National Cancer Institute

Advanced *In Vivo* Imaging to Understand Cancer Systems

Trans-Divisional Initiative:

Division of Cancer Treatment and Diagnosis
Division of Cancer Biology
Office of Technology and Industrial Relations

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Advanced *In Vivo* Imaging to Understand Cancer Systems

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Advanced *In Vivo* Imaging to Understand Cancer Systems

Imaging –

An enabling science that combines advanced technology and methods for data extraction, analysis, and display

The intent of this concept -

To develop and apply new imaging solutions to the elaboration of knowledge of *in vivo* systems beyond that possible with available platforms

Advanced *In Vivo* Imaging to Understand Cancer Systems

In Vivo Imaging –

Non destructive extraction and measurement of specific data from *in vivo* systems with insignificant perturbation of the system

Impact & Hypothesis

The knowledge of cancer systems and networks derived in part from *in vivo* imaging will be critical to the development of safer more effective therapies for cancer patients

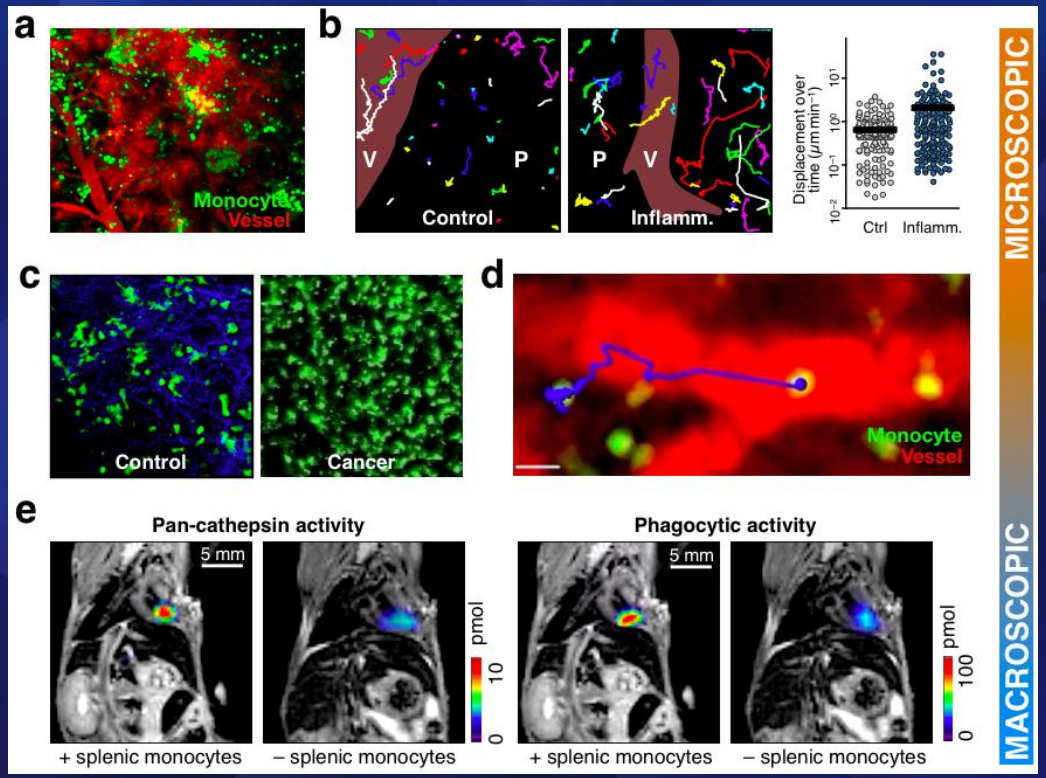
'Targeting cellular networks'

Nature Reviews Drug Discovery

November, 2007.

