ASU Complex Adaptive Systems
ARIZONA STATE UNIVERSITY

BIO 302:
APRIL 22, 2014

LECTURE 1:
DEVELOPING THERAPIES FOR CANCER: DRUG DISCOVERY, DEVELOPMENT AND REGULATION

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Confronting Cancer:
Changing Outcomes to Reduce the Massive Clinical, Economic and Personal Impact of a Devastating Disease

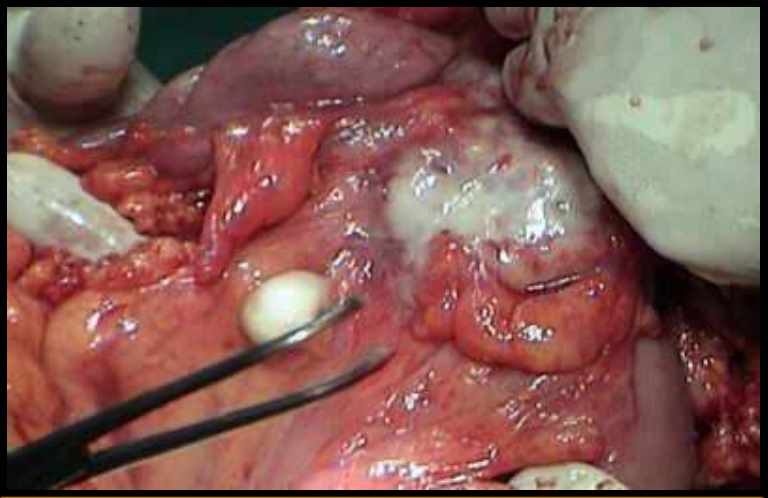
The Elusive Quest for Effective Cancer Treatments

- 134 new cancer drugs approved by FDA in last 28 years
- gains in disease-free interval/QOL but only limited gains in overall survival (OS)
- greater Rx progress in hematologic malignancies (HM) versus solid tumor (SM)
  - reduced cellular heterogeneity in HM?
- changing therapeutic paradigms
  - cytotoxic agents (1940s to present)
  - targeted therapies (1990s to present)
- unlikely prospect of major gains in OS without radical changes in therapeutic strategies
  - understanding the complex evolutionary ecology of tumors and their escape from homeostatic histiotypic control systems

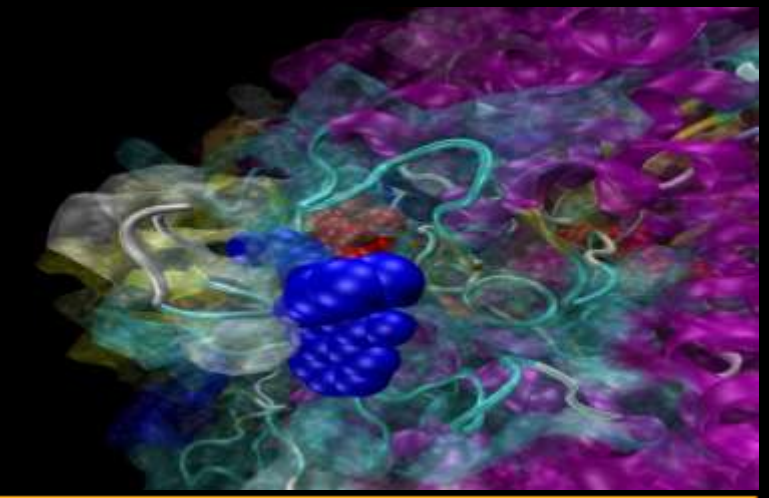
Dynamic Clonal Heterogeneity in Tumor Progression: The Most Clinically Dangerous Phenotypes

Evasion of Detection/Destruction by Host Immune System

Use of Host Systems to Promote Progression



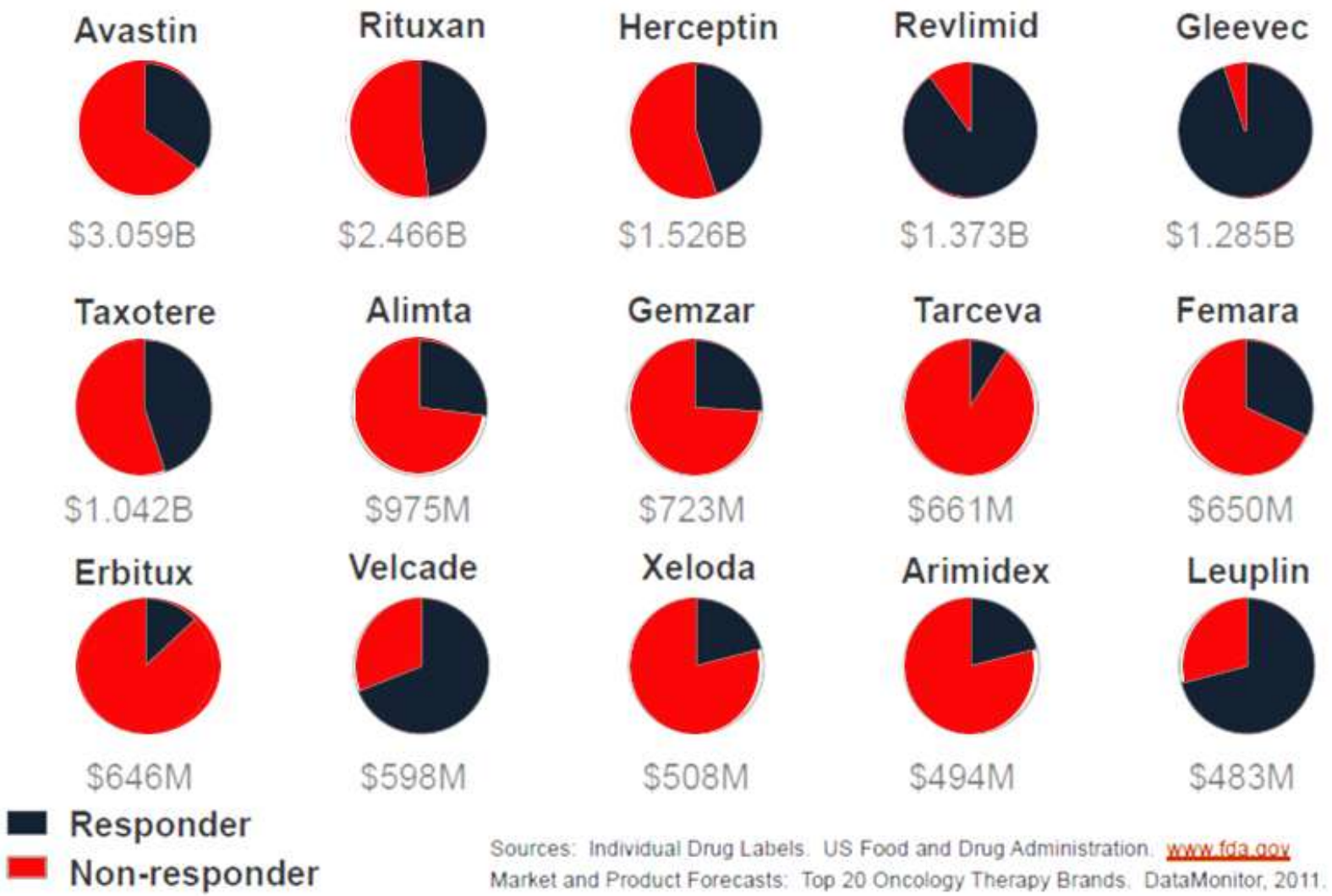
Invasion and Metastasis



Emergence of Drug-Resistant Clones

The Current Status of Too Many Therapeutic Decisions in Cancer

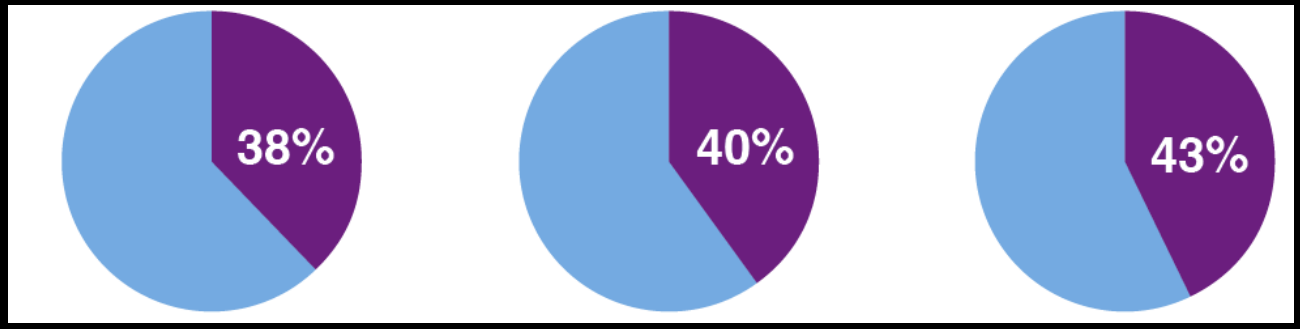
Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly



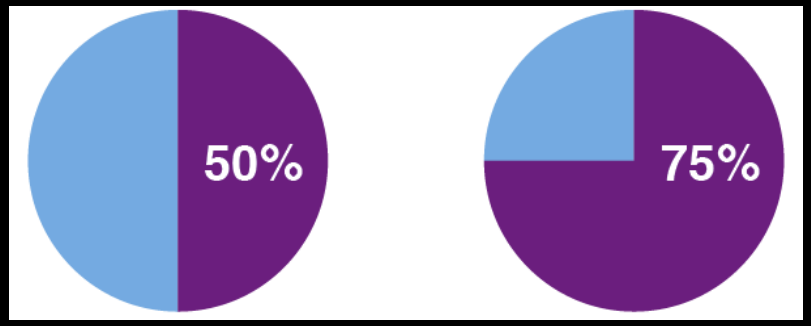
Sources: Individual Drug Labels. US Food and Drug Administration. www.fda.gov
Market and Product Forecasts: Top 20 Oncology Therapy Brands. DataMonitor, 2011.

