Understanding the disease, need, target population, and market

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Foundations in Cancer Therapeutics: Commercialization
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Goal of biotech entrepreneurship

Goal of biotech entrepreneurship

- eventually market a safe product to treat or cure disease

So,

- what is the “pain”?
- is there a market for mitigating pain?
- is the project relevant?

Early steps (before beginning project)

Relevance

- competition
- market
- industry interest
- funding possibilities (will eventually need industry/govt support for clinical trials)

Target product profile (i.e., what will the drug label say?)

- route of administration (e.g., oral, IV, topical, etc.)
- storage conditions (e.g., heat stable, refrigerate, etc.)
- dosage (e.g., chronic, prophylaxis, short window, etc.)
- price (e.g., what is the target demographic?)

Development path

- early pivotal derisking studies
- target & mechanistic validations
- cell culture systems
- animal model(s)
- clinical trial network

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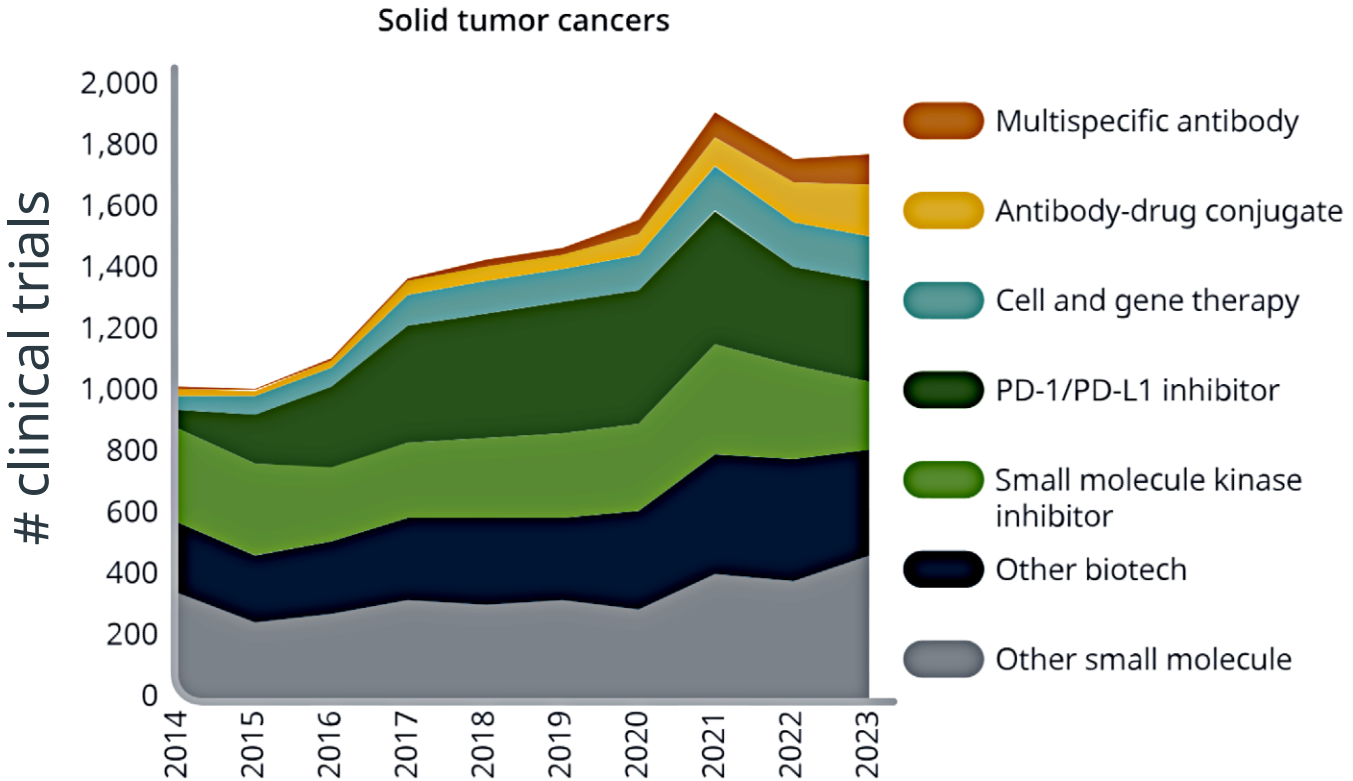
Competition

- cancer incidence is expected to rise significantly, particularly in lower-income countries
- annual new cases going from 20M (2021) to 32M (2050)
- ~2,000 new oncology clinical trials started in 2023 with novel modalities (e.g., cell & gene therapies, antibody-drug conjugates, multispecific antibodies, radioligands)
- cancer treatments have increased 9% annually since 2019



Source: Global Oncology Trends 2024: Outlook to 2028. IQVIA Institute for Human Data Science, May 2024

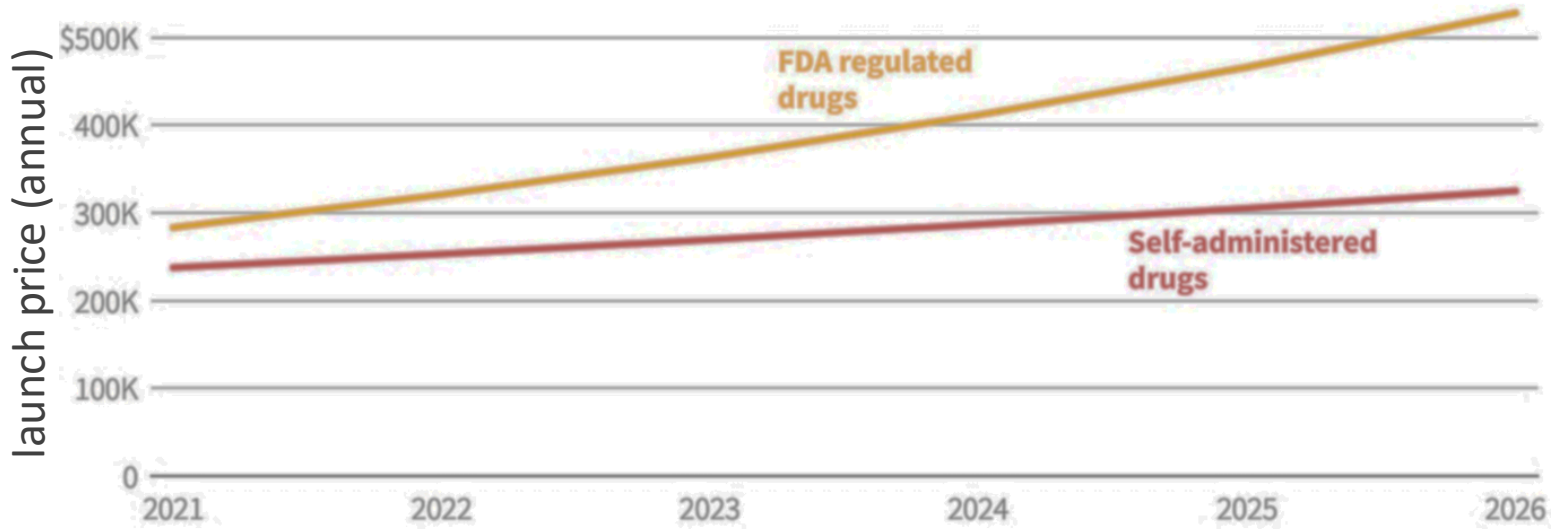
Market analysis – how hard can it be?

Market analysis

Quick & dirty market analysis is **almost always wrong**

Cancer drug costs will impact market size

- cancer is the second leading cause of death in the United States
- cancer treatments ~4x as costly as other therapies
- newly-launched cancer drug averages $283,000 (US, 2021)
- Medicare is required to cover all cancer medications
- Inflation Reduction Act impacts price of existing drugs, not launch prices



- in 2017, the most expensive new cancer tablet was Idhifa at $298,465/yr (to treat subset of leukemia patients). Study of Idhifa (2020) failed to show improved survival compared to standard care.

