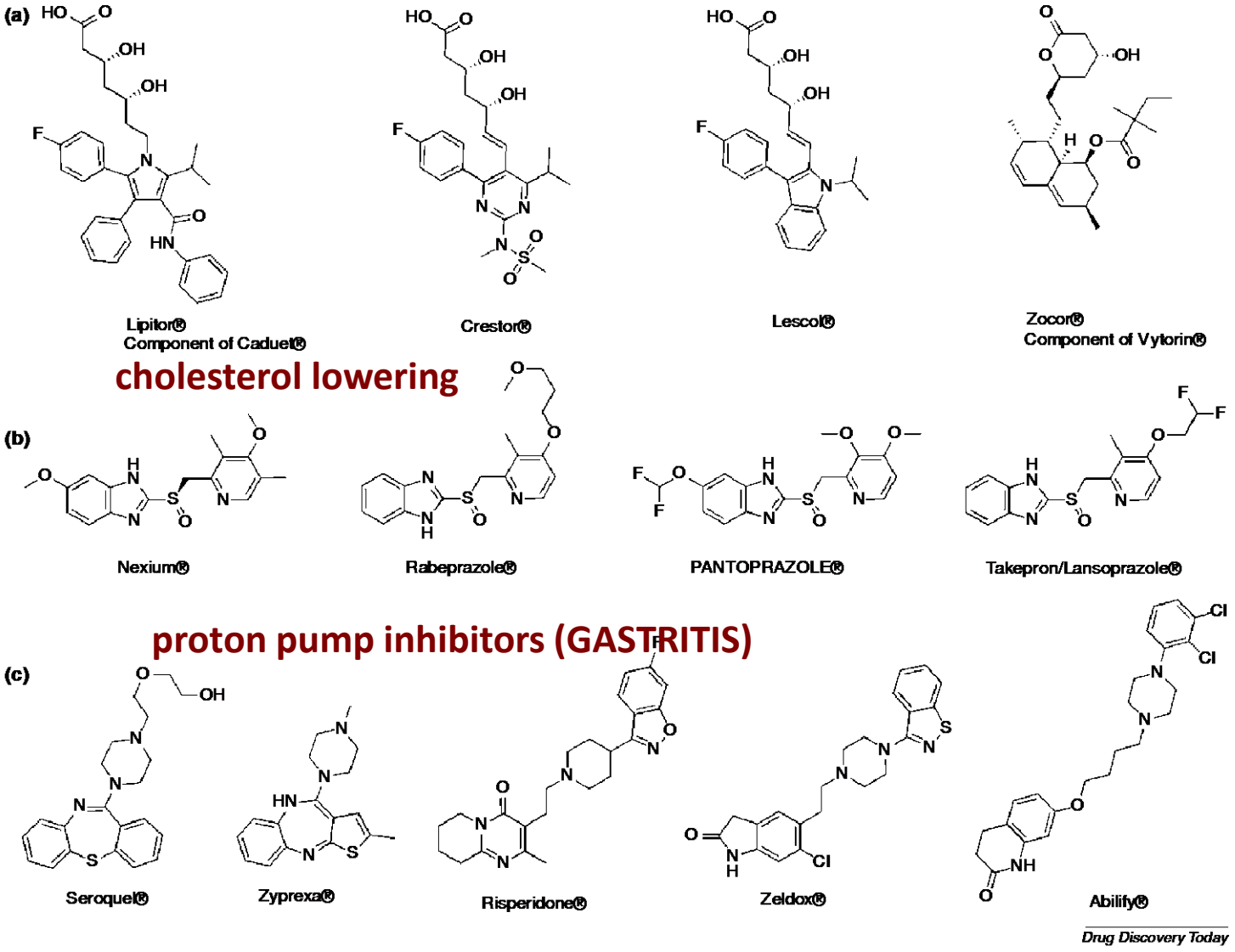
BEST-SELLING DRUGS IN 2009



schizophrenia, bipolar disorder, antidepressant

Best selling drugs in 2014: biologic medicines more than small molecules

Top 10 drugs 2014 sales ($m)				
Brand	**Indication**	**Company**	**2014 sales ($m)**	**2020 sales ($m)**
Humira	Autoimmune (various)	AbbVie	12543	14780
Sovaldi	Hepatitis C	Gilead	10283	16621
Remicade	Autoimmune (various)	J&J/Merck & Co.	9240	7601
Enbrel	Autoimmune (various)	Amgen/Pfizer	8538	7754
Lantus	Diabetes	Sanofi	8433	5497
Rituxan	Leukaemia/lymphoma	Roche	7550	5486
Avastin	Cancer (various)	Roche	7021	6480
Advair	Asthma/COPD	GSK	6971	2582
Herceptin	HER2+ breast cancer	Roche	6866	4573
Januvia	Diabetes	Merck & Co.	6002	9187

Source: Company reported data; Bloomberg

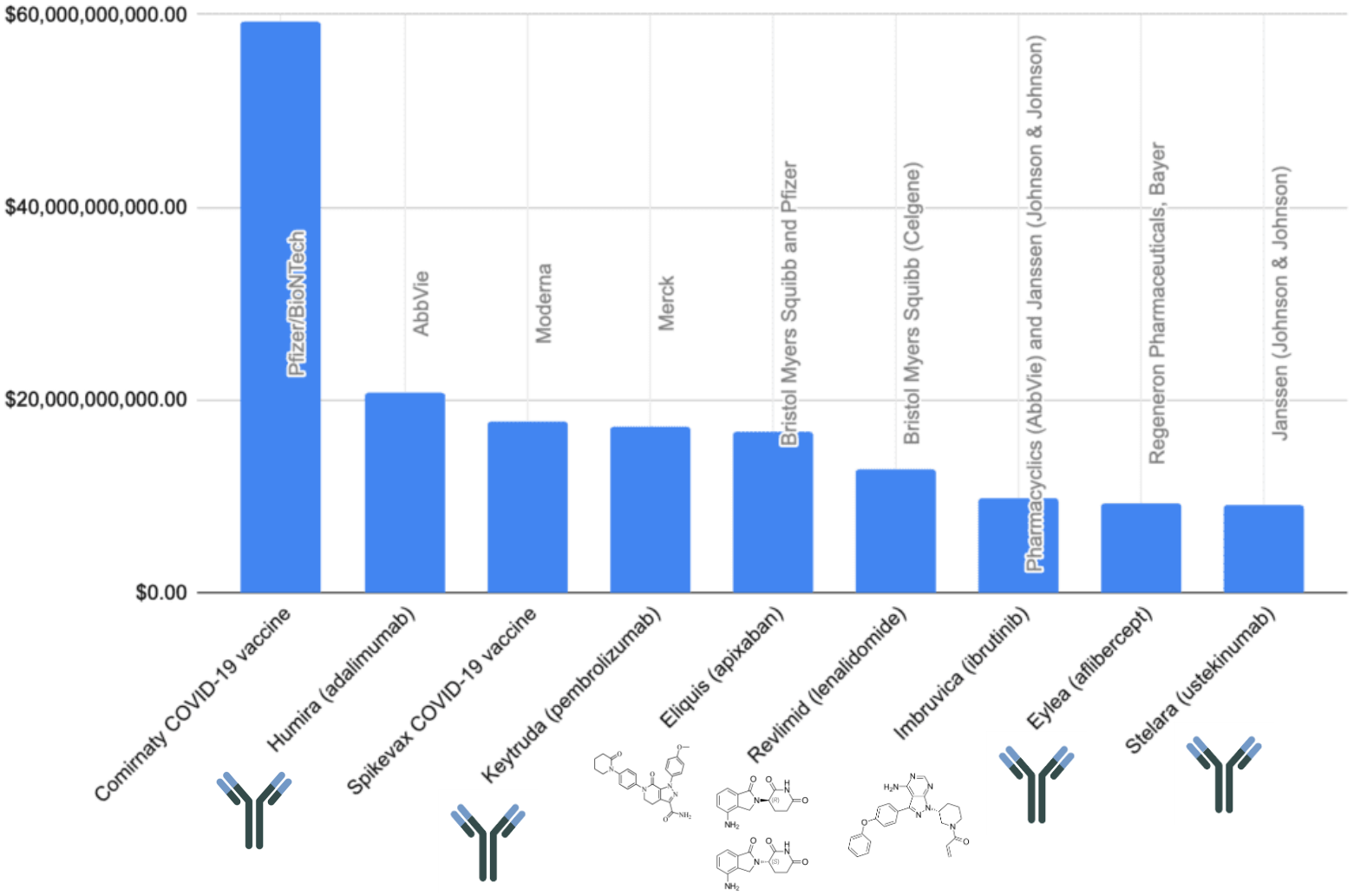
Drug marketed in the second quarter of 2018

Table 1 | **FDA new drug approvals in Q2 2018**

Date	Drug (brand name; company)	Mechanism	Indication	2024 global sales forecast
17 April[a]	Burosumab (Crysvita; Ultragenyx Pharmaceutical/ Kyowa Hakko Kirin)	FGF23 mAb	X-linked hypophosphataemia	$1,091 million
17 April	Fostamatinib (Tavalisse; Rigel Pharmaceuticals)	SYK inhibitor	Idiopathic thrombocytopenic purpura	$418 million
19 April	Palonosetron and fosnetupitant (Akynzeo IV; Helsinn Group)	5-HT_3 receptor antagonist and NK_1 receptor antagonist	Chemotherapy-induced emesis	NA
3 May[a]	Recombinant coagulation factor Xa; inactivated (AndexXa; Portola Pharmaceuticals)	Factor Xa inhibitor antidote	Reversal of anticoagulation	$987 million
16 May	Sodium zirconium cyclosilicate (Lokelma; AstraZeneca)	Potassium ion sorbent	Hyperkalaemia	$929 million
16 May[a]	Lofexidine (Lucemyra; STADA Arzneimittel)	α_2-adrenoceptor agonist	Opioid addiction	NA
17 May	Erenumab (Aimovig; Novartis/Amgen)	CGRP receptor mAb	Migraine	$1,708 million
21 May	Avatrombopag (Doptelet; Dova Pharmaceuticals)	Thrombopoietin receptor agonist	Thrombocytopenia	$399 million
24 May	Pegvaliase (Palynziq; BioMarin Pharmaceutical)	PAL replacement therapy	Phenylketonuria	$486 million
31 May	Baricitinib (Olumiant; Incyte/Eli Lilly)	JAK1/2 inhibitor	Rheumatoid arthritis	$1,415 million
14 June	Moxidectin (NA; Medicines Development for Global Health)	γ-aminobutyric acid and glutamate channel modulator	River blindness	NA
25 June[b]	Cannabidiol (Epidiolex; GW Pharmaceuticals)	Cannabinoid receptor agonist	Dravet syndrome; Lennox–Gastaut syndrome	$2,349 million
25 June[a,b]	Plazomicin (Zemdri; Achaogen)	Bacterial 70S ribosome inhibitor	Urinary tract infections	$312 million
27 June	Binimetinib[c] and encorafenib[c] (Braftovi and Mektovi; Array BioPharma)	MEK inhibitor and BRAF inhibitor	Melanoma	$743 million and $882 million

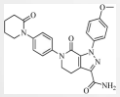
[a]Breakthrough therapy designation. [b]Fast track. [c]Both components of the combination are new molecular entities. 5-HT, 5-hydroxytryptamine; CGRP; calcitonin gene-related peptide; FGF, fibroblast growth factor; JAK, Janus-associated kinase; mAb, monoclonal antibody; MEK, mitogen-activated protein kinase kinase; NA, not available; NK, neurokinin; PAL, phenylalanine ammonia lyase; SYK, spleen tyrosine kinase.

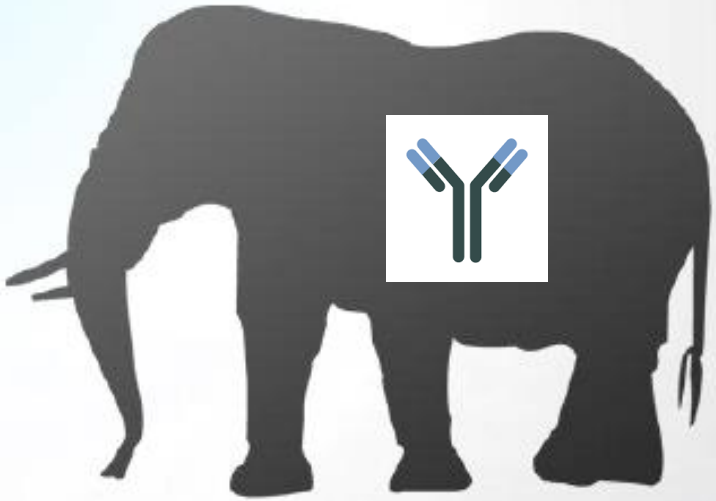
Best selling drugs in 2021



Small molecules vs biologic medecines

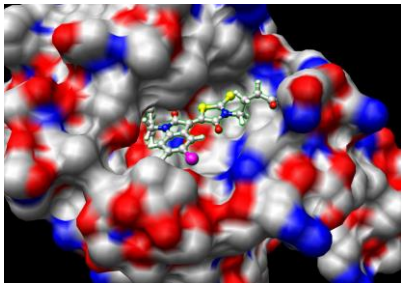
On average, biologic medicines are 100 to 1,000 times larger than small-molecule medicines



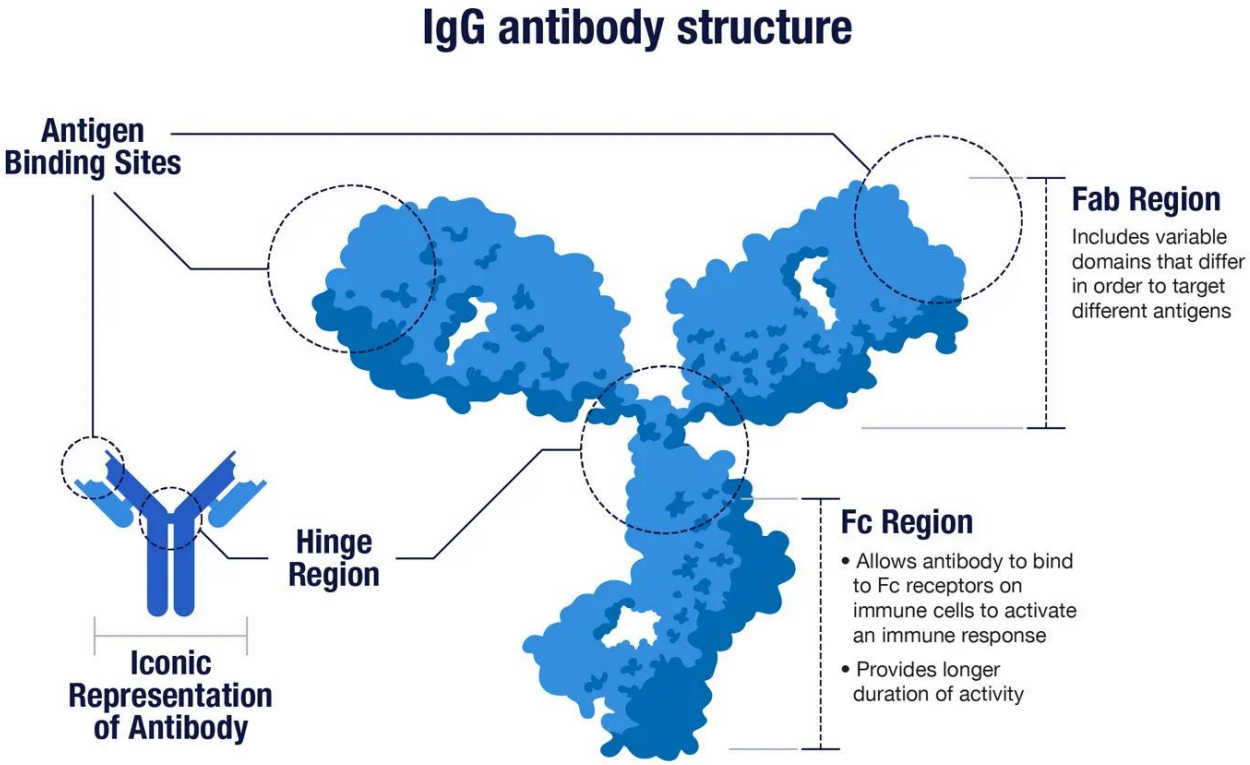


5 Weight (kg) 5,000

Affinity and specificity for the target



small molecule-protein interaction (μM to nM affinity)



Ab -protein interaction (nM to pM affinity)

Drug-target interactions:

