ASU Complex Adaptive Systems
ARIZONA STATE UNIVERSITY

BIO 302:
APRIL 30, 2015

WEEK 15, LECTURE 2:
THE FUTURE OF CANCER CARE: ECONOMIC OUTLOOK; CARE DELIVERY SYSTEMS; TECHNOLOGICAL INNOVATION; PREVENTION; PATIENT PARTICIPATION

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The Future of Cancer Care

- new technologies
- new treatments
- standards and quality of care
- cost of care
- quality of life

The Future of Cancer Care

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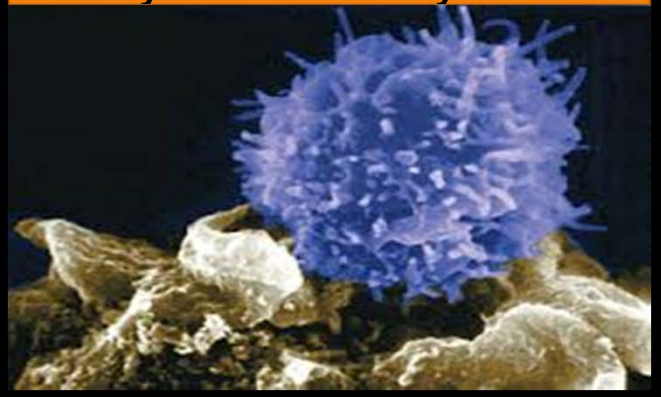
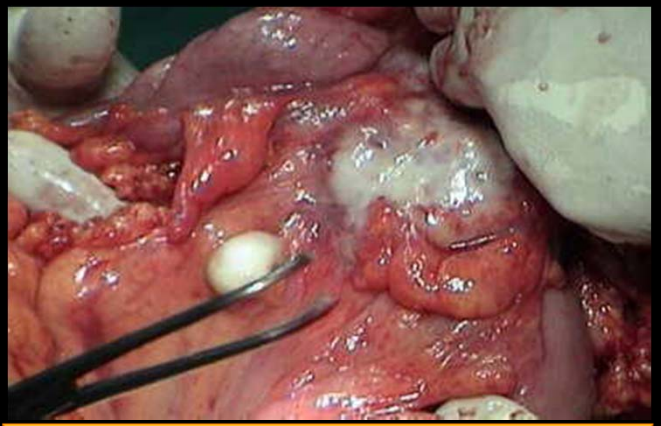
We Can No Longer Afford (Economically and Ethically) to Avoid Asking Tough Questions About The Adequacy of Current Approaches to Cancer Treatment and Care and the Urgent Need for Radical Change

Dynamic Clonal Heterogeneity in Tumor Progression: The Most Clinically Dangerous Phenotypes

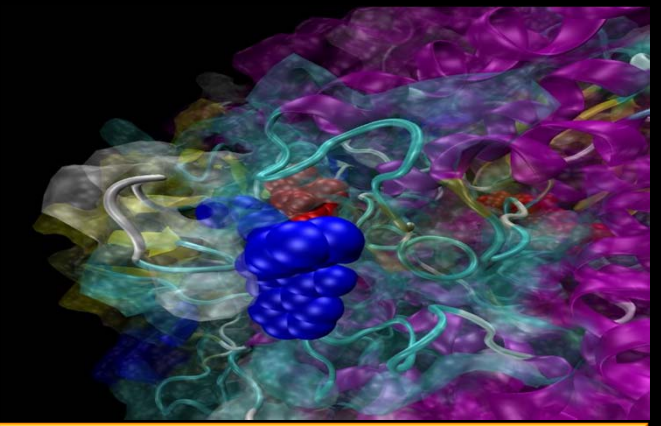
Evasion of Detection/Destruction by Host Immune System



Use of Host Systems to Promote Progression

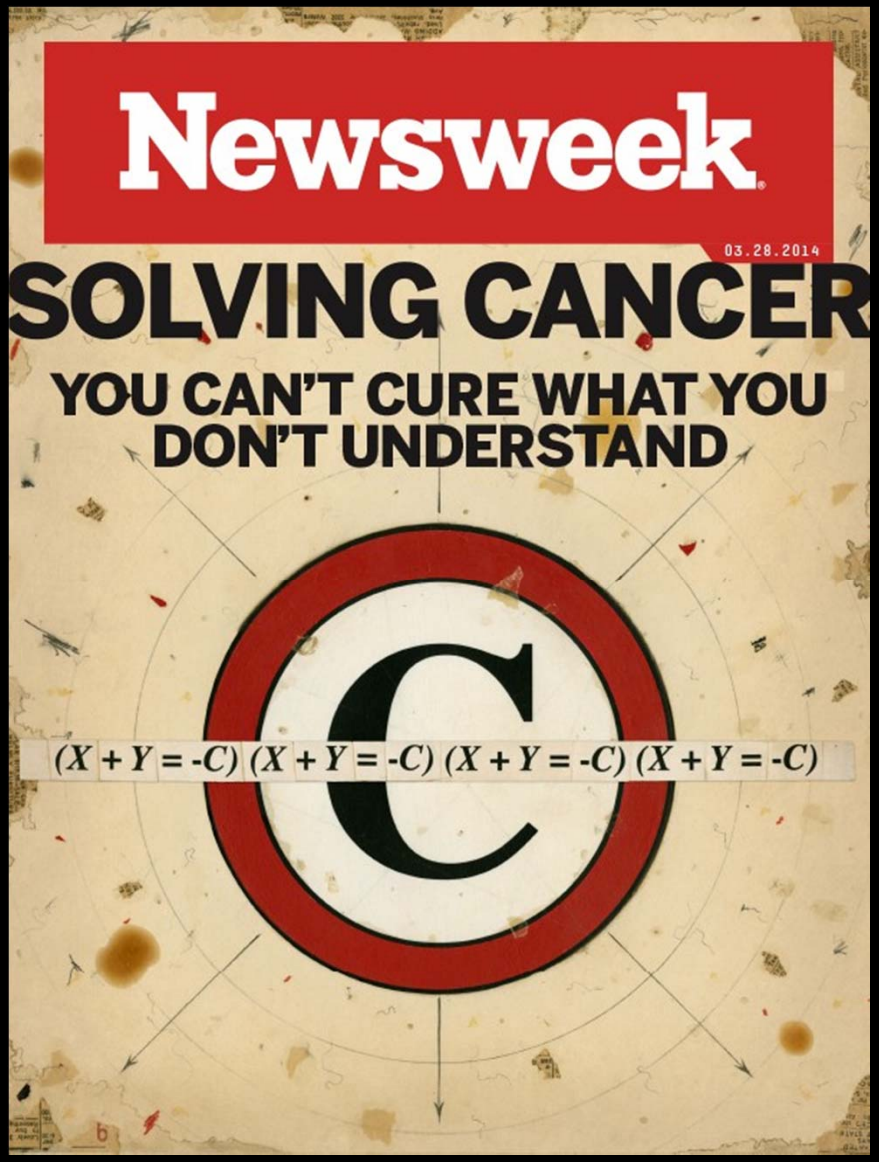


Invasion and Metastasis



Emergence of Drug-Resistant Clones

The Biological Complexity of Cancer: the Urgent Need to Improve Effectiveness of Current Therapy and the Design of New Treatment Strategies



- 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

A Hierarchy of Knowledge and Ignorance

Hon. D. Rumsfeld
US Secretary
of Defense

"known knowns"

- validated knowledge
- decisions with high degree of predictability of success

"known unknowns"

- known knowledge gaps (complete or incomplete) about relevant factors
- limitations of predictability and accuracy of decisions

"unknown unknowns"

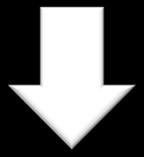
- conceptual and cognitive blank spaces
- rude shocks/disruption by unanticipated interactions between known factors or more likely completely new interactions between unknown/unrecognized factors

Rumsfeld's Rules and the Cancer Problem

"known knowns"	• genome mutations and genomic instability • role of host microenvironment in tumor progression • pattern and timing of metastatic spread • treatment resistance patterns
"known unknowns"	• epistasis and phenotypic diversity • RNA-mediated gene regulation • triggers of altered molecular signaling networks in different cancer subtypes in the same cell type • dynamics of evolution of metastatic and drug-resistant clones • roles of cancer stem cells (CSCs) and progenitor/differentiated (P/D) cell fractions in tumor behavior • plasticity of CSCs and P/D cellsand reacquisition of CSC properties by P/D cells
"unknown unknowns"	• by definition a black box with potential for rude surprises

Cancer Treatment

- molecular profiling (panOmics) and a new taxonomy for the classification of tumor subtypes
- understanding the dynamics of clonal diversification in tumor progression



- implications for future drug discovery
- need for new clinical trial designs and regulatory policies based on molecular profiling of patients and monitoring of clonal dynamics during tumor progression

The Problem and The Challenge

- how to hit multiple tumor clones?
- how to hit multiple tumor clones at multiple anatomic sites of metastatic disease?
- how to hit each new variant clone that may emerge as an escape variant driven by the selection pressure of treatment?

