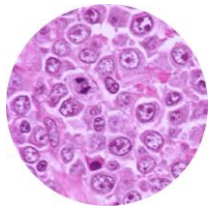
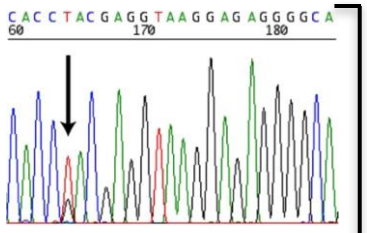
Validated Human Cancer Models to Develop Combination Targeted Therapies

Structural genomics

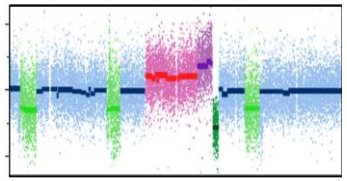
Functional genomics



Cancer biopsy



Sequence



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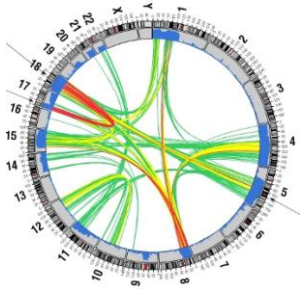
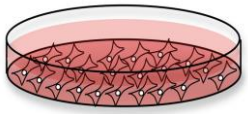
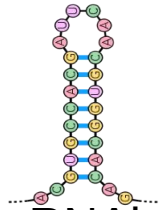


Rearrangements

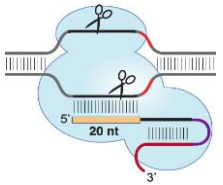
Putative driver genes



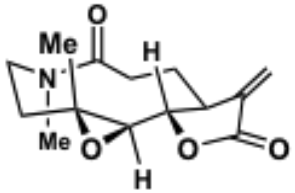
Develop relevant cancer model



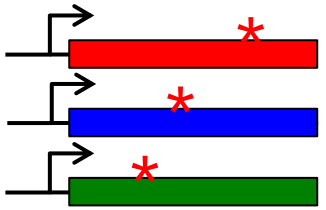
RNAi



CRISPR



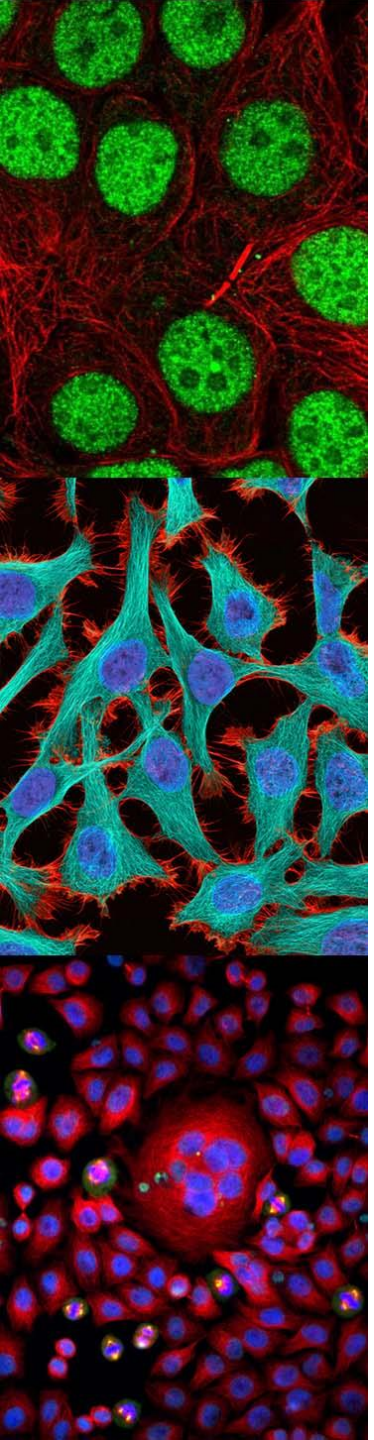
Small molecules



Mutant ORFs

Essential cancer pathways

Combination targeted therapy for cancer



Modeling the Diversity of Human Cancer: An Unmet Need

- Existing cancer cell lines have not been compared to the primary tumor and lack clinical annotations, including therapeutic response.
- Models do not exist for many recurrent genetic lesions in human cancer, and for common combinations of lesions.
- Models of rare cancer subtypes may be nonexistent or underrepresented.
- Existing models do not recapitulate the phenotypic variation and hierarchical relationships of tumor subpopulations.

GOAL – Create next generation cancer models with full genomic and clinical characterization.

Human Cancer Models Initiative (HCMI)

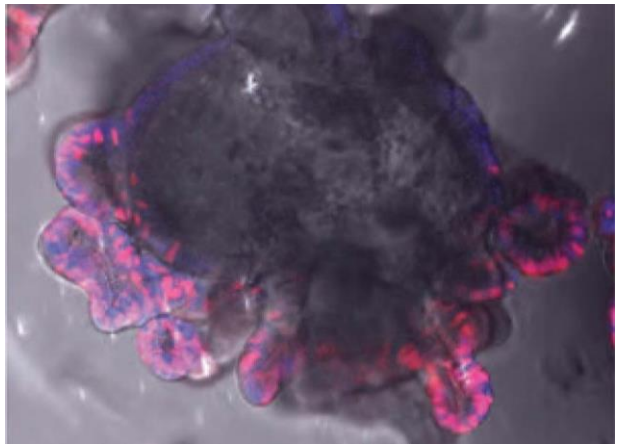
Launched in 2016

Molecular characterization

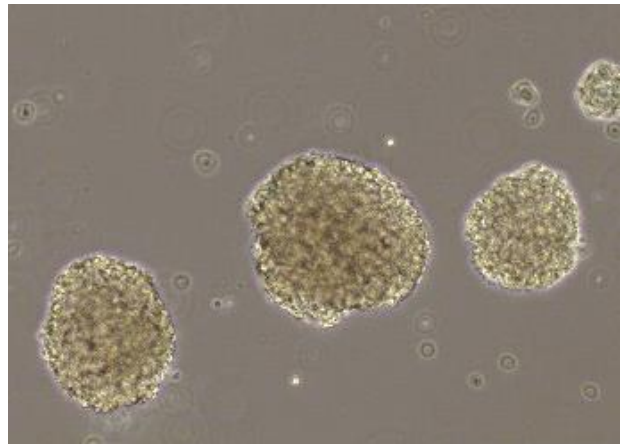
- Somatic and germline sequencing
- 15X tumor WGS
- 150X tumor WES
- 120 million read RNA-seq
- Infinium MethylationEPIC DNA Array

