ASU Complex Adaptive Systems
ARIZONA STATE UNIVERSITY

BIO 302:
APRIL 1, 2014

WEEK 11, LECTURE 1:
SYSTEMIC TREATMENT OF CANCER:
DRUGS, BIOLOGICALS AND IMMUNOTHERAPIES

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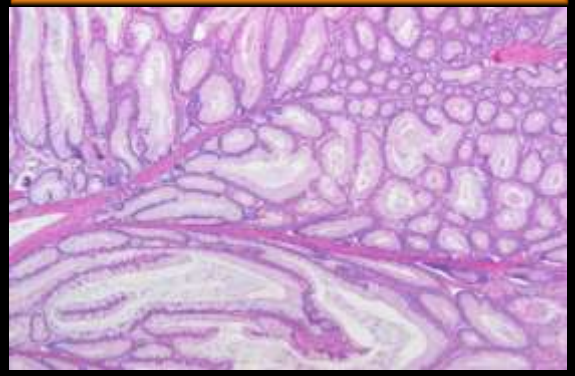
Cancer as a Complex Adaptive System: Emergent Phenomena and Tumor Progression (System State Shifts)

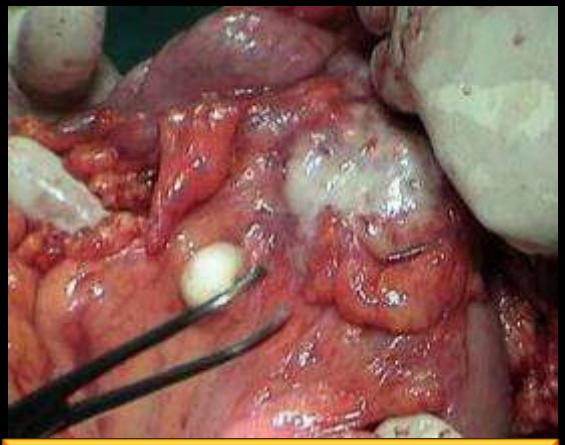
Escape From Controls for Normal Tissue Architecture



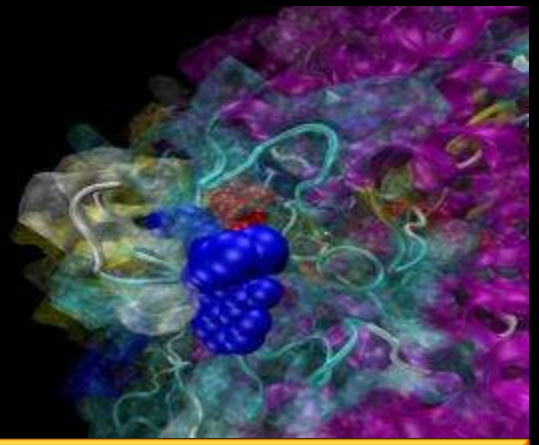
Genome Instability and Emergence of Clonal Variants

Evasion of Detection/Destruction by Host Immune System

Use of Host Systems to Promote Progression



Invasion and Metastasis



Emergence of Drug-Resistant Clones

Implications of Cancer as a Complex Adaptive System for the Development of More Effective Diagnostics and Therapies

Weeks 11 and 14

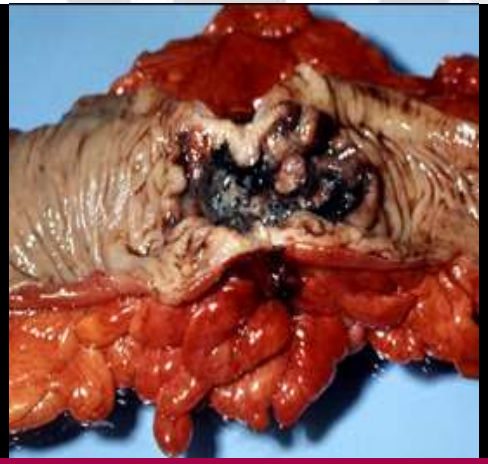
- current treatment practices and limitations
- confronting the tumor cell heterogeneity problem
- emerging treatment strategies and the particular promise of immunotherapy
- the time, cost and technical challenges of development of new diagnostics and therapies to achieve FDA approval and marketing

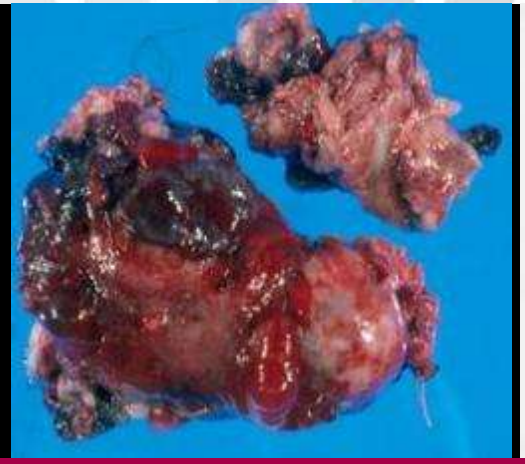
Meeting The Cancer Challenge

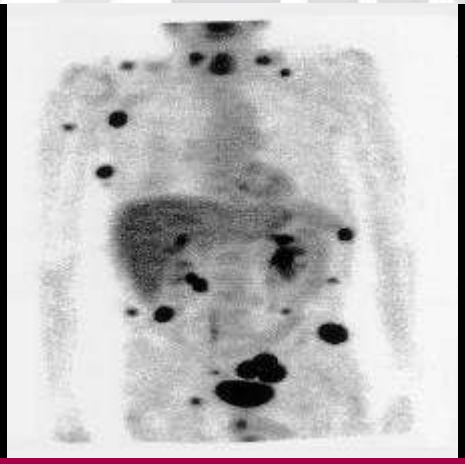
The Ideal

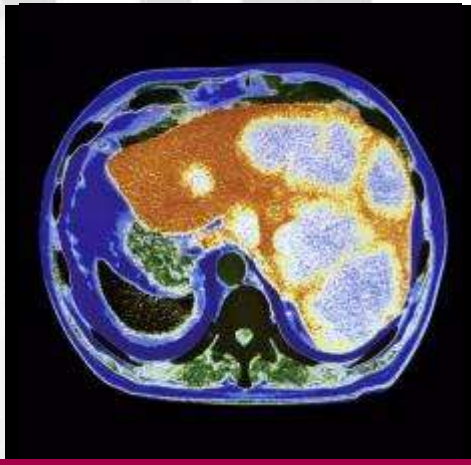
- prevention
- cure

US Cancer Deaths 2012









Progress in Reducing Disease Burden
Mortality 1970 – 2008*

• cerebrovascular disease	• 74%	↓
• heart disease	• 63%	↓
• accidents	• 33%	↓
• cancer	• 12%	↓ (largely since 1990)

*S. Soneji et al (2014) JCO 32, 444

US Cancer Prevalence Estimates 2010 and 2020

Site	# People (thousands) 2010	2020	% change
Breast	3461	4538	31
Prostate	2311	3265	41
Colorectal	1216	1517	25
Melanoma	1225	1714	40
Lymphoma	639	812	27
Uterus	588	672	15
Bladder	514	629	22
Lung	374	457	22
Kidney	308	426	38
Leukemia	263	240	29
All Sites	13,772	18,071	32

From: A.B. Mariotto et al. (2011) J. Nat. Cancer Inst. 103, 117

The Thin Line Between Hype and Hope

- celebrity populism and delusional belief that more money will solve everything

versus

- fundamental reassessment of why therapeutic success for metastatic solid tumors remains so elusive
- implications of cancer as a complex adaptive system
- clonal heterogeneity and evolutionary clonal dynamics during tumor progression as the major obstacle to effective therapy

The Principal Challenges in Cancer Treatment

- tumor cell heterogeneity and Rx effectiveness
- disseminated disease (metastasis)
- drug-resistance (intrinsic or acquired)
- treatment toxicities and complex clinical care
- treatment cost
- quality-of-life (in-treatment; post-treatment)
- timing of recommendation for palliative care versus interventional care
- end-of-life care

Ensuring That the Patient's Voice is Heard

- what is my prognosis?
- what are the treatment options?
- what is the toxicity of the treatment?
- how will treatment impact my quality-of-life?
- what is likely course of my disease if I don't take treatment?

Aspirations for Improved Cancer Diagnosis and Treatment

Better Approaches to Early Stage Disease

- earlier detection of subclinical disease
- earlier detection of clinical disease before metastasis occurs (surgery = cure)
- better methods to assess metastatic risk from primary tumor to evaluate need for exposure to adjuvant therapy
  - can tumors with metastatic potential be identified versus tumors that have low/no probability of metastatic spread?

Aspirations for Improved Cancer Diagnosis and Treatment

Improved Outcomes

- maximize the efficacy and safety of Rx interventions against advanced (metastatic) disease
  - circumventing variability in tumor cell clones to the selected Rx regimen (overcoming the heterogeneity problem)
  - dynamic monitoring of changing clonal dynamics during treatment for faster detection of drug-resistant clones

Clinical Standard-of-Care (SOC) Guidelines

- adjuvant therapy
  - (post-surgery/radiation)
- neoadjuvant therapy
  - (pre-surgery/radiation)
- palliative therapy
  - (non-curative Rx for advanced disease)
- end-of-life care
  - (last six months but more typically last month: ICU, hospice, in-home)

Therapeutics

- small (heterocyclic) molecules <1500 Daltons Mw
- biologicals
  - recombinant (r)proteins, antibodies (natural/engineered)
  - nucleic acids: antisense, miRNAs, aptamers
- gene therapy (and delivery vectors)
- vaccines
  - prophylactic, therapeutic
- novel drug formulations/drug delivery systems

FDA-Approved Anti-Cancer Drugs

DNA Damaging Agents

Generic Name	Trade Name	Approved Indication
altretamine	Hexalen	ovarian cancer
arsenic trioxide	Trisenox	certain leukemias
bendamustine	Treanda	multiple cancers
bleomycin sulfate	Blenoxane	certain lymphomas, squamous cell and testicular cancers
busulfan	Myleran, Busulfex	certain leukemias
carboplatin	Paraplatin, Paraplat	breast, lung and ovarian cancers
carmustine	BiCNU	brain tumors, certain lymphomas
chlorambucil	Leukeran	multiple cancers
cisplatin	Platinol-AQ	multiple cancers
cyclophosphamide	Cytoxan	multiple cancers
dacarbazine	DTIC-Dome	melanoma, certain brain cancers
dactinomycin	Cosmegen	multiple cancers
daunorubicin, daunomycin	Cerubidine	certain leukemias
doxorubicin hydrochloride	Adriamycin PFS, AdriamycinRDF	multiple cancers
epirubicin hydrochloride	Ellence	certain leukemias, breast and stomach cancers

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SUPPLEMENTAL MATERIALS

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Categories of Cancer Therapeutics

- expected to know different modes of action of anti-cancer drugs
- long lists of drugs posted on blackboard for reference only for those who want more information (no exam question on individual drugs)

Categories of Anti-Cancer Therapeutics

Cytotoxic Chemotherapy

- DNA synthesis inhibitors (anti-metabolites)
- DNA damaging agents
- cytoskeleton (microtubule) modifying agents

Hormonal Agents

- hormones (agonists)
- hormone blockers (antagonists)

Categories of Anti-Cancer Therapeutics

Targeted Chemotherapy

- small molecule cell signaling inhibitors
  - largely tyrosine kinase inhibitors (TKi's)
- angiogenesis inhibitors
  - again largely kinase inhibitors
- monoclonal antibodies
  - block growth factor receptors on tumor cells
  - induce tumor cell death
  - promote destruction by host defense cells (antibody dependent cellular cytotoxicity: ADCC)

Categories of Anti-Cancer Therapeutics

Epigenetic Modulators

- modify histones and gene expression

Proteasome Inhibitors

Cell Differentiation Agents

- induce terminal differentiation to non-replicating state (leukemias/lymphomas but not solid tumors to date)

Categories of Anti-Cancer Therapeutics

Immunotherapeutics

- anti-tumor monoclonal antibodies
- immune checkpoint modulators (overcome tumor-induced suppression of host defenses)
- immunomodulators (stimulate immune system)
- anti-cancer vaccines (prophylactic or therapeutic)

Inherited Cancer Risk

Cancer	Syndrome	Associated Gene
Leukemias and lymphomas	Ataxia telangiectasia	*ATM*
All cancers	Bloom syndrome	*BLM*
Breast, ovarian, pancreatic, and prostate cancers	Breast-ovarian cancer syndrome	*BRCA1, BRCA2*
Breast, thyroid and endometrial cancers	Cowden syndrome	*PTEN*
Colorectal cancer	Familial adenomatous polyposis (FAP)	*APC*
Melanoma	Familial atypical multiple mole–melanoma syndrome (FAMM)	*CDKN2A*
Retinal cancer	Familial retinoblastoma	*RB1*
Leukemia	Fanconi's anemia	*FACC, FACA*
Colorectal cancer	Hereditary nonpolyposis colorectal cancer/Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*
Pancreatic cancer	Hereditary pancreatitis/familial pancreatitis	*PRSS1, SPINK1*
Leukemias, breast, brain and soft tissue cancers	Li-Fraumeni	*TP53*
Pancreatic cancers, pituitary adenomas, benign skin and fat tumors	Multiple endocrine neoplasia 1	*MEN1*
Thyroid cancer, pheochromacytoma	Multiple endocrine neoplasia 2	*RET, NTRK1*
Pancreatic, liver, lung, breast, ovarian, uterine and testicular cancers	Peutz–Jeghers syndrome	*STK11/LKB1*
Tumors of the spinal cord, cerebellum, retina, adrenals, kidneys	von Hippel-Lindau syndrome	*VHL*
Kidney cancer	Wilms' tumor	*WT1*
Skin cancer	Xeroderma pigmentosum	*XPD, XPB, XPA*