Advanced *In Vivo* Imaging to Understand Cancer Systems

The Scope of this proposal is from Living Cell to Patient



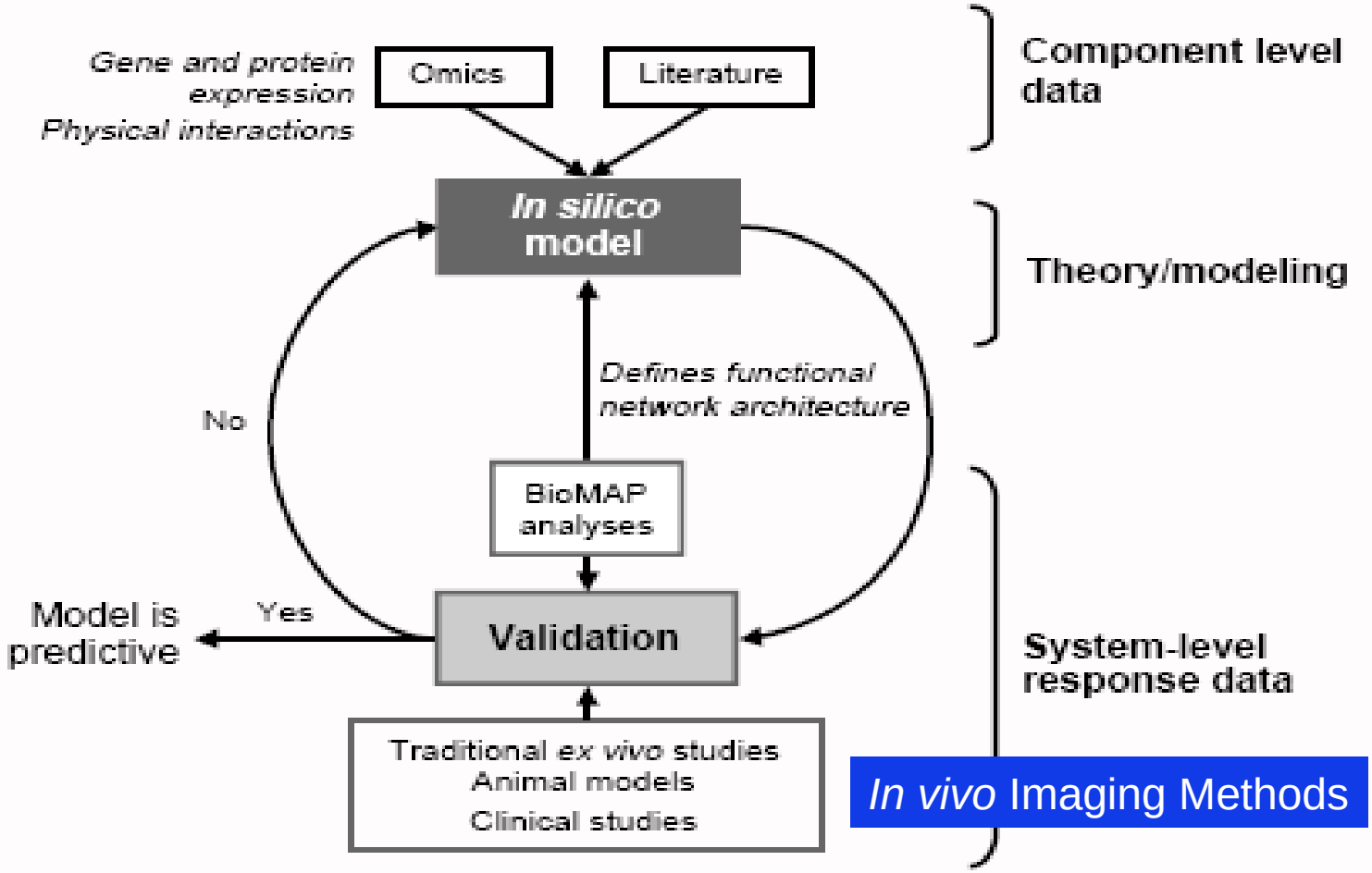
Integration of advanced imaging from micro to macro levels

Tracking of single cells *in vivo*

Informing clinical care

Science 325: 612, 2009: Monocyte Reservoir In Spleen

Analyzing Complexity in Biologic Systems



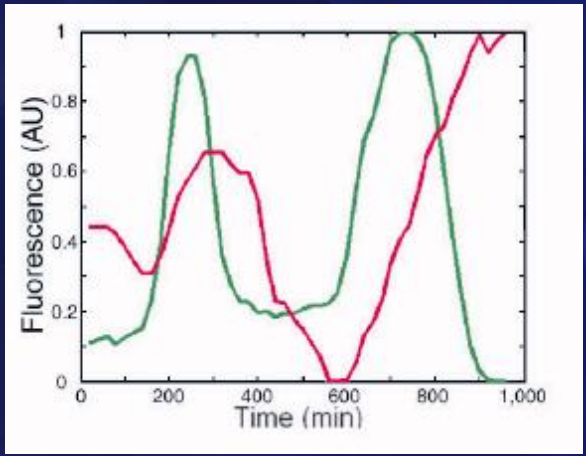
Butcher et. al. *Nature Biotechnology,* 2004

