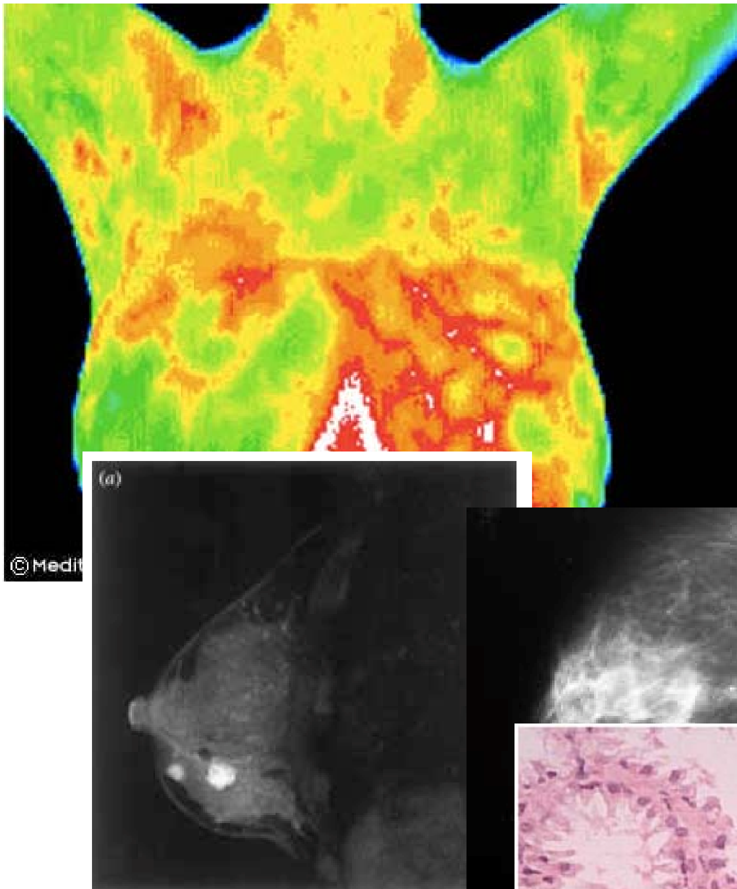
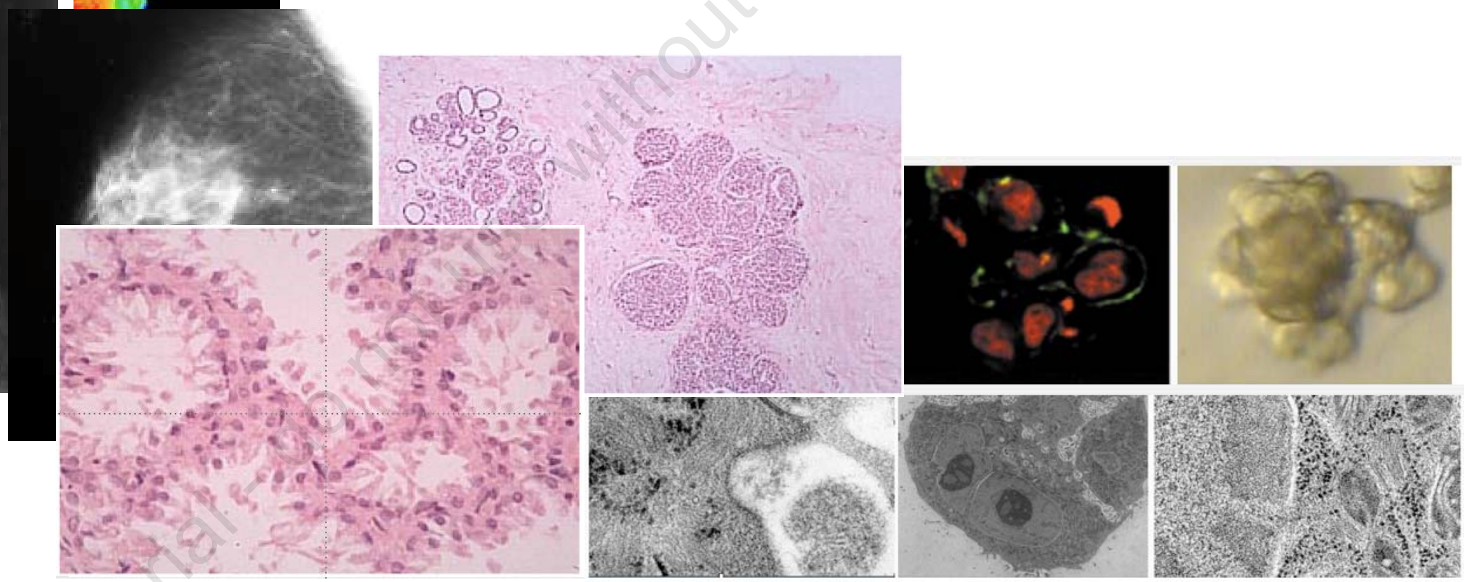
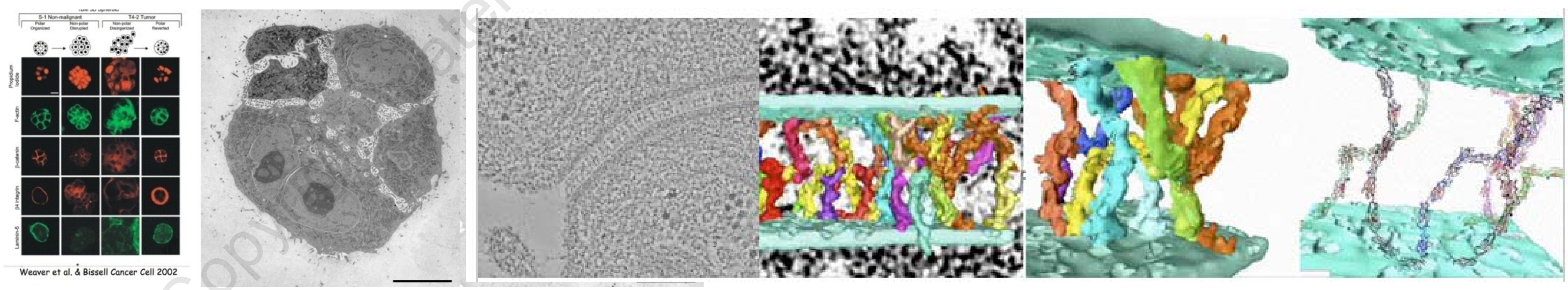
Cancer – looking at the wild life

The Gulliver Multi-Scale Imaging Project

What can we look at that will inform the management of the disease?







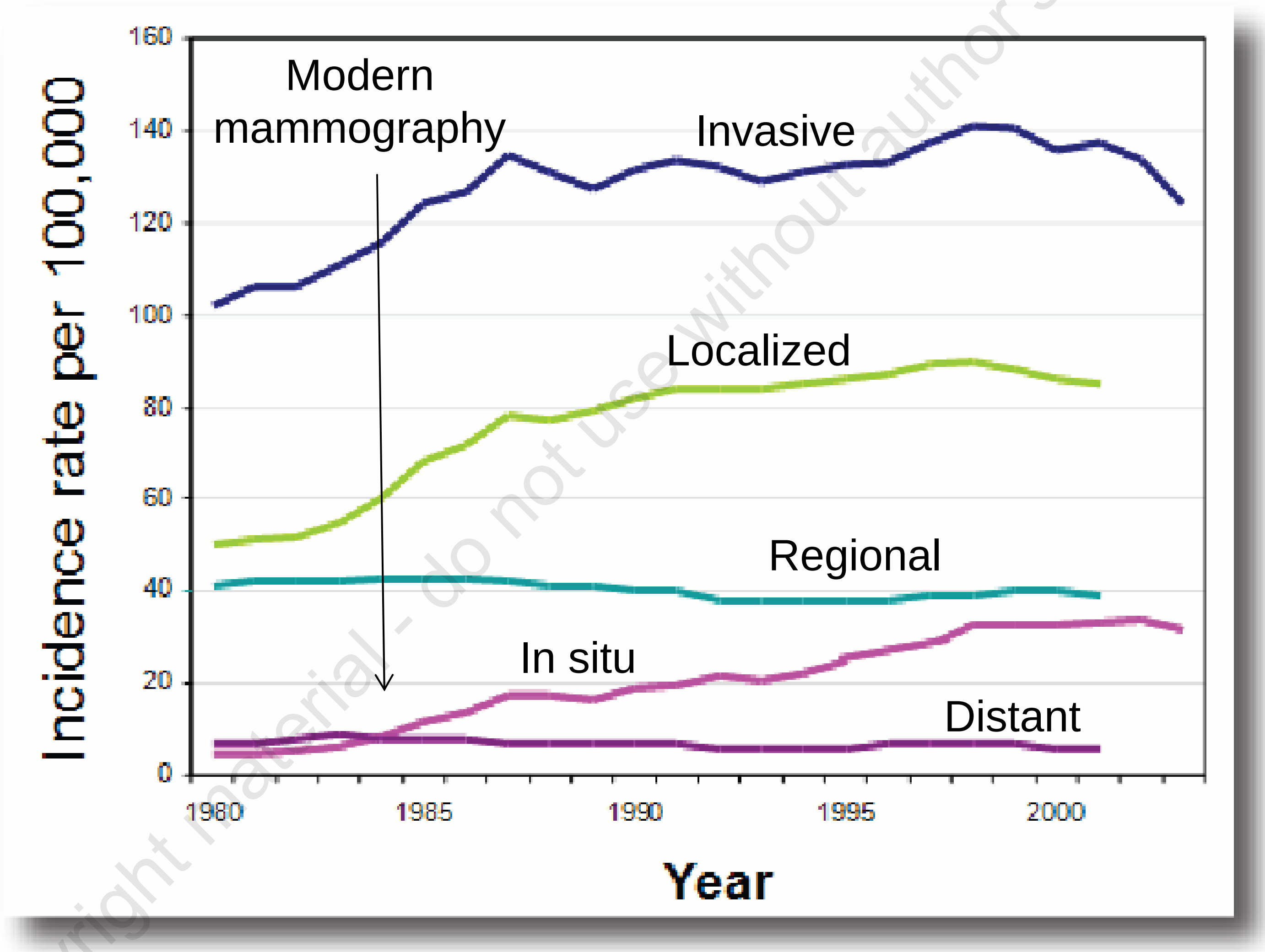
Talk overview

- Brief summary of three important problems in cancer management
- Examples where imaging can/is contributing to improve cancer management
- Imaging limitations/needs

