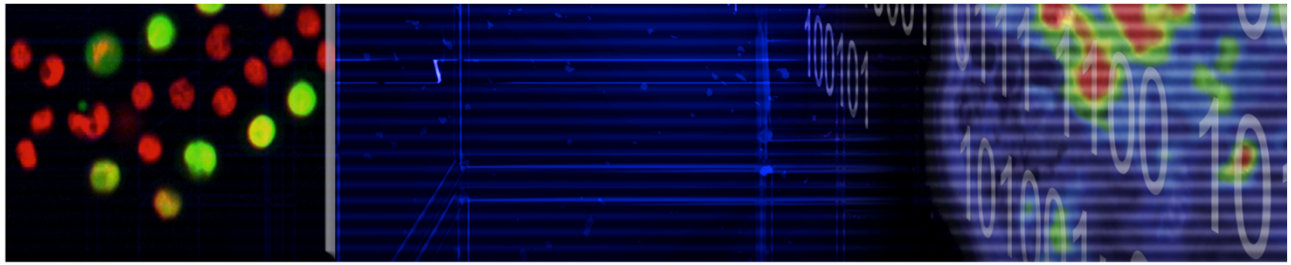
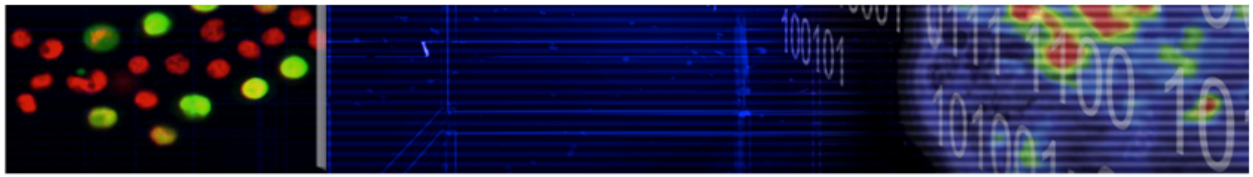
Advancing Research in Tumor Cell Heterogeneity



NCI-Frederick Advisory Committee (NFAC)

February 4, 2014



NATIONAL CANCER INSTITUTE

Integrative Cancer Biology Program:
Centers for Cancer Systems Biology

Vanderbilt-Ingram Cancer Center

Tumor Cell Heterogeneity Think Tank
December 2-3, 2013

- Steven Altschuler
- Mike Barrett
- Joan Brugge
- Jeff Engelman
- Sui Huang
- Joe Gray
- Garry Nolan
- William Pao
- Jennifer Pietenpol
- Sylvia Plevritis
- Kornelia Polyak
- Vito Quaranta
- Charles Sawyers
- Lani Wu

NATIONAL CANCER INSTITUTE

- Dinah Singer, Dan Gallahan, Suresh Mohla

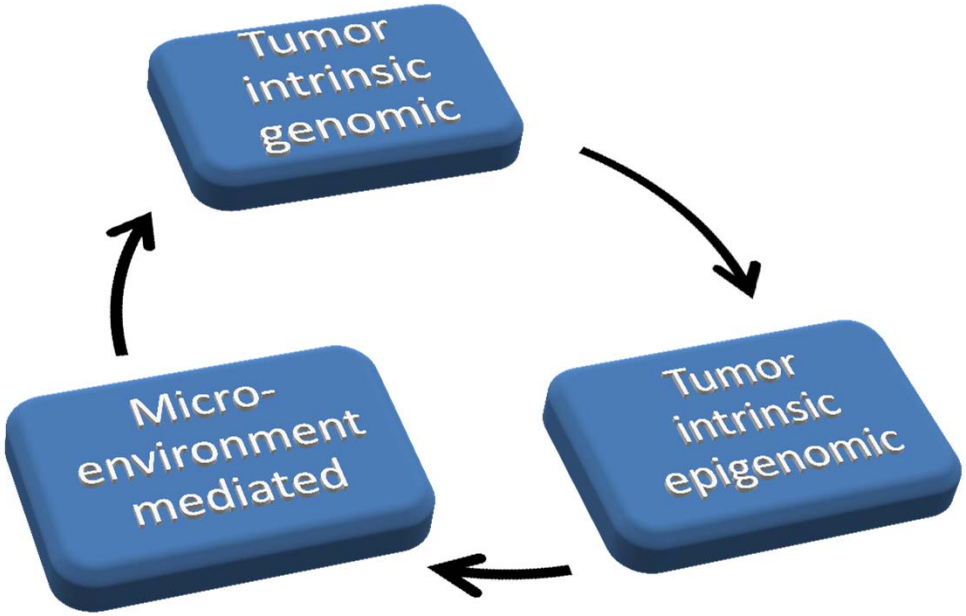
Data and concepts brought to you by:
NATIONAL CANCER INSTITUTE
Integrative Cancer Biology Program:
Centers for Cancer Systems Biology
Vanderbilt-Ingram Cancer Center
Current Topics in Cancer Systems Biology:
Tumor Cell Heterogeneity Workshop
December 2-3, 2013

Summary Observations From the Tumor Cell Heterogeneity Think Tank

- Heterogeneity likely arises from epigenomic and genomic events intrinsic to tumors and regulatory signals from diverse micro-environments.

- Tumor heterogeneity is a fundamental driver of therapeutic resistance in most human cancers. Understanding this is an urgent and unmet need in cancer treatment.

- Recent advances in measurement technology, data analytics and biological models enable new approaches to studies of tumor heterogeneity.



