A Systems Cancer Biomedicine Demonstration Project (SysCan)

NCI

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A partnership with FNIH

Identification of New FNL Projects

- **Think Tanks to identify possible projects for FNL**
- **Organized by Joe Gray, Ed Harlow, Sean Hanlon, Dinah Singer**
- **Invited leading cancer researchers from across the research continuum to discuss ideas for FNL projects**
- **Each workshop had ~12-15 participants. Each participant presented one idea, which was discussed by the group.**
- **11 workshops over a period of 8 months**
  - **9 were broad across all cancer research**
  - **1 was focused on RNA vaccines; 1 on population science**
- **All of the ideas were reviewed, organized by topic, assigned to be either FNL or NCI-appropriate**

Scientific Themes

- **Understanding and managing paraneoplastic syndromes, such as cachexia**
- **Next gen epidemiology.**
  - Population and age associations with risk.
  - Environmental determinants
  - Ancestry issues
- **Dormancy.** Mechanisms that drive dormancy and strategies to attack dormant cells.
- **Managing Co-morbidities.** Mechanisms and mitigations

FNL Themes

- **Spatial Systems Biology.** Although there is already considerable effort in this field, there is little coordination or integration that would allow the data being generated across the community to be actionable. There is also a need to provide broader access to the community.
- **Experimental Therapeutics.** Provide drugs and clinical workflows, cell and molecular analytics, data organization and dissemination, Car T resource, new drug screening infrastructure, project coordination.
- **Structural Biology Across Scales.** Instruments for CryoEM single particle structure, CryoEM tomography, 2D and 3D SEM. A central point for measurements and data analysis
- **Center for Perturbation Biotechnology.** The goal of the Center would be to coordinate clinical diagnostics, across a broad spectrum of perturbations, to generate a “perturbation” database that could be mined to establish clinical correlations and develop predictive models of therapeutic response.

Systems Cancer Biomedicine

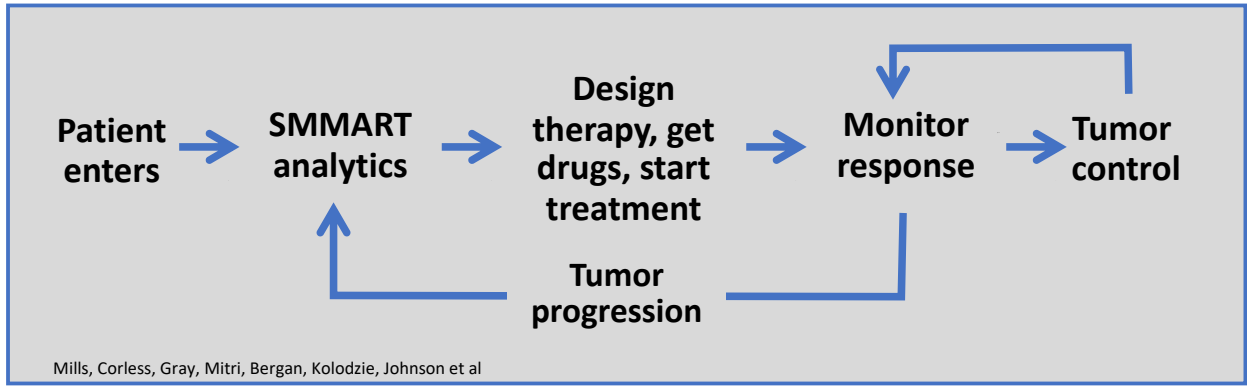
Dr. Joe Gray

A Systems Cancer Biomedicine Demonstration Project (SysCan)

