To advance the science and application of cancer etiology, prevention, and outcomes, and reduce the burden of cancer and its sequelae across all segments of the population, through collaborative multidisciplinary programs in clinical service, research and education.
Population Sciences – Goals

• Identify genetic and environmental factors contributing to the development of cancer

• Develop and test approaches for prevention and early detection of cancer

• Describe health-related outcomes and QOL in cancer patients

• Develop, implement and evaluate interventions to improve QOL and symptom management from diagnosis and treatment, through survivorship and end-of-life.

• Create educational programs to disseminate research and facilitate the adoption into clinical practice.

• Develop a Center for Cancer Survivorship
Etiopathogenesis of therapy-related leukemia

PAR-02-126, R01 HL083050
S Bhatia, R Bhatia
Forman, O’Connors

Therapy-related Leukemia

Genotoxic Insult

Genetic Susceptibility

Acquisition of Mutations

Proliferative stress

Clonal Hematopoiesis

Genomic Instability

Cytogenetic Abnormalities

Clinical/Morphologic MDS
Therapy-related Leukemia – Etiology and Pathogenesis

Funding: PAR-02-126, R01 HL083050

- Prospective, longitudinal study after autologous HCT for HL/NHL
  - Molecular pathogenesis of t-MDS/AML
  - Identify predictors of susceptibility.

- Investigate prevalence, nature and timing of occurrence of abnormalities in the course of development of t-MDS/AML
  - DNA repair mechanisms, cellular response to DNA damage, hematopoietic abnormalities, and telomeric shortening

- Investigate changes in gene expression patterns in CD34+ cells associated with the development of t-MDS

- Explore role of gene-environment interactions

# Goal 2: Develop and test approaches for prevention and early detection of cancer

### Genetic Cancer Screening and Risk Assessment
- *J Natl Cancer Inst* 2002;94:1773-79
- *Cancer Epidemiol, Biomarkers Prevention* 2005;14:1534-8

### Chemoprevention
- *Breast Cancer Res Treatment* 2003;82:1034
- *Breast Cancer Res Treatment* 2004;88:4002

### Early detection and monitoring of breast cancer
- *Breast Cancer Res Treatment* 2005;94:1018
Decreased contralateral breast cancer seen with aromatase inhibitor therapy suggests efficacy in breast cancer prevention

Dr. Chen (DCT) has demonstrated a previously unknown anti-aromatase effect with grape seed extract

Phase I human breast cancer chemoprevention trial (Dr. Palomares)
- Impact of GSE in significantly suppressing circulating estrogens in postmenopausal women at risk for breast cancer
- Gather preliminary dose information
- Determine bioavailability
- Evaluate safety and tolerability in postmenopausal women.

Funding: NCI, CBRP
Investigators: Palomares, S Chen, Synold, W Wen
Goal 3: Describe health-related outcomes and QOL in cancer patients

**Childhood and Adult Cancer Survivors**

*J Clin Oncol* 2002;20:4692-8  
*Blood* 2002;99:4257-64  
*Pediatrics* 2005;115:435-42  
*Blood* 2007;109:46-51

**Hematopoietic Cell Transplantation Survivors**

*Blood. * 2006; 1082867-73  
*Blood, * 2006, in press

**Health-related Outcomes in Underserved Populations**

*Blood* 2002;100:1957-64  
*JAMA* 2003;290: 2008-14  
*Cancer* 2004;101:450-65
Health-related outcomes after hematopoietic cell transplant
R01 CA078938 (Bhatia); P01 CA30206 (Forman)
Specific Aims

- Medical outcomes
- Sexual functioning
- Neuropsychological functioning
- Health-risk behaviors
- Access to/utilization of medical care
- Impact of outcomes on HRQL

Key publications:

Late effects in survivors of CML treated with HCT. *Blood* 2004;104:1898-1906.


Prevalence of conception and pregnancy outcomes after HCT. *BMT* 2006;37:1023-9


Diabetes, hypertension, cardiovascular events in HCT survivors. *Blood* 2006. (Epub)
Survival by Race/Ethnicity following Childhood ALL

Blood, 2002;100:1957-64
Possible reasons for observed differences in survival

Ethnic Differences in Survival

- Low systemic exposure to antimetabolites
  - Pharmacogenetics
  - Bioavailability
  - Non-adherence to therapy

Disease Biology

- Response to therapy
  - Cytogenetics
  - Age at Dx
Ethnic Differences in Survival after Childhood A.L.L.

121 participating institutions

Caucasians: 200
African-Americans: 200
Hispanics: 200
Asians: 120

Funding: R01 CA096670 (Bhatia)
Blood Specimen

To determine genetic differences in drug metabolizing enzymes and to determine adherence to 6MP

Questionnaires

To describe their pill-taking habits, and report any missed doses

MEMS Pill Bottles/Caps

Special pill bottles with electronic TrackCap to record bottle opening
Goal 4: Develop, implement and evaluate interventions to improve QOL and symptom management

**Interventions to overcome barriers to pain and fatigue**
Funding: R01 CA115323

Describe current status of pain and fatigue management in cancer patients
Incorporate recommendations from literature to develop innovative intervention model

**Interventions to improve QOL**

**HCT patients** – Structured Nursing intervention Protocol to evaluate improvement in QOL after discharge from HCT *(R01 CA107446)*