Molecular Profiling and Identification of New Targets for Rx Action

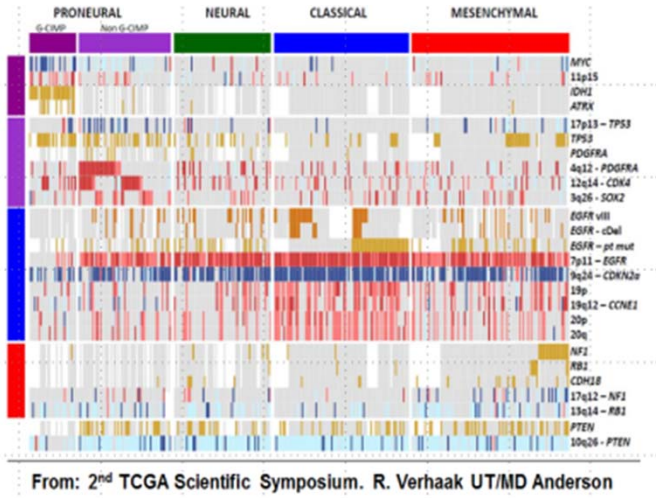
Monitoring Treatment Responses in Cancer

- earlier detection of lack of Rx efficacy
  - faster switch of Rx regimen(s)
- earlier detection of emergence of treatment-resistant clones
  - agile, anticipatory treatment to hit new resistant clones
  - greater current feasibility with ‘liquid’ hematopoietic tumors (leukemias, lymphomas) than solid tumors
  - new technologies and ‘liquid biopsy’ for solid tumors

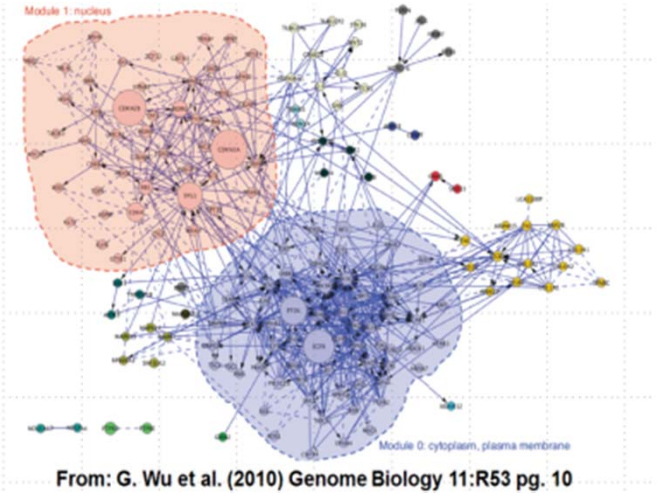
Cancer Treatment

- are current ‘chemo’ approaches doomed to inevitable therapeutic failure due to failure to address the complex biology of cancer?
  - clonal heterogeneity and need for broad Rx coverage
  - ‘escape’ pathways for Rx-resistant cells due to compensatory (redundant) molecular pathways
  - role of cancer stem cells as the critical, but elusive, target?

GBM Expression Subtypes and TF and miRNA-TF Regulatory Networks

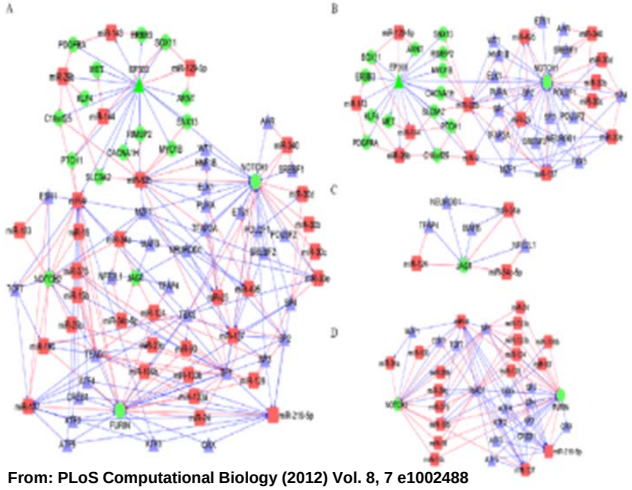


From: 2nd TCGA Scientific Symposium. R. Verhaak UT/MD Anderson



From: G. Wu et al. (2010) Genome Biology 11:R53 pg. 10

From: M. S. Carro et al. (2010) Nature 463, 318

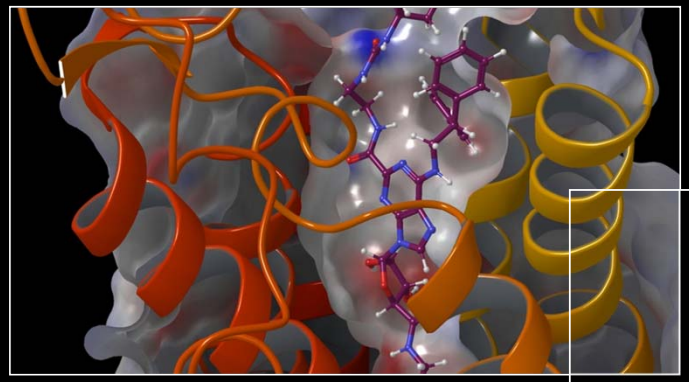


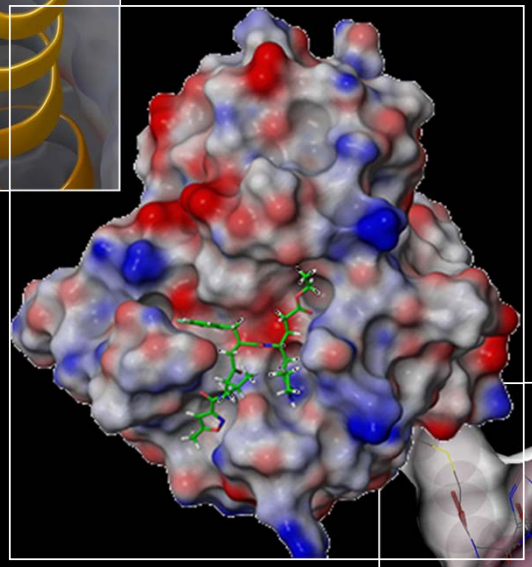
From: PLoS Computational Biology (2012) Vol. 8, 7 e1002488