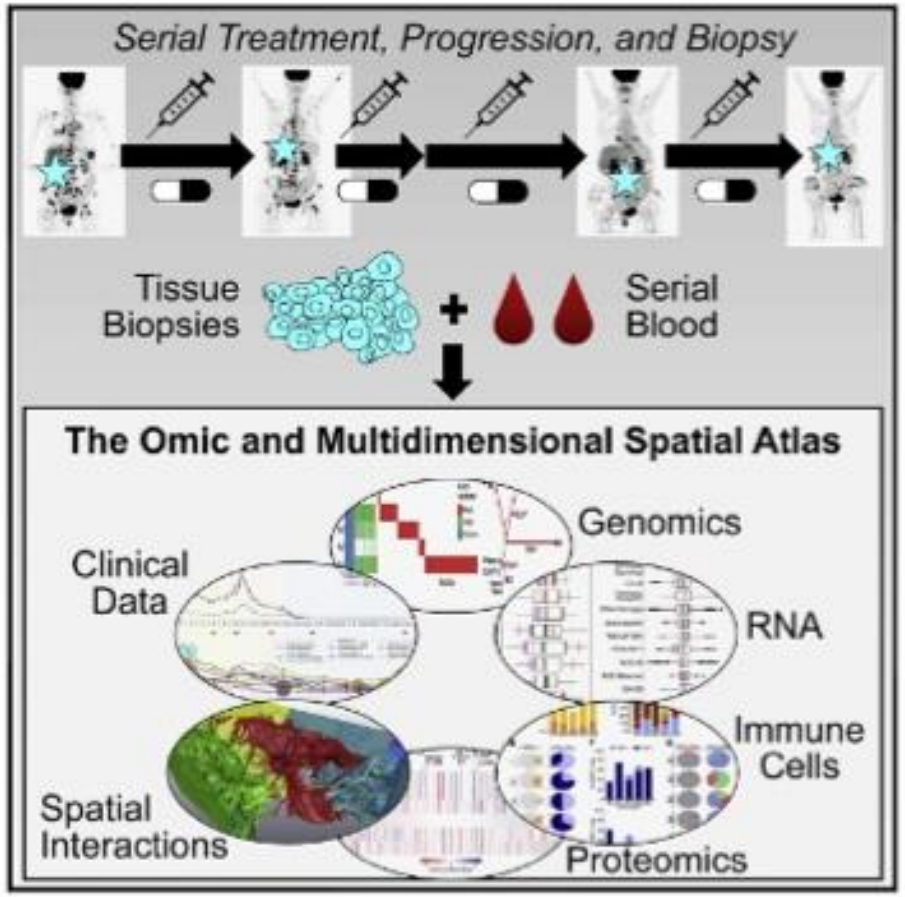
Topics for discussion

- Project background and concept
- Short and longer term goals
- A possible role for FNLCR

Serial Measurements of Molecular and Architectural Responses to Treatment (SMMART) Treatments



- Discover resistance mechanisms and therapeutic vulnerabilities
- Identify and act on tumor vulnerabilities in “real time” for individual patients
- Monitor and minimize toxicity
- Evolve treatment to counter emergent resistant mechanisms



