

Using “Big Data” to Discover Cancer Mechanisms

CRCHD Professional Development Workshop

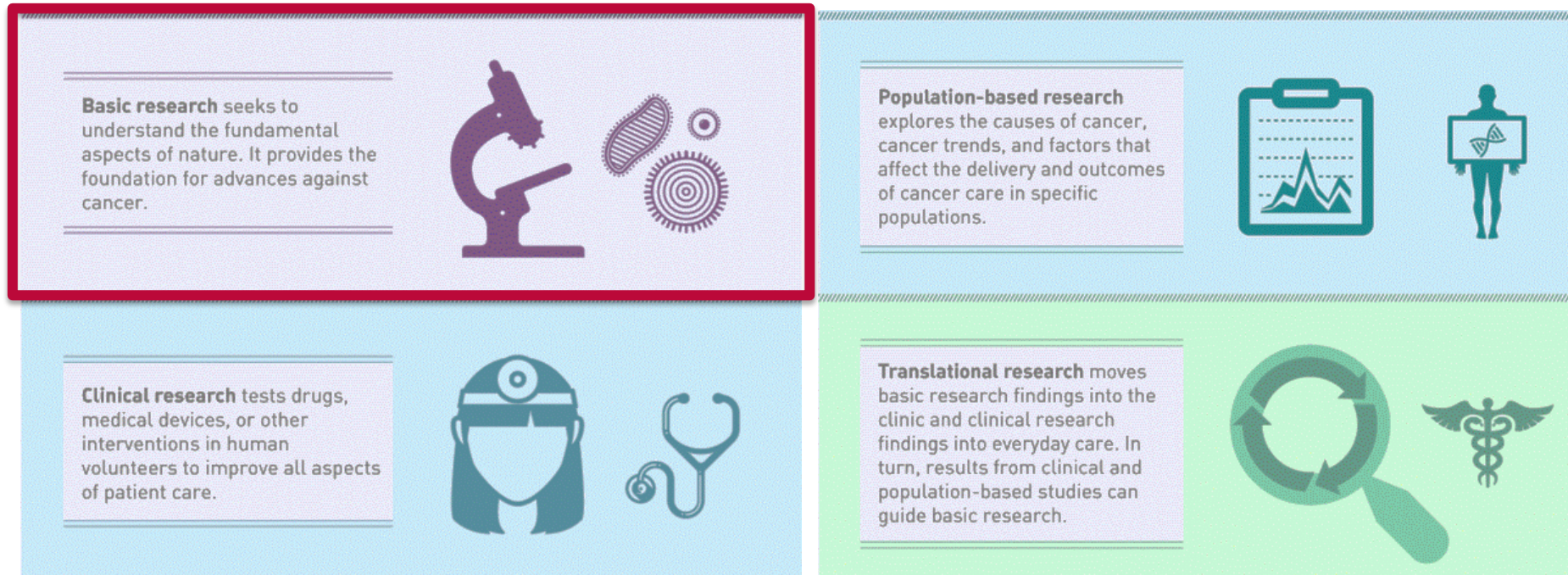
Shannon K. Hughes, Ph.D.

Program Director, Tumor Metastasis Branch

Division of Cancer Biology, NCI

The NCI supports cancer research across the disease spectrum.

Division of Cancer Biology



DCB supports the most basic cancer research at NCI, with an investigator initiated (R01/R21/P01) portfolio of ~2500 awards.

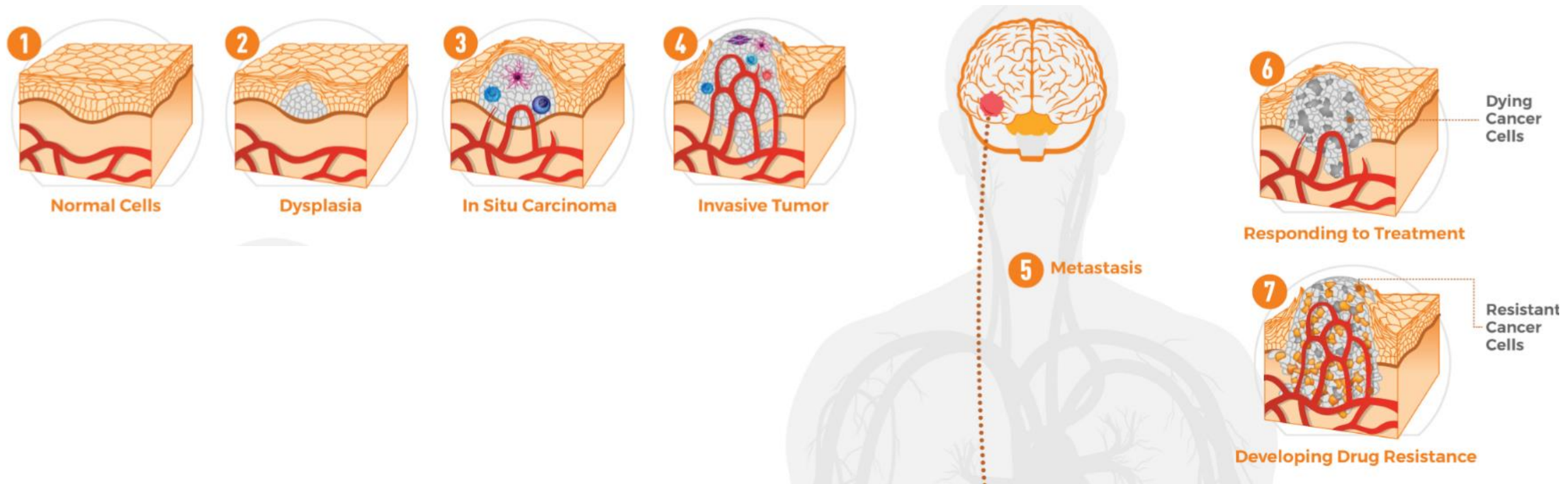
Adapted from cancer.gov/research/nci-role

Including a wide range of programs generating “Big Data” and **(importantly!)** computational approaches

- ✓ The Cancer Genome Atlas ([TCGA](#))
- ✓ Therapeutically Applicable Research To Generate Effective Treatments ([TARGET](#))
- ✓ Clinical Proteomics Tumor Analysis Consortium ([CPTAC](#))
- ✓ The Cancer Imaging Archive ([TCIA](#))
- ✓ Surveillance, Epidemiology, and End Results Program ([SEER](#))
- ✓ Cancer Target Discovery and Development ([CTD²](#))
- ✓ Informatics Technology for Cancer Research ([ITCR](#))
- ✓ Cancer Intervention and Surveillance Modeling Network ([CISNET](#))
- ✓ Physical Science in Oncology Network ([PS-ON](#))
- ✓ **The Human Tumor Atlas Network ([HTAN](#))**
- ✓ **Cancer Systems Biology Consortium ([CSBC](#))**

Cancer Moonshot Recommendation I: Generation of Human Tumor Atlases

Create dynamic 3D maps of human tumor evolution to document the genetic lesions and cellular interactions of each tumor as it evolves from a precancerous lesion to advanced cancer.