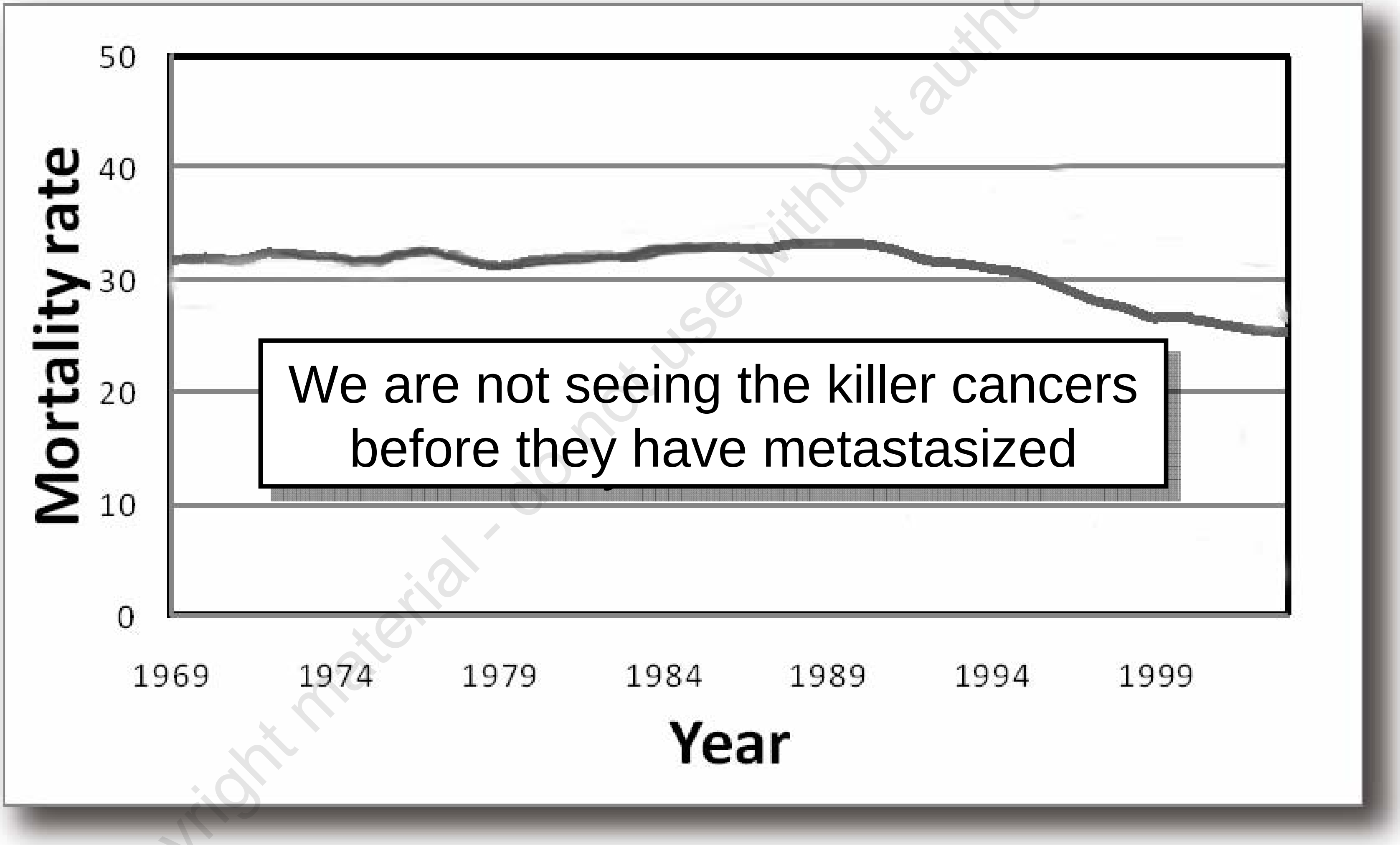
Big problems in cancer management

- Early detection technologies like mammography are not reducing cancer mortality as expected/hoped
- Treatment strategies for most metastatic solid tumors are not curative
- New drug development is time consuming, expensive and often fails

Early detection and treatment are not reducing late stage disease



Mortality rates remain high (SEER)



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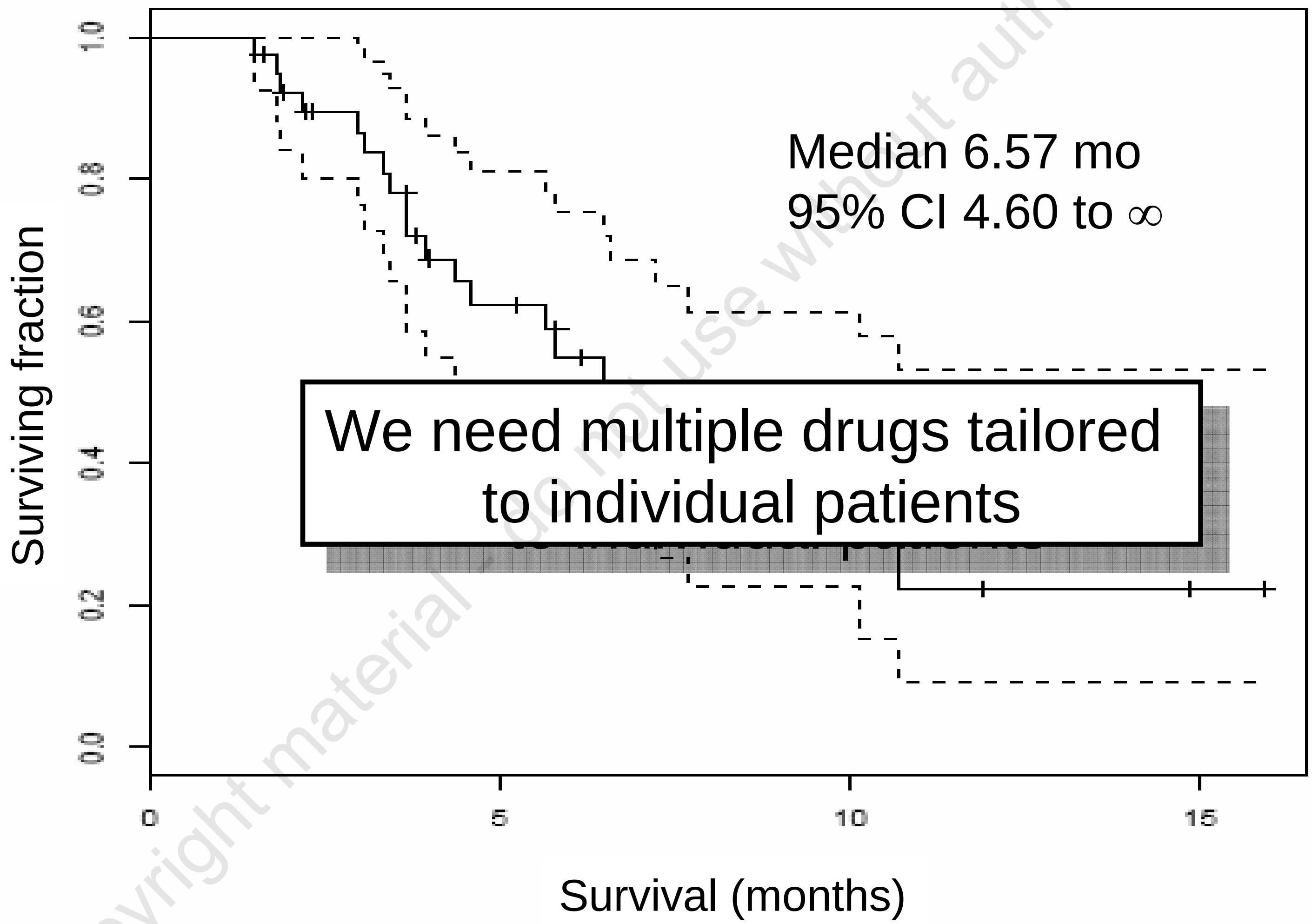
Survival of breast cancer patients with metastatic brain lesions treated with one of our best drugs



Lin et al. ASCO 2006;Abstract 503

Big problems in cancer management

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Experimental therapeutics

Approximately 100 drugs are now FDA approved for some cancer indication

Over 400 experimental drugs are now in Phase II/III trials

The typical cost per successful drug is greater than $1B and takes about 15 years

At the end of this, we still don't know who will respond well

Berkeley Lab 75 Years of World-Class Science 1931-2006

Our current approach to assessment of efficacy does not scale well

Cancer Type	Product/Compound												Total
	Nexavar	Sutent	AG-013736	Tarceva	ZD6474	Tykerb	Avastin	Erbitux	Vatalanib	Iressa	Vectibix	Recentin	
Bladder	2	2	0	2	0	0	2	1	1	2	0	0	12
Breast	1	8	0	4	0	28	32	5	0	0	0	3	81
Colorectal													125
Female repro													21
General/other													33
Head & Neck													72
Leukemia													14
Liver													16
Lung													145
Lymphoma													23
Melanoma													22
Mesothelioma													6
Myeloma													5
Multiple													17
CNS	3	1	0	12	1	3	14	1	4	6	0	2	47
Ovarian	3	0	0	1	0	2	3	0	1	0	0	0	10
Pancreatic	2	1	1	10	0	0	13	12	2	1	0	0	42
Prostate	4	3	0	5	0	2	9	0	2	0	0	0	25
Renal	14	10	0	4	1	0	10	0	1	0	0	3	43
Sarcoma	5	2	0	0	0	0	6	1	1	0	0	0	15
Solid	4	2	0	7	0	2	7	5	1	3	1	2	34
Thyroid	0	0	1	1	2	0	1	1	0	0	0	0	6
Total	70	53	3	128	12	48	279	103	18	55	14	31	769

Current tyrosine kinase inhibitor clinical trials

- 12 inhibitors
- 22 organ sites
- 769 separate trials
  - 81 in breast
- Typical time to approval 15 years
- Typical cost > $1B per approved drug

•Typical cost > $1B per approved drug

Source: Clinicaltrials.gov

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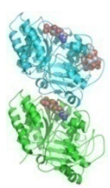
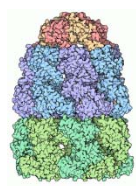
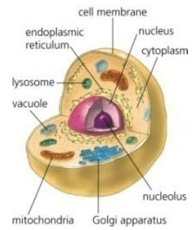


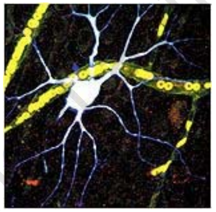
Molecules



Complexes



Cellular compartments



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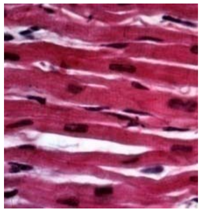
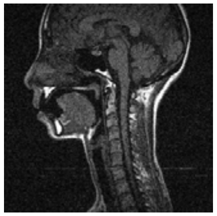


Tissues



Whole organisms

Cancer pathophysiology

Molecular parts list | Molecular function | Model organisms

Cancer detection

Molecular histopathology | Anatomic localization

Therapy

Molecular target definition and drug design | Therapeutic agent assessment *in vitro* and *in vivo* | Quantitative clinical response

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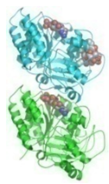

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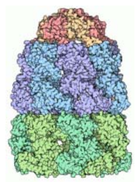

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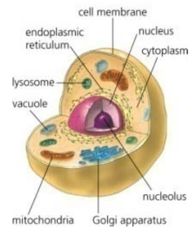

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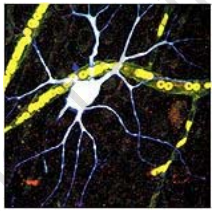

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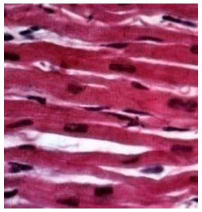

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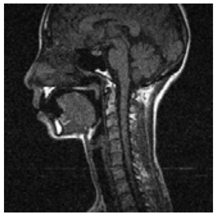

