

Translational Science Training Program

An overview of the drug development process

Rajesh Ranganathan, PhD

VP, & Head, Corporate Development
Sun Pharma Advanced Research Company (SPARC)

Apr 2023

Drugs and drug discovery

Drug:

Broadly defined as any chemical agent that affects processes of living

Drug discovery:

Process of discovery and/or design of drugs

Drugs and drug discovery

Drug:

Broadly defined as any chemical agent that affects processes of living

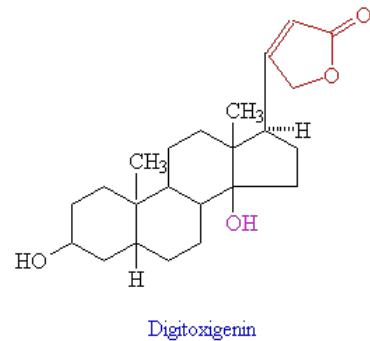
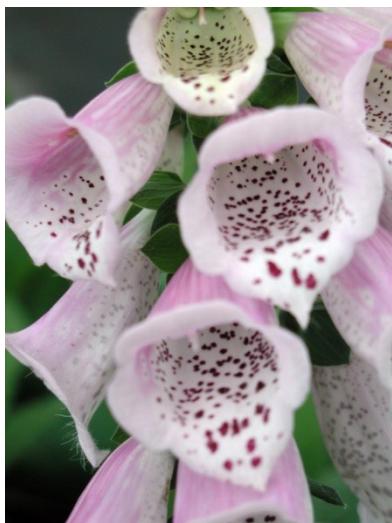
Drug discovery:

Process of discovery and/or design of drugs

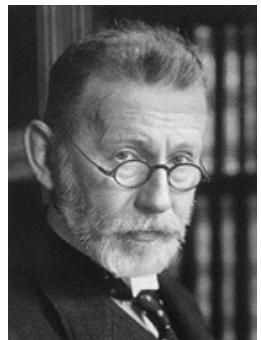
The beginning of drug discovery

Early drug discovery and pharmacology was purely observation-based, empirical and serendipitous discovery.

- **Herbal medicine**
 - **Purified compounds with medical use before 1900: morphine, digitalis, cocaine, atropine ...**



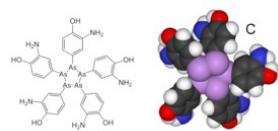
Drug discovery landmarks



Paul Ehrlich (1854 - 1915)

Nobel prize in physiology and medicine 1908

Aniline dyes bind to specific cells and structures in cells → receptor theory, later ‘chemotherapy’ ; “salvarsan” as one of the very first synthetic medicines, against syphilis.



Computing &
robotics

Combinatorial
chemistry

1920 1950 1960 1970 1980 1990 2000 2010 2020

Penicillin

The double helix

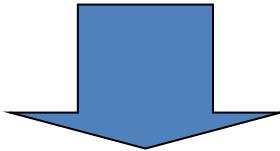
Monoclonal antibodies
Recombinant DNA technology

Transgenic animals
Polymerase chain reaction

Human genome sequence
CRISPR/gene therapy

In rare cases, mutation of a single
gene
can play a major role in disease

Genotype



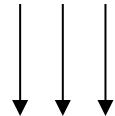
Disease



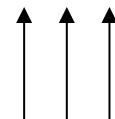
Environment

Most disease results from a combination of genes,
environment, behavior and bad luck

Genotype



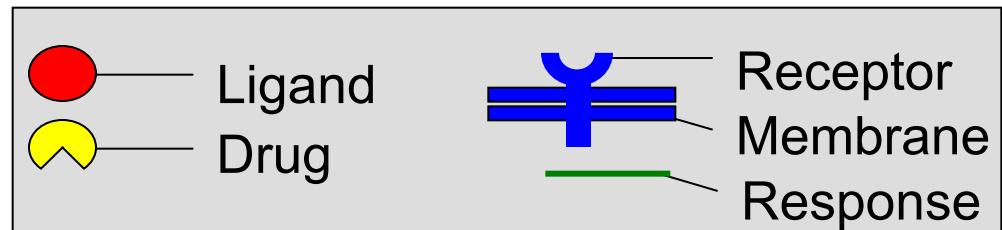
Behavior \rightleftharpoons Disease \rightleftharpoons Chance



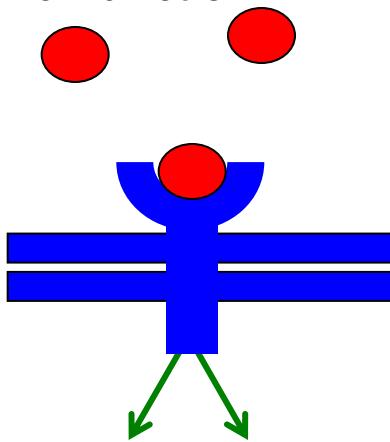
Environment

How pharmaceuticals work – membrane protein example

Histamine GPCR

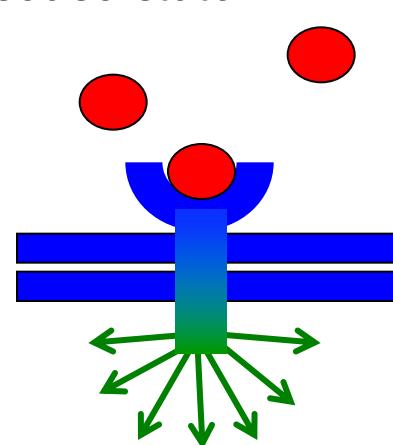


Normal function



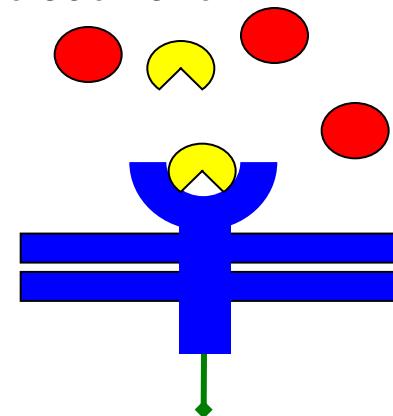
- Ligand binds to receptor
- Receptor transmits signal
- Physiological response
- *Example:* Dust binds to histamine receptor and activates immune response

Disease state



- Ligand binds to receptor
- Receptor transmits excessive signal
- Abnormal physiological response
- *Example:* Allergic response can result in runny nose and inflammation

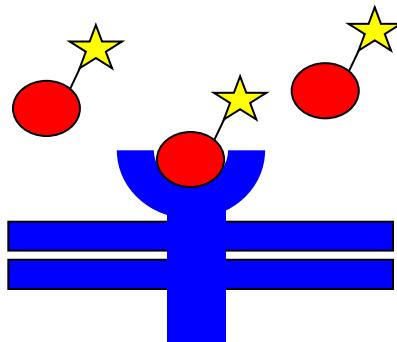
Drug treatment



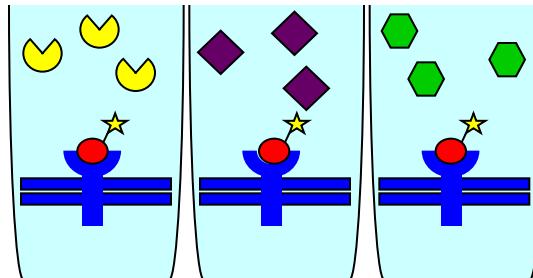
- Drug binds to receptor, blocking ligand
- Drug blocks receptor signal
- Physiological response abated
- *Example:* Claritin, an anti-histamine, mitigates the hyperinflammatory physiological response

A membrane protein binding assay is an example of a primary screen

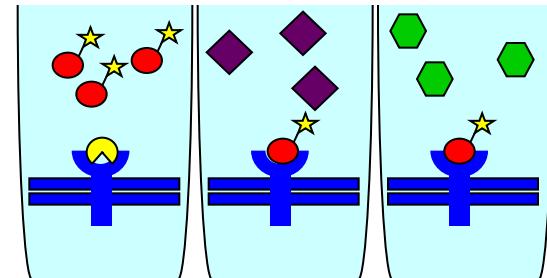
Membrane prep



Add compounds



Look for binding



+ - -

- Isolate protein target
- Incubate with labeled ligand
- Wash excess, unbound ligand
- Screen 100-300K compounds
- 1 compound per well
- 96, 384, or 1536 well format
- Binding of a compound displaces labeled ligand
- Examine wells for increase in free labeled ligand



Major factors controlling exposure of an individual to a drug:

Asorption: uptake of the drug into the body.

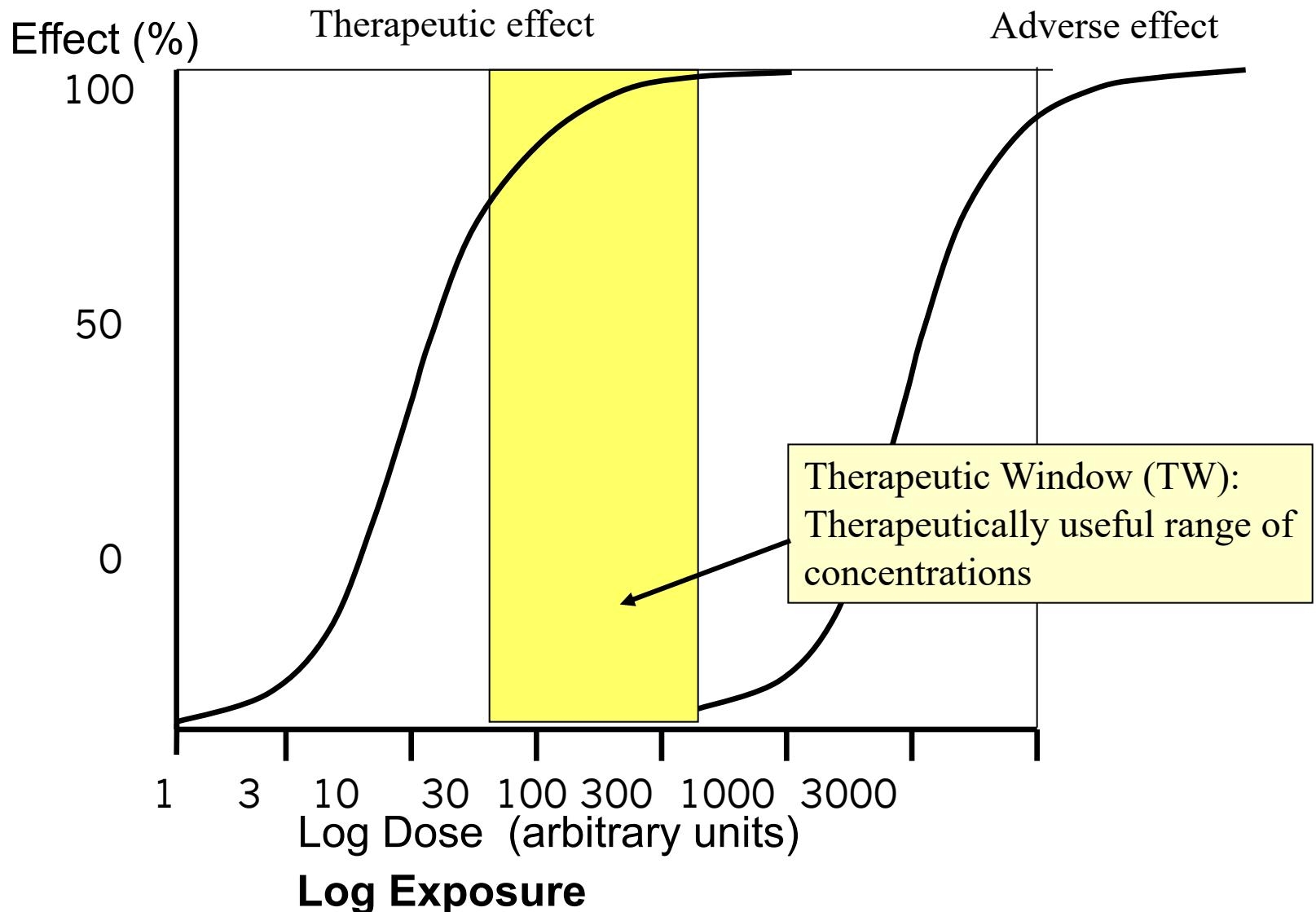
Distribution: diffusion of the drug into various body compartments, such as tissues and organs.

Metabolism: enzymatic processing of the drug to generate metabolites.

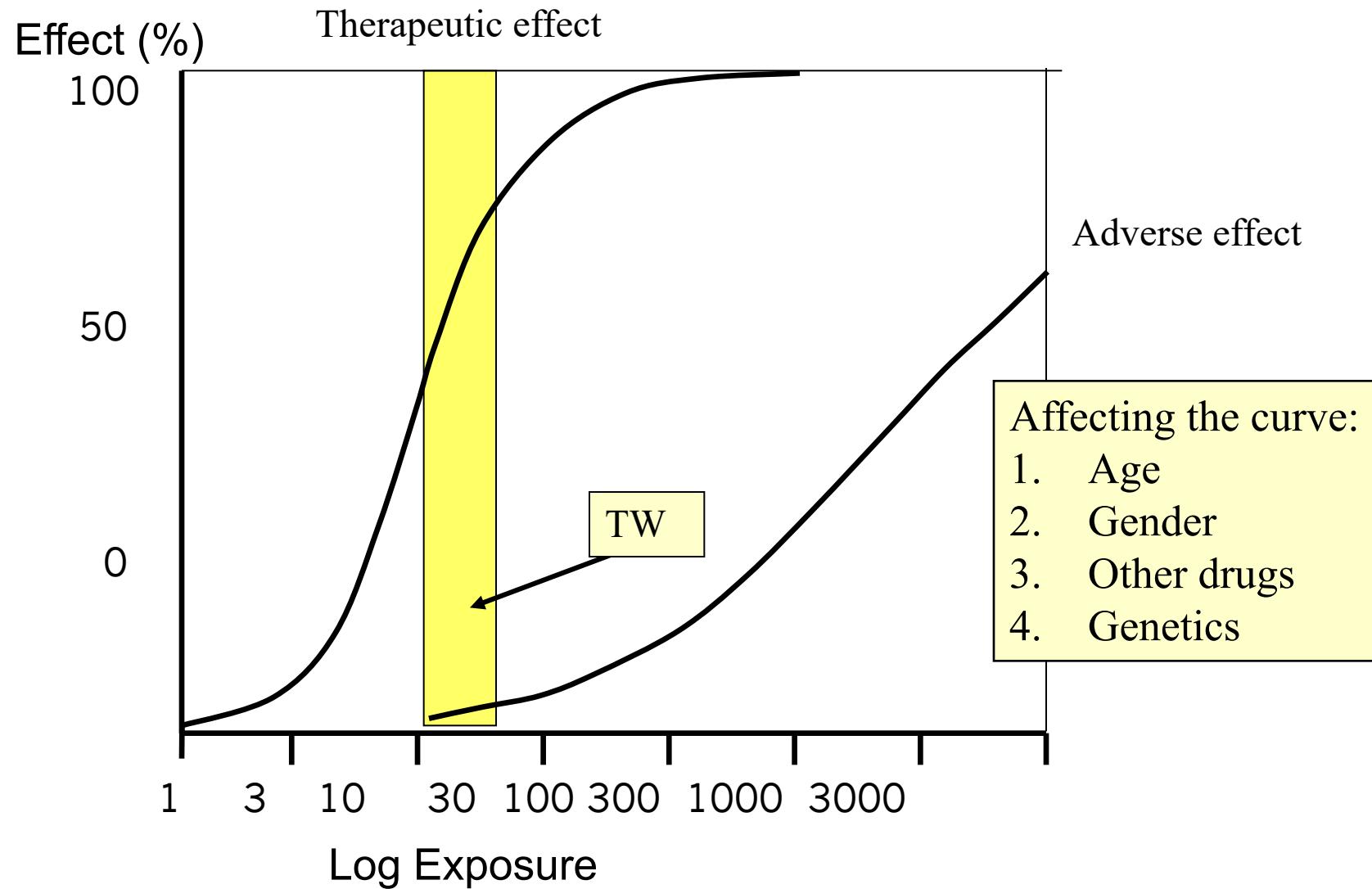
Excretion: elimination of the drug and its metabolites from the body.

Tox: toxicity due to drug and its metabolites
mechanism based vs. non-mechanism based

Measures of Efficacy vs. Safety: Therapeutic Index and Therapeutic Window



Dose response of side effects can narrow TW while TI remains constant



Drugs are Poisons

*“All substances are poisons;
there is none which is not a poison.
The right dose differentiates a
poison from a remedy.”*

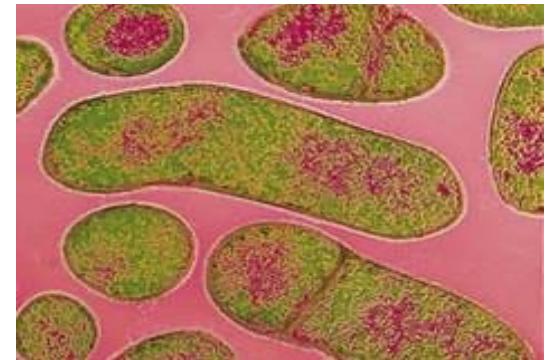
-Paracelsus (1493-1571)



Poisons Can Be Drugs

Botulinum toxin— from Clostridium botulinum

- **Most toxic poison known.**
- **Used therapeutically for focal dystonia and wrinkles**



Curare—purified from Strychnos toxifera

- **Arrow poison**
- **Muscle relaxant during anaesthesia**



Some general concepts

- Not all targets are druggable
- Not all small-molecule binders are drugs
- The drug has to reach the target in sufficiently high concentrations in order to produce a pharmacologic effect.
- Drugs must be metabolized in order to avoid accumulation to levels at which toxicity is manifest.
- Metabolites of a drug (or pro-drug) can have beneficial or undesirable effects.

What challenges are facing
pharmaceutical and biotechnology
companies today?

Perception of pharma companies

Key criticisms

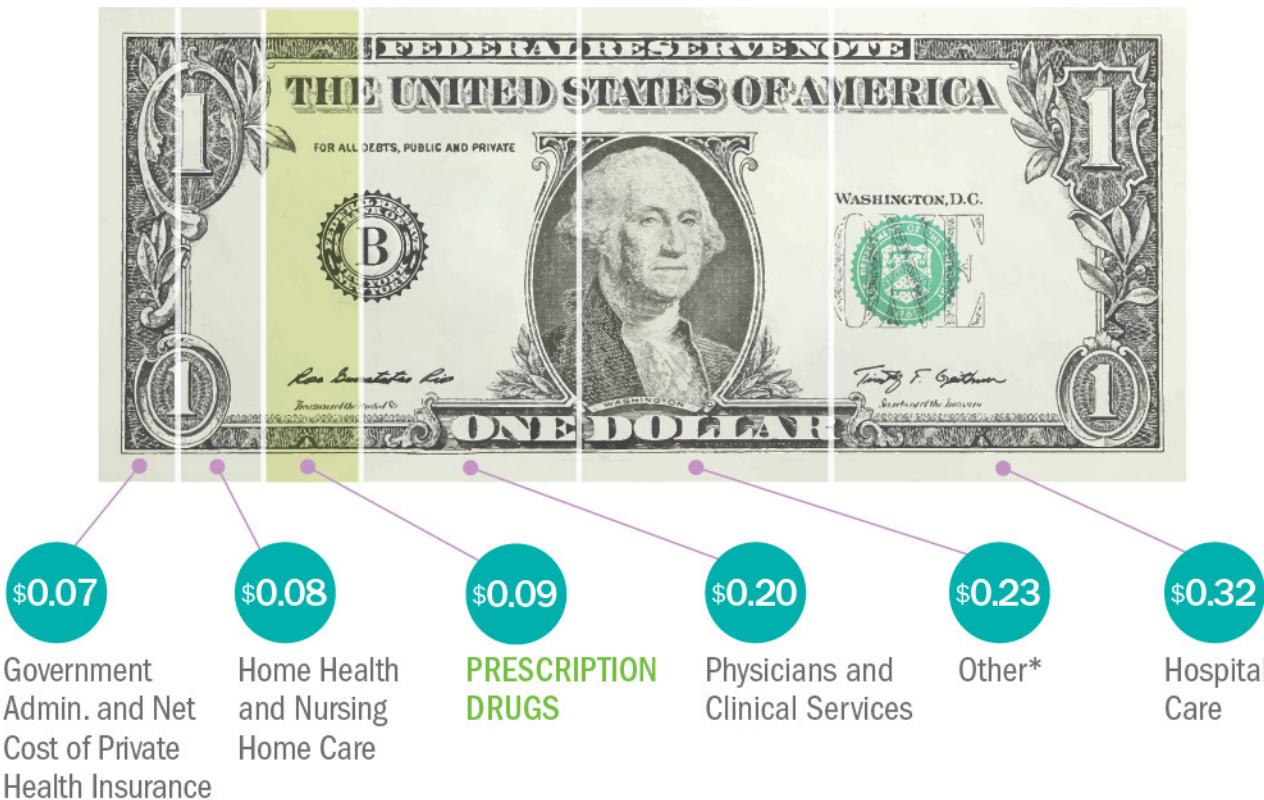
- **Develops only incrementally better products**
- **Is not innovative (no new targets)**
- **Neglects important diseases**
- **Develops unsafe products**
- **Earns excessive profits**

What percentage of total US healthcare expenditures (not merely out of pocket) comes from pharmaceuticals?

- A. 10%
- B. 20%
- C. 30%
- D. 50%
- E. >50%

Retail Spending on Prescription Medicines Is a Small Share of Total US Health Care Spending

2013 Health Care Dollar



What does the public think?

- Two-thirds of consumers estimated that prescription drugs account for between 40 and 79% of U.S. healthcare costs (Actual is ~ 10%)
- 80 percent of consumers say that when given a choice, they will consider a drug company's reputation when choosing which product to take

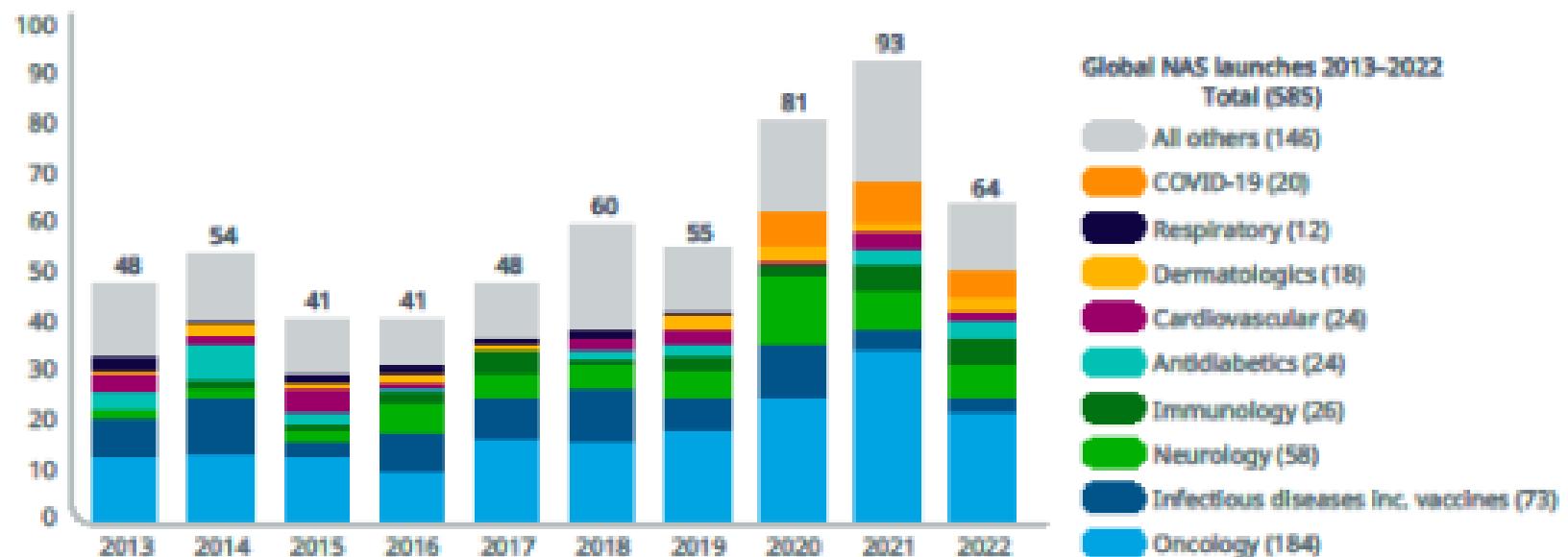
-Survey by PriceWaterhouseCoopers; January 9, 2007

Current status of drug discovery:

NEW DRUG APPROVALS AND LAUNCHES

A total of 64 novel active substances (NASs) were launched globally in 2022

Exhibit 27: Global launches of novel active substances (NAS) by therapy area, 2013–2022

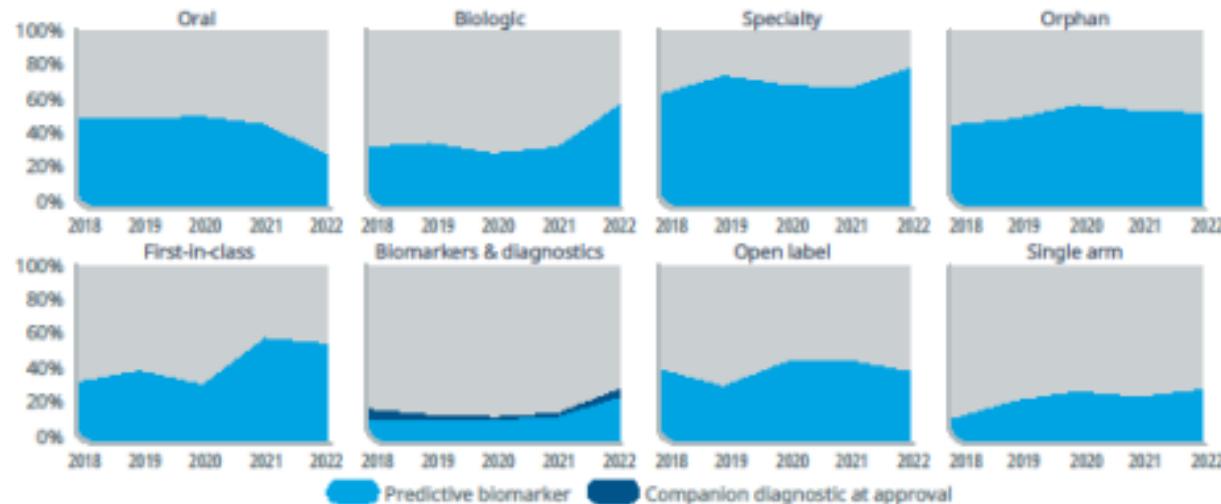


Source: IQVIA Institute, Jan 2023.

NEW DRUG APPROVALS AND LAUNCHES

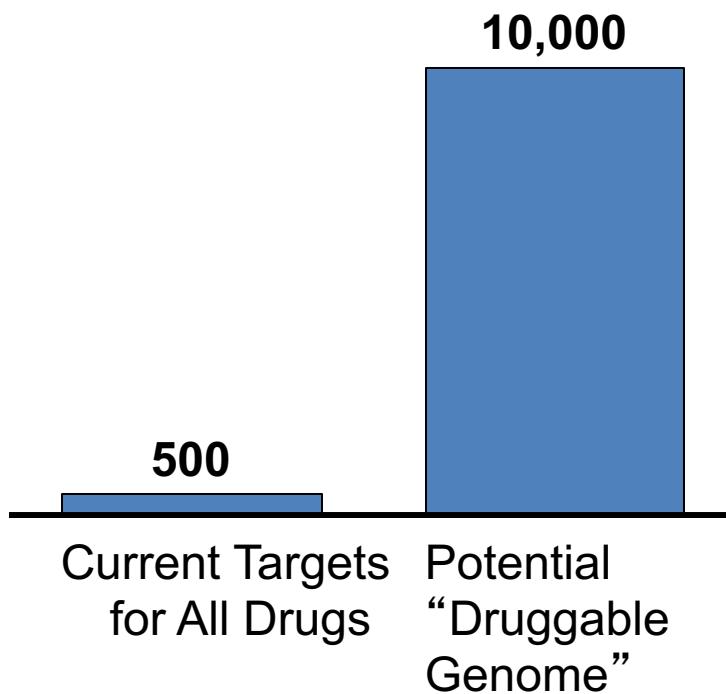
More than 60% of new launches in 2022 were first-in-class and more than half were biologic, up from 35% five years ago

Exhibit 29: U.S. novel active substances (NASs) by product attributes and characteristics of clinical trials used for approval, 2018–2022



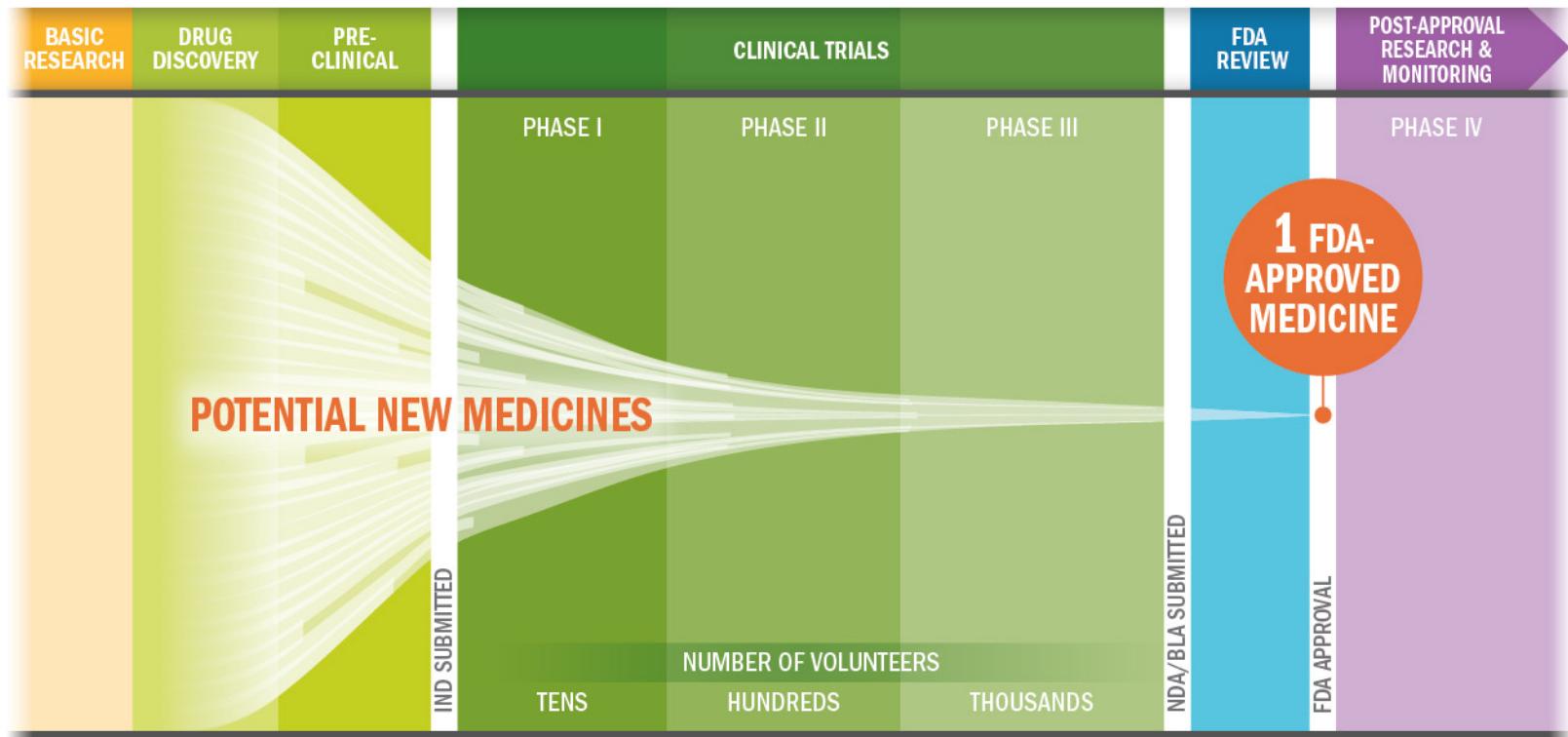
Source: IQVIA Institute, Jan 2023.

Still significant targets addressable



- Currently drugs affect roughly 500 different targets
- After completion of human genome project, it is believed that roughly 10,000 targets are “druggable”
- New technologies (e.g., antibodies, delivery tech) should increase target penetration
- In addition, there is room for significant clinical improvement with current targets (e.g., delivery, specificity, and dosing)

The Biopharmaceutical Research and Development Process



*The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be \$2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

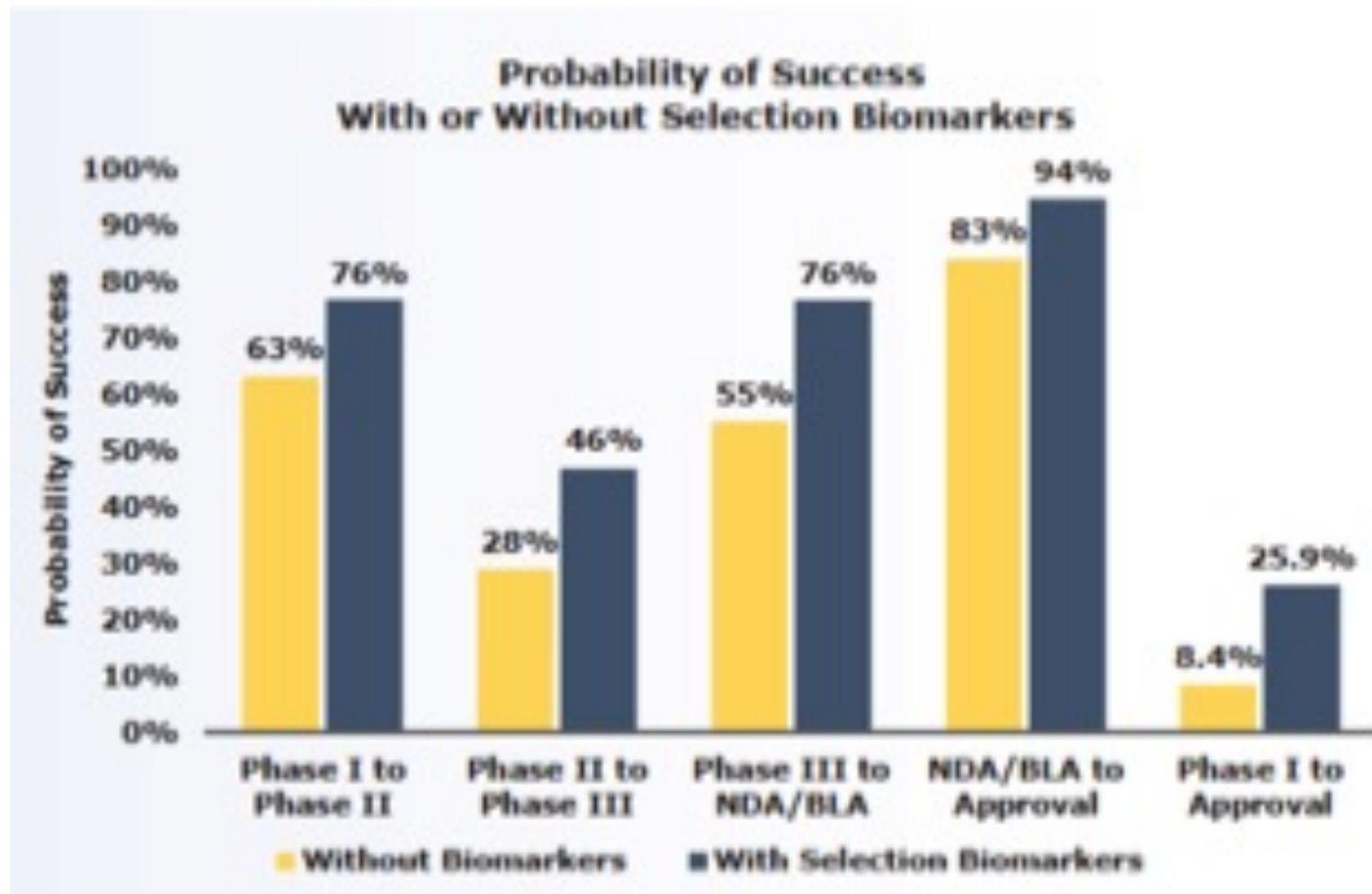
Only 13% success rate after entering human trials

Exhibit 35: R&D composite success rate and average phase success rates Phase I to filing, 2010–2022



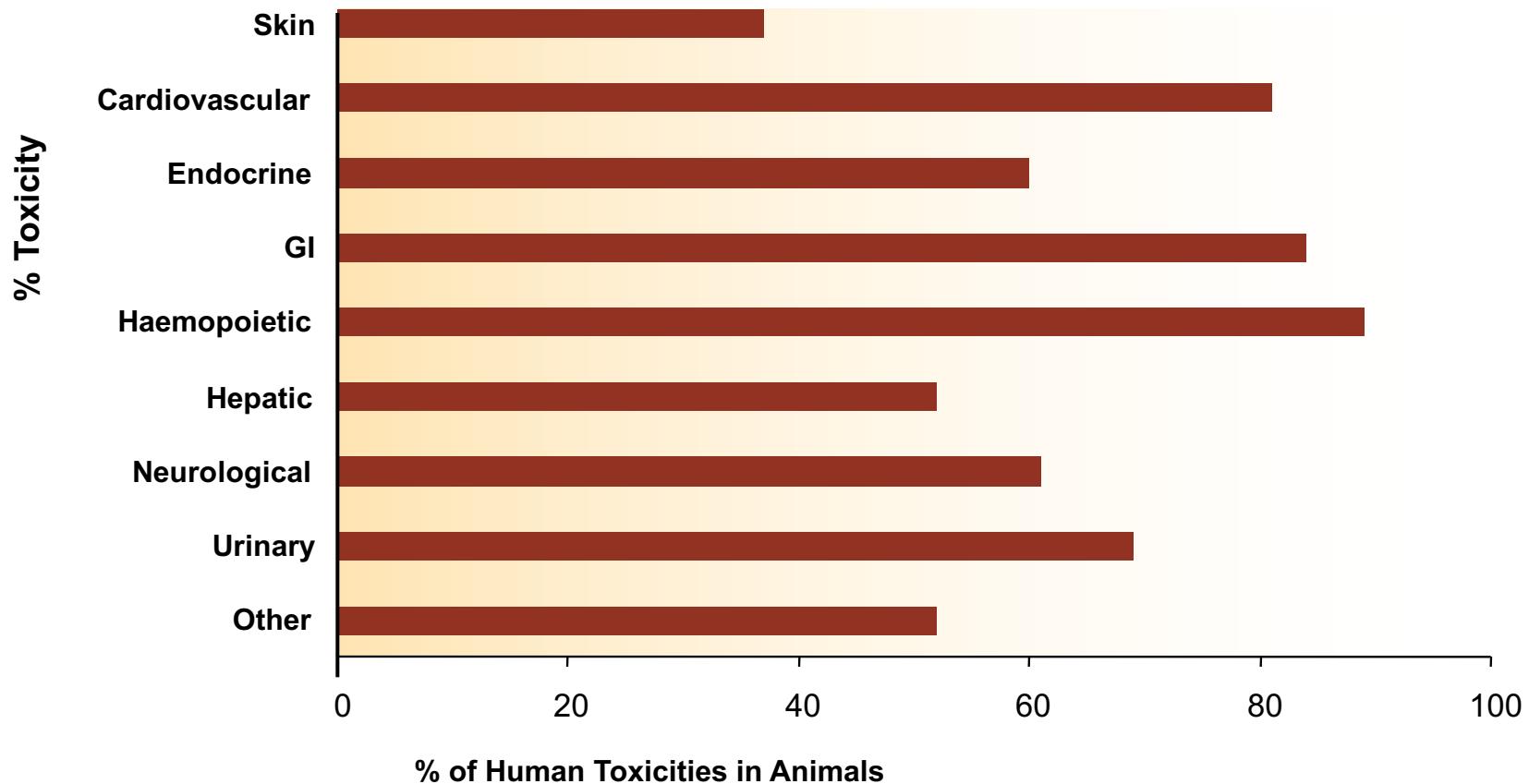
Source: IQVIA Pipeline Intelligence, Dec 2022; IQVIA Institute, Jan 2023.

Biomarkers improve success odds 3 fold

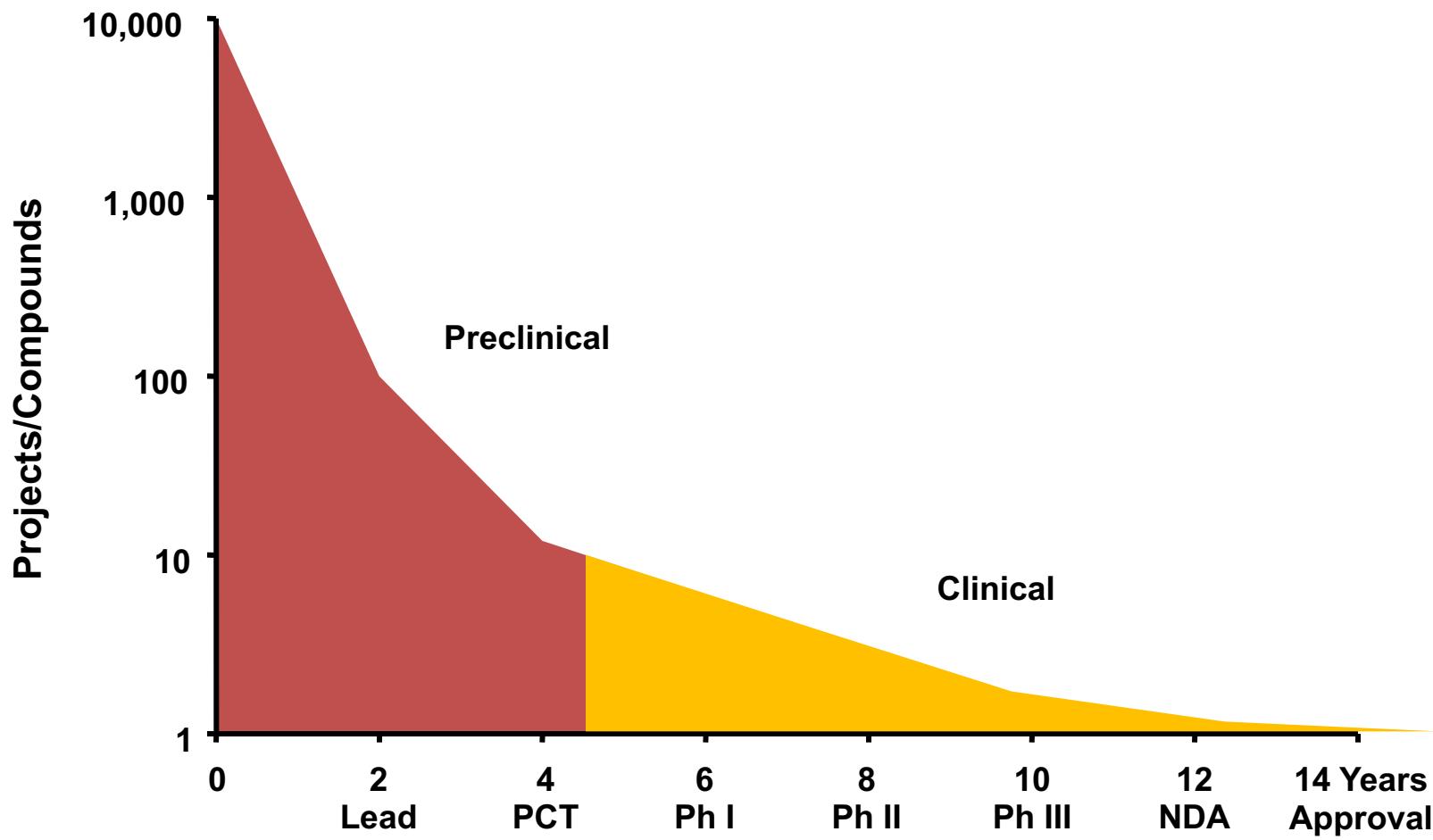


Animals are not humans

Percentage concordance between animals and human toxicities

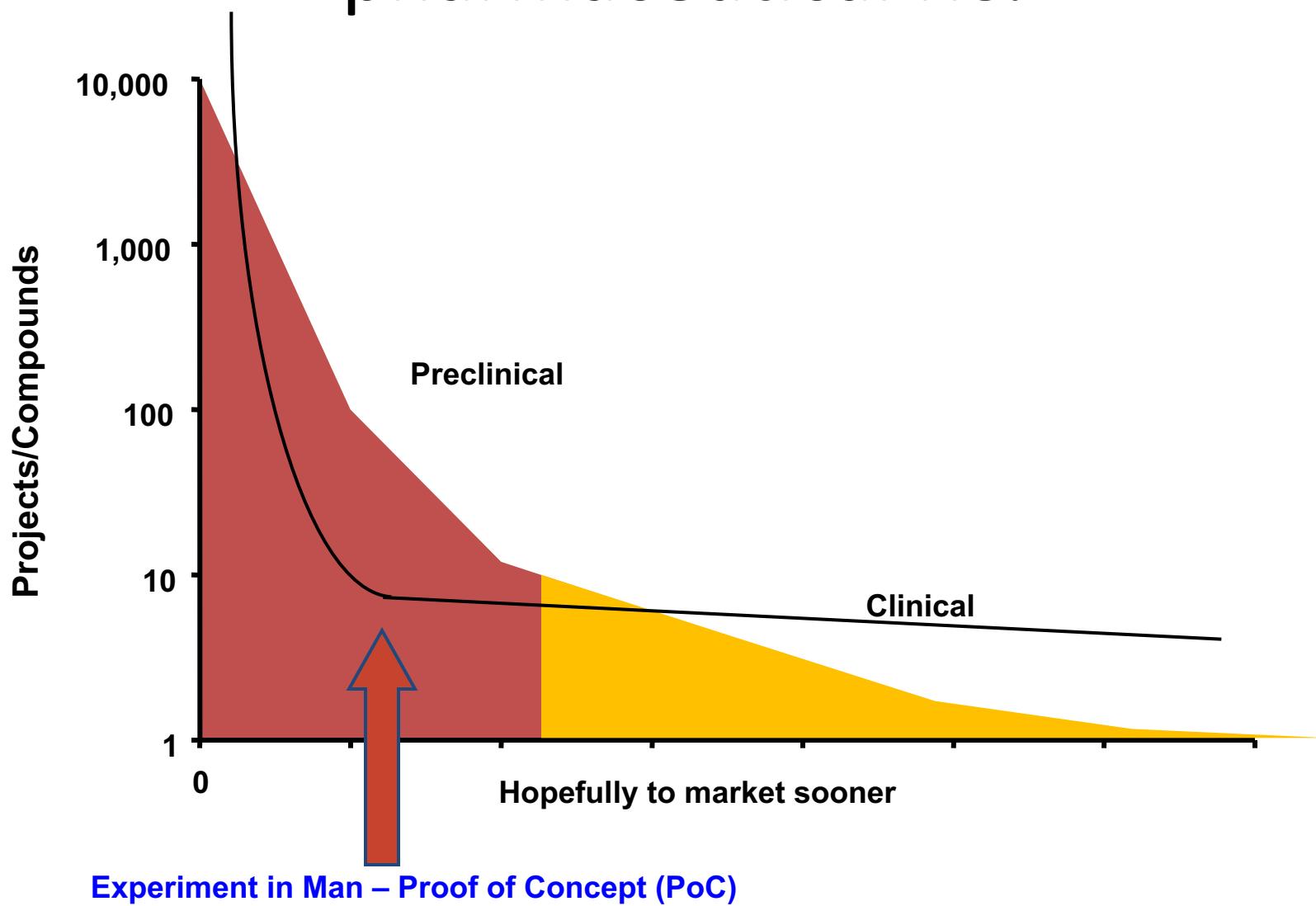


Compound attrition during pharmaceutical R&D



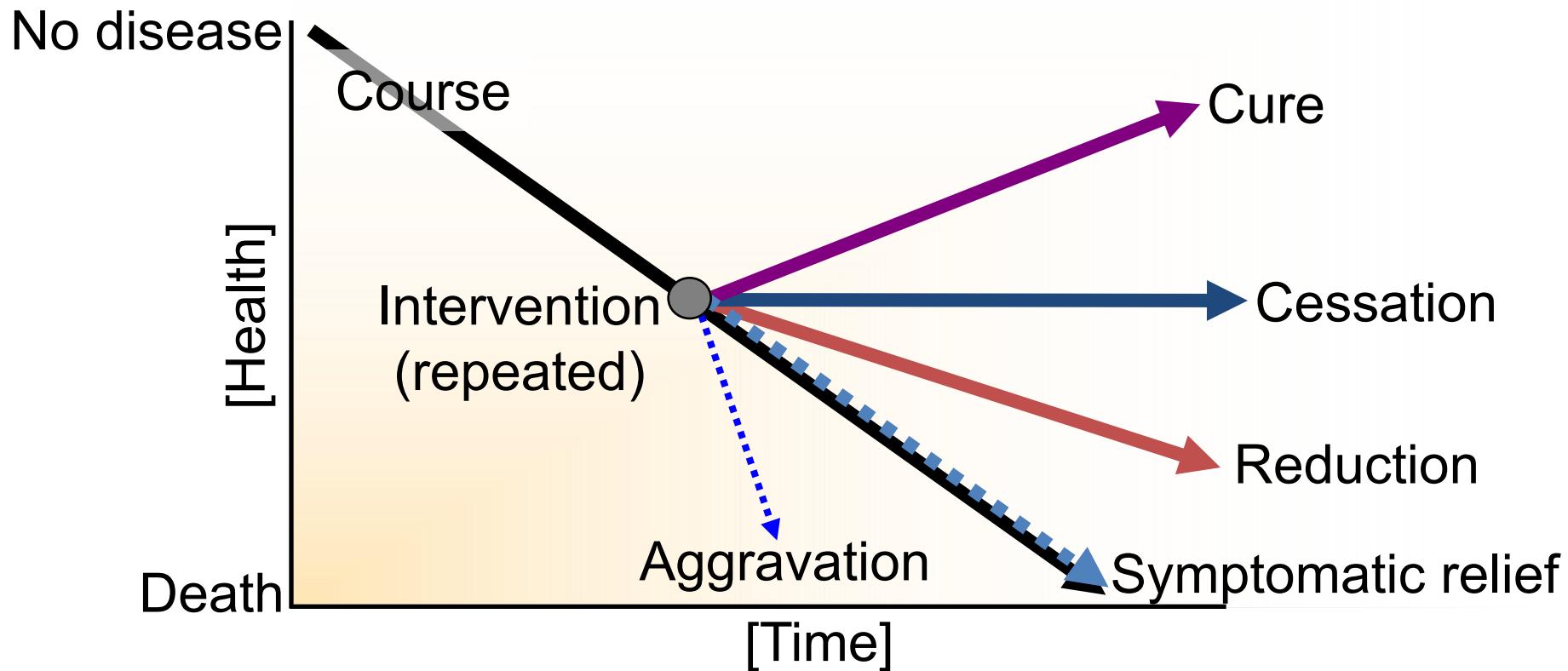
PCT = Pre-clinical testing

Compound attrition during pharmaceutical R&D

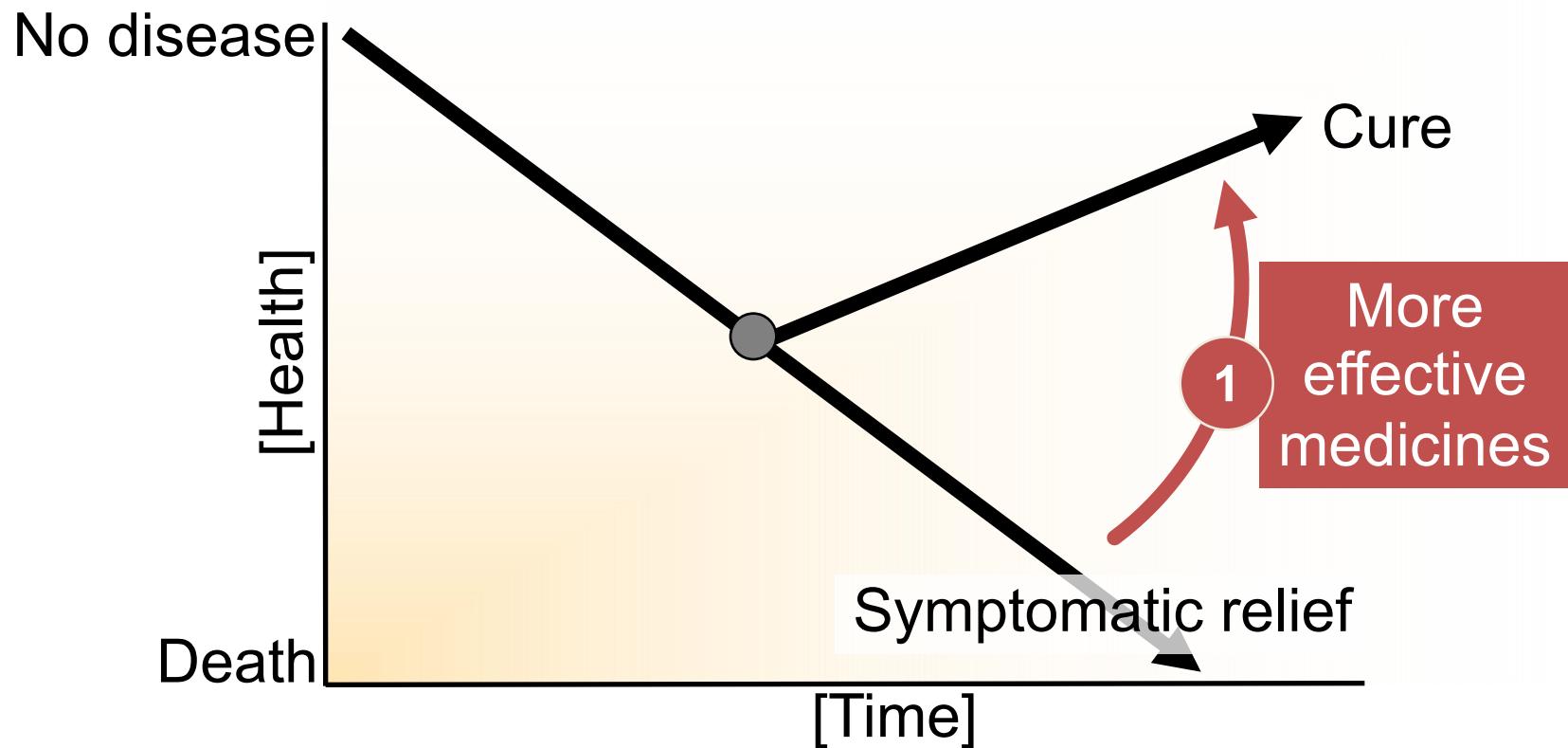


Unmet medical need:

