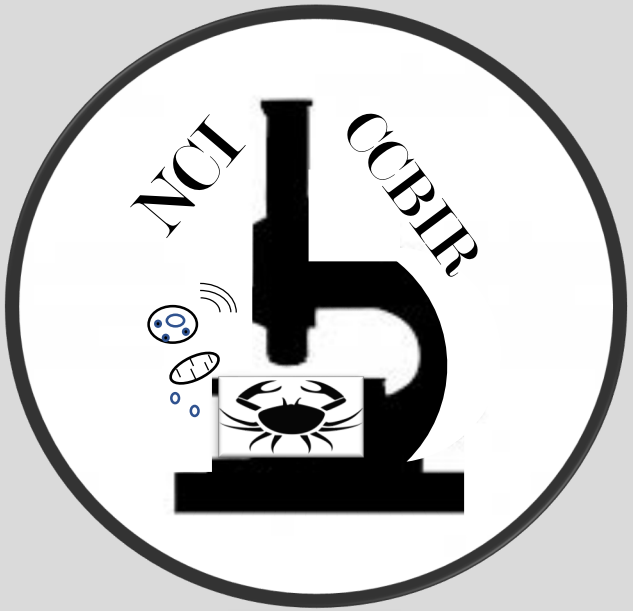
RFA Concept Proposal to the Board of Scientific Advisors
December 4, 2018

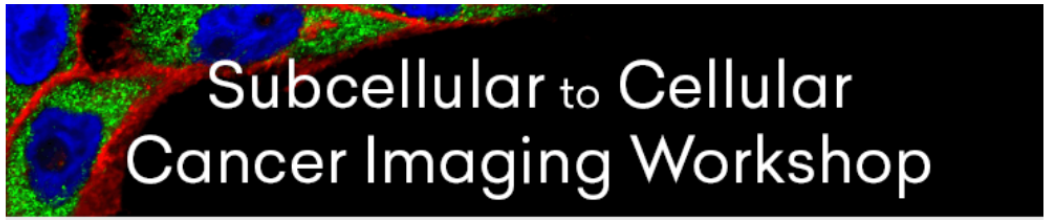
Cellular Cancer *B*iology *I*maging *R*esearch

"*CCBIR*" Program

Michael Graham Espey, Ph.D., M.T.(ASCP)
Program Director
NCI Division of Cancer Biology



Planning and Engagement Efforts *(a grassroots concept)*



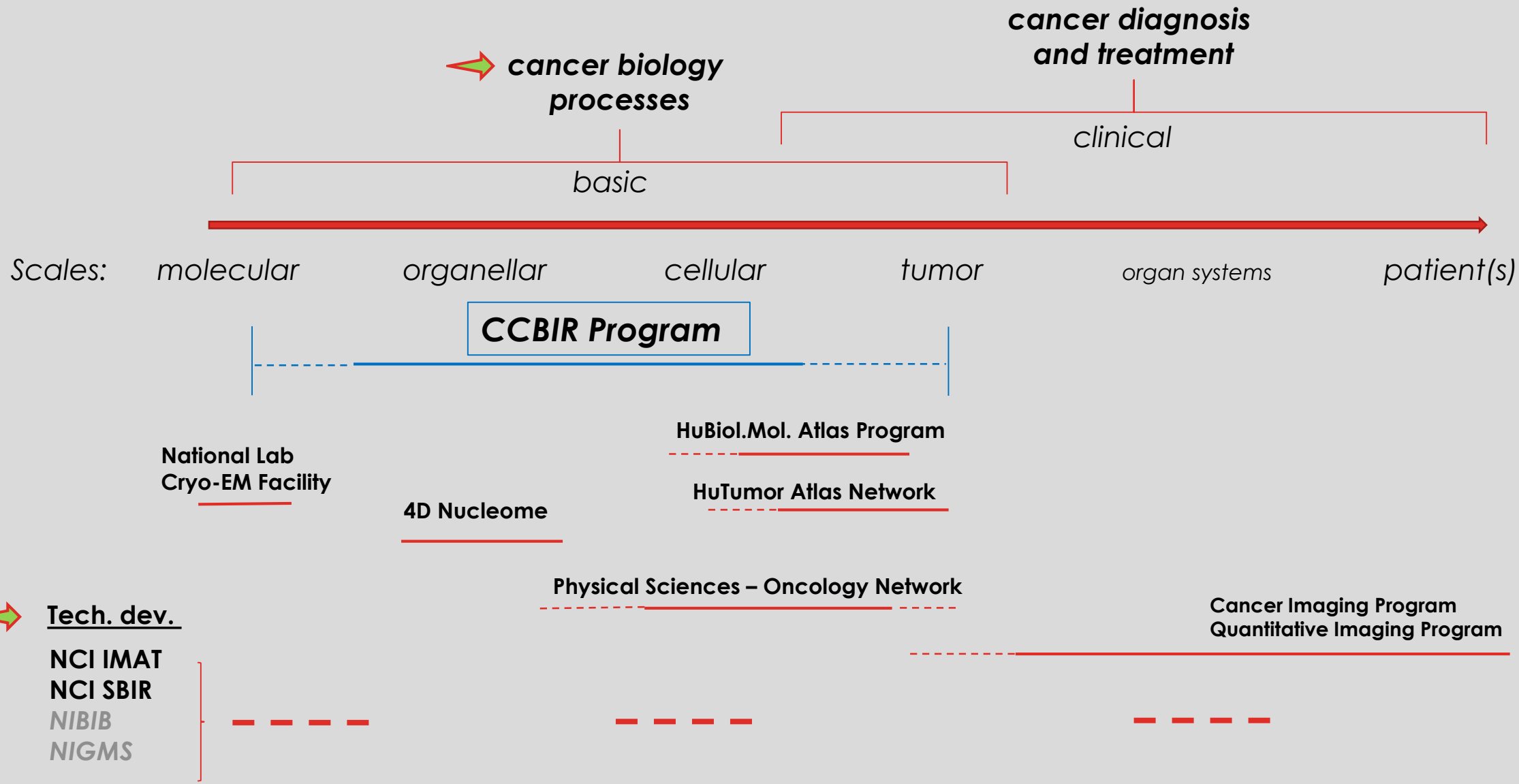
NCI in conjunction with the American Society for Cell Biology, held a Strategic Workshop in April, 2018:

