Declared Interests

Board of Directors
- Caris Life Sciences
- Monsanto
- Exelixis
- Bulletin Atomic Scientists

Scientific Advisory Boards
- Synthetic Genomics
- Burrill and Co.
- University of Michigan, Alfred Taubman Medical Research Institute

Advisory/Consultancy
- USG: Depts. of Defense and Homeland Security
- Institute of Medicine Global Forum on Health

Slides available @ http://casi.asu.edu/
Medical Progress:
From Superstitions to Symptoms to Signatures
Mapping The Molecular Signatures of Disease: The Intellectual Foundation of Rational Diagnosis and Treatment Selection

Genomics

Proteomics

Molecular Pathways and Networks

Network Regulatory Mechanisms

ID of Causal Relationships Between Network Perturbations and Disease

Patient-Specific Signals and Signatures of Disease or Predisposition to Disease
Precision (Personalized) Medicine

Molecular Profiling

- molecular diagnostics and disease subtyping
- improved outcomes and lower cost
- multiplex biomarkers and targeted therapies

Platforms
- new analytical and computational technologies

Impact

Rx selection
Mapping Causal Perturbations in Molecular Pathways and Networks in Disease: Defining a New Taxonomy for Disease

“Omics” Profiling to Identify Disease Subtypes (+ or - Rx Target)

Altered Network Structure and ID of Molecular Targets for MDx and/or Rx Action

Multiplex Profiling

Right Rx for Right Disease Subtype
Biomarkers, Disease Subtyping and Targeted Therapy: Companion Diagnostics - the Right Rx for the Right Disease (Subtype)

- Her-2+ (Herceptin) (Perjeta)
- EML4-ALK (Xalkori)
- K-ras (Erbitux) (Vectibix)
- BRAF-V600 (Zelboraf)
- CFTR-G551 (Kalydeco)
## Targeted Oncology Therapies in Molecularly Stratified Populations

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Target</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast carcinoma</td>
<td>HER2 amplification</td>
<td>Trastuzumab, Lapatinib</td>
</tr>
<tr>
<td>NSCLC</td>
<td>EGFR mutations</td>
<td>EGFR TKIs (erlotinib, gefitinib)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>EML-ALK</td>
<td>ALK inhibitors (crizotinib)</td>
</tr>
<tr>
<td>GIST</td>
<td>KIT and PDGFRA mutations</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Melanoma</td>
<td>BRAF-V600 mutation</td>
<td>BRAF inhibitor (vemurafenib)</td>
</tr>
<tr>
<td>Ewing's sarcoma</td>
<td>EWS-FLI translocation</td>
<td>anti-IGF1R ab (figitumumab)</td>
</tr>
<tr>
<td>Medulloblastoma BCC</td>
<td>PTCH1 or SMO mutations</td>
<td>SMO inhibitors (vismodegib)</td>
</tr>
<tr>
<td>Ovarian/ breast CA</td>
<td>BRCA1/BRCA2 mutations</td>
<td>PARP inhibitors (olaparib)</td>
</tr>
<tr>
<td>PRCC</td>
<td>MET mutations</td>
<td>MET TKIs (ARQ197. XL880)</td>
</tr>
</tbody>
</table>
Confronting the Clinical, Economic and Human Toll of Cancer

US Cancer Deaths (2013) 580,000
## US Cancer Prevalence Estimates 2010 and 2020

<table>
<thead>
<tr>
<th>Site</th>
<th># People (thousands)</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>2020</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>3461</td>
<td>4538</td>
</tr>
<tr>
<td>Prostate</td>
<td>2311</td>
<td>3265</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1216</td>
<td>1517</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1225</td>
<td>1714</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>639</td>
<td>812</td>
</tr>
<tr>
<td>Uterus</td>
<td>588</td>
<td>672</td>
</tr>
<tr>
<td>Bladder</td>
<td>514</td>
<td>629</td>
</tr>
<tr>
<td>Lung</td>
<td>374</td>
<td>457</td>
</tr>
<tr>
<td>Kidney</td>
<td>308</td>
<td>426</td>
</tr>
<tr>
<td>Leukemia</td>
<td>263</td>
<td>240</td>
</tr>
<tr>
<td>All Sites</td>
<td>13,772</td>
<td>18,071</td>
</tr>
</tbody>
</table>

$124$ billion and projected to rise to $207$ billion (66% increase) by 2020

Ini. = within 1 year of Dx; Con = continuing; Last = last year

World Cancer Report 2014

The State of Cancer Care in America: 2014

American Society of Clinical Oncology
Making a world of difference in cancer care
DELIVERING HIGH-QUALITY CANCER CARE
Charting a New Course for a System in Crisis

Toward Precision Medicine
Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease

Policy Issues in the Development of Personalized Medicine in Oncology
WORKSHOP SUMMARY