AACR Cancer Progress Report 2013, pg31

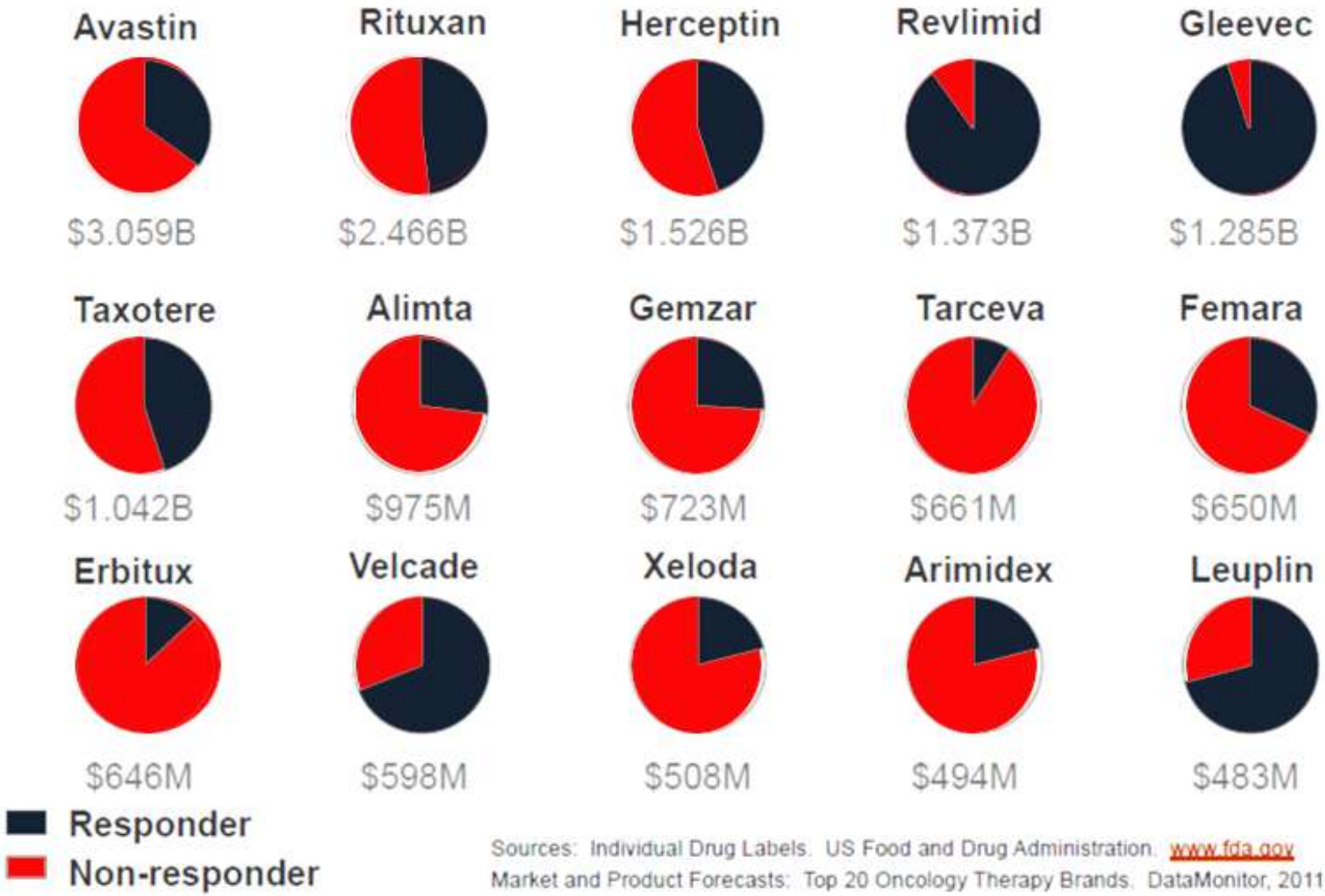
Screening and Cancer Prevention in Individuals with Inherited Germline Mutations in Cancer Predisposing Genes

- surgical removal of ‘at risk’ organ in high risk patients
  - mastectomy, oophorectomy (BRCA-1/2 carriers)
  - stomach (CDH1 mutation)
  - thyroid (RET mutation)
  - colon (APC mutation)
- detection of early cancer and surgical resection
  - elevated catecholamines (phaeochromocytoma)
  - elevated calcitonin (thyroid cancer)

The Current Status of Cancer Care

Flying Blind:
One-Size-Fits All Rx Approaches to Complex Multigenic Diseases

Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly



Sources: Individual Drug Labels. US Food and Drug Administration. www.fda.gov
Market and Product Forecasts: Top 20 Oncology Therapy Brands. DataMonitor, 2011.

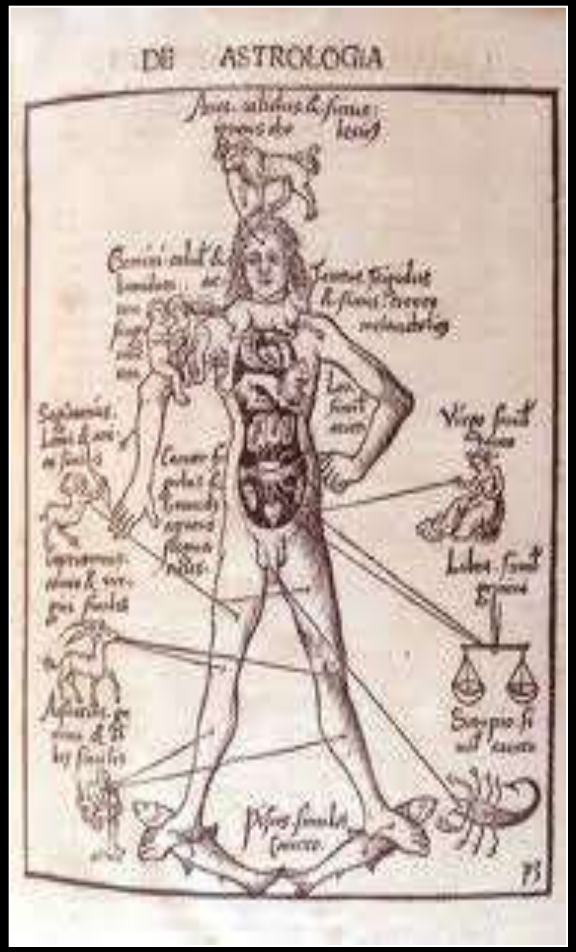
Ignoring The Obvious in Clinical Practice

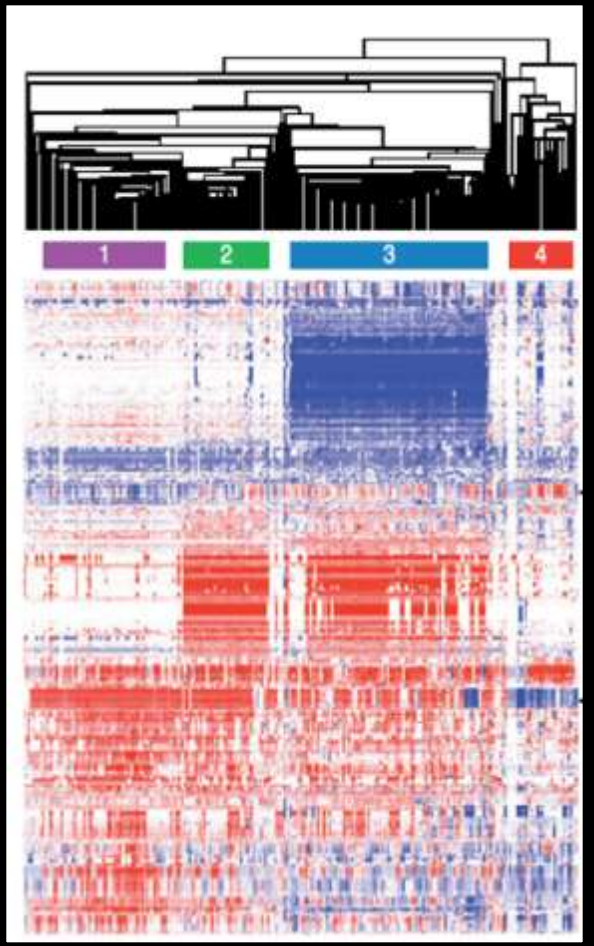
- diseases are not uniform
- patients are not uniform
- a “one-size fits all” Rx approach cannot continue
- ignores known variation in disease progression and therapeutic responses

- inefficiency and waste caused by empirical Rx
- cost of futile therapy
- risk to patients via AE’s
- first rule of radical ethics: do no harm!

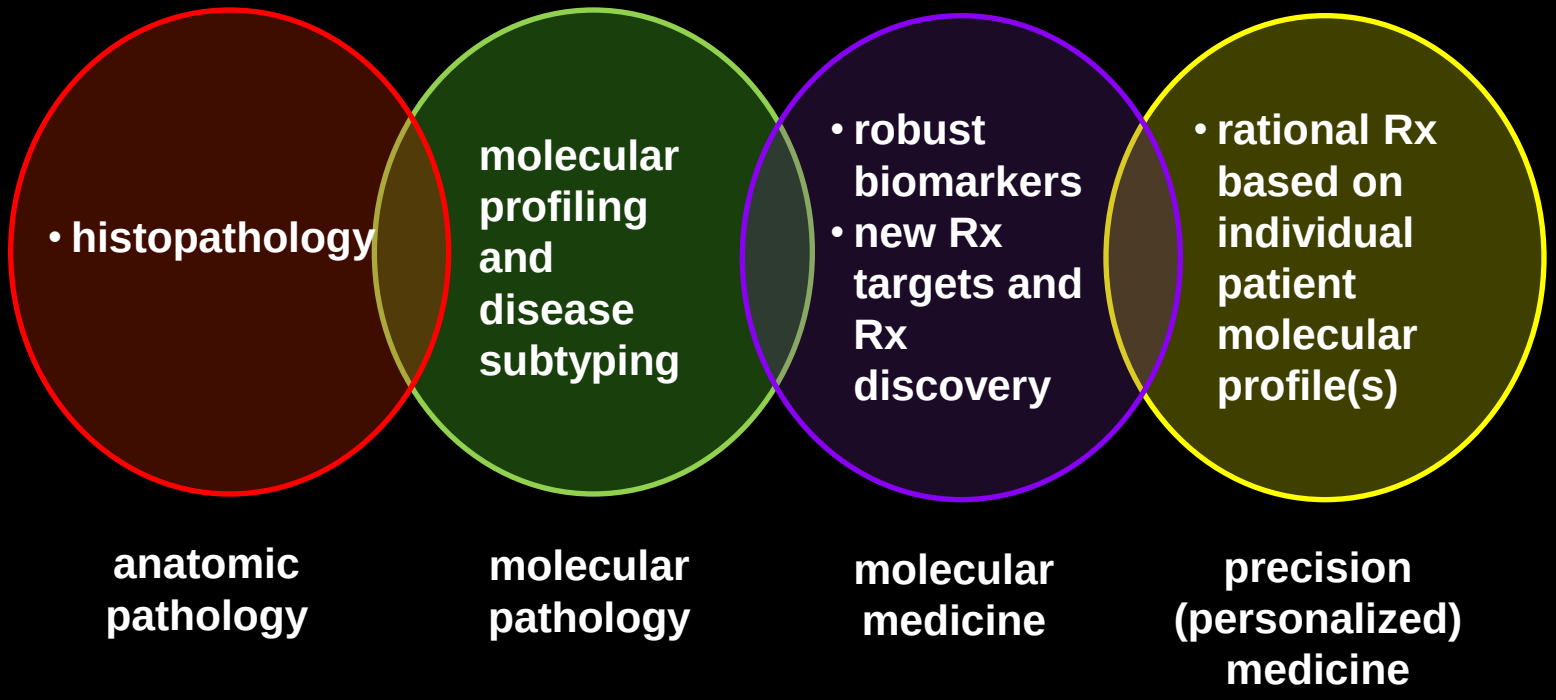
The Path to Precision (Personalized) Therapy

Medical Progress:
From Superstitions to Symptoms to Signatures

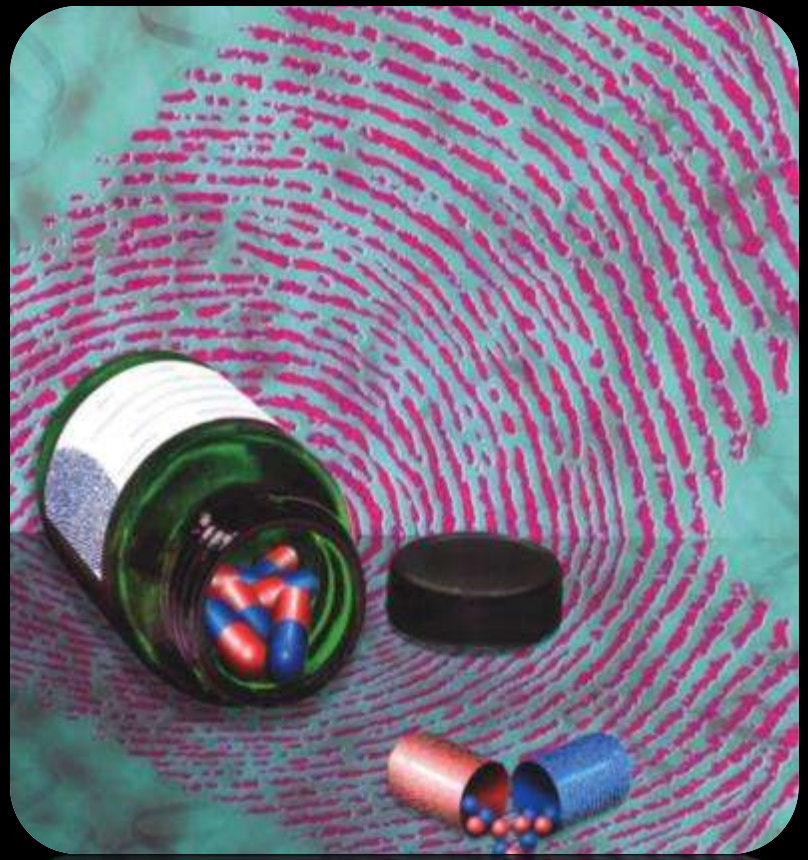




Understanding Cancer Biology and the Quest for Improvements in Cancer Care



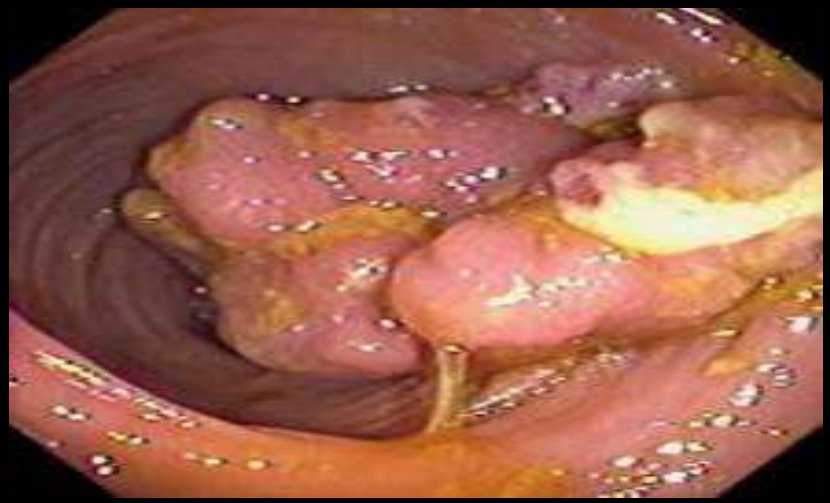
Precision Medicine

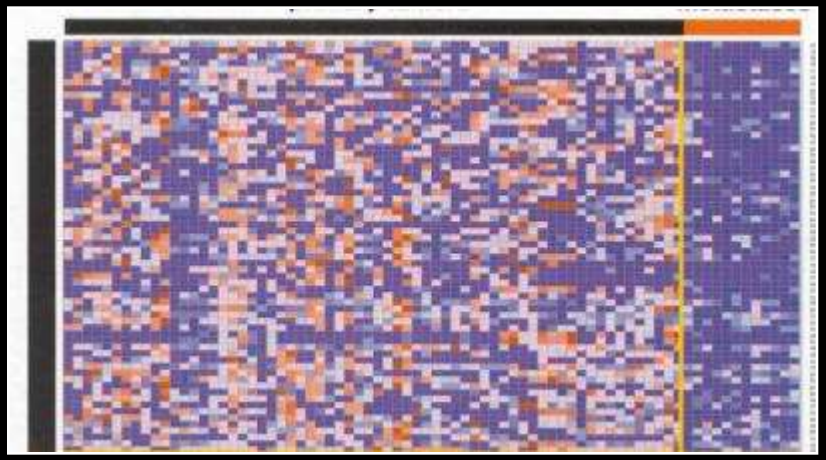


- right diagnosis and disease classification and subtyping by MDx
- right Rx for right disease subtype (efficacy)
- right Rx for right patient (efficacy and adverse event reduction)
- right dose, duration and timing (efficacy, safety and compliance)