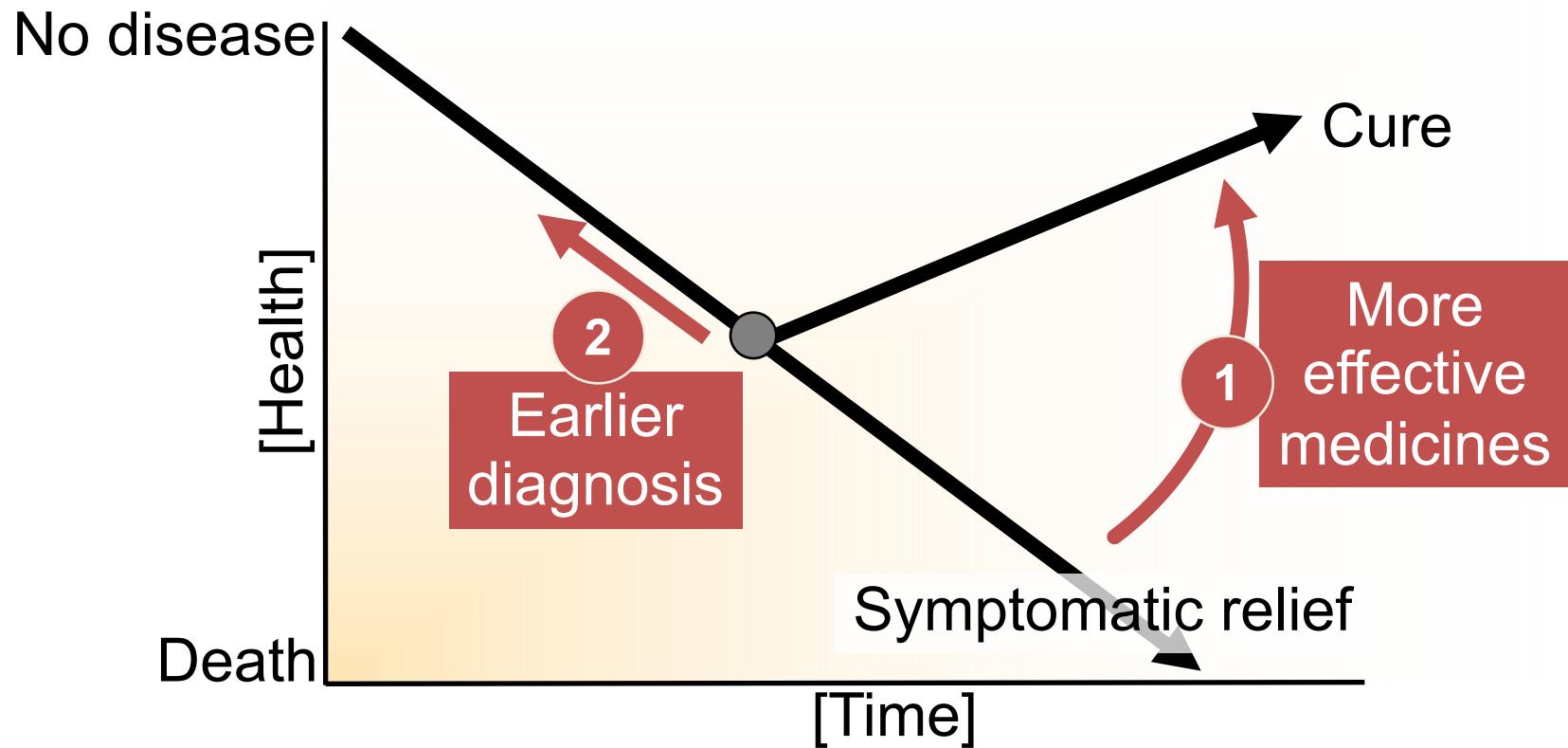
Disease modification?



The challenge



The challenge



Translational Science Training Program

Target Choice and Validation

Rajesh Ranganathan, PhD

VP, & Head, Corporate Development
Sun Pharma Advanced Research Company (SPARC)

Apr 2023

The drug discovery phases

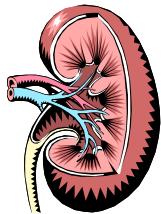


Discussion: What is a valid target ?



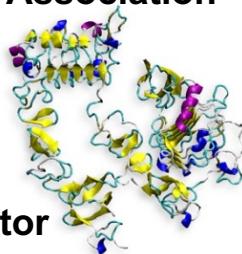
Many Ways to Choosing a “Valid” Target

Fundamental Understanding



Renin
Angiotensin
System

Association



EGF
Receptor

Human Genetics



Cystic Fibrosis
Spinal Muscular Atrophy

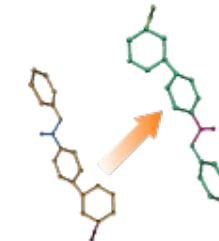
Validated
target

Serendipity and Folk Medicine

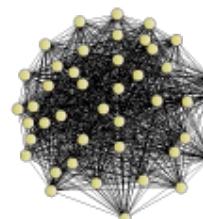


Opiates

Fast Follower

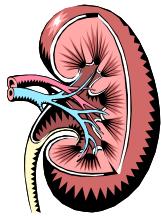


Pathway Genetics



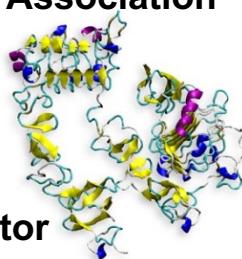
Many Ways to Choosing a “Valid” Target

Fundamental Understanding



Renin
Angiotensin
System

Association



EGF
Receptor

Human Genetics



Cystic Fibrosis
Spinal Muscular Atrophy

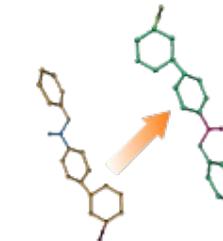
Validated
target

Serendipity and Folk Medicine

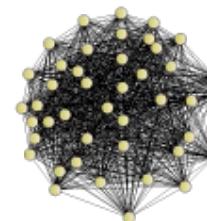


Opiates

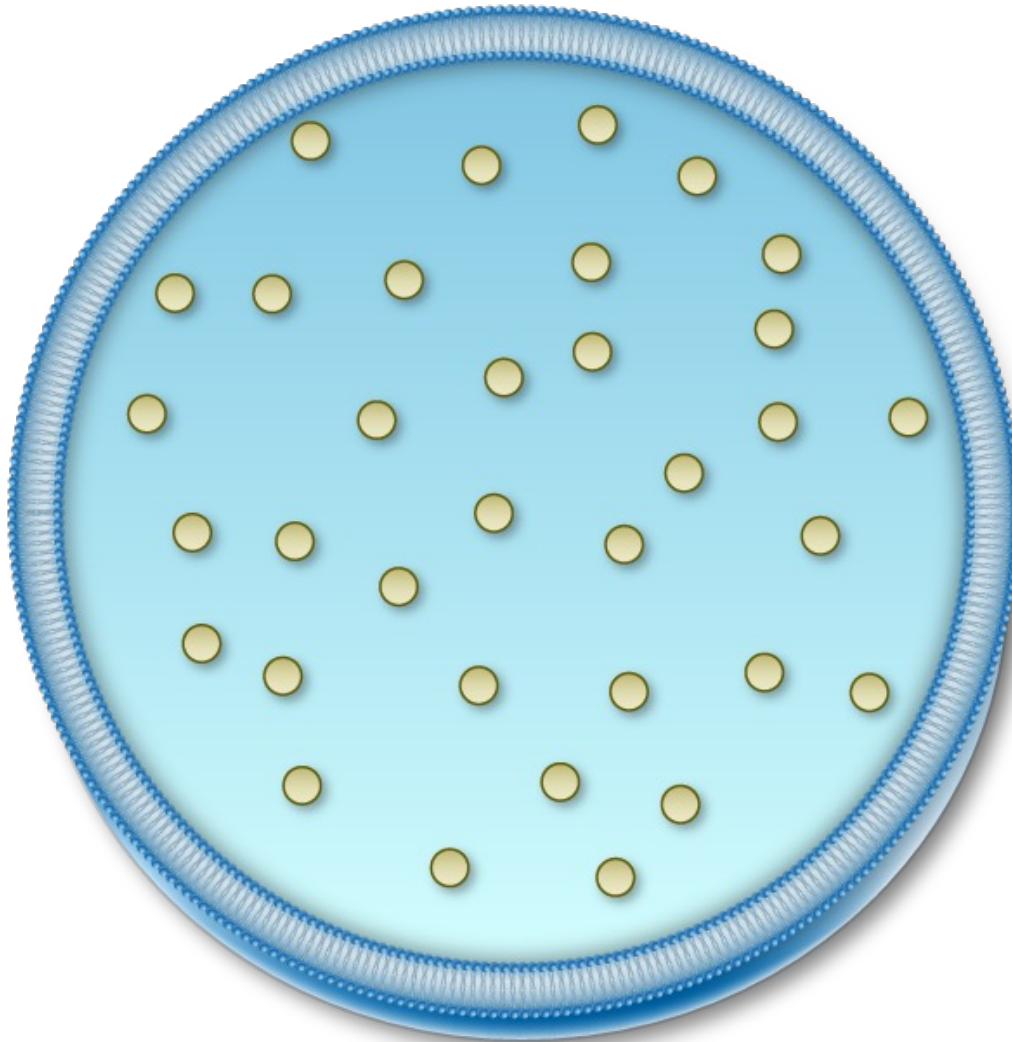
Fast Follower



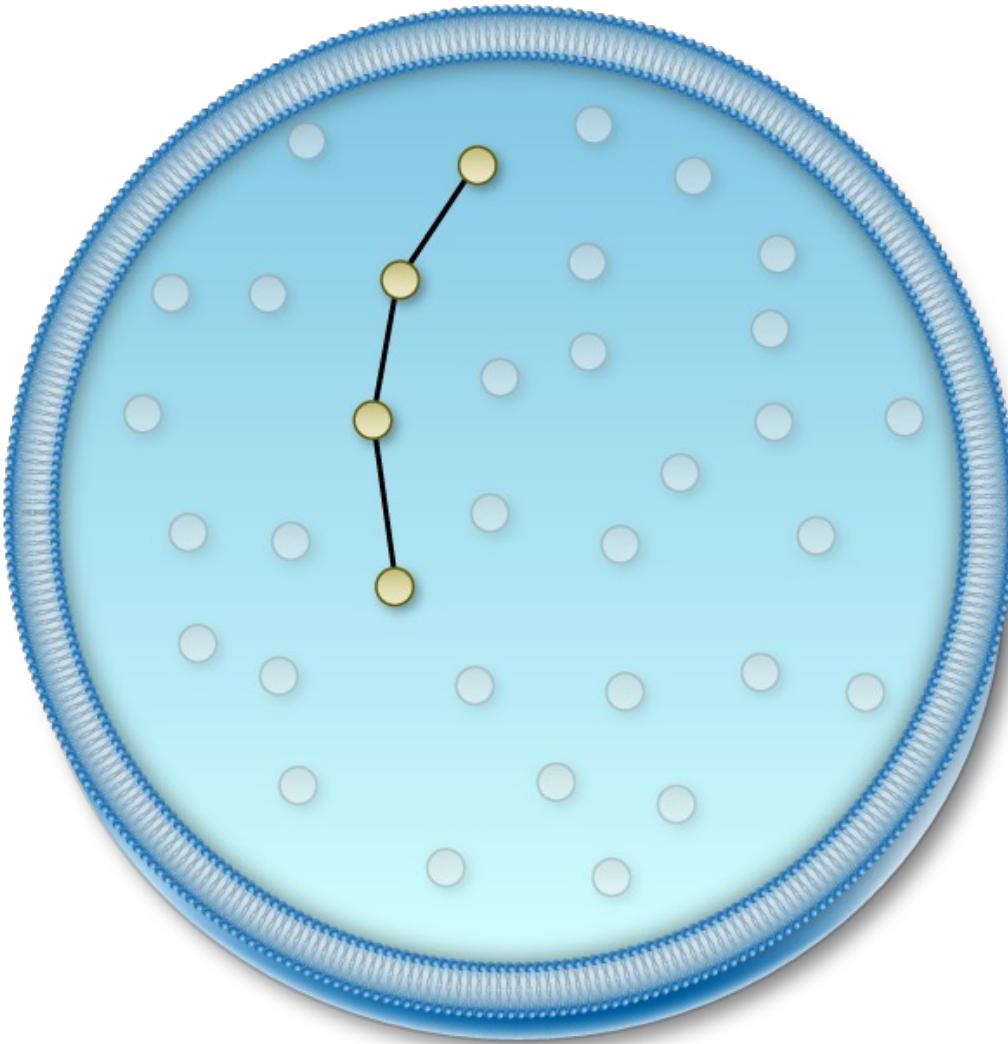
Pathway Genetics



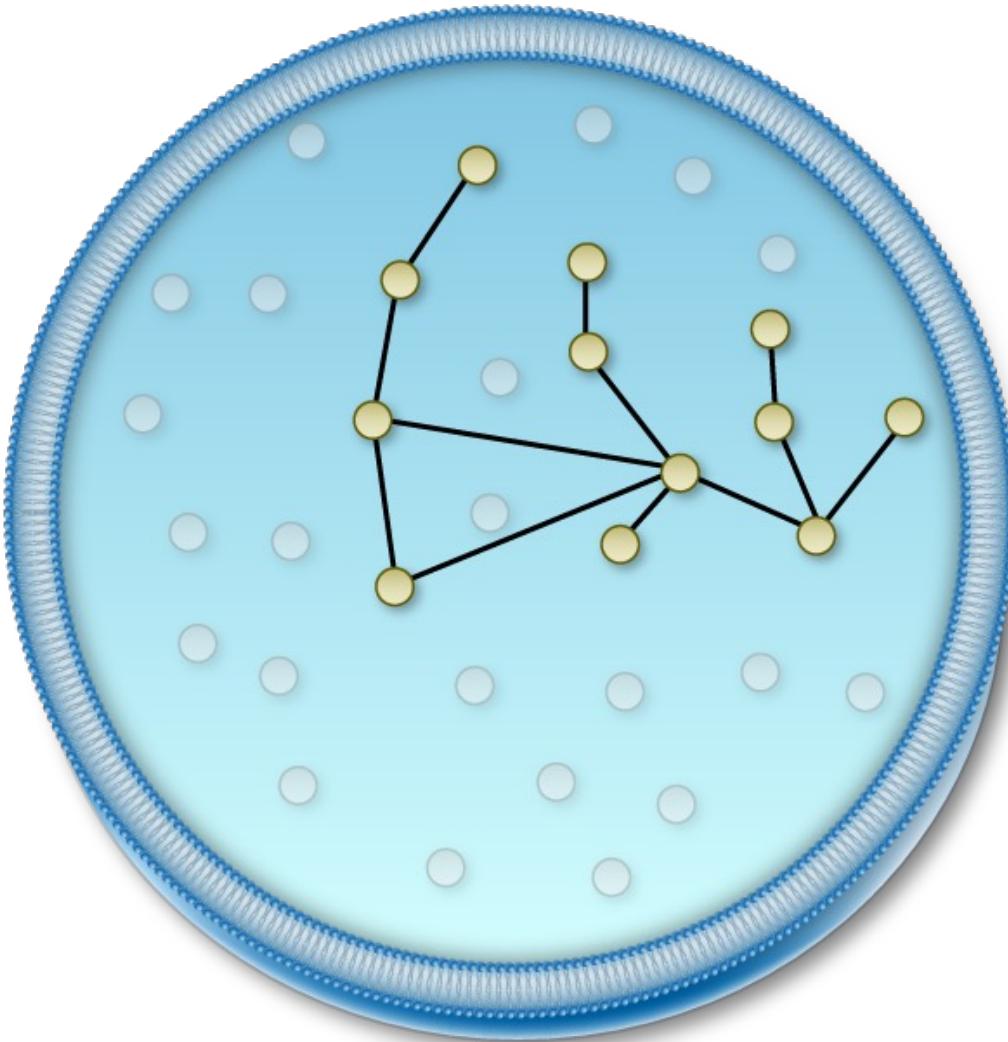
Many genes, few pathways



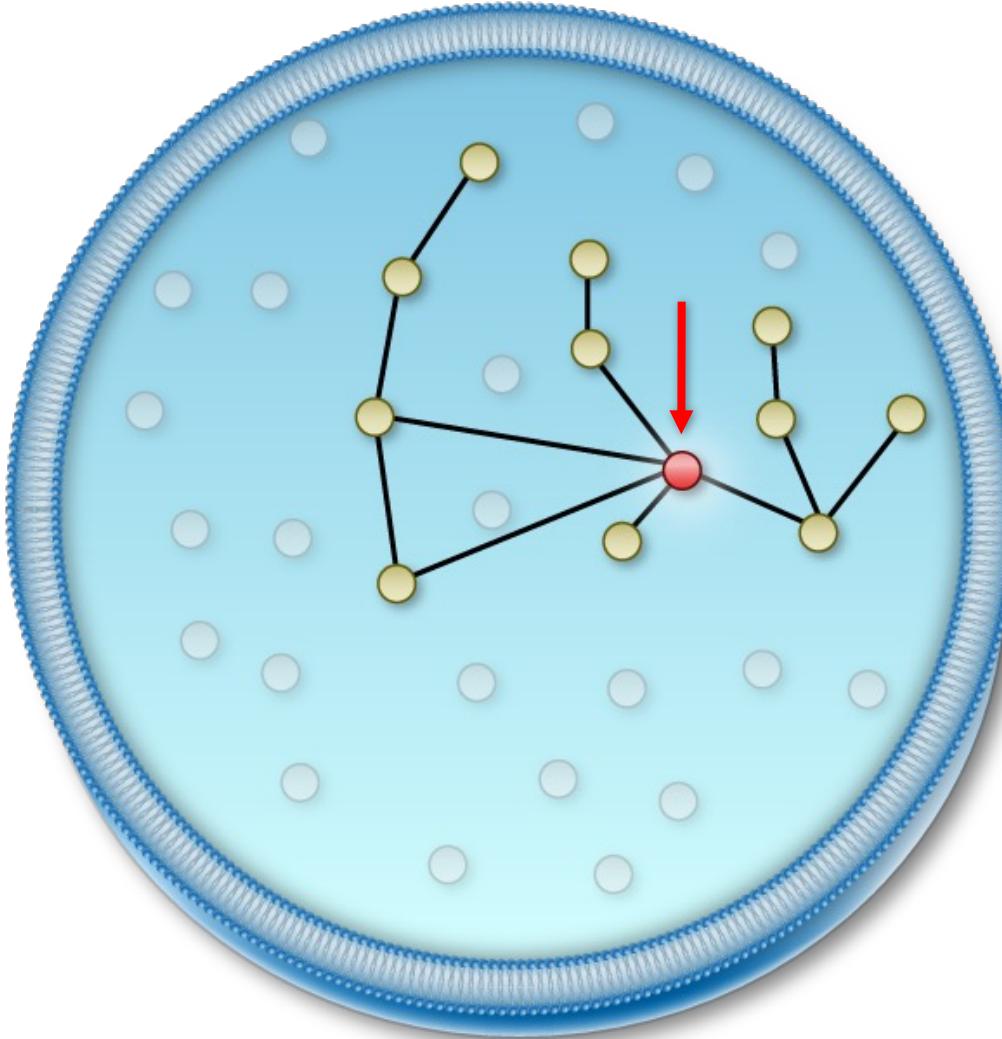
Building Networks



Building Networks



Building Networks to Discover Key Nodes

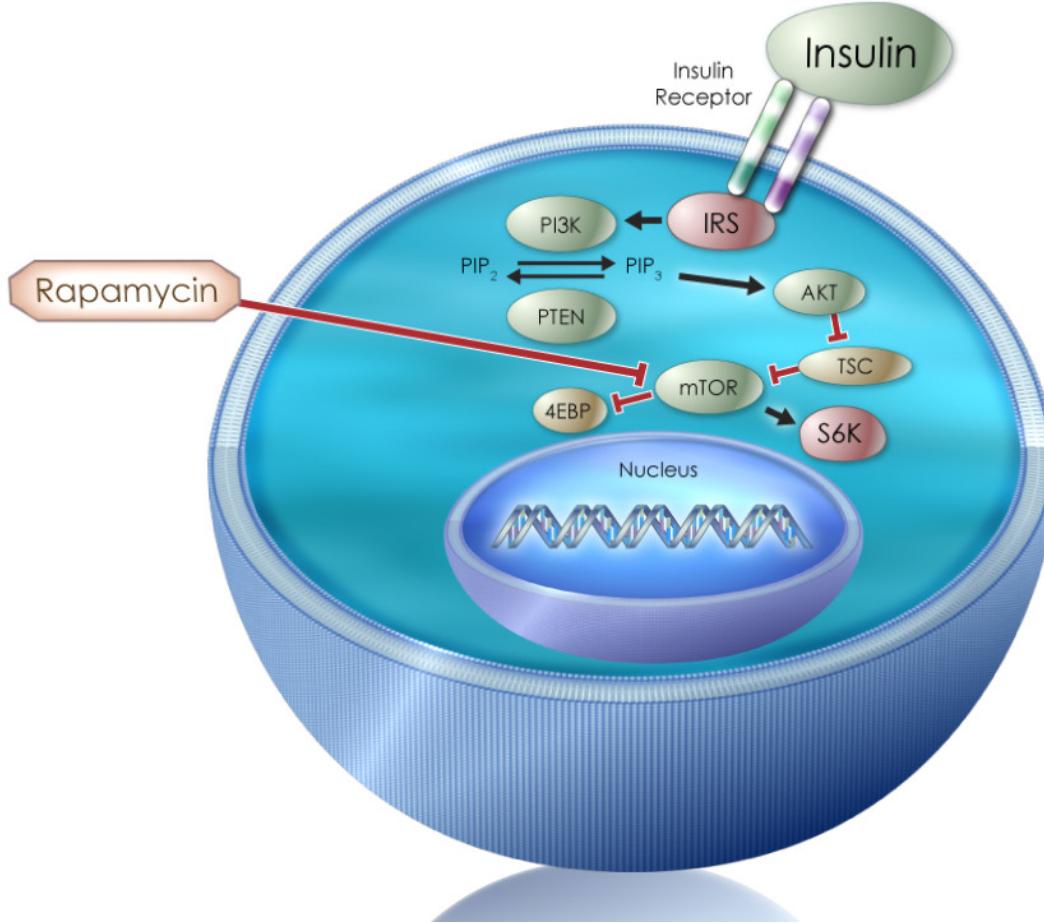


Building Networks

Pathways Run Like a Subway System

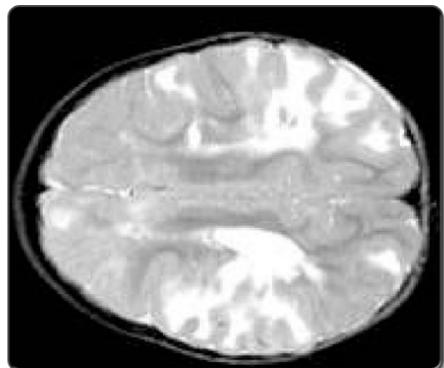


Targeting Key Nodes to Develop New Drugs



Pathways: Collections of Targets for Multiple Indications

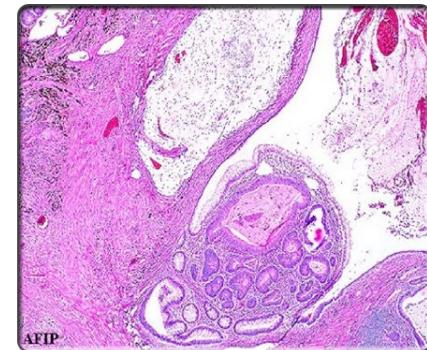
Tuberous sclerosis



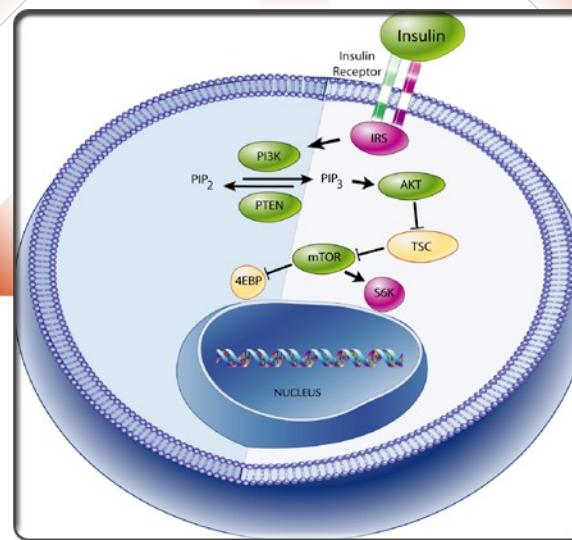
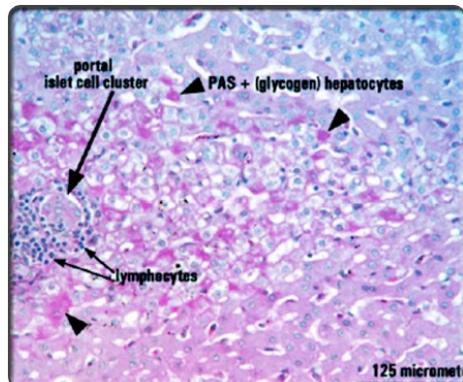
Retinitis pigmentosa



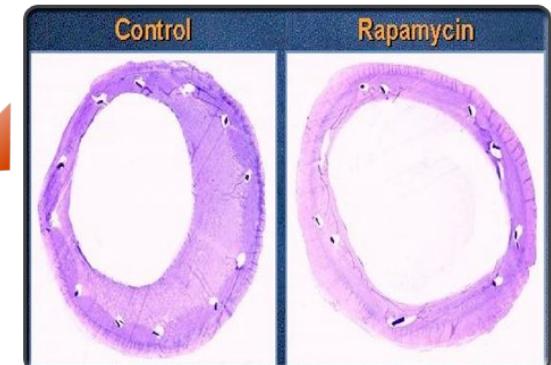
Cancer (colon/breast)



Immune diseases,
Tx rejection



Vascular proliferation
(stent implant)

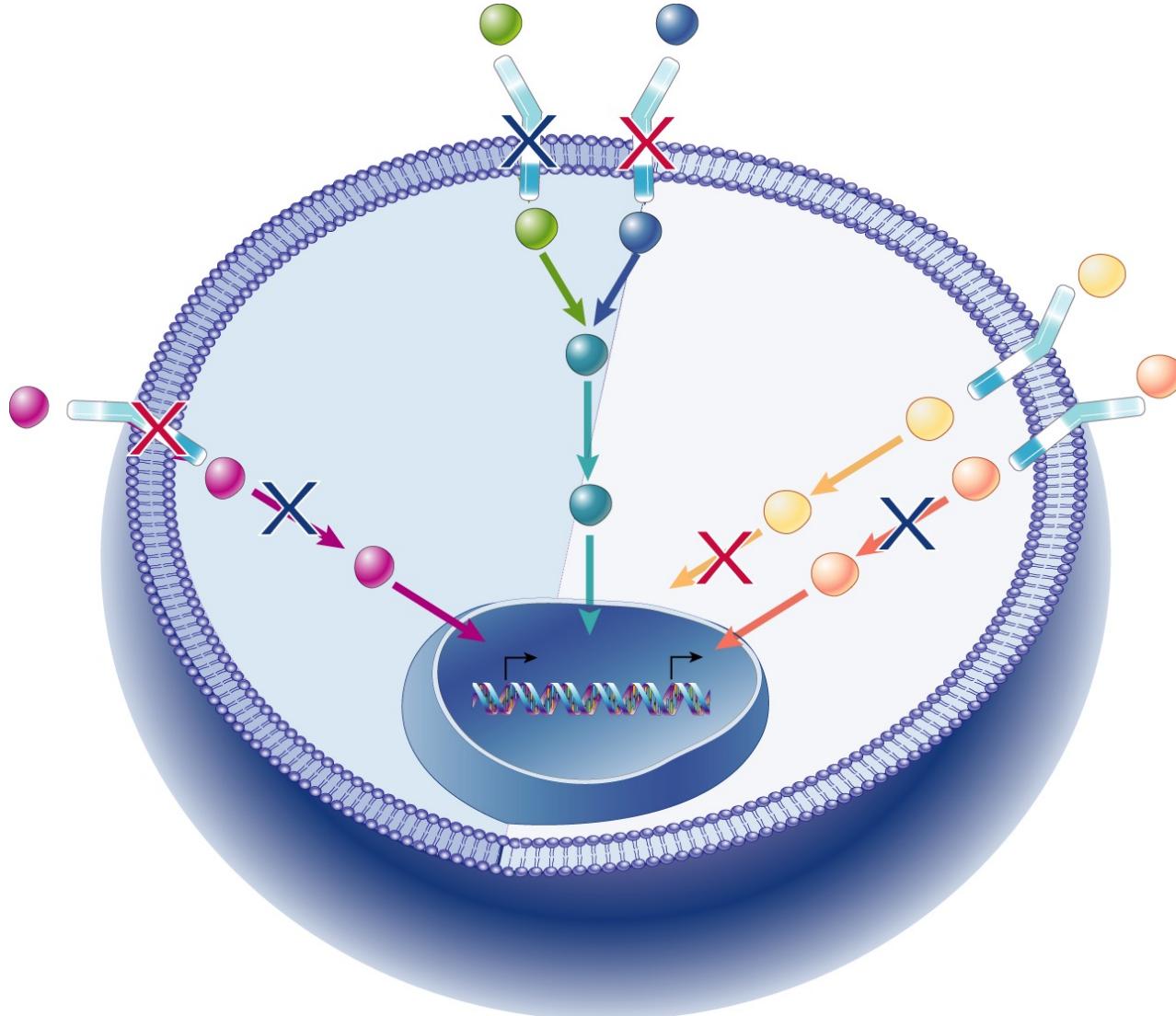


mTOR pathway

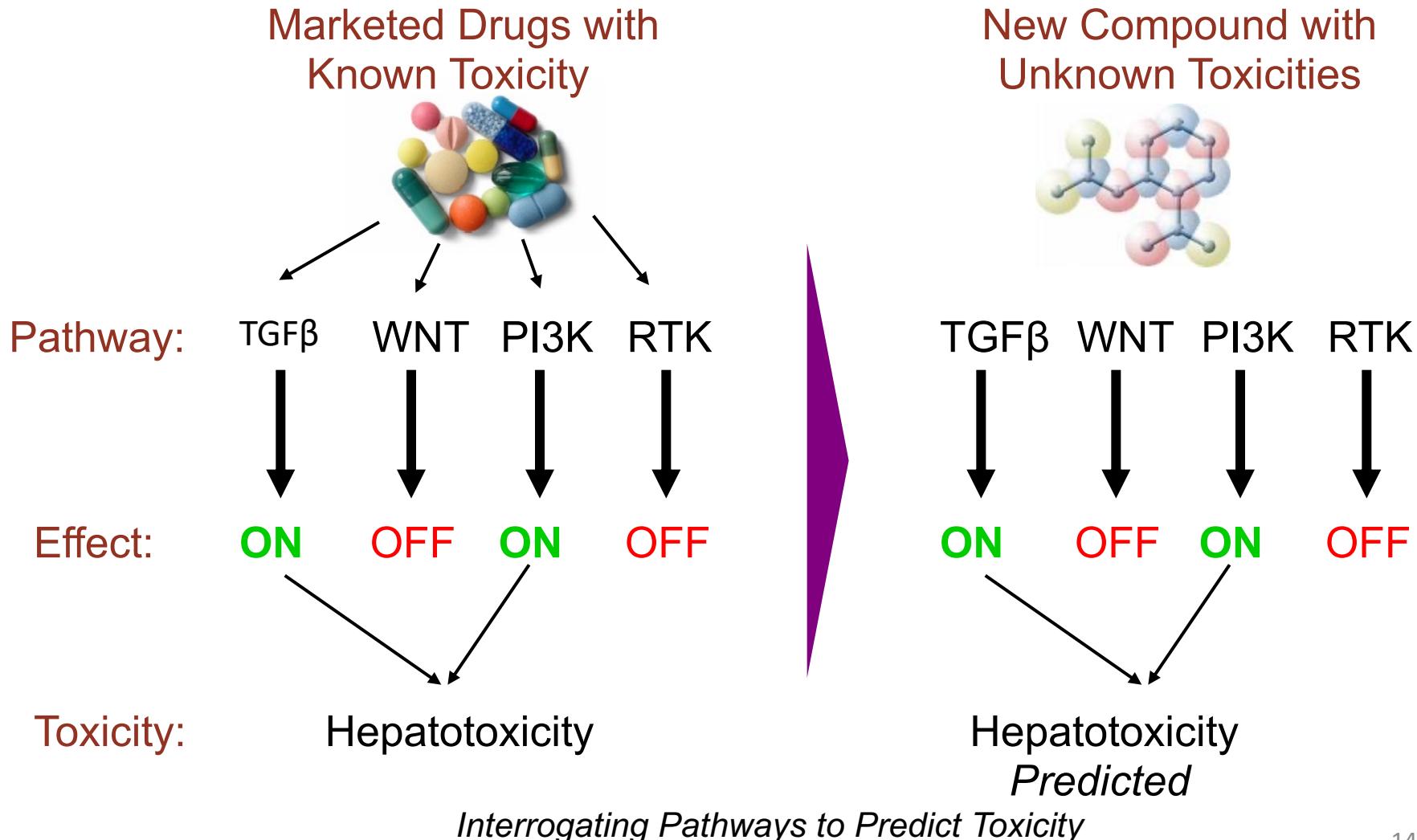
(Novartis portfolio example; used with permission)

Pathways

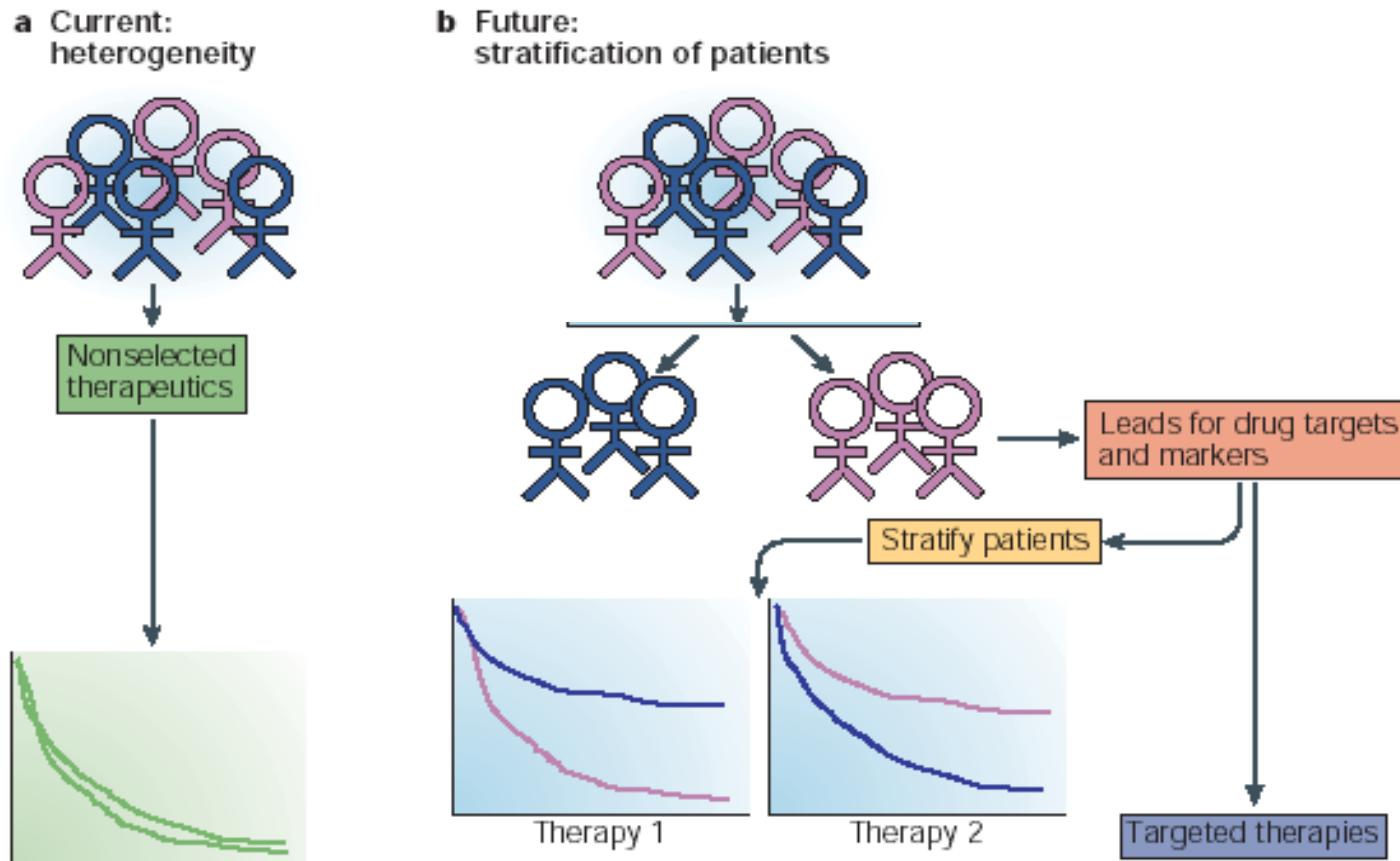
A Rational Approach to Drug Combinations



Utilizing Existing Pathways Knowledge To Understand ‘Science of Safety’



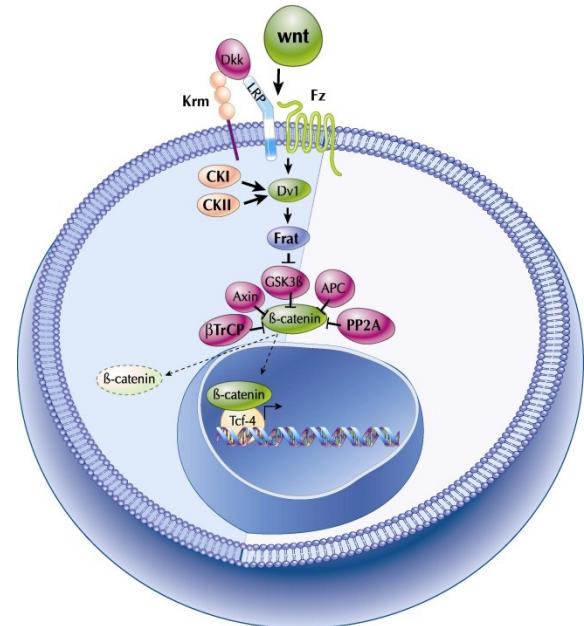
Patient stratification



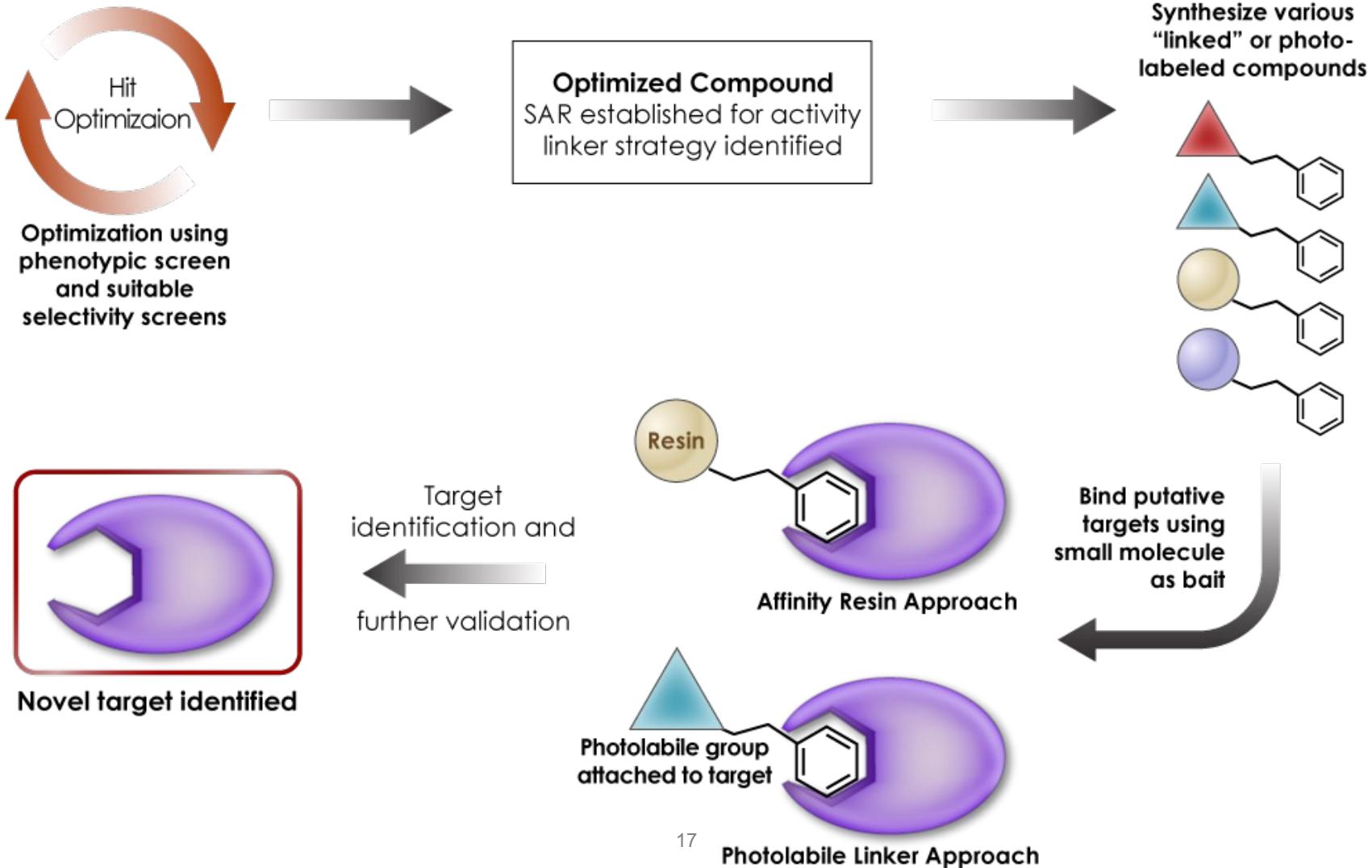
From Mischel et al. *Nature Reviews Neuroscience*, 2004

Summary: Why study pathways ?