Ionic interactions = 20 kJ/mol

Hydrogen bonds = 7-40 kJ/mol

Van der Waals interactions = 1.9 kJ/mol

Hydrophobic interactions

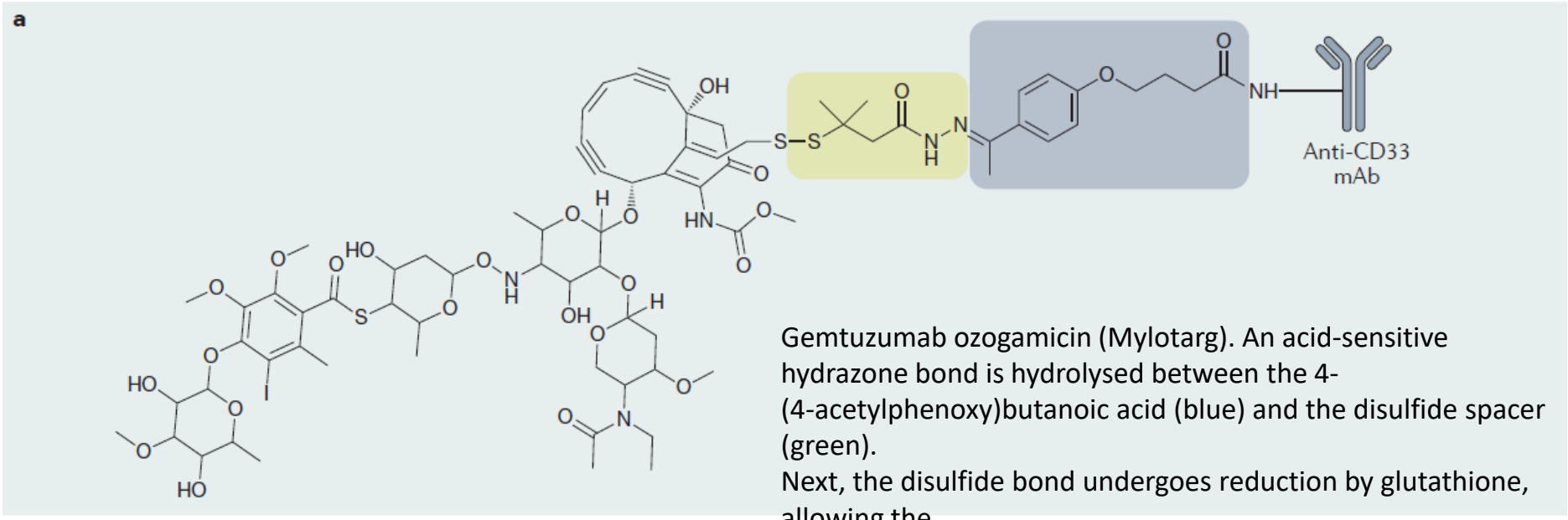
small molecules vs biologics: manufacturing and safety

Size	**- Small (single molecule) - Low molecular weight**	**- Large (mixture of related molecules) - High molecular weight**
Structure	Simple, well defined, independent of manufacturing process	Complex (heterogeneous), defined by the exact manufacturing process
Manufacturing	- Produced by chemical synthesis - Predictable chemical process - Identical copy can be made	- Produced in living cell culture - Difficult to control from starting material to final API - Impossible to ensure identical copy
Characterisation	Easy to characterise completely	Cannot be characterised completely the molecular composition and heterogenicity
Stability	Stable	Unstable, sensitive to external conditions

Antibody-drug conjugates (ADCs)

- Antibody–drug conjugates (ADCs) link an active drug to a monoclonal antibody, which specifically recognizes a cellular surface antigen and delivers the drug directly to the target cell (tumor cell).
- The chemical conjugation of the antibody to the cytotoxic drug has a major influence on the pharmacokinetics, selectivity and therapeutic index of the therapy. Because the conjugation is formed through a cleavable bond in most of the clinically used ADCs, these conjugates can be regarded as macromolecular prodrugs.

- This targeting strategy has been especially successful in the treatment of various cancers. For example, the enediyne anticancer agent calicheamicin is too toxic to be used as a chemotherapeutic. However, a slightly modified calicheamicin, linked to a humanized antibody through a spacer, was developed as gemtuzumab ozogamicin



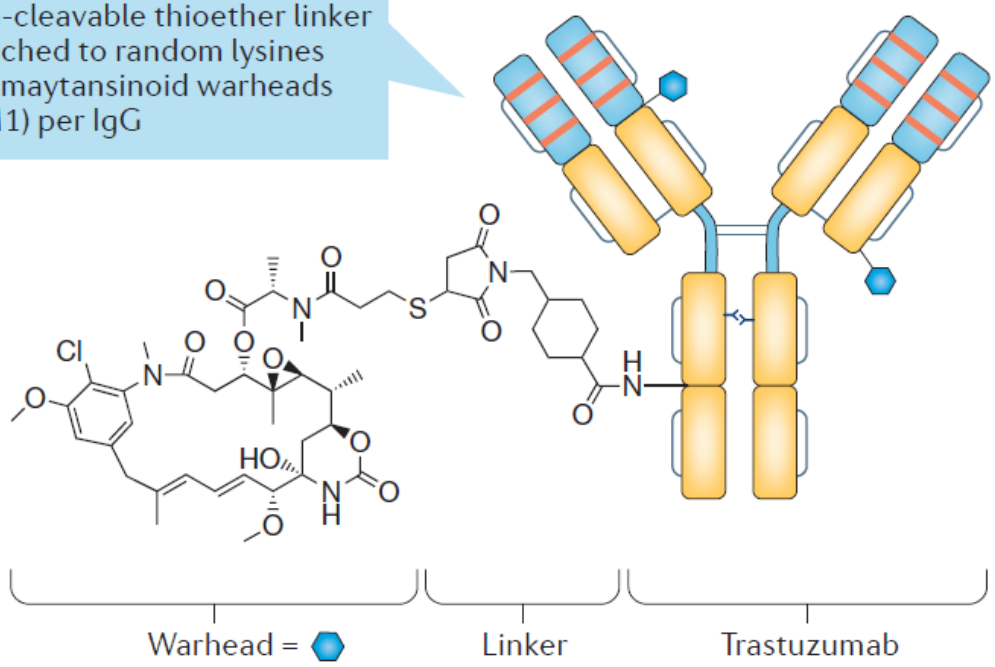
Gemtuzumab ozogamicin (Mylotarg). An acid-sensitive hydrazone bond is hydrolysed between the 4-(4-acetylphenoxy)butanoic acid (blue) and the disulfide spacer (green).
Next, the disulfide bond undergoes reduction by glutathione, allowing the
sulfhydryl intermediate to cyclize onto the enediyne core structure to form
a reactive species

Antibody-drug conjugates (antitumoral drugs)

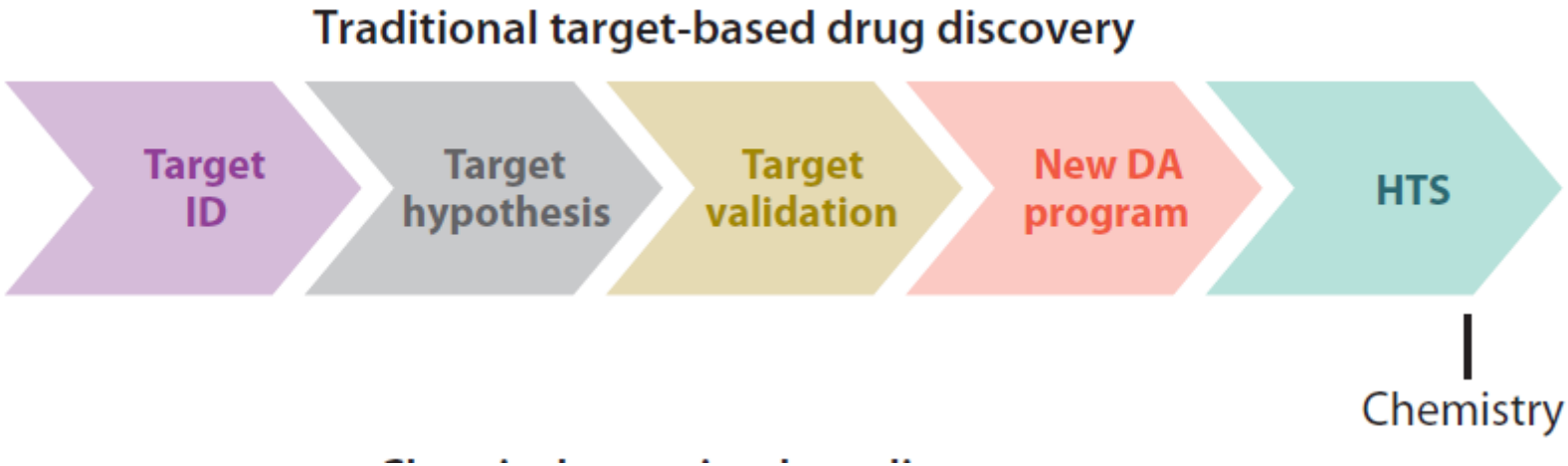
- Antibody–drug conjugates (ADCs) consist of recombinant monoclonal antibodies (mAbs) that are covalently bound to cytotoxic chemicals (known as warheads) via synthetic linkers.
- Such immunoconjugates combine the antitumour potency of highly cytotoxic small-molecule drugs (300–1,000 Da, with subnanomolar half-maximal inhibitory concentration (IC50) values) with the high selectivity, stability and favourable pharmacokinetic profile of mAbs.

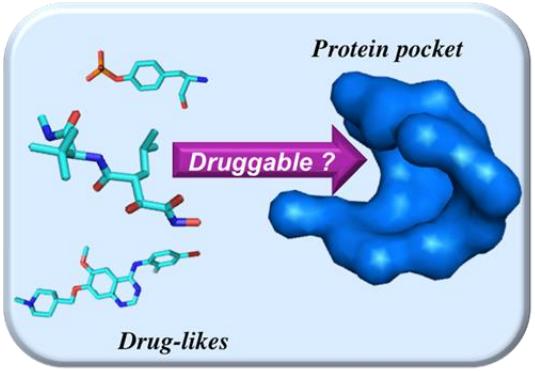
b **Trastuzumab emtansine**

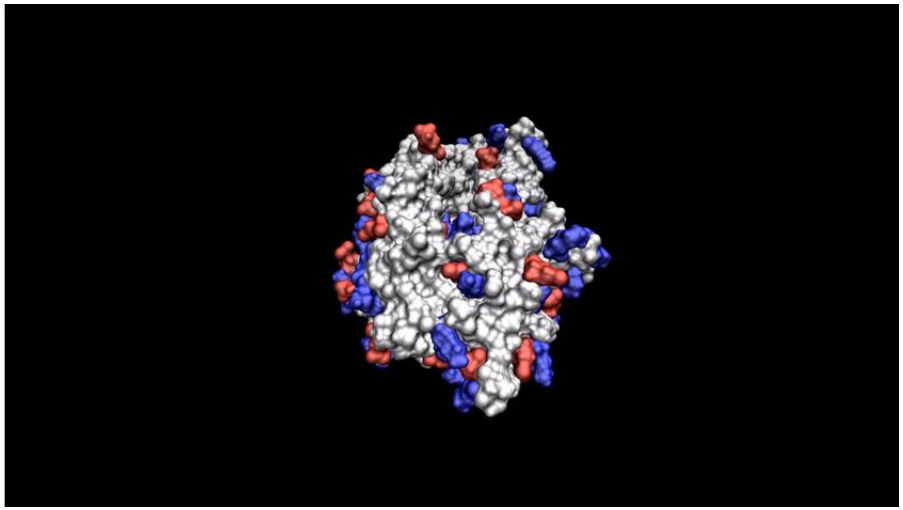
Second generation
- IgG1 mAb
- Non-cleavable thioether linker attached to random lysines
- 3–4 maytansinoid warheads (DM1) per IgG



Target-based DD







Target-based DD

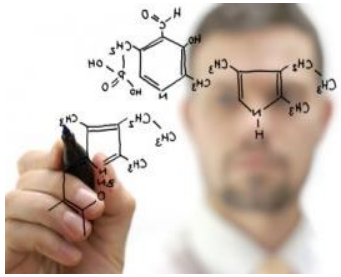
- Identify the pathology (medical need or economic revenue?)
- Target identification
- Dicovery of Hit compound (RDD, serendipity, combinatorial chemistry, from natural products)
- Hit to Lead: lead optimization (pharmacockinetic parameters (ADMET) including toxicity)
- Clinical trials (Phase I, II, III, IV)
- Market

Preclinical phase

HIT to LEAD: the DMTA cycles

- Standard small-molecule drug discovery approaches can conceptually be broken down into two components. The first component is an initial screen — often a high-throughput *in vitro* assay that can screen up to ~10^6 compounds — to identify compounds that show some level of the desired activity (hits). Setting up and analysing such screens typically takes 1 year[1].
- The second component is the optimization of hits into leads through design–make–test– analyse cycles (DMTA cycles), ultimately leading to the selection of a candidate drug. In addition to the desired biological activity, such optimization has to take into account other properties that are crucial for candidate drugs, including pharmacokinetics and safety.

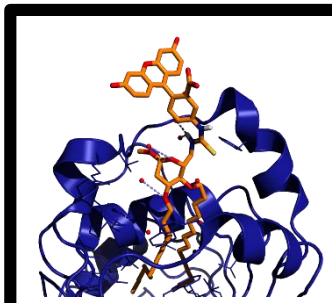
Hit to lead and DMTA cycle



Molecule design

DMTA cycle

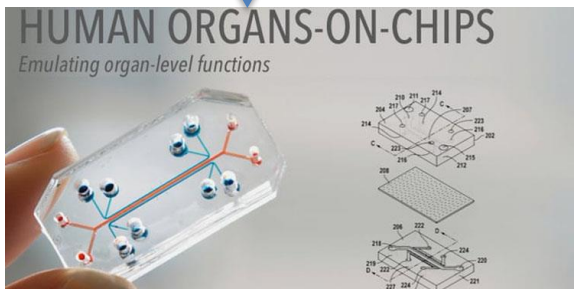
?