INFORMATICS NEEDS AND CHALLENGES IN CANCER RESEARCH
Workshop Summary
Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Clinical Challenge</th>
<th>Selection of Treatment Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Undefined standard of care <em>(How do I treat?)</em></td>
<td>Limited published evidence to guide treatment decisions</td>
</tr>
<tr>
<td>Aggressive</td>
<td>Limited standard treatment options <em>(How do I optimize any future treatment strategy?)</em></td>
<td>Limited time in face of poor prognosis</td>
</tr>
<tr>
<td>Metastatic and refractory diseases</td>
<td>Difficult to treat cancers <em>(What’s next; Am I beyond standard of care?)</em></td>
<td>Emerging data on novel drug: target associations revealed by molecular profiling</td>
</tr>
</tbody>
</table>
Molecular profiling identifies potential therapies not otherwise considered

<table>
<thead>
<tr>
<th>Drug</th>
<th>Associated Biomarker</th>
<th>On Compendium Tumor Types</th>
<th>Off Compendium Tumor Types</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>trastuzumab (Herceptin)</td>
<td>HER2</td>
<td>Breast</td>
<td>Ovarian</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastric</td>
<td>Gastroesophageal</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Colorectal</td>
<td>30%</td>
</tr>
<tr>
<td>nab-paclitaxel (Abraxane)</td>
<td>SPARC</td>
<td>Breast</td>
<td>Gastroesophageal</td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSCHC</td>
<td>Pancreatic</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Melanoma</td>
<td>41%</td>
</tr>
</tbody>
</table>

Caris Life Sciences data. 60,000+ tumors profiled data set. Information on file.
“There is a lack of evidence showing the impact of guidelines on clinical practice and patient outcomes.”

Dr. G. H. Lyman
University of Washington School of Medicine
Medscape 11 April 2014

- response to McKesson Speciality Health press release that CMS is considering proposal from NCCN, US Oncology and McKesson to use NCCN guidelines to control cost and promote more uniform medical practice
“Even within NCCN, certainly the majority of decision nodes that are enshrined in NCCN are not supported by high level evidence.”

Dr. Clifford Hudis
President, ASCO
Interview in Cancer Letter 22 Nov. 2013, 39
• should molecular profiling be conducted on all patients as SOC?

• should patients receive SOC if profiling indicates absence of molecular targets for the SOC regimen?
WILL
• Whole Genome Sequencing (WGS) Change Everything?

WHEN
• Will WGS Become Just Another Laboratory Test Value?

HOW
• Will WGS Affect Patient Care?
Introducing **NextSeq™**
A Whole Human Genome on Your Desktop

www.illumina.com/nextseq500
• The $1000 (or less) Whole Genome Sequence (WGS)

• The $ ? Interpreted WGS

• The $ ? Reimbursed WGS for Clinical Use
The Overly Simplistic and Deterministic Dangers of a Genome-Sequence Centric Perspective

The Over-Simplified Perspective That Whole Exome-and Whole Genome-Sequencing Will Reveal the Full Etiology of Disease Pathogenesis and Transform Treatment Options
The Need for Multiple Molecular Diagnostic Platforms to Maximize the Number of Actionable Drug: Target Associations to Guide Therapeutic Decisions

FISH = fluorescent in situ hybridization
CISH = chronogenic in situ hybridization
IHC = immunohistochemistry

- **FISH**
  - crizotinib
  - everolimus
  - lapatinib
  - pertuzumab
  - T-DM1
  - trastuzumab

- **CISH**
  - afatinib
  - cetuximab
  - erlotinib
  - gephitinib
  - imatinib
  - panitumumab

- **Sequencing** (Next-Gen Sanger)
  - dabrafenib
  - trametinib
  - vemurafenib

- **PCR**
  - afatinib
  - cetuximab
  - erlotinib
  - gefitinib
  - imatinib
  - panitumumab

- **IHC**
  - everolimus
  - hormone therapy
  - lapatinib
  - pertuzumab
  - T-DM1
  - trastuzumab
The Anticipated Need to Expand the ‘panOmics’ Analyte Repertoire for Comprehensive Diagnostic Profiling

Mapping Non-coding Regulatory Systems for Genes and Coupled Gene Networks
The Increasing Complexity of the RNA Universe

- m(messenger)RNA
- t(transfer)RNA
- r(ribosomal)RNA
- microRNAs (miRs, miRNAs)
- long non-coding RNAs (IncRNAs)
- competing endogenous RNAs (ceRNAs)
- circular RNAs (circRNAs)
- small nucleolar RNAs (snoRNAs)
- PIWI-interacting RNAs
- 3'-UTR RNA-binding proteins and mRNA stability
miRNA Network Dynamics in Cancer

- Down regulation of miR-200 family
  - Associated with worse overall survival in ovarian, renal and lung cancers
  - Improved clinical outcome in breast cancer except luminal subtypes in which low expression linked to worse survival
- IL-8 and CXC L-1 are targets for miR-200 family
  - Elevated levels of IL-8 associated with poor survival in ovarian, renal and lung carcinomas
- Inverse correlation of IL-8 expression and number of miR-200 family members
The Complex Regulation of the PTEN Tumor Suppressor Gene by Modulation of MicroRNAs (miRs) and Competing Endogenous RNAs (ceRNAs)