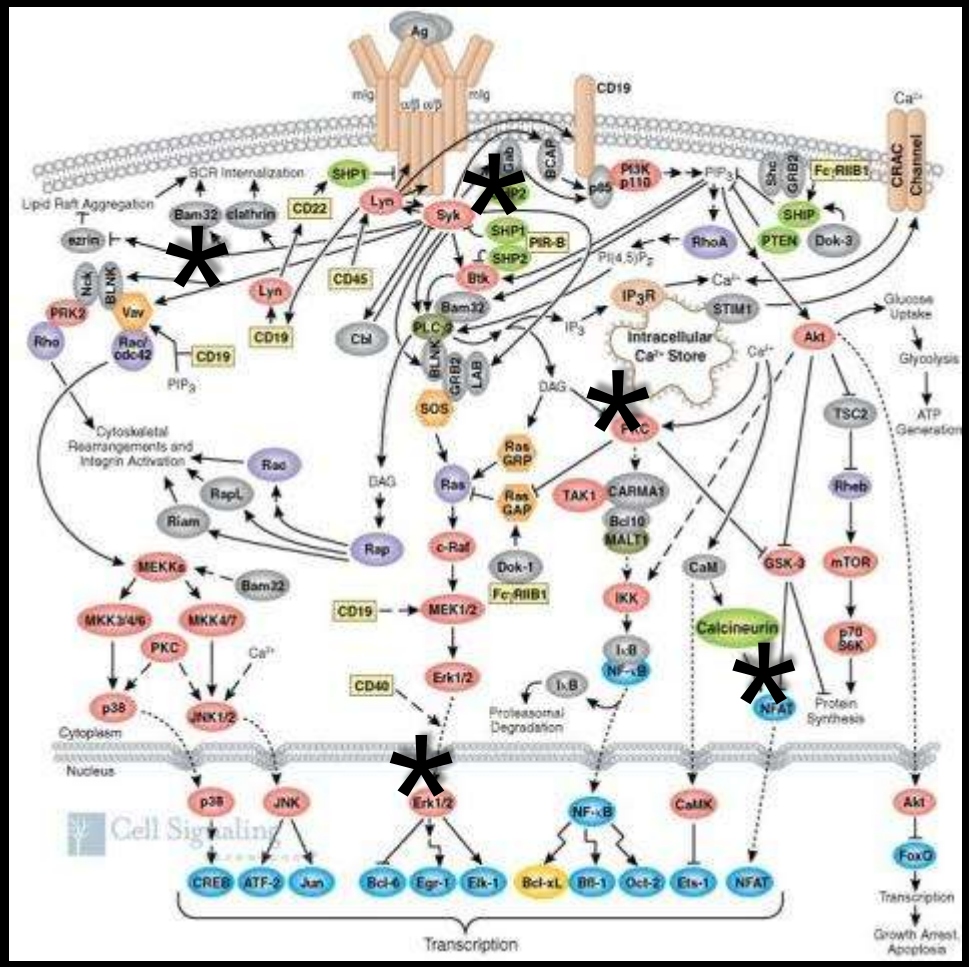
Mapping Causal Perturbations in Molecular Pathways and Networks in Disease: Defining a New Taxonomy for Disease

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

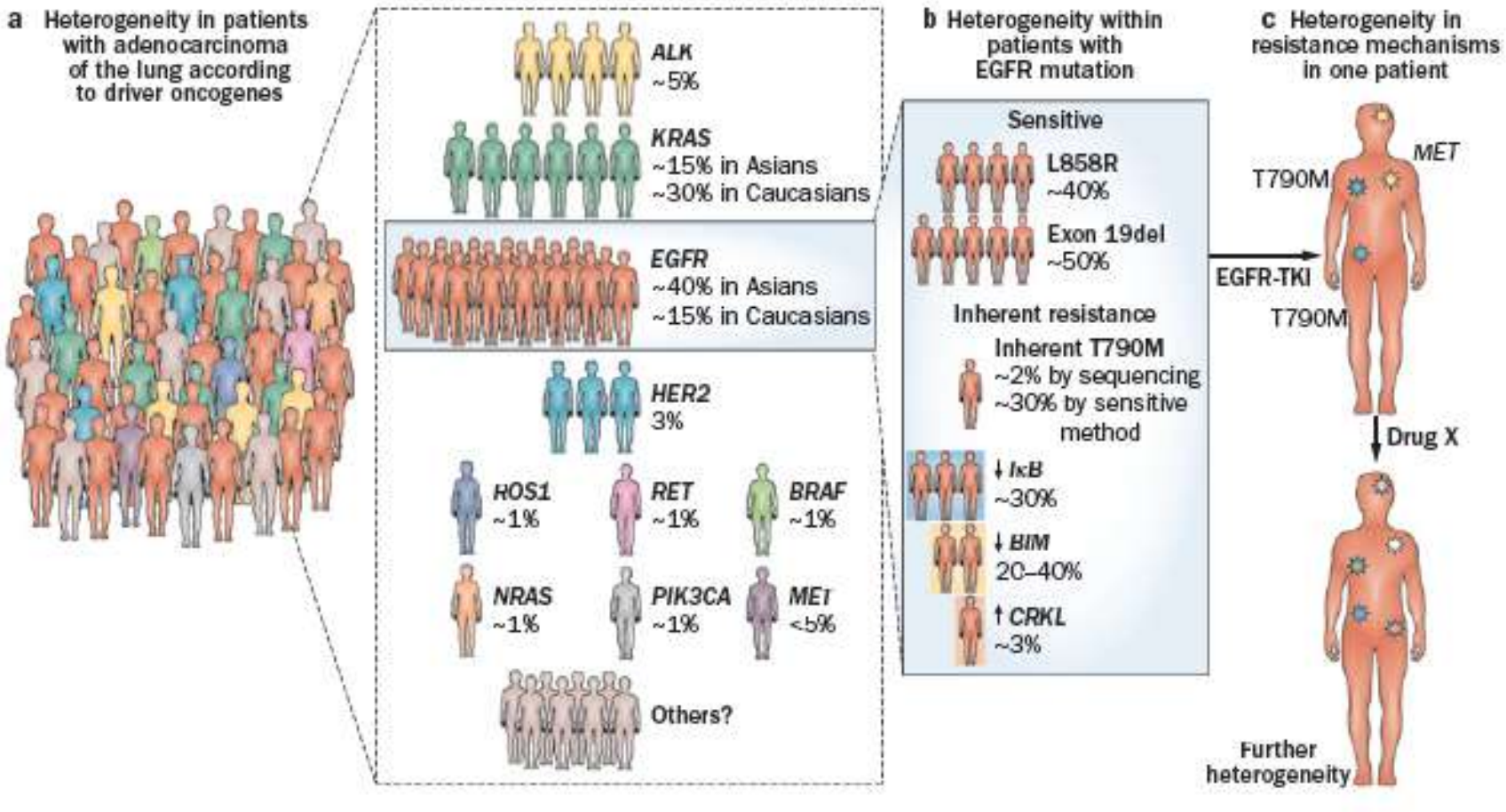




Altered Network Structure and ID of Molecular Targets for MDx and/or Rx Action

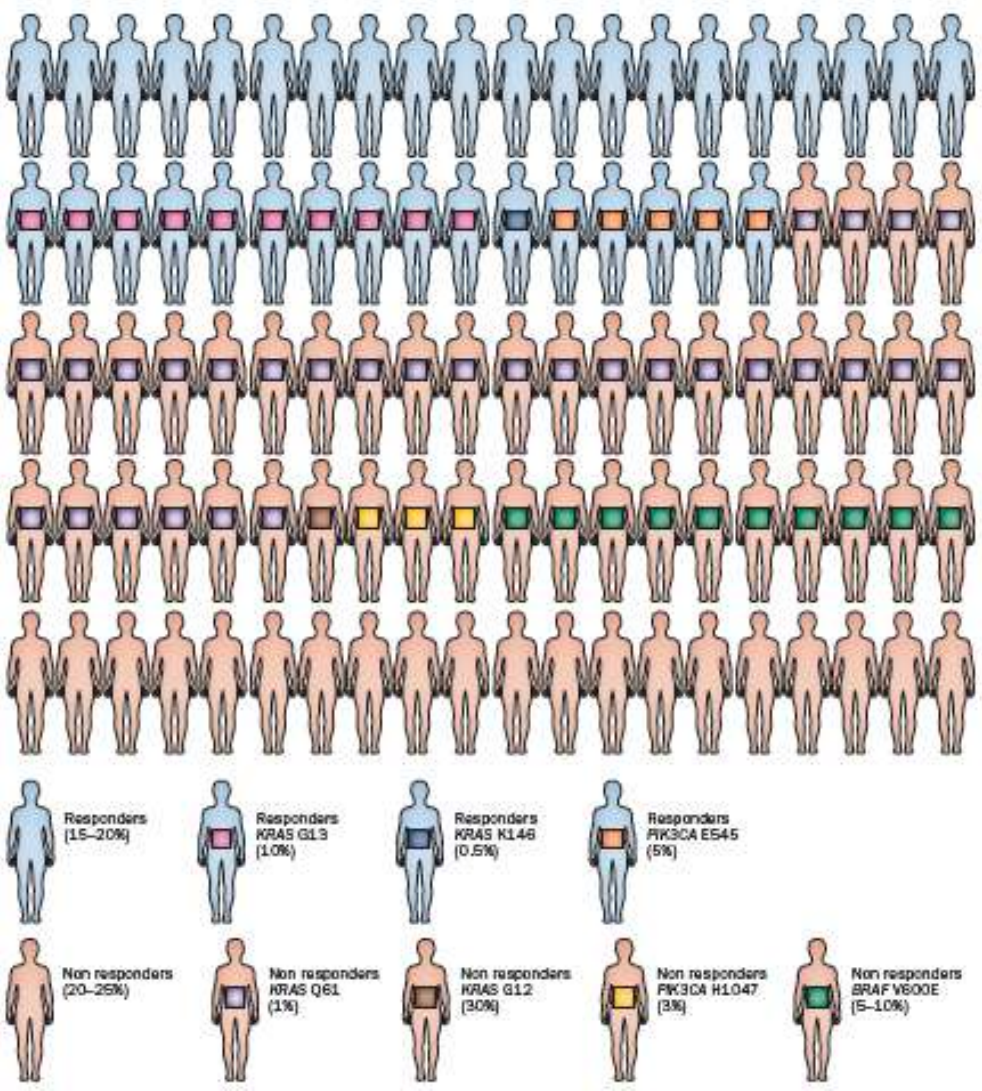


Heterogeneity of Driver Oncogenes in NSCLC



From: T. Mitsudomi et al. (2013) Nat. Rev. Clin. Oncol. 10, 235

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



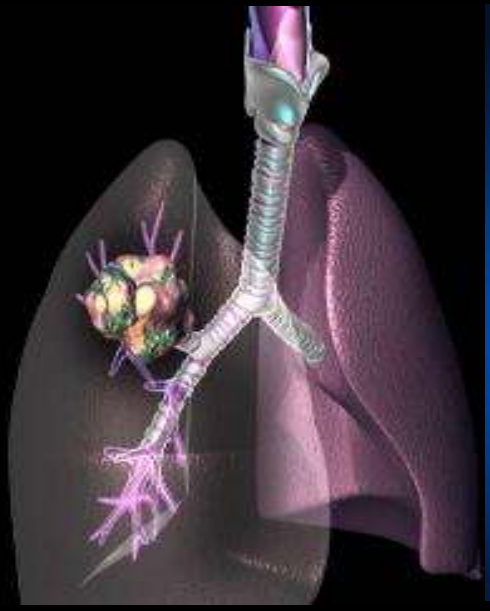
From: M. Martini et al. (2012) Nature Rev. Clin. Oncol.