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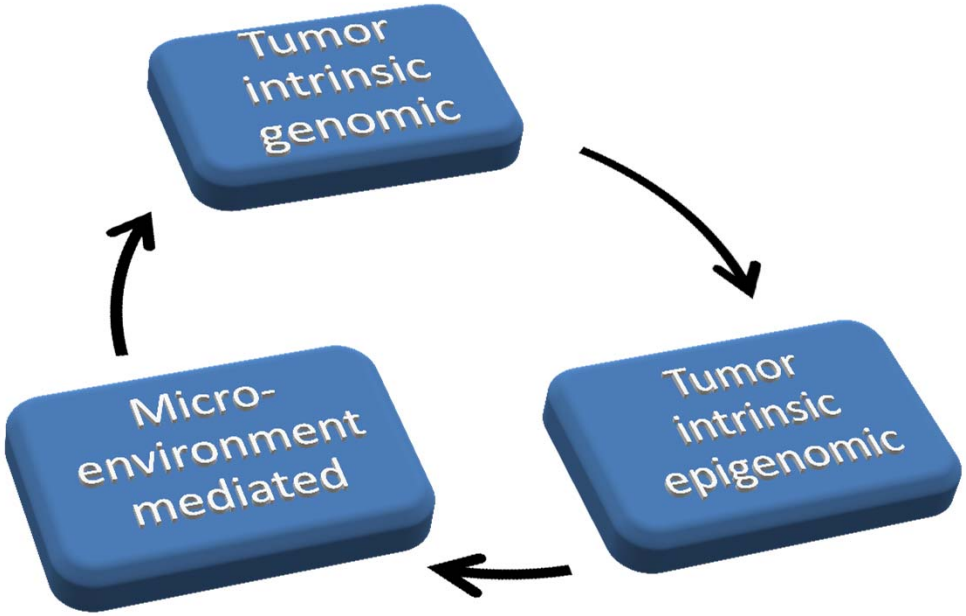
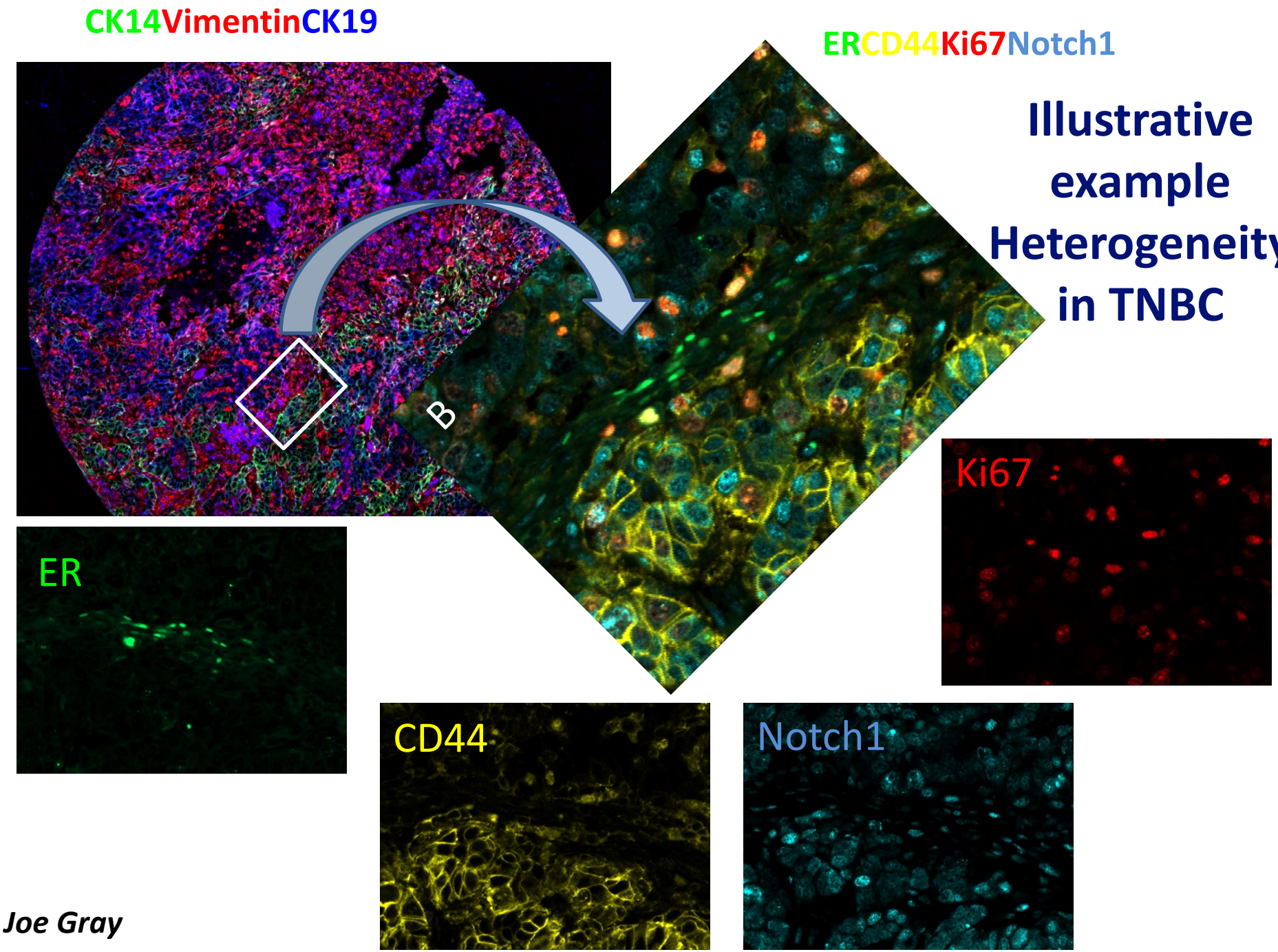


Illustrative example Heterogeneity in TNBC



Joe Gray

Genomic aberrations are well established as mechanisms of therapeutic resistance (NSCLC)

Gefitinib/Erlotinib (+ Afatinib) as an example

Activation of other receptor tyrosine kinases? (e.g. ERBB2 amplification)

FAS/NFκB activation?

Epithelial-mesenchymal transition? (AXL, Slug activation?)

Loss or spliced variant of BIM?

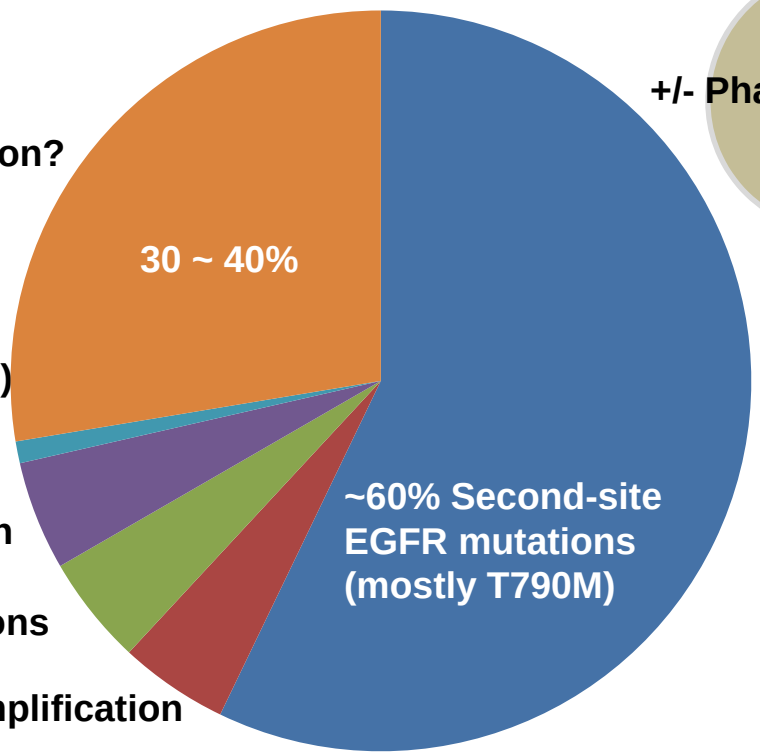
Other? (e.g. CRKL amplification)

