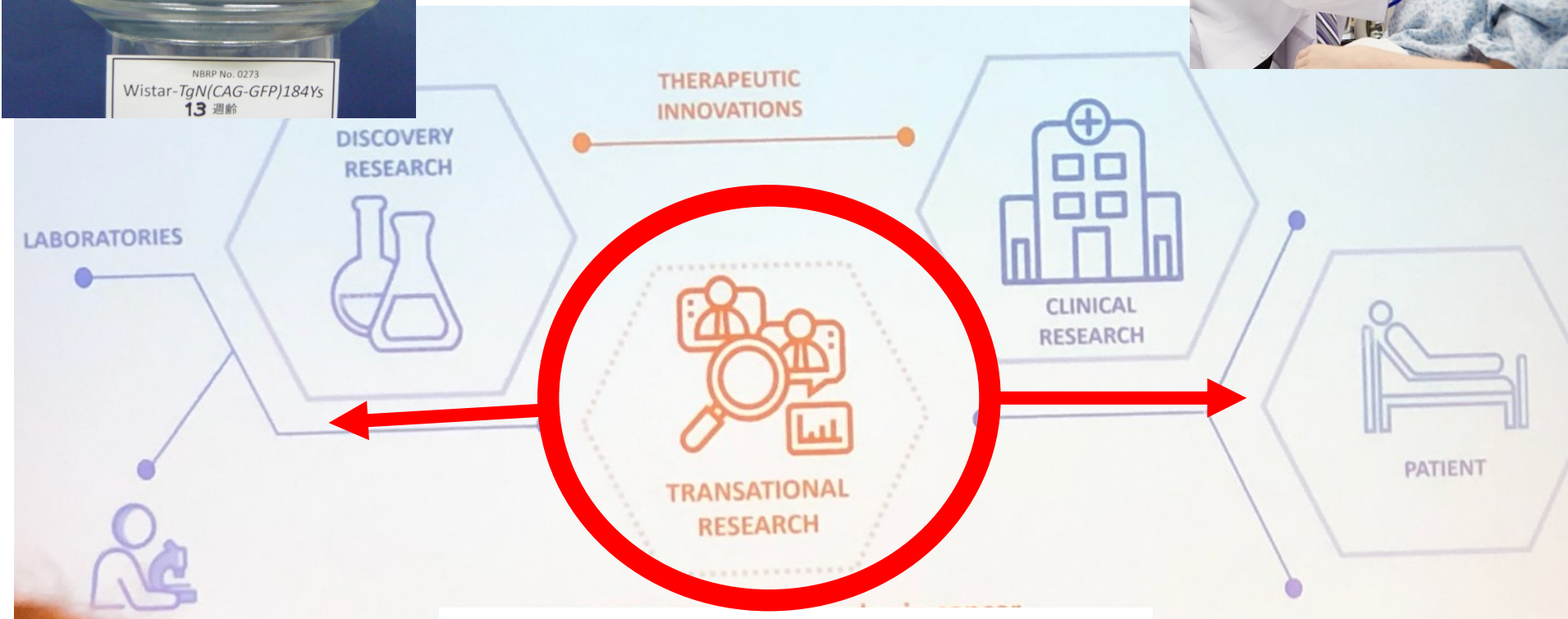


Translational research : a paradigm shift !



What is it : from bench to bedside
and back !



RESEARCH SCIENTISTS TALK TO PHYSICIAN SCIENTISTS
NOVEL THERAPEUTIC TARGETS AND THEIR ROLES
AI SCREENING FOR NOVEL THERAPEUTIC MODALITIES
IDENTIFYING MOLECULAR DIAGNOSTICS
UNDERSTANDING THERAPEUTIC DELIVERY ROUTES



Cc: Nathalie Brandenburg <nathalie.brandenberg@epfl.ch>, "Roger G. Clerc" <roger.clerc@epfl.ch>

Dear Colleagues,
Please be informed of this Thursday's

BIOENGINEERING SEMINAR

“Profiling T Cell Bispecific Antibodies in Colorectal Cancer Using Standardized Human Organoids”

Thursday, November 20, 2025, 16:00

in EPFL room [CM 0 13](#)

(no broadcasting over Zoom this time)

Nathalie Brandenburg, Ph.D.

EPFL Laboratory of Cell Membrane and Biology

host: Prof. Roger G. Clerc

Thank you for your attention.

Best wishes,
Dietrich

Dietrich REINHARD

Institute Manager / Adjoint du Directeur d'Institut

IBI - Institute of Bioengineering / Institut de bioingenierie
EPFL School of Life Sciences & School of Engineering

<https://bioengineering.epfl.ch> / twitter/X: [@EPFL_BioE](#)

R E G I S T E R N O W !

1,000,000,000 CHF investment

7,000,874 hours of work

6,587 experiments

423 researchers

1 medicine



THE MAKING OF AN INNOVATIVE MEDICINE

*Introductory workshops on translational biomedical research,
drug discovery and development*

**BIO-698 resumes Thursday September 11. 2025
4:15 PM @ CM013**



Judge Prof Dr med Olaia Naveiras



With Timothee Ferrari MD PhD cand



Sciences de la Vie -SV



With Justine Epiney MD PhD cand



Mehdi AliGadiri MD PhD cand



Prof Roger G. Clerc

The Making Of An Innovative Medicine – class schedule

Thursday's @ 4-6 PM except 04.12/11.12.25 @2-6 PM



- Session 1: Scope of the course _ general organization _ case study**
11.09.25 *Embracing a career at the heart of biomedical research !?*
CM013
- Session 2: Historical perspective: the modern pharmacy**
18.09.25 *Advent of modern medicines - placebo controlled drug development*
CM013
- Session 3: Introduction to translational research: crossing the bridge**
25.09.25 *A chasm has opened wide between biomedical research and patients in need*
CM013
- Sessions 4-5: Therapeutic target identification I & II**
02-09.10.25 *“me too” vs a wealth of innovative targets _ small MW cpds vs biologicals*
CM013
Early front loading of biomarker identification for cohort stratification
- Session 6: Structure based drug design _ medicinal chemistry_low/high throughput screening assays_ multiple parallel optimization_ML-powered screens**
16.10.25 *Setting up screening assays, the robotics, the million cpds libraries*
CM013
- Session 7: Therapeutic modalities biologicals–peptides : today’s - tomorrow’s pharmacy NBEs**
30.10.25 *Challenges (cost of goods - healthcare payers) and opportunities*
CM013

The Making Of An Innovative Medicine - class schedule

Thursday's @ 4-6 PM except 04.12/11.12.25 @2-6 PM



Session 8: Personalized Healthcare PHC _ precision medicine

06.11.25 *How PHC started: from a single case to a paradigm change*

CM013

Session 9: Pharmacogenetic polymorphisms, Pharmacogenomics

13.11.25 *Interindividual variability toxicity in response to medicines*

CM013

Session 10: In vivo pharmacology, investigative toxicology with Nathalie Brandenberg PhD eMBA CEO

20.11.25 *Preclinical research ends up with IDB's, FDA guidelines for FIH*

CM013

Session 11: Clinical research _ phase 0, phase I, II, III, IV with Michael Sommer PhD Bristol Myers Squibb

27.11.25 *The long and complex experimental procedures with human patients*

CM013

Intellectual property_ integrity in research_my genome vs our genomes

Why are patents essential to new medicine/biotech development

Session 12: Health Hackathon – Hacking medicine I with T. Ferrari & M. Ali Gadiri MD PhDs confirmed !

04.12.25 *Pitches –building teams – hacking problem - 5Ws – brainstorm*

starts @ 2PM ! CO017

Session 13: Health Hackathon – Hacking medicine II with judges Prof Olaia Naveiras - Prof James Habib

11.12.25 *Building up solutions – make it better - final presentations*

starts @ 2PM ! CO017

! NON EXHAUSTIVE LISTING - SUGGESTIONS WELCOME !

sessions	workshops	speaker/s
S02 (18-09-25)		
historical medicines	penicilin: impact, whose invention ?	
hopping on giant shoulders	prozac at the core of psychiatry	
	vaccine discovery:smallpoxJennerTodaymRNAvaccine	Eugenio
	artemisinin and malaria	
	insulin-Banting Best et al. beagle dog	
	slide51-X-ray image DNA--Rosalind Franklin	
	cyclosporin from soil sample to life saver	
S03 (25-09-25)		
translational research	expanding scope of translational therapies	
from bench to bedside and back	chronotherapy,circadian clock,sex,longevity	Solomon
	CAR-T, TCR-T cell therapies in "cold" tumors	
	Y chrom loss in immune cells drives cancer	
S04 (02-10-25)		
therapeutic target identification	th. target identification using a phenocopy screen	Justine
S05 (09-10-25)		
therapeutic target identification	nocosomial inf/MRSA/phage antibacterials	
	Crispr/Cas9 gene editing huntington disease	
	AI in drug discovery / ML-powered medicine	Lou
	AIDS - Lenacapavir : end of plague ?	
S06 (16-10-25)		
structure based drug design	macrocycles and non druggable targets	Benedikt
	chemoproteomics - NMEs	
	AIDS HIV from deadly virus to chronic disease	
S07 (30-10-25)		
therapeutic modalities - NBEs	rare diseases repurposing medicines	Jana
	biologics on the rise-MABs medicines & more	Eleni
	RNA therapeutics, antisense medicines	
	Wnt pathway - PROTACs vs molecular GLUEs	
S08 (06-11-25)		
PHC personalized healthcare	BRCA1/2 preventive surgery/tumor board	
Human genomics	4P medicine-GWAS-Personalized Health Care	Frederico
	disease enabling biomarkers/micro RNAs	
	AZ-biomarker BD-tau yet still no curative drug	
	centenarian host isoallo-LCA bile acid bacteria	
S09 (13-11-25)		
pharmacogenetic polymorphism	Pharmacogenomics	Greta
	deCODE Inc pharmgenomic/iceland genealogy	
	ageing and thanatophobia	
S10 (20-11-25)		
in vivo pharmacology	guest speaker : profiling MABs on organoids	Nathalie B
toxicology	organoids-drug discovery - CF patients	Tianhao + Alice
	thalidomide repurposing multiple myeloma	
S11 (27-11-25)		



Workshops The Making Of An Innovative Medicine (today's class)

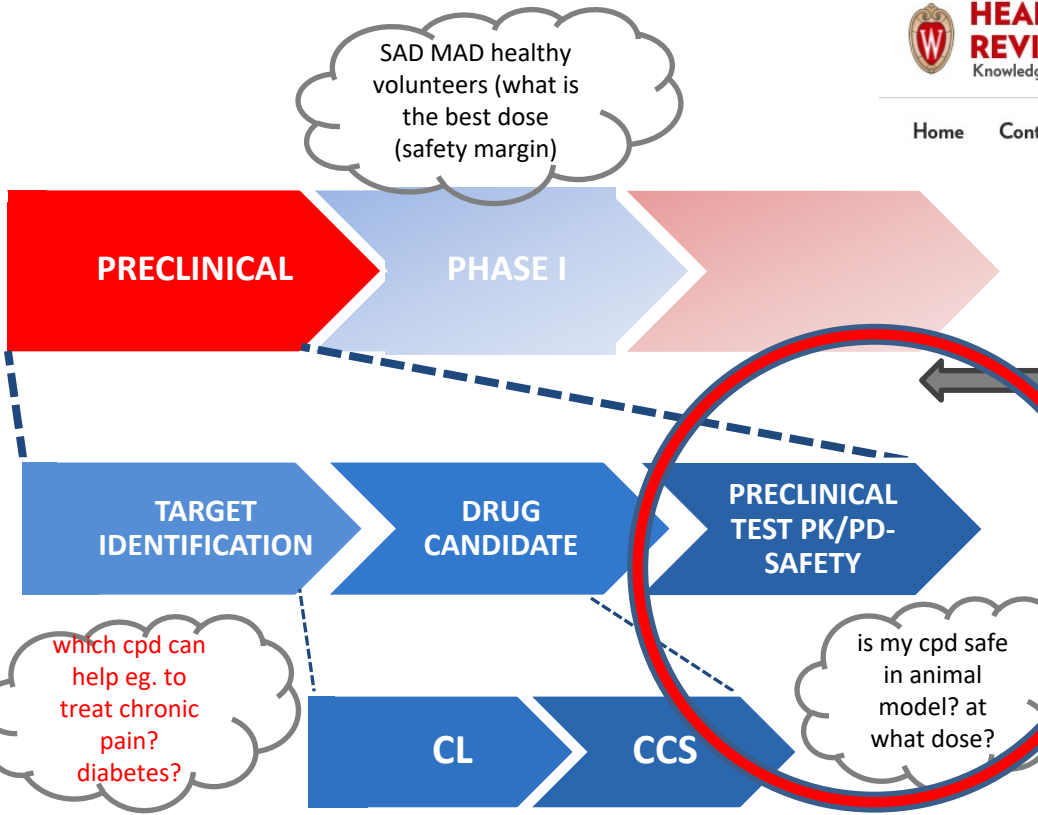


Prof O Naveiras



Prof J Habib

Drug Discovery: preclinical value chain _ ends up with IDB, IND, FDA application for FIH



Closing preclinical tests – PK, PD, SAFETY

Topics Map > Guidance > Submission Type Guidance

Guidance for the Submission of Investigator's Drug Brochures (IDBs) and Package Inserts

Version Date: May 21, 2018

In order to approve research studies under the Common Rule (45 CFR 46) or FDA regulations (21 CFR 56), an IRB must receive sufficient information about the effects of any drug under study to assess whether the risks to subjects are reasonable in relation to anticipated benefits and adequately minimized. For studies conducted under an investigational new drug (IND) application FDA guidance notes that an investigator's drug brochure (IDB) is usually required by the FDA (21 CFR 312.23(a)(5) and 312.55). In addition, FDA guidance states that even though 21 CFR 56 does not mention the investigator's brochure by name, much of the information contained in such brochures is "clearly required to be reviewed by the IRB" (FDA Information Sheets at <http://www.fda.gov/oc/ohrt/irbs/faqs.html>). The FDA provides flexibility to IRBs regarding when IDBs are required to be submitted, the format for submission, and how the IRB assesses the brochures.

When to Submit IDBs Versus Package Inserts

If a research study involves testing or evaluating drug(s) and their use in the research is covered under an IND, an IDB should be provided to the IRB. For any drugs being tested or evaluated as part of the research that are FDA-approved and an IND is not required for their use in the research, the study team should provide the IRB with package inserts rather than IDBs.

Note: Many studies involve using a combination of drugs, some of which may be covered by an IND and some of which may not be.

IDB investigators' drug brochure
IND Investigational New Drug
Application - FDA



- In vitro pharmacology
- In vivo animal pharmacology, PK, PD
AUC, C_{max}, DMPK, IDB, IND filing
- Safety assessment for FIH trials
- Investigative toxicology
(toxicogenomics)
- Drug-drug interaction
- “off target”

**THE BIGGEST RISK FOR
HUMAN BEEINGS IS NOT
TO GET A MEDICINE !**

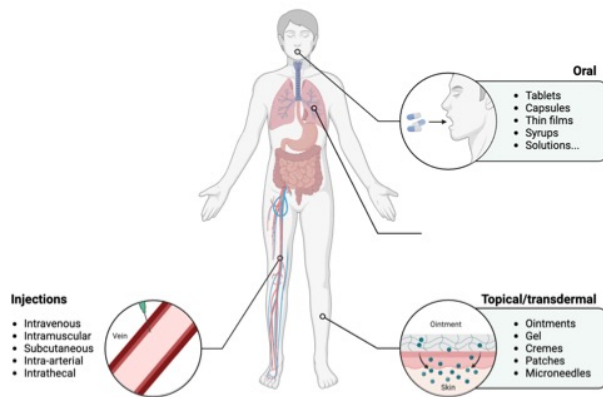


Pharmacology, DMPK, ADME

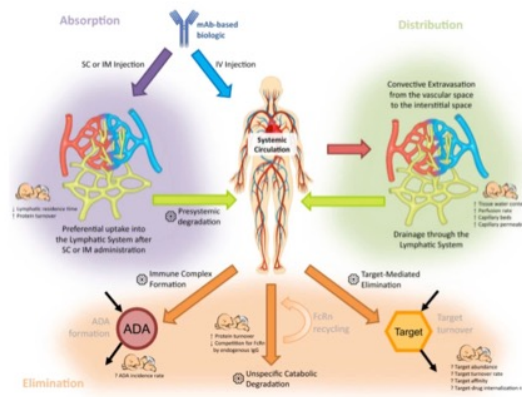


DMPK -drug metabolism and pharmacokinetics : considers the biotransformation of a drug and assessment of its pharmacokinetics

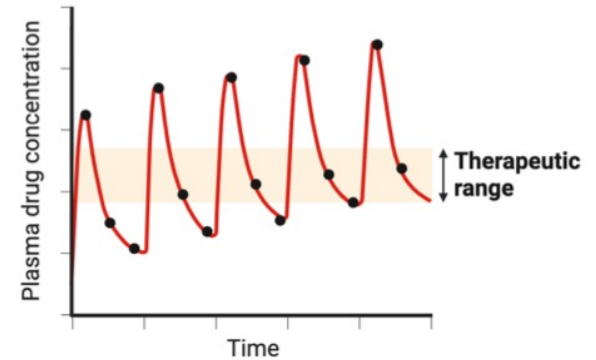
Pharmacokinetics is the description of a the drug journey from its administration to the elimination «body on drug»



Administration



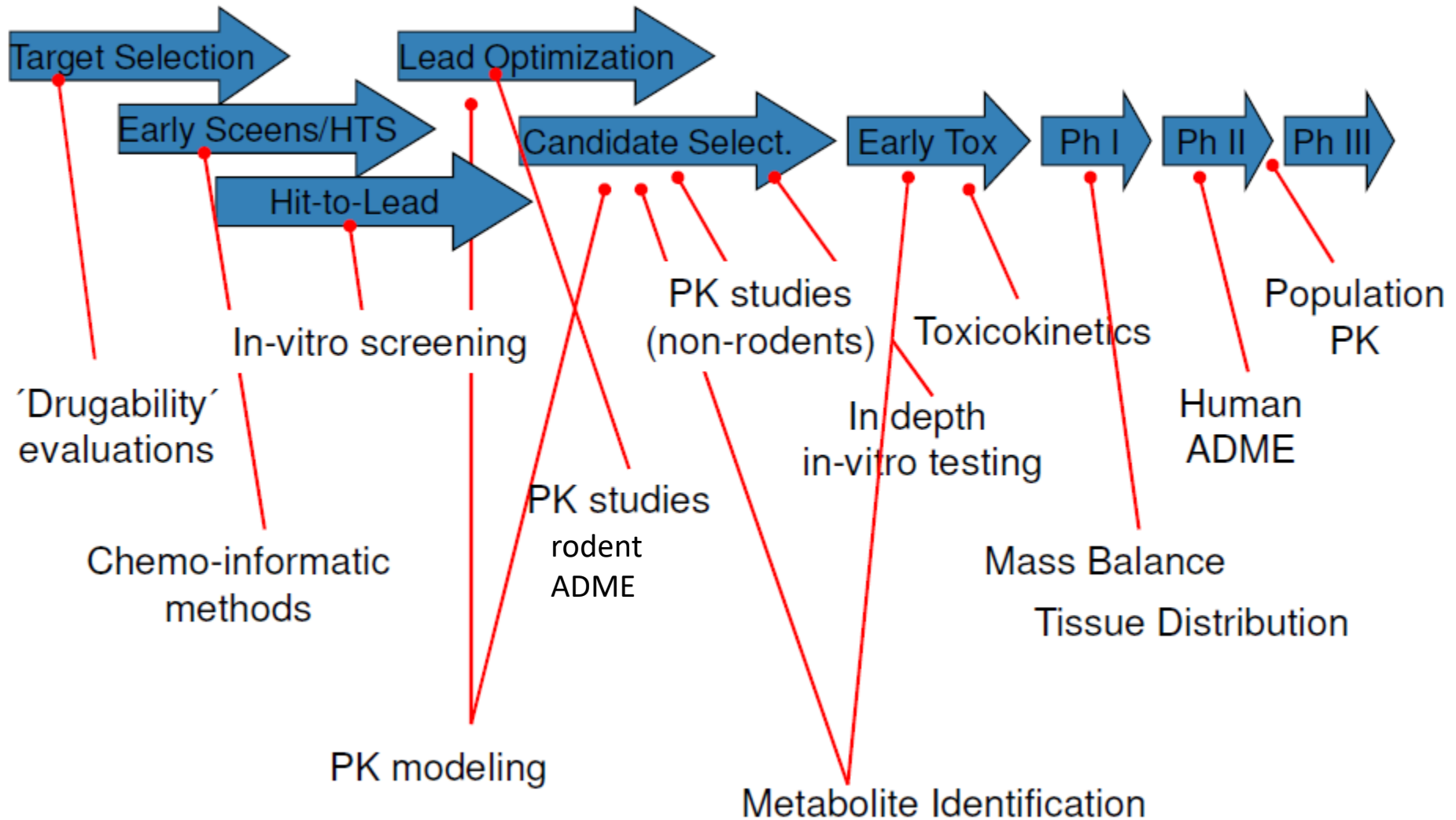
Disposition and elimination of the compound from the body



Plasma drug concentration allows to monitor and understand drug disposition

The biggest risk for human beings is not to get a medicine : when benefits outweigh the known risks

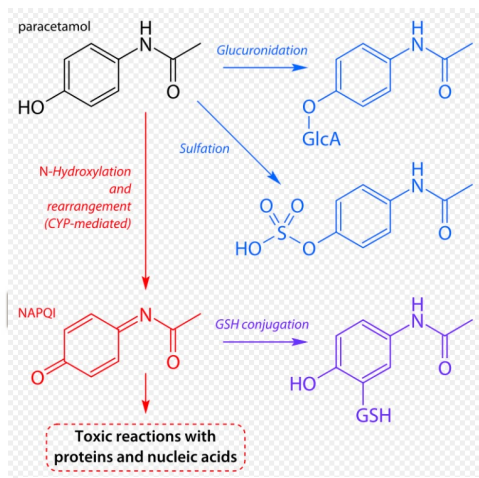
Pharmacology during preclinical and clinical development