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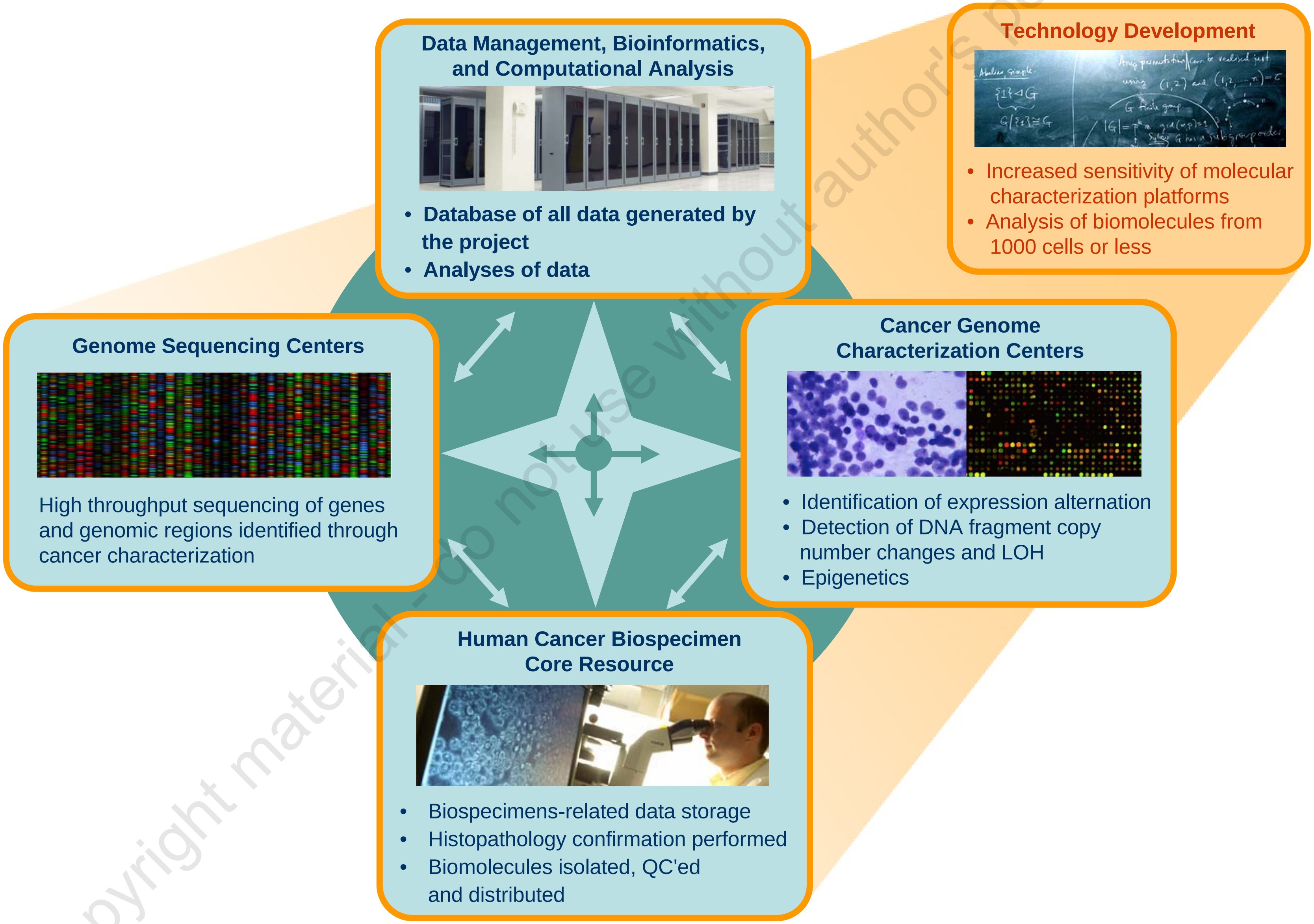
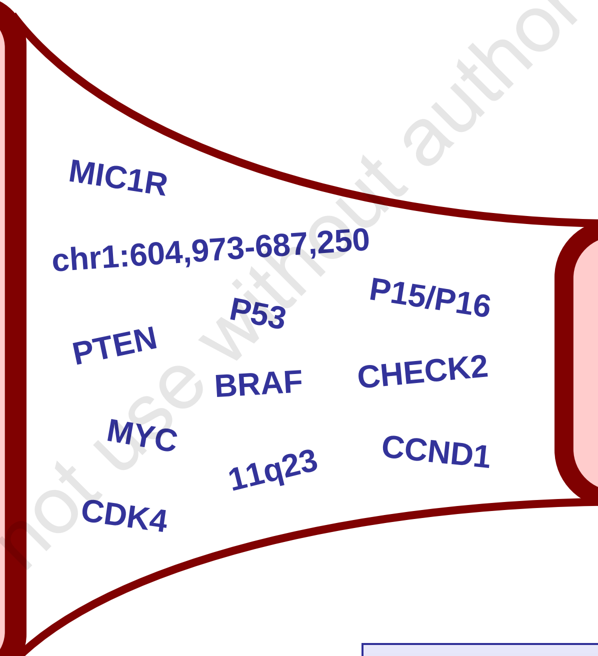
The Cancer Genome Atlas (TCGA) project



Genome Analyses Capabilities to Provide Robust Characterization of Cancers

Characterizations:

- Expression profiling
- Identification of genomic alterations
- Identification of epigenetic changes



Selection of candidate targets for sequencing

Clinical correlation and mechanistic insights

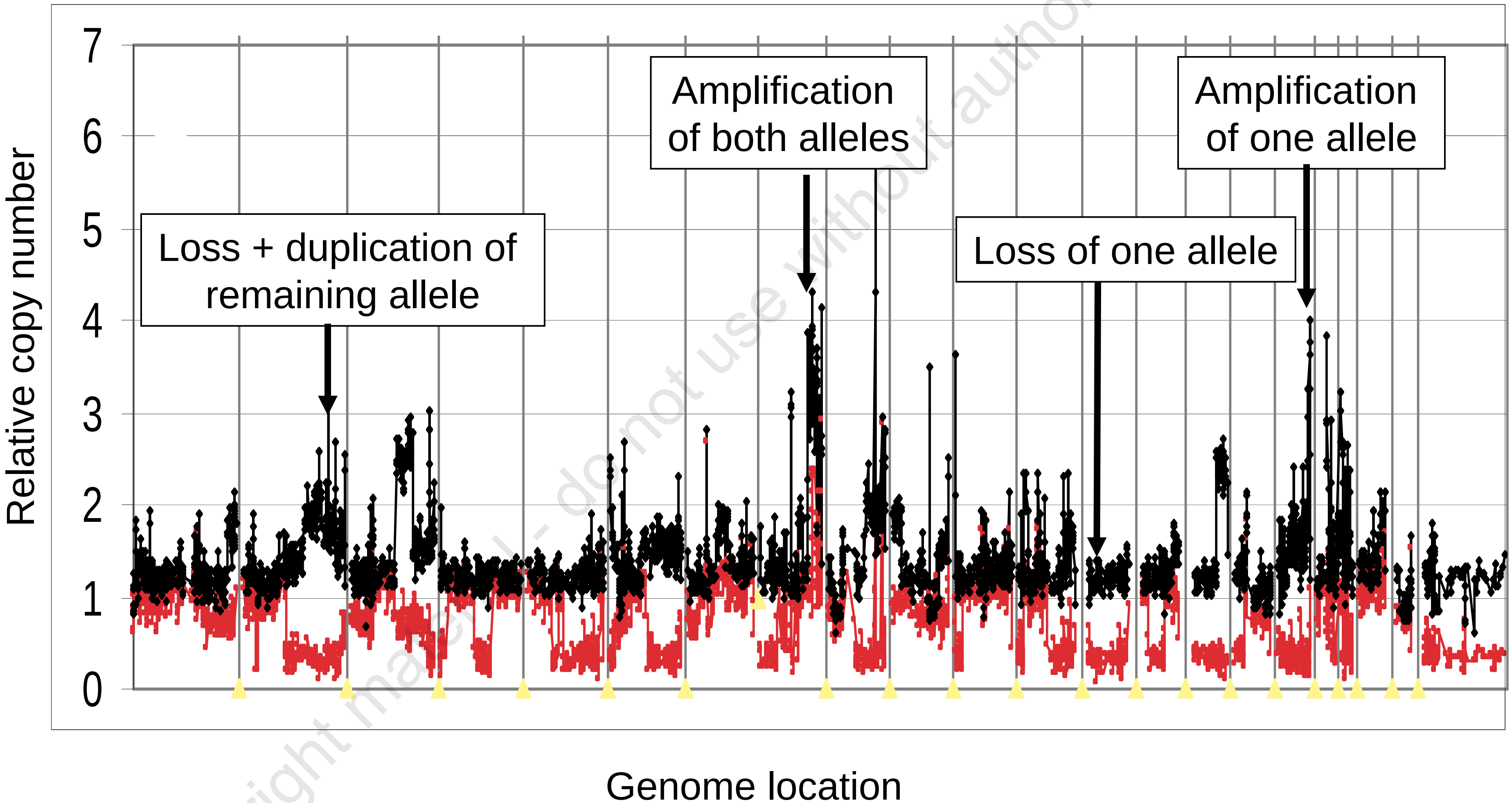
Glioblastoma
Lung cancer
Ovarian cancer

Remarks made on the completion of the first survey of the entire human genome, June 29, 2000

- “For let us be in no doubt about what we are witnessing today -- a revolution in medical science whose implications far surpass even the discovery of antibiotics, the first great technological triumph of the 21st century.” Prime Minister Blair

- “It is now conceivable that our children's children will know the term cancer only as a constellation of stars.” President Clinton

Tumor genomes can be remarkably complex

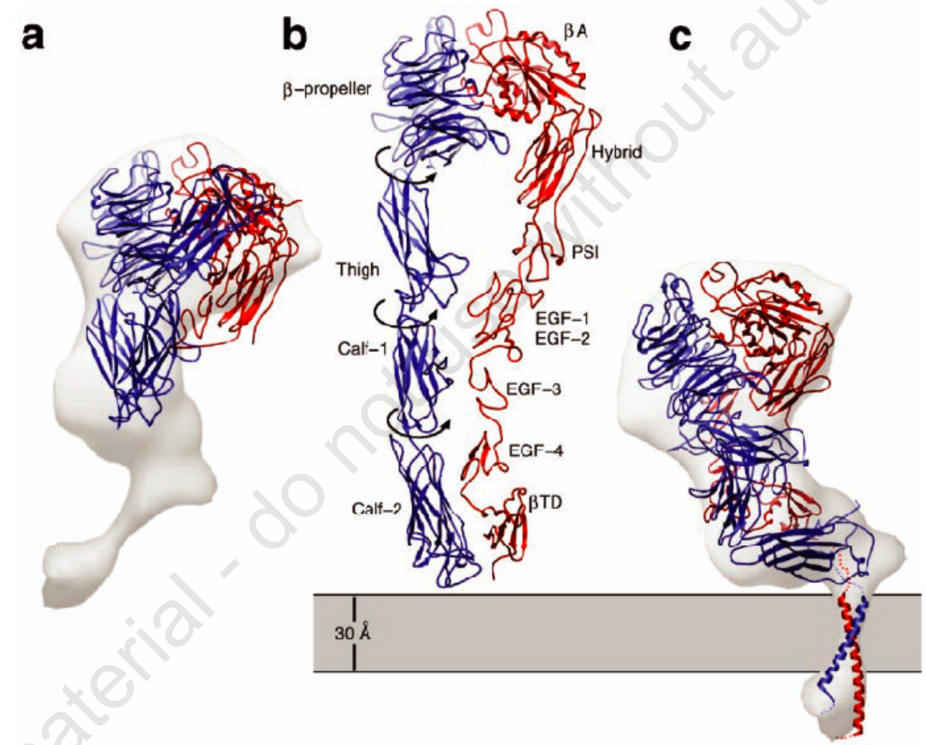


What we know so far

- The typical tumor will deregulate 30% of its genome (10,000 genes)
- 10% of the genome in a typical cancer type is recurrently aberrant (3000 genes)
- Several hundred gene mutations have been discovered
- These molecular features define cancer subtypes that progress and respond to therapy in unique ways