- CNOT6L
- VAPA
- ZeB2
- VCAN
- miR17 and 19 families
- miR17, 19, 26 families
- miR25, 92a, 181 and 200
- miR 136 and 144
- pseudogene PTENP1 miR 17, 19, 21, 26 and 214 families
Challenging Questions Regarding Future Directions in Cancer Research and Clinical Oncology
Cancer as a Complex Adaptive System

Sustained Tumor Growth, and Progression to Metastasis and Resistance to Treatment

determinants of clonal fitness: robustness, adaptability, evolvability

emergence of clones and subclones with diverse genotypes and phenotypes with tumor progression and metastasis

genotoxic insult(s), genome instability and dysregulation of molecular signaling networks in different cell types

Dynamics of Host:Tumor Co-evolution and Rx-Effects

Intra-and Inter-patient Variation Within Same Tumor Subtype

Tumor Subtypes in the Same Cell Type

SELECTION

HETEROGENEITY

DRIVERS
Major Knowledge Gaps in Understanding Clonal Dynamics and Fitness Landscapes in the Progression of Malignant Tumors

- mutation rates in different clones
- nature and frequency of selection pressures affecting clonal fitness
- fitness effects of different mutations and combinations
- fitness requirements for survival in different tissue microenvironments for metastatic success
- nature of competition and mutualism between co-evolving clones in same tumor or metastasis
- role of different therapeutic modalities and dosing regimens as selection pressures
The Selection Bottleneck (Selection Sweep) in Metastatic Dissemination

- Dominant clone and spectrum of lower frequency clones
- Zonal localization of individual clones
- Selection bottleneck for ‘fitness’ to complete multiple steps needed to successfully metastasize (note: often not the dominant clone the primary tumor)
- Selection for clonal phenotypes with preferred fitness for growth in specific organs?
- Further clonal diversification within individual metastases
Cancer Stem Cells

- divided opinions about their existence
- accumulating evidence to support their existence
- more purposeful efforts to resolve the issue
- if they exist they represent an obvious target for Rx/immune assault
  - more limited heterogeneity?
  - genomic canalization and constrained phenotypic diversity?
Are Current Targeted Treatments Attacking Both Stem Cells and Progenitor/Differentiated Cells or Largely Only the Latter?

If Stem Cells Are Surviving Unscathed then Therapeutic Failure is Inevitable and New Therapeutic Approaches to Selectively Attack Stem Cells Are Required
Implications of Different Cell-of-Origin Models for Cancer on Therapeutic Strategies

"malignant snowflakes": each cancer carries multiple unique mutations and other genome perturbations

disturbing implications for Rx and development of new Rx

Mutations in Individual Non-small Cell Lung Cancer

Drug Targets in Individual Non-Small Cell Lung Cancers

The Extravagant Landscape of Genomic Alterations in Cancer (Cell 2012, 150, 1107 and 1121)
Dynamic Clonal Heterogeneity in Tumor Progression:
The Most Clinically Dangerous Phenotypes

- Evasion of Detection/Destruction by Host Immune System
- Use of Host Systems to Promote Progression
- Invasion and Metastasis
- Emergence of Drug-Resistant Clones
The Problem and The Challenge

- how to hit multiple tumor clones?
- how to hit multiple tumor clones at multiple sites of metastatic disease?
- how to hit each new variant clone that may emerge as an escape variant driven by intrinsic genomic instability and/or by the selection pressure of treatment?
Clonal Heterogeneity and the Relentless Emergence of Drug-Resistant Clones (Intrinsic and/or Acquired Resistance)

Molecular Subtyping and RX Targets

Initial Rx-Response to Targeted Rx

Rx-Resistance via Redundant Molecular Pathways

B = 15 weeks Rx (Zelboraf®)
C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011) JCO 29, 3085)
# Mutations Responsible for Acquired Resistance to Targeted Therapies

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genetic mutation</th>
<th>Tumor type</th>
<th>Acquired drug resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>T790M</td>
<td>Advanced NSCLC</td>
<td>Gefitinib, Erlotinib</td>
</tr>
<tr>
<td>KRAS</td>
<td>Codon 12, 13 and 61</td>
<td>Colorectal cancer</td>
<td>Cetuximab</td>
</tr>
<tr>
<td>KIT</td>
<td>T670I</td>
<td>GIST</td>
<td>Imatinib</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>NS</td>
<td>NSCLC</td>
<td>Erlotinib, Gefitinib</td>
</tr>
<tr>
<td>ALK</td>
<td>C1156Y, L1196M</td>
<td>NSCLC</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>MEK1</td>
<td>C121S</td>
<td>Melanoma</td>
<td>Vemurafenib</td>
</tr>
<tr>
<td>BRAF</td>
<td>Amplification</td>
<td>Melanoma</td>
<td>Vemurafenib</td>
</tr>
<tr>
<td>NRAS</td>
<td>Q61K</td>
<td>Melanoma</td>
<td>Vemurafenib</td>
</tr>
</tbody>
</table>
EGFR Signaling Pathways in Cancer: Targeted Therapies and By-Pass Pathways for Drug-Resistance