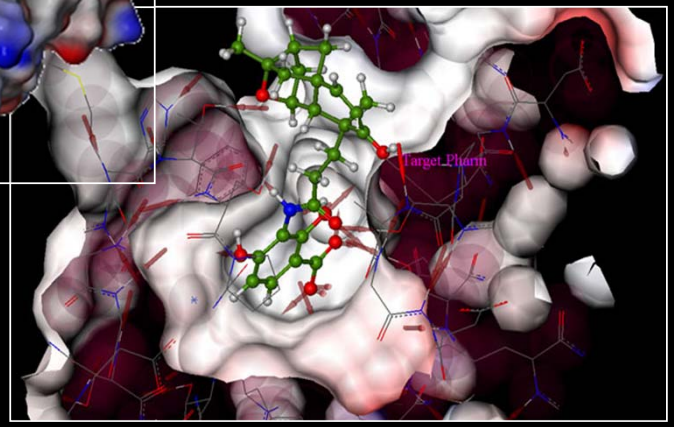
Cancer Treatment

- is the scale of disruption of molecular signaling networks in tumor clones in metastatic disease too large to be reversed by drugs that act on a single target?
  - role of by-pass signaling pathways in generation of drug-resistance
- technical, clinical and economic challenges of hitting multiple targets to limit compensatory by-pass resistance/escape pathways

Design of Candidate Rx via Detailed Structural Knowledge of 'Active Site' in the Target Molecule





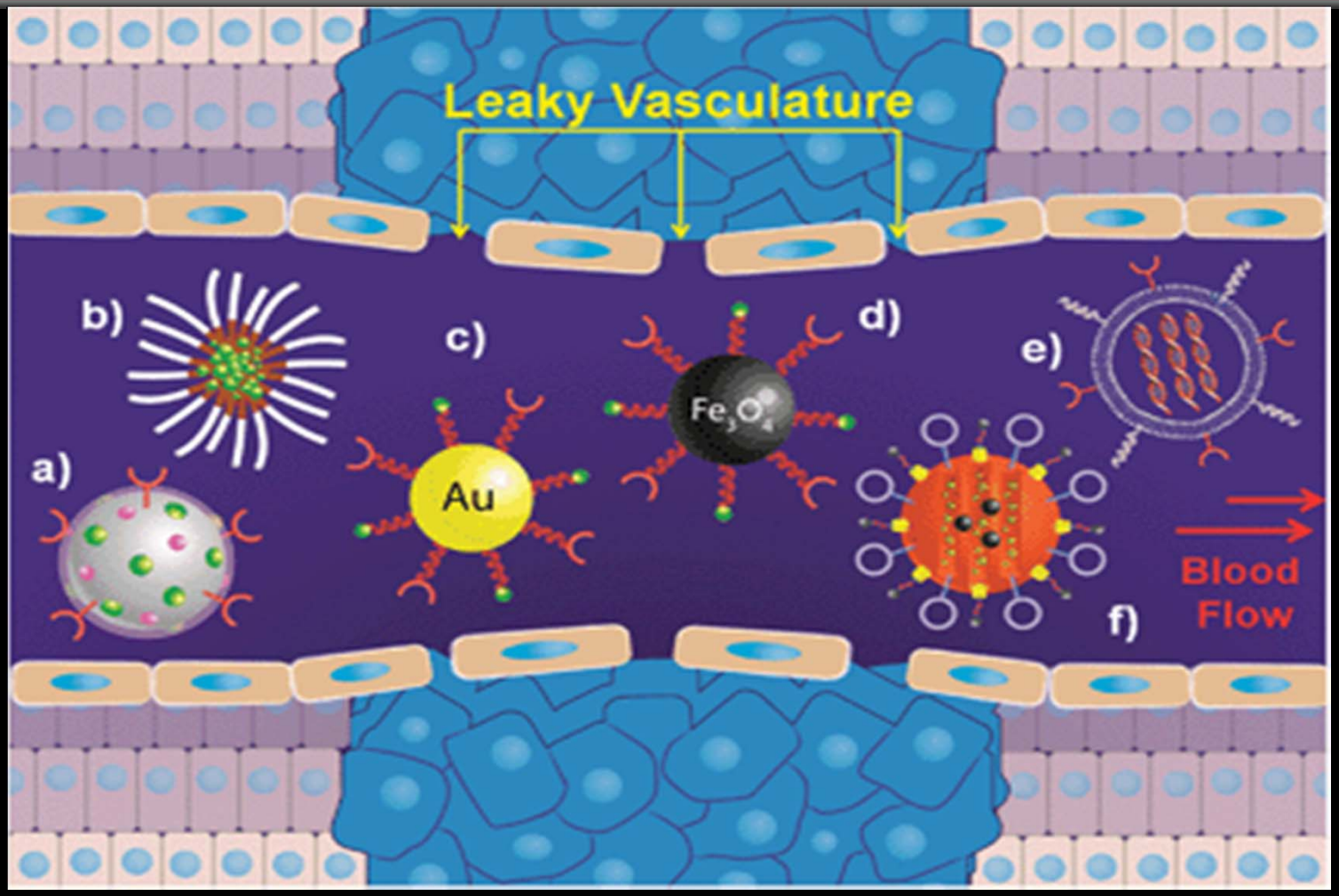


- specificity
- one target: no promiscuity
- limit off-target effects (side effects)

The Elusive Quest for Magic Bullets!

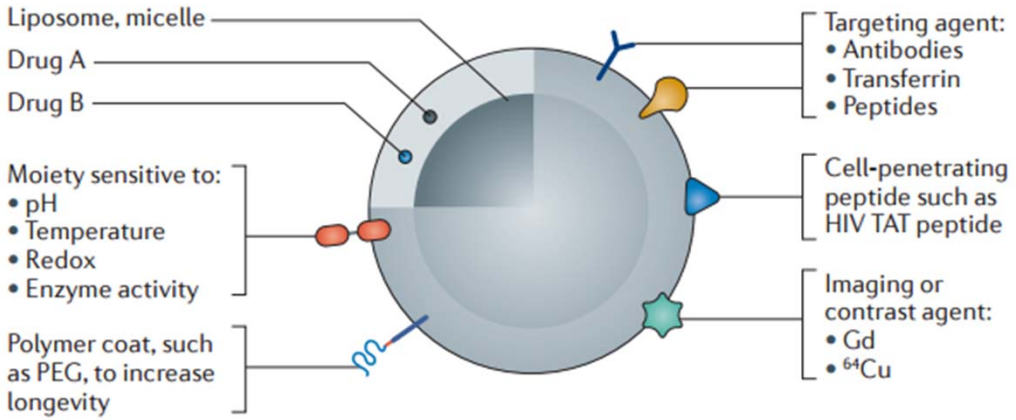
The Design of Drug Delivery Systems that Selectively 'Home-In' on Tumor Cells Based on Recognition of Surface Markers Expressed Selectively by Tumor Cells

Targeted Particulate Drug Carriers



Mesoporous silica nanoparticles in biomedical applications ...pubs.rsc.org

Multifunctional Environment-Sensitive Nanoparticulate -Systems for Drug Delivery



From: V. P. Torchilin (2015) Nat. Rev. Drug Disc. 13, 813

Targeted Drug Delivery Systems

- elegant molecular biology to ID targets for selective 'homing-in' on cancer cells

but

- target cell heterogeneity will likely require a spectrum of different 'homing' molecules to detect different clones

plus

- even if multiple clones can be recognized by using multiple 'homing' recognition molecules the problem of Rx-resistant clones (intrinsic or acquired) still looms


The lingering legacy of Deepwater Horizon pp. 11 & 22
The future of human genome editing p. 36
Drilling into engine oil antiwear films pp. 40 & 302
Science
$10
3 APRIL 2015
sciencemag.org
AAAS
SPECIAL ISSUE
Cancer Immunology and Immunotherapy

The Problem and The Challenge

- moving from limited narrow spectrum ‘chemo’ strategies to devise new ways to attack every clone
- harnessing the cognate (detection) and destruction (killing) of cancer cells by the body’s immune system
- how do cancers escape the immune system?
  - to allow initial tumor formation and subsequent metastatic spread?
  - clones that are not killed by immunotherapeutic Rx

The Need for Rethinking Therapeutic Strategies to Combat Cancer

Are We Looking at the Right Cellular and Molecular Target(s) in the Design of New Cancer Treatment Strategies?

Are We Looking at the Right Cellular Target(s) in the Design of New Cancer Therapeutic Strategies?