One Size Does Not Fit All: The Huge Economic Waste in Therapeutics

Percent of population for whom class of drugs do not work



Antidepressants Asthma Diabetes



Arthritis Cancer

Cost of Ineffective Rx

- 90% of drugs work in only 30-50% individuals

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

The Biological Complexity of Cancer and the Design of Future Treatment Strategies

- successful surgical removal of primary tumor assumed (except brain tumors)
- targeting metastatic disease and circumventing Rx resistance
  - subclinical (adjuvant Rx)
  - clinically evident advanced metastasis
  - minimal residual disease and tumor dormancy

The Biological Complexity of Cancer and the Design of Future Treatment Strategies

Formidable Performance Requirements

- hit all clones
- hit all clones in multiple metastases in multiple body locations
- hit all new emergent Rx-resistant clones

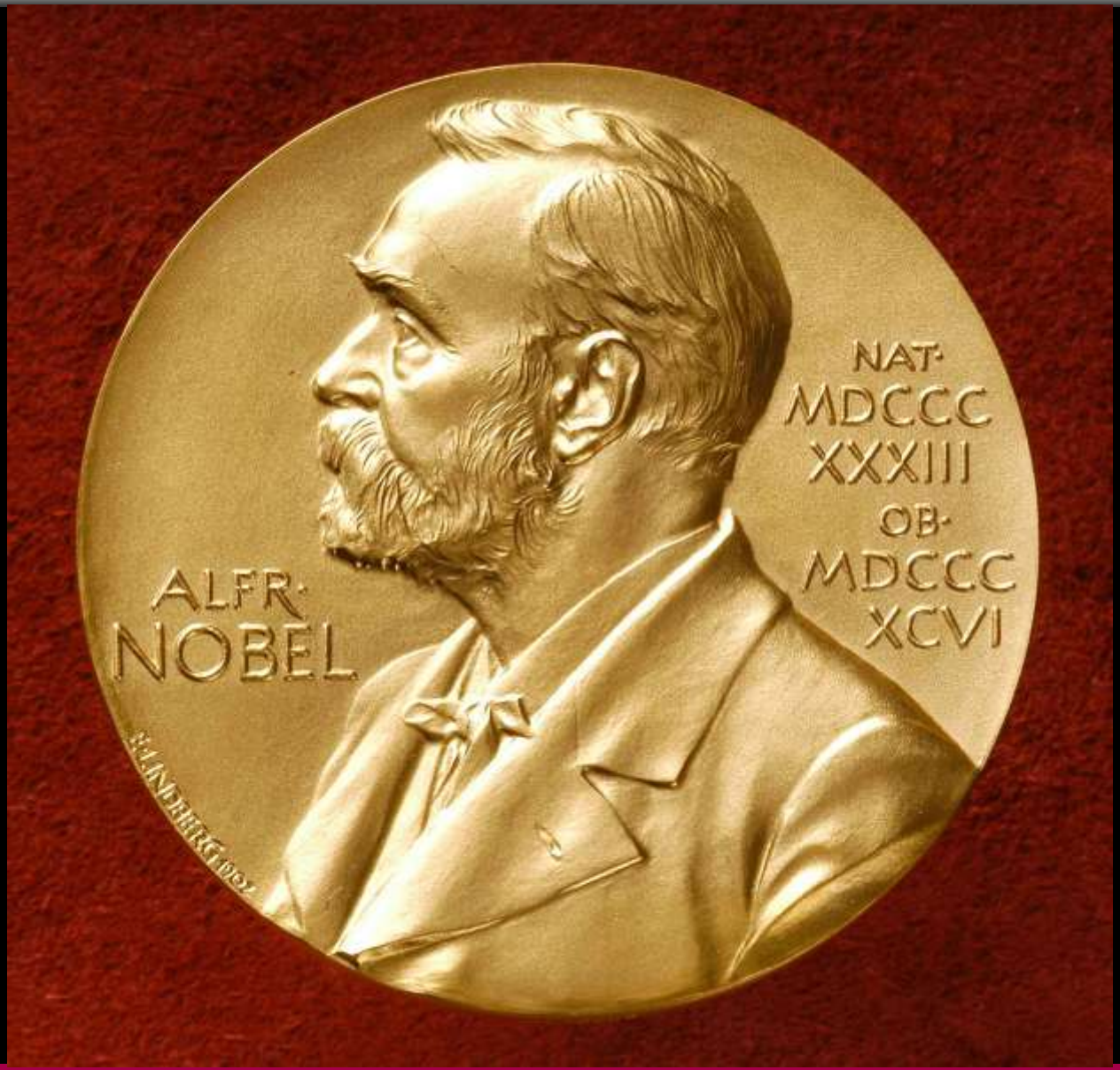
Future Innovation from the 2014 Class of Bio302?

ASU Complex Adaptive Systems

ARIZONA STATE UNIVERSITY

BIO 302:

The Discovery of Comptonomycin (panOncoRx)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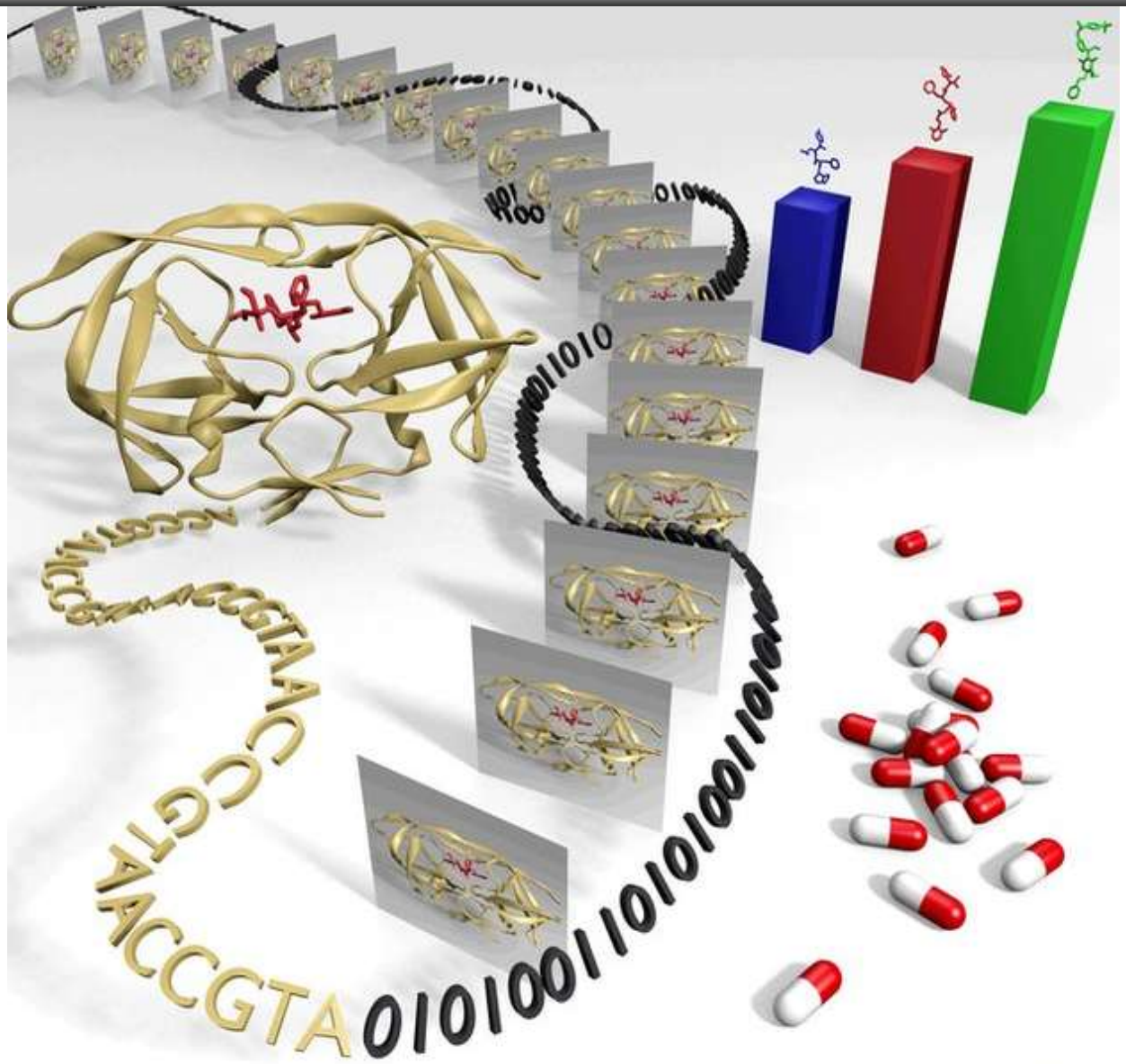
The Journey of Comptonomycin: From Discovery to Regulatory Approval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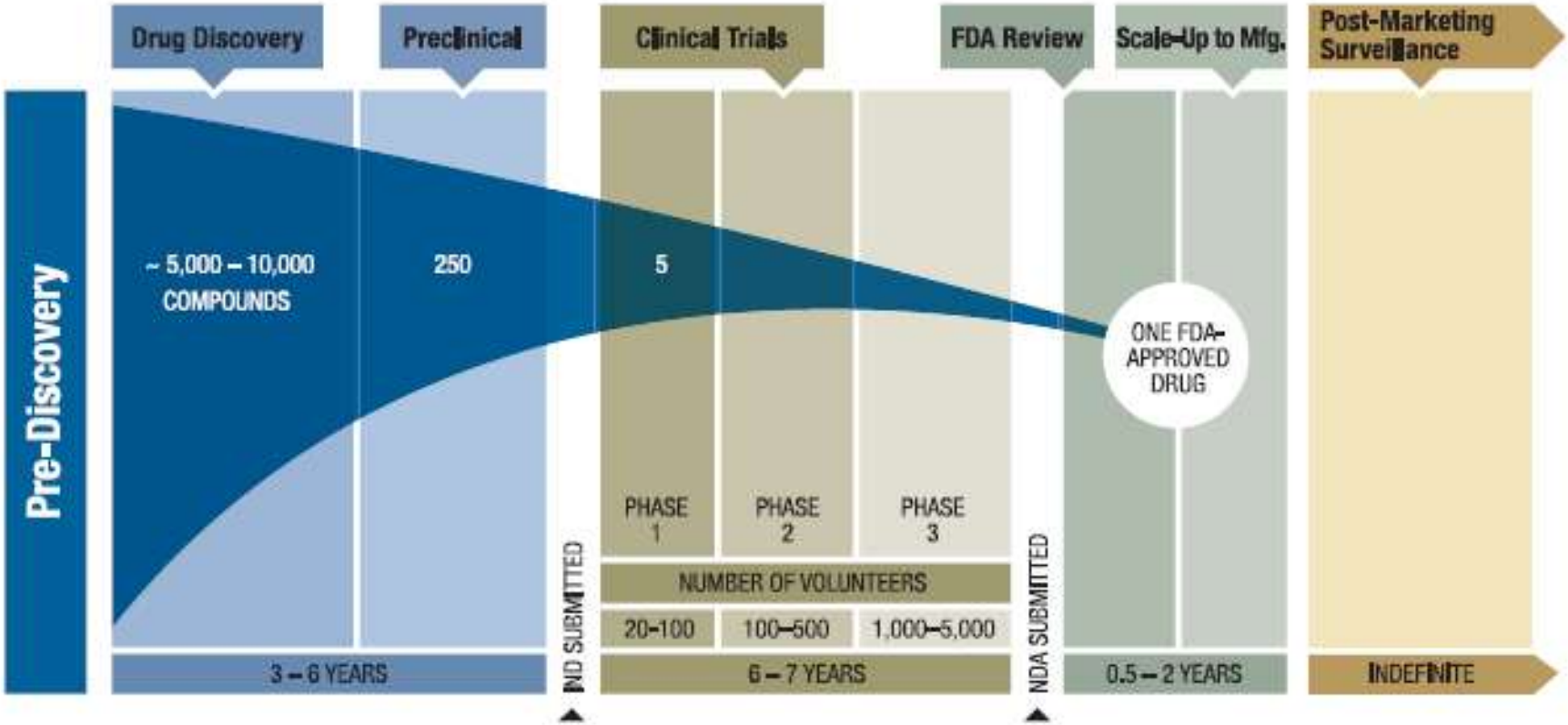
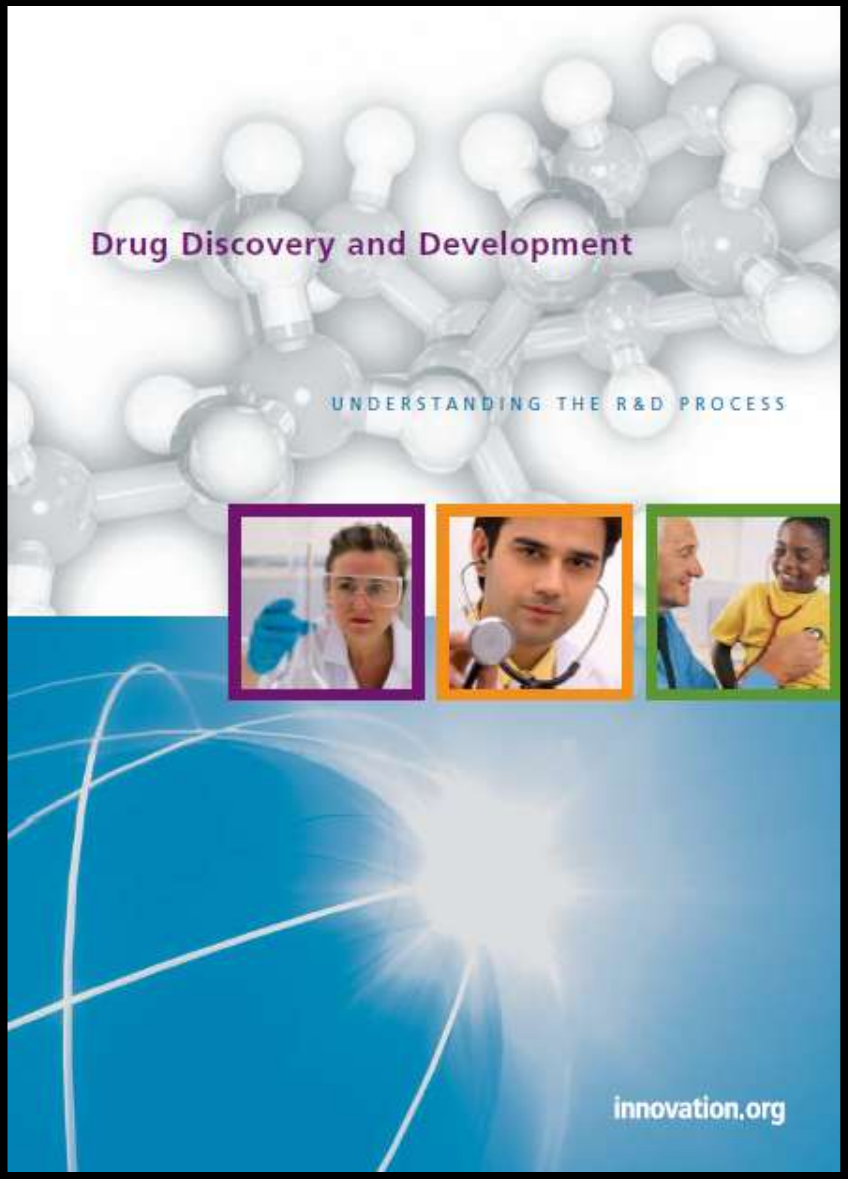
(Bio) Pharmaceutical R&D: How Much Does It Cost to Successfully Develop a New Pharmaceutical Drug or Biological Agent?