1) to examine the state of imaging science at the subcellular-cellular length scales;
2) to network the cell biology and cancer biology research communities;

Community feedback from this Strategic Workshop indicated that:

- **Advances in cellular-scaled imaging modalities offer transformative potential for cancer research;**
  - Engine to drive new mechanistic understanding in cancer biology;
  - Start point to reveal processes that could become new targets for therapy;
- **Cancer biology lags behind other fields in leveraging advanced cellular imaging tools;**
  - Access for smaller/isolated labs to cutting edge imaging infrastructure can be limiting;
  - Inertial barriers exists in moving cell biology imaging into cancer research;
    - Imaging cancer biology often requires specialized modifications to systems designed to study normal cell biology;
    - Technology dev. and discovery-based cellular imaging does not do well in cancer peer review

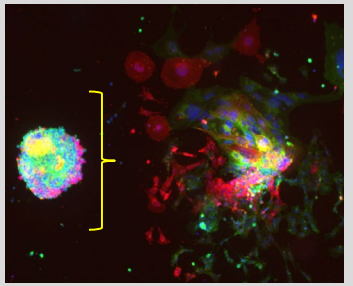
Portfolio niche areas having aspects of advanced imaging

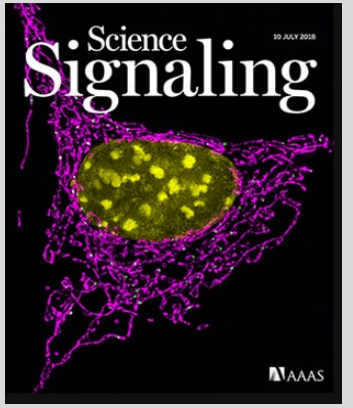


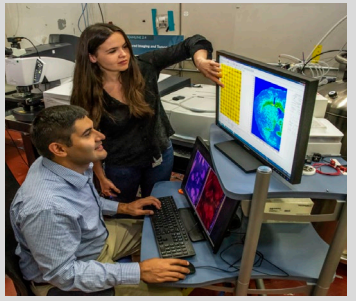
Cellular Cancer *B*iology *I*maging *R*esearch (*CCBIR*) Program

Goals of the RFA:

- To create resource centers that facilitate both development and use of advanced imaging technologies at the subcellular to cellular length scale to address basic cancer research problems;
- To foster a sustainable collaborative community between cellular imaging technology developers and basic cancer biology researchers across the NCI portfolio.







The UM1 Cooperative Agreement mechanism addresses this need:

- Enables a virtuous cycle of problem solving between tech. dev. and end-user adopters in defined areas of cancer biology research that leverage cellular imaging approaches;
- Programmatic "U added" opportunities:
  - Community-solicited pilot project process and interdisciplinary workforce development to stimulate broader impact and implementation;
  - Coordinate synergy with existing complementary NCI/NIH programs;
  - Potential to elevate as a "breeder" program that spins-off advances into multiple priority research areas.