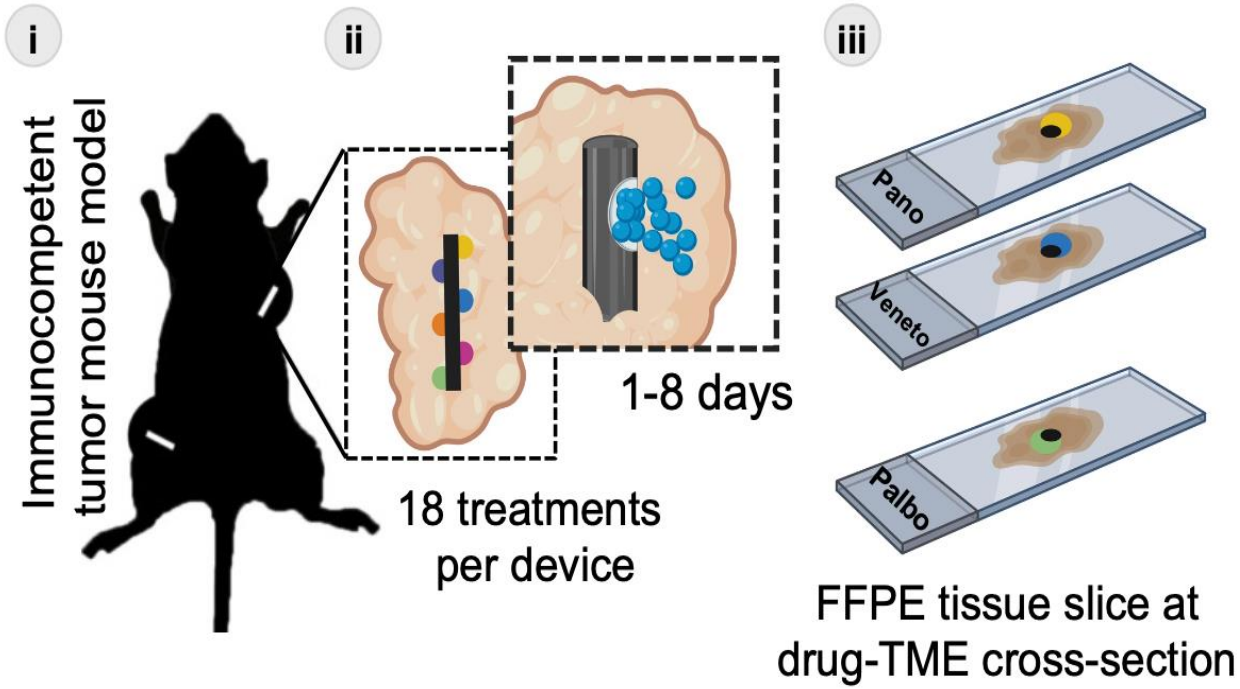
Cell Rep Med. 2022 Feb 15;3(2):100525.

SMMART Lessons Learned

- (Epi)genomic instability and migration generate therapeutic response heterogeneity that increases with time and treatment.
- In the end, it becomes impossible to find tolerable tumor targeted drug combinations that can control the heterogeneous lesions.
- Drugs designed to targets specific cancer cell vulnerabilities can have profound impacts on nontumor micro- and macroenvironments.