What is a human tumor atlas?

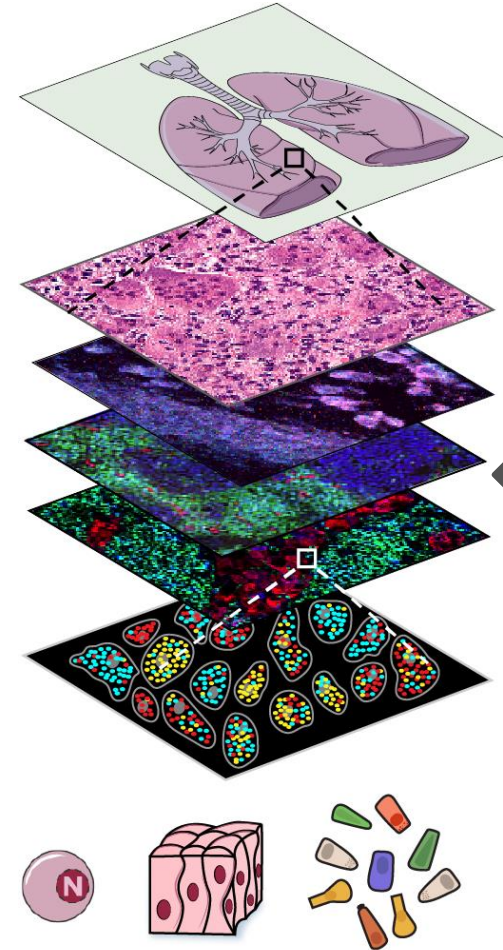
A comprehensive human tumor atlas is defined as the **multidimensional molecular, cellular, and morphological mapping** of human cancers, **complemented with critical spatial information** (at the molecular, cellular, and/or tissue level) that **facilitate visualization of the structure, composition, and multiscale interactions** within the tumor ecosystem.

Human Tumor Atlas Network (HTAN)

Constructing 3D atlases of the multidimensional cellular, morphological, molecular features of human cancers over time.

- Focus on *high-risk* cancers; including those responsive/non-responsive to immunotherapy; pediatric cancers
- Represent a *diverse patient population*, including minority and underserved patients
- Describe *transitions during cancer*: pre-malignant lesions to malignancy, locally invasive to metastatic cancer, and the development of therapeutic resistance
- Enable *predictive modeling* to refine therapeutic choices for patients.

Experimental Measurements



Computational Analysis

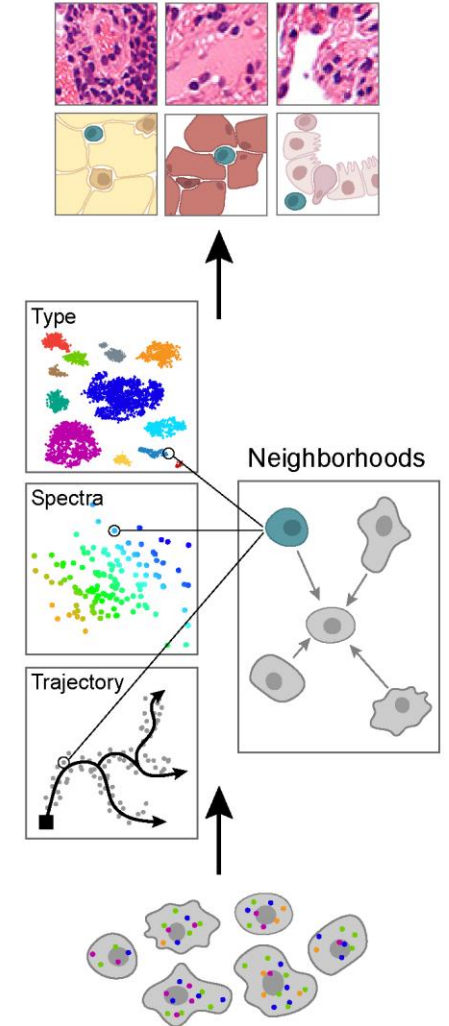
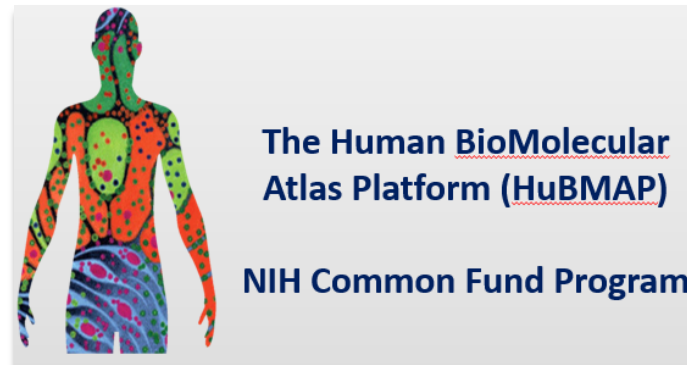


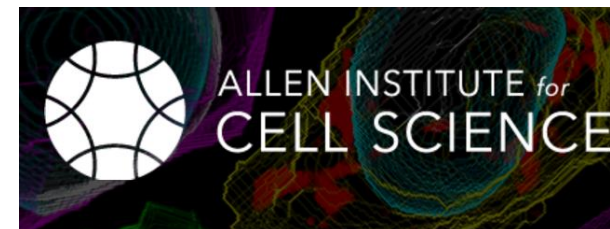
Figure from A. Regev and HTAPP Team

The HTAN in the context of other “Atlas” initiatives:

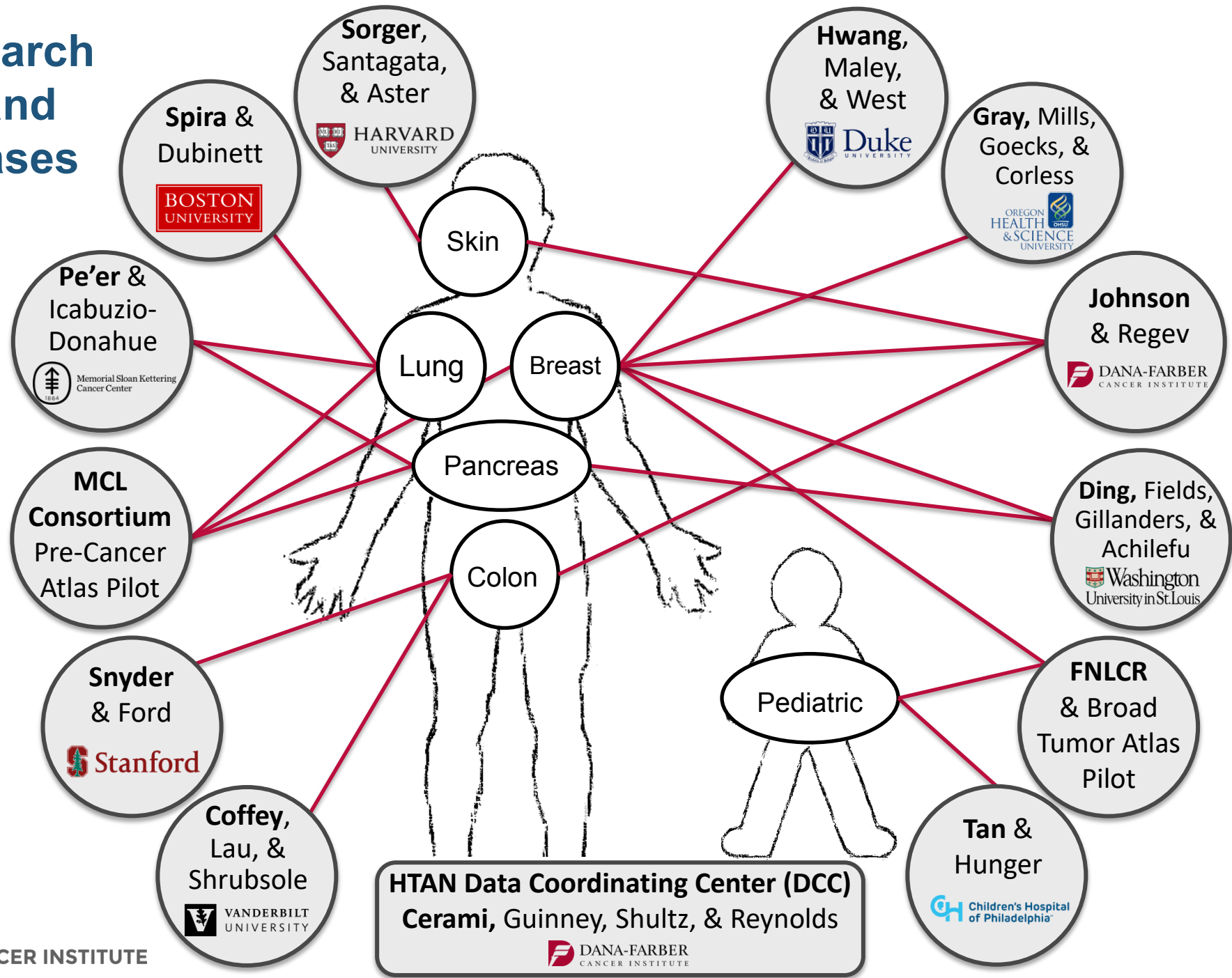


Human Tumor Atlas Network

- Emphasis on spatial relationships and interactions
- Prospective/longitudinal sample collection (time)
- Extensive clinical data
- Atlases describing disease transitions



HTAN Research Centers and Tumor Atlases



HTAN data sets will be highly multi-scale and multi-modal

Host level (microbiome, circulating factors)

Medical imaging modalities (radiomics)

Histology; Highly multiplexed 2D/3D imaging

Metabolomics (Mass Spectrometry, Imaging)

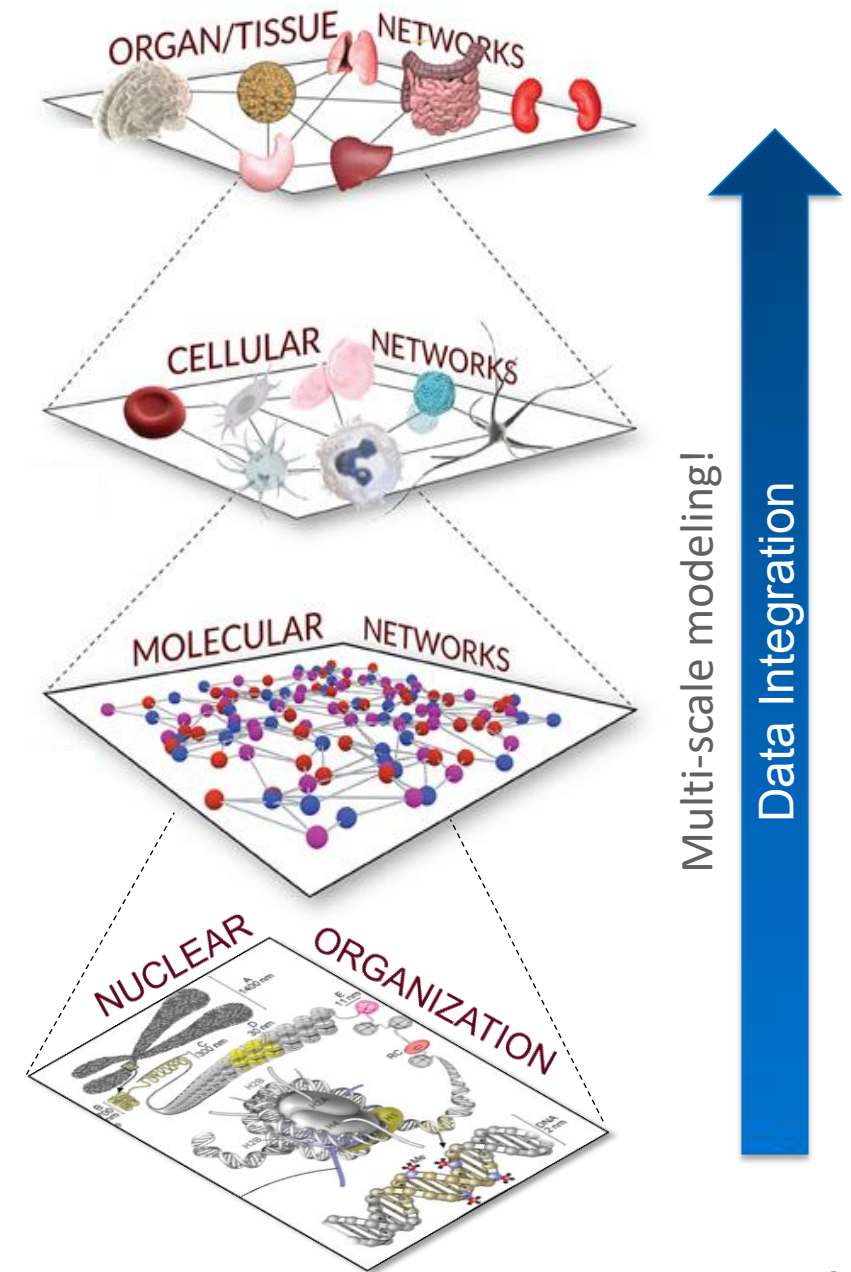
Proteomics (Mass Spectrometry, Imaging Approaches)

Transcriptomics (RNA-seq, in situ/FISH, etc.)