- $100 million?
- $250 million?
- $500 million?
- $1 billion?
- $1.5 billion?
- $2.5 billion?

The Complexity and Protracted Process of New Drug Development




Drug Discovery and Development
UNDERSTANDING THE R&D PROCESS
innovation.org

The Challenge of Successful Drug Delivery

Stage	Preclinical		Phase I		Phase II		Phase III		Regulatory Review
Percent Success	70%	X	50%	X	35%	X	50%	=	5% overall success
Cost $MM	10	X	15	X	100-150	X	300-1 billion	=	450 to 1 billion plus
Time Years	2	X	1.5	X	2	X	4-8	=	9.5 to 13.5

Drug Classes

(Bio) Pharmaceutical R&D

- small molecules (M_r typically <500 Daltons)
- biologicals (nucleic acids, genes, proteins, monoclonal antibodies, vaccines)

(Bio) Pharmaceutical R&D

- small molecules (M_r typically <500 Daltons)
  - proprietary drugs (on patent) and generic versions (off-patent)
- biologicals (nucleic acids, genes, proteins, monoclonal antibodies, vaccines)
  - proprietary biologicals (on-patent) and biosimilars (off patent)

Regulatory Criteria for Drug Approval

- safety
- efficacy

- safety
- efficacy
- cost-effectiveness
- separate review for regulatory approval (EU wide) and pricing (national)

- Center for Drug Evaluation and Research (CDER)
  - small molecules
- Center for Biologics Evaluation and Research (CBER)
  - biologicals
- Center for Devices and Radiological Health (CDRH)
  - diagnostic tests

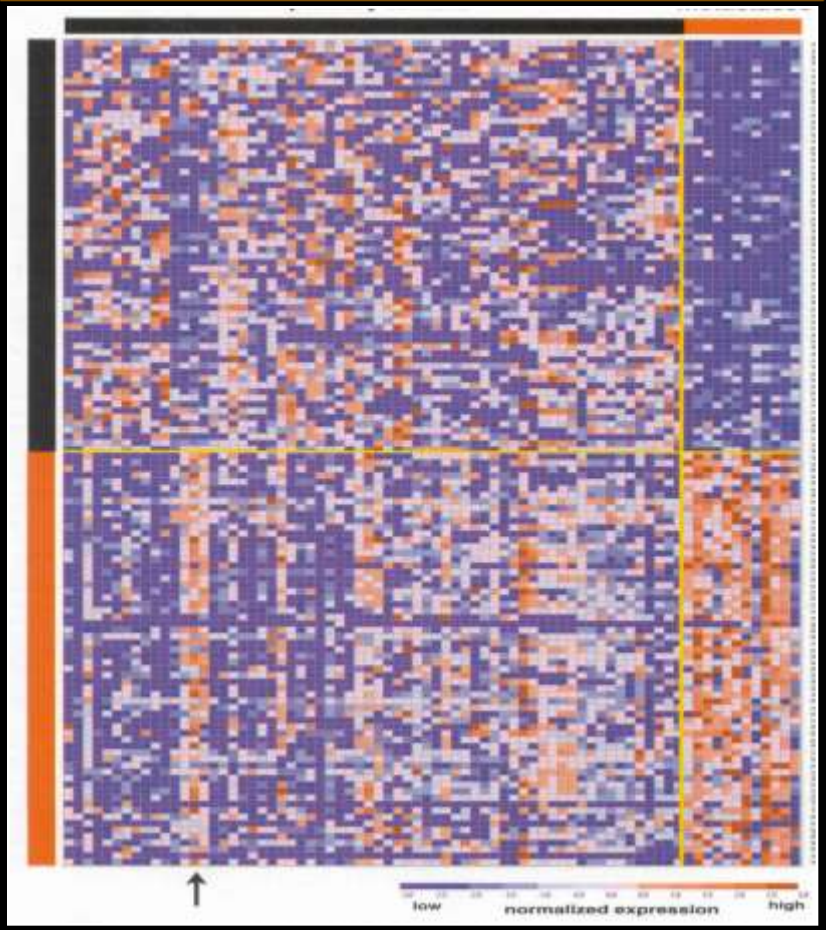
FDA Review and Approval of New Drugs and Vaccines

- Investigational New Drug (IND) application
- New Drug Application (NDA)
  - small molecular weight drugs
- Biological Licensing Application (BLA)
  - biologicals
  - vaccines
- approval and labeling
- post-approval obligations
  - REMS (risk evaluation measurement system)
  - SENTINEL (adverse event monitoring)

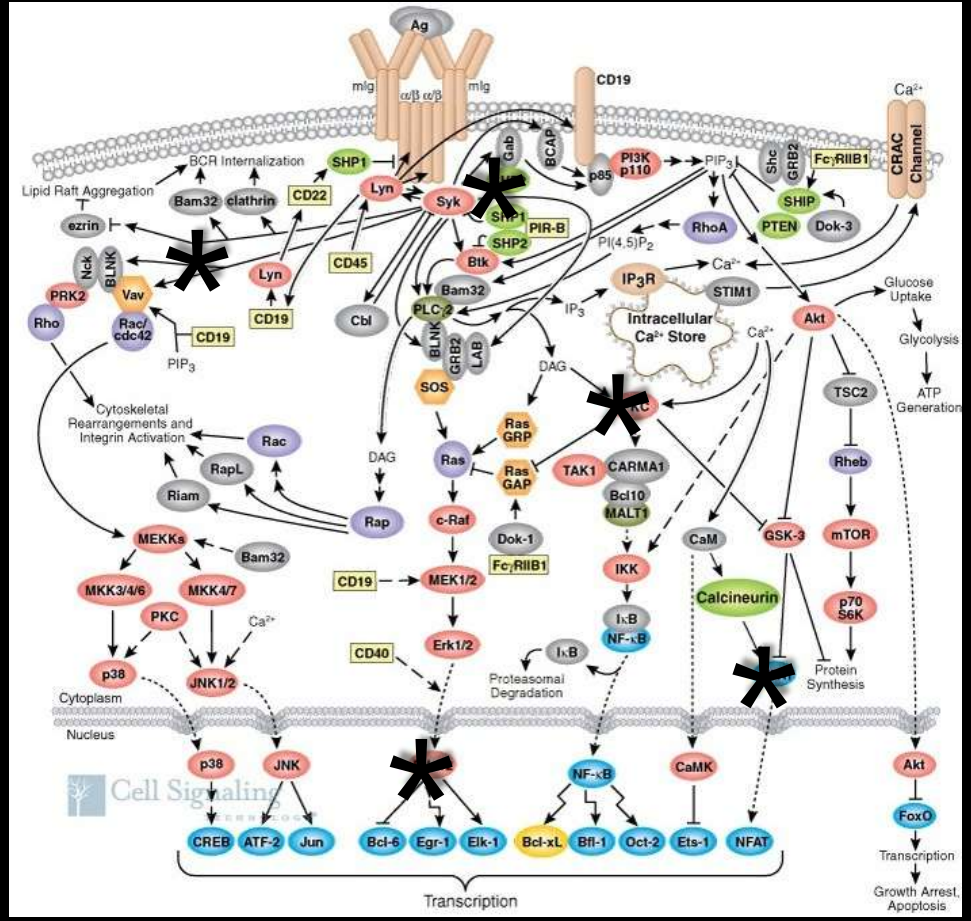
Drug Discovery

Mapping Dysregulation of Biological Networks in Disease

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



ID Molecular Targets for Rx Action and Blockade of Compensatory "By pass" Pathways



“Druggability”

Different Molecular Targets Pose Different Challenges for Drug Discovery

The Challenge of “Druggability”

- druggable targets
- non-druggable targets

The Challenge of “Druggability”

- surface receptors ● versus intracellular targets ● (access)
- target altered in disease ● versus normal cells ● (lower risk of toxicities)
- over-expression of the target in disease ● versus reduced expression/deletion in disease ●
- knocking out the target (antagonism) ● versus restoration of function (agonism) ●
- targets that are individual molecular nodes in a network ● versus ‘hubs’ connected to multiple nodes ●
- successful control of by-pass pathways as driver of Rx-resistance ●

Rx Blockade of Target Molecule Function (Antagonism) Is Easier to Achieve Than Restoration of Target Molecule Function (Agonist)

Cancer Driver Genes as Rx Targets

Oncogenes

- gain-of-function mutations
- antagonist Rx (targeted therapies to block activity)

