Sustainability in drug development

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Planetary Health

How we define sustainability in drug development?

Sustainable development is a development that meets the needs of the present without compromising the ability of the future generation to meet their own needs

Human population is aging ⟶ More medicine available

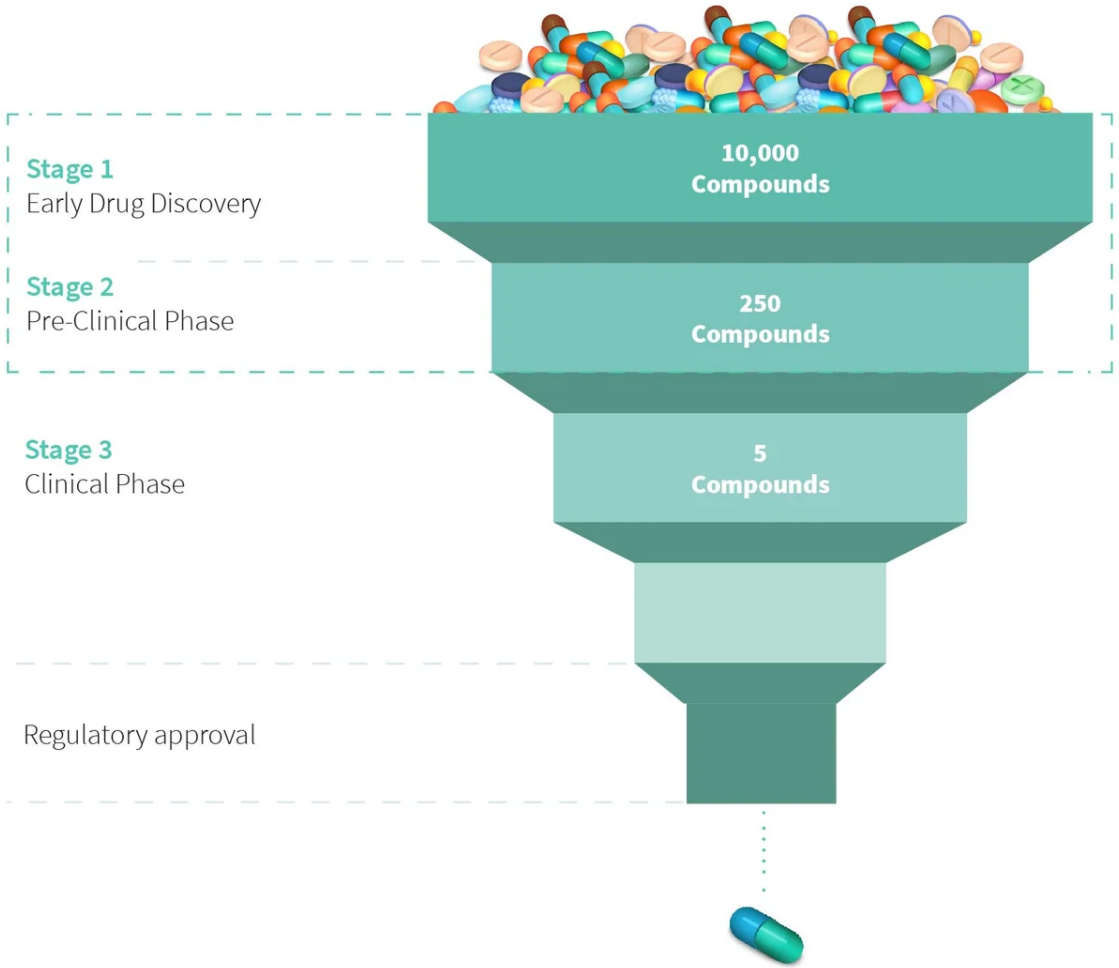
10 principle of sustainability in drug development

Table 1
Ten principles of sustainability applicable in drug discovery.

1	Ecological-environmental impact (benign-by-design)
2	Medical needs
3	Green chemistry
4	Artificial intelligence and big data
5	Root cause of illness
6	Risk and decision-taking models
7	Biomarkers and bioinformatics to support precision medicine
8	Cost-effective
9	Lean discovery process
10	Responsible research and innovation

Wynendaele et al. 2021

What is the process of drug development?



How long does it take to complete this process?

Which steps are done in the lab and which one in pharmaceutical companies?

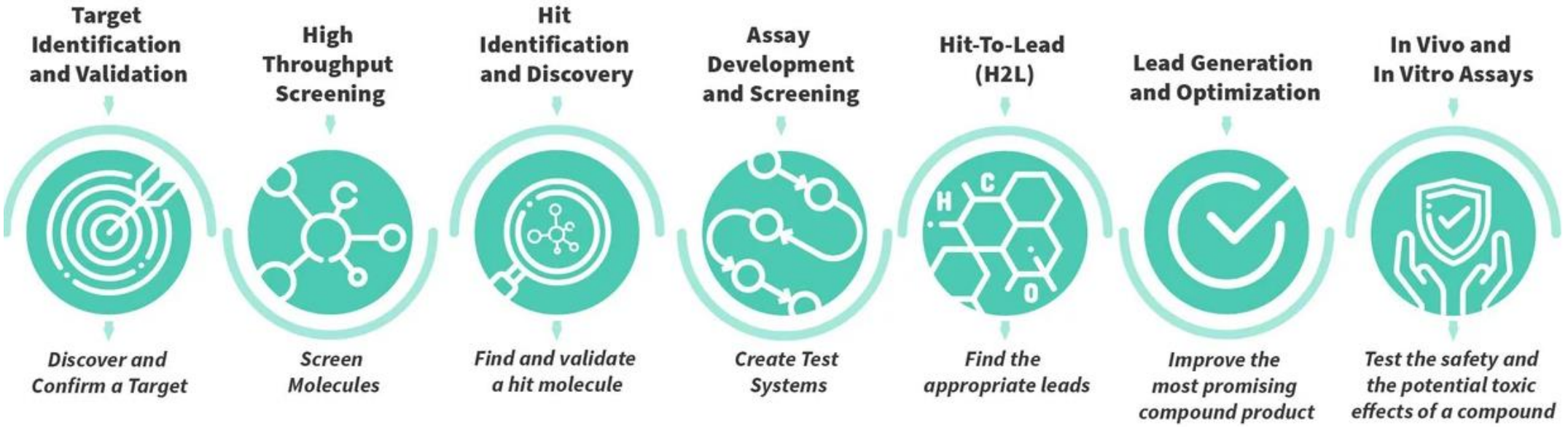
Early drug discovery process: lean process

Efficient experimental design: how can we start to discover a new therapeutic target or a new molecule?

1. Early Drug Discovery

The Early Drug Discovery Process involves many different actions and testing. Researchers collaborate to identify and optimize potential leads to a specific target. Essentially, the leads must elicit a desirable effect on a specific biological target implicated in a disease, in the hopes of treating it. Research at this point is performed in the laboratory using ***in silico*** **platforms, biochemical assays, cell cultures, and various animal models.** This stage flows through these sub-processes: **Target Identification and Validation**, **High Throughput Screening or High Content Screening**, **Hit Identification**, **Assay Development and Screening**, **Hit-To-Lead (H2L)**, **Lead Generation and Optimization,** and ***In vivo*** and ***In vitro*** Assays. Keep reading on to learn more about each of these different steps within the Early Drug Discovery process.

Early drug discovery process: lean process



Pre-clinical Phase

2. Pre-Clinical Phase

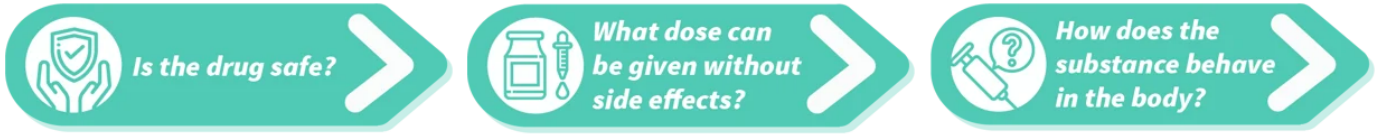
In keeping with the four major phases of the Drug Discovery process, the second stage is the **Pre-Clinical Phase**. In the Pre-Clinical Phase, **the substances identified during Early Drug Discovery are refined, optimized, and extensively tested in a laboratory and in animal or alternative models.** The aim is to provide sufficient evidence of safety and efficacy before Clinical Trials in humans can begin, and once this point is assured, it is also useful to calculate the appropriate doses to test in humans. Before the Clinical Trials start it must be ensured that the new substance is available in sufficient quantities during the clinical studies. Since only small quantities were previously required, production now has to be adapted to the significantly higher demand in the Clinical Phase.

Regulatory authorities require preclinical studies before submitting any investigational new drug application to progress to Clinical Phases.

Clinical phase

3. Clinical Phases

Clinical Trials are composed of four phases: **Phase I, II, III, and IV.** We will discuss each of these phases in greater detail further on. Nevertheless, in the first stage, the tolerance and safety of the drug candidate will be tested in a very small group of healthy subjects, usually 20 to 80. Phase I aims to answer the following questions:



For these studies, the active ingredient must first be **manufactured under GMP conditions.** That means strictly controlled according to the guidelines of "Good Manufacturing Practice."

After tolerance and effectiveness have been tested in a small group, **phases IIa, and IIb are started to examine the effectiveness, tolerability, and dosage** in a larger group. For this, the dosage form is first developed.

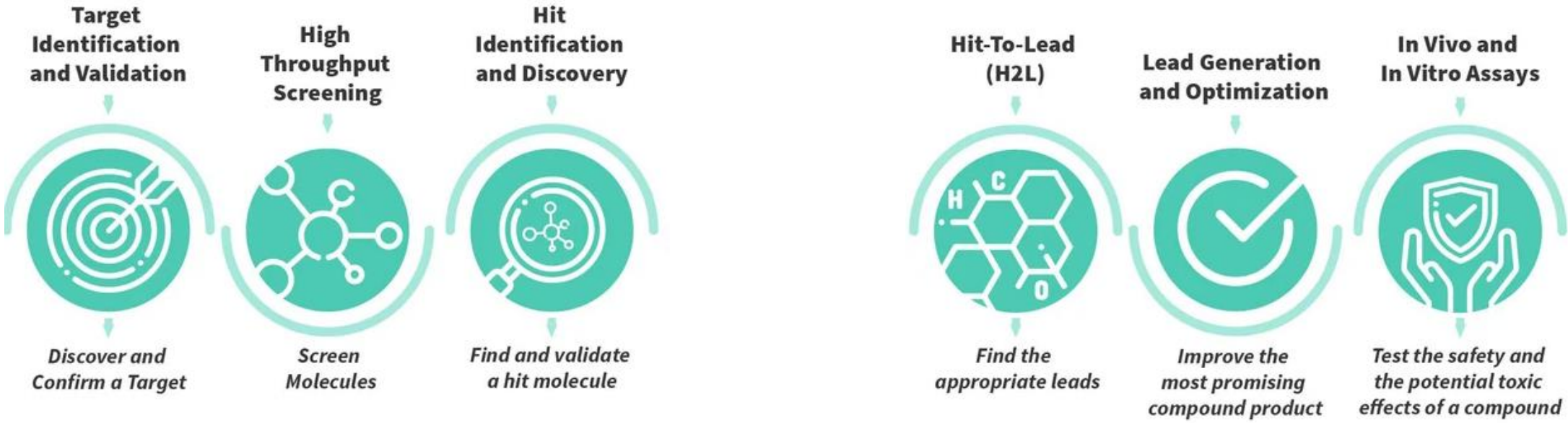
In phase IIa studies, **the therapy concept is primarily checked** (proof of concept); in phase IIb studies, **the aim is to find the right dose.** Phase II studies usually include 100 to 500 adult patients in the study.

Regulatory approval

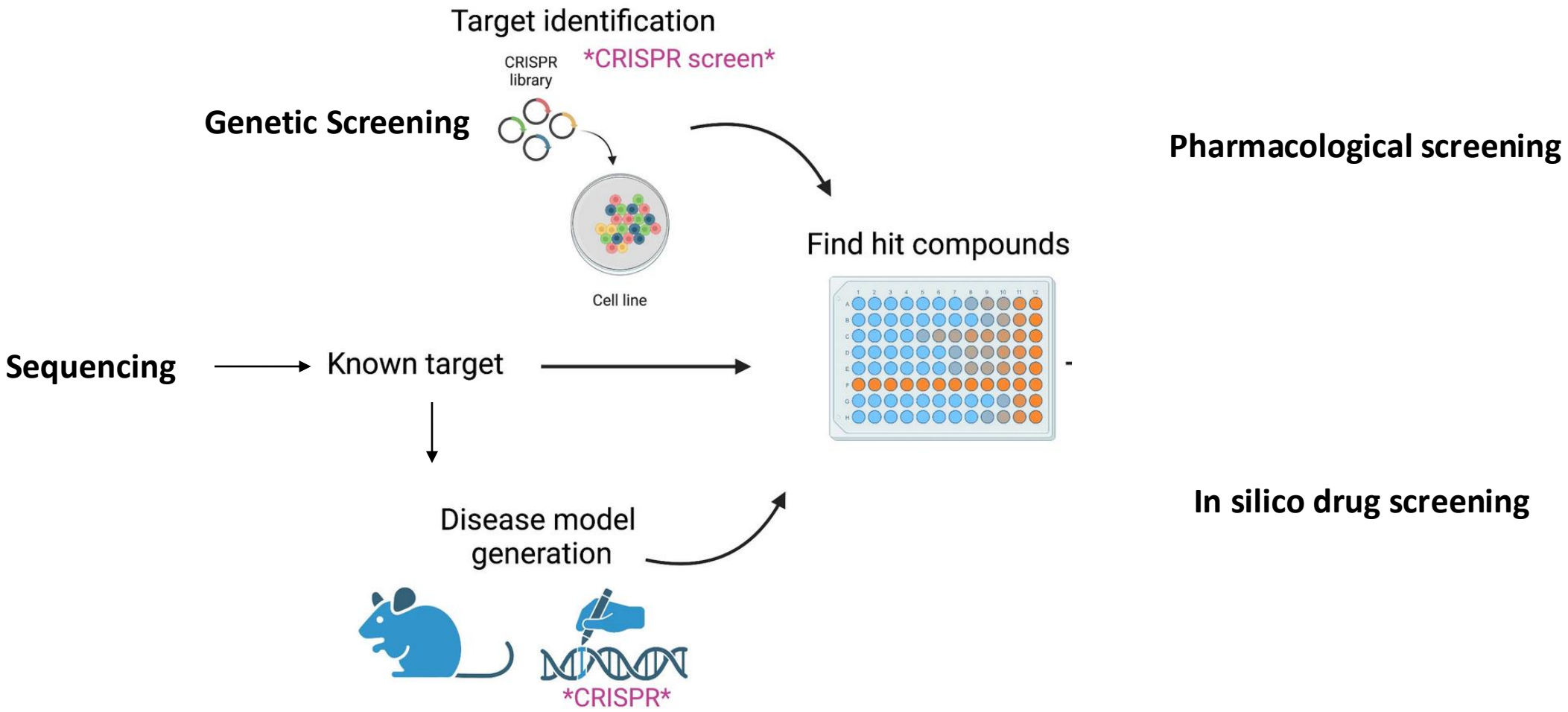
4. Regulatory Approval

When an active substance completes the Clinical Trials, the data is then collected and analyzed. Then, it can be submitted to the appropriate authorities for review. Before a drug or vaccine can be sold, **approval from a national regulatory authority or centralized process is required.** Ultimately, only one of a large number of compounds tested makes it through the process of clinical study phases and regulatory tests. Therefore, only one compound is approved as a drug or vaccine.

Early drug discovery process: lean process



Target identification and validation



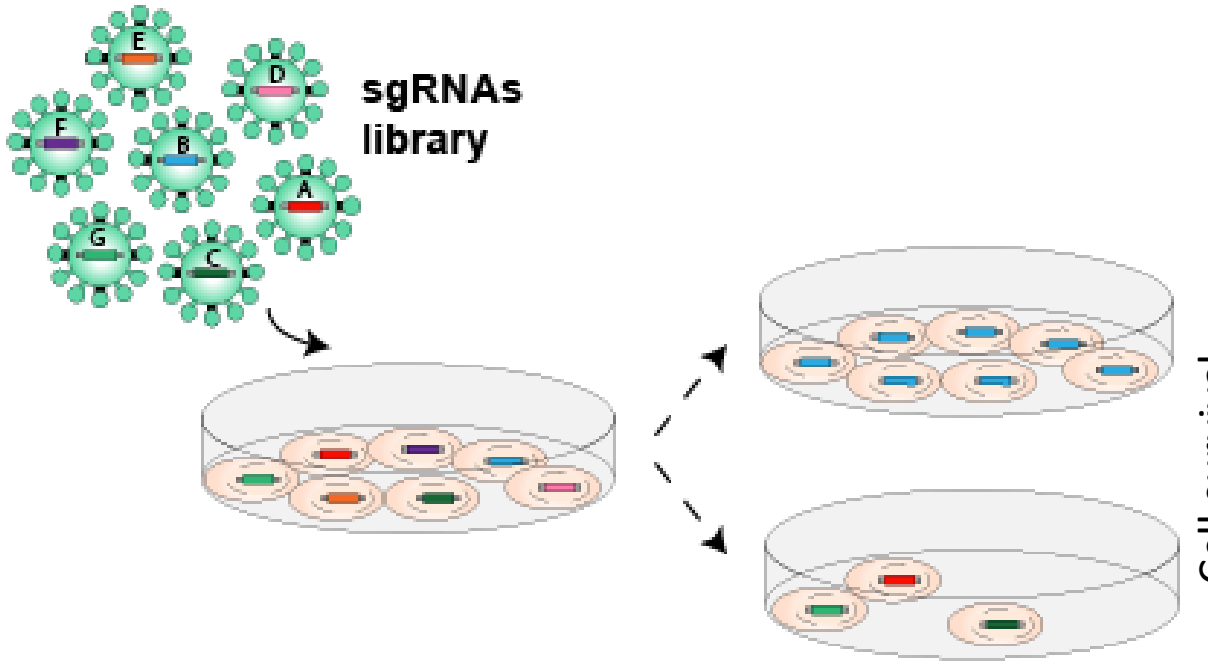
Genetic screening: new therapeutic targets

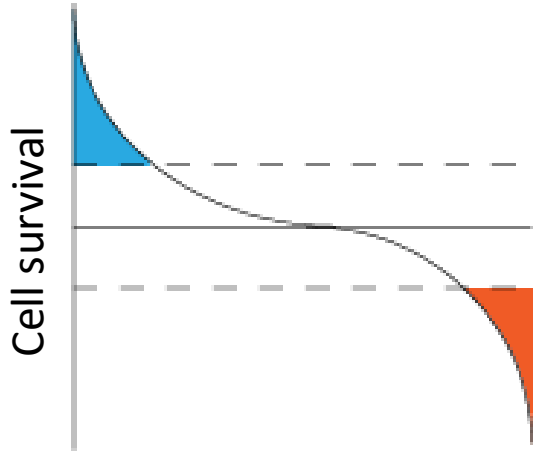
SIMULTANEOUSLY GENETICALLY MODIFY MULTIPLE GENES

Crispr Screen (introduce mutations in the gene sequence)
siRNA or shRNA screen (block gene expression, act on the mRNA)

Which gene is important for cancer cell survival?