Oncogene Addiction

- tumor cells become reliant on particular oncogene
- die if addictive oncogene is inhibited
- rationale for ‘targeted’ cancer therapy to selectivity inhibit the relevant oncogene

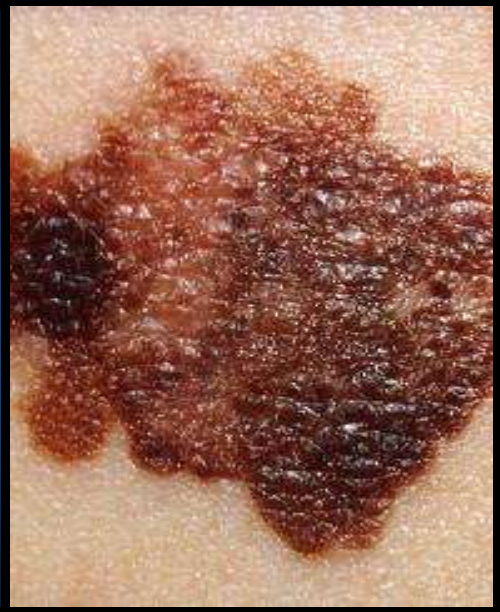
Biomarkers, Disease Subtyping and Targeted Therapy: Companion Diagnostics – the Right Rx for the Right Disease (Subtype)

Her-2+
(Herceptin)
(Perjeta)



EML4-ALK
(Xalkori)

KRAS
(Erbitux)
(Vectibix)

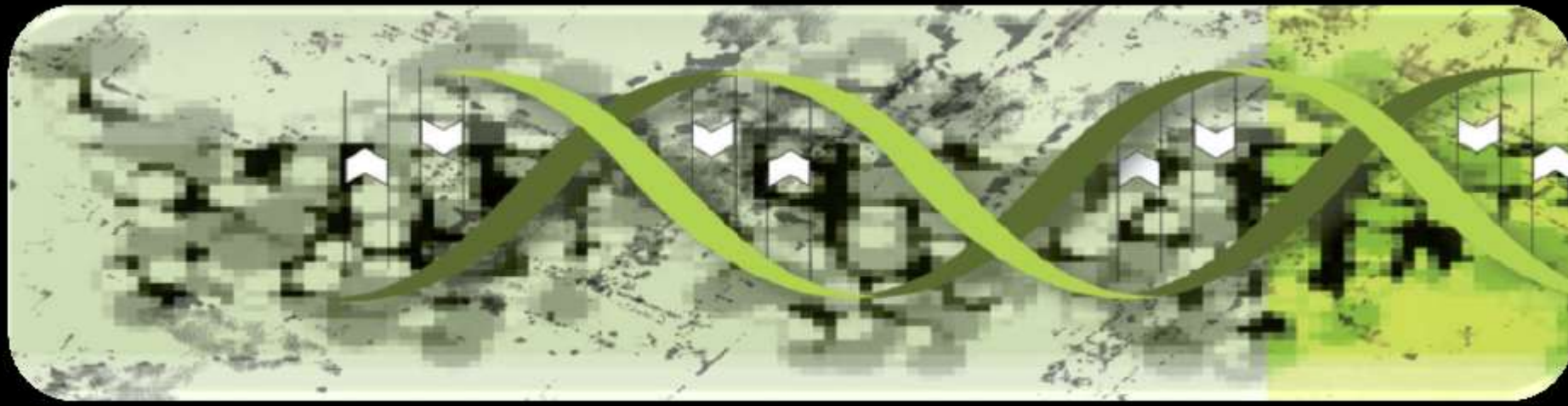


BRAF-V600
(Zelboraf)

Targeted Oncology Therapies in Molecularly Stratified Populations

Cancer	Target	Agent
Breast carcinoma	HER2 amplification	trastuzumab, lapatinib
NSCLC (adenoCA)	EGFR mutations	EGFR TKIs (erlotinib, gefitinib)
NSCLC	EML-ALK	ALK inhibitors (crizotinib)
GIST	KIT and PDGFRA mutations	Imatinib
Melanoma	BRAF-V600 mutation	BRAF inhibitor (vemurafenib)
Ewing's sarcoma	EWS-FLI translocation	anti-IGF1R mab (figitumumab)
Medulloblastoma BCC	PTCH1 or SMO mutations	SMO inhibitors (vismodegib)
Ovarian/ breast CA	BRCA1/BRCA2 mutations	PARP inhibitors (olaparib)
PRCC	MET mutations	MET TKIs (ARQ197. XL880)

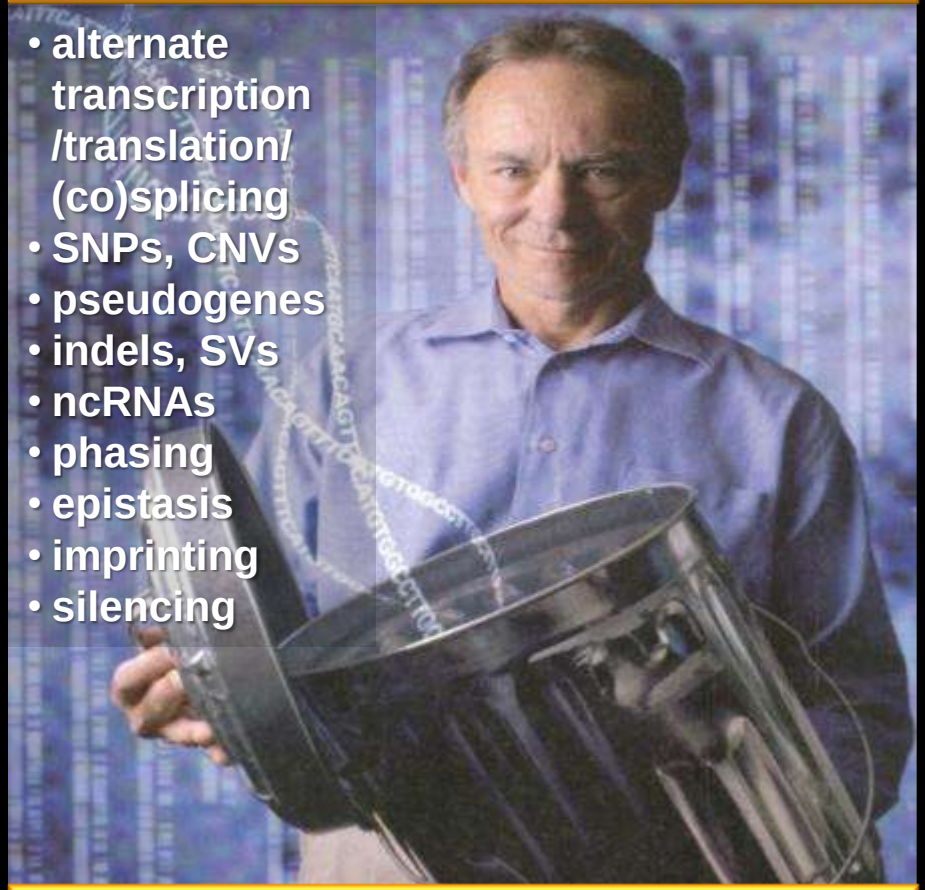
Genes For ….
The Overly Simplistic and Deterministic Dangers of a Genome-Sequence Centric Perspective



The Over-Simplified Perspective That Whole Exome-and Whole Genome-Sequencing Will Reveal the Full Etiology of Disease Pathogenesis and Transform Treatment Options

Individual Variation, Genome Complexity and the Challenge of Genotype-Phenotype Predictions

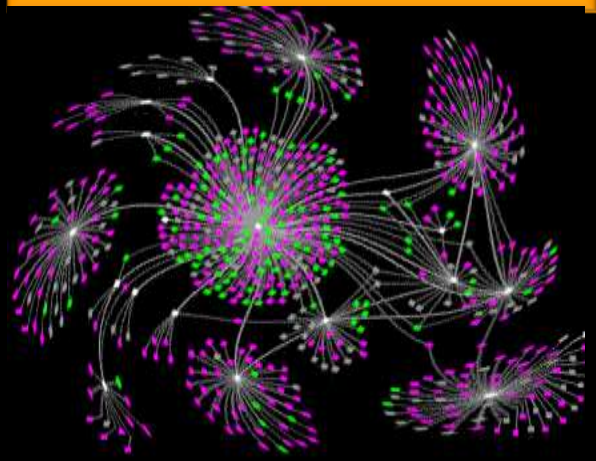
Junk No More: Pervasive Transcription



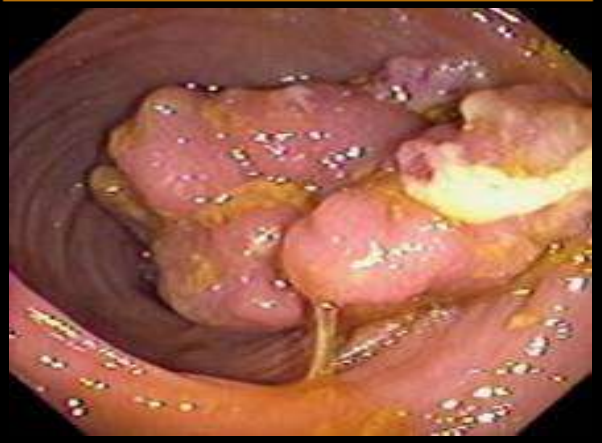
- alternate transcription /translation/ (co)splicing
- SNPs, CNVs
- pseudogenes
- indels, SVs
- ncRNAs
- phasing
- epistasis
- imprinting
- silencing

recognition of the complexity of genome organization and regulation

Cell-specific Molecular Interaction Networks



Perturbed Networks and Disease

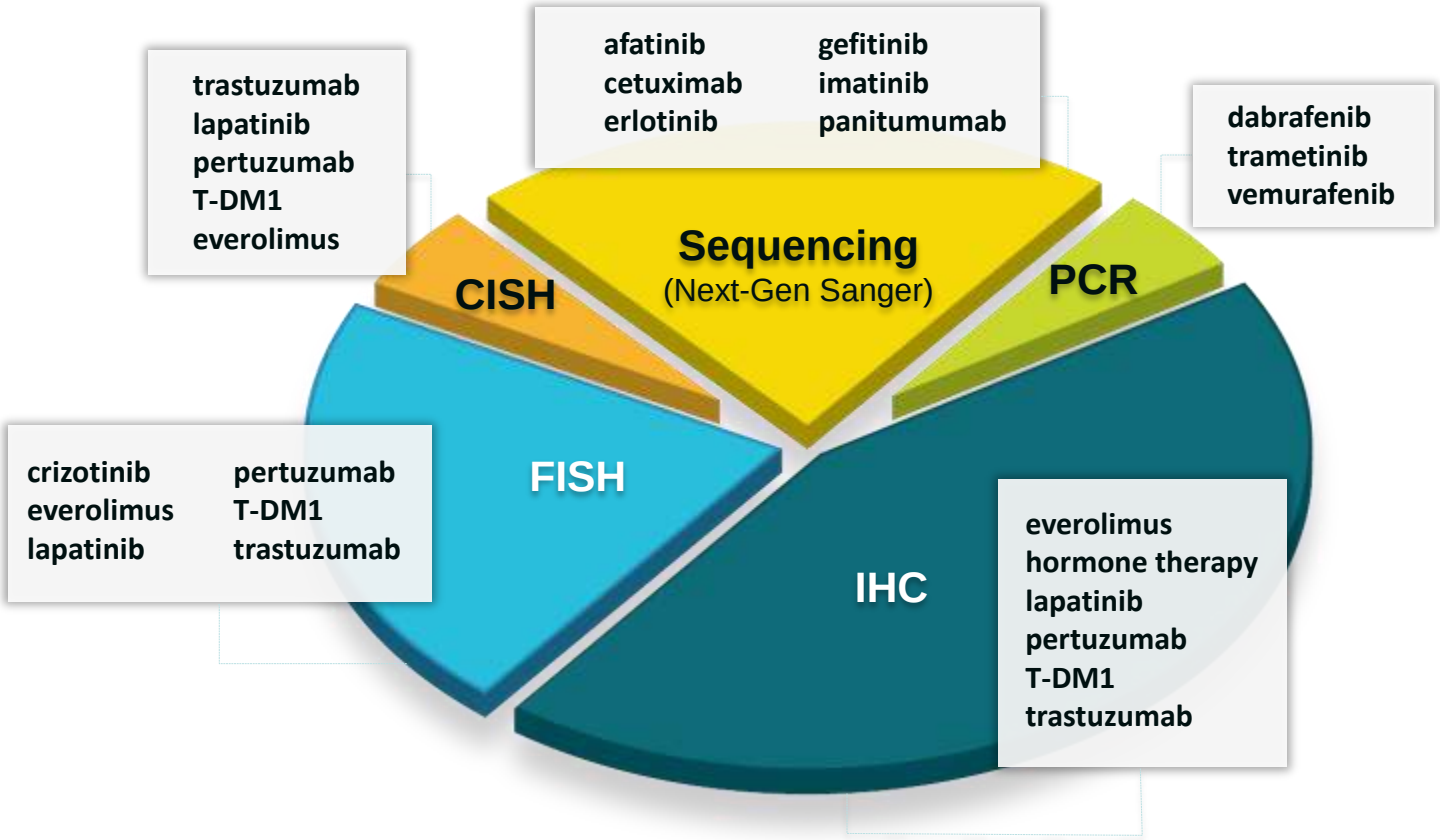


Profiling Changes in Biological Signaling Networks in Cancer: Understanding Cancer Requires a Holistic "Systems" Approach

- genome sequence data alone does not provide a sufficiently complete picture for either Dx or Rx decisions
  - need to understand cancer as a complex multi-component process

- mapping disruption in signaling pathways requires profiling of multiple aspects of both genotypic and phenotypic changes

The Need for Multi Molecular Diagnostic Platforms to Maximize the Number of Actionable Drug: Target Associations to Guide Therapeutic Decisions



FISH = fluorescent in situ hybridizaiton

CISH = chronogenic in situ hybrization

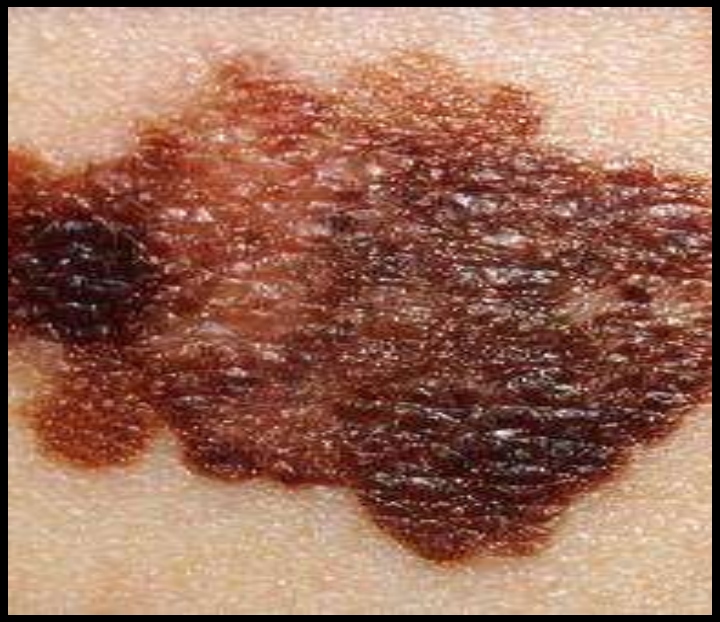
IHC = immunohistochemistry

Context:

Alteration of Rx Target in One Cancer Cell Type
May Not Always Translate to Rx Efficacy
in Cancers Arising in Different Cell Types

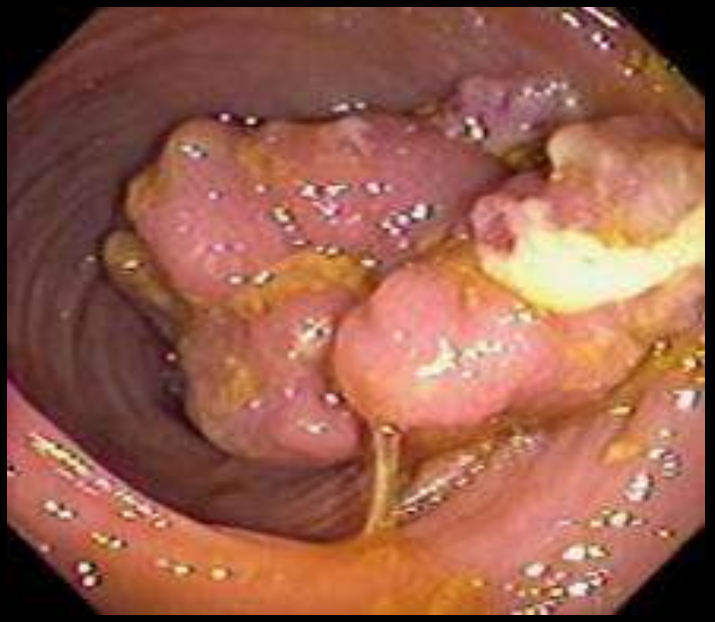
Expression of Same Mutation in Cancers Arising in Different Cell Lineages but with Different Response to Same Targeted Therapy

Melanoma
BRAF-V600



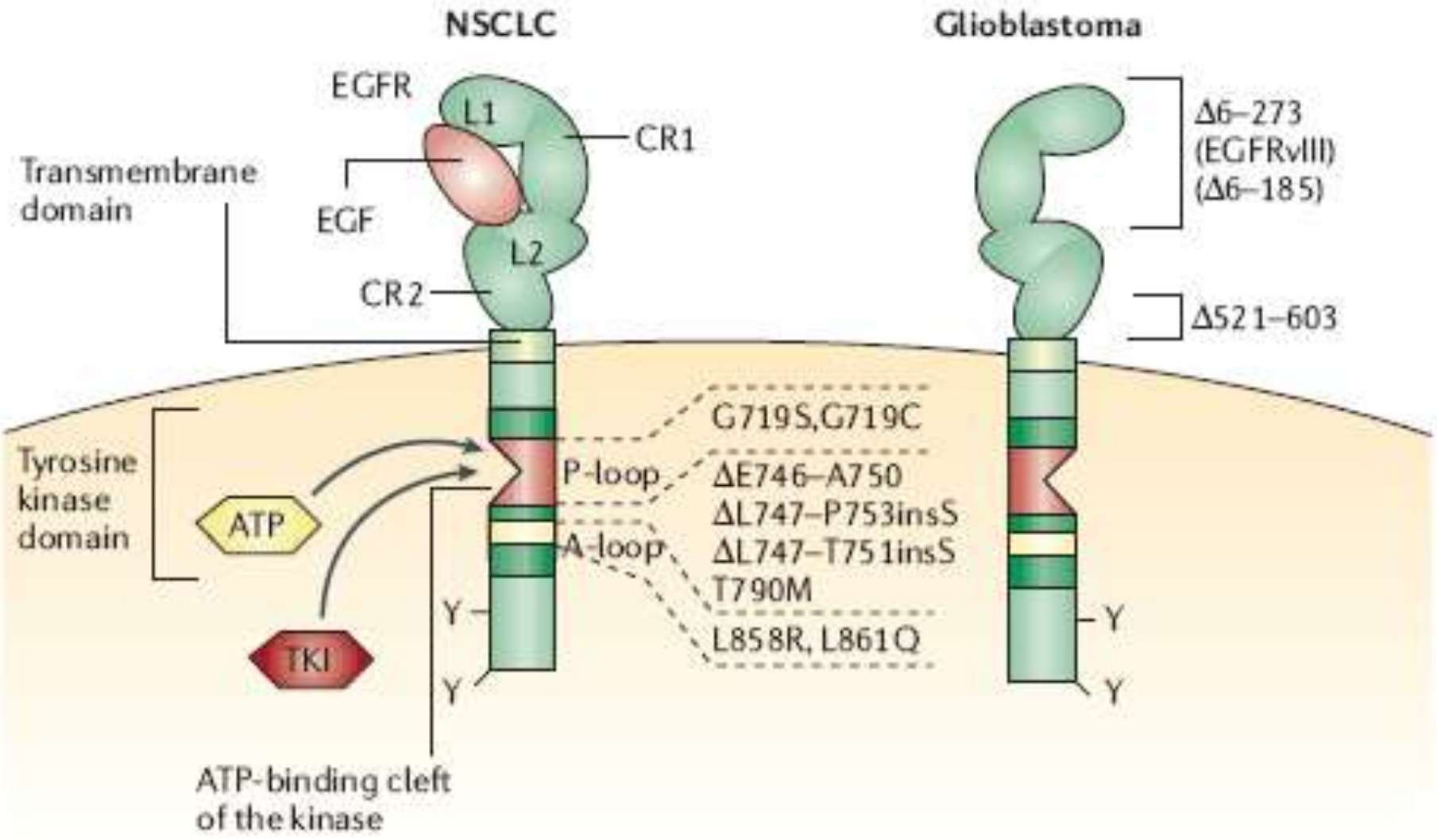
positive response
to
vemurafenib

Colorectal Cancer
BRAF-V600



10% patients carry mutation
but unresponsive to vemurafenib
due to compensatory activation
of EGFR

EGFR Mutations in Different Structural Domains



Source: Nat. Rev. Cancer 2006

Differential Sensitivity of Glioma-Versus Lung Cancer-Specific EGFR Mutations to EGFR Kinase Inhibitors

- EGFR mutations in lung cancer reside in the intracellular kinase domain
- EGFR mutations in glioblastoma multiforme (GBM) cluster in the extracellular domain
  - poor clinical results in GBM with erlotinib, gefitnib

The Three Most Dangerous Phenotypes in Tumor Cell Clones: metastasis; immunoevasion; and drug resistance

Dynamic Heterogeneity

Emergence and Adaptive Evolution of Different Tumor Clones and Subclones During Tumor Progression

Drug Resistance:
The Principal Challenge in Cancer Rx Therapy

Tumor Cell Heterogeneity: The Omnipresent and Greatest Challenge in Cancer Therapy

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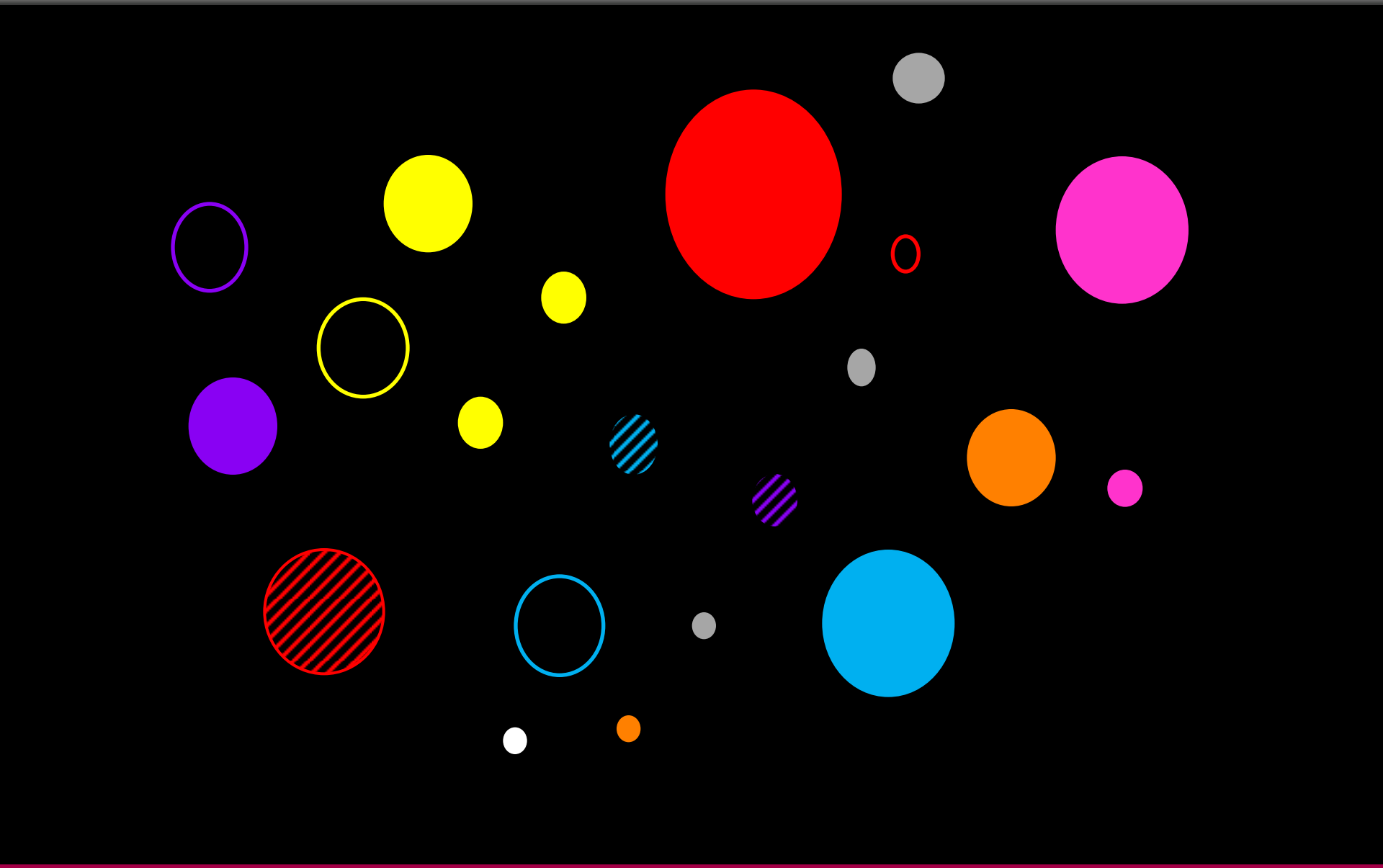
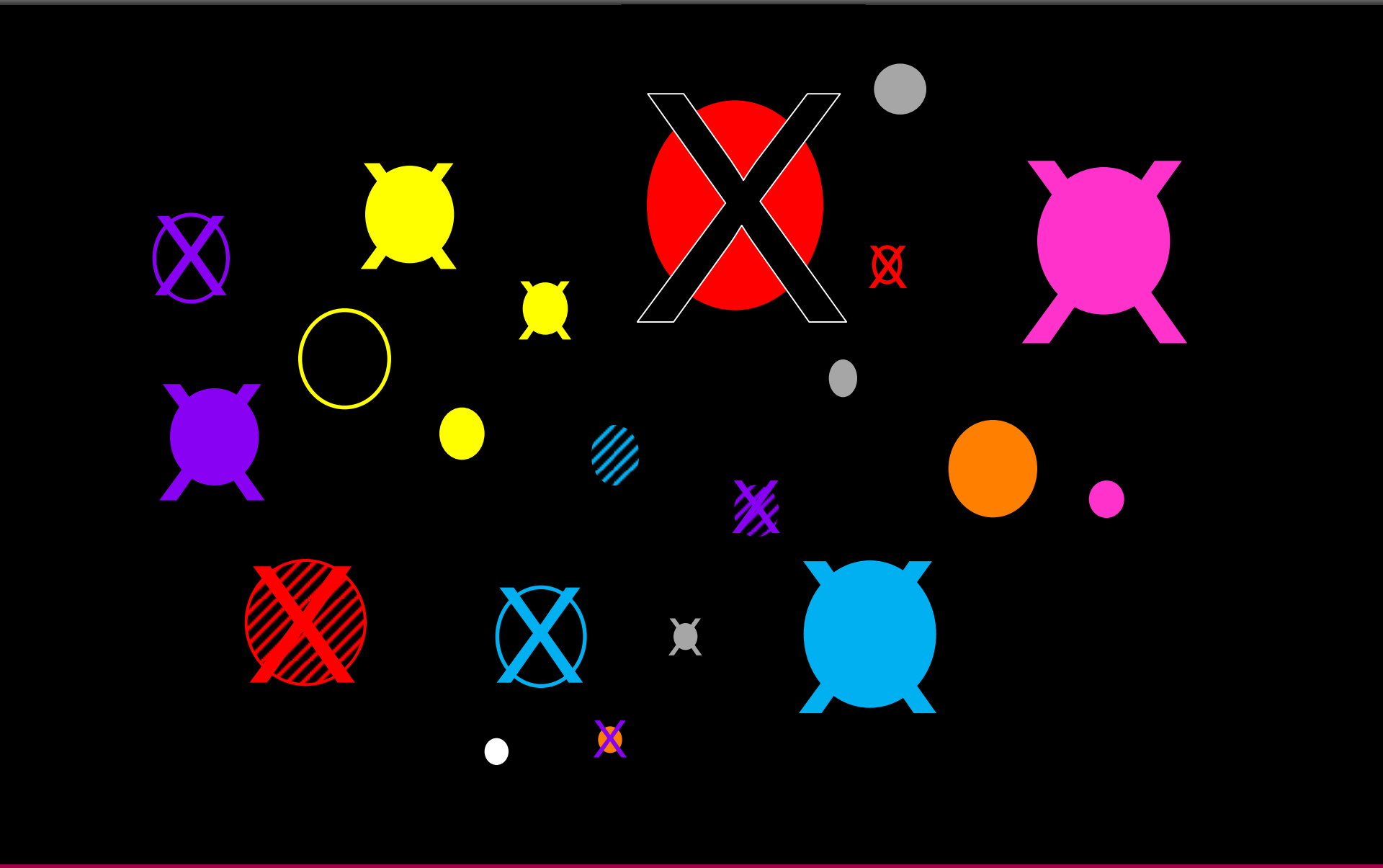
The Omnipresent and Greatest Challenge in Cancer Therapy



Tumor Cell Heterogeneity:
The Omnipresent and Greatest Challenge in Cancer Therapy