**The biggest risk for human beings is not to get a medicine :
when benefits outweigh the known risks**



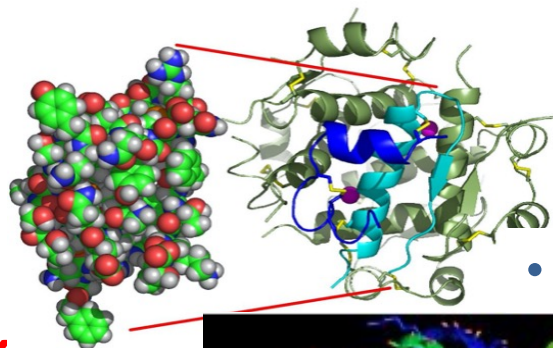
- Paracetamol



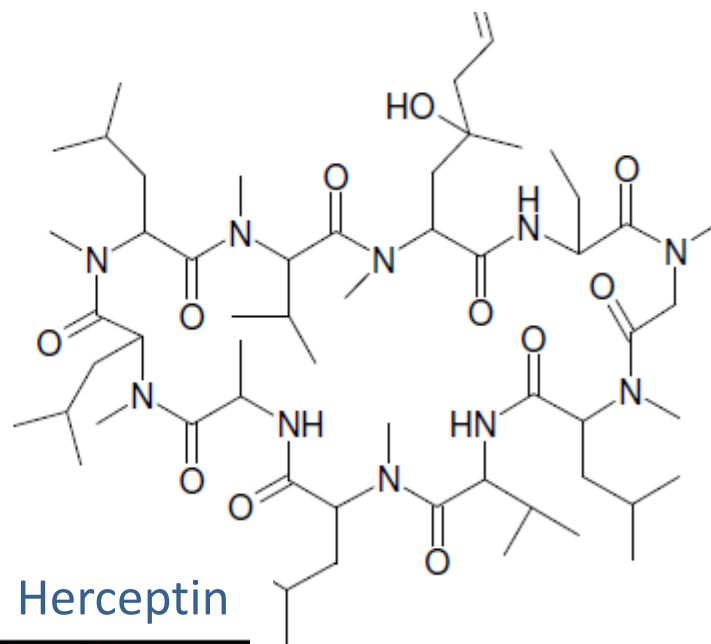
- Cyclosporin

- Insulin

- MABs



- Herceptin

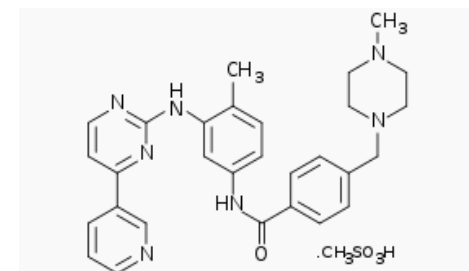


**WILL IT WORK
IN THE
CONTEXT OF A
LIVING
ORGANISM ?**



Modélisation de la molécule de trastuzumab

- Gleevec



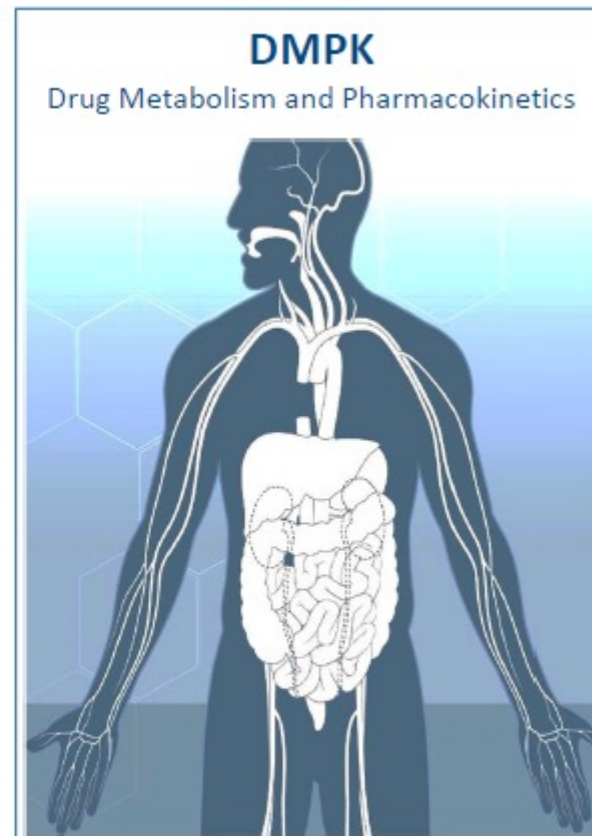
Structure chimique du mésilate d'imatinib



Pharmacology, DMPK, ADME



- **Pharmacokinetics (PK)** and **pharmacodynamics (PD)** are important fields of pharmaceutical sciences for investigating disposition profiles and the pharmacological efficacy of drugs under various experimental and/or clinical conditions.
- **Pharmacodynamics (PD)** is the study of the relationships between the concentration of a drug and the effect site (where target enzymes or receptors are located) and the magnitude of its pharmacological efficacy **(drug → body)**.
- **Pharmacokinetics (PK)** is the study of the way drug molecules behave in the body after administration **(body → drug)**.
- Four distinct and interrelated processes occur between the administration and elimination of drugs from the body. These sequential events are called **ADME** process, i.e., **absorption, distribution, metabolism, and excretion**.



PK : ADME process



A

Absorption:

The process (rate and extent) of compounds or drugs entering the blood circulation from their site of administration.

D

Distribution:

The dispersion or dissemination of compounds or drugs throughout the fluids and tissues of the body.

M

Metabolism (biotransformation):

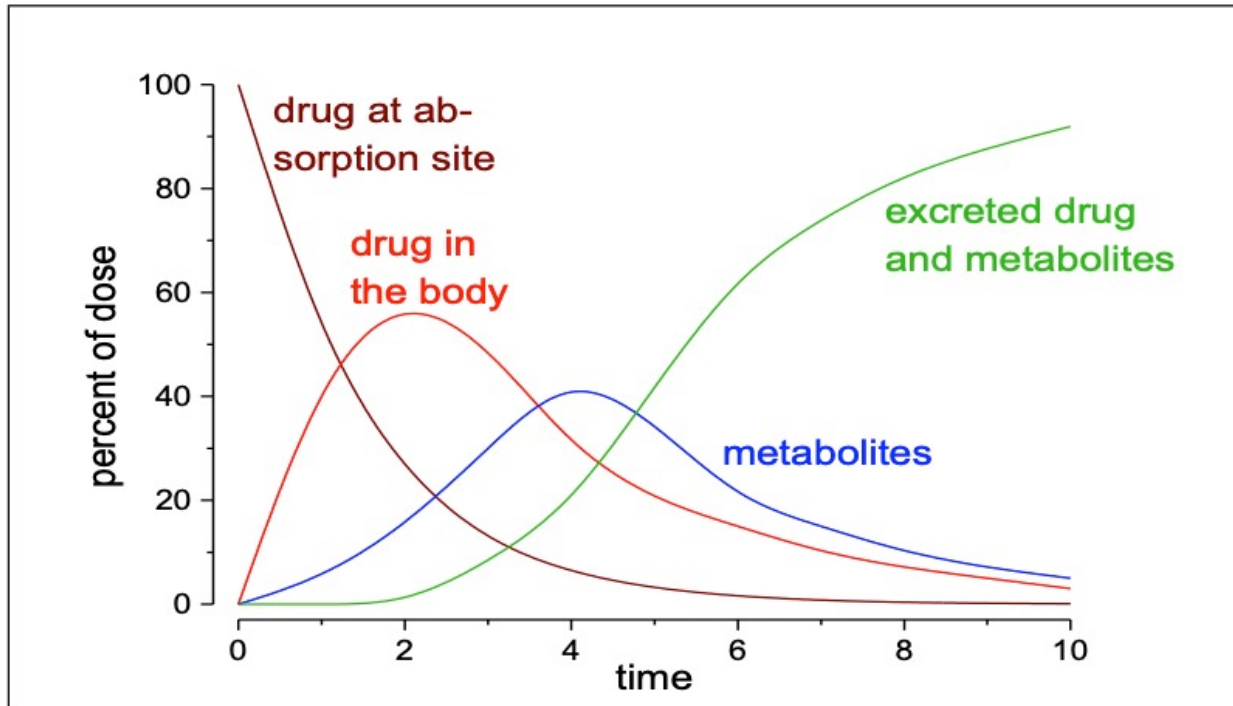
The transformation of (lipophilic) parent compounds or drugs into more hydrophilic metabolites that can be excreted into bile or urine.

E

Elimination/excretion:

The removal of compounds or drugs from the body either unchanged and/or as metabolites.

PK : drug exposure is key to efficacy



AUC = area under the concentration-time curve

C_{max} = maximum concentration

Clearance (CL) = Dose/AUC

Volume of distribution (Vd_{ss}) = MRT*CL

Half-life (t_{1/2}) = ln2 / lambda

Bioavailability (F) = (Dose IV * AUC_{po}) / (Dose PO * AUC_{iv})

PK : ADME process



Pharmacokinetic Aspect	Small Molecules	Monoclonal Antibodies (mAbs)
Absorption and Bioavailability	Typically administered orally ; absorbed through the gastrointestinal tract with varying bioavailability based on physicochemical properties.	Administered parenterally (e.g., intravenous or subcutaneous injection); poor absorption via the gastrointestinal tract; bioavailability depends on administration route and target antigens.
Distribution	Can diffuse across cell membranes to reach intracellular targets; small size facilitates widespread distribution, including the ability to cross the blood-brain barrier .	Predominantly remain in the extracellular space due to large size; cannot cross cell membranes ; limited to vascular and interstitial compartments, restricting access to intracellular targets.
Metabolism	Primarily metabolized in the liver by cytochrome P450 enzymes, leading to active or inactive metabolites.	Undergo catabolic processes rather than traditional metabolic pathways; broken down into peptides and amino acids by proteolytic enzymes with minimal liver enzyme involvement.
Elimination	Eliminated mainly through renal excretion or biliary secretion , based on size, charge, and lipophilicity.	Eliminated via target-mediated drug disposition (TMDD) ; drug-target complex is internalized and degraded, leading to nonlinear pharmacokinetics with varying clearance rates.
Half-Life	Generally have shorter half-lives , often requiring multiple daily doses to maintain therapeutic levels.	Exhibit longer half-lives (days to weeks), due to size, Fc receptor interactions, and recycling mechanisms, allowing for less frequent dosing.

PK : Absorption process



Drug specific factors affect eg. oral absorption of small molecules eg pK

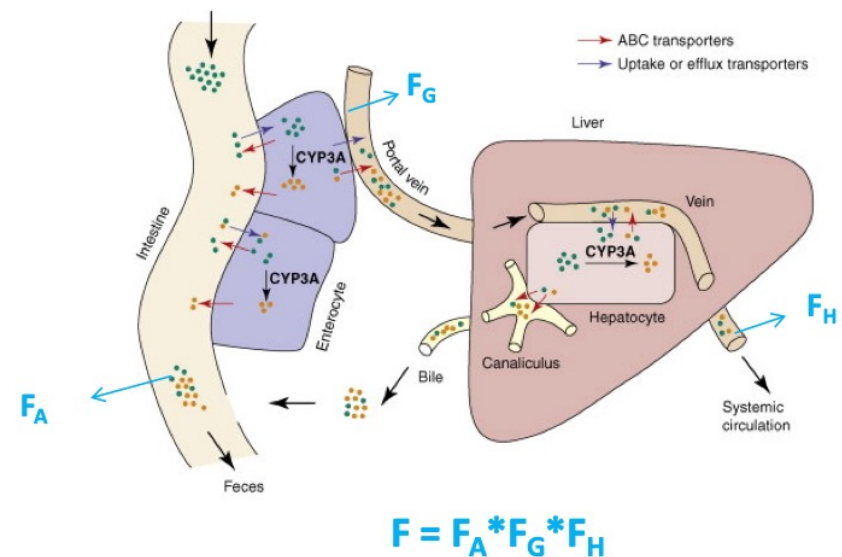
- Solubility/ Dissolution (pKa, lipophilicity, size)
- Stability in the GI tract
(chemical/enzymatic stability)
- Permeability (pKa, lipophilicity, size)
- Active and facilitated transport mechanisms

Absorption in vitro models

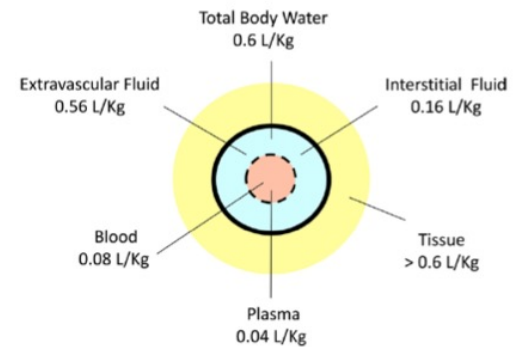
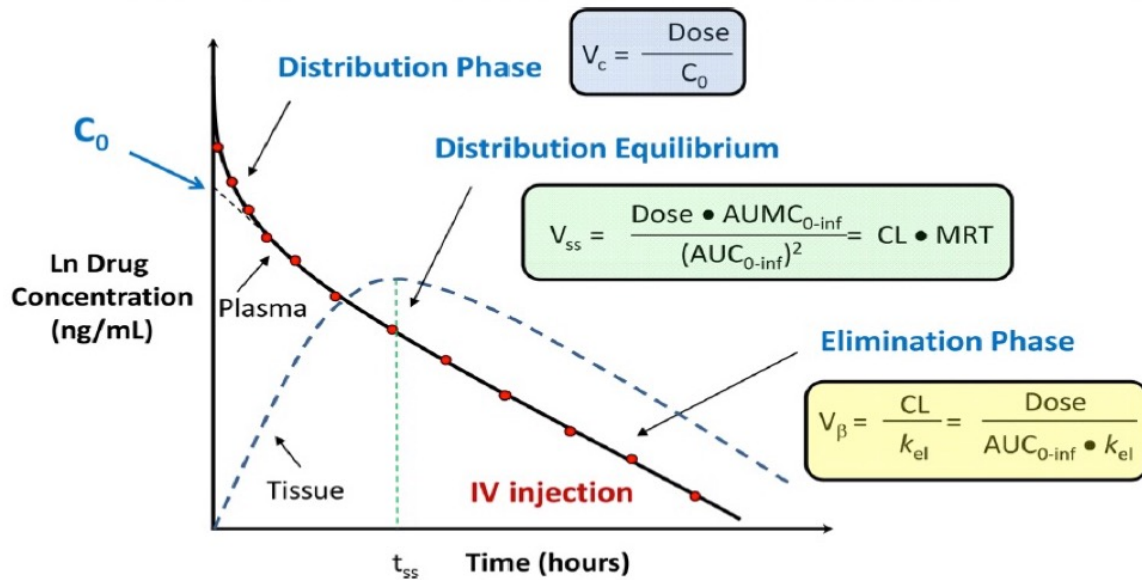
- Caco-2 cells
- MDCK cells
- PAMPA
- ORGANOIDS

System specific parameters affecting (oral) absorption:

pH, intestinal transit time, motility, transporter, enzyme expression



ADME : distribution process



$$V_{ss} = V_p + \sum \left(\frac{f_{u_p}}{f_{u_t}} \right) V_t$$

ADME : distribution process



Volume of distribution (Vd)

Definition: $V_d = \frac{\text{Amount of drug in body at equilibrium}}{\text{Plasma drug concentration}}$

- Volumes of distribution of small molecules range from 3 to 40,000 L in humans
- Plasma water ~ 3 L, extracellular water ~ 12 L, total body water ~ 27 L
- **How can Vd be as high as 40,000 L when the physical aqueous volume of a human being is ~ 27 L?**
 - Vd does not refer to a physical but an apparent volume
 - Drugs have different affinities to tissue protein, lipids or other constituents and this may result in significant bindings or partitioning of drug into tissue
 - Acids (e.g., flubiprofen, warfarin) show strong affinity to plasma proteins (low $f_{u,p}$) and have therefore typically much lower Vd compared to bases/ neutrals

Major drug-specific factors affecting the volume of distribution

- Lipophilicity
- pKa
- Plasma Protein Binding
- Transporters

ADME – metabolism and excretion process



Metabolism (chemically converted metabolites (may serve as biomarkers !
Genetical differences (polymorphisms) can lead to overdose !

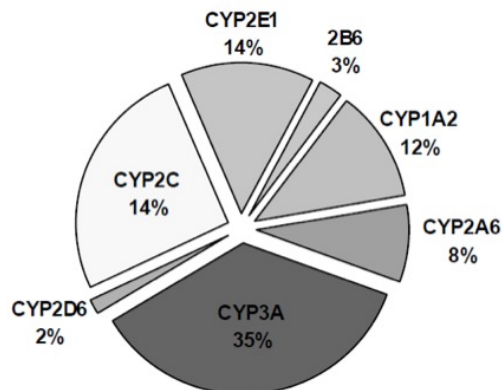
Hepatic metabolism

▪ Oxidative metabolism

- Referred to as **Phase I** metabolism as frequently the first metabolic step

▪ **Cytochrome P450** enzymes are key contributors to small molecule metabolism

- **CYP3A4** is the main enzyme



▪ Conjugation

- Referred to as **Phase II** metabolism as frequently following oxidative metabolism
- However, conjugation may also occur as first step
- UGT (glucuronidation) or SULT (sulfation) are primary conjugating enzymes

▪ Other metabolically active enzymes

- FMO (flavin mono-oxygenase), AD or XO (aldehyde or xantine oxidase), ADH (alcohol dehydrogenase), carboxylesterases

Small molecules

1, Paine et al. (2006) *Drug Metab and Dispos* 34: 880-6

Excretion : route dependent on size and physicochemical properties ; eg. alcohol expired as gas, larger less polar medicine in bile, small polar moieties in urine etc.

ADME – drug clearance

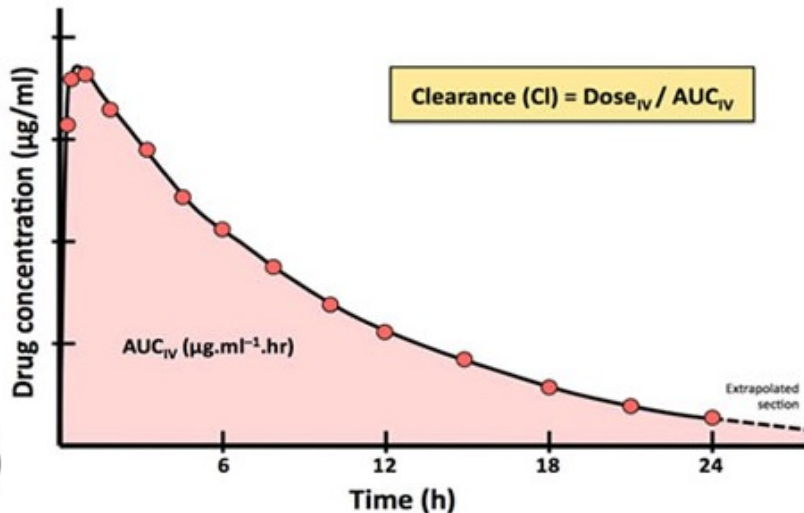
elimination rate over concentration



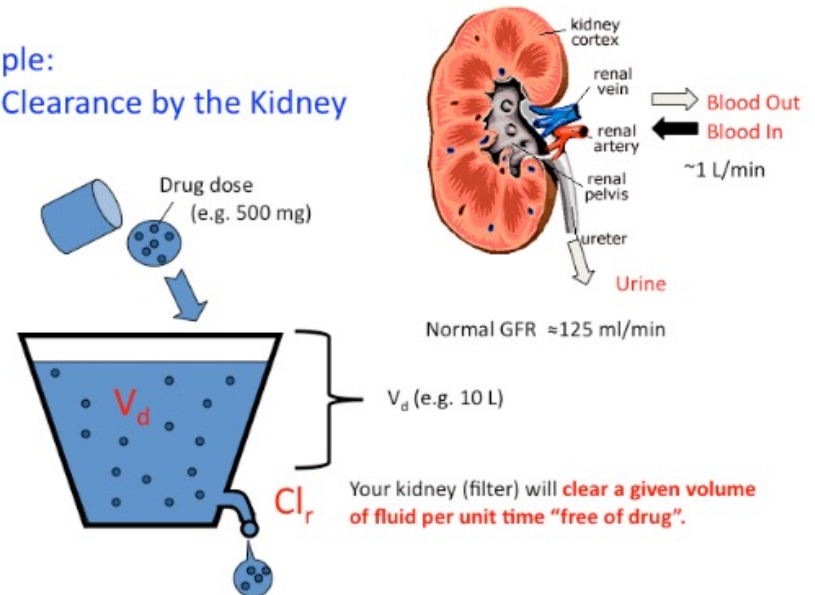
$$CL = \frac{\text{Dose}}{\text{AUC}}$$

CL represents the proportionality constant between concentration and rate of elimination or upon integration dose and AUC

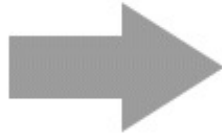
- **Apparent CL** refers to the observable clearance in blood or plasma (CL_b or CL_p)
- The apparent CL may be a composite of the contribution of various organs (**frequently liver and kidneys**)
 - Elimination of drug occurs by excretion and metabolism
- **Unbound intrinsic CL** ($CL_{u_{int}}$) refers to the actual cellular clearance without any limitations caused by tissue perfusion
 - $CL_{u_{int}}$ is not directly observable *in vivo*



Example:
Drug Clearance by the Kidney



Pharmacology during preclinical and clinical development: pharmaceutical formulation (galenics) is key



An active ingredient has to be incorporated into a suitable form of administration so that it can be transported to the part of the body where it is needed.