Exploring Drug-Microenvironment Interactions

Nanoliter drug volumes and device is non-immunogenic

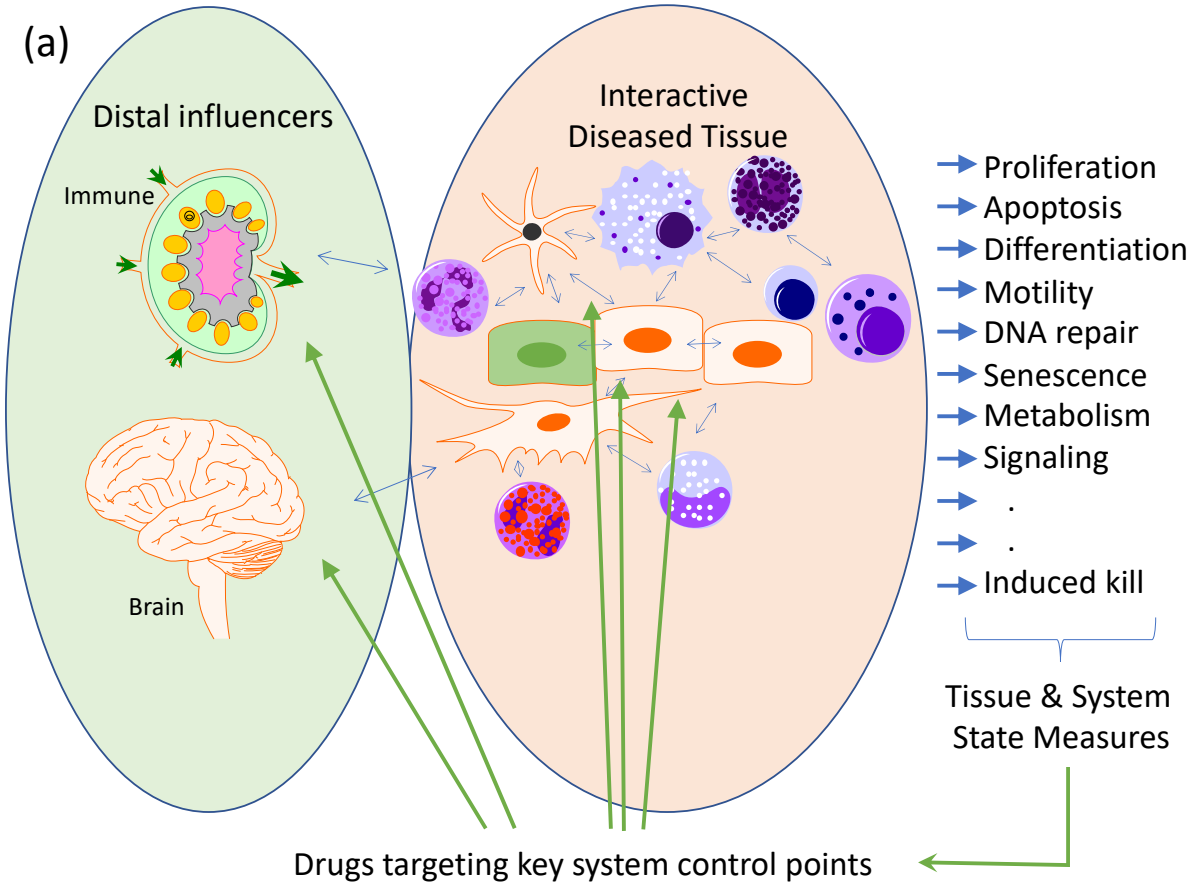


Multiplex Implantable Microdevice Assay (MIMA) System Nat Biotechnol. 40:1823, 2022. PMID: 35788566

Lessons Learned

- Confirms the profound effects that tumor targeted drugs have on the nontumor microenvironment
- Microenvironments can be either pro- or anti-tumor depending on the drug
- Multiple components of the microenvironment are influenced
- Treatment efficacy and tolerability can be increased by combining drugs to increase the antitumor nature of the nontumor microenvironment

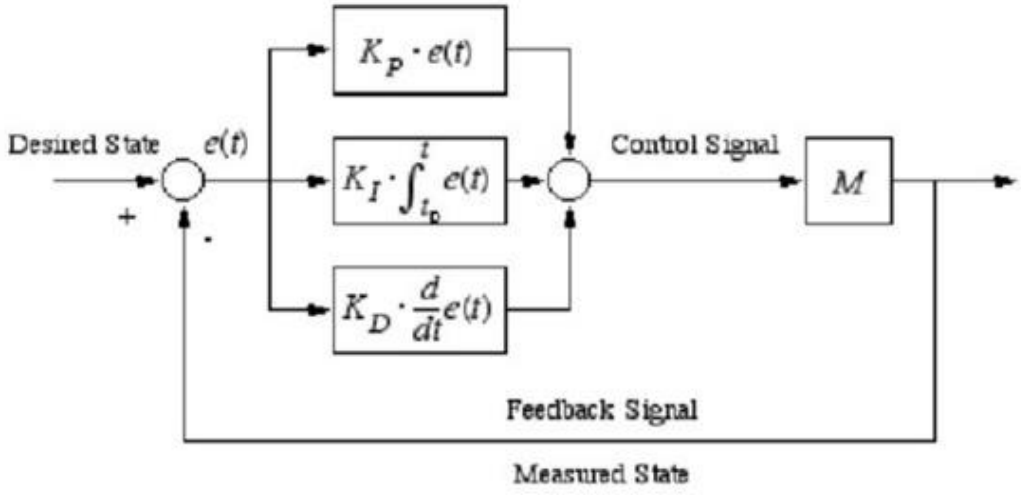
SysCan Goal



A FNIH/NCI demonstration project to develop, deploy, and test a systems biomedicine-based treatment strategy for *one important human cancer* that simultaneously attacks cancer cells directly *and* purposefully manipulates multiple intercellular interactions to create strong antitumor (i.e. tumoricidal) microenvironments