~1% BRAF mutations

~5% SCLC transformation

~5% PIK3CA mutations

5-10% MET amplification



+/- Pharmacokinetic failure

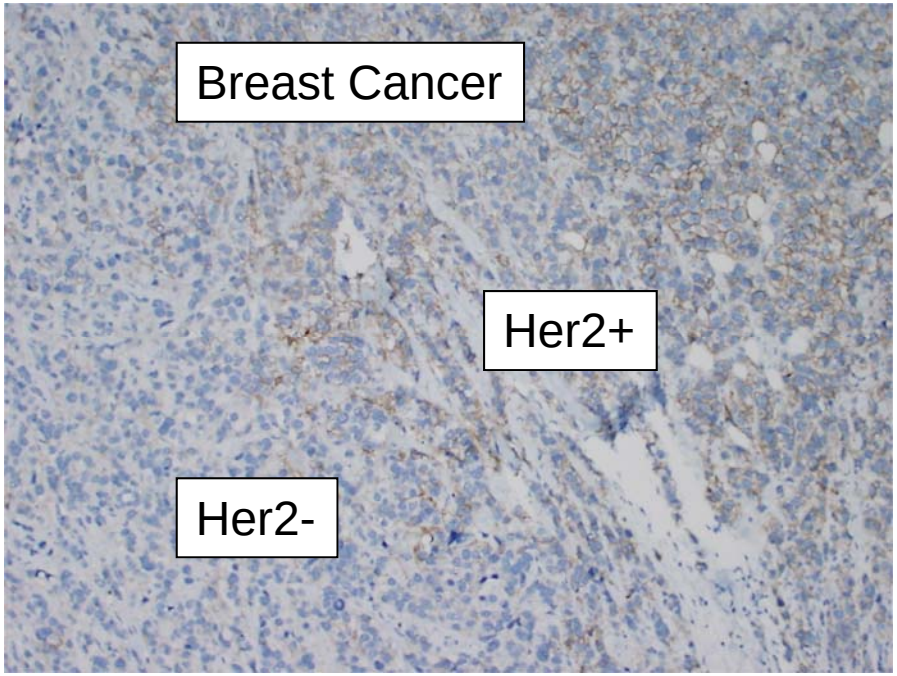
+/- Exogenous factors e.g. HGF, IL-6

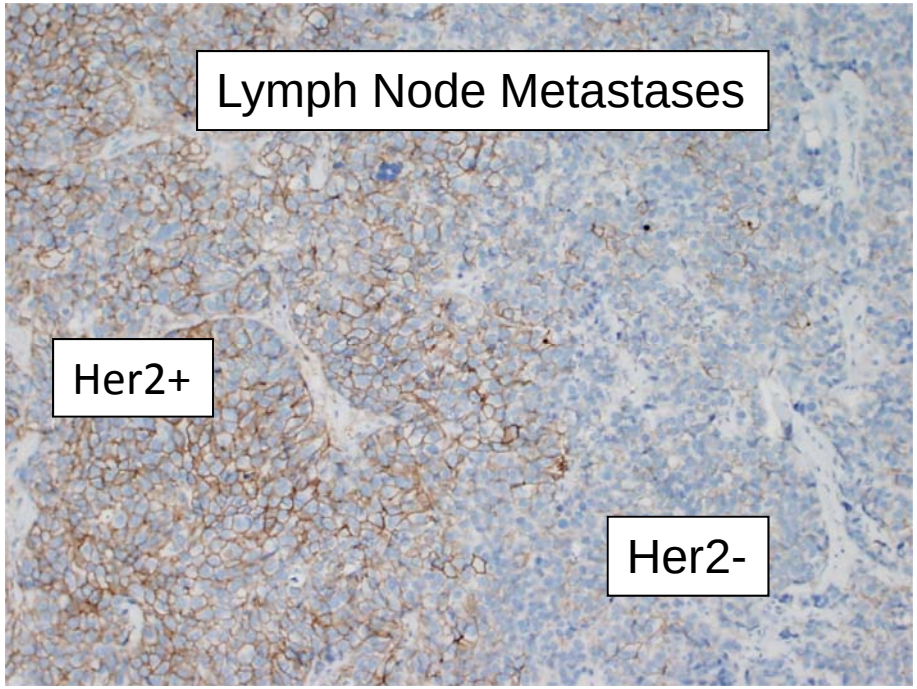
Ohashi et al '13

William Pao

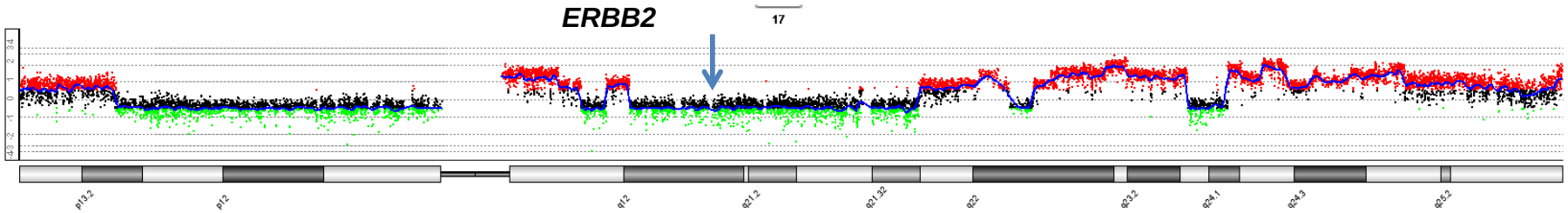
Jeff Engelman **Persister cells evolve through drug treatments; can generate a pie chart for each patient**