Clinical data

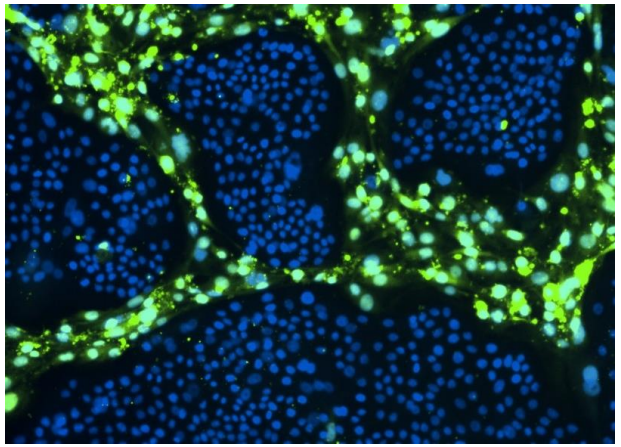
- Standardized case report forms
- Patient demographics
- Disease diagnosis, treatment and ~1.5 yr outcome information



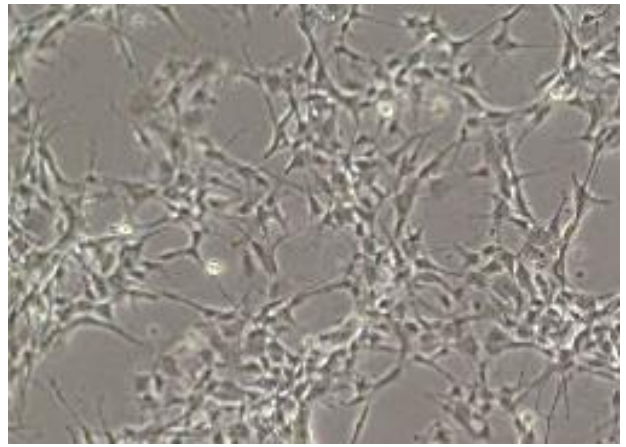
Organoids



Neurospheres

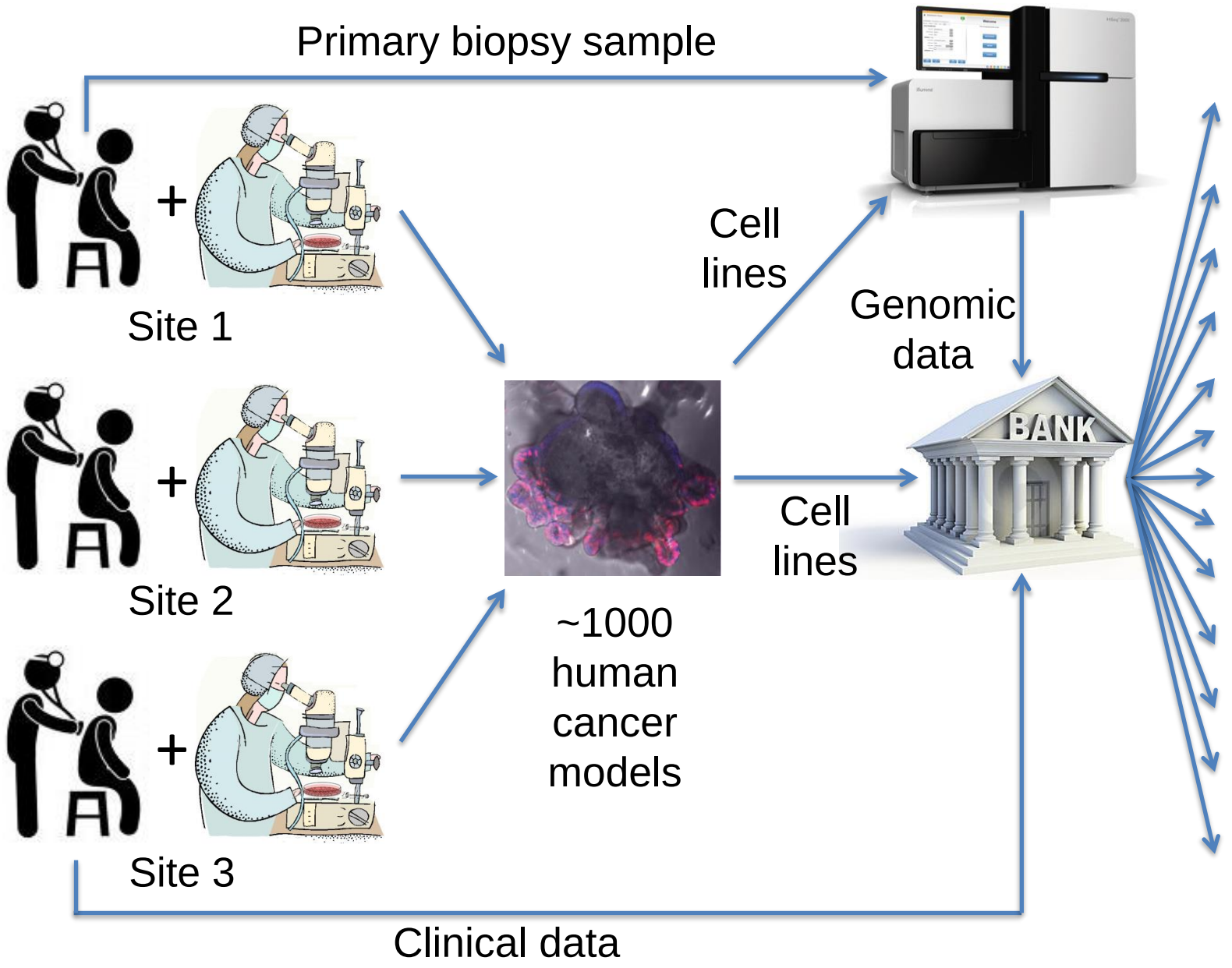


Conditionally Reprogrammed Cells

