Cigarette Restitution Fund at Johns Hopkins

The Sidney Kimmel Comprehensive Cancer Center

John D. Groopman
Martin D. Abeloff
Understanding the Molecular Basis of Cancer

Cancer arises from the accumulation of genetic changes.
CRF Research Program Impact

Prostate Cancer Demonstration Project and Early Detection Initiatives:

Viral Infection Epidemiology and Vaccines:

*From populations to individual therapy*

The Nrf2:Keap1 Pathway:

*Basic mechanisms translate into cancer prevention*
CRF Research Program Impact

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The Nrf2:Keap1 Pathway:
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Prostate Cancer Demonstration Project

Statewide Prostate Ca

Baltimore Prostate Ca

Mechanism(s) of Action
Proliferative Inflammatory Atrophy
May be a Precursor to Prostate Cancer*

Inflammation as a Cause of Prostate Cancer*

Faulty DNA repair gene linked to tobacco use is identified. DNA change predicts head and neck cancer. Gene profile identifies tissue at high risk of cancer. DNA change predicts head and neck cancer. DNA change predicts head and neck cancer.

**Additional Funding**

- NIH-RO1 Award: $970,000
- Damon Runyon Award: $200,000
- FAMRI Award: $108,000

**Collaborations**

- University of Maryland/JHU Project
- Johns Hopkins School of Public Health
- SKCCC Head & Neck Cancer SPORE
- Joseph Califano III, MD

A 2000 CRF grant initiated research to improve cancer outcomes and detect oral cancer early through DNA profiling.
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Cervical Cancer

Prevalence: 2,274,000 women have cervical cancer\(^1\)
Incidence: 510,000 new cases each year\(^1\)

2000 estimated incidence of invasive cervical cancer by selected region\(^2\):

- **14,845** United States/Canada
- **21,596** Central America
- **64,928** Europe
- **49,025** South America
- **151,297** Southcentral Asia
- **67,078** Africa
- **51,266** Eastern Asia
- **39,648** Southeast Asia
- **1,077** Australia/New Zealand

Mortality: Second leading cause of female cancer-related deaths (288,000 annually)\(^1\)
Epidemiology of Viral Infections and Vaccine Interventions: From Mapping to Translational Research: Maryland Cervical Cancer Mortality (1997-2001)
Trimble awarded CRF grants to investigate HPV vaccine and establish Cervical Diseases Center.

Established Cervical Diseases Center in East Baltimore to offer outreach and coordinated care for women with HPV disease.

Began investigating ways to stimulate an immune reaction against cells infected with HPV and prevent the progression to cervical cancer.

Leveraged CRF-funded research into a five year grant of $700,000 from the National Cancer Institute.

Launched Phase I clinical trials of a unique therapeutic cervical cancer vaccine, aimed at curing established disease. It is a landmark study because 1/3 of participants are minority women—more than double the National average.

Negotiating with a private industry partner for licensing and distribution of vaccine.
CRF Research Program Impact

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MARKET STAGE BROCCOLI

3 grams

150 grams

3-DAY SPROUTS

FREEZE-DRIED SPROUT EXTRACT

150 mg

All preparations contain the same quantity of detoxication enzyme inducer activity.
Basic Mechanisms in the Nrf2:Keap1 Pathway to Cancer Prevention

PNAS 101:2040-5, 2004
JBC 278:8135-45, 2003
Cancer Res 62:5196-203, 2002
**Nrf2: Molecular Target to Intervention Trials at SKCCC**

- **Identification of Inducers**
  - dithiolethiones
  - isothiocyanates (sulforaphane/broccoli)
  - triterpenoids

- **Biomarker Development and Validation**
  - gene expression markers
  - genotoxicity markers

- **Ongoing Phase I and II Clinical Interventions with Nrf2 Activators**
  - healthy volunteers
  - men undergoing prostatectomies
  - women undergoing breast reduction surgery
  - heavy smokers/high risk for lung cancer
  - high risk for liver cancer

