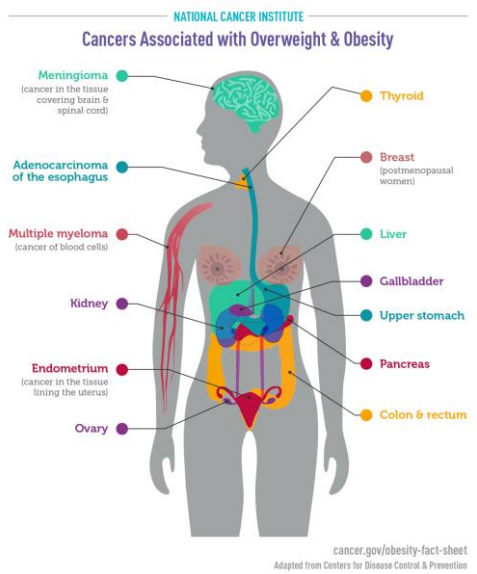


Trans-NCI Collaboration:

Division of Cancer Control and Population Sciences
Division of Cancer Biology
Division of Cancer Prevention
Center to Reduce Cancer Health Disparities

METABOLIC DYSREGULATION AND CANCER RISK:
A TRANSDISCIPLINARY APPROACH TO OBESITY-ASSOCIATED CANCER RESEARCH

TRAM KIM LAM

RFA CONCEPT PROPOSAL

DECEMBER 1, 2020
BSA

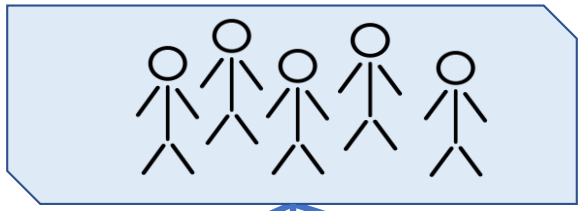
CONCEPT FRAMEWORK

Complements and extends current knowledge by focusing on **metabolic dysregulation as a key mechanism linking obesity to cancer risk.**

INTENT

To support transdisciplinary research that will enhance our knowledge of the dynamics, and underlying mechanisms, that link obesity, metabolic dysregulation, and cancer risk.