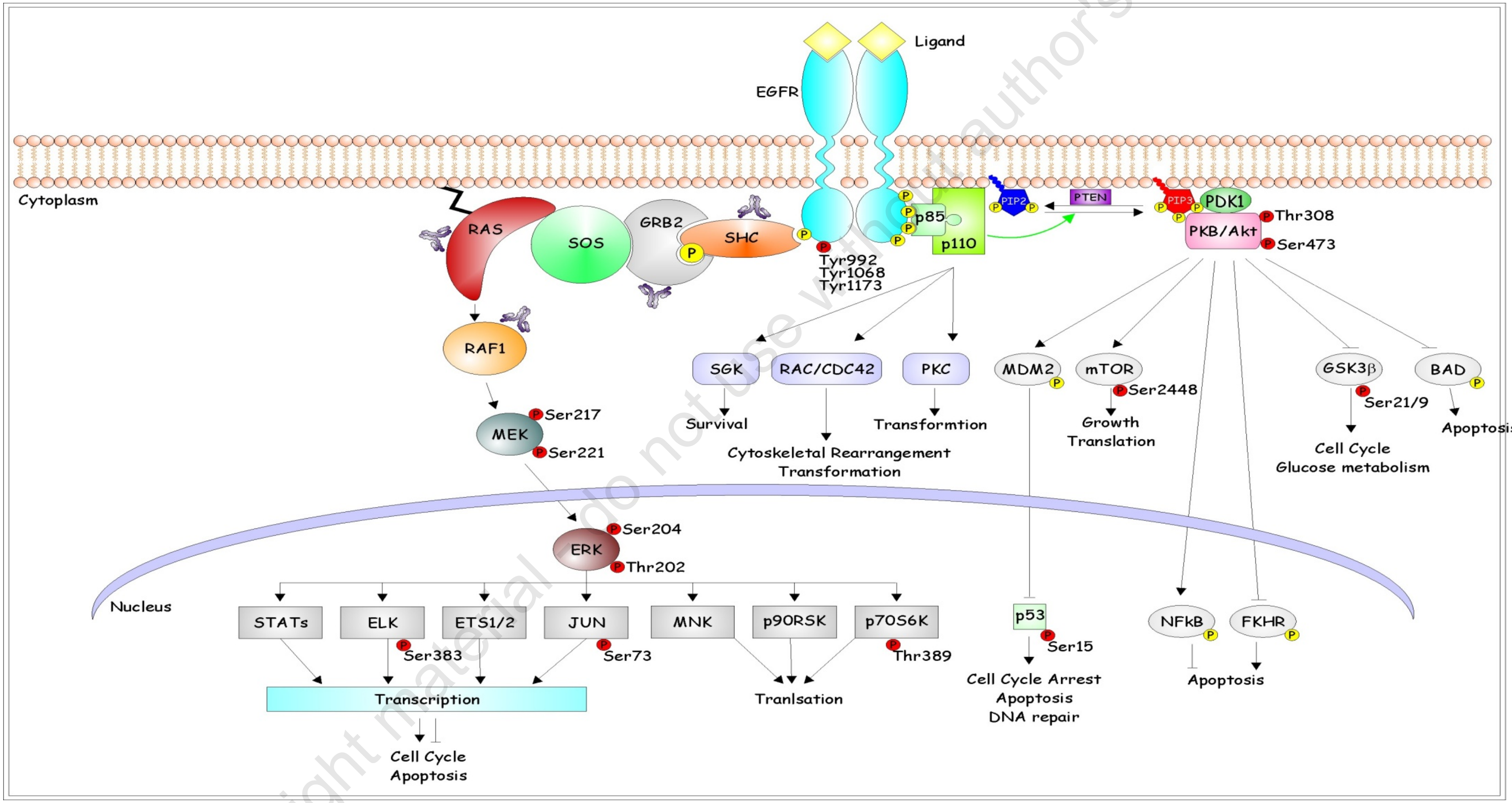
The structures, interacting partners and functions of most of these genes are not well understood

We need efficient tools to establish protein structure and function



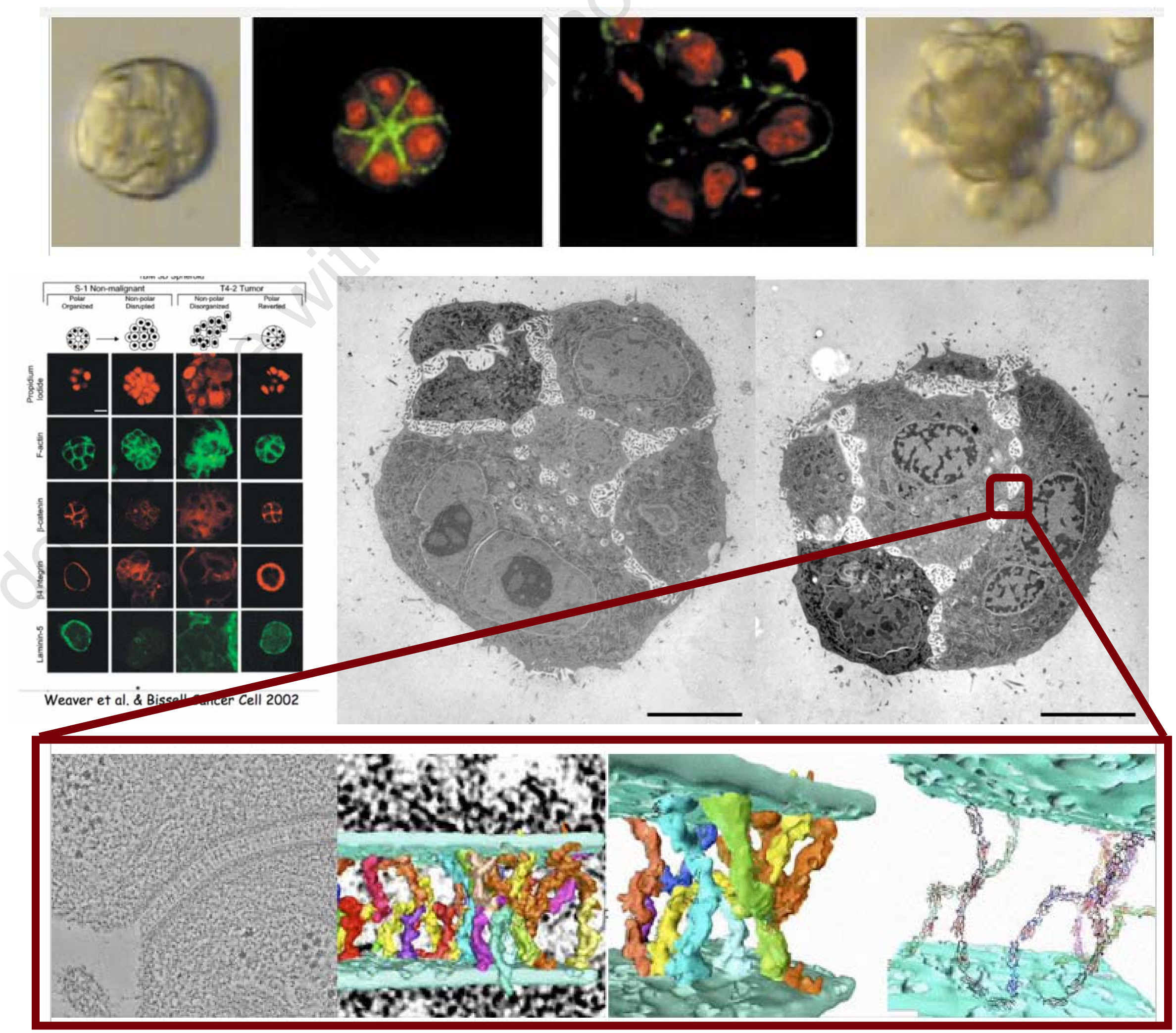
Integrin in inactive and active state - studying purified individual signaling proteins and complexes by single-particle cryo-EM, and docking of atomic structures obtained by X-ray diffraction into electron densities

We need tools to assess function in the cellular context



Correlative light and electron microscopy

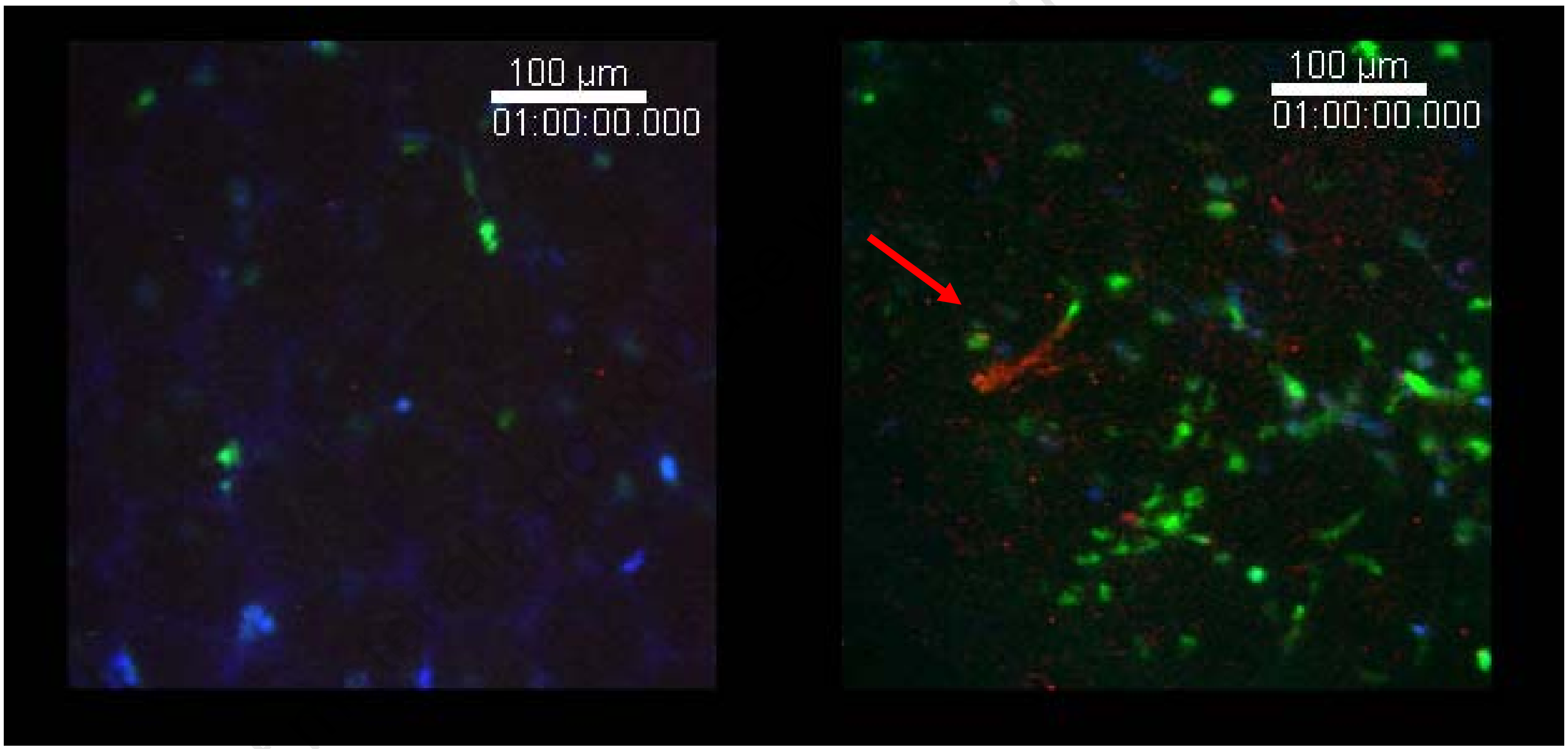
- Light microscopic phenotype
- Ultra-structural characterization
- Electron tomography for mol. resolution