CRISPRs SCREENING





Positive Screen= number of cell increase

Negative Screen = number of cells decrease

CRISPRs or shRNA SCREENING

STEP 1

GENERATE A LIBRARY OF sgRNA targeting the genes of interest

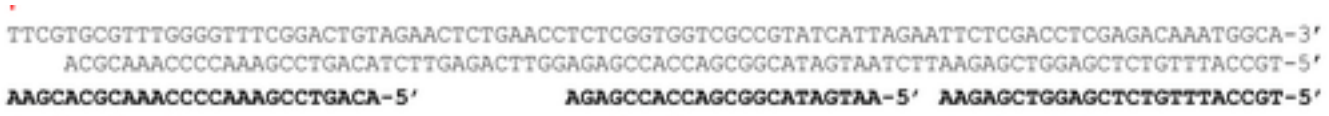
Each gene is targeted by multiple sgRNA to increase reproducibility

Library can be designed to target few genes or the whole genome

It is possible to study the function of non coding region

CRISPRs SCREENING
generate a sgRNA library

Gene-1

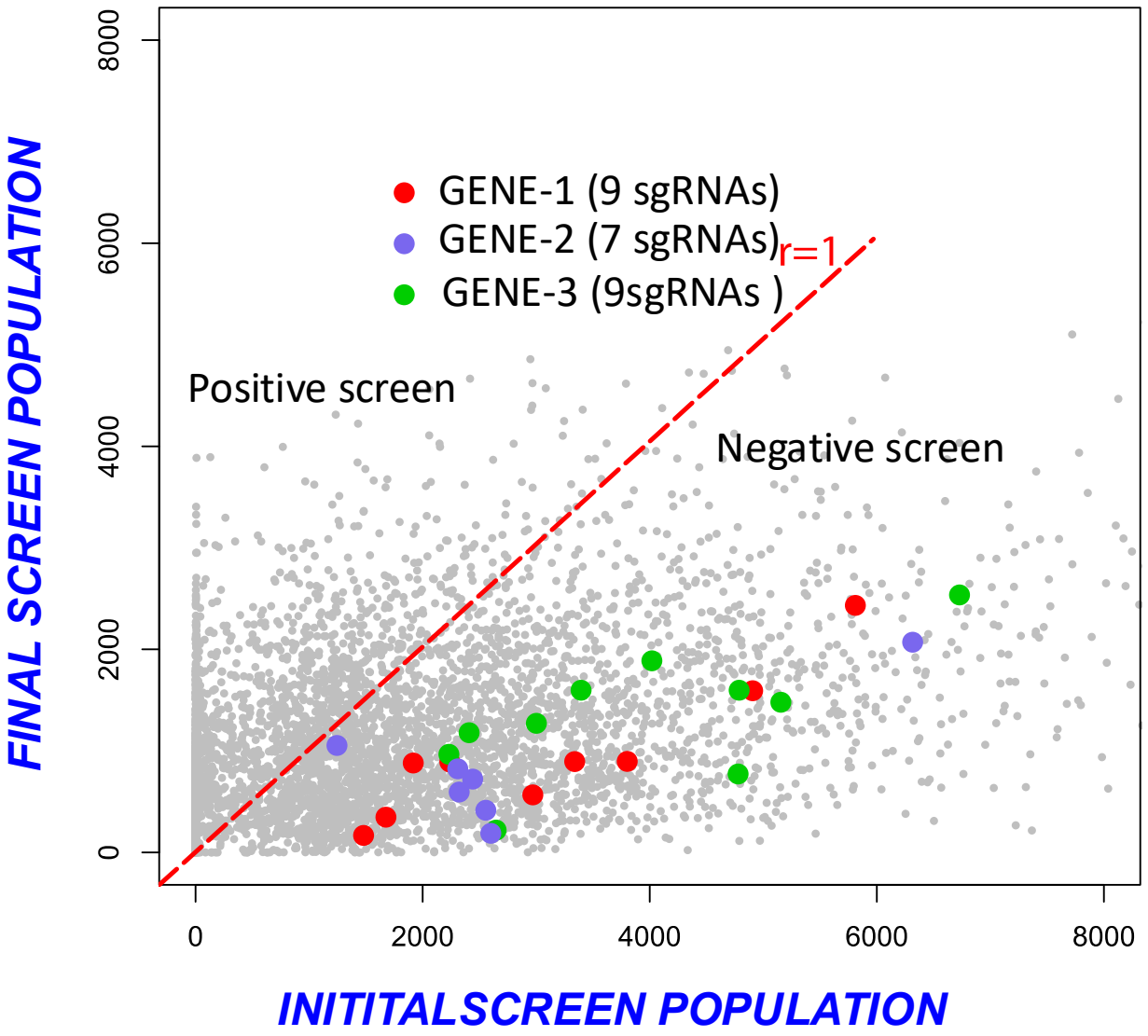


sgRNA-1 sgRNA-2 sgRNA-3

Genes in human are ~ 20000 = library has at least 60000 sgRNA

Target only gene with specific function (e.g. kinases)
500 genes = library with at least 1500 shRNA

CRISPRs SCREENING



Genetic screening: new therapeutic targets

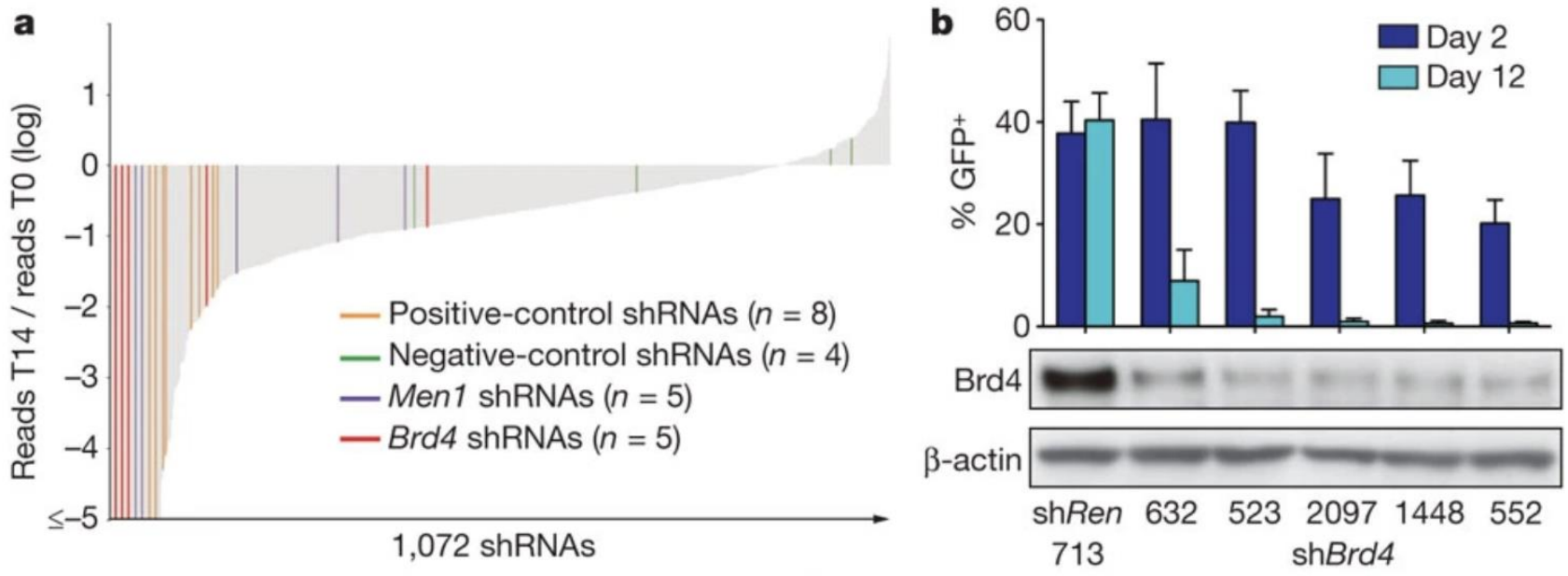
LETTER

doi:10.1038/nature10334

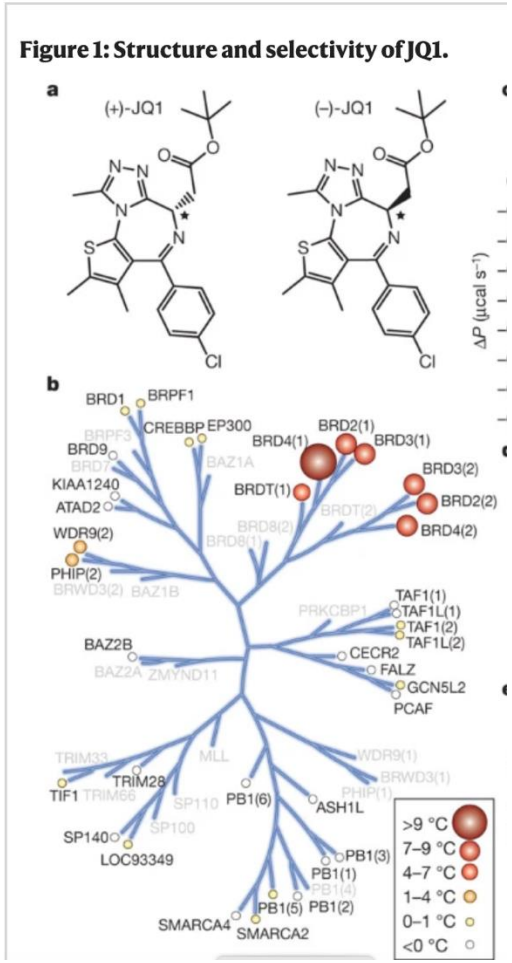
RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia

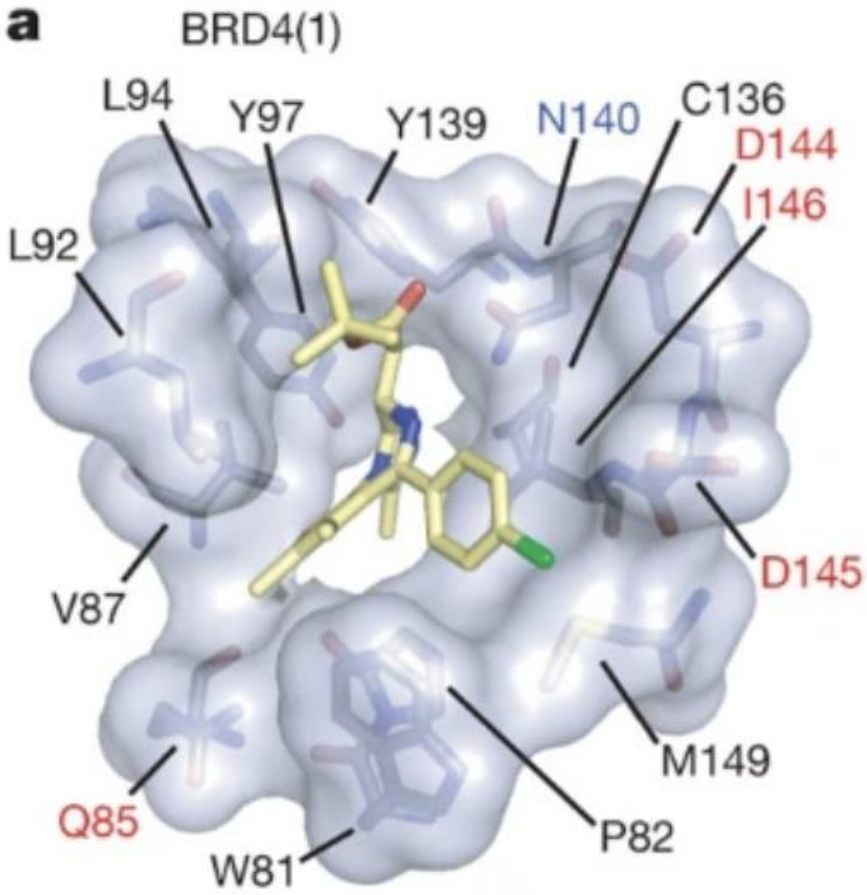
Johannes Zuber[1,2]*, Junwei Shi[1,3]*, Eric Wang[1], Amy R. Rappaport[1,4], Harald Herrmann[5], Edward A. Sison[6], Daniel Magoon[6], Jun Qi[7], Katharina Blatt[8], Mark Wunderlich[9], Meredith J. Taylor[1], Christopher Johns[1], Agustin Chicas[1], James C. Mulloy[9], Scott C. Kogan[10], Patrick Brown[6], Peter Valent[5,8], James E. Bradner[7], Scott W. Lowe[1,4,11] & Christopher R. Vakoc[1]

From: RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia

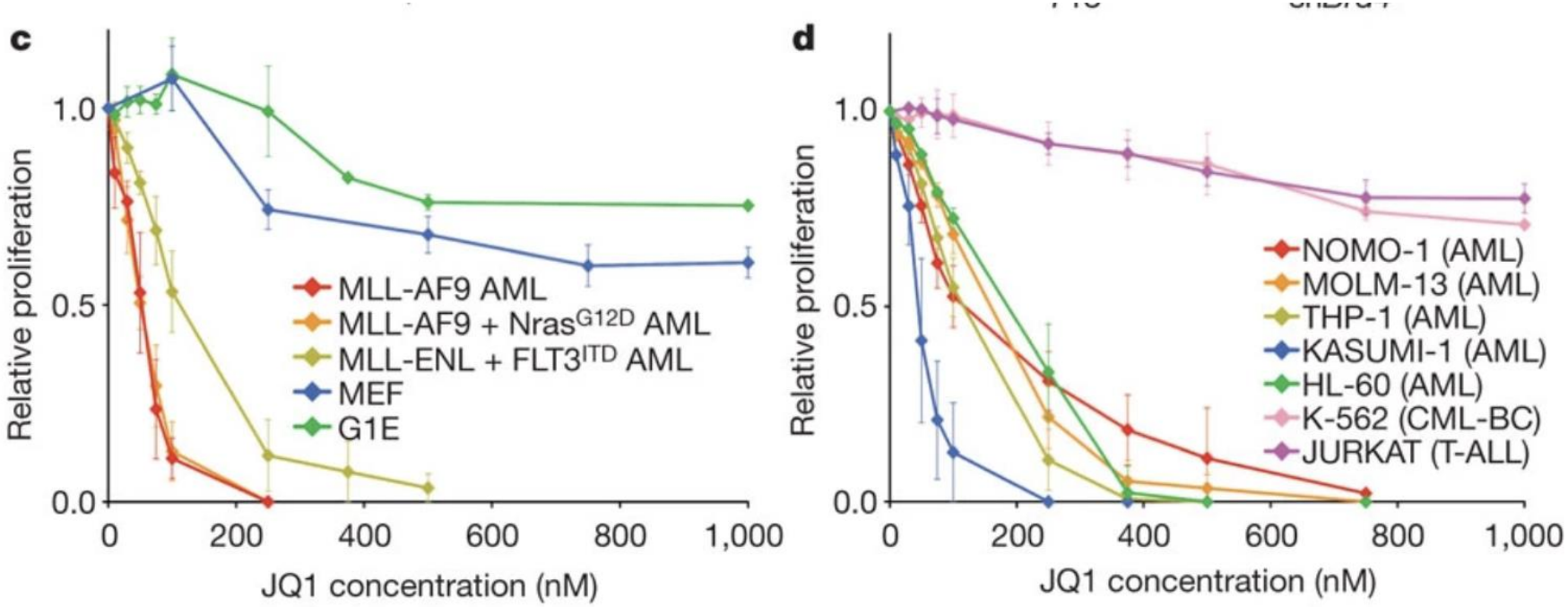


Genetic screening: new therapeutic targets

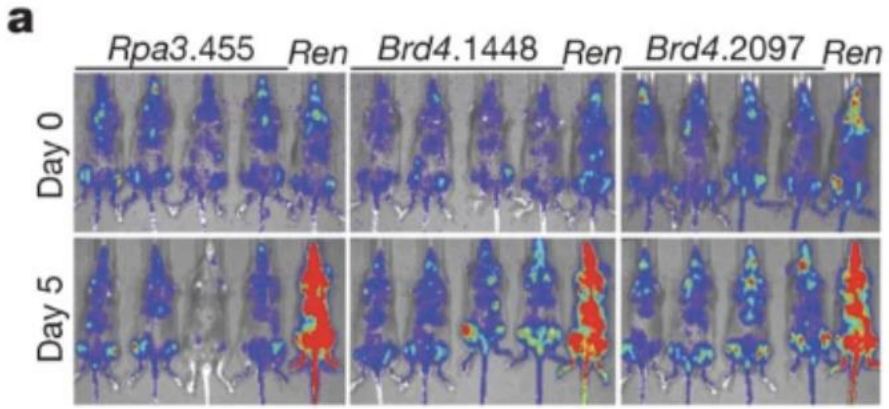


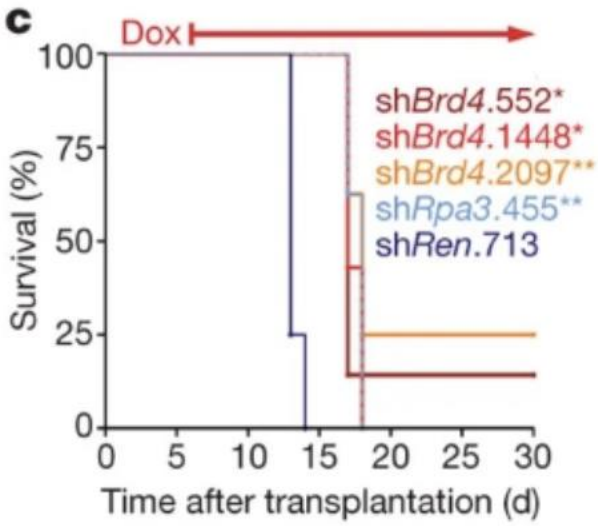


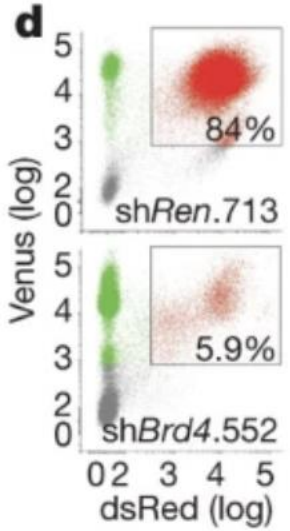
Genetic screening: new therapeutic targets