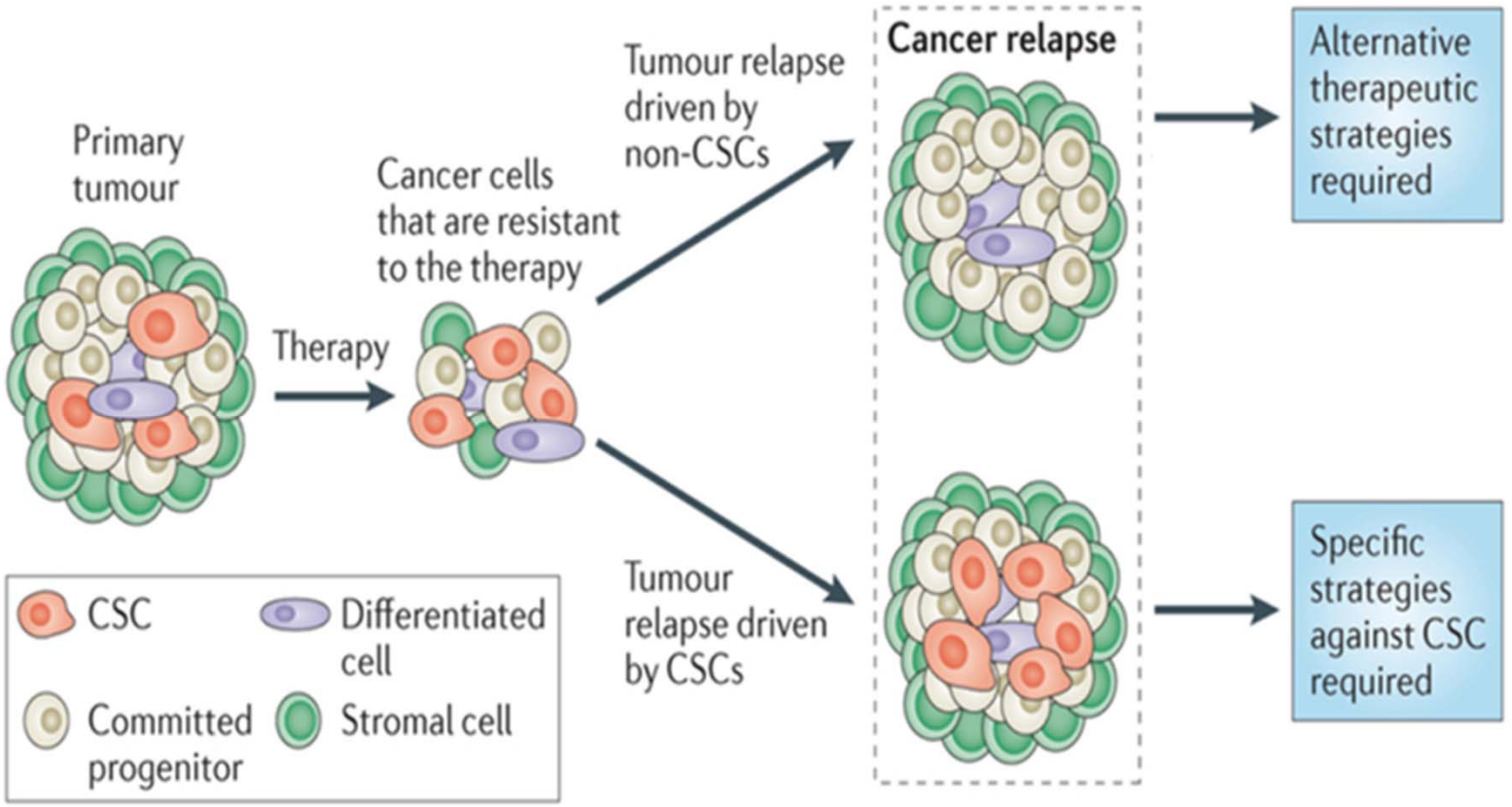
- what is/are the biologically relevant target/targets for effective destruction of cancer?

- cancer stem cells (constant renewal, Rx resistance and metastasis)?

or

- non-stem cell progeny (limited proliferative capacity) but which produce tumor bulk?

Implications of Different Cell-of-Origin Models for Cancer on Therapeutic Strategies



Adapted From: B. Beck and C. Blanpain (2013) Nature Rev. Cancer 13, 734

Shutting Down the Clonal Diversification Engine

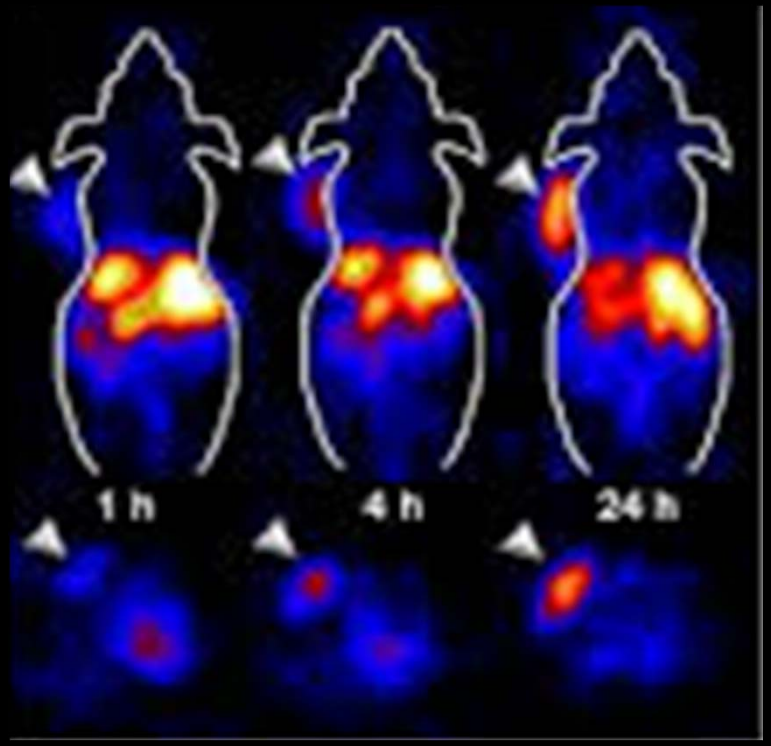
- better ID of cancer stem cells and therapies targeted to stem cells
- blockade of cell signaling pathways promoting clonal diversification and metastasis
- new findings of cross-communication between tumor clones that slow/accelerate clonal diversification
  - potential site Rx target?

Clinical Trials

- drug development is struggling
- high costs(>$1 billion)
- slow progress (5-12 years)
- high failure rates (75-95%)
- unsustainable business model in an era of economic constraint and mostly limited gains in PFS/OS