A computational systems control model is essential for SysCan success

A systems control approach to disease management



- Identify key components that comprise pro- and antitumor macro and microenvironmental systems
- Elucidate quantitative interactions between components and the functional consequences thereof
- Construct a dynamic interaction model that mirrors the behavior of perturbed model and human tumor systems.
- Computationally perturb the dynamic model to train an AI controller that will generate control strategies that produce strong antitumor control
- Test and refine the controller by testing against perturbed laboratory models and human tumors
- Use the control model to predict optimal control strategies to be tested clinically

Key SysCan Tasks/Needs to

- Specification of *one* tumor (sub)type
- Laboratory models that accurately mirror the intercellular interactions in the target human tumor
- Tools for improved longitudinal biosampling
- Diagnostic tools to quantify cellular and molecular compositions and functions, spatial organizations, and interactions that drive biological function
- Quantitative information about responses of model and tumors to existing tumor and/or microenvironment targeted drugs
- A computational model that encodes information about cellular types and interactions
- Metrics for the strong antitumor microenvironments that the SysCan will create
- New drugs targeting key associated micro- and macroenvironmental interactions.
- A clinical program to evaluate and refine candidate SysCan control strategies
- Regulatory strategies for systems-based treatments

SysCan Timelines, Deliverables, and Milestones

Planning phase (18 months)

- Engage leaders from the intramural and extramural research communities, potential pharma and biotech partners, relevant academic societies, patients and advocates, and regulatory agencies to refine the overall approach
- Public workshops to acquire multidisciplinary community input on the design of the project and to identify academic and private sector performance incentives
- Establish working groups to develop the overall proposal
- Establish policies for commercialization and availability of methods, biological models, measurements, computational tools, drugs, and technologies
- Curate biological and clinical information available for the target tumor type and biological models thereof
- Prepare and publish a research plan
- Establish steering committee and working groups to manage the project
- Assemble necessary partners

These activities will be led by our FNIH partners

SysCan Timelines, Deliverables, and Milestones

Implementation phase (4.5 years)