Network Pharmacology and Emergence of Drug-Resistant Cells

- Rx-sensitive pathway blockade and cell death
- Activation of downstream pathway component(s) resulting in Rx-resistance
- Activation of downstream pathway components via by-pass signaling from other pathways
Resistance to TKIs in EGFR-Mutant Lung Adenocarcinomas*
Development of Resistance to Gefitinib or Erlotinib in c.40% Patients After One Year

- additional mutations in Rx target
  - second-site resistance EGFR mutations (>50%)

- mutations/activation of downstream and/coupled pathways
  - amplification of MET receptor gene (5-10%)
  - mutations in PIK3CA encoding P110α subunit of downstream lipid kinase PI3K (<5%)
  - BRAF mutations (<1%)

- trans-differentiation
  - histologic transformation: EMT or small lung cancer (<5%)

* K. Ohashi et al. (2012) PNAS 109, 12282
Therapeutic Options for Multi-target Modulation of Dysregulation in Complex Biological Networks

- multisite action by single Rx in the same pathway
  - blockade of most likely predicted “escape” domains involved in Dr
- multi-target promiscuity by single Dx in different pathways
  - control of off-target AEs
- Rx combinations with multisite (single pathway) and/or multitarget actions (different pathways)
  - patient tolerance, cost,
  - clinical trial design for large Rx combinations
- new regulatory paradigms
## Limited Efficacy of Multi-Target Rx in Glioblastoma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>sorafenib</td>
<td>PDGFR-α,β, VEGFR-2,3, BRAF, c-Kit, Ras</td>
</tr>
<tr>
<td>imatinib</td>
<td>PDGFR-α,β, c-Kit, Bcr–Abl</td>
</tr>
<tr>
<td>tandutinib</td>
<td>PDGFR-α,β, c-Kit, Flt3 (Phase II)</td>
</tr>
<tr>
<td>dasatinib</td>
<td>PDGFR-α,β, Src, Bcr–Abl, c-Kit, EphA2 (Phase II)</td>
</tr>
<tr>
<td>afilibercept</td>
<td>VEGF-A, VEGF-B, PIGF</td>
</tr>
<tr>
<td>cediranib</td>
<td>VEGFR-1,2,3, PDGFR-α,β, FGFR-1, c-Kit</td>
</tr>
<tr>
<td>sunitinib</td>
<td>VEGFR-2, PDGFR-β, c-Kit, RET, Flt3</td>
</tr>
<tr>
<td>vandetanib</td>
<td>VEGFR-2, EGFR, RET</td>
</tr>
<tr>
<td>cabozantinib</td>
<td>VEGFR-2, Met, RET, c-Kit, Flt3, Tie-2</td>
</tr>
</tbody>
</table>

Irreversible Kinase Inhibitors and Cancer

- less potential for drug resistance phenotypes than reversible inhibitors?
- **Afatinib (B-Ingelheim)**
  - EGFR kinase inhibitor NSCLC (EMA and FDA approval)
- **Ibrutinib (Janssen:Pharmacyclics)**
  - FDA accelerated approval
  - Bruton’s TK (BTK) inhibitor
- **Dacomitinib (Pfizer)**
  - EGFR inhibitor NSCLC (III), brain, head and neck (II)
- **Neratinib (Puma)**
  - EGFR inhibitor, breast (III), NSCLC, Gastric (II)
Mapping Causal Perturbations in Molecular Pathways and Networks in Disease: Defining a New Taxonomy for Disease

panOmics Profiling to Identify Disease Subtypes (+ or - Rx Target)

Topology of Altered Network Structure and ID of Molecular Targets for MDx and/or Rx Action

The Challenge of Non-Linear Information Flow in Biological Networks
Omics” Technologies and the Elucidation of Perturbations in Molecular Network ‘Wiring’ in Complex Diseases

- the “dead hand” of reductionism and “the trap of linearity” as barriers to progress
- delusional pursuit of individual Rx ‘targets’ in face of known, extravagant network-wide perturbations
  - extensive network redundancy via pathway coupling and resulting rapid shifts to compensatory “wiring circuit” options to circumvent Rx efficacy
    - redundancy = Rx resistance
- time for a serious re-assessment of current Rx target discovery strategies?
is the scale of molecular network dysregulation and relentless ‘state shifts’ (clonal dynamics) in advanced metastatic disease so extreme that Rx-circumvention or reset of network stability (homeostasis) via Rx action at multiple sites in multiple pathways is not attainable?
- cancer as a complex adaptive system
- dynamics of clonal evolution during tumor progression and treatment
- clonal evolutionary dynamics as a complex interplay between tumor (evasion) and host (detection/destruction) activities
- the evolution of clonal heterogeneity is the core problem in effective therapy
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
Immunoevasion by Tumor Cells