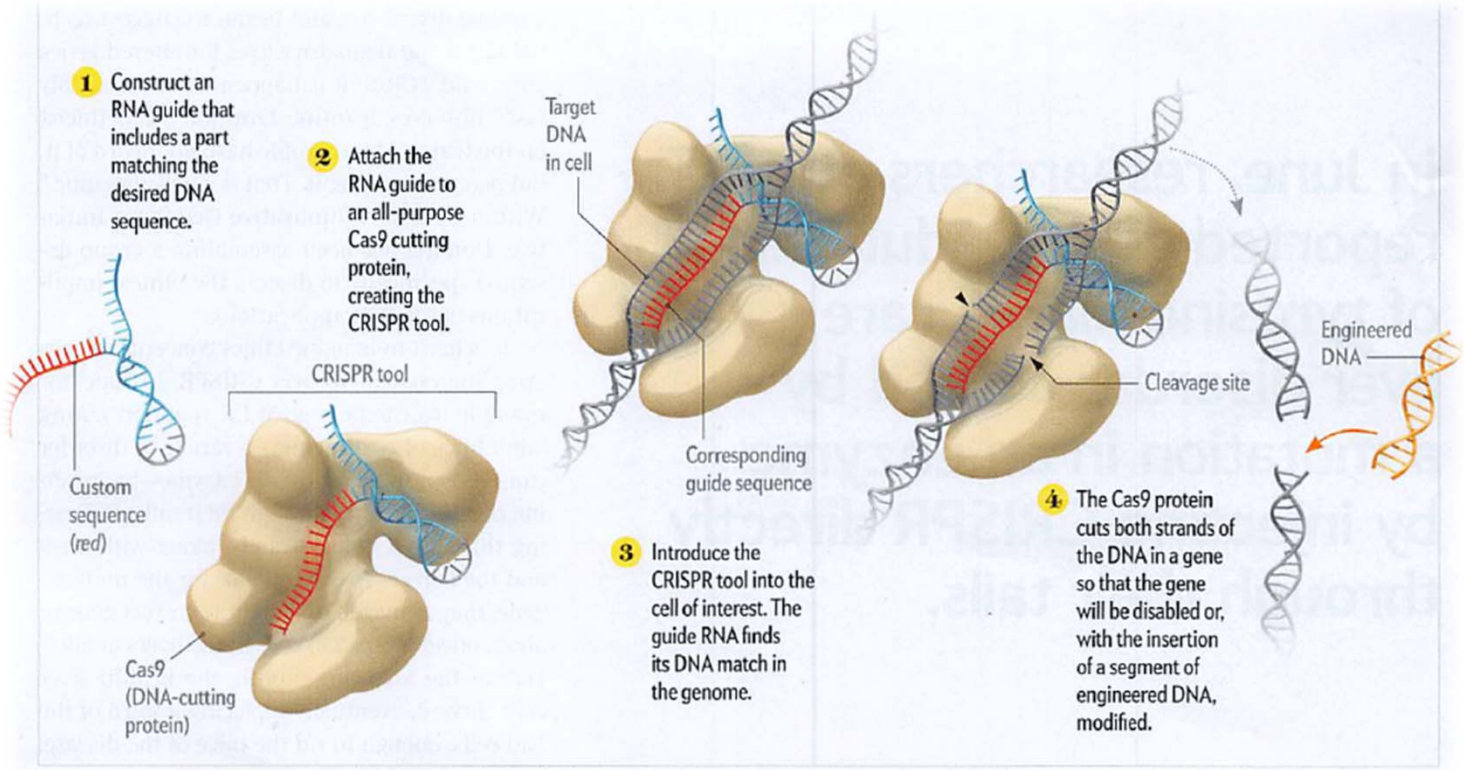
The Need for Better Preclinical/Laboratory Models That More Accurately Reflect the Genotypic/Phenotypic Properties of Human Cancer Cells for Selection of New Rx Agents