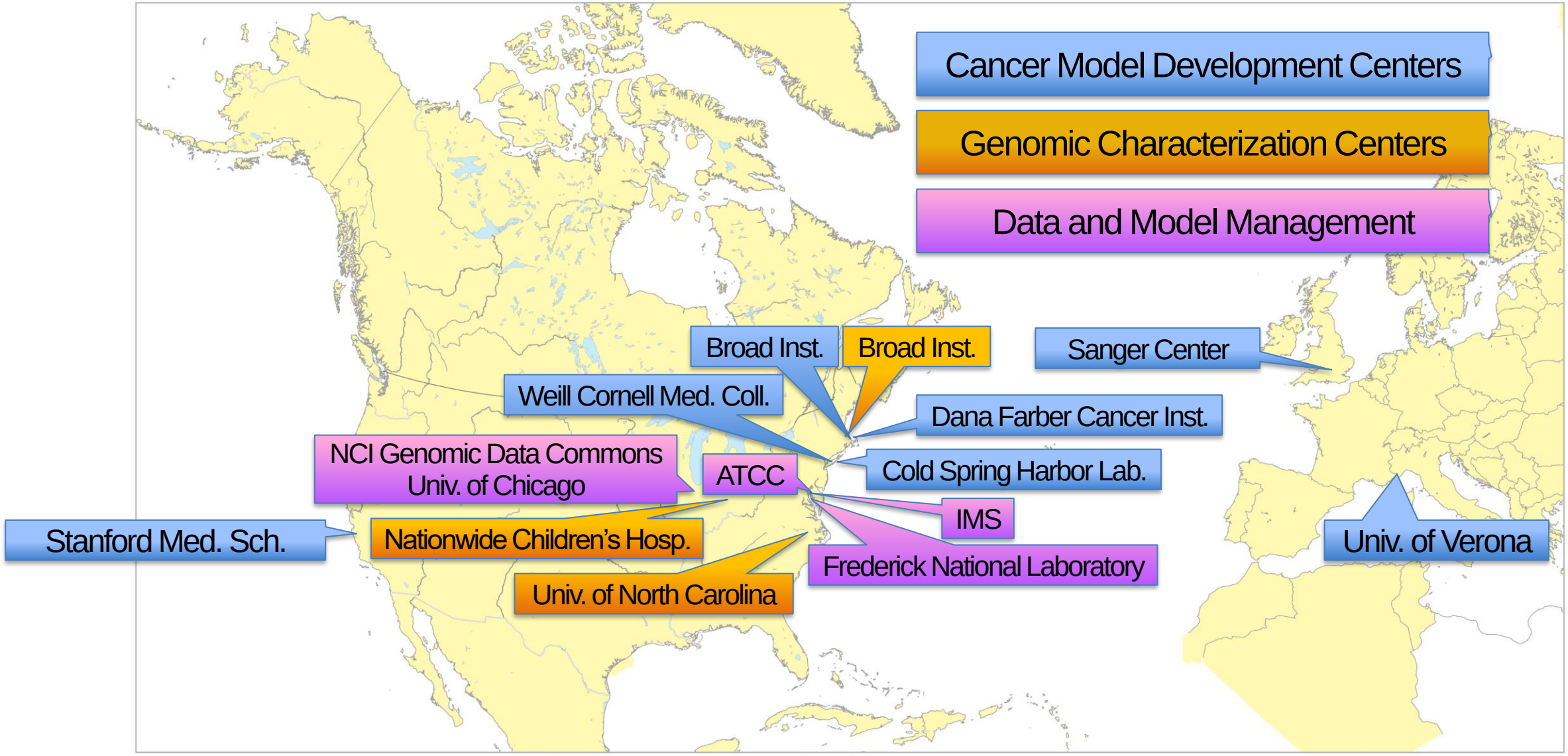


Novel Media Formulations

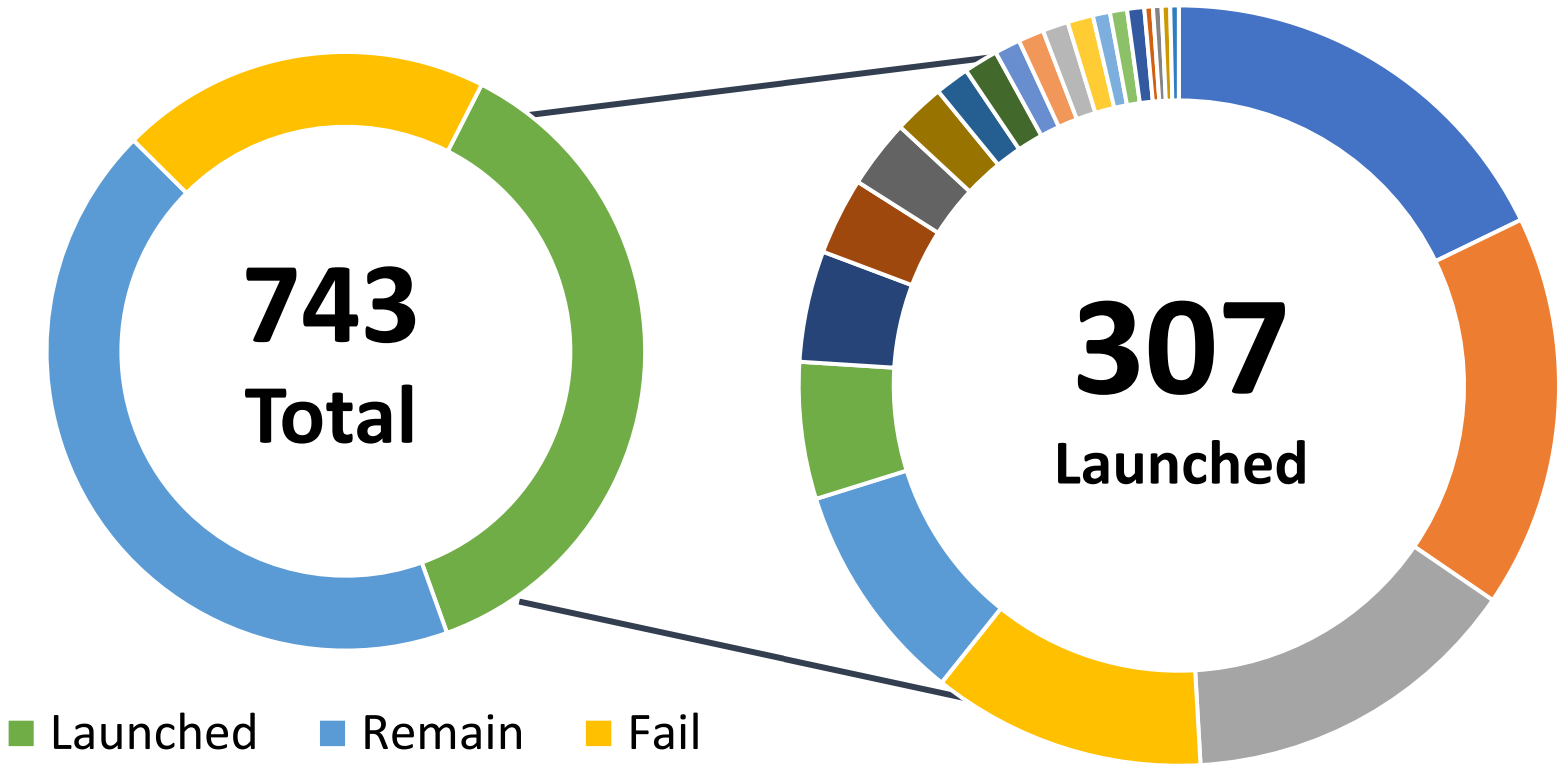
Human Cancer Models Initiative (HCMI) – Work Flow



Human Cancer Models Initiative (HCMI) – Many Moving Parts



HCMI Model Diversity Available to Researchers at ATCC



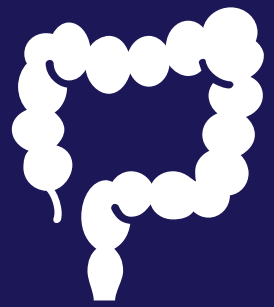
Top 10 tumor types

Brain	49
Pancreas	46
Colon	40
Esophagus	32
Skin	26
Rectum	16
Stomach	13
Connective tissue	9
Biliary tract	8
Lung	6

Complete list available at
atcc.org/hcmi

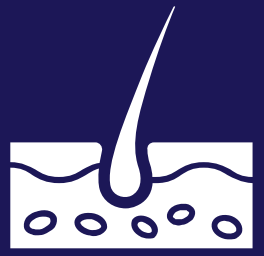
HCMI Models Harbor Recurrent Mutations Identified in TCGA tumors