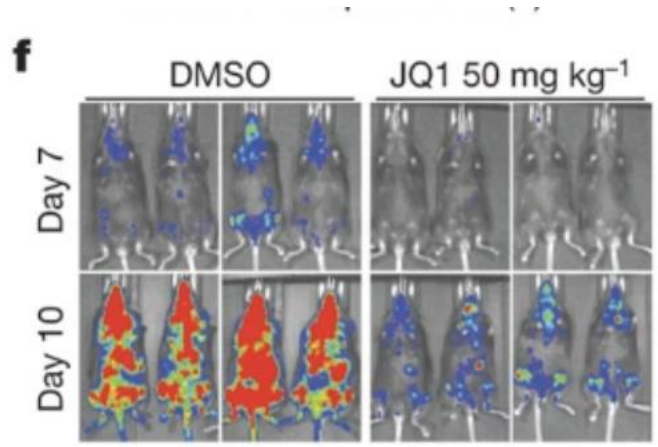


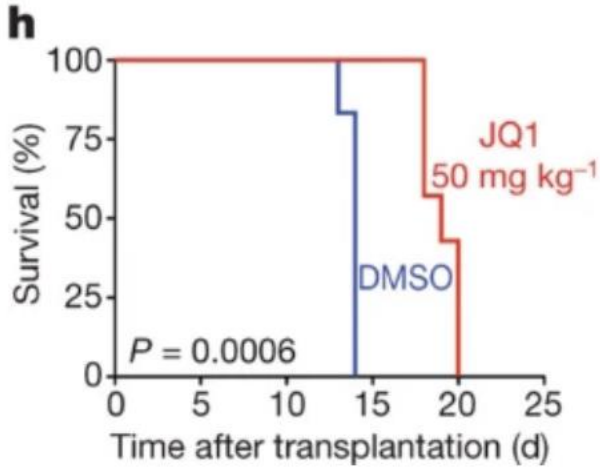
Genetic screening: new therapeutic targets









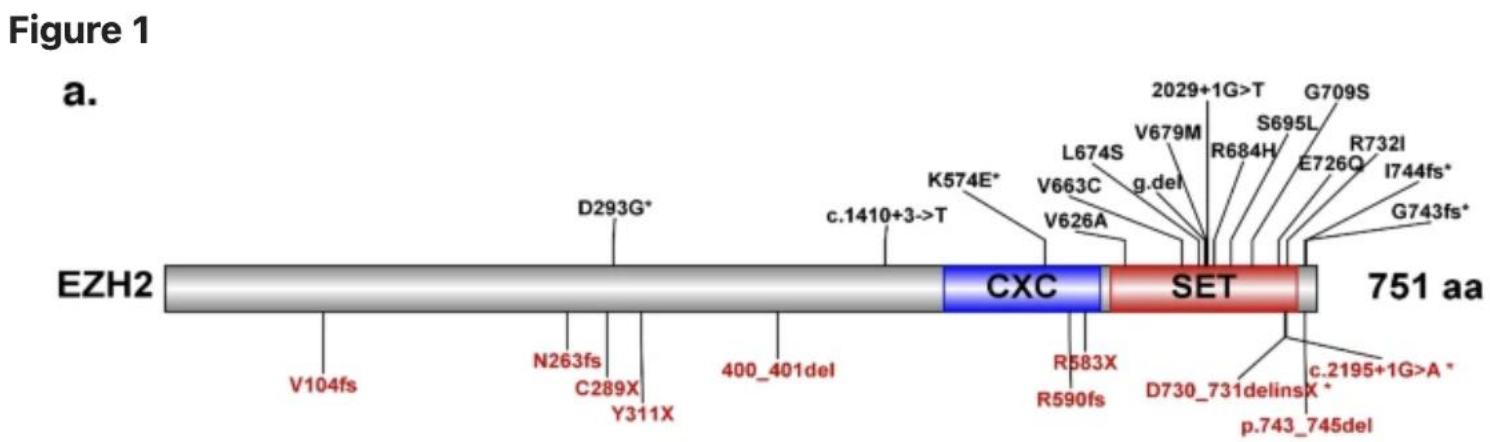


Known targets

Genetic disease driven by specific mutations

Mutated genes discovered by genomic sequencing

Pharmacological screening: known targets

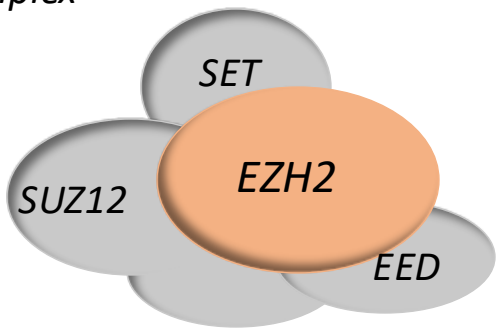


EZH2 has Gain of function mutations and over-expressed in many cancer type

Described for the first time in 2010

Chromatin regulators: EZH2 (writer) or HMT

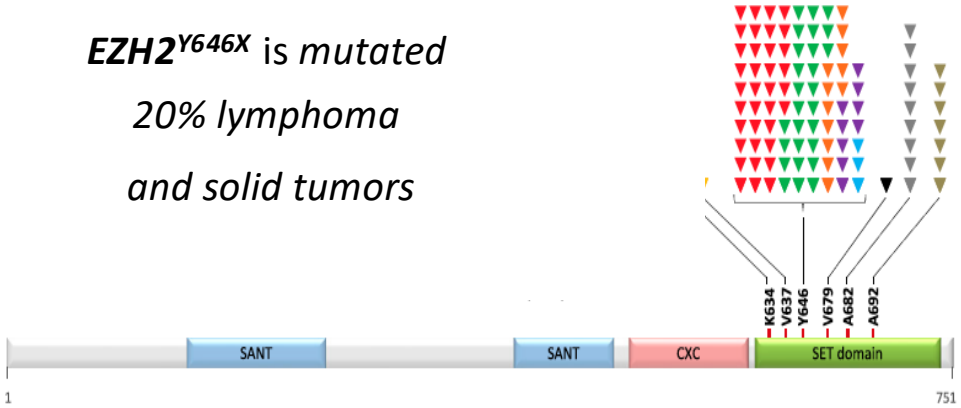
PRC2 complex



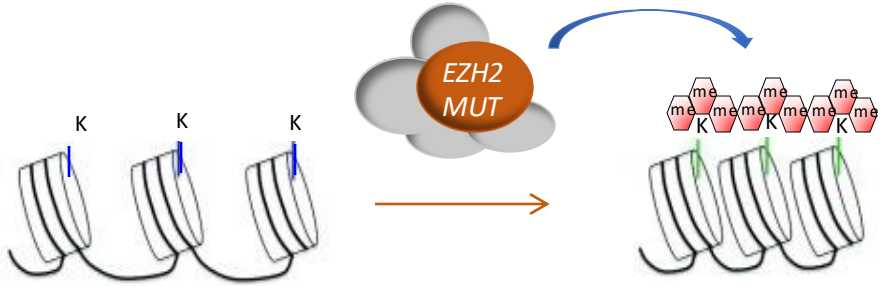
EZH2^{Y646X} *is mutated*

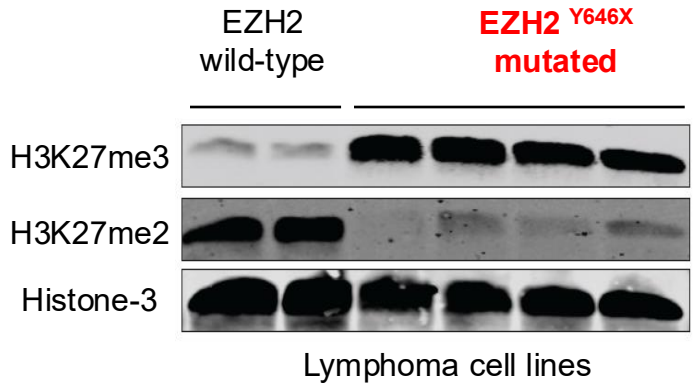
20% lymphoma

and solid tumors



EZH2^{Y646X} increases H3K27 tri-methylation





LETTER

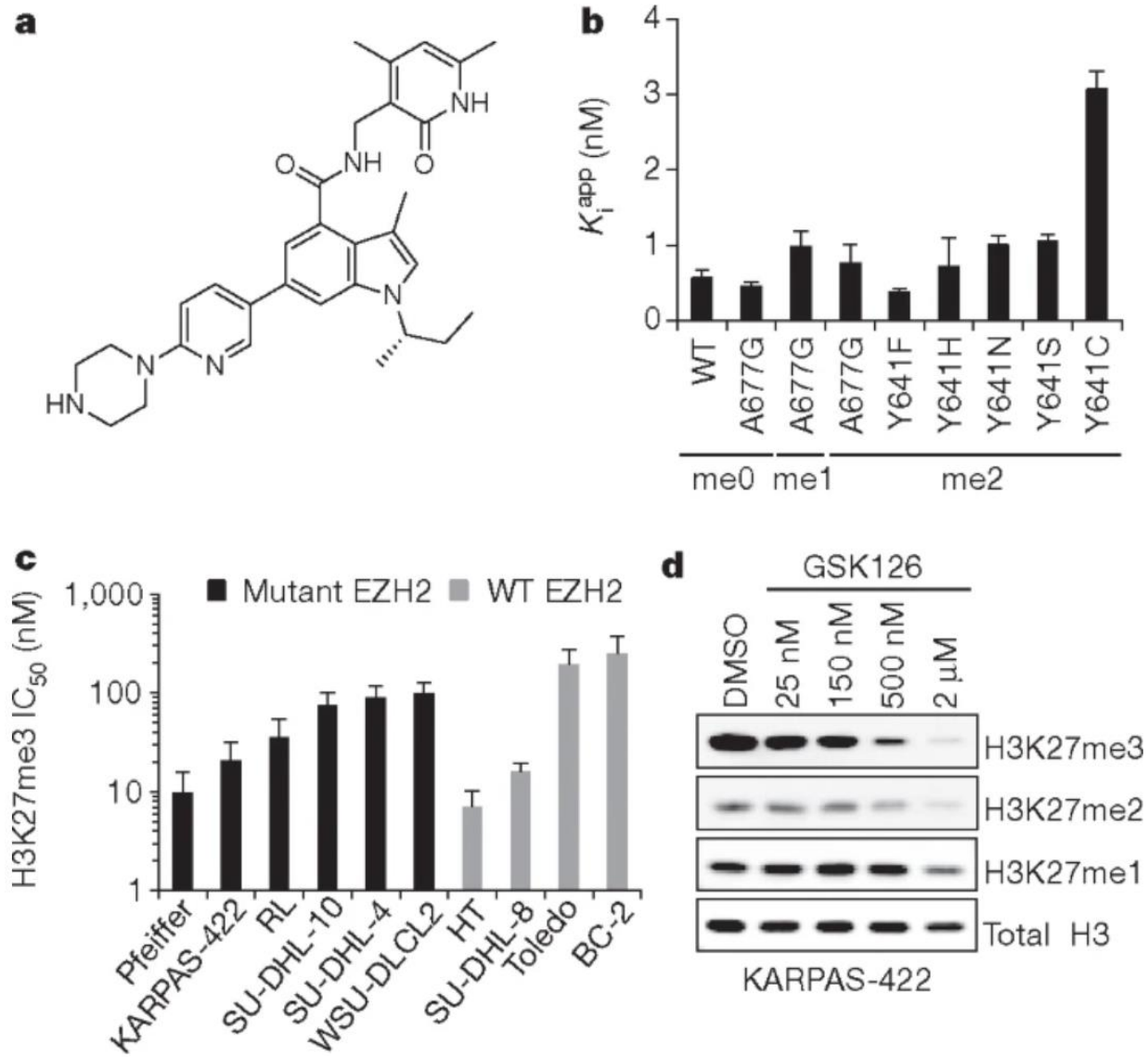
doi:10.1038/nature11606

EZH2 inhibition as a therapeutic strategy for lymphoma with EZH2-activating mutations

Michael T. McCabe[1], Heidi M. Ott[1], Gopinath Ganji[1], Susan Korenchuk[1], Christine Thompson[1], Glenn S. Van Aller[1], Yan Liu[1], Alan P. Graves[2], Anthony Della Pietra III[1], Elsie Diaz[2], Louis V. LaFrance[1], Mark Mellinger[1], Celine Duquenne[1], Xinrong Tian[1], Ryan G. Kruger[1], Charles F. McHugh[1], Martin Brandt[2], William H. Miller[1], Dashyant Dhanak[1], Sharad K. Verma[1], Peter J. Tummino[1] & Caretha L. Creasy[1]

Forst inhibitor published 2012

Figure 1: Biochemical and cellular mechanistic activity of GSK126.



Test EZH2 inhibitor in multiple lymphoma cells

Figure 2: GSK126 inhibits the proliferation of several EZH2 mutant lymphoma cell lines.