Human Tumor Xenografts and Drug Screening

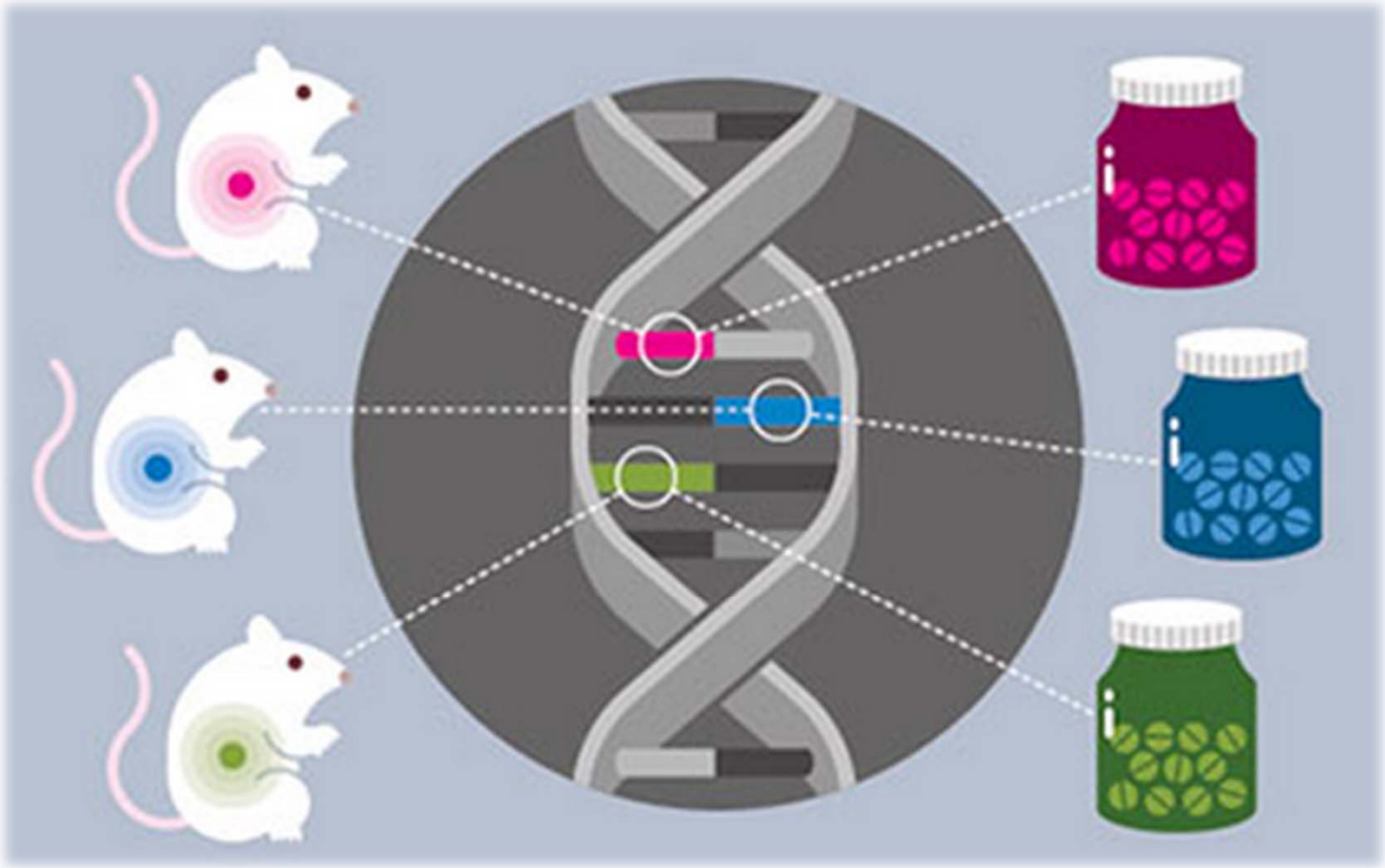


Targeted Introduction or Excision of Specific Genes or Gene Regulatory Domains

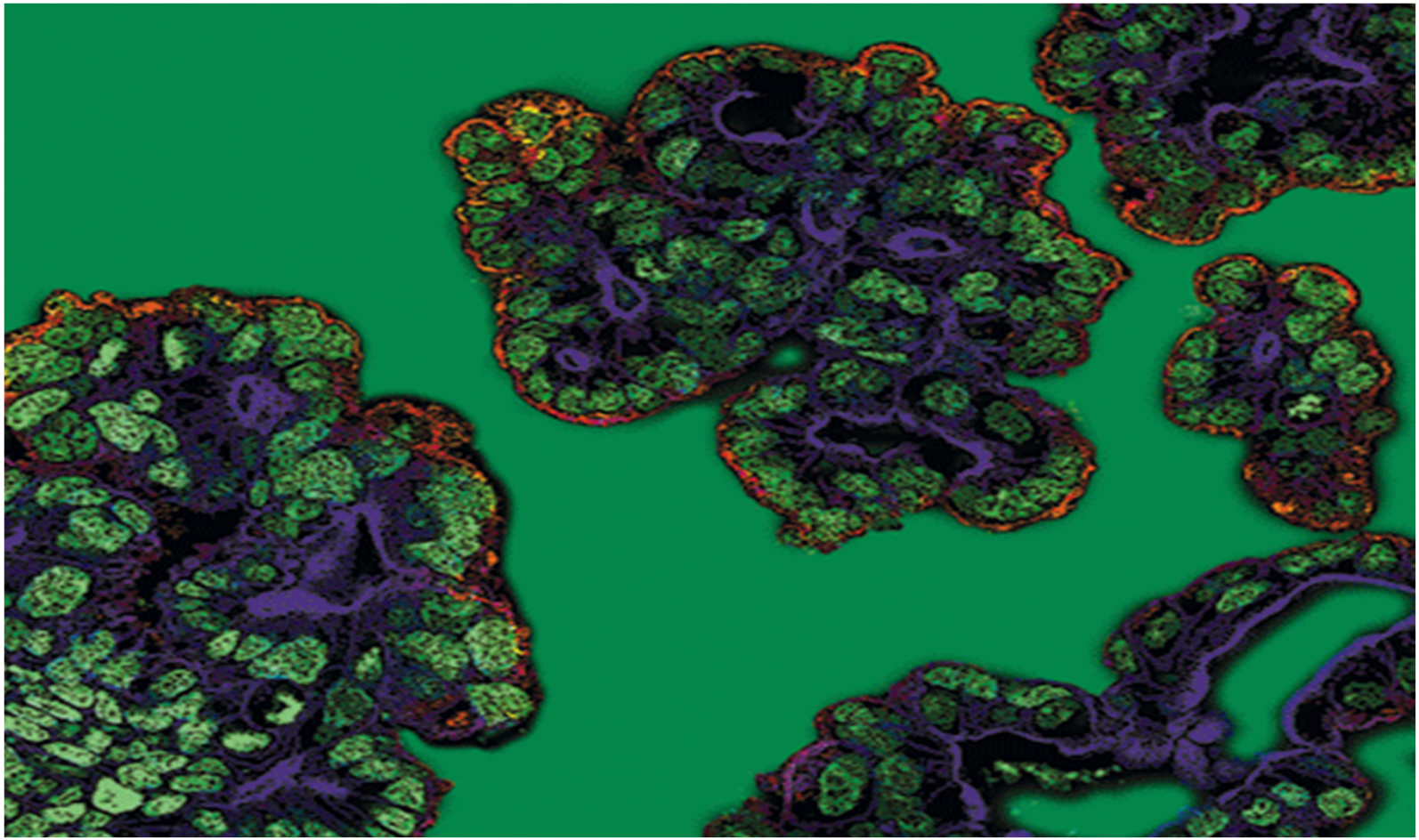
CRISPR-Cas9 and Genome Editing



Cancer Avatars: Engineering Tumor Xenografts That More Accurately Reflect the Molecular Pathway Disruptions of Human Cancers



CRISPR-Cas9–based Genome Editing to Recreate Human Tumor Organoid Models



From: Nature Medicine (2015) 21 (3) Cover

Rethinking Clinical Trial Design

Rethinking Clinical Trial Design

traditional

- randomized trials (RCTs)
- observational trials

new

- stratified trials
- adaptive trials
- basket trials

Will (Can) the Randomized Clinical Trial Design Remain Viable in an Era of Molecular Profiling and Identification of Disease Subtypes?

- Rx responder (Rx^+) and non-responder (Rx^-) subpopulations
- "one-size-fits all" trials must be larger to attain statistically significant difference between responder (Rx^+) and non-responder (Rx)
- continued inefficient and wasteful Rx use post-approval without ability to identify Rx^- non-responder patients
- exposure of non-responder Rx^- subpopulation(s) to potential toxicity risk

Stratified Trials

- molecular profiling of patients to ID drug target positive (T^+) versus T-negative (T^-) cohorts
- enroll only T^+ patients into the trials
- regulatory Rx approval and labeling only for use in T^+ patients
- obligate need for “companion diagnostic” test to profile patients before Rx can be prescribed

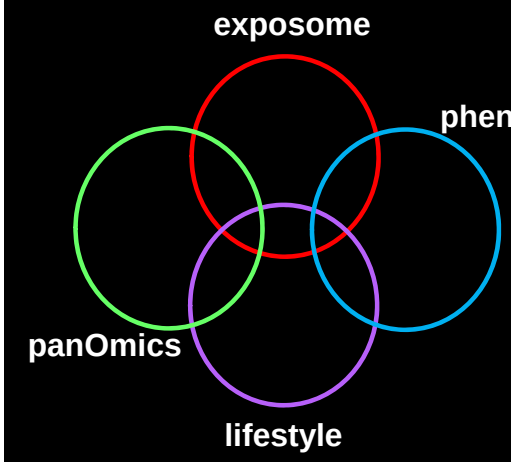
Healthcare Information Systems

Improving Healthcare Using Data

- better data on where money is spent and the results (outcomes)
- many MDs don't often know (or care) about the cost of recommended actions
- evidence-based tracking of waste, error and failure to adopt best practices
- informed patients
  - greater awareness and access of patients/families to information on treatment options and performance outcomes of different providers

The Progressive Evolution Healthcare as an Information-Intensive Enterprise

Information-Based Services for Increased Precision in Managing Risk in Healthcare



data curation and analysis

risk identification and mitigation + decision-support tools

- earlier detection of disease
- rational Rx
- monitoring of health status
- predisposition risk
- risk pre-emption

profiling

analysis

better informed decisions

The Progressive Evolution Healthcare as an Information-Intensive Enterprise

Big Data

- scale
  - V5: volume, variety, velocity, validity and value
- security
  - data privacy and compliance with different national requirements
- speed
  - real time collection
- superior decisions
  - improved outcomes and lower cost

Persistent Challenges Before Major Innovations in Research and Treatments Become Available

Demographics and the (Global) Cancer Burden

Unsustainable Costs and Need for Greater Focus on Quality-of-Life

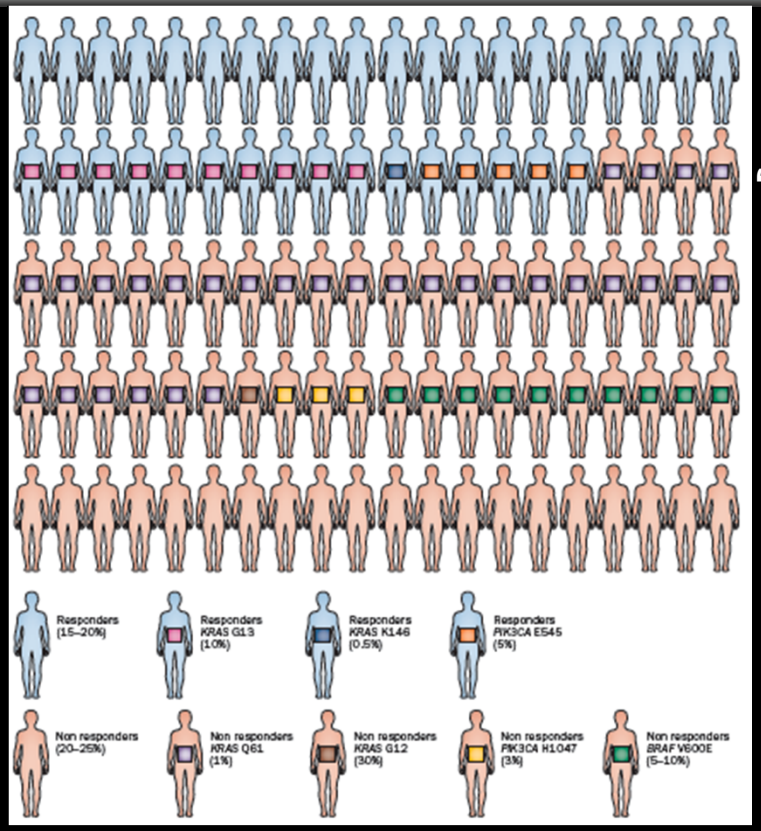
Are Oncologists' Financial Incentives Aligned with Quality Care?

Treatment At All Costs: How Far Should Treatment Go?