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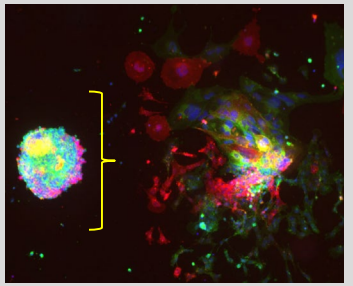

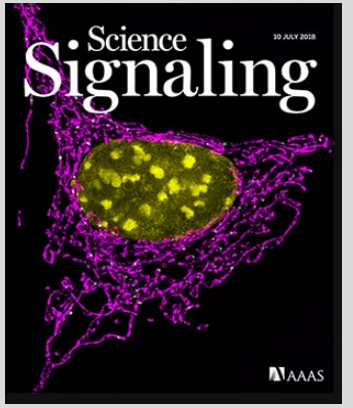

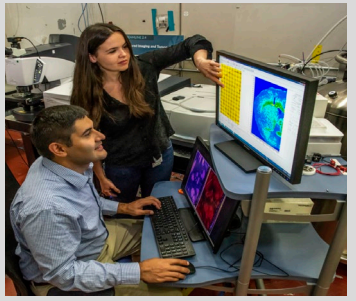

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  - Potential to elevate as a "breeder" program that spins-off advances in NCI's priority research areas.

CCBIR Program: Breadth and Scope

Technology development is best driven in the context of addressing a fundamental challenge

Examples of cancer biology thematic-priority areas responsive to this RFA concept could include:

- biophysical imaging of oncogenic signaling in live cancer cells;
- spatio-temporal resolution of metabolism and redox effectors in subcellular compartments;
- functional anatomy of cancer stem cells to aid lineage tracing and evolution of resistance;
- coupling single cell -omics with longitudinal imaging of metastasis;
- multiscale imaging (subcellular-to-cellular, time) of the tumor microenvironment;
- dynamic imaging of immune effector-cancer cell interactions.

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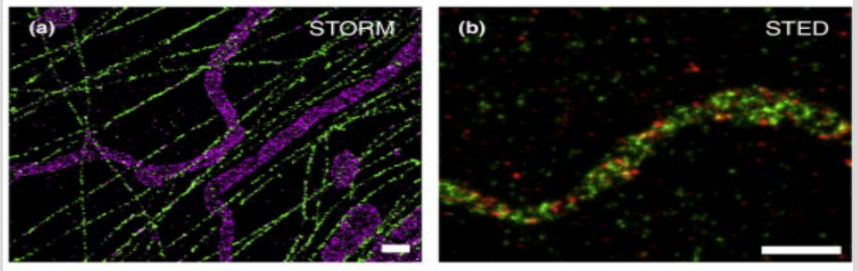
Examples of enabling imaging technologies:

- Super-resolution microscopy
- Spectroscopy imaging (MS, IR, Raman)
- Live cell morpho-dynamics, connect-omics
- Optogenetic, functionalized probes
- Genetically eng. lineage tracing
- Intravital microscopy



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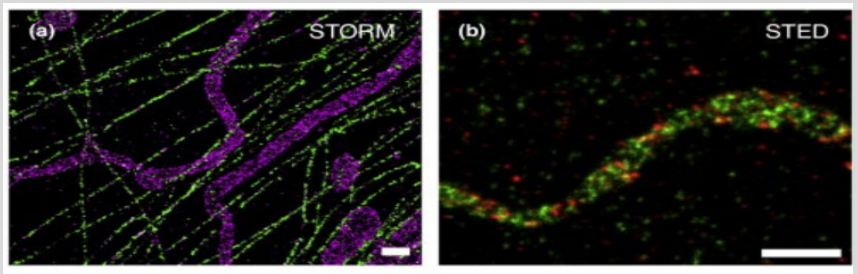
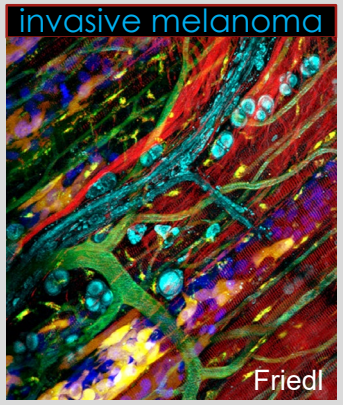
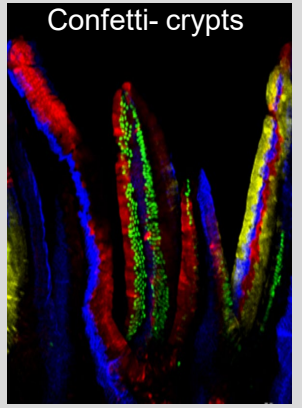
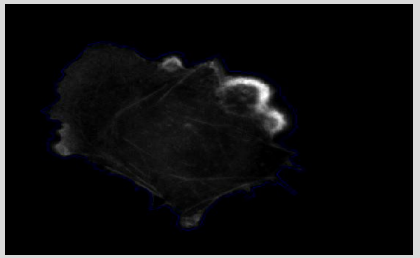