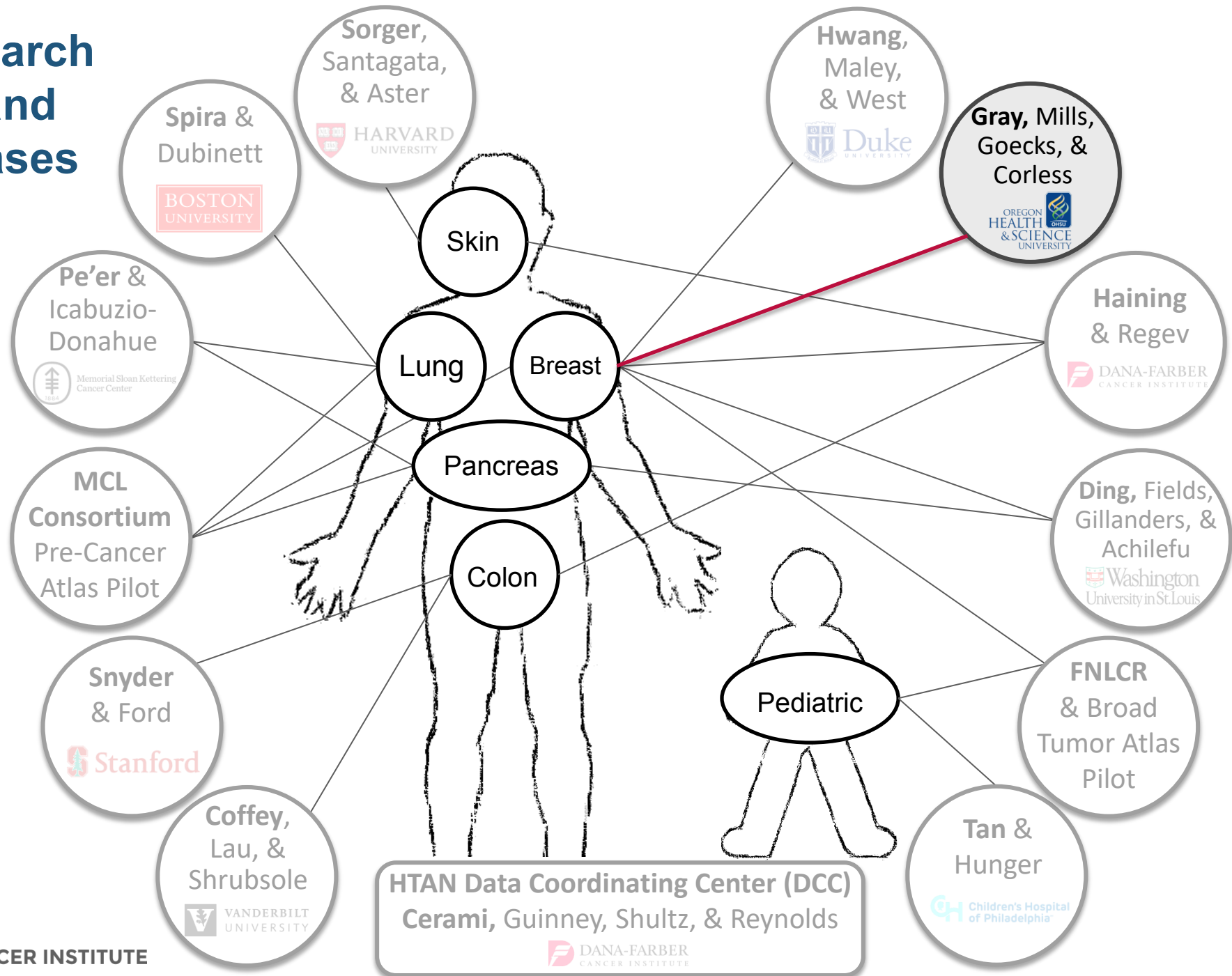
DNA-seq (whole genome, whole exome) and Epigenetics

EM imaging (2D, 3D)

