Translational and Basic Science Research in Early Lesions (TBEL) Initiative

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Early Lesion Clinical Dilemma & Biological Challenges

- Increasingly sensitive diagnostic technologies exist that readily detect precancers, early cancers and incidentalomas
- No effective means to phenotypically distinguish between lesions that are likely to progress and those that are indolent and are unlikely to be lethal
- Insufficient biological studies on the role of stroma as a co-organizer of early lesion fate
- Inability to organically coordinate basic and translational research gaps/challenges in order to characterize and distinguish phenotypically and biologically between indolent from aggressive early lesions

TBEL Overarching Objectives

To address these challenges and gaps by developing a comprehensive mechanistic understanding of early lesions and the determinants of their clinical trajectory to improve clinical management:

- Support multi-disciplinary studies that bridge the basic biology-translation gaps
- Gain biological insights on early lesion-specific blockers and drivers of disease progression
- Build upon established predictive markers, retrospective data/samples and computationally-derived and biologically-backed leads
- Improve the understanding of early lesion fate for better risk stratification
- Identify tumor and stromal targets that may improve existing screening methodologies, inform the development of new screening approaches to unscreened tumors, and establish biology-backed data to guide “precision prevention”

Stroma-Derived Influence on Neoplastic/Malignant Conversion (Important Mechanistic Leads but Insufficient Follow-Up)

Seminal Insights

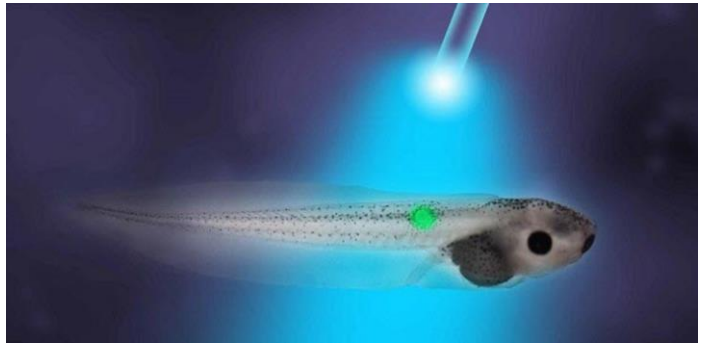
- **Cancer-Associated Fibroblast influence (CAF)**: Activated CAFs (but not normal fibroblasts) directly support tumor progression of initiated prostate epithelial cells in co-cultures and xenografts (AF Olumi, et. al., *Cancer Res* 1999)
- **Tissue Architecture**: Stromal MMP3 remodeling of the extracellular matrix influences initial tumor development and drives malignant conversion of mammary epithelial cells. (LM Coussens, MJ Bissell & Z Werb, *Chem Biol* 1996, *Cell* 1999)
- **Inflammation**: Chronic pulmonary inflammation-induced epigenetic silencing of p16 (CDKN2A) drives early lesion malignant conversion, without the acquisition of classic driver mutations. (D Blanco, et. al., *Neoplasia* 2007)
- **Aging Microenvironment**: Age-associated increase in mutation burden/genomic instability linked to decline in tissue levels of NAD^+ and downstream effects on PARP1-mediated DNA repair and BubR1-dependent mitotic checkpoint regulation. (J Li, et. al., *Science* 2017)

Stroma-Derived Influence on Neoplastic/Malignant Conversion
(Important models with potential in TBEL studies/new directions)

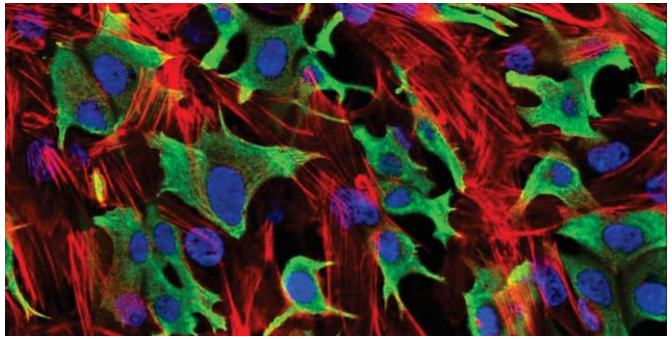
Key Questions:

- How does the bidirectional relationship between stroma and early lesion influence each other's phenotypic outcome?
- How can biologically significant parameters in stroma and early lesion inform clinical management?