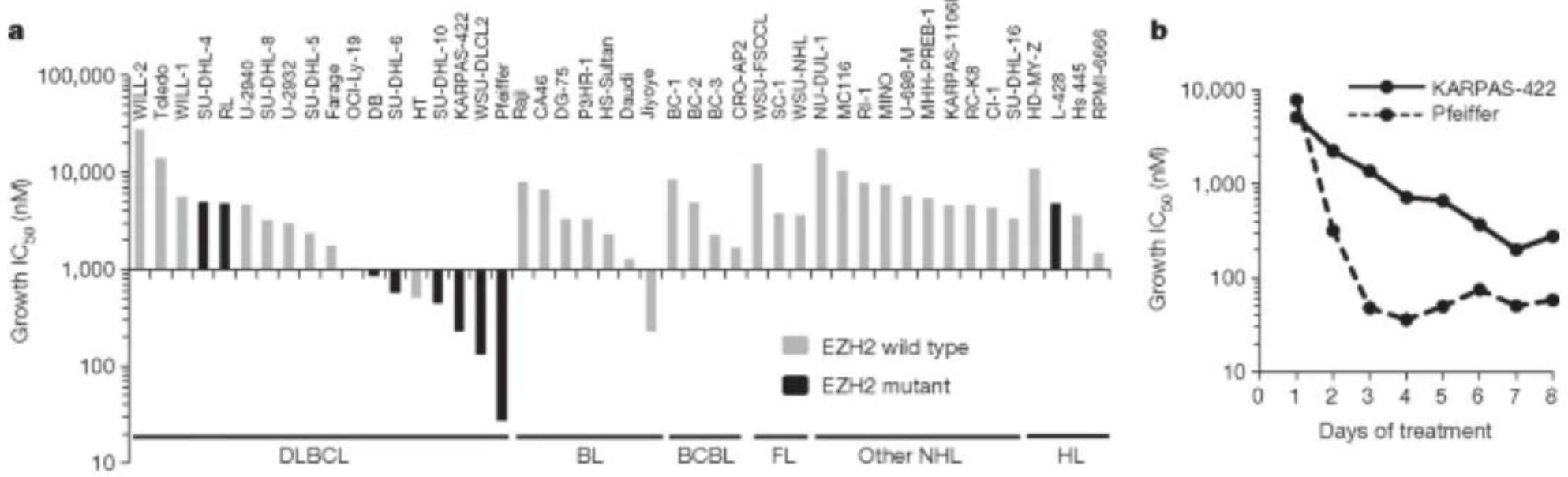
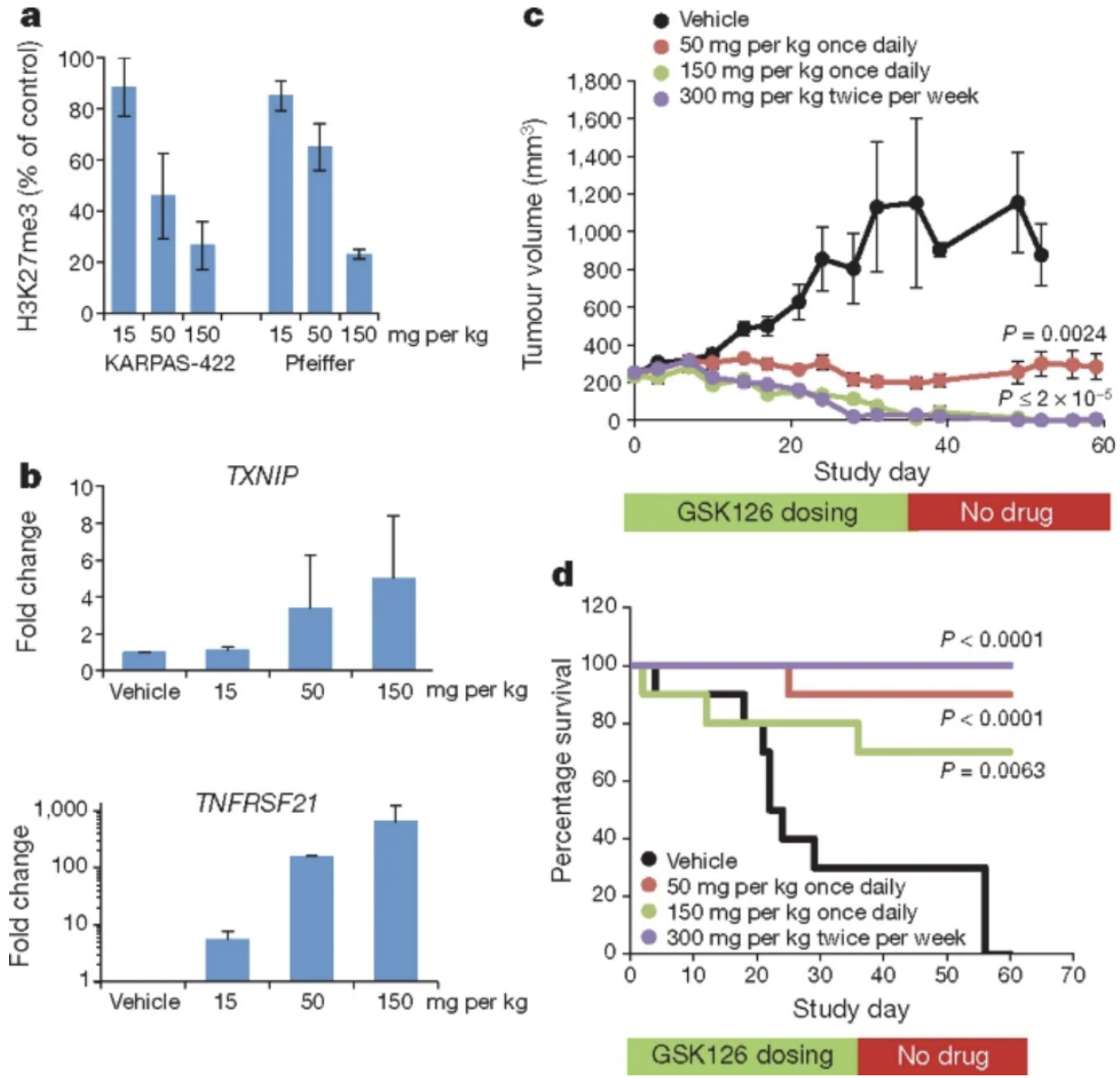


Figure 4: *In vivo* inhibition of H3K27me3 and tumour growth response with GSK126.



FDA approved

Epithelioid sarcoma

- **Date:** January 24, 2020
- **Indication:** Adult patients with advanced epithelioid sarcoma
- **Approval basis:** Results from a single-arm clinical trial showing a 15% overall response rate

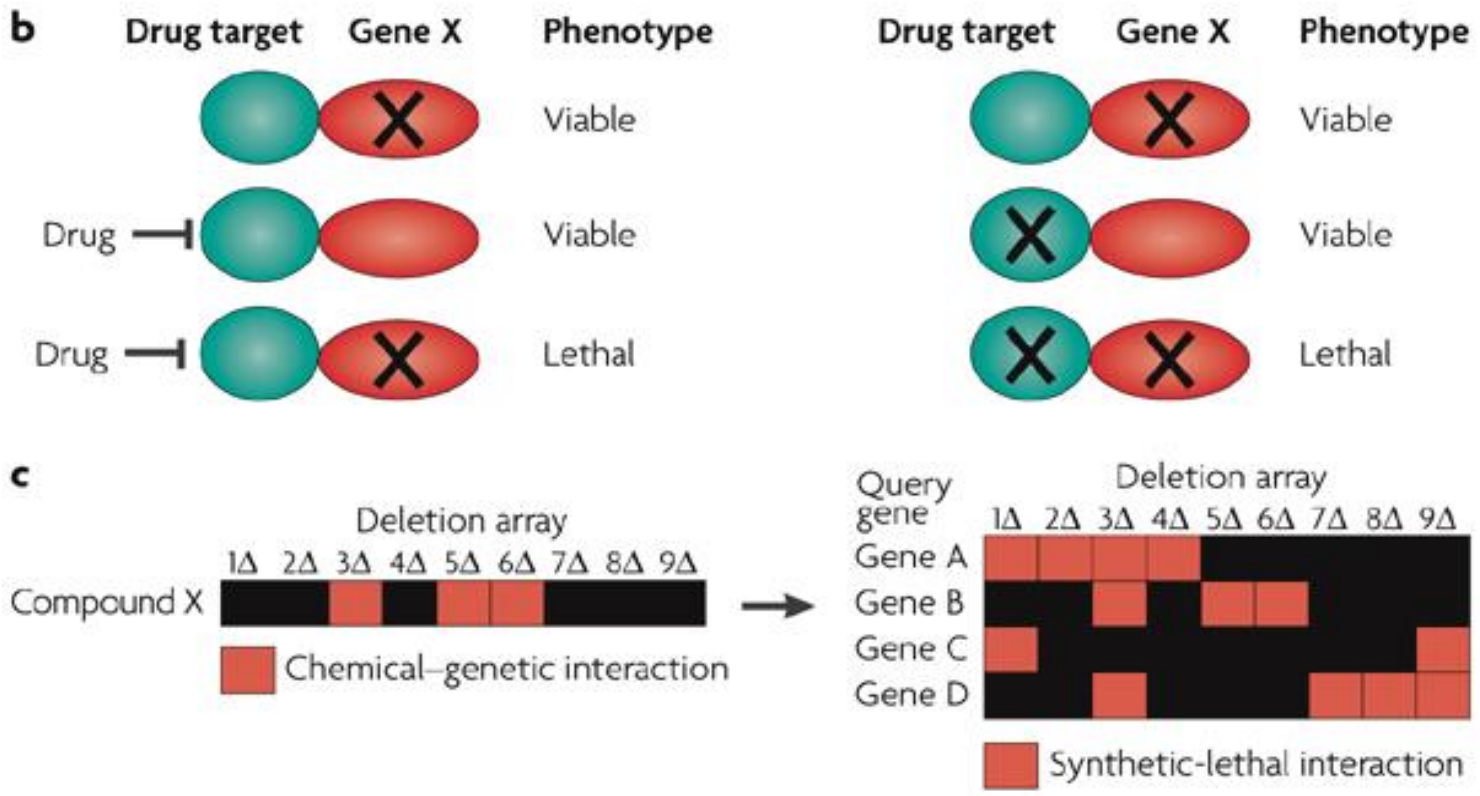
Follicular Lymphoma patient

- Adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) who have received at least two prior systemic therapies and whose tumors have an EZH2 mutation. It is also approved for adult patients with R/R FL who have no other satisfactory treatment options. This approval was granted on June 18, 2020.

Chemical genetic profiling in combination with synthetic lethal interactions

synthetic lethality between compound and gene X

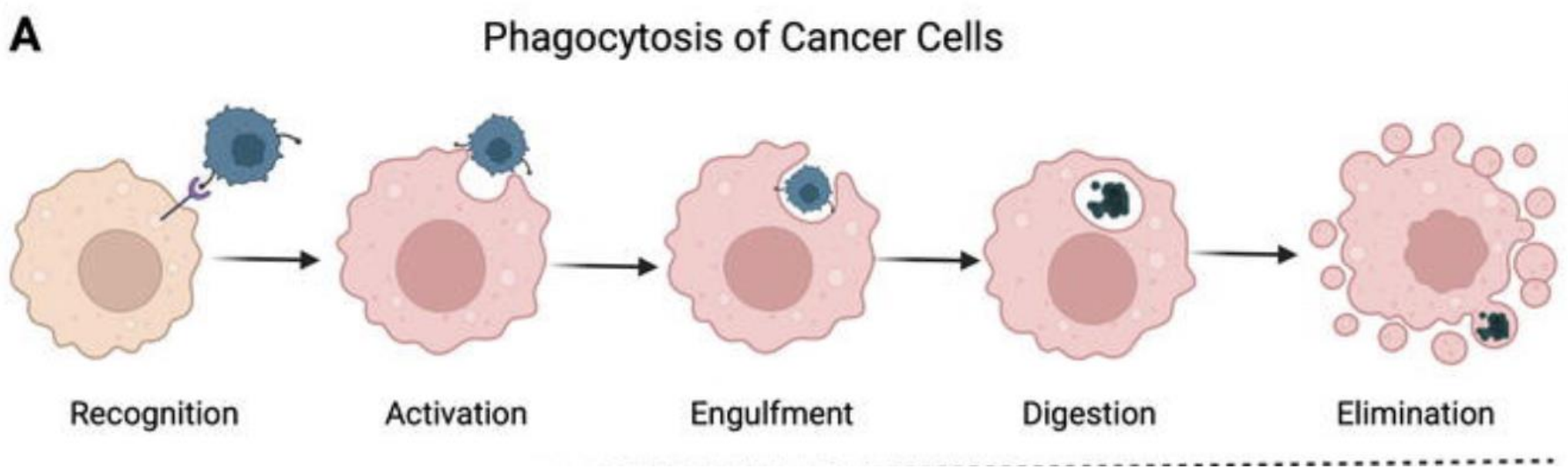
synthetic lethality between drug target and gene X



Pharmacological phenotypic screenings

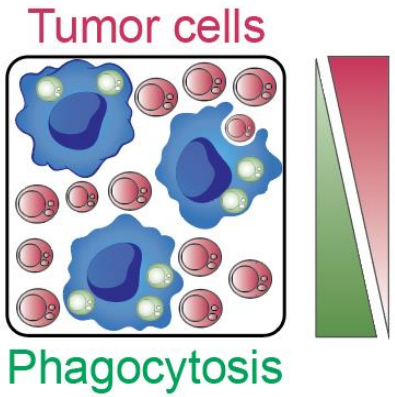
Phenotypic screening is a type of screening used in biological research and drug discovery to identify substances such as small molecules, peptides, or RNAi that alter the phenotype of a cell or an organism in a desired manner.[1] Phenotypic screening must be followed up with identification (sometimes referred to as target deconvolution) and validation,[2] often through the use of chemoproteomics, to identify the mechanisms through which a phenotypic hit works.[3]

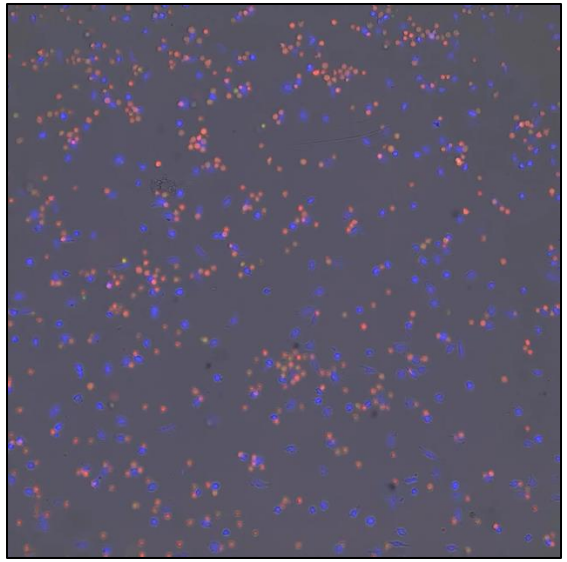
Phenotypic screening:
e.g. Increase phagocytosis of cancer cells