- Pathway perturbations cause disease; effective drugs may target such pathway imbalances in cells.
- Pathway knowledge is critical for mechanism of action analyses.
- Better understanding of fundamental pathways will identify opportunities across multiple indications.
- Aids patient stratification and the selection of PoC
- Aids the selection of combination therapy
- Aids in predicting tox signals



Chemical Genetics: Identification of targets from cell based assays

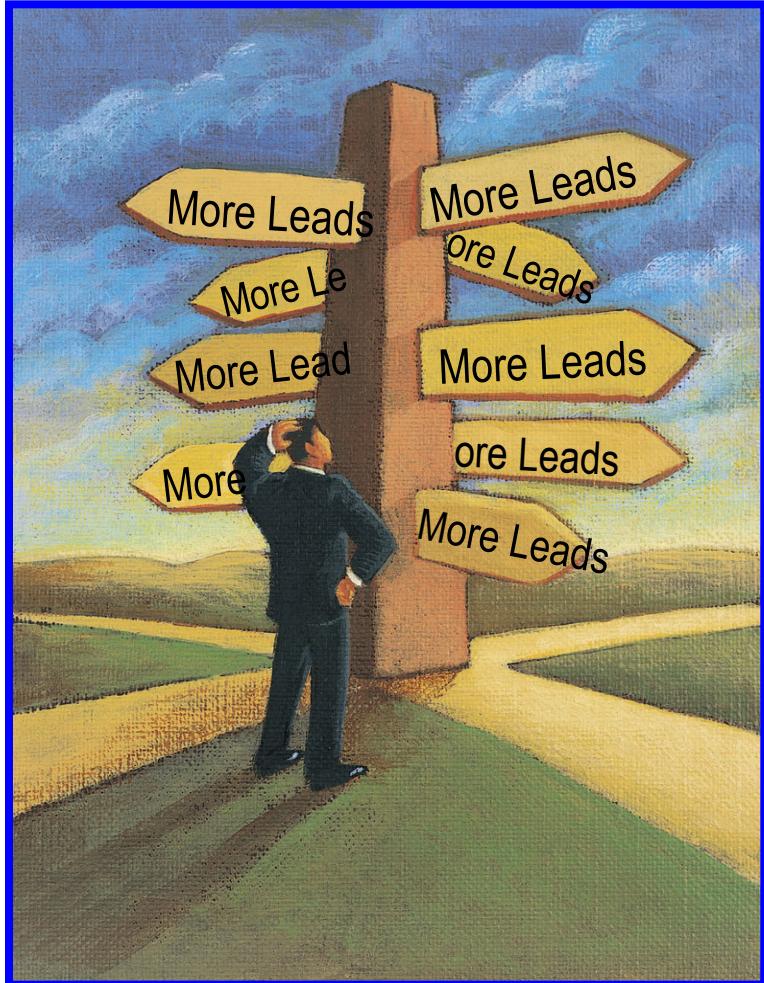


You picked a target – now choose a therapy

Multiple possibilities for therapeutic agents – different features

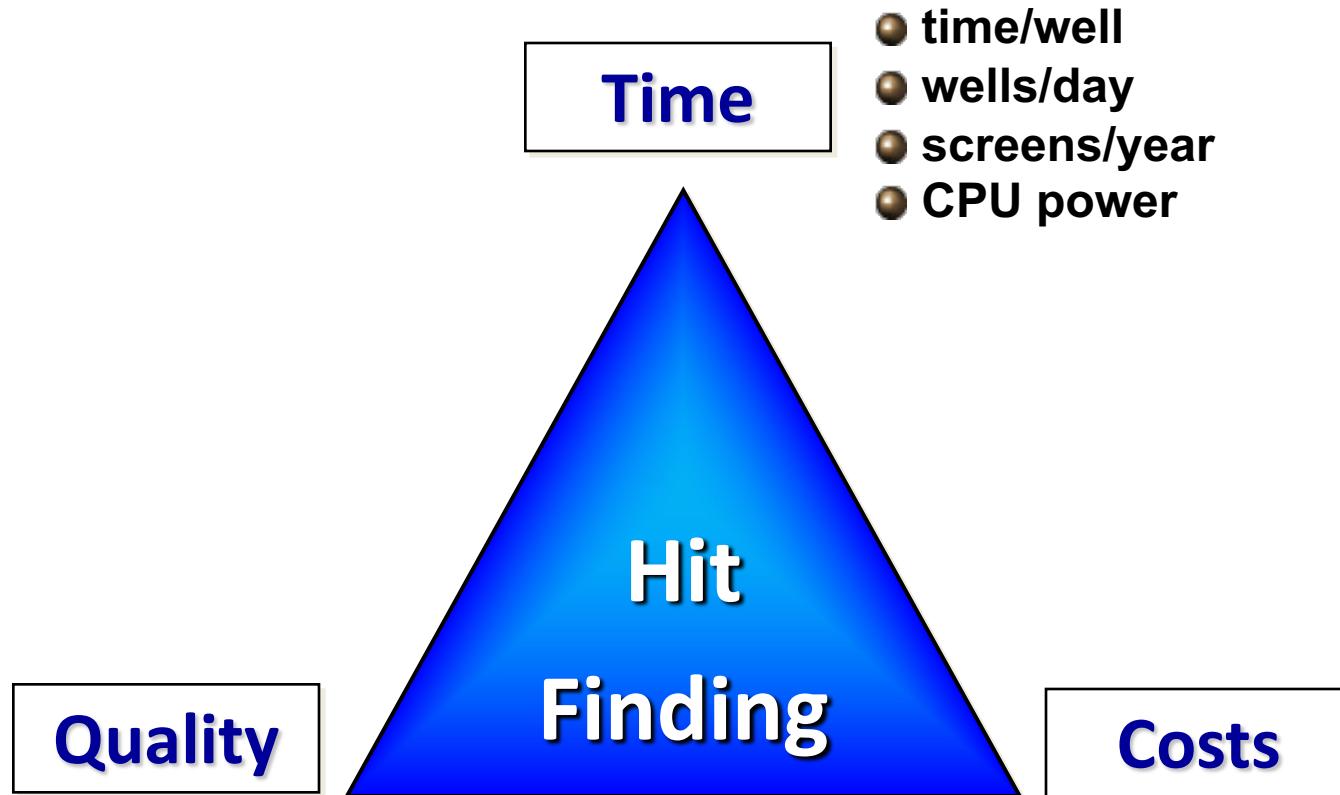
- Low molecular weight / small molecules
 - Antibodies
 - Proteins
 - siRNAs
- 
- Biologics

Approaches to hit finding



- ▶ **Patent “Busting”**
(to make use of existing patent literature
for synthesis of novel chemotypes)
- ▶ **Structural Biology/Chemistry**
in combination with CADD
(Computer Aided Drug Design)
- ▶ **HTS**
High-Throughput Screening
(of chemical compound libraries)
- ▶ **FBS**
Fragment Based Screening
(of small fragment libraries)
- ▶ **Peptidomimetic**
- ▶ **HTD**
High Throughput Docking
(of large compound libraries)
- ▶ **Combinations of approaches**

“Magic triangle”

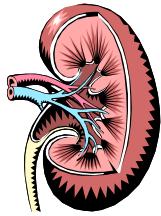


- compound collection
- analysis tools
- few false positive hits
- few false negative hits
- S/N, H/L, Z'-factor

- reagents
- consumables
- instrumentation
- in silico tools

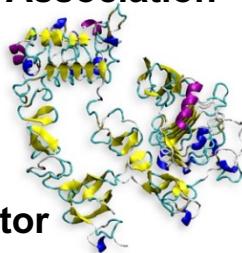
Many Ways to Choosing a “Valid” Target

Fundamental Understanding



Renin
Angiotensin
System

Association



EGF
Receptor

Human Genetics



Cystic Fibrosis
Spinal Muscular Atrophy

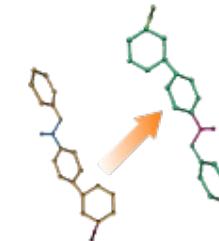
Validated
target

Serendipity and Folk Medicine

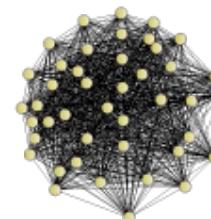


Opiates

Fast Follower



Pathway Genetics



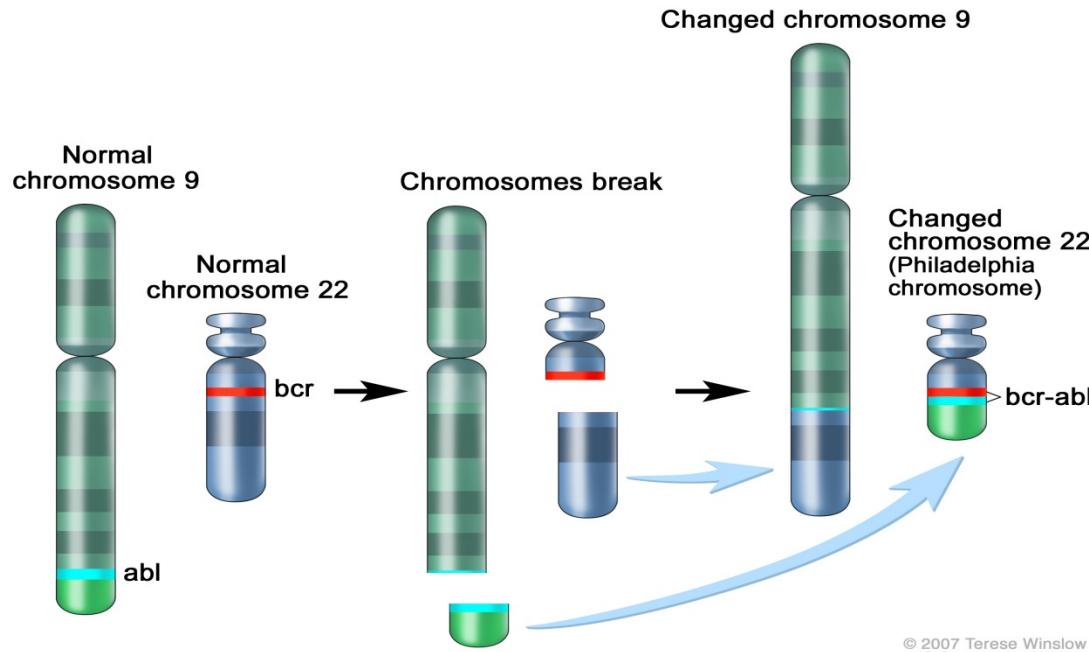
Philadelphia Chromosome



Source: Fox Chase Cancer Center

- In 1959, when David A. Hungerford, in collaboration with Peter C. Nowell, detected a tiny abnormality in the chromosomes from cultured blood cells taken from two patients with chronic myelogenous leukemia (CML).
- Part of chromosome 22 appeared to be missing. The abnormality proved to be an exchange, or translocation, of material between chromosomes 22 and 9.

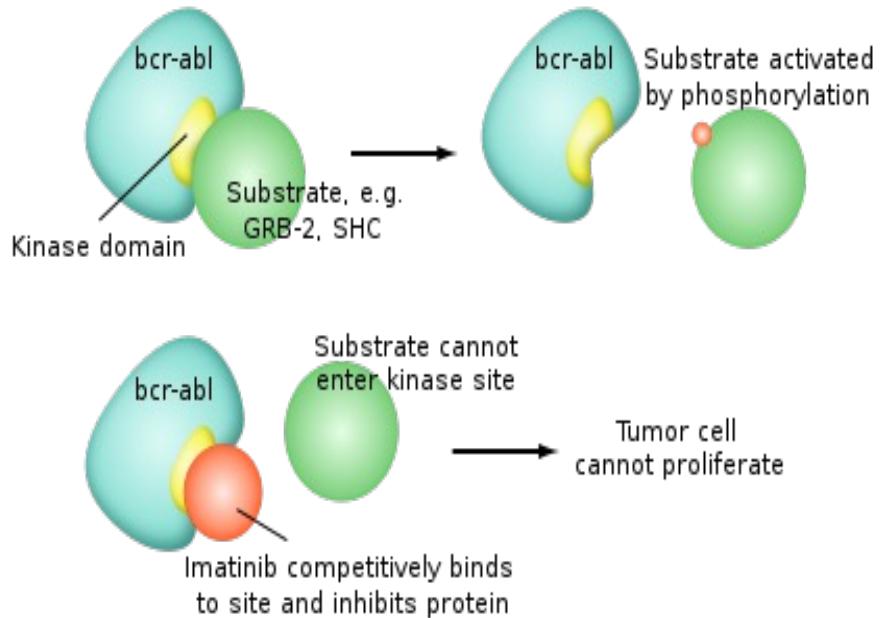
BCR-ABL Fusion Protein



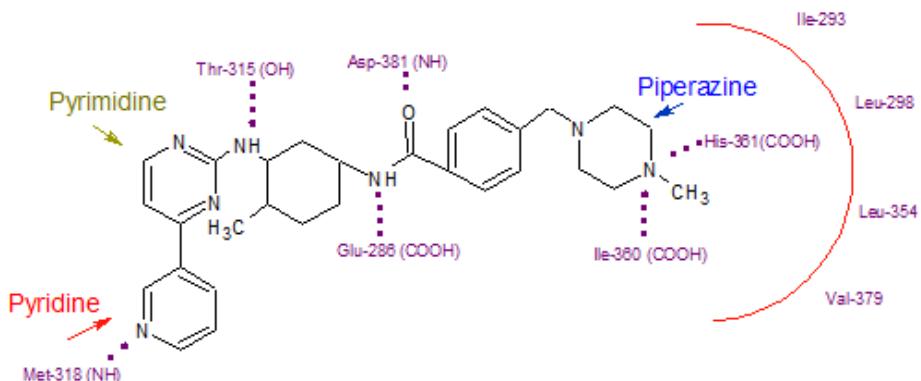
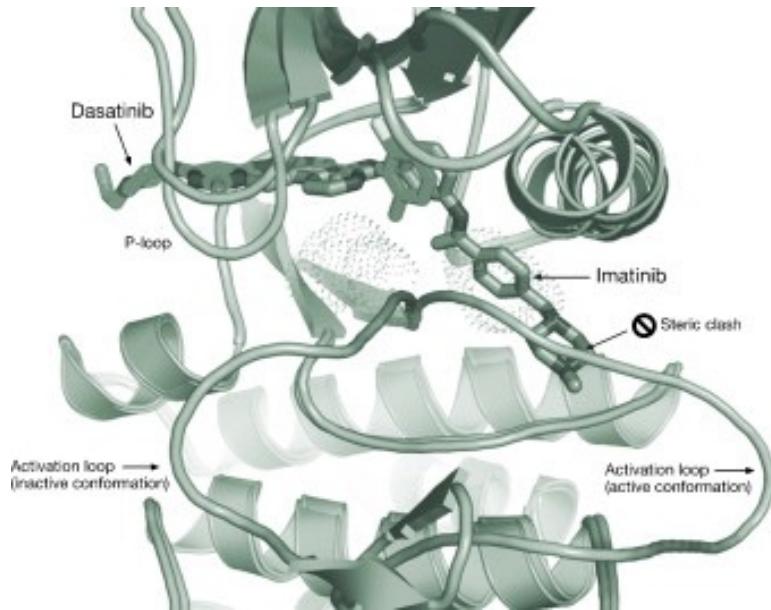
- The protein is found in most patients with chronic myelogenous leukemia (CML), and in some patients with acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia (AML). Inside the leukemia cells, the ABL gene from chromosome 9 joins to the BCR gene on chromosome 22 to form the BCR-ABL fusion gene, making the fusion protein.
- Since ABL activates a number of cell cycle-controlling proteins and enzymes, the result of the BCR-ABL fusion is to speed up cell division. Moreover, it inhibits DNA repair, causing genomic instability and potentially causing the blast crisis in CML.

Target Validation for Imatinib (Gleevec)

- The fused BCR-ABL kinase is continuously active and does not require activation by other cellular messaging proteins. In turn, BCR-ABL activates a cascade of proteins that control the cell cycle, speeding up cell division.
- CML is characterized by the increased and unregulated growth of myeloid cells in the bone marrow and the accumulation of these cells in the blood. 95% of patients with CML have Ph+ chromosome (containing BCR-ABL).
- Imatinib (GLEEVEC®) works by binding to the kinase domain site of the BCR-ABL protein and blocking its activity.

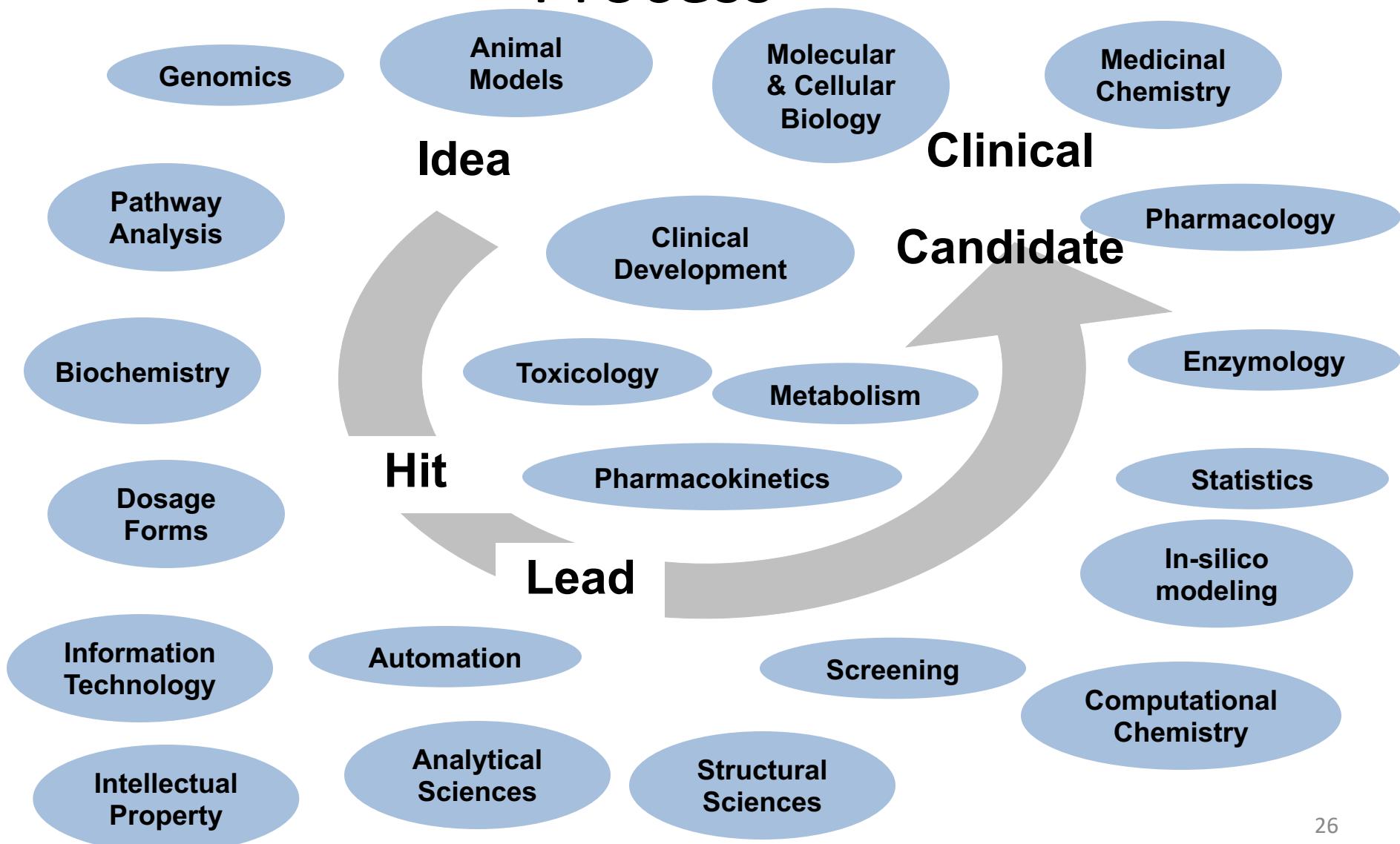


Imatinib Binding



- Imatinib functions by binding in the ATP binding site and stabilizing the inactive conformation of BCR-Abl. The Thr 315 residue is known as the gatekeeper residue and it shifts to allow binding of Imatinib and gives Imatinib its remarkable binding specificity.

Drug Discovery: A Multidisciplinary Process





Pre-Clinical Development & IND-Enabling Studies: Assay Development, Medicinal Chemistry and *in vivo* Pharmacology

TSTP, April 2023

matthew.hall@nih.gov



@cispt2

MATTHEW D. HALL

CHIEF, EARLY TRANSLATION BRANCH

NIH Center for Advancing Translational Sciences (NCATS)

National Institutes of Health



NIH
National Center
for Advancing
Translational Sciences

Outline

Pre-Clinical Development

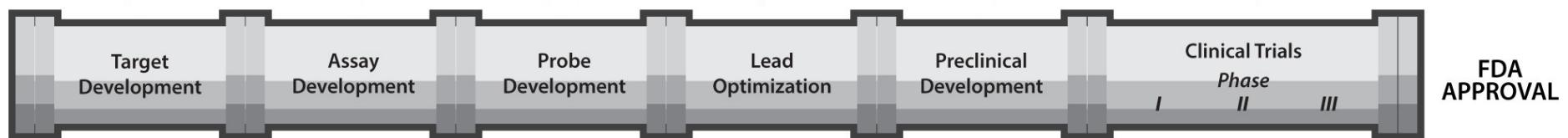
Assay Development

Medicinal Chemistry

In vivo Pharmacology

IND enabling studies

“Basically we are looking for you to cover the entire Preclinical development landscape.”



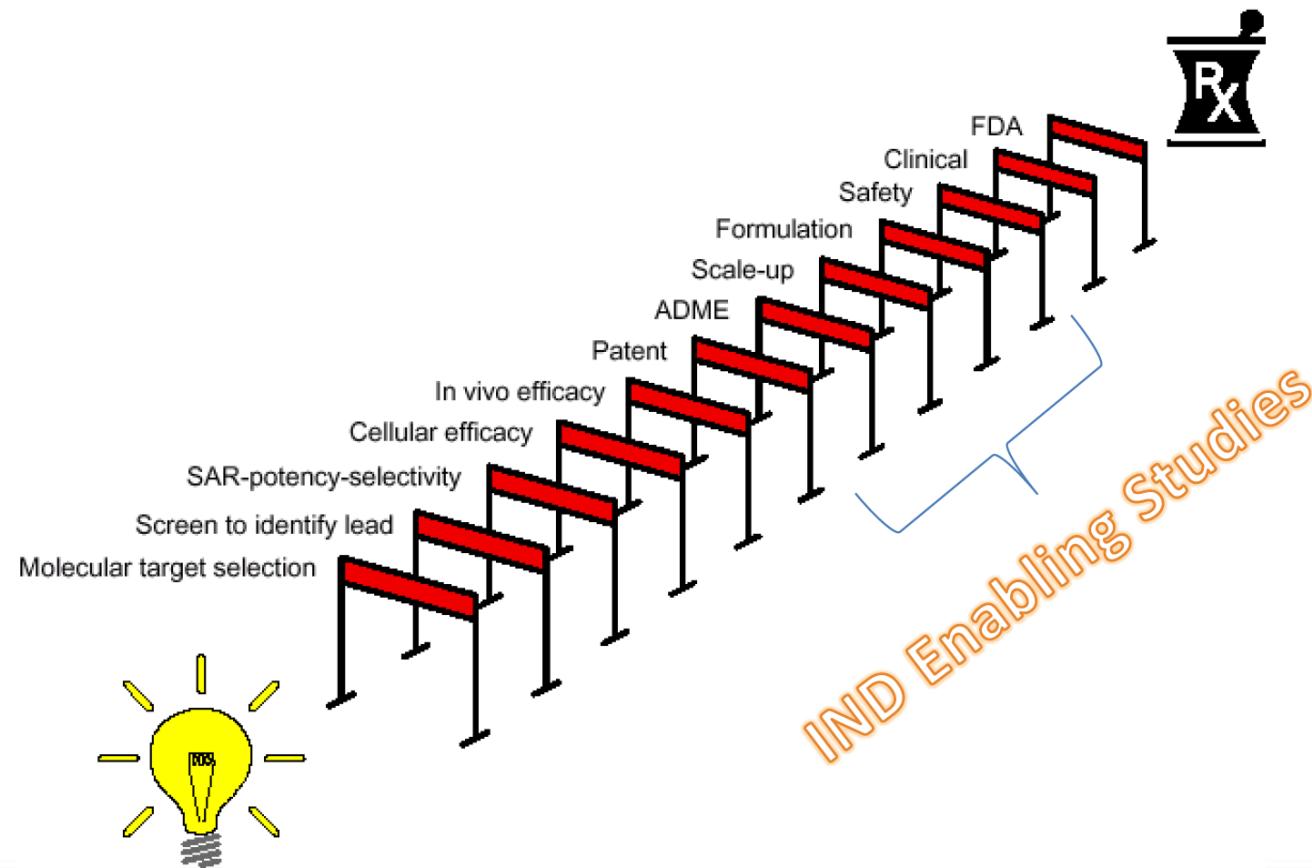
What is translational science?

Translational science is the field of investigation focused on understanding the scientific and operational principles underlying each step of the translational process

NCATS studies translation as a scientific and organizational problem

“Its focus areas are the common causes of inefficiency and failure in translational research projects (for example, incorrect predictions of the toxicity or efficacy of new drugs, lack of data interoperability and ineffective clinical trial recruitment).”

Translation is a team sport!



What is an Investigational New Drug (IND) Application?

A document package submitted to US FDA

- **To seek the permission for human administration of unapproved investigational drugs**
- **Prior to first in human administration**

Sponsored by individual investigator, pharmaceutical company or research institution

FDA has 30 days review before sponsor starts trial

- **Major consideration:** potential safety risks to human subjects

FDA acceptance permits:

- The planned Phase 1 clinical trial
- Shipment of experimental drug among states
 - The Federal Food, Drug and Cosmetic Act – 21CFR Part 312

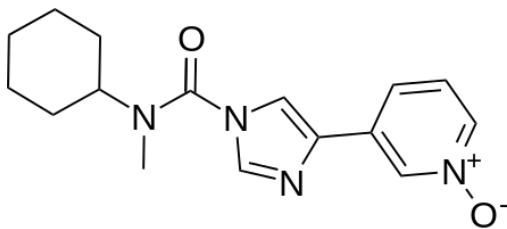
IND Enabling Studies

U. S. 21 CFR 312.23 IND Requirements

“Adequate information about the **pharmacological and toxicological** studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is **reasonably safe to conduct the proposed investigations in humans.** . . .

Why are IND-enabling studies critical?

BIA 10-2474 is part of a family of FAAH-enzyme inhibitors that can have an impact on pain and anxiety by boosting the endocannabinoid system involved in appetite control, pain sensation, mood and memory.



According to the document, which is in French, participants in this particular study group were to receive €1900, including travel expenses; in return, they agreed to stay at Biotrial's facility in Rennes for 2 weeks, swallow a drug on 10 consecutive days, undergo extensive medical tests, and provide at least 40 blood samples.



The study was halted on Monday, and all six patients who had taken the drug were hospitalized; one is brain-dead, four others have neurological symptoms of varying severity, while one is under observation but without symptoms, neurologist Gilles Edan of the University of Rennes Hospital Center said yesterday. MRI imaging has shown "deep, necrotic, and hemorrhagic lesions in the brain[s]" of the patients, Edan said.

What went wrong?

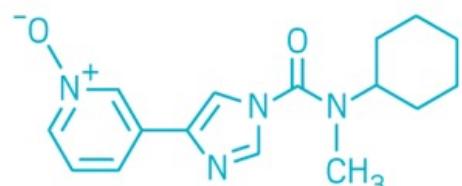
BIA 10-2474 is part of a family of FAAH-enzyme inhibitors that can have an impact on pain and anxiety by boosting the endocannabinoid system involved in appetite control, pain sensation, mood and memory.

The trial was designed so that 6 doses (2.5 mg up to a maximum of 100 mg) would be tested on one group of volunteers. The researchers would then multiply the quantity by two each time a new dose was administered--but this was not applied between dosages of 20 mg and 50 mg.

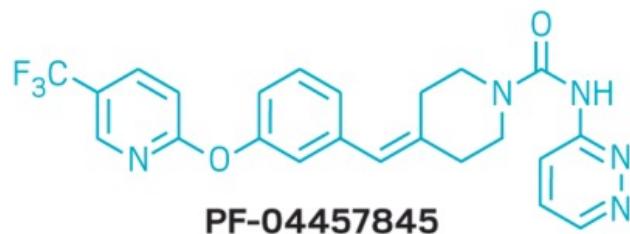
One question the experts want answered is why so much animal testing had preceded the human trials. They said it was surprising to see that rats, mice, dogs and monkeys were all used - raising the question whether the lab had suspicions about toxicity.

What went wrong at a molecular level?

Off-target effects



BIA 10-2474



PF-04457845

Highly specific FAAH inhibitor, also in human clinical trials

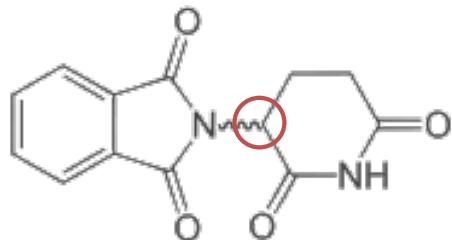
BIOCHEMISTRY

Activity-based protein profiling reveals off-target proteins of the FAAH inhibitor BIA 10-2474

This analysis revealed that the drug inhibits several lipases that are not targeted by PF04457845, a highly selective and clinically tested FAAH inhibitor. BIA 10-2474, but not PF04457845, produced substantial alterations in lipid networks in human cortical neurons, suggesting that promiscuous lipase inhibitors have the potential to cause metabolic dysregulation in the nervous system.

Enzyme	Treatment	IC ₅₀ (μM)		
		BIA 10-2474	BIA 10-2639	PF04457845
FAAH	In vitro	7.5	4.1	0.004
FAAH	In situ (4 hours)	0.049	0.049	0.011
FAAH2	In situ (4 hours)	0.40	0.10	0.59
ABHD6	In situ (4 hours)	0.081	0.079	>10
CES2	In situ (4 hours)	2.0	0.63	>10
ABHD11	In situ (4 hours)	>10	2.3	>10
PNPLA6	In situ (24 hours)	11	ND	>50

Thalidomide: the drug that started safety?



- Introduced as a sedative in the late 50's
- Particularly effective against morning sickness
- Found to cause teratogenicity
- Withdrawn from use in 1961

- While in use, over 10,000 cases associated with birth defects occurred
- About 40% of thalidomide victims died before their first birthday

WHAT HAPPENED?

Teratogenic: causes abnormality in development

The drug that started safety?

Developed by a German pharmaceutical company

Launched in October 1957

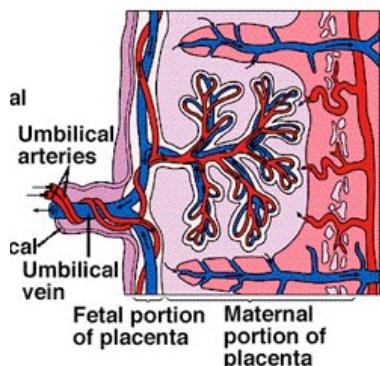
Tranquilizer and painkiller

Marketed as a “wonder drug” for insomnia, flu, etc.

Also an effective antiemetic, including “morning sickness”

As a result many pregnant women took thalidomide

At the time of development, it was not believed that any drug could cross the blood-placenta barrier (similar to blood-brain barrier)



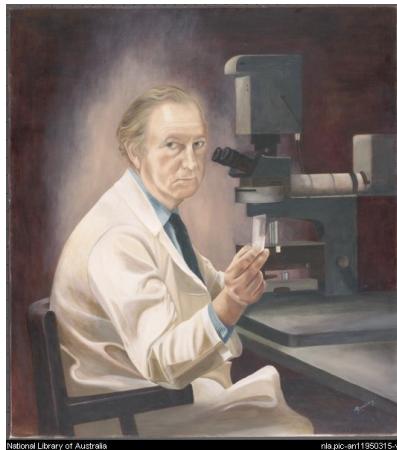
- Tight junctions prevent diffusion-mediated crossing
- Transfer of oxygen, nutrients (transporter regulated)
- Efflux pumps prevent entry of many drugs
- Similar to the BBB in function
- So... if it enters the brain, it can cross the placenta
- Neuroactive = potentially harmful to child, or its development (alcohol, nicotine, antidepressants, etc.)

The drug that started safety?

William McBride (b. 1927), Australian ob/gyn

- Observed multiple deformities
- Submitted a paper of observations to *Lancet* – they declined to publish it!
- Then wrote a ‘letter’ on his observations to *The Lancet* (rather than manuscript for peer review)

Precipitated withdrawal of drug



THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ('Distaval') during pregnancy, as an anti-emetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales.

W. G. McBRIDE.

12

Physician



Meanwhile in America.....

Thalidomide approved for use across the globe
NEVER approved in the United States.

Enter Frances (Frances Oldham Kelsey, 1914 - 2015)

- Canadian physician
- Reviewer at the FDA
- Had concerns about thalidomide side-effects in application for registration
- Insisted that the drug be “fully tested”, delaying its registration
- Side-effects reported in the meantime, and the drug was withdrawn worldwide

- Awarded the President's Award for Distinguished Federal Civilian Service by JFK
“Only twenty” cases of teratogenicity were reported in America, due to imported thalidomide. But thousands of doses were provided to women by doctors as part of a clinical trial.

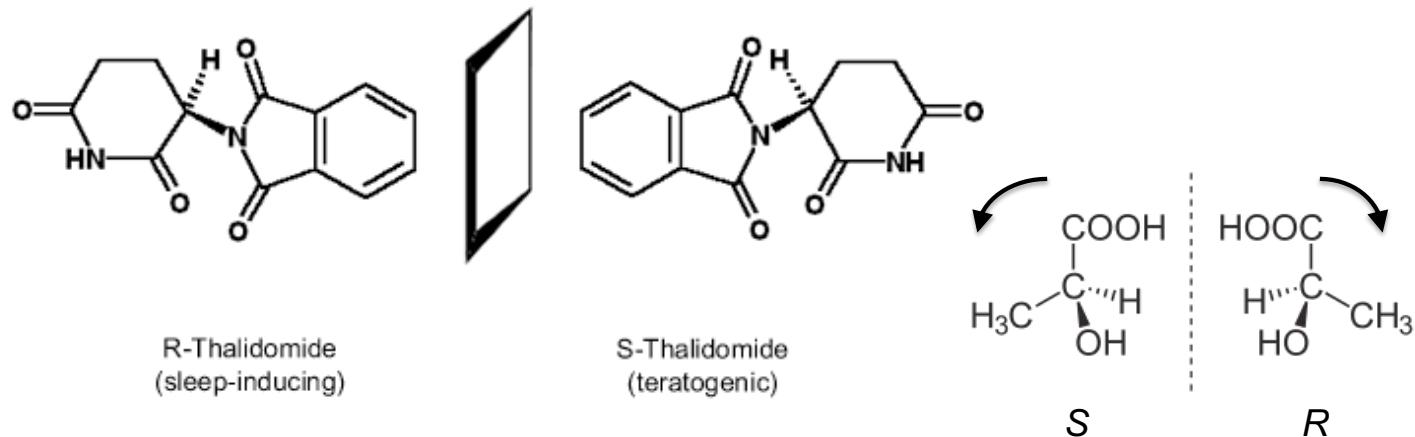


FDA reviewer



The cause?

Thalidomide was formulated as a **racemate** of two **enantiomers**

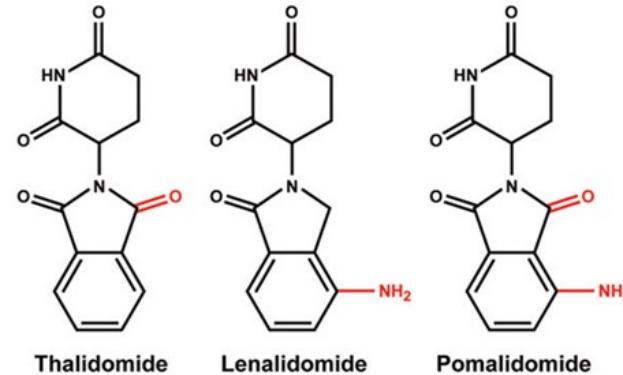


Racemate: Contains equal amounts of left- and right-handed molecules (enantiomers)

Solution: Administer only the enantiomer that has pharmacologic effect, without the teratogenic effects

Enantiomerically pure thalidomide interconverts to the racemate over time

Not the end of the line?



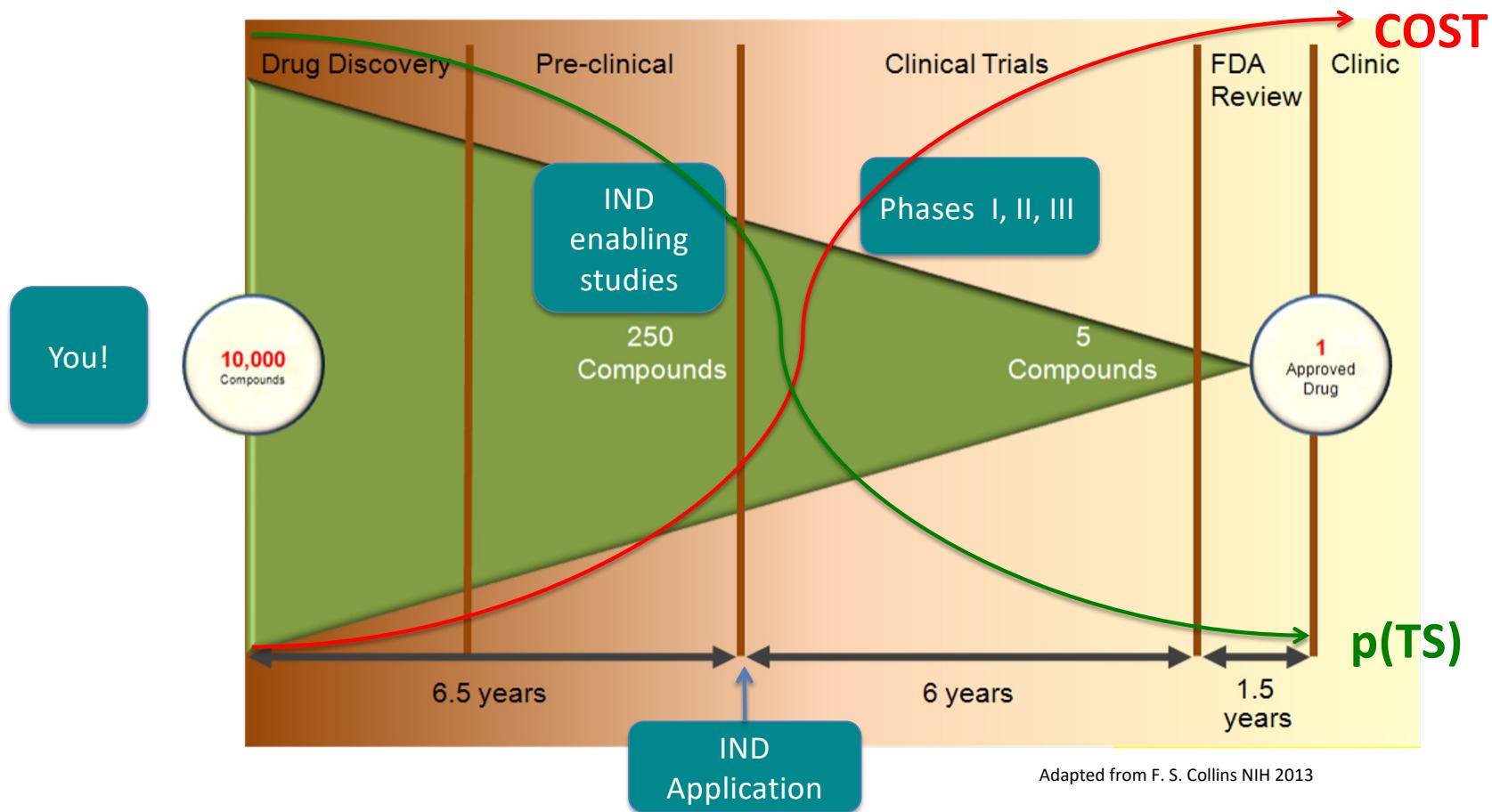
Lenalidomide has been used to successfully treat both inflammatory disorders and cancers in the past 10 years

In vivo, lenalidomide induces tumor cell apoptosis by inhibition of bone marrow stromal cell support, by anti-angiogenic and anti-osteoclastogenic effects, and by immunomodulatory activity

On a molecular level, lenalidomide has been shown to interact with the ubiquitin E3 ligase cereblon and target this enzyme to degrade the Ikaros transcription factors IKZF1 and IKZF3.

Lenalidomide costs \$163,381 per year for the average U.S. patient, and Revlimid made almost \$3.8bn for Celgene in 2012

Drug discovery: it's a long hard road!



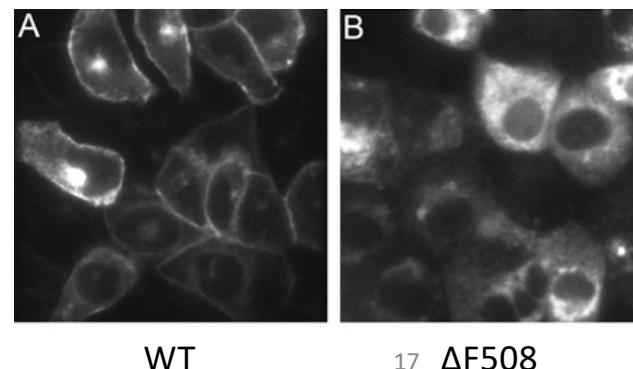
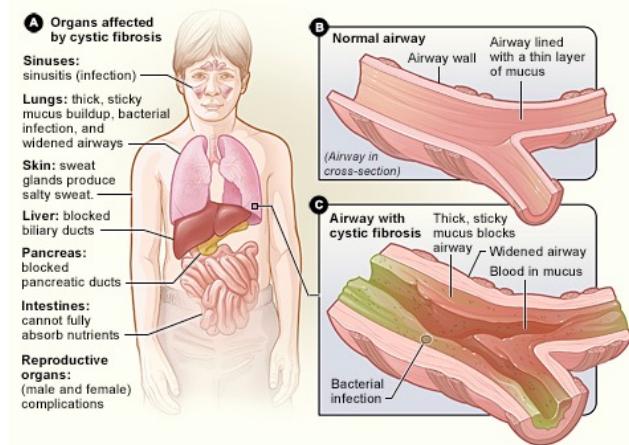
Why DO we need new drugs?

Unmet need

- Diseases/disorders with no available drug therapy
- Why is no therapy available?

Is the disorder understood? i.e. is there a target?

Cystic fibrosis, mutation in chloride transporter ***CFTR*** (*MRP7, ABCC7*) makes it inactive. No therapy to directly resolve the disorder currently available.

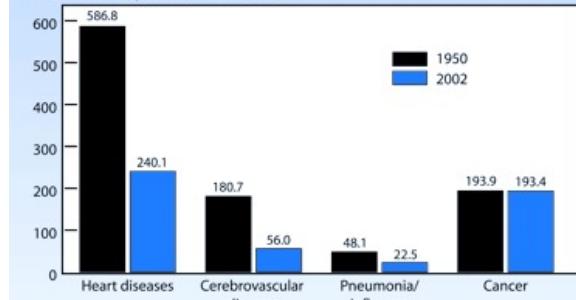


STAT BITE

Changes in the U.S. Death Rate by Cause, 1950 and 2002

The U.S. mortality rate for cancer in 2002 was about 193 per 100,000—nearly identical to the rate in 1950. Although there were large declines in cancer mortality in many age groups during that time period, the rates increased by about 12% among 65–74-year-olds and 75–84-year-olds and by 19% among those older than age 85. In addition, lung cancer mortality increased by 269%—from 14.9 deaths per 100,000 in 1950 to 55.1 deaths per 100,000 in 2002.

U.S. death rate* by cause, 1950 and 2002:



*Rates are per 100,000 and are age-adjusted to the 2000 U.S. standard population.

Sources: Cancer Statistics 2005 (American Cancer Society 2005), access at www.cancer.org; Cancer Statistics Review, 1975–2002 (National Cancer Institute 2005), access at seer.cancer.gov.

10.1093/jnci/djj294

New drugs for cystic fibrosis

The New York Times

INTERNATIONAL BUSINESS

Vertex's 2-Drug Cystic Fibrosis Pill Shows Promise

By ANDREW POLLACK JUNE 24, 2014



EMAIL

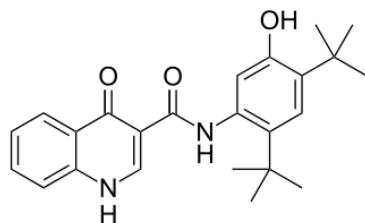


FACEBOOK

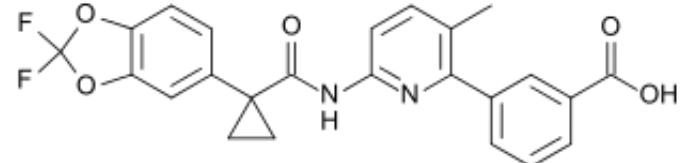


TWITTER

Vertex Pharmaceuticals said on Tuesday that a combination of two of its drugs had successfully treated cystic fibrosis in closely watched clinical trials, potentially clearing the way for approval of a new option for nearly half the patients with the genetic disease.



Ivacaftor
(VX-770)
Activates transporter



Lumacaftor
(VX-809)
Corrects folding defects

The cost of ivacaftor is \$311,000 per year !!!! 18

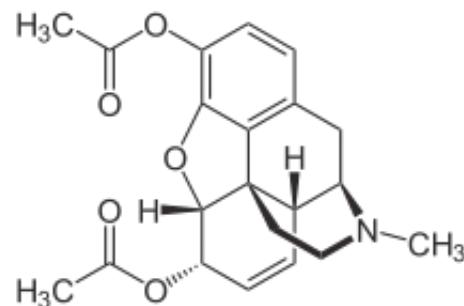
Why DO we need new drugs?

- To **improve** efficacy/treatment, and lower unwanted side effects (including toxicity).



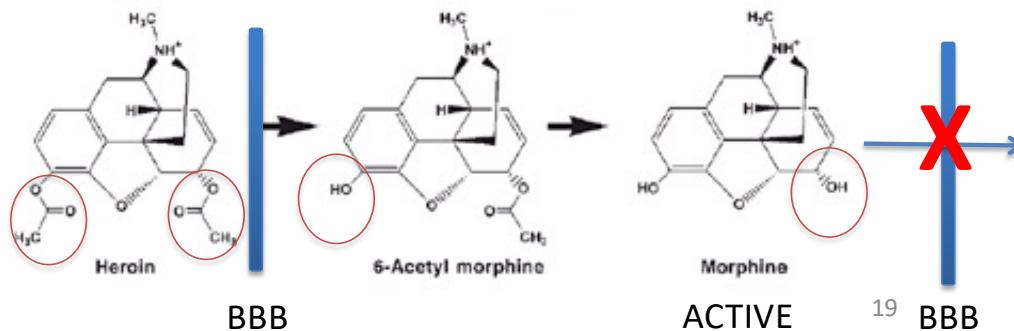
Heroin, from the opium poppy.
An excellent painkiller, but....

- Addiction
- Tolerance



1b

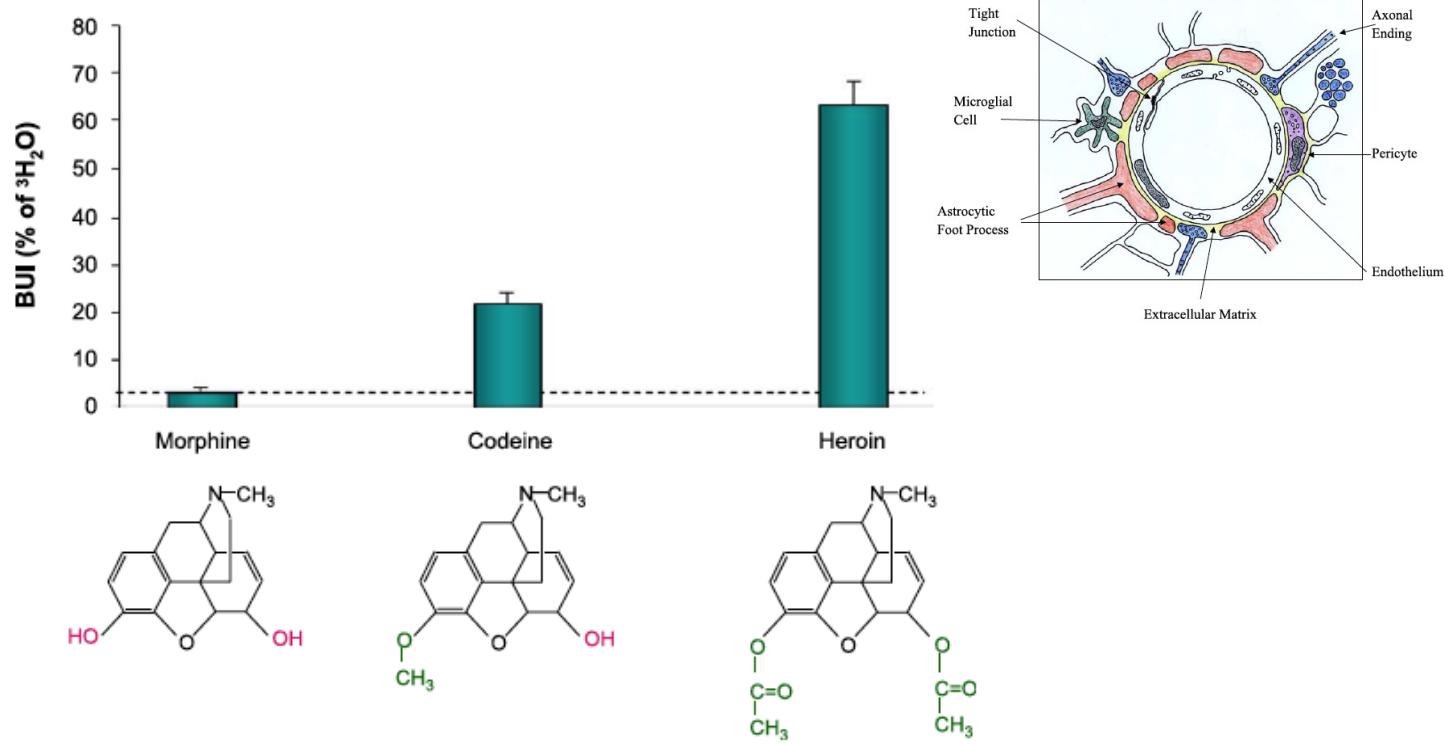
Hydrolysis of heroin



19 BBB

Delivering drugs to the brain is a huge challenge

Small changes in structure make a big difference!



BUI = brain uptake index

Whence came drugs? (good and bad)

Mithridate – a remedy taken as an antidote for poison!

*When he tried to kill himself, he could not find
any poison that would have an effect*

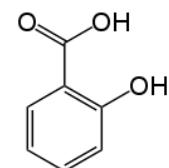
Mithridates VI (120-63 BC)



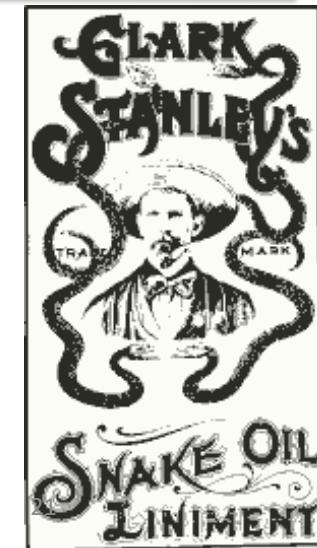
Historically: Known use of ‘natural products’, herbs, and traditional medicines to remedy disease. Some worked, many didn’t.

‘Oil of Wintergreen’ - Methyl salicylate

Willow bark – Salicylic acid
(pain and fever reducers)



Materia medica (gen.) – published body of knowledge on therapies and treatments available.

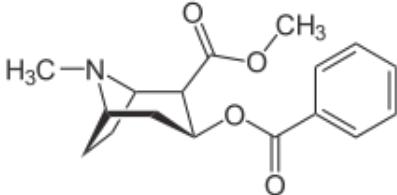


Whence came drugs? (good and bad)

19th century – morphine and cocaine natural products isolated

Morphine and cocaine – prescribed for use, as well as abused.

Coca leaf



Cocaine

Now: Coca leaf processed in NJ (regulated by the DEA) – cocaine removed and processed for medicinal purposes, and cocaine-free leaves for flavoring generated for incorporation into Coca-Cola.

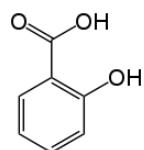
Cocaine is processed to cocaine hydrochloride (requires DEA approval for use)

Morphine (1805), Quinine (1823), Atropine (1834)

General anesthetic (surgery from 1842): diethyl ether (1842), nitrous oxide (1845)
chloroform (1847).

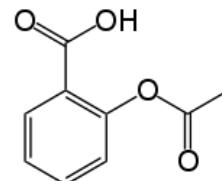
Hypodermic needle: 1857

Whence came drugs? (good and bad)



Salicylic acid as analgesic 1860's
gave aspirin (1897)
Relieves pain, reduces fever

Acetylsalicylic acid



Acetylation

Gastric irritation, ulceration, bleeding

Nobel prize!
Modern medicinal medicine: **Ehrlich** and Hata

- 'Magic bullet'
 - Blood-brain barrier
 - Syphilis treatment through medicinal chemistry
- **Before:** Got syphilis? Take mercury salts!
- **After:** Got syphilis? Take arsenic!