Tumor Suppressor Genes

- loss-of-function mutations
- agonist Rx (restore function)

Cancer Driver Genes as Rx Targets

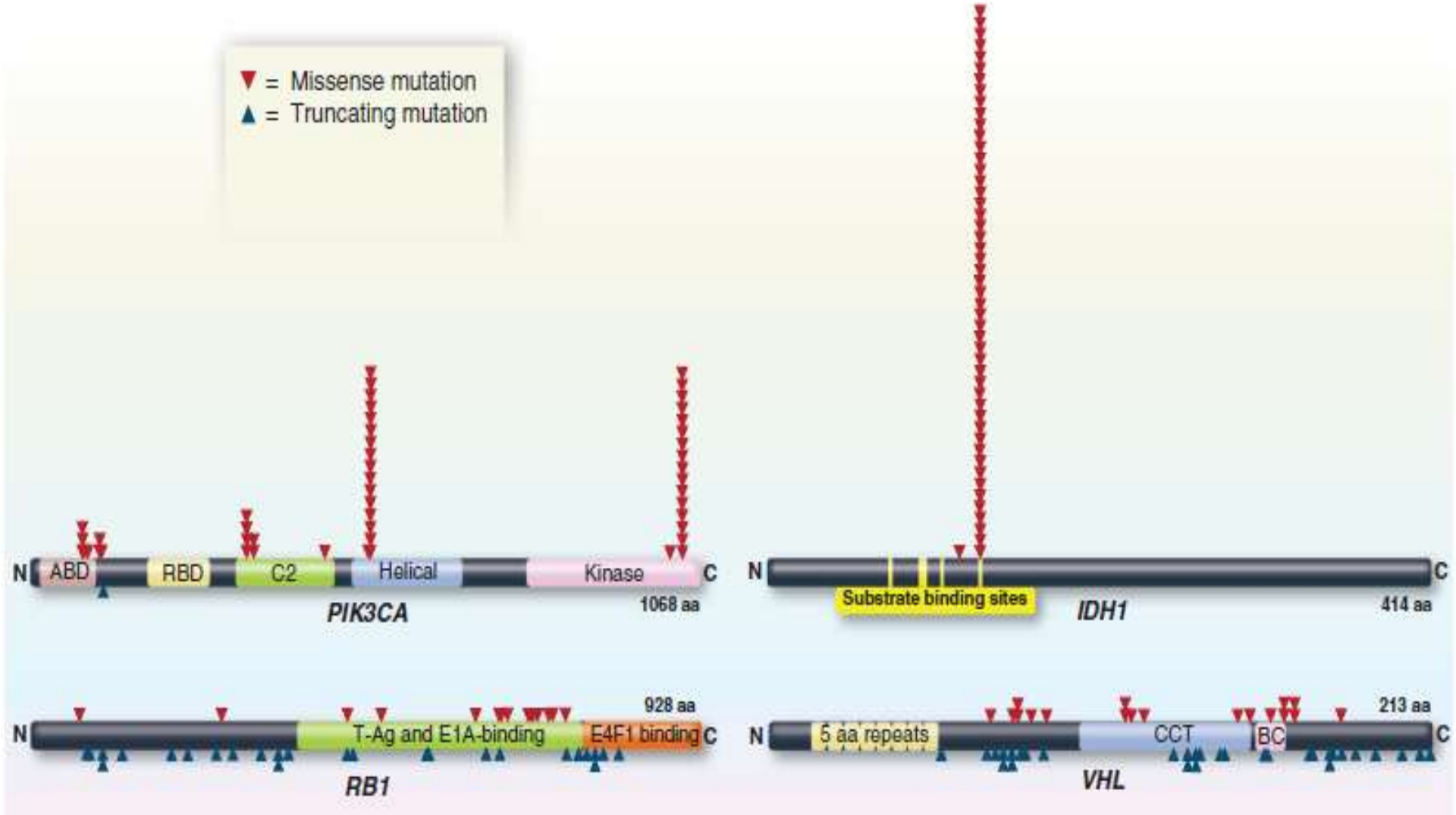
Oncogenes

- gain-of-function mutations
- antagonist Rx (targeted therapies to block activity)
- range of Rx design options

Tumor Suppressor Genes

- loss-of-function mutations
- agonist Rx (restore function)
- far more difficult Rx design (very few examples in any therapeutic area)

Distribution of mutations in two oncogenes (PIK3CA and IDH1) and two tumor suppressor genes (RB1 and VHL)

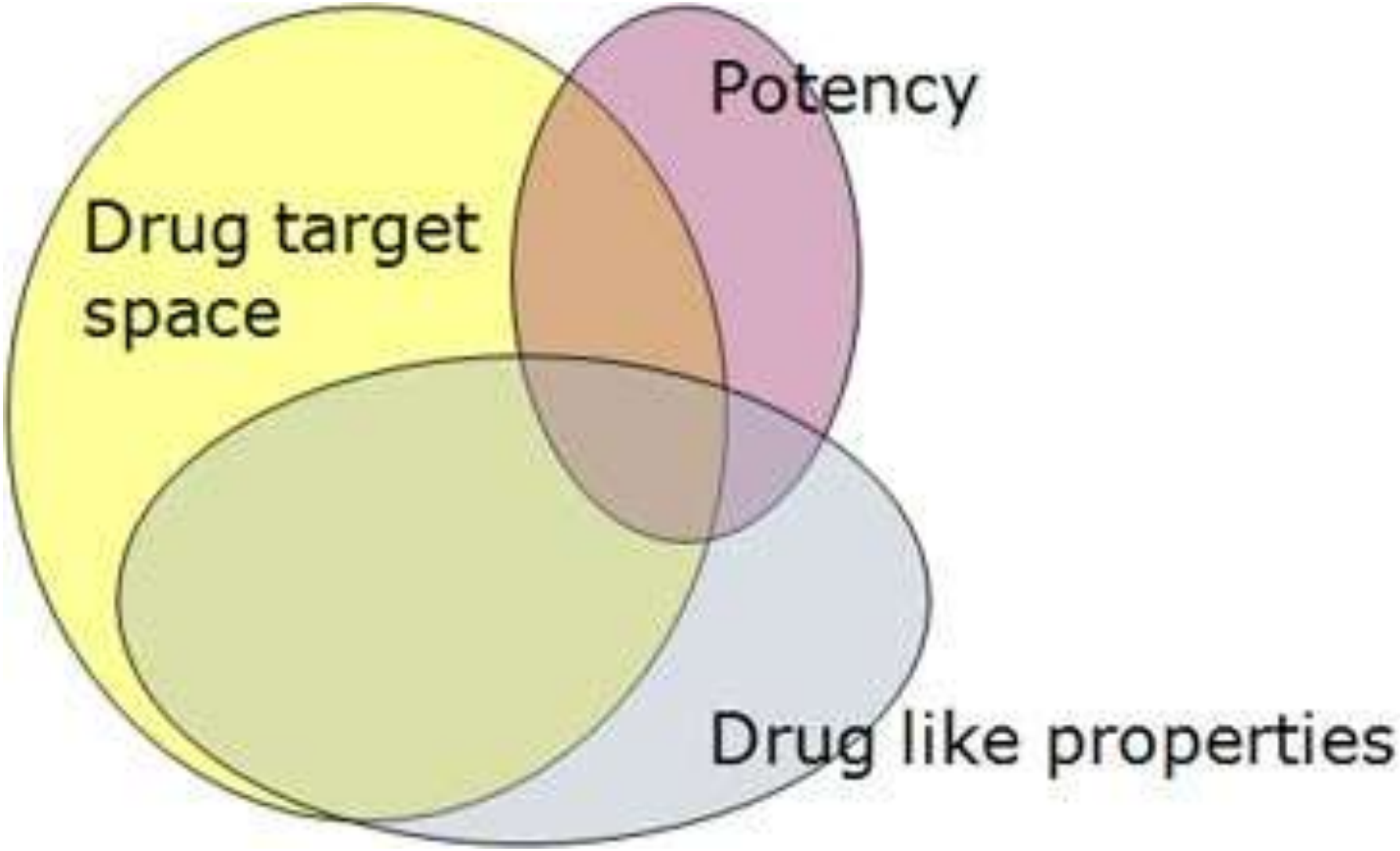


From: B. Volgelstein et al. (2013) Science 339, 1546

Targeting the Elusive Mutated K-RAS Gene in Cancer

- 30% of human tumors
- 90% of pancreatic cancers
- 40% of colon cancers
- 20% of non-small cell lung cancers

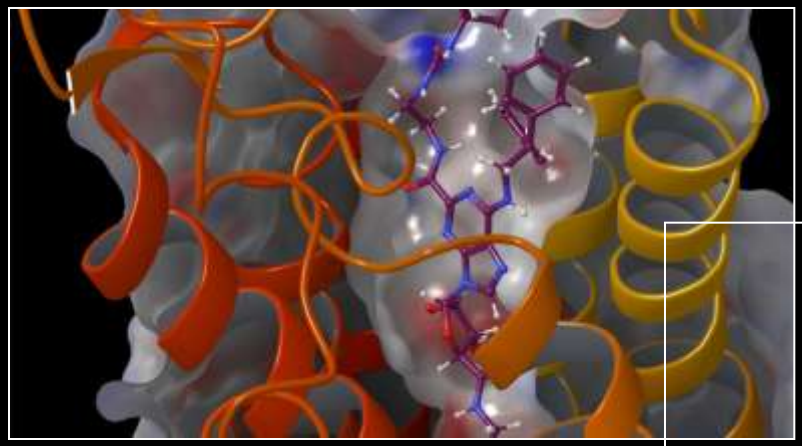
Matching Drug Candidates to Molecular Targets

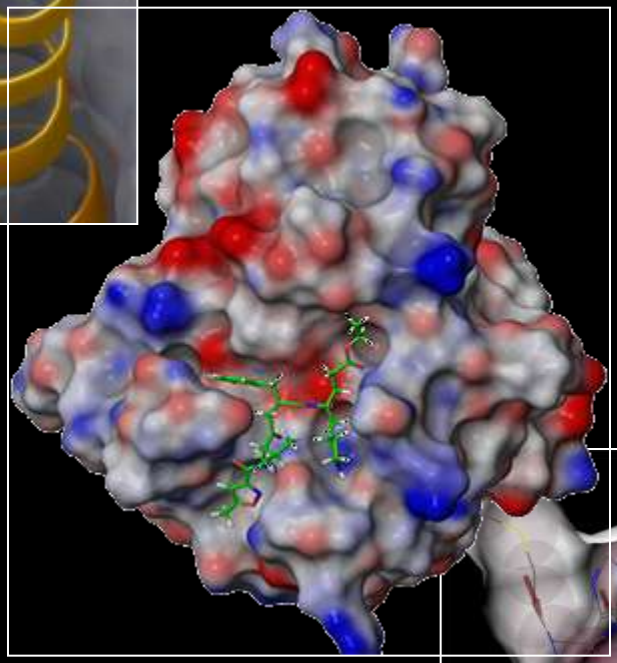


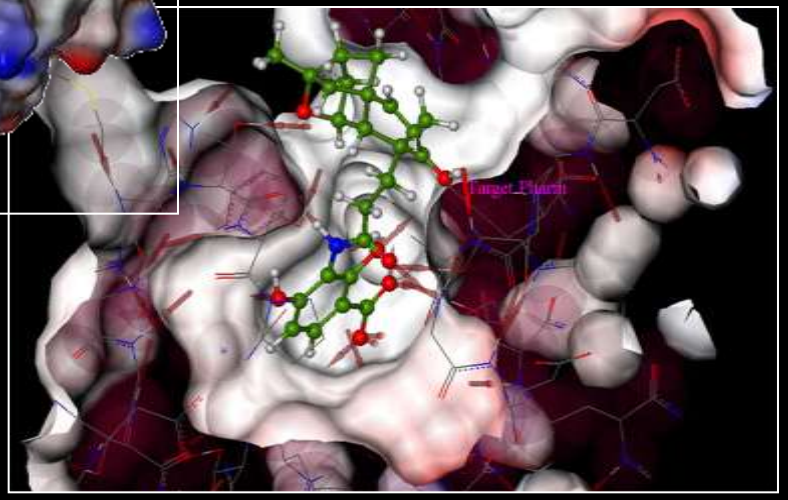
Drug Discovery: Two Approaches

- rational drug design based on knowledge of detailed structure of the desired target
- screening of libraries of structurally diverse molecules against desired target(s) to identify ‘hits’ for subsequent refinement as potential candidate Rx

