Attachment I Date Prepared: __9-1-2009____ **REQUEST FOR EC/BSA CONCEPT APPROVAL REQUESTS FOR APPLICATIONS (RFAs)/CONTRACTS (RFPs)** **Title: Barrett's Esophagus Translational Research Network (BETRNet)**	
RFA _X_ Coop. Ag. _X__ RFP____ Activity Code (e.g. R01) ___U01, U24 Limited Comp. __ New X Reissue ___	
Division/Office/Center: __DCP___ **Division/Office/Center Co-sponsor(s): _____DCB___**	**Program Director: Asad Umar DVMPhD (ER)** **(Signature)** **Division/Office/Center Director: Peter Greenwald (KHJ for) (Signature)**
Length of Award (Yrs.) _____5_____ **Anticipated Award Date:___2011___**	**Source of Funds: RPG _X_Centers____ Other Res:___X___ Construct _____ NRSA _____**
RFAs (Set Aside): (single issuance only) **Amount of Set Aside 01 Year:$7.0 Million**	**Est. Number of Awards:_____5_____ Est. Cost for Total Project Period:_$35.0 Million____**
Justification for Use of RFA/RFP Mechanism: Attached: Yes_____ **Congressional Mandate:_____** **Other: _____**	**New issuance:** **Are evaluation criteria included? Yes_____** **Reissuance:** **Is the evaluation included?** *(Large infrastructure only)*

Introduction:

This concept proposes a multi-institutional, multi-disciplinary translational research network of exceptional investigators to address the challenges presented by the increase in the incidence of esophageal adenocarcinoma (EA) and the opportunities associated with understanding its only accepted precursor lesion, Barrett's Esophagus (BE). Critical research advances can only be achieved through interdisciplinary collaboration among investigators with expertise in varied areas. The mission of this research network is to help the scientific community integrate and transform important research findings generated from individual laboratory-based, clinical, or population studies into clinical applications to reduce EA incidence, morbidity, and mortality.

1. Background:

Significance of Esophageal Adenocarcinoma While the overall incidence and mortality rate of cancers have declined in recent years, the incidence of EA has continued to rise[1]. EA now accounts for at least 2% of US cancer-related deaths in men and has the fastest growing incidence of all cancers in the United States[1]. In the past three decades, EA incidence has increased more than 600%[2] in men aged 65 years and older[3] and notwithstanding progress in multimodality therapies, the overall 5 year survival rate is still estimated at 15%[4]. Furthermore, esophagectomy with or without neoadjuvant radiation therapy often incurs early postoperative complications and long term devastating functional abnormalities are common[5]. Likewise, medical therapies are still highly toxic, and remain unsatisfactory in response duration and overall survival benefit[6]. The completion of any therapy for EA is most often followed by tumor recurrence or distant metastasis that leads to severe morbidities and eventual death. The natural course of the disease is insidious and debilitating, becoming clinically apparent only in advanced stages that are refractory to treatment and are resource-intensive. Needless to say, more effective cancer preventive measures will benefit not only affected individuals but also the public at large. Decreasing the suffering and death associated with EA will have a substantial effect on the cancer burden in the US.

Significance of Barrett's Esophagus Central to the development of cancer preventative and clinical management measures is to advance the understanding of the etiology of EA. Neoplastic progression in the esophagus is a multi-decade process characterized by genomic instability and accumulation of molecular alterations in cell clones[7, 8]. Histologically, EA is thought to arise from the injury of the esophageal mucosa by frequent reflux of gastric contents that result in a sequence of metaplasia to low-grade dysplasia, high-grade dysplasia, and carcinoma. The metaplasia to dysplasia phase of this sequence is known as Barrett's esophagus (BE) and is diagnosed in approximately 10% of patients who are referred to endoscopy for gastroesophageal reflux disease (GERD) symptoms[9]. BE is defined as the replacement of the normal squamous epithelium of the distal esophagus by columnar epithelium with intestinal metaplasia. BE is the only widely accepted precursor lesion to EA. Patients with BE are at least 30 times more likely to develop EA than patients without BE.