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Source: Office of Us Rep. Porter; Reuters, Nov 2, 2022

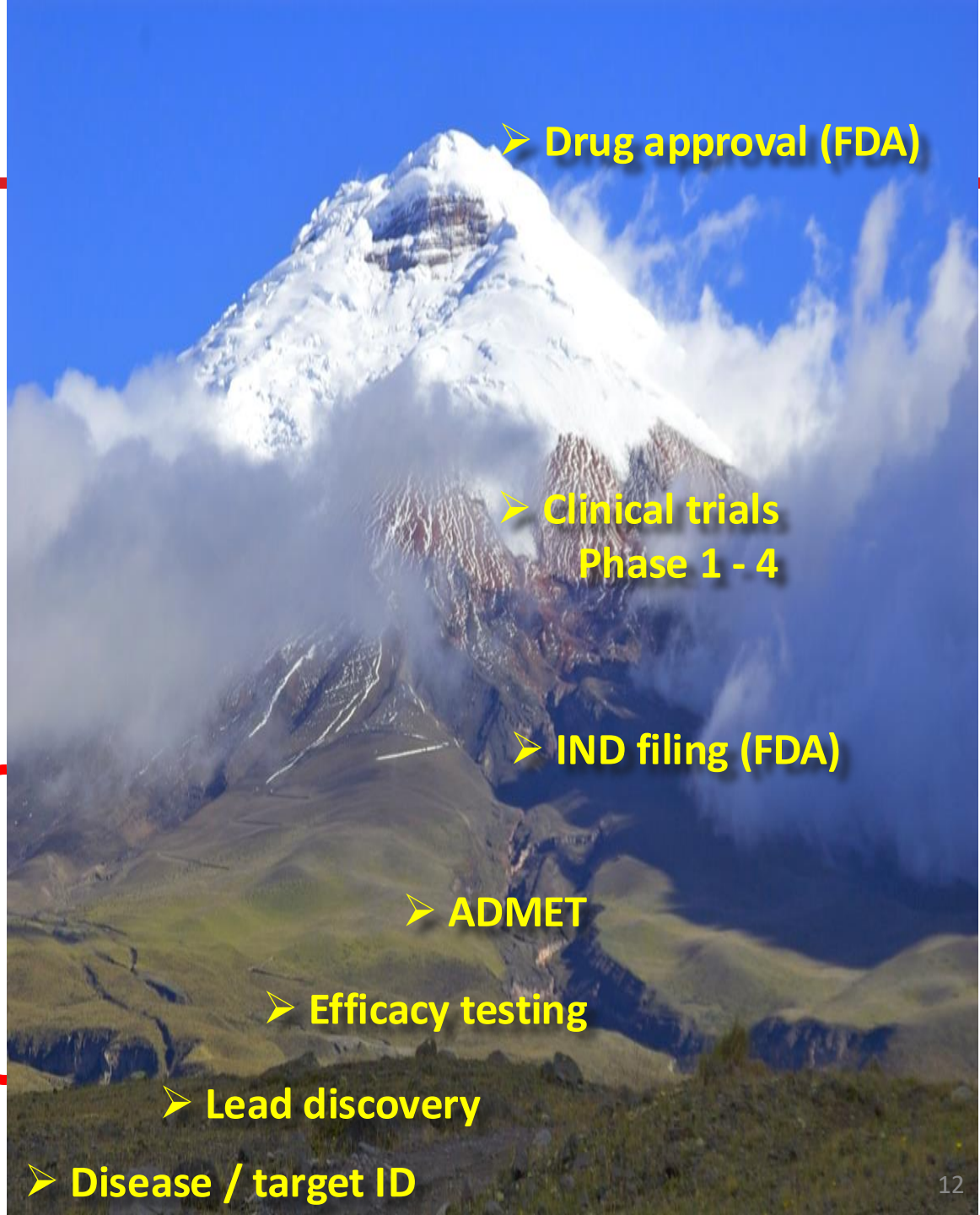
Market analysis - talk to the “customer”

Market analysis - talk to the “customer”

- for academic researcher, your “market” is pharma

Drug commercialization

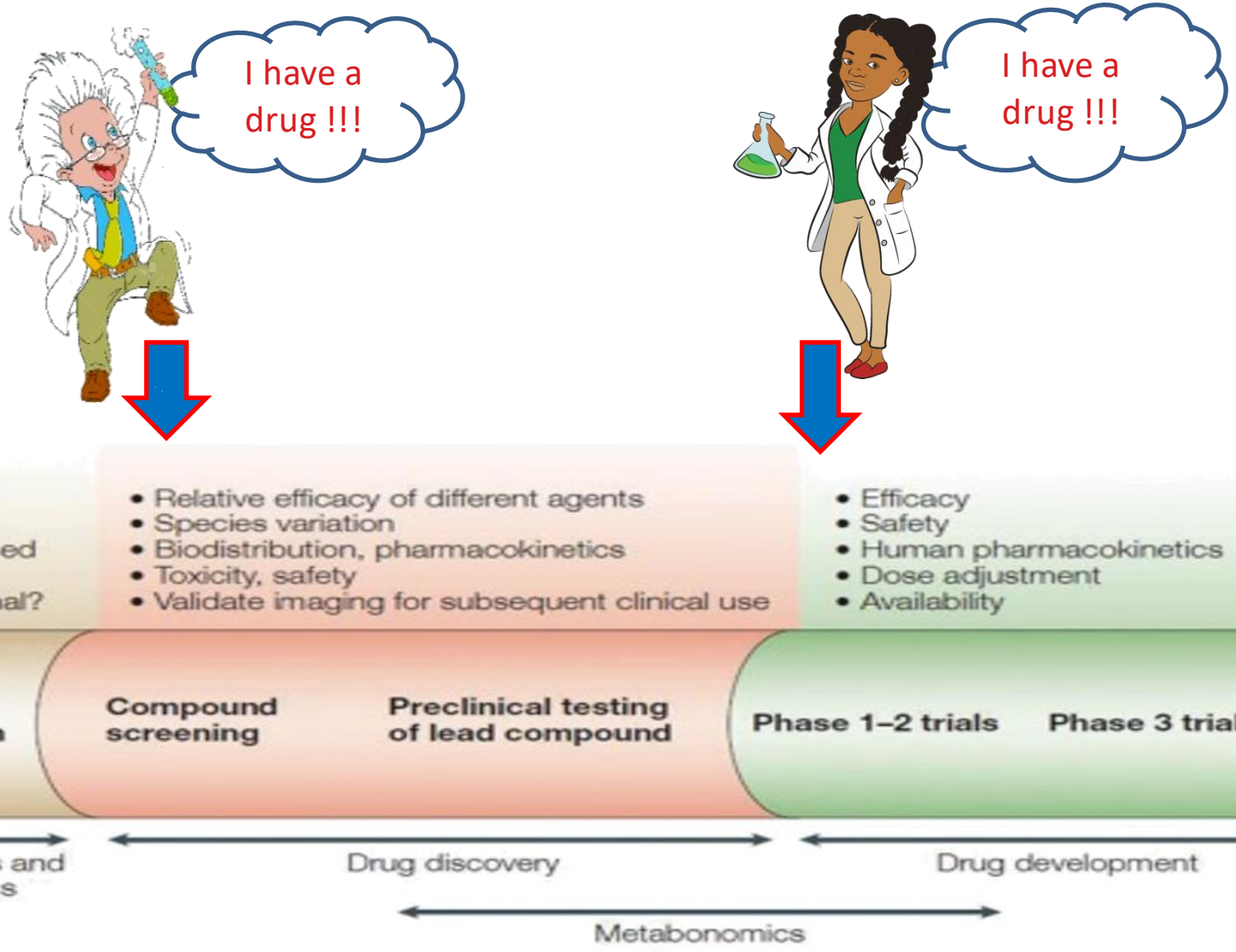
- process is very challenging
- requires dedication & perseverance
- efficacy & ADMET can occur in parallel
- clinical trials are sequential



Sample Target Product Profile (ex. Chagas disease)

	Acceptable	Ideal
Target label	Chronic Indeterminate CD	Chronic Indeterminate + Reactivations (Immunocompromised)
Spp.	TcI+TcII	TcI+TcII
Distribution	All areas	All areas
Target population	Immunocompetent	Immunocompetent + immunocompromised
Adult/children	Adult	All
Clinical efficacy	Superiority over benznidazole in all endemic regions (parasitological)	70% (parasitological and serological) > 95% cure for reactivated patients (parasitological and serological)
Resistance	Active against nitrofuran- and nitroimidazole-resistant T. cruzi strains	Active against nitrofuran- and nitroimidazole-resistant T. cruzi strains
Safety	Superiority to benznidazole 3 Clinical Evaluation plus 2 standard Laboratory Evaluation during treatment	Superiority to benznidazole No Clinical Evaluation or Laboratory Evaluation needed during treatment
Contraindications	Pregnancy/lactation	None
Precautions	No genotoxicity; No prolongation of QTc interval	No genotoxicity; No teratogenicity; No negative inotropic effect; No prolongation of QTc interval
Interactions	No clinically significant interaction with anti-hypertensive, anti-arrythmic and anticoagulants drugs	None
Presentation	Oral	Oral
Stability	3 years, climatic zone IV	5 years, climatic zone IV
Dosing regime	Comparable to systemic antifungal treatments	b.i.d./60 days

Do you have a drug?