Colon



APC	FAT4
TP53	MUC16
KRAS	LRP1B
CSMD3	ROBO2
ACVR2A	ALK

Skin



MUC16	GRIN2A
LRP1B	MECOM
CSMD3	FAT4
FAT3	DCC
FAM135B	COL1A1
TP53	BRAF
NRAS	NF1

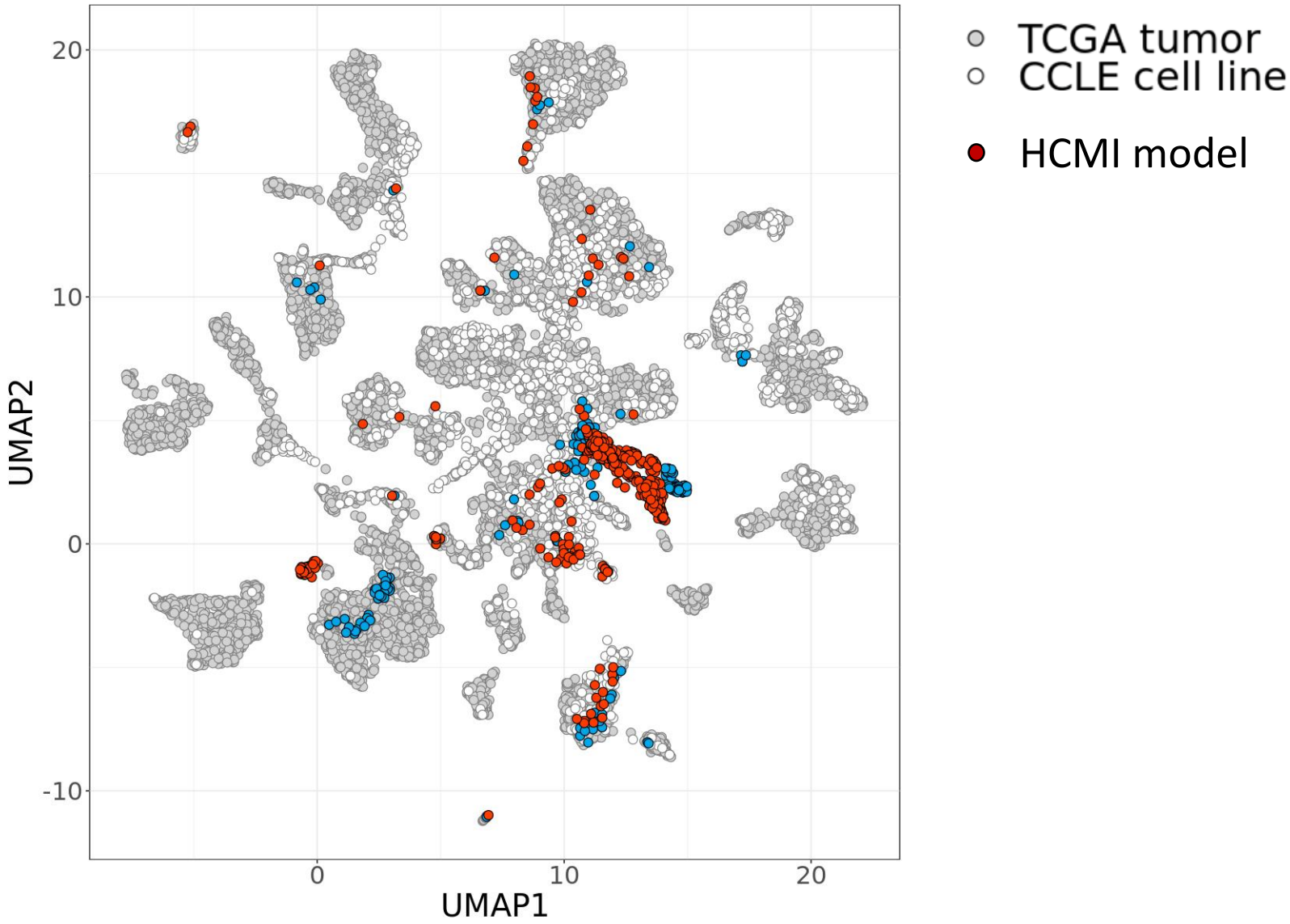
Brain

PTEN	PIK3CA
TP53	CSMD3
EGFR	BCOR
CNTNAP2	NF1
PIK3CR1	FAT1

Pancreas

KRAS	MUC4
TP53	MUC16
SMAD4	KMT2D
CDKN2A	FAT3
ACVR2A	RHOH

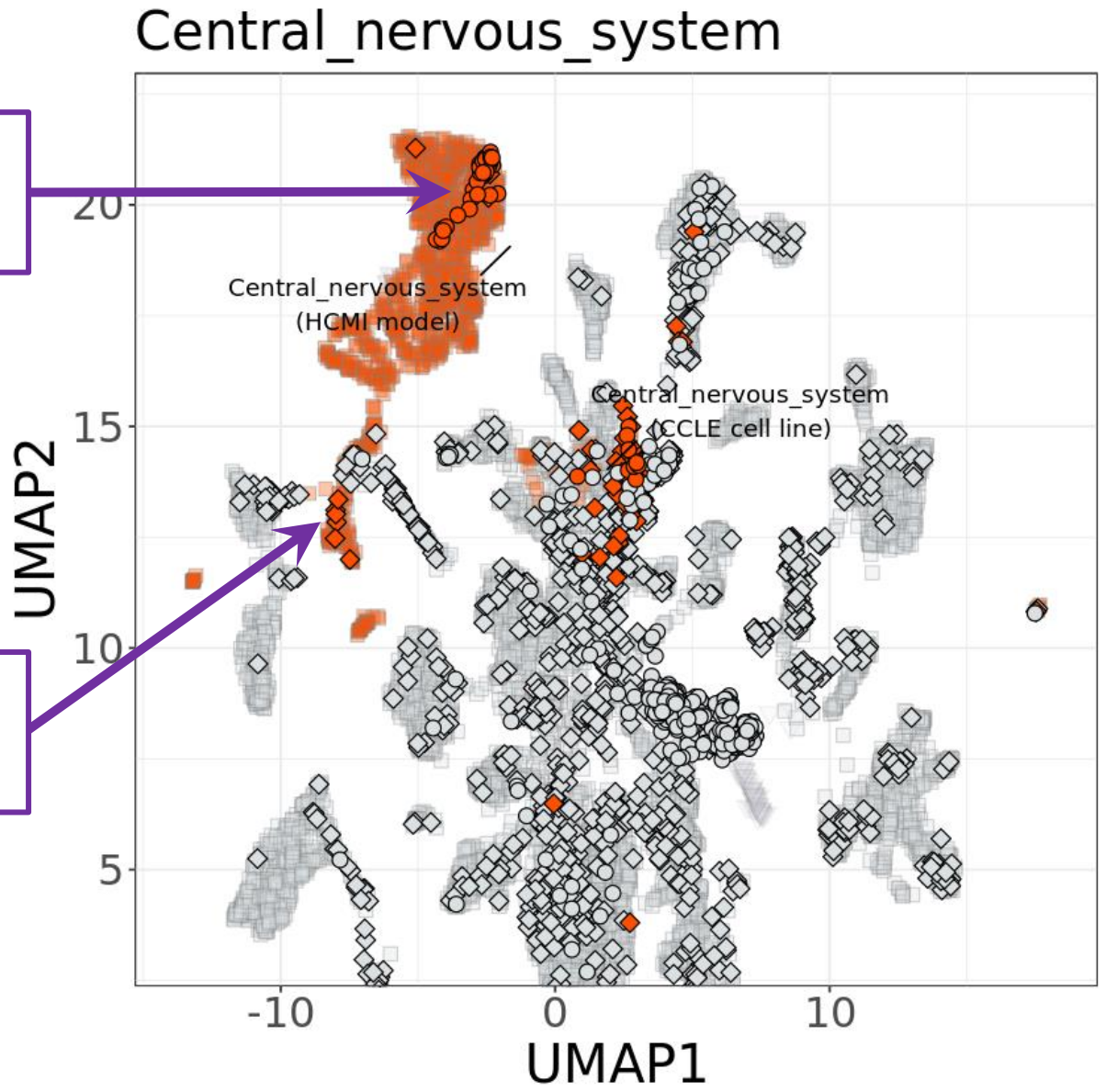
HCMI Models Match Transcriptional State of HCMI and TCGA Tumors