computational studies

Chemical Synthesis

In vitro experiments

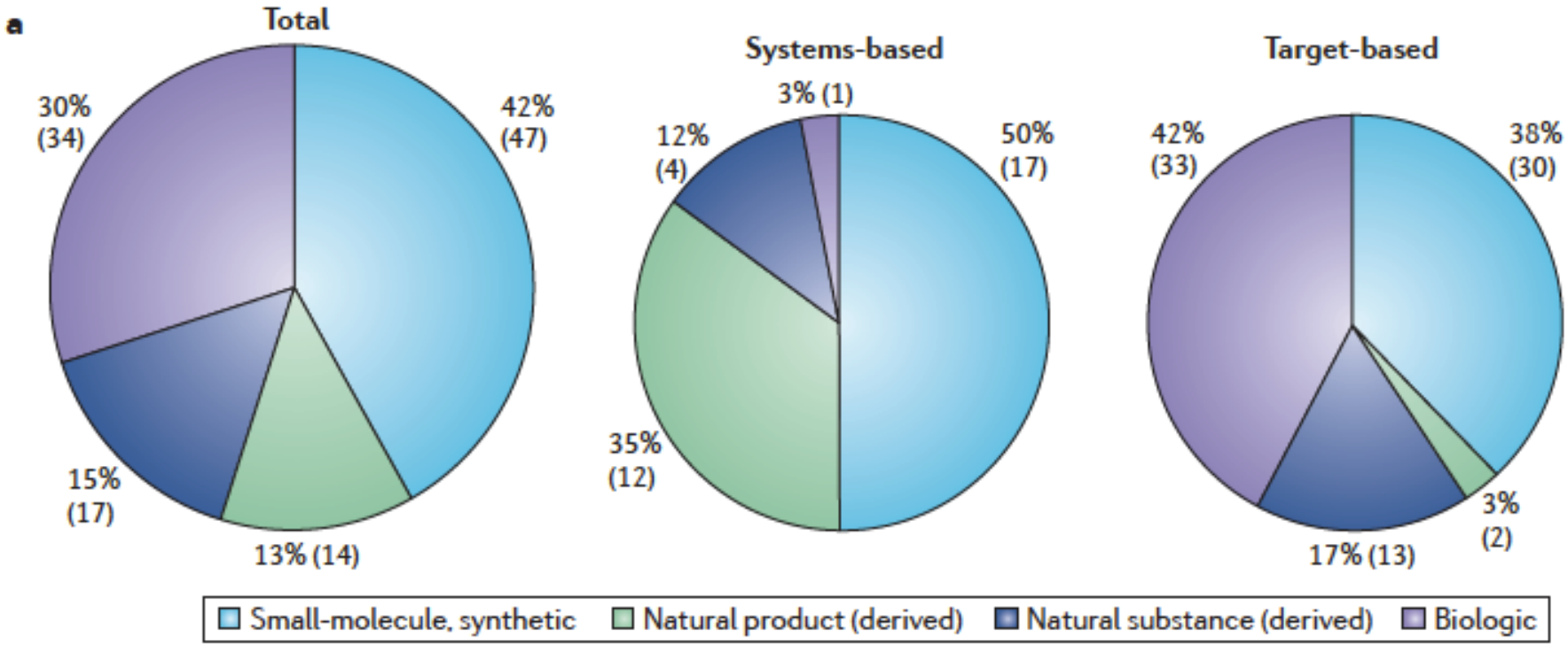


In vivo experiments

The discovery of first-in-class drugs: origins and evolution

Jörg Eder, Richard Sedrani and Christian Wiesmann

Nat Rev Drug Discov 2014



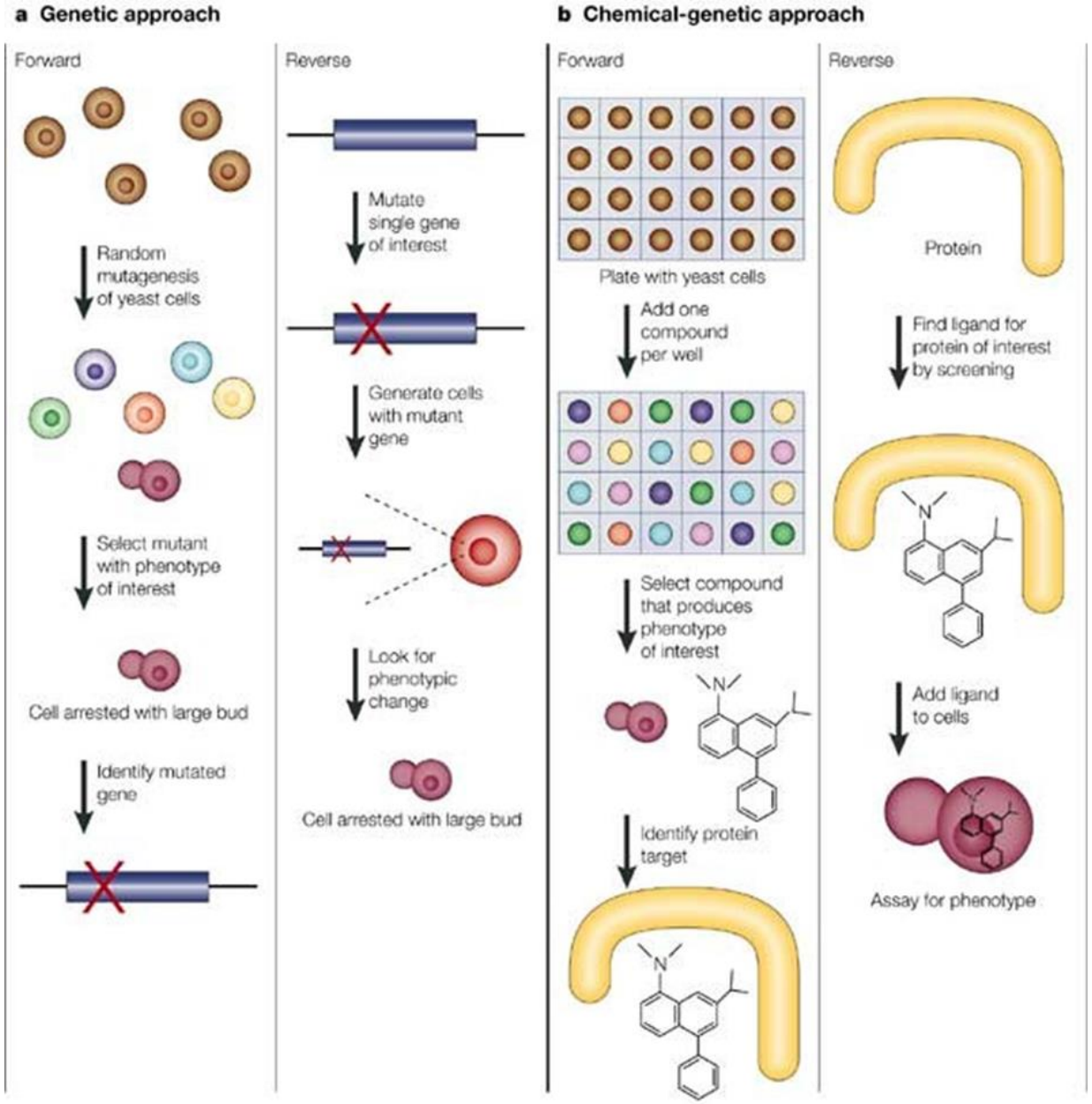
Failure of the target-based approach

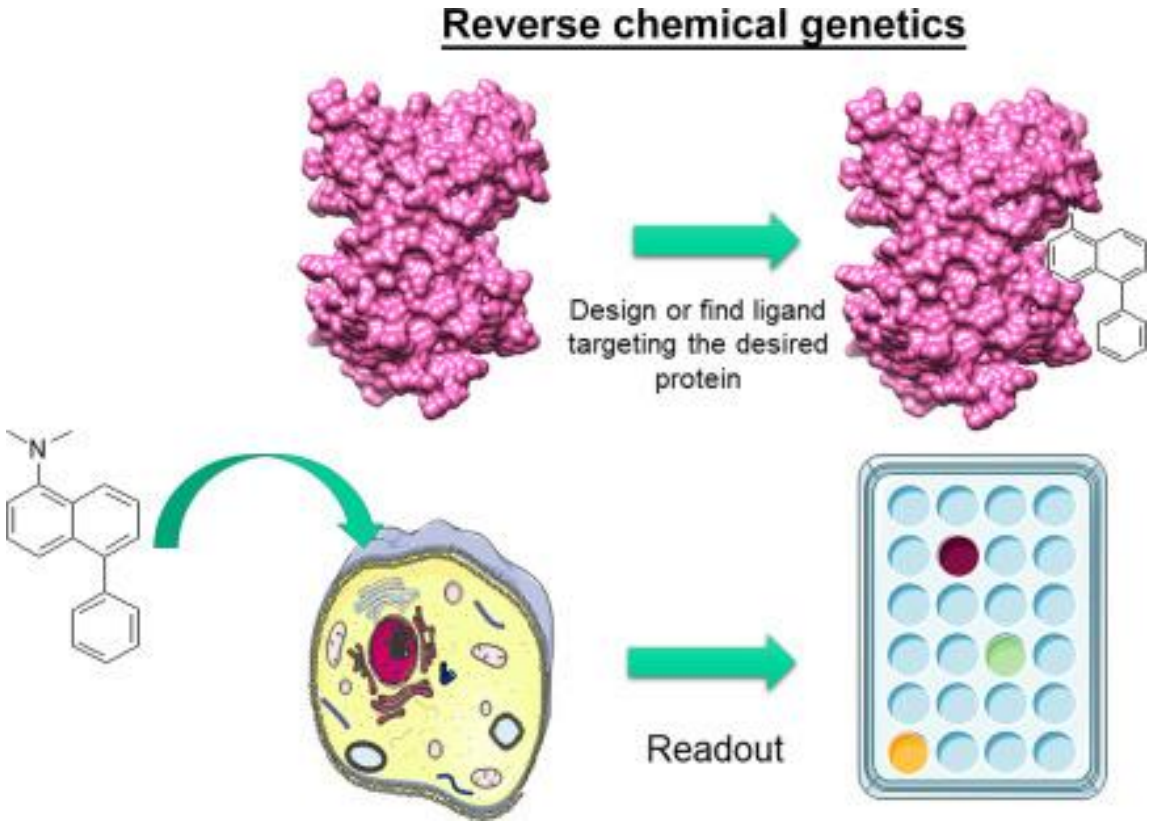
- the discovery and validation of novel disease-relevant targets continue to be low, and many disease-relevant targets and pathways have remained “undruggable.” It may be fair to say that the recent decline in innovative drugs is largely due to exhaustion of validated and tractable targets, but a counterargument can be made that the traditional approach to drug and target discovery no longer works.
- To maintain a healthy pipeline of novel validated targets for drug discovery, pharmaceutical companies must apply new and innovative approaches.

Genetics vs chemical genetics

- interpreting the functions of a given gene by eliminating its expression is an oversimplified approach, especially in the context of identifying pharmacological tractable mechanisms.

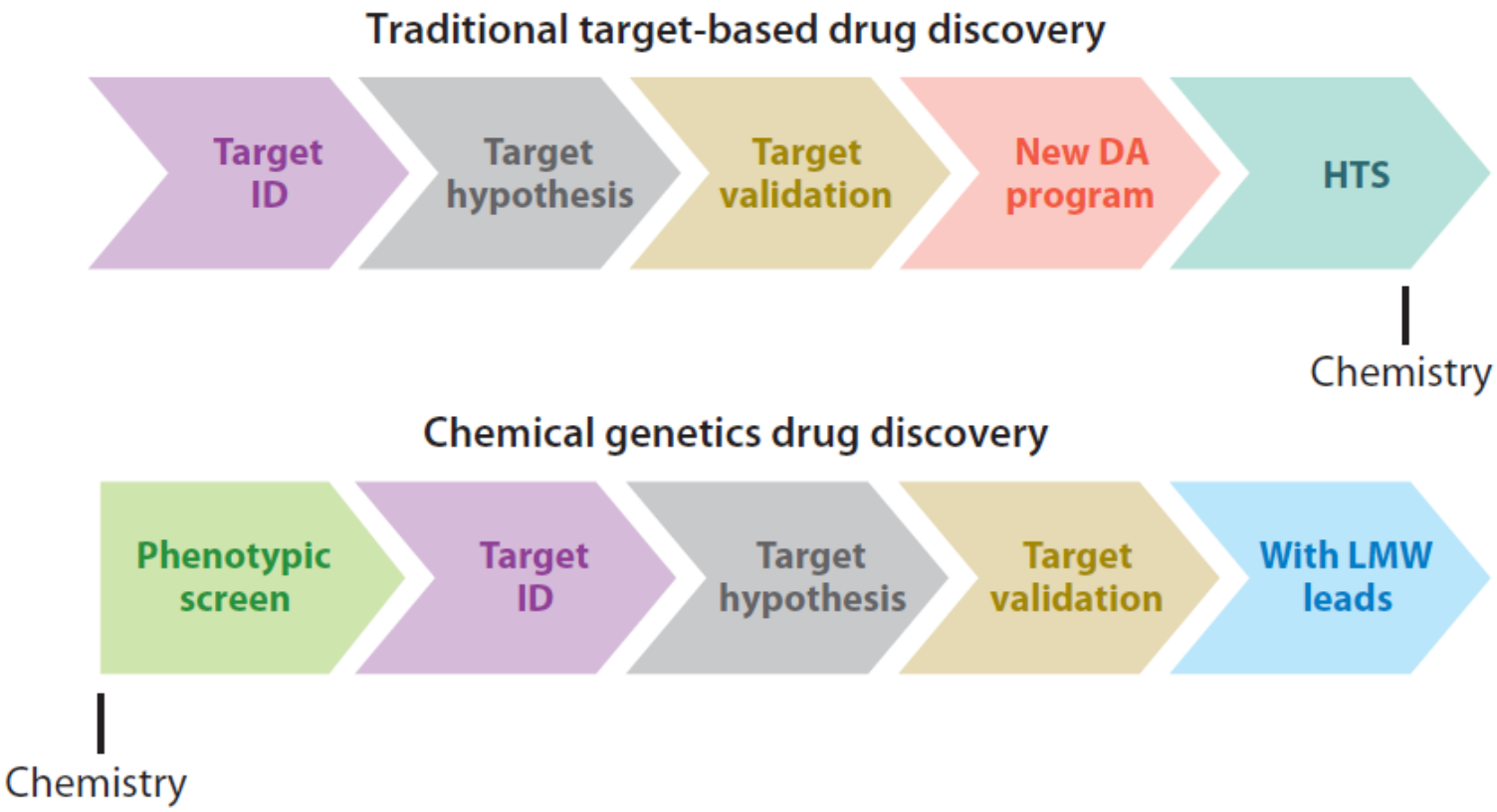
- As an alternative approach for target discovery, chemical genetics, the study of genes through small-molecule perturbation, holds many advantages over traditional genetics . Disease can be caused by an imbalance in molecular signaling pathways; thus, chemicals that rebalance these pathways should have therapeutic potential


a Genetic approach
b Chemical-genetic approach
Forward
Random mutagenesis of yeast cells
Select mutant with phenotype of interest
Cell arrested with large bud
Identify mutated gene
Reverse
Mutate single gene of interest
Generate cells with mutant gene
Look for phenotypic change
Cell arrested with large bud
Forward
Plate with yeast cells
Add one compound per well
Select compound that produces phenotype of interest
Identify protein target
Reverse
Protein
Find ligand for protein of interest by screening
Add ligand to cells
Assay for phenotype

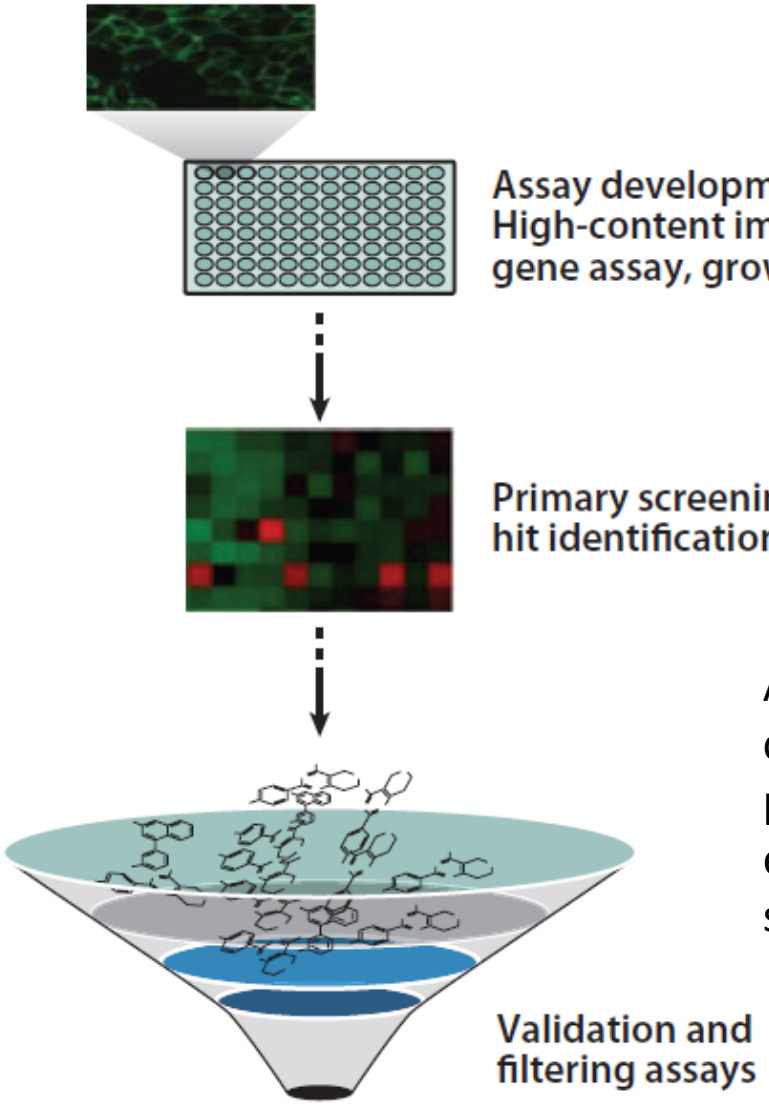


- Unlike the traditional target-based screen that relies on a predefined, often poorly validated target, the (reverse) chemical genetics–based phenotypic screen probes the entire pathway for the most “druggable” node

Chemical Genetics–Based Target Identification in Drug Discovery



Compounds screen and hit selection



A primary cell-based assay that captures pathways or phenotypic readouts is established and validated to screen a compound library.

