Early Detection Research Network (EDRN)
A National Infrastructure for Biomarker Development

Pre-Application Meeting for RFA-CA-16-009
April 21, 2016

Sudhir Srivastava, Ph.D., MPH
Chief, Cancer Biomarkers Research Group
EDRN Program Objectives

- Establish an investigator-initiated infrastructure to support development and validation of early detection biomarkers and markers of progression
- Foster interaction between academic, clinical and industry leaders
- Standardize biomarker validation criteria
- Develop a quality assurance program
- Bring biomarkers to clinical use
Organization of EDRN

Discovery

Assay Development

Validation

Validation Informs Discovery

Network Consulting Team
Chair: Larry Norton, M.D.

Steering Committee
Chair: Ian Thompson
Co-Chair: Joshua Labaer

Data Management and Coordinating Center
Director: Ziding Feng, Ph.D.
Biomarker Developmental Laboratories (BDLs) conduct discovery, development, characterization and testing of new, or the refinement of existing, biomarkers and biomarker assays for:

- Risk assessment
- Molecular Detection
- Molecular Diagnosis and Prognosis of Early Cancer
Clinical Validation Centers: Scope

• Clinical Validation Centers (CVCs) conduct biomarker validation studies

• Partner with other networks with available biospecimens for biomarker validation (e.g., NCTN, Cohort Consortium, HMOs)

• Serve as a Collaborative Resource for the Network

• Partner with EDRN Biomarker Developmental Laboratories (BDLs) and EDRN Reference Laboratories (BRLs)
Biomarker Reference Laboratories (BRLs) serve as Network resources for the validation of biomarkers for clinical or laboratory use. Their responsibilities include:

- Testing of candidate biomarkers
- Assay design and development
- Assay optimization and refinement
- Assay methods and protocol standardization
Data Management and Coordinating Center: Scope

• Network Coordination
• Data Management and Protocol Development
• Validation Infrastructure and Services
• EDRN Core Fund Management
Partnering Organizations

- National Institute of Standards and Technology
- Center for Prostate Disease Research, DOD
- Pacific Northwest National Laboratory, DOE
- Jet Propulsion Laboratory, NASA
- Canary Foundation of America
- Lustgarten Foundation N.Y.
- International collaborations: China (C-EDRN), Cancer Research-UK, Turkey, Japan, Chile, Israel
- Industry (15 active)
- Associate Members (>200)
## EDRN Milestones:
From Structure to Process to Outcomes

### 2000-2005
**Coordinate, Communicate and Collaborate**
- 33 Principal Investigators
- Steering Committee Attendance: 85; Workshop 300
- Associate Membership Program Initiated; 32 Associate Members
- Initiated EDRN-Human Proteome Organization Plasma Proteome Project
- Guidelines for Biomarker Discovery and Validation
- Project Management Tools Created
- Multi-center Trial Informatics Infrastructure created, verified
- Virtual Specimen Bank Established
- IRB Approvals Monitored: 38 sites

### 2005-2010
**Learn, Improve and Deliver**
- 45 Principal Investigators
- Steering Committee Attendance: 120; Workshop 300
- 123 Associate Members
- 2 EDRN-Gordon Research Workshops (2005, 2007)
- MOUs signed With Canary Foundation, Lustgarten Foundations, Turkey
- OVA1 FDA Approved
- EDRN-FDA Educational Biennial Workshop
- EDRN-NIST Workshop on Standards
- IRB approvals monitored: About 80 sites

### 2010-Present
**Productivity, Outcome and Dissemination**
- 57 Principal Investigators
- Steering Committee Attendance: 150; Workshop: 350
- 231 Associate Members
- DCP and AFP-L3 FDA Approved for Liver Cancer and ROMA for Ovarian Cancer
- proPSA and PCA-3 FDA Approved for Prostate Cancer
- 11 CLIA-approved Diagnostic Tests
- 10 Clinical Reference Sets completed and stored at Frederick, MD
- IRB Approvals Monitored: 216; 200 Protocols; 100 MTAs
Study Designs for Biomarker Development

