ASU Complex Adaptive Systems
ARIZONA STATE UNIVERSITY

BIO 302:
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LECTURE 2:
DEVELOPING THERAPIES FOR CANCER: DRUG DISCOVERY, DEVELOPMENT AND REGULATION

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Clinical Trials

Design and Evaluation of Rx Efficacy and Safety

Clinical Trials

- conducted in accord with a definitive “protocol” reviewed by FDA and IRB at participating institutions (study centers)
  - patient eligibility criteria
  - medication and dosages
  - all tests and procedures
  - randomization methods
  - statistical analysis
  - length of study
  - independent drug safety monitoring board
  - clinical endpoints for phase III pivotal studies

Making Progress: The Transition from Preclinical to Clinical Development

- IND (investigational new drug) submission to FDA to begin trials
- FDA does not strictly approve but must raise any concerns about IND submission package within 30 days
  - otherwise OK to proceed to human trials
- parallel requirement for Institutional Review Board (IRB) review and approval by institutions where the trials will be conducted

Institutional Review Boards

- mandated Federal regulation for institutions participating in investigational clinical trials
  - drugs, diagnostics, vaccines, devices
- independent review of trial protocol
  - scientifically valid
  - ethical
  - risks are as low as possible with the potential benefit(s)
  - rights of trial participants protected

Institutional Review Boards

- membership
  - physicians, statisticians, lay representative
  - other expert opinion as deemed relevant
- challenge of technology acceleration and convergence
  - panOmics and statistical validation of molecular profiling assays for disease subtyping
  - adaptive clinical trial design
  - new combination trials: Rx + MDx; Rx + sensors

Informed Consent

- objectives of the study?
- benefits?
- risks (harms)?
- what treatments, procedures, tests are involved?
- study site and number of anticipated visits?
- length of the study?

Informed Consent

- availability of other treatments
- ability to leave the trial
- use(s) of data
- ownership of data

Informed Consent

- specific
  - limited to specific clinical study or research experiments
- broad
  - ability for study data/specimens to be used in further studies on additional questions beyond the purpose of the original study

Informed Consent

- written at level of 8th grade education
- additional translational needs for non-English speaking individuals
- special needs populations
  - pediatric (parents or legal guardian)
  - physically/mentally impaired (appointment of enduring power of health attorney)

Informed Consent

- who will cover the cost of participation?
- continuity of care (and access to investigational Rx after study ends?)
- who is the sponsor of the study?

Data Privacy

- identifiable data
  - direct link to specific patient
- de-identified data
  - donor identity not revealed directly but can be linked via trusted custodian
- anonymized data
- destruction of data

Clinical Trials

phase I

- first human testing
- initial trial in small cohort (20-80 people)
- evaluation of safe dosage range and potential side effects
- healthy volunteers (but paid) for most Rx classes
- cancer drug trials initiated directly in patients
- evidence of efficacy valuable but not the primary objective or endpoint assessment (safety is primary focus)

Clinical Trials

phase II

- evaluation in larger patient population with disease
- typically 100-300 patients
- establish evidence of efficacy and optimum dosage for phase III trials
- typically ‘single arm’ trial without comparison to placebo/standard Rx
- additional assurance on safety profile

Clinical Trials

phase III

- “pivotal” trial to demonstrate efficacy and safety for regulatory approval to market
- randomized clinical trial (RTC) protocols dominated trial design until recently

Phase III Clinical Trials: Clinical Endpoints

- prospective definition before trials begin
- primary endpoints
  - efficacy performance
- secondary endpoints
  - lower side effects versus current available Rx
  - QOL parameters
  - reduced hospitalization stay, faster return to higher performance status (work, school, etc.)

Efficacy Endpoints in Cancer Clinical Trials

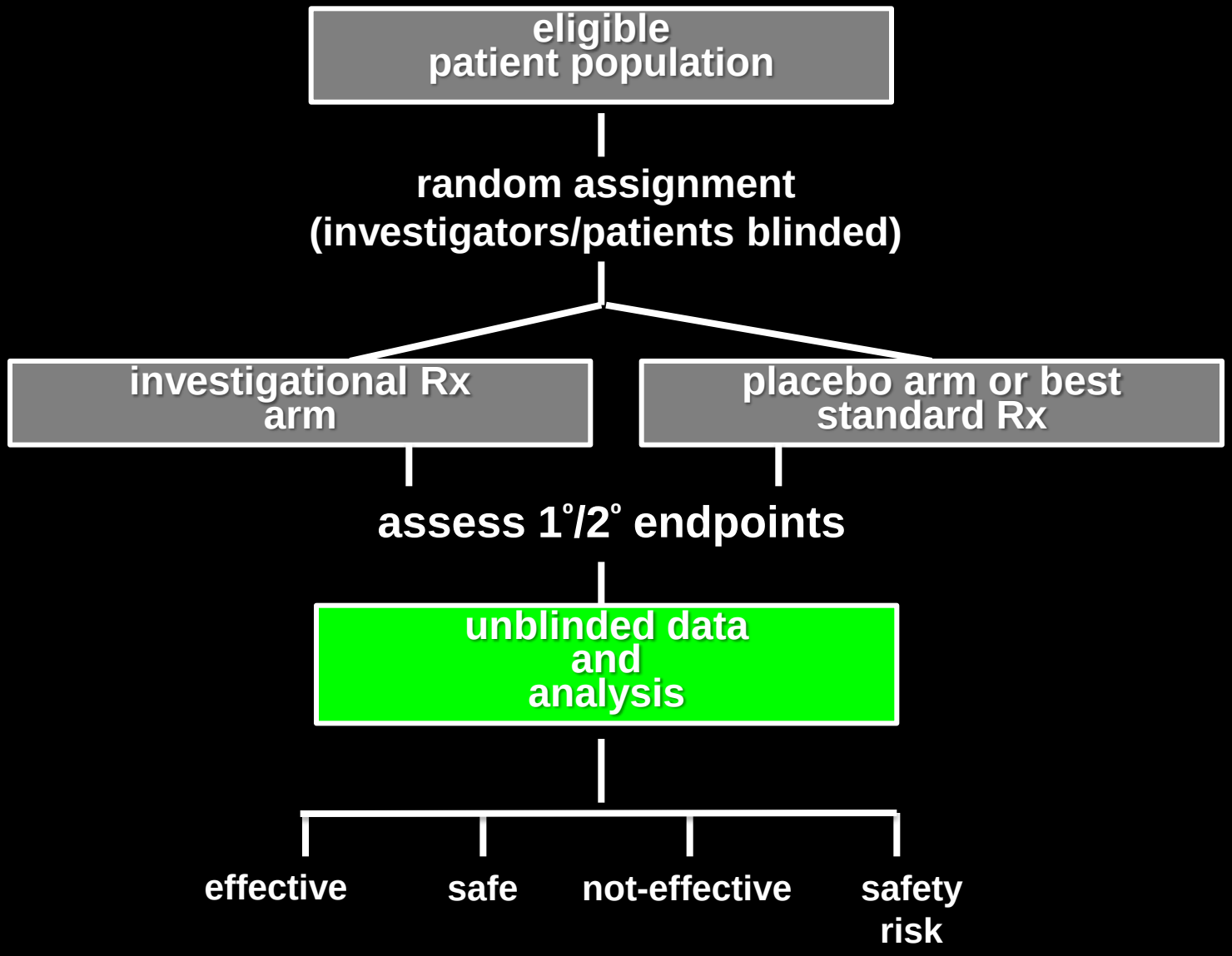
- no response (NR), partial response (PR) or complete response (CR)
- durable stable disease
  - time to progression (TTP): progression-free survival (PFS)
- overall survival (OS)
- recurrent disease in patients previously viewed as having minimal residual disease or no disease
- terminal disease