Medicines are required to:

- Contain an accurate dose
- Make active substance available for absorption
- Be stable
- Be convenient to administer and easy to take
- Be produced economically according to Good Manufacturing Practice (GMP)

**The biggest risk for human beings is not to get a medicine :
when benefits outweigh the known risks**



drug formulation

The biggest risk for human beings is not to get a medicine :
when benefits outweigh the known risks

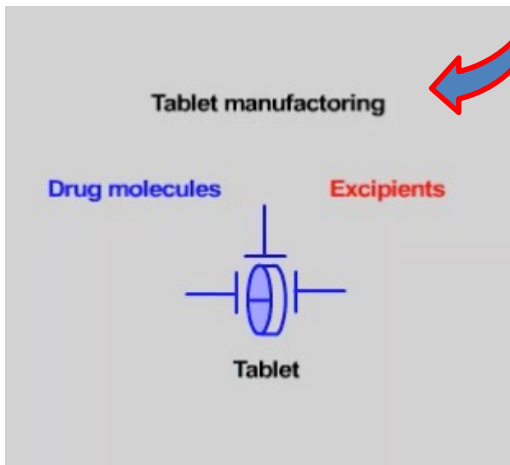
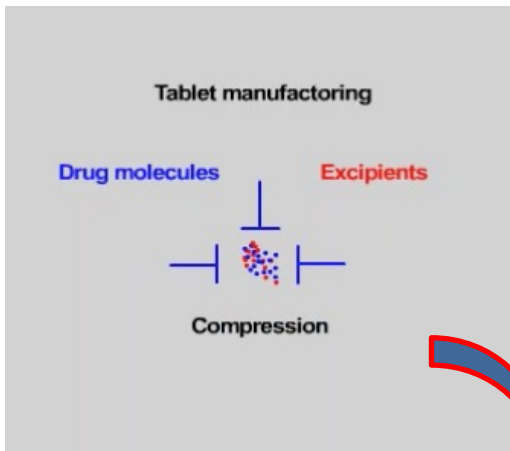
In vivo pharmacokinetics and galenics



tissue delivery/exposure, classical vs high tech galenic formulations

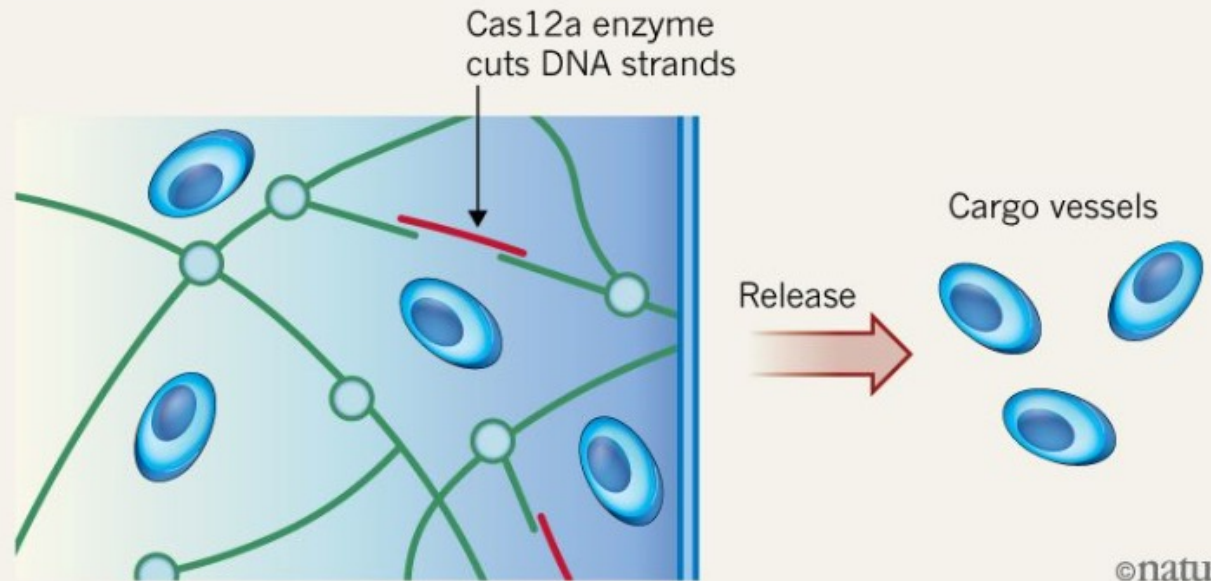
today's galenics

tomorrow's galenics



CRISPR-CONTROLLED GEL

Researchers have created a smart hydrogel material that is held together by DNA. The CRISPR-Cas12a protein cuts the DNA strands, changing the gel's shape, which can be controlled to release drugs, particles or even switch an electronic circuit.



Adapted from D. Han et al. Science <https://doi.org/10.1126/science.aay4198> (2019).

In vivo pharmacokinetics and prodrug : eg release of tissue esterase-sensitive prodrugs



tissue delivery/exposure, prodrug overcome pharmacokinetic barriers

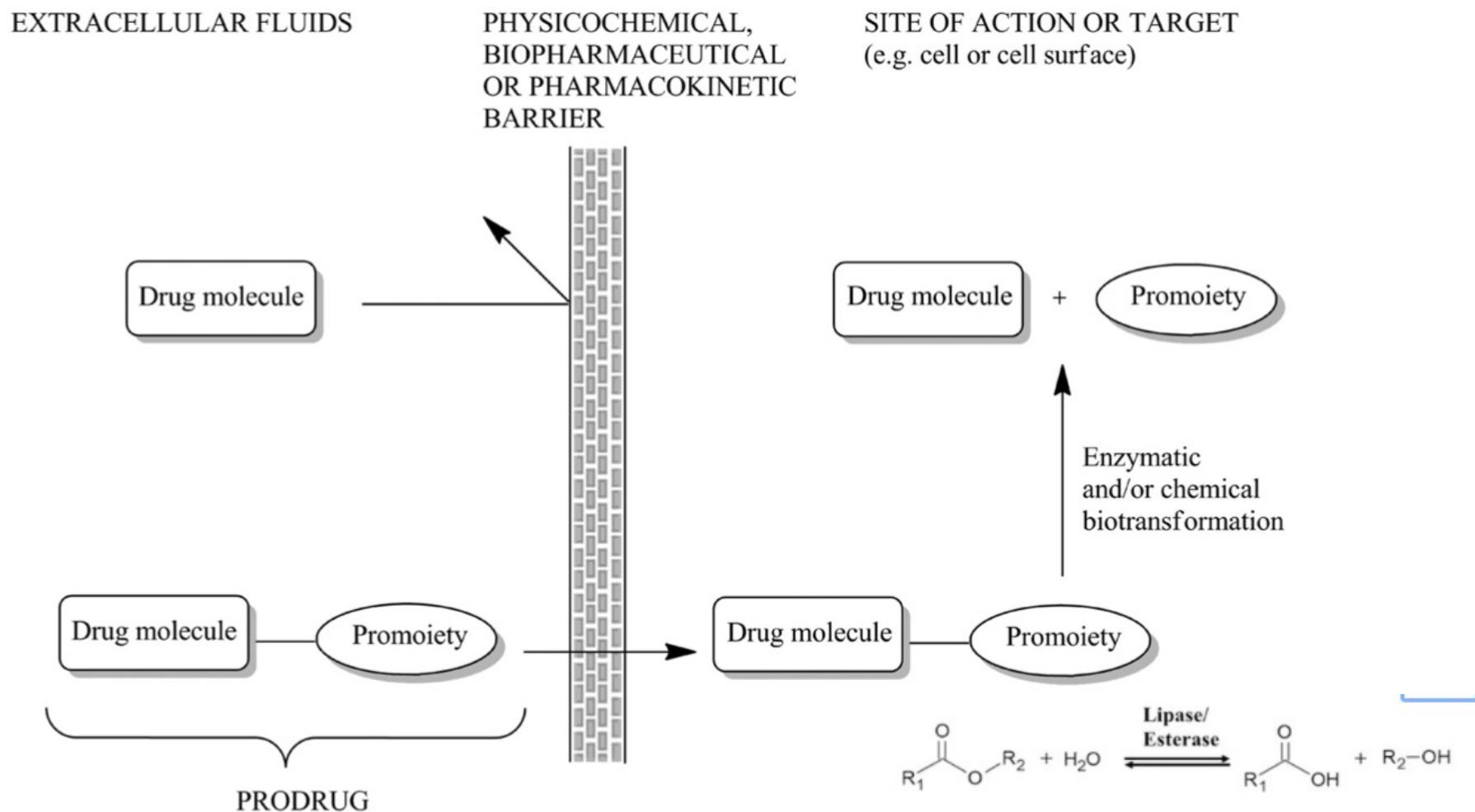


FIG. 1. A simplified illustration of the prodrug concept.

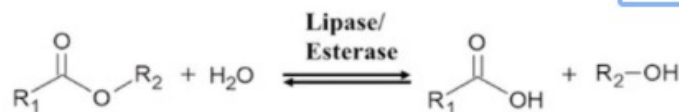
In vivo pharmacokinetics and prodrug : eg release of tissue esterase-sensitive prodrugs



tissue delivery/exposure, prodrug overcome pharmacokinetic barriers

TABLE 4
The occurrence of prodrugs among the world's 100 top-selling pharmaceuticals in 2009

Prodrug Name (Trade Name) and Therapeutic Area	Functional Group	Prodrug Strategy
Proton pump inhibitors Esomeprazole (Nexium) Lansoprazole (Prevacid) Pantoprazole (Protonix) Rabeprazole (Aciphex)	Formation of active sulfonamide form	Bioprecursor prodrugs that are converted into their respective active sulfonamide forms site-selectively in acidic conditions of stomach
Antiplatelet agent Clopidogrel (Plavix)	Formation of the active thiol	Bioprecursor prodrug that selectively inhibits platelet aggregation
Antiviral agent Valacyclovir (Valtrex)	L-Valyl ester of acyclovir	Bioconversion by valacyclovir hydrolase (valacyclovirase) Transported predominantly by hPEPT1 Oral bioavailability improved from 12–20% (acyclovir) to 54% (valacyclovir)
Hypercholesterolemia Fenofibrate (Tricor)	Isopropyl ester of fenofibric acid	Lipophilic ester of fenofibric acid
Antiviral agent Tenofovir disoproxil (Atripla)	Bis-(isopropoxy-carbonyloxymethyl) ester of tenofovir	Bioconversion by esterases and phosphodiesterases The oral bioavailability of tenofovir from tenofovir disoproxil is 39% after food
Psychostimulant Lisdexamfetamine (Vyvanse)	L-Lysyl amide of dextroamphetamine	Bioconversion by intestinal or hepatic hydrolases Reduced potential for abuse due to prolonged release of active drug
Influenza Oseltamivir (Tamiflu)	Ethyl ester of oseltamivir carboxylate	Improved bioavailability compared with oseltamivir carboxylate, allowing oral administration



In vivo animal pharmacology, PK, PD, ADME



In vivo efficacy, exposure, safety margins, IB, FDA documents



BalbC mouse



Beagle dog



Vervet Cynomolgus



DIO rat

- In common experimental animals (same species as for in vivo pharmacology and toxicology)
 - Most common are rats and dogs
 - Cynomolgus as non-human primate species
 - Less common are rabbits, minipigs, mice, hamsters guinea pigs etc.
- Analytical method for the determination of drug in blood or plasma needed
 - Sensitivity requirements are set by the pharmacological and safety properties of a drug



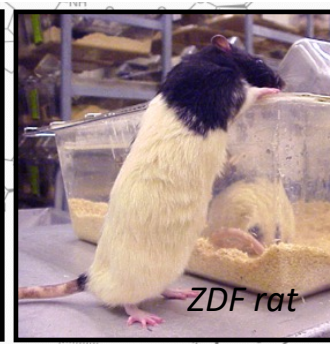
dbdb mouse



obob mouse



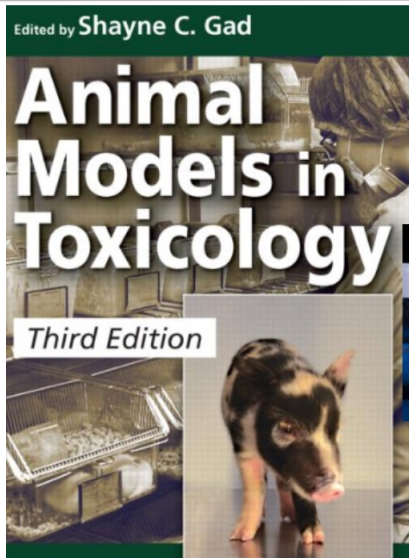
critecus mesocritecus
golden hamster



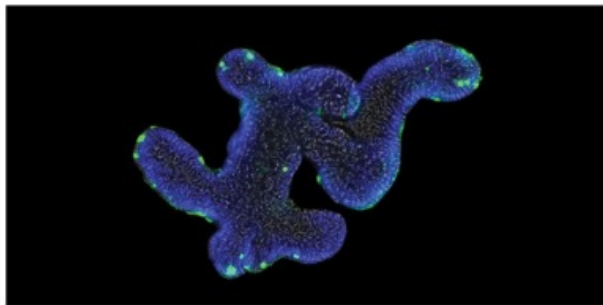
ZDF rat



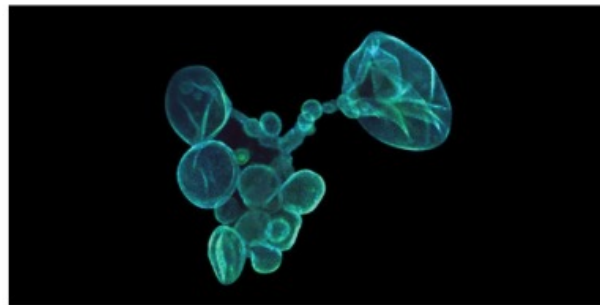
3R initiative in safety toxicology : can organoids help ?



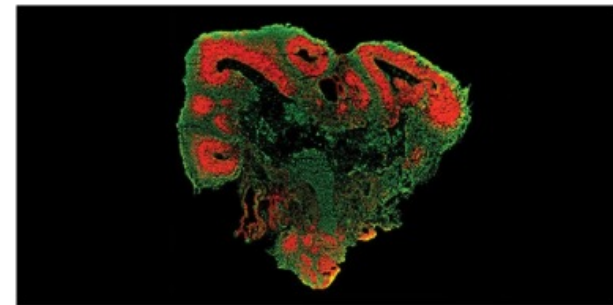
3R



Intestinal Organoids



Liver Organoids



Neural Organoids

Strategic Focus on 3R Principles Reveals Major Reductions in the Use of Animals in Pharmaceutical Toxicity Testing

Elin Törnqvist, Anita Annas, Britta Granath, Elisabeth Jalkestén, Ian Cotgreave, Mattias Öberg

Published: July 23, 2014 • <https://doi.org/10.1371/journal.pone.0101638>



www.3ragrocarbon.com

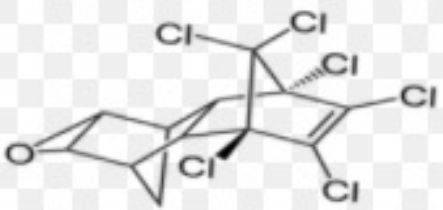
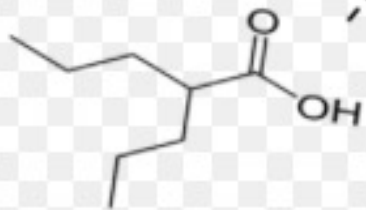
3R initiative in safety toxicology : are patient's safety in danger ?



"If I'd known the dogs were dead, I wouldn't have risked my life for €1,900. I wouldn't have signed up. I'm not crazy." a phase 0 BIA 10-2474 healthy volunteer trial survivor

Modes of action;
Targets;
Drugs, Chemicals

Human safety
?
Human health



Medicine safety (adverse effects) is what patients care first !!
THE BIGGEST RISK IN DRUG DEVELOPMENT IS NOT TO GET A MEDICINE : "FAIL EARLY" STRATEGY

3R initiative in safety toxicology and animal pharmacology : *in vivo* vs *in vitro*



Antispeciesism : against animal pharmacology/experiments vs 3Rs - while billions of wild mice exterminated yearly by cats !

What about pets in custody, small apartments ? And over consumption of meat?

Against scientific process ? biomedical research

[< Retour au sommaire](#)



Lancement d'un programme national de recherche sur la thématique « animaux, recherche et société »

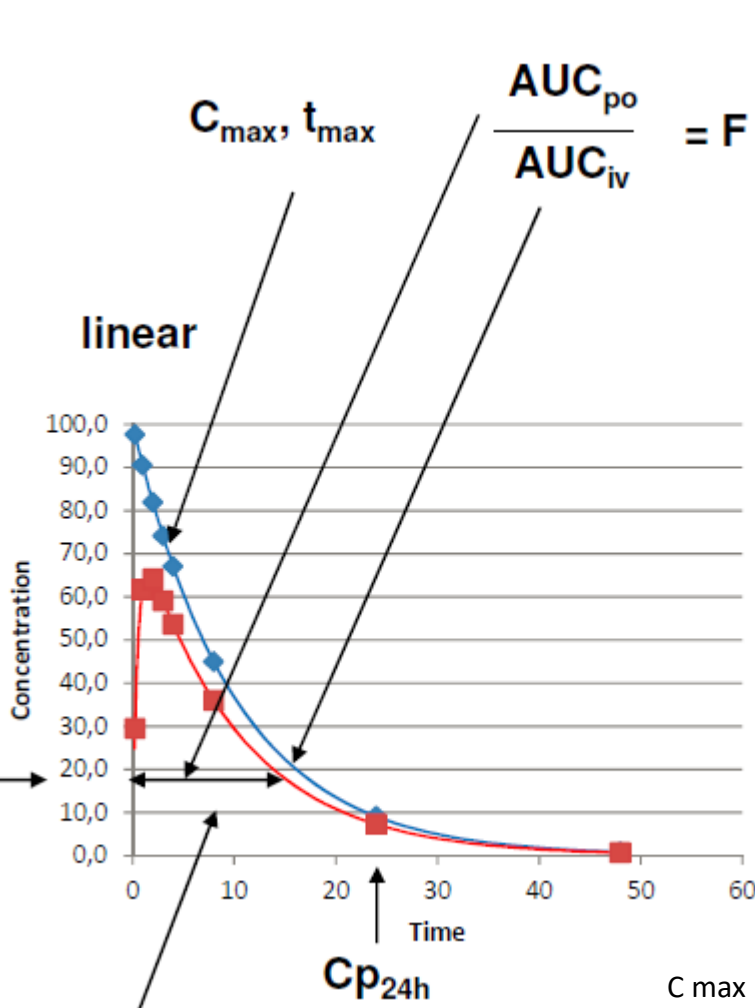
Berne, 03.02.2021 - Le 3 février 2021, le Conseil fédéral a lancé un nouveau programme national de recherche intitulé « Advancing 3R – animaux, recherche et société », qui vise principalement à faire diminuer le nombre d'expérimentations animales dans la recherche scientifique, à les améliorer et à définir des principes de bases pour les aspects éthiques et sociétaux dans ce domaine. Ce programme est doté de 20 millions de francs et s'étend sur une durée de cinq ans.

Le programme national de recherche (PNR) 79 « Advancing 3R – animaux, recherche et société » vise d'une part à faire diminuer le nombre d'expérimentations animales dans la recherche scientifique et, de ce fait, à réduire proportionnellement celui des animaux de laboratoire. Il a également pour but de réduire au maximum les contraintes subies par les animaux de laboratoire pendant leurs expériences et de leur détention. D'autre part, ce PNR traitera des questions éthiques, juridiques, sociétales, culturelles et économiques de la transition vers une exploitation animale.

Le programme vise à promouvoir les principes de « remplacement », « réduction » et « raffinement ». Les expérimentations visent les objectifs suivants : remplacer autant que possible les



PK *in vivo* – "body on drug"



— iv
— po

- AUC Area under the curve (from PK data analysis)
- C_{max} Peak Concentration (from PK data analysis)
- T_{max} Peak time (from PK data analysis)
- Elimination Rate Constant (λ_z , from PK data analysis)
- Elimination Half-life $t_{1/2} = \ln(2)/\lambda_z$
- F Bioavailability = AUC (po)/AUC (iv)
- Volume of Distribution $V(t)$
 - $V_z = CL/\lambda_z$
 - $V_c = D/C(0)$
- CL: Total Body Clearance $D / F = AUC_{po} * CL = AUC_{iv} * CL$

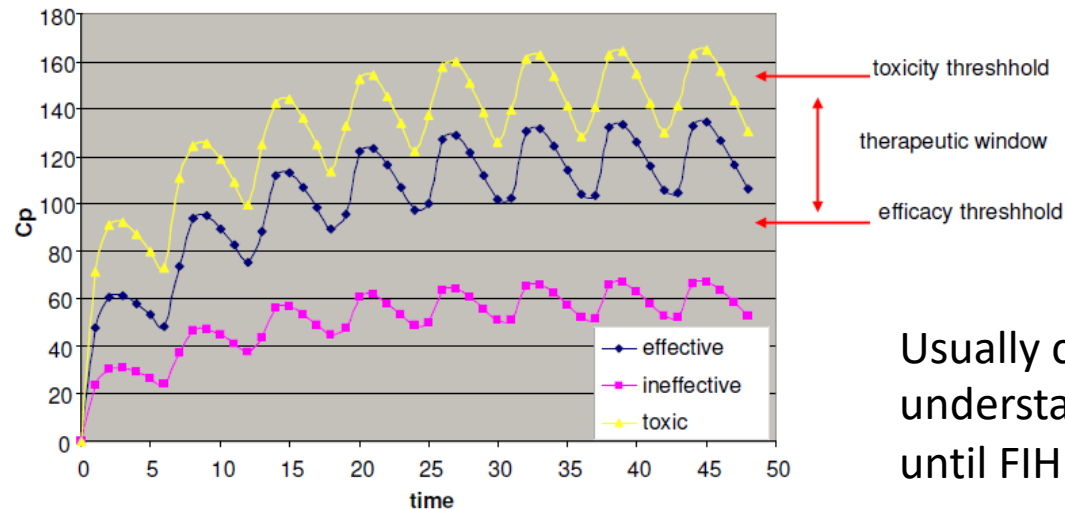
C_{max} : the peak serum concentration of a therapeutic drug

T_{max} : The amount of time that a drug is present at the maximum concentration in serum.