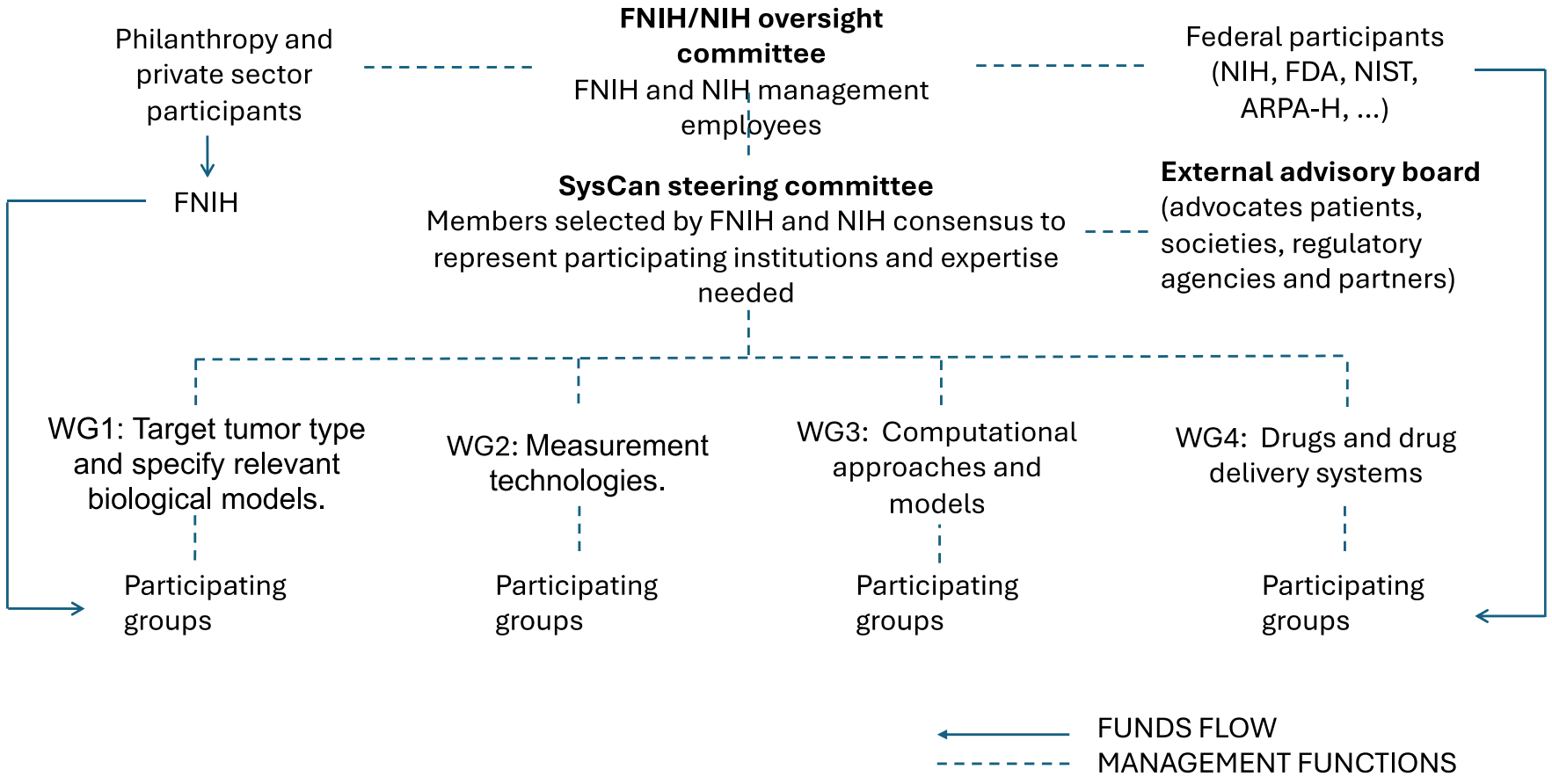
- Acquire access to or develop tools for tissue acquisition, digital pathology and assessment of systems responses.
- Develop biological and computational models of the target cancer.
- Train an AI systems control model
- Acquire or develop drugs and drug compositions designed to purposefully manipulate key micro and macroenvironments.
- Develop multidrug delivery technologies enable dynamic delivery of multiple tissue control drugs
- Develop and test candidate SysCan tumor control strategies in animal models of the targeted tumor type.
- Design and execute clinical trials that deploy and test systems biomedicine-based treatments in one target cancer.
- Effectuate the uploading of all data to the NCI Cancer Research Data Commons to be made publicly available.