Emergence of Drug-Resistance Mutations in Tumor Progression

mutation(s) in Rx-naïve patients

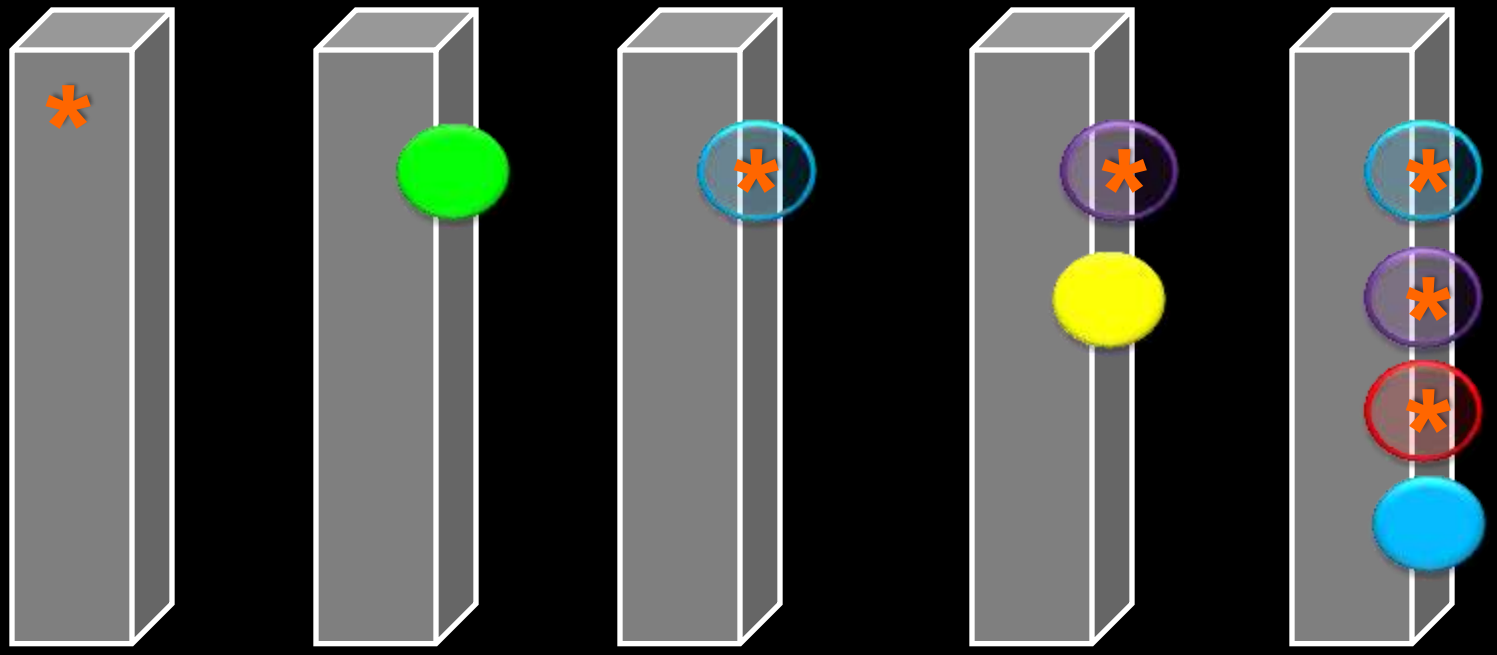
- "intrinsic resistance" to specific Rx
- exist prior to Rx

mutation(s) in Rx-treated patients

- "acquired resistance" to specific Rx
- Rx as selective pressure (cf. antibiotic resistance in bacteria)

Point Mutation$^{(M)}$-Driven Resistance to Targeted Anticancer Drugs

Evolution of Rx-Resistant Clones During Tumor Progression



Rx-sensitive

Rx-resistant

Rx-sensitive

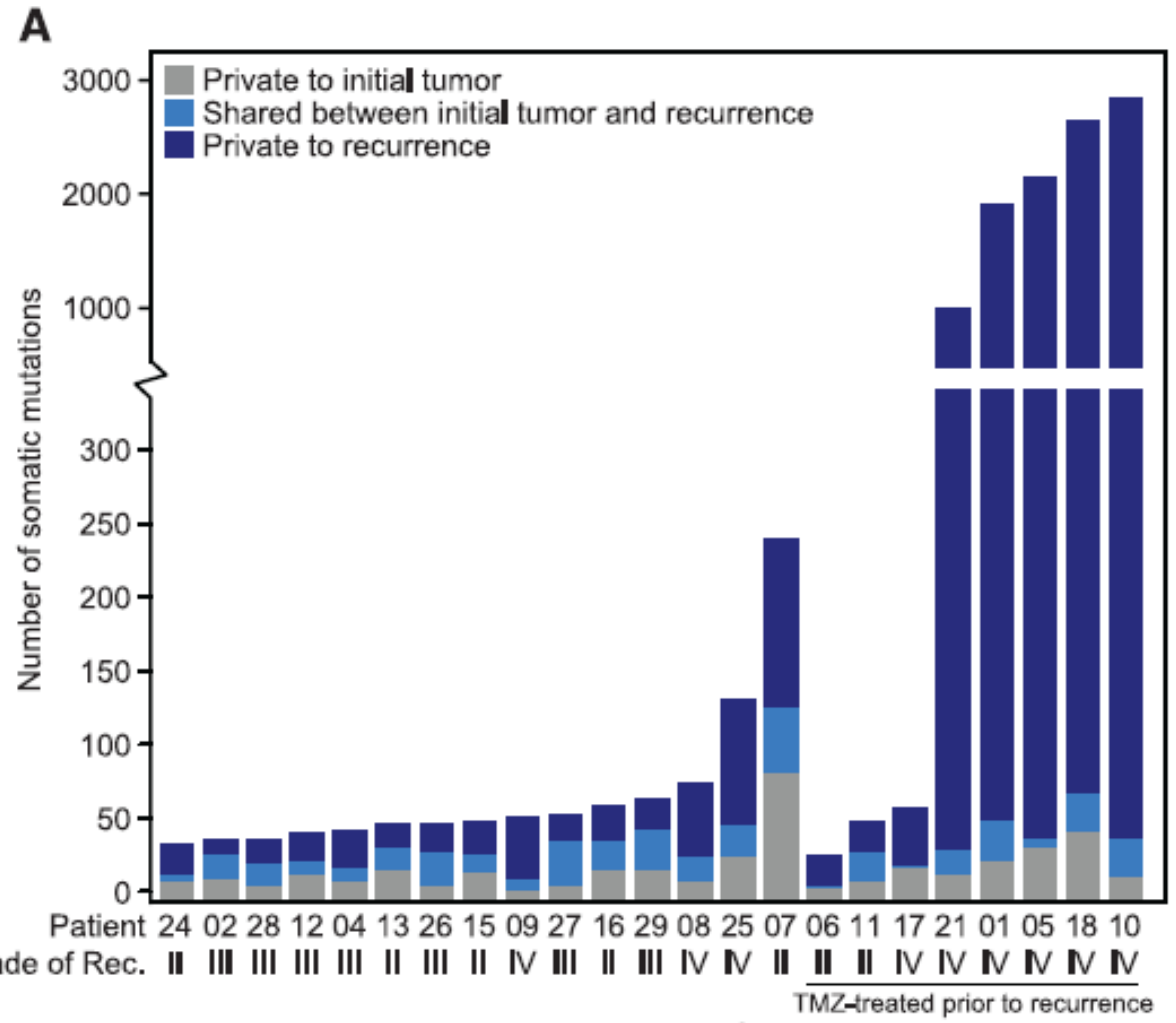
Rx-resistant

refractory resistant disease

Mutations Responsible for Acquired Resistance to Targeted Therapies

Gene	Genetic aberration	Tumor type	Acquired drug resistance
EGFR	T790M	Advanced NSCLC	Gefitinib Erlotinib
KRAS	Codon 12, 13 and 61	Colorectal cancer	Cetuximab
KIT	T670I	GIST	Imatinib
PIK3CA	NS	NSCLC	Erlotinib Gefitinib
ALK	C1156Y L1196M	NSCLC	Crizotinib
MEK1	C121S	Melanoma	Vemurafenib
BRAF	Amplification	Melanoma	Vemurafenib
NRAS	Q61K	Melanoma	Vemurafenib

Mutation Profiling of 23 Glioma Patients and Hypermutation in Temozolomide (TMZ) Treated Patients



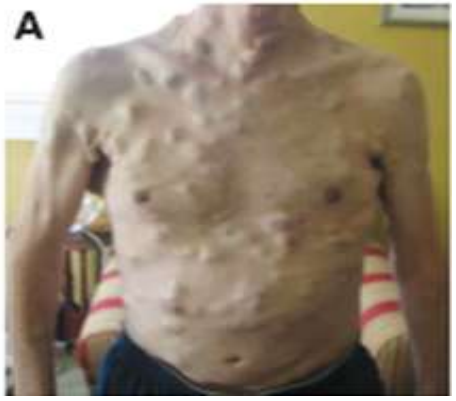
From: B. E. Johnson et al. (2014) Science 343, 189

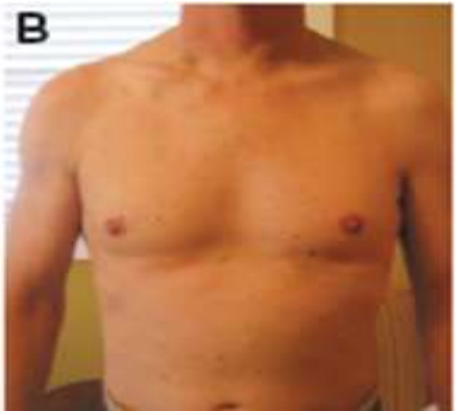
Emergence of Drug Resistance to Targeted Therapy in Melanoma

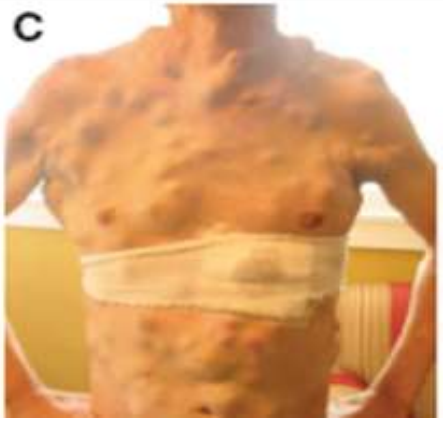
Initial Rx-Response to Targeted Rx

Rx-Resistance via Alternate Molecular Signaling Pathway (Network Redundancy)

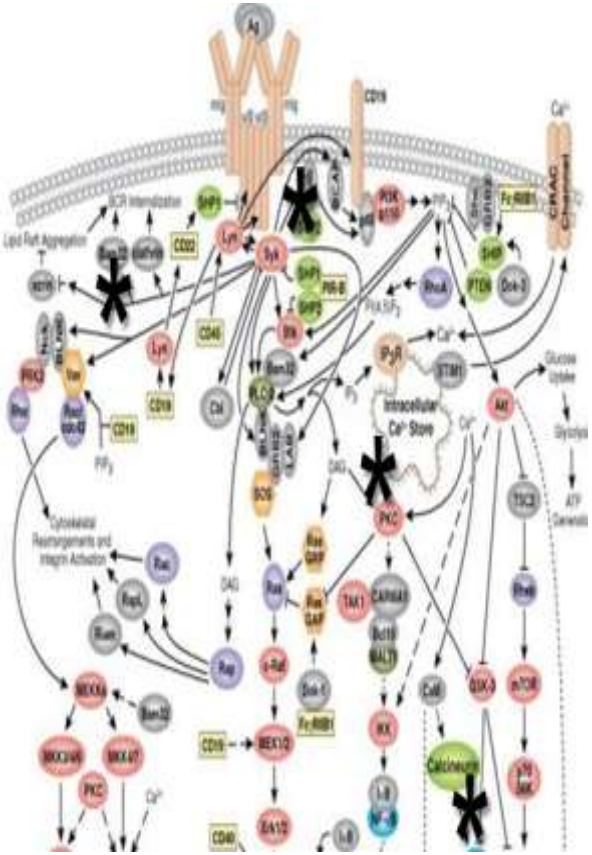
Circumvention of Rx-Resistance Requires Multi-site Blockade of Connected Signaling Pathways





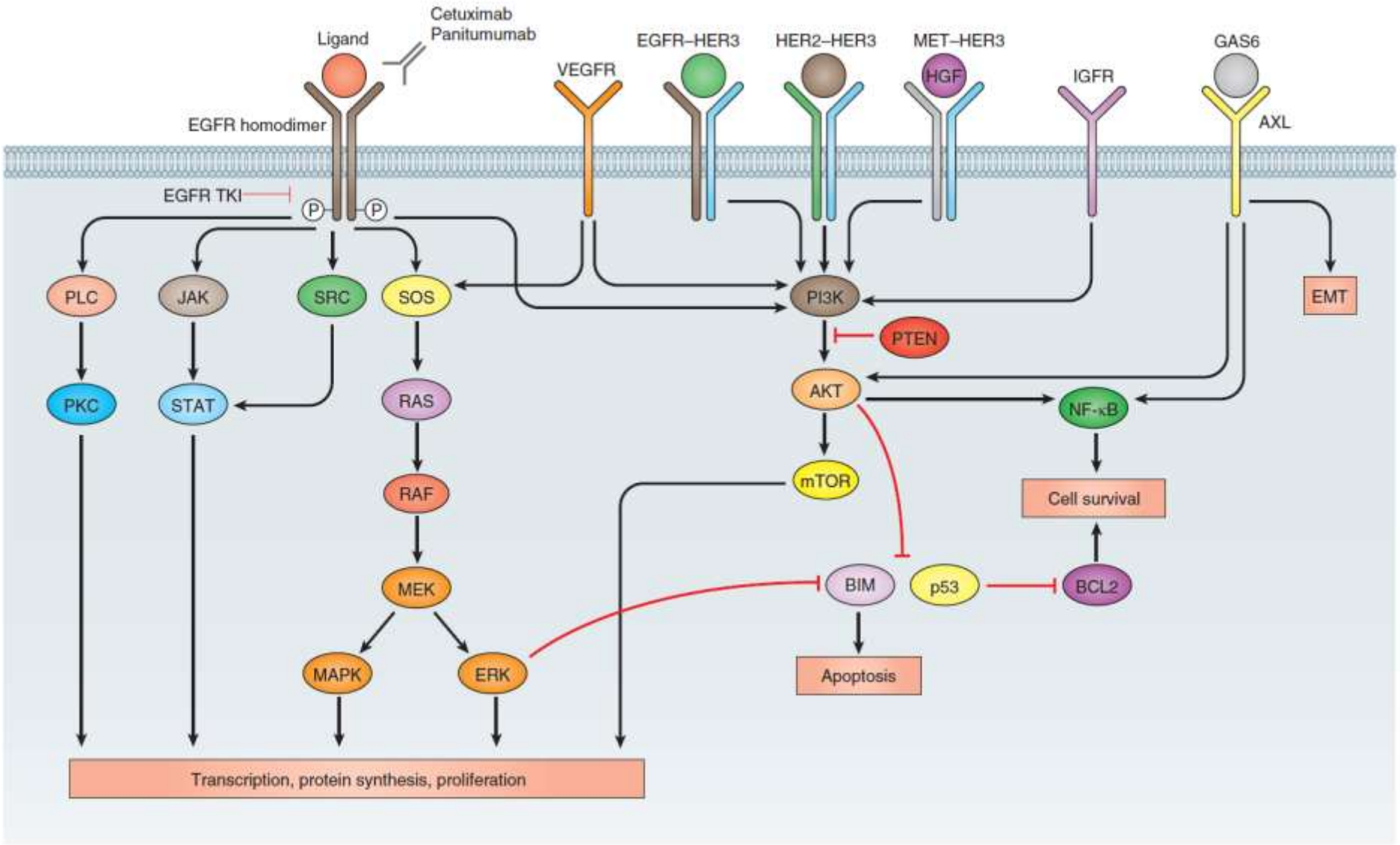


B = 15 weeks Rx (Zelboraf®)
C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011) JCO 29, 3085)