**Phases of Biomarker Discovery and Validation**

- **Preclinical Exploratory** (PHASE 1): Promising directions identified
- **Clinical Assay and Validation** (PHASE 2): Clinical assay detects established disease
- **Retrospective Longitudinal** (PHASE 3): Biomarker detects preclinical disease and a “screen positive” rule defined
- **Prospective Screening** (PHASE 4): Extent and characteristics of disease detected by the test and the false referral rate are identified
- **Cancer Control** (PHASE 5): Impact of screening on reducing burden of disease on population is quantified

**References**

Phases of Biomarker Development for Early Detection of Cancer
Margaret Sullivan Pepe et al.

Pivotal Evaluation of the Accuracy of a Biomarker Used for Classification or Prediction: Standards for Study Design
Margaret Sullivan Pepe et al.
J Natl Cancer Inst 2008; 100:1432-1438
Salient Features of EDRN

• Provide **Integrated Infrastructure**
• **Build Resources** for Biomarker Research
• **Establish Standardized Criteria** for Biomarker Discovery and Validation
• **Quality Assurance** Programs
• Ensure Research **Reproducibility**
• Improve Screening and Diagnostic **Tests for Common Clinical Dilemmas**
Building Resources for Clinical Studies

- Platform for multi-center biomarker validation studies
- Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories to develop and test assays using GLP and GMP
- Centralized statistical center for data analysis and informatics infrastructure to share data
- Mechanism for biomarker triaging prior to large, expensive validation studies (use of Reference Sets)
- >100,000 clinically-annotated biospecimens using common data elements (CDEs)
Building Resources for Clinical Studies: Informatics and Bioinformatics (Jet Propulsion Lab)

- VSIMS for multicenter validation studies
- eSIS for study management
- ERNIE for Virtual Specimen Banks (tracks >100,000 biospecimens)
- Prioritized Biomarker Database
- >2600 Common Data Elements
- Validation data collected through LabCAS (proteomic and genomic data) and eCAS
- Crowd-sourcing being considered on stored data

http://edrn.nci.nih.gov/informatics/informatics
Biomarker Development Laboratories (RFA-CA-16-009 U01)

The application in response to this FOA must be focused on cancers of the breast, prostate and other genitourinary organs, and lung. In addition, cancers with rapidly rising incidence rates, e.g., endometrial, hepatocellular, kidney, thyroid, oropharyngeal cancers, and/or cancers with unique etiology, e.g., mesothelioma, will be responsive.

All of the components of EDRN are funded through the Cooperative Agreement Mechanisms in which there is substantial involvement of the NCI staff.
General Requirements of this FOA

- Adhere to FOA-specific scope, specific requirements, page limitations, and other details
- Describe study designs
- Describe statistical analyses
- Collaborate with cohort, consortia, HMOs, Cooperative Groups, and other relevant entities for a shovel-ready biospecimen collection for development of biomarkers
- Pay attention to review criteria when preparing your application
- Describe licensing and IP plan, if applicable
Purpose of this FOA

This FOA solicits applications for EDRN Biomarker Developmental Laboratories (BDLs) to discover and develop biomarkers and molecular and cellular signatures for risk assessment, detection, and diagnosis and prognosis of early cancers.
### Key Responsibilities of BDLs in the Five-Phase Development of Biomarkers

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical Exploratory</td>
<td>PHASE 1  Promising directions identified</td>
</tr>
<tr>
<td>Clinical Assay and Validation</td>
<td>PHASE 2  Clinical assay detects established disease</td>
</tr>
<tr>
<td>Retrospective Longitudinal</td>
<td>PHASE 3  Biomarker detects preclinical disease and a “screen positive” rule defined</td>
</tr>
<tr>
<td>Prospective Screening</td>
<td>PHASE 4  Extent and characteristics of disease detected by the test and the false referral rate are identified</td>
</tr>
<tr>
<td>Cancer Control</td>
<td>PHASE 5  Impact of screening on reducing burden of disease on population is quantified</td>
</tr>
</tbody>
</table>

Examples of Biomarker Discovery Research

• Development of molecular signatures based on integrated ‘omics’ approaches to assess risk; to identify pre-cancerous lesions and early stage cancer; and to identify of cancers that are likely to progress.