Clinical Trials

phase III

- pivotal trial to demonstrate the level of efficacy and safety required for regulatory approval to market
- patients randomized to different ‘arms’ of the trial
  - candidate Rx versus placebo or standard therapy
  - candidate Rx plus standard therapy versus standard therapy alone (standard for cancer drugs)

The Randomized Clinical Trial



Clinical Trials

phase III

- randomized clinical trials (RCTs)
- large number of patients per arm (2-5000) to achieve adequate statistical power
- high cost ($100’s millions)
- complex sophisticated logistics to coordinate and monitor trials at multiple study centers and multiple countries

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

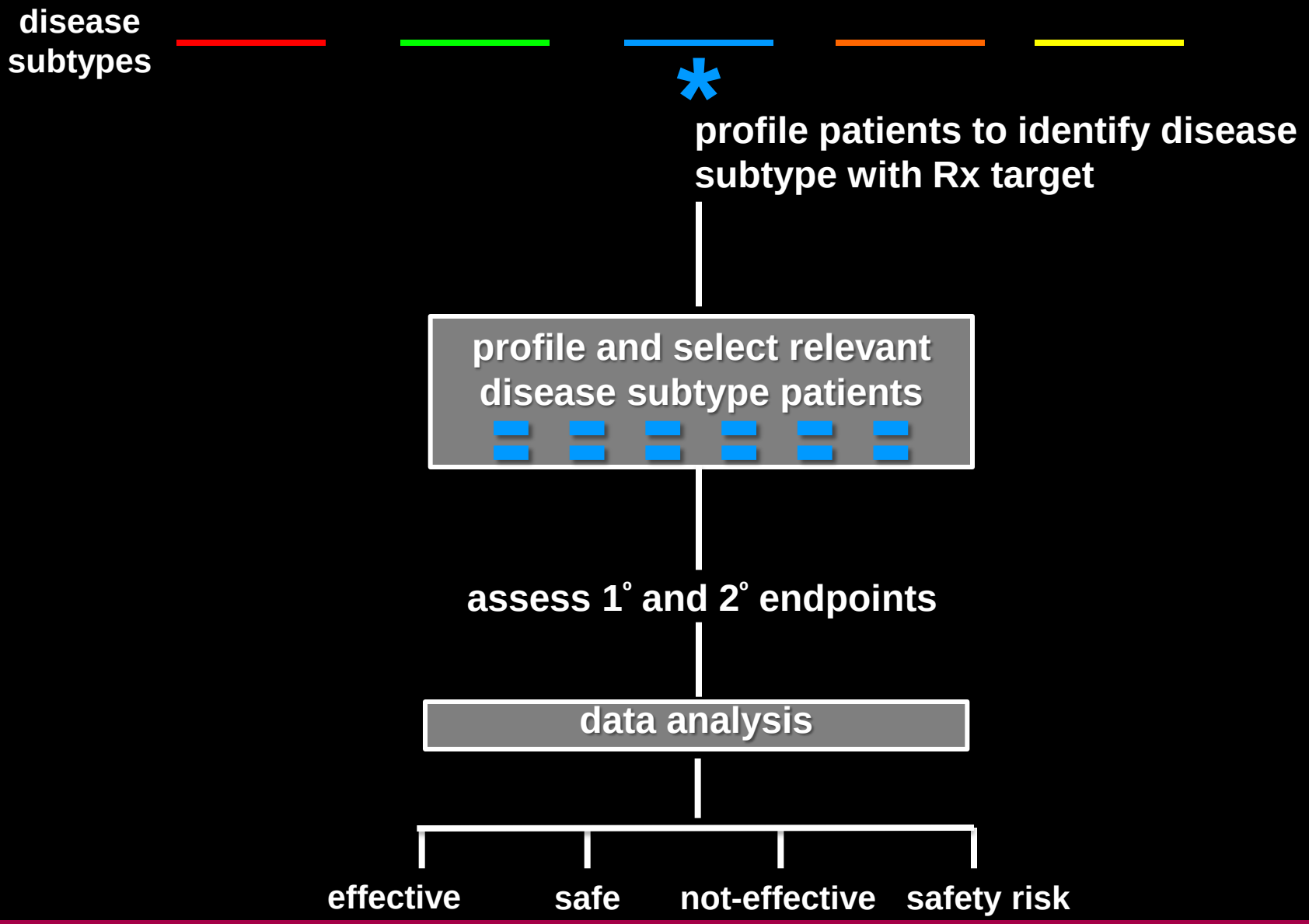
- Rx responder (Rx^+) and non-responder (Rx^-) subpopulations
- larger trial needed to attain statistically significant difference between responder (Rx^+) and non-responder (Rx)
- inefficient and wasteful Rx use post-approval without ability to identify Rx^- non-responder patients
- exposure of non-responder Rx^- subpopulation(s) to potential toxicity risk

Clinical Trials

phase III

- large size of RCTs dictated by historical lack of methods to ‘stratify’ patients based on disease subtypes
- inclusion of patients with different disease subtypes with likely different Rx responses increases the fraction of “non-responders” and need to study much larger populations to obtain statistically significant efficacy