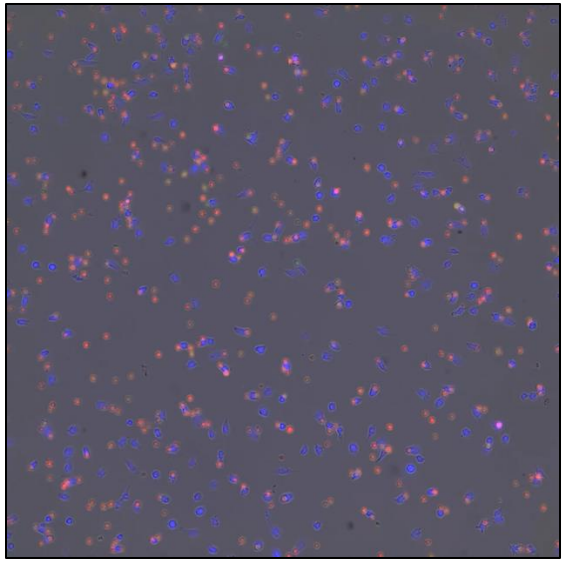
Macrophages can “eat” cancer cells

Phenotypic screening:
e.g. Increase phagocytosis of cancer cells



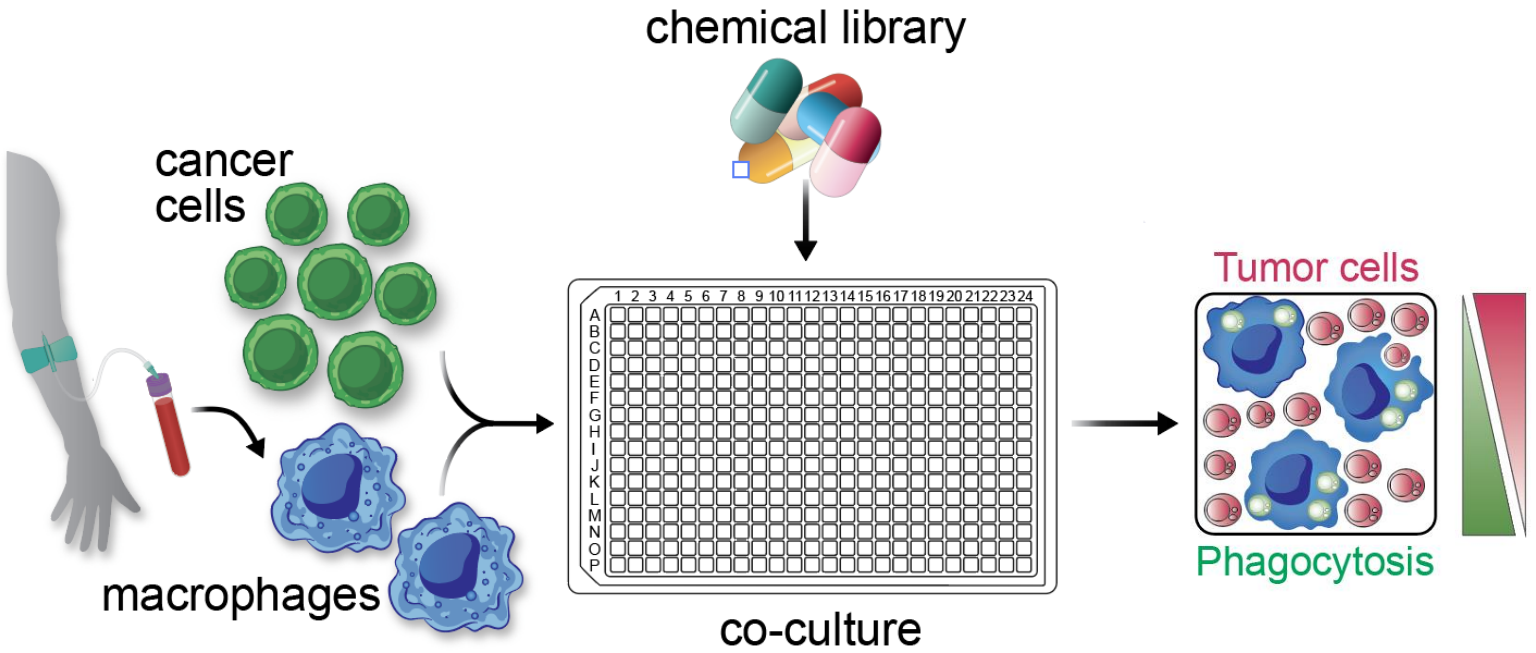


Tumor cells **macrophages**

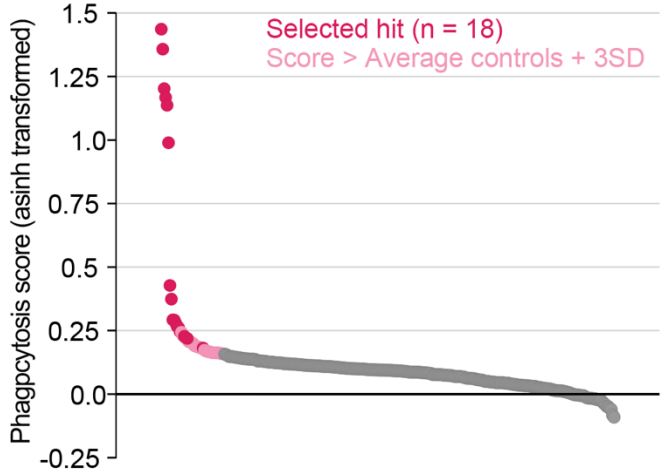


Tumor cells **macrophages**

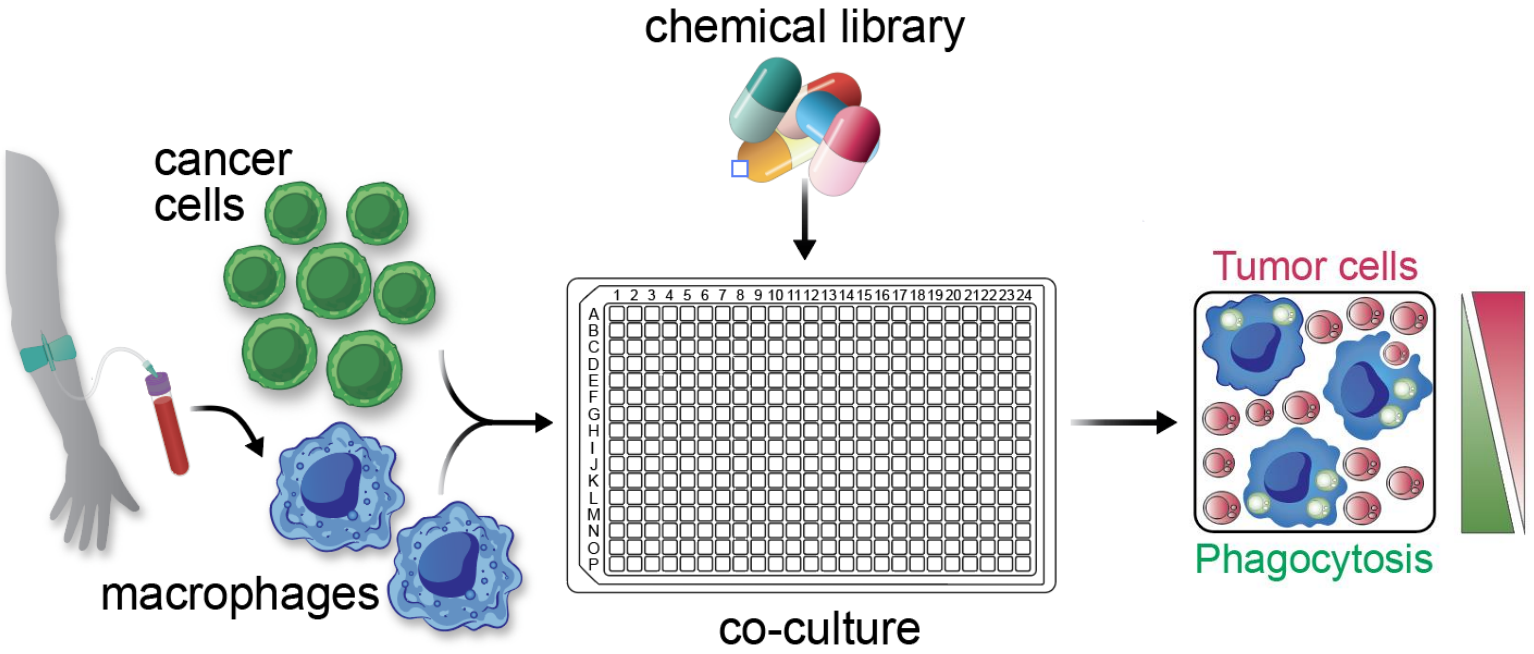
Small molecule screening



7640 small molecules → **300** hits validations

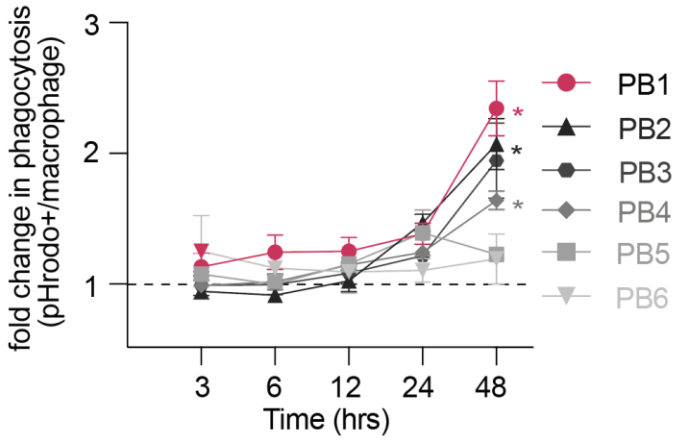


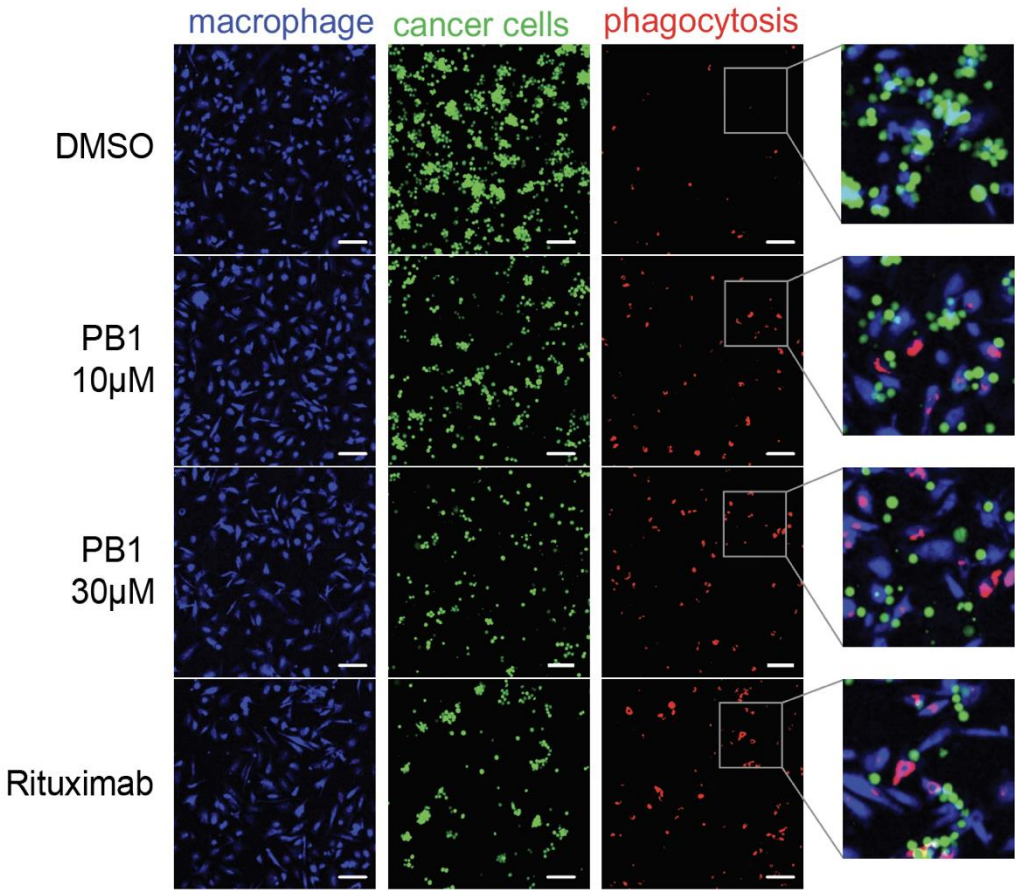
Small molecule screening

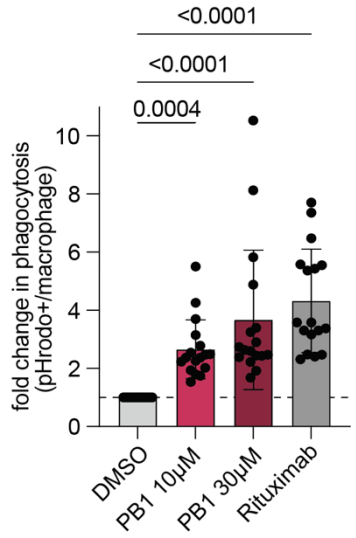


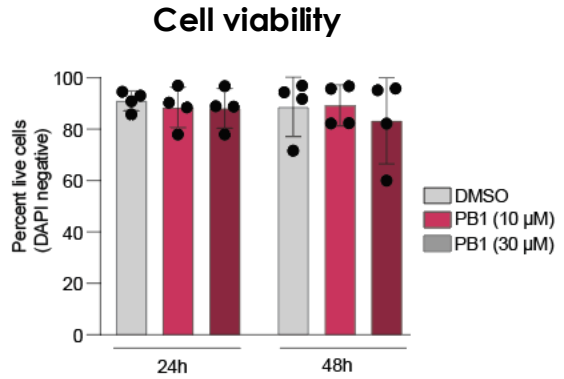
7640 small molecules → **300** hits validations → **18** dose response → **6** hits confirmed

Small Molecule 1 (SM1)

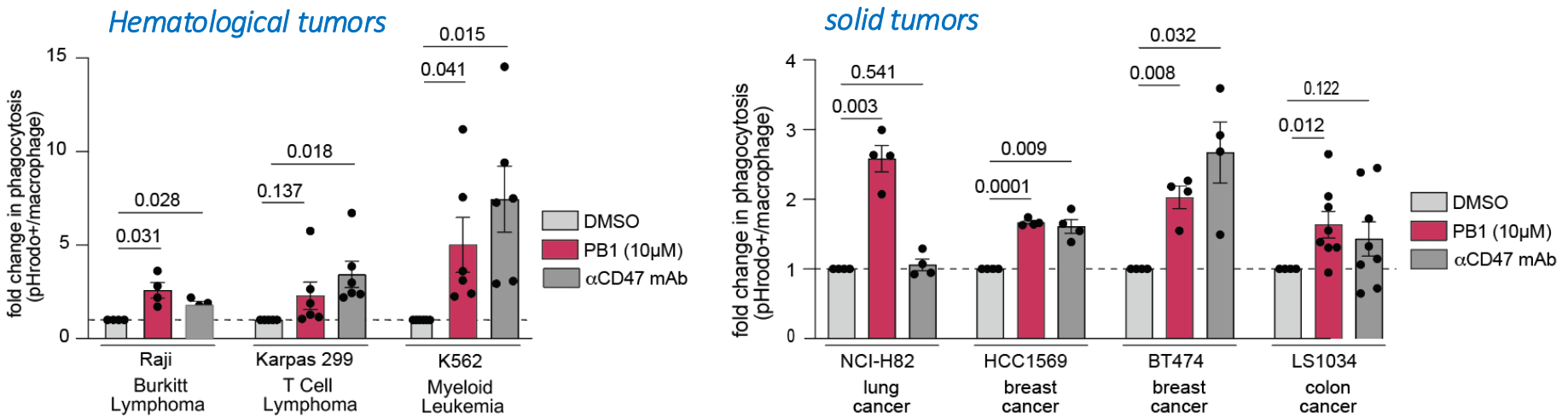








SM1 enhances phagocytosis of several tumor types

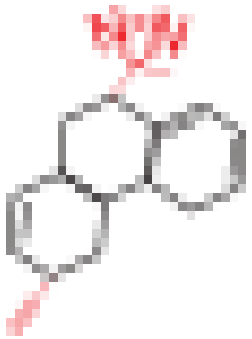


Who is the target of SM1 target?

Who is the target of SM1?

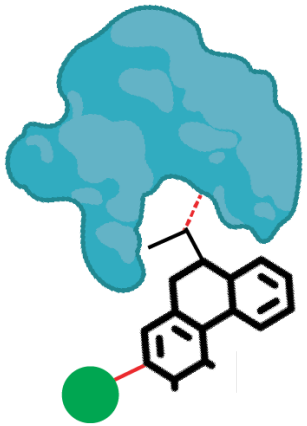
Photoaffinity labeling (PAL)
+ SILAC

Photolinker



Alkene clickable handle

SM1+ photolinker +alkene =B2



UV exposure forms a covalent bond

biotin to pull down

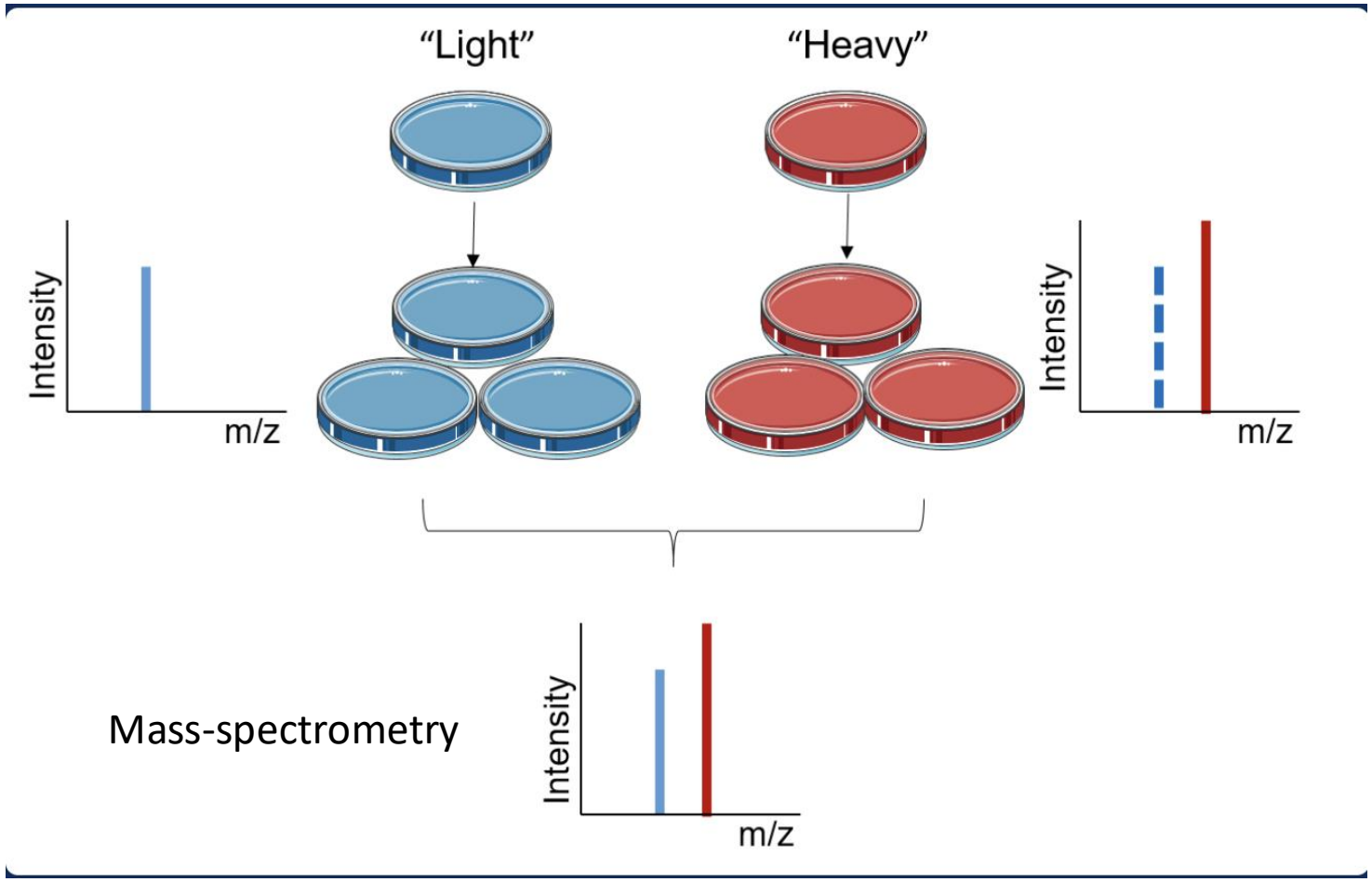
SILAC: **S**table **i**sotope **l**abeling using **a**mino acids in cell culture (SILAC) is a powerful method based on mass spectrometry that identifies and quantifies relative differential changes in protein abundance.