Intra-tumor heterogeneity in targeted genomic aberration





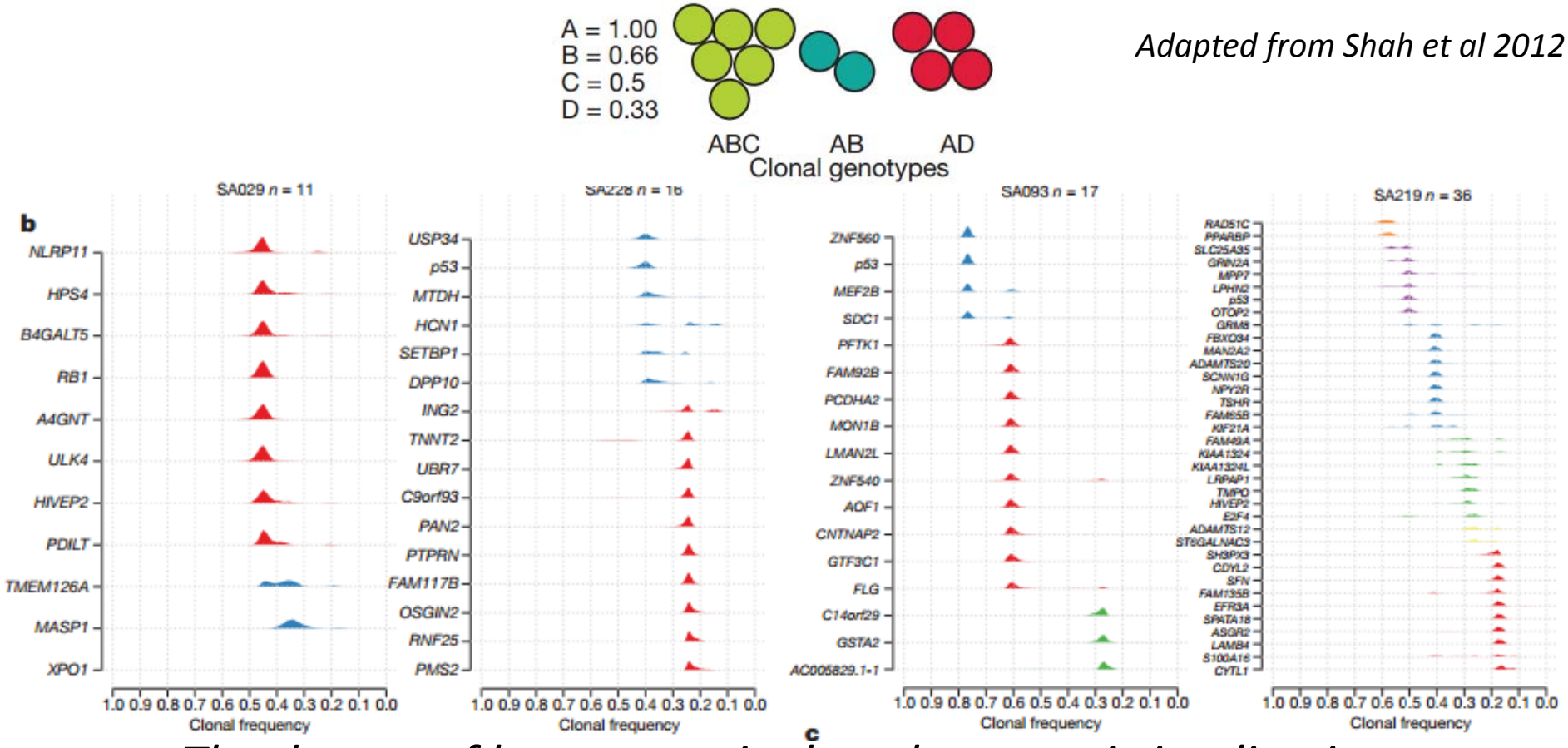
- Both the breast cancer and lymph node have Her2 staining
- Note, abrupt boundaries of expression
- Where the core biopsy is taken makes a difference – <u>tumor sampling bias</u>



Mike Barrett

The degree of heterogeneity can vary substantially between TNBC tumors; what are the drivers

Adapted from Shah et al 2012



The degree of heterogeneity has therapeutic implications

Understanding the biology and therapeutic responses of patients with TNBC will require the determination of individual tumor clonal genotypes

Jennifer Pietenpol

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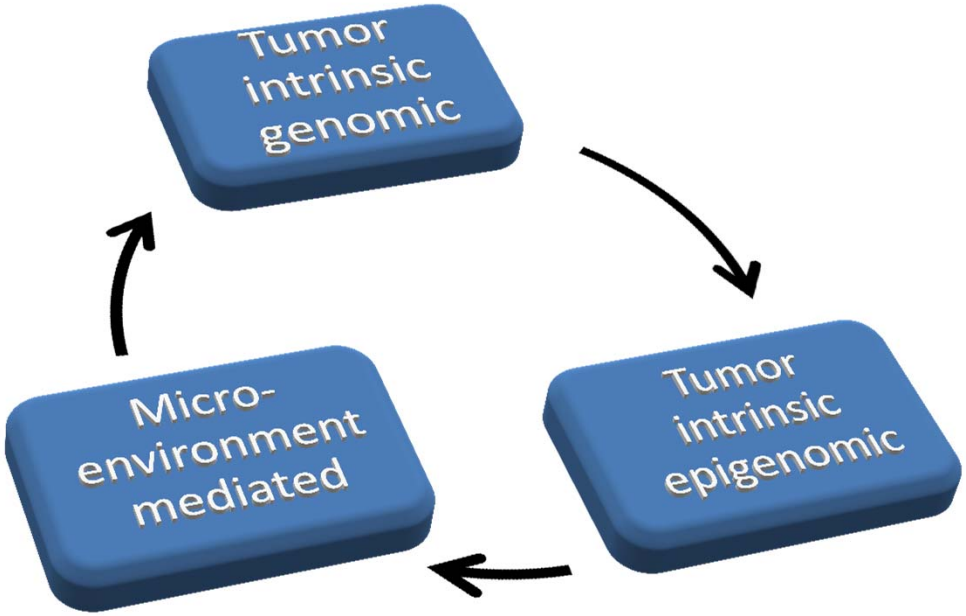
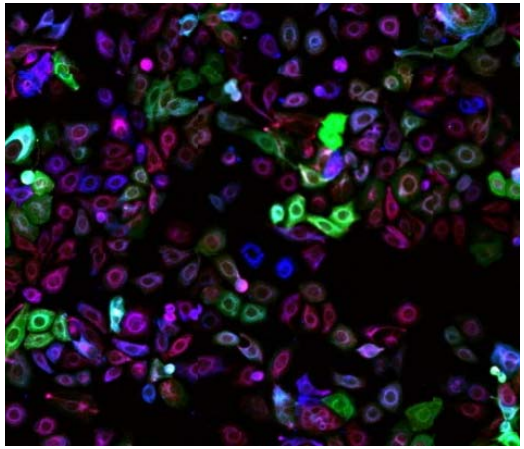