Multi-color functional analysis in vivo

Phagocytic response to a tumor

Spinning disk, multi-color confocal microscopy



Alexa-647-dextran
Tumor debris (CellTracker Red)
c-fms-eGFP phagocytes

Mikala Egeblad (Zena Werb)

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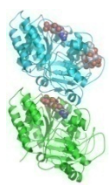

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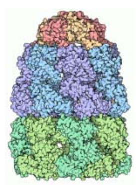

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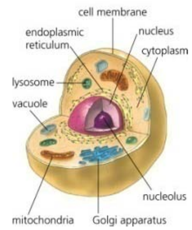

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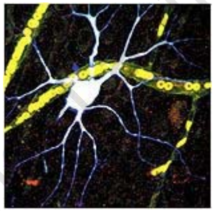

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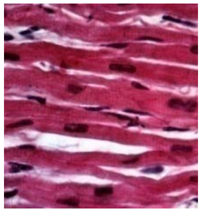

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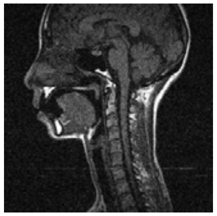

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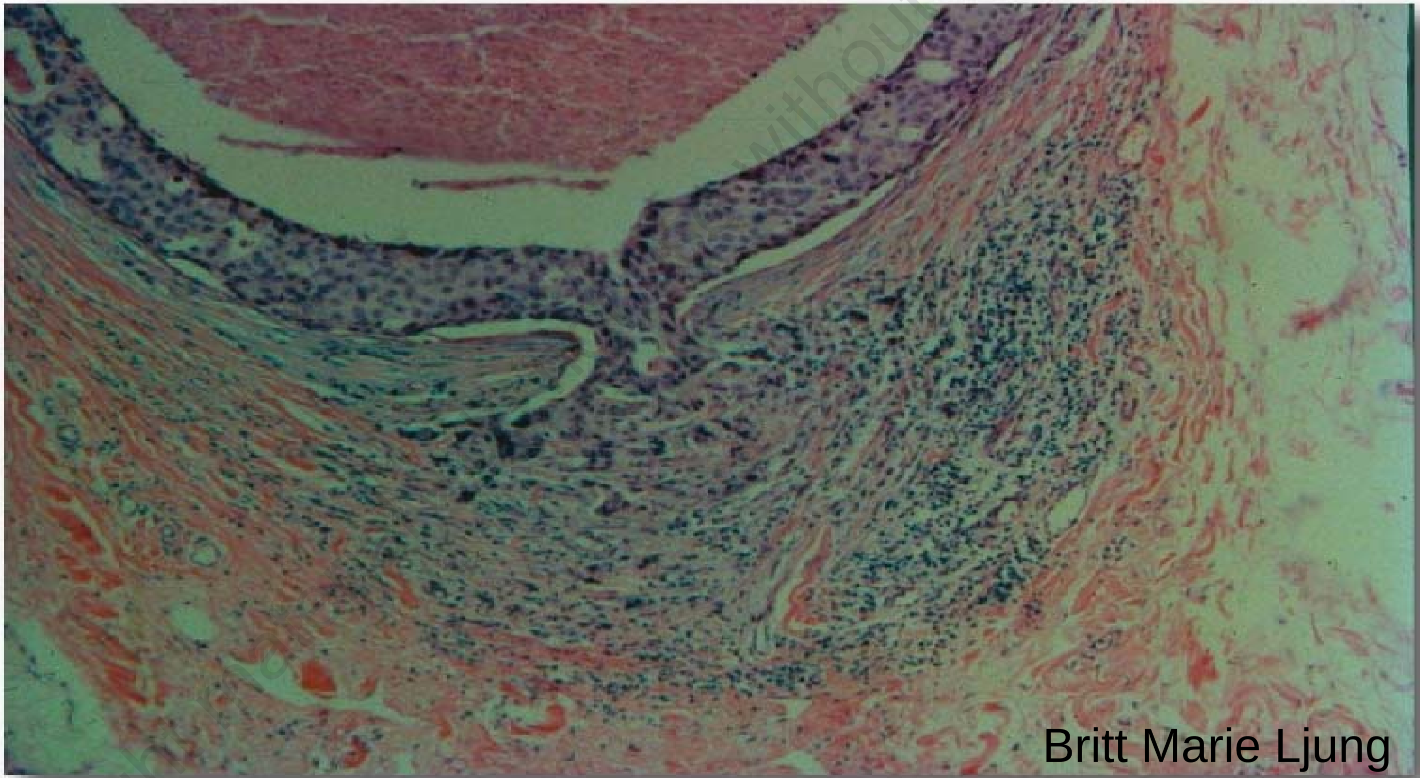
We need to understand the molecular mechanisms and extent of invasion

Microinvasion in breast cancer



Scanning mass spectrometry is particularly appealing for protein specific imaging

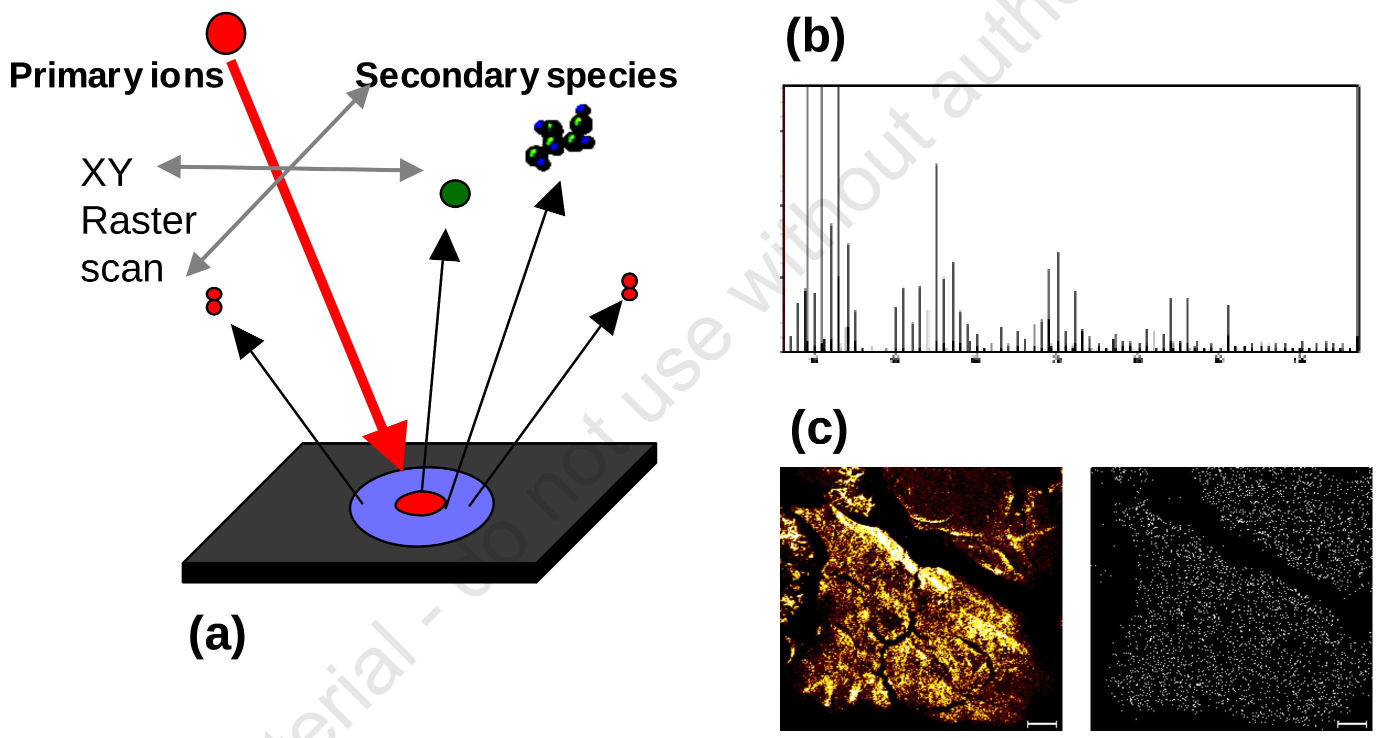
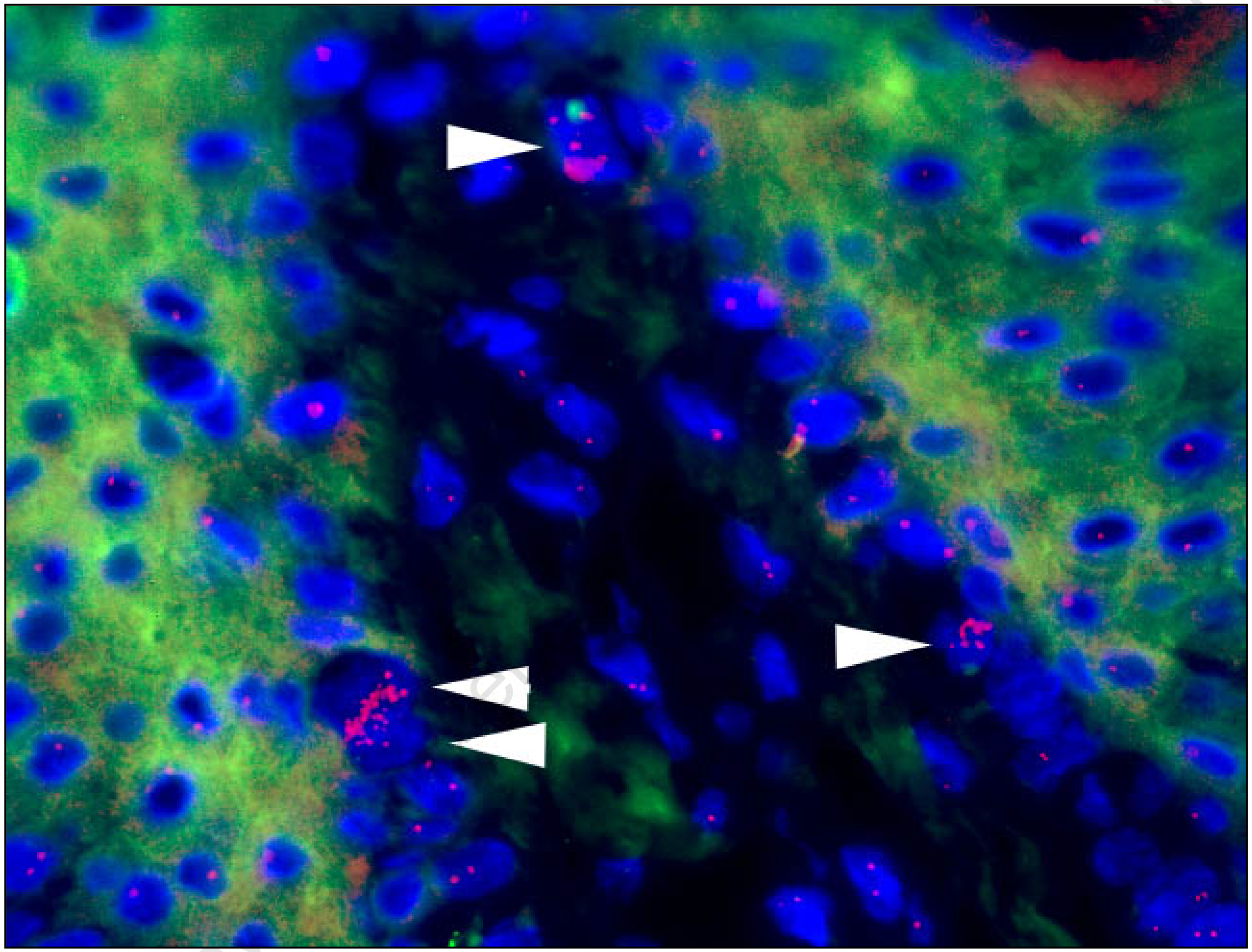


Figure 3. Principles of ToF-SIMS. Panel a. Raster scan of tissue section. Panel. B. Mass spectrum showing amounts of secondary ions. Panel c. Secondary-ion-specific images of histological sections.