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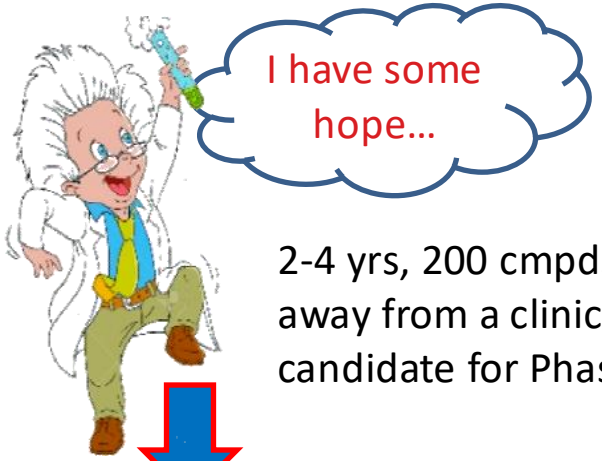
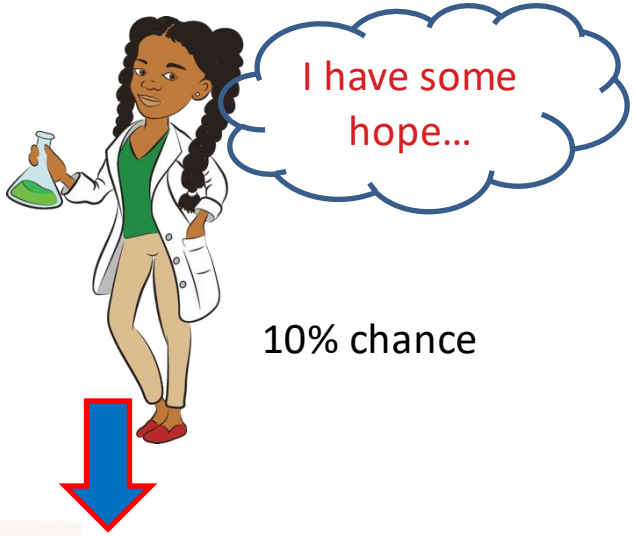
Slide adapted from Duxin Sun, Univ Michigan

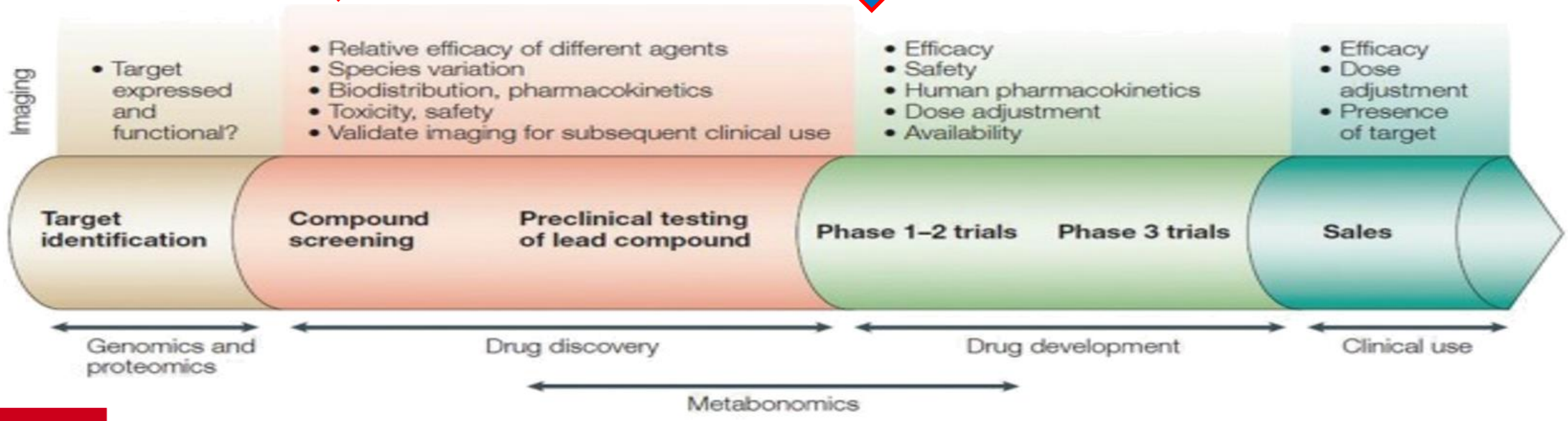
Doubtful you have a drug



2-4 yrs, 200 cmpds, $3-10M away from a clinical candidate for Phase I trial



10% chance



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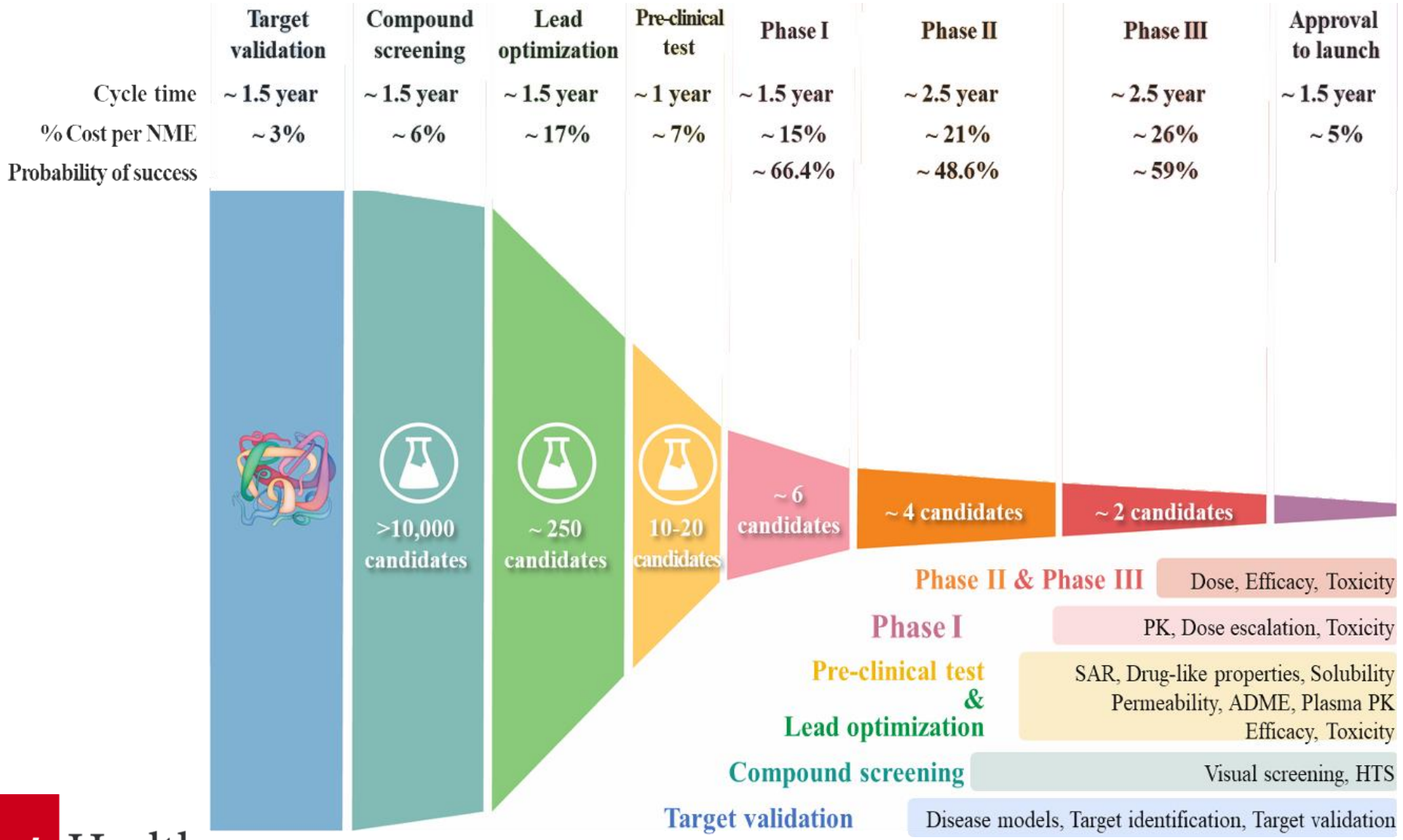
Drug development process & risks