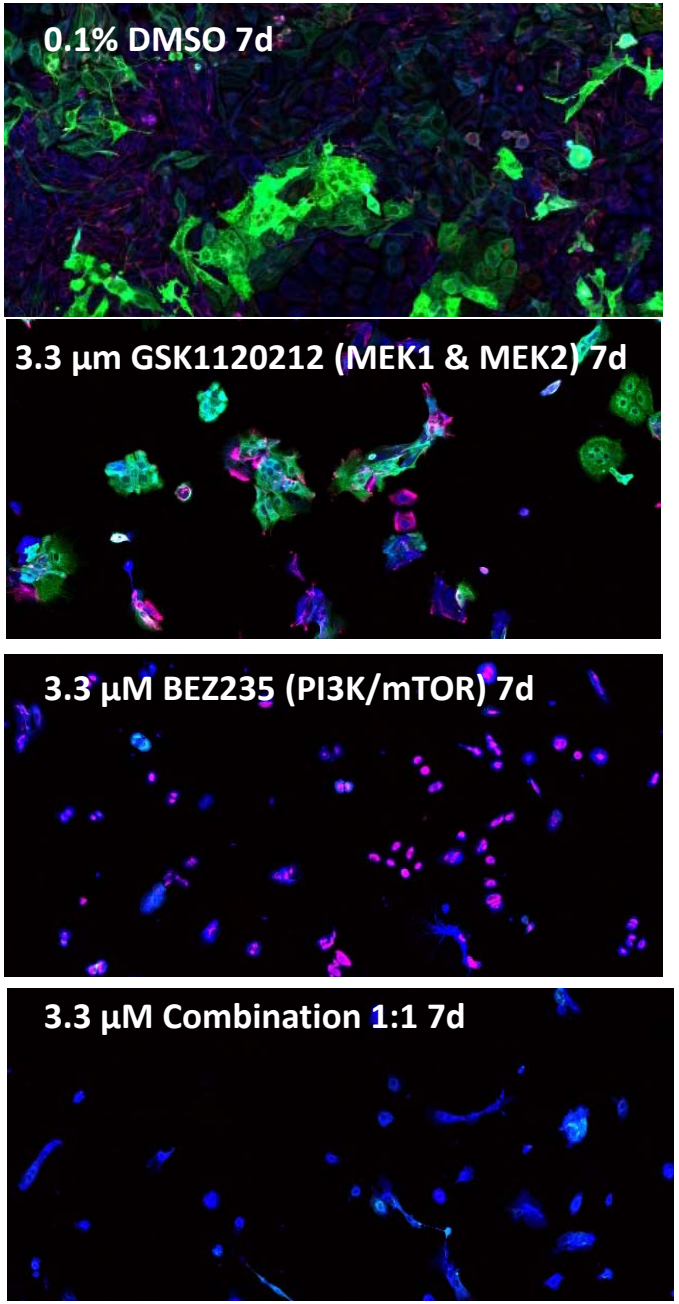
Model systems display intrinsic heterogeneity and can be used to study multi-drug steering strategies and mechanisms

HCC1143 (not actual starting density)



CK14VimentinCK19

Incubate cells in presence of compound(s) for 3-7days



Selection versus steering to a more homogenous state?

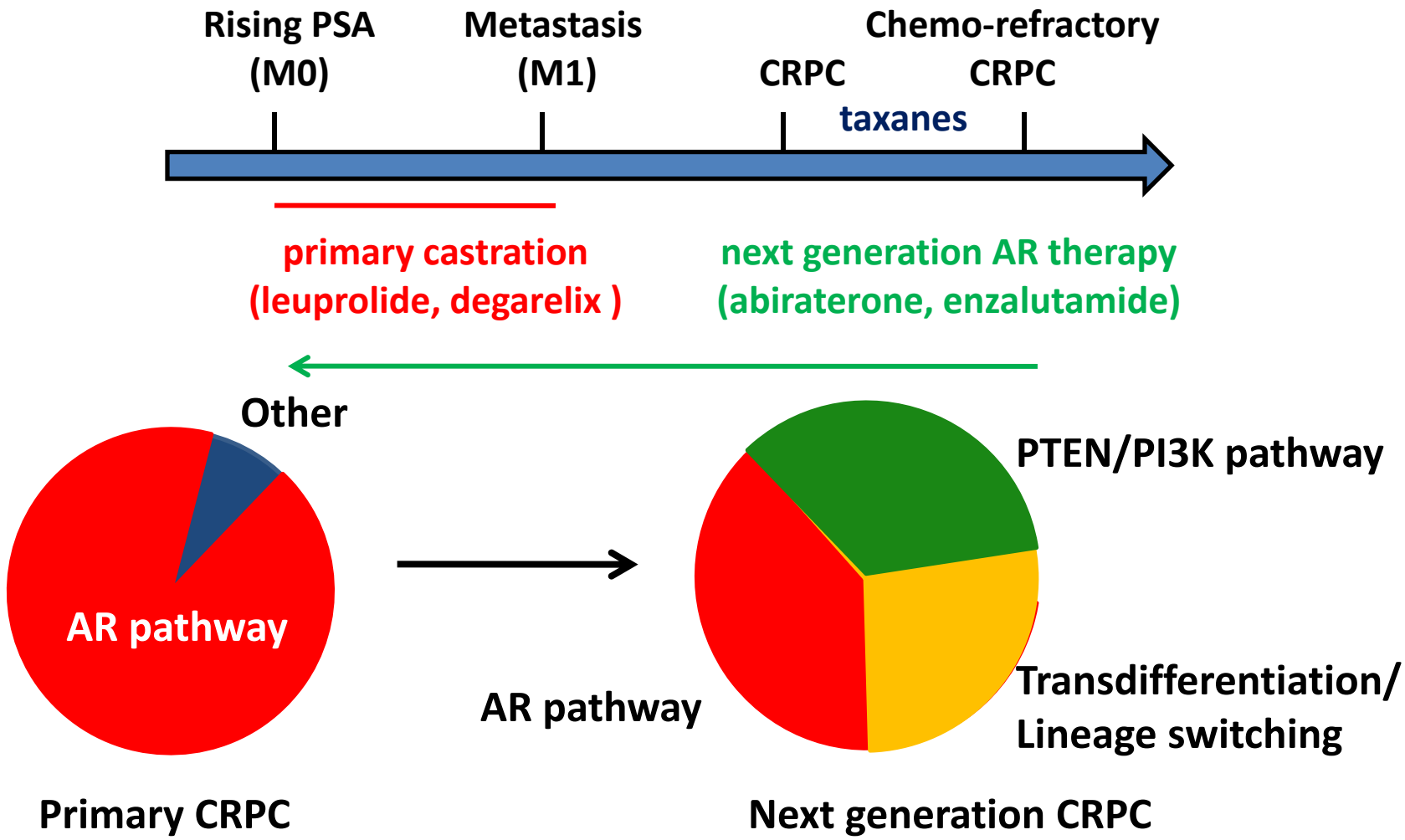
Sequential single agents vs combinations

Genotype or state of differentiation?