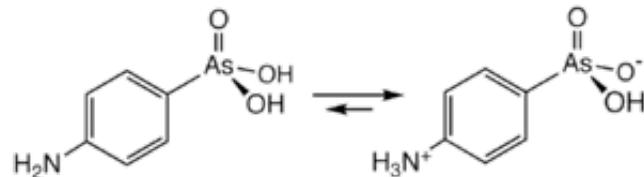
1971: COX inhibitor ->



Salvarsan: Compound 606

Syphilis is a sexually transmitted infection caused by the spirochete bacteria

Ehrlich reasoned that SCREENING toxic compounds might identify a compound toxic towards syphilis bacteria. His starting point was **arsanilic acid**

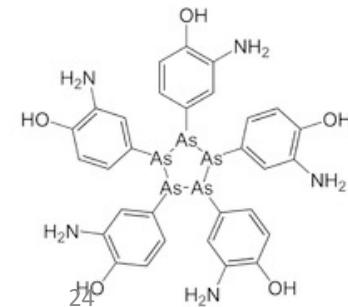
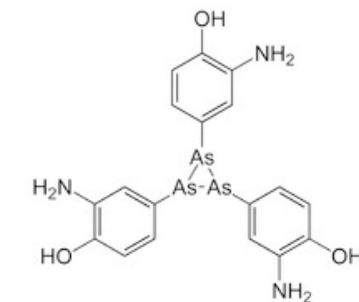
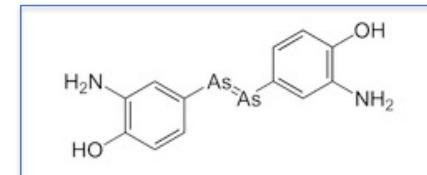


Systematic chemical modifications to the **lead compound** were made and each new compound tested for **efficacy**.

Salvarsan was found to be highly active.

Standard treatment for syphilis till **penicillin** in the 1940s.

Ehrlich received the Nobel prize in 1908

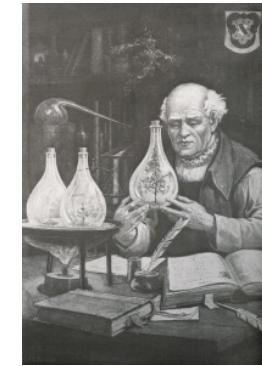


Arsenic can make you better?

A poison? A heavy metal?

Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy.

Paracelsus (1493-1541)



Arsenic — New Life for an Old Potion

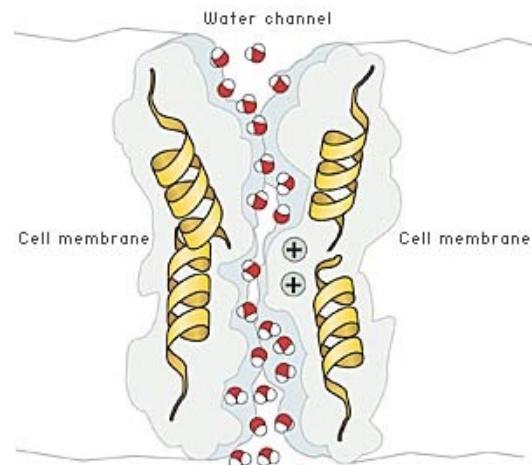
The NEW ENGLAND
JOURNAL of MEDICINE

Arsenic is still in use in medicine today against acute promyelogenous leukemia (APL), giving 85% remission rates.

Arsenic trioxide (As_2O_3) – trade name Trisenox.

Enters cancer cells via aquaporin (N!), the water uptake transporter (molecular channel) on the cell surface.

So how do we decide if a toxic substance like arsenic is acceptable for pharmaceutical use?



Understanding safety of a drug is critical

Ehrlich:

$$\text{Chemotherapeutic index} = \frac{\text{Minimum curative dose}}{\text{Maximum tolerated dose}}$$

The lower the number, the safer the drug.

NOW:

$$\text{Therapeutic index} = \frac{\text{LD}_{50}}{\text{ED}_{50}}$$

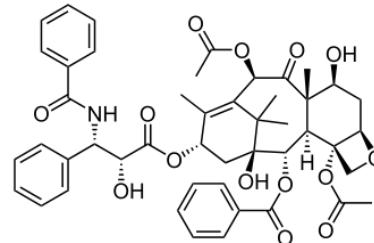
Lethal dose for 50% of mice
Effective dose for 50% of population (humans)

A high ratio (33,000:1) is safe, and a low ratio (2:1) requires careful monitoring or patient blood sampling. **Why blood sampling?**

In humans, TD_{50} is used instead = Toxicity in 50% of patients

Where do lead drugs come from?

- Screening of local folk remedies
- Plant sources
- Marine sources
- Microorganisms (pen)
- Animal sources
- **Synthetic chemistry libraries
(Medicinal chemistry)**

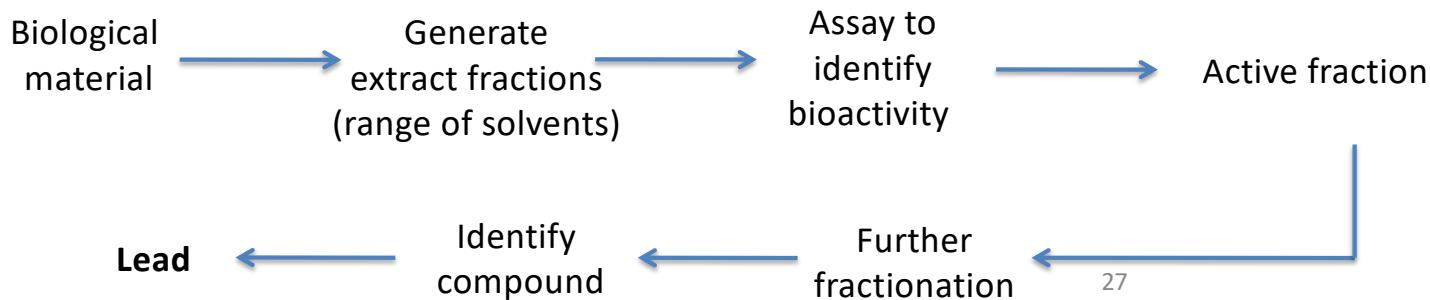


Paclitaxel

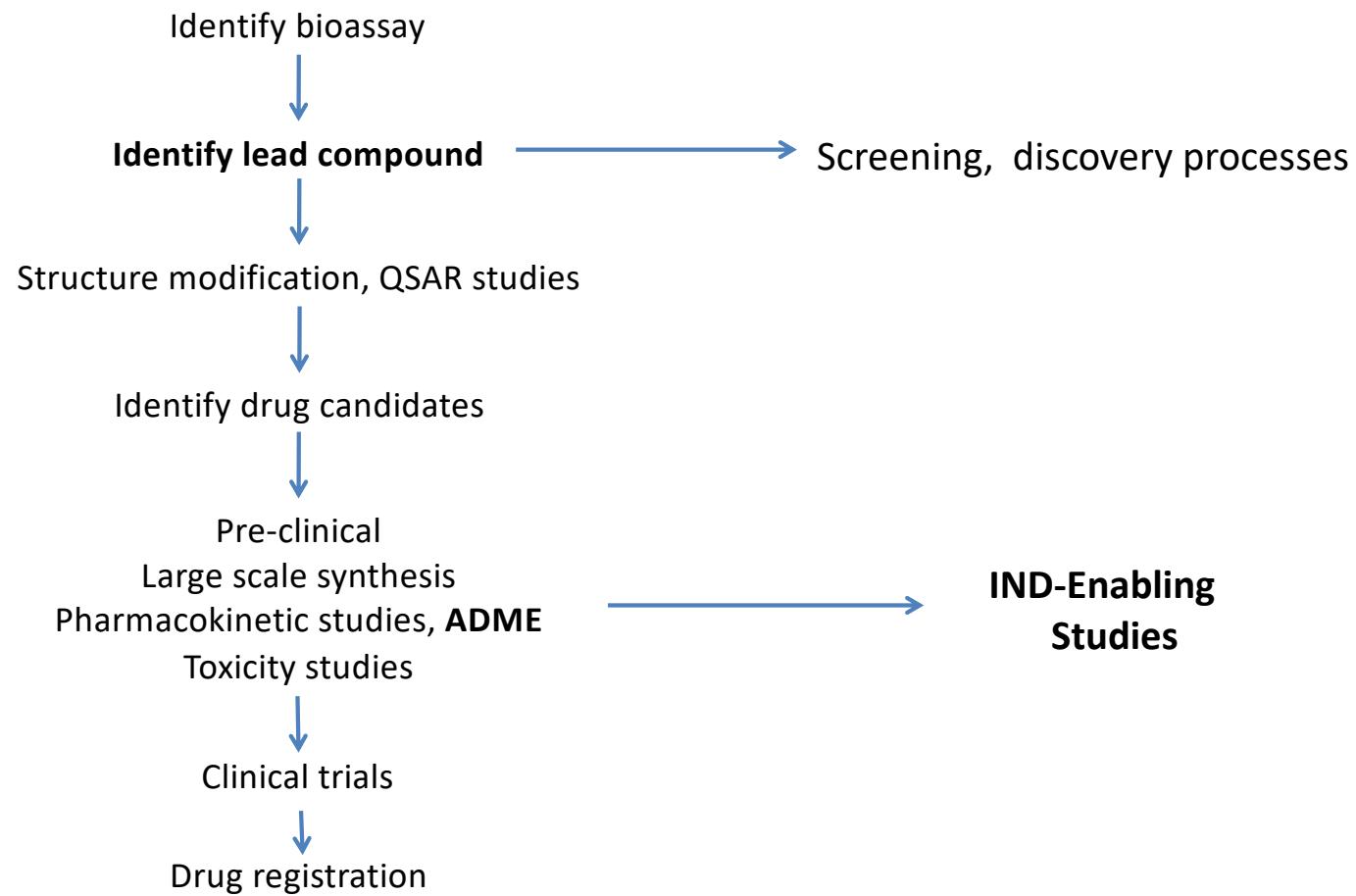
- Anticancer drug
- From bark of the Pacific yew
- Supply limited by slow growth of tree
- *Solution???*
- Virtually insoluble –
-but too good to ignore

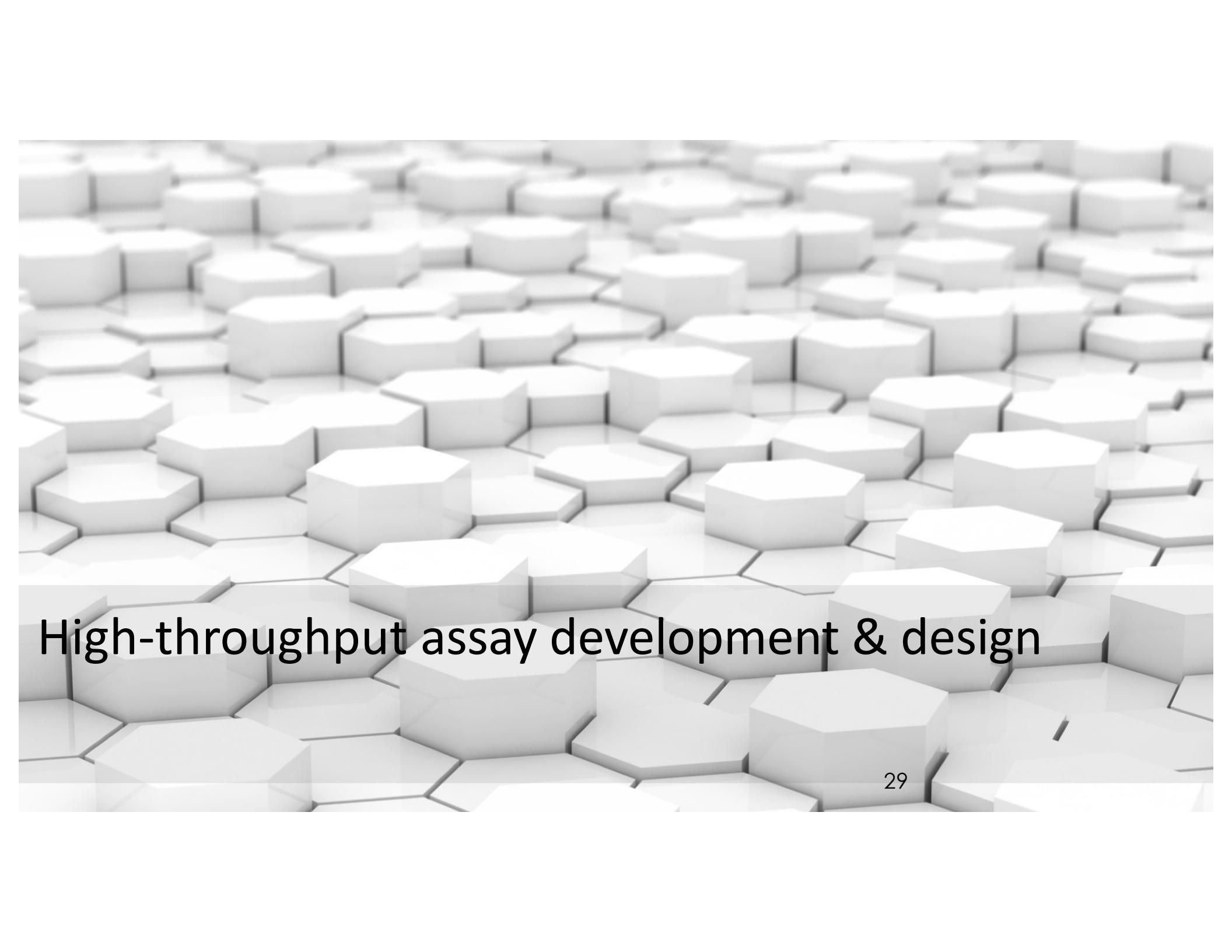
Many toxins sourced.... Why?

Which of the above sources would be easiest to screen?



General stages of modern drug discovery





High-throughput assay development & design

Where do drugs really come from? Then: Serendipity in drug discovery

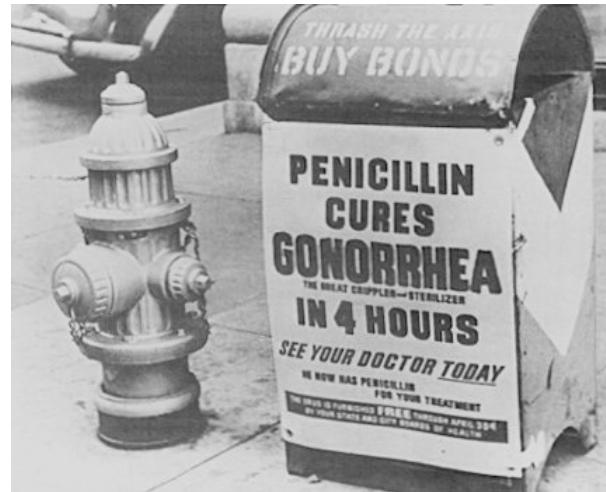
The most exciting phrase to hear in science, the one that heralds new discoveries,

is not "Eureka" but "That's funny..."

- Isaac Asimov (1920–1992)

"Chance favors only the prepared mind."

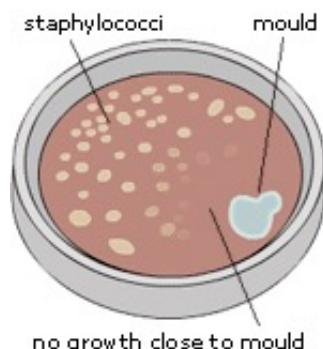
- Louis Pasteur (1822-1895)



Penicillin

"When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionize all medicine by discovering the world's first antibiotic, or bacteria killer,"

Alexander Fleming (1881-1955)



1928

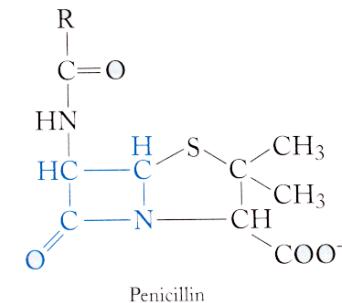
"Originally noticed by a French medical student, Ernest Duchesne, in 1896."

Isolate
fungus



Penicillius
(fungus)

identify
compound

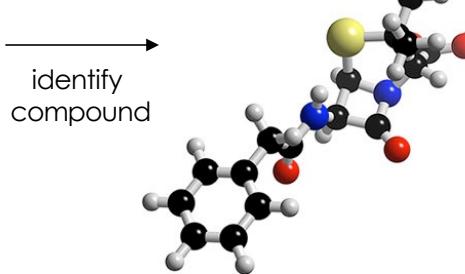
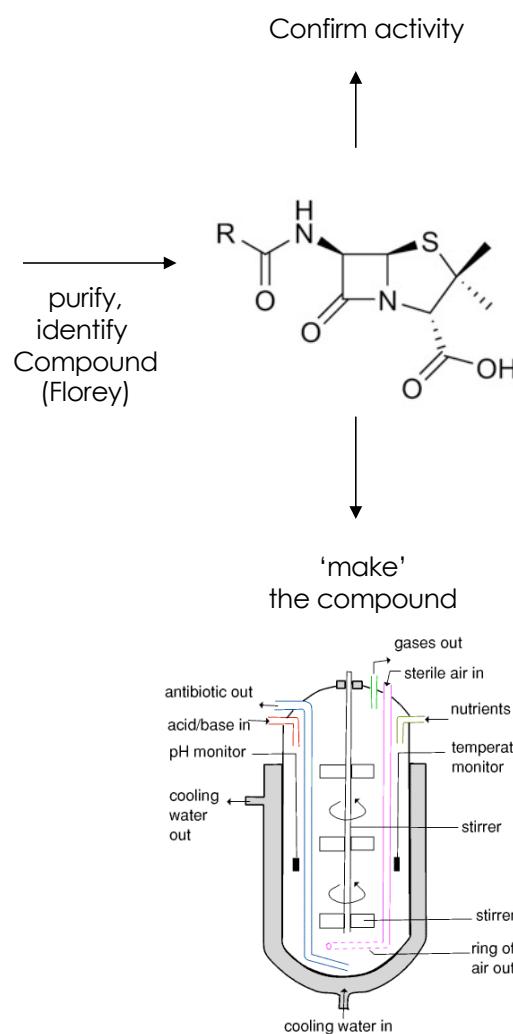


Synthesise
the compound



Clinical trials to evaluate the compound

Penicillin



Dorothy Crowfoot Hodgkin

Nobel Chemistry 1968
1910 Cairo
1994 England

penicillin in 1945
cholesterol in 1937
vitamin B12 in 1954
insulin in 1969

Fermentation

"after a worldwide search, it was a strain of penicillin from a moldy cantaloupe in a Peoria (Illinois) market that was found and improved to produce the largest amount of penicillin when grown in the deep vat"

Penicillin

- They proved it harmless and effective on mice. First patient was a terminal cancer patient – to check its toxicity! Developed a fever due to an impurity.
- Their attempts to treat humans failed due to insufficient volumes of penicillin (the first patient treated was Reserve Constable Albert Alexander). They even recovered penicillin from patient urine.
- On March 14, 1942, John Bumstead and Orvan Hess became the first in the world to successfully treat a patient using penicillin
- Penicillin production was quickly scaled up and available in quantity to treat Allied soldiers wounded on D-Day.
- As production was increased, the price dropped from nearly priceless in 1940, to \$20 per dose in July 1943, to \$0.55 per dose by 1946.

"People sometimes think that I and the others worked on penicillin because we were interested in suffering humanity. I don't think it ever crossed our minds about suffering humanity. This was an interesting scientific exercise, and because it was of some use in medicine is very gratifying, but this was not the reason that we started working on it."

Howard Florey, Baron Florey



The horror of diseases such as blood poisoning is easily forgotten. These pictures, taken in 1942 shortly after the introduction of penicillin, show the improvement in a child with a bacterial infection four (photo 3) and nine (photo 4) days after treatment, and fully recovered (5&6)

Drug discovery: *then* and **now**

DRUG DISCOVERY

THEN:

Hunches, serendipity and sheer luck

Nature (plants, fungi, bacteria, animals)

Test tube, larger formats

By hand (grad students)

Dozens/day? **THROUGHPUT?** >1,000,000 wells/day

NOW:

HOW?

HTS, virtual screening, rational drug design (and still luck!)

SOURCE

Screening libraries

ASSAYS

Microplate-based (up to 1536, 3456-well!)

LABOR

Robotics/automated (even cell culture!)

The most exciting phrase to hear in science, the one that heralds new discoveries,
is not “eureka” but “that’s funny...”

- Isaac Asimov (1920–1992)

"Chance favors only the prepared mind."

- Louis Pasteur (1822-1895)



What is an assay?

AN ASSAY IS a defined set of reagents that produce a detectable signal allowing a biological process to be quantified (i.e. a specific experiment)

Assays can be used to measure any number of biological markers:

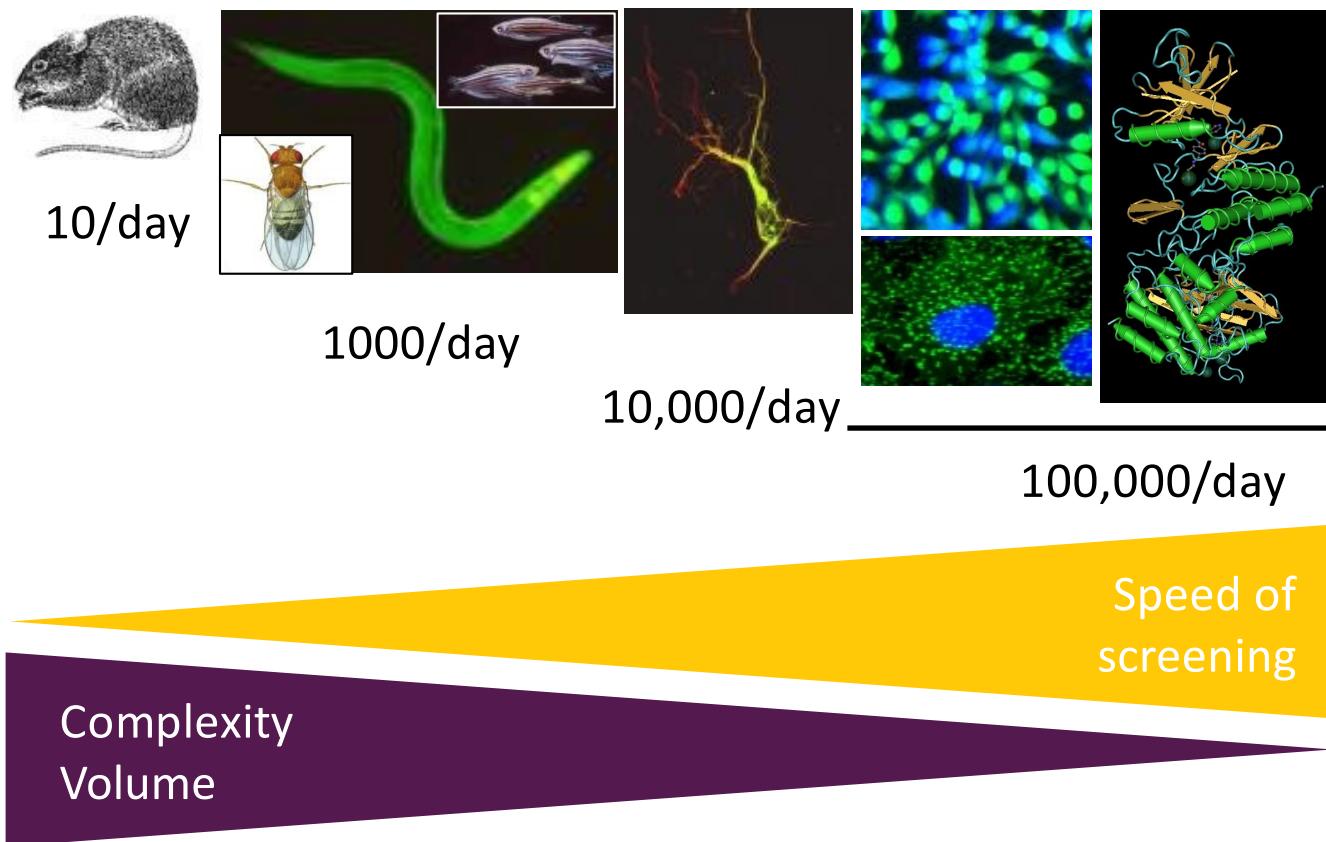
- Protein levels in cell lysate (Bradford assay)
- Cell viability in presence of compound (MTT assay)
- Activity of isolated kinase enzyme (kinase assay)
- Cell migration and motility (wound-healing/scratch assay)

Assays are used in all aspects of science to measure specific phenomena

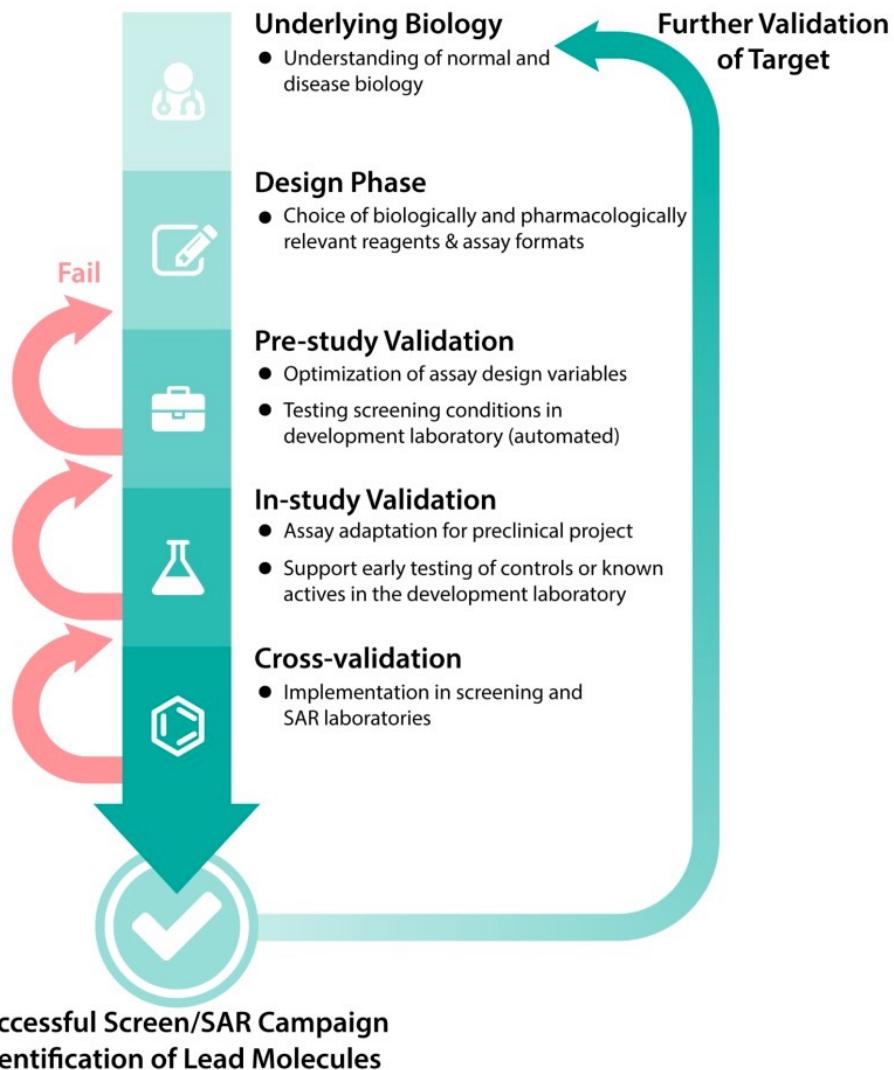
In the context of this talk, assays are specifically those that can be adapted to perform high-throughput screening in the biotechnology and drug discovery fields



What can be assayed?



Assay Development Cycle



What is high-throughput screening?

High Throughput Screening (HTS) is a drug-discovery process widely used in the pharmaceutical industry. It leverages **automation** to quickly assay the **biological or biochemical activity of a large number of drug-like compounds**.

3-5 days/screen

100,000 – 500,000 compounds - **High-throughput screen, (HTS)**

25,000– 50,000 compounds – **Medium-throughput screen**

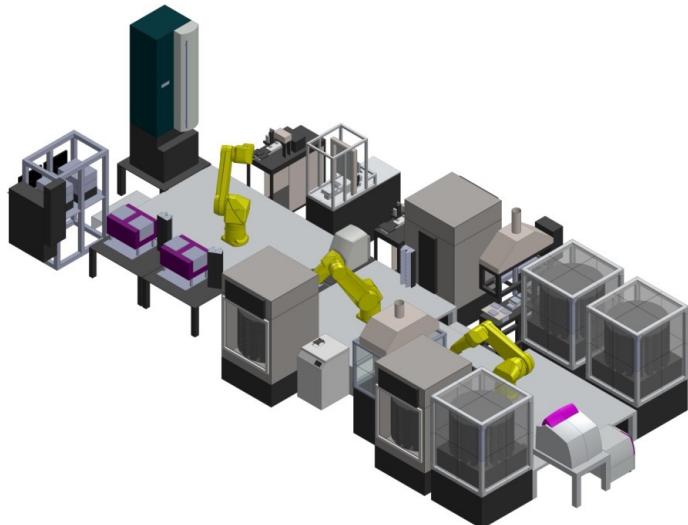
10,000- 25,000 compounds – **Low-throughput screen**



Structure Activity Relationship (SAR) Assays

50-100 compounds tested/ week

High-throughput screening automation

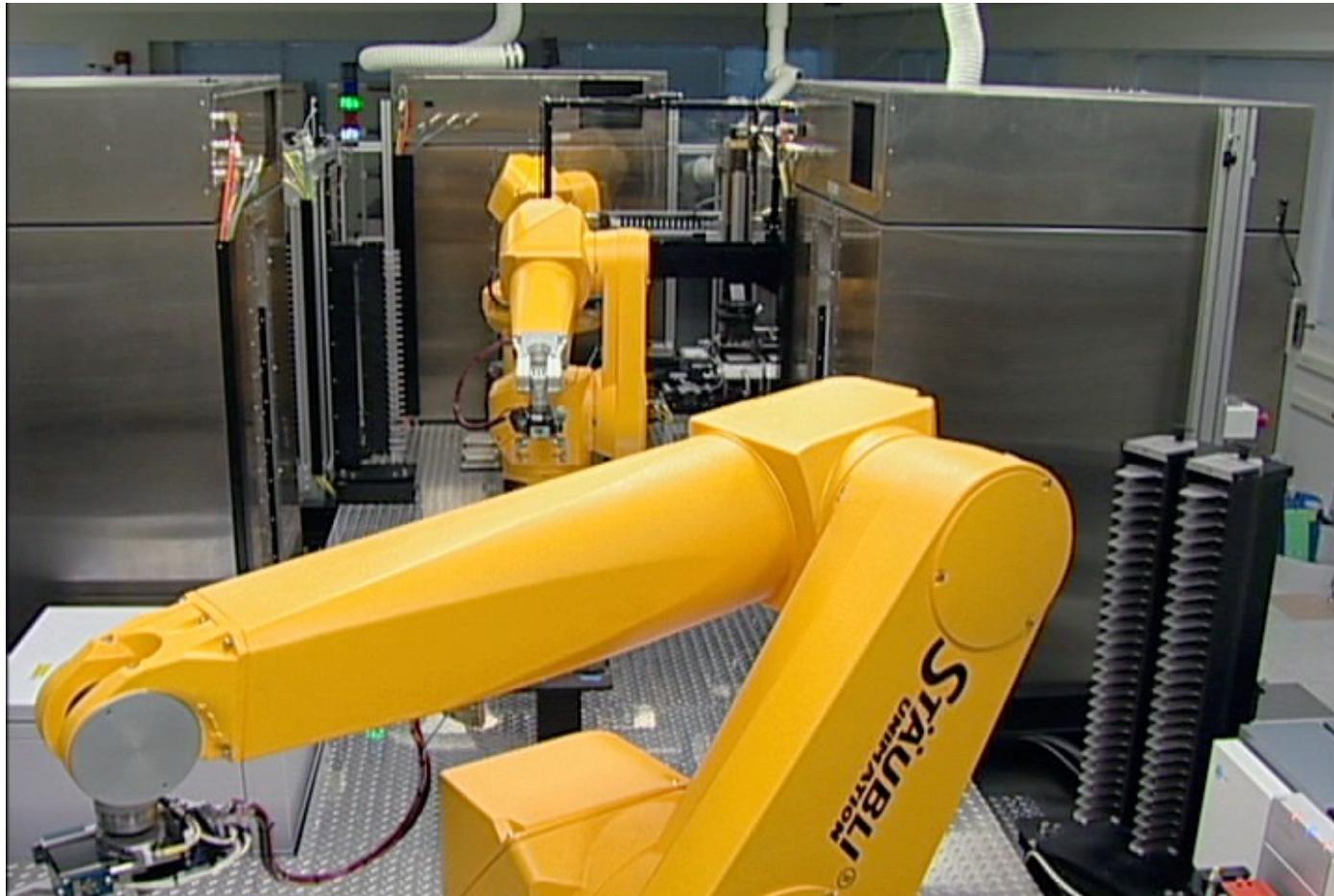


Robotic Screening System

Parameter	Value
Assay Plate Storage	1,134 plates
Compound Plate Storage	2,079 plates
Compounds	~525,000
Throughput	~480 plates/day
Low Volume Dispensers	3
Compound Transfer Devices	3
Plate Readers	6

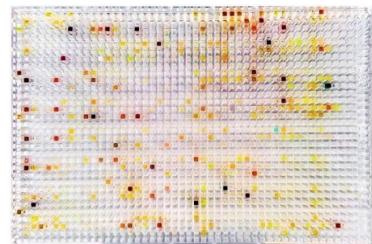
Same instruments as our "offline" assay development lab (AKA the bench)

NCATS High-throughput screening automated platform

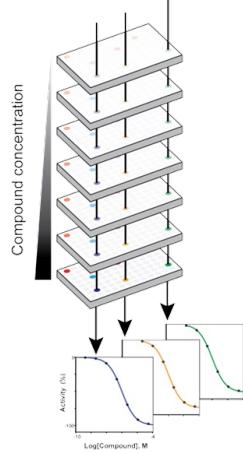


The NCATS screening paradigm

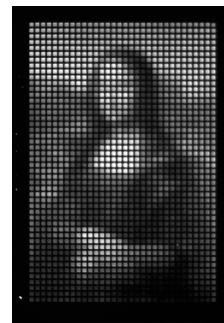
- 1 Diverse, curated libraries (+550,000 compounds)



- 2 Quantitative HTS (dose-response)



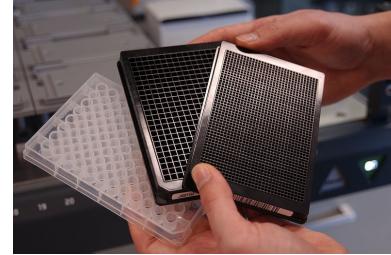
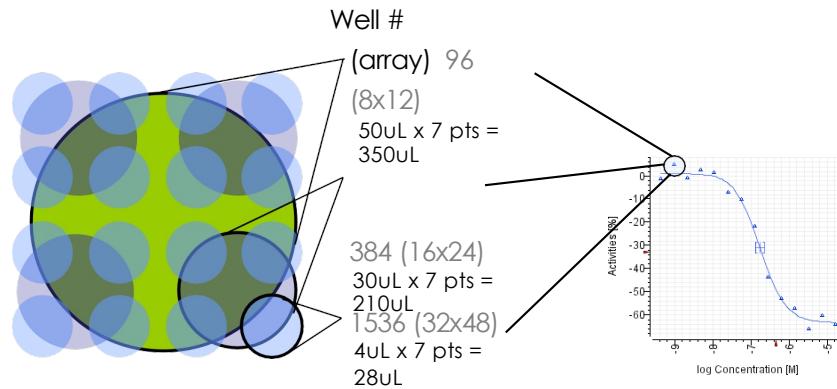
- 3 1536-well format



- 4 Automated screening platform



The power of scale



Higher Throughput Assay Formats

• PROS:

- Allow for more compounds to be tested
- More efficient use of reagents (both assay reagents and compounds)
- Enables dose-response testing in primary screen

	96	384	1536
Plates per 100,000 compounds:	1,042	261	66
Assay volume (µL):	50-200	30-50	2-8
Adherent cell seeding density:	~10,000	~2,000	~500

• CONS:

- May require use of automation for plating, dispensing, treating
- Larger assays generate more data
- Assay "physics" change at lower volumes (e.g. impact of well surface area-to-liquid ratios)

Controls: choose wisely

Assay statistics are **garbage in : garbage out!**

These values are only predictive when calculated using controls that approximate or mimic the desired conditions of actual hits/inactives



Assay performance statistics

Commonly calculated assay parameters

- Standard deviation (SD)
- Signal-to-background (S:B)
- Coefficient of variation (%CV)
- Z prime or Z factor (Z')

What are ideal values for these?

- Lower = better
- Higher = better
- <10% ideal
- > 0.5 is excellent

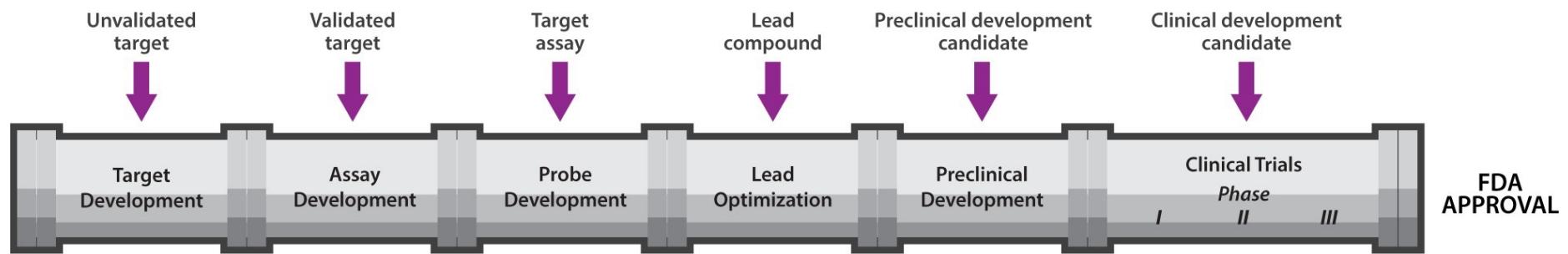
People tend to focus on meeting these benchmarks

BUT what do they actually mean??



Assays & screening are only the beginning...

Project entry point:



The Assay Guidance Manual

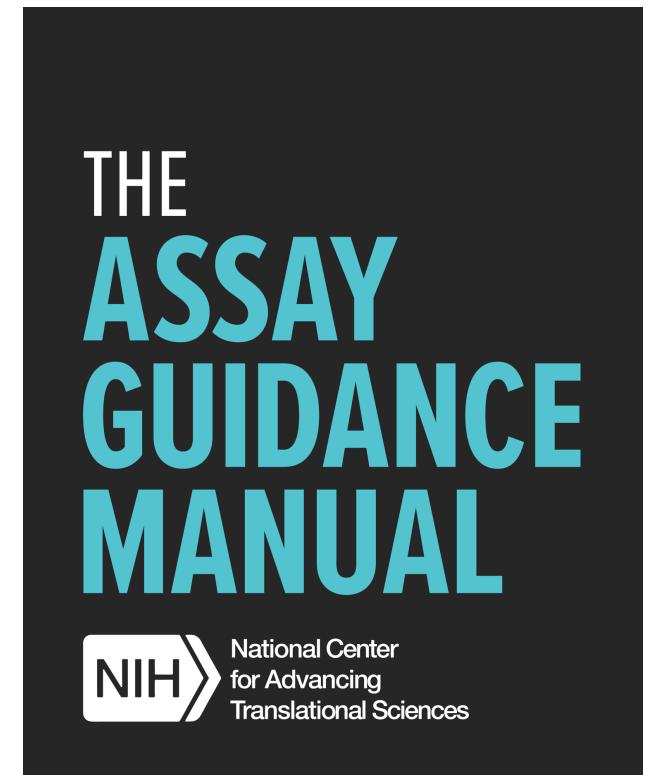
46 Chapters and 1,338 printed pages

The AGM has been a free and publicly available resource since 2005, accessible as an eBook on the NLM, NCBI Bookshelf

In its current form as a dynamic, readily updatable eBook with continued renewal and expansion of content, the AGM is widely accessed (>30,000 views/month in 2017) by scientists from pharma, biotech, government, and academic research laboratories

32 editors with extensive preclinical assay development and drug discovery

Table of Contents	
Preface	
Considerations for Early Phase Drug Discovery	1 Chapter
<i>In Vitro</i> Biochemical Assays	10 Chapters
<i>In Vitro</i> Cell Based Assays	19 Chapters
<i>In Vivo</i> Assay Guidelines	2 Chapters
Assay Artifacts and Interferences	4 Chapters
Assay Validation, Operations and Quality Control	5 Chapters
Assay Technologies	2 Chapters
Instrumentation	2 Chapters
Pharmacokinetics and Drug Metabolism	1 Chapter
Glossary of Quantitative Biology Terms	1 Chapter



<https://ncats.nih.gov/expertise/preclinical/agm/training>

ASSAY GUIDANCE WORKSHOP FOR
HIGH-THROUGHPUT SCREENING AND LEAD DISCOVERY

OCTOBER 18-19, 2022 • FREE TO REGISTER
BUILDING 35A • NIH MAIN CAMPUS • BETHESDA, MD

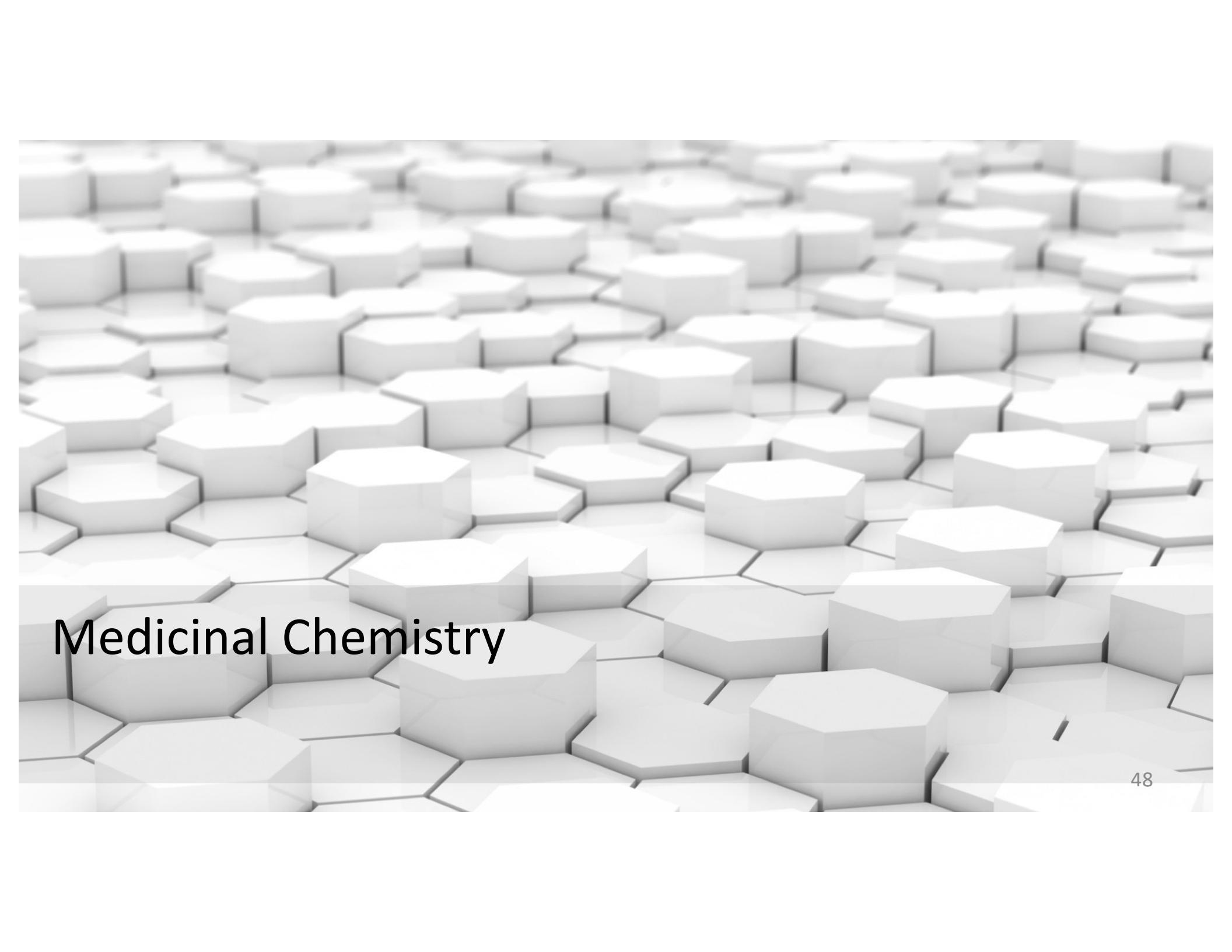
 16 TALKS INCLUDING CASE STUDIES BY EXPERTS FROM GOVERNMENT, INDUSTRY AND ACADEMIA

Topics include: reproducibility, assay development, HTS data analysis, biophysical techniques, medicinal chemistry, DNA-encoded libraries and 3D tissue models for drug discovery

Sponsored by
 National Center
for Advancing
Translational Sciences
THE ASSAY GUIDANCE MANUAL

REGISTER AT
<https://ncats.corsizio.com/c/626855c6a72266e768c48416>

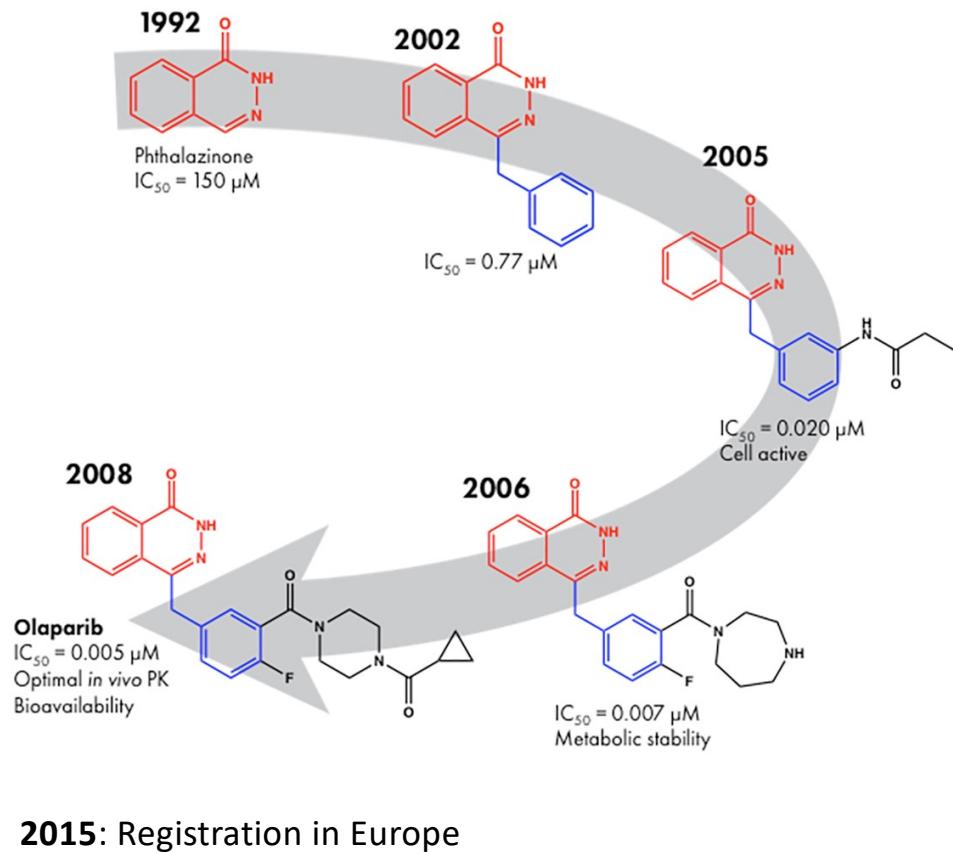




Medicinal Chemistry

Example of a Structure-Activity Relationship (SAR)

Bioactivity modulation

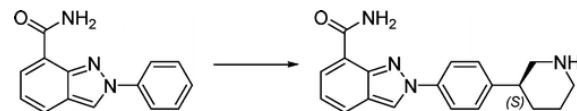


Olaparib

- PARP inhibitor

- improves DNA-damage-induced cell death

**Journal of
Medicinal Chemistry**



PARP-1 $IC_{50} = 3.8 \text{ nM}$
BRCA1- CC₅₀ = 33 nM
BRCA1wt CC₅₀ = 860 nM

J. Med. Chem., 2009, 52 (22), pp 7170–7185

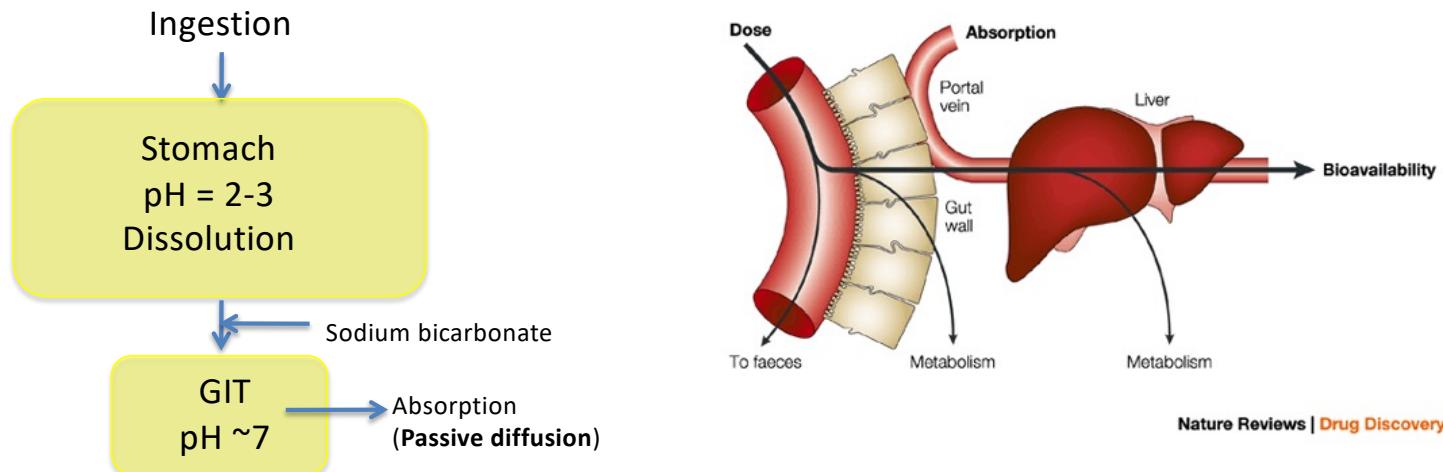
Medicinal chemist



Bioavailability

“Fraction of drug found in circulation” – a molecule must be ‘bioavailable’.*
(Section 11.5 of Thomas)

*Assumes ORAL administration of drug.