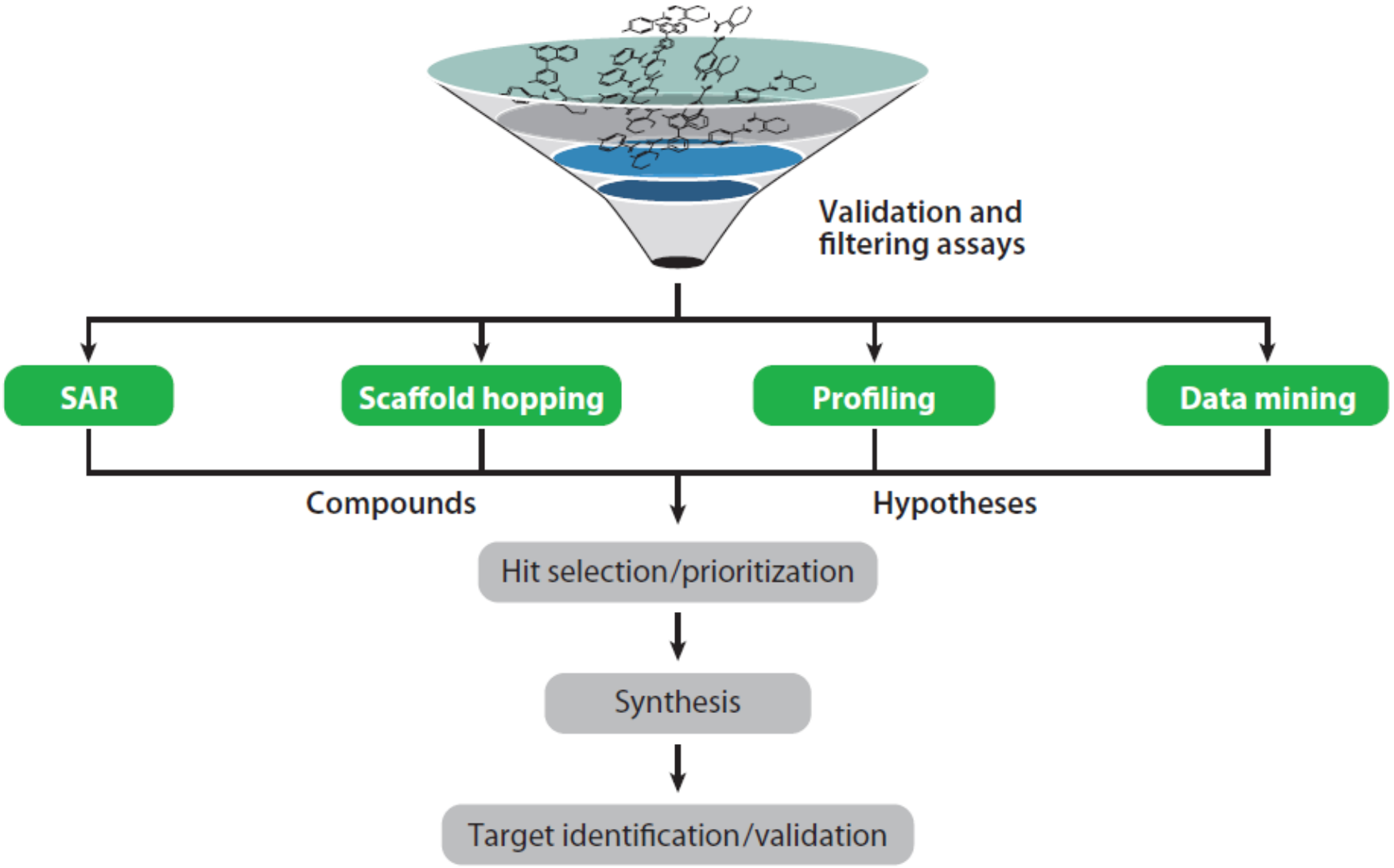
The workflow

- Owing to the frequent off-target effects of primary screen compounds, it is essential to implement counter screens and secondary screens to filter nonspecific hits in order to arrive at a group of high-confidence hit compounds.
- In silico methods for scaffold hopping and compound similarity searching can be utilized to select groups of similar molecules to generate structure-activity relationships (SAR) data to better understand the relevant "warhead."
- In parallel, profiling and data mining can also arrive at hypotheses and facilitate hit selection and prioritization.

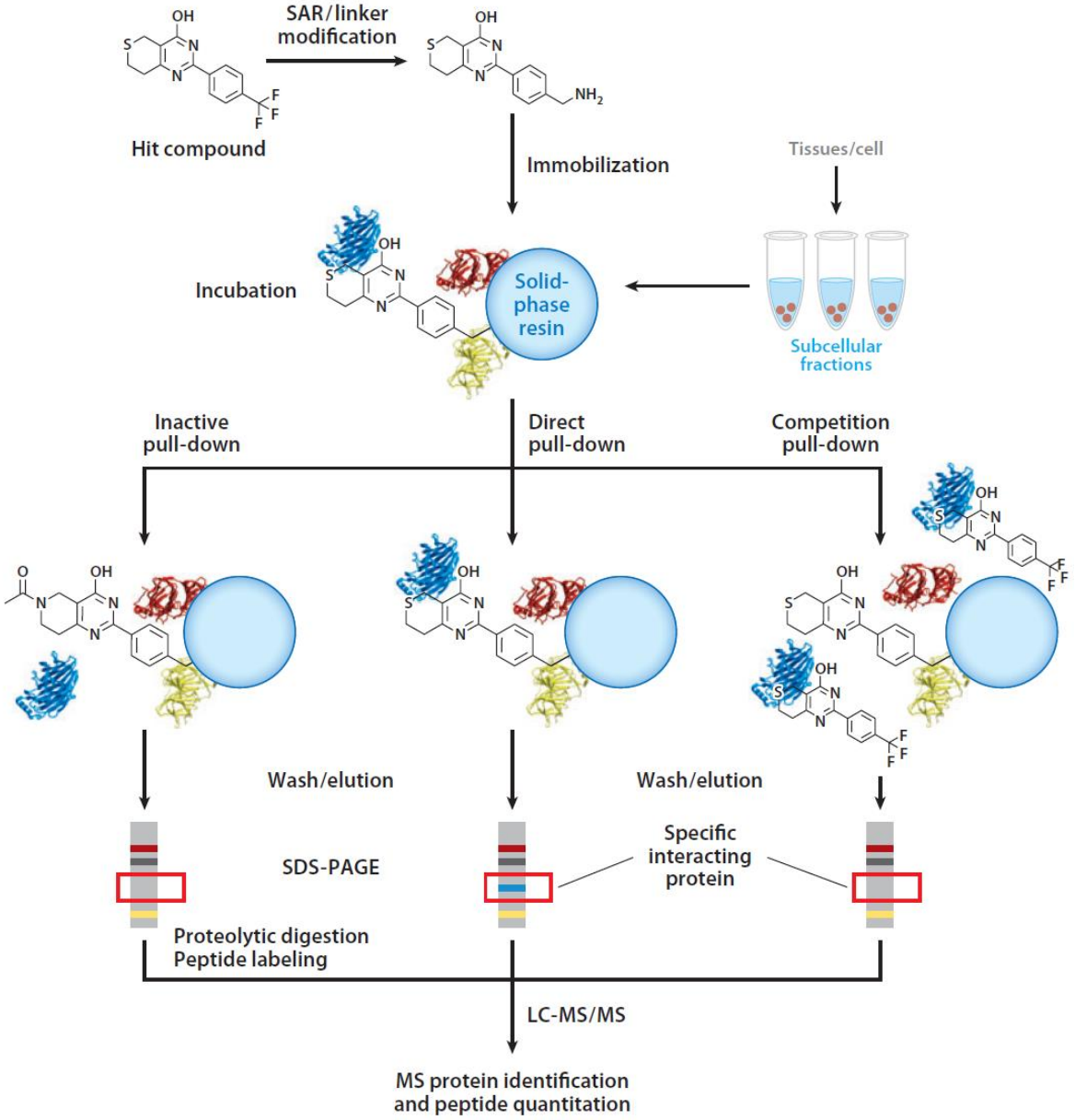
- Next, chemistry is initiated to expand the SAR for the hit and to identify sites for linker modification or prepare chemical probes.

- Target identification is conducted with the compound-linked beads by affinity purification of interacting proteins.
- This is followed by protein identification and quantification through the use of liquid chromatography–tandem mass spectrometry (LC-MS/MS) or other chemical probes.
- The final step is target validation through genetic, biochemical, or biophysical means.

Hit selection/prioritization



Chemical proteomics

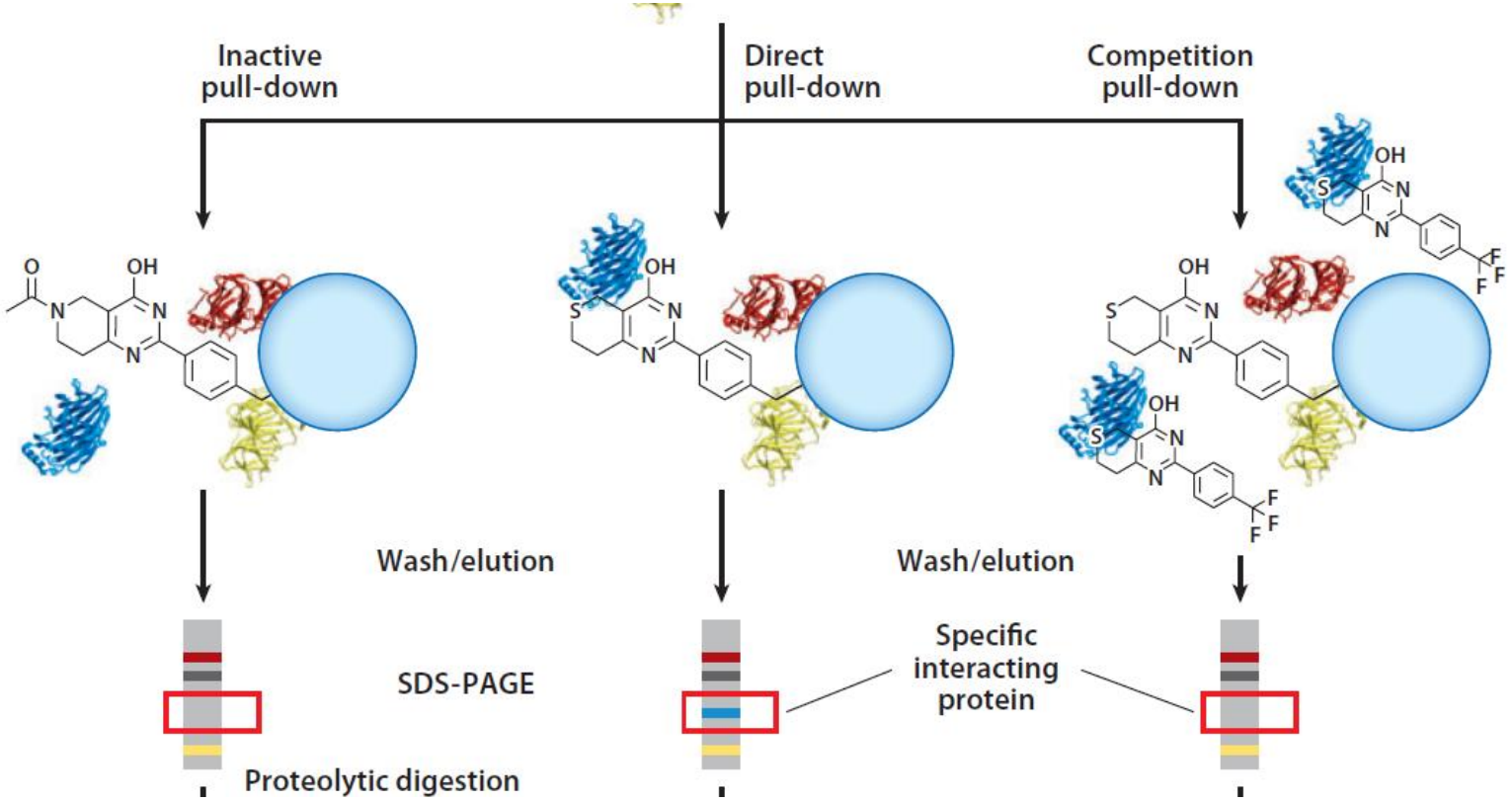


Chemical proteomics represents a key approach for target identification . It consists of the classical drug-affinity chromatography and modern high-resolution mass spectrometry (MS) analysis for protein identification

drug-affinity chromatography

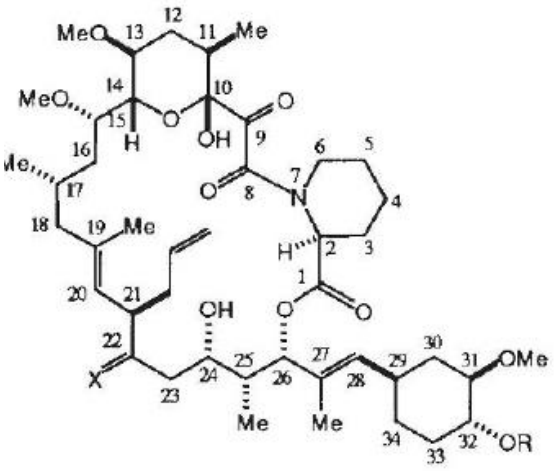
- The compound-immobilized resin is incubated with lysate prepared from whole cells/tissues or subcellular fractions. In direct pull-down mode (middle), the resin-enriched proteins are separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE).
- The specific bands are then proteolytically digested, and the proteins are identified by liquid chromatography–tandem mass spectrometry (LC-MS/MS). To better discern specific binding proteins from nonspecific binders, parallel experiments are performed: incubation with an immobilized inactive compound (left) or incubation with a free active compound (right). In both of these pull-down modes, the specific binding proteins are removed while the nonspecific binding proteins remain.
- Quantitative comparison of these experiments can be performed using isobaric tags for relative and absolute quantitation (iTRAQ) labeling of the peptides after separation and proteolytic digestion of the proteins through MS/MS. For quantification using stable isotope labeling by amino acids in cell culture (SILAC), the affinity purifications with light and heavy labeled cell lysates are performed in parallel (not shown) and combined immediately before protein separation by SDS-PAGE.

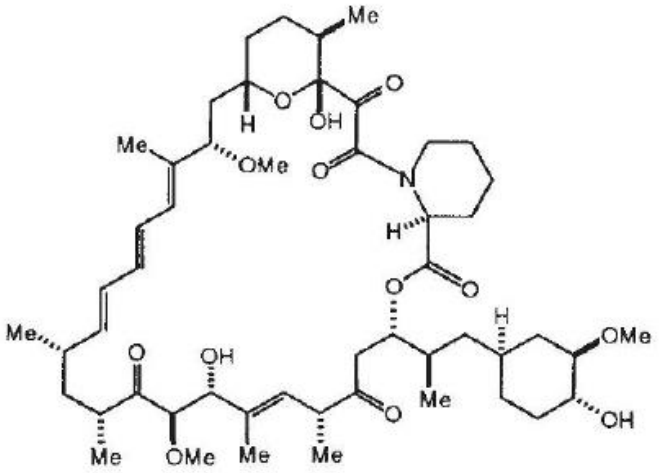
Metodi per evitare falsi postivi



A receptor for the immunosuppressant FKS06 is a cis-trans peptidyl-prolyl isomerase

Matthew W. Harding, Andrzej Galat, t
David E. Uehlingt & Stuart L. Schreibert





5 (rapamycin)

1 X = O, R = H (FK-506)

↓ L-Selectride

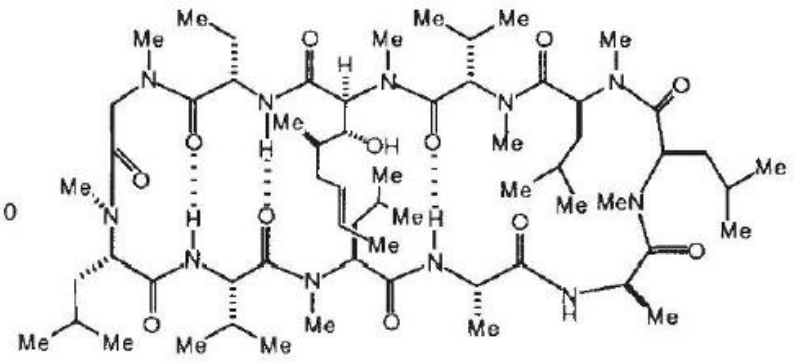
2 X = α-OH, β-H

↓ 1. $N_3(CH_2)_2COCl$
2. $HS(CH_2)_3SH$
3. affigel-10

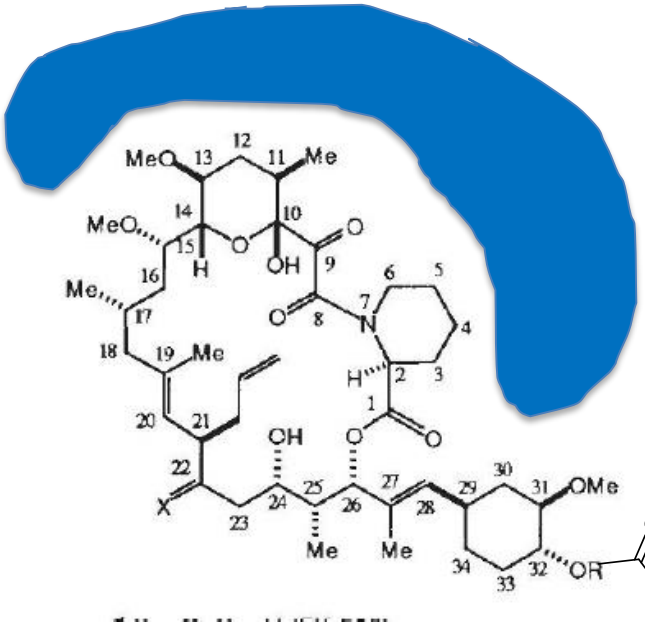
3 X = α-OH, β-H
R = -(C=O)$(CH_2)_2$NH(C=O)-affigel-10