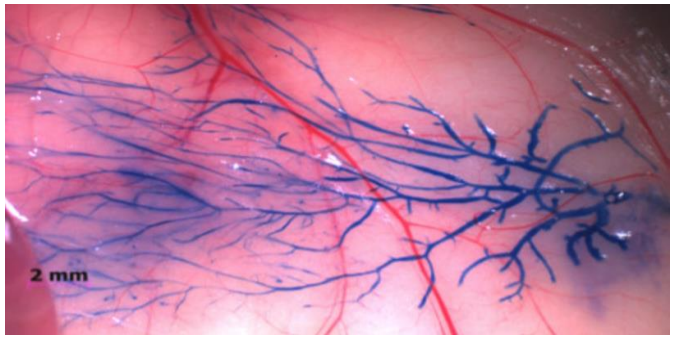
Stromal Optogenetics Manipulation



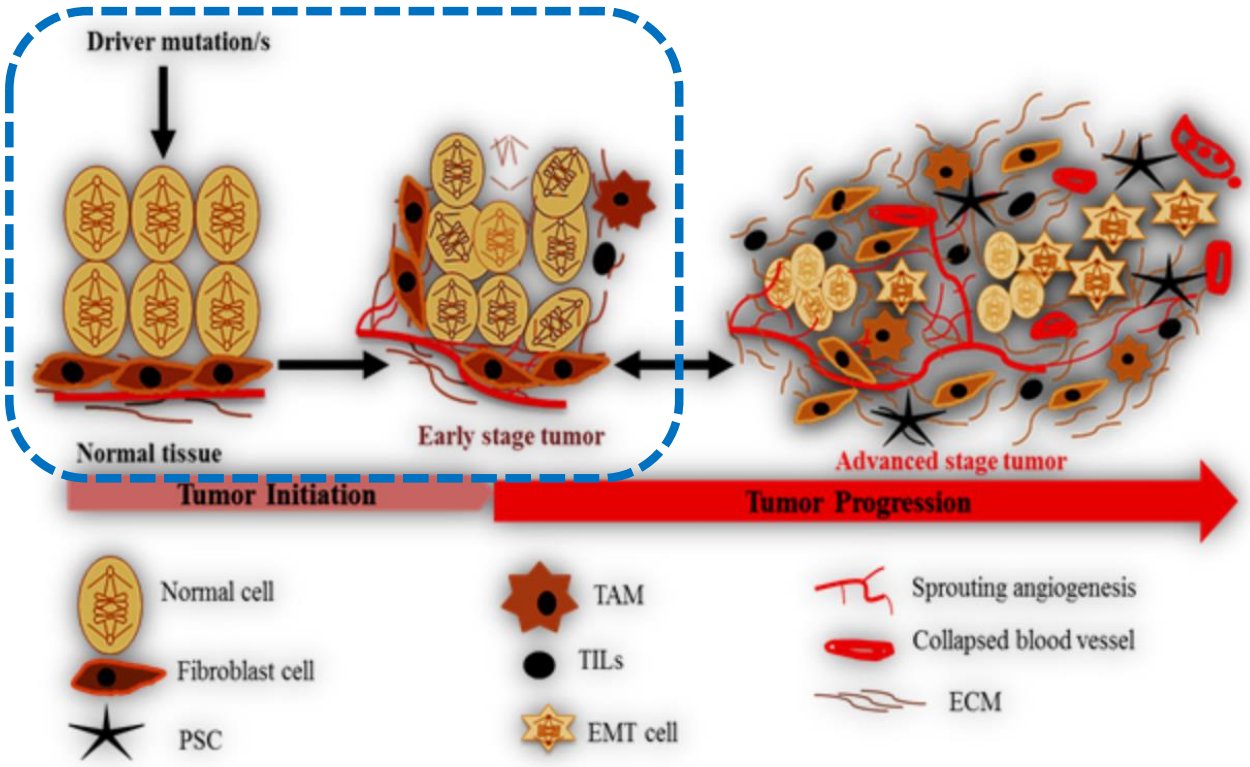
Microenvironment Barcoding



Mammary Intraductal (MIND) Approach



TBEL Objectives: Basic Biology Gaps to be Filled



- Limited studies dedicated to elucidating the complex, multi-dimensional aspects of early lesion-microenvironment dynamics
- Paucity of basic scientists dedicated to early lesion-microenvironment biology research
- Lack of knowledge on **the role of stroma in shaping the fate of early lesions** – and as an equal partner/modulator of malignant conversion
- Insufficient knowledge of early vs late stage-specific disease modulators
- Lack of coordination with translational research