Clinical Management of at Risk Patients is Inadequate Currently, chronic GERD patients are screened for BE and if diagnosed, they are managed by endoscopic surveillance[9].The

role of endoscopic surveillance is supported by studies that demonstrated that patients with malignancy detected at surveillance endoscopy have cancers at an earlier stage and better survival than those with no surveillance[9, 10]. The significance of surveillance, however, is questioned by other studies demonstrating that only about 60% of patients diagnosed with EA have a prior diagnosis of GERD and less than 5% have BE[11]. Furthermore, although the increased risk of EA in BE patients has been observed consistently, studies have shown that only 0.5% of endoscopically monitored BE patients progress to EA per year (with the high-grade dysplasia patients progressing at an annual rate of 5% to 20%) [12].This suggests that despite decades of research, current management of EA progression is still inadequate. It also suggests that very few patients who are screened and monitored for progression have benefited and that most of those whose disease might have been prevented or detected early through endoscopy were not identified. With the threat of a highly lethal cancer and without a randomized trial that could determine criteria for screening and endoscopic surveillance, both patients and physicians typically opt for the most aggressive strategies for treatment and surveillance even with procedure-related risks. This has perpetuated the extremely low yield from current strategies and a tremendous drain on healthcare dollars. Only with better understanding of the biology of EA carcinogenesis, including host and environmental factors, will cancer risk evaluation be more individualized for improved patient care.

BE is an Ideal Model to Study the Biology of Cancer Formation and Its Targeted Intervention BE is an ideal model to study the malignant transformation process, offering opportunities for rapid scientific and clinical advances that could be applied to other cancers. From a clinical management perspective, BE is unique among premalignant lesions in that once identified, rather than being completely excised (like colon adenomas), it is left in place and monitored endoscopically over time with relative ease and safety. BE's long asymptomatic premalignant phase allows sequential collection of tissues and other specimens that can be used to study the genetics and molecular biology of cancer formation as well as the changes caused by environmental exposures, response to interventions, and the impact of risk and protective factors. From a biological perspective, molecular alterations associated with Barrett's metaplasia such as COX-2 over-expression, inactivation of p53, aneuploidy, and DNA methylation are common to many solid tumors and can function as biomarkers of cancer risk identification, neoplastic progression, and serve as targets for preventative and therapeutic agents.

Understanding the mechanisms that promote the progression of BE to EA and the true significance of this precursor lesion, especially at the genomic and proteomic levels, could lead to novel interventions to prevent malignancy and/or control the progression of intervention-resistant clones. Once potential interventions are identified, they must be tested in adequately powered, well-controlled clinical trials that include prospective, tissue-based molecular and cellular characterizations of response.

Team Science Approach to BE-EA Research While promising insights are emerging from Barrett's research, endoscopic surveillance for the detection of dysplasia remains the main strategy to monitor cancer progression in BE[9]. Many molecular alterations associated with Barrett's metaplasia and EA have been defined, but the significance of

these pathways for the Barrett's-EA transformation is unclear and needs to be assessed in a more systematic approach. For example, while progression from Barrett's metaplasia to adenocarcinoma is thought to be a process of clonal evolution driven by genetic instability, new evidence supports a link between clonal diversity and neoplastic progression suggesting that Barrett's phenotypic and genotypic heterogeneity arise from clonal diversity[10, 13]. Validation of cutting edge hypotheses requires access to adequate numbers of research participants and their tissue samples, which is extremely difficult for individual investigators. Interdisciplinary collaboration between investigators and institutions is essential to moving the science forward. This "team science" approach to translational research with shared resources has been difficult to promote without an established network and NCI programmatic oversight.