**Phase I/II trial participants** – Simultaneous Care Educational Intervention *(R25 CA95260)* combines supportive care with education

**Ovarian Cancer** – Educational intervention to improve QOL *(ONS)*

**Underserved patients** – Culturally competent intervention to improve psychosocial functioning in breast and cervical cancer patients *(ACS)*
Cancer Survival, 0-14 Years of Age
SEER Program 1976-1997

More than 270,000 childhood cancer survivors
1 in 1000 is a childhood cancer survivor
1 in 500 (18 to 35 year-old) is a childhood cancer survivor
Cancer Survivors – all ages – US

64% of adults are alive five years from diagnosis (US, 2001)
Long-term Sequelae in Childhood Cancer Survivors

<table>
<thead>
<tr>
<th>Health-related Quality of Life</th>
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<tbody>
<tr>
<td>Growth and development</td>
</tr>
<tr>
<td>linear growth</td>
</tr>
<tr>
<td>skeletal maturation</td>
</tr>
<tr>
<td>intellectual function</td>
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<td>emotional/social maturation</td>
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<td>sexual development</td>
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<td>Vital Organ Function</td>
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<td>Vision/Hearing</td>
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<td>Fertility and Reproduction</td>
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<tr>
<td>Fertility</td>
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<tr>
<td>Health of Offspring</td>
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<tr>
<td>Second Neoplasms</td>
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<tr>
<td>Benign</td>
</tr>
<tr>
<td>Malignant</td>
</tr>
</tbody>
</table>
Second Cancers in Survivors

Cumulative incidence

Years since diagnosis

SMN
Breast Cancer after HD in Girls

Special Education Services

- All: 23%
- Leukemia: 8%
- CNS: 36%
- Survivors: 70%

SMN
25% at 25 yrs.
The implications of cure are not trivial

*Burden of morbidity in survivors of childhood cancer is substantial*
Long-term Complications – etiology

- Age
- Gender
- Radiation
- Chemotherapy

Environmental/lifestyle
  - smoking
  - diet

Genetic susceptibility

Interactions
Chronic health conditions after childhood Cancer

- Approximately 75% experience at least one therapy-related chronic health condition
  - 40% experience severe/life-threatening conditions

- **Radiation**
  - Secondary breast and thyroid cancers and brain tumors
  - Coronary artery disease
  - Stroke

- **Alkylating agent- and topoisomerase II inhibitor**
  - Therapy-related leukemia

- **Anthracyclines**
  - Cardiac dysfunction

- **Steroids**
  - Avascular necrosis

- **Dose-response relationship between therapy and adverse events**
  - Wide variation in individual sensitivity
    - Possibly explained by genetic susceptibility
Case-Control Study of Key Adverse Events after Childhood Cancer

- COG – Chair, S Bhatia
  - 138 institutions
  - Coordinating Center – COH

Funding: Lance Armstrong Foundation
Planned submission to NCI – June, 2007
Goals

Establish a mechanism within COG to identify key adverse events developing in patients diagnosed and treated for childhood cancer.

Obtain blood samples from patients who develop these outcomes (cases) as well as randomly selected controls.

Explore genetic susceptibility and gene-environment interactions.
Key Adverse Events

- Congestive Heart Failure
- Ischemic Stroke
- Osteonecrosis
- Second malignant neoplasms

Selection of adverse events based on presence of:
- High incidence anticipated among childhood cancer survivors
- Clear association with specific therapy used for primary malignancy
- Chronic nature of adverse events
  - Morbidity or mortality
Methodology

• Candidate gene approach
  – Targeting of functional polymorphisms
  – Identification of genes based on association with similar “de novo” disease
  – Impact on pharmacogenetics or pharmacodynamics of the therapeutic exposure associated with adverse event

• Genome-wide scans will be used to identify additional candidate genes and polymorphisms
**Study Design - Case Control**

**Case**
Key adverse events developing in patients diagnosed with a primary cancer under 21 years of age, irrespective of current age.

**Controls**
Patients diagnosed with a primary cancer under 21 years of age, irrespective of current age who have not developed the event of interest.

**Matching criteria**
- Primary diagnosis
- Time at risk from Dx
- Date of dx of primary ca
- Race/ethnicity

**Case: control::1:3**
Future Directions…

Division of Population Sciences
Center for Cancer Survivorship

Goal

Provide comprehensive long-term follow-up care for cancer survivors in the setting of clinical research
Aims

• Provide state-of-the-art comprehensive care to cancer survivors

• Serve as an invaluable resource for research
  – Outcomes
  – Genetic susceptibility
  – QOL assessment
  – Interventions to reduce morbidity and mortality

• Healthcare Professional Training
  – Post-graduate Fellowship Program in Cancer Survivorship
    • clinicians (physicians, NPs, PAs)
    • researchers planning careers in cancer survivorship

• Support
  – Develop specialized support services for survivors
    • Counseling (work, school, insurance issues)
Center for Cancer Survivorship

Aims

- Use the childhood cancer survivor paradigm to survivors of adult cancer
  - Breast cancer
  - Prostate cancer
  - Colorectal cancer
  - Bone marrow transplant
  - Other cancers
Thank you