- “stealthy” tumor cell strategies that reduce detection and/or killing by body’s immune defenses, therapeutic monoclonals and anti-cancer vaccines
New Therapeutic Strategies to Circumvent Tumor-Mediated Suppression of Anti-Tumor Immune Responses

- circumventing tumor-mediated activation of T regulatory (Treg) cells to limit activity of anti-tumor killer T cells

- immune checkpoint modulation
  - “releasing the brakes” on the immune system
  - “removing the blindfold”
  - “unleashing the killer instinct”
The Promise of Immune Checkpoint Modulation Versus The Drug Resistance Problem in Targeted Therapy

clones with different Rx sensitivities

- $Rx_1$
- $Rx_2$
- $Rx_3$
- $Rx_4$
- $Rx_5$

targeted drugs

Cytotoxic T cells

- Immune checkpoint modulation agents

Rx-resistant clones/
Rx refractory disease

adaptive evolution of immune response and expanded cytotoxic T cell responses
Immune Checkpoint Modulation

- CTLA-4; ipilimumab (BMS approved)
- PD-1 antibodies and PD-1 ligands (Phase I/II/III)
- OX4; nivolumab (Phase III)
Engineering Killer T Cells for Cancer Therapy

- killer T cells harvested from cancer patients
- harvested cells genetically engineered in vitro to express T cell receptor(s) (TCRs) or chimeric antigen receptors (CARs) that recognize tumor antigen(s)
  - TCR/CAR genes delivered by viral vectors
  - TCRs must be genetically matched to the patients immune type
Three Component Chimeric Antigen Receptors (CARs)

- **T Cell**
- **Tumor Cell**

**co-stimulatory molecules and activation of T cell cytotoxic killing**

**antigen recognition/binding protein**

**tumor antigen**
production cost and technical complexity of individualized treatment

- local versus centralized production
- facilities and expertise
- regulatory review
Major Conceptual and Technical Barriers in Understanding the Role of Immunity in Protection and Disease

- limited metrics for multiplex functional monitoring of status of the immune system
  - poor predictive potential of animal models for humans
  - diverse cell classes
  - complex repertoire of cell-cell and cell-mediator interactions
  - monitoring of antigen expression dynamics in tumor clones
  - anatomic compartmentalization and lack of sampling tools
  - evolution of immune-escape variants
The Urgent Need for New Diagnostics and Molecular Profiling Tools for Improved Monitoring of Tumor Progression

From ‘Static Snap Shot’ at Initial Diagnosis to Dynamic Monitoring of Clonal Population Dynamics
RECIST (Response Evaluation Criteria in Solid Tumors) as sanctioned regulatory evaluation criteria for clinical trials
- significant inter-reader variation in tumor lesion feature extraction
- estimates of tumor burden and treatment response do not always correlate with time-to-progression and OS (particularly for non-cytotoxic Rx)

methods of recording both qualitative and quantitative features in free text reports handicaps automated data analysis
The Liquid Biopsy: The Need for New Diagnostic Tools for More Sensitive Longitudinal Monitoring of Tumor Progression

- faster detection of emergence of Rx-resistant/immune evasion clones
  - pre-exist prior to Rx
  - acquired resistance driven by Rx regimen(s)
  - minimal residual disease and relapse risk

- scientific foundation for more agile shifts in treatment regimens
  - clinical care
  - new clinical trial designs
• emergence of new KRAS mutations in CRC patients treated with cetuximab (Misale et al. 2012. Nature 486, 532)
• pre-existing ‘minor’ clones with KRAS mutations identified in metastases
• new clones sensitive to investigational Rx targeting MEK
• mutant clones detected in blood as early as 10 months before cetuximab resistance and disease progression documented
Anticipation-Based Chemotherapy in CLL

The Liquid Biopsy: The Urgent Need for New Minimally Invasive Diagnostic Tools for More Sensitive Longitudinal Monitoring of Tumor Progression
The Liquid Biopsy: The Urgent Need for New Minimally Invasive Diagnostic Tools for More Sensitive Longitudinal Monitoring of Tumor Progression

- circulating tumor cells
- circulating tumor-derived DNA/miRNA
- tumor-associated proteins (?)
- exosomes
At diagnosis = APC and KRAS (Wild Type)
emergence = KRAS and NRAS mutations and MET amplification clones

Exploration of the Role of Exosomes in Tumor Progression

• cancer-specific signatures
  – miRNA, mRNA, proteins
  – identify tissue of origin
  – ‘cargo’ changes with progression
• role in modulating host immune defenses?
• role in epithelial-mesenchymal transition?
• role in ‘preconditioning’ of organs for metastatic seeding?
• potential value in Dx?
  – minimally invasive versus biopsy
  – longitudinal disease monitoring in patients
• potential value as markers of Rx response/resistance/relapse?
Carisome™

• a blood-based technology to detect and profile tumor-derived biomarkers
• proprietary microvesicle isolation technology
• minimally invasive method to detect and monitor cancer progression and changing clonal dynamics on therapy
• potential in diagnosis and therapeutic response monitoring
• more than $100 million R&D investment to date
Redesigning Traditional Clinical Trial Paradigms in an Era of Molecular Profiling and Disease Subtyping
Oncology Therapeutics: An Unsustainable Enterprise Using Current Approaches?