Stratified (Enrichment) Clinical Trials



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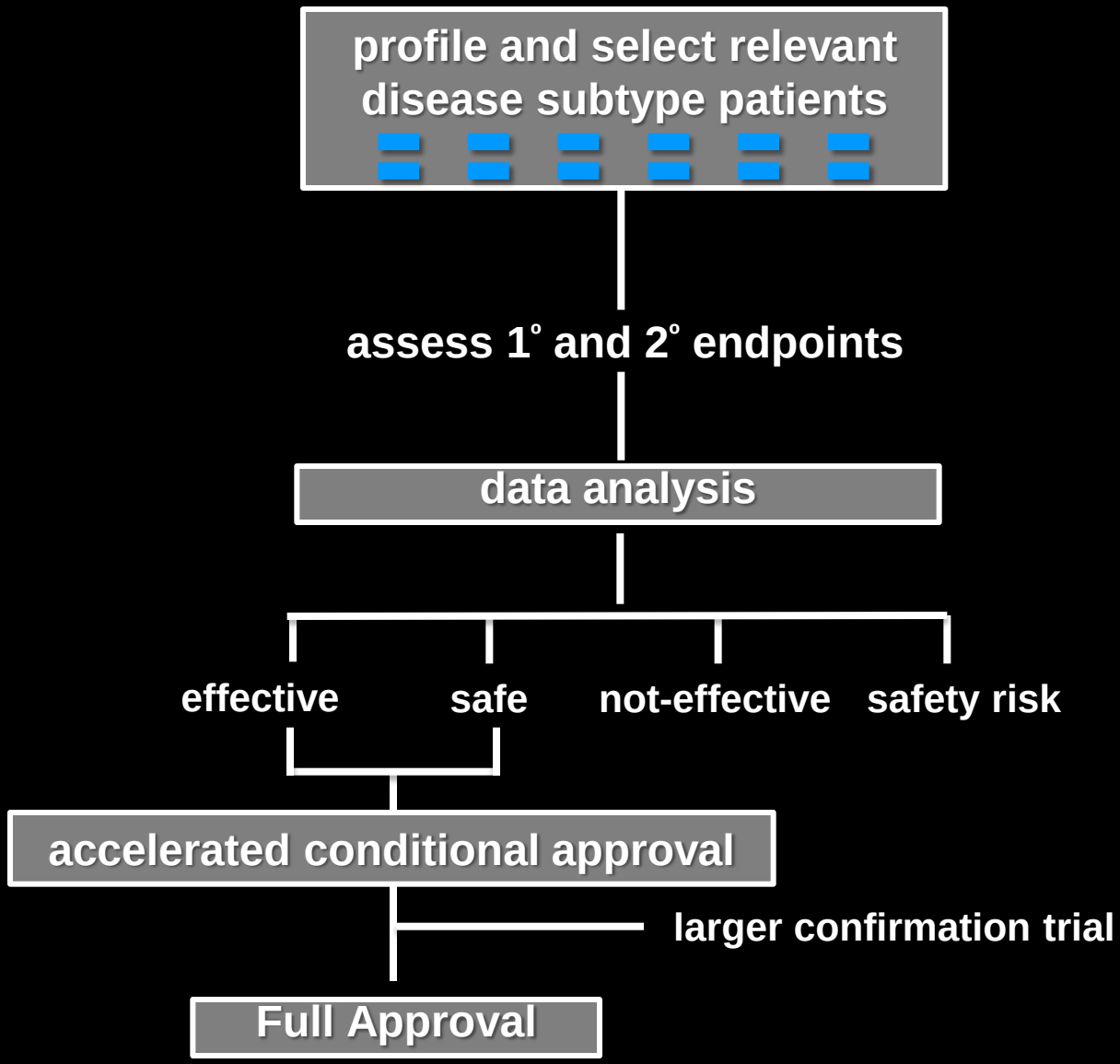


Monitoring Treatment Responses in Cancer

RECIST

- **R**esponse **E**valuation **C**riteria **I**n **S**olid **T**umors
- imaging of size and volume of tumor metastases
- not sufficiently sensitive to detect emergence of treatment-resistant tumor cell clones

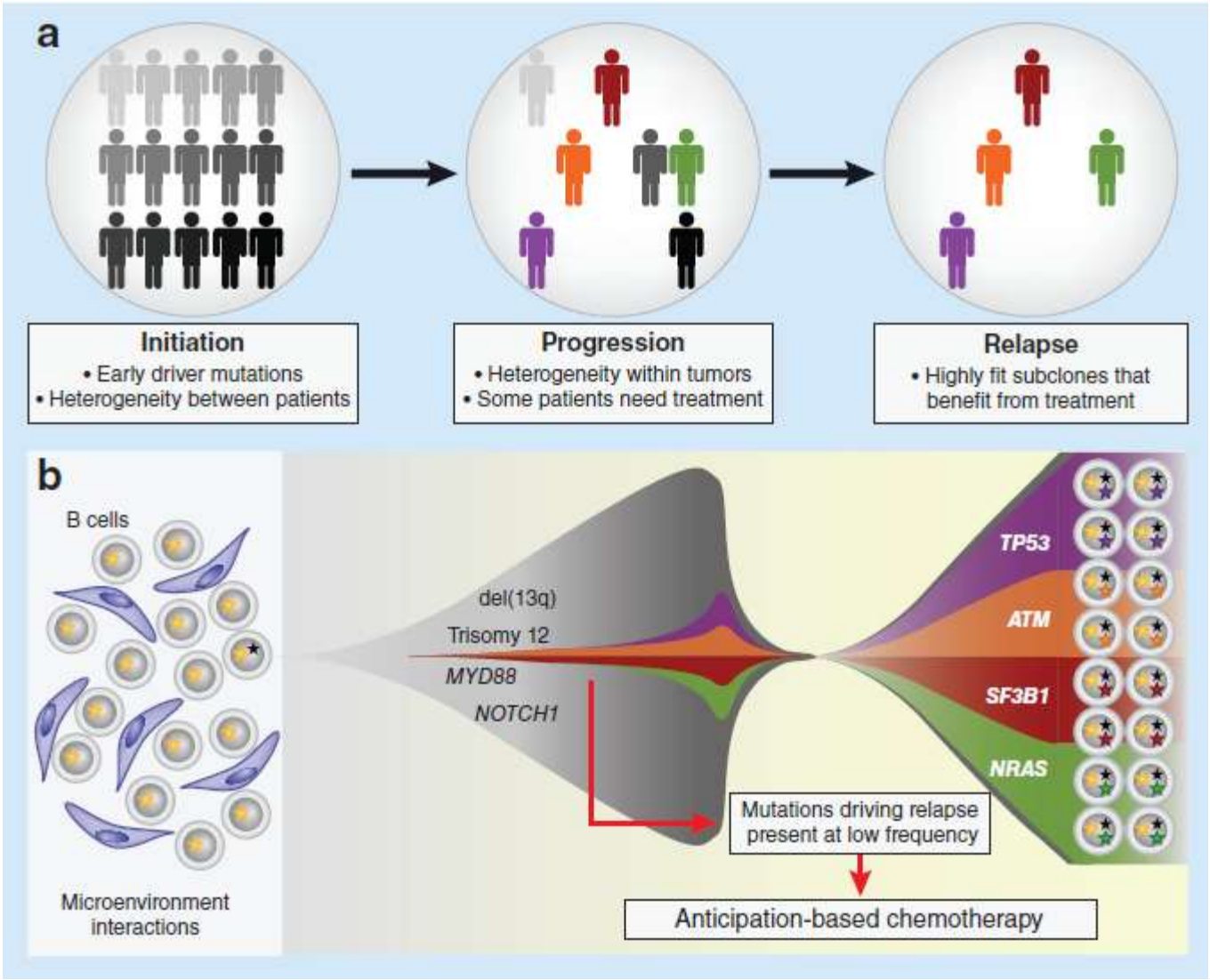
The Urgent Need for New Diagnostics and Molecular Profiling Tools for Improved Monitoring of Tumor Progression