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



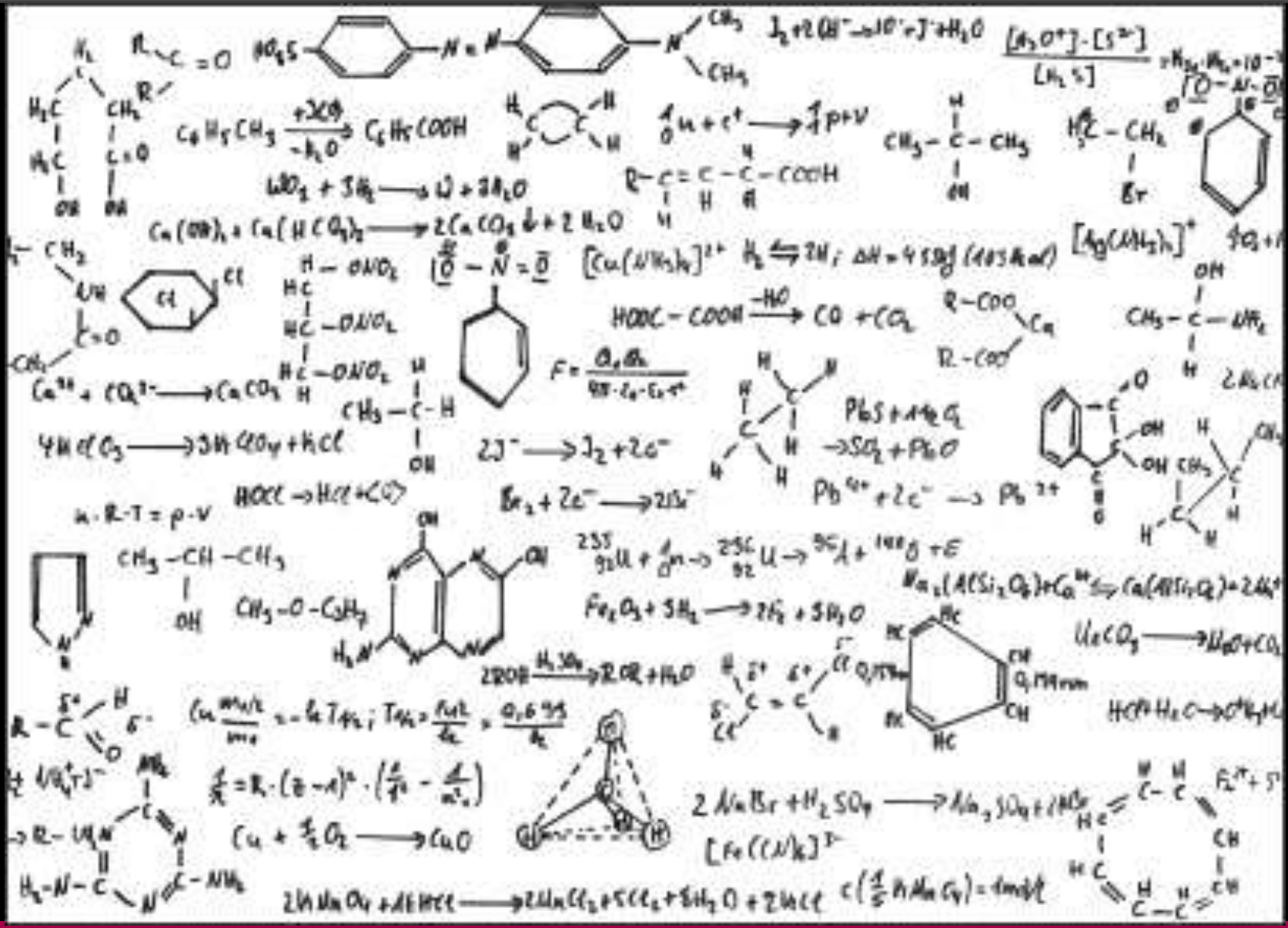




Drug Discovery
Rational Drug Design of Small Molecule Candidates

- low molecular weight heterocyclic molecules
- prediction of likely desired activity of a candidate molecule based on its chemical structure/reactivity and knowledge of the tertiary (3D) structure of the target
- databases of accumulated knowledge of drug-like properties and structure activity relationships (SAR) of particular classes of chemical structure

The Value of Experience and Creativity



Understanding How Different Chemical Structures Interact with Different Target Molecules

DrugBank

Therapeutic Targets Database

BIDD
Bioinformatics and Drug Design group

PDTD [Potential Drug Target Database]

SNOMED® INTERNATIONAL

DRUGDEX

CTSA Pharmaceutical Assets Portal

The NCGC Pharmaceutical Collection version 1.0.19

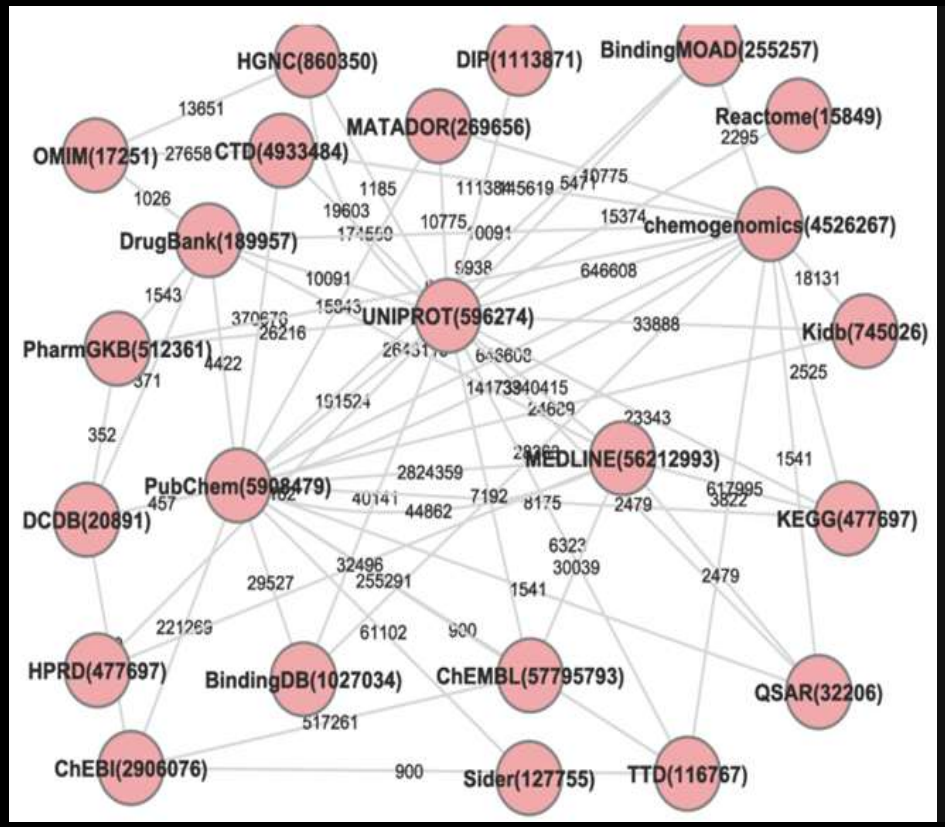
PharmGKB
Pharmacogenomics Knowledge Base

Drug-Disease Knowledge Base (DrDKB)