What to expect from DMPK – PK, PD data allow relating safety with efficacy

- Dose dependence of efficacy and safety
- Frequency of dosing
- Exposure of target organs
- Differences in efficacy and safety
 - Between species
 - For special populations and ethnicities
 - Individual differences
- Drug-drug-interactions
- Best choice of animal species for toxicological studies
- Supporting data for new formulations
- Supporting data for safety assessment
- In vitro/in silico
 - Microsomes, hepatocytes, enzymes, cell cultures
 - Computer models for in vitro-in vivo-correlation
- Laboratory animals
 - Rodents, dogs, rabbits, non human primates
- Phase I studies (<20 healthy individuals)
 - Human PK or metabolism data
- Phase III studies (>1000 individuals)
 - Population models
- Patients (therapeutic drug monitoring)
 - Individual analysis



Usually clear understanding up until FIH

PK, ADME, PD - in silico simulation

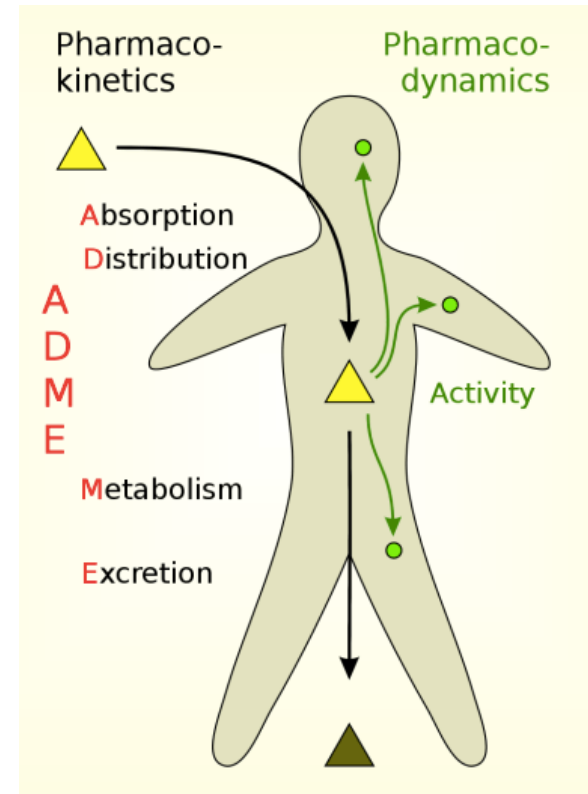
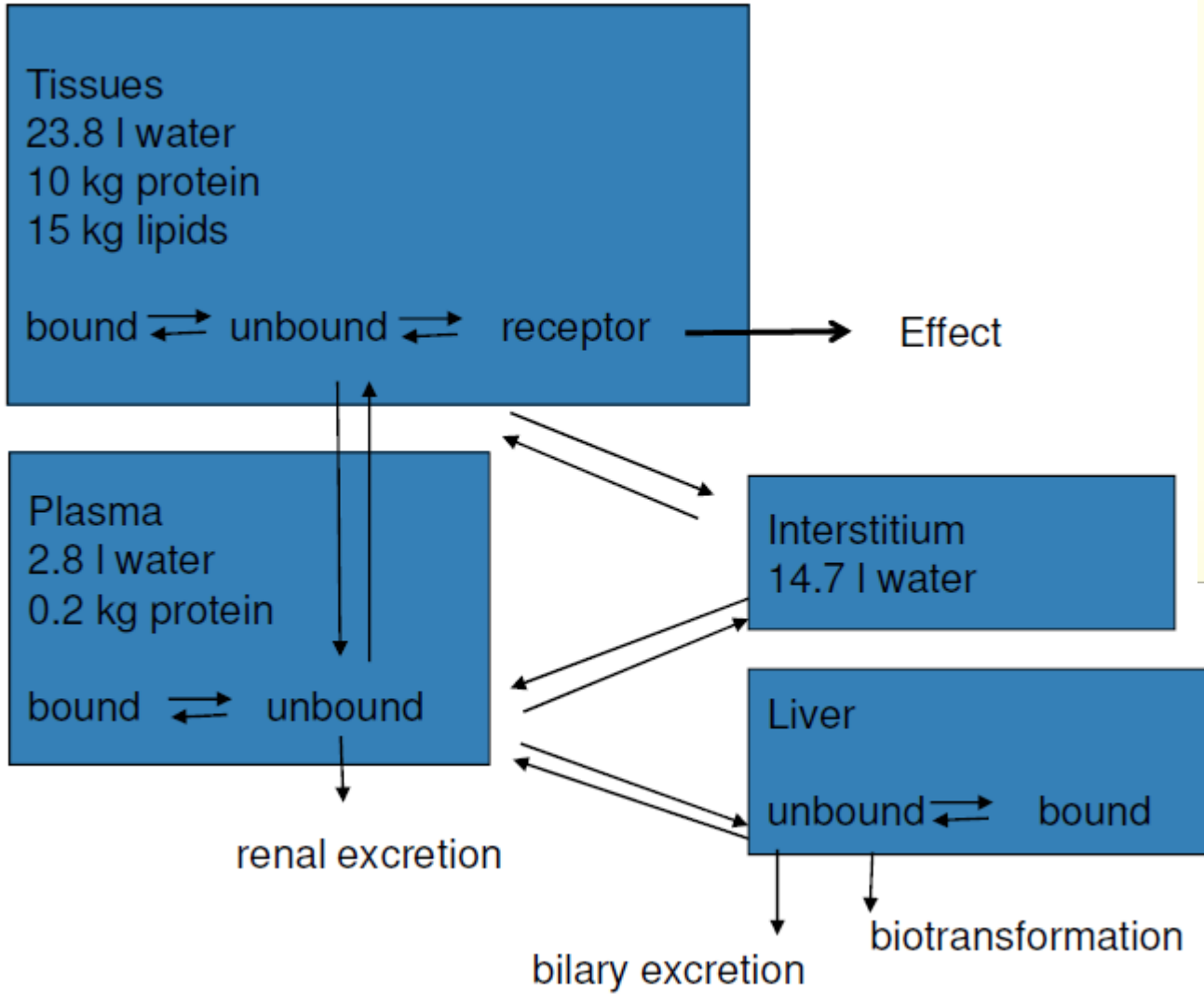


Fraction unbound

$$f_u = \frac{A_{unbound}}{A_{total}}$$

A_ amount of drug

C=concentration of drug



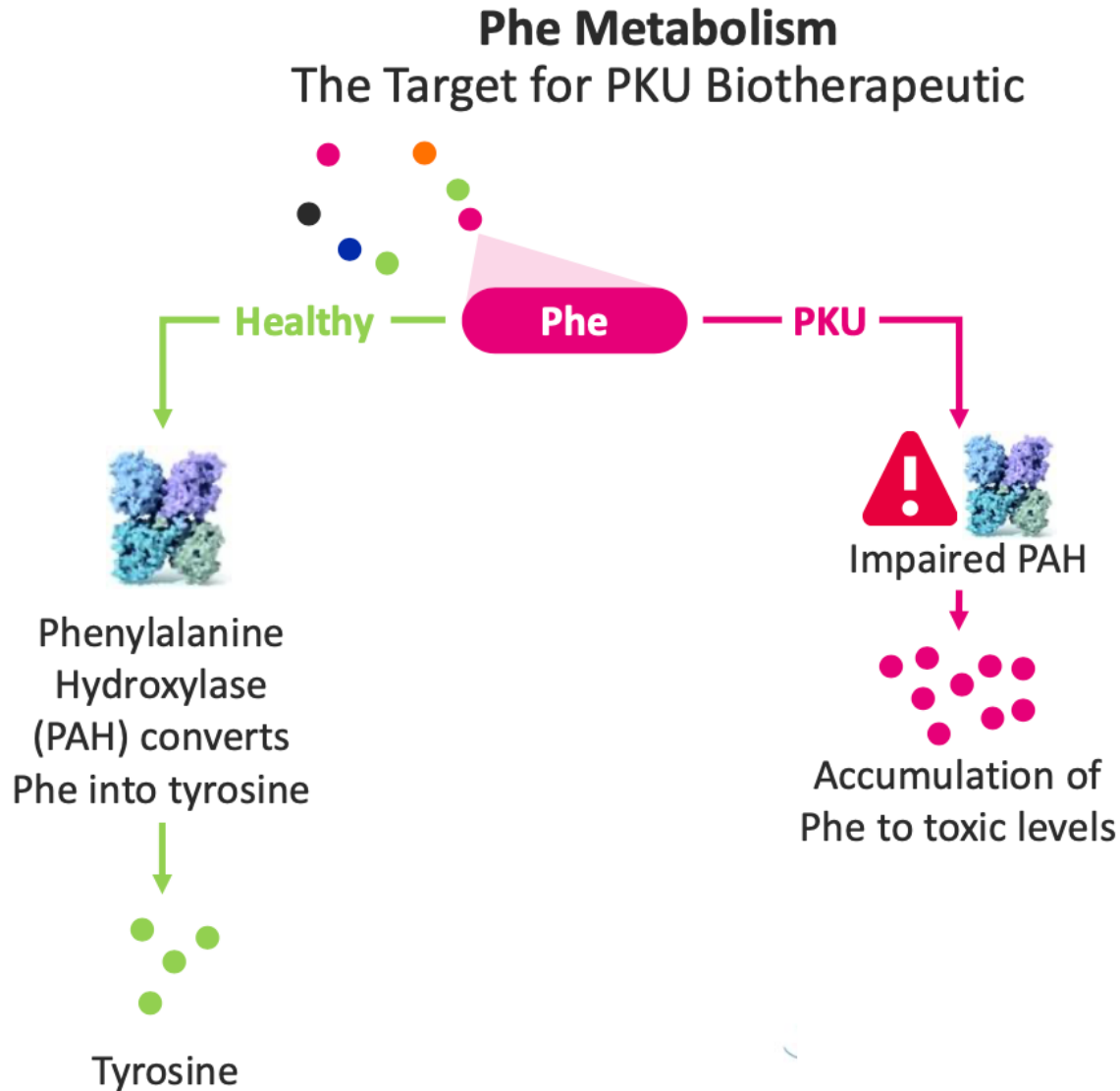
In vitro pharmacology, DMPK, ADME



In vitro efficacy, safety margins,

Characteristic	Description	Example value	Symbol
Dose	Amount of drug administered.	500 mg	D
Dosing interval	Time between drug dose administrations.	24 h	τ
C_{\max}	The peak plasma concentration of a drug after administration.	60.9 mg/L	C_{\max}
t_{\max}	Time to reach C_{\max} .	3.9 h	t_{\max}
C_{\min}	The lowest (trough) concentration that a drug reaches before the next dose is administered.	27.7 mg/L	$C_{\min,ss}$
Volume of distribution	The apparent volume in which a drug is distributed (i.e., the parameter relating drug concentration to drug amount in the body).	6.0 L	V_d
Concentration	Amount of drug in a given volume of plasma .	83.3 mg/L	C_0, C_{ss}
Elimination half-life	The time required for the concentration of the drug to reach half of its original value.	12 h	$t_{\frac{1}{2}}$
Elimination rate constant	The rate at which a drug is removed from the body.	0.0578 h^{-1}	k_e
Infusion rate	Rate of infusion required to balance elimination.	50 mg/h	k_{in}
Area under the curve	The integral of the concentration-time curve (after a single dose or in steady state).	1,320 mg/L·h	$AUC_{0-\infty}$
			$AUC_{\tau,ss}$

Phenylketonuria : a rare disease (1:23'000 live births) (recessive autosomal)



Phenylketonuria : facts and clinical figures



Symptoms of PKU

Newborns with PKU rarely have symptoms right away, although sometimes they are sleepy or eat poorly. Symptoms develop slowly over several months as phenylalanine builds up in the blood. If not treated, affected infants progressively develop intellectual disability over the first few years of life, which eventually becomes severe. Other symptoms include

- Seizures
- Nausea and vomiting
- Eczema-like rash
- Lighter skin, eye, and hair color than their family members
- Aggressive or self-injurious behavior
- Hyperactivity
- Sometimes psychiatric symptoms

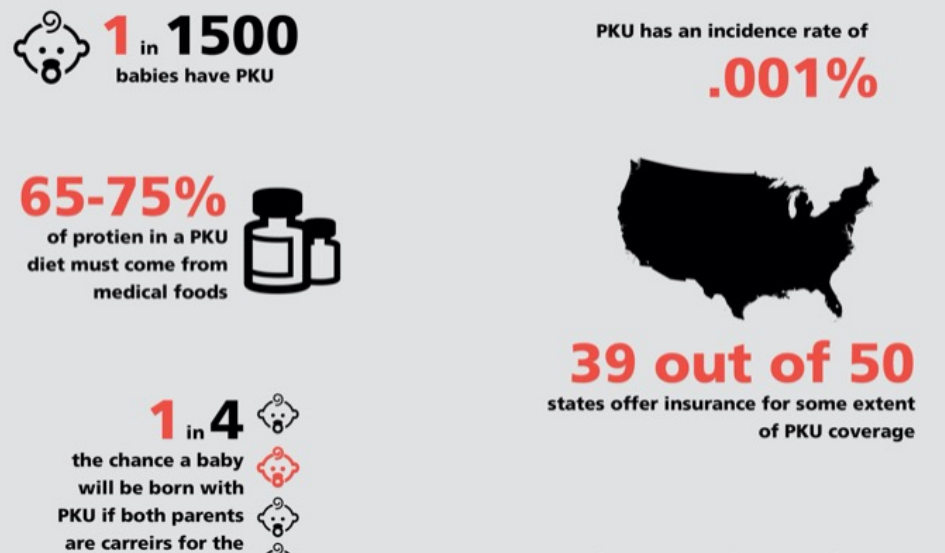
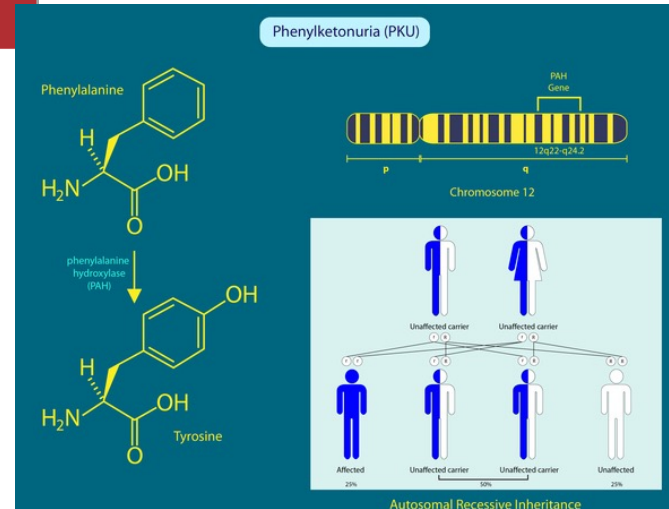
Untreated children with phenylketonuria often give off a mousy or musty body odor in their urine and sweat. This odor is the result of phenylacetic acid, which is a by-product of phenylalanine.

Diagnosis of PKU

- Newborn screening test
- Prenatal screening tests

Phenylketonuria is usually diagnosed with a routine [newborn screening test](#).

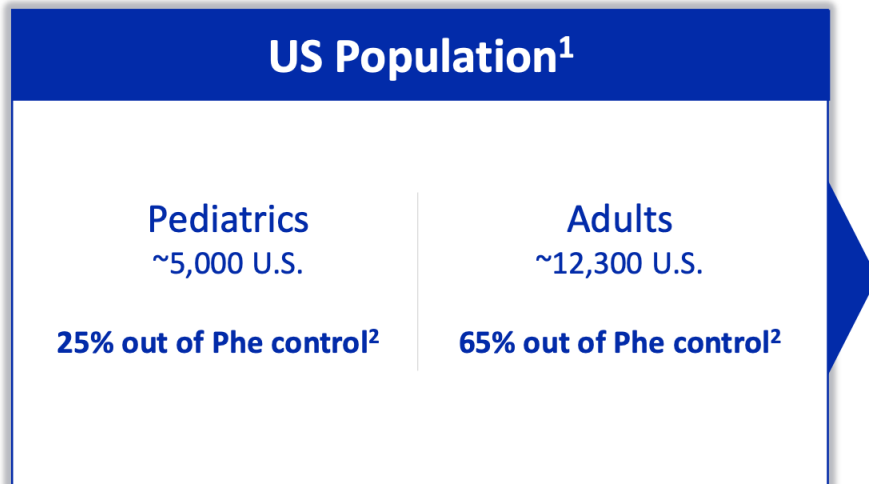
Autosomal recessive inheritance : globally 0.45 million individuals have PKU, with global prevalence 1:23,930 live births (range 1:4,500 [Italy]–1:125,000 [Japan]).



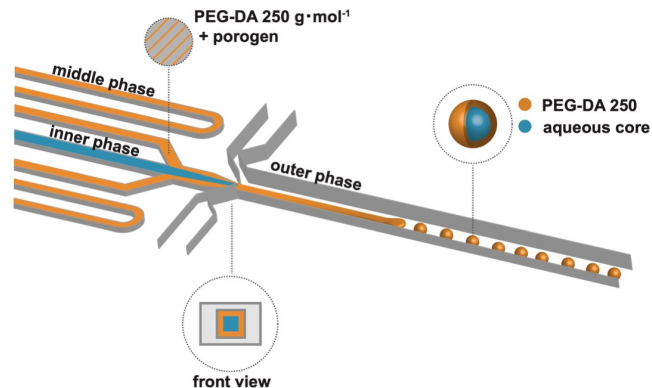
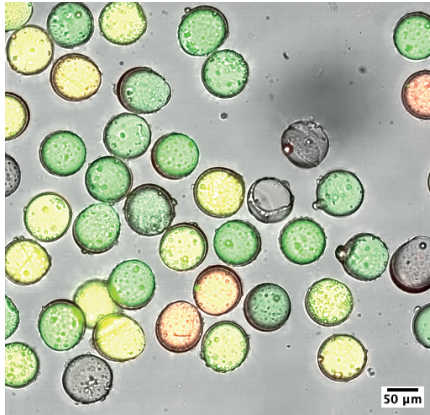


PKU: Significant Need Remains for New Treatment Options

Challenges



- Significant risk for **neurocognitive impairment** if untreated
- Extremely challenging diet with **low compliance**
- **Low response** to current oral therapies: 80% fail to respond³
- Most adult patients **out of Phe control** and difficulties in **executive function**
- Substantial need for increased intake of **natural protein**



Direct encapsulation of biological active substances in semi-permeable PEG microcapsules

Grégoire Michielin MD PhD

advisor:

Professor S. Maerkl, LBNC, EPFL

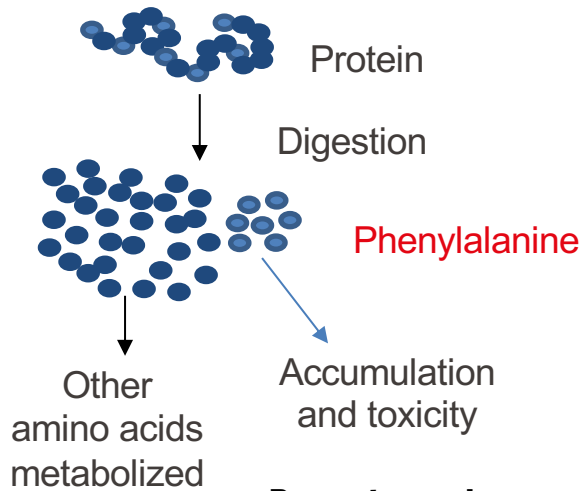


Phenylketonuria : galenics 2.0

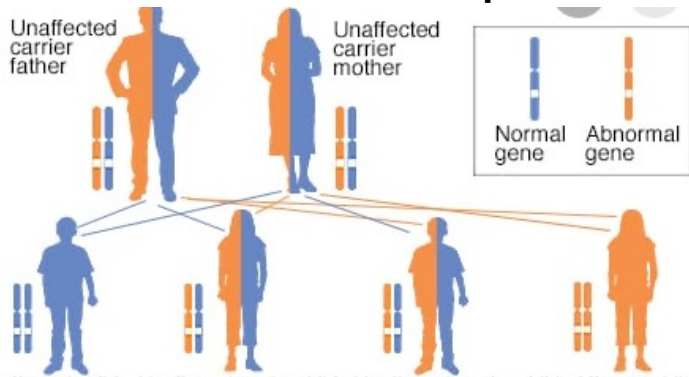


Context Grégoire Michielin

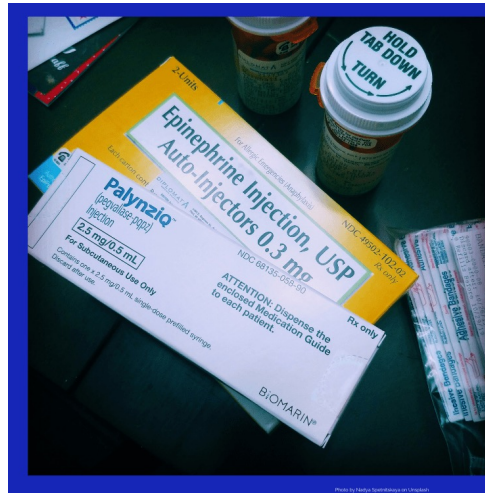
Phenylketonuria



Rare autosomal recessive disorder
1:10'000 birth
0.5 millions patients ww

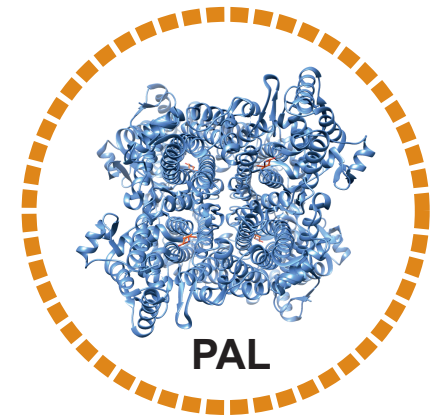


Enzyme replacement therapy by injection



<https://prosperouspku.com/2021/04/01/dietary-transition-pku/>
 pegylated phenylalanine hydroxylase

This projet: Treatment by oral delivery !