Many at single-cell resolution, longitudinal, & with spatial information



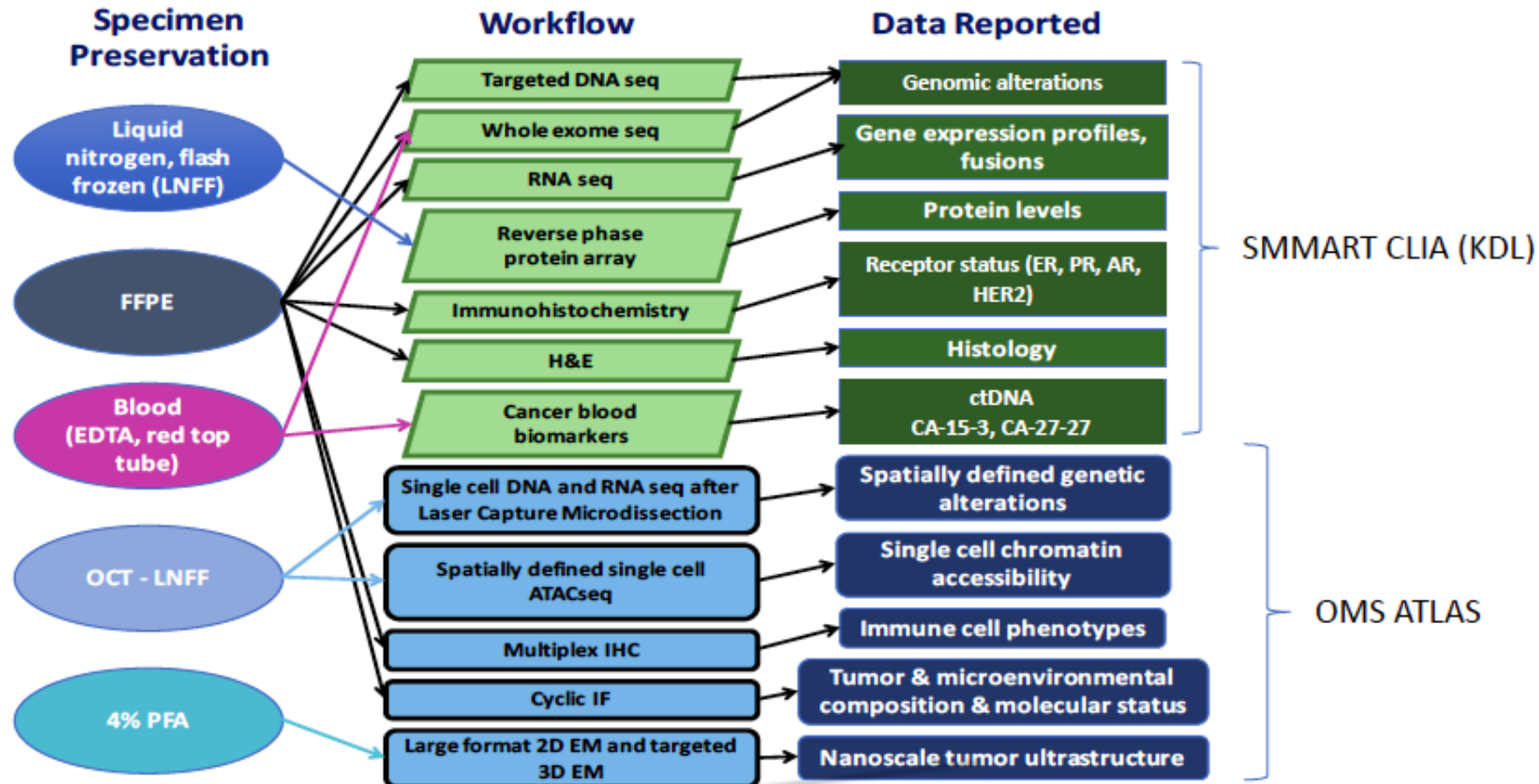
HTAN Research Centers and Tumor Atlases



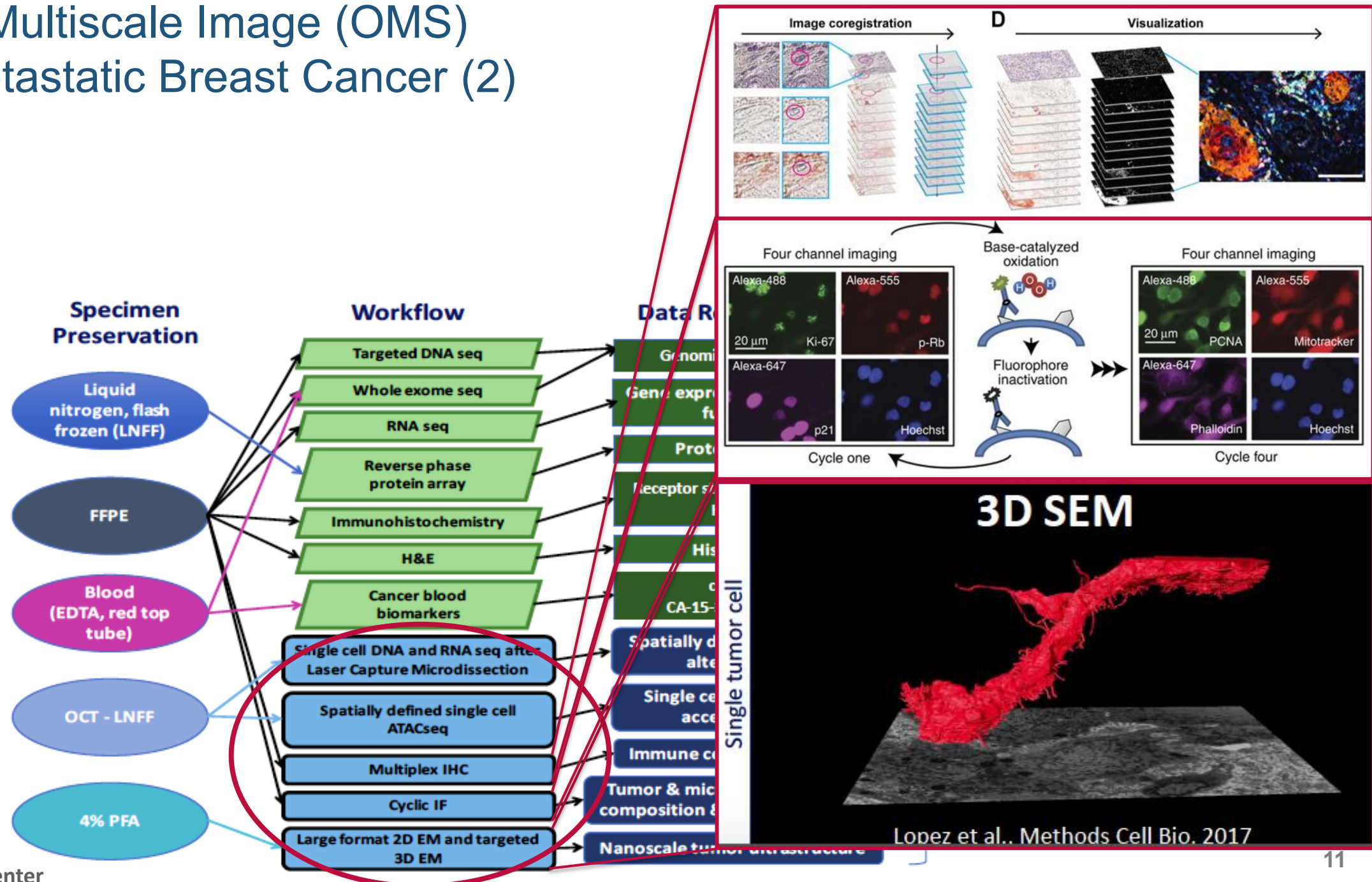
Omic and Multiscale Image (OMS) Atlas of Metastatic Breast Cancer

Overarching goal: Identify **therapeutic vulnerabilities** and mechanisms of **resistance** in evolving metastatic breast cancers.