- highest failure rate in clinical trials of any therapeutic class (8% success)
- slow adoption of new clinical trial designs using stratified patient subpopulations
- testing of new investigational drugs on late-stage patients with advanced and/or refractory disease
  - cellular composition likely unrepresentative of tumors at initial presentation
  - effect of repeated Rx cycles on clonal phenotypes and immune system damage
### Large Scale Profiling of Cancer Patients to Identify Cohorts Expressing Low Frequency Rx Target(s) for Phase II Trials

<table>
<thead>
<tr>
<th>Target</th>
<th># Patients Screened</th>
<th># Eligible Patients</th>
<th># Centers</th>
<th># Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML4 ALK(^+): lung cancer(^*)</td>
<td>1500</td>
<td>82</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>HER2(^+): gastric cancer(^**)</td>
<td>3803</td>
<td>549</td>
<td>122</td>
<td>24</td>
</tr>
</tbody>
</table>

\(^*\) E.L. Kwak et al. (2010) NEJM 363, 1693  
\(^**\) Y. Bang et al. (2010) Lancet 376, 687
Adaptive Trials

- use accumulating data during the trial
- add or drop agents in complex multi-arm trials (e.g. I-SPY; S-1400)
- critical need for robust validated biomarkers to assess Rx response and more agile changes in regimen
- more complex statistical designs
- uncertainty in planning drug supply
- cooperation between Rx sponsors for use of multiple investigational agents
Enrichment and Adaptive Trials Using MDx-Stratified Patients: Consequences of Foregoing Phase III RCTs

- appeal of faster trials and patient access to promising Rx (terminal diseases)
- less definitive evidence regarding safety and efficacy (smaller ‘N’)
- more complex regulatory filings for ‘combination’ protocols (Rx^n, MDx^n)
- accelerated approval should require reciprocal agreement for market withdrawal if confirmatory trials are negative
  - “fast on, fast off”
  - lessons from Avastin
Precision Medicine and Escalating Technical Complexities

The Need for Agile, Adaptive Regulatory and Reimbursement Policies
Precision Medicine: Key Drivers

Science

Policy

Cost and Outcomes
The Difficult but Largely Ignored Central Questions in Oncology and Cancer Care Delivery

What is a meaningful advance in Rx effectiveness?

Can we continue to afford the high cost of anti-cancer drugs for modest gains in PFS/OS and limited QOL?
How Many Drugs Acting on the Same Target Can The Market Support?
### Failed Phase III Clinical Trials of anti-VEGF Agents