Non-invasive imaging and Systems/Network Biology

Dynamics of the p53-Mdm2 feedback loop in individual cells

Galit Lahav[1], Nitzan Rosenfeld[1], Alex Sigal[1], Naama Geva-Zatorsky[1], Arnold J Levine[2], Michael B Elowitz[3] & Uri Alon[1]

…the p53-Mdm2 feedback loop generates a 'digital' clock that releases well-timed quanta of p53 until damage is repaired or the cell dies.



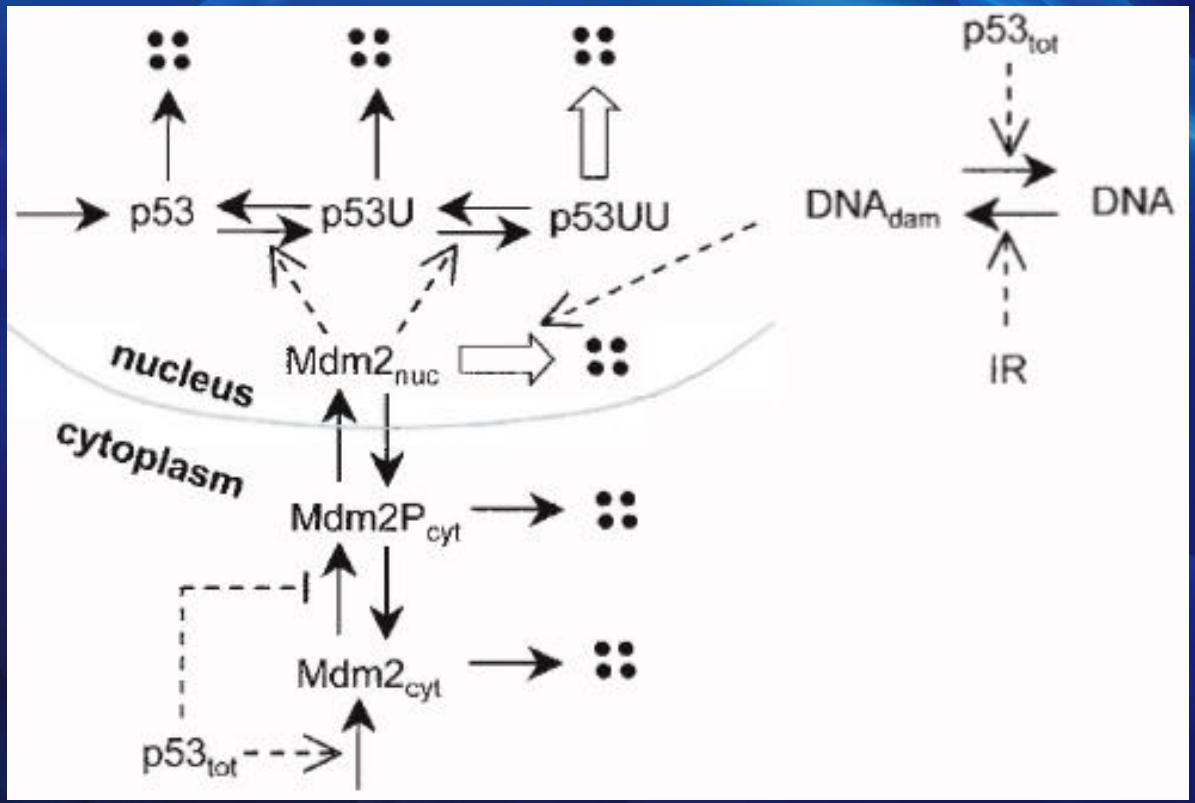
P53 – green

Mdm2 - red

Nature Genetics, February 2004.