Felton et al

Targeted labeling strategies are highly informative

Histologically normal tissue in vicinity of an acral melanoma



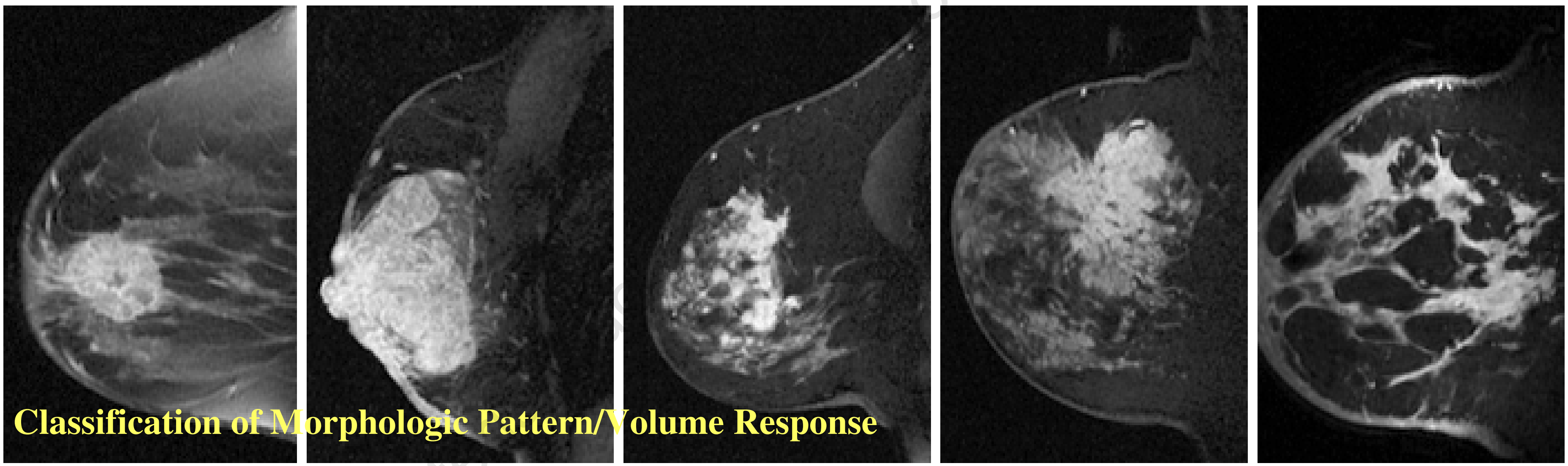
Cells with high-level amplifications are present <u>before</u> there is a histologically recognizable tumor.

<u>Field Cells</u> beyond excision margins may result in local recurrence.

Pinkel, Bastian et al

We need to be able to “see” the anatomic extent and molecular subtype

We know the molecular characteristics of tumors that are likely to invade early – we need to be able to “see” them



Morphologic heterogeneity in ductal carcinoma in situ

Esserman, Hylton et al

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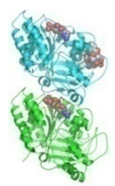

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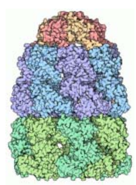

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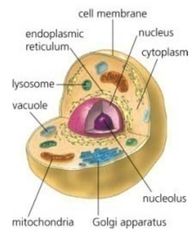
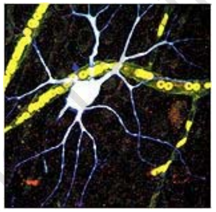


Cellular compartments



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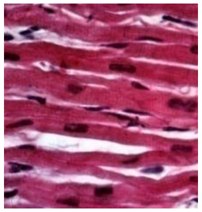
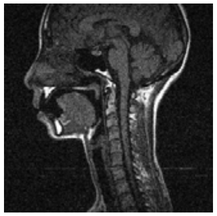


Tissues



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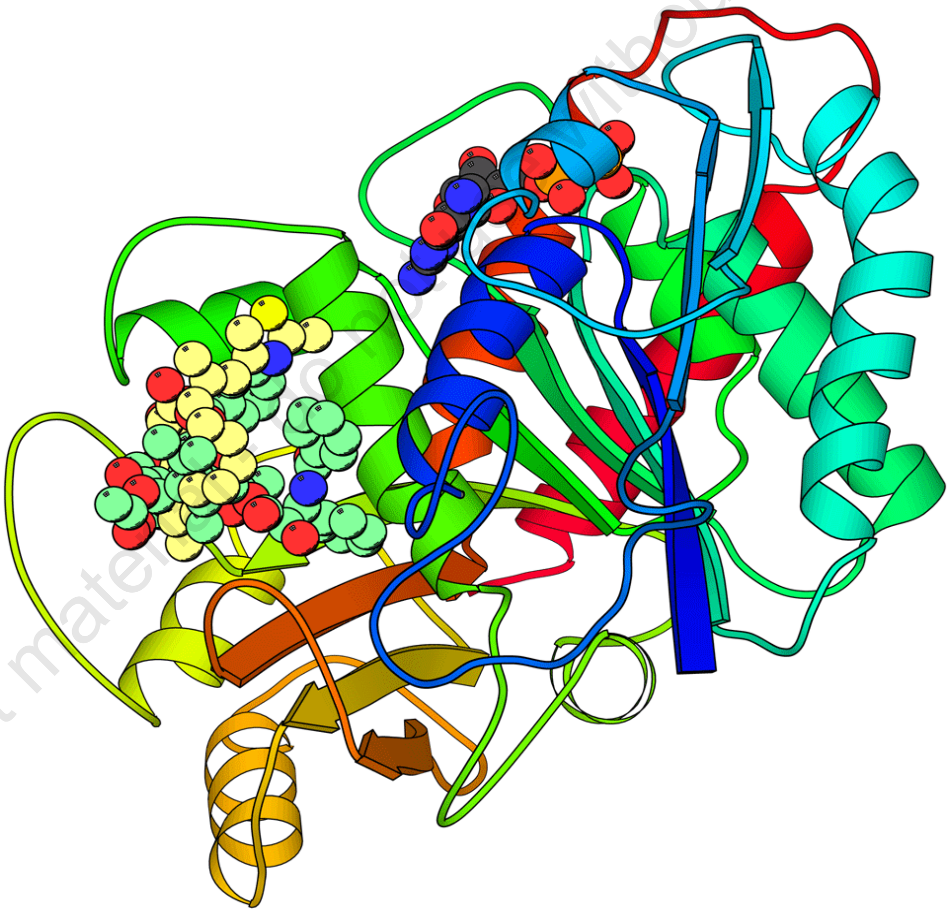
We need more efficient tools for structure guided drug design

Therapeutic targets in one breast cancer subtype
66 genes amplified, over-expressed and associated with poor outcome

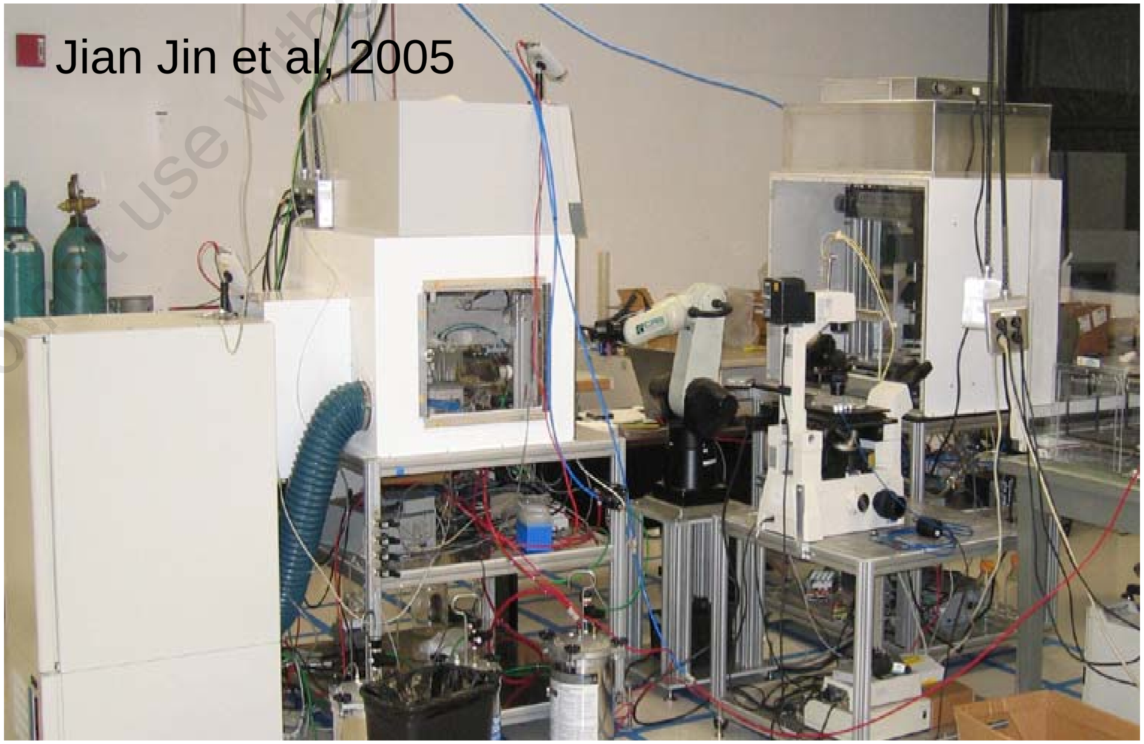


We need better tools for identification of molecular determinants of individual response and resistance