Research Project Grant

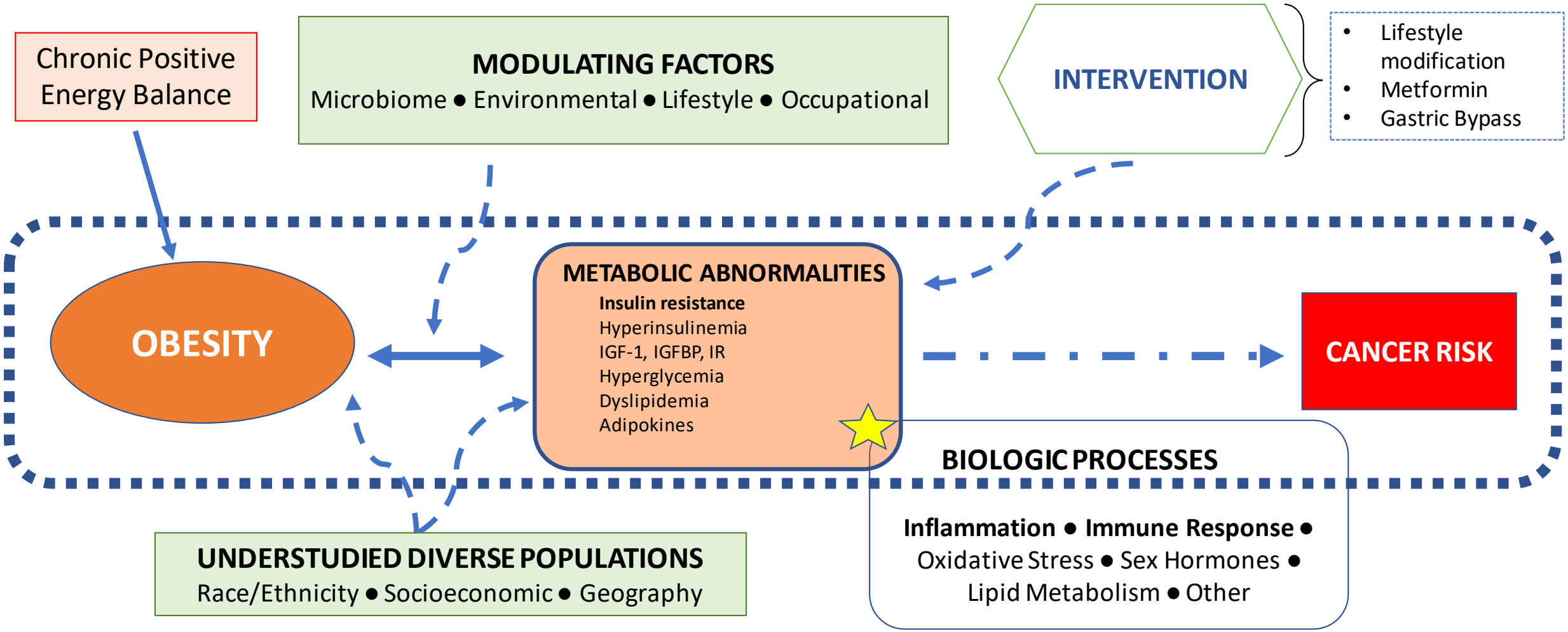


PRE-CLINICAL **OBSERVATIONAL** **INTERVENTIONAL**

OBJECTIVES

1. Investigate the mechanistic role of metabolic dysregulation underpinning the obesity-cancer link.
2. Characterize an altered metabolic profile (e.g., metabolic-related markers) to identify high-risk individuals.
3. Test interventions designed to modify obesity altered-metabolic pathways to decrease cancer risk.

THE OBESE STATE → Metabolic-dysregulated "Disease" State



IGF-1: Insulin-like growth factor-1; IGFBP: Insulin-like Growth Factor Binding Protein; IR=Insulin receptors; PI3K: Phosphatidyl inositol-3 kinase; MAPK: mitogen-activated protein kinase; mTOR: mammalian target of rapamycin

RESEARCH PRIORITIES

- What is the relationship between insulin resistance and cancer risk?
- How does metabolic dysregulation affect anti-tumor immune and inflammatory response in relation to cancer risk?
- Are overweight/obese individuals with a metabolic dysregulation profile at higher risk of cancer compared to those (overweight/obese or nonobese) with a normal metabolic profile?
- Can weight loss or other clinical interventions improve abnormal metabolic profiles (i.e., insulin resistance) and modify cancer risk?

RESPONSIVE APPLICATIONS

MUST INCLUDE

1. Focus on obesity-associated metabolic dysregulation
   - metabolic-related phenotypes
2. Use objective measures of adiposity
3. Address a pressing need or gap in obesity-cancer research
4. Accept the inclusion of common measures and participation in collaborative research
5. Comprehensive Data Sharing Plan