2. Purpose of RFA:

The purpose of this concept is to request an RFA that will advance translational research in BE-EA by establishing a multi-disciplinary, multi-institutional research network of basic and clinical investigators, coordinated and administered by a Coordinating Center (CC) and linked by existing NCI infrastructures, to support centralized and focused research programs with shared resources and technologies. The goal of the network is to initiate and foster long-term productive collaborations among investigators with the common objective of achieving a more comprehensive understanding of EA carcinogenesis as the foundation for innovative high impact clinical research that will lead to development of validated diagnostic tools for EA as well as improved patient management.

Patient registry/virtual repository

Central to realizing the potential of this collaborative network is the development of a multi-institutional patient registry that will include clinical, longitudinal, and epidemiological data and data sets associated with the biospecimens that are collected and available at each participating site. The cohort of patients will include individuals at all levels of risk for BE and EA, providing opportunities for understanding the natural history of the disease and determining risk stratification criteria (molecular, environmental, and epidemiological). Such a registry/virtual repository will represent a centrally coordinated shared resource, that dramatically increases opportunities to study interventions that target malignant processes and to develop and assess novel invasive and noninvasive technologies for patient stratification, ultimately improving patient management and outcomes.

To achieve this goal, the Division of Cancer Prevention (DCP) and the Division of Cancer Biology (DCB) jointly propose a BE Translational Research Network (BETRNet) composed of 4 Translational Research Centers supported by a Coordinating Center and the NCI's Cancer Biomedical Informatics Grid (CaBIG) applications. Each Center will be composed of multiple research institutions that collaborate on projects under the direction of designated Principal Investigators (PIs) and the overall Center Director. The BETRNet team would encompass expertise in clinical research, genomics, evolutionary biology, molecular biology, computational biology and biostatistics. Individual center applications submitted under this initiative should propose a multi-disciplinary approach for understanding EA formation as a basis for its prevention with projects that focus on the following areas defined by the RFA:

BIOLOGY OF BE-EA SEQUENCE

a) The cell of origin in BE

- Identification of the cell of origin in BE
- Characterization of the mechanisms that promote differentiation of esophageal stem cells
- Mapping the cellular pathways in the evolution of BE in experimental models and in human tumors

b) The role of mucosal injury and repair in the BE-EA progression

- Identification of the mechanisms that control mucosal response to injury induced by acid reflux, bile and other factors and their role in progression
- Identification of the role of the inflammatory cells, immune cells, and inflammatory mediators in initiation and progression
- Characterization of the effects of chronic inflammation on progression

c) Unique molecular pathways that promote the BE-EA transition

- Identification of molecular pathways that promote the transition of BE-EA
- Validation of the utility of unique molecular pathways as biomarkers for transformation

d) The role of tumor stem cells in BE-EA transition

- Identification of tumor stem cells and factors that control their behavior
- Characterization of the role of esophageal cancer stem cells in Barrett's progression to cancer

e) Genetic and epigenetic alterations in BE-EA transition

- Identification of genetic and epigenetic changes in BE and their role in its transition to EA
- Defining the significance of gene-environment interaction for BE-EA transition

DEVELOPMENT & VALIDATION OF MOLECULARLY-TARGETED INTERVENTIONS

- Characterization of molecular targets for intervention
- Development of chemopreventive interventions

CHARACTERIZATION OF PATIENT OUTCOME-ASSOCIATED BIOMARKERS

- Biomarkers of screening and surveillance
- Biomarkers of risk assessment
- Biomarkers of disease progression
- Biomarkers of intervention response

DEVELOPMENT OF NOVEL TECHNOLOGIES AND MODELS

- Development of novel preclinical models
- Development of molecular profiling technologies to identify unique biomarkers for BE and its transition to EA
- Development of dynamic and real-time in vivo imaging technologies to study BE-EA