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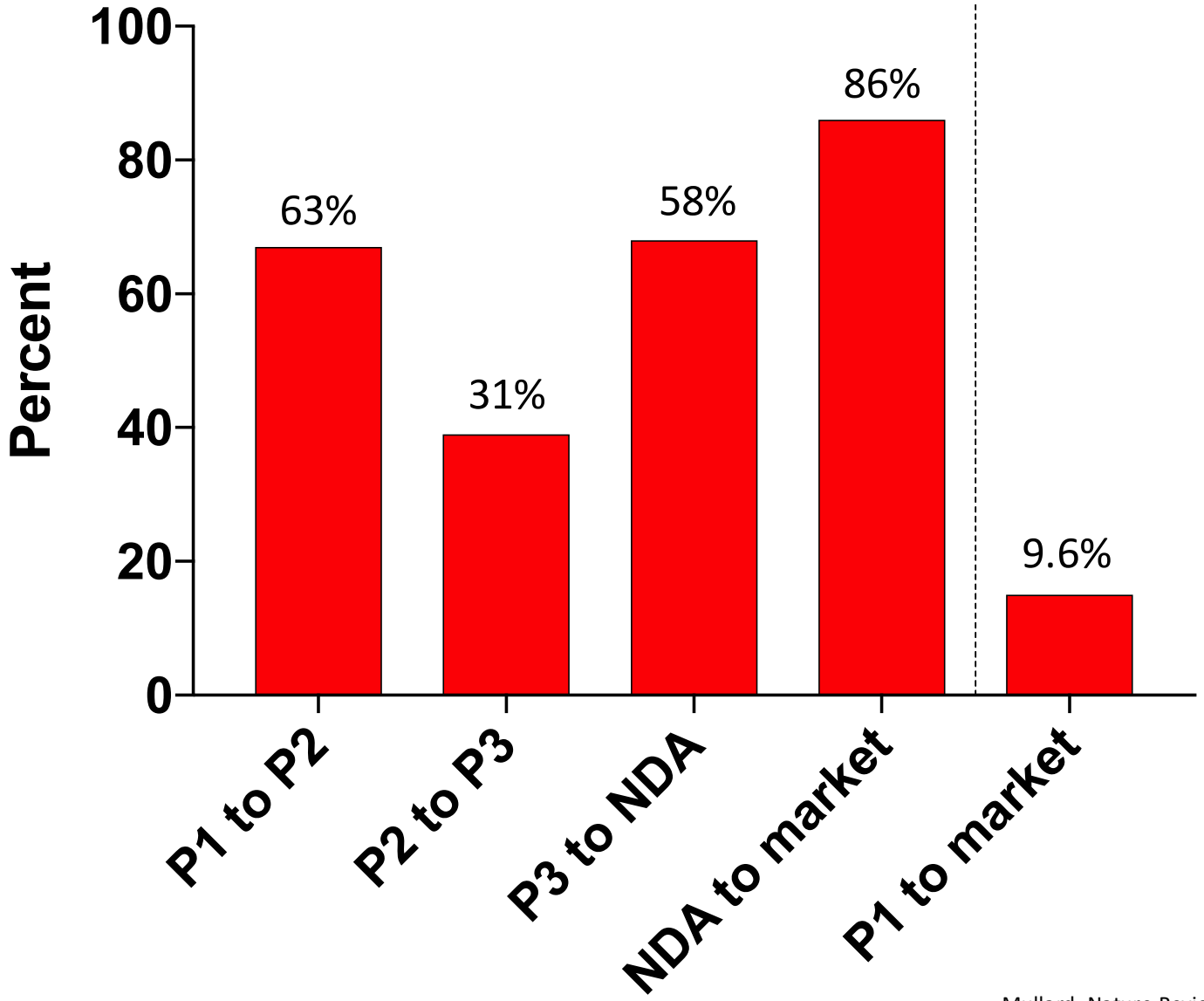
Clinical trial success rates

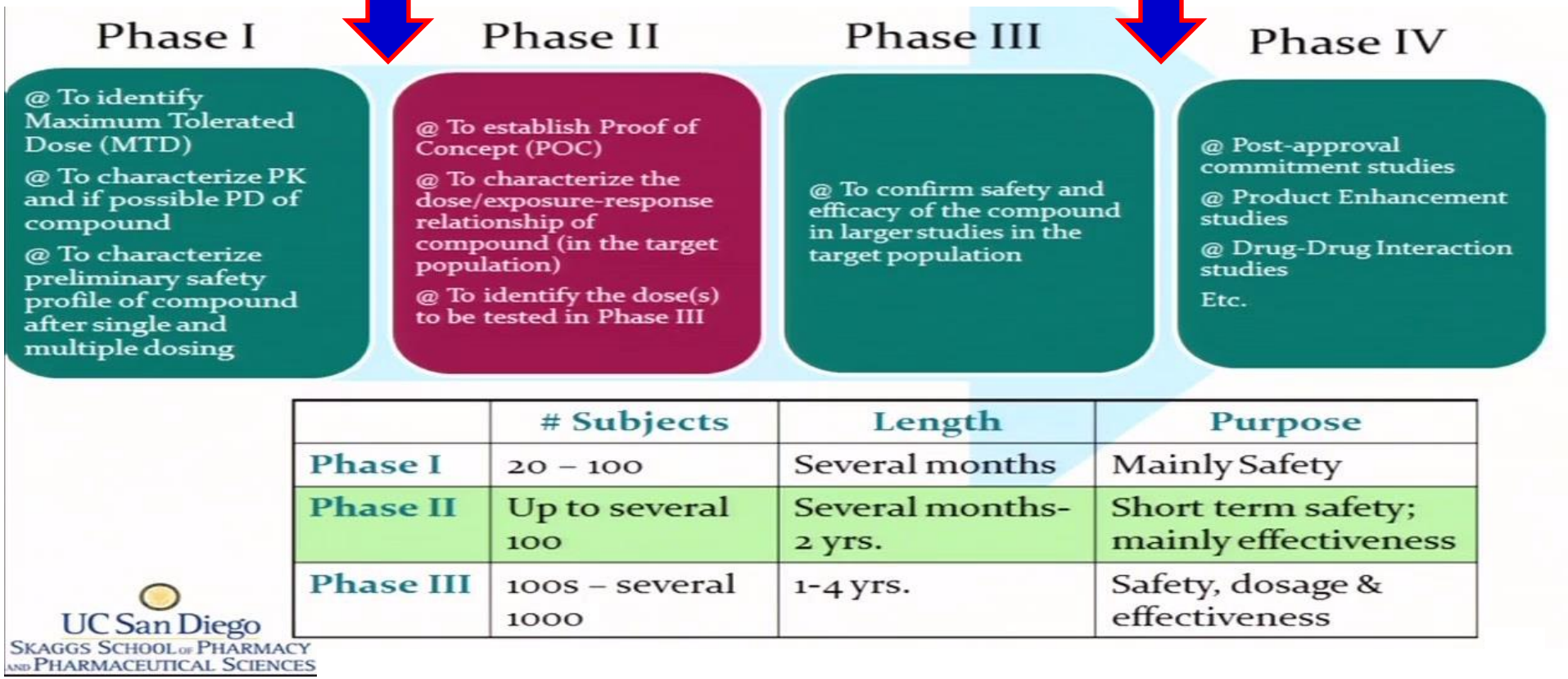


Mullard, Nature Reviews of Drug Discovery, 2016

Clinical studies of a drug candidate (90% failure rate)

Randomized, double-blind, placebo-controlled, multi-center

NDA



	# Subjects	Length	Purpose
Phase I	20 – 100	Several months	Mainly Safety
Phase II	Up to several 100	Several months-2 yrs.	Short term safety; mainly effectiveness
Phase III	100s – several 1000	1-4 yrs.	Safety, dosage & effectiveness