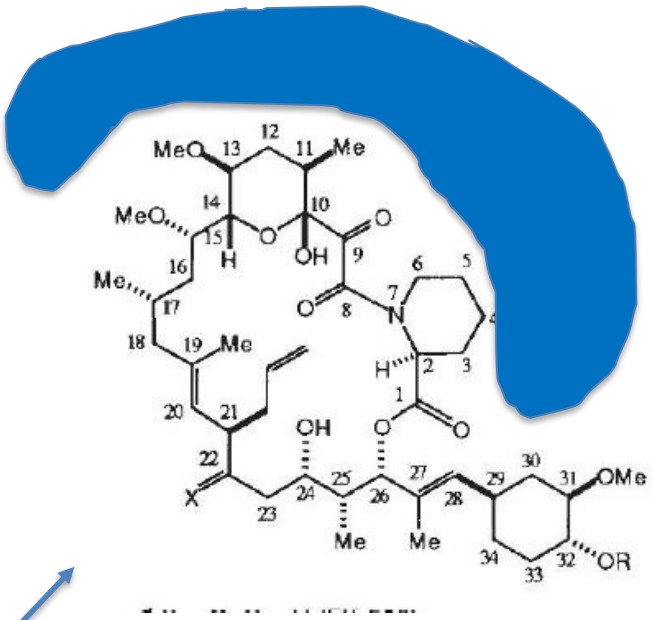
↓ ^{14}C-benzoyl chloride

4 X = O
R = -(^{14}C=O)C_6H_5



6 (cyclosporin A (CsA))


MeO
Me
OH
OMe
OR
Me
Me


MeO
Me
OH
OMe
OR
Me
Me

A receptor for the immunosuppressant FKS06 is a cis-trans peptidyl-prolyl isomerase

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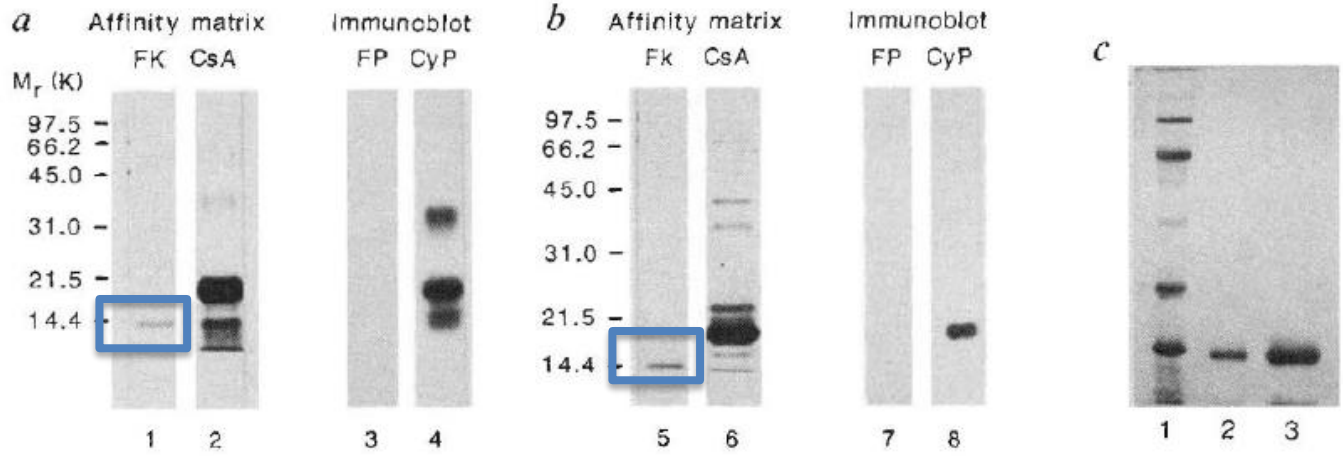
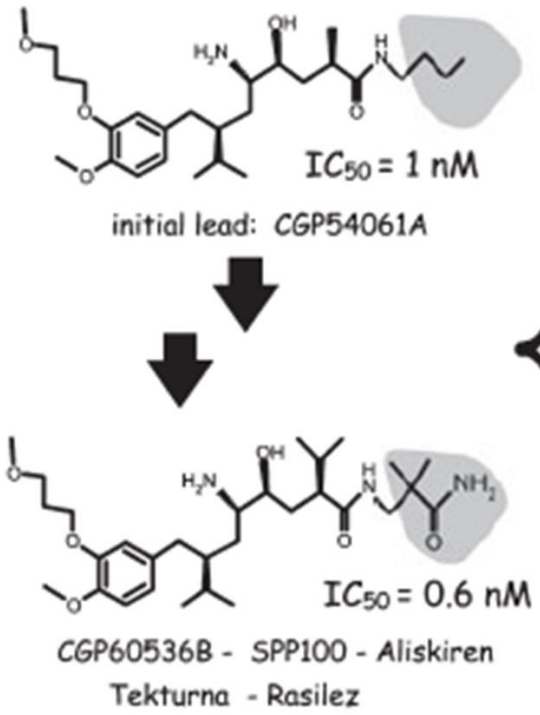


When cytosol extracts of bovine thymus and of human spleen were adsorbed onto the FK506 matrix and the column eluted with FK506, a single protein of -14K was obtained (Fig 2, lanes 1 and 5).

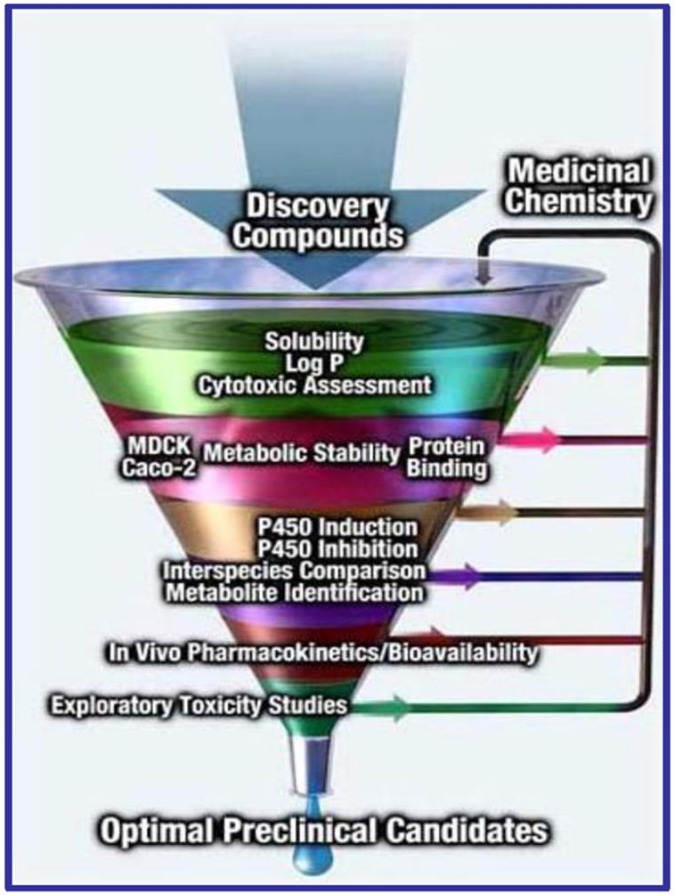
FK506 also displaced a 14K protein from the FK506 matrix in experiments with cytosol extracts of bovine kidney, human and murine liver, and EL4 cells.

Hit to lead optimization (PD + PK) preclinical phase

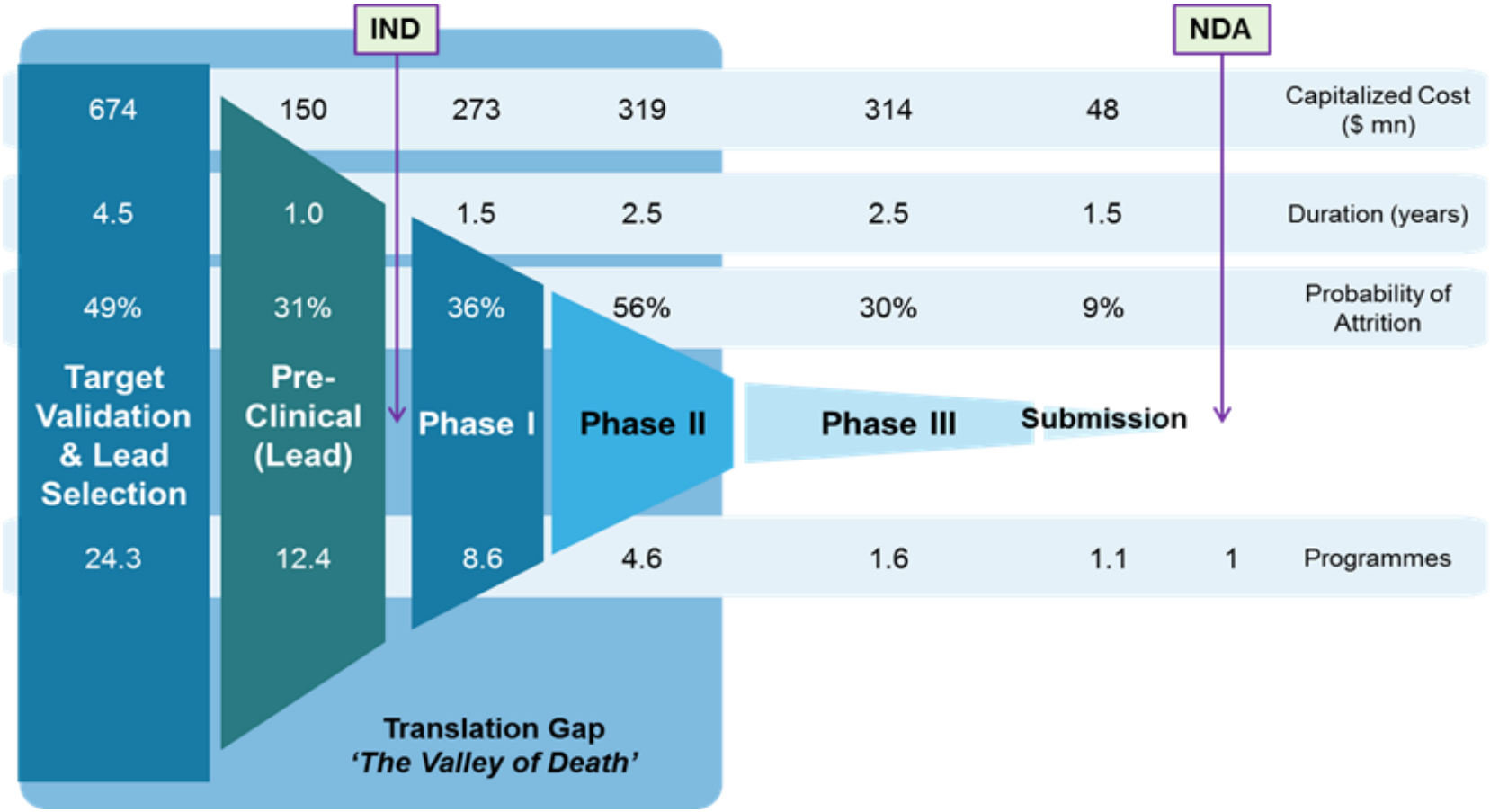


Optimization

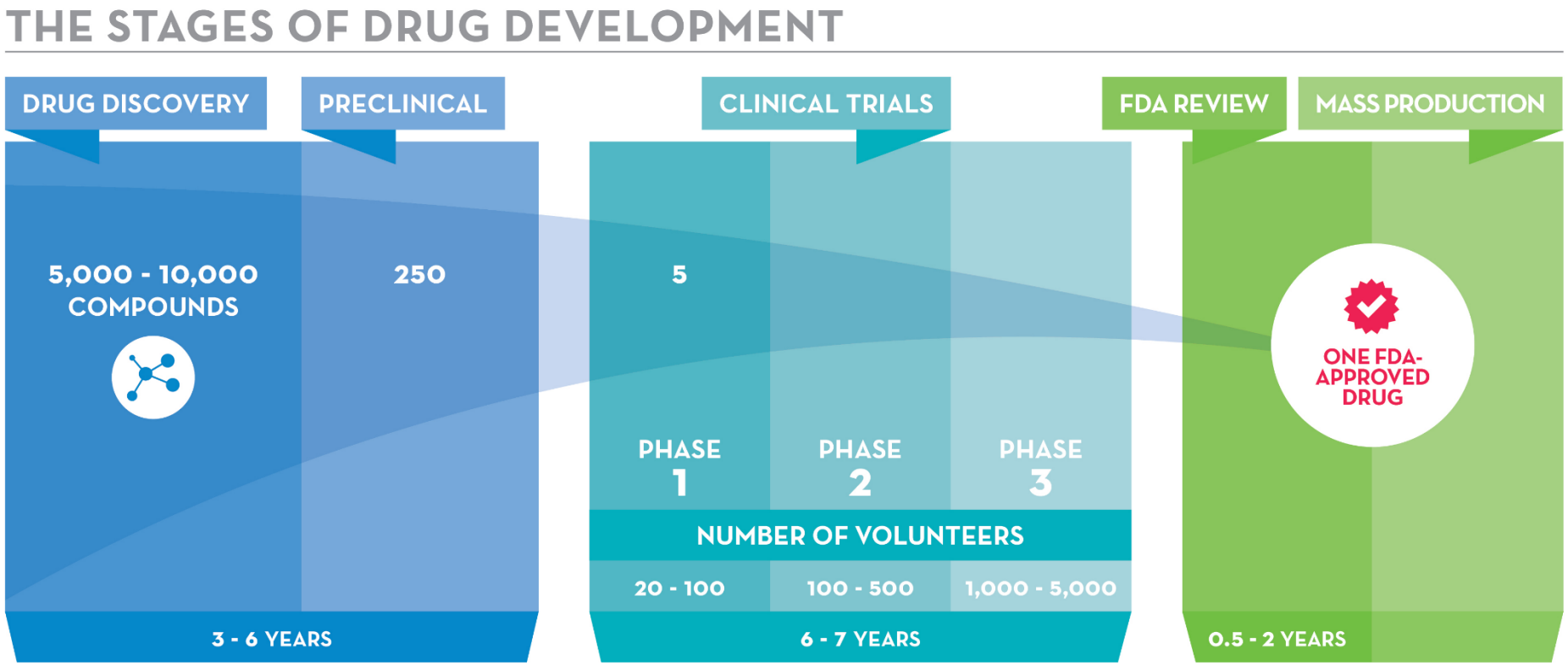
- Potency
- Aqueous solubility
- logP
- Stability
- Specificity (enzymes
- Specificity (species)
- Toxicity



Drug development is a highly risky process



From 10.000 hits to 1 approved drug!



Clinical stages of DD

Phase I:

Phase I studies are carried out in healthy volunteers, which are small in number – usually 20 to 100. The purpose of phase I studies is to identify metabolic and pharmacological effects of drug in humans and to determine the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects is required.

The purpose of phase I studies is to mainly determine safety profile.

Phase II:

Phase 2 includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred people.

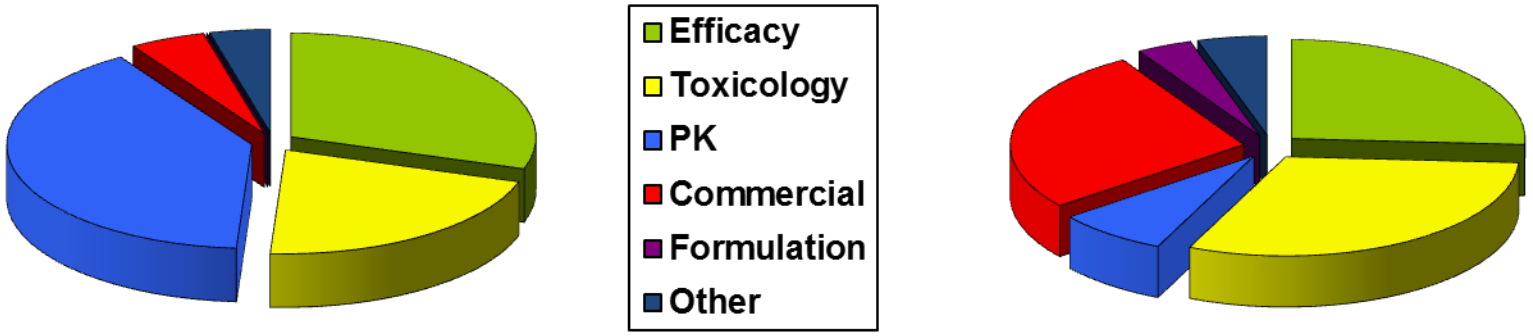
Phase III:

Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in Phase 2, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Phase 3 studies also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labeling. Phase 3 studies usually include several hundred to several thousand people .

Phase IV:

In addition to these three phases, Phase IV, also known as Post Marketing Surveillance is also carried out once the drug is approved and marketed. The aim of Phase IV is to find out safety profile in large patient pool across the world and to establish the safety profile of the drug. It is estimated that success rate of drugs making to market from lab is very less. One drug, from among the thousands tested, makes it to the market.