Structure of the BETRNet

The BETRNet will be comprised of four Translational Research Centers (BTRCs) that are linked by NCI CaBIG applications and coordinated by a Coordinating Center (CC). The CC will provide critical services for study design (e.g., developing the theoretical and statistical approaches to the problem of simultaneous pattern analysis with multiple markers), implementation (e.g., standardization of clinical site reporting including data entry for patient registry) and oversight (e.g., regulatory submissions and compliance, human subjects protection and clinical site monitoring). Each BTRC will establish a data resource of annotated specimens available at the various sites and research findings from the network through *caTissue* Suite, which will allow them to harmonize specimen/data collection and sharing according to the NCI's best practices in addition to technologies and research data sharing. BETRNet will also organize a pathology panel, with representatives from each that will meet twice a year to review the histology of the specimens used by the projects in the network. BETRNet will operate under the guidance of a BETRNet Steering Committee (BSC) composed of BTRC directors and scientific staff from DCP and DCB involved in the development of the RFA. The BSC will serve as the governing scientific and administrative board. The network will carry out joint research that would not be possible to conduct expeditiously, if at all, in the absence of this vehicle of collaboration and funding support.

Key to the success of the network will be the incorporation of existing consortia or Barrett's research groups with a history of productive collaboration into the translational research centers. Centers will be encouraged to form a collaborative relationship among ongoing NCI programs such as the Early Detection Research Network (EDRN), DCP Prevention Consortia, Minority Based Community Clinical Oncology Programs (MBCCOP), Barrett's and Esophageal Adenocarcinoma Consortium (BEACON), SPORES, and the Mouse Models of Human Cancer Consortium (MMHCC). New collaborations can formulate new projects that can compete for funds through the RPG mechanisms or for pilot funds associated with this RFA that will be managed by DC and DCB based on recommendations from the BSC.

Support from External Experts Through their management of grant portfolio, meeting attendance, and communications with the scientific community, NCI scientific staff has recognized an important opportunity to further progress in this area of translational research. In 2002, the NCI's Stomach Esophagus Progress Review Group, a large group of multidisciplinary experts met for a series of meetings to identify gaps in research and provide recommendations for translational research opportunities that would include: 1) Profile the molecular, cellular, and epidemiological features of esophageal tumors and their precursor lesions to identify diagnostic, prognostic, predictive, preventive, and therapeutic targets; 2) Define host and molecular/biologic tumor characteristics that will

help customize treatment and best predict recurrence and/or survival; 3) Develop prevention strategies based on the mechanisms of host/environment interactions that lead to metaplasia and neoplasia of the esophagus; and 4) Evaluate their effectiveness in at-risk populations.

In January 2008, DCP re-convened its Barrett's Esophagus Translational (BETR) Working Group to provide recommendations for the national translational research agenda. The expert group provided the perspectives of the research community who uniformly concluded that a multi-disciplinary, multi-institutional translational research network is needed to accelerate the pace of BE-EA research and provide opportunities for bench to bedside transition in a concerted manner. Such a network will provide investigators with access to specimens from different stages of the disease for studies on its biology, facilitate the development of novel preclinical models, and pool generated mechanistic data on BE and its transformation to EA. Sharing of resources will be a condition mandated by the RFA. Through collaboration of multi-disciplinary scientists and potentially, private industry, the burden of this malignancy on society can be reduced.

In response to the recommendations provided by the 2008 BETR Working Group Meeting and NCI scientific staff as well as prior analysis of portfolio gaps, DCP and DCB have collaborated to draft this concept for the RFA to stimulate research on BE and its transformation to EA. The RFA would support translational research informed by clinical needs and the promotion of clinical research that is based on relevant preclinical findings to address important research questions that are currently underrepresented in the NCI extramural grants portfolio.

DCB and DCP have agreed to collaboratively develop and manage such an RFA. In addition, DCEG has also agreed to support the effort by promoting collaboration with BEACON, an established consortium of population scientists, molecular epidemiologists, clinicians and translational researchers. Potential collaborations with BEACON include mutual access to ongoing cohorts for clinical and epidemiological trial participation and specimen sharing.