Nature Reviews | Drug Discovery

The drug must be able to enter the gut, cross into the bloodstream, avoid first-pass metabolism/excretion in the liver, and circulate in the bloodstream.

Exception: **Intravenous** (i.v.) administration.

Undesirable due to patient comfort factors

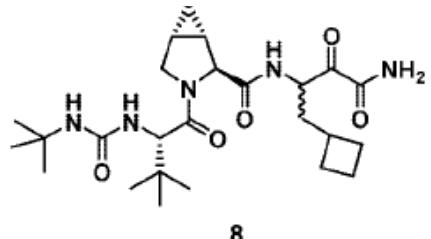
What about topical administration? Other?

Challenges in Modern Drug Discovery: A Case Study of Boceprevir, an HCV Protease Inhibitor for the Treatment of Hepatitis C Virus Infection

F. GEORGE NJOROGE,* KEVIN X. CHEN, NENG-YANG SHIH,
AND JOHN J. PIWINSKI

Schering-Plough Research Institute, 2015 Galloping Hill Road,
Kenilworth, New Jersey 07033

RECEIVED ON MAY 4, 2007



Boceprevir
(SCH 503034)
 $K_i^* = 14 \text{ nM}$
 $EC_{90} = 0.35 \mu\text{M}$
 $\text{HNE/HCV} = 2200$

- Targets NS3 (non-structural 3) in HCV
- NS3 is a serine protease
- Developed by Schering-Plough
Taken on by Merck (SP acquisition)
- FDA registered in 2011
- Withdrawn 2014 (competition)

The approach

- Challenge in HCV is rapid resistance due to high mutation rates
- Screening efforts failed
- Embarked on a structure-based design approach
- Means they have crystals/structure of the protein of interest
- Challenge: models of HCV
- Studying a serine protease, so used a ‘serine trap’ strategy
 - (Serine + electrophile = trapping of transition state)
 - Inhibition is slowly reversible

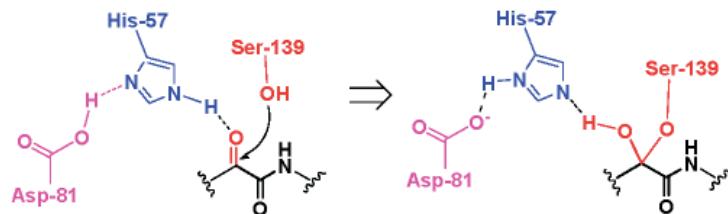


FIGURE 2. Nucleophilic attack of the α -ketoamide by Ser139 led to a covalent tetrahedron intermediate stabilized by residues His57 and Asp81.

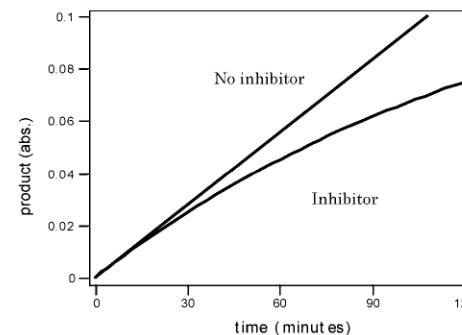
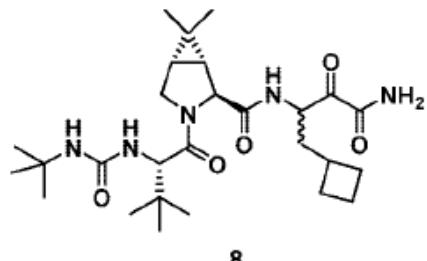


FIGURE 3. Progress curve of peptide substrate hydrolysis by the HCV protease domain showing the time-dependent inhibition.

‘Our research... was greatly aided by X-ray structures of inhibitors bound to NSC3 and continuous drug metabolism/PK evaluation’

How was it discovered?



$K_i^* = 14 \text{ nM}$
 $EC_{90} = 0.35 \mu\text{M}$
HNE/HCV = 2200

Owing to the fact that the NS3–NS4A protease is playing a critical role in HCV viral replication, it has been viewed as an ideal target for the creation of new HCV therapy.^{8,13} However, developing HCV protease inhibitors as drugs was no trivial task. At the onset of our work, there were no viable lead structures from which to develop potential drug candidates. Our screening effort of four million compounds did not generate any meaningful leads to initiate a drug discovery effort.

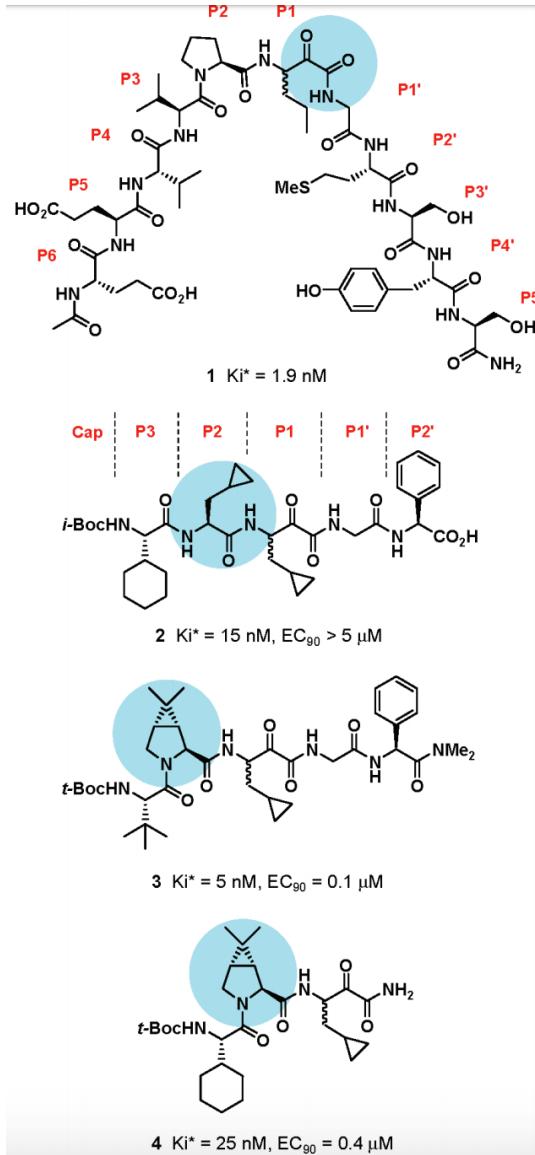


TABLE 1. Mean ($n = 3$) Pharmacokinetic Parameters of **8** Following Oral Dosing

species	mouse	rat	dog	monkey
dose (mg/kg)	10	10	3	3
AUC (po, $\mu\text{M} \cdot \text{h}$)	0.93	1.5	3.1	0.12
bioavailability (%)	34	26	30	4
MAT (h)	1.2	1.4	0.5	1.4
C_{\max} (μM)	2.3	0.66	2.3	0.09

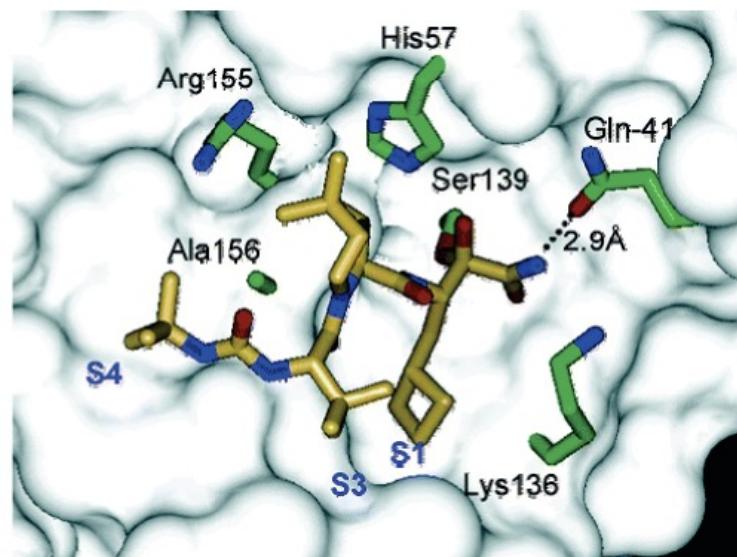
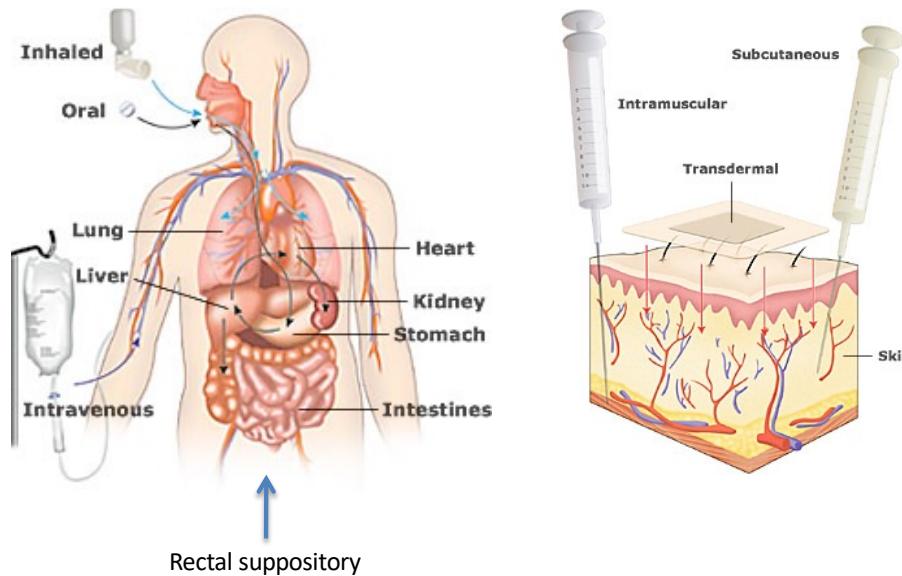


FIGURE 10. X-ray structure of inhibitor **8** bound to the HCV protease.

Administration (getting it in)

Dosage form: liquid, semisolid (cream), solid

Contains: Active component (drug), other (excipients)



Enteral: absorption through gastrointestinal tract.

PARENTERAL: those which avoid the GIT

Administration

Route of administration is affected by many factors – patient comfort, age of patient, their ability to self-administer, health-care setting, cost.

Some (but not all!!!!) considerations:

Oral – patient comfort, ease of administration, some side-effects (NSAIDs cause stomach irritation/ulceration)

Suppository – local action, circumvents acidic environment of stomach, unconscious or vomiting patient

Subcutaneous – local introduction of drug (e.g. local anesthetic)

Intramuscular – slow release of drug over time (monthly basis)

Transdermal – slow release across skin for systemic (nicotine) or local purposes (pain). Systemic transdermal patches control dose and release (if used as advised).

Intravenous – Administration of large doses of drug, circumvents bioavailability issues.

Inhalation – local action (asthma), or fast systemic distribution away from health-care setting (also drugs of abuse).

Administration

Effective, reliable administration critical for drug efficacy.

Dosage regimen – need to understand pharmacokinetic properties of drug
rates of absorption, metabolism and excretion

A drug may be ineffective if the wrong dose is given

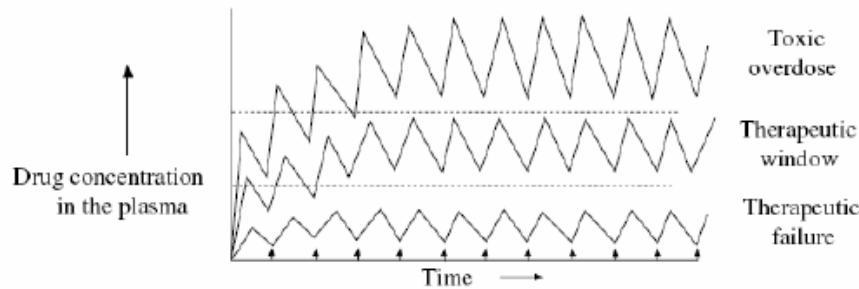


Figure 1.11 A simulation of a therapeutic window for a drug, given in fixed doses at fixed time intervals (\uparrow)



**Philippus Aureolus Theophrastus Bombastus von Hohenheim
(1493-1541)**

"German: 'Alle Ding sind Gift und nichts ohn' Gift; allein die Dosis macht,
das ein Ding kein Gift ist.
English: All things are poison and nothing (is) without poison; only the dose
makes that a thing is no poison."

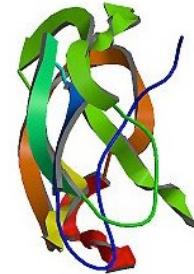
57





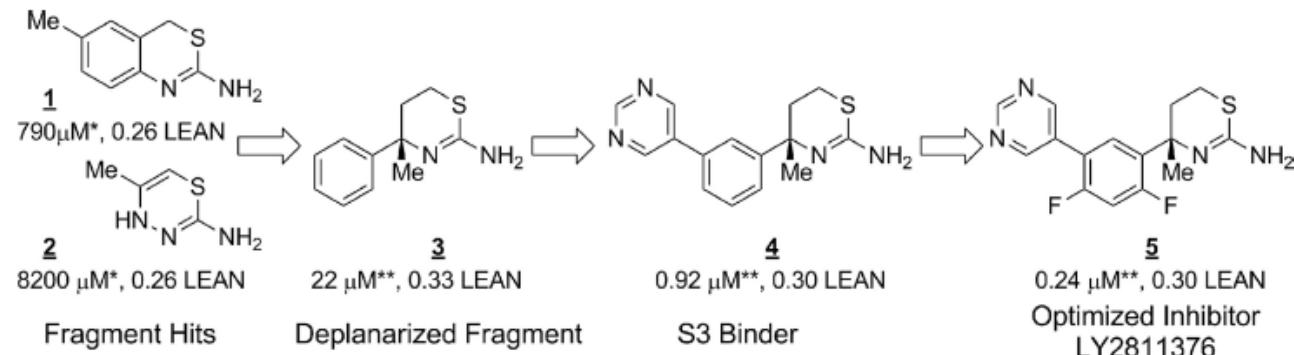
In vivo Pharmacology, Safety
& IND enabling studies

“Robust Central Reduction of Amyloid- β in Humans with an Orally Available, Non-Peptidic β -Secretase Inhibitor”



J. Neurosci., November 16, 2011 • 31(46):16507–16516

According to the amyloid cascade hypothesis, cerebral deposition of amyloid-peptide ($A\beta$) is critical for Alzheimer’s disease (AD) pathogenesis. $A\beta$ generation is initiated when β -secretase (BACE1) cleaves the amyloid precursor protein.

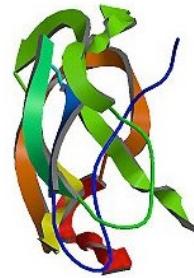


The first orally available non-peptidic BACE1 inhibitor

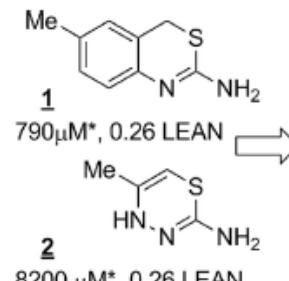
J. Neurosci., November 16, 2011 • 31(46):16507–16516

“Robust Central Reduction of Amyloid- β in Humans with an Orally Available, Non-Peptidic β -Secretase Inhibitor”

J. Neurosci., November 16, 2011 • 31(46):16507–16516

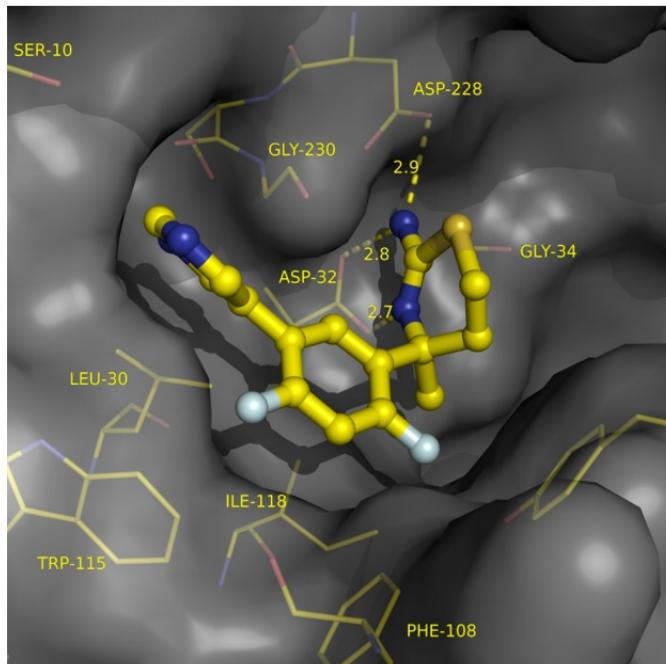


According to the α
peptide (A) is criti
initiated when β -s

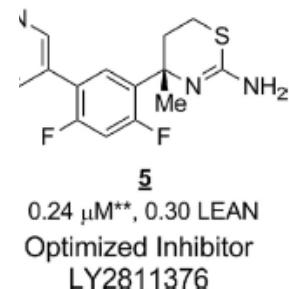


Fragment Hits

The 1



of amyloid- β generation is
r protein.



or

, 2011 • 31(46):16507–16516

Figure 2. Co-crystal structure of LY2811376 in BACE1 active site (flap not shown for clarity). Structure factors and protein coordinates to be deposited into Protein Data Bank.

Preclinical validation: in vitro

Table 2. Potency of LY2811376 in BACE1 and related aspartyl protease assays

Assay	hBACE1 MBP–C125 _{Swe}	hBACE1 mcaFRET	hBACE2 mcaFRET	Cathepsin D FRET	Pepsin FRET	Renin FRET
IC ₅₀ ± SD (nM)	249 ± 309 (4)	239 ± 73 (8)	2880 ± 19 (2)	15700 ± 1830 (2)	32567 ± 13947 (2)	39027 ± 1720 (2)

Data are given as mean ± SD of two to eight independent assays conducted as described in Materials and Methods. *n* values are in parentheses.

Table 3. Potency of LY2811376 cellular APP processing assays

Assay	HEK293 _{Swe} Aβ _{1–40}	HEK293 _{Swe} Aβ _{1–42}	HEK293 _{Swe} Cytotoxicity	PDAPP 1° neuronal Aβ _{1–40}	PDAPP 1° neuronal Aβ _{1–42}	PDAPP 1° neuronal cytotoxicity
IC ₅₀ ± SD (nM)	303 ± 112 (5)	299 ± 58 (4)	>100,000(5)	115 ± 42 (4)	106 ± 46 (5)	>50,000 (4)

Data are given as mean ± SD of four to five independent assays conducted as described in Materials and Methods. *n* values are in parentheses.

- Biochemical & cell based assays
- Selectivity in aspartyl proteases
- Selectivity in cells with mutation and primary neurons
- Reduction in 1-40 and 1-42 Ab peptides

Swedish double mutation = N670L671

PDAPP Mouse = V717F

Preclinical validation: in vivo (mice, dogs)

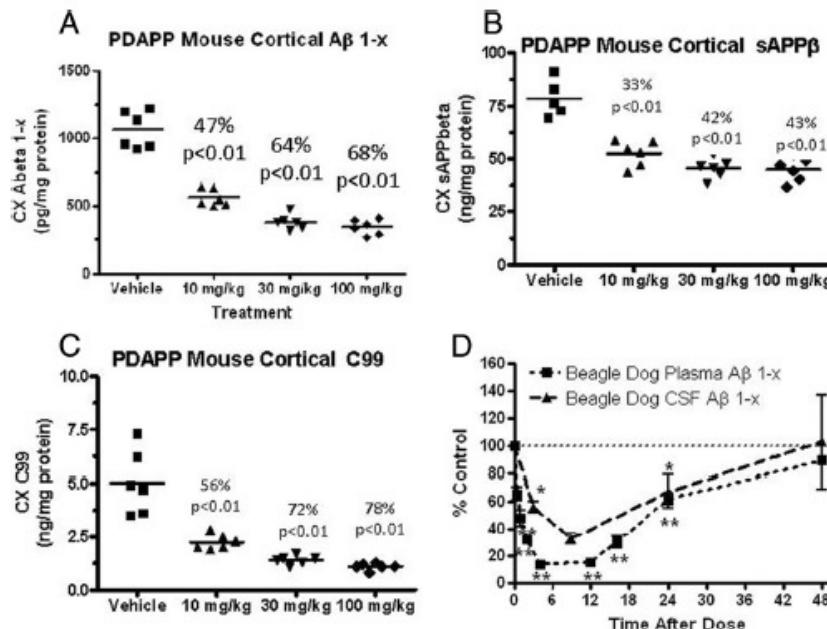


Figure 3. Pharmacologic effects in vivo of oral administration of LY2811376. A–C, PDAPP mice ($n = 6$ per group) were treated with increasing doses of LY2811376 or vehicle, and Ab (A), sAPP (B), or C99 (C) levels were determined from cortical extracts obtained 3 h after dosing. LY2811376 produced dose-dependent decreases in all APP-related PD markers of BACE1 inhibition in PDAPP mice, $p < 0.01$ versus vehicle control, ANOVA/Dunnett's post hoc analysis. D, Beagle dogs ($n = 4$) were treated sequentially with vehicle or 5 mg/kg LY2811376, and plasma and CSF samples were collected at various times after dosing. The average predose baseline plasma A1-x was 340 \pm 14.2 pg/ml (mean \pm SEM, $n = 4$). The average vehicle baseline CSF A1-x was 12409 \pm 1014 pg/ml (mean \pm SEM, $n = 4$). LY2811376 produced robust and time-dependent decreases in A1-x in both plasma and CSF of dog compared with baseline control values. * $p < 0.05$, ** $p < 0.01$ versus baseline controls, ANOVA/Dunnett's post hoc analysis.

J. Neurosci., November 16, 2011 • 31(46):16507–16516

Pharmacologist



Preclinical validation: in vivo (Phase 1 safety/PK)

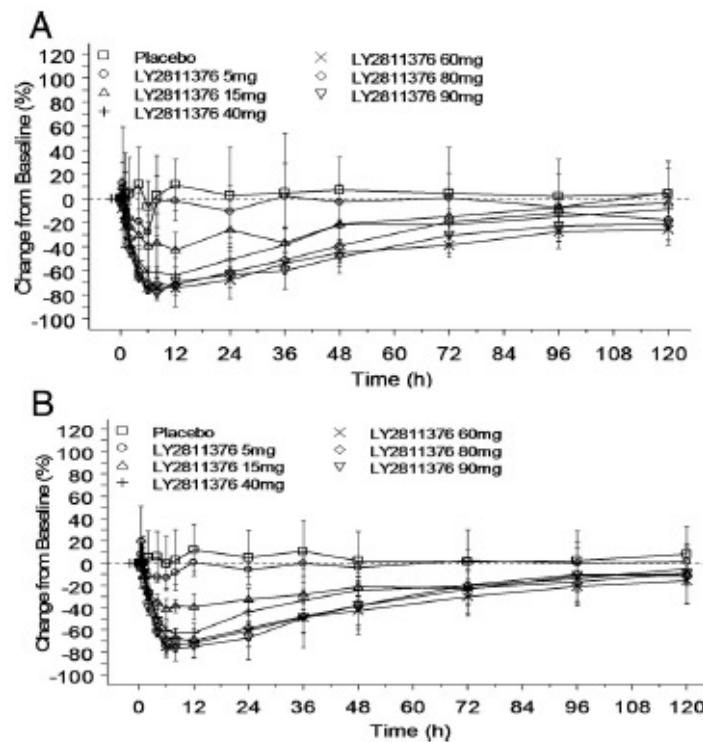
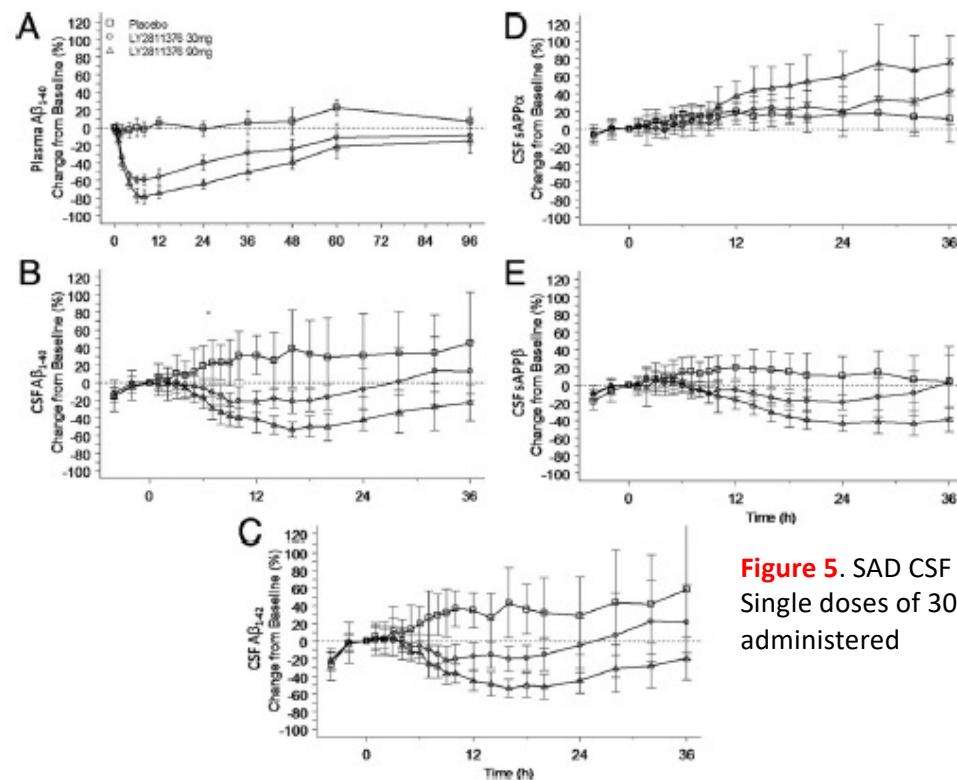


Figure 4. SAD study in healthy volunteers. Mean plasma A1-40 (A) and A1-x (B) change from baseline after single doses of LY2811376. After single doses of LY2811376 between 5 and 90 mg, plasma concentrations of both A1-40 and A1-x decreased, reached a nadir, and then slowly returned to their predose baseline values. The time at which the nadir occurred ranged from a mean of 6–12 h and appeared to be independent of dose. The magnitude of the decrease in plasma A1-40 and A1-x, as measured by either the nadir or the average reduction over the first 24 h tended to increase with increasing doses of LY2811376. Plasma concentrations of A1-40 and A1-x after the highest dose of 90 mg did not fully return to their predose baseline values within the 120 h sampling period of the study. Plasma A1-40 and A1-x PD response provided guidance for dose selection to the second part of the trial looking at PD effect in CSF.

Preclinical validation: in vivo (Phase 1 biomarkers)



A – Plasma conc. Ab 1-40

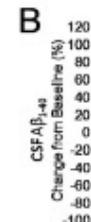
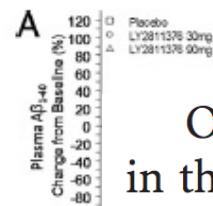
B-C: CSF conc. of Ab 1-40 and Ab 1-42

D-E: Swe APP-b and Swe APP-a

Figure 5. SAD CSF sampling study in healthy volunteers. Single doses of 30 or 90 mg of BACE inhibitor LY2811376 administered

J. Neurosci., November 16, 2011 • 31(46):16507–16516

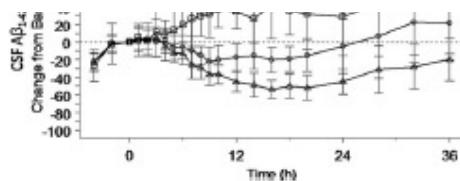
Preclinical validation: in vivo (Phase 1 biomarkers)



Overall, LY2811376 was well tolerated in the CSF study. There were no serious adverse events, and all 27 treatment-emergent adverse events were mild or moderate in severity. The most frequent treatment-emergent adverse events were procedural headache ($n = 15$) and catheter site pain ($n = 7$). There were no clinically significant alterations in vital signs, laboratory analytes, or electrocardiograms associated with LY2811376 treatment during the dosing period.

** $p < 0.01$ versus baseline

Ab 1-42



LY2811376
administered

J. Neurosci., November 16, 2011 • 31(46):16507–16516

Preclinical validation: in vivo (toxicology)

In parallel to the phase 1 studies in healthy volunteers, a 3 month rat toxicology study was performed to prepare for longer exposures in phase 2 clinical trials.

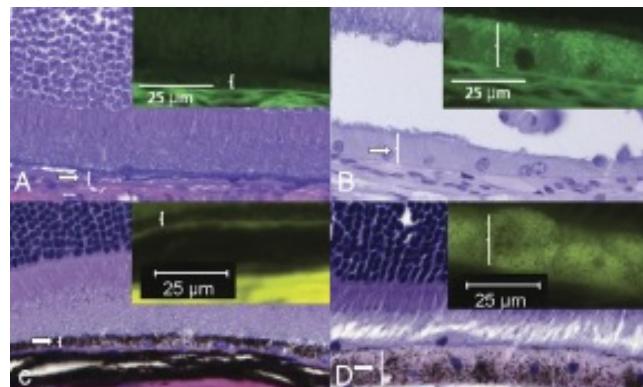


Figure 6. LY2811376-related changes in the retinal epithelium of Sprague Dawley [Crl:CD(SD)] rats (top) and BACE1 knock-out (BACE1tm1Pcw) mice (bottom). Retinas from the vehicle treated rats (A) and mice (C) were normal. Retinal epithelial cells from LY2811376-treated rats (B) and mice (D) were enlarged and distended with autofluorescent granular material (insets). The retinal epithelial layer is labeled with arrow and/or bracket. Note the brown pigment granules within the retinal epithelial layer and underlying choroid, which are a normal feature of the eye from this strain of pigmented mouse (C,D) but absent in the eye from the albino Sprague-Dawley rat (A,B). Additionally, the bright yellow-green zone in the bottom right of the inset for C is attributable to autofluorescence of the scleral collagen, a normal structure that is not included in the insets for A, B, or D. H&E stain. Insets are H&E-stained sections viewed with epifluorescence.

J. Neurosci., November 16, 2011 • 31(46):16507–16516

Preclinical validation: in vivo (toxicology)

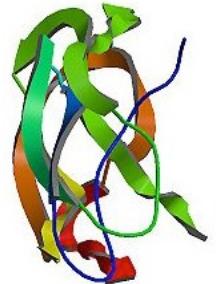
In parallel to the phase 1 studies in healthy volunteers, a 3 month rat toxicology study was performed to prepare for longer exposures in phase 2 clinical trials.

Importantly, as soon as these preclinical pathology data became available, clinical dosing of LY2811376 was discontinued, the Food and Drug Administration was notified, and the studies were terminated in agreement with the Food and Drug Administration. As a safety follow-up, all study participants were contacted for follow-up eye examinations. The examinations were conducted ~6–10 months after completion of the trial. They revealed no clinically significant observations in the 45 of the 61 enrolled subjects, who agreed to participate.

distended with autofluorescent granular material (insets). The retinal epithelial layer is labeled with arrow and/or bracket. Note the brown pigment granules within the retinal epithelial layer and underlying choroid, which are a normal feature of the eye from this strain of pigmented mouse (C,D) but absent in the eye from the albino Sprague-Dawley rat (A,B). Additionally, the bright yellow-green zone in the bottom right of the inset for C is attributable to autofluorescence of the scleral collagen, a normal structure that is not included in the insets for A, B, or D. H&E stain. Insets are H&E-stained sections viewed with epifluorescence.

J. Neurosci., November 16, 2011 • 31(46):16507–16516

Study conclusions



Reasonable potency and efficacy *in vitro* and *in vivo*

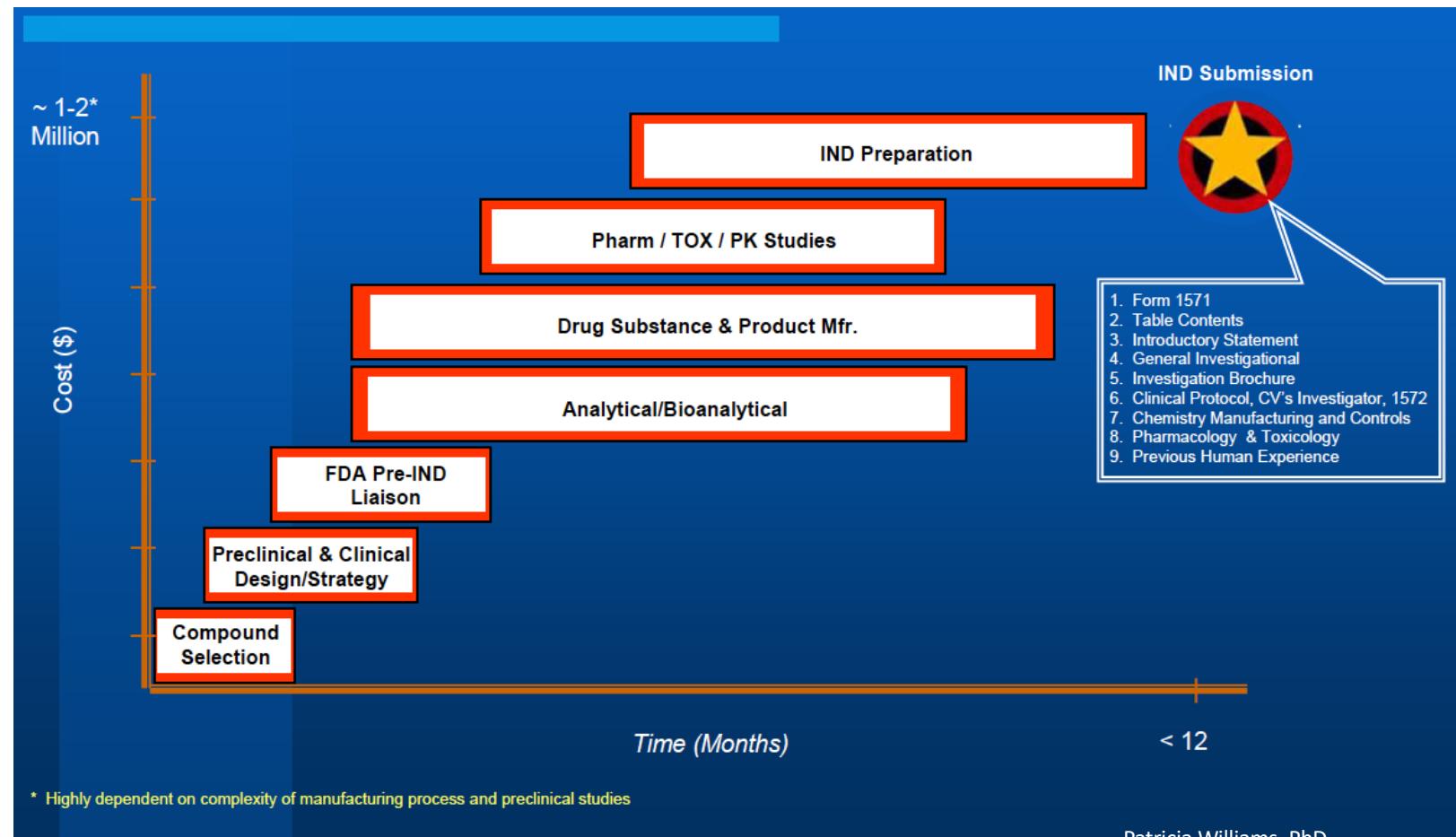
Appear to be safe in SAD studies in healthy volunteers

Retinal toxicity albino Sprague-Dawley rats.

“Because of toxicology findings identified in longer-term preclinical studies, this compound is no longer progressing in clinical development”.

J. Neurosci., November 16, 2011 • 31(46):16507–16516

IND enabling studies



IND enabling studies: pharmacology

- **Rationale for Human Benefit**
- **Extrapolate from Animal Data Projected Doses or Blood Concentrations for Human Efficacy**
- **Identification of Unintended Actions Which May Impact Safety**
- **Estimate Therapeutic Index from Pharm/Tox Data**

IND enabling studies: toxicology

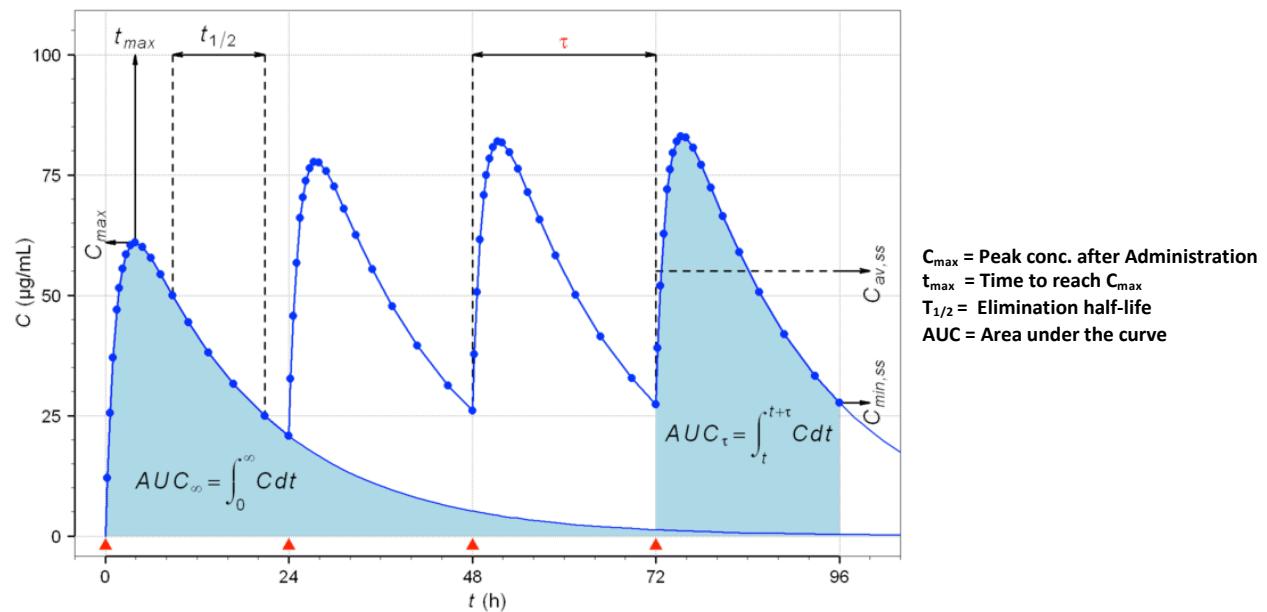
- Identify Target Organ Toxicity
- Identify Non-Toxic and Toxic Dose Levels
- Provide Evidence of Safety for the Duration of Phase 1 Clinical Trial
- Provide Evidence of Safety for the Dosing Regimen

IND review process

- 30 Day Review By FDA
- FDA Will Convene Internal Meeting
- Questions May Be Posed
- Requests May Be Made (Data, Changes)
- IND May Be Put On Clinical Hold

Absorption, Distribution, Metabolism and Elimination (ADME)

Pharmacokinetics: What the body does to the drug!



ADME/PK Scientist



Pharmacodynamics

What the drug does to the body

Biochemical and physiological effects of drugs on the body

Mechanisms of drug action and the relationship between drug concentration and effect.

Cellular membrane disruption

Chemical reaction with downstream effects

Interaction with enzyme proteins

Interaction with structural proteins

Interaction with carrier proteins

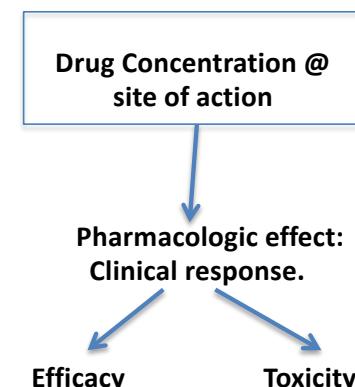
Interaction with ion channels

Ligand binding to receptors:

Hormone receptors

Neuromodulator receptors

Neurotransmitter receptors



Preclinical Pharmacology

- In vitro and in vivo pharmacodynamics results
 - Demonstrate efficacy of a drug candidate
 - Various in vitro assays (enzyme or cell based assays)
 - Efficacy in animal models (POM in target specific model or disease model)
 - e.g. MMP-12 as a target for the treatment of COPD
 - Target model (short term model): Ear swollen model in mice
 - Disease model: Smoke model in mice
 - Minimum efficacious dose or ED_{50} with in vivo model systems
 - Enzymology and kinetics of target engagement
 - Validate how moderating the target affects the disease (e.g., knock out models)
 - PK/PD correlation (efficacious drug concentration in plasma or target site)
 - Establish MABEL (minimum anticipated biological effective level)
 - Therapeutically window assessment
- Identify biomarkers and develop assays

Preclinical Pharmacokinetics (PK)

- Information related to Absorption, Distribution, Metabolism and Excretion (ADME)
 - In vitro ADME useful, especially in human:
 - Species comparison in metabolism, plasma or tissue protein binding, human CYP inhibition/induction, inhibition for major transporters
 - Animal pharmacokinetics
 - PK parameters (C_{\max} , C_{\min} , T_{\max} , AUC, $t_{1/2}$, V_d , Cl, F)
 - Animal efficacy species, toxicology species, intended routes of administration in human
 - Linearity of exposure with dose
 - Radiolabel useful for tissue distribution, drug metabolism, excretion (mass balance study)
- PK/PD relationships - related to dose and route
- Projection of human PK efficacy dose and regimen
- DDI potential assessment
 - CYP inhibition, induction, and transporter inhibition that affect PK
- Bioanalytical method

Preclinical toxicology

- Preclinical Toxicity Studies Provide Data for Determining First Human Dose
 1. Safety margin
 2. NOAEL - no observed adverse effect level - highest dose level without toxic effect
 3. Dose limiting toxicity - MTD, most sensitive endpoint to watch for in human dosing
 4. Genotoxicity - indicators of possible carcinogenicity
- FDA will allow escalating dosing from NOAEL up to MTD
- MTD determined by indicators (e.g., liver enzyme increase, histopathology) and by how much risk tolerated based on disease and patients
- NOAEL determined by the most sensitive of the two species tested
- First human dose - based on NOAEL using scaling factors and safety margin (see FDA Guideline)

Histopathologist



Toxicologist



Preclinical toxicology

- Safety Pharmacology In Vivo
 - Effect on systems (CV, CNS, Lung, GI, kidney, liver, urinary, blood)
- Toxicology studies in animals
 - Two species: one rodent and one non-rodent
 - Cover human metabolites
 - Single and repeat dose studies with toxicokinetics (TK) components
 - Genotoxicity (Ames , Mouse, erythrocyte micronucleus in rat)
 - If available: carcinogenicity, reproductive
 - Off target effects
- Safety margin and relationship to human dose
- Previous results in human - useful

Formulation & Dosing

Oral administration:

- solution, suspension
- tablets, capsules

IV administration

Inhalation dosing

Transdermal dosing

Excipients and additives

Stability of formulations

Frequency of dosing

Packaging and storage

Formulation chemist



So much to worry about!!

- IND enabling studies involve detailed/thorough characterization of a drug candidate
 - Physical/chemical properties of API and drug product
 - In vitro activity and in vivo efficacy in animal models for the intended use
 - Pharmacokinetic (ADME) properties
 - Safety profiles
- To reduce the failure rate in the preclinical development, key issues (risk factors) need to be identified as early as possible
- Knowledge gained from the IND enabling studies will guide the design of clinical study protocols

Intellectual Property and the Patent Process

Translational Science Training Program

Sue Ano, Ph.D.

Director, NINDS Technology Transfer



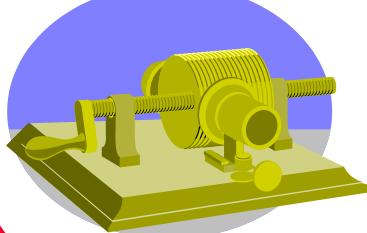
Outline

- ▶ Patents
- ▶ Typical Process
- ▶ Knowledge in Action - Gleevec
- ▶ Takeaways



Four Major Categories of Intellectual Property (IP)

Patents



Copyrights



Trademarks



and Trade
Secrets



Authority for IP Patents?

Article I section 8 of the Constitution

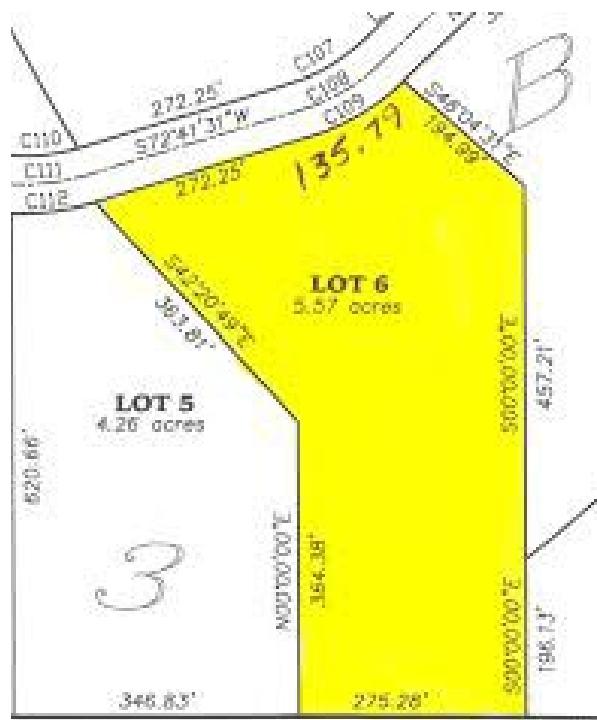
“Congress shall have power... to promote the progress of science & the useful arts by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries.”

PATENTS

- ▶ Protects new new embodiments of useful ideas, plants, and designs for a fixed, limited term (up to ~20 years)
- ▶ Benefits
 - ◆ Societal trade-off: full disclosure for right to exclude others
 - ◆ Reward to creator (over one who merely copies)
 - ◆ Economic engine

Letters Patent

- ▶ In United States, Letters Patent are primarily:
 - ▶ Intellectual Property (IP) Patents
 - ▶ Land Patents



What really is a patent?