Automated cell culture and high content imaging for assessment of Rx response

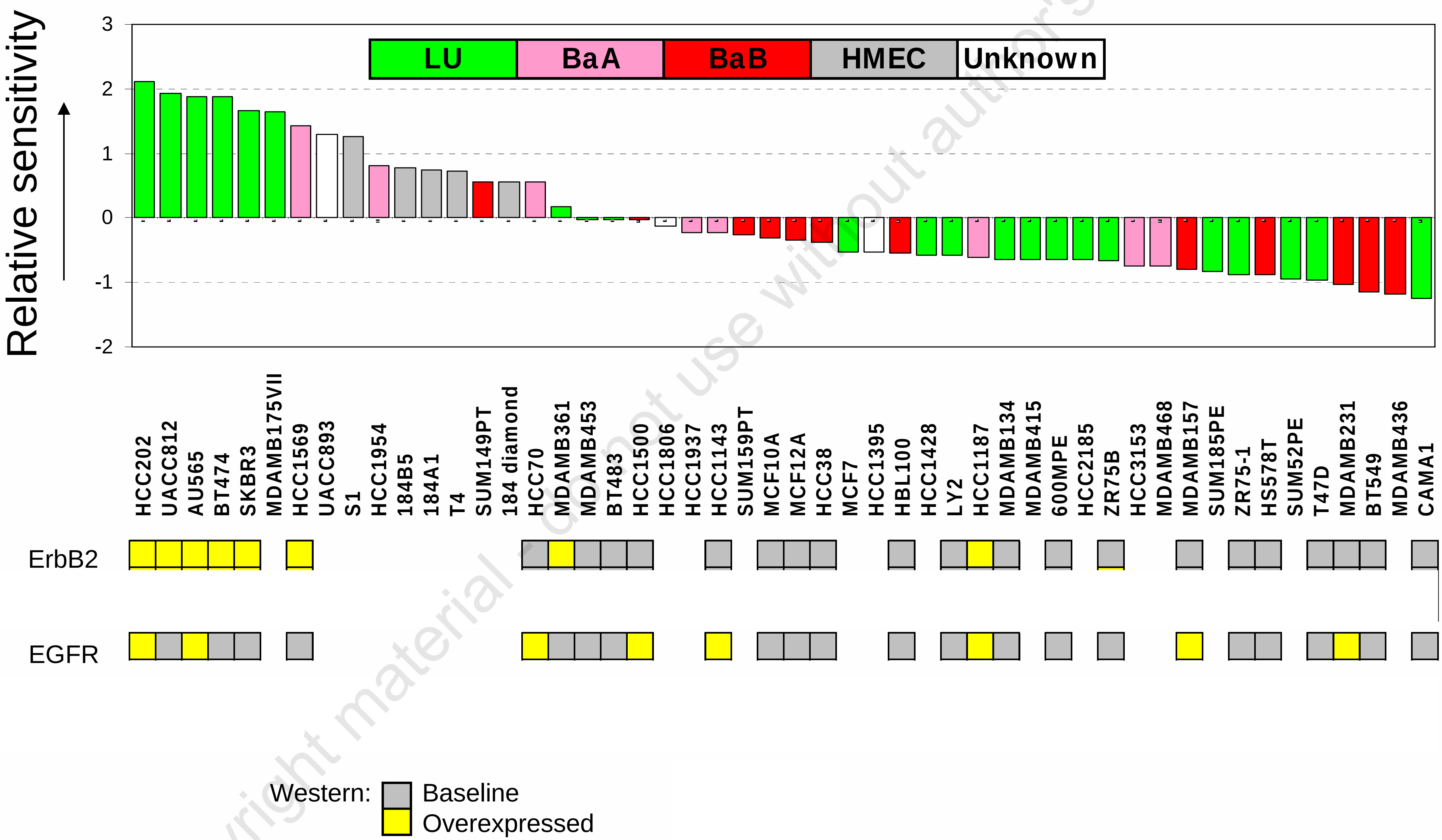
- ~60 breast cancer cell lines in 2D and 3D culture
- Molecular profiling
  - DNA, RNA, methylation, protein
  - DNA sequence
- Semi-automated cell culture
- High content imaging
  - Apoptosis
  - Motility
  - Proliferation
  - Protein localization

Kuo, Neve, et al,



Molecular determinants of response

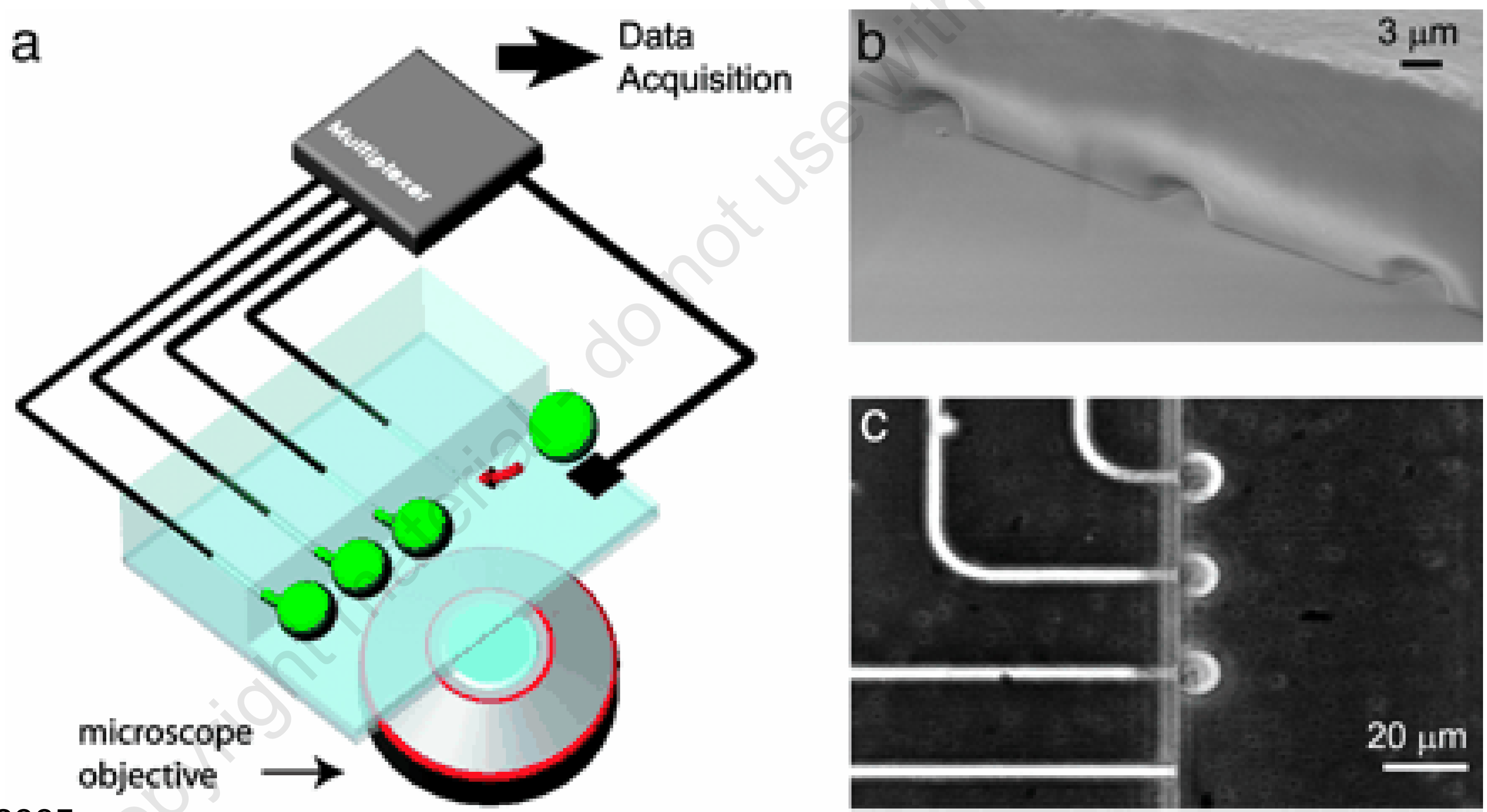
The ErbB2/ERGF inhibitor lapatinib as an example



Kuo, Neve, Das et al., 2007

Technological opportunities

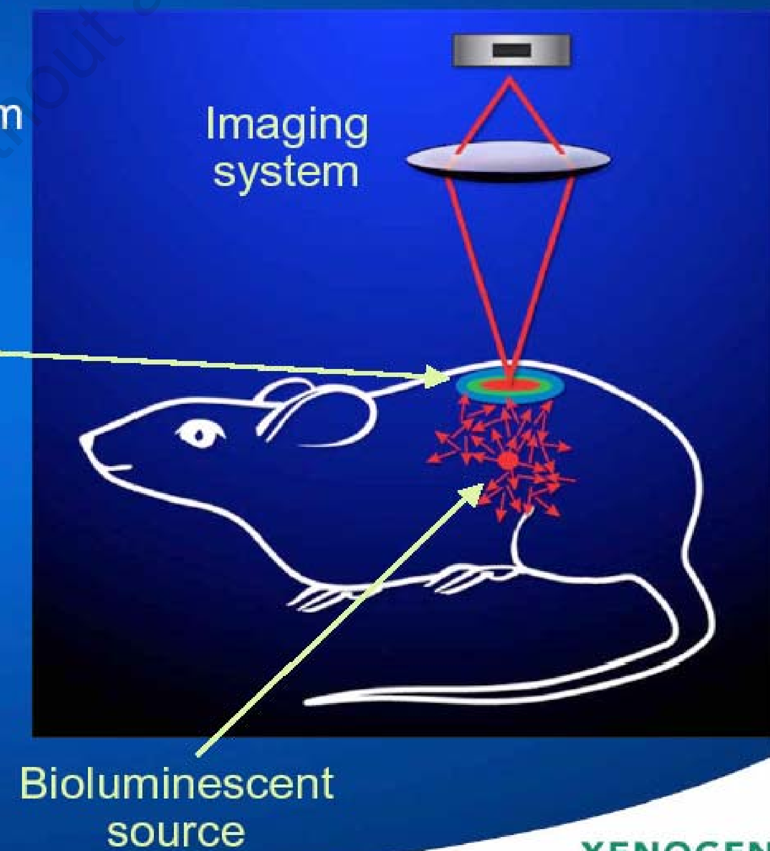
Current system is too expensive and slow to test thousands of compounds – Microfluidics and detectors (e.g. Luke Lee at UCB)



PNAS 2005

Imaging facilitates assessment of response in model organisms

- Light diffuses (scattering >> absorption) through "turbid" medium such as tissue
  – Absorption low for wavelengths > 600 nm

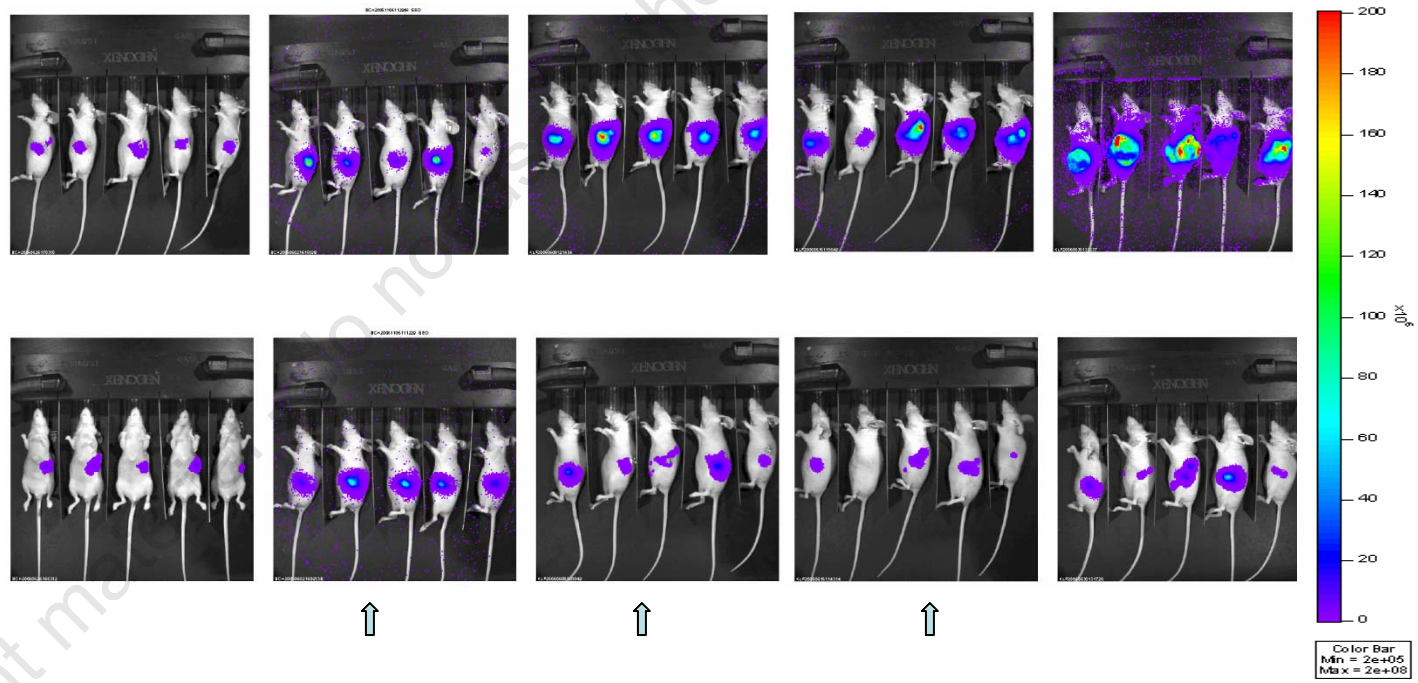


- Surface intensity depends on:
  – Source depth
  – Source shape and brightness
  – Surface shape (curvature)
  – Wavelength
  – Tissue optical properties