Non-invasive imaging and Systems/Network Biology

Steady States and Oscillations in the p53/Mdm2 Network



Ciliberto A, Novak B. and Tyson J, *Cell Cycle 2005.*

Non-invasive imaging and Systems/Network Biology

Table 1 **Differential equations for the p53/Mdm2 network model**

$$\frac{d[p53_{tot}]}{dt} = k_{s53} - k_{ds53}\cdot[p53_{tot}] - k_{es53}\cdot[p53UU]$$

$$\frac{d[p53U]}{dt} = k_1\,[Mdm2_{nuc}]\,[p53] + k_{-1}\,[p53UU] - [p53U]\,(k_{-1} + k_1\,[Mdm2_{nuc}]) - k_{ds53}\cdot[p53U]$$

$$\frac{d[p53UU]}{dt} = k_1\,[Mdm2_{nuc}]\,[p53U] - [p53UU]\,k_{-1} - [p53UU]\,(k_{es53}+k_{ds53})$$

$$\frac{d[Mdm2_{nuc}]}{dt} = V_{cyt\,n}(k_t\cdot[Mdm2P_{cyt}] - k_{tn}\cdot[Mdm2_{nuc}]) - k_{d2}\cdot[Mdm2_{nuc}]$$

$$\frac{d[Mdm2_{cyt}]}{dt} = k_{s2}' + \frac{k_{s2}\,[p53_{tot}]^{n_1}}{J_{s2}^{n_1} + [p53_{tot}]^{n_1}} - k_{d2}'\,[Mdm2_{cyt}] + k_{dcph}\,[Mdm2P_{cyt}] - \frac{k_{ph}}{J_{ph} + [p53_{tot}]}\,[Mdm2_{cyt}]$$

$$\frac{d[Mdm2P_{cyt}]}{dt} = \frac{k_{ph}}{J_{ph} + [p53_{tot}]}\,[Mdm2_{cyt}] - k_{dcph}\,[Mdm2P_{cyt}] - k_t\,[Mdm2P_{cyt}] + k_{tn}\,[Mdm2_{nuc}] - k_{d2}'\,[MdmP_{cyt}]$$

$$\frac{d[DNA_{dam}]}{dt} = kDNA[IR] - kdDNA\,[p53_{tot}]\,\frac{[DNA_{dam}]}{J_{dna} + [DNA_{dam}]}$$

$$k_{d2} = k'_{d2} + \frac{[DNA_{dam}]}{J_{dam} + [DNA_{dam}]}\,k''_{d2}$$

$$[p53] = [p53_{tot}] - ([p53U] + [p53UU])$$

$$[Mdm2_{tot}] = [Mdm2_{cyt}] + \frac{1}{V_{cyt\,n}}[Mdm2_{nuc}] + [Mdm2P_{cyt}]$$