Reasons for the failure of a new drug in clinical phase
PK: pharmacokinetic



1991
PK 40% tox 21%

2000
PK 8% tox 31%

The translational gap

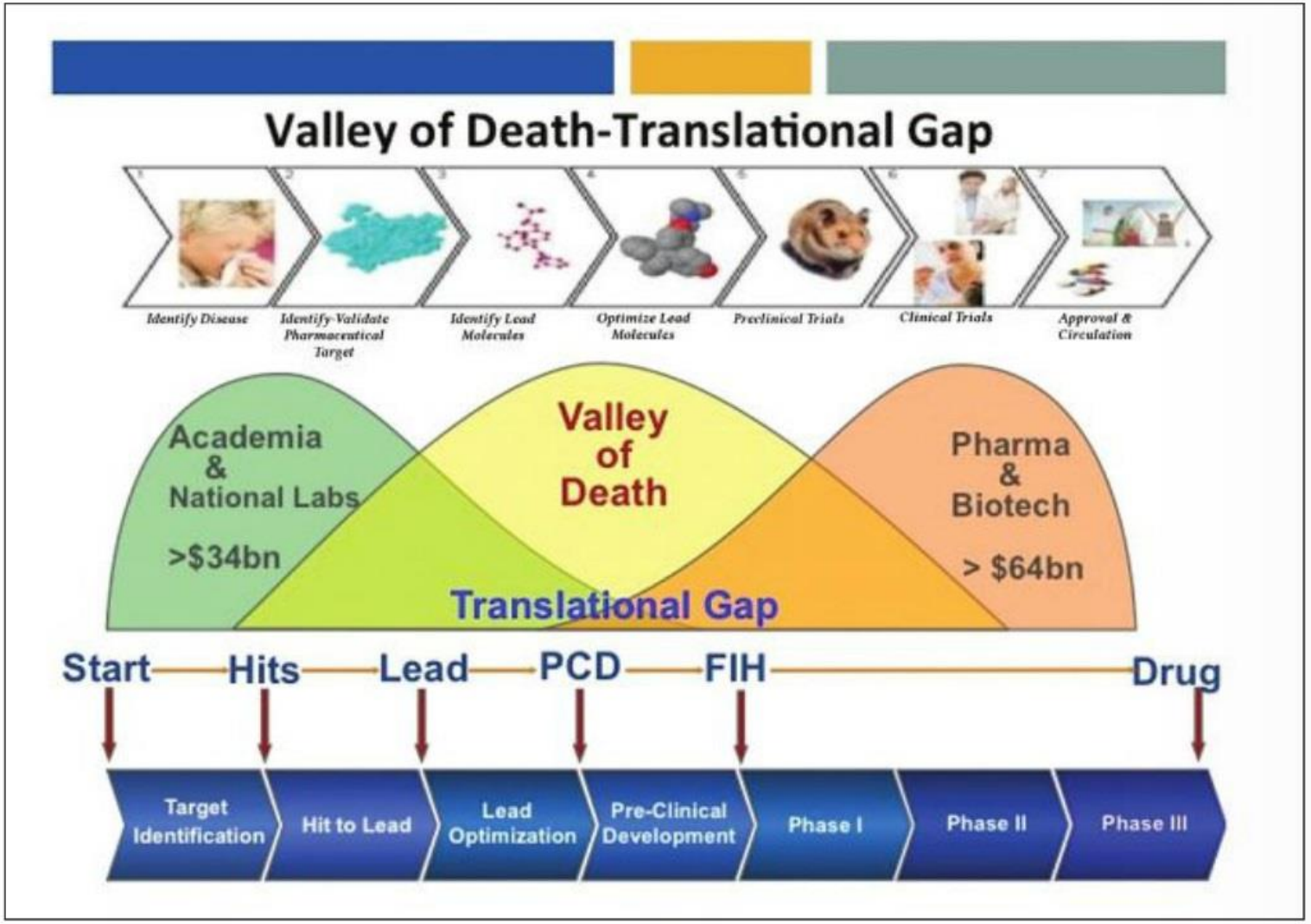


Figure 8 The map of valley of death-translational gap

Perché i modelli cellulari per lo sviluppo preclinico non sono soddisfacenti

A GUIDE TO DRUG DISCOVERY

OPINION

Screening out irrelevant cell-based models of disease

Peter Horvath, Nathalie Aulner, Marc Bickle, Anthony M. Davies, Elaine Del Nery, Daniel Ebner, Maria C. Montoya, Päivi Östling, Vilja Pietiäinen, Leo S. Price, Spencer L. Shorte, Gerardo Turcatti, Carina von Schantz and Neil O. Carragher

- **Limitations of traditional disease models**

- Traditional cell culture methods typically rely on cancer cells or immortalized cells grown within artificial environments, on non-physiological substrates such as functionalized plastic and glass.
- Although these methods have facilitated the discovery of many basic biological processes, they often fail to provide an adequate platform for drug discovery owing to their inadequate representation of key physiological characteristics. These problems can be broadly categorized into the following limitations.

Limitazioni attuali:

- ***Limitations due to cells.*** Most cell-based assay screens have traditionally been performed using transformed or immortalized cell lines.
- ***Limitations due to lack of appropriate cell culture substrates and bioengineering tools.*** The two-dimensional (2D) planar substrates on which cells are typically grown are stiff, demonstrating high (gigapascal) tensile strength and mechanical resistance to deformation, unlike most substrates found in the human body (which are on the millipascal to kilopascal scales), with the exception of bone and cartilage
- ***Limitations due to lack of appropriate co-culture methods.*** Cell-culture screening assays traditionally use a single cell type, whereas cells *in vivo* are either in direct contact or communicate over a long range with many different cell types

Modelli più avanzati ed affidabili:

- ***Primary and patient-derived cell models.*** The adaptation of patient-derived primary cell samples, as well as fresh human tissue samples, for *ex vivo* and *in vitro* translational research applications aims to overcome many of the disadvantages of using transformed cell lines for drug discovery
- ***Induced pluripotent stem cell technology.*** Although primary human and patient-derived *ex vivo* models are considered to be of high value, the availability of the relevant tissue is a limiting factor for modelling many disease phenotypes.
- iPSCs have several advantages as a platform for drug screening. They represent normal primary cells with a mostly stable genotype compared with transformed cell lines, and they possess an intrinsic capacity for self-renewal, facilitating their propagation and expansion for drug screening.

3D cell cultures

- ***Three-dimensional cell culture models.***
- Culturing cells in 3D environments can favour the formation of multicellular tissues with the appropriate cell–cell and cell–ECM interactions and architecture that are important drivers of tissue differentiation and function. The use of 3D cellular models for *in vitro* disease modelling and screening is especially useful in instances where aberrant tissue organization is associated with disease pathology and progression: for example, in **neurodegenerative disorders, fibrosis, solid cancers and cystopathies**

Cells in the natural environment are embedded in the extracellular matrix (ECM), forming a complex three-dimensional (3D) structure [11].
The ECM plays the role of regulating cell-to-cell interactions, cell adhesion, differentiation, and growth [12–14].
Therefore, an understanding of ECM composition and structure is critical for the development of novel 3D cultures for predicting biological mechanisms and therapeutic effects.

Mounting evidence has shown that physiologically more relevant factors can be revealed by imitation of the components and structure of the ECM in the natural environment [13,15,16]. In particular, cells cultured in a 3D microenvironment with ECM components showed realistic morphology and expressed several genes that failed to be expressed in a 2D culture [5–7].

Moreover, these cells synthesized ECM as they do in vivo for regeneration [11–14]. Thus, 3D cell culturing requires the use of biomaterials with a high level of similarity with the ECM for the enhancement of cellular functions.

Biomaterials are available for 3D cell culture

Table 1. Types of biomaterials used in three-dimensional (3D) cell culture and their advantages and disadvantages.

Type	Advantage	Disadvantage	References
Hydrogel	Tissue like flexibility Easily supplies water-soluble factors to cells	Low mechanical resistance	[5,11,13,17,18]
Solid scaffold	Various materials can be used Physical strength is easily adjusted	Difficulty in homogeneous dispersion of cells	[15,16,19–21]
Decellularized native tissue	Provides complex biochemistry, biomechanics and 3D tissues of tissue-specific extracellular matrix (ECM)	Decrease of mechanical properties (roughness, elasticity, and tension strength) of the tissues as compared to the native group	[22–26]
Ultra-low attachment surface	Provides an environment similar to in vivo conditions	Difficulty in mass production Lack of uniformity between spheroids	[27–31]

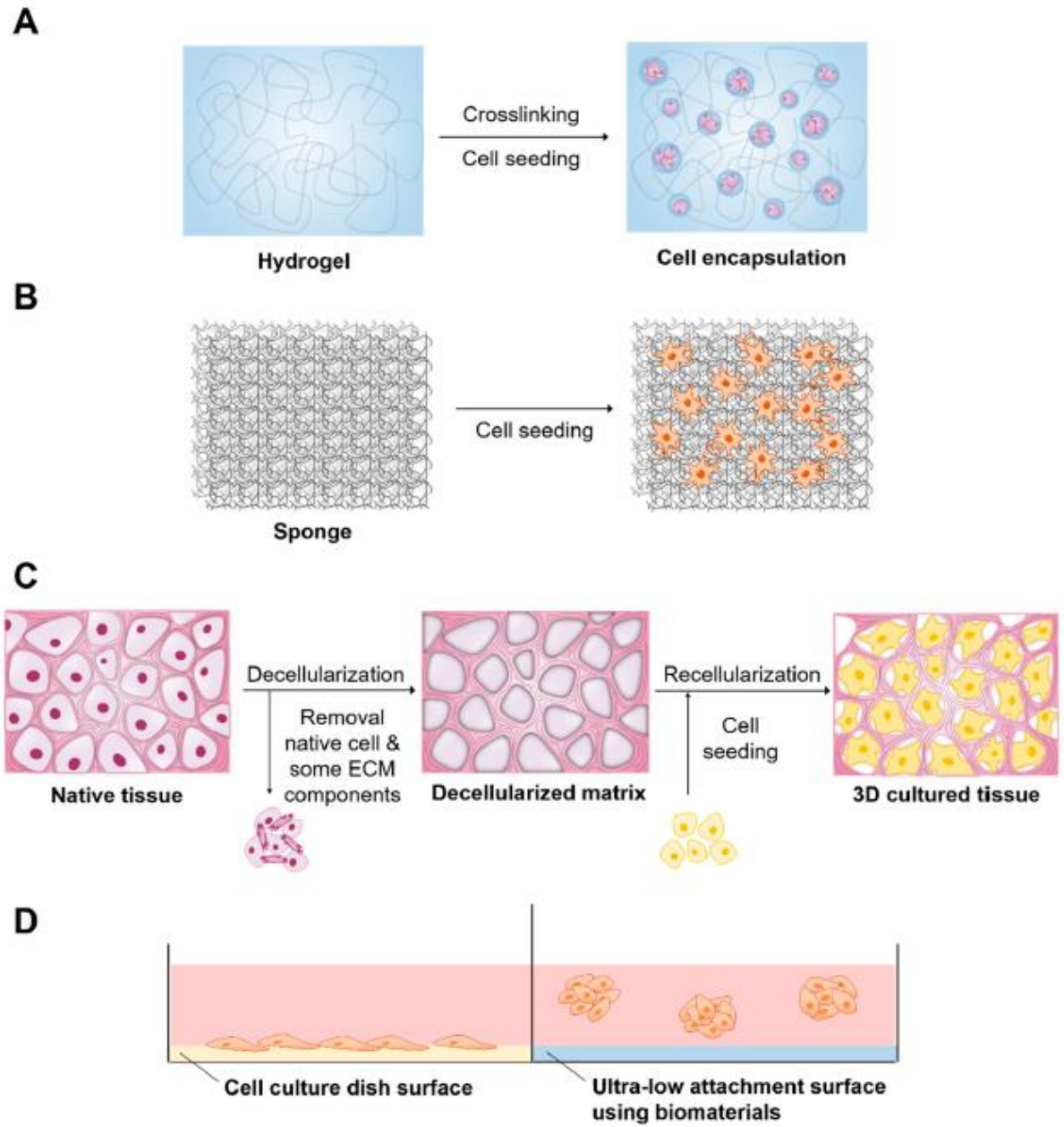


Figure 1. Biomaterials and related method of three-dimensional (3D) cell culture preparation. (**A**) Hydrogel, (**B**) Solid scaffold, (**C**) Decellularized native tissue (**D**) Ultra-low attachment surface.

Stem cells-derived organoids

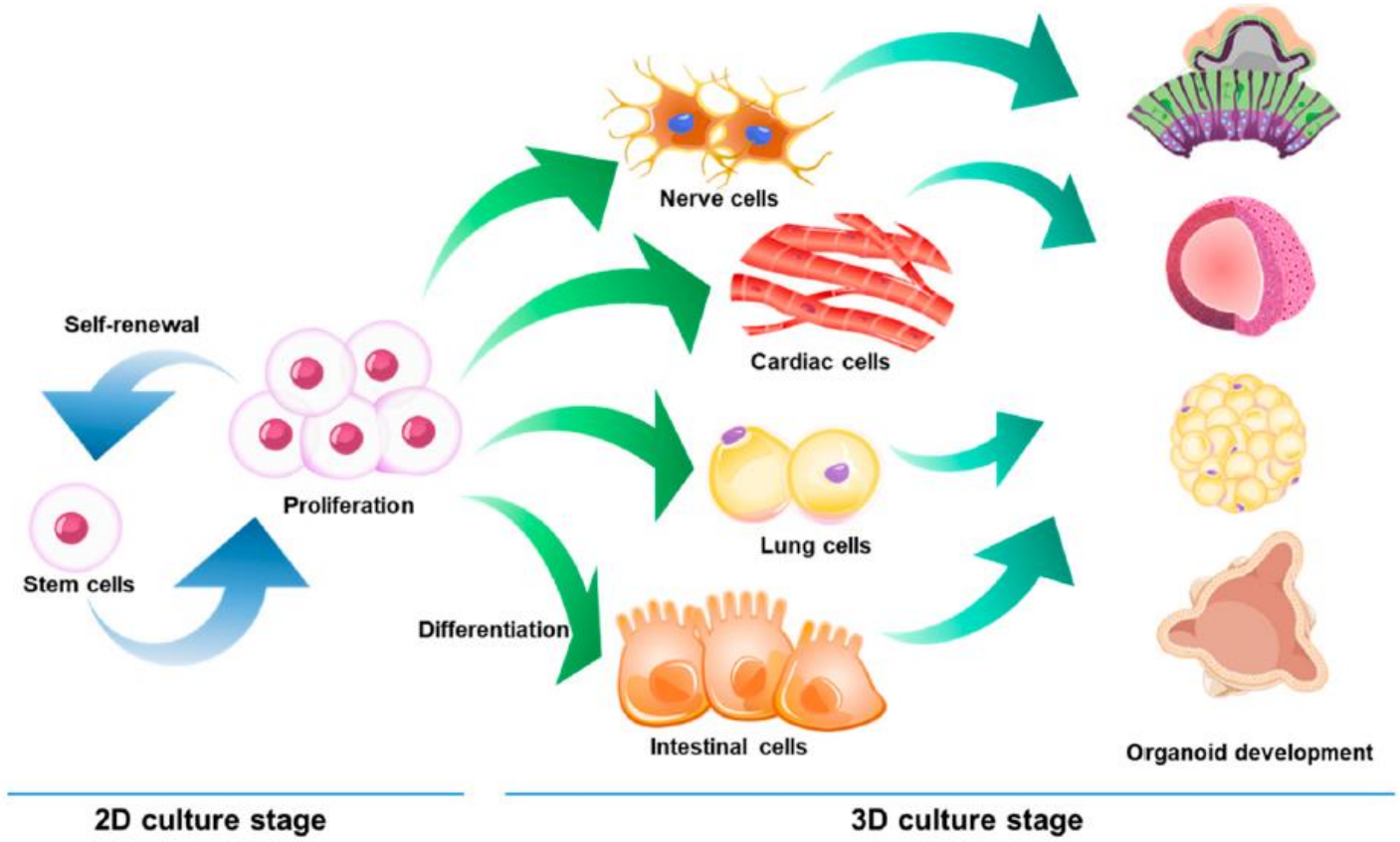


Figure 2. Stem cell-derived organoids.

INNOVATION

Directing evolution: the next revolution in drug discovery?

Andrew M. Davis, Alleyn T. Plowright and Eric Valeur

DMTA and evolution

- The classical DMTA cycle in medicinal chemistry has many similarities to the evolutionary processes in biology mediated through traits encoded in the genomes of organisms. The medicinal chemistry design hypothesis could be viewed as analogous to genetic information.