XENOGEN®

Response of a pancreatic tumor

We need to be able to see the molecular response



Hann

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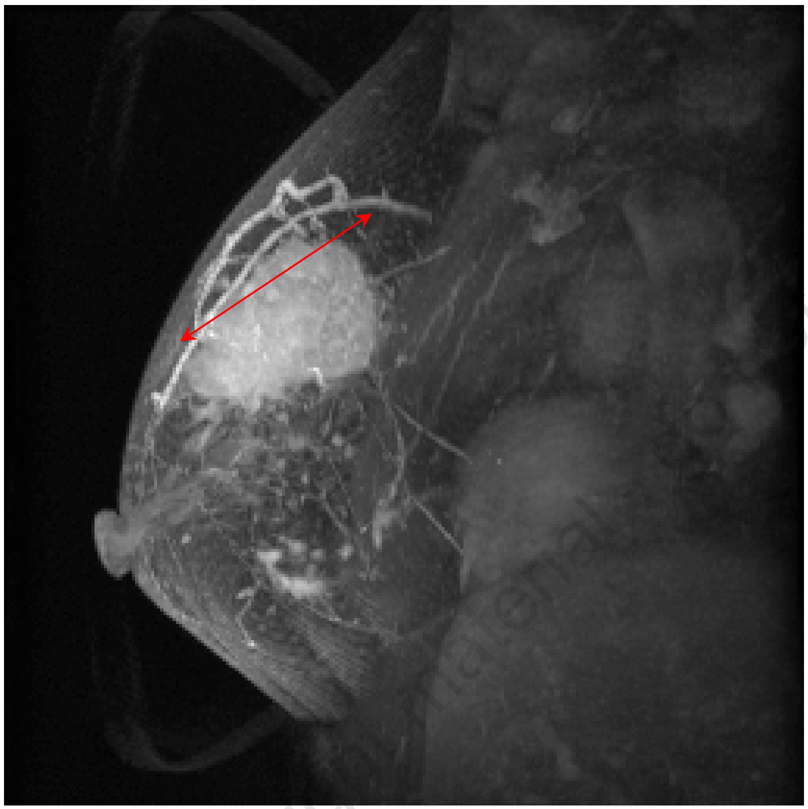
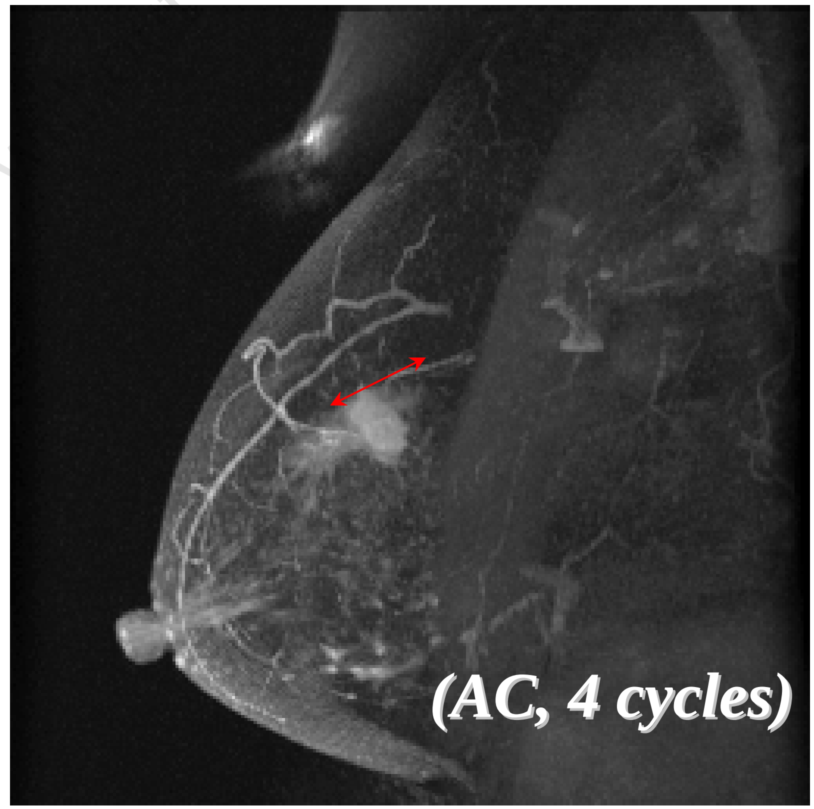
MRI assessment of response

We need to be able to "see" the molecular response

Pre-chemotherapy



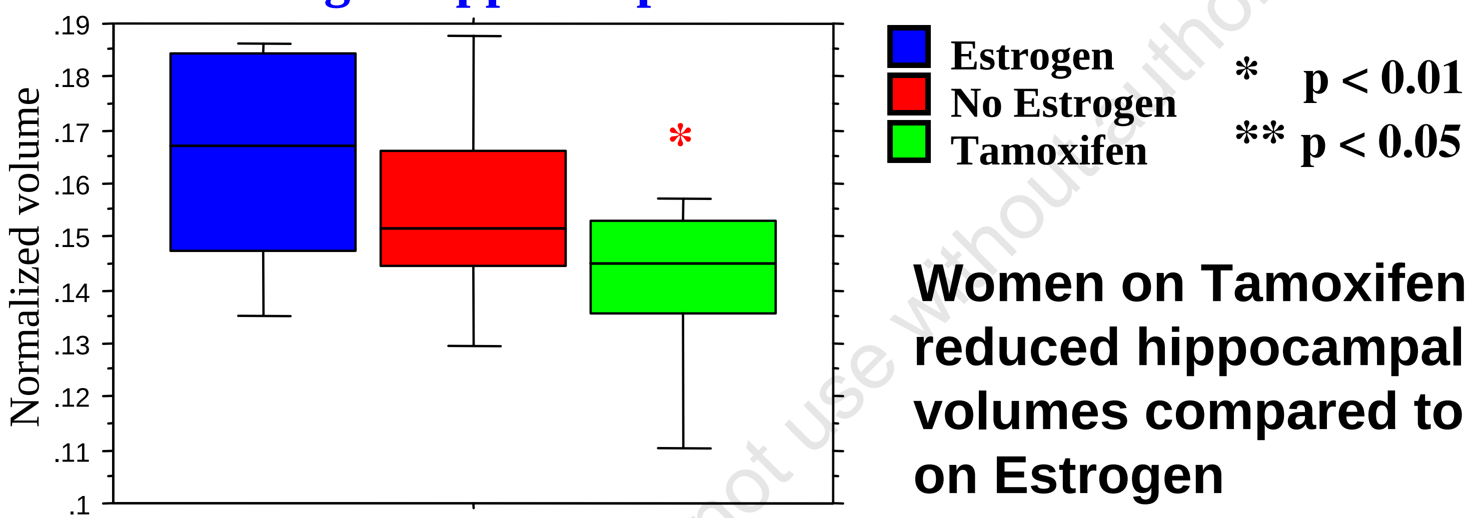
Post-chemotherapy



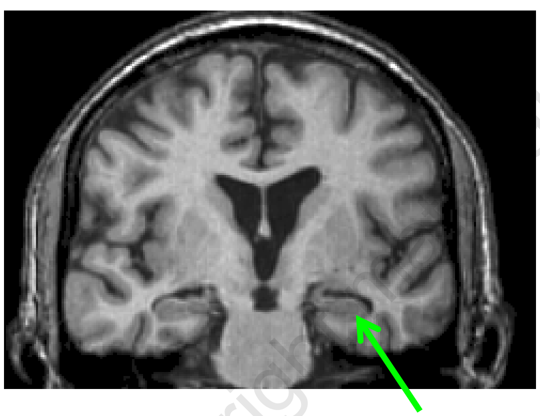
Hylton, Esserman

Assessment of off target drug effects

Right hippocampus



Women on Tamoxifen show reduced hippocampal volumes compared to women on Estrogen



Atrophic Hippocampus

Eberling, Jagust et al

Normal Hippocampus

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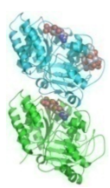
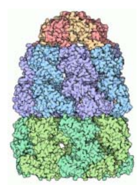
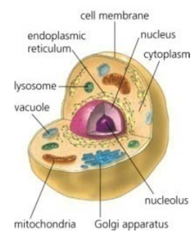


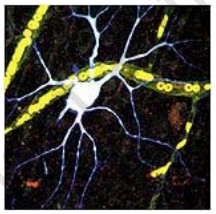
Molecules



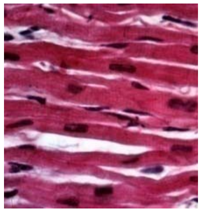
Complexes



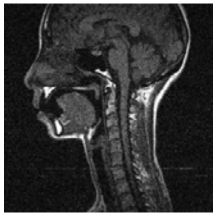
Cellular compartments



Cells



Tissues



Whole organisms

Cancer pathophysiology

Molecular parts list

Molecular function

Model organisms

Cancer detection

Molecular histopathology

Anatomic localization

Therapy

Molecular target definition and drug design

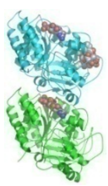
Therapeutic agent assessment *in vitro* and *in vivo*

Quantitative clinical response

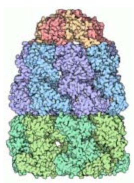
What is missing/needed?

Size (m)

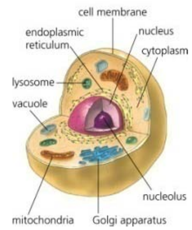
10^{-8}	10^{-7}	10^{-6}	10^{-5}	10^{-4}	10^{-3}	10^{-2}	10^{-1}	1



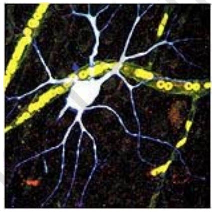
Molecules



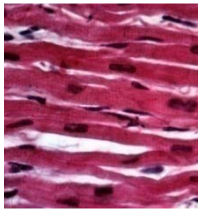
Complexes



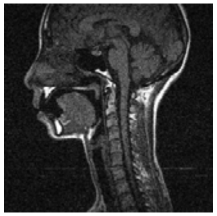
Cellular compartments



Cells



Tissues



Whole organisms

Throughput in structure-function determinations, drug design

We need multiplex, molecular labeling techniques that work at all scales

Multiplex, molecular imaging in living cells/animals

Molecular imaging to reveal tumor type and target response

The Gulliver multi-scale imaging project

DOE-GTL (JBEI)

Bioremediation
Cellulose degradation
Biofuel cells
Carbon sequestration

Low dose

Damage response
Cellular interactions

Imaging technologies

EM: phase contrast, large area
X-ray: tomography, diffraction, detectors
Mass spec: Ion beam, SELDI
Light: structured illumination, selective plane, dynamic
PET: detectors, CT/MRI
Chem: mol. tags, reporters, immuno, in situ hybe, radiopharm, tracers
Comp: multi-scale overlay, pattern recog, atlas dev, quant.

Pathophysiology

Cancer
Neurophysiology

Cell biology

Signaling biology
DNA repair
Chromatin structure