**Table 1: Failed phase III clinical trials of anti-VEGF agents**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Tumour type and setting</th>
<th>PFS</th>
<th>OS</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab plus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XELOX and cetuximab</td>
<td>CRC (1st line)</td>
<td>–</td>
<td>NR</td>
<td>CA1992** (n = 755)</td>
</tr>
<tr>
<td>Docetaxel-based or irinotecan-based chemotherapy and panitumumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX</td>
<td>CRC (adjunct)</td>
<td>–</td>
<td>NR</td>
<td>NSABP-C01** (n = 2,872)</td>
</tr>
<tr>
<td>Capcitabine and oxaliplatin</td>
<td>CRC (2nd line)</td>
<td>–</td>
<td>–</td>
<td>MYSTIC** (n = 426)</td>
</tr>
<tr>
<td>Eribulin</td>
<td>NSCLC (2nd line)</td>
<td>+</td>
<td>–</td>
<td>BC4114 (n = 698)</td>
</tr>
<tr>
<td>Capcitabine or i所得税 and irinotecan</td>
<td>GC (3rd line)</td>
<td>+</td>
<td>–</td>
<td>NUGAST12** (n = 77.4)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>PC (1st line)</td>
<td>–</td>
<td>–</td>
<td>CALGB031381 (n = 536)</td>
</tr>
<tr>
<td>Gemcitabine and eribulin</td>
<td>PC (2nd line)</td>
<td>+</td>
<td>–</td>
<td>Avastin** (n = 30.1)</td>
</tr>
<tr>
<td>Docetaxel and prednisone</td>
<td>PR (1st line)</td>
<td>+</td>
<td>–</td>
<td>CALGB040117** (n = 1,030)</td>
</tr>
<tr>
<td>FOLFOX or XELOX</td>
<td>CRC (adjunct)</td>
<td>–</td>
<td>NR</td>
<td>AVANT22 (n = 3,460)</td>
</tr>
<tr>
<td><strong>Antibody plus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>PC (2nd line)</td>
<td>NR</td>
<td>–</td>
<td>VANILLA** (n = 2,052)</td>
</tr>
<tr>
<td><strong>Sunitinib plus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>MBC (2nd line)</td>
<td>–</td>
<td>–</td>
<td>SUN1107** (n = 700)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>HCC (2nd line)</td>
<td>–</td>
<td>NR</td>
<td>SUN11170**</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>MBC (2nd line)</td>
<td>–</td>
<td>NR</td>
<td>SUN10344**</td>
</tr>
<tr>
<td>Capcitabine</td>
<td>MBC (2nd line)</td>
<td>–</td>
<td>–</td>
<td>SUN10909** (n = 442)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>MBC (2nd line)</td>
<td>–</td>
<td>NR</td>
<td>SUN10056** (n = 694)</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>CRC (3rd line)</td>
<td>–</td>
<td>–</td>
<td>SUN11122**</td>
</tr>
<tr>
<td>Eribulin</td>
<td>NSCLC (2nd line)</td>
<td>+</td>
<td>–</td>
<td>SUN10687**</td>
</tr>
<tr>
<td>Pemetrexide</td>
<td>PR (2nd line)</td>
<td>NR</td>
<td>–</td>
<td>SUN11290** (n = 813)</td>
</tr>
<tr>
<td><strong>Sorafenib plus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboptatin and paclitaxel</td>
<td>MM (2nd line)</td>
<td>–</td>
<td>NR</td>
<td>PINEM1** (n = 270)</td>
</tr>
<tr>
<td>Carboplatin and paclitaxel</td>
<td>NSCLC (3rd line)</td>
<td>–</td>
<td>–</td>
<td>ESCLP** (n = 926)</td>
</tr>
<tr>
<td><strong>PINK167 plus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX</td>
<td>CRC (2nd line)</td>
<td>+</td>
<td>–</td>
<td>CONFIRM2** (n = 655)</td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>CRC (3rd line)</td>
<td>+</td>
<td>–</td>
<td>CONFIRM1** (n = 1,106)</td>
</tr>
<tr>
<td><strong>Saxumant plus</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX</td>
<td>CRC (3rd line)</td>
<td>+</td>
<td>–</td>
<td>NCT00012821**</td>
</tr>
<tr>
<td><strong>Leukemias and Myeloid</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX</td>
<td>CRC (2nd line)</td>
<td>–</td>
<td>–</td>
<td>NCT0004252**</td>
</tr>
<tr>
<td><strong>Avastin plus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>PC (1st line)</td>
<td>NR</td>
<td>–</td>
<td>MOE0228* (n = 639)</td>
</tr>
<tr>
<td><strong>Vandetanib plus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>NSCLC (2nd line)</td>
<td>–</td>
<td>–</td>
<td>TEST1** (n = 1,141)</td>
</tr>
<tr>
<td>Perifosine</td>
<td>NSCLC (2nd line)</td>
<td>–</td>
<td>–</td>
<td>ZEAL** (n = 534)</td>
</tr>
<tr>
<td><strong>Dendritic plus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX</td>
<td>CRC (3rd line)</td>
<td>–</td>
<td>NR</td>
<td>HOV1Z0N III** (n = 1,076)</td>
</tr>
<tr>
<td>Monotherapy or temsirolimus</td>
<td>GEM (2nd line)</td>
<td>–</td>
<td>–</td>
<td>REGALL** (n = 321)</td>
</tr>
</tbody>
</table>

*No further available. **This was not reported. Abbreviations: PFS, progression-free survival; OS, overall survival; GC, gastric cancer; CRC, colorectal cancer; MBC, metastatic breast cancer; MM, multiple myeloma; NSCLC, non-small cell lung cancer; PR, not reported; OS, overall survival; PC, pancreatic cancer; MET, murine epidermalgrowth factor receptor; SSTR, somatostatin receptor 2; ERCC, excision repair cross-complementation group 1; HRR, homologous recombination; BEV, bevacizumab plus anything; CA1992, panitumumab plus FOLFOX; DCC, docetaxel plus cetuximab; NSABP-C01, irinotecan plus capcitabine; BC4114, bevacizumab plus oxaliplatin plus EGFR plus Tax; NUGAST12, panitumumab plus FOLFOX; CALGB031381, cetuximab plus oxaliplatin plus irinotecan; Avastin, bevacizumab plus eribulin; CALGB040117, bevacizumab plus docetaxel plus prednisone; AVANT22, cetuximab plus irinotecan; VANILLA, bevacizumab plus eribulin; SUN11070, eribulin plus gemcitabine plus paclitaxel; SUN11170, paclitaxel plus S1; SUN10344, irinotecan plus gemcitabine; SUN10909, gemcitabine plus eribulin plus bevacizumab; SUN10056, gemcitabine plus bevacizumab; SUN11122, eribulin plus gemcitabine; SUN10687, eribulin plus gemcitabine; SUN11290, eribulin plus gemcitabine; PINEM1, eribulin plus gelatin; ESCLP, eribulin plus gemcitabine; CONFIRM2, eribulin plus gemcitabine; CONFIRM1, eribulin plus gemcitabine; NCT00012821, bevacizumab plus eribulin plus gemcitabine; NCT0004252, bevacizumab plus gemcitabine plus paclitaxel; MOE0228, bevacizumab plus gemcitabine plus paclitaxel; TEST1, eribulin plus gemcitabine plus paclitaxel; ZEAL, eribulin plus gemcitabine plus paclitaxel; REGALL, eribulin plus gemcitabine plus paclitaxel.