"Why do they put nails in coffin lids?
To stop oncologists having one last try….."

C. Chatfield
Prospect July 2012, p.16

Molecular Diagnostics and Identification of Responder/Non-Responder Patients for Rational Rx



Frequencies of Molecular Alterations in CRC and Responsiveness to Cetuximab or Panitumumab

From: M. Martini et al. (2012) Nature Rev. Clin. Oncol.

"The problem with all these tests, soon I'll have nothing (treatments) I can offer my patients"

"Eminent Oncologist" (journal's designation) Drug Discovery World. Spring 2011, p. 61.

Dangerous Arrogance?

**"The problem with all these tests,
soon I'll have nothing (treatments)
I can offer my patients."**

**Eminent Oncologist
(journal's designation)
Drug Discovery World, Spring 2011, p.61**

So is it better to go ahead and prescribe Rx of no value?
- ethics?, malpractice?
- financial incentives?

Are Oncologists Financial Incentives Misaligned with Optimum Treatment?

- uncritical payer acceptance of high cost of new oncology drugs (US)
  - $50K-120K/year
- estimated 80% annual income for community oncologists tied to Rx use
- no incentives to select less expensive Rx or palliative care
- physician/payer refuge in slow pace of change in SOC guidelines to incorporate obligate molecular diagnostic profiling for Rx selection
- unacceptable levels of use of new Rx regimen(s) in last two weeks of life

Reform in Current Oncology Drug Prescribing

- create new financial rewards to limit use of expensive drugs (particularly I.V.) and increased use of end-of-life conversations/palliative care recommendations
- uncouple relationship between physician prescribing patterns and income
- new compensation and incentive schemes for clinical actions and services that enhance/maintain QOL and reflect patient/family preferences

Choosing Wisely®

An initiative of the ABIM Foundation

American Society of Clinical Oncology

ASCO

American Society of Clinical Oncology

Five Things Physicians and Patients Should Question - 2013

http://www.asco.org/sites/www.asco.org/files/asco_choosing_wisely_top_five_list_2013.pdf

Palliative Care:
Treatment With No Longer a Curative Intent

Economic (Payors) and Evidence-Based Pressure for Increased Use of Palliation versus Repeated Aggressive Cycles of Different Rx Without Clinical Benefit and Major Impact on QOL

Palliative Cancer Treatment

- reduce or eliminate symptoms and complications
- non-curative intervention
- greater emphasis on quality-of-life (QOL)

Factors Linked to Survival Benefit of Palliative Care in Cancer Patients

- limit futile Rx and impact of QOL and cost
- limit repeated testing and hospitalizations
- reduction of physical symptoms due to disease progression
  - pain, nausea, CV complications
- reduction of psychological symptoms
  - anxiety, depression, impaired cognition
- active engagement and education of patients and family members on value

Approaching Death: Care At End of Life

Dying with Dignity

New Expectations for the Level of Intervention(s) in Late Stage Terminal Illness

Dying with Dignity

disease-related concerns

- pain and physical impairments
- cognitive and communication deficits

psychological and spiritual well being

- emotional functioning
- acceptance of disease
- at peace for death
- concern for surviving family members

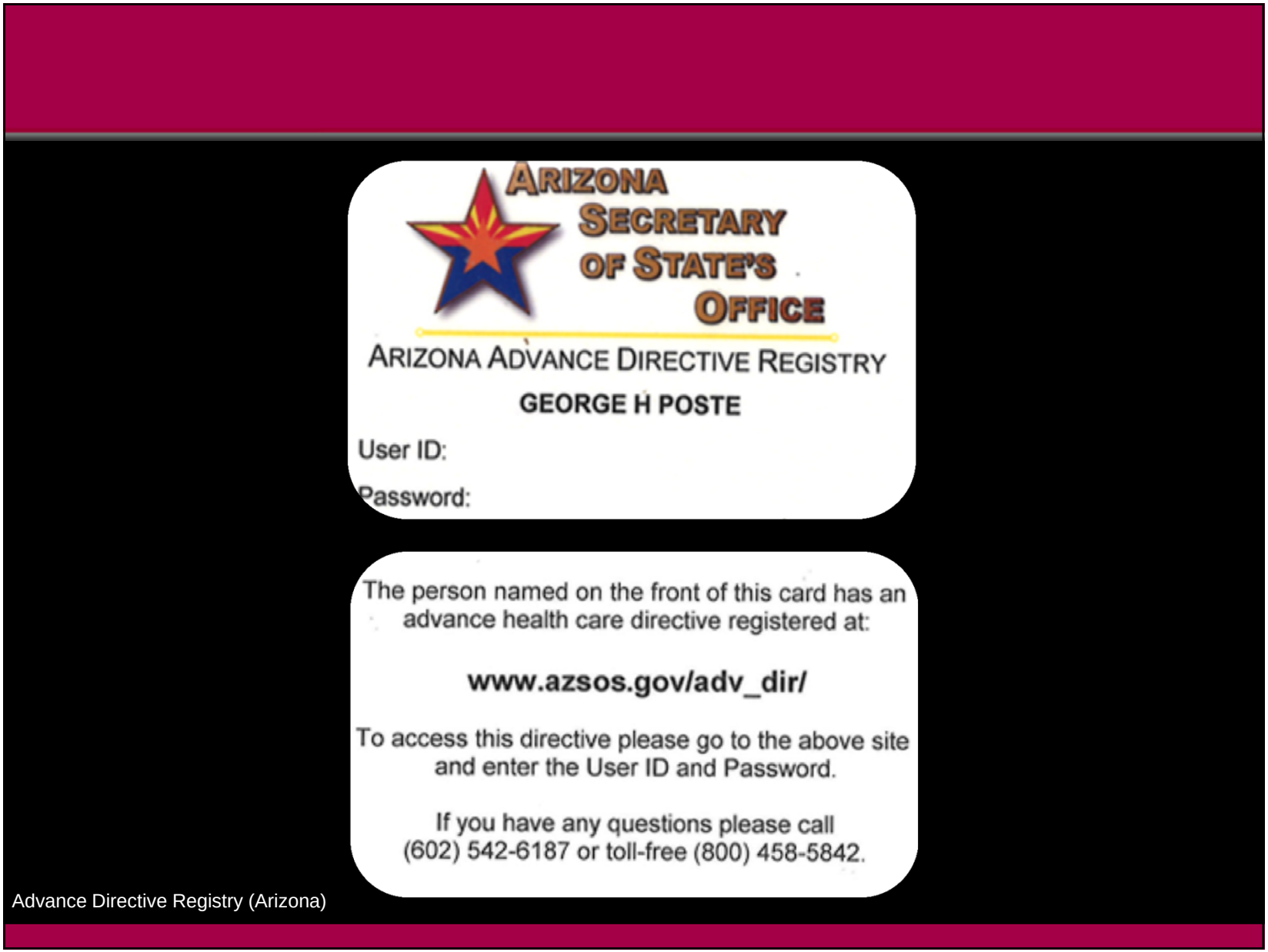
Dying with Dignity

autonomy, competency and decision-making

- performance status
- clarity of patient preferences in advanced directive
- power of health attorney in place
- provider and/or family pressures for actions against patients stated desire
- end-of-life (EOL) decisions explained to patients and family in timely fashion

Advance Directives

- discussions of death and dying largely avoided in patient management
- fewer than half cancer patients who died in 2011 had documented preferences
  - end-of-life care, resuscitation
  - durable power of attorney for health decisions
- typically only discussed in last 30 days of life or even less
- less than 15% ambulatory patients with advanced cancer have advanced directives
- see J.H. Von Roden (2013) JCO, 31, 663