UC San Diego
Skaggs School of Pharmacy and Pharmaceutical Sciences

Success of Phase I: 60%; Phase II: 30-40%; Phase III: 50-60%; Overall: ~10%

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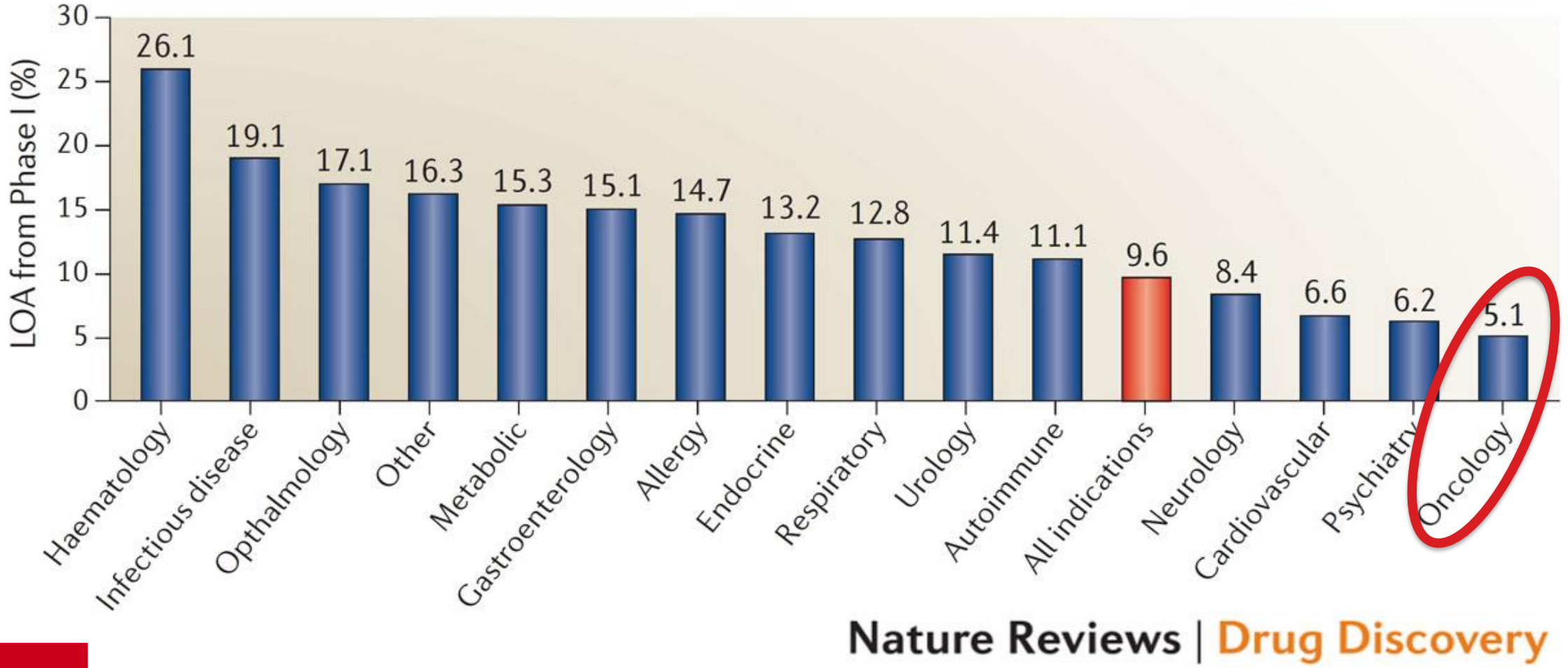
https://www.youtube.com/watch?v=66vK4Sfda9o

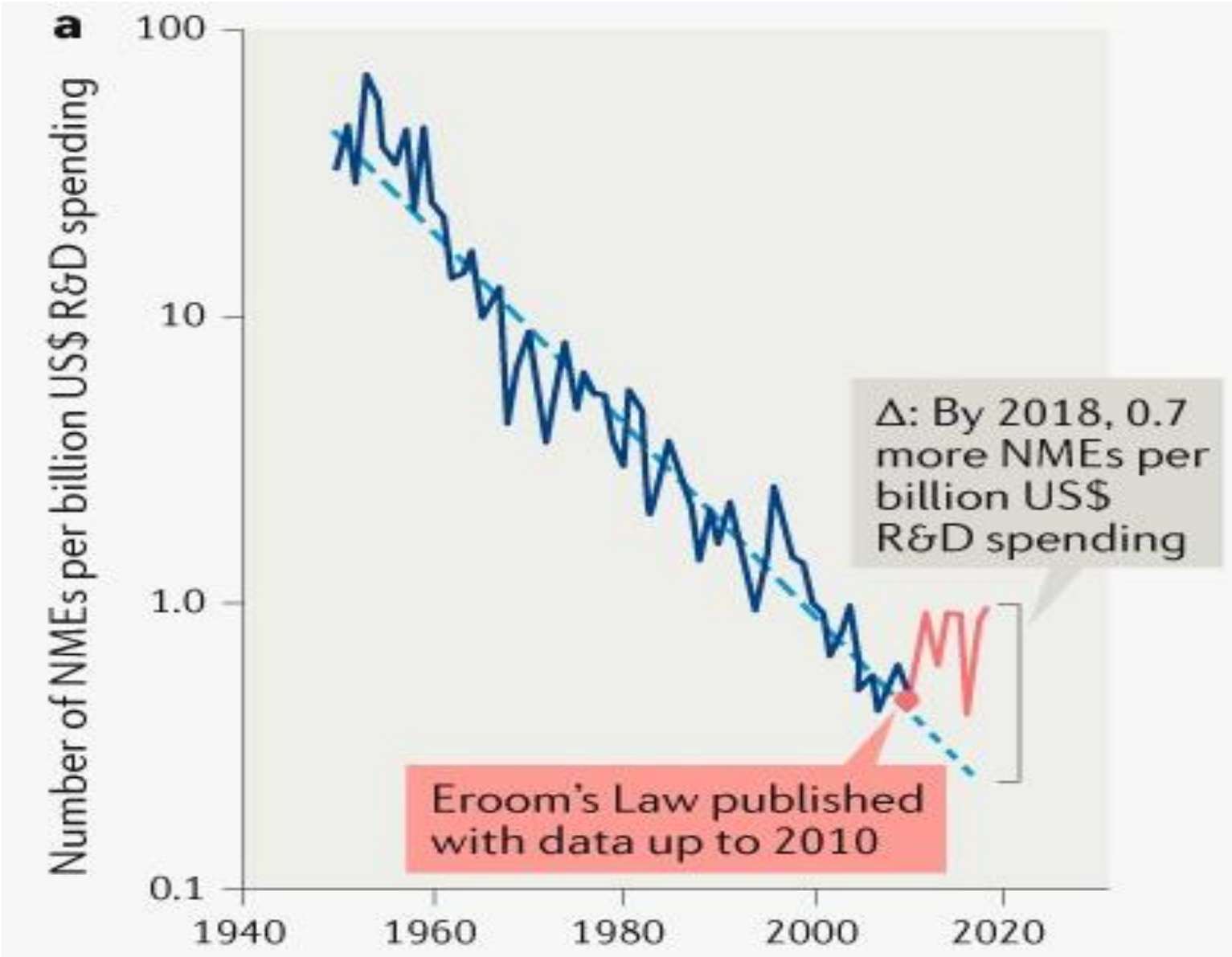
Clinical trial success, by indication

- only 10% of clinical drug development succeeds from Phase I to approval



Drug development is expensive

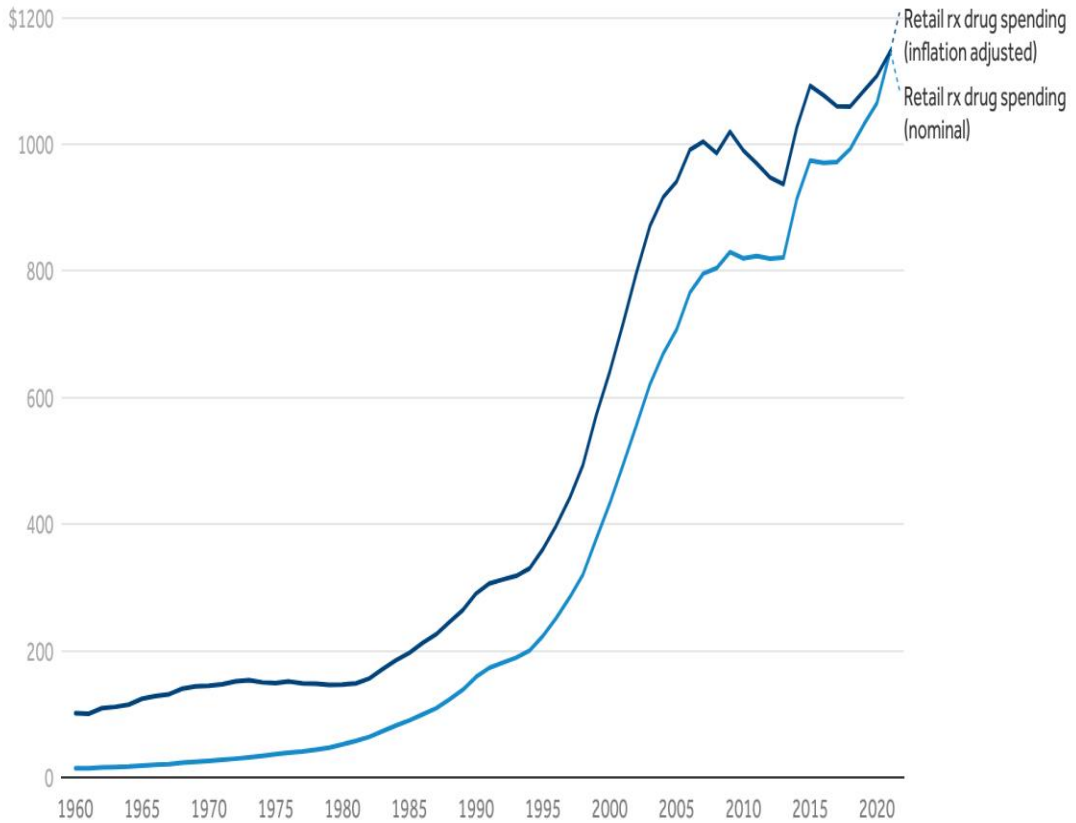
- Eroom's "Law" updated
- ~$1B per new drug