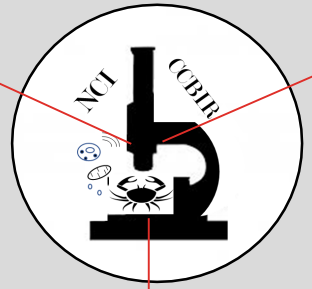




Proposed UM1 *CCBIR* Program Structure

- Instrumentation, probes, computational & data science;
- Fosters interoperability of modular cellular imaging systems

TECH: Cellular-scaled imaging **Tech**nology innovation & development



Pilot projects

Training and dissemination

CE: **C**ommunity **E**ngagement

- Collaborative Pilot projects e.g., ½ inside + ½ outside Institution

RTB: **R**esearch **T**est **B**ed

- RTB provides wet-lab context for demonstration-refinement of TECH;
- Iterative - virtuous cycle of increasing experimental sophistication with time;
- Breadth and scope of each UM1 is defined by a theme;

Oncogenic signaling

Metabolism - organelles

Cancer Stem cells

Microenvironment

Metastasis

Immuno-Oncology

Proposed Initiative: NCI UM1 *CCBIR* Program

- RFA with set-aside of $12M x 5 years = $60M
  - UM1 grant mechanism to allow for programmatic guidance
  - anticipate 3 - 4 UM1 Centers (approx. $3.0 M total costs/UM1)
  - one receipt date

- Each UM1-CCBIR would be thematically centered in a basic cancer research priority area
  - UM1s collectively would be autonomous, with programmatic coordination as appropriate (e.g., pilot projects, workshops, interfacing with other NCI imaging programs/activities)

- DEA Special Emphasis Panel review would best cover the needed broad interdisciplinary expertise in cell-scaled imaging and basic cancer research;

- Receipt beginning July, 2019; April, 2020 award start; Active in FY20 – FY25

Initial questions from the BSA sub. comm. reviewers:

- Q: Can the RFA emphasize that the UM1 center must focus on a question or problem in cancer biology, with imaging being the technology to support that line of investigation?

  A: Yes, the intent is for the "imaging tech" to be driven by the unique cancer biology questions each UM1 center is addressing.
  - the relationship between cancer biology and tech. dev. is iterative with increased sophistication over time;
  - the balance and synergy between TECH, RTB and CE will be a special review criteria;
  - will be emphasized to both applicants during the pre-application period and to peer reviewers during pre-review orientation.

- Q: Why not structure this RFA as many U01s with a U24 coordinating center to encourage and support more ideas?

  A: The UM1 mechanism allows for TECH, RTB and CE elements to be uniquely interwoven to achieve the RFA's programmatic goals:
  - CE pilot projects provide a pipeline to invigorate UM1 with new ideas, and are a vehicle to democratize the scientific engagement to a wider participant base beyond the individual UM1 home institution;
  - UM1 structure focuses a suite of interoperable "TECH" systems toward solving the overarching cancer biology problem;
  - Through this RFA, NCI is piloting this unique UM1 structure.

❖ Q: What are your measures of success? Provide specific examples.
A: The measures of CCBIR program success are as follows:

- Iterative optimization of *CCBIR* tech. ultimately becomes enabling to advance or open up new specific priority sectors of mechanistic cancer biology research;
  - spatio- temporal dynamics of oncogenic signaling leading to new targets;
  - predictive biomarkers at sub-to-cellular length scales that inform on efficacy/resistance;

- Permeation of *CCBIR* technological and conceptual innovation into the broader cancer research community across NCI's basic research portfolio.
  - generates spin-offs of successful research awards via other mechanisms (P01, U01, R01);

- *CCBIRs* stimulates dissemination of scalable imaging approaches into the commercial sector;
  - commercialization of cancer biology tools broadens the base of adopters increasing opportunities for discovery and national impact.

Questions?

Extra slide- definition of the UM1 mechanism:

UM1 Cooperative Agreement Research Project With Complex Structure

- The UM1 mechanism provides support for large-scale research activities with complicated structures that cannot be appropriately categorized into an available single component activity code.
- The components represent a variety of supporting functions and are not independent of each component.
- Substantial Federal programmatic staff involvement is intended to assist investigators during performance of the research activities, as defined in the terms and conditions of the award.