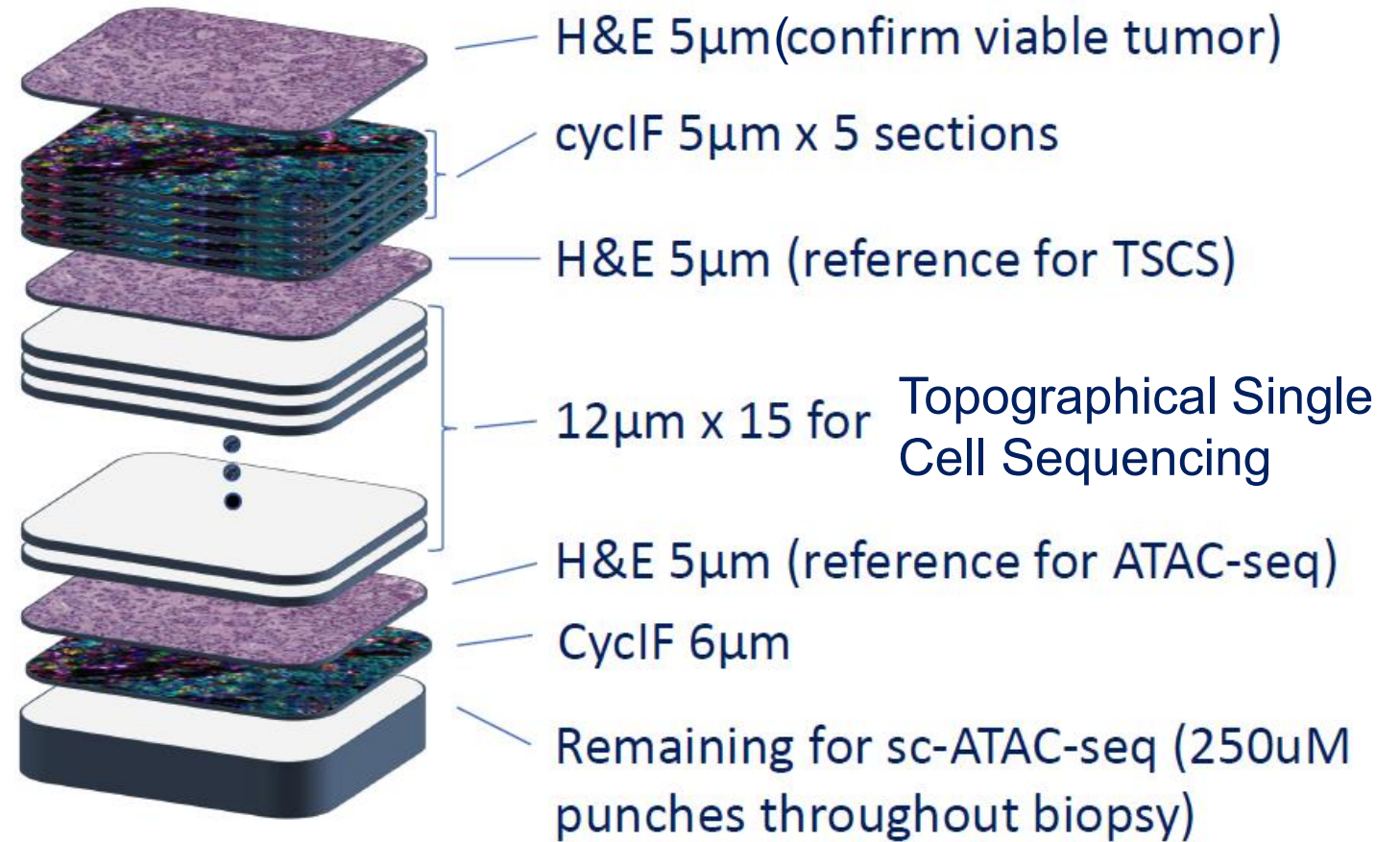
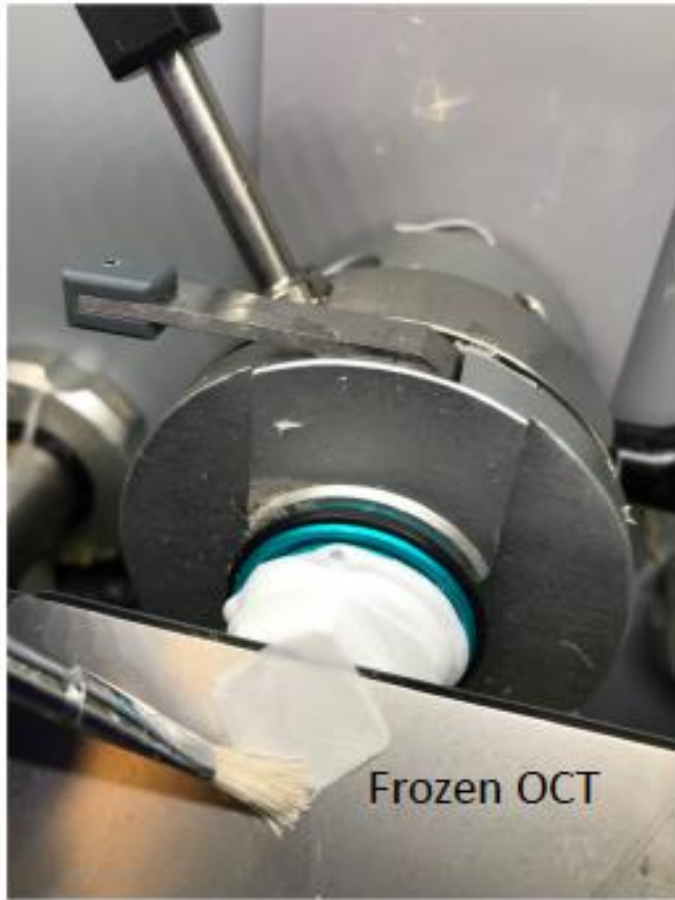
- HRBC treated with CDK4/6 inhibitors + anti-estrogen
- TNBC treated with PARP inhibitor + immune checkpoint inhibitors



Omic and Multiscale Image (OMS) Atlas of Metastatic Breast Cancer (2)



Tissue processing to facilitate spatial registration of cyclF, TSCS and sc-ATAC-seq



NCI Cancer Systems Biology Consortium (CSBC)

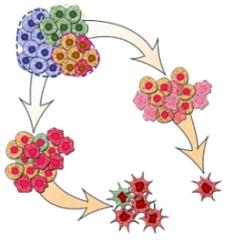
- In the CSBC we define systems biology as the **explicit integration of experimental biology and computational or mathematical modeling** to build, test and/or validate hypotheses or ideas



Currently: 13 Research Centers (multi-project) and 13 Research Projects

New U01 Funding Opportunity Announcement: [PAR-19-287](#)

Follow @NCISysBio!