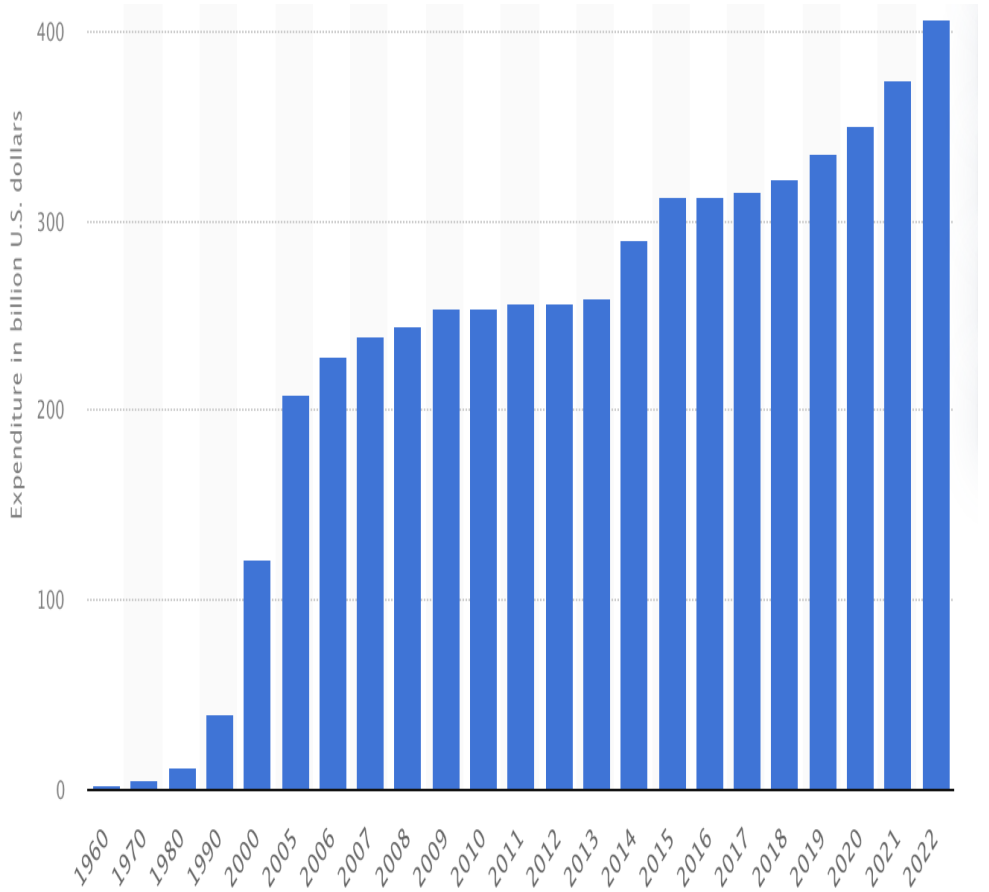


Lengthy, high-risk, expensive … why do it?

Lengthy, high-risk, expensive … why do it?

- US prescription drug spending $1147/person (2021)
- total US spending on pharmaceuticals ~$400B (2021)
- small molecule drugs totaled >$300B





Statista; KFF analysis of National Health Expenditures Accounts

Oncology drugs are largest Rx drug sector

- U.S. spending on oncology was $65B in 2019, increased to $99B in 2023
- U.S. spending on oncology drugs expected to reach $180B in 2028

- global spending on cancer therapies was $223B in 2023; projected to reach $409B in 2028
- US accounts for 45% of global spending

Potential reasons for clinical trial high failure rates

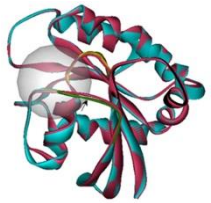
Target validation incomplete or misread

- Is the molecular target the cause of human disease?
- Is the molecular target the drug's actual target?

Unbalanced drug optimization process

- Misleading drug candidate selection
- Incorrect balance of clinical dose, efficacy, & safety

Is the molecular target the root cause of disease?



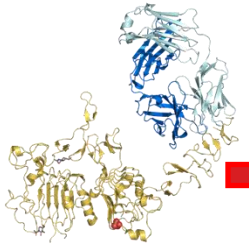
https://www.spandidos-publications.com/10.3892/ol.2019.10325

K-Ras G12D

https://www.express.co.uk/lifestyle/health/1515934/pancreatic-cancer-symptoms-top-ten-signs-evg

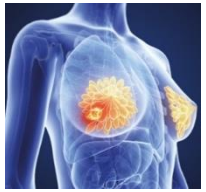
Pancreatic Cancer (PDAC)

(90% PDAC has Kras mutation,
36% PDAC has G12D)



https://en.wikipedia.org/wiki/HER2/neu

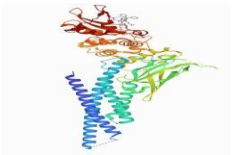
HER2



https://www.wcrf.org/just-one-alcoholic-drink-a-day-increases-breast-cancer-risk/

Breast Cancer

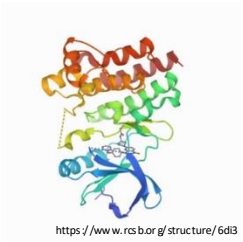
(15% BC is Her+)



https://www.rcsb.org/structure/6NJS

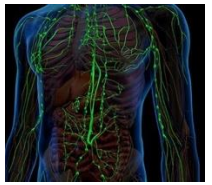
STAT3

Disease?



https://www.rcsb.org/structure/6dl3

Bruton tyrosine kinase (BTK)

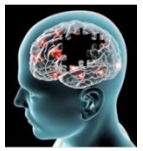


https://www.medicinenet.com/mantle_cell_lymphoma_md/article.htm

Mantle Cell Lymphoma (MCL)

% of MCL is BTK dependent?

Molecular Target?



Alzheimer's Disease

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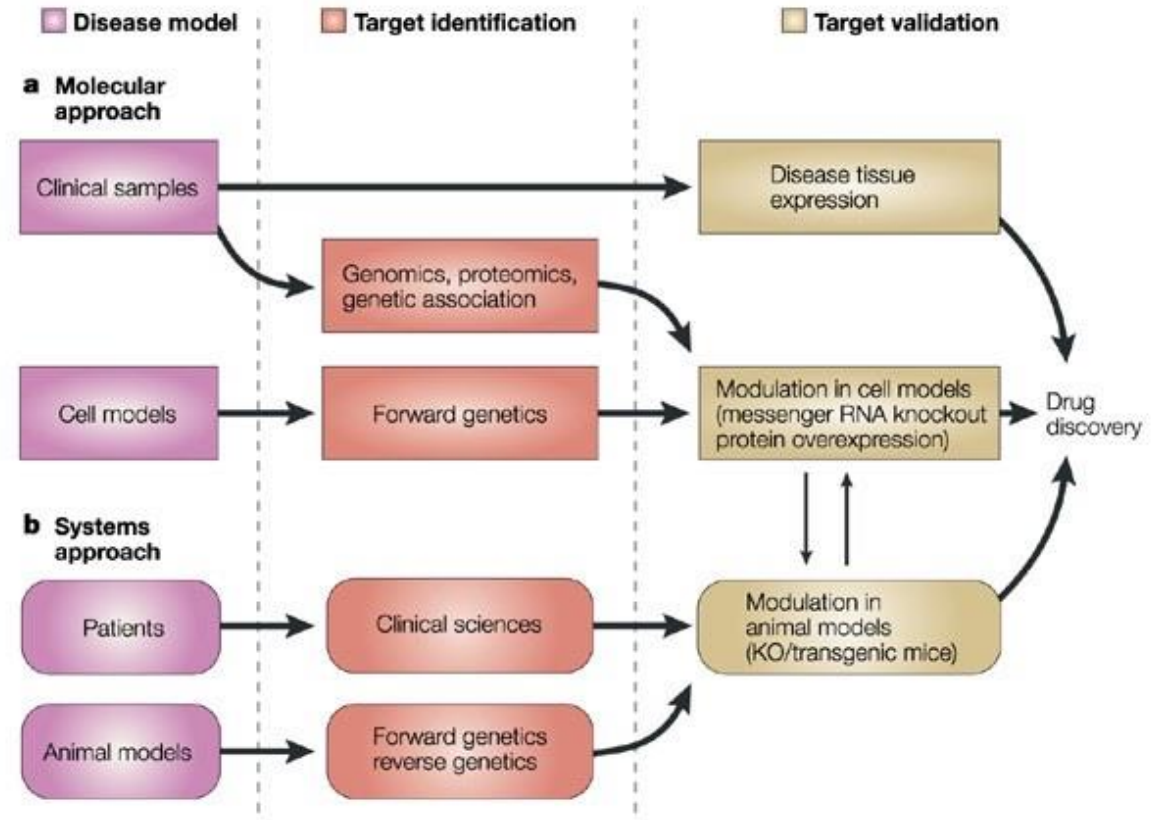
Slide adapted from Duxin Sun, Univ Michigan

Rigorously validate the putative disease target

- Is the target the cause of the human disease?
- What is target expression pattern in patients?
- Is target manipulation (mutation, knockout, expression) clinically relevant?
- Is the stimulus to activate target-dependent processes disease-relevant?
- Are the animal models relevant to human disease?