Clinical Challenges: Overdiagnosis and Incidentalomas (a major health care burden)

Cancer type	Overdiagnosis (estimates)	Screening modality
Breast	25%	Mammography
Prostate	50–60%	PSA
Lung	13–25%	CT
Melanoma	50–60%	Population trend-based crude estimate
Kidney	Two-fold increase in incidence (but no increase in deaths)	abdominal CT
Thyroid	Two-fold increase in incidence (but no increase in deaths)	Incidental detection by imaging or palpitation

PSA, prostate-specific antigen; **CT**, computed tomography. **Srivastava et al., Nat Rev Cancer. 2019**

Incidentalomas:
Highest percentage occurred in the breast (42%), followed by ovaries, thyroid, and kidney, where cancer was found about 25% of the time as the result of US, CT, MRI for unrelated diseases.
BMJ 2018;361:k2387

- No effective means of predicting whether an early lesion is progressive or indolent and how to best manage it.
- Filling in the biology gap will help inform future precision-based clinical management

TBEL Objectives: Translational Research

- Develop approaches and define technologies informed by biology to assess the predictive and/or stochastic behavior of early lesions.
- Develop morphometric algorithms for distinguishing indolent from aggressive lesions through the integration and co-registration of early lesion imaging and '-omics' data along with clinical annotation.
- Develop statistical modeling using combined basic and patient-derived early lesion '-omics' data to uncover pathways and sequences of events driving early lesion progression.
- Stimulate/support biologically-backed translational research; and integrate the molecular and genomic alteration analysis in precancerous lesions with wide-ranging stromal elements and clinically annotated screen detected or incidentalomas and interval lesions.

Areas of Programmatic Interest & Integration

Basic Biology

- Tumor & stromal landscape of lesion drivers and suppressors based on position-dependent functional organization/heterogeneity/reciprocal interactions.
- Mediators of chronic inflammation, metabolic crosstalk, and/or phenotypic switching/cellular plasticity.
- Development of novel or repurposed early lesion platforms (and companion human resources) to interrogate complex ECM-stromal cell-nascent tumor cell interactions in malignant progression.

Translational Science

- Molecular "-omic" evaluation of recurrent and non-recurrent screen-detected lesions, interval lesions and incidentalomas to identify unique and/or shared aggressive or indolent features.
- Integrating phenotypes of the cellular and stromal components in early lesions with molecular signatures that may predict increased cancer-specific mortality.
- Adopting sequential imaging approaches to elucidate dynamic changes in progressive disease to provide insights into molecular and cellular events linked to lethal cancer versus non-lethal disease.

Early Lesion & Microenvironment Basic Biology Portfolio Analysis

Research Focus	Active grants (#)
Immuno-Oncology	28
Multi-Component/ Complex Microenv	9
ECM	9
Microbiome	4
Fibroblast	3
Nerves	1
TOTAL=	**54**

- **NCI-Wide Basic Biology with TME**, but **Tumor as Organizer** = 54 awards
- **Program Emphasis: Early Lesion & Stroma as Co-Organizers** in shaping tumor initiation & malignant conversion