From ‘Static Snap Shot’ at Initial Diagnosis to Dynamic Monitoring of Clonal Population Dynamics

Tumor Profiling and Optimum Treatment Selection

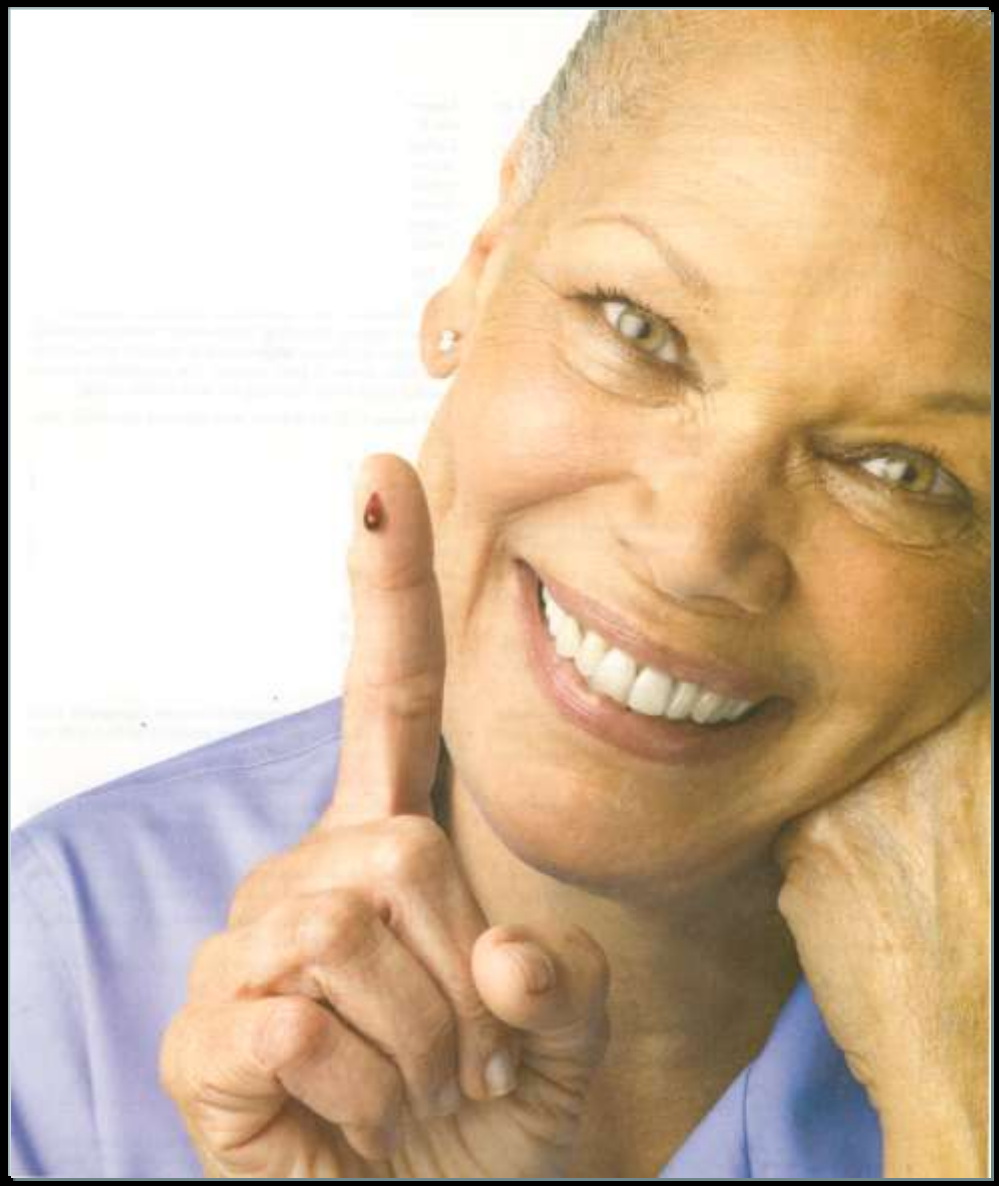
- initial diagnosis (‘static snapshot’)
- longitudinal profiling during treatment for earlier detection of emergence of drug-resistant clones
- more agile shifts in Rx regiment to reflect changing clonal dynamics driven by Rx selection pressure(s)