- **Pre-Clinical Efficacy in vivo**
  - pharmacology/toxicology
  - chemoprevention models

- **Genetic Models: Nrf2 Knockout Mice**
  - increased sensitivity to:
    - environ. carcinogens
    - smoke-induced emphysema
    - oxidative stress
Genes ➔ Proteins ➔ Cell Structure & Function ➔ Tissue Structure & Function ➔ Organ Structure & Function ➔ Clinical Medicine

35,000+ genes ➔ 100,000+ proteins ➔ 300+ cell types ➔ 4 tissue types ➔ 10 organ systems ➔ 1 body

Toxins and Toxicants ➔ Biological Response

Adapted from Sasisekharan and Essigmann, 2005
The state of cancer in Maryland

**Western Maryland:**
- Smoking-related cancers
- Carcinogens in drinking water
- Cancer risk from arsenic exposure
- Youth smoking cessation

**Before and After**

**Before CRF:**
Maryland ranked fourth nationally in cancer deaths in 1990.

**AFTER CRF:**
Maryland now ranks 17th nationally in cancer deaths.

**Before CRF:**
Maryland cancer mortality rates remained steady.

**AFTER CRF:**
Maryland's cancer mortality rates are dropping at twice the national average.

**Before CRF:**
Overall cancer death rates were 27 percent higher among Maryland's minorities when compared to whites.

**AFTER CRF:**
In 2001, cancer death disparities between Maryland whites and minorities declined significantly.

Cancer research is targeted specifically to reducing the cancer burden among the state's minority populations.

**Before CRF:**
There was no central Core Population Resource for the collection and study of blood samples.

**AFTER CRF:**
A Core has been established and more than half of patients and their friends and family members have said they want to provide blood samples to help identify biomarkers for cancer prevention and control.

**Statewide**
- Carcinogens in Maryland's air, water, and soil
- Smoking-related cancer detection and prevention
- Breast cancer gene pathways
- New cancer drug discoveries
- Analysis of genetic risk for colon cancer
- GIS survey of environmental risks for colon cancer
- Inflammation and cancer risk
- Core Resource for cancer biomarker discovery.
- Overcoming breast cancer treatment resistance
- Familial and early markers of pancreatic cancer.
- Cholesterol-lowering drugs for prostate cancer prevention.

**When Maryland Invests, Others Do Too.**
Direct funding leveraged through CRF:
- Sidney Kimmel: $150 million
- FAMRI: $15 million
- Dept. of Defense: $10 million
- Avon Foundation: $1.5 million

* Flight Attendants Medical Research Institute

**Central Maryland (Includes Baltimore City)**
- Oral cancer screening
- Faith-based cancer prevention and control
- Youth smoking cessation
- Lung cancer risk factors for women
- Biomarkers for colon cancer
- Racial/ethnic differences in prostate cancer
- Cancer prevention in African Americans
- Cervical cancer prevention in Hispanics
- Cadmium exposure and prostate cancer risk
- Genetics of lung cancer
- Urban disparity cancer reduction
- HPV infection and oral cancer screening

**Southern Maryland (Includes Suburban D.C. Area):**
- Racial/ethnic variations in prostate cancer
- Cancer biomarkers and prevention
- Cancer risk from arsenic exposure

**Eastern Shore:**
- Carcinogens in drinking water
- Cancer risk from arsenic exposure
- Youth smoking cessation
- Cervical cancer vaccine
- Environmental exposures to carcinogens
- Racial disparities and cervical cancer
- Metroway contamination and cancer risk
- Prostate, breast and colon cancer screening

**CRF Community Outreach**
Through the CRF Public Health Grant, more than 1.9 million citizens have been reached. More than 17,000 have met with a cancer educator to learn about cancer screening for early detection. Over 2,000 have been screened for prostate cancer resulting in ten diagnoses of cancer.