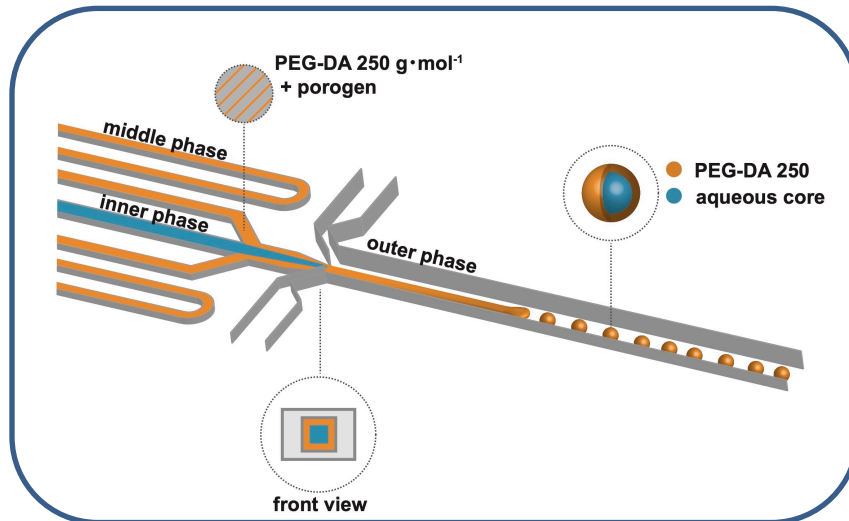


pegylated phenylalanine amoniac lyase (30KDa)
 (hydrolysis of Phe)

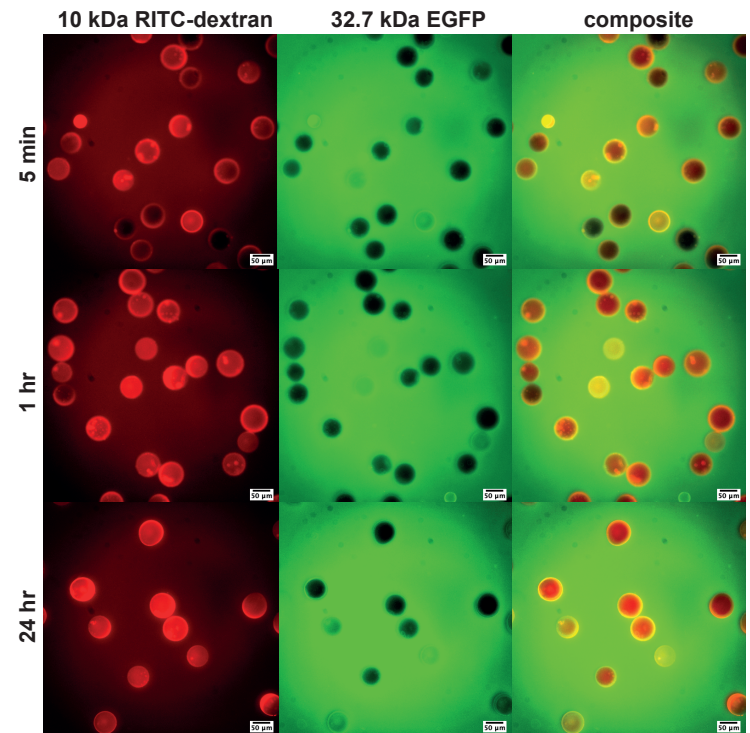


Results (1) Grégoire Michielin

Droplet microfluidics



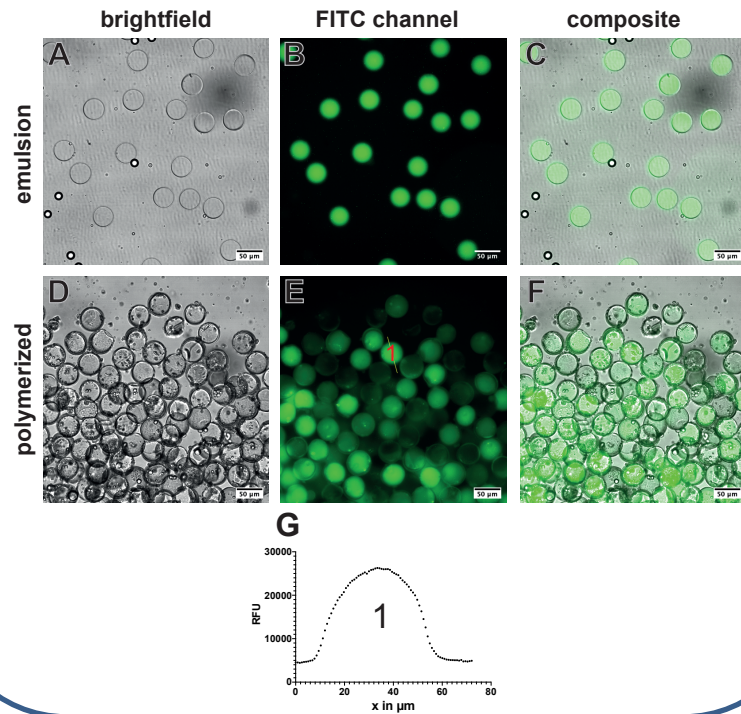
Semi-permeable capsules



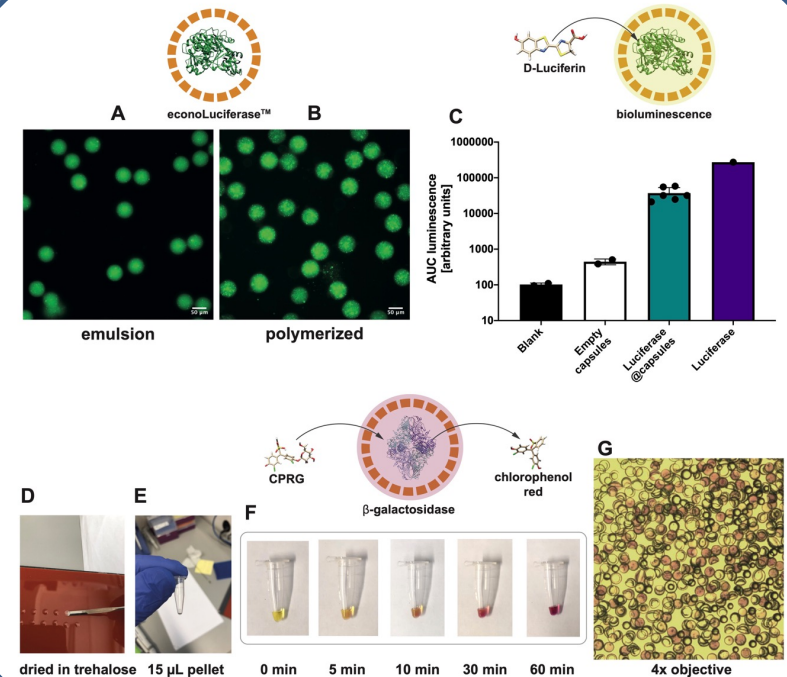


Results (2) Grégoire Michielin

Encapsulation of proteins

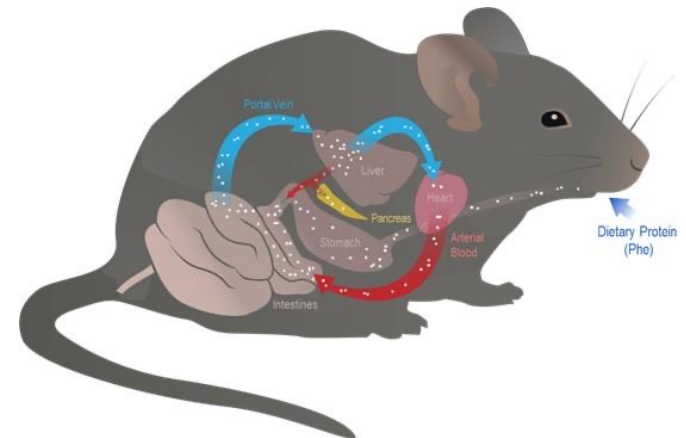


And active enzymes





Deliverables Grégoire Michielin



Isabella VM, Ha BN, Castillo MJ, Lubkowitz DJ, Rowe SE, Millet YA, et al. Nature Biotechnology. Nature Publishing Group; 2018 Aug 13;36(9):857–64.

- Next steps
- Smaller pores (avoid PAL proteolysis)
- Co-encapsulation of protease inhibitors

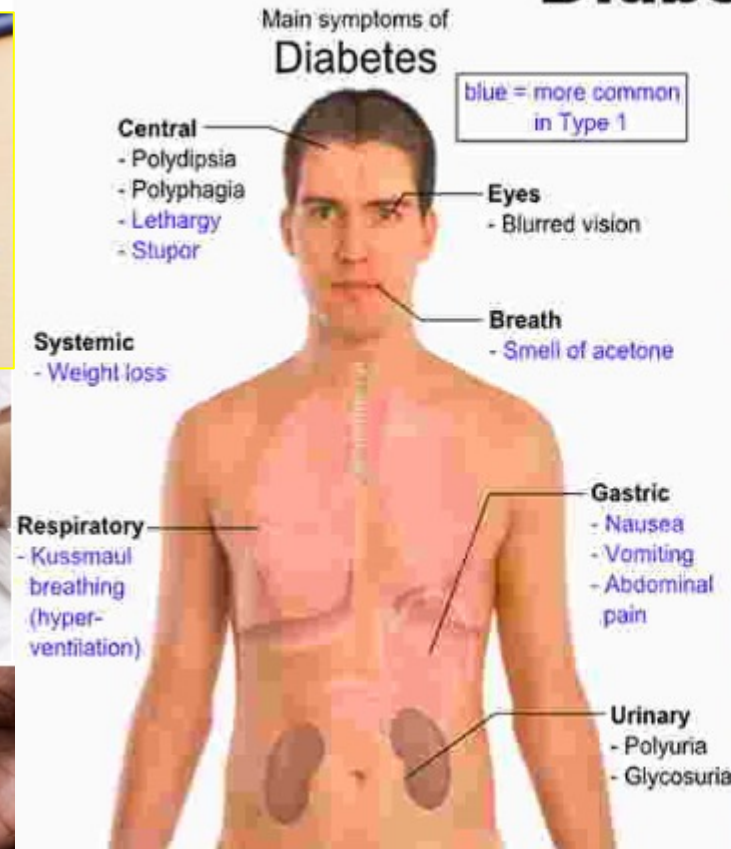
- Next steps in vivo validation
- Preclinical studies
- Mouse/pig model of PKU

Case study : type 2 diabetes novel medicines : the impact of animal pharmacology and safety

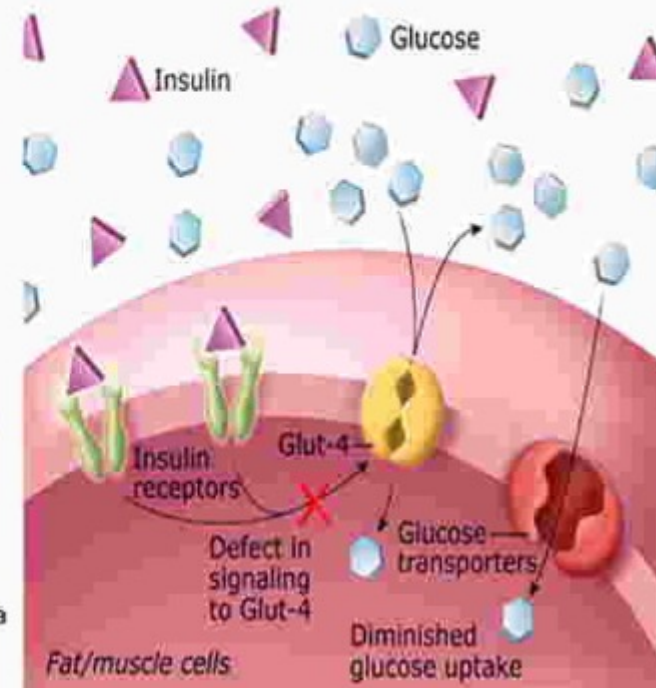


ULTIMATE THERAPEUTIC SOLUTION IN TYPE II DIABETES

Diabetes mellitus type 2



Type 2 Diabetes: Insulin Resistance



PROGRESSIVE DISEASE (5-10 years) : micro- (kidney failure) and macro vascularization pathologies (CVD, stroke etc) **PANDEMIA ONGOING** : WHO - hundred millions cases worldwide ! **AT DIAGNOSIS** : major losses (!) in pancreatic β -cells due to insulin resistance **DISEASE ENABLING BIOMARKER** urgently needed : read Wigger L. et al ... and Thorens B. (2017) *Plasma dihydroceramide are diabetes type 2 susceptibility biomarkers both in human and rodents*. Cell Reports 18: 2269-2279

elevated fasting blood glycemia > 1.3g/l

Type II diabetes and metabolic syndrome pandemia _ 2025 : WHO



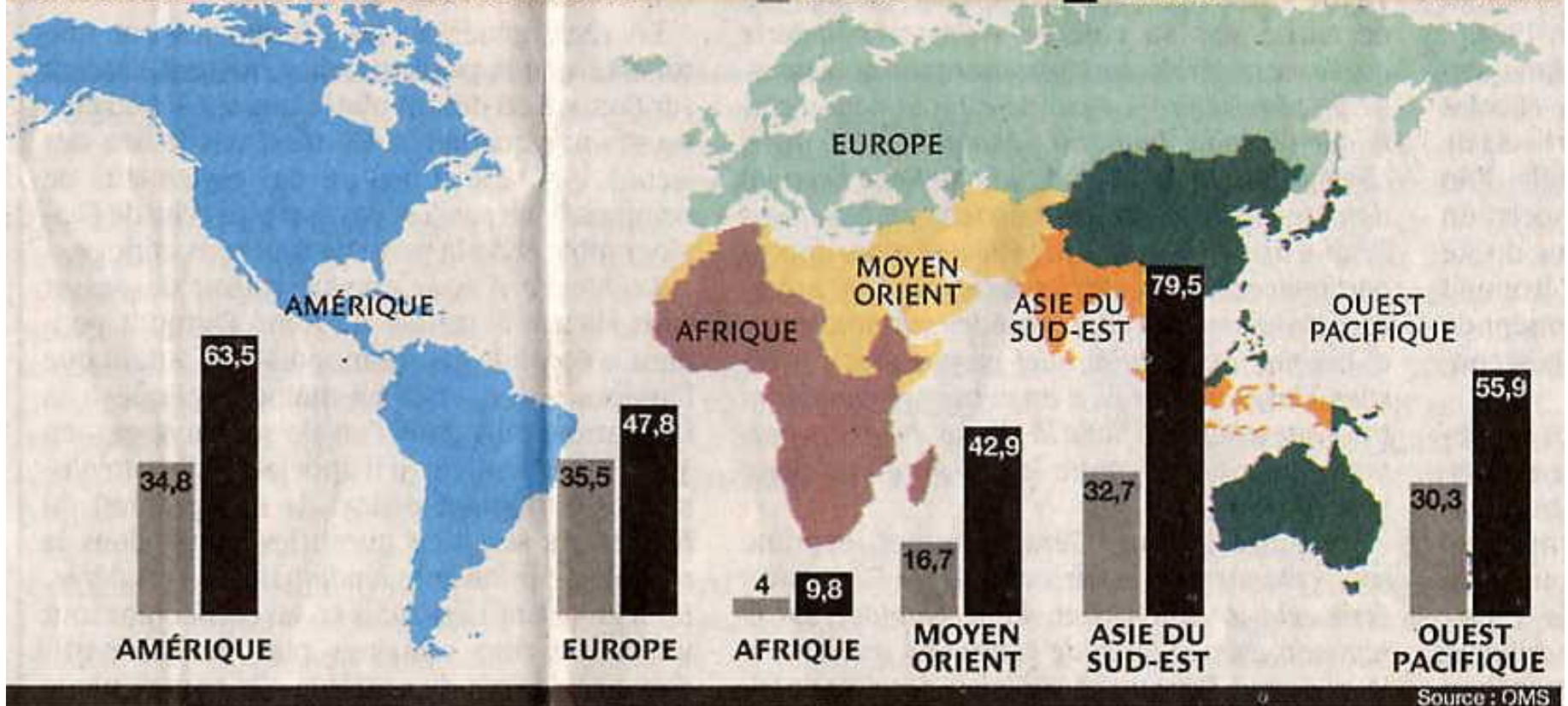
300 millions de malades en 2025

NOMBRE DE CAS DE DIABÈTE DANS LE MONDE

EN 2000

EN 2025

en millions

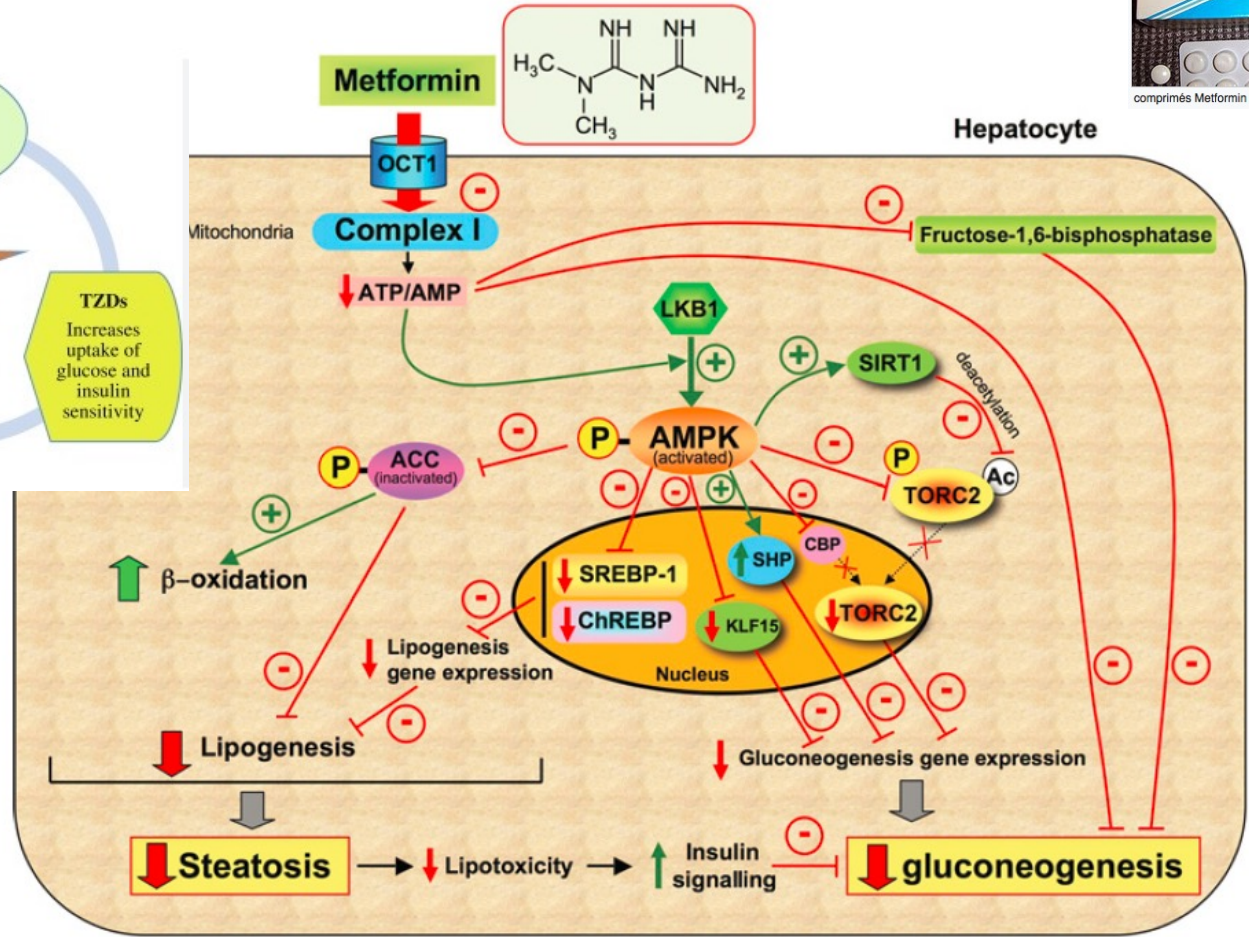
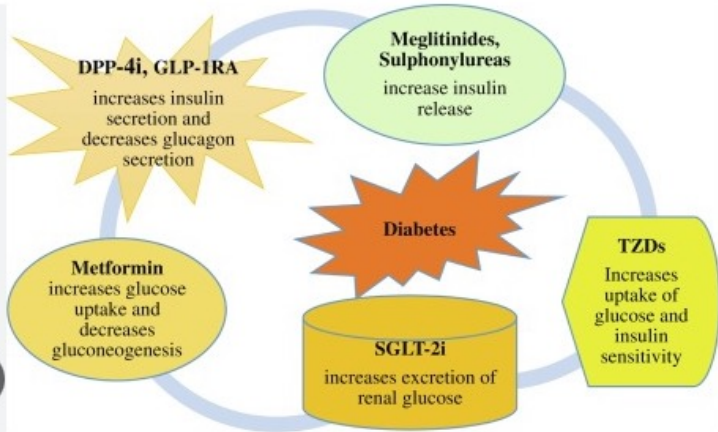


Source : OMS

Type 2 diabetes current future therapies



Improve standard of care : metformin

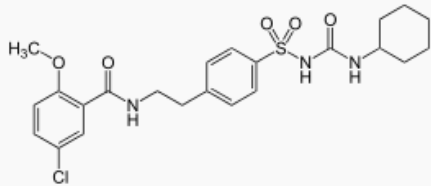


anti hyperglycaemic action of Metformin mainly associated with activation of AMPK and decrease of hepatic glucose production

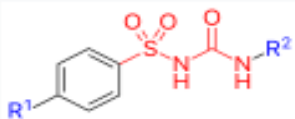
Type 2 diabetes current therapies



Glibenclamide

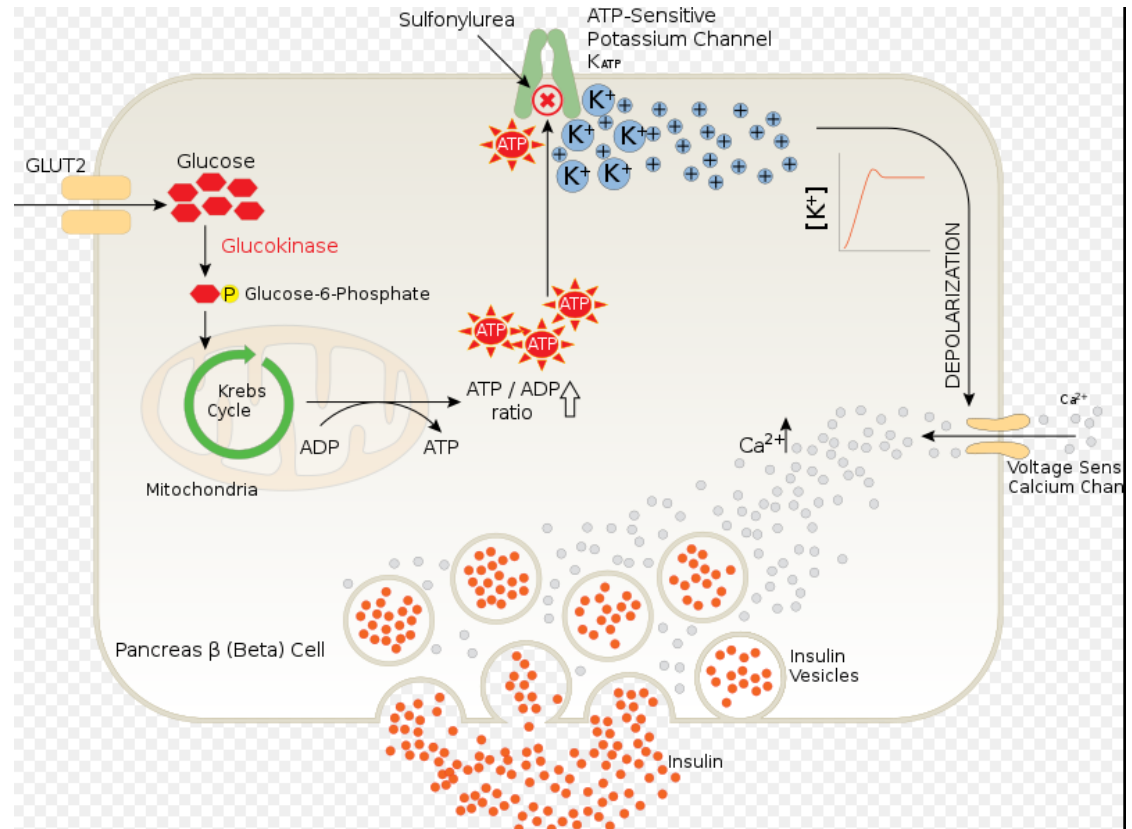


Structure du glibenclamide



General formula of a sulfonylurea, showing the sulfonylurea backbone itself in red and the side chains that distinguish each compound in blue.