• Development of biomarkers in preclinical specimens to discriminate between screen-detected aggressive lesions and indolent or slow-growing lesions to reduce the burden of overdiagnosis and overtreatment.

• Development of biomarkers for risk stratification; improve risk stratification by improving pathological classification, especially of early lesions.

• Molecular signatures for risk of and early stage disease due to infectious agents, pathogens, or environmental agents.
Examples of Biomarker Discovery Research (Cont’d)

- Development of **integrated approach** based on **imaging modalities and molecular/‘omic’ biomarkers** for risk assessment, early detection, diagnosis and early prognosis.

- Effectively delineate disease **genotypes** and **phenotypes of pre-cancerous and cancerous lesions that are likely to progress**.

- Determine the potential of **perturbed network- and pathway-based biomarkers**.
Biomarker Developmental Laboratories: Expectations

- Laboratory scientists with extensive biomarker research experience and experience with knowledge and principles of biomarker discovery
- Biomarkers addressing specific clinical question(s) in the realm of early detection (Phase 1 and Phase 2)
- Discovery based on EDRN’s five-phase biomarker development criteria and PRoBE or a similar study design
- Availability of quality specimens for discovery as opposed to “convenience samples”
- Robust study design and appropriate statistical approach to minimize false discovery (plan to adjust for multiplicity, plan to minimize chance, bias, overfitting, etc.)
- Decision criteria for triaging candidate biomarkers
- Achievable timeline of proposed research
- Collaboration to complement expertise and resources; IP and licensing plan to ensure that collaboration is not affected
Page Limitations

All page limitations described in the SF424 Application Guide and the Table of Page Limits must be followed, with the following exception:

For this specific FOA, the Research Strategy must not exceed 30 pages.
Requirements and Key Components for a BDL

Facilities and Resources

- Specialized or unique resources important for achieving objectives
- PDs/PIs must have their own research laboratories and demonstrate they have expertise in the technologies they propose to use

Key Personnel (include or have access to)

- Pathologist – expertise in your disease focus
- Clinical epidemiologist/biostatistician – understands PRoBE study design, power calculations for a strong study design
- A designated Project Manager who will be the main point-of-contact regarding the details and activities of the study

Part 2. Section IV: Application and Submission Information.
Budget

• Direct costs may not exceed $250K/yr for single-PI or $400K/yr for multi-PD/PI awards, including the 30% set-aside.

• The lead PD/PI must commit a minimum of 1.8 person-months effort per year. For multiple PD/PI awards, the other PDs/PIs must devote a minimum of 1.2 person-months effort per year.

• Set aside 30% of the annual budget for Network collaborative studies from Year 1 onward. Release of these funds must be reviewed by the EDRN Steering Committee and approved by NCI.

• Travel and per diem expenses for PD/PI and an additional senior investigator to attend:
  • Planning (Orientation) and a Steering Committee Meeting in the first year (two meetings)
  • Two Steering Committee Meetings per year
  • One Network Workshop or Symposium every 18 months
An example of 1st year restricted travel budget for 2 PIs attending 2 Meetings

### C. Equipment Description

List items and dollar amount for each item exceeding $5,000

<table>
<thead>
<tr>
<th>Equipment Item</th>
<th>Funds Requested ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional Equipment: [Add Attachment] [Delete Attachment] [View Attachment]

Total funds requested for all equipment listed in the attached file: [ ]

Total Equipment: [ ]

### D. Travel

1. Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions) \((2 \text{ PIs} \times 2 \text{ Mtgs} \times $2,000)\) 8,000
2. Foreign Travel Costs

Total Travel Cost: 8,000

### E. Participant/Trainee Support Costs

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other

<table>
<thead>
<tr>
<th>Funds Requested ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

Number of Participants/Trainees: [ ]
Total Participant/Trainee Support Costs: [ ]
All applicants must set aside 30% of their budget from the 1st year onward for Network collaborative studies.