Anticipation-Based Chemotherapy in CLL

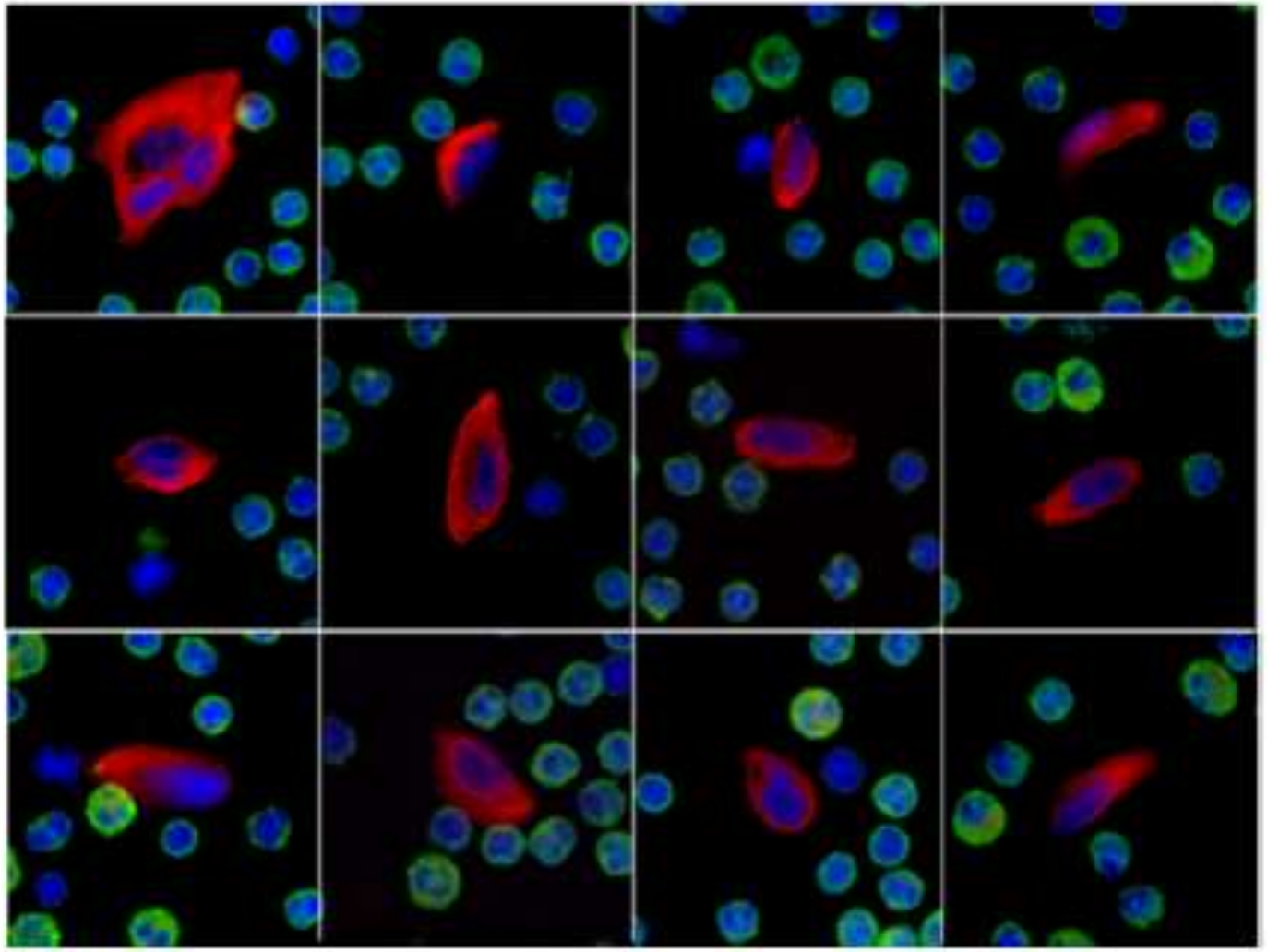


From: X. S. Puente and C. López-Otín (2013) Nature Genetics 45, 230

The Liquid Biopsy:
The Quest to Profile Disease Status and Rx Efficacy from Blood-based Biomarker



Gallery of representative HD-CTCs found in cancer patients. Each HD-CTC is cytokeratin positive (red), CD45 negative (green), contains a DAPI nucleus (blue), and is morphologically distinct from surrounding WBCs.

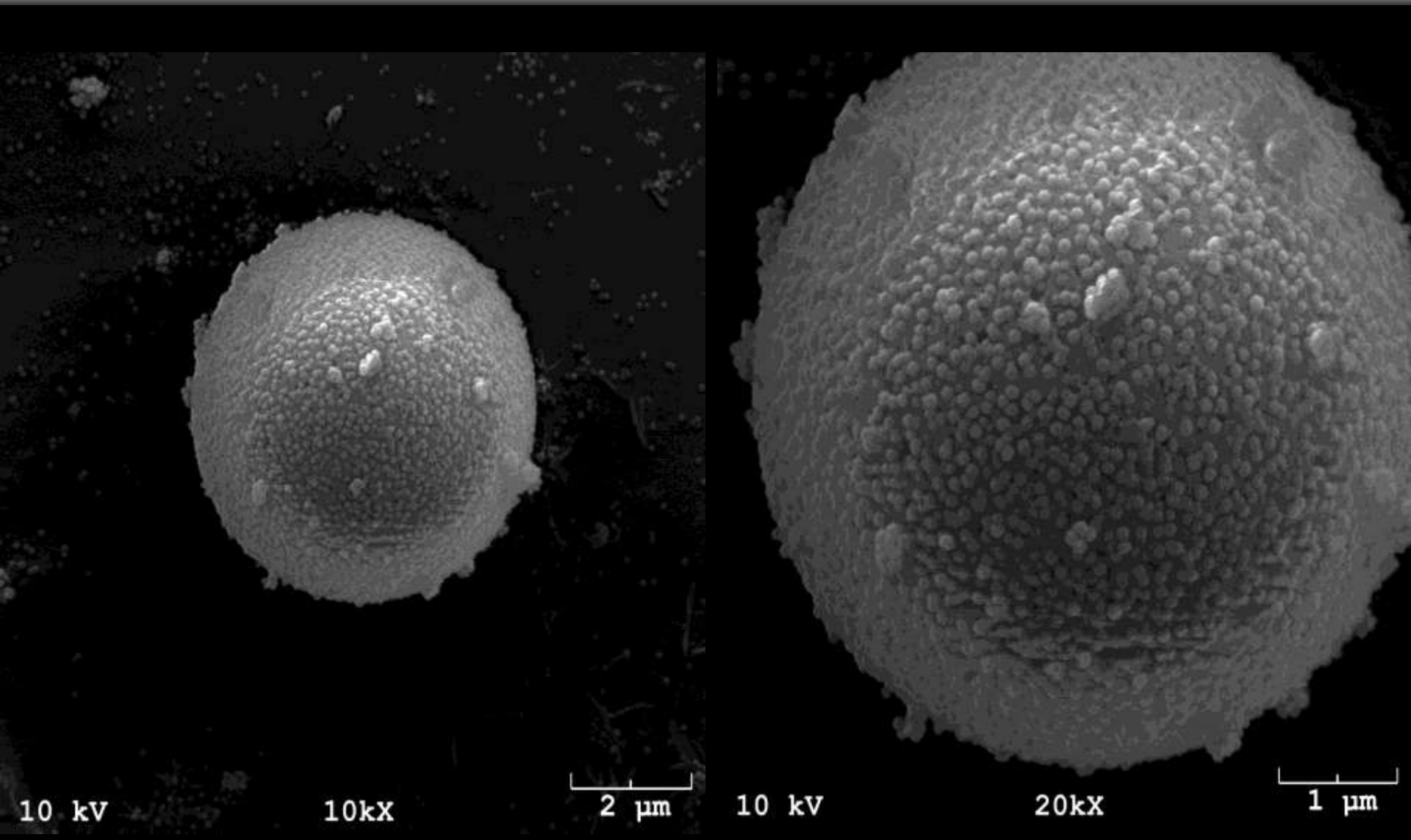


From: D. Marrinucci et al. (2012) Phys. Biol. 9, 016003

Detection of Tumor-Associated Biomarkers in Blood: 'The Liquid Biopsy'

- cell-free nucleic acids
  - DNA, miRNAs
- circulating tumor cells(CTC)
- exosomes

Exosomes (Cariosomes™) and Profiling of Blood-based Biomarkers in Cancer



From: Caris Life Sciences

Pharmaceutical Dosage Forms and Route of Drug Administration

Infusion Clinics
Ambulatory Patients

Hospitalized Patients

Oral

Aerosol

Routes of Rx Administration

small molecules

- oral
- IV
- nasal
- aerosol
- trans-dermal
- specialized delivery devices

biologicals

- IV (dominant)
- subcutaneous/ intramuscular
- nasal/aerosol
- specialized delivery devices

