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)

We are not seeing the killer cancers before they have metastasized
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
Survival of breast cancer patients with metastatic brain lesions treated with one of our best drugs

Median 6.57 mo
95% CI 4.60 to $\infty$

We need multiple drugs tailored to individual patients

Lin et al. ASCO 2006; Abstract 503
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
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
Our current approach to assessment of efficacy does not scale well.

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

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Source: Clinicaltrials.gov
What can we “look at” that will inform the management of the disease?

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**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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The Cancer Genome Atlas (TCGA) project

- Identification of expression alternation
- Detection of DNA fragment copy number changes and LOH
- Epigenetics
- Biospecimens-related data storage
- Histopathology confirmation performed
- Biomolecules isolated, QC’ed and distributed

- Increased sensitivity of molecular characterization platforms
- Analysis of biomolecules from 1000 cells or less

- Database of all data generated by the project
- Analyses of data

- High throughput sequencing of genes and genomic regions identified through cancer characterization

- Identification of expression alternation
- Detection of DNA fragment copy number changes and LOH
- Epigenetics

- Genome Sequencing Centers
- Technology Development
- Cancer Genome Characterization Centers
- Human Cancer Biospecimen Core Resource
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

Glioblastoma
Lung cancer
Ovarian cancer

Clinical correlation and mechanistic insights
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

- Amplification of both alleles
- Amplification of one allele
- Loss + duplication of remaining allele
- Loss of one allele

Relative copy number vs. Genome location
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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We need to understand the molecular mechanisms and extent of invasion

Microinvasion in breast cancer

Britt Marie Ljung
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.
Targeted labeling strategies are highly informative

Histologically normal tissue in vicinity of an acral melanoma

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

Field Cells 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.

Classification of Morphologic Pattern/Volume Response

Morphologic heterogeneity in ductal carcinoma in situ

Esserman, Hylton et al
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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)
Imaging facilitates assessment of response in model organisms

- Light diffuses (scattering $\gg$ 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
Response of a pancreatic tumor

We need to be able to see the molecular response

Day 0  7  14  21  35
HBSS control

C225-targeted liposomal CPT11

First dose  Second dose  Third dose

Hann
MRI assessment of response

We need to be able to “see” the molecular response

Pre-chemotherapy

Post-chemotherapy

(AC, 4 cycles)

Hylton, Esserman
Assessment of off target drug effects

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

Eberling, Jagust et al
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What is missing/needed?

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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

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