- 30% of the $400K (direct cost) = $120K (direct cost)

- The remaining budget, $400K - $120K = $280K (direct cost) will be used towards the proposed BDL studies.
All standard SF424 instructions for PHS 398 Research Plan must be followed along with the additional items noted below:

**Specific Aims**

In addition to a brief description of the specific aims and approach(es) to be employed, applicants must outline the scope of the proposed research and its relevance to a specific unmet clinical need in the management of human malignancies.

**Research Strategy**

**Sub-section A: Overview** – Team structure, relevant partnerships or collaborations, data & resource sharing

**Sub-section B: Previous Accomplishments** – Related to biomarker discovery

**Sub-section C: Research Project** – What you propose to do

**Sub-section D: Project Management Plan**

1. Timeline
2. Milestones (quantifiable)
3. Decision-tree scheme (when to stop or continue with biomarkers)

Section IV: Application and Submission Information.
Multiple PD/PI Leadership Plan
In addition to following standard instructions, applicants should explain how the multiple PDs/PIs will divide their scientific responsibilities in terms of focus on different platforms for biomarker discovery and development. In this context, it is expected that each PD/PI will be responsible for a different platform (although overlap in types of tumors of focus across PDs/PIs is acceptable).

Letters of Support
In addition to standard items, provide letters of commitment for resources and/or technology made available by industry partners involved in the proposed research.

Resource Sharing Plan
1. Specimen Sharing
2. Intellectual Property Management Plan
Receipt and Other Schedules

• Letter of Intent Due Date: April 23, 2016

• Application Due Date: May 23, 2016 (by 5:00 PM local time of applicant organization)

• Peer Review Date: July 2016

• Advisory Council Review: August 2016

• Earliest Anticipated Start Date: September 2016
Summary

- Propose biomarker Phase 1/Phase 2 biomarker discovery studies addressing unmet clinical needs
- Highlight key personnel, incorporation of PRoBE design, relevant statistical considerations of study design, and measurable research milestones
- Collaboration with national networks and NCI-supported programs for access to high quality specimens
- Access to specific patient populations for prospective specimen collections
- Partnership with other EDRN components (visit www.cancer.gov/edrn)
- Project management plan with timelines and quantitative milestones
- Resource and data sharing plan, and Intellectual Property management plan
Application Checklist

- Is application organized per instructions in the RFA?
- Have the review criteria been addressed in the proposal?
- Are the proposed specific aims achievable in a given time frame?
- Has collaboration been established and partners on board?
- Has a contact PI been identified for multi-PI proposal and communication and management plan developed?
- Have the special requirements been followed in developing the proposal, e.g., page limit, team structure, study designs, etc.?
NCI PD Contacts

- Jacob Kagan, M.Sc., Ph.D. (Prostate and Other Urological Cancers)  
  kaganj@mail.nih.gov
- Karl Krueger, Ph.D. (Lung and Upper-Aerodigestive Cancers, Glycomics)  
  kruegerk@mail.nih.gov
- Lynn Sorbara, Ph.D. (Lung and Upper-Aerodigestive Cancers)  
  lynns@mail.nih.gov
- Christos Patriotis, Ph.D. (Breast and Gynecologic Cancers)  
  patriotisc@mail.nih.gov
- Sharmistha Ghosh-Janjigian, Ph.D. (Breast and Pancreatic Cancers)  
  ghoshjanjigias@mail.nih.gov
- Wendy Wang, Ph.D. (Breast Cancer, International Collaborations)  
  wangw@mail.nih.gov
- Richard Mazurchuk, Ph.D. (Imaging)  
  richard.mazurchuk@nih.gov
- Jo Ann Rinaudo, Ph.D. (GI Cancers)  
  rinaudoj@mail.nih.gov
- Matt Young, Ph.D. (GI Cancers)  
  youngma@mail.nih.gov
Thank you