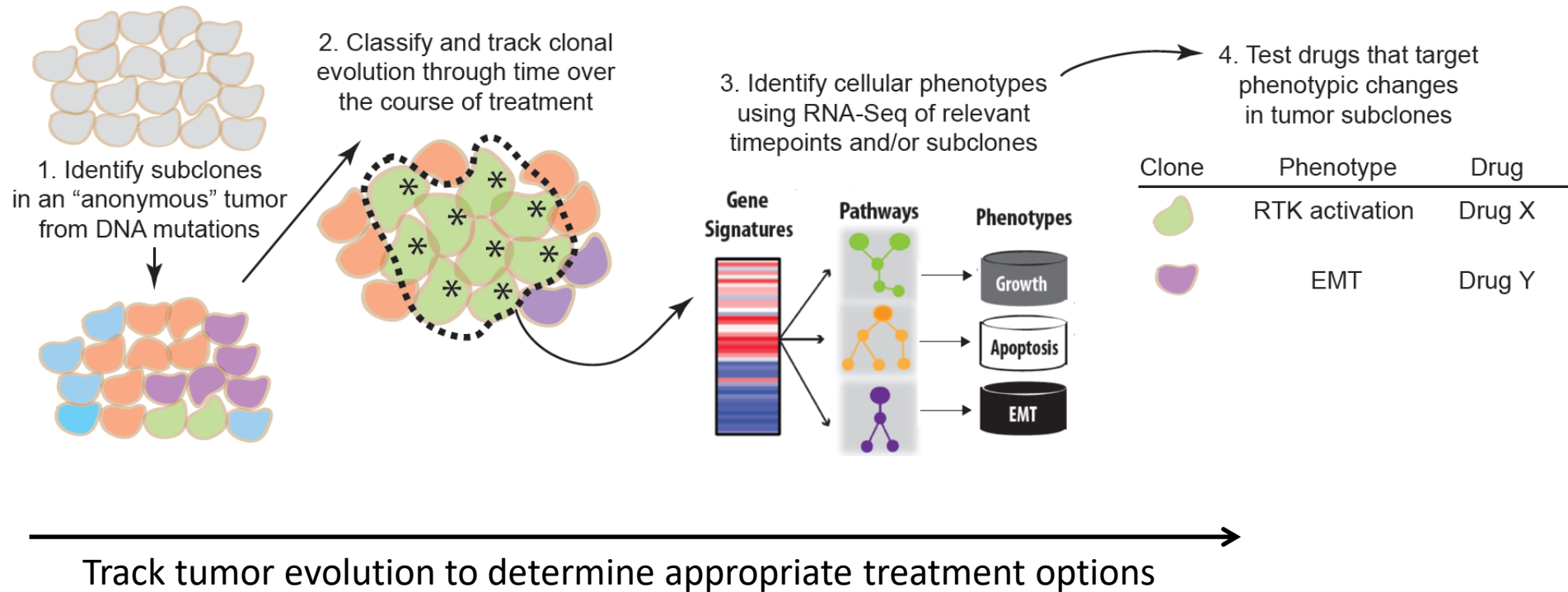


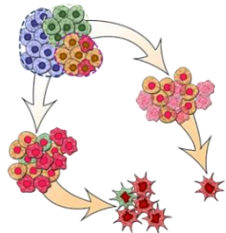
CSBC Center of HoPE (Heterogeneity of Phenotypic Evolution)

PI: Andrea Bild



Combating subclonal evolution of resistant cancer phenotypes



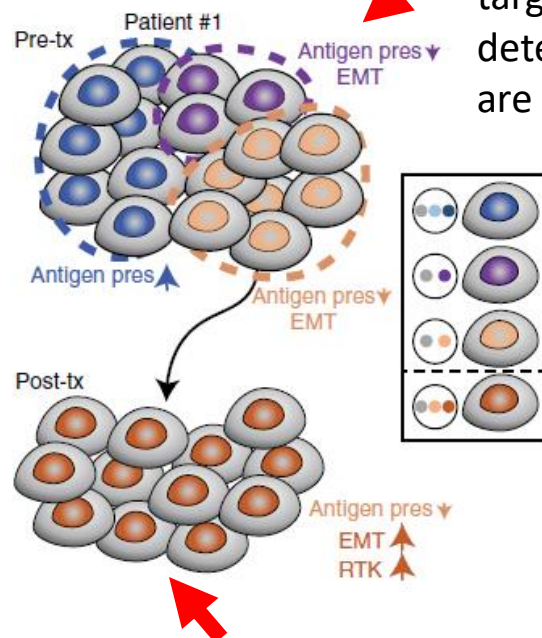


CSBC Center of HoPE (Heterogeneity of Phenotypic Evolution)

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Combating subclonal evolution of resistant cancer phenotypes

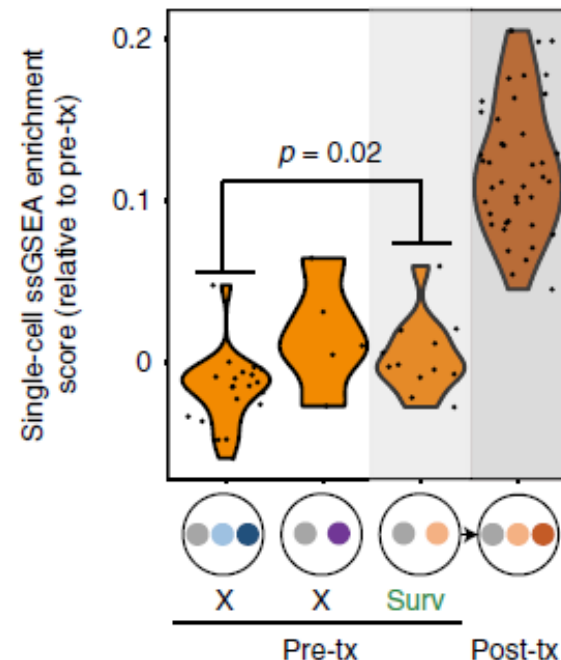
1) Combination of bulk WGS, WES and targeted single-cell DNA Seq to determine what mutations (subclones) are present in the tumor



Dot = mutation
Collection of dots = subclone

2) Over time, use single-cell RNASeq to determine which pathways are active in particular clones

Epithelial-to-Mesenchymal Transition Signature (Invasive Characteristic)



The banner features a dark teal background on the right with the title in white. The left side is decorated with a pattern of stylized orange and blue cells. Below the title, a row of logos for partner organizations is displayed.

Tumor Deconvolution DREAM Challenge

DREAM
CHALLENGES
powered by Sage Bionetworks



Sage Bionetworks

Stanford

Launch: June 3, 2019

510 pre-registered participants

<https://www.synapse.org/tumorDeconvolutionChallenge>

Contact: brian.white@sagebase.org

Don't worry. AI/DL/ML will solve it.