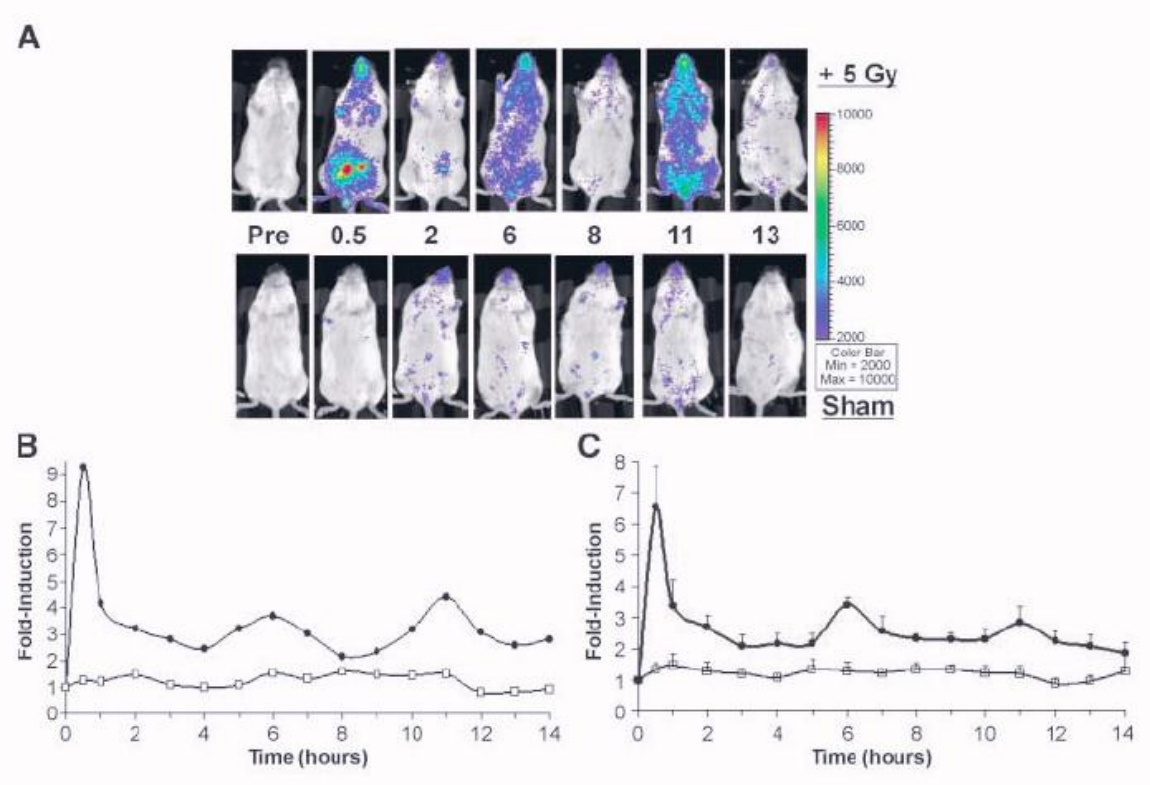
$$IR = ampl\cdot heav(10 < t < 20)$$

Ciliberto A, Novak B. and Tyson J, *Cell Cycle 2005.*

Non-invasive imaging and Systems/Network Biology

Real-time Evaluation of p53 Oscillatory Behavior *In vivo* Using Bioluminescent Imaging

University of Michigan ICMIC – Brian D. Ross PI

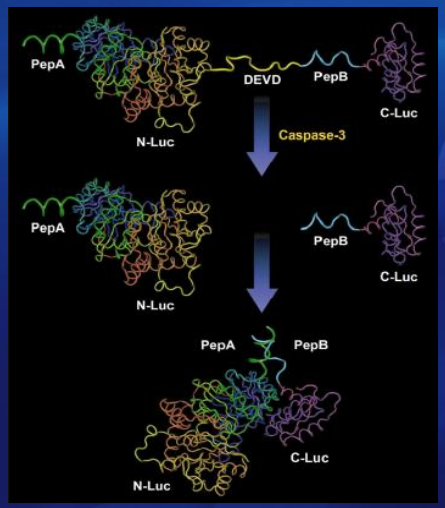


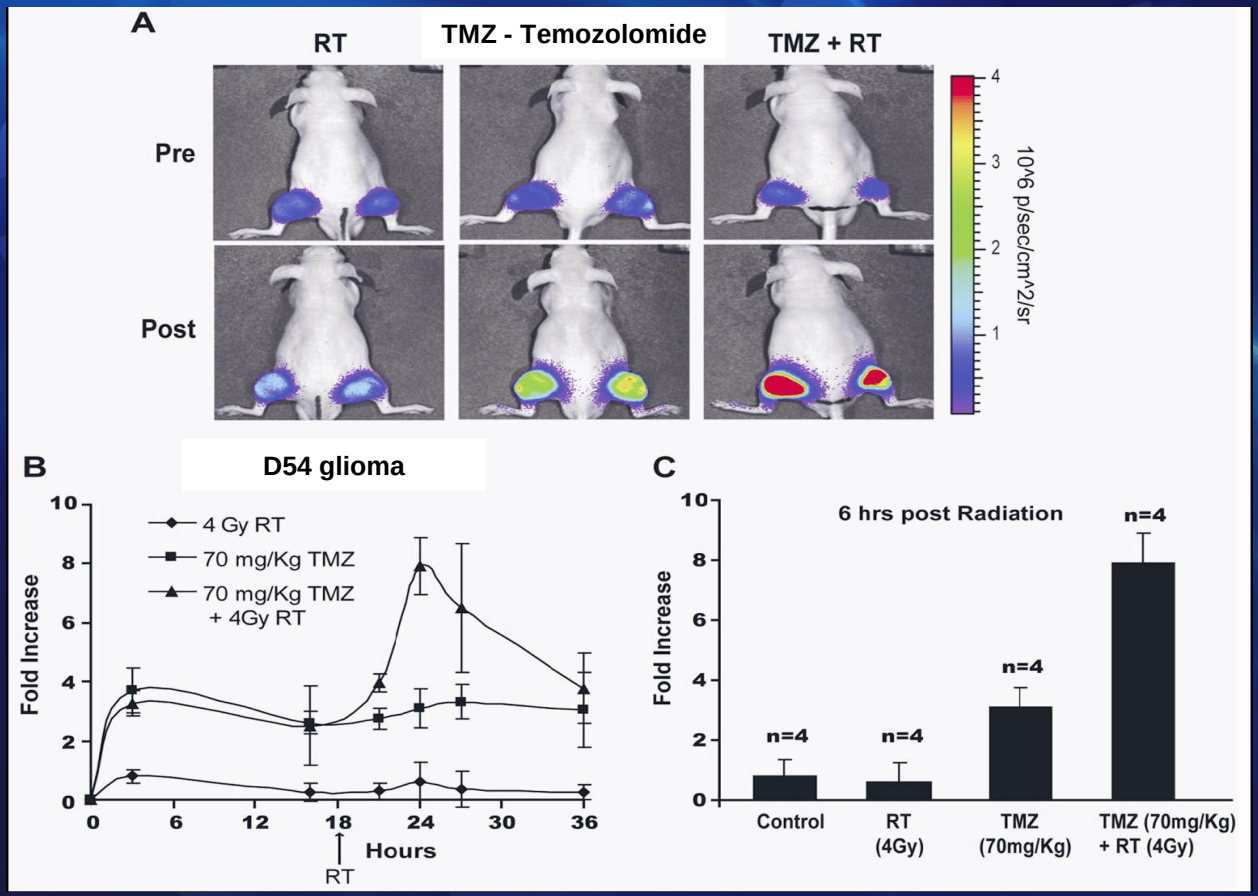
Luciferase gene expression dependent on the p53-responsive P2 promoter from Mdm2 gene.