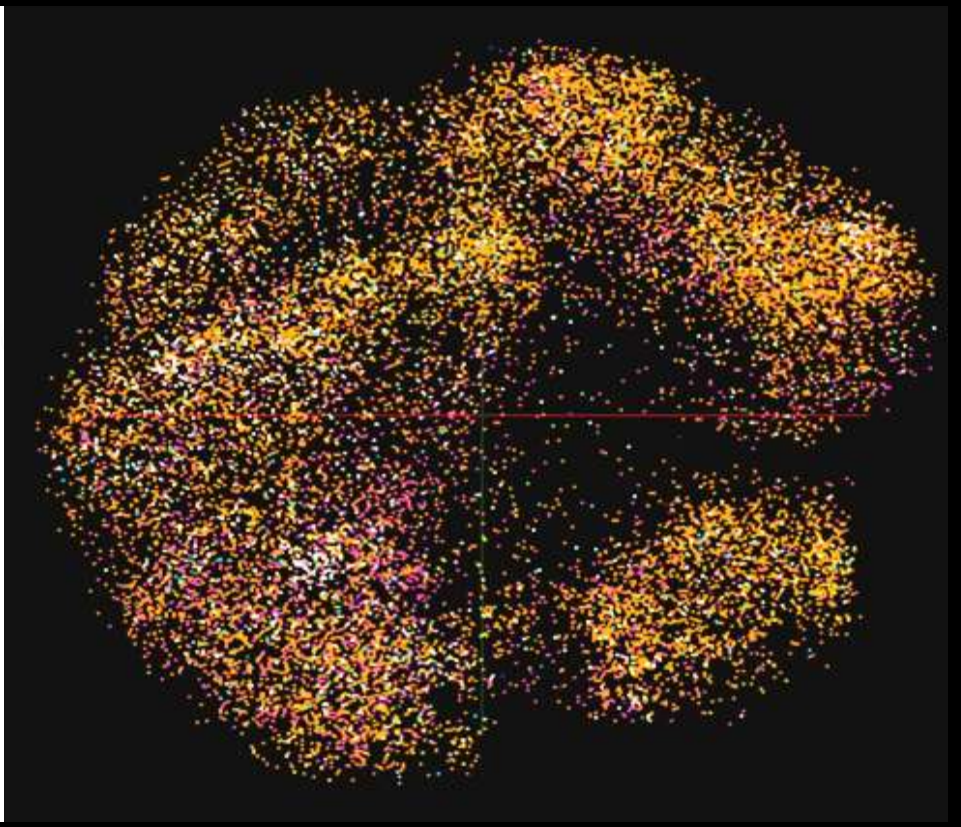
chem2bio2rdf

Big Data in Drug Discovery

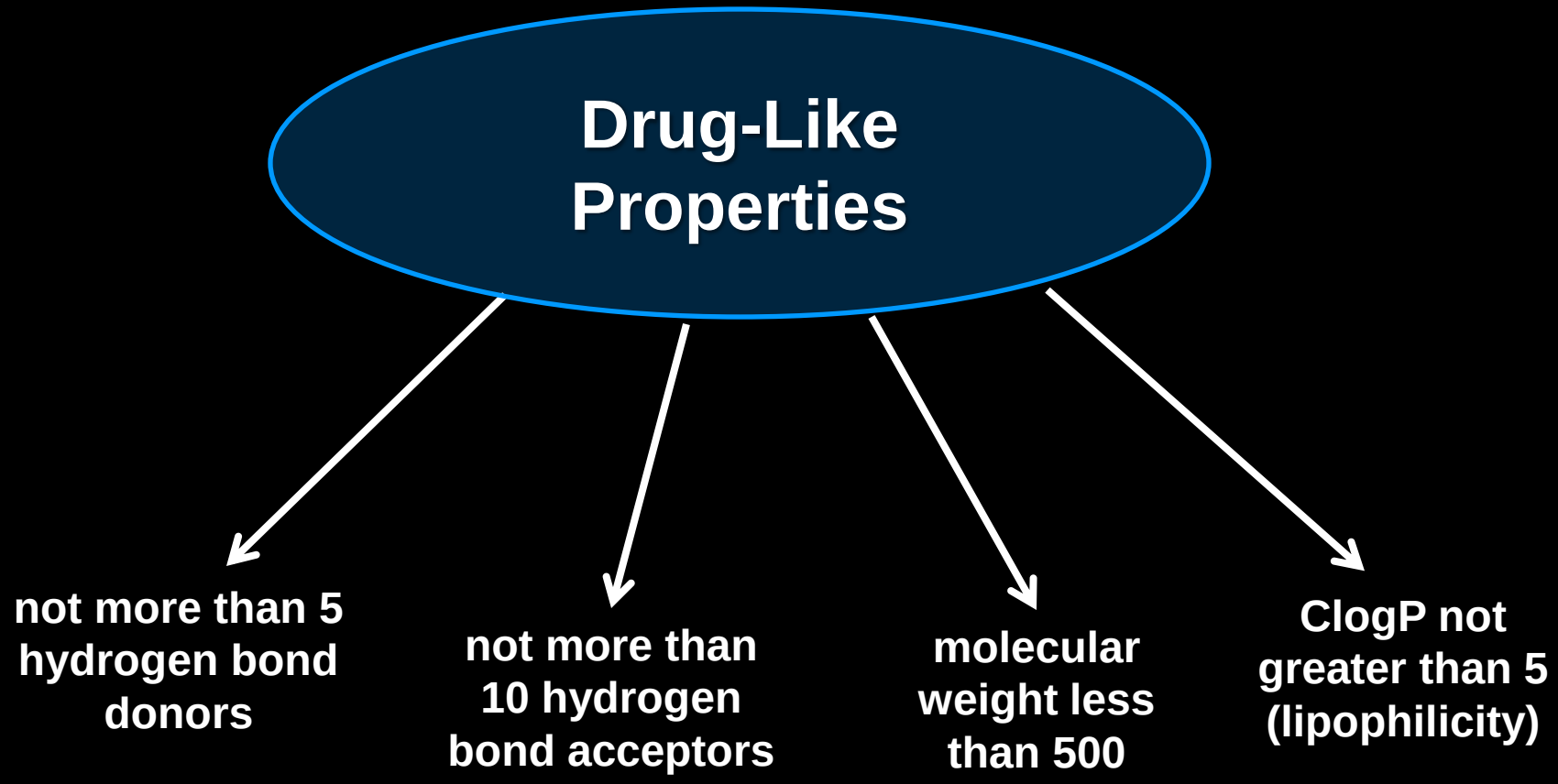
Chem2Bio2RDF



Mapping Large Scale Chemoinformatics Space



Lipinski's Rule of Five for Drug-Like Properties for Small Molecules



Automated High Throughput Screening of Structurally Diverse Chemical Libraries to Identify ‘Hits’ as Leads for Drug Discovery

Drug Discovery
Automated High Throughput Screening (HTS) of Small Molecule Candidate Rx

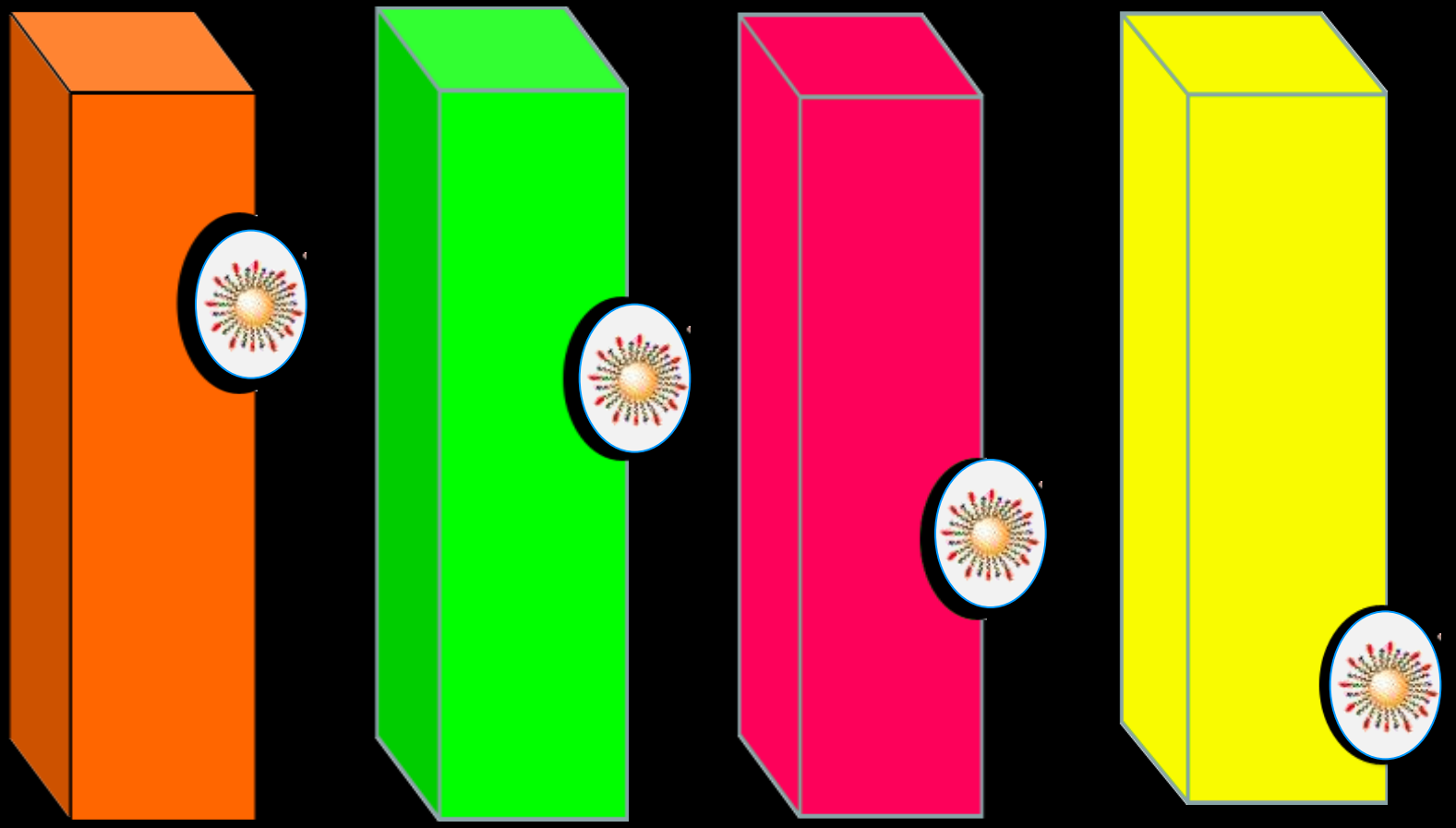
- screen large ‘libraries’ of compounds for interaction with proposed target
  - 100,000 or more chemical candidates
- screen ‘focused’ libraries of 5-10,000 compounds based on prior knowledge of likely potential to interact with the target
- identification of ‘leads’ (5-10) for more detailed exploration of action of the target
  - target specificity or promiscuity for multiple targets?
  - binding affinities

Assessment of Rx Activity

pharmacodynamics

- interaction of Rx with molecular target(s)
- agonist or antagonist?
- binding affinity and kinetics: reversible or irreversible?
- direct action at active site on the target or allosteric effects?

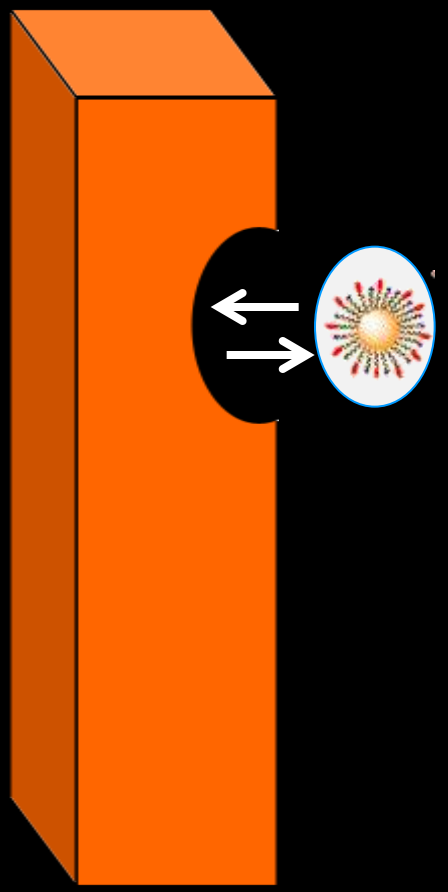
Pharmacodynamics



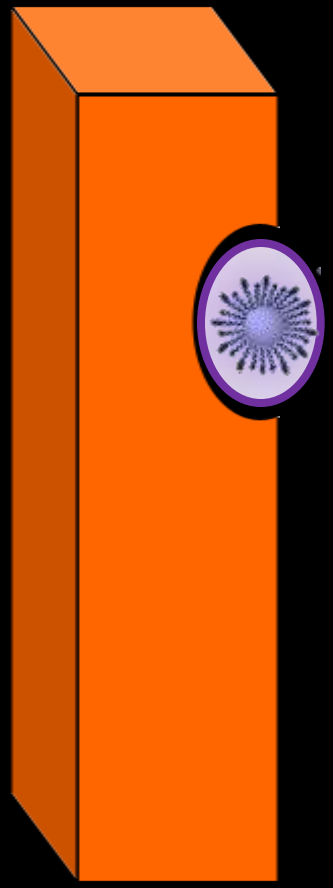
desired target molecule

off-target binding to non-target molecules with structurally-related binding sites (benign effects or toxicity)