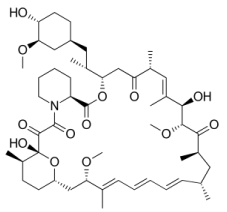


Emmerich, et al. Nature Reviews of Drug Discovery, 2020

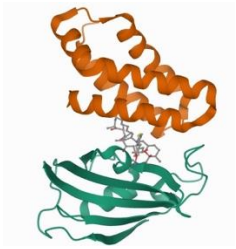
Slide adapted from Duxin Sun, Univ Michigan

Does drug modulation of the target give expected effect

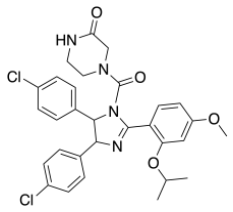
- FKBP12 inhibitor (rapamycin) and MDM2 inhibitor (nutlin-3a) inhibit cancer cell growth
- target-dependent using CRISPR-knockout cells



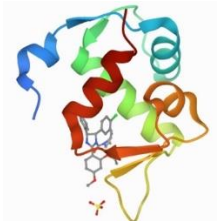
Rapamycin



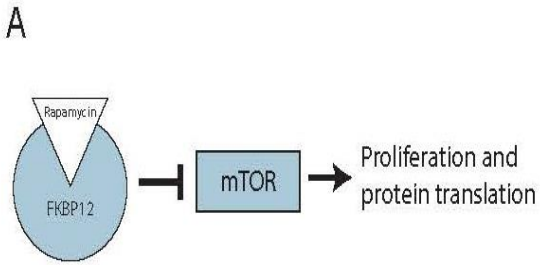
FKBP12

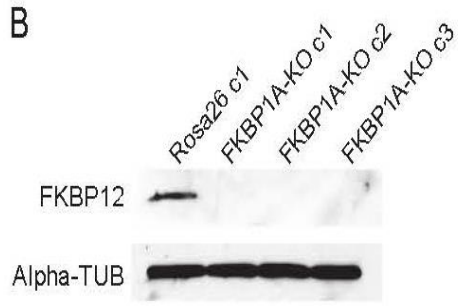


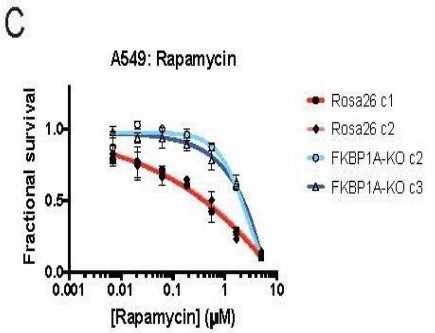
Nutlin-3a

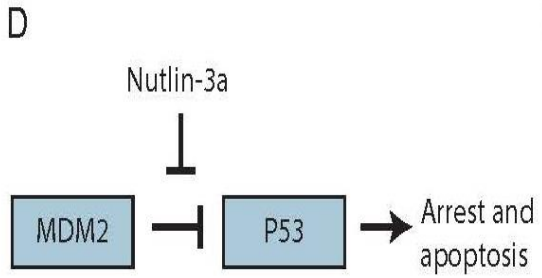


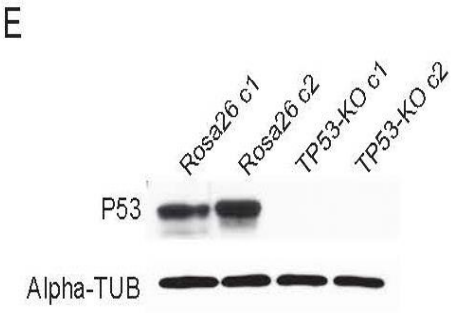
MDM2
(human homolog of murine double minute 2)

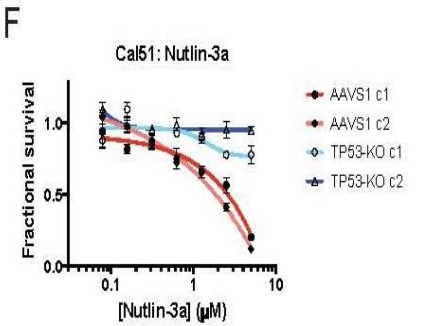






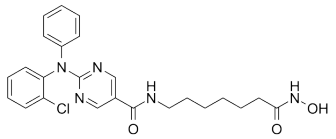




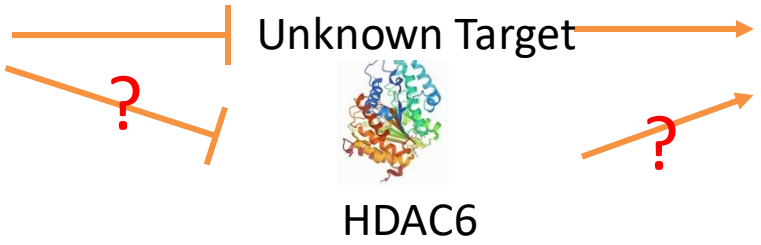


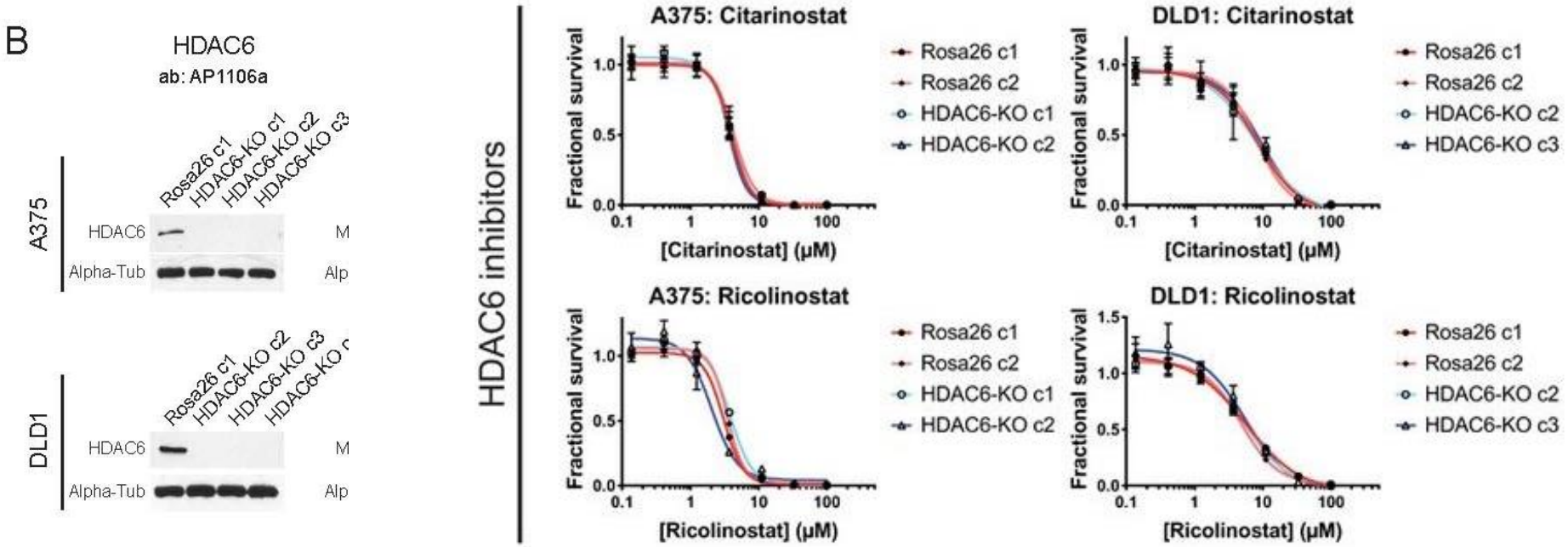
Does drug modulation of the target give expected effect

- HDAC6 inhibitor (Citarinostat, in clinical trial) inhibits cancer cell growth with/without HDAC6 using CRISPR-knockout cells