Hamstra D, Bhojani M, Griffin L, Laxman B, Ross B, and Rehemtulla A. *Cancer Res*. 2006.

Non-invasive imaging of apoptosis and its application in cancer therapeutics

University of Michigan ICMIC – Brian D. Ross PI





Coppola J, Ross B, and Rehemtulla A. *Clin Cancer Res*. 2008

Input from Extramural Experts "Virtual Workshop"

NCI Staff discussed broad topic with Drs. Ralph Weissleder & Peter Sorger

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Drs. Weissleder, Sorger and Colleagues submitted White Paper

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White Paper was circulated amongst broader community of experts

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White paper and all comments were incorporated into final Concept

Purpose of this request

Key issues – complexity, range of expertise required and collaboration

Goal of proposal – enable collaboration and team science on a scale beyond that previously achieved

Strategy – provide opportunity and incentive for NCI funded programs with established expertise and infrastructure to form collaborations including outside partners that can achieve the level of team science required

High Priority Objectives

To provide an opportunity for new collaborative projects among cancer complexity researchers and cancer imagers that address the 4 major areas of research identified through the virtual workshop:

1. **Technologies and methods to advance high resolution intra-vital, *in vivo* microscopic imaging**
2. **Development and validation of cancer-specific *in vivo* probe and reporter systems**
3. **Integration of micro- and macroscopic data ("Google Earth" for cancer imaging)**
4. **Development of new approaches of modeling, integrating and visualizing multi-scale imaging data**

Proposed mechanism of request:

Leverage of highly relevant NCI funded programs

DCTD

In vivo Cellular and Molecular Imaging Centers (ICMICs)

Multidisciplinary *in vivo* imaging approaches to cancer detection, diagnosis and response to therapy.

DCB

Integrative Cancer Biology Program (ICBPs)

Analysis of cancer as a complex biological system through the integration of computational models and experimental biology.

Tumor Microenvironment Network (TMEN)

Stroma in normal tissues, its roles in tumor initiation, progression, and metastasis and mechanisms of tumor-stroma interaction

Mouse Models of Human Cancer Consortium (MMHCC)

Integration of mouse models into basic, translational, epidemiological, and clinical cancer research.

Centers of Cancer Nanotechnology Excellence (CCNE)

Development and applications of nanotechnology and nanoscience solutions to the diagnosis and treatment of cancer.

INVESTIGATOR COMMUNITY

Proposed mechanism amendment

Following reviewer comments and suggestions we propose changing the submitted concept from encouraging inclusion of participation of investigators outside the specified groups to a requirement of applications

INVESTIGATOR COMMUNITY

THE REQUEST

4-6 five-year Collaborative U01s

$0.75 - $1.25M/year total costs/award

$5M/year total costs/1 year

$25M total costs/5 year