3. Current Portfolio Analysis:

In fiscal year 2008, NCI funded 35 BE/EA projects for a total cost of $13,170,739. This number includes training grants such as K and small grants like R03 and R21. Only a small proportion of the grants represent translational research, likely due to the lack of cross-disciplinary collaborations. In FY 2008, NIDDK funded 20 awards totaling $4,758,278 that focused mainly on BE. In FY02, NCI co-sponsored an RFA with NIDDK that garnered 50 applications. The RFA funded 8 R01 applications (3 by NCI) and 5 R21 applications (1 by NCI), most of which resulted in publications and were hypothesis generating. These findings should now be evaluated through organized collaboration for their potential utility in risk stratification and clinical management of patients.

4. Justification for the Use of RFA Mechanism:

The use of this mechanism is justified because critical advances to understand

neoplastic progression in the esophagus are urgently needed and are not supported by the small research base of individual grant projects. Furthermore, there is a lack of adequate sharing practices of high quality biospecimen and data, which are needed for rigorous clinical/translational studies, and research outcomes through a common integrating platform. The NCI portfolio of BE and EA research is rather fragmented and does not focus on some of the more important areas that will significantly impact patients. The specific allocation of NCI resources will ensure collaborations that produce new insights into the pathogenesis of EA and a bench to bedside translation of knowledge of public health importance.

In addition, the responses to the RFA will be reviewed by a special panel convened by DEA that will be selected based on diverse expertise in genomics, technology, cancer biology, clinical management and analyses. This is the most appropriate way to assess the multidisciplinary groups and integrative functions needed to achieve the goals of BETRNet.

5. Justification for Use of Cooperative Agreement:
The BETRNet RFA will utilize the NIH cooperative agreement mechanism for the Translational Research Centers (U01) and for the Coordinating Center (U24). Success of this program will require a high degree of integration and coordination amongst researchers from diverse specialty areas. A cooperative agreement with an active steering committee, NCI program involvement, and CaBIG infrastructure will ensure that a network of disparate investigators in the field of BE-EA research will collaborate and develop their data sharing and resource sharing plans to maximize the outcomes of research projects. A cooperative agreement ensures that NIH staff has meaningful input into the network organization, management, protocol development, DSMB review and shared resources. Current funding mechanisms using unsolicited R01, R21, and R03 grants are inadequate for this activity.

6. Budget:
$7.0 million/year for 5 years. This will include $1.5 million per BTRC per year, $500,000 per year for the CC and $500,000 per year to be shared by DCP and DCB for funding collaborative pilot projects.

7. Evaluation Criteria:
Continuous improvement of BETRNet's performance through ongoing evaluation will be a priority. An external review process (ERP) will be established to determine the extent to which BETRNet is fulfilling its aims. An external review panel of at least 3 independent scientists will be selected to conduct an evaluation approximately in the middle of the funding period, which is based on measurable performance criteria that will include:

- Participation in administrative and scientific committees and/or other BETRNet activities
- Participation in study development within the network and new collaborative projects within and outside the network

- Timely publication of study findings
- Timely and accurate submission of required data to CaBIG, including data on specimens/cohort availability
- Accrual of adequate number of eligible patients to clinical studies
- Rigorous adherence to clinical protocols and NCI best practices
- Development of models and clinical applications from research findings generated by the network

In addition to the above criteria, funded projects will be monitored for progress annually through the evaluation of progress report and discussion at the annual BSC meeting. Progress will also be shared and discussed at a national conference that will include the participating scientists in the program and the scientific leaders from the extramural community who provided advice during the development of the RFA. This conference will be organized toward the end of the network funding. All analyses of publication records and confirmation of accomplishments will be conducted in collaboration with the NCI OSPA to assure complete and objective analysis. A synthesis of the OSPA evaluation and the evaluation by both extramural scientific staff and extramural academic advisors will be reported to the Executive Committee and the Office of the Director.

References

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