HCMI Models Match Transcriptional State of HCMI and TCGA Tumors

GBM space enriched in HCMI models

GBM space enriched in CCLE models



CNS tumors

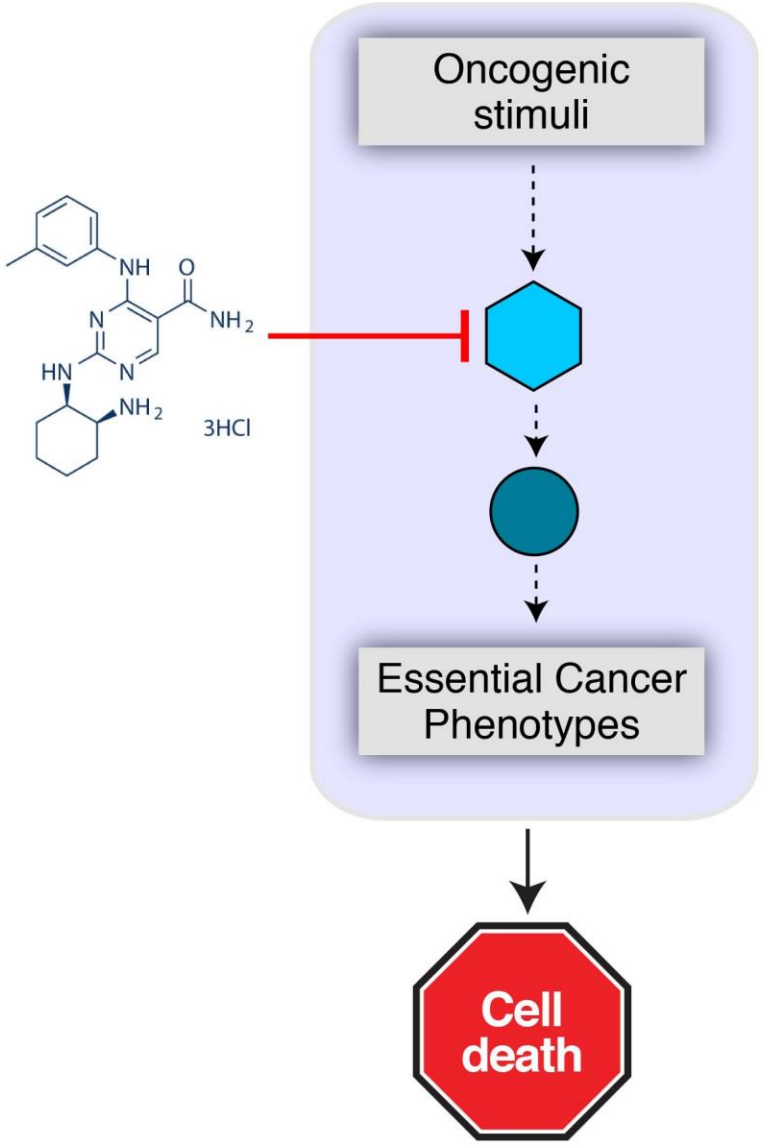
CCLE cell line
TCGA tumor
HCMI tumor
HCMI model

Next-Gen Cancer Signaling Networks and Predictive Cancer Therapeutics

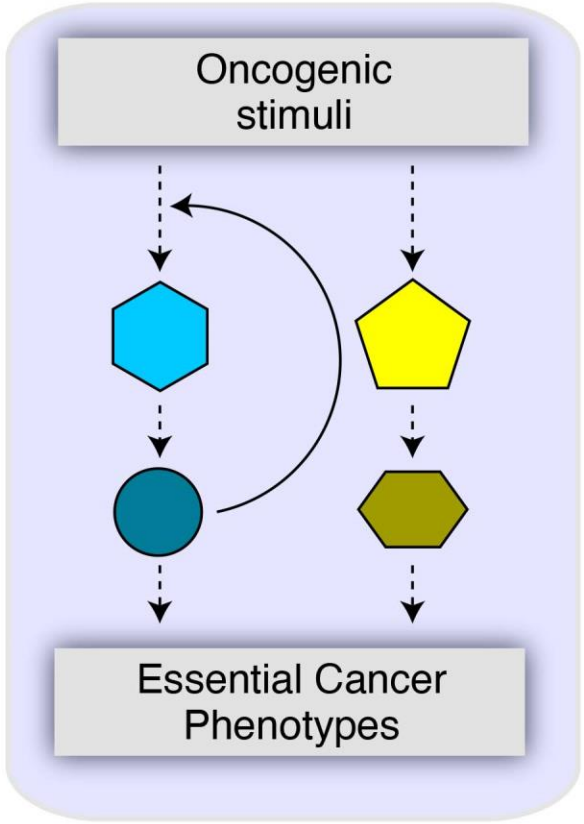
The Problem

- Targeted monotherapy of cancer has had some limited success, but resistance emerges frequently.
- Combination therapy of cancer has been empirical and not based on deep knowledge of regulatory networks.
- Current models of signaling/regulatory networks in cancer do not account for:
  - Cancer type-specific epigenetic differences
  - Influence of oncogenic alterations
  - Network redundancy, feedback circuits, complexity
- Current network models are descriptive, not predictive, and are static, not dynamic.
- Next generation cancer network models are needed to rationally design combination therapies for cancer.