Ligh amino acid

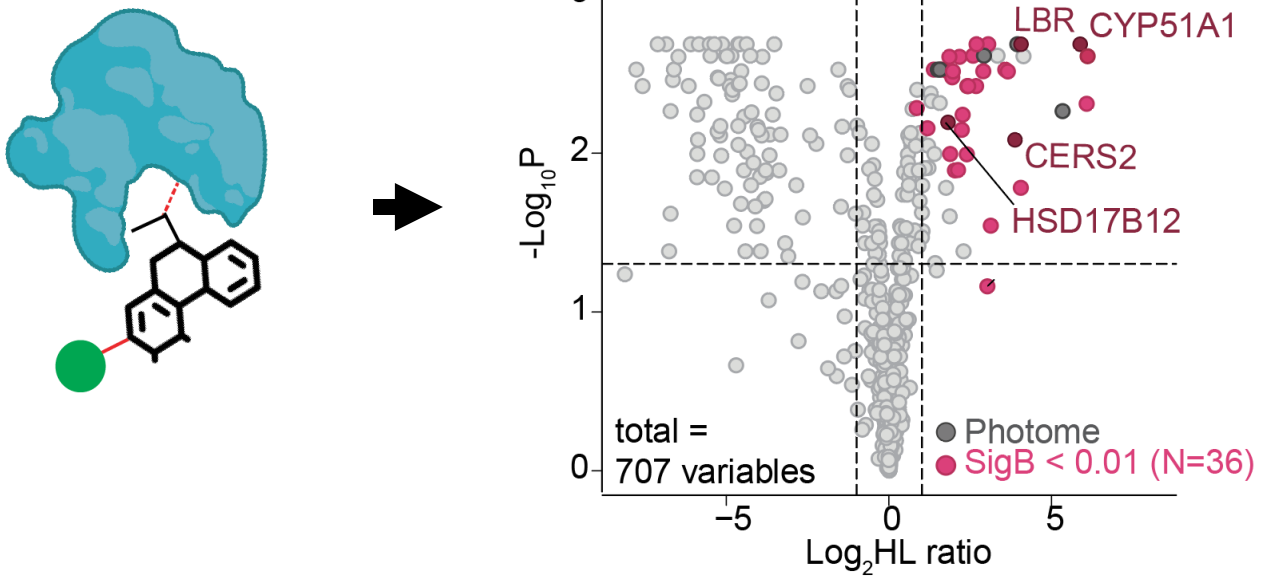
^{12}C

heavy amino acid

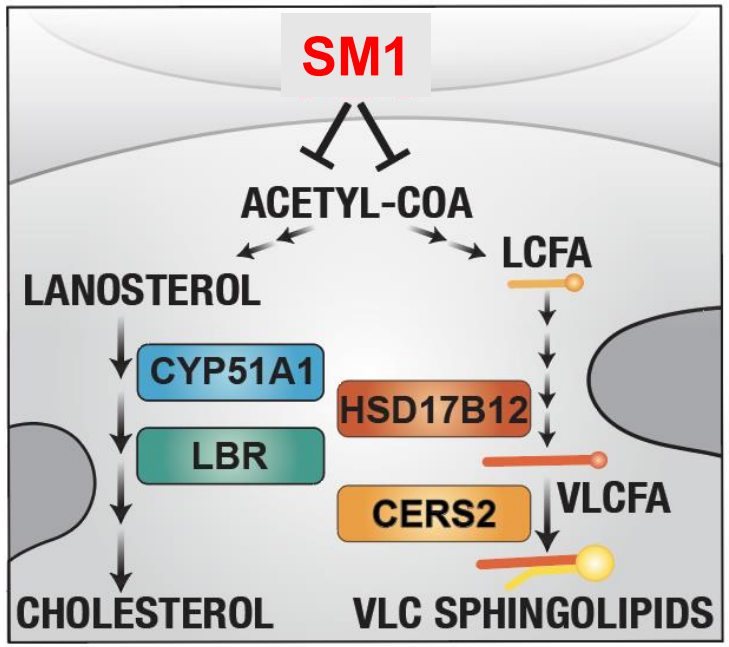
^{13}C

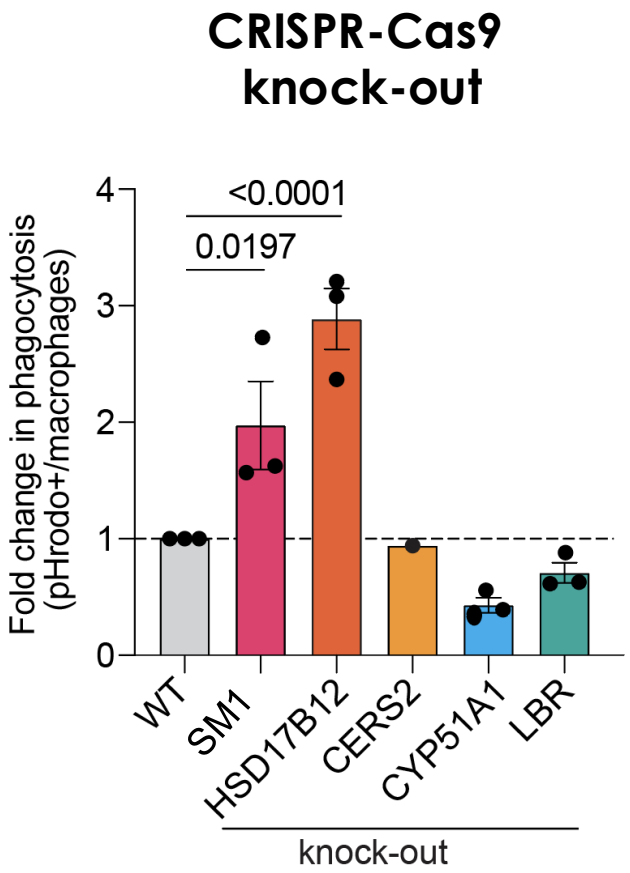


Who is the target of SM1?



Who is the target of SM1?





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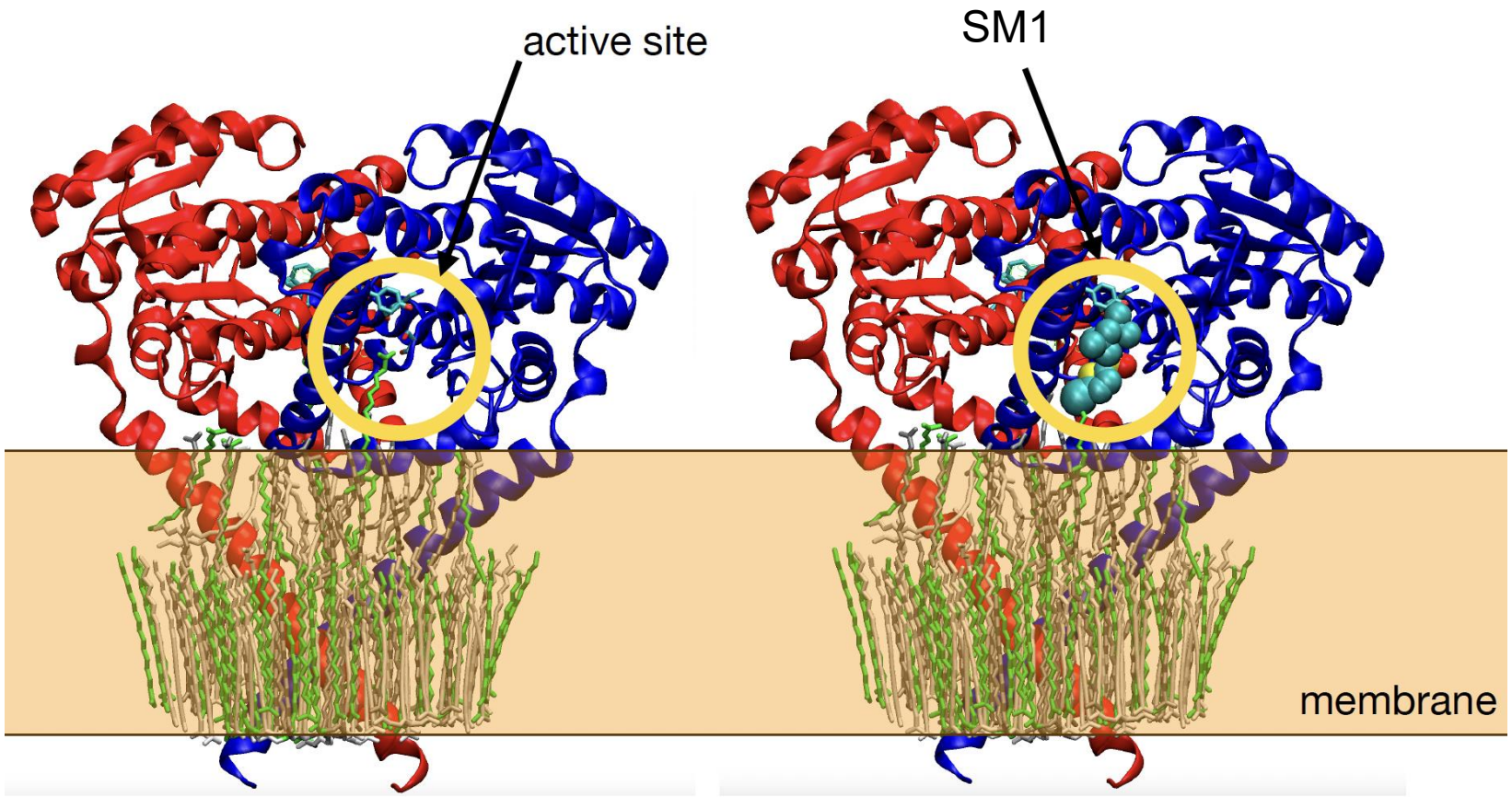
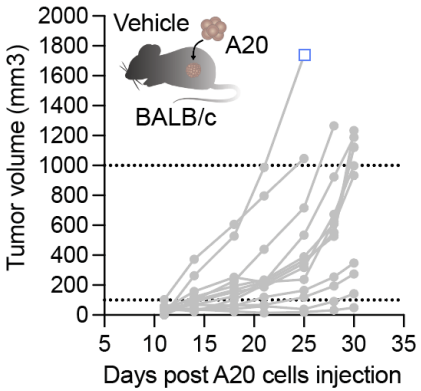
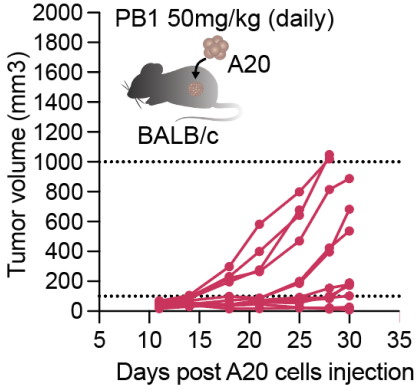
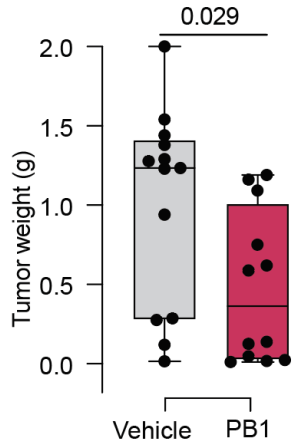


Pre-clinical studies

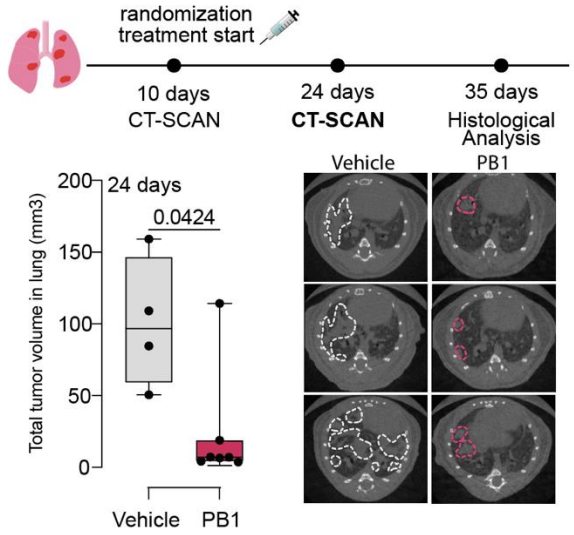
Lymphoma

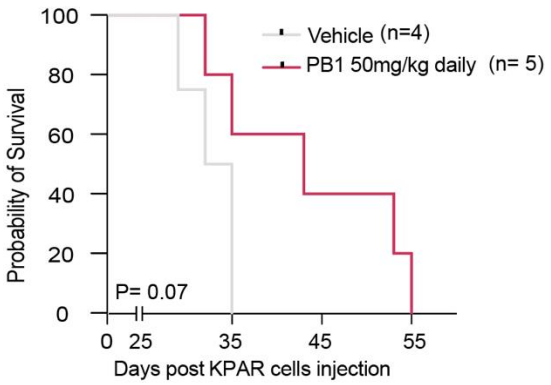






Lung cancer





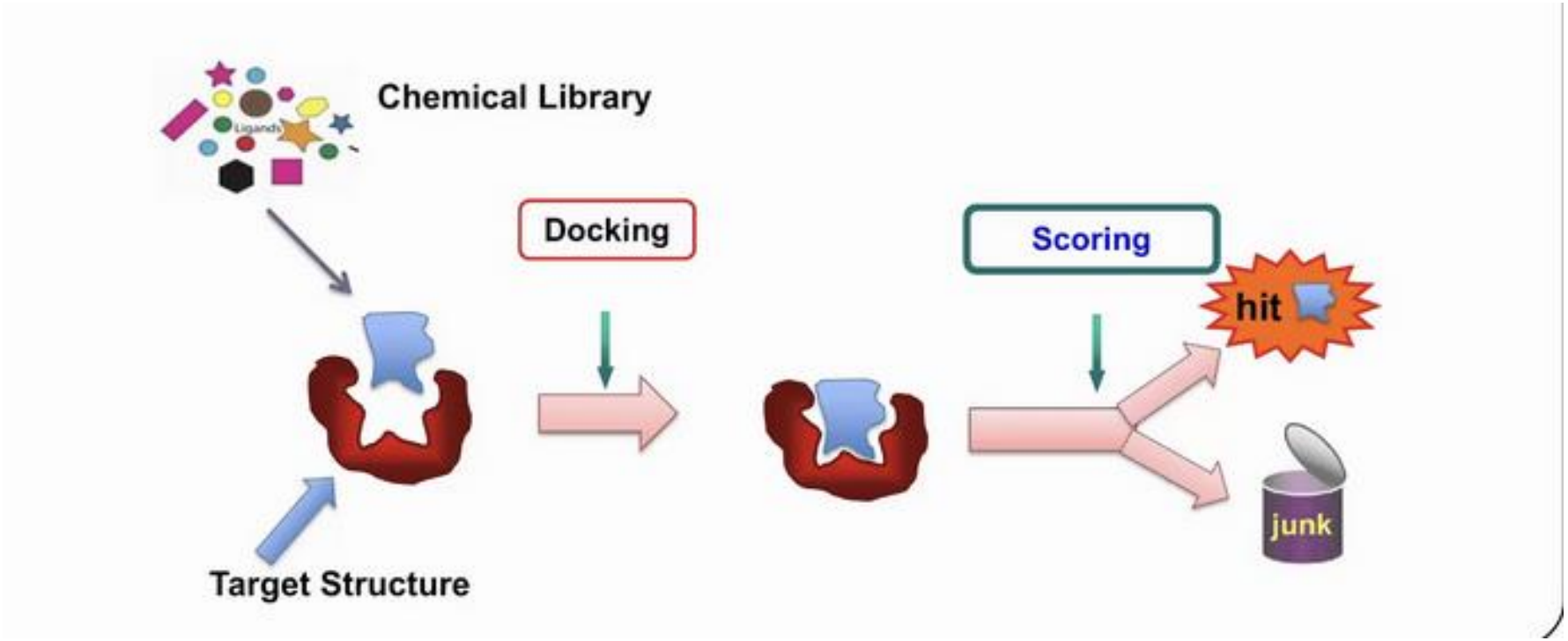
Early drug discovery process: lean process

Efficient experimental design: how can we start to discover a new therapeutic target or a new molecule?

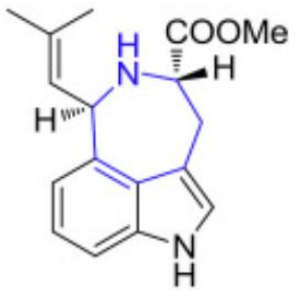
1. Early Drug Discovery

The Early Drug Discovery Process involves many different actions and testing. Researchers collaborate to identify and optimize potential leads to a specific target. Essentially, the leads must elicit a desirable effect on a specific biological target implicated in a disease, in the hopes of treating it. Research at this point is performed in the laboratory using ***in silico*** **platforms, biochemical assays, cell cultures, and various animal models.** This stage flows through these sub-processes: **Target Identification and Validation**, **High Throughput Screening or High Content Screening**, **Hit Identification**, **Assay Development and Screening**, **Hit-To-Lead (H2L)**, **Lead Generation and Optimization,** and ***In vivo*** and ***In vitro*** Assays. Keep reading on to learn more about each of these different steps within the Early Drug Discovery process.