The right to exclude others from making, using, selling, or importing what the patent claims - not necessarily the direct right to practice the invention

If Inventor A invents the airplane,
and Inventor B invents the jet engine,

NO ONE, not even the inventors,
can make a jet airplane without the
consent of BOTH inventors



This means they must either grant each other a license, or make something new ("design around")

Patents - Three types in the US:



- ▶ Utility: New things and processes that are useful
 - Term is 20 years from earliest application
- ▶ Plant: new plants propagated by means other than seeds or tubers
 - Bred plants: protected by another, non-patent law
 - Transgenic plants: protected by utility patents
 - Term is 20 years from earliest application
- ▶ Design: Ornamental, original, non-functional features
 - Term is 14 years from issuance of patent

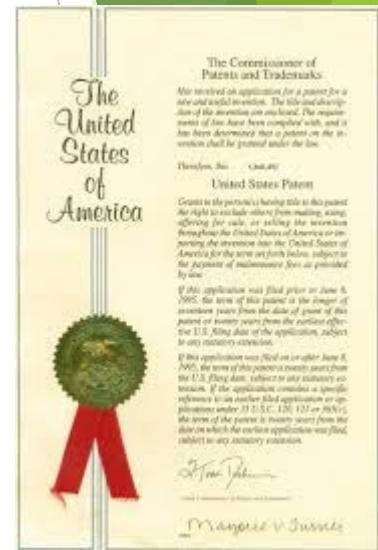


Patent myths

- ▶ Things found in nature can be patented (sort of)
- ▶ Inventor must physically make the invention, and it must work as claimed, to be entitled to a patent
- ▶ To be patentable, the invention must work (significantly) better than everything that came before it
- ▶ Informal conversations with friends & colleagues have no impact on patent rights
- ▶ Inventor need not disclose everything to patent attorney or Patent Office

Criteria for Utility Patents

- ▶ An inventor is ***entitled*** to a patent on appropriate subject matter (35 USC § 100), ***if*** the invention:
 - ◆ has a credible, substantial, and specific “use” (§ 101);
 - ◆ is “novel” (§ 102);
 - ◆ is not “obvious” (§ 103); ***and***
 - ◆ is adequately described in writing (§ 112)
- ▶ Each underlined term means something very different from a typical dictionary definition
- ▶ Patents are country specific

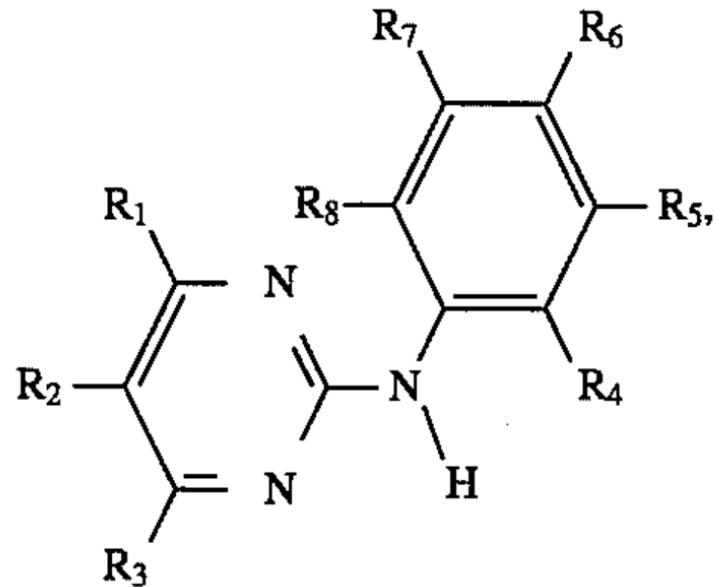


Anatomy of a patent

- ▶ Specification (10s of pages)
 - ◆ Written Description
 - ◆ Drawings
- ▶ Claims (~1-2 pages, at most)
 - ◆ What inventor is entitled to exclude others from doing, if patent issues
 - ◆ Invention is defined by the claims of a patent

US patent 5,521,184

- ▶ One of five patents in FDA orange book for Gleevec®
- ▶ 19 page patent (1 page correction)
- ▶ Specification = 15 pages
- ▶ Claims = 3 pages



Appropriate Subject Matter:

Machines



Articles of Manufacture

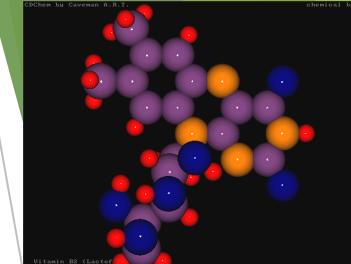


Or any combination of these

But *not*:

math, properties of nature, items found in nature, broad/nonspecific strategies, and anything properly covered by other forms of IP (e.g., text, artistic works, trade names)

Compositions of matter



Processes, including
- methods of *making*



- methods of
processing data



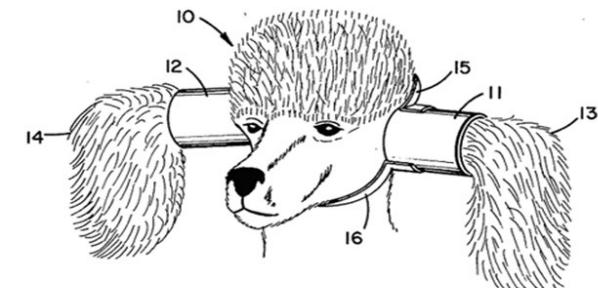
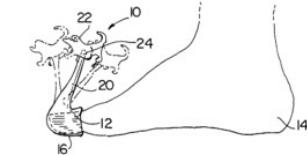
- methods of *using*



Utility

- ▶ “Useful” means *any* practical use that the inventor has reason to believe will work
- ▶ The use must be **credible** (no perpetual-motion machines), **substantial** (not merely “land fill”), and **specific**
 - ◆ “useful” ≠ better than existing alternatives
 - ◆ “useful” ≠ safe
 - ◆ “useful” ≠ scientific merit or societal benefit

United States Patent		[19]	Patent Number:	5,830,035
Budreck		[45]	Date of Patent:	Nov. 3, 1998
[54]	TOE PUPPET	3,911,618	10/1975	Gent
[76]	Inventor: David J. Budreck, 109 E. Woodruff St., Port Washington, Wis. 53074	3,918,180	11/1975	Chamberlin
[21]	Appl. No. 794,294	4,434,830	3/1984	Fitz et al.
[22]	Filed: Feb. 3, 1997	4,473,842	11/1979	Buhler
		4,518,366	5/1985	Fultz et al.
		4,590,320	5/1987	Wolff et al.
		5,209,967	4/1994	Gilbert
FOREIGN PATENT DOCUMENTS				
[63]	Continuation of Ser. No. 553,885, Nov. 6, 1995, abandoned.	7644	5/1922	Germany
[51]	Int. Cl. A63H 03/14	1,301,960	8/1969	Germany
[52]	U.S. Cl. 446,366, 446,261, 446,327	2,120	of 1900	United Kingdom
[58]	Field of Search 446,329, 486, 359, 365, 366, 387			
[56]	References Cited			
	U.S. PATENT DOCUMENTS			
D. 292,811	11/1997 Fogarty et al. D21/153			
D. 341,025	10/1999 Dickens D22/153			
731,752	12/1998 Feltz et al. D22/153			
J,008,619	11/1911 Spear 446,099			
J,269,610	1/1918 Clegg 446,366			
1,545,120	1/1925 Lepre 446,327			
2,155,065	4/1939 Lepre 446,366			
2,387,700	1/1945 Lepre 446,327			
2,621,440	12/1952 Stone 446,327			
2,624,155	1/1953 Boyce 446,367			
3,226,849	1/1960 Rosen 446,329			
3,442,372	7/1969 Feltz et al. 446,328			
3,501,144	3/1970 Schmidt 446,328			
3,611,628	10/1971 Noble et al. 446,328			
[57]	ABSTRACT			
	A prop is adapted to be mounted on a single human digit for providing animated motion of a figurine responsive to movement of the single human digit. The puppet comprises a hollow, elastic cap having an inner wall defining a cavity for receiving a single human digit and a neck portion. The cap includes a resilient neck portion for supporting the figurine at a distance spaced from the single human digit such that movement of the single human digit causes the neck portion and the figurine to oscillate to and fro under the influence of the weight of the figurine.			
	11 Claims, 1 Drawing Sheet			

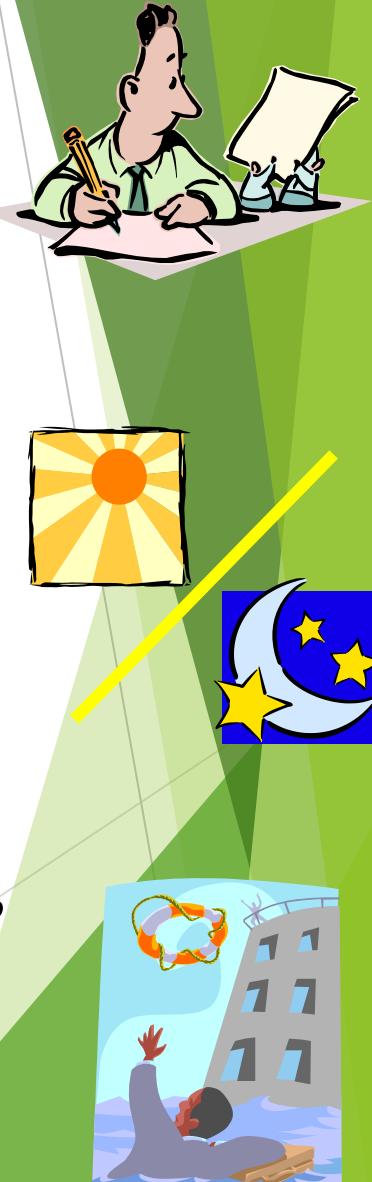


“Novelty”

“Novel” means the inventor invented and filed a patent application before the first effective disclosure of the invention (“prior art”).

“Novelty” is a bright-line test for the date on which the entire, enabled invention first appears in a single disclosure.

In most of the world, novelty is “absolute;” the US has a 1-year “grace period”



“Obviousness”

- ▶ The claimed invention is “obvious” if --
 - ◆ a person having “ordinary skill in the art,”
 - ◆ looking at all pertinent prior references,
 - ◆ would find the claimed improvement insubstantially different (“obvious”),
 - ◆ in light of any two or more prior references (“prior art”) when combined.
- ▶ The exercise: the hypothetical “average” colleague (called a “*person having ordinary skill in the art*”) in the “infinite room”



What is “prior art”?

► Disclosure before patent filing date

- ◆ Meet all the limitations of the claims (novelty)
- ◆ Combination meets all of the limitations of the claims (obviousness)
- ◆ Publicly available anywhere
- ◆ Printed publication/patent anywhere



What sorts of disclosures count towards “prior art”?

COMMON EXAMPLES INCLUDE:

- ✓ Abstracts and Posters
- ✓ Journal articles
(even titles)
- ✓ Talks & slide shows



- ✓ Internet postings
- ✓ Offers to license or sell
- ✓ Commercial beta-testing
- ✓ Free/promotional prototypes

- ✓ Even graduate theses can qualify



Patenting Process

Types of Applications and Prosecution Process

Considerations for Filing Patent Application

Inventorship, Ownership and Authorship

Types of Patent Applications

- ▶ U.S. Provisional (PRV) Patent Application
 - ◆ 12 months
 - ◆ Not examined/never matures into patent
- ▶ PCT Application
 - ◆ 30 months (18 if filed PRV first)
 - ◆ Not formally examined/never matures into patent
 - ◆ Can add new data
- ▶ National Stage Filing
 - ◆ Includes U.S. Patent Application (non-provisional)
 - ◆ Examined on the merits
- ▶ Country validation or registration
 - ◆ EPO Validation
 - ◆ Supplemental Patent Certificates (SPC)

Patent Strategy Timelines

US provisional application
(1 year)

PCT application
(18 months)

National stage filing(s)
(~3-5 years)

PCT application
(30 months)

National stage filing(s)

National stage filing(s)

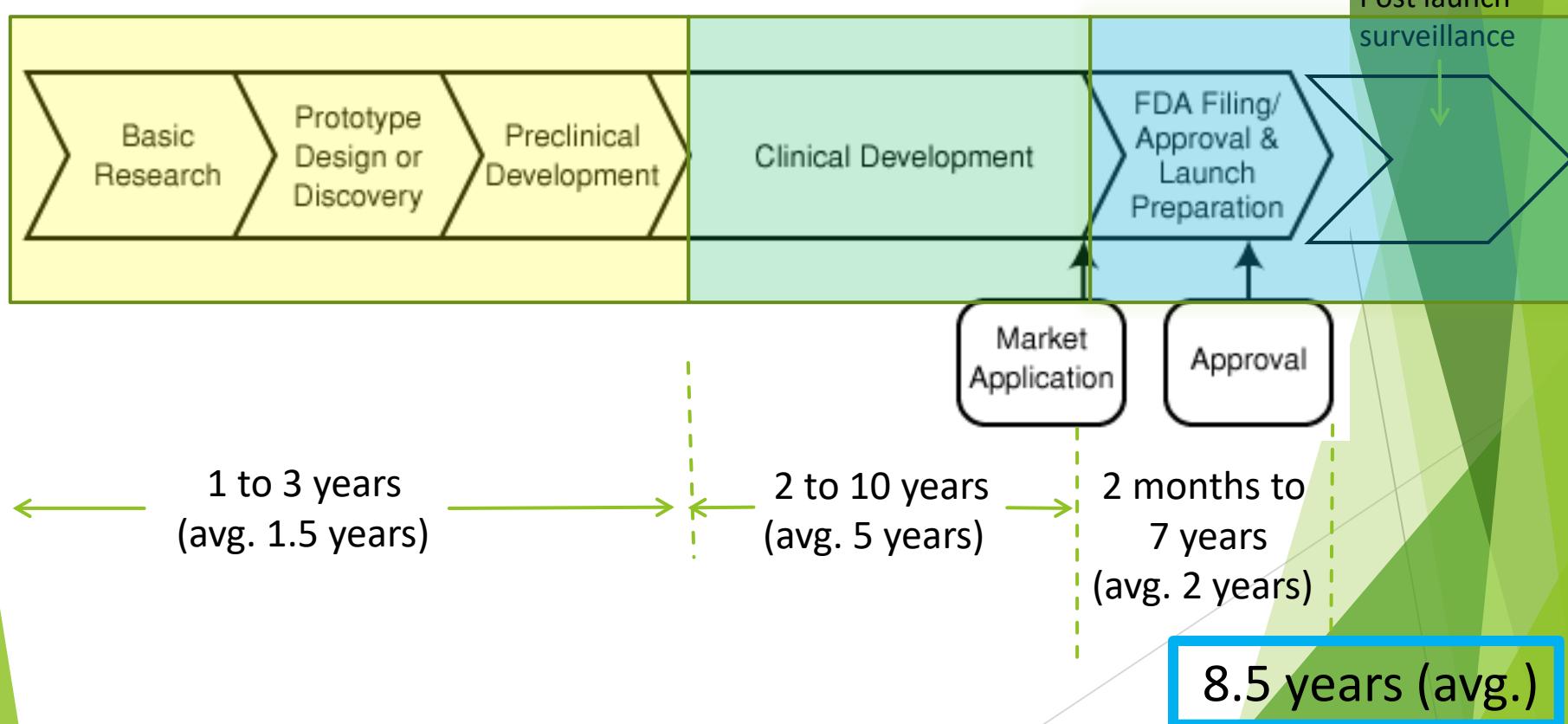
Patent Application Examination (Prosecution)

- ▶ Applicant asserts it is entitled to a patent because:
 - ◆ appropriate subject matter (§ 100)
 - ◆ useful (§ 101);
 - ◆ novel (§ 102);
 - ◆ is not “obvious” (§ 103); *and*
 - ◆ is adequately described in writing (§ 112)
- ▶ Patent Office asserts applicant is NOT entitled to a patent and why
- ▶ Arguments, claim amendments, and discussions lead to either issued patent or application abandonment

Considerations for Patent Filing and Prosecution

- ▶ Is it patentable (novel, non-obvious, and written description)?
- ▶ Has it been disclosed? Will it be disclosed? When?
- ▶ First in class product or “me-too”?
- ▶ Commercial potential
- ▶ Licensing interest
- ▶ Probability of obtaining a patent
 - ◆ Scope and breadth of claims
- ▶ Cost and cost recovery
- ▶ Patent term
- ▶ Product development pathway

Drug/Biologic Development



www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077262.htm

www.campbellfamilyinstitute.ca/our-research/focus/Platforms/Clinical-Trials/Clinical-Phases.aspx

Inventorship (US), Ownership, and Authorship

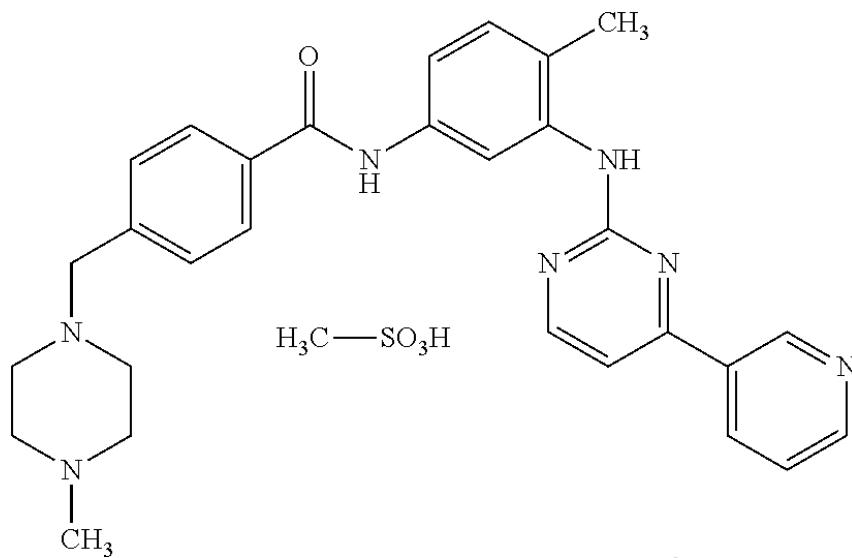
- ▶ An inventor is a person who contributes to the claims of a patentable invention
 - ◆ Can be just one claim
 - ◆ Not just “a pair of hands”
- ▶ Author not necessarily inventor
- ▶ Inventor usually NOT patent owner
- ▶ Order of inventors not important

Knowledge in Action

Gleevec case study

Gleevec/glivec (Imatinib mesylate)

- ▶ Tyrosine kinase inhibitor
- ▶ US FDA approved in 2001
- ▶ Treatment for chronic myelogenous leukemia (CML)
- ▶ Approved for additional indications



GLEEVEC TIMELINE

- ▶ 1960 Discovered CML patients have short chromosomes in blood marrow
- ▶ 1973 Discovered translocation of chromosomes 22 and 9 is source of shortened chromosome
- ▶ 1980s Discovered translocation resulted in fusion of two genes to create new gene, BCR-ABL
- ▶ 1986 BCR-ABL shown to cause body to produce abnormally active form of tyrosine kinase
- ▶ 1993 Nicholas Lydon (Ciba-Geigy; now Novartis) starts collaboration with Brian Druker (Oregon Health Science University), who had been working on TKs as target
 - ▶ Screening compounds developed in Lydon lab
 - ▶ Druker identified compound STI571 (aka CPG 57148) as more effective than others

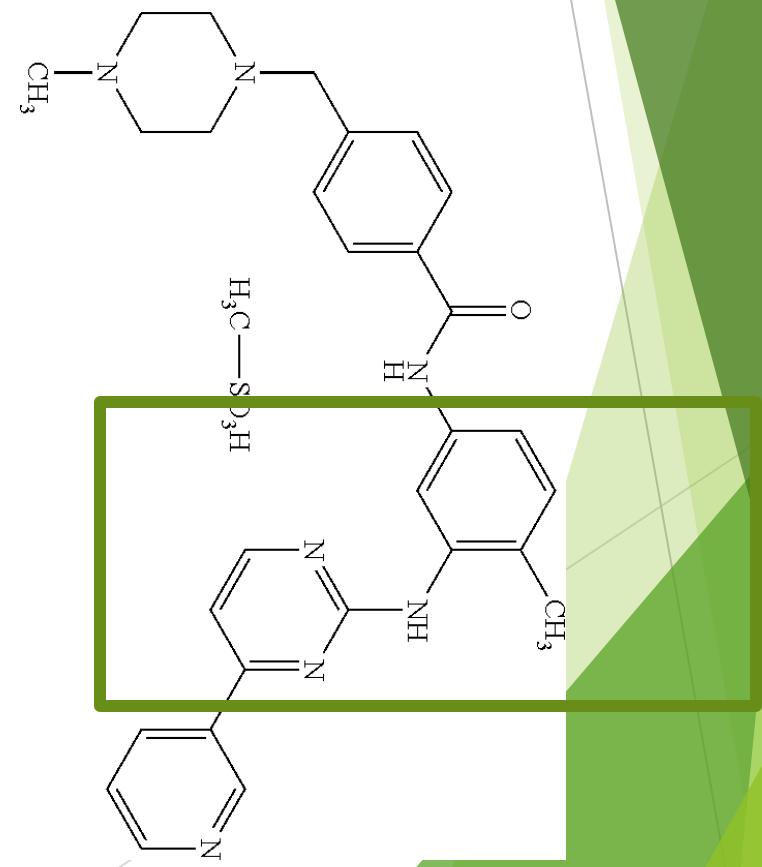
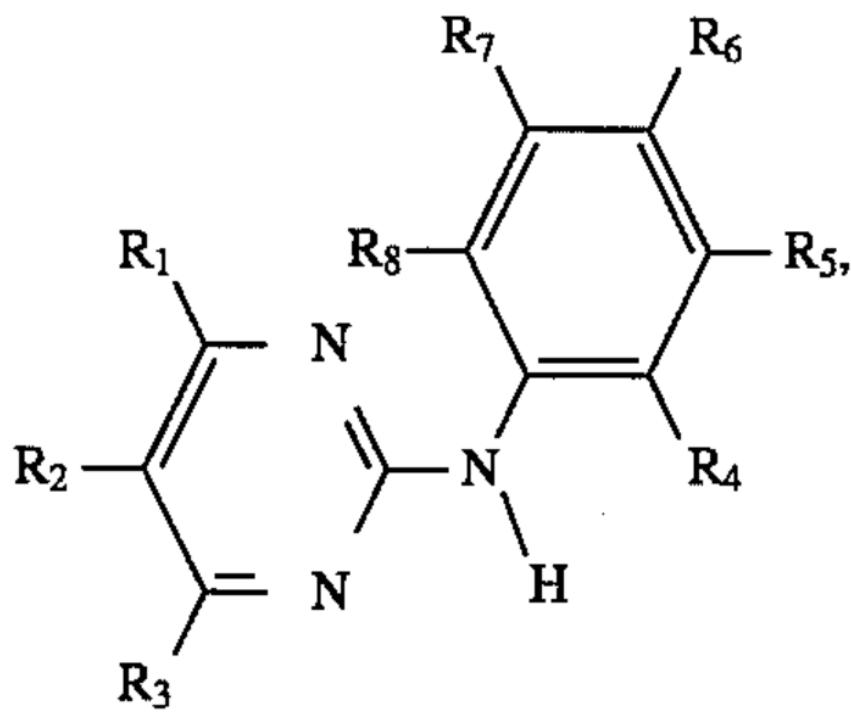
First Patent Filed?

GLEEVEC TIMELINE

- ▶ 1960 Discovered CML patients have short chromosomes in blood marrow
- ▶ 1973 Discovered translocation of chromosomes 22 and 9 is source of shortened chromosome
- ▶ 1980s Discovered translocation resulted in fusion of two genes to create new gene, BCR-ABL
- ▶ 1986 BCR-ABL shown to cause body to produce abnormally active form of tyrosine kinase
- ▶ 1993 Nicholas Lydon (Ciba-Geigy; now Novartis) starts collaboration with Brian Druker (Oregon Health Science University), who had been working on TKs as target
 - ▶ Screening compounds developed in Lydon lab
 - ▶ Druker identified compound STI571 (aka CPG 57148) as more effective than others

Winner, winner - 1990s

US Patent 5,521,184: patent with earliest priority date (1992)



First Publication?

May 1996

Nat Med. 1996 May;2(5):561-6.

Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells.

Druker BJ¹, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, Zimmermann J, Lydon NB.

How many are inventors?

Gleevec Patent Filings (FDA Orange Book)

Priority Filing Date	Patent Number	Issue Date	Inventor(s)
April 3, 1992	5,521,184	May 26, 1996	Jürg Zimmermann (Novartis)
July 18, 1997	6,894,051	May 17, 2005	Three inventors (Zimmermann)
October 27, 2000	6,958,335	October 25, 2005	Ten inventors (including Druker and Buchdunger; 3 co-owners)
July 18, 1997	7,544,799	June 9, 2009	Three inventors
July 18, 1997	RE43932	January 15, 2013	Three inventors

Why multiple patents?

Why multiple patents?

Patent Number	Claims
5,521,184	Original Imatinib (Gleevec) composition, general salts
6,894,051	Monomethanesulfonic acid addition salt (certain conditions), b-modification and method of treatment
6,958,335	Method of treatment of gastrointestinal stromal tumors
7,544,799	Monomethanesulfonic acid addition salt (conditions different than US Patent 6,894,051)
RE43932	Reissue of 7,544,799 to fix priority claim

Why multiple patents?

- ▶ Patent term ~20 years
 - ◆ 1992
 - ◆ 1997
 - ◆ 2000
- ▶ Gleevec/Glivec ~\$4.7B worldwide sales (2015)
- ▶ Expired 2015 (US); 2016 (EU); 2016 (Japan)
- ▶ Generics 2016
 - ▶ 2016 US sales \$3.3B
 - ▶ 2017 US sales \$1.9B (source Novartis annual report)
- ▶ Successor drugs Tasigna \$1.8B (2018; US only; expires 2023)
Scemblix (approved 2021)

Gleevec Patent- Publication Timeframe

A Matter of Balance

- ▶ Company controls disclosure and therefore impact on patent
- ▶ Federal/academic labs mandate to disclose research results
- ▶ Federal/academic organizations file patent applications early in the research process
 - ◆ May not work
 - ◆ May be improved

No Patent in India for Glivec

- ▶ Equivalent of US patent 6,894,051 (mesylate salt in β -crystal form) not issued in India
- ▶ Indian patent office said it claimed a modified version of an existing drug (“not innovative”)
- ▶ Legal proceedings for 7+ years
- ▶ Novartis lost

Gleevec Patent Filings

(FDA Orange Book)

July 29, 2019 - NIH Funding Identified!

Priority Filing Date	Patent Number	Issue Date	Inventor(s)
April 3, 1992	5,521,184	May 26, 1996	Jürg Zimmermann (Novartis)
July 18, 1997	6,894,051	May 17, 2005	Three inventors (Zimmermann)
October 27, 2000	6,958,335	October 25, 2005	Ten inventors (including Druker and Buchdunger; 3 co-owners)
July 18, 1997	7,544,799	June 9, 2009	Three inventors
July 18, 1997	RE43932	January 15, 2013	Three inventors

<http://blog.petrieflom.law.harvard.edu/2019/10/11/novartis-dana-farber-oregon-health-science-university-wait-18-years-to-disclose-nih-funding-in-key-gleevec-patent/>

Why does Government funding matter?

- ▶ Patent 6,958,335 expires June 19, 2022
- ▶ Gleevec pricing tripled between 2001 and 2016
- ▶ Not disclosing Government rights can have consequences, including Government taking over patent
- ▶ Bayh-Dole “March-In Rights”
 - ▶ Some organizations make case for using these rights to address drug pricing issues
 - ▶ Senators Bayh and Dole expressly stated that March-In was not intended to address pricing

But that's a presentation for another day....

Take aways

- ▶ Patents are a negative right (“right to exclude”)
- ▶ Entitled to patent if invention is:
 - ◆ Appropriate subject matter
 - ◆ Useful, novel, not obvious, and adequately described
- ▶ Many factors to consider before patent filing
 - ◆ Balance against disclosure
- ▶ Criteria for authorship and inventorship are different



The NDA/BLA Evaluation and Review

Dr. Pedro L. Del Valle
FDA-CDER-Office of New Drugs
Office of Cardiology, Hematology, Endocrinology & Neurology
DPT-CHEN
Supervisor Interdisciplinary Scientist

Presented at the NIH Office of Intramural Training and Education's Translational Science Training Program (TSTP)
Bootcamp

Bethesda, MD April 3, 2022

Disclaimer

The opinions expressed in this presentation are those of the presenter and do not necessarily reflect official support or endorsement by the Food and Drug Administration

I have no conflict of interest to report

Glossary

- AC – Advisory Committee
- ALL – Acute Lymphoblastic Leukemia
- BLA – Biologic License Application
- CMC – Chemistry, Manufacturing and Controls
- CRS – Cytokine Release Syndrome
- eCTD – Electronic Common Technical Documents
- EFD – Embryo Fetal Developmental Study
- FDASIA – FDA Safety and Innovation Act
- HSCT – Hematopoietic Stem Cell Transplantation
- NDA – New Drug Application
- NHP – Nonhuman primates
- PLLR - Pregnancy and Lactation Labeling Rule
- PDUFA – Prescription Drug User Fee Act
- PMC – Postmarketing commitment
- PMR – Postmarketing requirement
- REMS – Risk Evaluation and Mitigation Strategy
- RTF – Refuse to file

Topics for Discussion

- Example of Translational Research – Bispecifics Abs
- When to submit a Marketing Application
- NDAs/BLAs Application Organization
- PDUFA & Goals of the 21st Century Review Process
- CDER Timelines for review
- NDAs/BLAs Reviewed by CDER-OND
- NDA/BLA Review Team
- Example of a Review by Pharm/Tox
- Basis for NDA/BLA Approval
- FDA-CDER Programs for Serious Conditions
- Summary

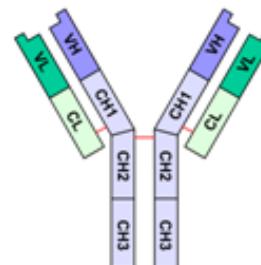
Bispecific Constructs Discovery

- 1959 Gerald M. Edelman & Rodney R. Porter proposed the antibody structure
- 1960-1961 Alfred Nisonoff Used pepsin to generate (Fab)2 with dual specificity
- mAbs development advanced rapidly
- However, complete cure has not been achieved
- Bispecifics endured a long process for production. Three methods to produce bispecific antibodies

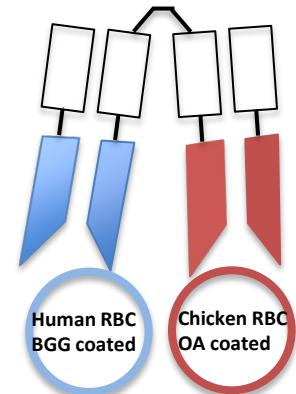
- 1 – Quadroma
- 2 – Chemical conjugation
- 3 – Genetic approaches using recombinant DNA

- **Translational Research is now occurring more rapidly**
- **More than 60 INDs with bispecific antibodies CD3-XX or XX-XX**

Edelman – disulphide bonds
Porter – papain to split 3 parts



Nobel Prize in Physiology or Medicine 1972



OKT3 Muronomab CD3	Rituxan Rituximab CD20	Blincyto
--------------------------	------------------------------	----------

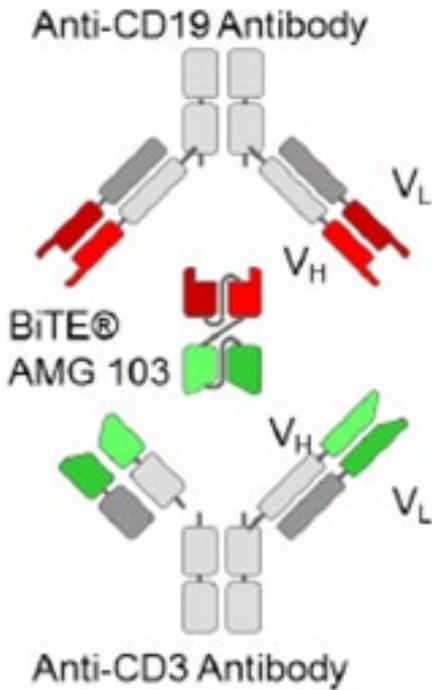
Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 7021–7025, July 1995
Immunology

A small bispecific antibody construct expressed as a functional single-chain molecule with high tumor cell cytotoxicity

MATTHIAS MACK, GERT RIETHMÜLLER, AND PETER KUFER

Institut für Immunologie, Goethestrasse 31, D-80336 Munich, Germany

Communicated by Gunter Blobel, The Rockefeller University, New York, NY, April 14, 1995

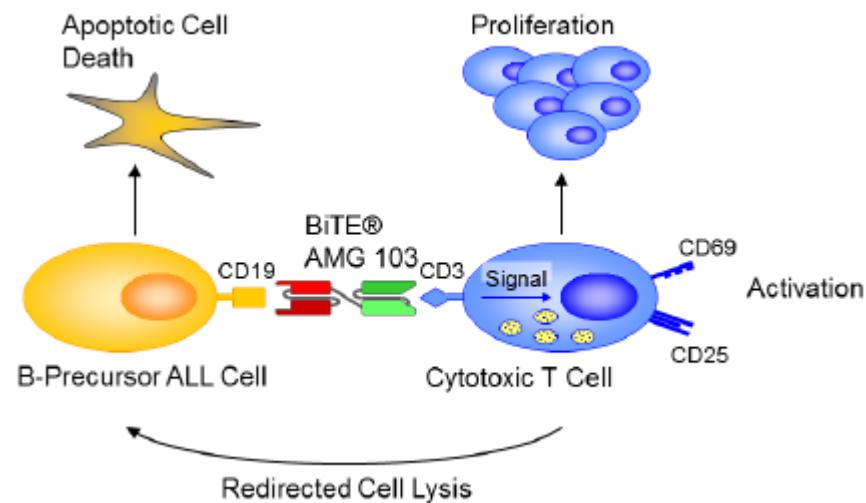


The immune system was involved in the fight against cancer

- Immune Checkpoint Modulators
- Immune Cell Therapy
- Therapeutic Antibodies
- Cancer Treatment Vaccines
- Immune System Modulators

Blincyto (Blinatumomab)

- A single-chain antibody construct which acts as a bi-specific CD-19 directed CD-3 T-cell engager (BiTE®)
- Designed to transiently engage CD19+ target B cells with CD3+ T cells, resulting in activation of the T cells to kill the bound target cell
- Treatment of patients with Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (B-cell ALL), an uncommon form of ALL (2014)
- Treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children (2017)



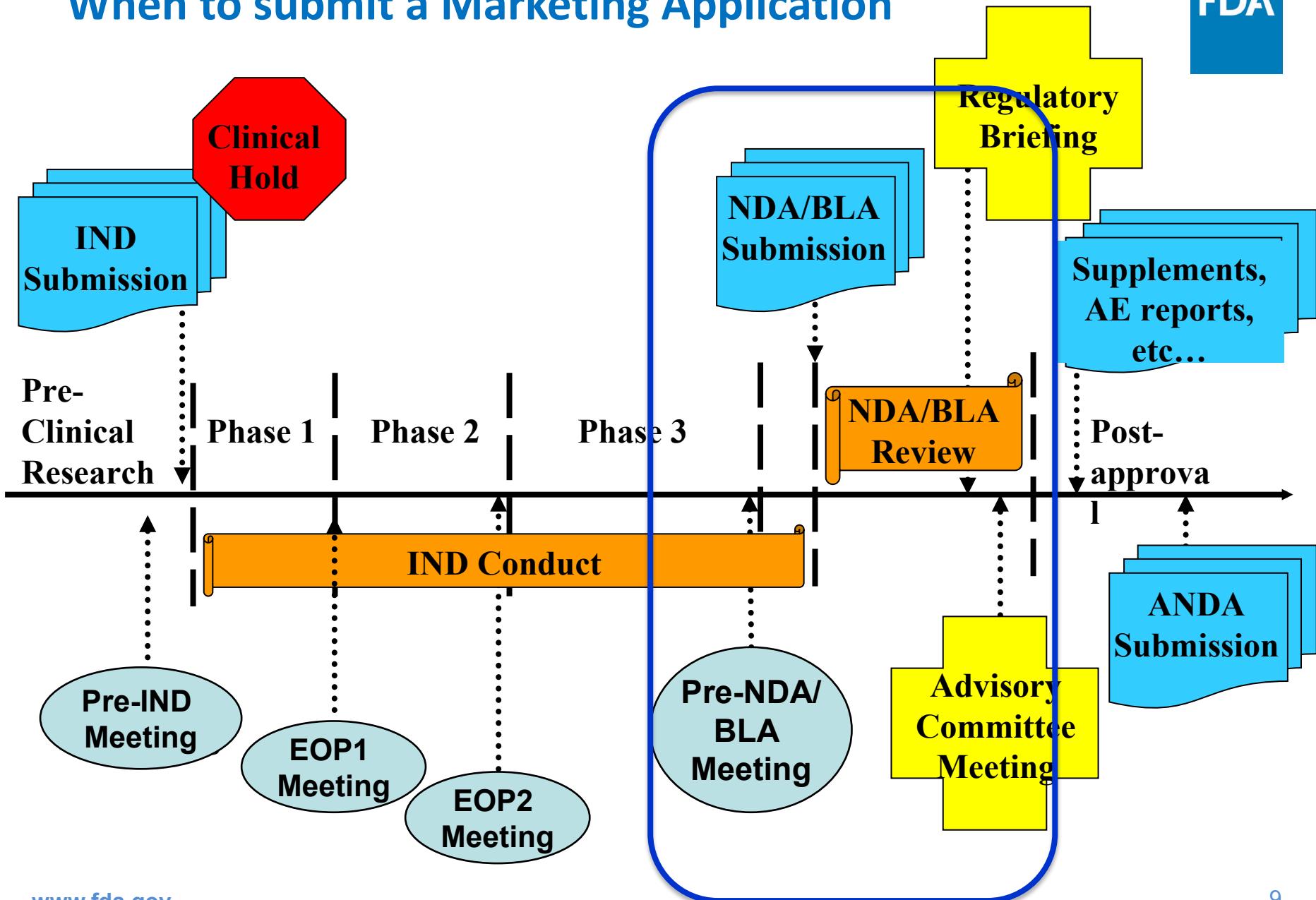
Blincyto (Blinatumomab) Regulatory Highlights

- IND filed on August 18, 2006
- NDA filed on September 19, 2014
- Accelerate approval December 2, 2014 for patients with relapsed-refractory children and adults with B-cell ALL Ph+ negative
- Less than 3 months FDA approval (1995-2014)
- July 12, 2017 Blincyto granted full approval based on results of a Phase 3 trial
- BiTEs have now an FC for extended
- Half-life avoiding continuous dosing
- **GAME CHANGER**
- More than 40 INDs with bispecific antibodies CD3-XX or XX-XX
- BiTEs have now an FC for extended
- Half-life avoiding continuous dosing

Saber, H., Del Valle P.L., Ricks, T., Leighton, J.K. "An FDA oncology analysis of CD3 bispecific constructs and first-in-human dose selection" *Regulatory Toxicology and Pharmacology*, 90:144-154 (2017)

When to submit a Marketing Application

FDA



eCTD Organization

Marketing applications have 5 modules:

- Module 1. Regional - region-specific administrative and prescribing information
- Module 2. Common Technical Document Summaries
- Module 3. Information on product quality
- Module 4. Nonclinical study reports
- Module 5. Clinical study reports

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>

Prescription Drug User Fee Act (PDUFA)

- Created by Congress in 1992. Authorizes FDA to collect fees from companies that produce certain human drug and biological products.
- PDUFA must be reauthorized every five years, and was renewed in 1997 (PDUFA II), 2002 (PDUFA III), 2007 (PDUFA IV), and 2012 (PDUFA V).
- The Food and Drug Administration Reauthorization Act (FDARA) signed **Aug 18, 2017**, included PDUFA VI to cover Fiscal Years 2018-2022.
- The **current legislative authority for PDUFA VI expires in September 2022**. At that time, new legislation ([PDUFA VII](#)) will be required for FDA to continue collecting prescription drug user fees in future fiscal years.

21st Century Review Initiative: Goals



- Performance standards CDER follows during reviews
- Provide timeline and milestones
- Improve review process
- Good Review Management Principles and Practices
- Reduce number of review cycles
- Address application problems
- Review team members are accountable for raising and addressing differing points in a timely manner

[CDER 21st Century Review Process: Desk Reference Guide](#)

CDER Review Timelines- Prescription Drug User Fee Act PDUFA VI

- New Molecular Entities NDAs, BLAs
- PDUFA Clock start from filing day (Day 60)
 - 10 months standard (S)... for a total of 12 months from day of submission
 - 6 months for priority (P)... for a total of 8 months from day of submission

[CDER 21st Century Review Process: Desk Reference Guide](#)

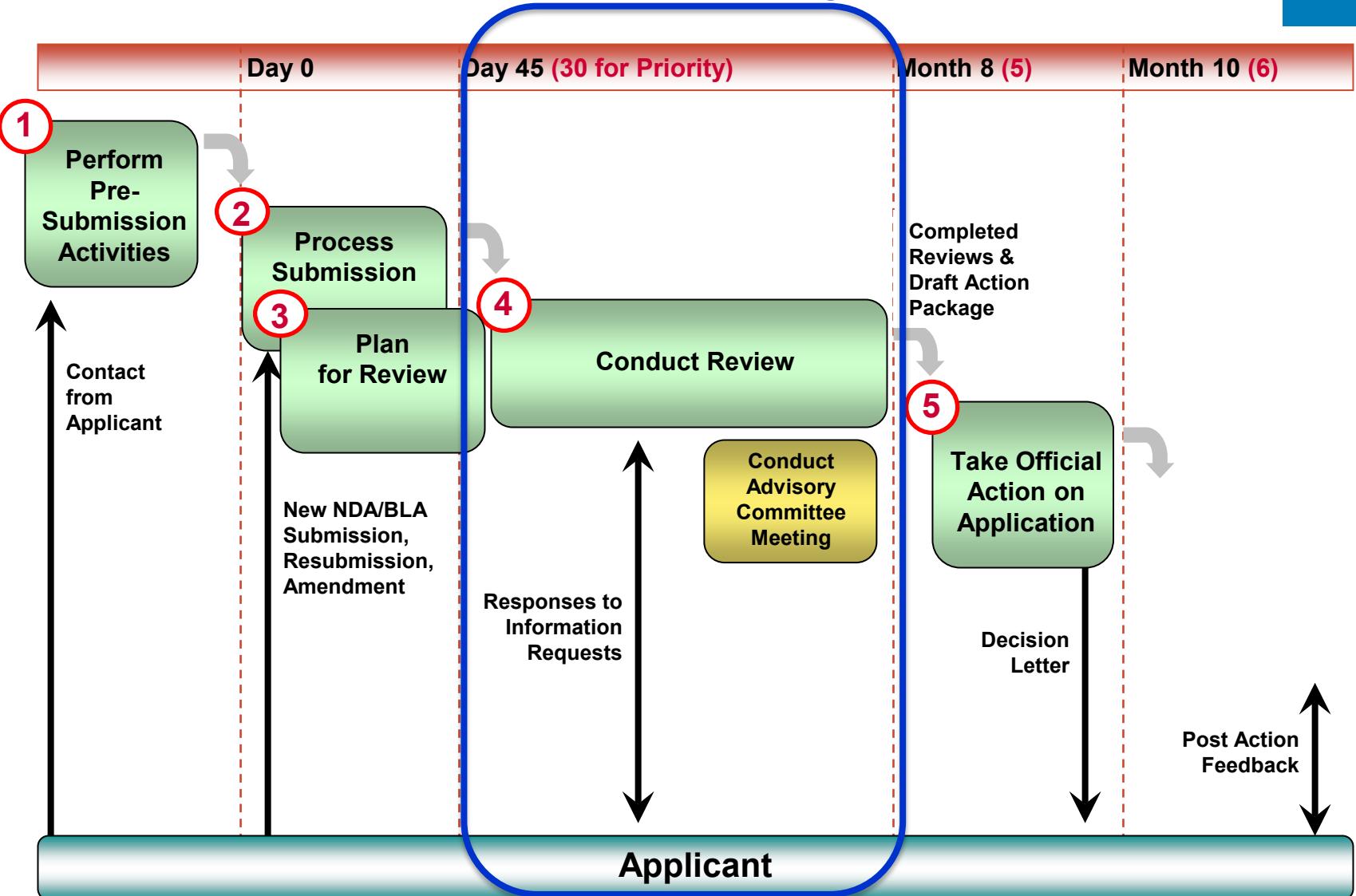
NDAs/BLAs Reviewed by CDER

- New Drug Applications (NDA)
 - [21 CFR 314](#)
 - In general, small molecules
 - 505(b)(1), 505(b)(2)
- Biologics License Application (BLA)
 - [21 CFR 601](#), BPCI Act 2009
 - Large proteins (enzymes, MAbs), Biosimilars-CDER
 - Other biologics reviewed in CBER, e.g., vaccines, blood products, gene therapy products (any “virus, therapeutic serum, toxin, antitoxin, or analogous product...”)

NDA/BLA Review Team

- Regulatory Project Manager - RPM
- Cross-Discipline Team Leader - CDTL
- Clinical - Assesses drug efficacy and safety
- Statistical Reviewer - Assesses drug efficacy
- Pharm/Tox - Assesses pre-clinical data
- Clinical Pharmacology
 - Assesses drug metabolism, drug-drug interaction, clinical PK
- Chemistry - Assesses drug purity, sterility, CMC
- Biosimilars- Therapeutic Biologics and Biosimilar Team

The 6 Steps of the 21st Century Review Process



Step 4 – Conduct Review Highlights

- Perform scientific and regulatory reviews, consult with fellow team members and team leaders
- Mid-cycle meeting
 - Standard: by month 5
 - Priority: by month 3
- Mid-cycle communication
 - Within 2-w following the mid-cycle meeting
 - Provide update on the status of the review
- Complete 1°, 2°, and CDTL reviews
- Initiate internal labeling, PMR/PMC discussions
- Discuss need for an Advisory Committee

Step 4 – Conduct Review Highlights

- Late-cycle communication
 - Opportunity for enhanced communication
 - Not to focus on the regulatory decision
- Wrap-up meeting
 - Internal meeting
 - Reviews are complete
 - Facilitates the development of a comprehensive understanding of the safety, efficacy and quality of the proposed drug product
 - Discuss preliminary decision on the regulatory action

Pharmacology-Toxicology Review of Blincyto BLA

- Three Pharmacology-Toxicology Reviewers assigned
- Total of 15 Pharmacology studies reviewed
- Total of 6 Toxicology studies reviewed
 - 5-w IV repeat-dose in Chimpanzees (3)
 - 13-w Subcutaneous (SC) and 4-w IV repeat-dose in mice
 - Embryo-fetal development (EFD) in mice
 - Cross-reactivity, cytokine release, hemolysis studies
- Applicant produced a murine surrogate of blinatumomab for use in studies with mice

Toxicology Review of Blincyto BLA

- Blinatumomab-related toxicities in animals included:
 - Infusion in chimpanzees associated with T-cell activation and ↑ in body temperature and heart rate and ↓ in blood pressure, in addition to increases in cytokines IL-2, IL-6, and INF- γ. Findings consistent with the Cytokine Release Syndrome (CRS) observed in the clinical trial in patients with ALL
 - No clear signs of CNS toxicity detected in animal toxicology and CNS safety pharmacology studies

BLINCYTO® (blinatumomab) for injection, for intravenous use
Initial U.S. Approval: 2014

**WARNING: CYTOKINE RELEASE SYNDROME and
NEUROLOGICAL TOXICITIES**

See full prescribing information for complete boxed warning.

- Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. (2.3, 5.1)
- Neurological toxicities, which may be severe, life-threatening, or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. (2.3, 5.1)

Toxicology Review of Blincyto BLA

- Blinatumomab-related toxicities in animals included:
 - ↓ lymphocyte levels including CD19+ and CD20+ B cells and CD3+/CD4+ and CD3+/CD8+ T cells in chimpanzees and mice
 - Immunophenotypic findings in mice corresponded with microscopic findings of ↓ cellularity and ↓ germinal center development in the lymph nodes (mandibular, mesenteric and inguinal) and Peyer's patches

Toxicology Review: ReproTox

- No drug-related effects in male or female reproductive organs in non-terminal chimpanzee studies
- The murine surrogate of blinatumomab did not show effects in male or female reproductive organs, embryo-fetal toxicity or teratogenicity
- Murine blinatumomab crossed the placenta; fetal exposure at pharmacologically active concentrations: potential for fetal lymphocyte depletion

PLLR Labeling of BLINCYTO® (blinatumomab)

FDA

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BLINCYTO may cause fetal harm including B-cell lymphocytopenia when administered to a pregnant woman [*see Clinical Pharmacology (12.1)*]. There are no data on the use of BLINCYTO use in pregnant women. In animal reproduction studies, a murine surrogate molecule administered to pregnant mice crossed the placental barrier [*see Data*]. Advise pregnant women of the potential risk to a fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Due to the potential for B-cell lymphocytopenia in infants following exposure to BLINCYTO in-utero, the infant's B lymphocytes should be monitored before the initiation of live virus vaccination. [*see Warnings and Precautions (5.11)*].

Data

Animal Data

Animal reproduction studies have not been conducted with blinatumomab. In embryo-fetal developmental toxicity studies, a murine surrogate molecule was administered intravenously to pregnant mice during the period of organogenesis. The surrogate molecule crossed the placental barrier and did not cause embryo-fetal toxicity or teratogenicity. The expected depletions of B and T cells were observed in the pregnant mice, but hematological effects were not assessed in fetuses.

Pregnancy and lactation Labeling Rule – PLLR 2014

Implemented June 2015

PLLR Labeling of BLINCYTO® (blinatumomab)

8.2 Lactation

Risk Summary

There is no information regarding the presence of blinatumomab in human milk, the effects on the breastfed infant, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from BLINCYTO, including B-cell lymphocytopenia, advise patients not to breastfeed during and for at least 48 hours after treatment with BLINCYTO.

8.3 Females and Males of Reproductive Potential

Based on its mechanism of action, BLINCYTO may cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

Pregnancy Testing

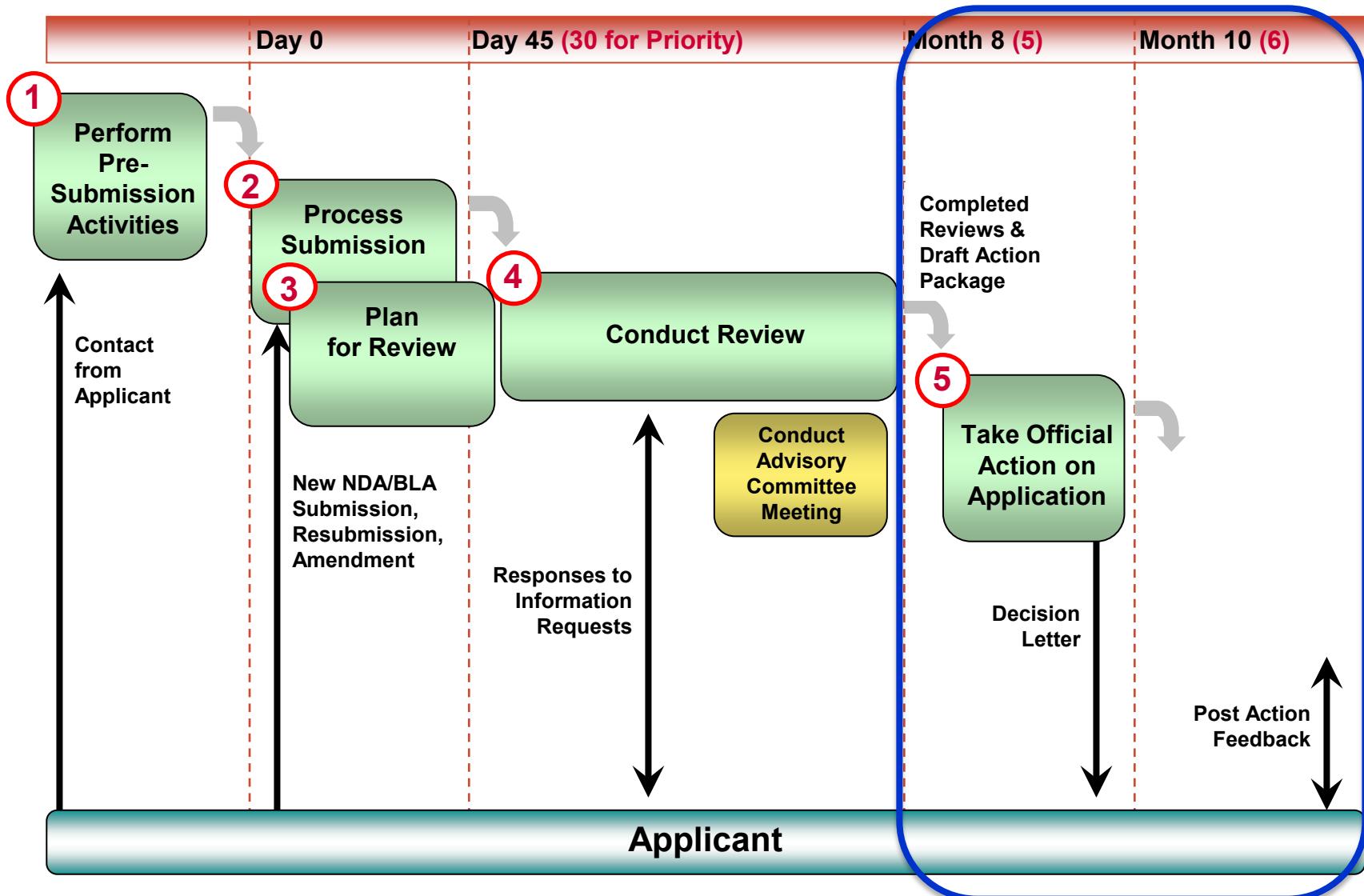
Verify the pregnancy status of females of reproductive potential prior to initiating BLINCYTO treatment.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for at least 48 hours after the last dose of BLINCYTO.

Step 5 – Action on Application



Basis for NDA/BLA Approval

- ***Demonstration of efficacy*** with acceptable safety in adequate and well-controlled studies
- ***Ability to generate product labeling*** that
 - Defines an appropriate patient population for treatment with the drug
 - Provides adequate information to enable safe and effective use of the drug
- ***Adequacy of the manufacturing facilities***
 - Manufacturing methods and controls are sufficient to preserve and consistently provide product that meets the defined identity, strength, quality and purity specifications (BLAs: add potency)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BLINCYTO™ safely and effectively. See full prescribing information for BLINCYTO.

BLINCYTO (blinatumomab) for injection, for intravenous use
Initial U.S. Approval: 2014

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES

See full prescribing information for complete boxed warning.

- Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. (2.3), (5.1)
- Neurological toxicities, which may be severe, life-threatening, or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. (2.3), (5.2)

—INDICATIONS AND USAGE—

BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). **This indication is approved under accelerated approval.** Continued approval for this indication may be contingent upon verification of clinical benefit in subsequent trials. (1)

DOSAGE AND ADMINISTRATION

- Dosage
 - Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. (2)
 - A single cycle of treatment consists of 4 weeks of continuous intravenous infusion followed by a 2-week treatment-free interval. (2.1)
 - For patients at least 45 kg in weight, in Cycle 1, administer BLINCYTO at 9 mcg/day on Days 1–7 and at 28 mcg/day on Days 8–28. For subsequent cycles, administer BLINCYTO at 28 mcg/day on Days 1–28. (2.1)
- Administration
 - Premedicate with dexamethasone 20 mg intravenously 1 hour prior to the first dose of BLINCYTO of each cycle, prior to a step dose (such as Cycle 1 day 8), or when restarting an infusion after an interruption of 4 or more hours. (2.2)
 - Administer as a continuous intravenous infusion at a constant flow rate using an infusion pump. (2.2)

- The IV bag should be infused over 24 hours or 48 hours. (2.2)
- BLINCYTO should be infused through a dedicated lumen. (2.2)
- Preparation
 - IV Solution Stabilizer is provided and is used to coat the prefilled IV bag prior to addition of reconstituted BLINCYTO. (2.4)
 - Reconstitute BLINCYTO with Sterile Water for Injection, USP, only. (2.4)
 - Aseptic technique must be strictly observed when preparing the solution for infusion since BLINCYTO does not contain antimicrobial preservatives. (2.4)
 - Use the specific volumes described in the admixing instructions. (2.4)

—DOSAGE FORMS AND STRENGTHS—

- For injection: 35 mcg of lyophilized powder in a single-use vial for reconstitution. (3)

—CONTRAINDICATIONS—

- Known hypersensitivity to blinatumomab or to any component of the product formulation. (4)

—WARNINGS AND PRECAUTIONS—

- Infections: Monitor patients for signs or symptoms and treat appropriately. (5.3)
- Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO is being administered. (5.6)
- Preparation and Administration Errors: Strictly follow instructions for preparation (including admixing) and administration. (5.9)

—ADVERSE REACTIONS—

- The most common adverse reactions ($\geq 20\%$) were pyrexia, headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, tremor, rash, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

—USE IN SPECIFIC POPULATIONS—

There is limited experience in pediatric patients. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2014

NDA/BLA Process Output

- Final action decision: approval vs complete response
- Final labeling if approved
- Reviews to explain/support the action
- CDER used ***diverse regulatory pathways*** to facilitate increased flexibility, efficiency, and interactions between CDER staff and drug developers:
 - ***Shorter review times to speed the availability of new therapies to patients with serious conditions***

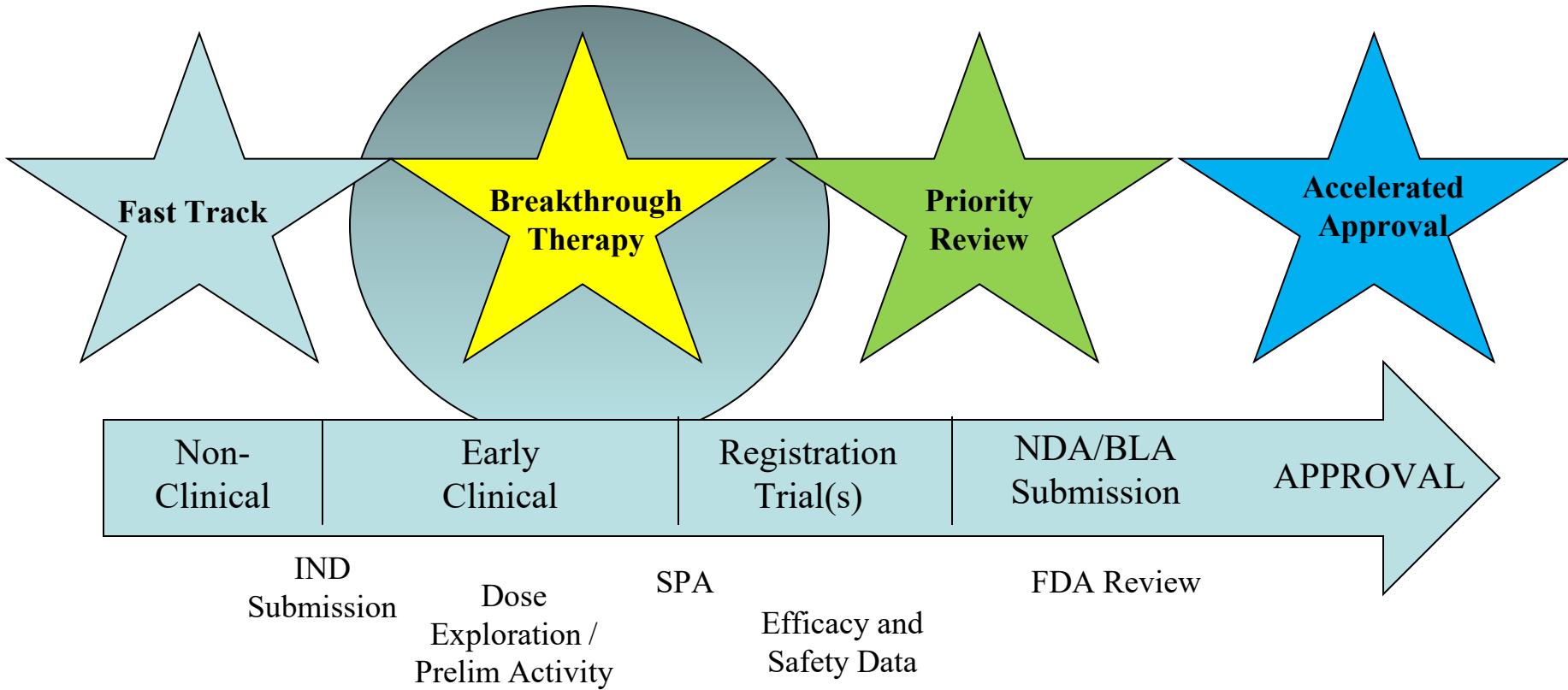
FDA-CDER Methods for Expediting Innovative Novel Drugs to Market

- Fast Track Designation (FT)
- Breakthrough Therapy Designation
- Priority Review Designation
- Accelerated Approval
 - Source: [FDA-CDER 2021 Annual Report Summary](#) Dr. Patrizia Cavazzoni

HOMEWORK

In 2021 **CDER approved 50 novel drugs**, either as new molecular entities (NMEs) under New Drug Applications (NDAs), or as new therapeutic biologics under Biologics License Applications (BLAs)

FDA Expedited Programs



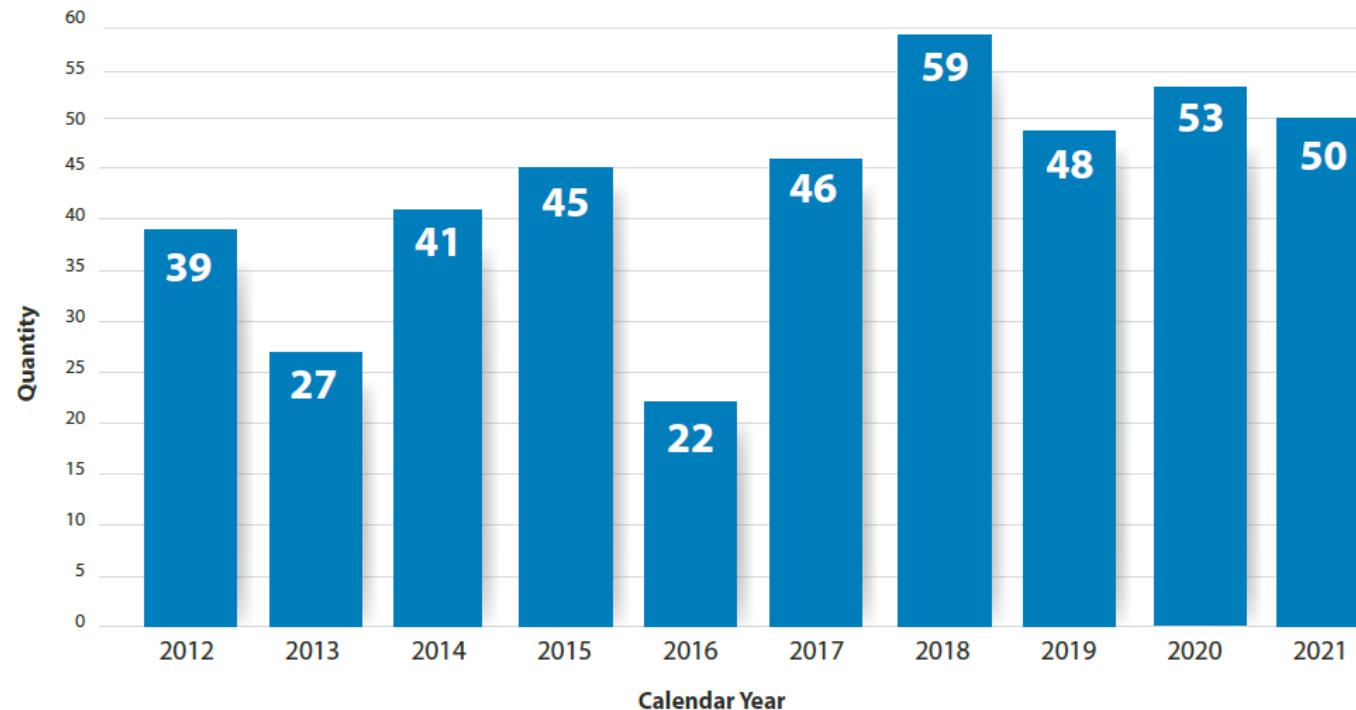
- ★ If considering accelerated approval, post-marketing clinical trials should be underway at the time of approval.

FDA-CDER Summary 2021

In 2021 CDER approved 50 novel drugs:

Fast track: 18 (36%); Breakthrough: 14 (28%); Priority Review: 34 (68%); Accelerated approval: 14 (28%).

From 2011 through 2021, CDER has averaged about 43 novel drug approvals per year

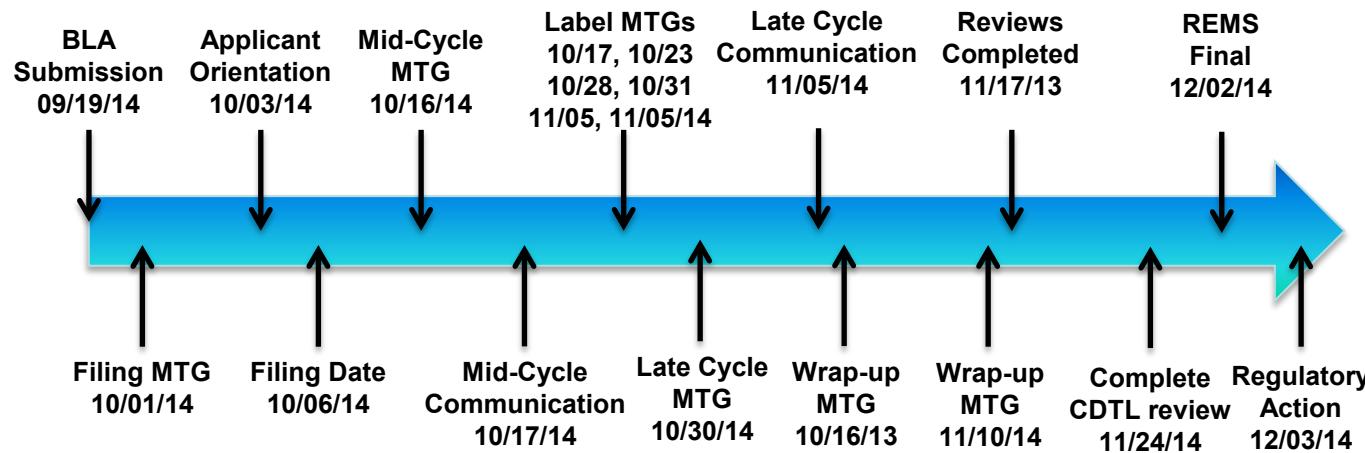


[FDA-CDER 2021 Annual Report Summary](#) Dr. Patrizia Cavazzoni
[Nature Reviews Drug Discovery](#)

Blincyto (Blinatumomab) Expedited Review (Breakthrough, Priority, Orphan Product and Accelerated Approval)

Total time for Expedited Review: 3 months

PDUFA goal 8 months: May 19, 2015



Summary

- CDER executes a structured-high performance organized program to review NDAs/BLAs - 21st Century Review Process
 - Defined goals, expectations and timelines
 - Optimal teamwork and collaboration across disciplines
 - Better management of the process
 - Provide transparency
- CDER has Expedited Programs for approval of new drugs/biologics
 - experience with these programs will identify areas for improvement
- CDER continue meeting or exceeding most PDUFA goal dates for application review, agreed to with the pharmaceutical industry and approved by Congress

Topics for Discussion

- Example of Translational Research – Bispecifics Abs
- When to submit a Marketing Application
- NDAs/BLAs Application Organization
- PDUFA & Goals of the 21st Century Review Process
- CDER Timelines for review
- NDAs/BLAs Reviewed by CDER-OND
- NDA/BLA Review Team
- Example of a Review by PharmTox
- Basis for NDA/BLA Approval
- FDA-CDER Programs for Serious Conditions
- Summary

QUESTIONS????





Relevant Laws

- Federal Food, Drug, and Cosmetic Act
- FDA Safety and Innovation Act (FDASIA) 2012
- Food and Drug Administration Reauthorization Act (FDARA) 2017
- Prescription Drug User Fee Act PDUFA VI Fiscal Years 2018 - 2022
- Public Health Service Act--Part F Licensing of Biological Products and Clinical Laboratories

Relevant Guidances

- IND regulations (both drugs and biologics) 21 CFR 312
- NDA (drugs) regulations--21 CFR 314
- Product licensing (biologics)--21 CFR 601
- Protection of human subjects and informed consent regulations--21 CFR 50
- IRB regulations--21 CFR 56
- Good Review Practices (GRPs) - MAPP CDER
- Good Laboratory Practices (GLP) 21 CFR 58

More information about approved drugs at

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>

More information about Guidance's at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/default.htm>

Laws

- Federal laws establish the legal framework within which FDA operates.
- The Federal Food, Drug, and Cosmetic Act (FD&C Act) can be found in the United States Code, which contains all general and permanent U.S. laws, beginning at 21 U.S.C. 301.
- USC = US Code official compilation of the general and permanent Federal Statutes

<https://www.fda.gov/AboutFDA/Transparency/Basics/ucm194909.htm>

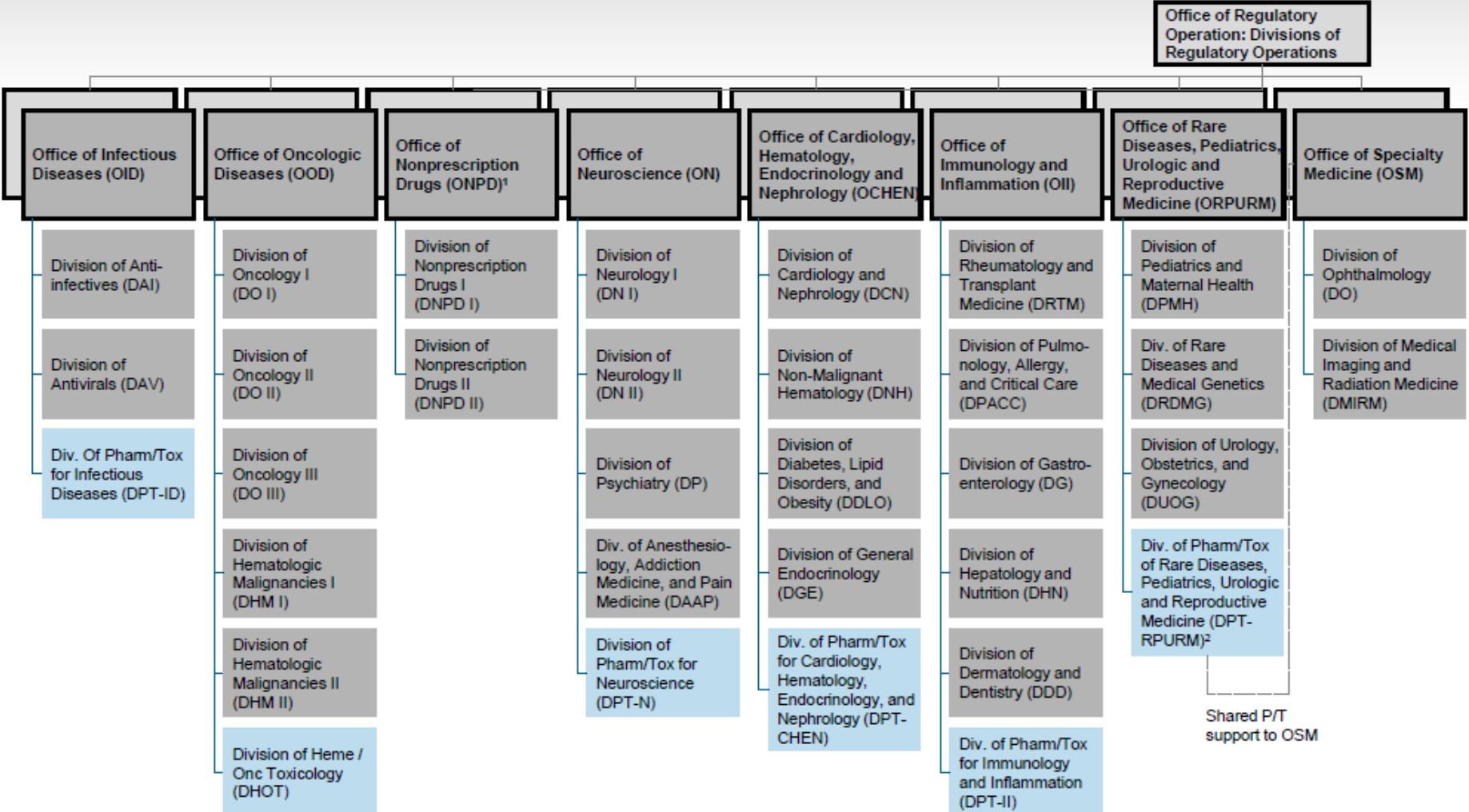
Guidances

- FDA develops regulations based on the laws set forth in the FD&C Act or other laws under which FDA operates.
- FDA follows the procedures required by the Administrative Procedure Act, another federal law, to issue FDA regulations.
- FDA regulations are also federal laws, but they are not part of the FD&C Act.
- FDA regulations can be found in Title 21 of the Code of Federal Regulations (**CFR**).

Clinical and Pharm/Tox Structure



Office of Regulatory Operation: Divisions of Regulatory Operations



¹ ONPD P/T staff in the ONPD IO given the small current size of P/T staff.

² Single P/T division with staff supporting both ORPURM and OSM; PT DD will have dotted line reporting to ORPURM and OSM for P/T issues, and solid line to ORPURM Office Director for PMAP, etc.

CLINICAL DEVELOPMENT TRIALS I, II, AND III AND GOOD MANUFACTURING PRACTICES (GMP)

Todd Parsley, Ph.D., Director, Infectious Disease Research

Noble Life Sciences, Inc.

OUTLINE

- 1) Overview of Clinical Drug Development
- 2) I filed my IND now what? - Executing the plan.
- 3) Making Clinical Material – GMP production of drug substance and drug product
- 4) Clinical trials
 - Phase I - Is it safe?
 - Phase II - Can it work?
 - Phase III - Really, does it work?
- 5) Are you ready to start your NDA/BLA –
 - Did we do it the correct way, and can we prove it?
- 6) Phase IV – Post approval – Does it work in the real world?
- 7) Case study – Gleevec. A targeted therapy success story

FDA DRUG APPROVAL PROCESS

A DRUG IS ANY PRODUCT THAT IS INTENDED FOR USE IN THE DIAGNOSIS, CURE MITIGATION, TREATMENT, OR PREVENTION OF DISEASE, AND THAT IS INTENDED TO AFFECT THE STRUCTURE OR ANY FUNCTION OF THE BODY



Who reviews new drug submissions?

A team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists review the drug sponsor's data and proposed labeling of drugs.



NDA REVIEW

FDA's New Drug Application (NDA)Review

Drug Labeling

10



FDA reviews the drug's professional labeling and assures appropriate information is communicated to health care professionals and consumers.

Application Reviewed

8-9



After an NDA is received, FDA has 60 days to decide whether to file it so it can be reviewed. If FDA files the NDA, the FDA Review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.

NDA Application

7



The drug sponsor formally asks FDA to approve a drug for marketing in the United States by submitting an NDA. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured.

Review Meeting

6



FDA meets with a drug sponsor prior to submission of a New Drug Application.

11

Facility Inspection



FDA inspects the facilities where the drug will be manufactured.

FASTER APPROVALS

The Accelerated Approval program allows earlier approval of drugs that treat serious diseases and that fill an unmet medical need. The approval is faster because FDA can base the drug's effectiveness on a "surrogate endpoint," such as a blood test or X-ray result, rather than waiting for results from a clinical trial.

The Fast Track program helps reduce the time for FDA's review of products that treat serious or life-threatening diseases and those that have the potential to address an unmet medical need. Drug sponsors can submit portions of an application as the information becomes available ("rolling submission") instead of having to wait until all information is available.

12 FDA

Drug Approval

FDA reviewers will approve the application or issue a response letter.

POST-MARKETING

FDA's Post-Approval Risk Assessment Systems

Because it's not possible to predict all of a drug's effects during clinical trials, monitoring safety issues after drugs get on the market is critical. The role of FDA's post-marketing safety system is to detect serious unexpected adverse events and take definitive action when needed.



Once FDA approves a drug, the post-marketing monitoring stage begins. The sponsor (typically the manufacturer) is required to submit periodic safety updates to FDA.

www.fda.gov/medwatch
(800) FDA-1088 (322-1088) phone
(800) FDA-0178 (322-0178) fax



FDA's MedWatch voluntary system makes it easier for physicians and consumers to report adverse events. Usually, when important new risks are uncovered, the risks are added to the drug's labeling and the public is informed of the new information through letters, public health advisories, and other education. In some cases, the use of the drug must be substantially limited. And in rare cases, the drug needs to be withdrawn from the market.

PDUFA

Prescription Drug User Fee Act

Since the PDUFA was passed in 1992, more than 1,000 drugs and biologics have come to the market, including new medicines to treat cancer, AIDS, cardiovascular disease, and life-threatening infections.

PDUFA has enabled the Food and Drug Administration to bring access to new drugs as fast or faster than anywhere in the world, all while maintaining the same thorough review process. Under PDUFA, drug companies agree to pay fees that boost FDA resources, and FDA agrees to time frames for its review of new drug applications.

WHAT IS AN INVESTIGATIONAL NEW DRUG APPLICATION (IND)?

IND is a document submitted to the FDA for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions.

Must show data to address three questions:

- 1) Is it reasonably safe?
- 2) Can you produce and supply consistent batches of the drug?
- 3) Are you qualified to fulfill the clinical trial duties?

IND goes into effect 30 days from the filing unless the FDA notifies sponsor of deficiency.

WHAT DID YOU PROMISE IN THAT IND:

CMC – chemistry manufacturing and controls

- Can you make it correctly (cGMP production)?
- Assure identification, quality, sterility and strength of the drug
- Stability – is it the same today as a year from now – material needs to be maintained on stability protocol
- Drug substance (API) and Drug product (dosing material)
- Qualified/validated analytical methods

Pharmacology/Toxicology Data

- Conduct pharmacokinetic and toxicity studies using the *same schedule, duration, formulation, and route* as proposed clinical trial
- Need qualified/validated bioanalytical methods for pK studies

Clinical Protocol and Investigators Brochure

- How it will used in the clinic.
- Why it should be used in the clinic.

IT'S NOT JUST THE FDA YOU HAVE TO CONVINCE

1) IND body – details to allow FDA to assure safety and rights of patients, and that the data generated will be sufficient quality to evaluate the drugs activity.

2) Clinical protocol – for FDA and Institutional Review Board (IRB).

- Detailed description of each clinical study planned, including estimated number of patients, exclusion criteria, details of dose delivery, and safety monitoring.
- Amendments allow necessary changes to Clinical Protocol

3) Investigators Brochure –

- Targeted to the Clinical investigators that will enroll patients on trial.
- Includes summary of why it should work, expected pK and side effects
- Should answer “why should I put my patient on your trial”

4) Informed consent form – tells the patient risks and reasons

DRUGS MUST BE MANUFACTURED CORRECTLY

1. Good Manufacturing Practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards. Legally mandated and legally enforced
2. They are used to **prevent** product defects. Not all defects can be detected by testing so process must be controlled
3. FDA determines current GMPs (cGMP) based on its experience and knowledge. Procedures that are feasible and valuable.
4. Required for Phase II and later trials.

Drug Substance is the manufactured active pharmaceutical ingredient (API). The stuff in the barrel.

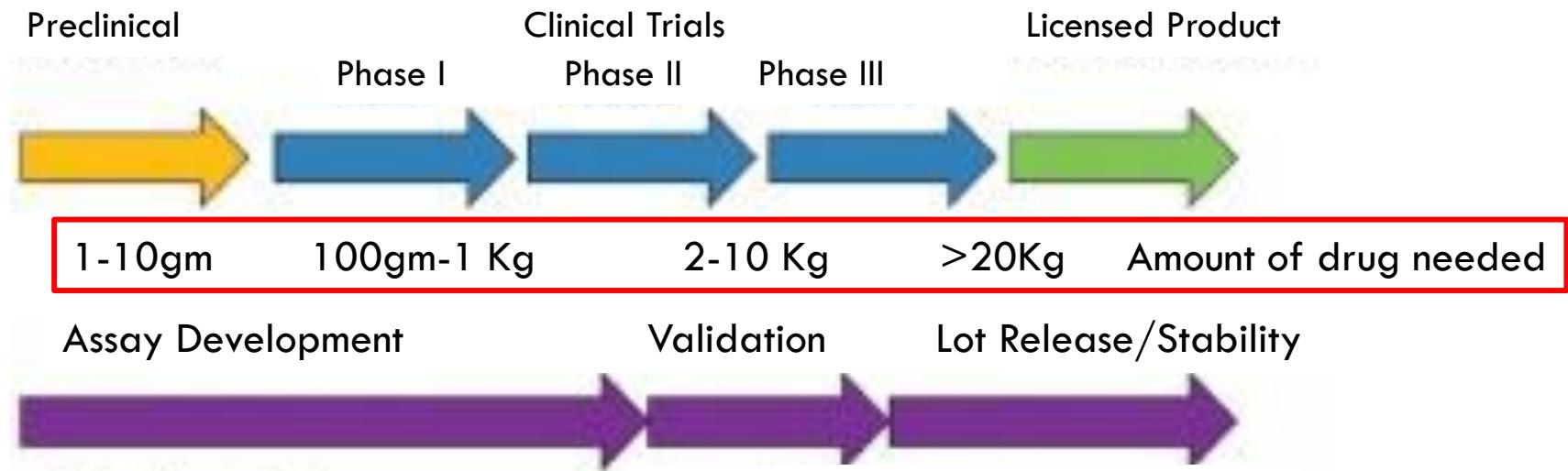
Drug Product is the formulated API that will be dosed to the patient. The stuff in the bottle



KEY COMPONENTS OF CGMP PROCESS

- **Quality Systems –**
 - Defined records and inspections
 - Quality Control / Quality Assurance
- **Facilities and Equipment Systems**
 - Facility inspections
 - Monitoring and Maintenance. Specifications and calibrations
- **Materials and Production Systems**
 - Documentation, controls and knowledge of source material
 - Manufacturing process and validation
- **Packaging and Labeling Systems**
 - Process and controls to appropriately identify materials
 - Correct and complete description of contents
- **Laboratory Control Systems**
 - SOPs and Training

HOW MUCH STUFF DO YOU NEED



- Limited quantitative information
 - Wider range allowed
 - Assay in development
- Assay validated
 - Parameters for assay defined and accepted
 - Adequate to support lot release and stability testing

CLINICAL TRIAL PHASES

- Phase 0 - Determine human pharmacokinetics (microdose of compound)
- Phase I - Establish the safe recommended dose and/or schedule of new drugs
- Phase II - Obtain preliminary data on whether the drug works in people who have a certain disease or condition
- Phase III - Generate statistically valid disease response and compare the new treatment with the current standard of care.
- Phase IV -drug's effectiveness and safety are monitored in large, diverse populations

CLINICAL TRIAL DESIGNS – MANY OPTIONS

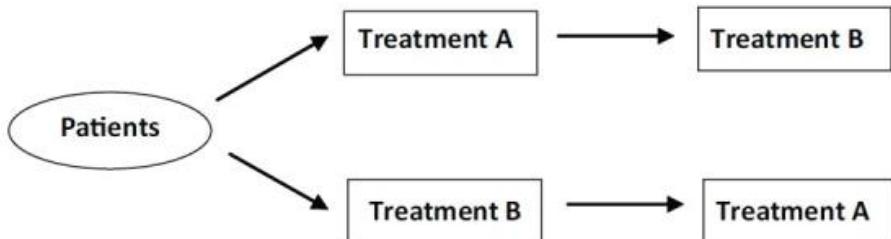
Open Trial



Randomized Controlled Trial



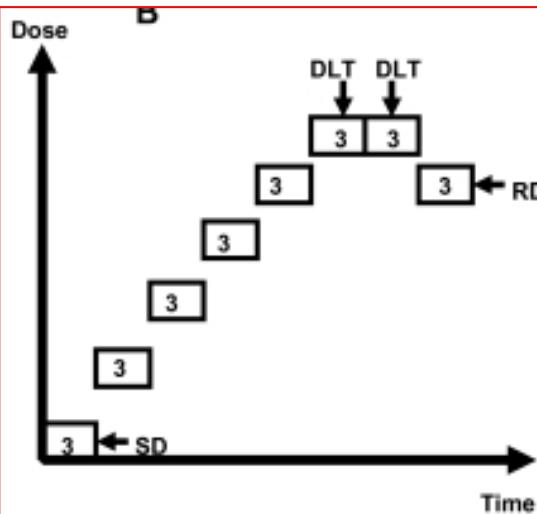
Randomized Crossover Trial



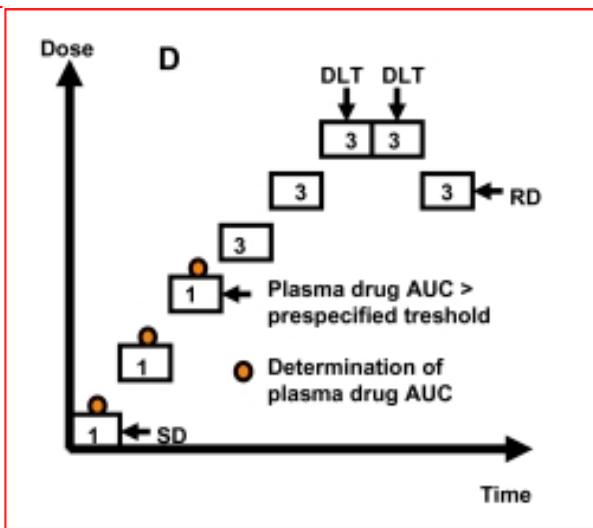
1. **Open-Label** – all parties know treatment
2. **Single blind** – subject blind
3. **Double blind** – Both patient and clinical staff blind

INNOVATIVE ESCALATION METHODS: GETTING TO EFFECTIVE DOSE EFFICIENTLY

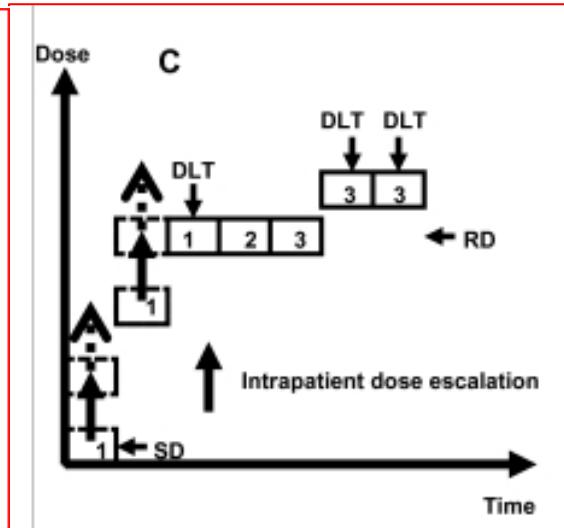
1. Traditional 3+3 Design



2. Pharmacologically guided



3. Accelerated titration design



Le Tourneau, et al., J Natl Cancer Inst. 2009 May 20; 101(10): 708–720.

PHASE I CLINICAL TRIAL

- Determine the Safety, Tolerability and Pharmacology.
- 20-80 subjects (healthy volunteers or patients)
- Dose escalation in an iterative schedule
- Identify side effects and appropriate Identify dose/schedule for further studies
- Exposure in people: Pharmacokinetics, Clearance
- Activity: Pharmacodynamic and Clinical response
- \$3-5M, 2-3 years

PHASE I CLINICAL TRIALS –

What you need to do

- Determination of safety
 - Predetermine how you will carefully monitor patients.
Define both clinical assays and analytical tools.
- Pharmacology
 - Need to determine drug blood levels after single dose and multiple doses, and clearance.
 - Need GLP pK method and stability (not validated yet).
- What you should do
 - Pharmacodynamic activity – need tool and plan for determining drug exposure
 - Clinical response – what is expected interim response measure.
Imaging, progression
 - Most patients will not be at maximum dose (dependent on trial design)

PHASE II CLINICAL TRIALS

- Determination if it is efficacious
 - Performed in Patients with disease
 - Has to be powered appropriately
- Evaluation of long-term safety
- Is this optimal dose/schedule
- Test patient selection criteria
- Still limited number of patients treated (30-100's)
- Examination of patients for preexisting conditions, drug-drug interactions, predictive markers of toxicity
- Start testing combination strategies
- Much more expensive \$10-20M

PHASE III CLINICAL TRIALS

- Requires demonstration of statistically significant clinical benefit in traditional endpoint, such as survival or accepted clinical endpoint
 - Accelerated approval can use a surrogate endpoint, but requires subsequent confirmation of benefit post approval
- Typically compared directly to standard of care or placebo
- Detailed prospective statistical analysis with documented efficacy
- Typically, need at least two multisite well controlled trials
- Address product/formulation issues: Scale-up and linking to-be-marketed formulation with clinical trial formulation
- Very expensive and slow – 300-1000 patients, \$20-50 of million, 5-10 years

BASIS FOR NDA APPROVAL

- Does it work?

- Demonstration of efficacy with acceptable safety.
- Does it have a therapeutic window
- Does it work better than approved standard of care?

- Who should use it?

- Ability to generate product labeling that defines an appropriate patient population for treatment with the drug
- **You get approval for the patients/disease/indication you tested it on.**
- Other indication/patient populations need additional trials.

- Are you sure?

Performed under Good Clinical Practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and **reported results are credible and accurate**, and that the rights, integrity, and confidentiality of trial subjects are protected.

TO USE YOUR DRUG IN COMBINATION YOU NEED TO RUN ANOTHER CLINICAL TRIAL

Clinical trials combining anti PD-1 inhibitors with other agents

1. Anti-CTLA-4 agents: 251
 2. Chemotherapies: 170
 3. Radiotherapies: 64
 4. Anti-VEGFA agents: 43
 5. Chemoradiotherapy combos: 42

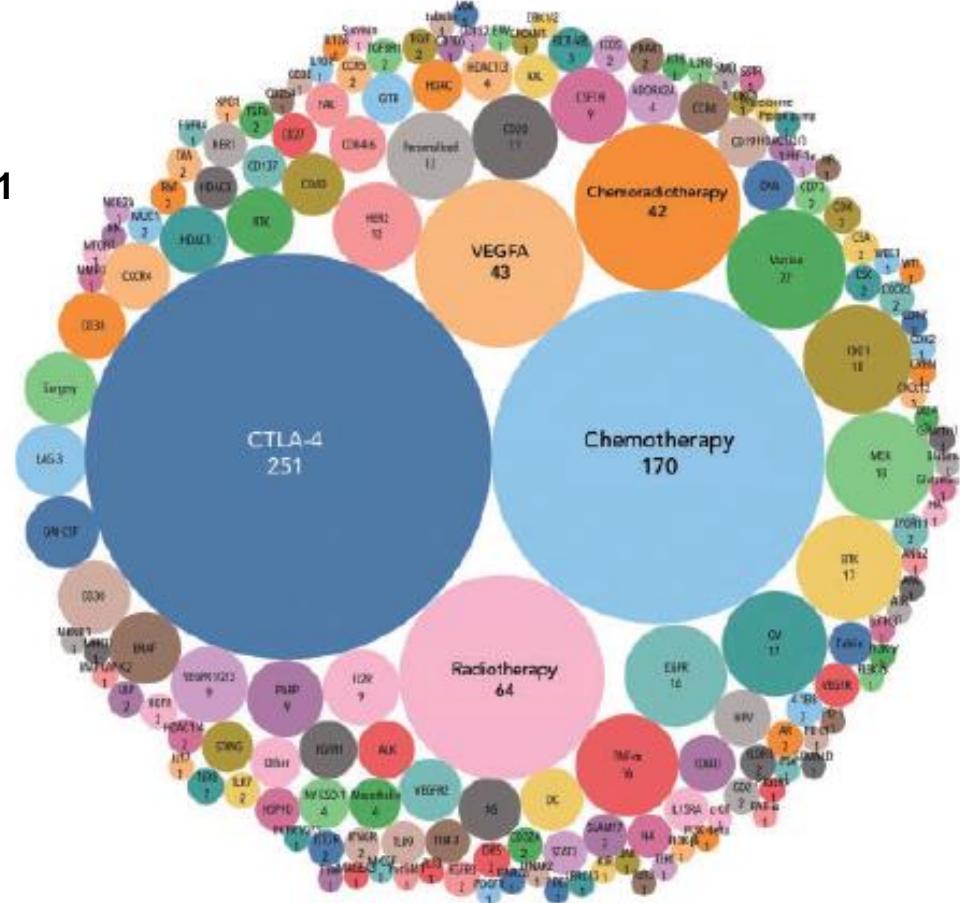


Figure 7. The landscape analysis of targets of anti-PD-1/L1 combination trials. The size of the bubble correlates to the number of trials.

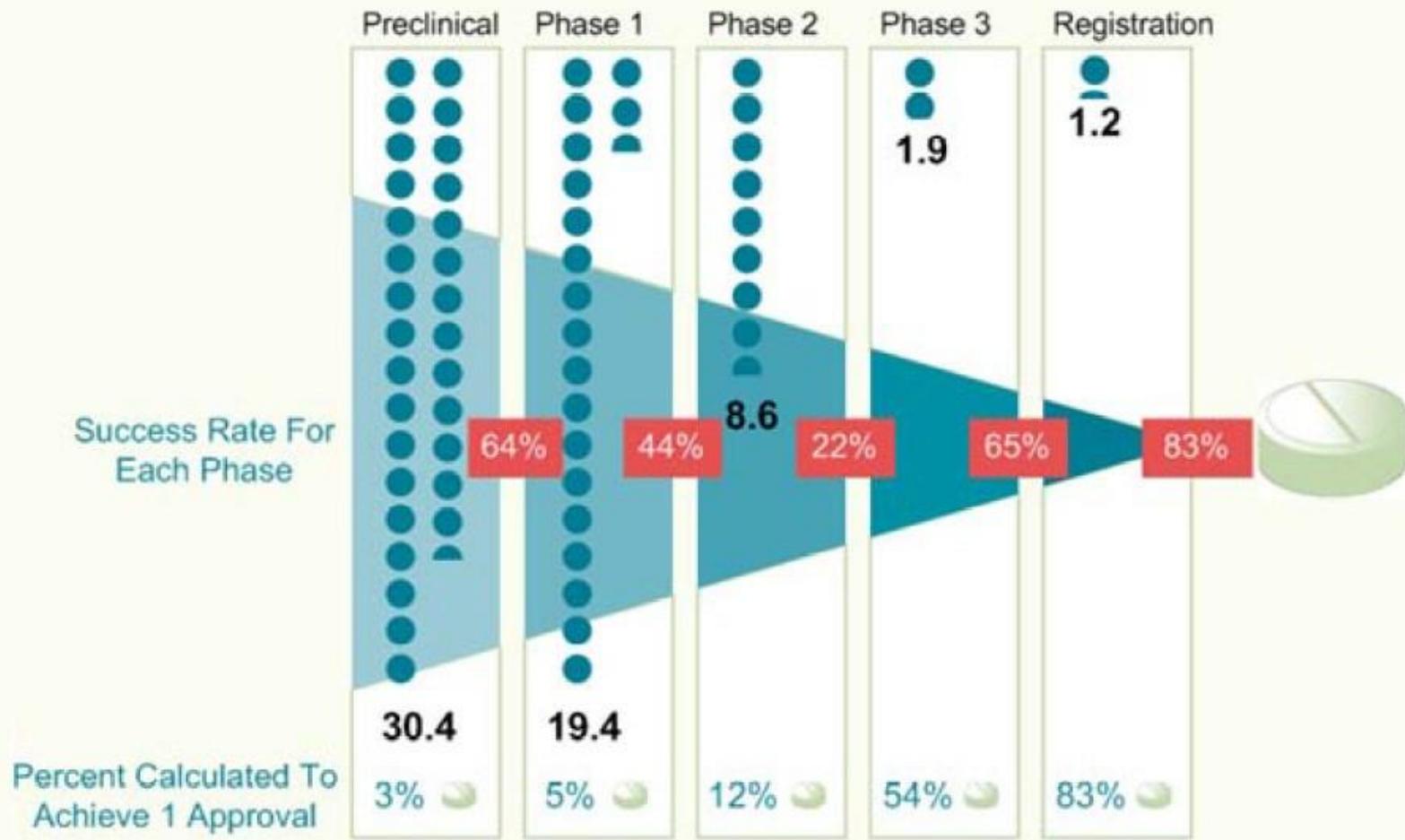
Comprehensive analysis of the clinical immuno-oncology landscape. Ann Oncol. 2018 Jan 1;29(1):84-91

PHASE IV CLINICAL TRIAL – POST-MARKETING SURVEILLANCE

- Monitoring the use of the drug after approval
- How is it used in the “wild” – no longer at experienced centers
- How well does it work when used more widely
- Identify any rare adverse effects that have not been observed previously
- Understand frequency and severity of expected adverse effects
- Any economic issues that interfere with correct use

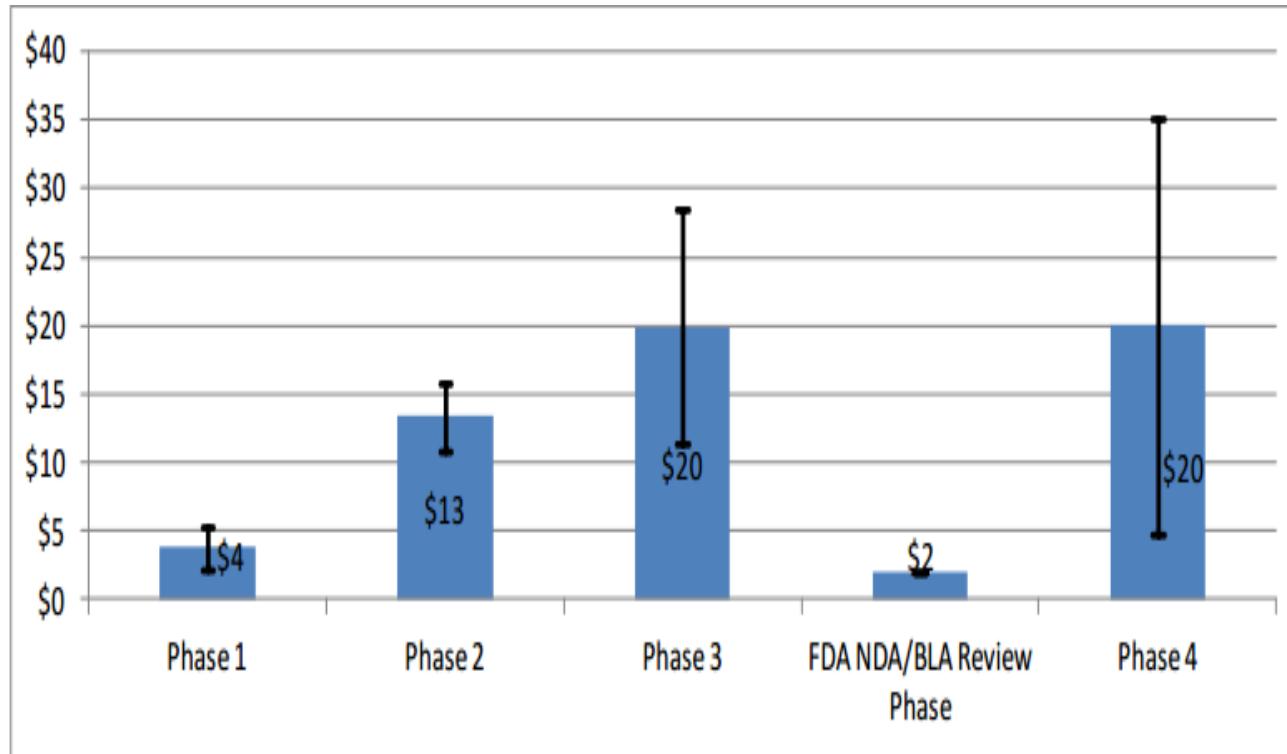
Development Success Rates

NME Success Rates By Phase And Overall 2007-2011 Industry Portrait, Pure



WHERE IS THE CASH SPENT

Average Per-Study Costs by Phase (in \$ Millions) Across Therapeutic Areas

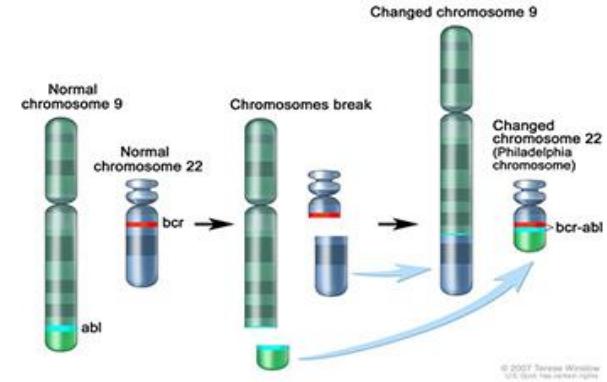


HOW MUCH DO THE TOP SELLING DRUGS MAKE?

Rank	Trade name	Type	Main indications	Company	Sales (USD millions/2021)
1	Comirnaty	Biologic	SARS-CoV-2	Pfizer, BioNTech	36,800
2	Humira	Biologic	Rheumatoid arthritis	AbbVie Inc.	20,700
3	Spikevax	Biologic	SARS-CoV-2	Moderna	17,700
4	Keytruda	Biologic	Melanoma, non-small cell lung cancer,	Merck & Co.	17,200
5	Eliquis	Small molecule	Nonvalvular atrial fibrillation, deep vein thrombosis and pulmonary embolism	BMS, Pfizer	16,730
6	Revlimid	Small molecule	Multiple myeloma MDS	BMS, Pfizer	12,800
7	Imbruvica	Small molecule	Mantle cell lymphoma, Chronic lymphocytic leukemia	AbbVie, J&J	9,800
8	Stelara	Small molecule	Plaque psoriasis	J&J	9,100
9	Eylea	Biologic	macular degeneration	Regeneron Pharmaceuticals, Bayer	8,900
10	Biktarvy	Small molecule	HIV	Gilead	8,600
11	Opdivo	Biologic	Melanoma, non-small cell lung cancer,	BMS, Ono Pharmaceutical	8,500
12	Xarelto	Small molecule	Nonvalvular atrial fibrillation, deep vein thrombosis, pulmonary embolism and coronary artery disease	Bayer, J&J	7,500
13	REGEN-COV/Ronapreve	Biologic	SARS-CoV-2	Regeneron, Roche	7,500
14	Trulicity	Biologic	Type 2 diabetes, cardiovascular risk reduction	Eli Lilly	6,500
15	Darzalex	Biologic	Multiple myeloma	J&J	6,000

CHRONIC MYELOGENOUS LEUKEMIA

- CML is slow growing but progressive leukemia
- 5-10K new cases/year
- CML cells have a BCR-ABL translocation
- Target discovered with a microscope
- The BCR-ABL translocation dysregulates the ABL tyrosine kinase
- BCR-ABL also found in 10-20% Acute Lymphocytic Leukemia.
- Cytogenetics and PCR provide diagnostic and pharmacodynamic biomarkers
- Conventional therapy was IFNa and BMT
- **1-year survival 50-75%, 5 years survival <30%.**



© 2007 Temple University
U.S. Copy, free reprint rights

GLEEVEC

- Gleevec purposely (kind of) developed to target the ABL kinase in CML
- First targeted cancer drug
- Tyrosine Kinase inhibitor
- Accelerated Approved in 2001
- **Post Gleevec approval 5-year survival is 89%**
- Relapse rate of only about 17%
- 2nd generation kinase inhibitors now available

GLEEVEC, PHASE 1 STUDY -1998

- Patients in chronic phase CML who had failed IFN therapy
- Single daily dose, conventional dose escalation design. Oral dose once per day
- **Pharmacokinetics** @ >400 mg/day dose: Cmax > 1 uM, Half life = 19 h and Dose proportional
- **Responses:** Hematologic responses at >140 mg/day
- 53/54 showed Complete Hematological response at >300 mg/day
- **Adverse Events:** mild nausea, diarrhea, periorbital edema and skin rashes.

Myelosuppression (efficacy)

At 300mg/day only Grade 3 or 4 event was Neutropenia.

- Maximum tolerated dose not identified, but did have expansion of Gr. 3 and 4 events
- Study expanded to include patients in blast crisis and patients with relapsed or refractory Ph+ ALL. Active but Results in these populations less impressive.

COMPLETE RESPONSE DOES NOT MEAN NO RESIDUAL DISEASE

TABLE 3. HEMATOLOGIC RESPONSES.

DOSE (mg/DAY)	ALL PATIENTS	PATIENTS WITH RESPONSES		PATIENTS WITH COMPLETE RESPONSES
		no.	no. (%)	
25 or 50	6	2 (33)	0	
85	4	2 (50)	1 (25)	
140	3	3 (100)	1 (33)	
200 or 250	16	16 (100)	9 (56)	
300–1000	54	54 (100)	53 (98)	
Total	83	77 (93)	64 (77)	

TABLE 4. CYTOGENETIC RESPONSES.