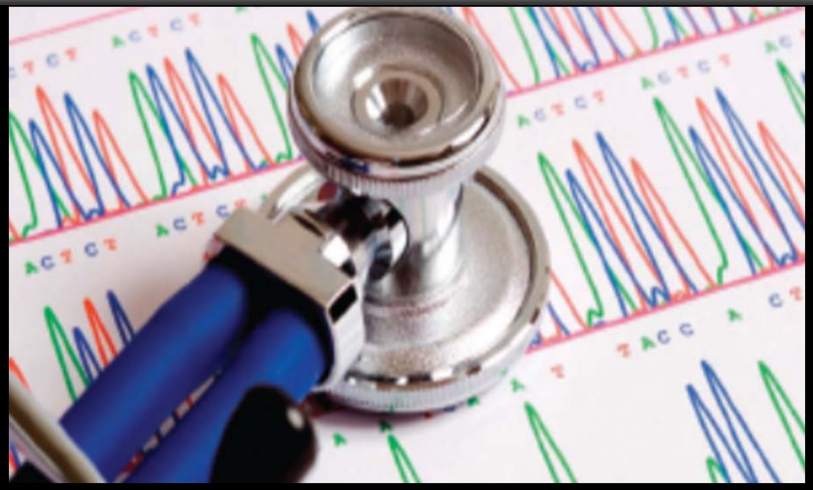
Advance Directive Registry (Arizona)

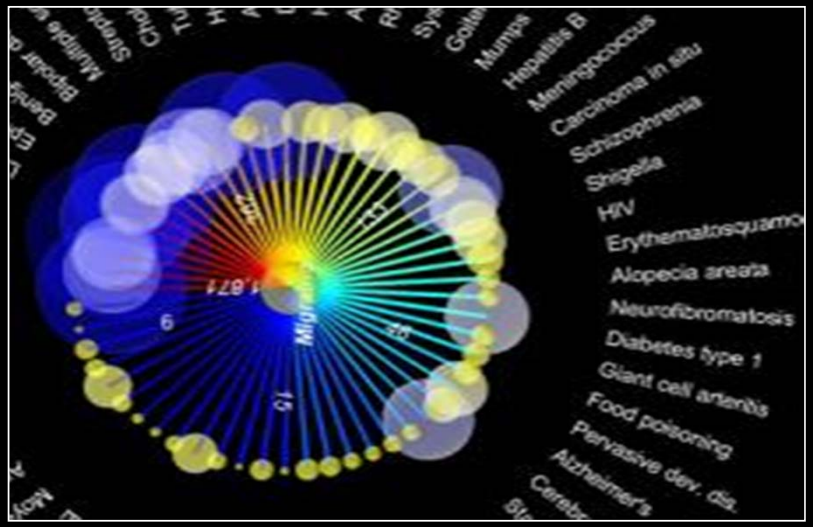
End-of-Life Care

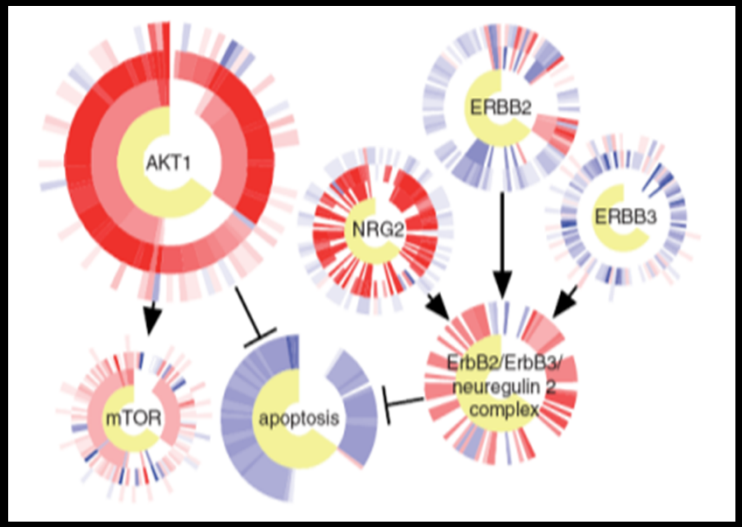
Assisted Death:
the most perplexing issue in medical ethics, law and religious discourse

Major Education and Competency Gaps in the Translation and Clinical Adoption of Molecular Profiling for Precision Medicine

The Growing Education and Knowledge Gaps in Comprehension of Molecular Medicine Concepts Among Healthcare Professionals



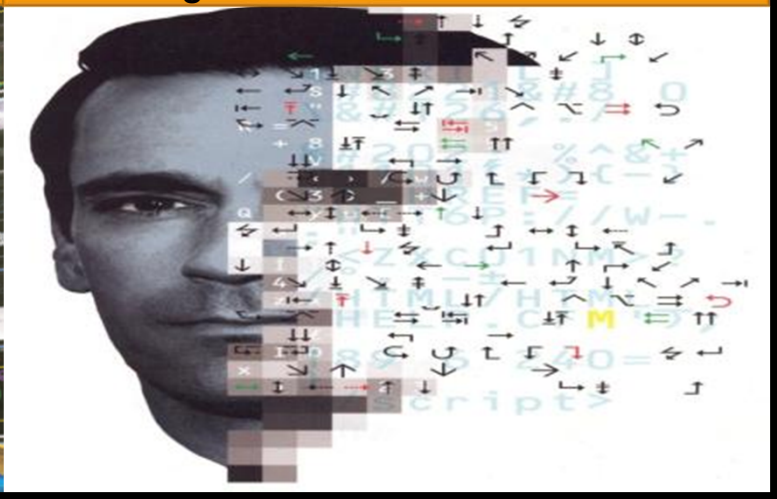


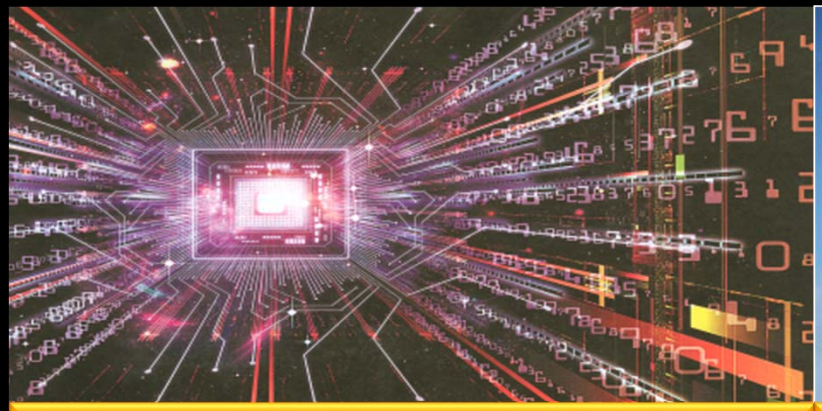


Technology Acceleration and Convergence: The Escalating Challenge for Professional Competency, Decision-Support and Future Education Curricula

Data Deluge

Cognitive Bandwidth Limits





Automated Analytics and Decision Support

Facile Formats for Actionable Decisions

New Skills and Professional Specialties in an Era of Molecular Medicine

- clinical specialists with panOmics expertise
  - molecular genetics, pathology, genetic counseling
  - “molecular medicine 101” and CME for healthcare professionals
- informaticians
  - informatics (analytics)
  - database design and curation for optimized data flows for clinical decisions
  - data customization and visualization for different end-users
- empowered patients social media and medical apps.

Optimizing Palliative Care: A Team-Based Process

- physicians, nurse specialists, other HCPs
- physical therapists
- expertise in psychological support and spiritual care
- home-based care services
- ‘the family unit’

BioIT World 2011 - by **Sorena Nadaf, M.S. M.MI**
Director - Translational Informatics, CIO

Healthcare 2030: An Information-Based, Science-Based Enterprise

- molecular profiling is routine and enables earlier detection and/or prevention of disease
- computerized decision tools dominate, monitoring, diagnosis and treatment selection
- healthcare services integrated from cradle to grave and facile use of information to mitigate disease risk/optimize treatment compliance
- patients are empowered but are required to take greater responsibility for sustaining their health
- most healthcare services not exclusively MD (physician)-centric but provided by multi-disciplinary teams
- new business models and incentives for care delivery: the wellness premium

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