POSSIBLE STUDY STRATEGIES

OBSERVATIONAL

- Case-control; Cohorts
  - Molecular Pathological Epi
- + Preclinical model

INTERVENTIONAL

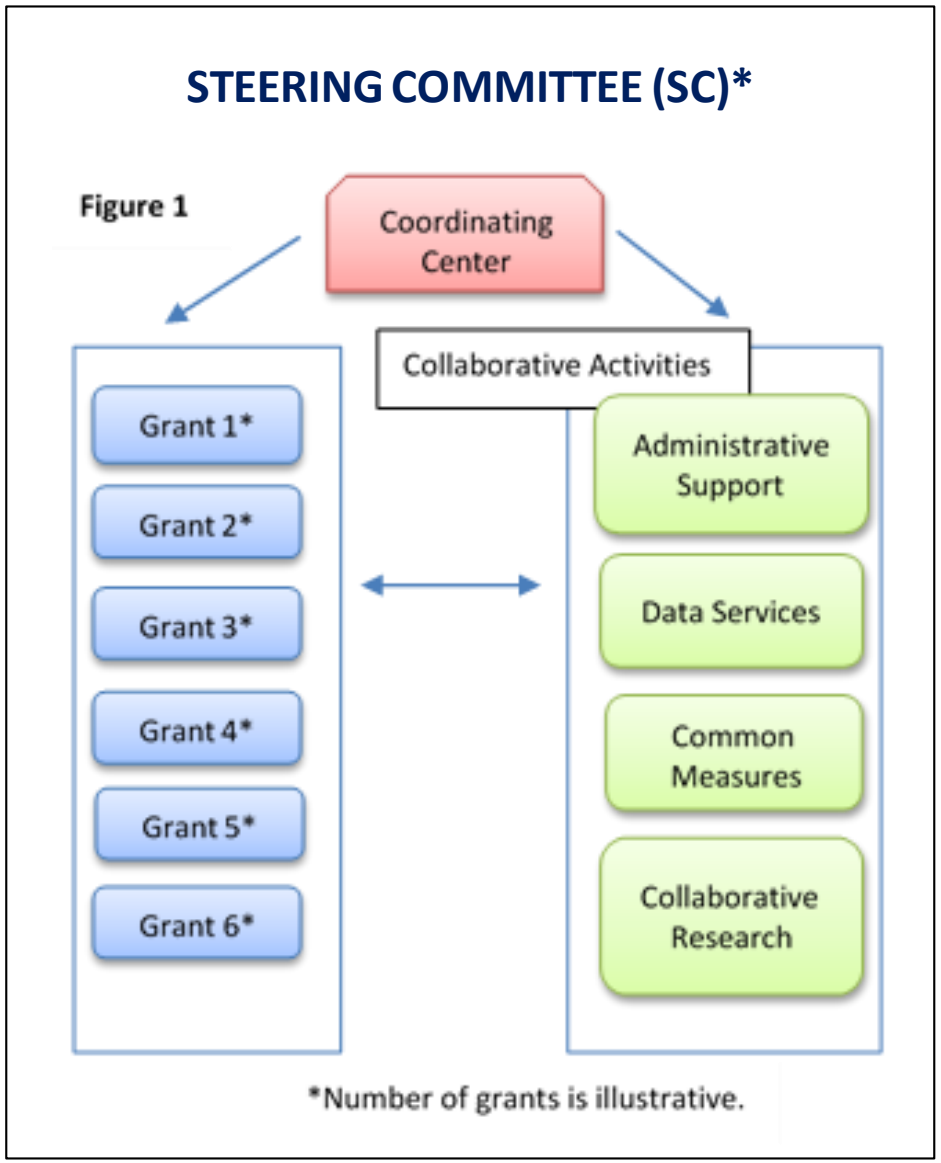
- Interventional (INT)
- Clinical trial
- + Preclinical model

POSSIBLE ENDPOINTS

- Cancer risk; cancer precursors
- Markers of carcinogenesis
- Metabolic-related markers (INT/Trials)

RFA: U01/COOPERATIVE AGREEMENT

CLINICAL TRIALS OPTIONAL



Program Staff

Pre-Submission/Submission

* Assess responsiveness of applications
* Provide programmatic guidance
* Identify common themes from applicants

Steering Committee

Award

* Identify common themes across projects
* Identify common measures that could be assessed by two or more projects
* Identify possible collaborative projects

Program Staff with SC

Post-Award

* Provide programmatic and scientific guidance to address gaps
* Provide support to foster investigation of emerging concepts that will require collaborative science

*Steering Committee: NCI staff, funded PIs, and coordinating center

BUDGET

- Total Costs: $40M for 5 years
  - $8M per year
- Research Project Grants: $7M total cost per year
  - 6 projects (average $1.15M per grant)
- Coordinating Center: $1M total cost per year

SHORT-TERM GOALS

- Understand the mechanisms of how obesity-related metabolic dysregulation affects cancer risk.
  - Insulin resistance
- Characterize cross-talks between metabolic dysregulation and key biologic processes* in obesity-related cancer risk.
  - Inflammation; immune response
- Develop common measures and readouts of obesity-related metabolic dysregulation for different cancer types.
  - Enable synergy across studies and inform pilot collaborative projects

***BIOLOGIC PROCESSES:** Inflammation ● Immune Response ● Oxidative Stress ● Sex Hormones ● Epigenetic Changes…

REVIEWERS' COMMENTS and CLARIFICATIONS (Drs. White, Beckerle, and Brawley)

- Broad potential for topics, suggest greater clarity of examples that are responsive to FOA
  - *Areas of research priorities to be emphasized in the FOA language:*
    - *Insulin resistance and cancer risk; how does insulin resistance influence cancer risk?*
    - *Effects of metabolic dysregulation on immune and inflammatory response and cancer risk*
  - *Programmatic guidance at pre-application stage to answer questions in advance of submission deadline*
- Clarification for the opportunities for synergy within the consortium
  - *Identification of common data/measures*
  - *Pilot collaborative projects to investigate emerging concepts guided by the SC*
- Clarification, pre-clinical models do include animal models
  - *FOA language will clarify the inclusion of animal models to investigate mechanisms*