Rosalie Sears, Joe Gray

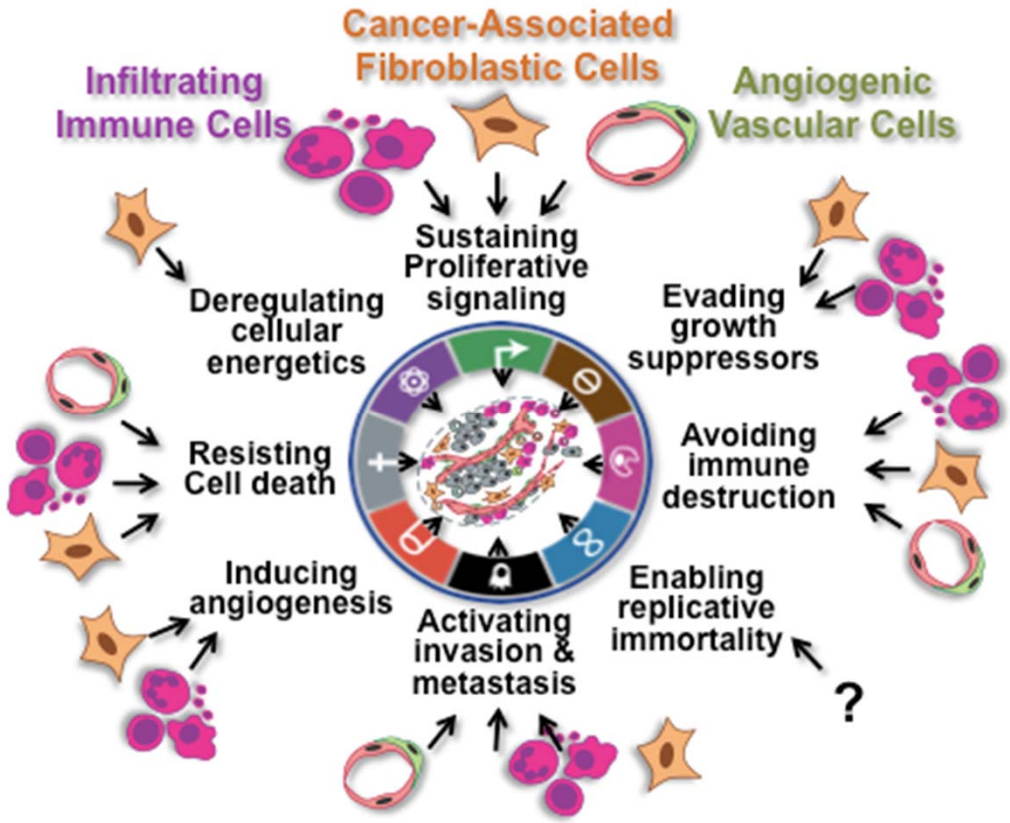
Both genomic and epigenomic mechanisms influence therapeutic response evolution clinically

Changing Landscape of Castration Resistant Prostate Cancer (CRPC)



Charles Sawyers

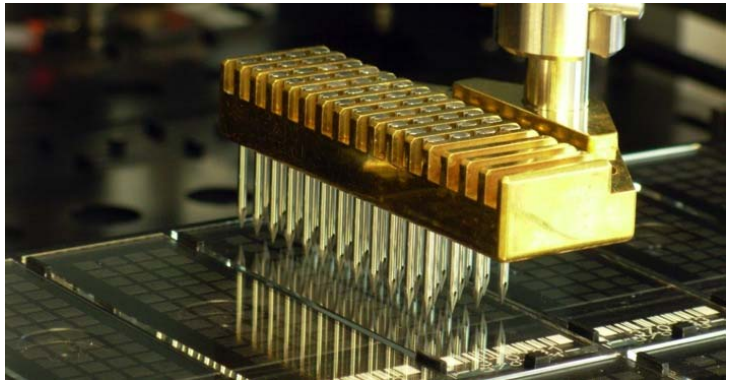
Extrinsic signals from the microenvironment also drive heterogeneity

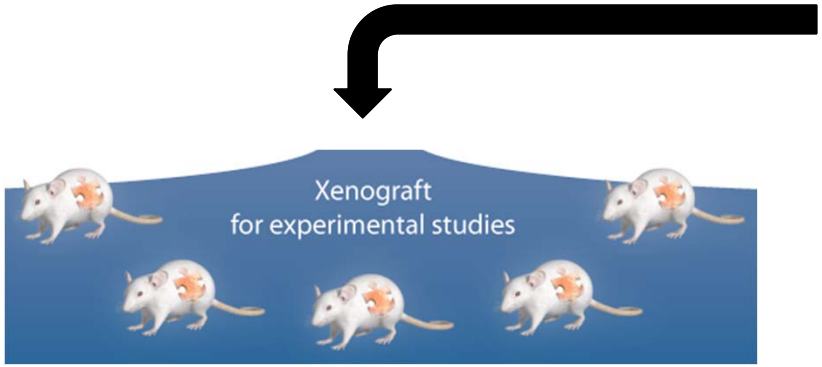


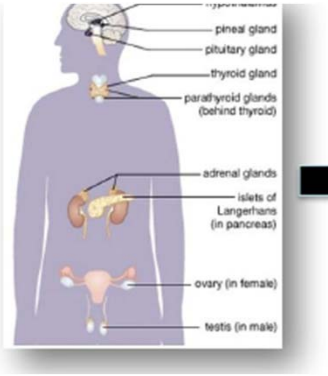
Hanahan & Coussens, Cancer Cell (2012)

Biological systems can be engineered to study the impact of specific extrinsic signals

- Growth on thousands of combinations of ECM and signaling proteins - cancer cell lines are adhered to array spots
- Heterogeneous “printed” 3D tissue structures and PDX models derived from tumor biopsies from patients on clinical trials