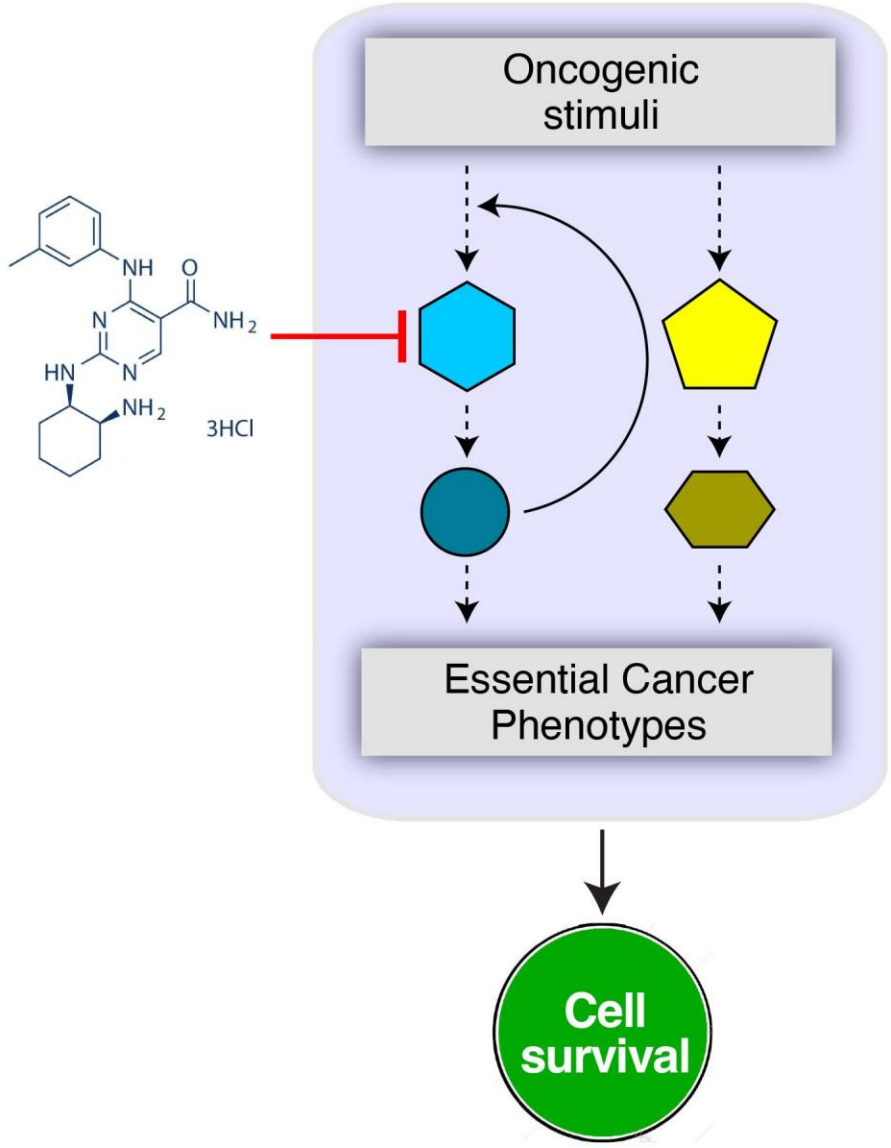
Next-gen Regulatory Networks to Develop Combination Cancer Therapies



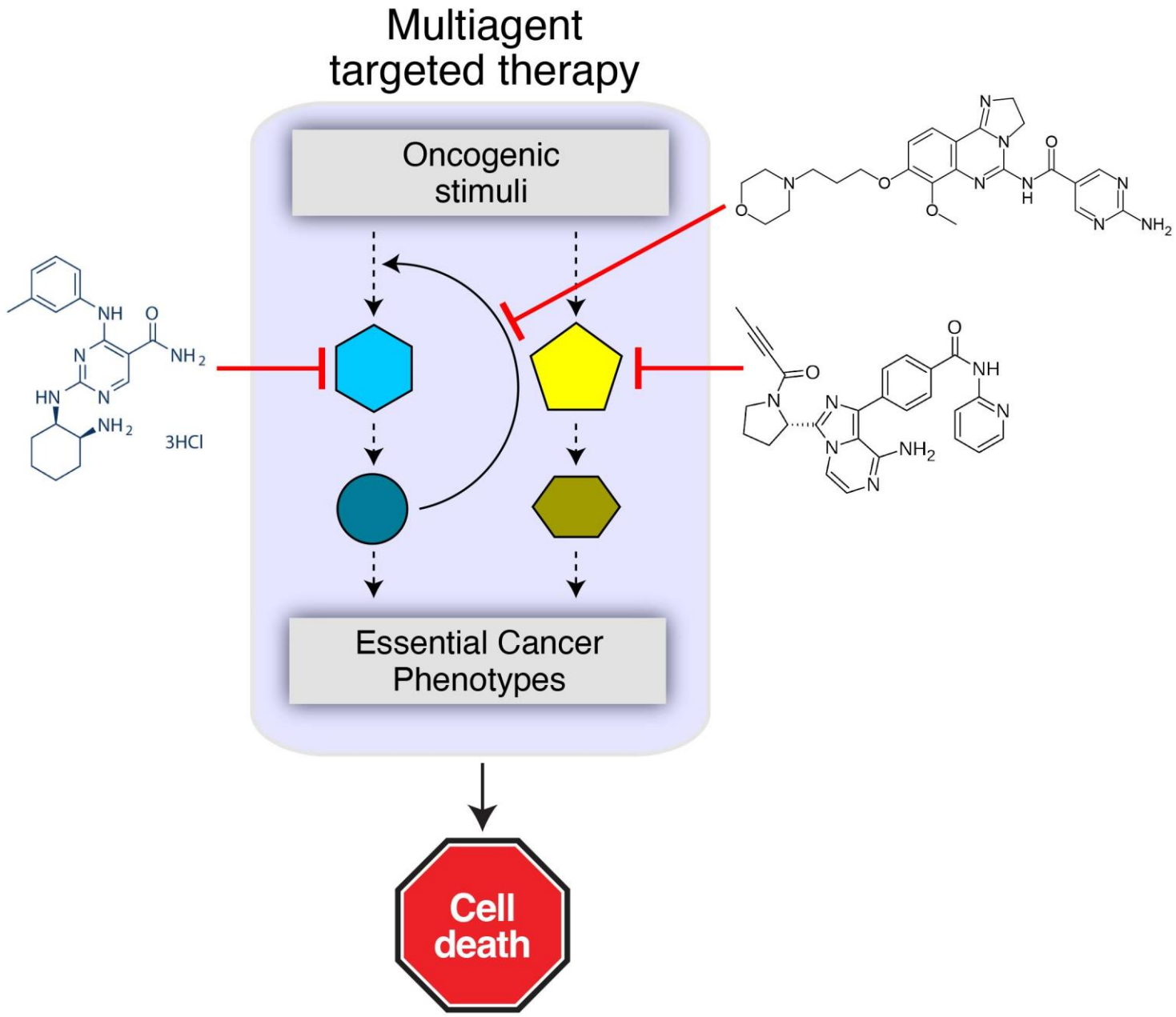
Next-gen Regulatory Networks to Develop Combination Cancer Therapies