SysCan Timelines, Deliverables, and Milestones

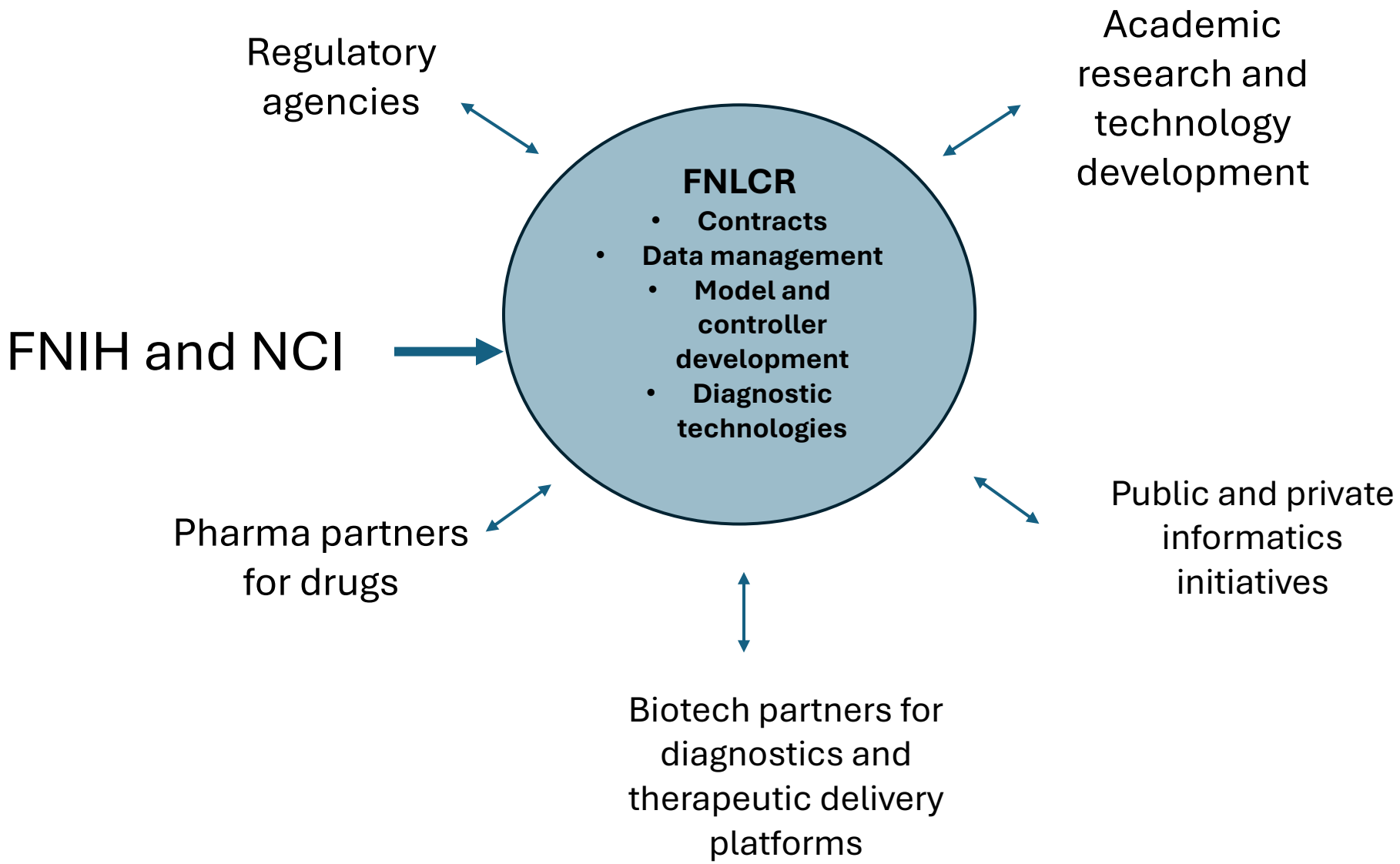
Implementation phase (4.5 years)

Technology	**Modeling and Data**	**Biology**	**Clinic**
Acquire access to or develop tools for tissue acquisition, digital pathology and assessment of systems responses.	Develop computational models of the target cancer.	Develop biological models of the target cancer.	Design and execute clinical trials that deploy and test systems biomedicine-based treatments in one target cancer.
Develop multidrug delivery technologies enable dynamic delivery of multiple tissue control drugs	Train an AI systems control model		
Acquire or develop drugs and drug compositions designed to purposefully manipulate key micro and macroenvironments	Effectuate the uploading of all data to the NCI Cancer Research Data Commons to be made publicly available.		
Develop multidrug delivery technologies enable dynamic delivery of multiple tissue control drugs			

SysCan Operations



A Coordinating Function for FNLCR?



Thank you!