Sulfonylurea(s) : secretagogue with risk of hypoglycemia



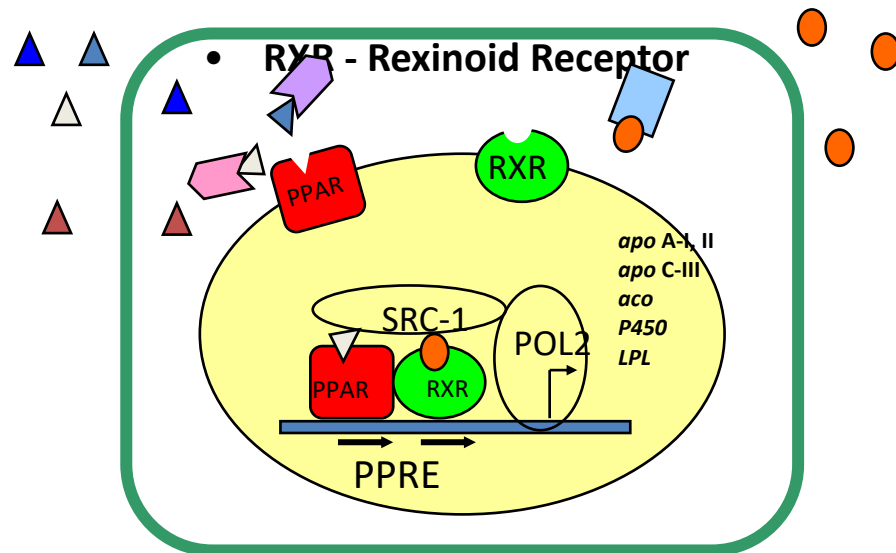
INSULIN SECRETAGOGUE action of sulfonylureas mainly associated with binding/closing ATP-sensitive K^+ channels of β cells which in turn depolarize voltage gated Ca^{2+} channels and increase degranulation of proinsulin vesicles

Case study: My story in the development of innovative medicine



The Aleglitazar Story
 Challenged by developing
 a balanced **non TZD PPARalpha**
PPARgamma agonist
 profiled in insulin resistant and
 cardiovascular patients
 in clinical phase III

- PPAR - Peroxisome Proliferator Activated Receptor



- PPAR/RXR-dependent nuclear signaling

Common blueprint of the nuclear hormone receptors

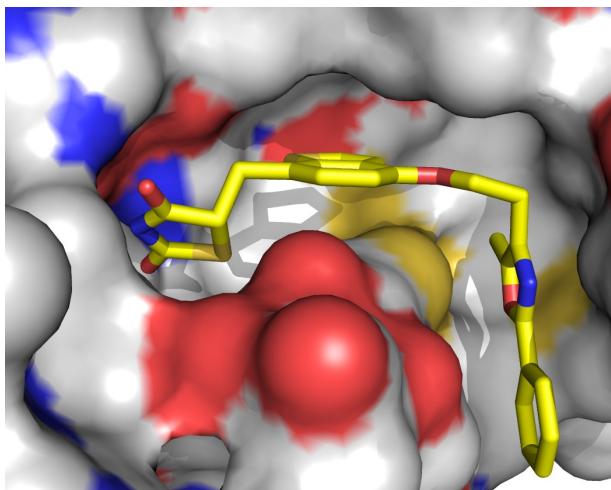


Case study: a balanced PPAR's agonist - the aleglitazar story



The Aleglitazar Story

Challenged by developing
a balanced **non TZD PPARalpha**
PPARgamma agonist
Profiled in insulin resistant and
cardiovascular patients
In clinical phase III



LBD = ligand binding domain

CPDs SCREENING CASCADE

PPAR α receptor binding assay (IC50)

RXR PPAR Heterodimer assay

Db/db mouse screening

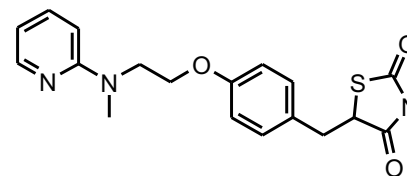
HDL assay in DIO mice and hamster

Safety margin IDB

Non human primate monkey

First dose in man

Clinical trials

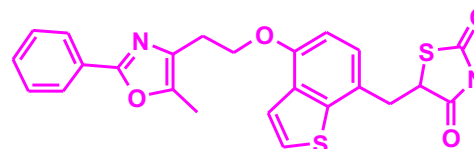


Rosiglitazone (Prototypical PPARgamma Agonist)

GSK-Tail (Phenyloxazole)



Benzothiophene Spacer (Boehringer "Invention")



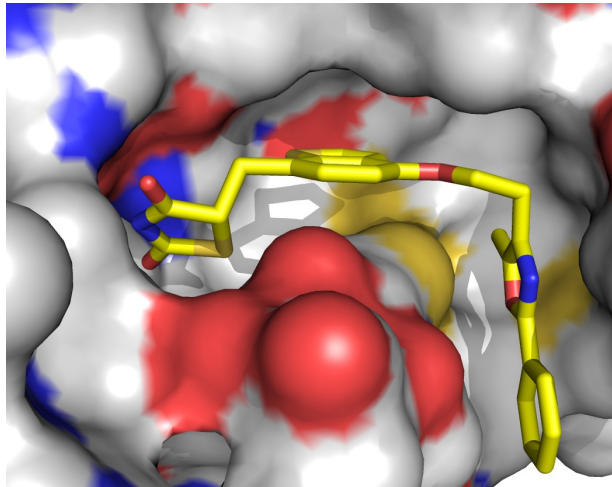
Aleglitazar

Balanced PPAR's agonist - the thiazolidinedione class of cpds



The Aleglitazar Story

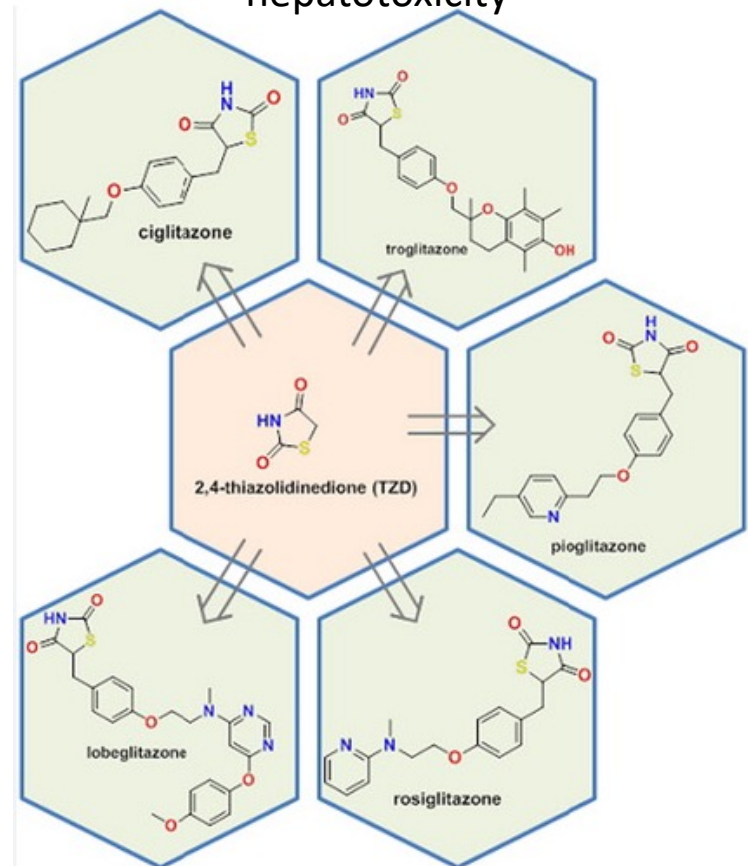
Challenged by developing
a balanced **non TZD PPARalpha**
PPARgamma agonist
Profiled in insulin resistant and
cardiovascular patients
In clinical phase III



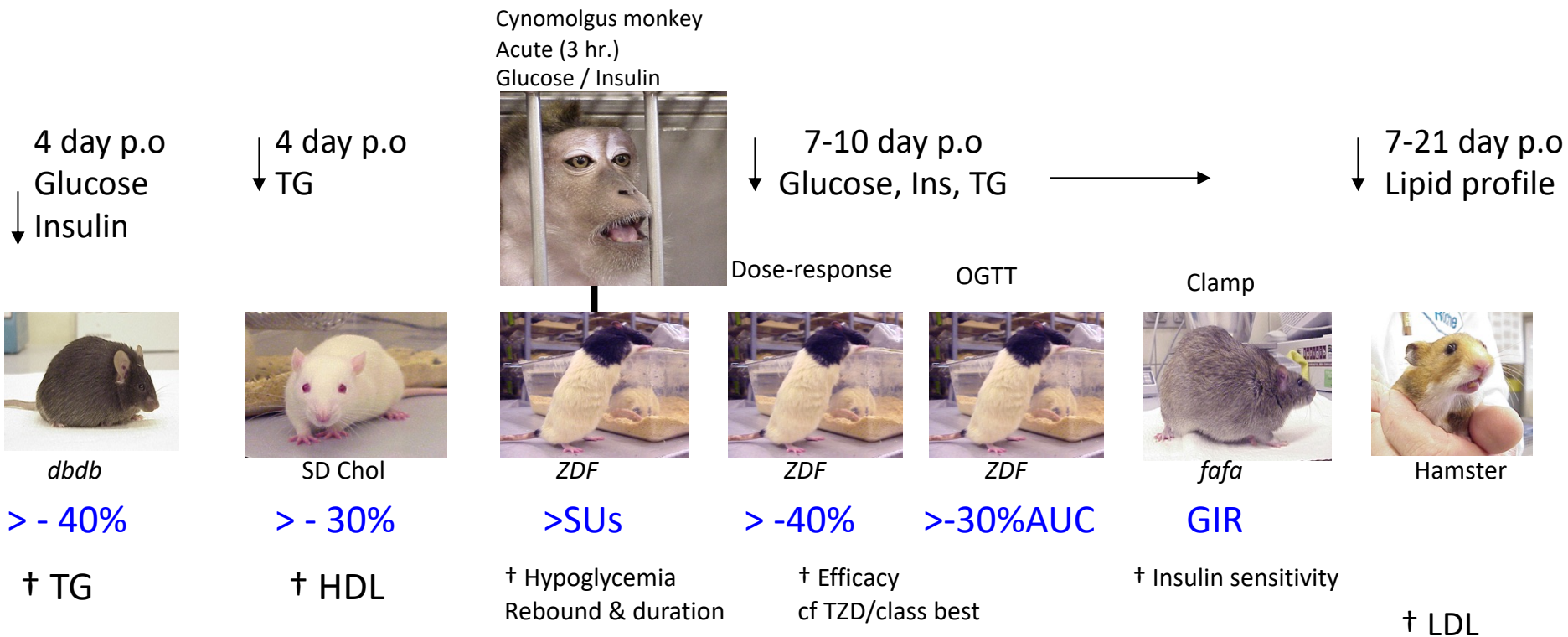
LBD = ligand binding domain

Adverse effects

- **weight gain** due to fluid retention (hemodilution)
- Increased deposition of subcutaneous fat
 - Increased of heart failure and MI
 - hepatotoxicity



Case study: a balanced PPAR's agonist - the aleglitazar story



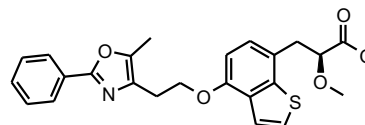
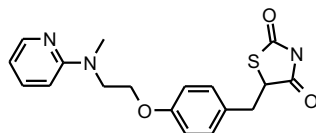
Only the combination of SEVERAL CRITICAL ANIMAL PHARMACOLOGICAL MODELS may predict the therapeutic value of an innovative medicine in future first-in-human clinical settings/trials

Case study: a balanced PPAR's agonist - the aleglitazar story



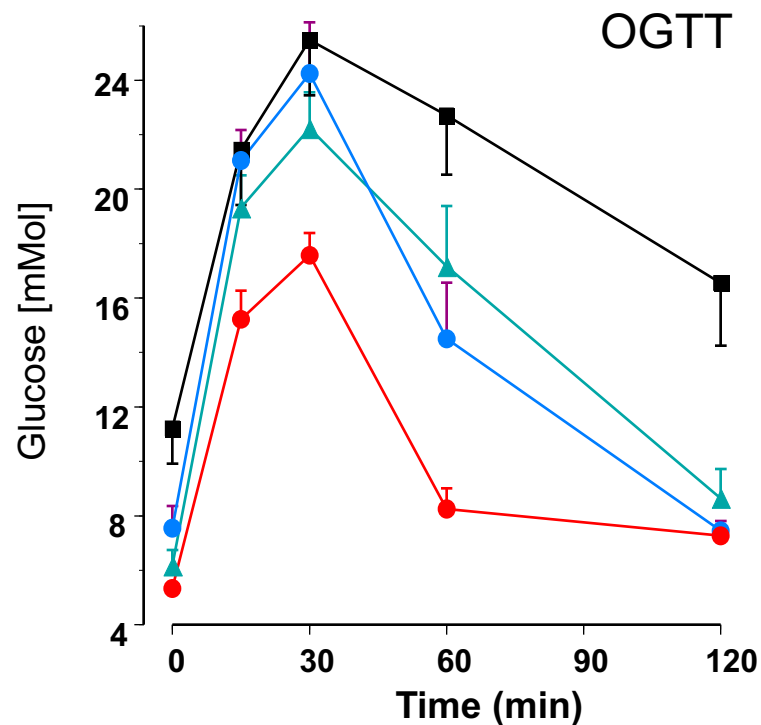
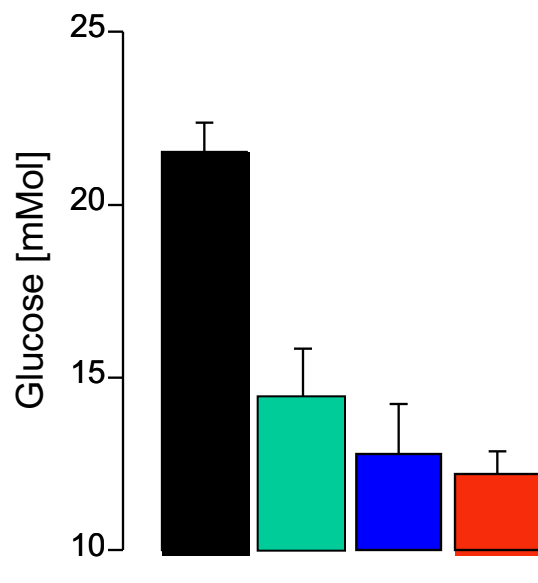
Treatment of db/db mice for 12 days

Rosiglitazone



Aleglitazar

non fasted glucose



■ Placebo ■ RSG 3 mkd

■ RO072000 0.3 mkd

■ RO072001 3.0 mkd

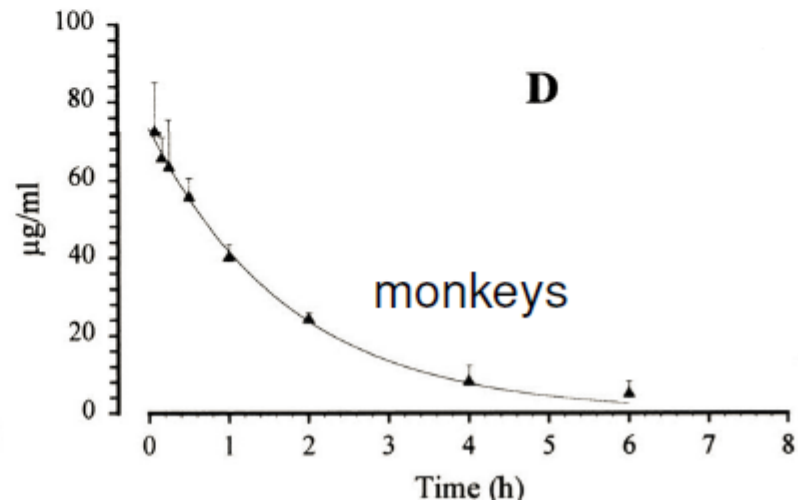
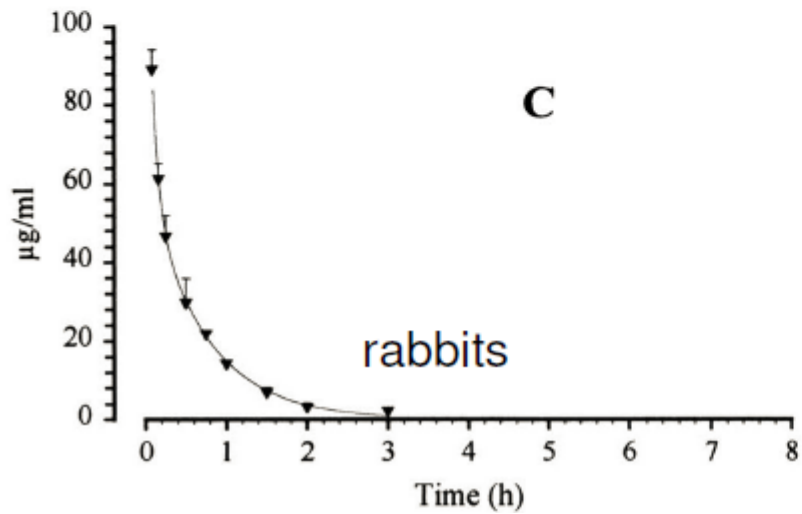
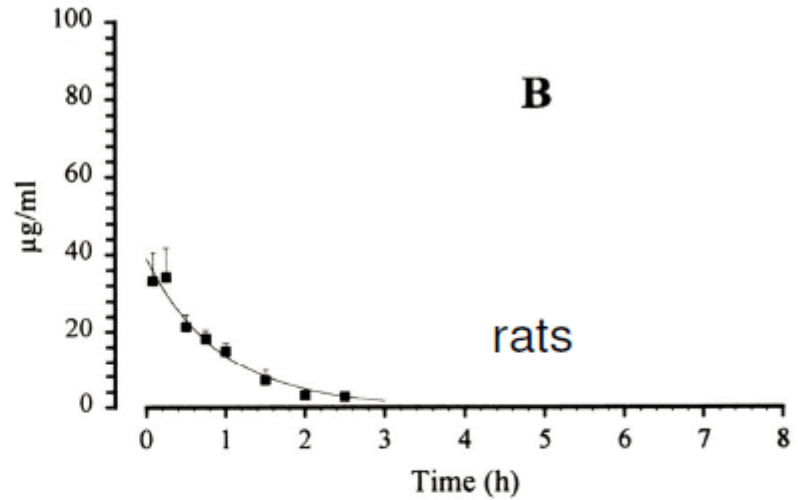
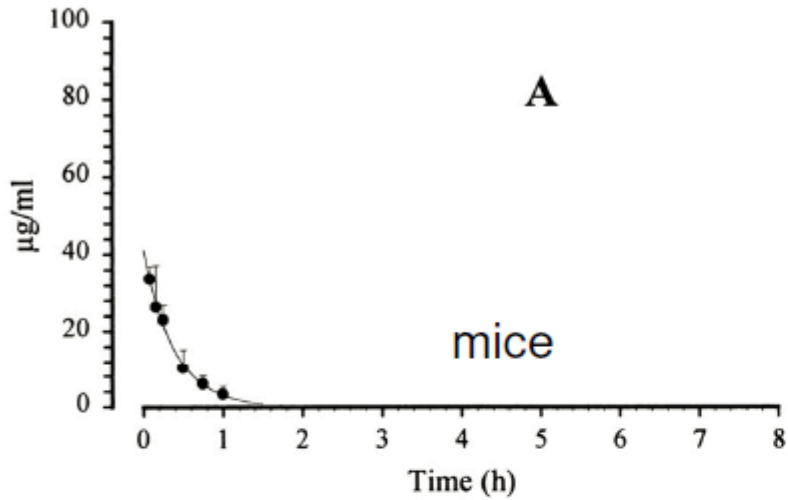
Case study: a balanced PPAR's agonist - the aleglitazar story



Pharmacokinetics (Rat)	Total clearance	6.2 ml/min/kg	1.6 ml/min/kg
	Vss	1.3 l/kg	0.4 l/kg
	Bioavailability	70 %	68 %
	T1/2	4 h	12.9 h
Safety (<i>in vitro</i>)	Cyp	3A4 19; 2C9 4.0; 1A2 >50	2D6 >50; 2C19 12 μM
	hERG	negative	
	Ames/MNT	negative	
	Phospholipidosis	negative	
	Phototoxicity	negative	

(Cyno-
monkey)

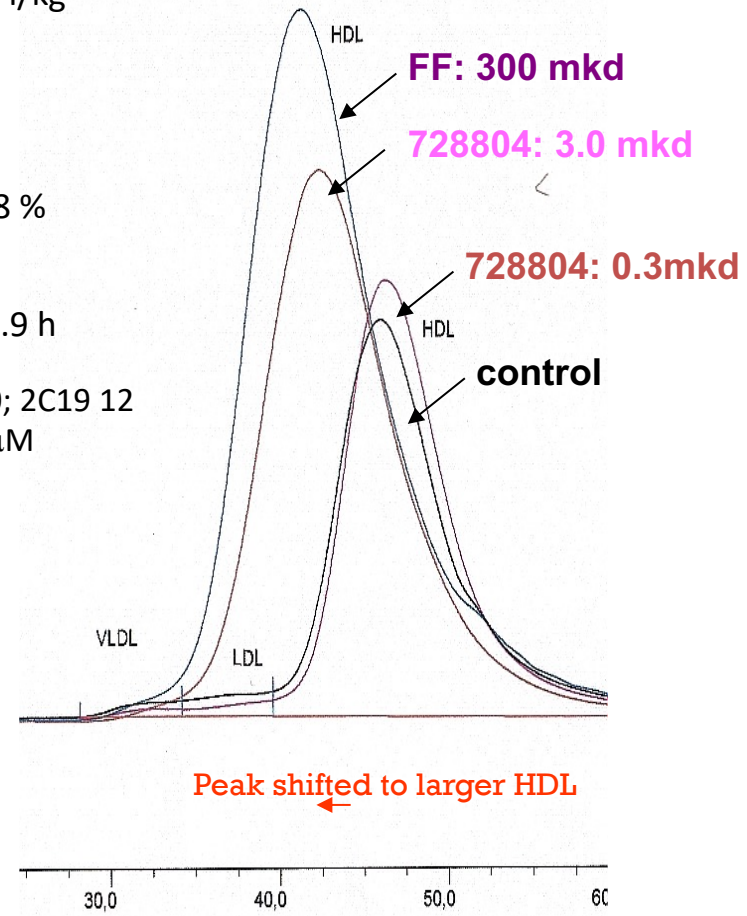
PK PD *in vivo* different species tested