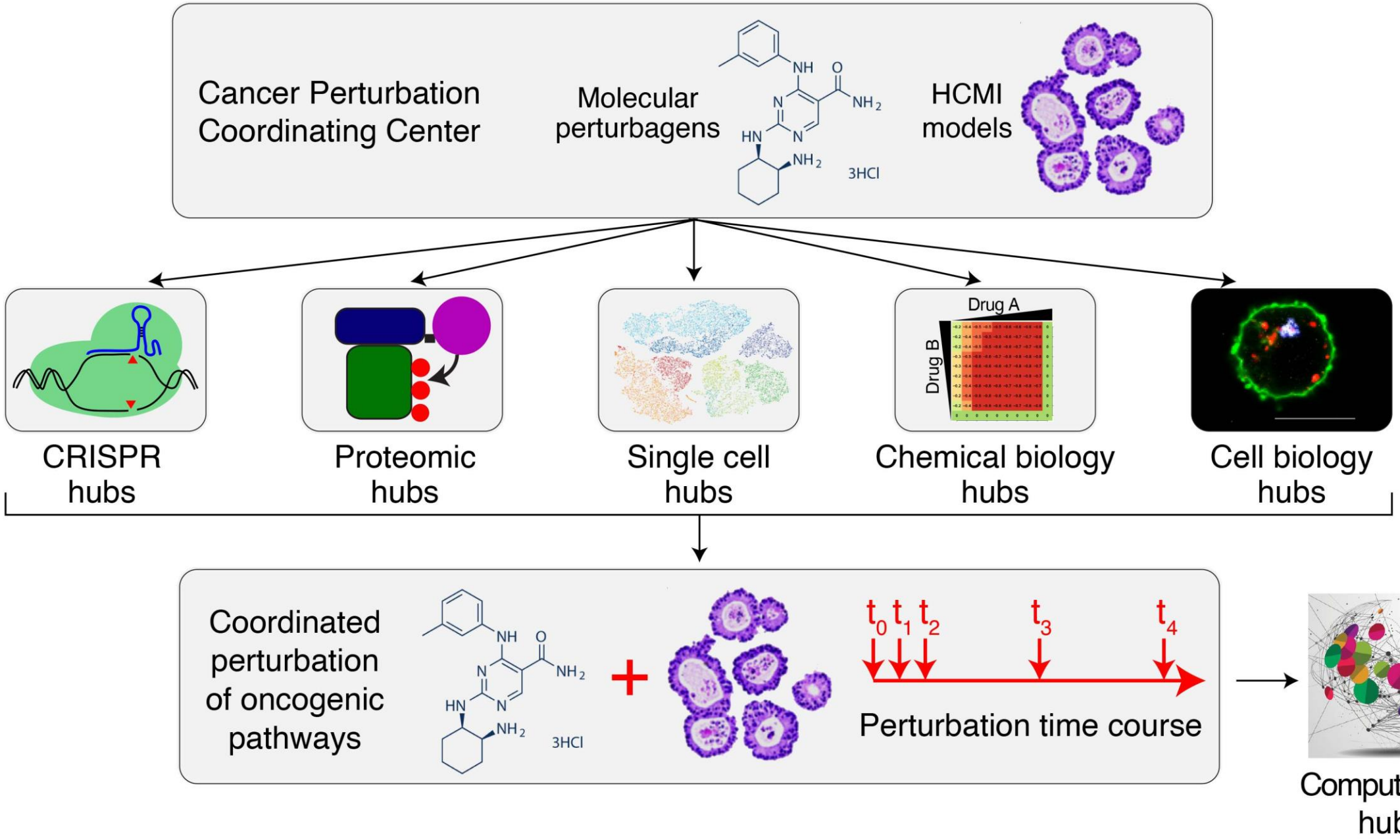
Next-gen Regulatory Networks to Develop Combination Cancer Therapies



Next-gen Regulatory Networks to Develop Combination Cancer Therapies



A “Functional TCGA” Initiative



A “Functional TCGA” Initiative - Deliverables

Computational Hubs

→

Next-gen models of cancer regulatory networks

=> Reference perturbation datasets distributed to cancer researchers in real time.

=> Detailed wiring diagrams of intracellular networks in cancer. How does cancer type/differentiation alter networks?

=> Identify synthetic lethal relationships with clinically available drugs.

=> Define new targets for therapeutic development based on the most vulnerable regulatory nodes.

=> Devise combination drug strategies to overcome network redundancy and feedback mechanisms.

=> Initiate phase I trials to test drug combinations predicted to be safe and effective in particular cancer types.