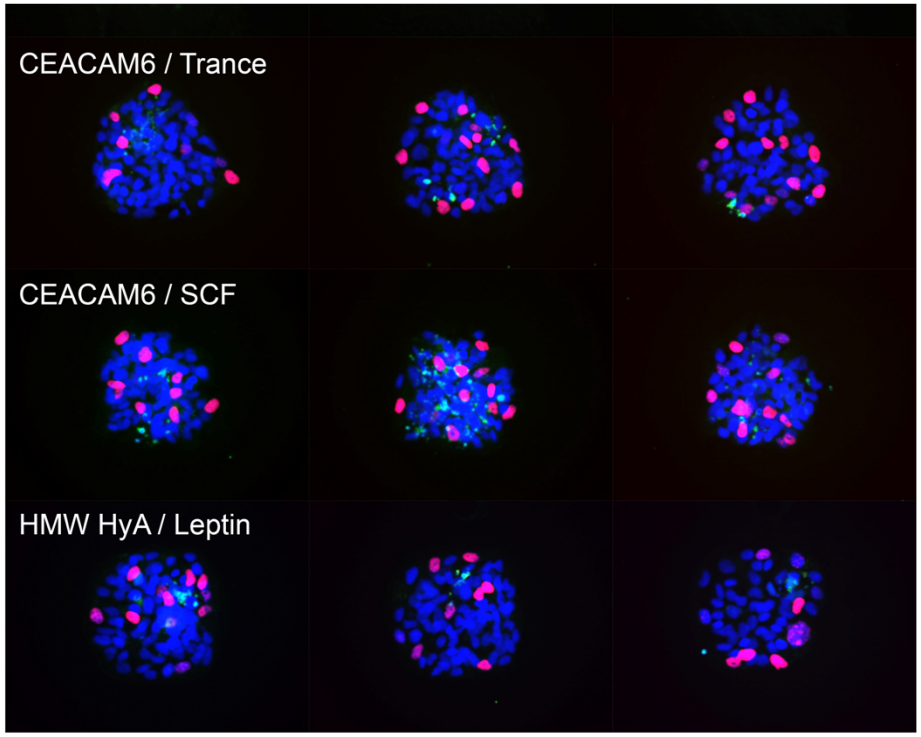




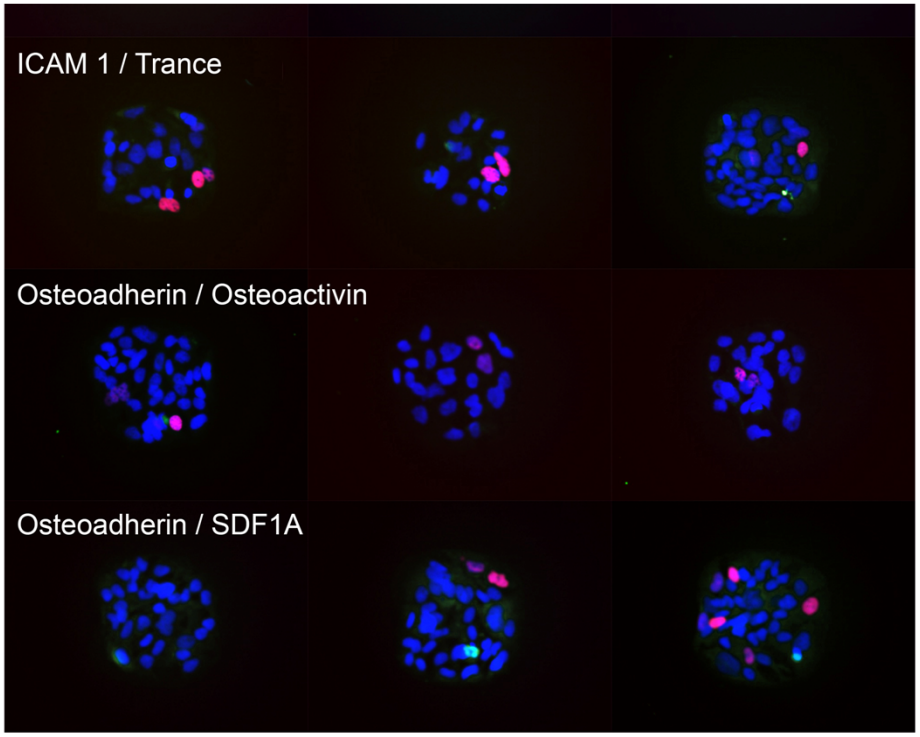
Selected microenvironment proteins influence therapeutic response

EdU incorporation 48 h after lapatinib in ERBB2^{AMP} cells

Resistant environments



Responsive environments



EdU incorporation vs. DAPI

Watson, Korkola, Gray

Competition within a tumor environment - Barcode system to quantitatively analyze interactions between clones

Ovarian Ascites

Equal ratio mix

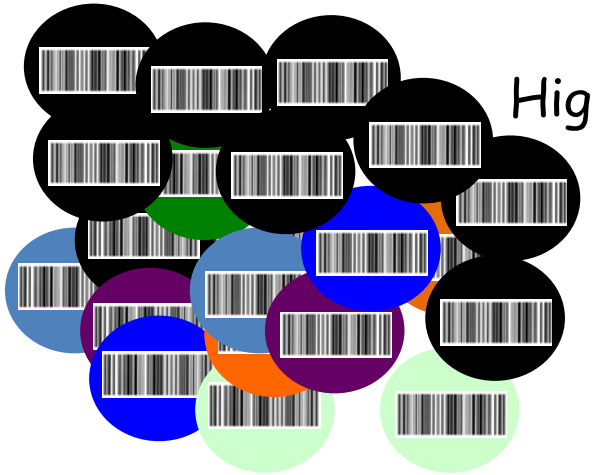
Injection to mice

Collect tumors

Genomic DNA

PCR- to amplify the Barcode region

High throughput sequencing (Ion torrent)



- Provides evidence that crosstalk between clonal populations can promote cancer progression and aggressiveness.

