagus.

9. Development of a Genome-wide Model of Urinary Bladder Progression from Clinically Occult Precancerous Lesions to Invasive Cancer The project will develop new technology to allow early diagnosis of bladder cancer and tobacco-related cancers and for monitoring efficacy of prevention and therapeutic strategies.

10. Examination of Early Genetic Changes Following Exposure of the Tobacco Containing Cancer Causing Agent, 4-Amino Biphenyl, the Development of a 3-D Model for Normal Urothelium and Bladder Cancer and Identification of Urothelial Specific Promoters This project will examine early genetic alterations occurring in bladder epithelial cells after exposure to the tobacco carcinogen and will develop new models and methods for prevention and therapeutic strategies.

11. Development of a Preclinical Model for Intravesical Bladder Gene Therapy and Prevention of Recurrence Using a Broad Spectrum Tumor Suppressor Gene This will develop a new model of superficial bladder cancer and test whether gene therapy using a variant of the retinoblastoma gene will decrease bladder cancer progression.

FY 2000-2001 Biennial Budget for Tobacco Carcinogenesis Programs		
	<u>FY '00</u>	<u>FY '01</u>
Faculty Salaries	\$ 152,000	\$ 152,000
Other Salaries	538,000	538,000
Equipment, Supplies, start-up costs	500,000	900,000
Cancer Prevention	<u>110,000</u>	<u>110,000</u>
Total	\$1,300,000	\$1,700,000

SPECIAL PROJECTS

1. Pilot Projects For Research On Tobacco-Related Diseases

Purpose: Funds will be made available to support the initiation of new, innovative research projects on any aspect of tobacco-related diseases not covered in the preceding programs. This will allow investment in unanticipated opportunities for pursuing new research directions that appear promising. Funds will be allocated based on a peer review system and will be used to support pilot studies.

2. Support for Physician-Scientist Program in Tobacco-related Diseases

Purpose: To produce a small number of intensely trained physicians who understand the complexities of biomedical research as it relates to tobacco-related cancers and who are thus able to facilitate the development of more effective measures for preventing and curing these cancers. The program provides a structured training environment for broadening the research skills of promising research-oriented physicians who are interested specifically in tobacco-related diseases.

FY 2000-2001 Biennial Budget for Special Projects		
	<u>FY '00</u>	<u>FY '01</u>
Special Projects	\$1,000,000	\$1,076,094

FY 2000-2001 Biennial Budget UTMDACC Tobacco Initiatives			
	<u>FY '00</u>	<u>FY '01</u>	<u>TOTAL</u>
	\$ 9,931,064	\$12,347,628	\$22,278,692

<u>Note:</u>	<u>FY '00</u>	<u>FY '01</u>	
Source of funds: \$	4,500,000	\$ 4,500,000	Interest from \$100M Endowment
	1,639,346	1,639,346	Permanent Health Fund Allocation
	<u>3,791,718</u>	<u>6,208,282</u>	One-time Appropriation by the Legislature
Total:	\$ 9,931,064	\$12,347,628	