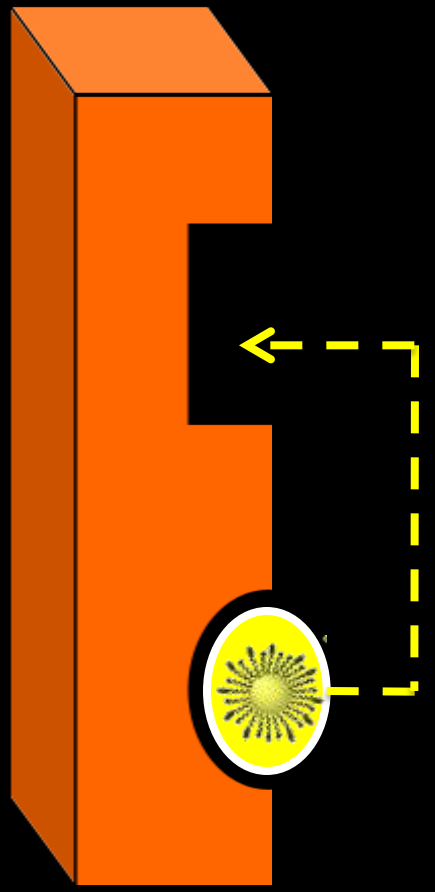
Pharmacodynamics



reversible binding to active site on the target



irreversible binding to active site on the target



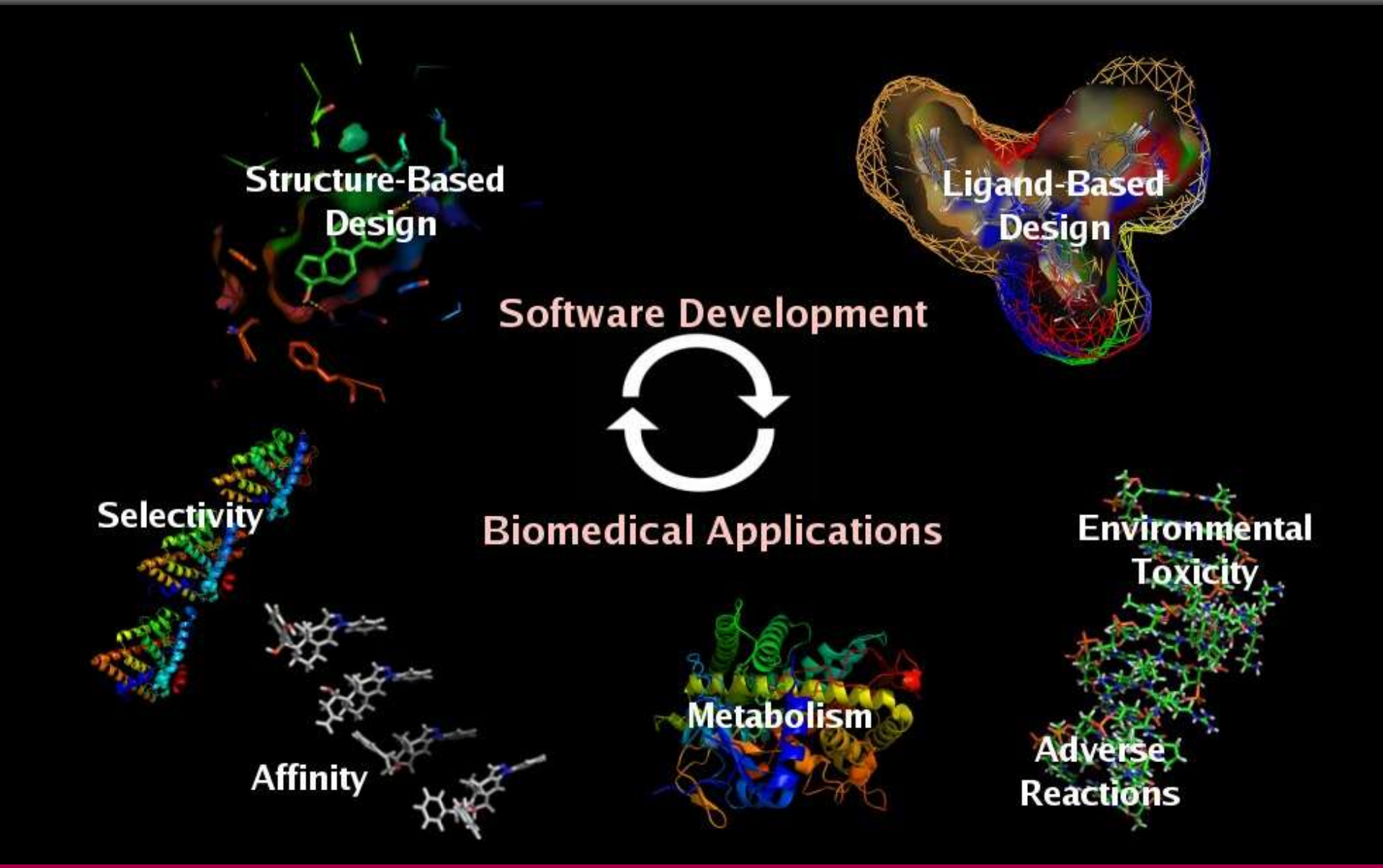
allosteric binding to target at non-active sites induces structural change in active site

Thinking About ‘Downstream’ Development Challenges

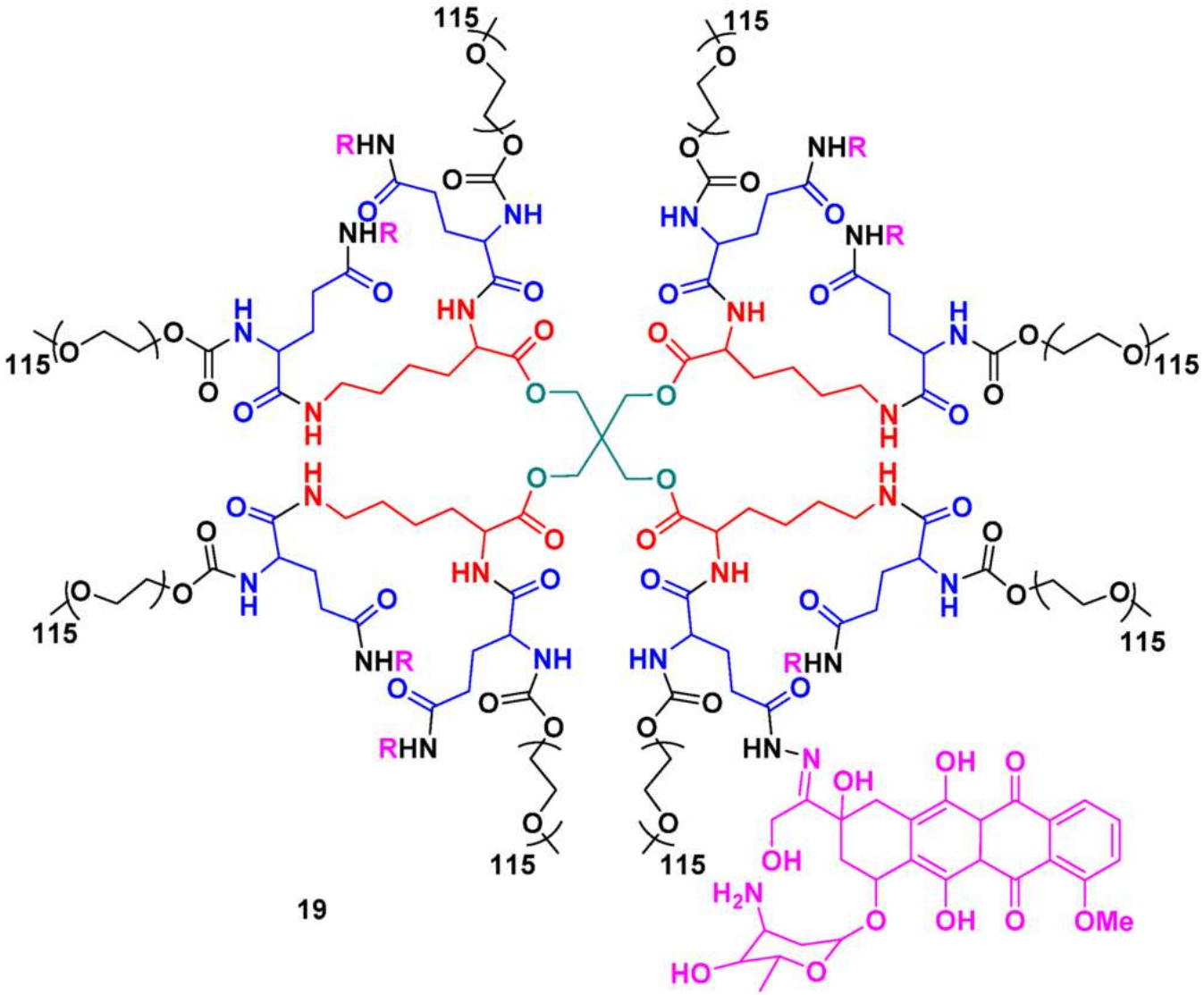
Thinking About ‘Downstream’ Development Challenges

- pharmacokinetics
- toxicology
- pharmaceutical formulation
- cost and complexity of scale up of chemical synthesis for clinical trials and eventual marketing

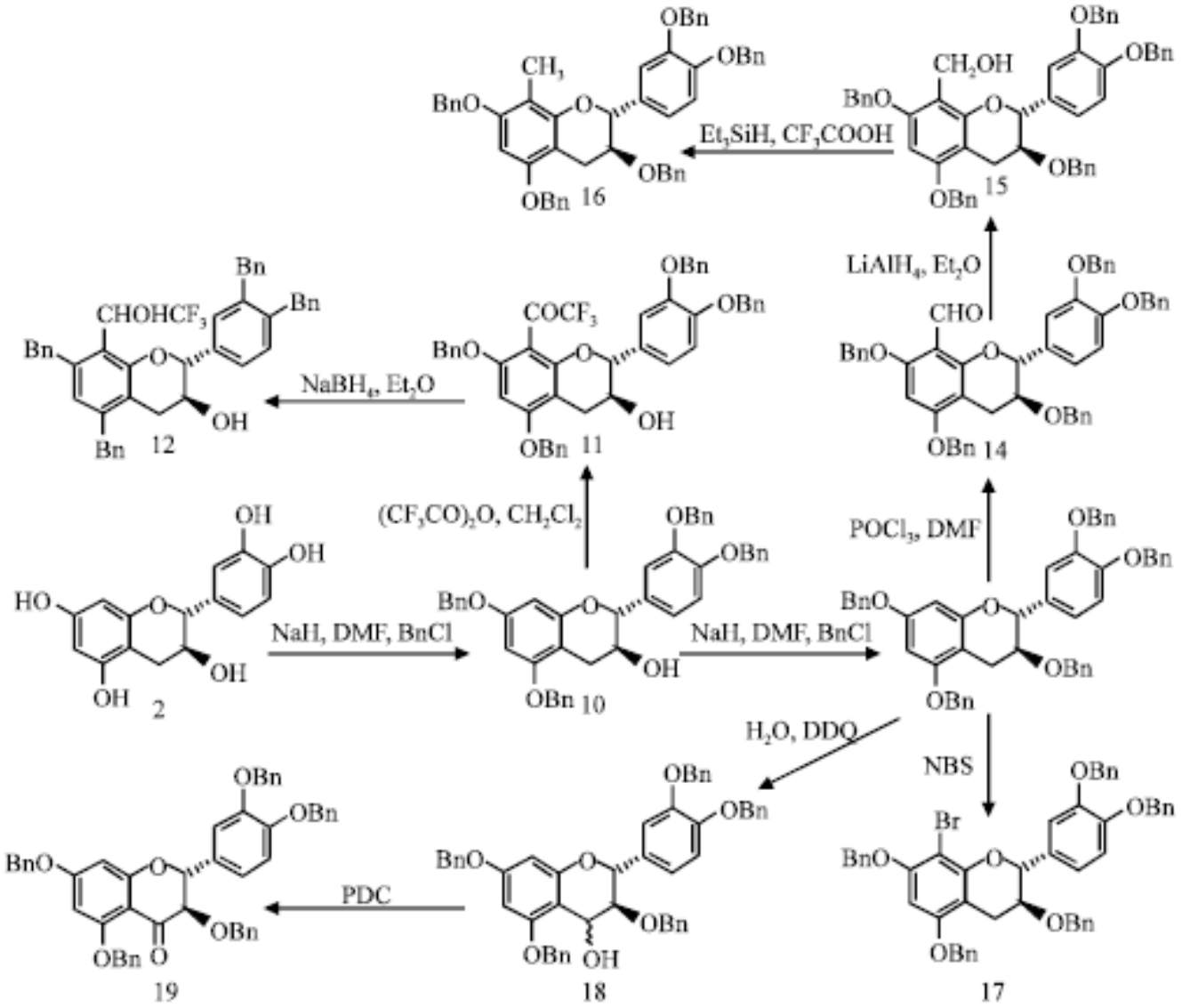
Computer-Aided Drug Discovery



Structural Complexity as Barrier to Cost Effective Large Scale Chemical Synthesis