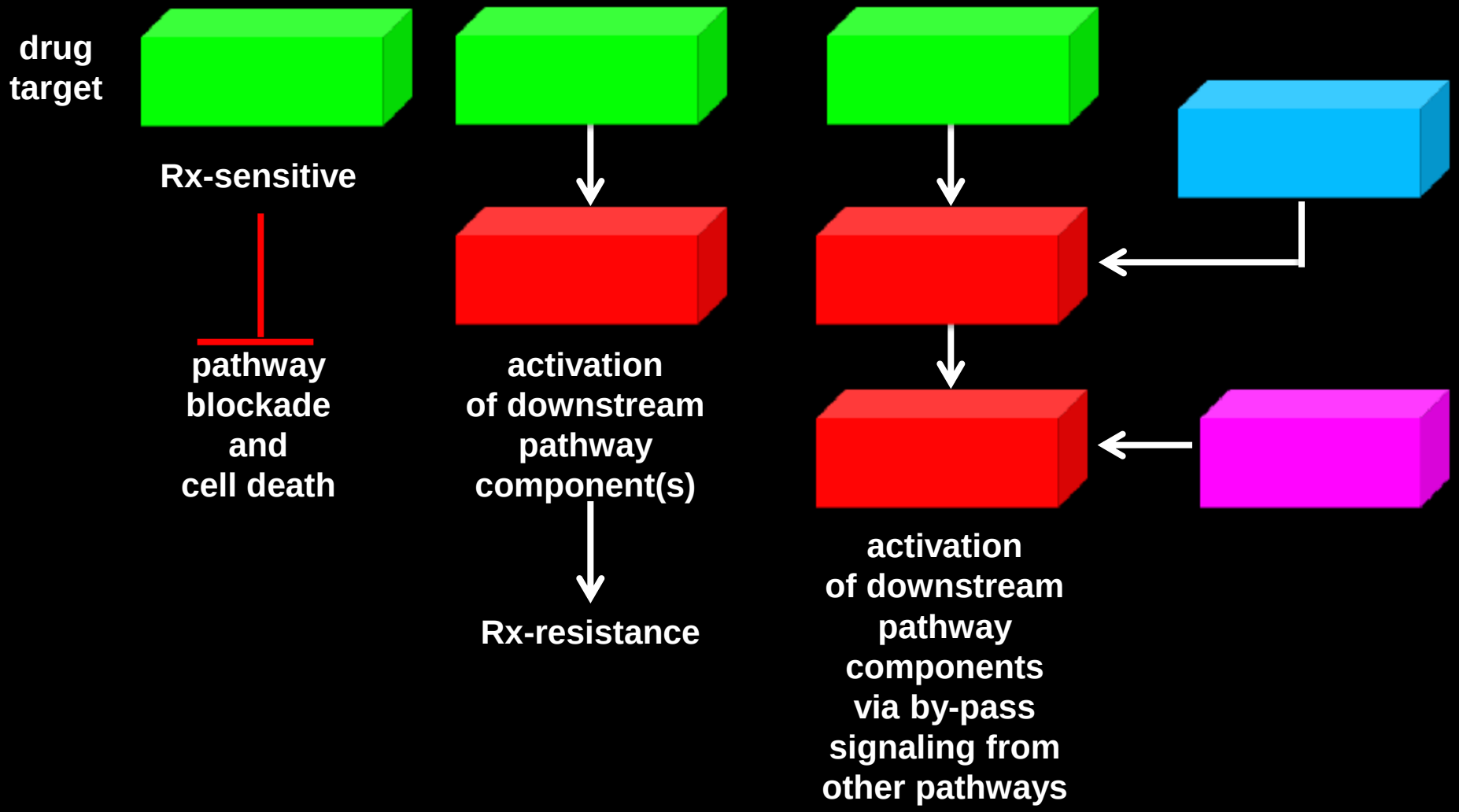
‘Compensatory’ Signaling Pathways and Drug Resistance

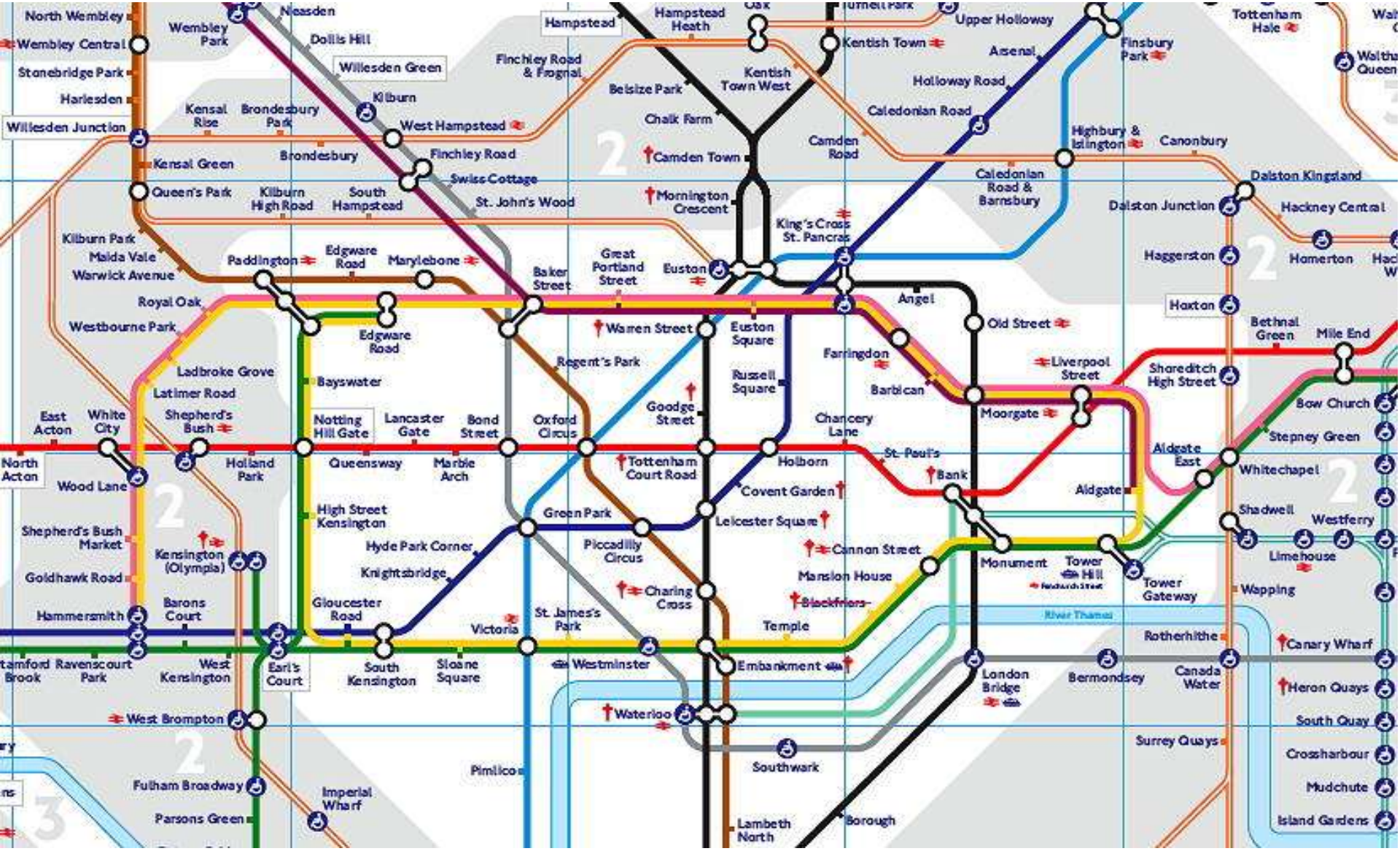
Linkage (Connections) Between Different Signaling Pathways Offers a Major By-Pass for Cancer Cells to Develop Rx Resistance



From: C. R. Chong & P. A. Jänne (2013) Nature Medicine 19, 1389–1400
DOI: doi:10.1038/nm.3388

Network Pharmacology and Emergence of Drug-Resistant Cells





Drug Resistance Can Arise from Both Mutations in the Drug-Target Plus Use of By-Pass Pathways

Resistance to TKIs in EGFR-Mutant Lung Adenocarcinomas*

- development of resistance to gefitinib or erlotinib in c.40% patients after one year
- resistance via additional mutations
  - second-site resistance EGFR mutations (>50%)
- resistance via downstream or other by-pass pathways
  - amplification of MET receptor gene (5-10%)
  - mutations in PIK3CA encoding PI10α subunit of downstream lipid kinase PI3K (<5%)
- histologic transformation: EMT or small lung cancer (<5%)

* K. Ohashi et al. (2012) PNAS 109, 12282

Monitoring Treatment Efficacy

Monitoring Treatment Responses in Cancer Patients

- no, partial or complete response
- progression-free survival (interval) (PFS)
- progressive disease
- chronic, stable disease
- regulatory parameters: PFS and overall survival (OS)
- recurrent disease in patients previously viewed as having no or minimal residual disease
- terminal disease

RECIST
(Response Evaluation Criteria In Solid Tumors)

RECIST Version 1.1 Update | RECIST in Practice

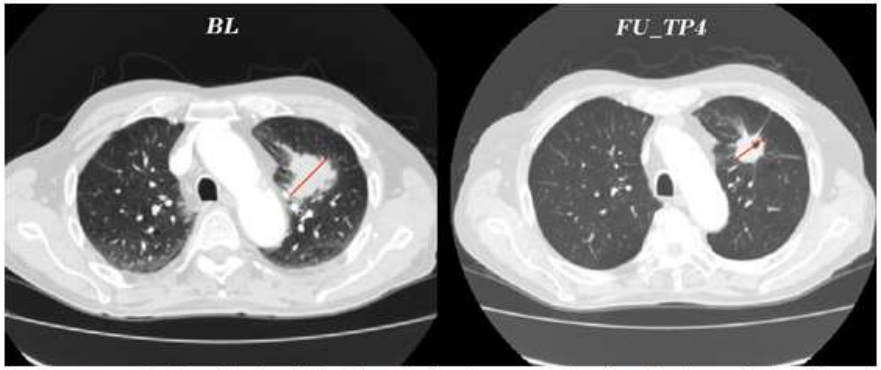
Topics

1. RECIST - Definitions
2. Measure the longest in plane diameter
3. Target Measurement Rules
4. Selecting Target Lesions
5. Importance of Imaging Consistency
6. Importance of IV-Contrast
7. Importance of i.v.-contrast and proper timing, scanning delay
8. Imaging: Anatomy for CT/MRI
9. Target Measurement Rules at Follow-up
10. Progression by Non-Targets only
11. Reappearing Lesion
12. Splitting Lesions
13. Merging Lesions
14. Merging lesions example
15. Variable Enhancement
16. Lung Lesion develops cavity
17. Lymph Node Measurements, CT
18. Lymph Node Measurements, MRI
19. Bone mets
20. MRI
21. PET
22. Overview: RECIST vs. RECIST 1.1

Topic 16

< Prev Next >

Lung Lesion develops cavity



Continue measuring target lesions in their longest diameter, even when they develop central cavities or necrosis.