Hit to Lead: virtual screening

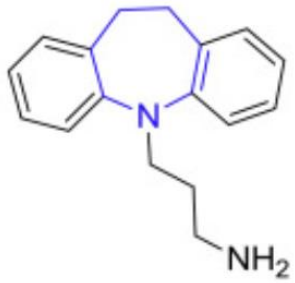


Hit to Lead: physical screening



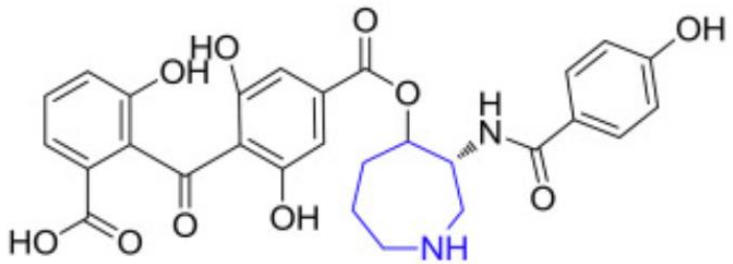
2

Claviciptic acid



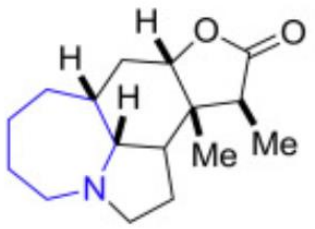
3

Imipramine



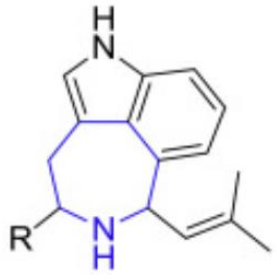
4

Balanol

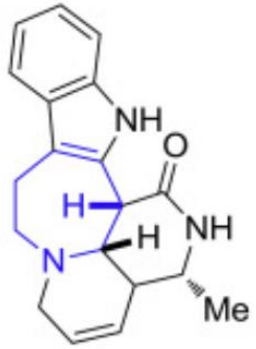


5

Stenine

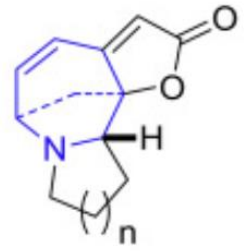


6, R = H, Aurantioclavine
7, R = COOH, Clavicipitic acid



8

Arboflorine



9, n= 1, Norsecurinine
10, n= 2, Securinine

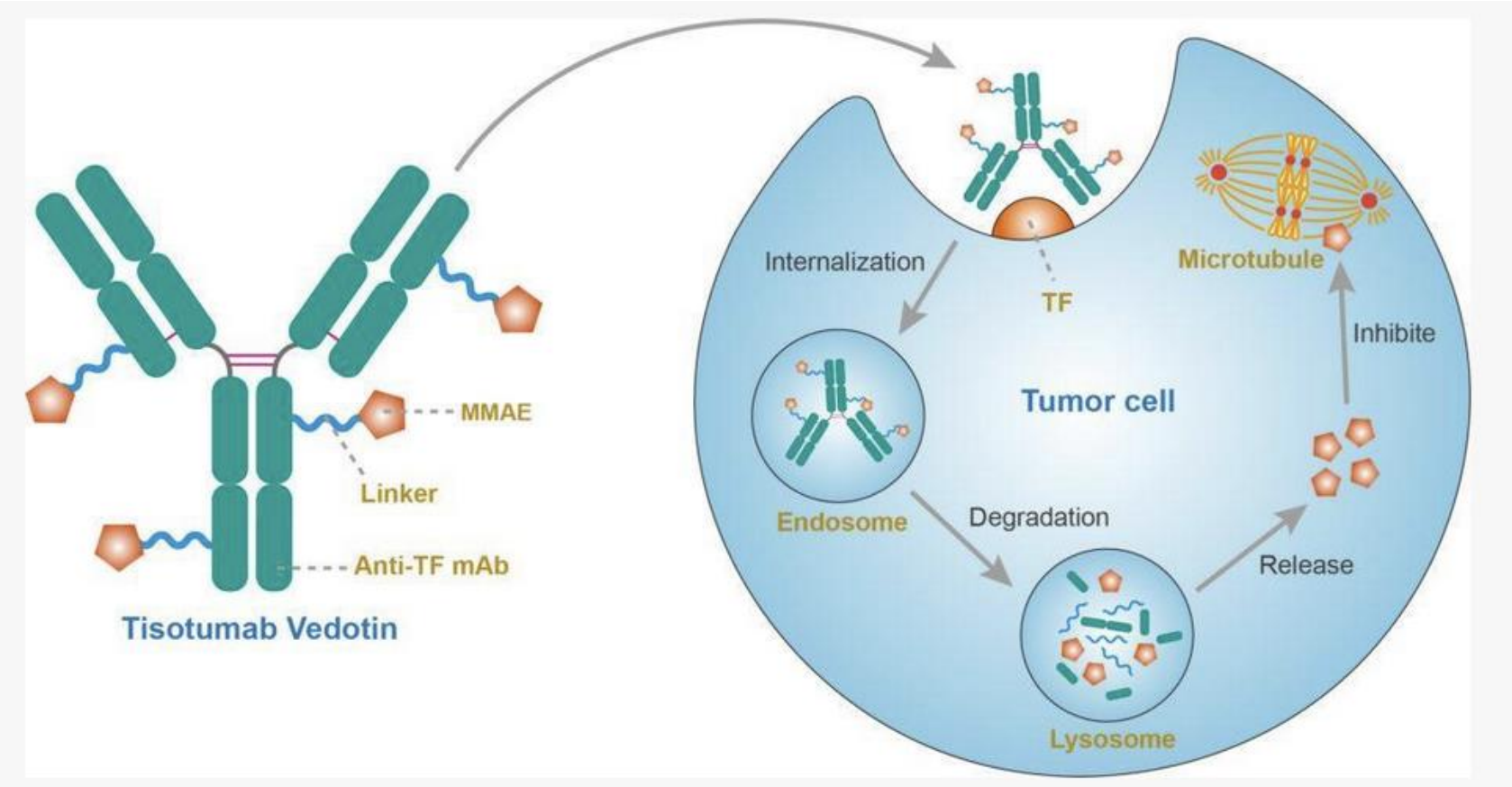
Small molecules vs biologics

Feature	Small Molecules	Biologics
Size / Structure	Low molecular weight, simple, well-defined chemical structures	Very large, complex molecules (proteins, antibodies, nucleic acids), difficult to fully characterize
Method of Production	Chemical synthesis	Produced in living systems (cells, bacteria, yeast)
Administration	Often oral (tablets/capsules)	Usually injectable (IV, SC) because they degrade in the GI tract
Mechanism of Action	Typically act on intracellular or enzyme targets; broad tissue penetration	Often highly specific to extracellular targets (e.g., cytokines, receptors)
Stability	Stable; long shelf life; tolerant to heat and pH changes	Sensitive; require cold storage (cold chain)
Immunogenicity	Low risk of immune response	Higher risk of immune reactions due to protein nature
Manufacturing Cost	Less expensive; scalable	Very expensive and complex manufacturing
Regulatory Pathway	Generic versions easier to produce	Biosimilars are challenging due to molecular complexity
Examples	Aspirin, ibuprofen, statins, beta-blockers	Insulin, monoclonal antibodies (e.g., adalimumab, trastuzum

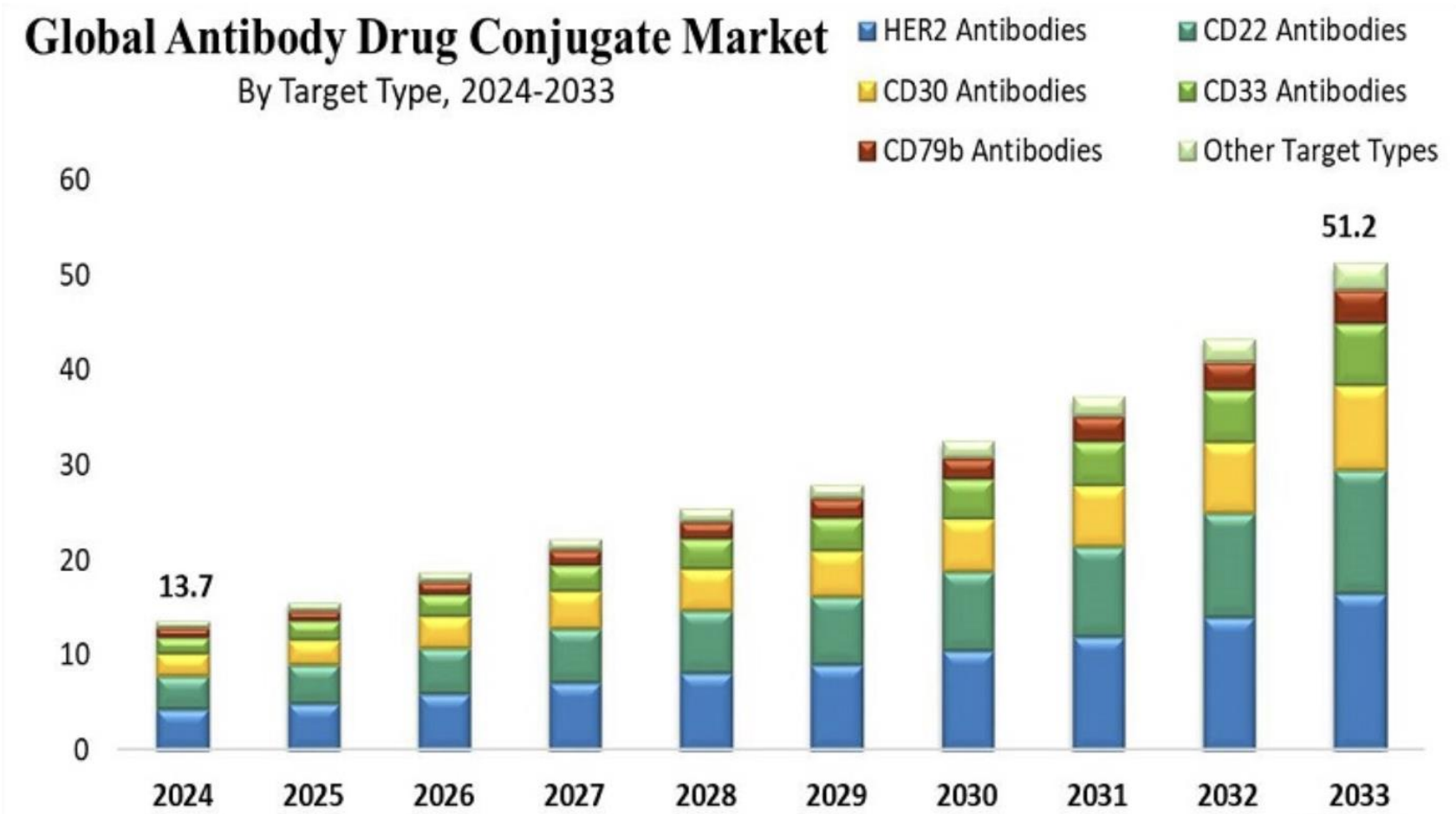
Drug development pipeline

Stage of Pipeline	Small Molecules	Biologics
Target Identification	Often enzyme, receptor, or ion-channel targets; wide diversity of intracellular targets	Usually extracellular or cell-surface targets (e.g., receptors, cytokines); often focus on immune-modulating pathways
Hit Discovery	High-throughput screening (HTS) of large chemical libraries; computational docking	Typically involves antibody generation platforms, phage display, hybridoma technology, or rational protein engineering
Lead Optimization	Extensive medicinal chemistry to improve potency, selectivity, ADME, and toxicity	Protein engineering to improve affinity, stability, half-life; glyco-engineering; humanization of antibodies
Preclinical Testing	Strong emphasis on ADME/PK optimization, metabolic stability, off-target safety	**Focus on immunogenicity**, PK in relevant species, and ensuring biological activity; fewer metabolism concerns because proteins degrade naturally
Manufacturing Development	Chemical process optimization; typically scalable and reproducible	**Cell-line development (CHO, HEK, yeast), bioprocess optimization, purification; significantly more complex and costly**
Formulation	Often oral formulations; stability is usually high	Typically injectable formulations; require cold-chain; stability and aggregation are major concerns
Clinical Trials – Phase I	Evaluate safety, dose, PK/PD; usually faster and cheaper	Often first-in-human antibody or protein studies; **immunogenicity** closely monitored
Clinical Trials – Phase II/III	Larger patient cohorts; generics easier to develop later	Larger trials needed for biologics; biosimilar development requires extensive analytical comparison
Regulatory Pathways	Relatively straightforward generics pathway; full molecular characterization possible	Complex regulatory requirements due to structural variability; biosimilar approval is challenging
Time & Cost	**Generally shorter timelines and lower cost**	**Longer timelines, high production cost, complex scale-up**

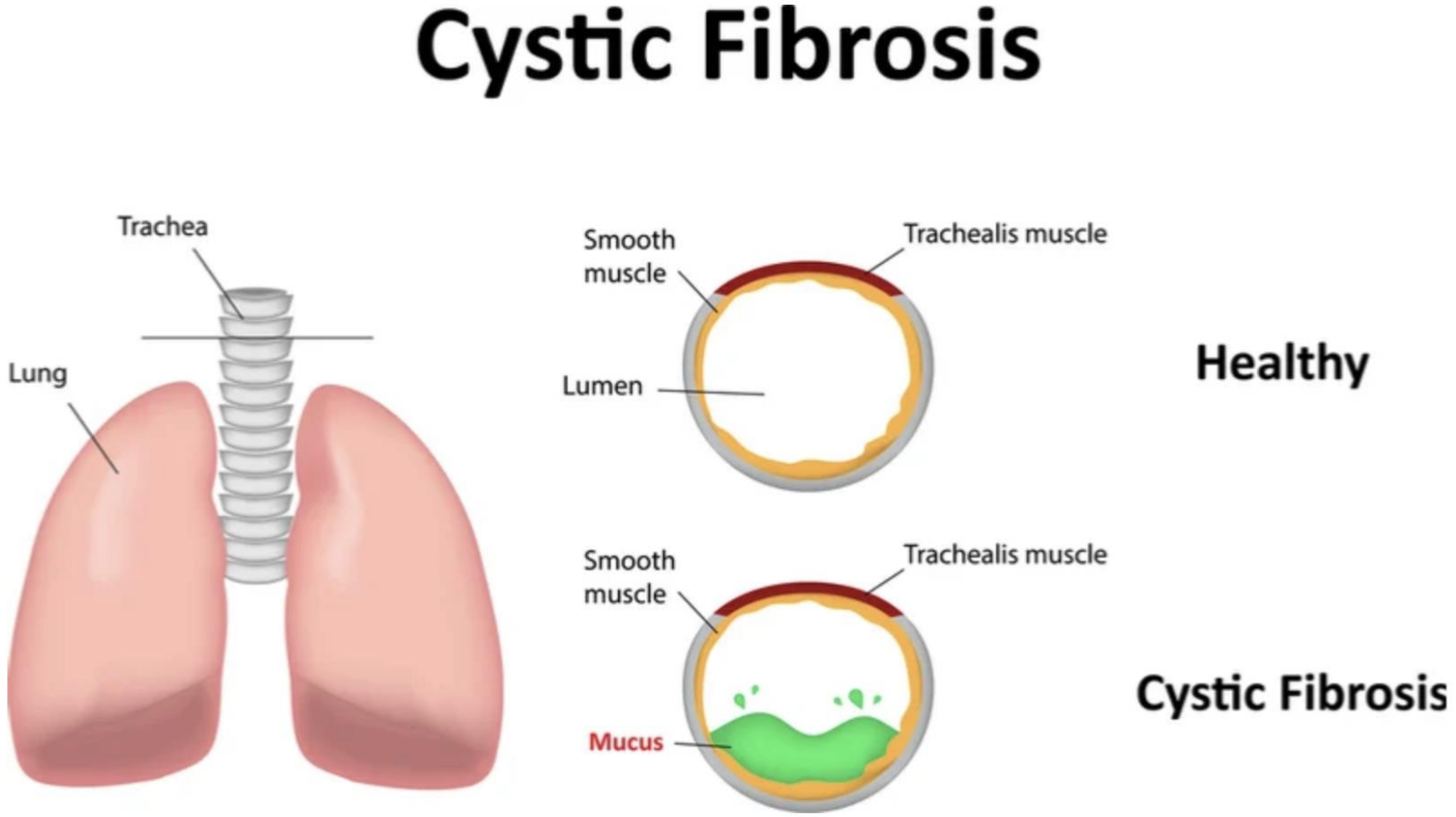
Antibody drug conjugates



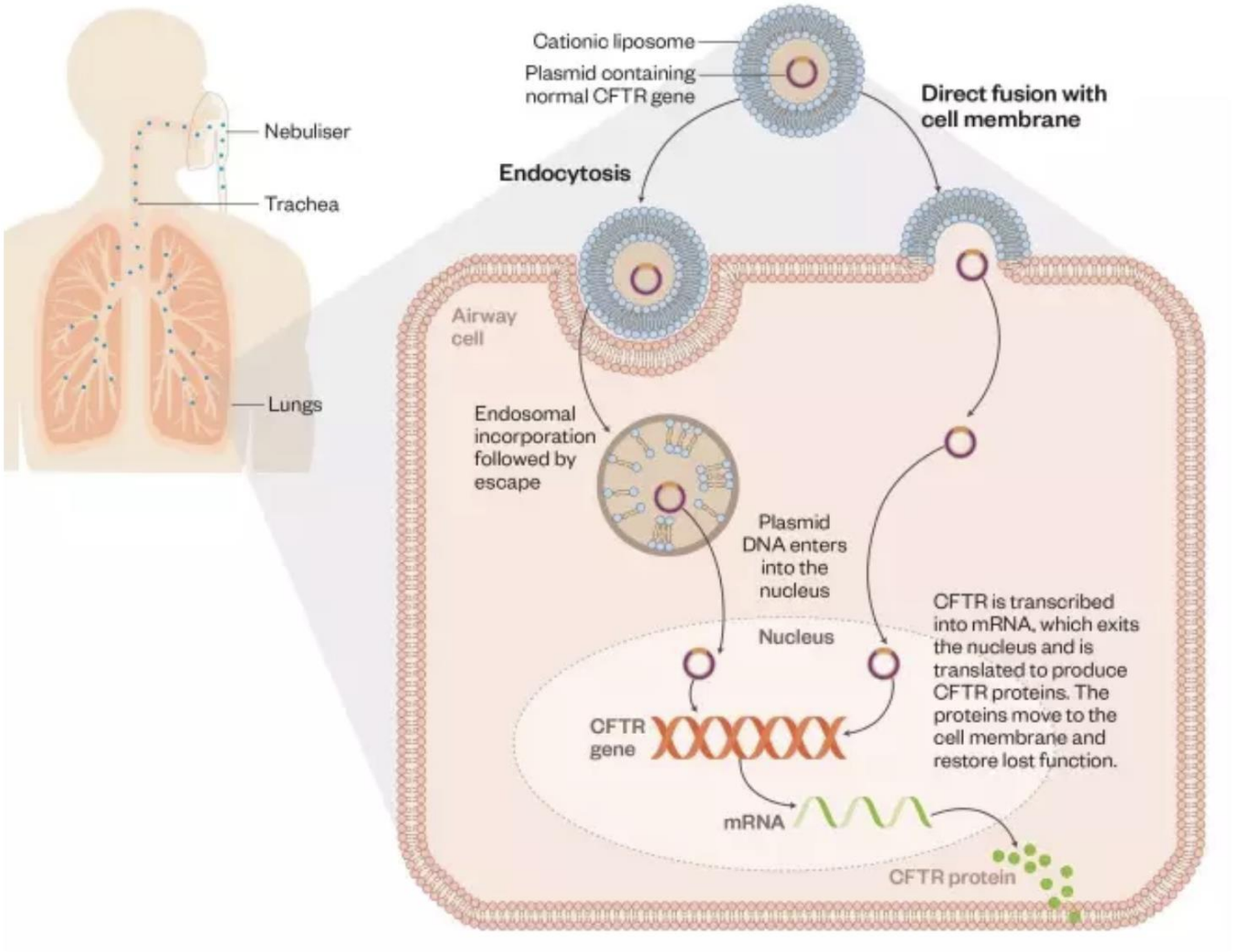
Market development in the next 10 years



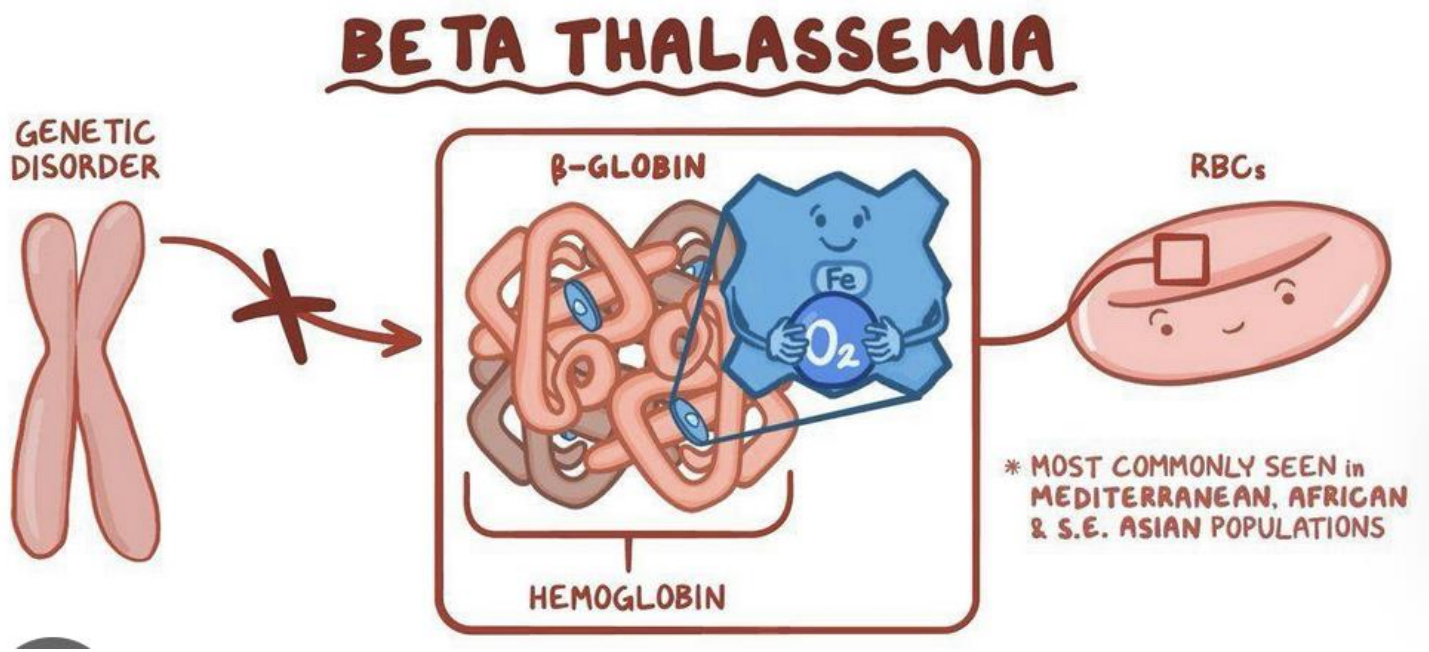
Gene therapies:



Gene therapies

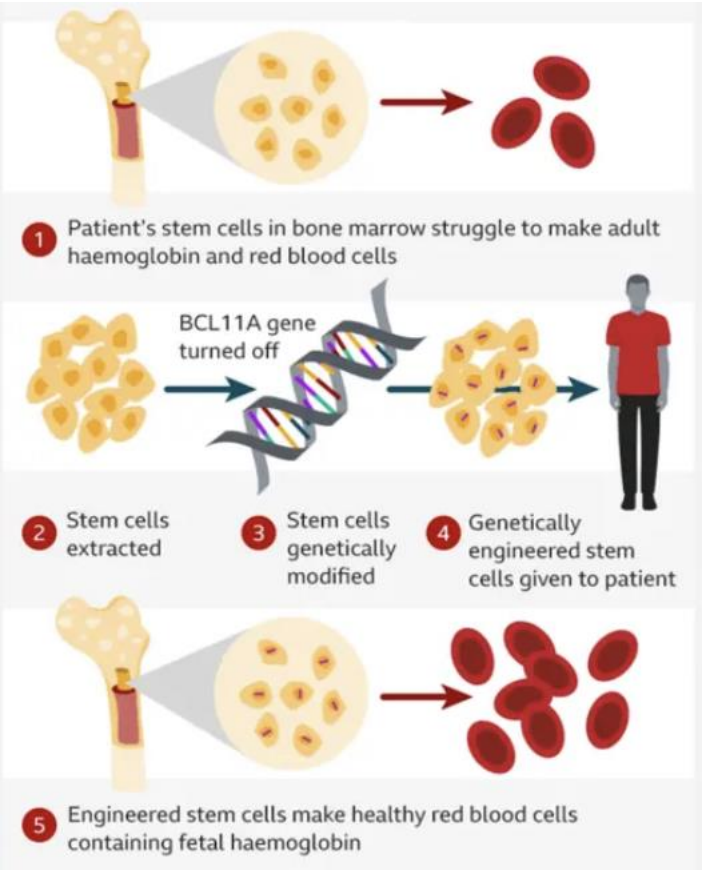


Gene editing based therapies



Gene editing based therapies

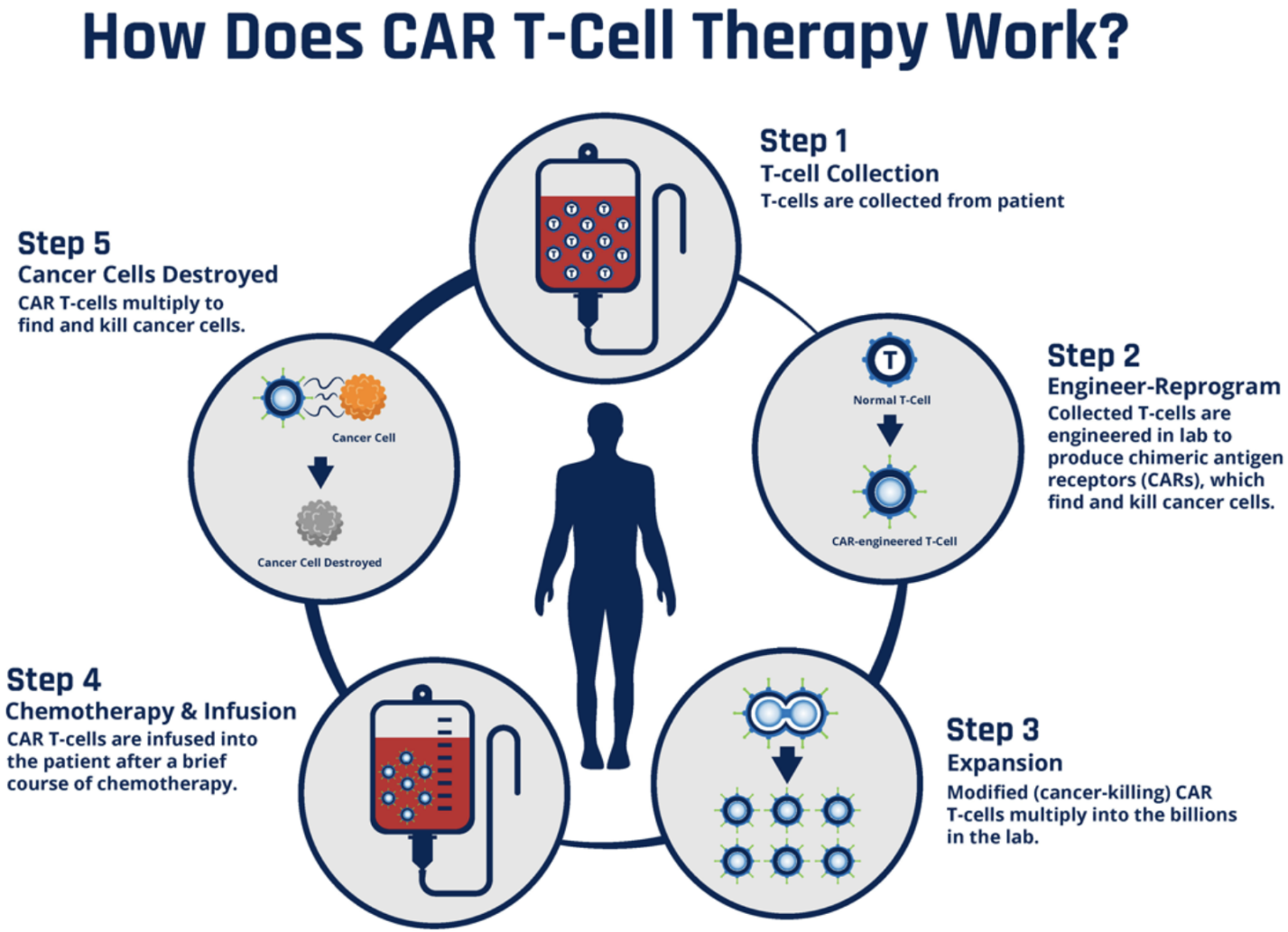
The UK has approved the world's first CRISPR-based genome editing therapy, called **Casgevy**, to treat severe sickle cell disease and beta-thalassaemia. The treatment is available through the NHS in England for patients aged 12 and over who have these conditions and cannot find a suitable stem cell donor. It involves editing a patient's own stem cells to correct the genetic mutation causing the disease.



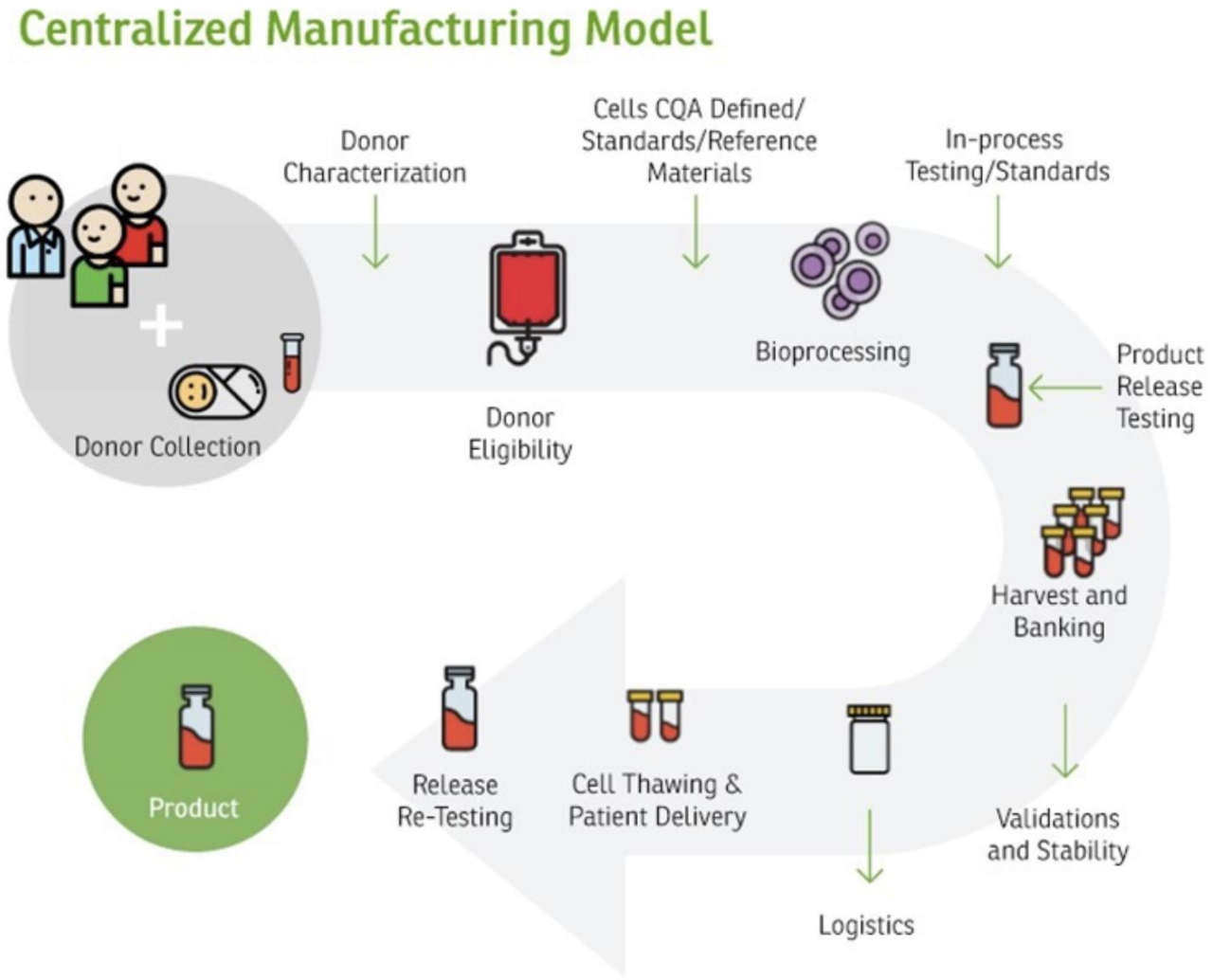
How the therapy works

- A patient's stem cells are collected.
- The cells are sent to a lab where they are edited using CRISPR technology to correct the gene that causes the blood disorder.
- The patient undergoes chemotherapy to prepare their body for the new cells.
- The edited stem cells are then infused back into the patient.

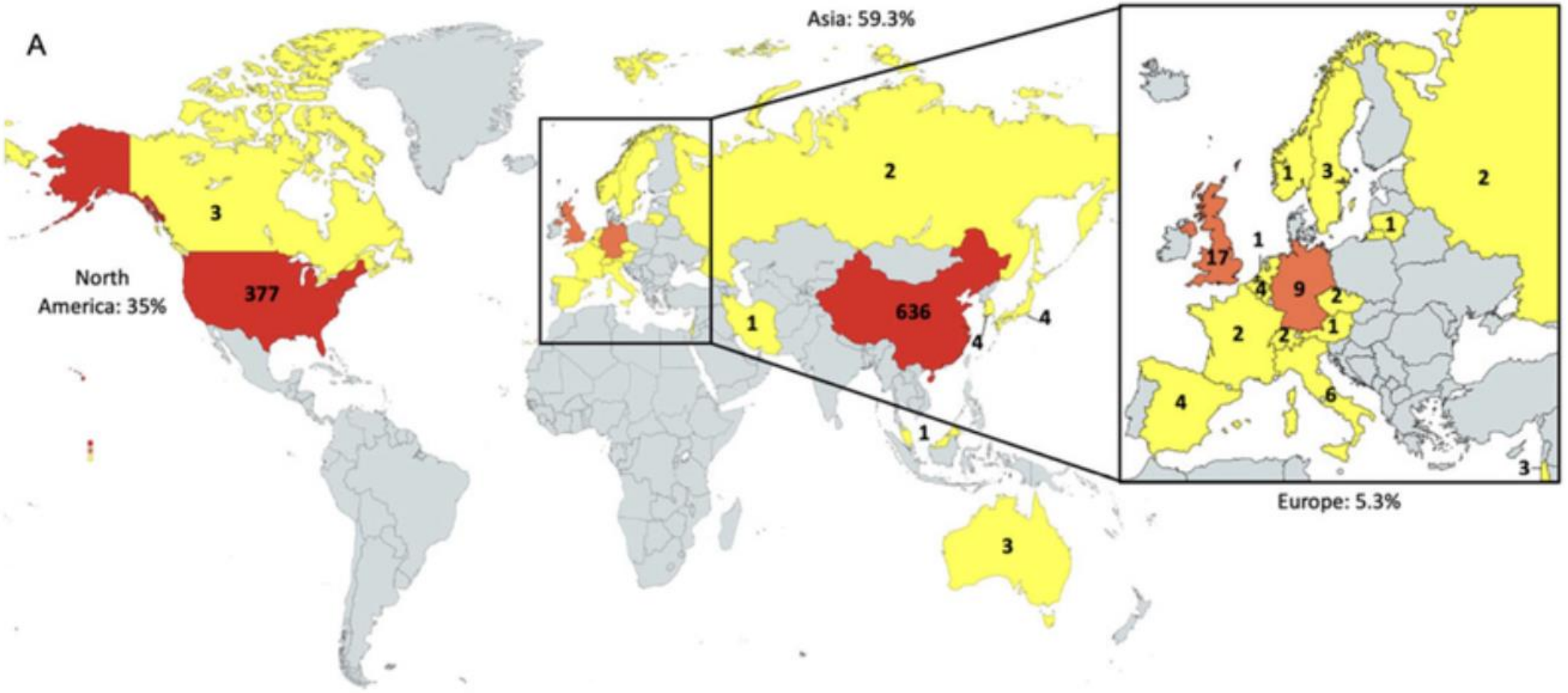
Cell based therapies: Car-T cell therapies



Manufacturing and distribution



Car-T cell therapy trial in 2022



Comparison of the cost

Therapy Type	Approximate Cost / Patient	Key Cost Drivers / Notes
CAR-T Cell Therapy	*One-time treatment:* ~ US$ 373,000–475,000 for the CAR-T product alone *Total median real-world cost:* ~ US$ 608,100 over the peri-CAR-T period for B-cell lymphoma (study) *European list price:* ~ €307,200–350,000 per treatment, + ~ €50,000 for pre-/post-infusion costs **Highly variable**: depending on region/regimen: ~US$ 450–1,200 per cycle	Manufacturing (engineering T cells), hospitalization, monitoring for side effects (like cytokine release syndrome), leukapheresis, lymphodepletion, ICU stays can drive cost very high.
Chemotherapy	Classic chemotherapy regimens in non-hospitalized settings (older studies): e.g., CHOP in non-Hodgkin's lymphoma ~ US$ 3,120 total for 4 cycles (in one economic evaluation) – In non-small-cell lung cancer (follow-up costs): around US$ 1,745/month in first months post-chemo in one Canadian study. (cancercare.mb.ca)	Drug cost (which depends heavily on the specific chemo agents), number of cycles, hospital vs outpatient administration, supportive care (anti-nausea, transfusions), imaging and blood tests all impact total cost.
Antibody-Drug Conjugates (ADCs)	US$ 12,000- to 23,900	Drug acquisition is a major driver, but because ADCs are given in cycles, repeated dosing costs matter. Also, adverse event management, infusion costs, and hospital visits add up.

Exercise

https://www.sciencedirect.com/science/article/pii/S2590098620300622

The exam will be after Prof McKinney's exam

It will be 5 open questions (1 questions will be on the paper of the exercise)