- The ‘make’ stage (chemical synthesis or purchase) corresponds to the translation of genetic information into proteins. The ‘test’ and ‘analyse’ stages are similar to the identification of organisms that have particular characteristics (differential fitness), and deduced structure–activity relationships lead to new designs. The good features are kept, and the bad features are discarded from the design hypothesis for the next round of synthesis, a process that is comparable to the mutation and recombination of the genetic information that occurs during reproduction and hereditability of fitness

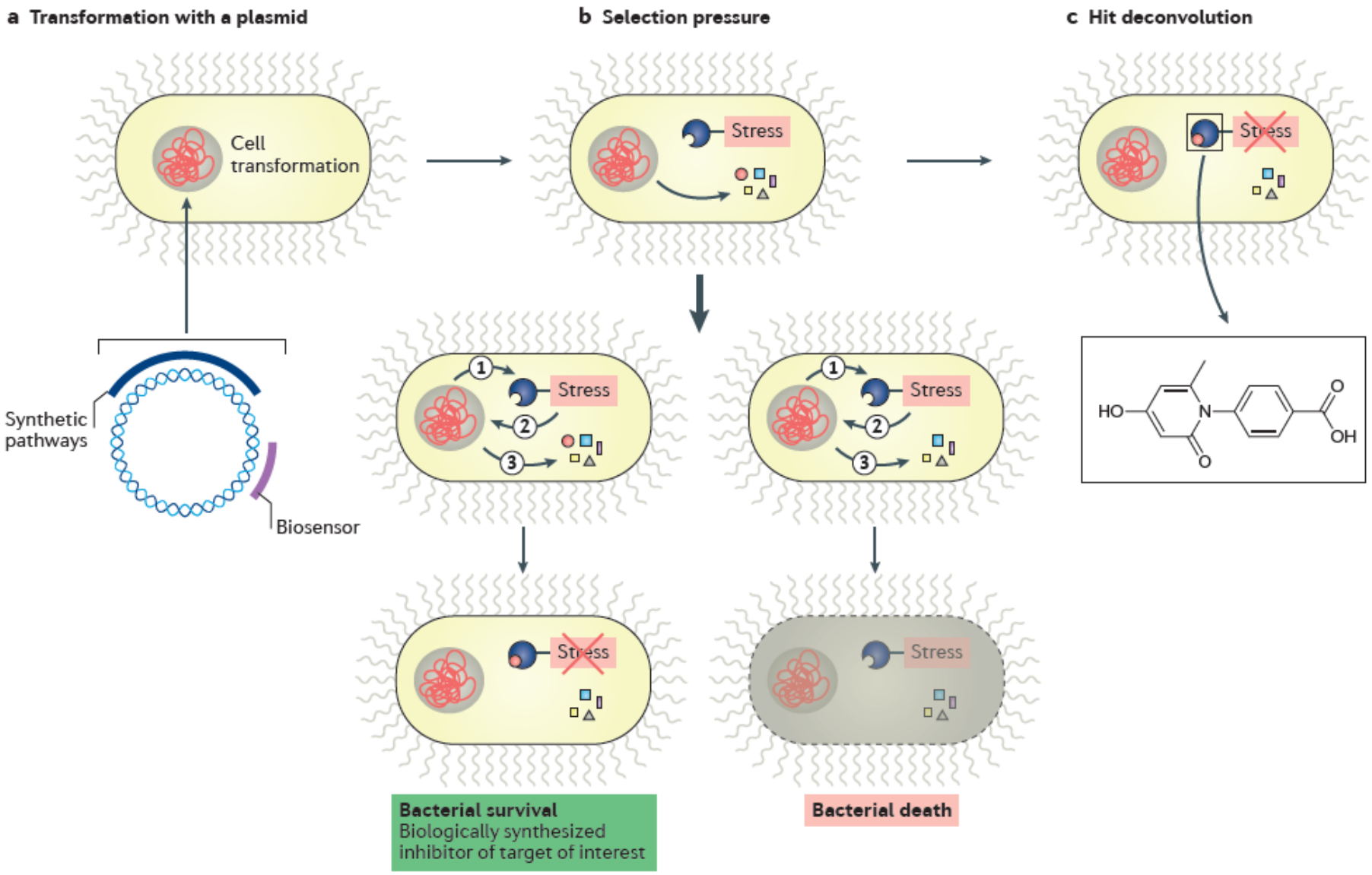
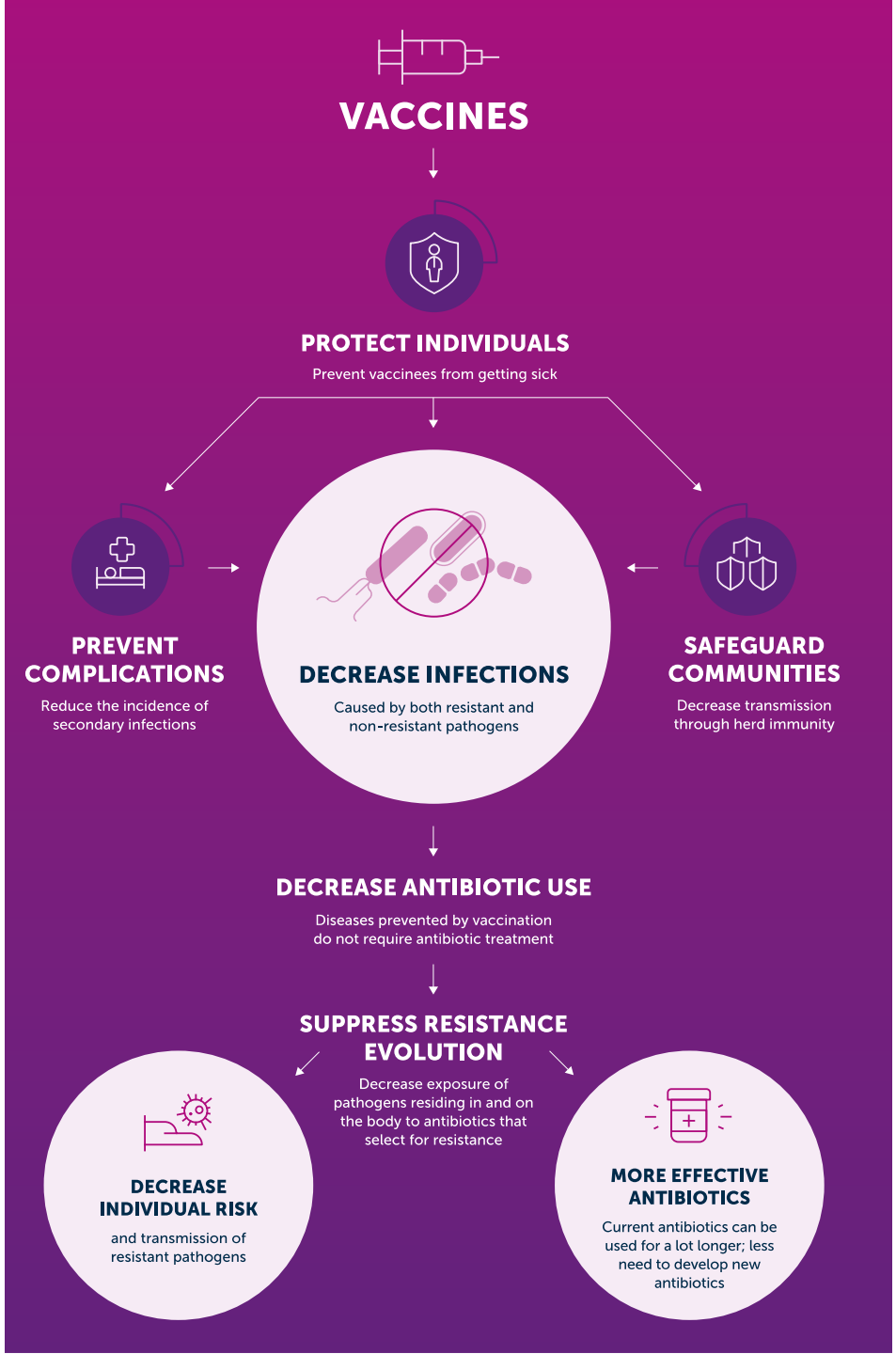


Figure 1 | **Vision for harnessing evolutionary pressure in drug discovery.** By coupling the production of new molecules to biosensors, it is possible to drive cells under a mutational stress and a selection pressure through evolutionary cycles to optimize a ligand of interest. **a** | Enzymatic synthetic pathways are introduced and randomized within a plasmid. Biosensors are also introduced into the plasmid. Cells are then transformed with this plasmid. **b** | Selection pressure follows: the stress inducer (pressure) is expressed (step 1), triggering mutations (step 2) and leading to the synthesis of potential inhibitors (step 3). Only the 'fittest' cells — those able to generate an inhibitor — survive, while other cells die. **c** | For stress-surviving cells, hit deconvolution is carried out to identify the chemical structures of the inhibitors.



Bacterial vaccines in clinical and preclinical development:
an overview and analysis.
World Health Organization; 2022

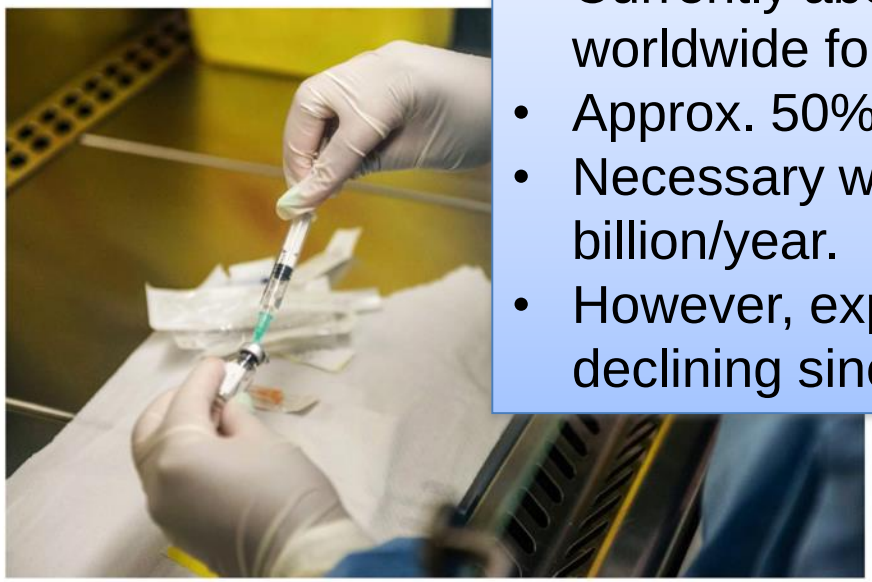
The New York Times

GLOBAL HEALTH

Vaccines Against H.I.V., Malaria and Tuberculosis Unlikely, Study Says

Unless the $3 billion spent annually on research triples, the world may not be able to invent vaccines or rapid cu

- Currently about $3 billion/year worldwide for vaccine research.
- Approx. 50% come from the USA
- Necessary would be about $9 billion/year.
- However, expenditures have been declining since 2000



An experimental vaccine against the AIDS virus in Soshanguve, South Africa in Nov. 2016.
Mujahid Safodien/Agence France-Presse — Getty Images

By Donald G. McNeil Jr.

Sept. 7, 2018

Vaccines against H.I.V., malaria and tuberculosis — three major killers of the world's poor — are unlikely to be produced in the foreseeable future unless vastly more money is committed to finding them, a new study has concluded.

Gates Open Research

Gates Open Research 2018, 2:23 Last updated: 28 AUG 2018

Check for updates

RESEARCH ARTICLE

REVISED Developing new health technologies for neglected diseases: a pipeline portfolio review and cost model [version 2; referees: 2 approved, 1 approved with reservations]

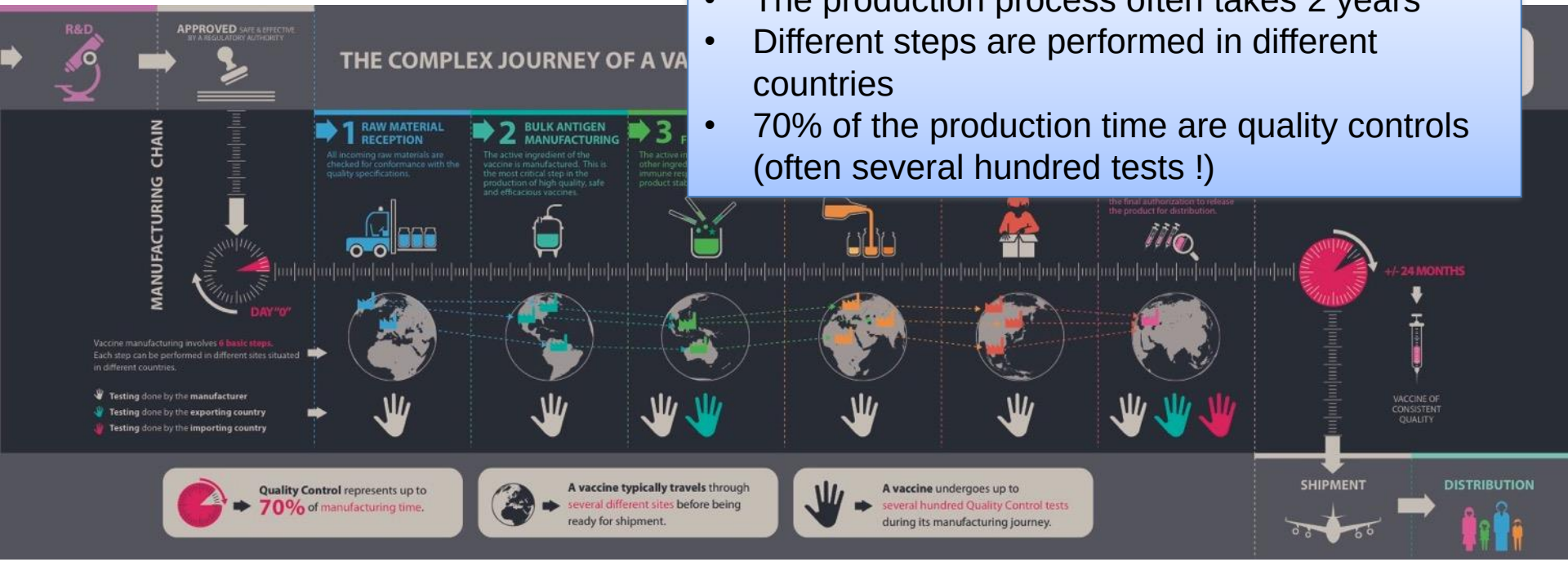
Ruth Young [1], Tewodros Bekele [1], Alexander Gunn [1], Nick Chapman [2], Vipul Chowdhary[2], Kelsey Corrigan[3], Lindsay Dahora [4,5], Sebastián Martinez[6], Sallie Permar[4,7], Johan Persson[6], Bill Rodriguez[8], Marco Schäferhoff[6], Kevin Schulman [9], Tulika Singh[4,10], Robert F Terry [11], Gavin Yamey [1]

Archetype	Number of products needed at preclinical phase	Cost ($, millions)	Length of time until launch (yrs)
Simple vaccine	11.0	406.6	10
Complex vaccine	34.6	1057.4	13
Unprecedented vaccine	243.9	5550.0	13

Young, R. et al. (2018). *Gates Open Research*, *2*, 23.

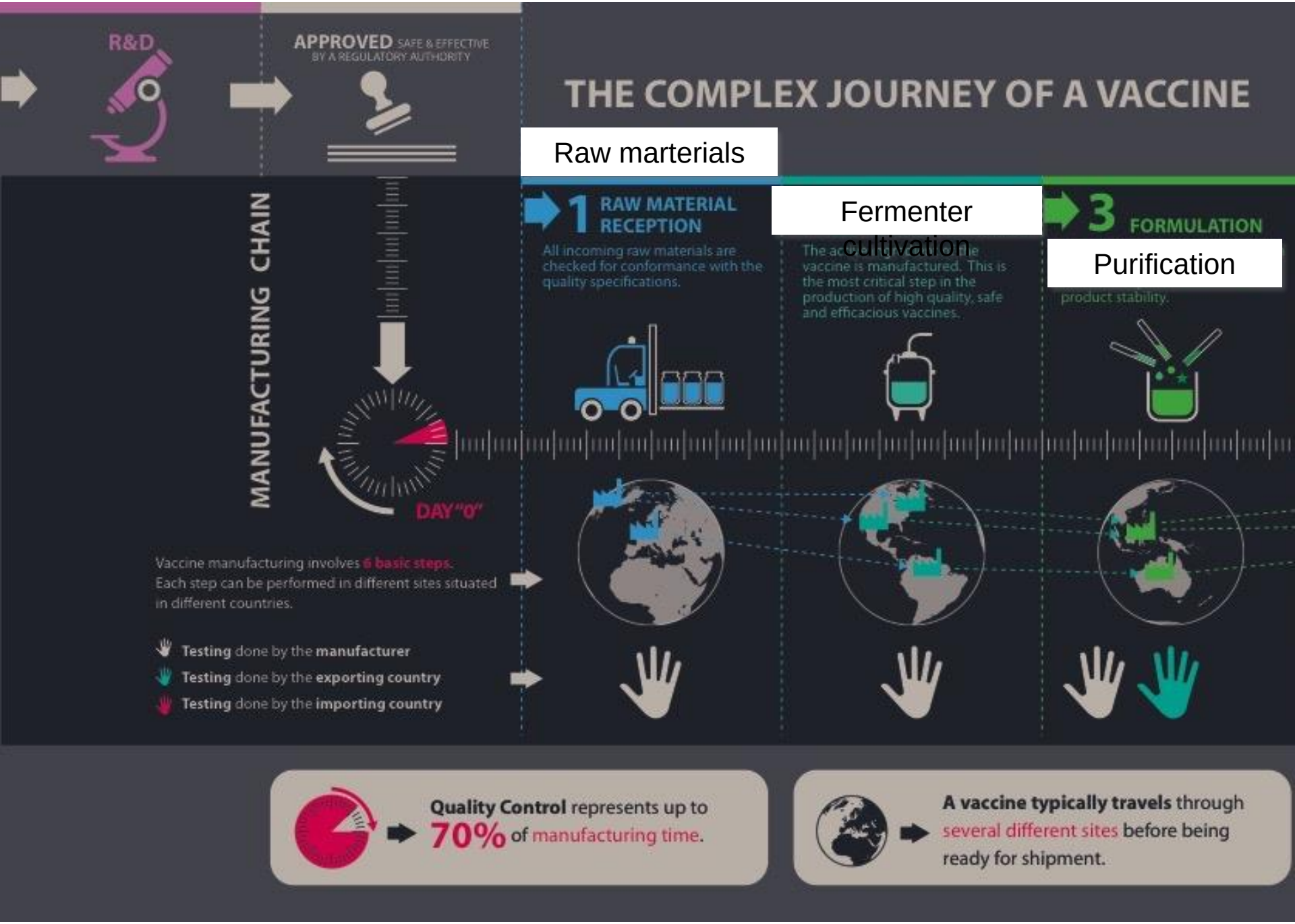
Vaccine production

- The production process often takes 2 years
- Different steps are performed in different countries
- 70% of the production time are quality controls (often several hundred tests !)