If the sum of diameters does not accurately reflect the patient's response assessment, a different assessment may be provided, accompanied by explanatory comments justifying so

< Prev Next >

Monitoring Treatment Responses in Cancer

RECIST

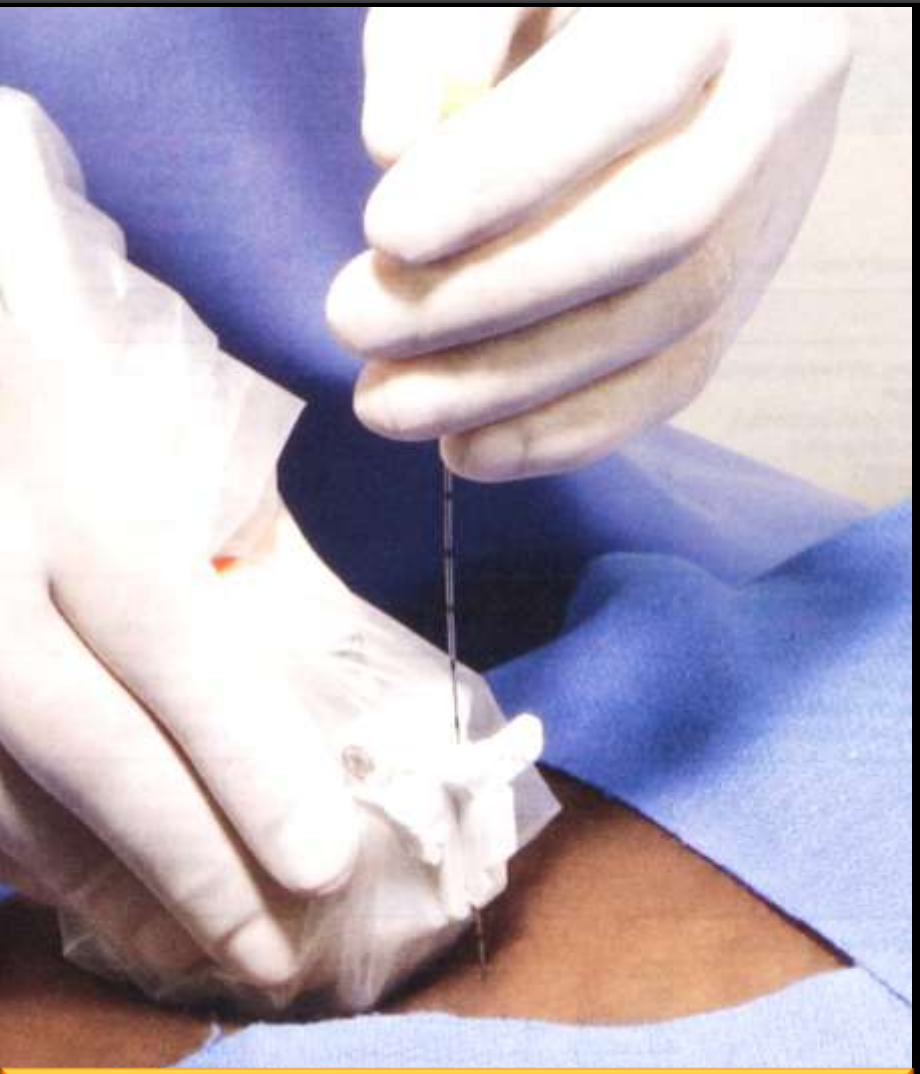
- **Response Evaluation Criteria In Solid Tumors**
- **imaging of size and volume of tumor metastases**
- **not sufficiently sensitive to detect emergence of treatment-resistant tumor cell clones in solid tumors**

Monitoring Treatment Responses in Cancer

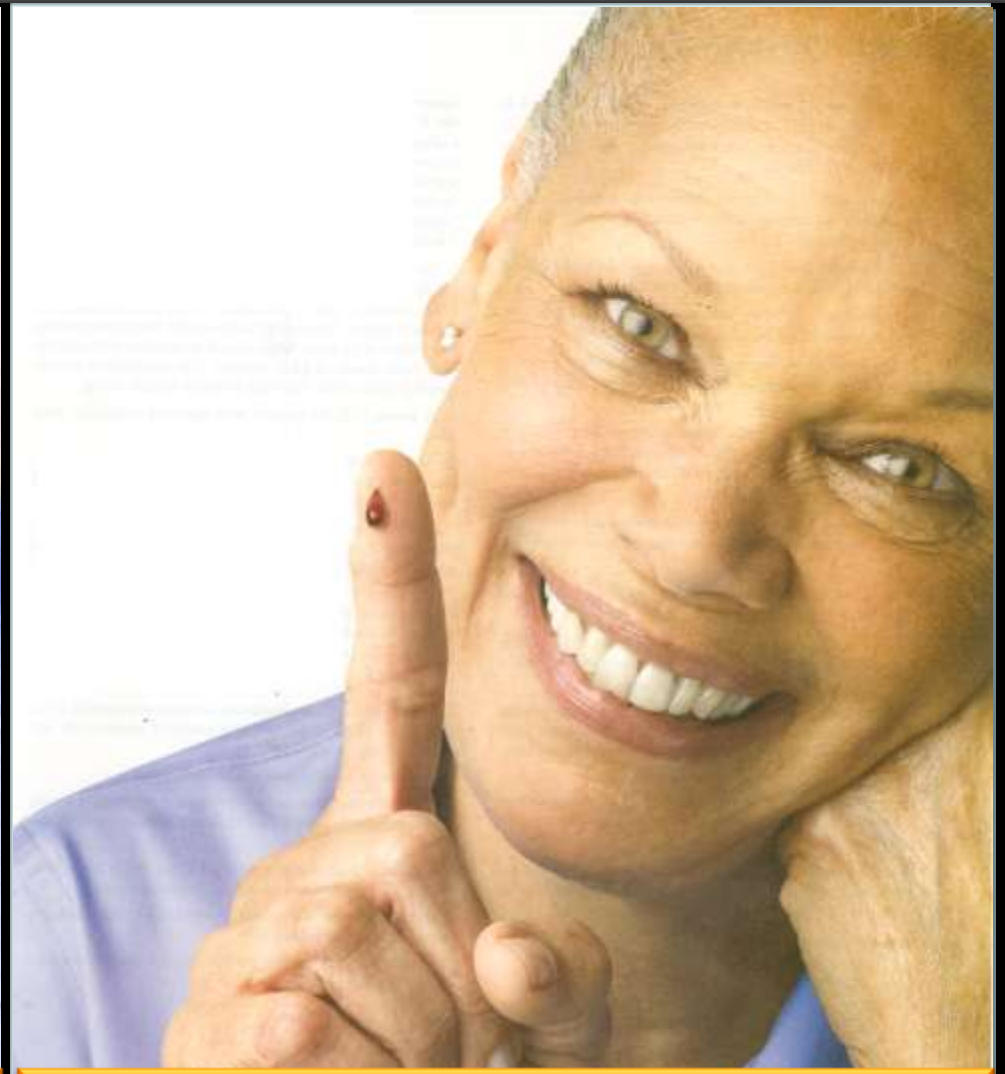
- earlier detection of lack of Rx efficacy
  - switch Rx regimen
- earlier detection of emergence of treatment-resistant clones
  - agile, anticipatory treatment to hit new resistant clones
  - greater current feasibility with ‘liquid’ hematopoietic tumors (leukemias, lymphomas) than solid tumors

Molecular Profiling and Rx Selection in Cancer Treatment

- given the high frequency (inevitability?) of emergence of Rx-resistant clones (intrinsic or acquired resistance) how can their emergence be best monitored?

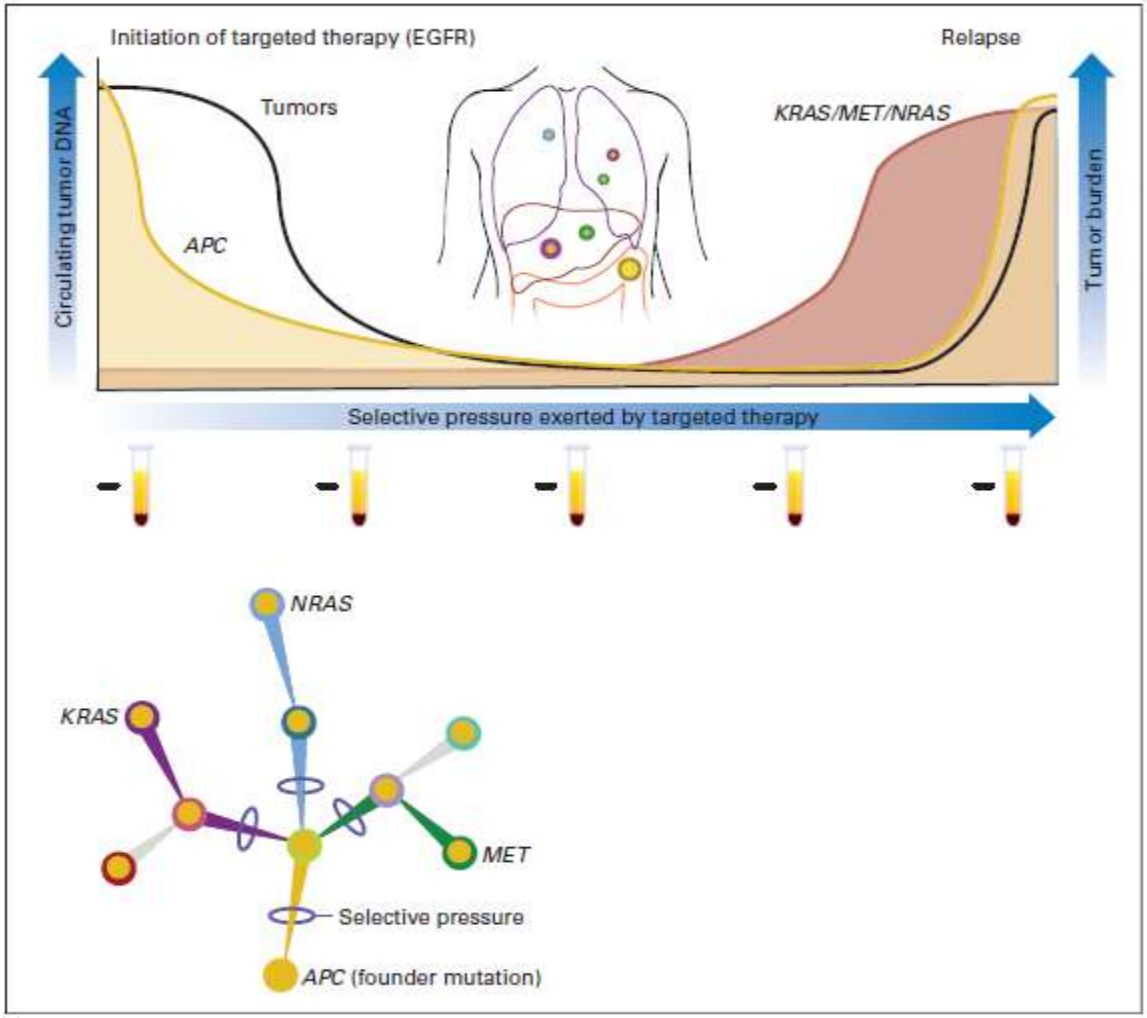


Fine Needle Aspiration (FNA) Biopsy



Minimally-Invasive Profiling
(Blood/Other Body Fluids)

"Liquid Biopsy"
Monitoring of Changing Clonal Dynamics by Monitoring Tumor Specific Biomarkers in CRC



At diagnosis = APC and KRAS (Wild Type)
emergence = KRAS and NRAS mutations and MET amplification clones
From: L. A. Diaz Jr and A. Bardelli (2014) J Clin Oncol 32, 579

Mapping the Dynamics of Clonal Diversification in Tumor Progression

- urgent need for new technologies for minimally invasive profiling of the full spectrum of clones present in a patient and changes occurring over time with treatment
- difficult to sample (biopsy) multiple metastases in solid tumors
- the quest to create a ‘liquid biopsy’ for profiling clonal dynamics for solid tumor profiling from analysis of blood samples
  - exosomes
  - circulating tumor cells
  - cell-free (cf) DNA or miRNAs from tumor cells

Mapping the Dynamics of Clonal Diversification in Tumor Progression

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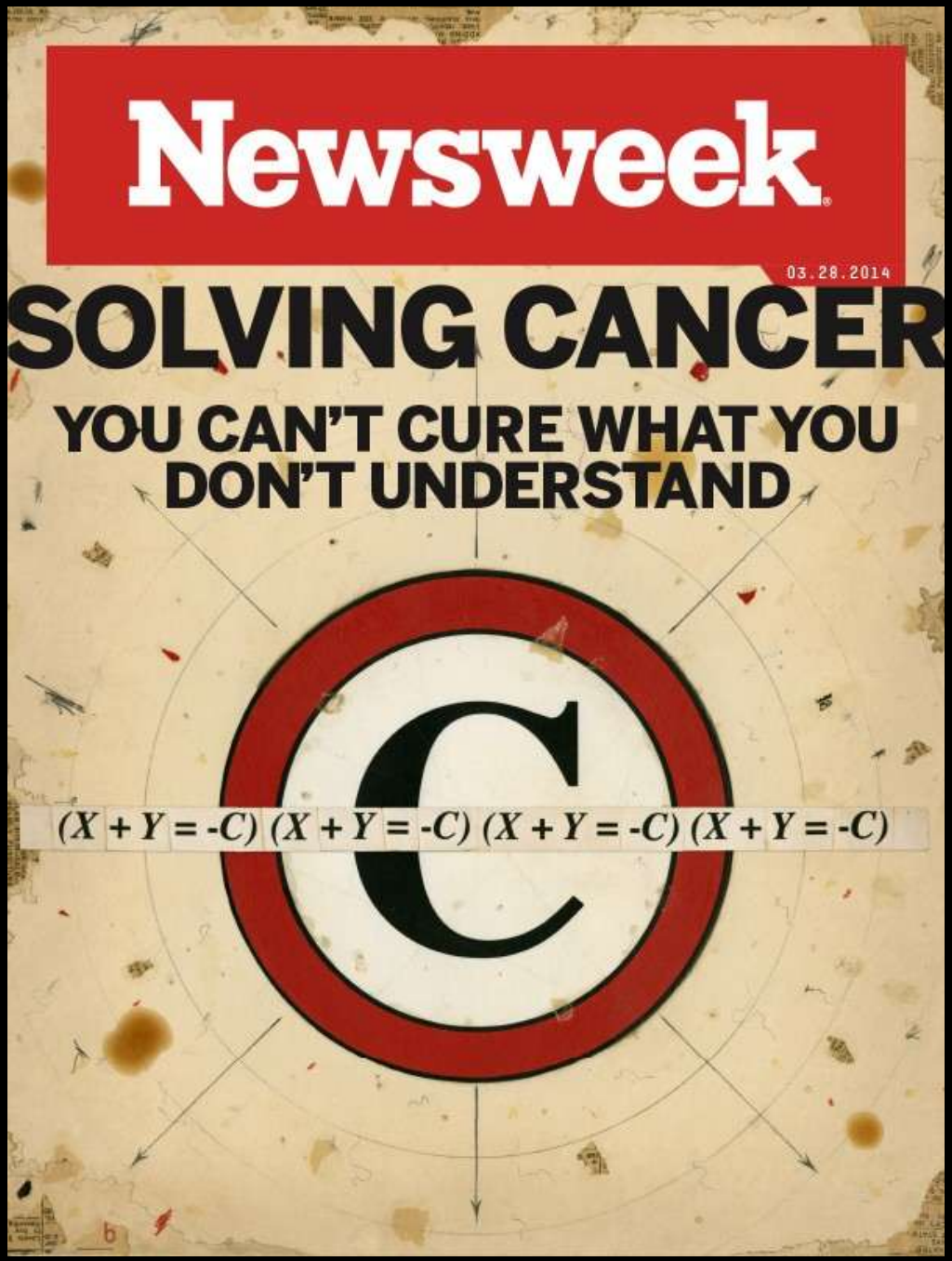
- the quest to create a ‘liquid biopsy’ for tumor profiling from analysis of blood samples

Lecture in Week 14 on Drug Development



- 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

Lecture 2: Cancer Treatment

- rethinking current chemotherapeutic approaches
- the promise of immunotherapy
- post-treatment clinical challenges for cancer survivors
- the impact of advanced cancer on body function and quality-of-life
- palliative care (non-curative)
- end-of-life care