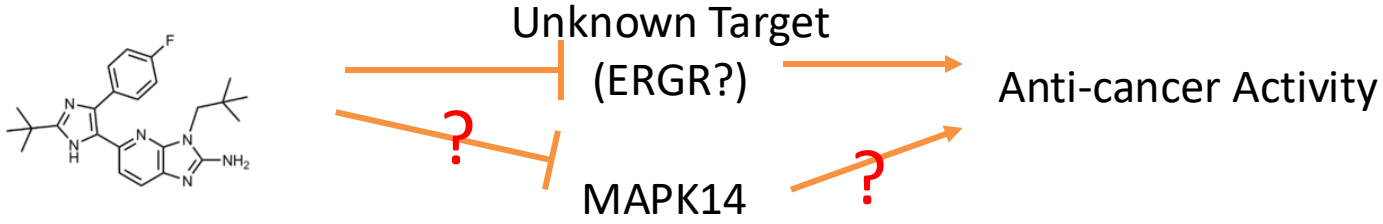
Citarinostat



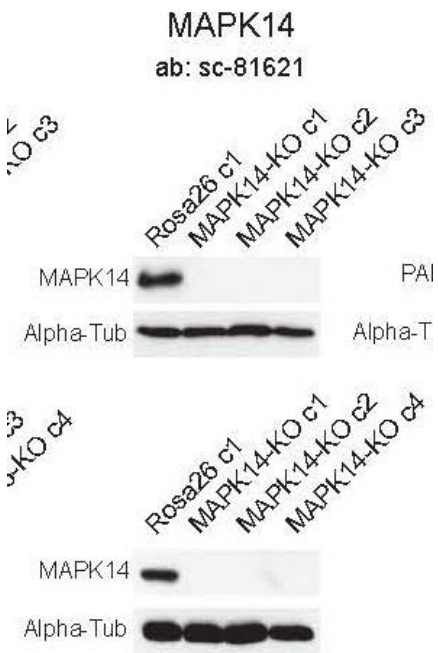


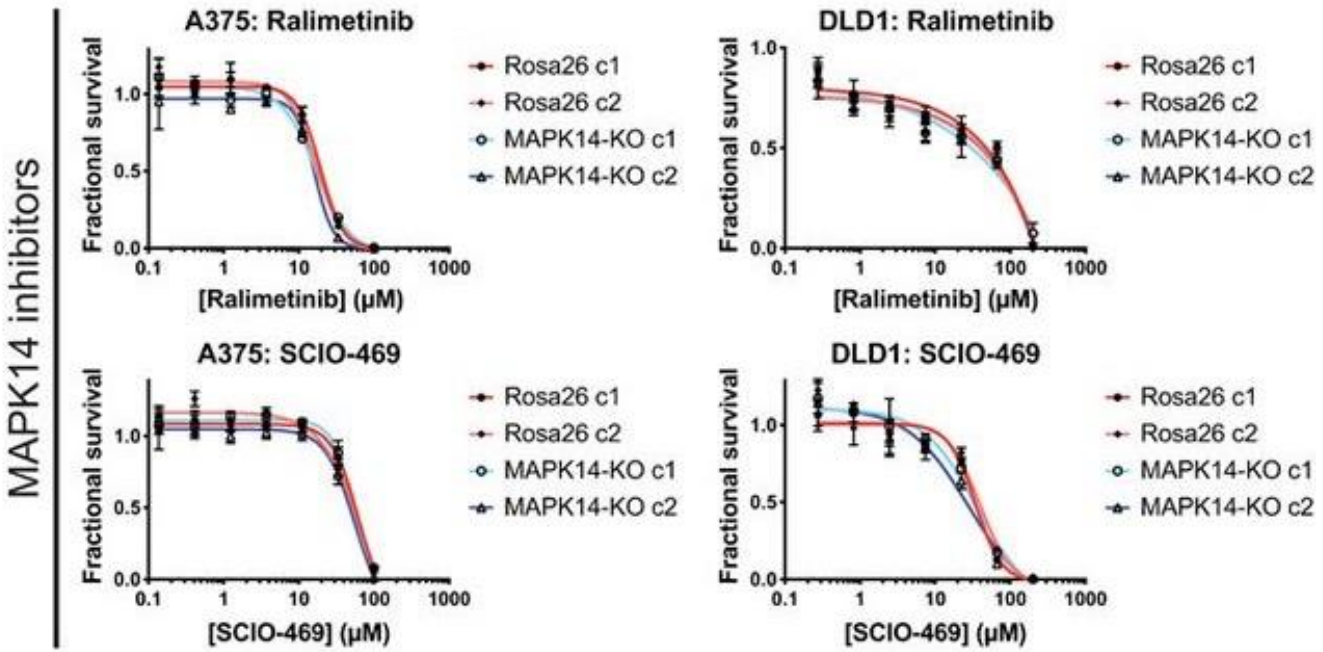
Does drug modulation of the target give expected effect

- MAPK14 inhibitor (ralimetinib, Eli Lilly, in clinical trial) inhibits cancer cell growth with/without MAPK14 using CRISPR-knockout cells
- modest to little improvement in Phase 1b/2 study



Ralimetinib





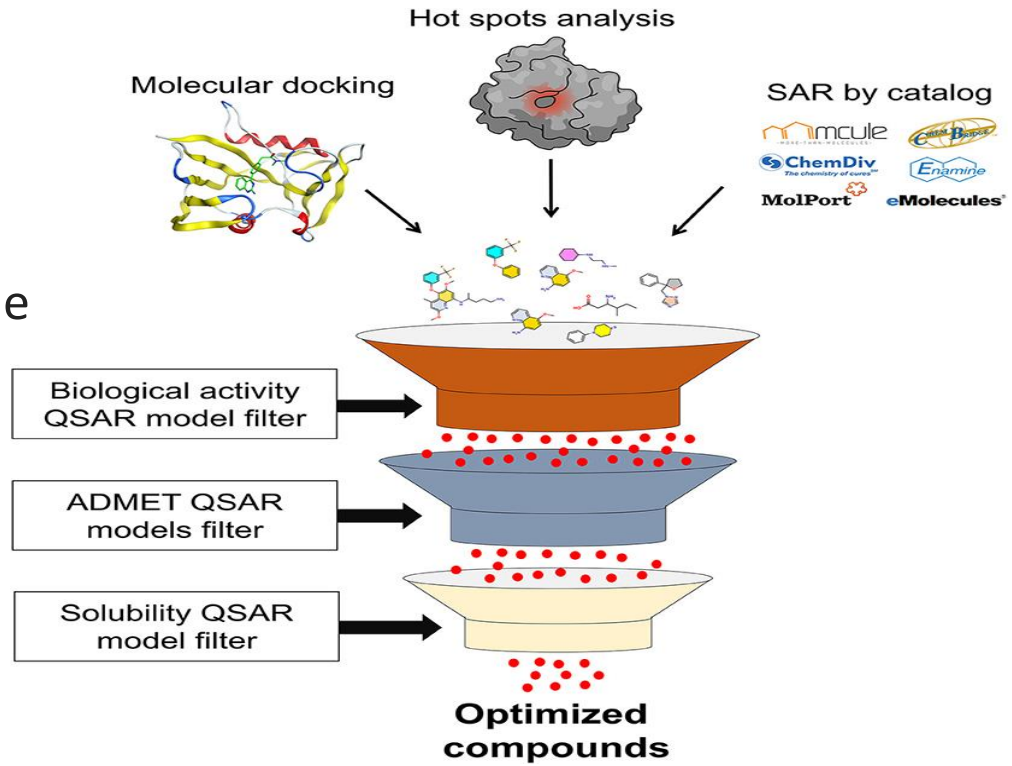
Lin, et al. Science Translational Medicine, 2019, 11

Slide adapted from Duxin Sun, Univ Michigan

Unbalanced drug candidate “optimization”

Emphasizes one aspect at the expense of others: potency vs. specificity vs. ADMET

- structure or AI-based “rationale” drug design
- IC50 and Ki in cell-free protein and cell-based assays (nM)
- interpretable structure–activity relationship (SAR)
- cross-validating the results using different assays
- compound binds to the target by crystal structure
- inactive or low-potency analogues as controls
- compound modulation of the target, and explainable downstream events?
- main off-target effects?



Dahlin, Nature Reviews of Drug Discovery, 2015

Jumper, et al. Nature volume 596, pages 583–589 (2021)

Slide adapted from Duxin Sun, Univ Michigan

Clinical trial failures

These two aspects are inter-dependent and DOSE-dependent

Lack of Efficacy (40-50%)

- does not mean that the drug did not work
- it worked in animal model
- biological difference between animal and human disease?
- if higher dose, the drug would work
- but high dose would cause toxicity in vital organs (not in animal, but in human)

Toxicity (30%)

- if lower dose, the drug would not show toxicity
- but lower dose would have no efficacy
- increased dose causes toxicity in vital organs before any efficacy in disease organs

"Optimized" clinical candidate

- high potency/specificity inhibiting target without off-target effect
- high drug exposure in disease organs for efficacy at clinical dose (ideally even at low dose)
- minimal drug exposure in vital organs to avoid toxicity at clinical dose (ideally even at high dose)