Development of Pharmaceutical Formulations

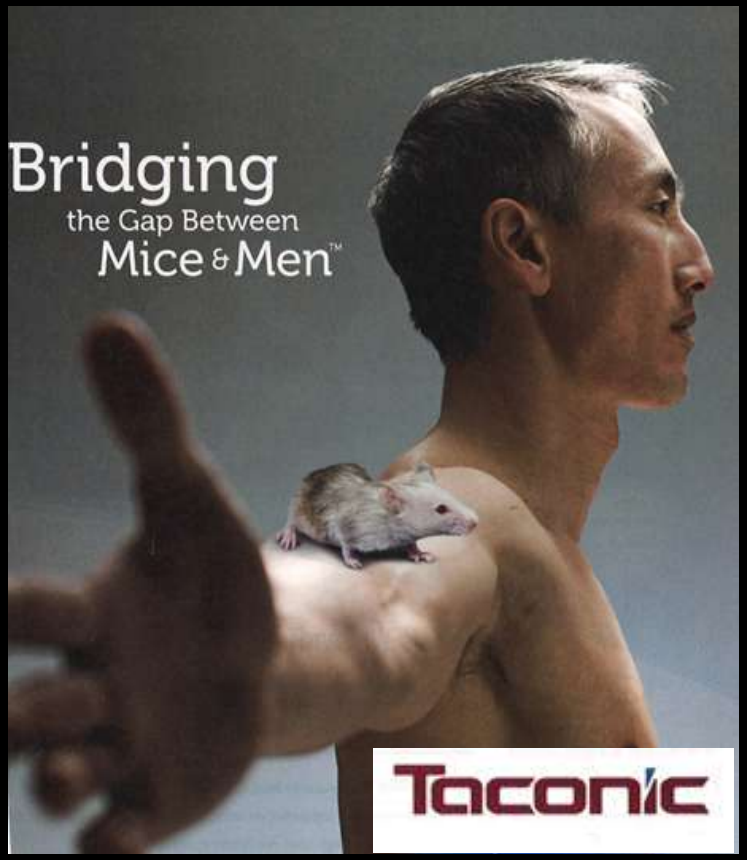
- development of ‘dosage form’ to achieve optimum Rx efficacy and patient convenience
  - frequency of dosing
  - ease of dosing (oral versus non-oral)
  - need for specialized delivery devices
- selection of dosage forms to achieve optimum Cmax (maximum concentration in blood/tissues) and optimum half-life for clearance
  - efficacy and toxicity issues
- special populations
  - pediatric, pregnant, aged

Dose and Dosage Formulation Will Influence Efficacy (Pharmacodynamis) and Risk of Adverse Events Pharmacokinetics

- time target cells are exposed to effective Rx concentration
- risk of adverse events
  - drug concentration and duration of exposure
  - pharmacogenetics (inter-individual genetic variation in drug metabolism)
  - effect of co-existing diseases/other drugs on Rx metabolism