DOSE (mg/DAY)	ALL PATIENTS	PATIENTS WITH COMPLETE OR MAJOR RESPONSES		PATIENTS WITH MINOR RESPONSES
		no.	no. (%)	
300–350	13	5 (38)	2 (15)	
400	6	3 (50)	2 (33)	
500	6	1 (17)	1 (17)	
600	8	4 (50)	4 (50)	
750	6	2 (33)	0 (0)	
800	8	1 (12)	2 (25)	
1000	7	1 (14)	1 (14)	
Total	54	17 (31)	12 (22)	

Seven patients had complete cytogenetic response

Two patients were negative by BCR-ABL FISH

One Patient was negative by rt-PCR

GLEEVEC, PHASE 2 STUDIES – APPROVAL FOR FAILED STANDARD OF CARE PATIENTS

Three multisite studies in patients with Ph+ CML

- Single arm, open label
- Enrollment criteria
 - Chronic phase disease after IFN failure
 - Accelerated phase disease (IFN does not work)
 - Myeloid blast crisis (IFN does not work)

Basis for US approval for treatment of chronic phase disease after IFN failure

GLEEVEC, PHASE 3 STUDY APPROVAL FOR FRONT LINE THERAPY

Chronic phase CML, newly diagnosed patients

- Large (n=1106)
- open label

Randomized study

- Gleevec vs. IFN+AraC

Endpoints

- Primary – Progression Free Survival
- Secondary – major cytogenetic response, hematologic response, time to accel. Phase or blast crisis, survival

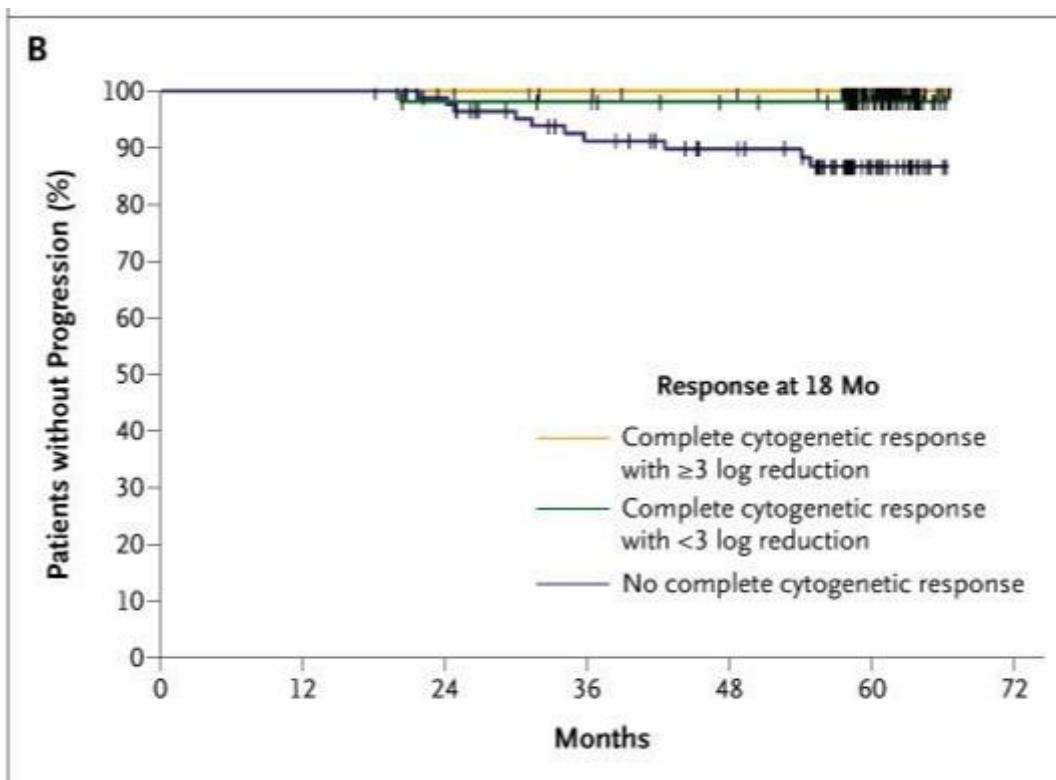
Approval for first line treatment in US and EU

PHASE IV (kind of) - 5 YEAR FOLLOW UP DATA SUPPORTS INITIAL RESULTS

Table 3. Responses to imatinib versus IFN plus cytarabine in newly diagnosed patients with CML in chronic phase

	CHR, %	MCR, %	CCR, %	Progression-free survival, 14 mo
Imatinib, n = 553	95.3	85.2	73.8	92.1
IFN + cytarabine, n = 553	55.5	22.1	8.5	73.5
P	.001	.001	.001	.001

Median duration of follow-up equaled 19 months. CHR indicates complete hematologic response; MCR, major cytogenetic response; and CCR, complete cytogenetic response.



Druker et al., N Engl J Med 2006; 355:2408-2417

I Deininger et al., Blood 2005; 105:2640

GLEEVEC TODAY

Approved front line in CML

Development of resistance is common from mutations in ABL kinase domain

2nd and 3rd generation ABL inhibitors can be used effectively

Expanded clinical use in other indications

ALL with BCR-ABL translocations – more complicated clinical response, but effective when used appropriately

Gastrointestinal stromal tumors with cKIT kinase activation

Systemic Mastocytosis with cKIT kinase activation

Dermatofibrosarcoma Protuberans with PDGF-beta activations

Chronic Eosinophilic Leukemia with PDGFa activations

Marketing and the Launch of Gleevec

May 1, 2023



TSTP May 2023

Marketing and the Launch of Gleevec

May 1, 2023

Subtitle:

***A journey to the dark side and
why that may be important***

Session Agenda

Part 1 - Marketing 101

- *Why is marketing important?*
- *What is marketing?*
- *What are the critical elements of marketing?*

Part 2 – Launching Gleevec

- *Building the Launch Plan 2001*

Why is marketing important

3. The “best” product in a market is generally not the market leader.
2. Adapting to the market and the market dynamics can enhance product development.
1. Investors get a return only when your product or service is sold. Therefore, they will not invest in your company unless they are convinced that your product meets a customer need and your plan will lead to sales.

What is marketing?

AMA Definition

- Identifying particular wants and needs of a target group of customers
- Satisfying those customers better than the competitors
- Conducting market research on customers, analyzing their needs
- Making strategic decisions about product design, pricing, promotion and distribution

What is marketing?

WAB* Definition

- Optimizing the features, advantages and benefits of your product or service within it's competitive environment
- Developing the product promotional strategy, tactics and tools
- Defining the “sizzle”

*** World according to Brad**

Marketing vs. Sales

Marketing

- Tactical strategies
- Interacts with customers in groups or segments
- Focus on product **features** and **advantages**

Sales

- Strategic tactics
- Most customer interaction is one-on-one
- Focus on product **benefits**

Some definitions

- | | |
|-------------------|---|
| Features | <ul style="list-style-type: none">• The physical and ideological attributes of your product or service |
| Advantages | <ul style="list-style-type: none">• The differences that make your product or service superior to the competition |
| Benefits | <ul style="list-style-type: none">• The perceived value that the customer receives from the advantages of your product or service |

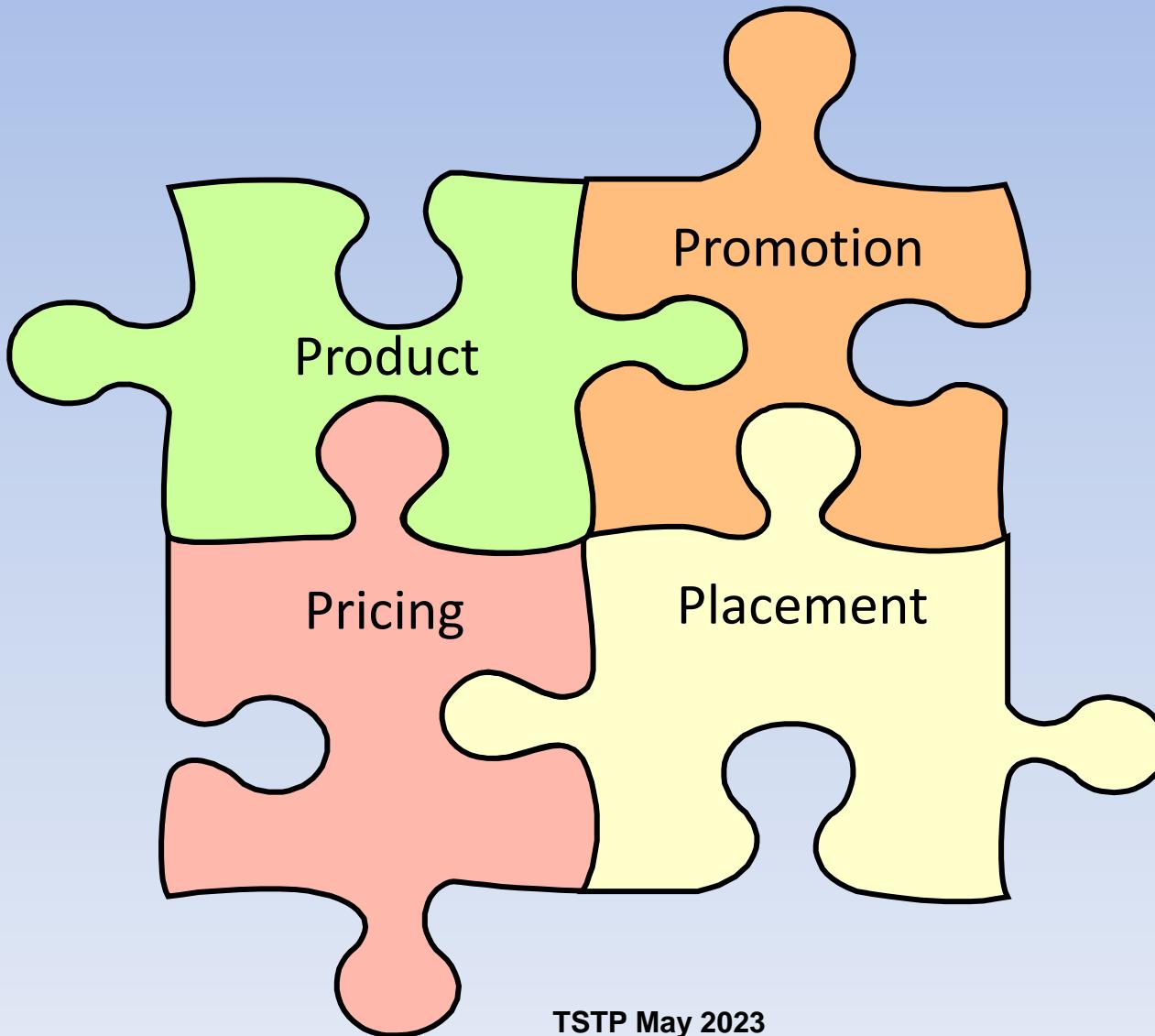
Market Dynamics

All markets are constantly evolving and shifting

- **Market size**
 - Dollars / Units
- **Market growth**
 - Product vs. market or relevant comparator
- **Customer buying processes and patterns**
- **Competitive products and strategies**
 - Attaining and maintaining your edge
- **Relevant industry trends**
 - Market shifts
 - Pharmaceutical pricing reform

Marketing Levers

The 4 P's



Marketing Levers

Product	Placement	Price	Promotion
Functionality	Channel members	List price	Message
Appearance	Channel motivation	Discounts	Personal selling
Quality	Market coverage	Allowances	Advertising
Packaging	Locations	Financing	Public Relations
Brand	Logistics	Leasing Options	Media
Warranty	Service levels		Geography
Service/Support			Budget

Product attributes

- An initial market “landscape” may identify new or unfulfilled areas of customer need
- Product design and/or study design may be revised to incorporate advantages to leverage a market niche
 - **Target product profile:** The product attributes that will allow you to take advantage of a market opportunity
- Remember that the market is dynamic
- Quantifying this analysis can help attract investors

GASTRIC CANCER COMPETITIVE LANDSCAPE

Investigational Therapies Clinical Trial Timeline Table

1st Line Therapies

XP: capecitabine (Xeloda) + cisplatin (Platinol). EOX: epirubicin + oxaliplatin + capecitabine (Xeloda). ECX: epirubicin + cisplatin + capecitabine (Xeloda). TC: docetaxel (Taxotere) + cisplatin.

Therapy	Study	Details	Status	2008	2009	2010	2011	2012	2013	2014
Erbitux (cetuximab, EGFR mAb)	Phase III 1st Line, Advanced (EXPAND) NCT00678535	N = 870 (Germany, Spain, Korea, Taiwan) XP +/- cetuximab	Recruiting Start: Jun 2008 FPI: Jul 8, 2008 Data: Jul 2010 End: Mar 2012							
Herceptin (trastuzumab, HER2 mAb)	Phase III 1st Line, Advanced, HER2+ (ToGA) BO18255	N = 584 (International) chemo +/- trastuzumab 8 mg/kg » 6 mg/kg q3w	No longer recruiting Start: Sep 2005 Data: Jun 2009 MMA filed: 3Q 2009 sBLA filing: 1H 2010							
Vectibix (panitumumab, VEGFR/EGFR inhibitor)	Phase III 1st Line, Advanced (REAL 3) NCT00824785	N = 730 (UK) EOX +/- panitumumab	Recruiting Start: May 2008 Data/End: Feb 2013							
Avastin (bevacizumab, VEGF-A mAb)	Phase III 1st Line, Advanced (AVAGAST) NCT00548548	N = 760 (US) XP +/- bevacizumab	Active, not recruiting Start: Nov 2007 Data: Dec 2010 (ClinicalTrials.gov reports Nov 2011 for data, but OS data will likely be available in 2010)							
	Phase III 1st Line, Advanced NCT00887822	N = 200 (China) Arm 1: bevacizumab + XP Arm 2: placebo + XP	Recruiting Start: Mar 2009 End: Jul 2013							
	Phase II/III 1st Line Neo-/Adjuvant, Resectable (CDR0000536013) NCT00450203	N = 1100 (UK) ECX +/- bevacizumab	Recruiting Start: Oct 2007 Data: Jun 2012							
Recentin (cediranib, VEGFR inhibitor)	Phase I Prev Untreated, Loc-Adv/Met, Unresectable NCT00960349	N = 18 (Japan) Arm 1: cediranib + cisplatin + S-1 Arm 2: cediranib + XP	Recruiting Start: Aug 2009 Data: Dec 2009 End: Feb 2010							
Nexavar (sorafenib, VEGFR inhibitor)	Phase II 1st Line, Unresectable, Met, Loc-Adv (ECOG-E5203) NCT00253370	N = 38 (US) sorafenib + TC	Active, not recruiting Start: Oct 2005 Data: Jul 2009							

Investigational Therapies Comparative Efficacy Table

Targeted Agent	Phase	Line	Setting	N	Regimen	ORR%	Median (months)			Source
							TTP	PFS	OS	
Erbitux	II	1 st	Adv	49 (GC:34)	cetuximab + IF (irinotecan + 5FU + leucovorin)	42		8.5	16.6	AIO IF Ph 2: Moehler, ECCO15 ESMO34, Sep 2009: abstr P-6579
	II	1 st	Adv, Met	51	cetuximab + oxaliplatin + irinotecan	63	5.75		9.5	AGMT Gastric-2 (1st efficacy results w/35 evaluable pts): Woell E et al. ASCO 2009 abstr 4538.
	II	1 st	Met	52 (GC:27)	cetuximab + FUFOX	65.2	7.6		9.5	AIO FUFOX Ph2 Final Results: Lordick, et al. ASCO 2007, abstr 4526.
	II	1 st	Adv	38 (GC:34)	cetuximab + FOLFIRI	44.1	8		16	FOLCETUX study (34 eval pts): Pinto, et al. Ann Oncol, 2007 vol 18 is 3.
	II	1 st	Adv	40	mFOLFOX6 + cetuximab	50	5.5		9.9	Korean mFOLFOX6 (38 eval pt): Han SW et al (2009). Br J Cancer 100(2):298–304.
Herceptin	III	1 st	Adv, HER2+	294	trastuzumab + capecitabine + cisplatin + 5FU	47.3	7.1	6.7	13.8	ToGA: Kang, et al. ASCO 2009; presentation abstr LBA4509
				290	capecitabine + cisplatin + 5FU	34.5	5.6	5.5	11.1	
						p=0.0017	p=0.0003	p=0.0002	p=0.0046	
Avastin	II	1 st	Met	47	bevacizumab + cisplatin + irinotecan	65			12.3	Shah, et al. JCO 2007
	II	1 st	Met	32	bevacizumab + docetaxel + cisplatin + irinotecan	63				Enzinger, et al. ASCO 2008, Abstr 4552.
	II	1 st	Adv	42	bevacizumab + mDCF	67	12	16.2		Jhawer, et al. GI ASCO 2009, Abstr 10.
Nexavar	I	1 st	Adv	16	sorafenib + XP	62.5		10	14.7	Kim, C. et al. ECCO15 ESMO34 September 2009: abstract P-6563 and posters
	II	1 st	Adv, Met	44	sorafenib + docetaxel + cisplatin	40.9	5.8	13.6		
Sutent	II	2 nd	Adv/Met	78	sunitinib 50mg	2.6	2.5	2.5	7.4	A6181054

Marketing Levers

Product	Placement	Price	Promotion
Functionality	Channel members	List price	Message
Appearance	Channel motivation	Discounts	Personal selling
Quality	Market coverage	Allowances	Advertising
Packaging	Locations	Financing	Public Relations
Brand	Logistics	Leasing Options	Media
Warranty	Service levels		Geography
Service/Support			Budget

Three Key Pillars of Placement

- **Segmentation**
 - Separating the groups within a market where the members are as similar as possible within the segment, and as different as possible between segments.
- **Targeting**
 - Comparing the attractiveness of various segments and then selecting the most attractive - pick your niche.
- **Positioning**
 - Determining where your product best fits in your ***customer's*** mind relative to your competitors.

Segmentation

A viable customer segment is:

- Measurable
- Accessible
- Durable
- Substantial enough to be profitable
- Different in its response to promotion

Types of segmentation

Geographic: Region, climate, population density, population change

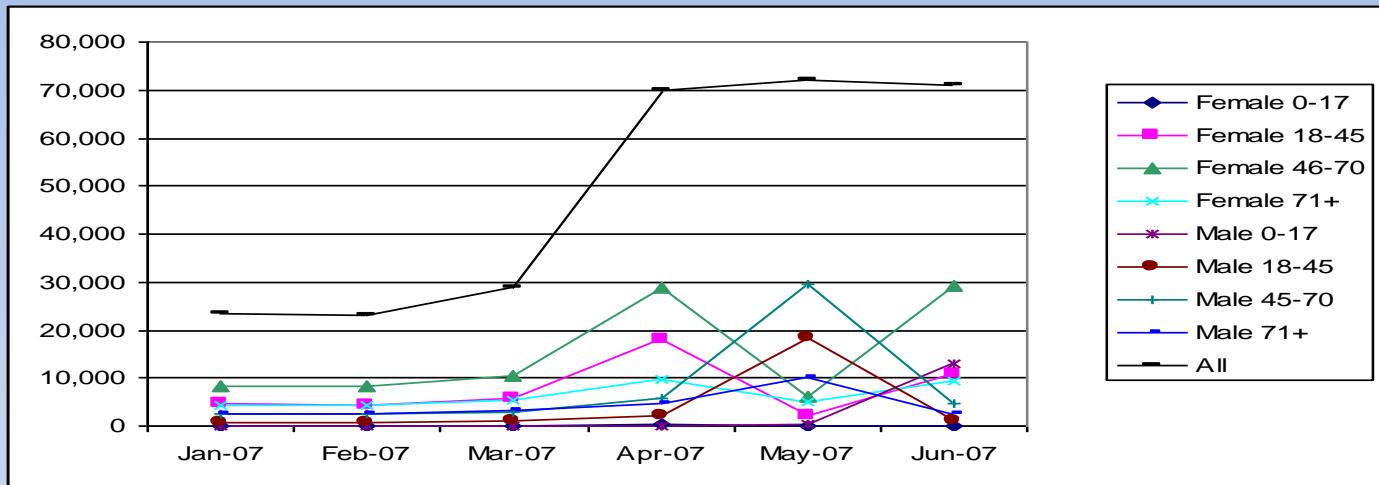
Demographic: Age, gender, ethnicity, education, occupation, income, family status

Psychographic: Values, attitudes, life style

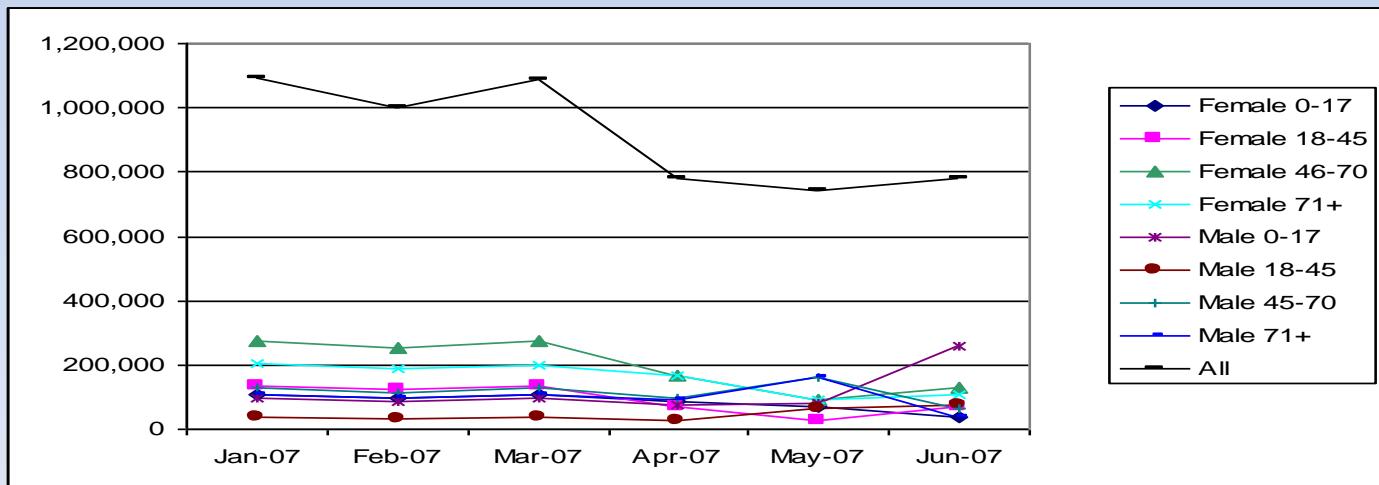
Behavioral: Consumption patterns, price sensitivity, brand loyalty

Age / Gender Segmentation

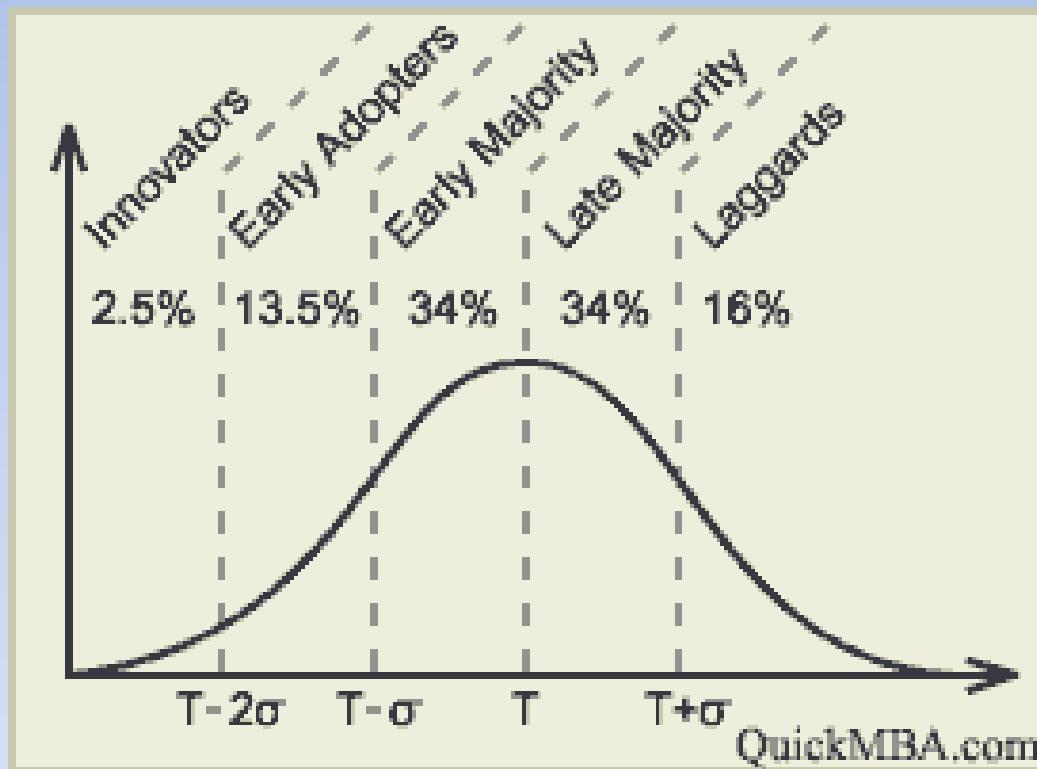
Amitiza



Rest of Market



Product Adoption



Physician Segmentation

Decile	# of GEs	# of PCPs	Total # of MDs	Avg. Zel TRx	Avg. PEG TRx (1)	Avg. Mkt TRx
10	557	49	671	338	665	1,074
9	1,058	200	1,424	153	342	537
8	1,363	676	2,360	95	196	326
7	1,435	1,878	3,818	61	111	197
6	1,146	3,951	5,970	39	72	131
5	876	6,402	9,035	24	55	95
4	723	9,180	13,552	14	44	72
3	594	13,253	21,052	8	33	52
2	656	22,000	38,228	4	20	32
1	1,121	78,238	190,125	1	5	9
0	551	40,838	126,060	-	-	3
Total	10,080	176,665	412,295	5	14	24

Source: IMS prescription data

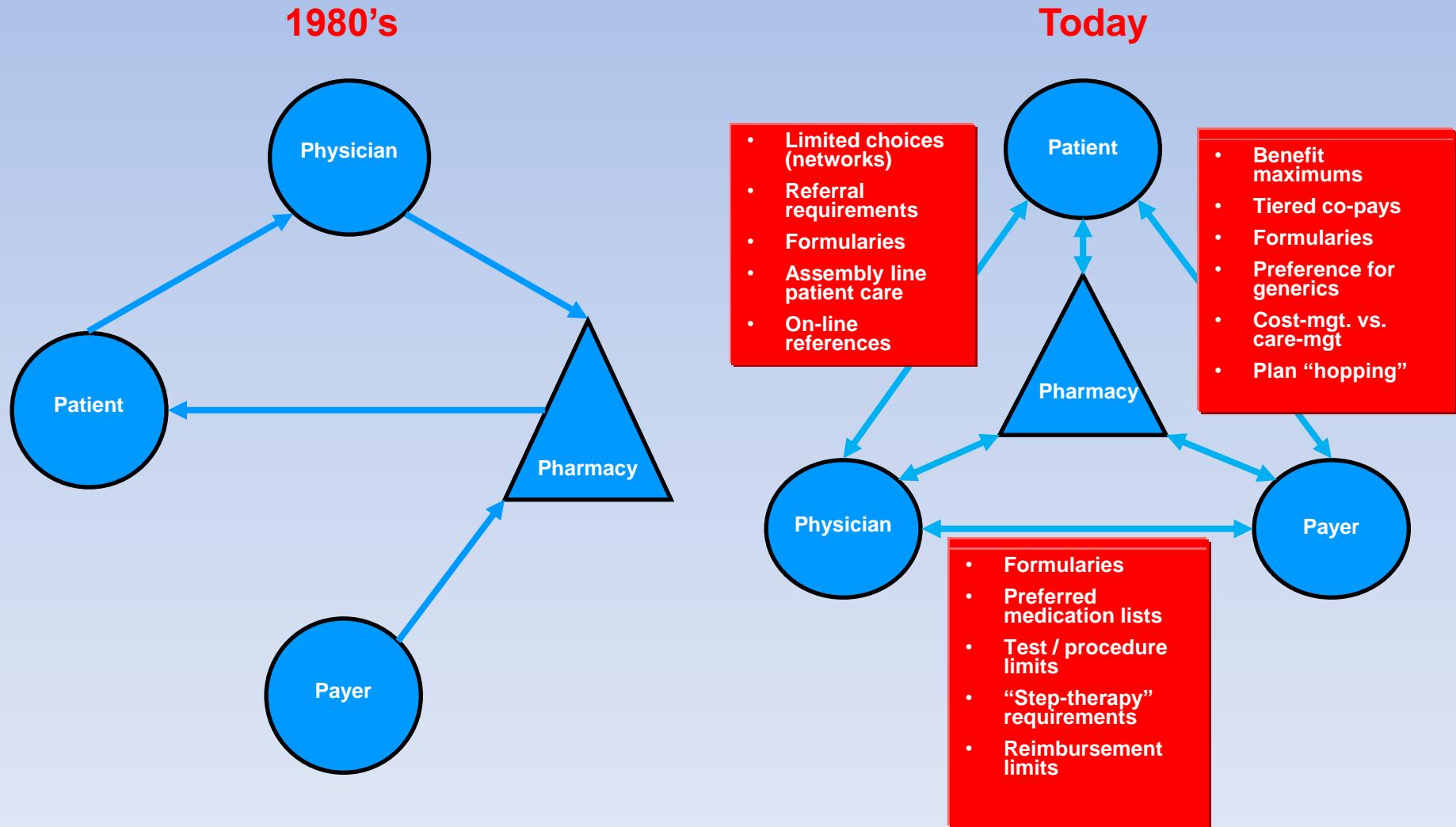
1. PEG TRx includes MiraLax, Glycolax, and Polyethylene Glycol

Targeting

- Who buys?
- Who pays?
- Who decides?
- Who uses?
- Who regulates?



Increasing difficulty of targeting

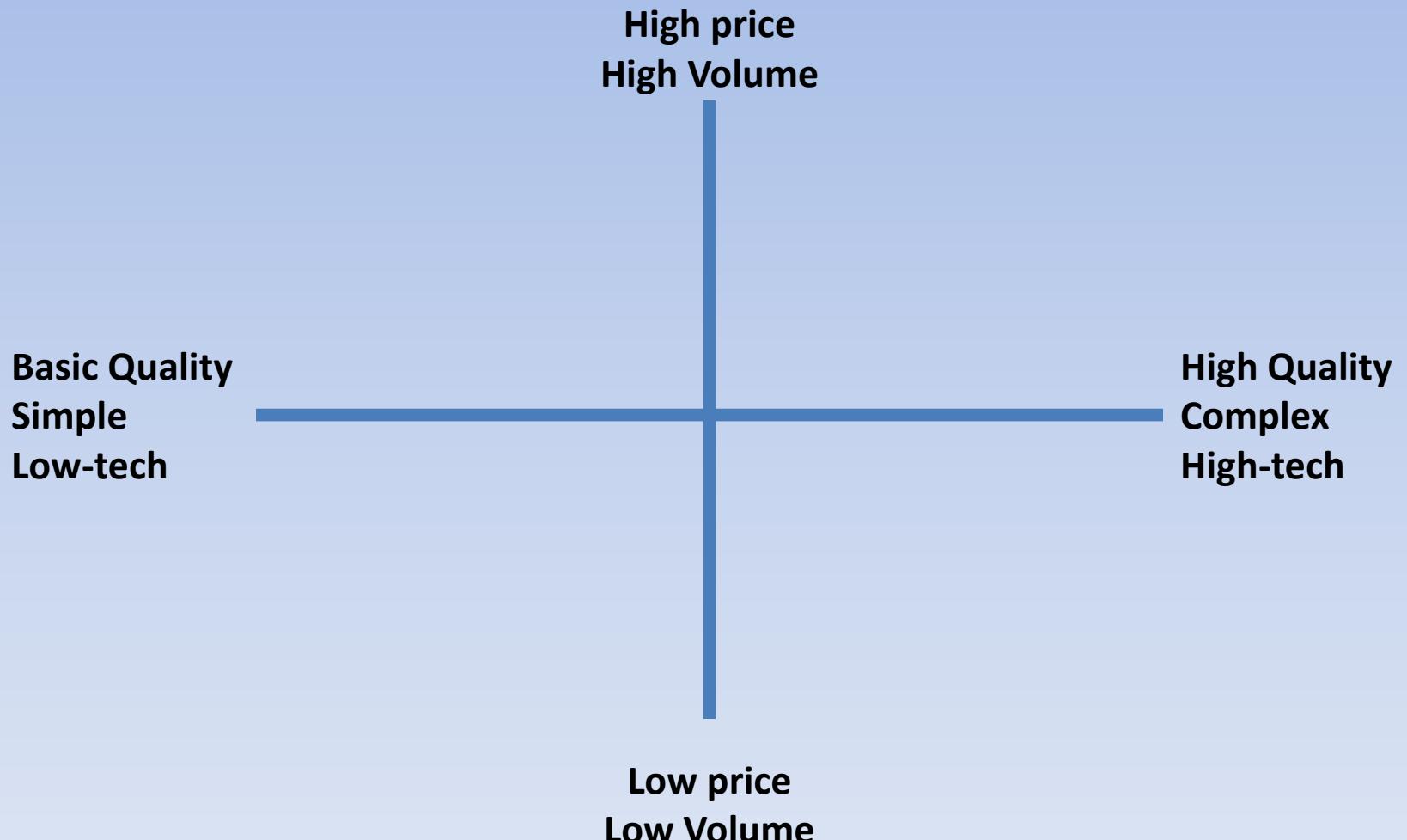


Positioning

Defining your product or service in terms the perceptions of your target customer segment

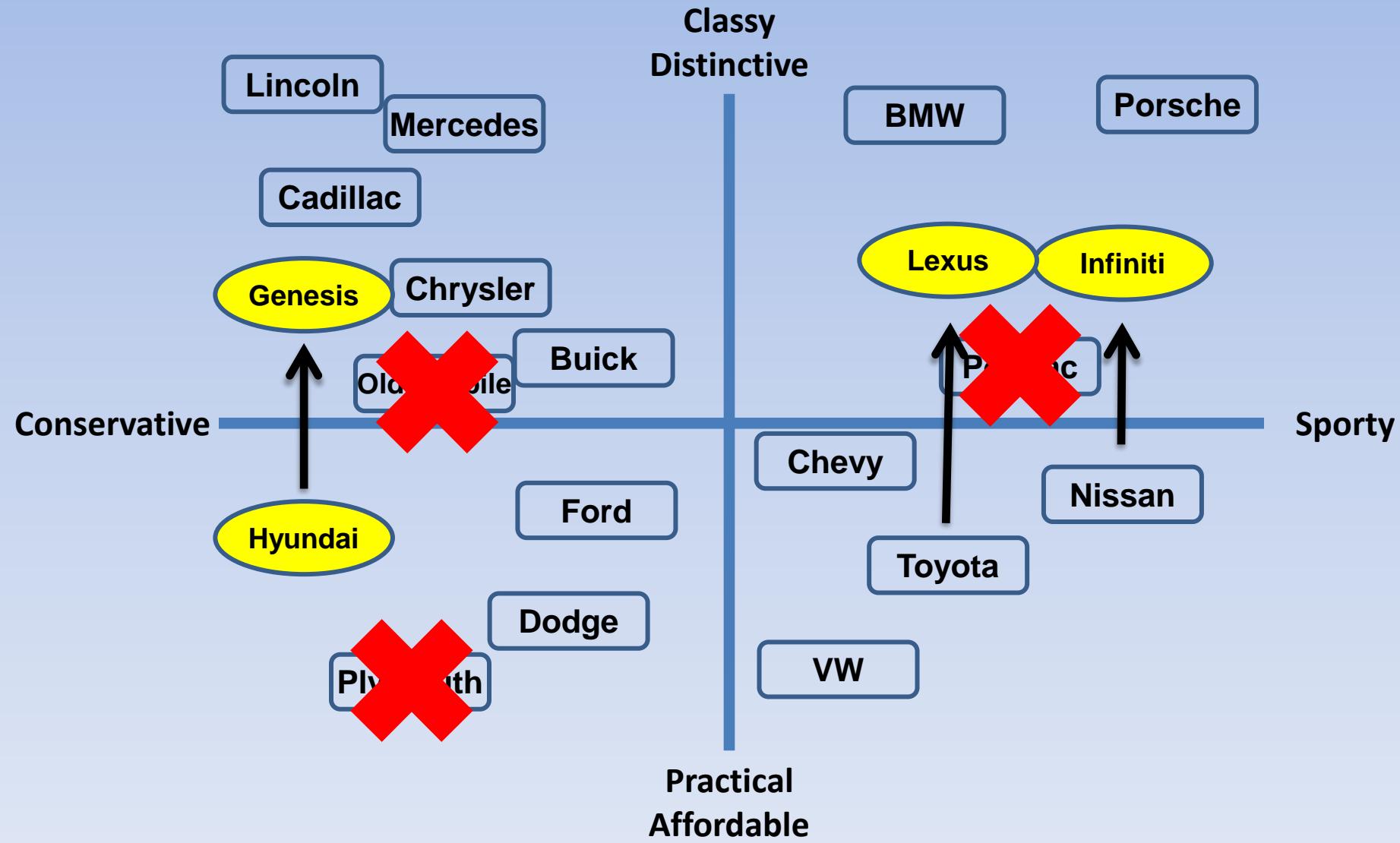
- Based on attributes valued by customers
- Relative to your competition
- Ideally a niche that is otherwise unoccupied in mind of customer
 - Improved performance vs. the competition
 - Similar performance vs. the competition, better price
 - Reshape the competitive landscape

Perceptual Map



Perceptual Map

US Automobile industry



Defining Your Optimal Position

Factors for consideration

Market factors

- Size / growth
- Life cycle
- Barriers to entry

Competitive factors

- Number and strength of competitors
- Unmet need
- Elasticity of pricing

Defining Your Optimal Position

Factors for consideration

Market factors

- Size / growth
- Life cycle
- Barriers to entry

Competitive factors

- Number and strength of competitors
- Unmet need
- Elasticity of pricing

Environmental / regulatory factors

- Approval process and timing
- Legal environment
- Technology change

Will likely require a Competitive Landscape and Market Research analyses

Marketing Levers

Product	Placement	Price	Promotion
Functionality	Channel members	List price	Message
Appearance	Channel motivation	Discounts	Personal selling
Quality	Market coverage	Allowances	Advertising
Packaging	Locations	Financing	Public Relations
Brand	Logistics	Leasing Options	Media
Warranty	Service levels		Geography
Service/Support			Budget

Pricing in the health Care Industry

Pricing drivers in health care have changed more in the past five years than in the previous 100 years. This trend will likely continue over the next three to five years.

- As individuals pay a higher portion of their health care costs there will be increased public awareness and outcry over healthcare costs
- There will be increased management and regulation of the marketplace
- Cost and treatment value may become part of the approval process
- True innovation will continue to allow for premium pricing

Components of Price

- Cost of production (fixed and variable)
- Cost of promotion
- Premiums & discounts (relative to competition)
- Standard vs. custom
- Profit required
- Industry margins

The ability to leverage efficient product development and promotion to create a price benefit in the market place can lead to competitive advantage.

Marketing Levers

Product	Placement	Price	Promotion
Functionality	Channel members	List price	Message
Appearance	Channel motivation	Discounts	Personal selling
Quality	Market coverage	Allowances	Advertising
Packaging	Locations	Financing	Public Relations
Brand	Logistics	Leasing Options	Media
Warranty	Service levels		Geography
Service/Support			Budget

Promotion

Critical Questions

- What are the key messages to communicate to your target audience?
- How will you reach your audience?

And sometimes:

- How do your competitors do their promotions?
- When is the best time to promote?
- Where can I best promote?

Marketing Message

A Definition

The overall theme that describes the features, advantages and benefits of your product or service

- Related to your target audience's perceptions of product attributes
- Denotes a communication regarding these attributes that is received and understood
- May start with a **SWOT** (**S**trengths, **W**eaknesses, **O**pportunities, **T**hreats), then ranked in priority order from many possibilities with the use of market research

Marketing Message Some Good Examples

“A 15 minute phone call could save you 15%”

Geico Insurance

“Your bags fly free.”

Southwest Airlines

“When you can’t, _____ can.”

Michael and Son Plumbing and Heating

And a bad one

“It’s not for women”

Dr Pepper Cherry

Reaching the Target Audience

Marketing Mix

- **Personal promotion**
 - Sales force (Internal or Outsourced)
 - Medical sciences
 - Managed marketing / trade
 - E-detailing
- **Media advertising**
 - Print (medical, lay press)
 - Direct mail
 - Patient-based literature
 - TV
 - Social media
- **Public relations**
 - Product guarantees
 - Indigent care programs

Marketing Mix

Additional Considerations

- **Competitive promotion**
 - “Watch your competitors, don’t copy them”
 - May set level of “voice” required or indicate strategy changes
- **The timing of promotion**
 - Seasonality
- **Geography**
 - Regulatory environment
 - Differences in disease incidence

The Launch of Gleevec in the US

May 2001

- 1. Market landscape**
- 2. Gleevec general description**
- 3. SWOT analysis**
- 4. Prioritizing the P's**
- 5. Promotional strategy**

Ph⁺ CML and Treatment in 2001

The overall incidence for CML in the US was approximately 1.5 / 100K (approx. 400,000) and rising very slightly. 5000 new diagnoses / year

The standard of care was interferon-alpha (Roferon, Roche and Intron A, Shering Plough), sometimes in combination with Cytarabine (various manf.)

- Route of administration: IV
- Response rate @ 1 year: 15 – 20% (CCR, Complete cytogenic response)
- Side effects: Flu-like symptoms , leukocytopenia, thrombocytopenia, anemia

Compounds in development

- Dasatinib (Sprycel, BristolMyersSquibb) FDA approval: June 2006
- Nilotinib (Tasigna, Novartis) FDA approval: October 2007
- Ponatinib (Iclusig, ARIAD) FDA approval: December 2012

The routes of administration for the bulk of all cancer treatments at this time were injections or infusions

Gleevec (Imatinib)

- Tyrosine kinase inhibitor (TKI)
- First “rationally designed targeted therapy”
- NDA submitted December 2000, Original FDA approval for Ph+ CML in May 2001
- Oral formulation, 100 mg and 400 mg scored tablets
- Daily dose: 400 mg QD, up to 800 mg / day on a BID schedule
- Efficacy:

PIII trials	Complete hematologic,	95.3% vs. 55.5%
	Major cytogenetic,	85.2% vs. 22.1%
- Dose response: PI trials

Daily dose 400mg – 800mg	65% (22 / 34)
All other doses	45% (9 / 20)
- Most common side effects*:
 - Fluid retention, Muscle cramps, pain, or bone pain, Abdominal pain, Anorexia, Vomiting, Diarrhea, Decreased hemoglobin, Hemorrhage, Nausea, Fatigue, Rash

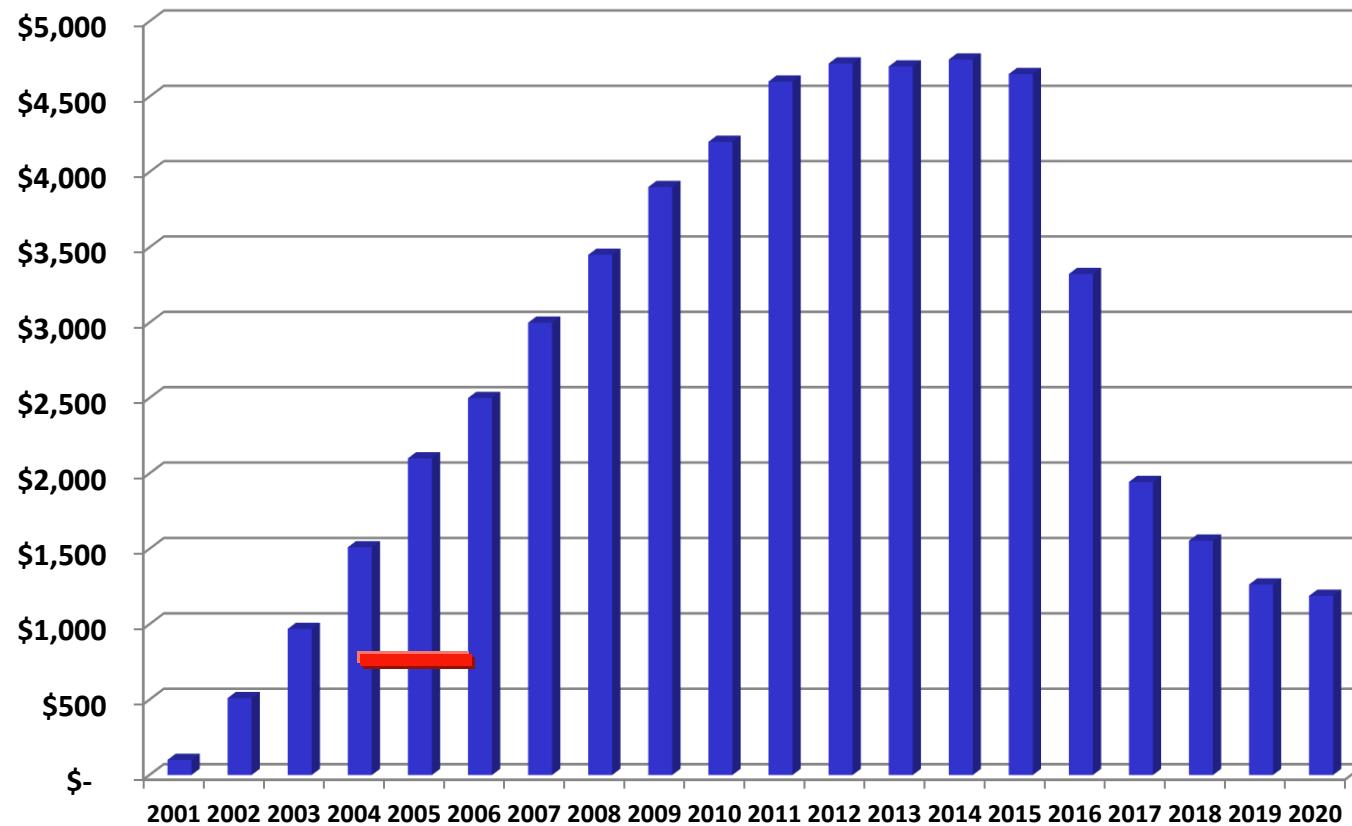
* “Almost all patients treated with GLEEVEC experience side effects at some time” - Gleevec patient information

Gleevec

Gleevec / Glivec Worldwide Sales

2001 - 2020

Million USD



— 2001 Industry analyst projections for 2005

Gleevec

Product Life Cycle Management

- The first generic Imatinib entered the market in Europe, November 2012
- The US marketing exclusivity received an extension from May 2013 to January 2015
- What happens?

A product loses approximately 90% of its revenues within 12 months of the first generic competitor

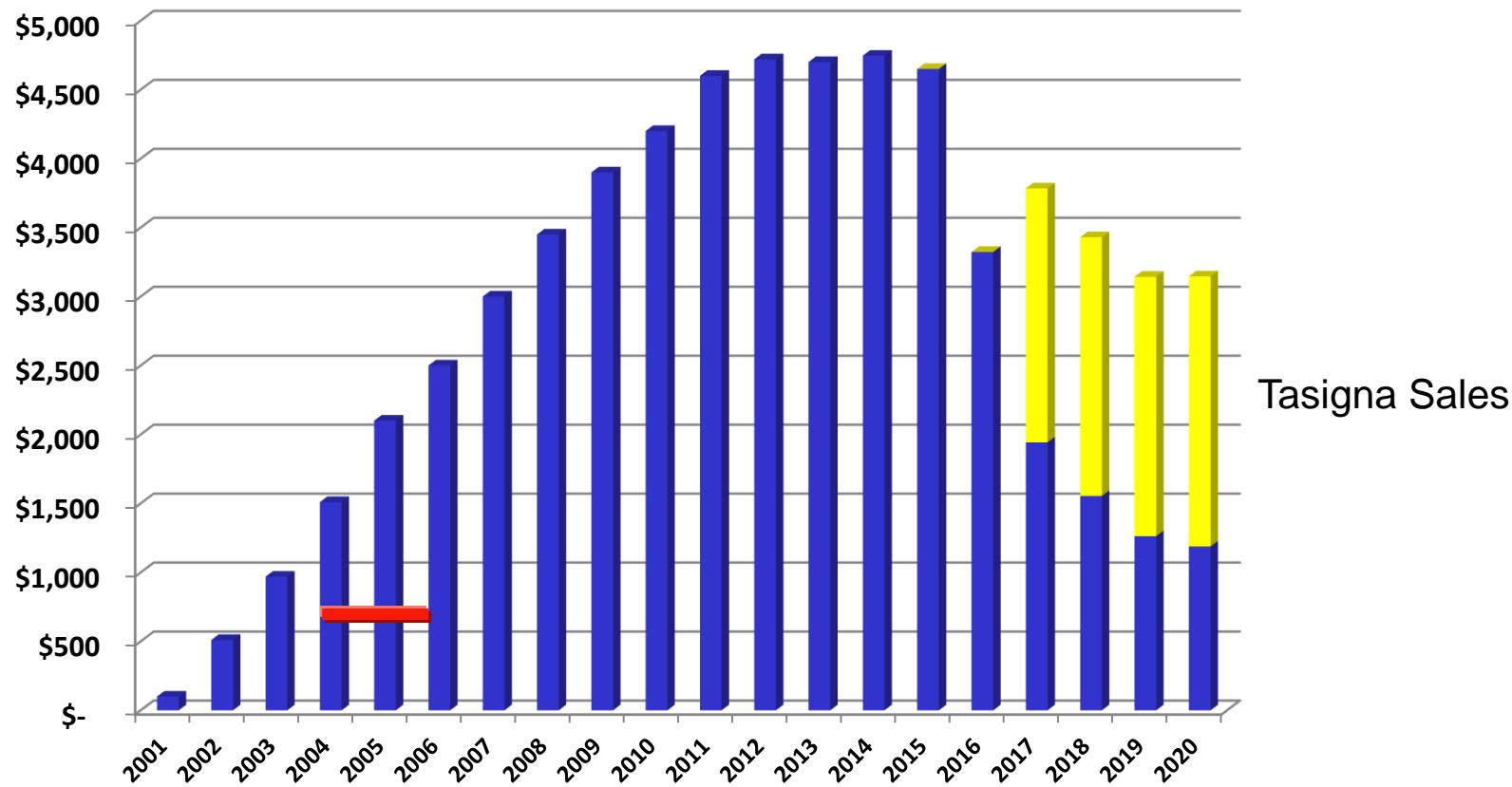
Life Cycle Management Strategies

- Pediatric indication
- Indications / usage extensions
- Pricing / Rebating programs
- Follow-on compound

Gleevec / Glivec Worldwide Sales

2001 - 2020

Million USD



— 2001 Industry analyst projections for 2005

Gleevec