Multi-step Synthesis as an Economic Barrier to Cost-Effective Large Scale Synthesis



Drug Discovery:
A Complex Multi-Disciplinary Exercise

Drug Discovery
A Complex Multi-Disciplinary Exercise

- multiple specialized “ologies”
  - oncology, gastroenterology, neurology, cardiology, nephrology….
  - physiology, pathology, toxicology
- analysis and curation of large scale datasets
  - V4: volume, variety, velocity, validity
  - computational science, informatics
  - novel algorithms for big data

Drug Discovery
A Complex Multi-Disciplinary Exercise

- chemistry
  - synthetic, analytical
  - scale up technologies
  - formulation technologies
  - materials science

Drug Discovery
A Complex Multi-Disciplinary Exercise

- specialized support services
  - animal facilities
  - biobanks
  - large scale instrumentation resources (mass spec., electron microscopy, ‘panOmics’…..)
- regulatory compliance
  - Good Laboratory Practice (GLP)
  - verifiable records for FDA inspection
  - relentless QC/QA audit

Progress:
The Transition to Preclinical Development

Preclinical Development

- complex series of tasks to fulfill regulatory requirements for first human tests
- large scale chemical synthesis
- pharmacokinetics
- toxicology
- pharmaceutical formulation and purity

Pharmacokinetics

Assessment of Rx Activity

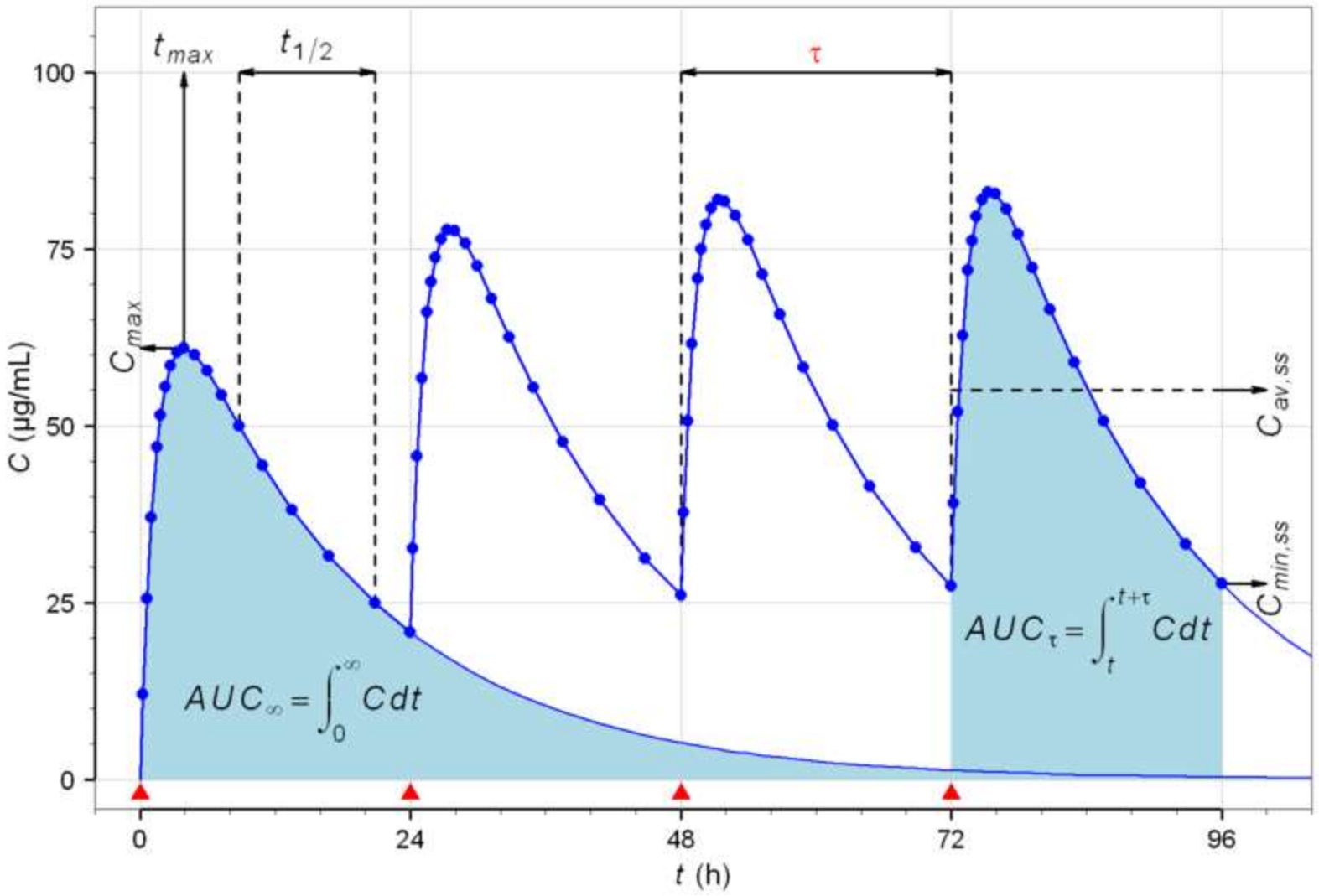
pharmacokinetics

- timing and pattern of accumulation of Rx and its metabolites in tissue and body fluids

Preclinical Development: Pharmacokinetics

- ADME
- Absorption, Distribution, Metabolism and Excretion
- typically studied in three species
  - rodents or rabbits, dogs, primates

Plotting Rx Pharmacokinetics: Concentration and Clearance



Preclinical Development: Pharmacokinetics

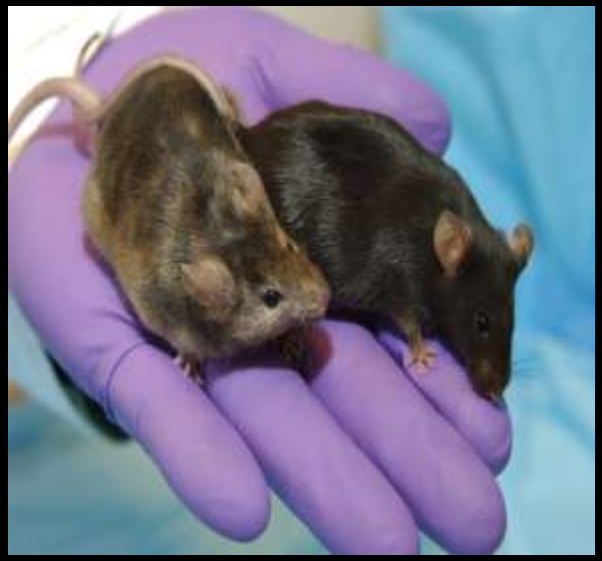
- ADME: **A**bsorption, **D**istribution, **M**etabolism and **E**xcretion
- kinetics and sites of tissue uptake (A and D)
- time to maximum concentration in blood/tissue and kinetics of clearance (A, D and M)
- ADME variation with different dosage levels
- ADME variation with extended dosing
  - acute vs chronic administration
  - drug tolerance (tachyphylaxis)

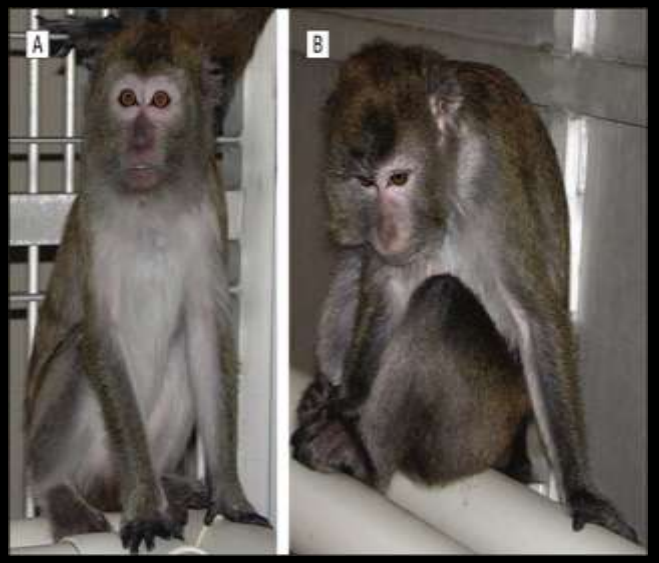
Preclinical Development: Pharmacokinetics Metabolism (M)

- characterization of metabolic sites and molecular pathways for metabolic degradation
- liver > GI > kidney as typical metabolic sites
- identification of different class I/II drug metabolism enzyme isoform pathways
- impact of genetic variation in drug metabolism enzymes on clearance (pharmacogenetics)
  - slow, intermediate and fast metabolizers

Preclinical Toxicology Testing

Drug Safety Testing in Laboratory Animals





Drug Safety Testing in Laboratory Animals

- contentious issue but formal regulatory requirements
- the 3R's
  - refine, reduce, replace
- the 'fourth R' (relevance)
  - relevance to human disease processes
  - cultured cell lines largely inadequate
- variable validity for extrapolation of laboratory animal data to human trials

Preclinical Development: Toxicology

- acute, subacute and long term toxicology assessment
  - 30 days, 6 months, 2 years
- assessment of multiples of anticipated human dose
  - input from preclinical pharmacokinetic studies of peak plasma/tissue concentrations to establish dose multiples

Preclinical Development: Toxicology

- 30 day (acute) profiling typically sufficient to initiate human Phase I trials
  - rodents, rabbits and larger mammals (dogs, pigs)
- 6 month and 2 year trials
  - rodents
- selective use of non-human primates/primates
  - depends on Rx mode-of-action and whether it is active in lower species

Scale-Up of Drug Synthesis

Purity, Stability and Cost

Preclinical Development

- rigorous QA/QC compliance and FDA inspection
- scale up synthesis method ‘locked in’ to ensure that initial clinical trials conducted with identical materials to those used in preclinical testing
- all instrumentation calibrated an documented at defined intervals
- all processes, procedures and documentation must fulfill FDA Good Laboratory Practice (GLP) requirements

Preclinical Development: Pharmaceutical Formulation

- stability of Rx substance
  - 2 year shelf-life requirement
- storage requirements
  - room temp. or refrigerated (most biologicals)
  - thermotolerance in more extreme climates
- interaction with components in Rx containers or delivery systems

The Great Day Arrives!
Comptonomycin is Ready to Begin Human Clinical Trials