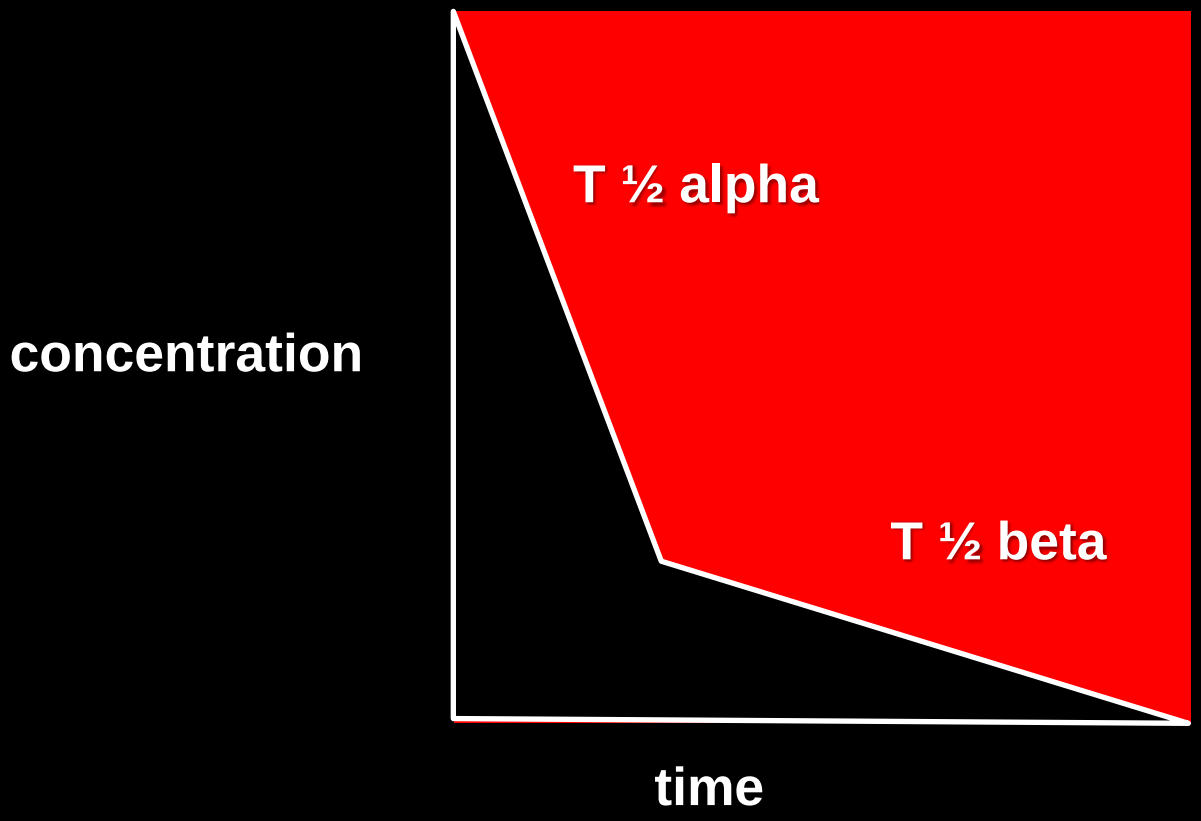
Human Pharmacokinetics

Human Pharmacokinetics

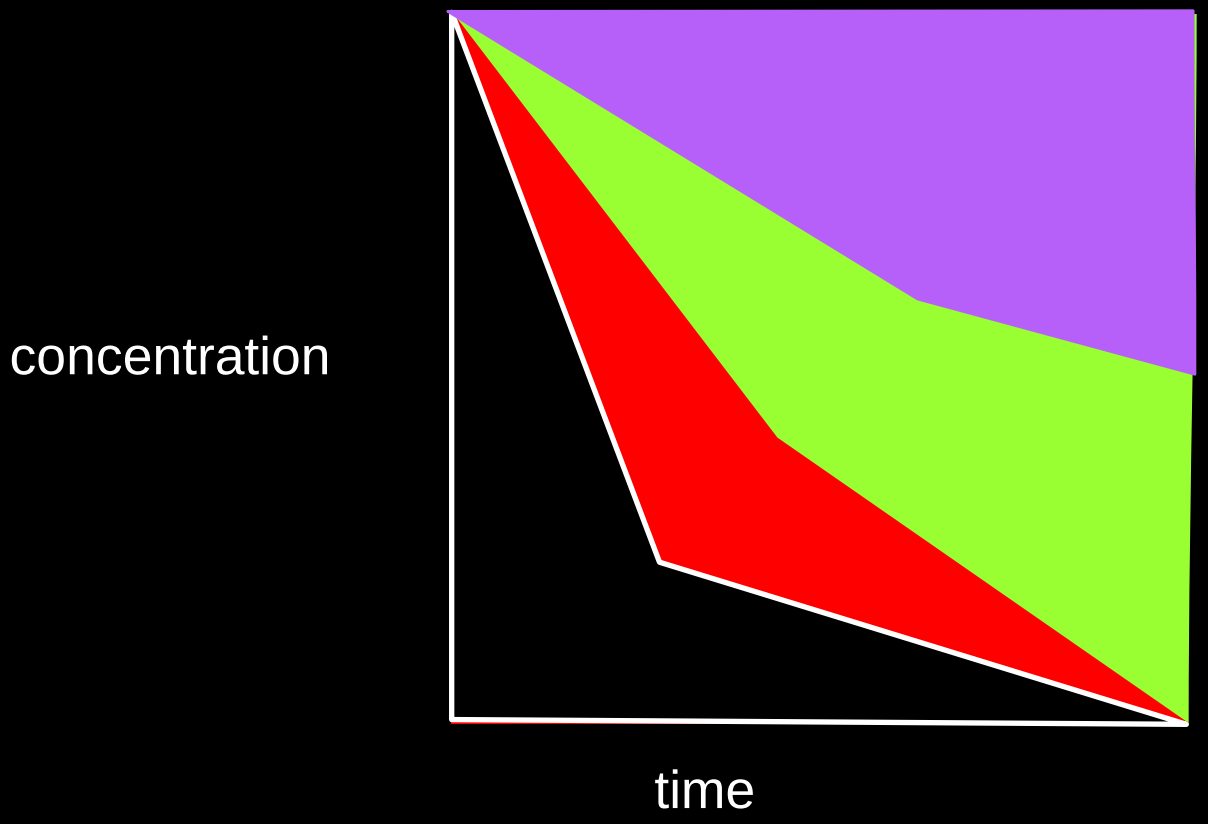


- often biggest variation from data obtained in animal studies
- critical factor in Rx efficacy and safety (Cmax; off-target exposure)
- impact of disease in altering ADME

Pharmacokinetics: Biphasic Drug Clearance Patterns



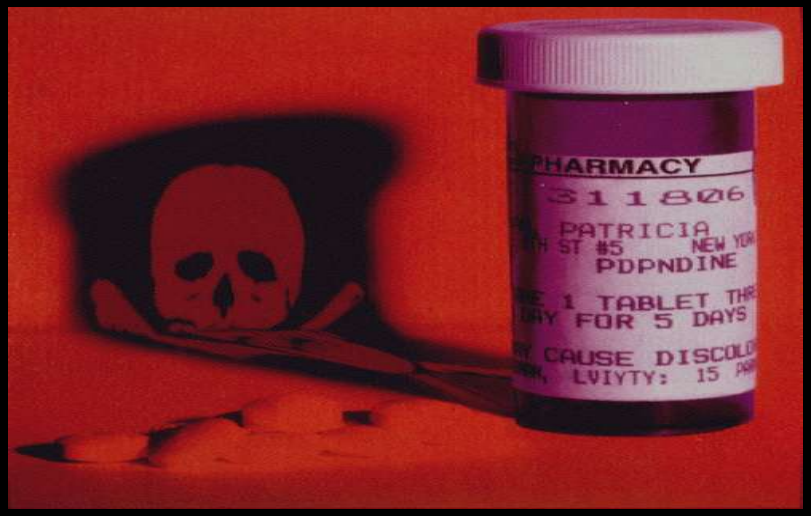
Effect of Disease, Disease Co-Morbidities or Other Drug Treatments on Drug Metabolism and Clearance



Repeated Measurement of Rx Pharmacokinetics to Ensure Consistent Bioavailability and Metabolic Pattern

Mapping the Genetics of Drug Metabolism: Profiling Patient Risk to Adverse Drug Reactions

Right Rx for the Right Patient



- 1.5 to 3 million annual hospitalizations (US)
- 80 to 140 thousand annual deaths (US)
- est. cost of $30-50 billion

- Rx AE risk for “slow metabolizers”
  - genetic variation in type I/II drug metabolism enzymes
- HLA-related drug toxicities
- GI microbiome and metabolism of drugs/carcinogens

Pharmacokinetic Pharmacogenetics (PKPG)

Individual Variation in Drug Metabolism Enzymes			
Metabolic Profile	slow metabolizer	intermediate metabolizer	fast metabolizer
Drug Efficacy	high	high to intermediate	low to none

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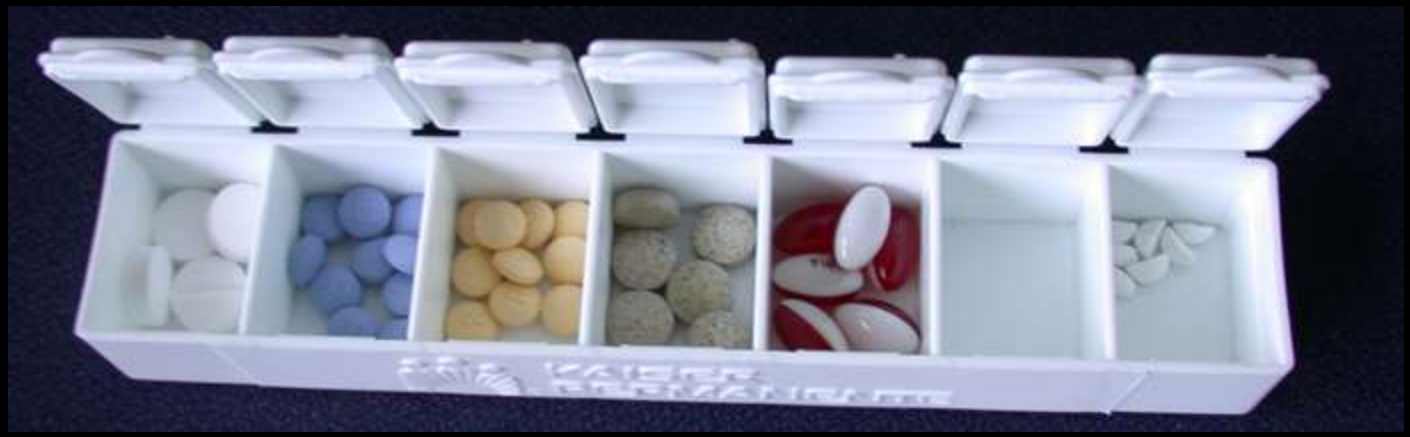
Drug Efficacy	high	high to intermediate	low to none
Toxicity Risk	highest	intermediate	low to none