Translational Research Portfolio Analysis

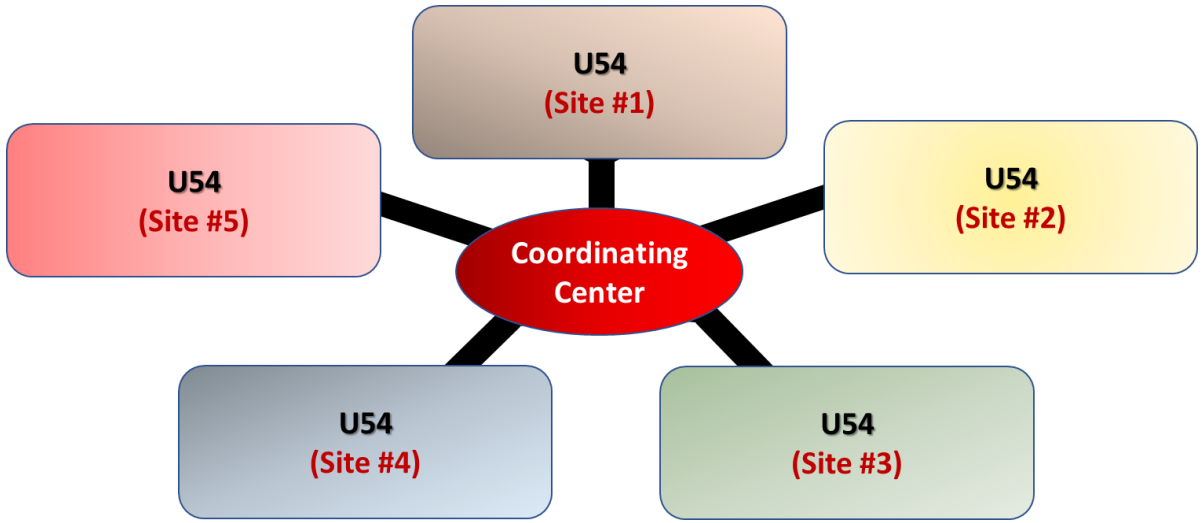
Funded Programs/Activities	Active Grants (#)
EDRN	**3**
MCL Consortium*	**7**
Moonshot PCA	**5**
Other initiatives: BETRNet*, SCLC Consortium, Alliance of Glycobiologists, Liquid Biopsy for Early Cancer, Consortium of Imaging and Biomarkers	**10**
R01, R35, R37	**23**
TOTAL =	**48**

* **Expiring Programs**

- **NCI-wide** (all funding mechanisms) = 48 awards with a translational research component focusing on overdiagnosis, early lesion progression and microenvironment

- **Program Emphasis:** Distinguish between indolent and aggressive, screen-detected or interval (symptom)-detected early lesions and incidentalomas based on unique biologically-backed, molecular/imaging measures

TBEL Mechanisms & Structure



- Broad focus: Lung, Kidney, Thyroid, Bladder, Pancreas, Breast, Prostate, Hematopoietic
- Identify unique and/or common pathways & determinants of indolence/aggressiveness

Structure:

- 5x U54 Specialized Centers
- 1x U24 Coordinating & Data Management Center
- U54: Complementary Multi-PI & integrated Projects
  - **2** Basic + **1** Translational projects
    OR
  - **1** Basic + **2** Translational projects
  - Dedicated core for unique resources, tool development/optimization

Networking and Synergy:

- **Restricted funds** for inter-U54 collaborations (15%)
- **Working group** activities to address common goals, challenges and opportunities
- **Sharing** of tools, reagents and resources
- Required **Steering Committee-led meetings**
- Inclusion of **Associate Members** (from relevant NCI programs)

Potential Long-Term Impact of TBEL

- Expand understanding of early lesion biology and clinically relevant trajectories through comprehensive analysis of stage-specific lesion-microenvironment dynamics.
- Develop biology-backed parameters to improve and expand screening modalities and perform more effective risk stratification and inform “precision prevention.”
- Reduce health burden associated with inadequate screening, overdiagnosis and overtreatment.
- Build on and expand resources and knowledge from other NCI-funded programs (and vice-versa): HTAN-PCA, SPOREs, CSBC, NCI/CR-UK Cancer Grand Challenges, etc.
- Potential trans-NIH partnership (NIDCR)

TBEL Evaluation Criteria

- Publication of center-specific & collaborative research findings
- Collaboration & participation in new pilot study development within and outside the network
- Sharing of human specimens between centers to answer collaborative research questions
- New grant applications generated by cross-TBEL studies
- Novel models and resources to be shared with the broader scientific community
- Development of research tools & applications for patient management

TBEL Initiative: Proposed Budget

Funding Mechanism	No. of Awards	Funding Level	Recommended Total Costs
U54	5	Each award max. $1 M DC	$9 M (First year)
U24	1	$500 K DC	
			Total for the Program $45 M (5 years)

THANK YOU!

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