- might be true in some contexts
- but maybe (very likely) not for others



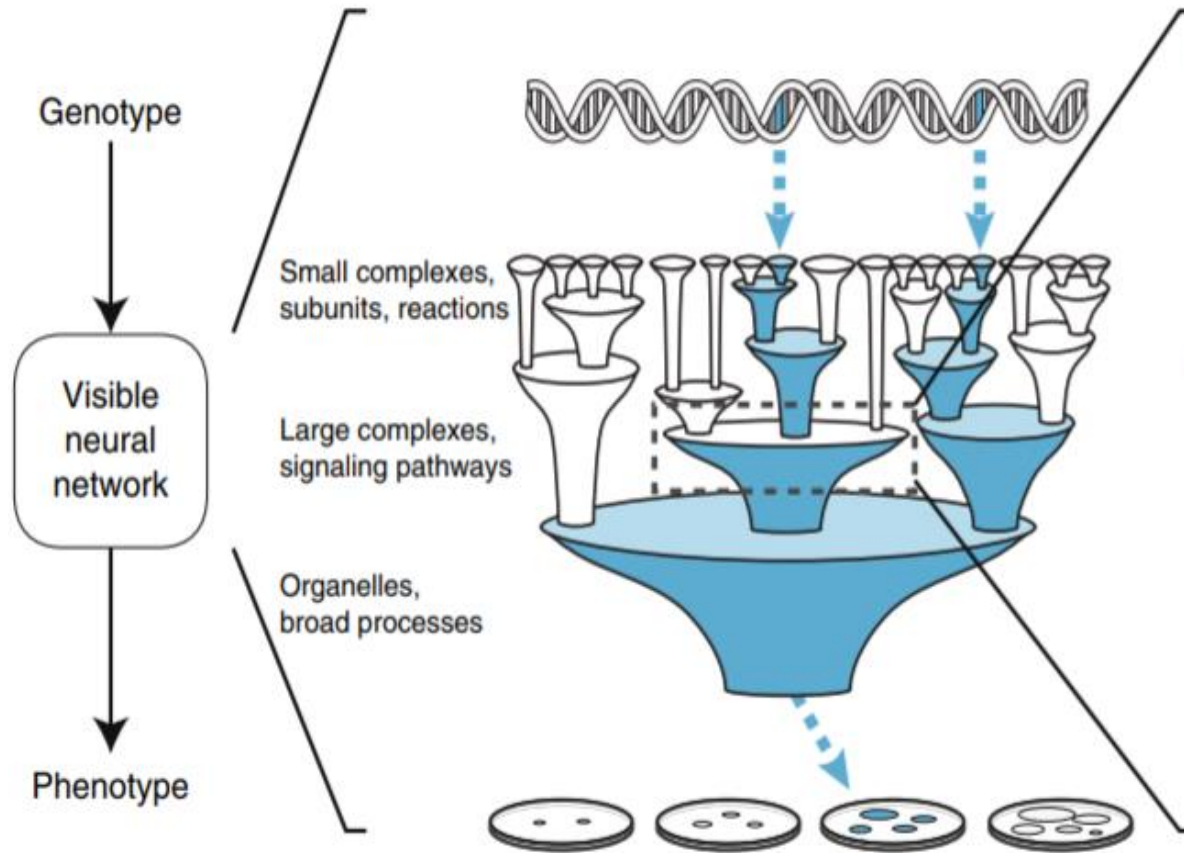
Ideker Lab UCSD

Ma et al. *Nature Methods* May 2018 [doi:10.1038/nmeth.4627](https://doi.org/10.1038/nmeth.4627)



The Cancer Cell Map Initiative

PIs: Nevan Krogan (UCSF) & Trey Ideker (UCSD)



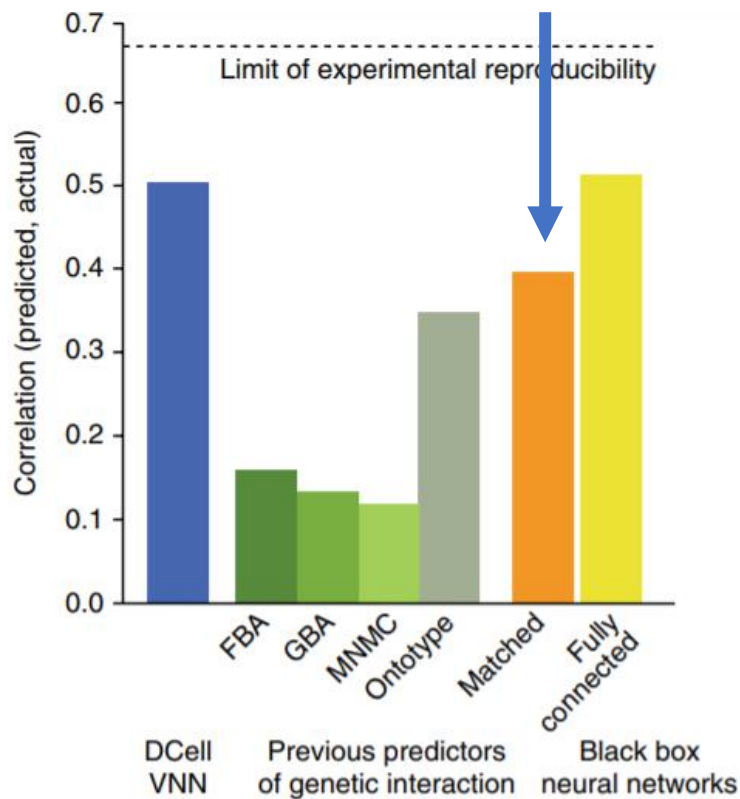
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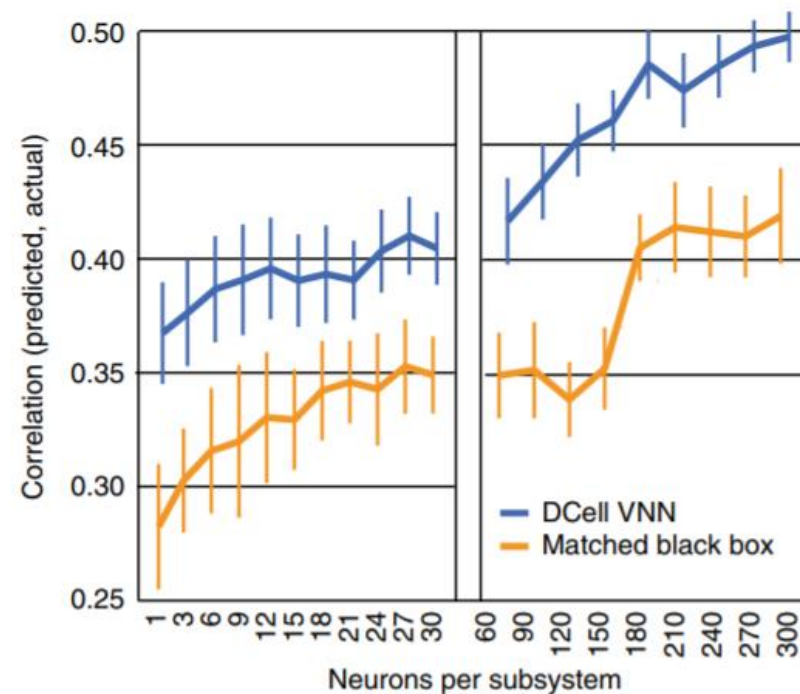
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Same structure, but ontology information is randomized



Information is lost if biology is not used to inform the model



Ideker Lab UCSD

Ma et al. *Nature Methods* May 2018 [doi:10.1038/nmeth.4627](https://doi.org/10.1038/nmeth.4627)

Please contact me with questions:
shannon.hughes@nih.gov

Follow us on Twitter: @NCISysBio and @NCIHTAN
Check out currently funded projects: www.csbconsortium.org

CSBC U01 Funding Announcement: [PAR-19-287](#)

Informatics Technologies for Cancer Research (ITCR) Funding
Announcements: <https://itcr.nci.nih.gov/> (R21/U01/U24)