BARRETT’S ESOPHAGUS TRANSLATIONAL RESEARCH NETWORK (BETRNet)

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Unanimous recommendation:

- Formation of a multidisciplinary, multi-institutional translational research network to lead the bench to bedside transition
- Accelerate the pace of BE-EA research
Esophageal Adenocarcinoma

Incidence on the Rise

Change in rate from 1975

Rate ratio (relative to 1975)


Esophageal Adenocarcinoma
Melanoma
Prostate
Breast
Lung
Colorectal

Pohl & Welch 2005 JNCI
Esophageal Adenocarcinoma

Risk / Protective Factors

- GERD (Gastric Acid & Bile Reflux)
- Obesity
- Tobacco
- Diet
- NSAIDs
- H. pylori
Esophageal Adenocarcinoma Carcinogenesis

Adapted from Buttar & Wang 2004 Nature Clinical Practice Gastroenterology & Hepatology
Mutant clones expand and drive other clones extinct within the segment

Measures of clonal diversity have been shown to be useful in predicting progression to EA
Esophageal Adenocarcinoma
Ideal Model for Carcinogenesis Research

• A model for epithelial carcinogenesis
• Unique access to specimens
  • Serial & safe biopsies
  • Availability of biospecimens
• Natural history
• Response to intervention
• Motivated patients

Data from these proposed multi-institutional, multi-disciplinary clinical studies must be aggregated to define statistically significant at-risk populations, risk & protective factors, natural history of EA
Promoter Hypermethylation of NEL-like Gene

- → gene silencing
- Appears early in Barrett’s-associated neoplastic progression
- Common in EA
- Potential biomarker of poor prognosis in early-stage EA

Jin et al., 2007 Oncogene
Chromosomal Instability by SNP Arrays

Li et al., 2008 Cancer Prev Res
## Esophageal Adenocarcinoma
Incidence, Different Baseline Abnormalities & NSAID Use

<table>
<thead>
<tr>
<th>Abnormal Markers</th>
<th>2 y</th>
<th>6 y</th>
<th>10 y</th>
<th>RR (95% CI), P-value</th>
<th>Non-users</th>
<th>Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (n=85)</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>12% (3)</td>
<td>Baseline</td>
<td>1 / 25</td>
<td>2 / 59</td>
</tr>
<tr>
<td>One (n=104)</td>
<td>0.96% (1)</td>
<td>5.65% (5)</td>
<td>19.88% (8)</td>
<td>1.8 (0.48-6.87), &gt;0.38</td>
<td>4 / 34</td>
<td>4 / 70</td>
</tr>
<tr>
<td>Two (n=32)</td>
<td>16.83% (5)</td>
<td>28.40% (8)</td>
<td>35.56% (9)</td>
<td>9.0 (2.4-33.3), &lt;0.001</td>
<td>6 / 13</td>
<td>3 / 19</td>
</tr>
<tr>
<td>Three (n=22)</td>
<td>40.20% (8)</td>
<td>79.12% (14)</td>
<td>(14)</td>
<td>38.7 (10.8-138.5), &lt;0.001</td>
<td>10 / 12</td>
<td>4 / 9</td>
</tr>
</tbody>
</table>
BETRNet Proposed Infrastructure

= CaBIG Apps

= Pt. Registry

Coordinating Center = CC

BETRNet Translational Research Center = BTRC

Collaborating PI
BETRNet

Translational Research Areas of Focus

• Biology of EA Carcinogenesis
  – Cell of Origin
  – Mechanisms of esophageal stem cell differentiation
  – Pathway mapping

• Development of Novel Technologies & Models
  – Novel preclinical models
  – Molecular profiling technologies
  – Dynamic & real-time *in vivo* imaging technologies

• Patient Outcome-Associated Biomarkers
  – Screening & surveillance
  – Risk assessment
  – Disease progression
  – Intervention response

• Development & Validation of Molecularly-Targeted Interventions
Independent Evaluation Criteria

- Evaluation based on measurable performance criteria
  - Progress in BETR areas of focus
  - Collaboration with other NCI programs
  - Development of research studies within BETRNet
  - Participation in scientific committees
  - Publications
  - Progress reports
  - Development of new tools & applications for patient management
Barrett’s Esophagus / Esophageal Adenocarcinoma
Current Portfolio Analysis

• In FY 2008, NCI funded 35 projects on EA, including BE (TC: $13,170,739)
  – Including training/small grants e.g., K, R03 & R21

• NIDDK funded 20 awards (TC: $4,758,278); focused mainly on BE

• FY02 RFA → 50 applications
  – Funded 8 R01 (3 by NCI) 5 R21(1 by NCI)
Justification

• Funding Mechanism
  – Cooperative Agreement

• Allows Meaningful Partnership with NCI
  – Steering Committee
  – Ensure Collaboration
  – Centralized Patient Registry
Budget Request

• $7 Million per year for 5 years
  – Translational Research Centers
    • ~$1.5 Million for 4 Centers
  – Coordinating Center
    • $500,000
  – Pilot Projects Funds
    • $500,000