Pharmacokinetics: Drug Interactions

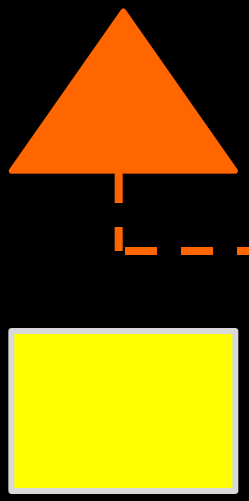
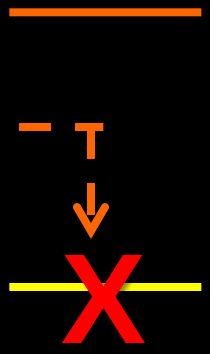
- test candidate Rx in concert with other (approved) Rx likely to be used in patients receiving the candidate Rx
- direct inhibitory effects on drug metabolism pathways for other Rx
- indirect effects caused by metabolites (by-products) produced by metabolism of the candidate Rx



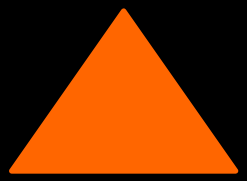
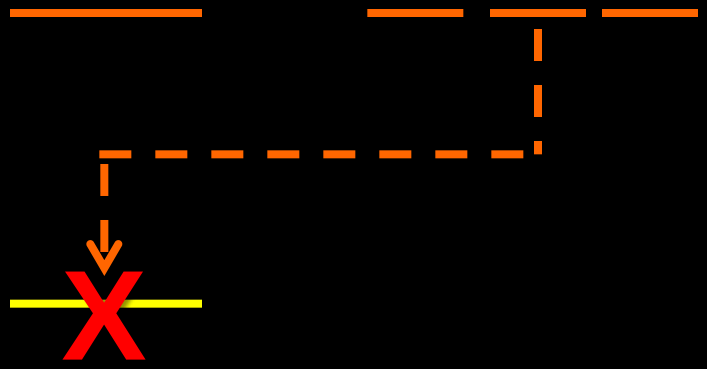
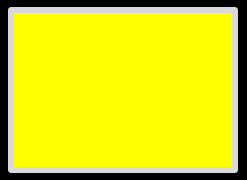
Common Co-Existing Diseases (Co-Morbidities) in Cancer Patients

- cardiac disease and other vascular diseases
- diabetes
- Alzheimer's disease and other neurodegenerative diseases (Parkinsonism)
- aging and frailty

Drug Interaction Toxicities:
Direct Blockade of Drug Metabolism Pathway for Concomitant Rx

Drug	Metabolic Pathway	Adverse Event Risk
		No
		Yes

Drug Interaction Toxicities: Blockade of Metabolism of Concomitant Drug by Metabolite(s) from Drug #1

Drug	Metabolic Pathway	Metabolites	Adverse Event Risk
			No
			Yes

Evaluation of By-Stander Exposure to Excreted Rx Product and/or Metabolites

Pharmacokinetics: Excretion

- sites (routes) of excretion
- proportion of non-metabolized Rx versus metabolites
- potential biological effects of both categories on by-standers
  - manufacturing personnel
  - HCPs, family members and other by-standers
  - environmental accumulation (e.g. endocrine disrupters)

Pharmaceutical Manufacturing

Pharmaceutical Manufacturing

Pharmaceutical Manufacturing

- cost-effective large scale production methods
- methods and drug chemical specifications used for ‘pivotal’ Phase III trials must be identical to those used post-approval (“lock-in”)
- rigorous QA/QC and FDA inspection audits
- highly specialized and expensive production facilities
  - physical separation of production areas for different Rx: air handling, water systems

Clinical Trial Monitoring and Audit

Clinical Trial Monitoring and Audit

- sponsor (Rx company) responsibility
- study sites comply with ALL aspects of the defined protocol
- all protocol violations reported to FDA
- ‘spot-check’ unannounced audits by both sponsor and FDA

Clinical Trial Monitoring and Audit

- highly complex logistics to ensure timely coordination of work in trial study centers
  - 10s-100s sites/investigators
  - increasing # of countries

Clinical Trial Monitoring and Audit: Large Scale Data Capture, Curation and Integration into the Dossier for Regulatory Approval

Clinical Trial Monitoring and Audit

Big Data

- scale
  - V4: volume, variety, velocity, validity
- security
  - data privacy and compliance with different national requirements
- speed
  - real time collection
  - preparation of regulatory dossier

Speed: Accelerating Time to Market

- impact of avoidable delays in completion of clinical trials and regulatory review
- new drug with annual sales of $100 million

Delay	Negative Impact on Lost Sales
1 day	$273,972
1 hour	$11,410
1 second	$190

- ‘blockbuster drugs’ typically have sales of $500 million to low billions (multiply above #s by 5-25)

Fingers Crossed: Decision Day
The Un-blinding of Clinical Trial Data

Submission of New Drug Application (NDA) or Biological Licensing Application (BLA) to the FDA

Drug Approval and Labeling

- specific (disease) indications
- dosing
- adverse events
- contraindications
- drug-interactions
- additional testing before use
- ‘black box’ labeling

- PDUFA: Prescription Drug User Fee Act (1992)
- two-tiered review system
- priority review
  - drugs that offer major advances in treatment
  - treatments for which no adequate therapy exists
  - 6 month review time
- standard review
  - drugs that offer only minor improvements over existing marketed therapies
  - 10 month review time

Breakthrough Therapy Designation

- FDA Safety and Innovation Act 2012 (FDASIA)
- serious or life threatening diseases
- “substantial improvement” over “existing therapies”
  - one or more clinically significant endpoints

The Quest for Faster Drug Approvals: New Designations

- fast-track (unmet medical needs)
- accelerated approval
- priority review
- breakthrough therapy

Comptonomycin (panOncRx™) Wins FDA Approval

Approval to Market Comptonomycin (panOncRx)

- demonstrating product value in an increasingly cost-constrained environment
- competition
- comparative effectiveness
- meeting Wall Street's expectations
- achieving a return on investment (ROI) to recover sunk R&D cost

The Future of Cancer Care

- demographics and increased disease incidence (burden)
- cost of care and cost control
- defining value in healthcare: a complex problem that goes well beyond cancer
- societal priorities: three “’ics”
  - genomics, economics and ethics

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YOUR ROLE!
MAKING A DIFFERENCE