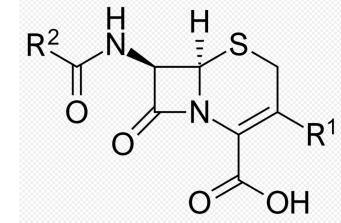
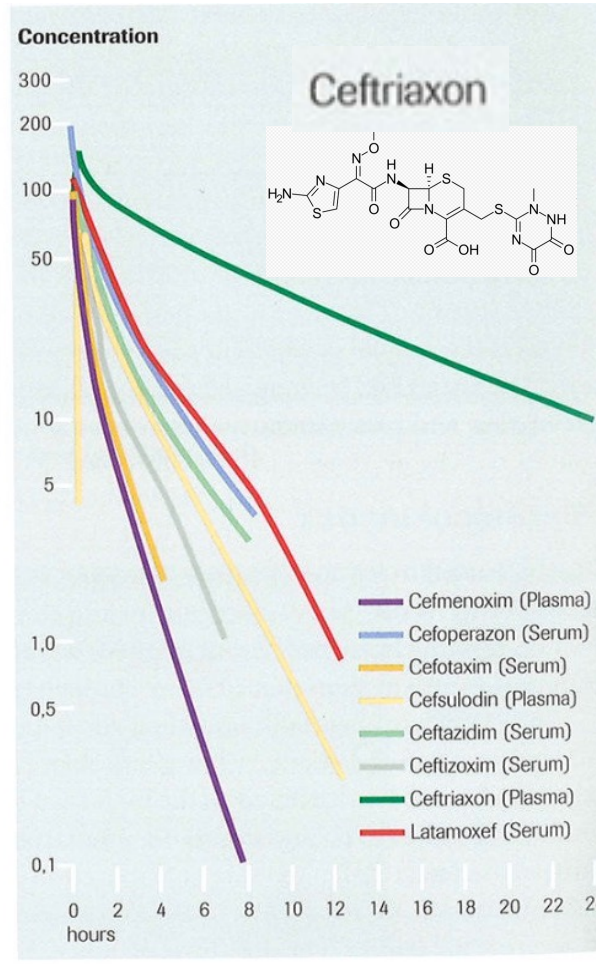
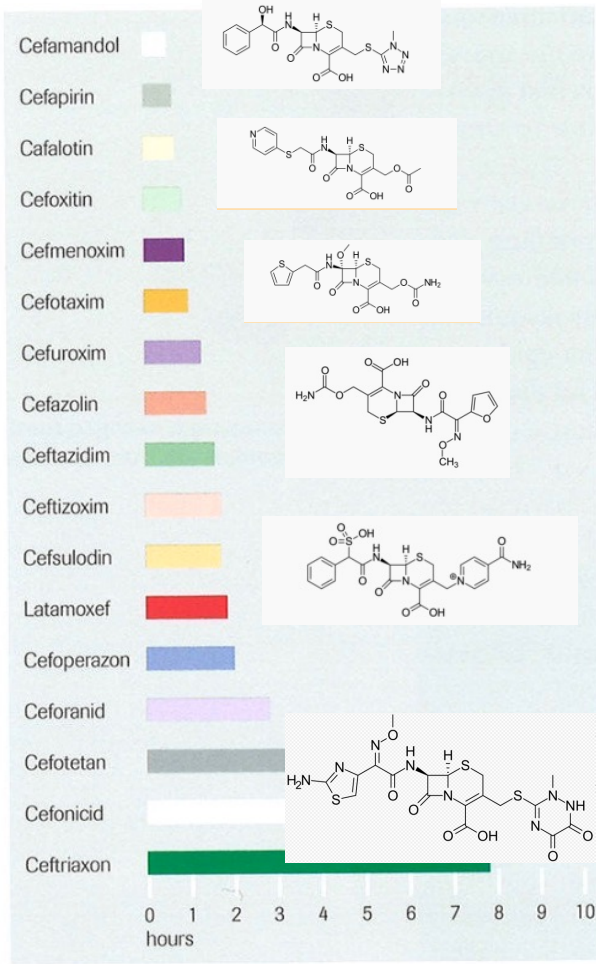
Case study: a balanced PPAR's agonist - the aleglitazar story



		(Rat)	(Cynomolgus)	
Pharmacokinetics	Total clearance	6.2 ml/min/kg	1.6 ml/min/kg	7-21 day p.o Lipid profile
	Vss	1.3 l/kg	0.4 l/kg	
	Bioavailability	70 %	68 %	
	T1/2	4 h	12.9 h	
Safety (<i>in vitro</i>)	Cyp	3A4 19; 2C9 4.0; 1A2 >50	2D6 >50; 2C19 12 μM	
	hERG	negative		
	Ames/MNT	negative		
	Phospholipidosis	negative		
	Phototoxicity	negative		



Today's world most prescribed cephalosporin: unique PK "once a day" ceftriaxone or how to get the job done !



R2 benzylalcohol
R1 thio-methyltetrazol

R2 mercaptopyridine
R1 methylester

R2 methylthiophen
R1 aminoester

R2 aminoester
R1 methoxyimine furane

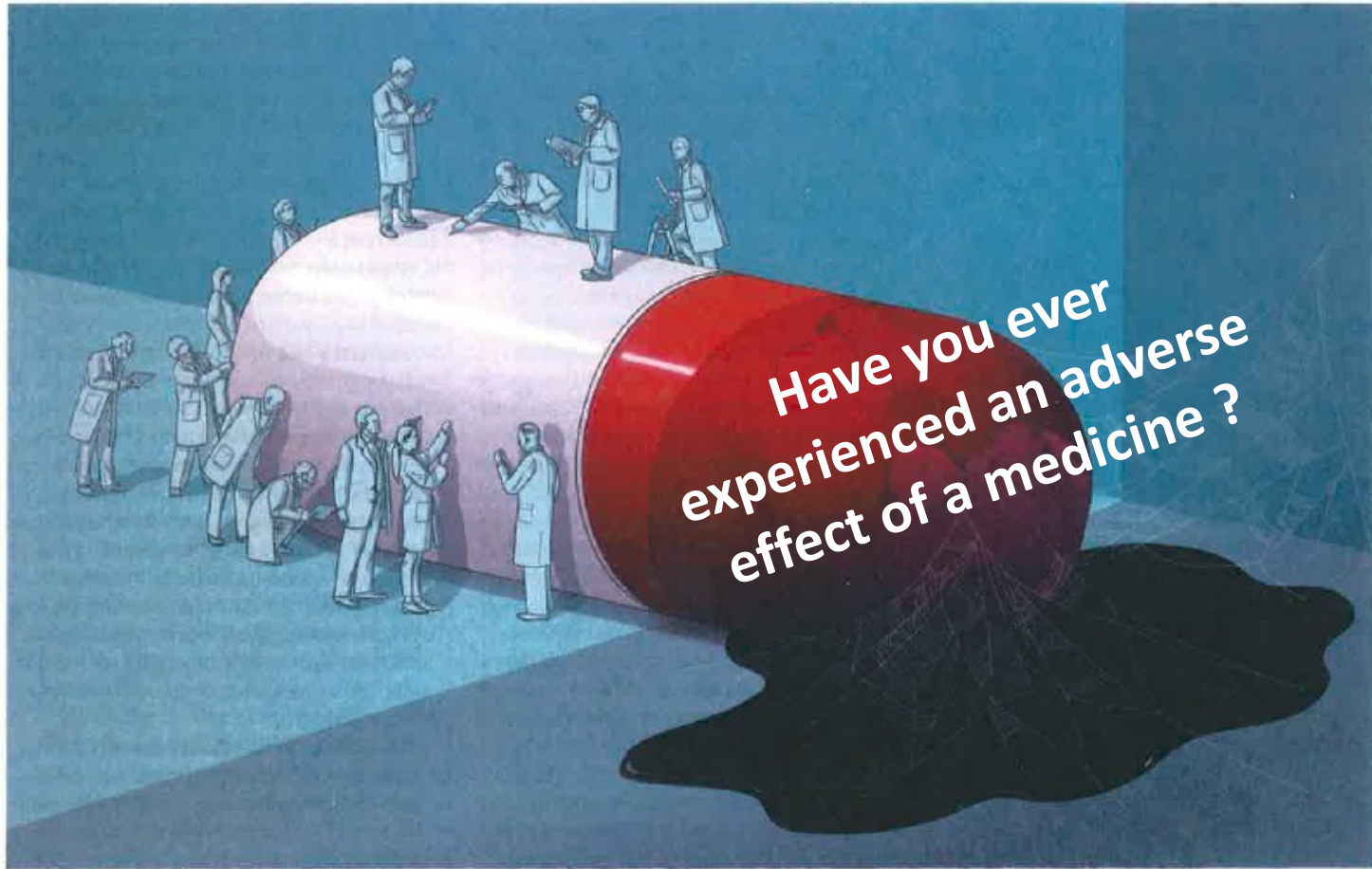
R2 aminotriazol N-methoxyimine
R1 thiotriazindione

a remarkable example of mastering t_{1/2} half life of an iv/im cpd

Efficacy yes, but safety (adverse effects) is what patients care first !

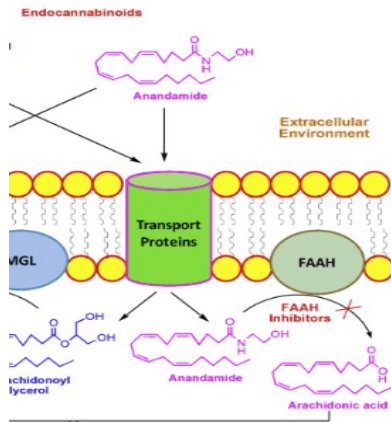


ILLUSTRATION BY RICHARD WILKINSON



Consider drug efficacy and safety before first-in-human trials - FIH

Safety (adverse effects) is what patients care first



Survivor of lethal French drug trial speaks out :

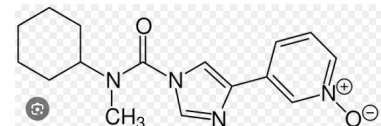
dogs and a monkeys died from same drug before it was tried on humans

BIA 10-2474 was an experimental fatty acid amide hydrolase (FAAH) inhibitor. Documents from a prospective volunteer forwarded to French media described BIA 10-2474 as a "product in development for the treatment of different medical conditions from anxiety to Parkinson's disease, but also for the treatment of chronic pain of sclerosis, cancer, hypertension, or the treatment of obesity."

Kimmelman J et al. 2017 Nature 542: 25-27

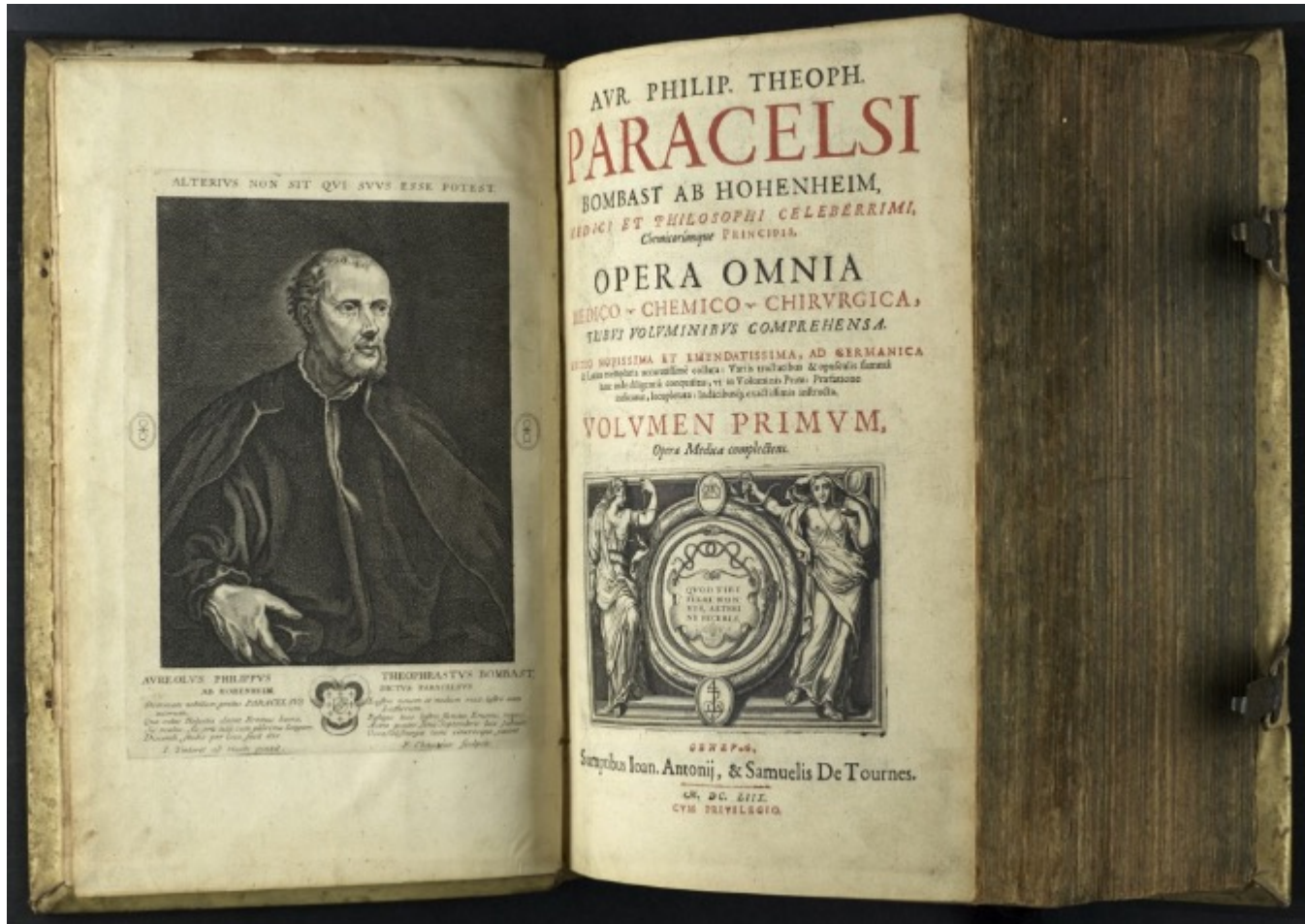
"If I'd known the dogs were dead, I wouldn't have risked my life for €1,900. I wouldn't have signed up. I'm not crazy." a phase 0 BIA 10-2474 healthy volunteer trial survivor

- On January 17, 2016, a healthy man was declared brain dead after receiving an experimental drug in a first-in-human (FIH) trial in France.
- After the authorities asked for the Investigator Drug Brochure (IDB) from the drug developer Bial in Portugal (sponsor) they realized that the 63 pages long document barely contained TWO pages on drug efficacy and desired pharmacological profile.
- Moreover, the cpd had been tested at a range of doses in mice that **MADE IMPOSSIBLE TO ESTIMATE** the most likely safe and effective dose in humans!



Swiss physician «Paracelsus» : the beginning of toxicology

«every medicine is a poison in disguise»



Philippus Aureolus Theophrastus Bombastus von Hohenheim

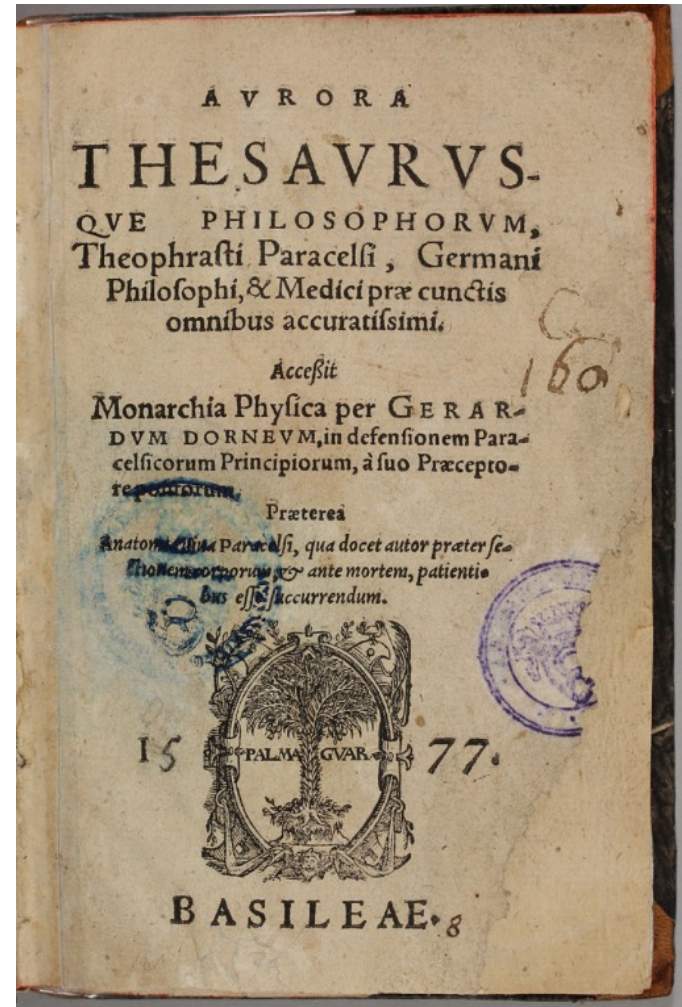
1493-1541

“Paracelsus” practiced medicine at University of Basel Switzerland (oldest swiss university since April 4, 1460 on !)

“solely the dose makes it a poison or not” (*sola dosis facit venenum*)

Swiss physician Paracelsus : the beginning of toxicology

«every medicine is a poison in disguise»



Philippus Aureolus Theophrastus Bombastus von Hohenheim
“Paracelsus” practiced medicine at University of Basel Switzerland (founded April 4, 1460)
“solely the dose makes it a poison or not” (*sola dosis facit venenum*)

Safety assessment : Paracelsus in the belgian comic strips !



Risque = danger x exposition

1 in 1,000,000 1 in 10,000

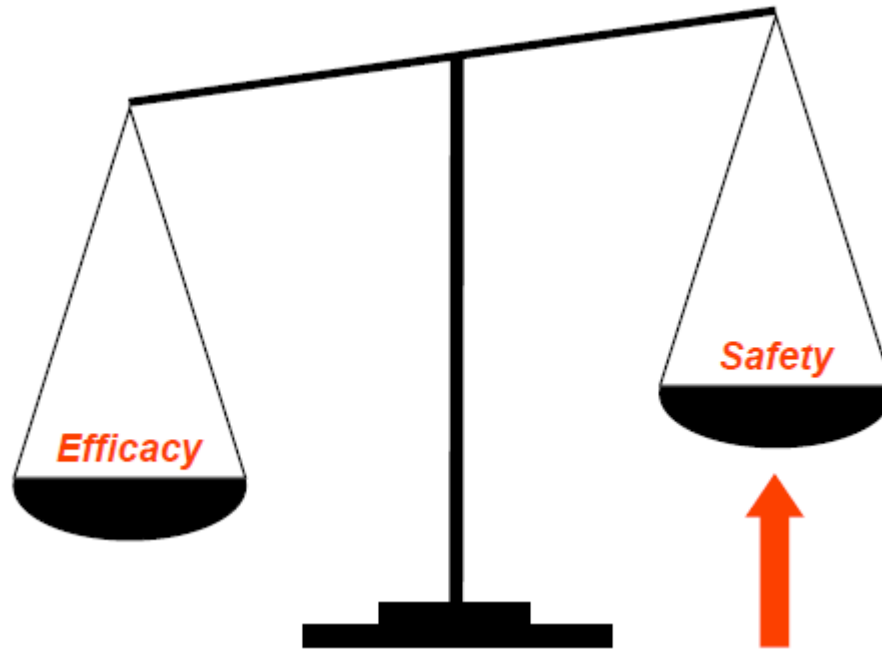
Une larme...
Un soupçon...

La suffit...
Merci...

DOSIS SOLA FACIT VENENUM

“solely the dose makes it a poison or not”

Safety (adverse effects) is what patients care first ! a balancing act in pharmacology



- Depakine
- Opioid
- Thalidomide
- and more tox catastrophes

- A BALANCING ACT : NO THERAPIES WITHOUT ADVERSE EFFECTS !
- ANY THERAPEUTIC PHARMACOLOGICAL INTERVENTION SHOULD HOWEVER BE SAFE : **TODAY'S INVESTIGATIVE TOXICOLOGY IS KEY !**
- Paracelsus -16th cent : “every drug is a poison in disguise” (*sola dosis facit venenum*)

Safety (adverse effects) is what patients care first ! a balancing act in pharmacology



- Thalidomide
- Depakine
- Opioid
- Benfluorex
- and more tox catastrophes

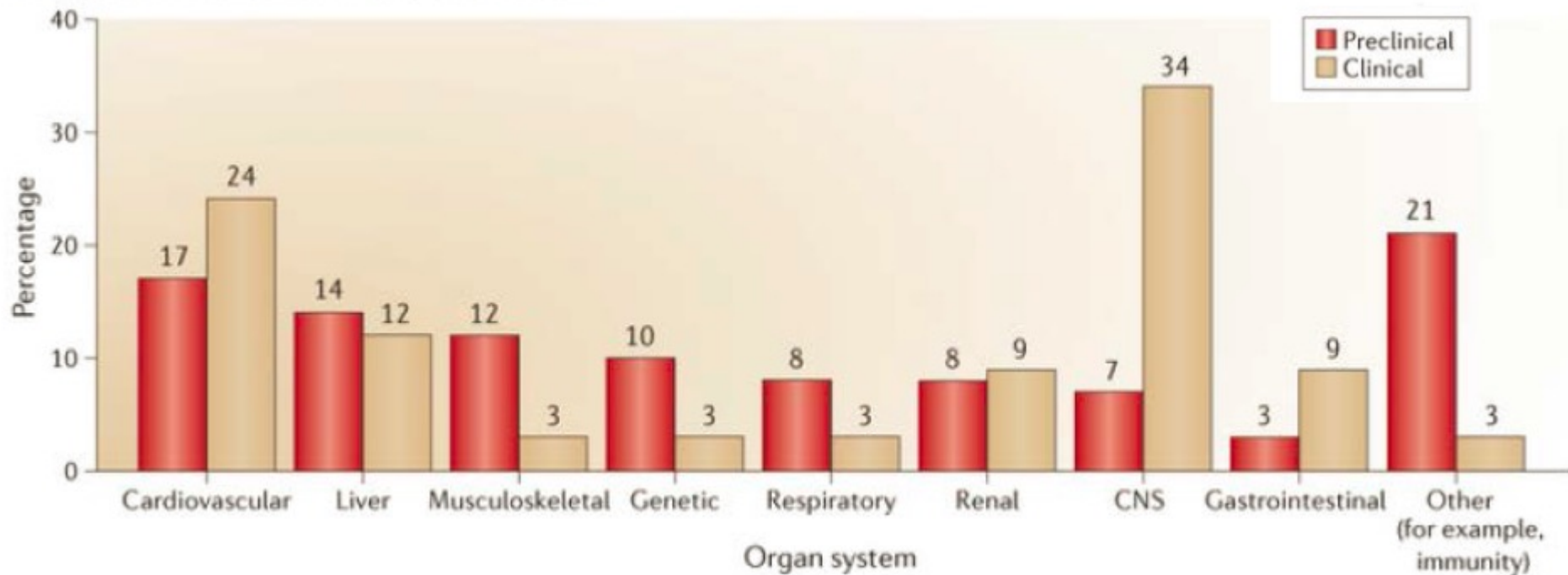
• A BALANCING ACT : NO THERAPIES WITHOUT ADVERSE EFFECTS !
• ANY THERAPEUTIC PHARMACOLOGICAL INTERVENTION SHOULD HOWEVER BE SAFE : **TODAY'S INVESTIGATIVE TOXICOLOGY IS KEY !**