International Federation of Pharmaceutical Manufacturers & Associations

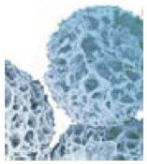
IFPMA


R&D
APPROVED SAFE & EFFECTIVE BY A REGULATORY AUTHORITY
THE COMPLEX JOURNEY OF A VACCINE
Raw marterials
Fermenter cultivation
Purification
MANUFACTURING CHAIN
DAY "0"
1 RAW MATERIAL RECEPTION
All incoming raw materials are checked for conformance with the quality specifications.
vaccine is manufactured. This is the most critical step in the production of high quality, safe and efficacious vaccines.
3 FORMULATION
product stability.
Vaccine manufacturing involves 6 basic steps.
Each step can be performed in different sites situated in different countries.
Testing done by the manufacturer
Testing done by the exporting country
Testing done by the importing country
Quality Control represents up to 70% of manufacturing time.
A vaccine typically travels through several different sites before being ready for shipment.

2,000 l

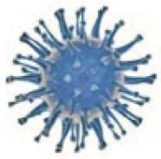
20,000 l

Molecule design | Cell design and selection | Cell culture | Product recovery (2–3×) | Capture | Polishing | Drug substance | Drug product



Vero cells
grown on Cytodex™ microcarriers

Seed train bioreactor
(ReadyToProcess WAVE™ 25 system)



Virus production

Culture medium
(HyClone™ SFM4MegaVir)

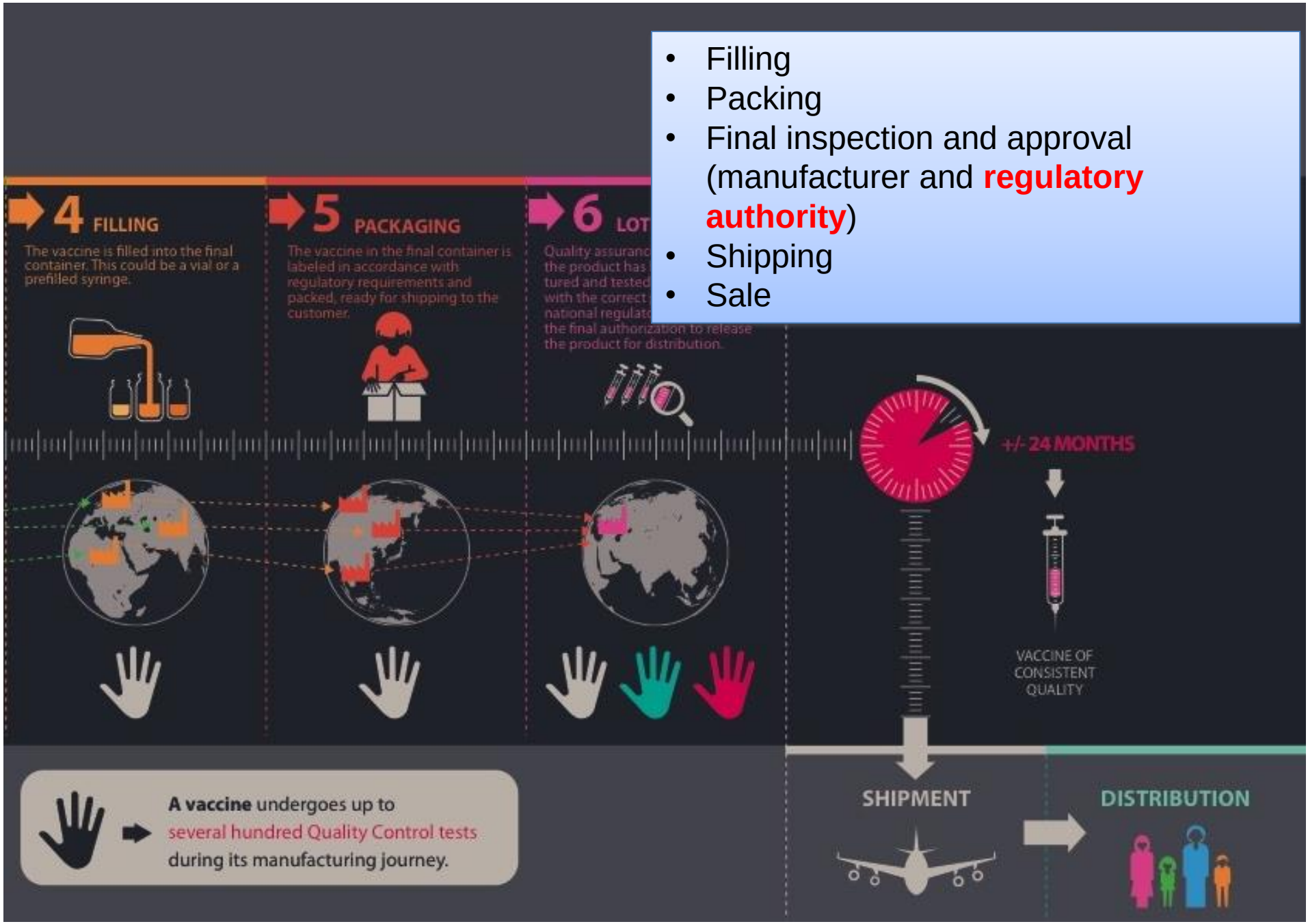
Production bioreactor
(Xcellerex™ XDR systems)

Clarification
(ReadyToProcess™ hollow fiber filters operated through the ÄKTA readyflux single-use filtration system)

Chromatography
(ReadyToProcess columns operated through the single-use ÄKTA™ ready chromatography system)

Final filtration
(ReadyToProcess hollow fiber filters operated through the ÄKTA readyflux single-use filtration system)

- Filling
- Packing
- Final inspection and approval (manufacturer and **regulatory authority**)
- Shipping
- Sale



“Challenges” of Combination Vaccines

- Combination vaccine formulations are much more complex than a single mixture of several antigens
  - physical compatibility and stability has to be tested
- Extra doses of some antigens are sometimes administered increasing the risk of adverse events
- Manufacturing is long and complex requiring strict and expensive quality control
- In case of allergic reactions or adverse events, it can be difficult to single out the responsible component
- Clinical evidence demonstration is more challenging (i.e. potential interference of antigens)
- In general, combination vaccines are more expensive

Obando-Pacheco et al., Vaccine 36 (2018) 5485–5494

"The production of a conventional drug is as difficult as building a car, the production of a biological drug is similar to the production of an A380. The production of a combination vaccine is as complex as building a space shuttle.“

John McGrath, Senior Vice President von Global Industrial Operations Vaccines von GSK

PLOS PATHOGENS

PEARLS

Polyvalent vaccines: High-maintenance heroes

Barbara Schlingmann[1¤], Katelyn R. Castiglia[2], Christopher C. Stobart[2], Martin L. Moore[1,3¤*]

1 Department of Pediatrics, Emory University, Atlanta, Georgia, United States of America, **2** Department of Biological Sciences, Butler University, Indianapolis, Indiana, United States of America, **3** Children's Healthcare of Atlanta, Atlanta, Georgia, United States of America

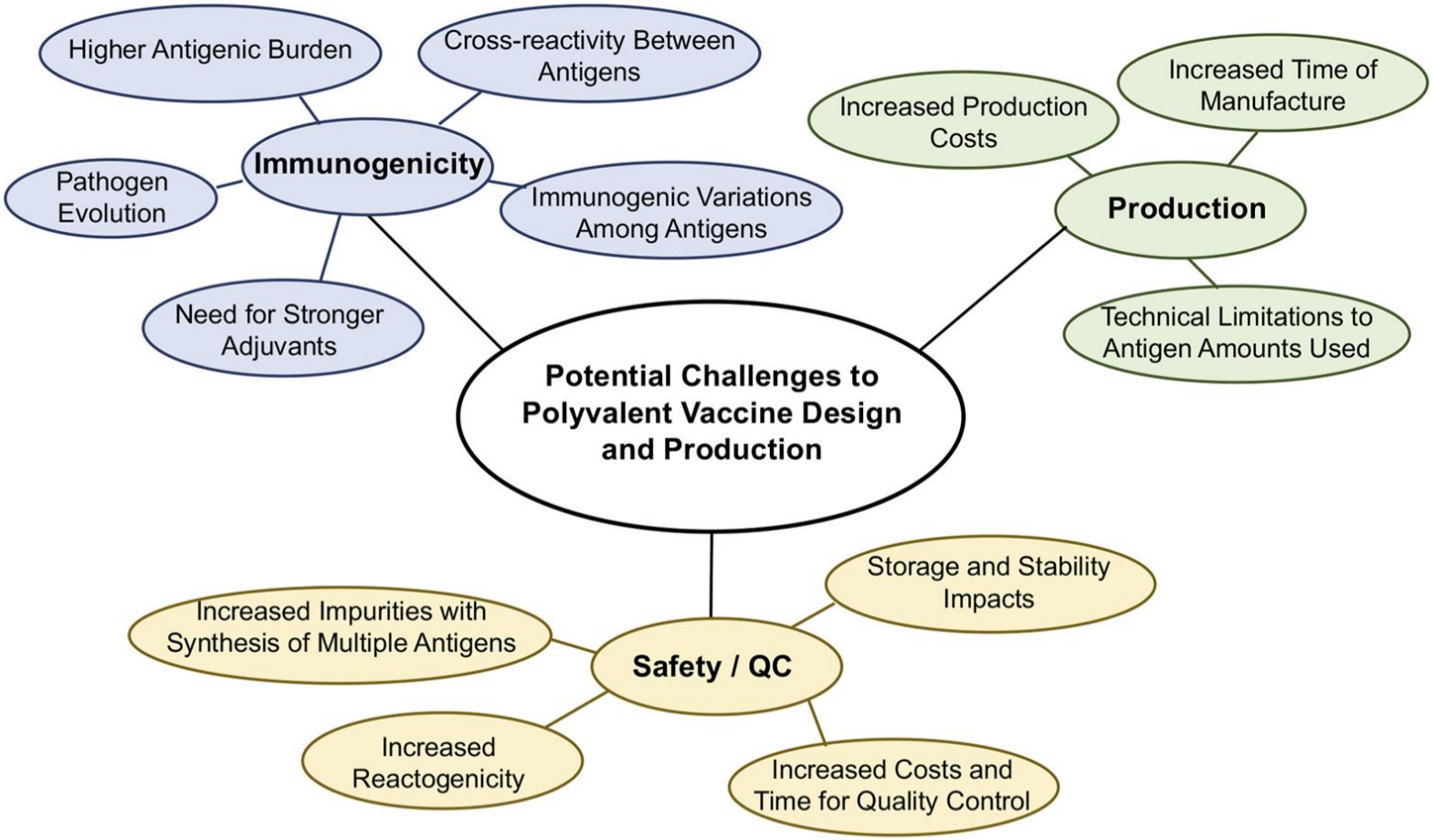
¤ Current address: Meissa Vaccines, Inc., South San Francisco, California, United States of America
* martin.moore@emory.edu

troduction

ccines are the most efficient tools to battle infectious diseases, with an estimated prevention 2–3 million deaths per year [1]. Vaccine development, however, is costly and challenging, ecially when the target pathogen can be subdivided into serologically distinguishable types rotypes) that individually cause disease. Broad protection against serotypes can be achieved h either polyvalent vaccines of mixed serotype-specific immunogens or by discovery and of a good immunogen conserved among serotypes. The latter is preferable but technically sive. The poliovirus vaccine (containing three poliovirus serotypes) was first used as a poly- ent vaccine, beginning with the establishment of the Global Polio Eradication Initiative in 88, reducing poliomyelitis by 99% [2]. Polyvalency has been arguably more useful than using conserved immunogens to target multiple serotypes, and polyvalency has steadily advanced despite complexity and barriers to manufacturing. Here, we review challenges and developments in polyvalent vaccines.

Citation: Schlingmann B, Castiglia KR, Stobart CC, Moore ML (2018) Polyvalent vaccines: High-

Challenges to Polyvalent Vaccines



Schlingmann et al. PLoS Pathogens 14:e1006904

Clinical Development of Vaccines

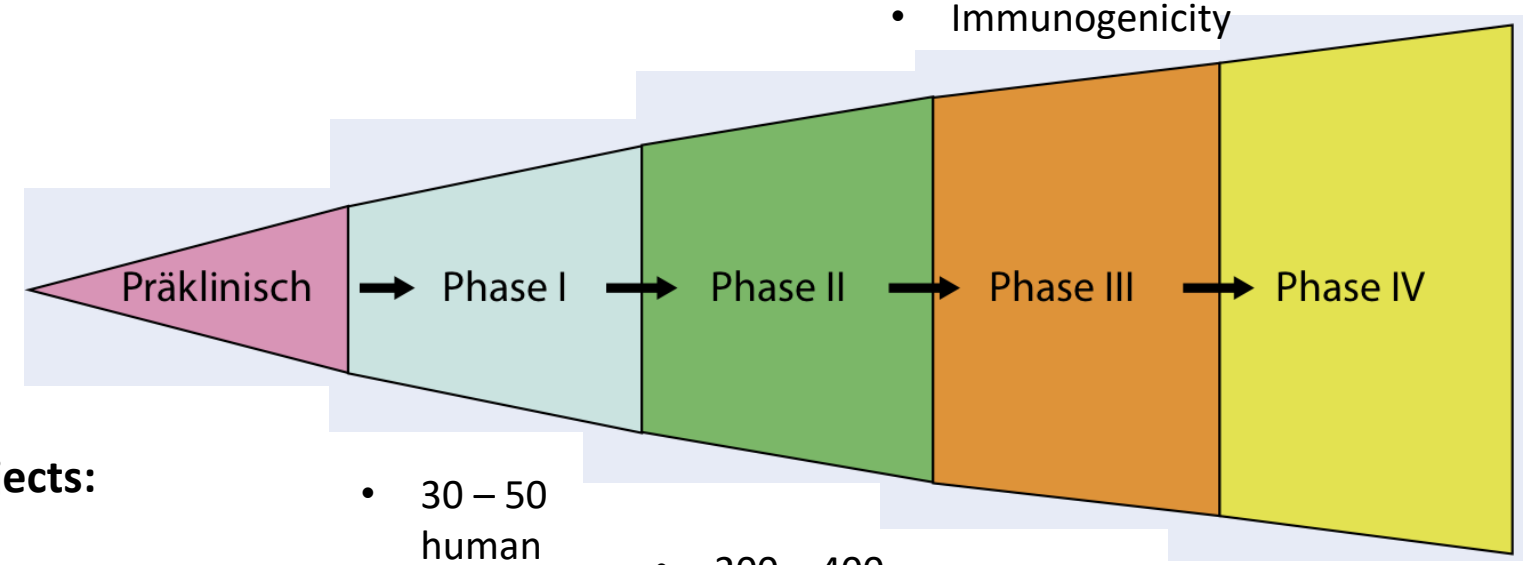
GOALS:

- Immune response ?
- Protection ?

- Dose finding
- Safety
- Immunogenicity

Proof of Concept
- Safety
- Immunogenicity

Pivotal Study
- Vaccine efficacy
- Safety
- Immunogenicity



Subjects:

- animals
- 30 – 50 human volunteers
- 200 – 400 human volunteers
- 3000 – 10,000 human volunteers