Cost of Recently Approved Anti-Cancer Drugs

- brenfuximab (Adcetris) $216,000/course
- ipilimab (Yervoy) $123,000/year
- cabazitaxel (Jevtana) $96,000/year
- sipuleucel-t (Provenge) $93,000/year
- vismodegib (Erivedge) $75,000/course
- petuzumab (Perjeta) $70,800/year
- vemurafenib (Zelboraf) $61,000/year
- abiraterone (Zimiga) $60,000/year
- premetrexed (Alimta) $30,000/course
Educating Payors on the Value of Molecular Profiling in Healthcare: Shift from Cost-Based Pricing to Value-Based Reimbursement to Incentivize Biomarker R&D
Regulatory Considerations for Molecular Diagnostic Tests

- increasing R&D cost complexity of new molecular diagnostic tests versus LDTs
- need for greater FDA oversight based on technical complexity
  - 510(k) and pre-market approval (PMA)
A Study in Reimbursement Policy Contrasts: Targeted Therapeutics (Rx) Versus Molecular Diagnostics (MDx) in Oncology
Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MDx) and Therapeutics (Rx) in Oncology

MDx and Omics Profiling

MDx profiling to ID Rx response/resistance

segmentation of major cancers into ever smaller cohorts

MDx and Omics Profiling

SOC Rx guidelines

‘one size-fits all’ Rx regimens

multi-line Rx versus palliation

aggressive end-of-life Rx
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- SOC Rx guidelines
- MDx profiling to ID Rx response/resistance
- Scientific Foundation for Precision Diagnosis and Rational Treatment Selection
- Propagation of Therapeutic Strategies with Limited Effectiveness

- ‘one size-fits all’ Rx regimens
- multi-line Rx versus palliation
- aggressive end-of-life Rx

segmentation of major cancers into ever smaller cohorts
The Need for Value-Based Reimbursement of New Molecular Profiling Services: A Market Failure that Threatens Innovation in Precision Medicine

MDx and Omics Profiling

SOC Rx guidelines

Cost-Based Versus Value-based Pricing

Uncritical Acceptance of Rx Pricing

Barriers to Innovation and Recovery of Increasing R&D Cost

Incentives to Sustain Flawed Discovery Strategies and Clinical Care
The Imminent Arrival of the Zettabyte (10^{21}) Era
The Omics Data Storage Challenge
(J. Starren et al. 2013 JAMA 309, 1237)

- typical EHR
  - 375 KB/patient
- radiologic picture archiving and communication system (PACS)
  - 104 MB/patient
  - x277 > EHR
- WGS
  - 3-10 million variants/individual
  - 5-10 GB/individual
  - x50 > imaging
PanOmics Profiling and the Data Deluge

- anatomic pathology + single analyte Dx
- multiplex ‘panOmics’ MDx
- whole exome sequencing (WES)
- whole genome sequencing (WGS)
- epigenome profiling

V5 data
- volume
- velocity
- variety
- veracity
- value

infrastructure
integration
intelligence at ingestion
education/training of HCPs
Cross-Domain Convergence, Complexity and Increasing Dependency on Data-Intensive Methods and New Knowledge Networks

systems-focused, big data sets mining and analytics

reductionist, investigator-centric datasets and hypotheses

hypothesis driven

unbiased datasets and pattern mining
Assimilation of Concepts of Molecular Medicine into Routine Practice and Health Records
Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency, Decision-Support and Future Education Curricula
Analytical and Clinical Validation of Molecular Determinants of Disease (Subtypes) and Treatment Options

disease biomarkers and molecular variants

massive data: volume, velocity, variety, veracity

evidentiary standards for regulation/reimbursement

clinical utility and adoption

outcomes and values
Identification and Validation Biomarkers: A Complex, Multi-Dimensional Challenge

OPTIMIZED DECISIONS FOR IMPROVED OUTCOMES AT LOWER COST
The Caris Approach to Precision Oncology and Clinical Oncology Information Services

**Molecular Profiling**
- Caris Molecular Intelligence
- Multiple technology platforms

**Research**
- Caris Registry
- Biorepository
- Carisome platform

**Evidence Ranking**
- Advanced bibliometric analysis and ranking

**Information Services**
- MI Portal
- Clinical Trials Connector
- EMR Integration

**Actionable Drug: Target Associations**
- CMI™ Report
  - Actionable Drug: Target Associations
  - Evidence

**Reimbursement**
- Billing group
- Appeals support

**Client Support**
- Physician consults
- On-line tools