Barrett’s Esophagus Translational Research Network (BETRNet) Renewal Concept

Division of Cancer Biology
Division of Cancer Prevention

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Barrett’s Esophagus Translational Research Network (BETRNet)

- DCB/DCP multi-disciplinary and multi-institutional program
- Collaboration among multiple centers, with basic and clinical researchers and resource sharing, to tackle a rare cancer
- Significant oversight and active participation by NCI staff allows real-time modifications to the program based on scientific needs and accomplishments
- Enable a deeper understanding of EA biology and its putative precursor lesion, Barrett’s esophagus (BE), provide strategies for EA prevention, and better define individuals at risk
- Funded by NCI in 2011; 3 Research Centers and 1 Coordinating Center
Esophageal Adenocarcinoma

- Highly morbid and highly lethal cancer
- Unexplained dramatic rise in incidence and mortality
- BE confers increased risk
  - ~11-30 fold greater than average risk
  - 80-90% of EA cases have no prior diagnosis of BE

Hvid-Jensen F et al, NEJM 2011; 365:1375
Dulai GS et al, Gastroenterology 2002; 122:26
BETRNet Organization

RC2: University of Michigan
University of Washington
Mayo Clinic

RC1: Columbia University
University of Pennsylvania
Mayo Clinic

RC3: Case Western Reserve University
Fred Hutchinson Cancer Center
Johns Hopkins University
Mayo Clinic
Washington University St. Louis
University of North Carolina
University of Pennsylvania

First transgenic (L2-IL-1β) mouse model of Barrett’s-like metaplasia with multiple tumors at 12 months - developed by RC1

- BE/EA may arise from a stem/progenitor cell in the gastric cardia; this model challenges the dominant thinking in the field about the origin of BE/EA
- BE gene signature more closely resembles cardia than squamous epithelium

Accelerated validation of the mouse model through the consortium

- Testing of chemopreventives (e.g., statins, obeticholic acid) in RC2
- Validation of imaging markers for high grade dysplasia and EA (e.g., EGFR, Transglutaminase 2) in RC3
• Protective role of GSTT2 gene in African American esophagus
  ▪ Aimed to explain the increased prevalence of EA in Caucasians versus African Americans (ratio 4-6:1)
  ▪ GSTT2 enzyme has a protective role against oxidative damage; however, in Caucasian GSTT2 is less expressed

• Study made possible by combining rare esophageal cancer specimens from multiple BETRNet institutions

• Study completed and manuscript in preparation
• Whole-exome sequencing reveals alternative model for EA development through genomic doubling
• Challenges the prevailing hypothesis of stepwise accumulation of genetic mutations
• Supported by BETRNet collaboration
BETRNet Coordinated Outreach

• Pilot projects with flexible funds to exploit emerging ideas advertised to outside investigators

• Cross-BETRNet focused sessions at national and international meetings included outside investigators

• Leading experts invited to BETRNet Steering Committee meetings

• Publications in major journals
Patient Registry-Virtual Biorepository

- Access to specimens available through collaboration with BETRNet
- Review of proposals by an access committee
- 3901 unique specimens available as of November 2015
- Current revision to the PR-VR “public face” for easy access by the larger scientific community
BETRNet Program Evaluation
(Performed During Year 4)

• RFA provided the necessary infrastructure to break down silos and support collaborative research to synergize science and accelerate opportunities for translational studies

• BE could be a model for understanding the development of other adenocarcinomas with unknown or inaccessible precursors

• Noted Significant Accomplishments
  ▪ EGFR probe with great potential for clinical use
  ▪ Epigenetics and exome sequencing- an important foundation for future application
  ▪ Registry-tissue repository - exceptionally valuable for a wide range of research studies
  ▪ Cross-Center collaborations
  ▪ Interactions with other NCI-supported entities such as the EDRN and CISNET
BETRNet Program Renewal (RFA Reissuance)

• **Research Centers (U54)**
  
  Multi-institutional, trans-disciplinary research groups to support:
  