Joan Brugge

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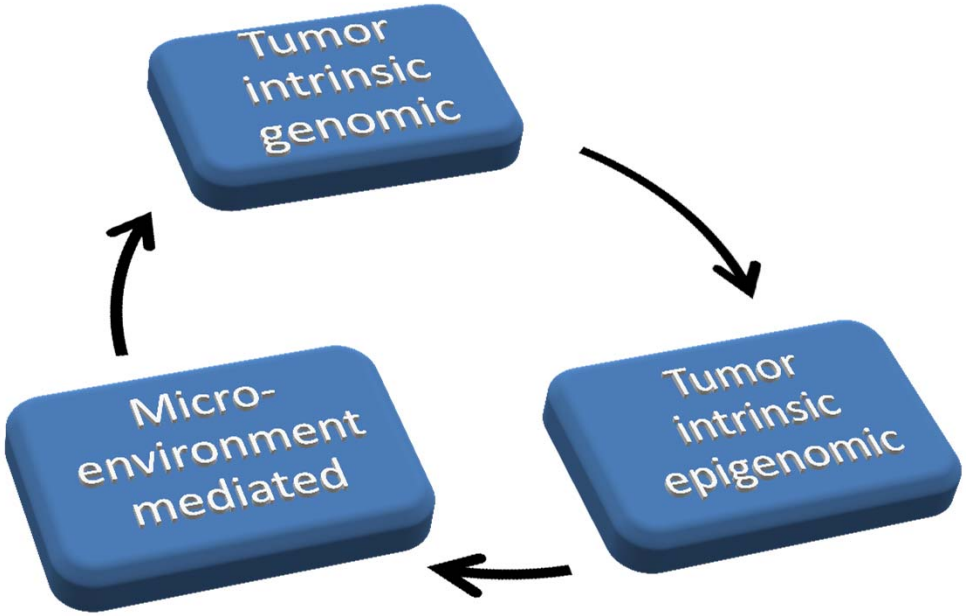
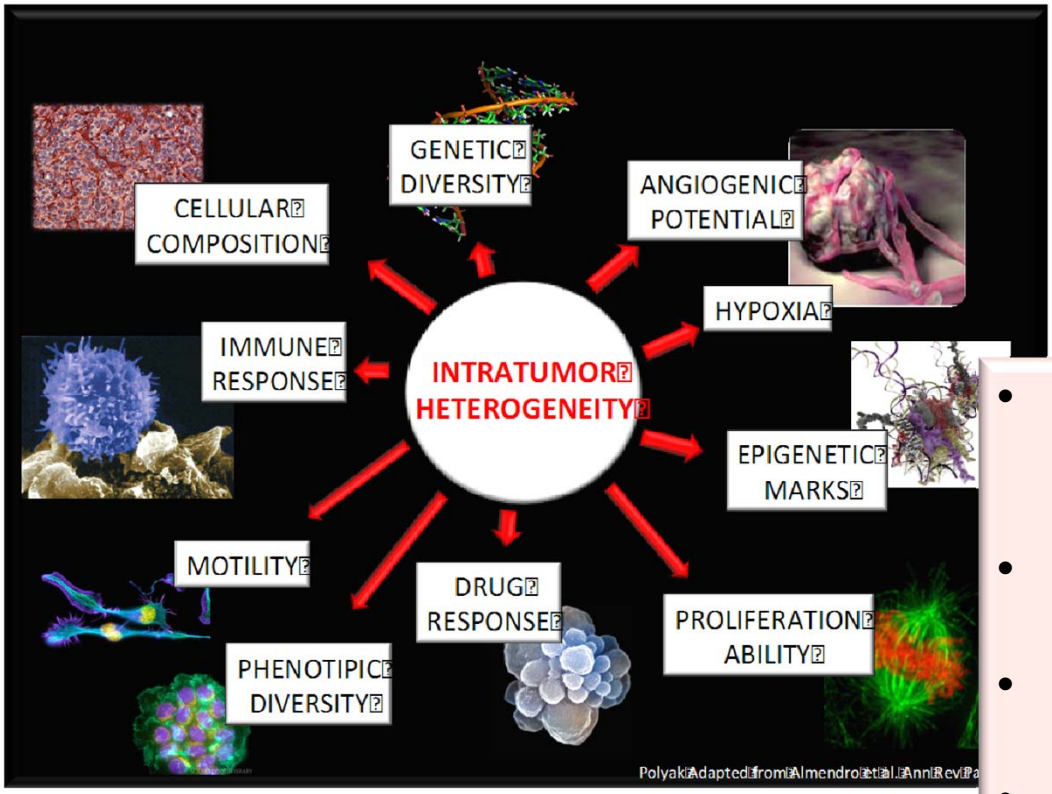


New experimental tools to facilitate study of heterogeneity

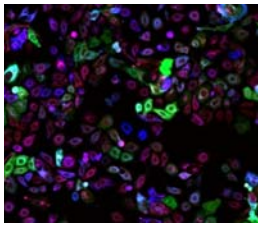
- Vital imaging to study dynamic changes in population composition
- Mass cytometry for high dimensional assessment of heterogeneity (CyTOF)
- Multi-color super resolution fluorescence microscopy
- Nanometer resolution 3D electron microscopy
- Relatively low cost, single cell sequencing
- Computational-based tools

Overall conclusion - heterogeneity influences most aspects of tumor biological and clinical behavior



Polyak Adapted from Almendro et al. Ann Rev Pa

- Tumors are heterogeneous in every way possible
- Drivers of heterogeneity not understood
- Heterogeneity affects response to Rx
- Need to control heterogeneity for durable response to therapy
- Tools and models available to study; need to leverage resources to accelerate discoveries



Questions from research community

- What are the intrinsic and extrinsic mechanisms that drive heterogeneity?
- What are the dominant heterogeneity drivers? Genome instability? Epigenomic instability? Extrinsic influences?
- How do mechanisms that influence heterogeneity interact/synergize?
- Does treatment cause state change via selection or epigenomic state change or both?
- What are the best strategies to counter heterogeneity?
- What are the resistance states and how do we target them?

& Tumor Heterogenity

PQB – 4: ***What methods can be devised to characterize the functional state of individual cells within a solid tumor?***

PQC – 4: ***What in vivo imaging methods can be developed to portray the "cytotype" of a tumor — defined as the identity, quantity, and location of each of the different cell types that make up a tumor and its microenvironment?***

PQD – 4: ***What are the mechanistic bases for differences in cancer drug metabolism and toxicity at various stages of life?***

PQE – 4: ***What are the best methods to identify and stratify subgroups of patients with particular co-morbidities who will benefit from defined cancer therapies?***

Frederick National Laboratory for Cancer Research

FNLCR as an integrator and enabler of efforts to understand and manage tumor heterogeneity

- Develop and offer tools to study heterogeneity (imaging, biological models, experimental & computational methods, antibodies, reagents)
- Coordinate clinical trials to enable analysis of mechanisms that influence heterogeneity-mediated resistance (e.g. NCI-MATCH)
- Establish a national "clearing house" to collect, organize, and disseminate clinical and basic science data applicable to the study of tumor heterogeneity (e.g. in depth analysis of cell lines, PDXs, GEMMs and tumors from pre-clinical and clinical studies)
- Facilitate collaborative, pre-clinical and clinical studies across the national cancer program, aimed at deciphering and targeting heterogeneity-based resistance

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