  ▪ Well-defined and NCI coordinated platform to advance research on a rare cancer
  ▪ Collaborative accrual of sufficient cohorts/specimens that could not be collected at a single institution
  ▪ Collaborative approach to new research directions and expertise sharing to permit adequate hypothesis testing (lesson learned)

• **Coordinating Center (U24)**
  
  ▪ Administration of the consortium and continued expansion of the virtual biorepository

• **NCI Staff**
  
  ▪ Active role in program organization, management, and performance evaluation to maximize integration and coordination of the complex U54 research structure with diverse scientific areas
  ▪ Partnership with BETRNet investigators to prioritize and support research and outreach activities
Research Questions - New RFA

**Cell of Origin**
- Biology and development of esophageal stem cells and whether they are slow dividing cells or proliferative progenitors
- Effects of acid and inflammation on esophageal stem cells and their modulation by preventive agents
- Role of esophageal or other stem cells in the development of EA

**Genomics of EA**
- Impacts of spatial distribution of genetic alterations in BE on the evolution of EA
- The genomics of tumor heterogeneity and tumor plasticity and their impacts on the progression of EA
- The genomics of obesity and their effects on the risk of EA to inform molecular targeting for chemoprevention
Research Questions (continued)

**Microbiota**
- Alterations in BE and EA microbiota, their role in BE-EA transition and potential modulation for cancer prevention

**Technologies and Models**
- New technology for minimally invasive screening and surveillance
- Models such as engineered mice, PDX models, cell lines, and organoids that could provide a platform for understanding human esophageal epithelial transformation
Proposed Budget

Set aside request: $5.5 million in total costs (TC) per year for 5 years

- 4 Research Centers
  - $1.28 million TC per year each

- 1 Coordinating Center
  - $375,896 TC per year

- Invited speakers/small workshops
  - $15,000 per year (administered by DCB - DCP)

- Total requested set aside for entire project period:
  - $27.6 million
Portfolio Analysis - Fiscal Year 2014

- NCI Extramural: ~ $17.2 million in total costs (TC)
  - BETRNet, R01s, U01s and P01
- NCI Intramural: $670,804 TC
- Other NIH institutes: $2.2 million TC
  - K awards, some R01s
- No existing multi-disciplinary collaborative programs
Correlation of BETRNet (2011-2105) With the Landscape of EA Research

Publications 2003-2015

Note: Citation count data is unavailable for papers published prior to 2003.

Competing NIH Awards
2007-2015
Program Evaluation Metrics (New Program)

• **Detailed scientific understanding of EA formation (years 1-4)**
  - Validation of the initial cell of origin findings in animal models and humans
  - Validation of the genomic doubling hypothesis underlying the molecular risk for EA formation
  - Sharing of scientific expertise and valuable specimens to tackle these research questions
  - Publication of the team research findings

• **Improved PR-VR availability to the larger scientific community (years 1-5)**
  - Enhanced PR-VR accessibility for review by the larger scientific community (year 1)
  - Promotion of specimens availability for collaborative research studies (years 1-5)
  - Invitation of outside investigators to contribute specimens for collaborative research studies (years 1-5)

• **New research tools and technologies for patient management (years 1-5)**
  - Development of non-endoscopic and imaging devices for screening and surveillance
  - Development and validation of biomarker for risk stratification
  - Development of chemopreventive approaches

• **Model organisms, GWAS, data and resource sharing (according to NIH policies) (years 3-5)**
  - Links to data public sites available through the Coordinating Center website
  - Links to publications from outside investigators utilizing the resources
Questions?
Additional BETRNet Accomplishments

• First-in-human trial
  – Image guided endoscopic biopsy using fluorescent peptides to bind with cell surface markers (e.g., epidermal growth factor receptor)
  – Aberrant *vimentin* methylation - common in upper GI neoplasia
    o Novel non-endoscopic device study is underway
Additional Program Evaluation Criteria

- Collaboration and participation in new pilot studies within the network and outside the network
- Sharing of human specimens between centers to answer collaborative research questions
- New grant applications from cross-BETRNet studies
- New models and resources to be shared with the scientific community
- New research tools & applications for patient management
- Active participation in Steering Committee meetings, focused scientific committees, and other BETRNet activities
- Publication of collaborative research findings