• Paracelsus - 1526 : "every drug is a poison in disguise" (*sola dosis facit venenum*)

Looking at attrition rate from AstraZeneca portfolio (2005-2020)

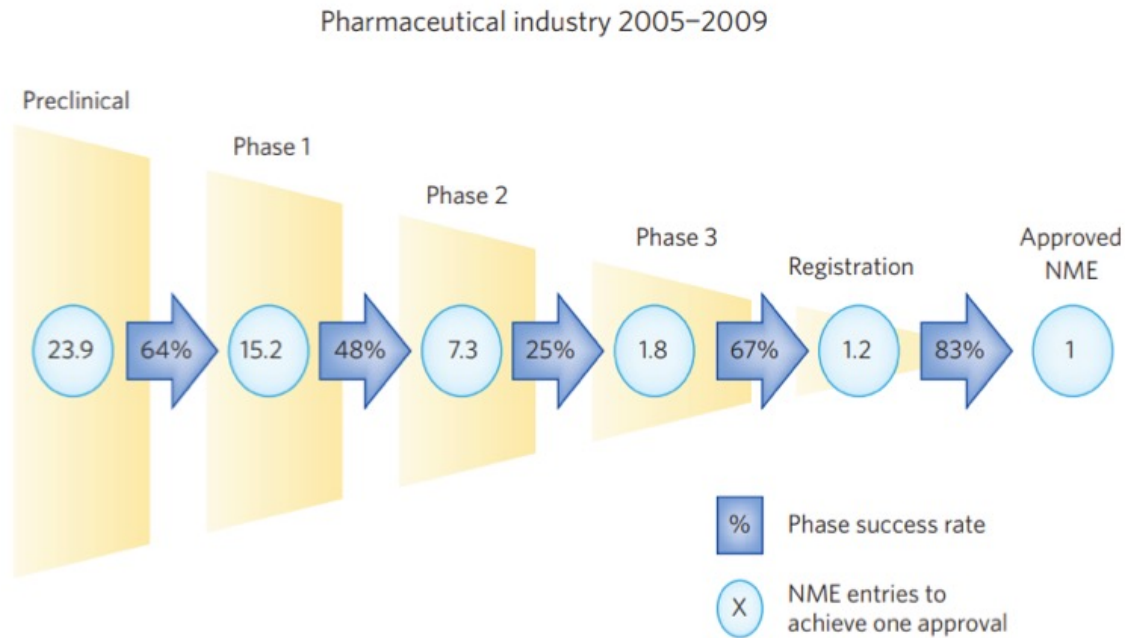


a Organ systems involved in safety failures



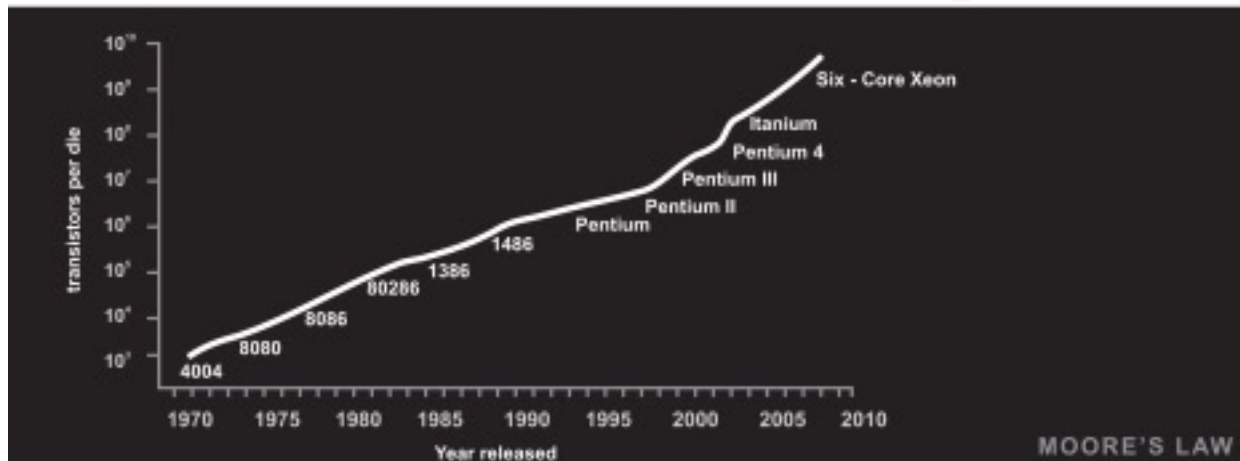
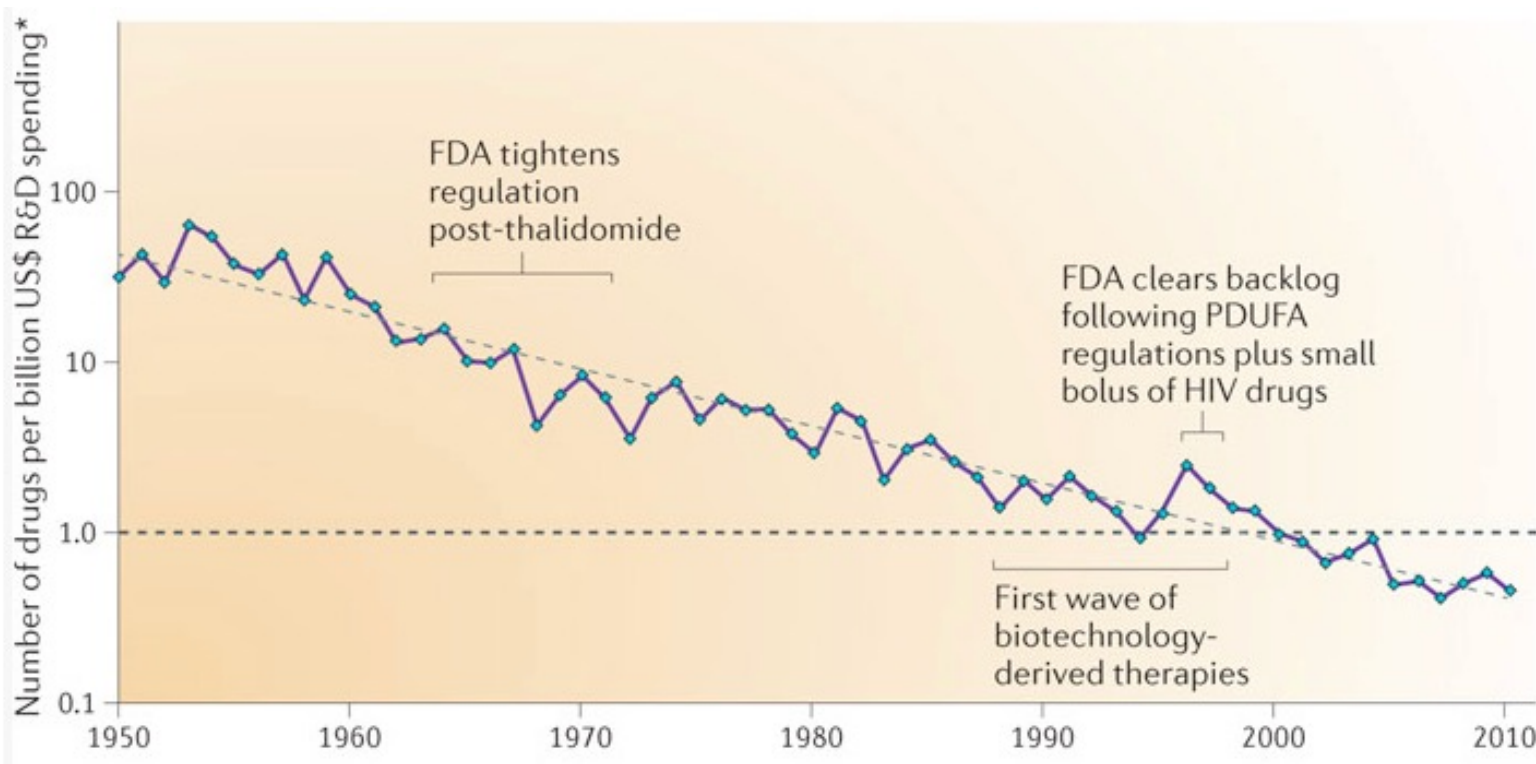
Food for thoughts : the biggest risk for human beings is not to get a safe and efficacious medicine !

Pharma challenge : the biggest risk for human beings is not to get a safe and efficacious medicine !



The 'big pharma' dilemma: develop new drugs or promote existing ones?

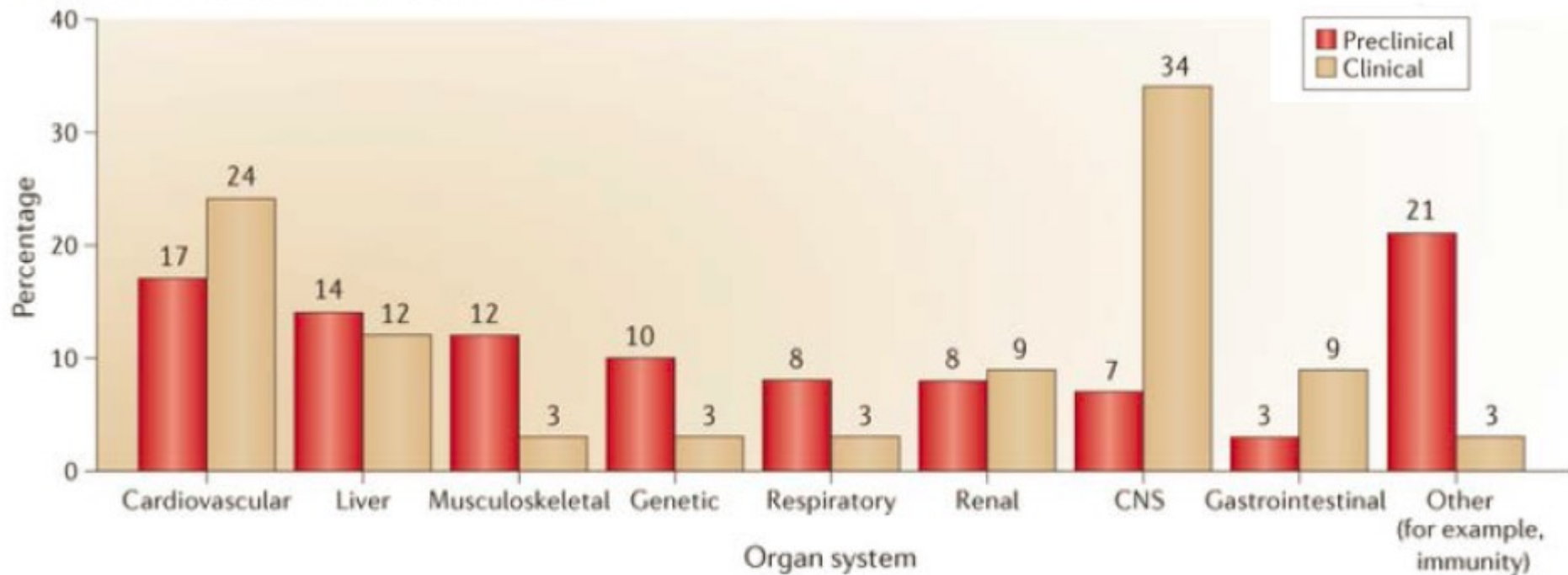
The biggest risk is NOT to get a medicine !



Looking at attrition rate from AstraZeneca portfolio (2005-2020)

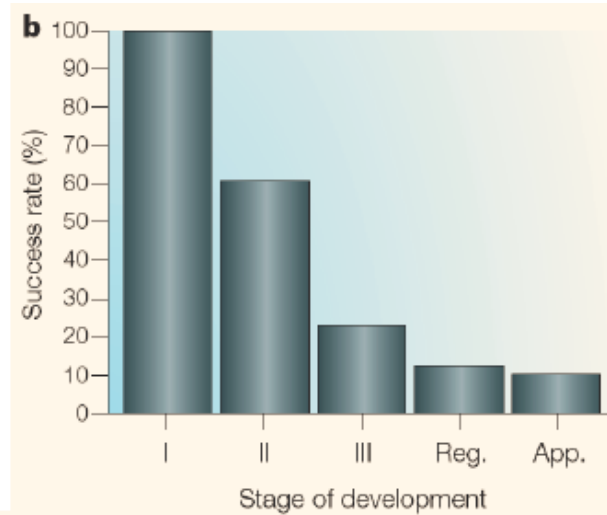


a Organ systems involved in safety failures

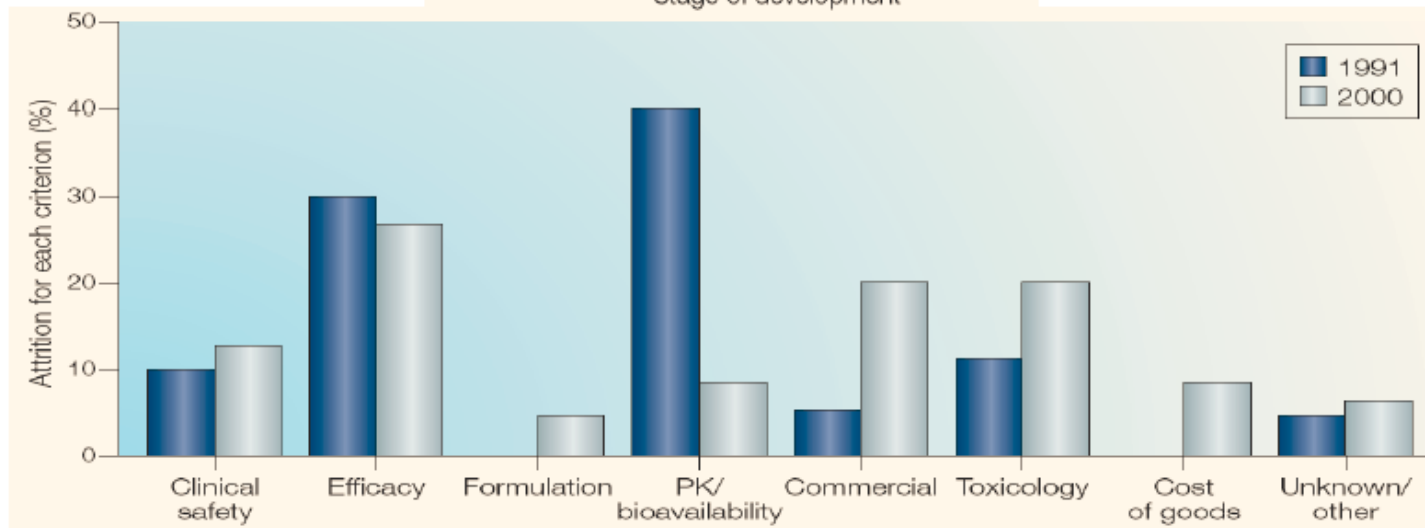


Food for thoughts : the biggest risk for human beings is not to get a safe and efficacious medicine !

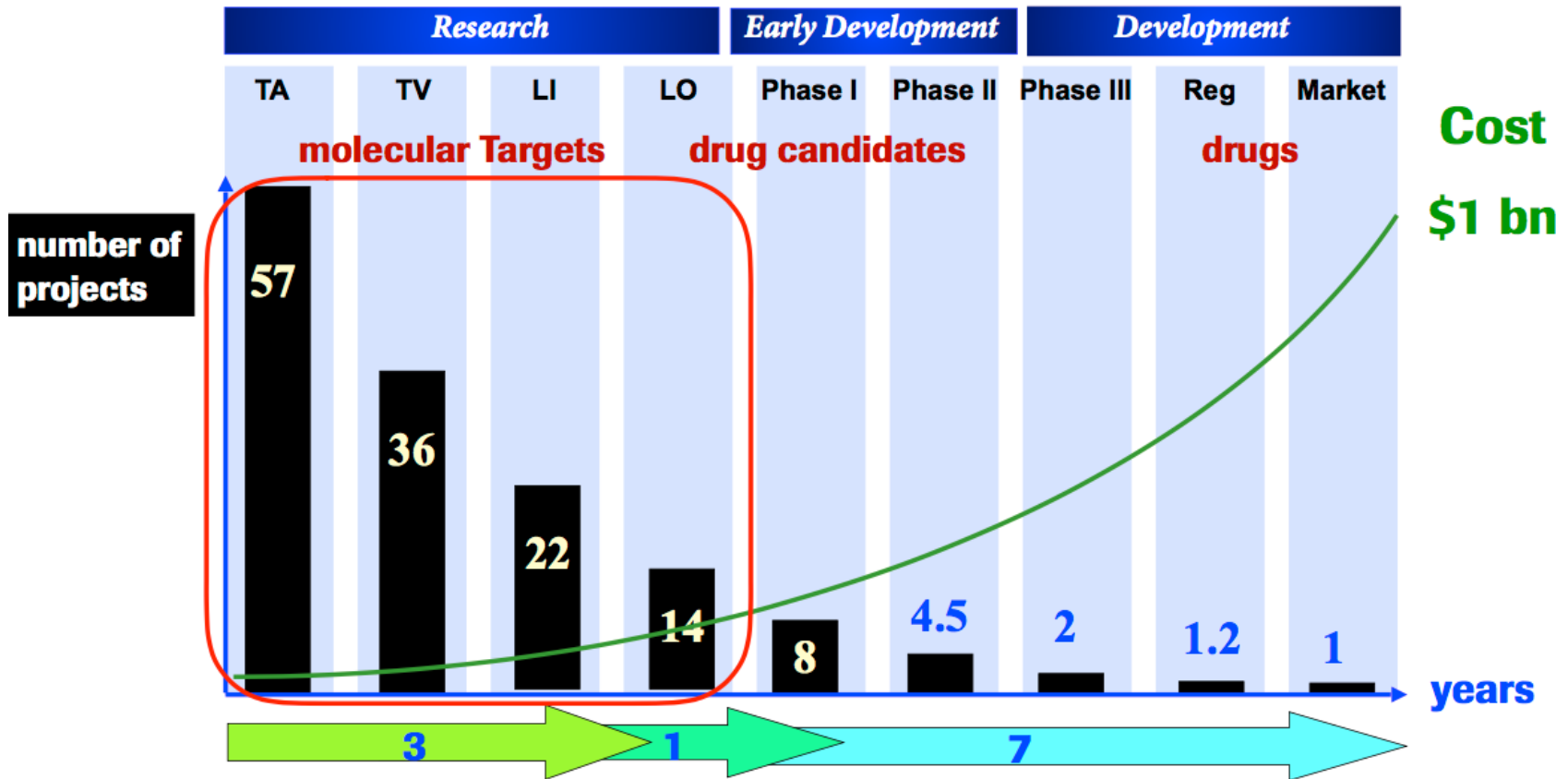
Safety vs Efficacy : drug development success rate overall and by criteria



[Nat Rev Drug Discov. 2004 Aug;3\(8\):711-5](#)



High attrition rate : only very few experimental medicine makes it to the clinical practice

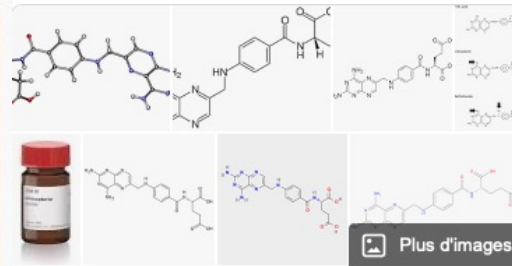


>95 % attrition rate : the sooner the better !

«Poisoning the atmosphere» or when poison turns a medicine : *Sydney Farber antifolate in leukemia and Paul Ehrlich arsenic in syphilis*



Le Docteur Sidney Farber, en 1966

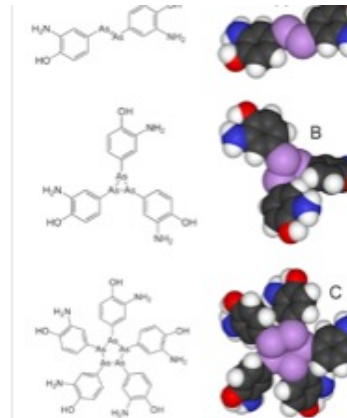


Aminoptérine (Aminopterin)

Médicament

L'aminoptérine est un médicament antagoniste de l'acide folique prescrit comme antinéoplasique qui

Arsphenamine, also known as **Salvarsan** or **compound 606**, is a drug that was introduced at the beginning of the 1910s as the first effective treatment for syphilis and African trypanosomiasis. This organoarsenic compound was the first modern antimicrobial agent.



Paul Ehrlich
FRS

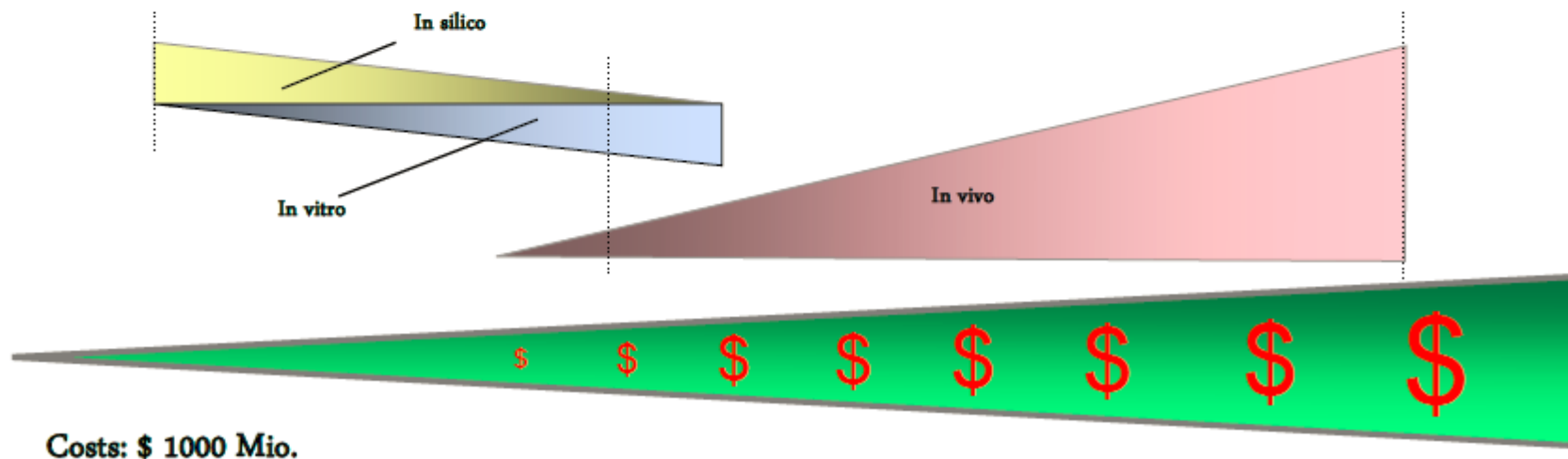
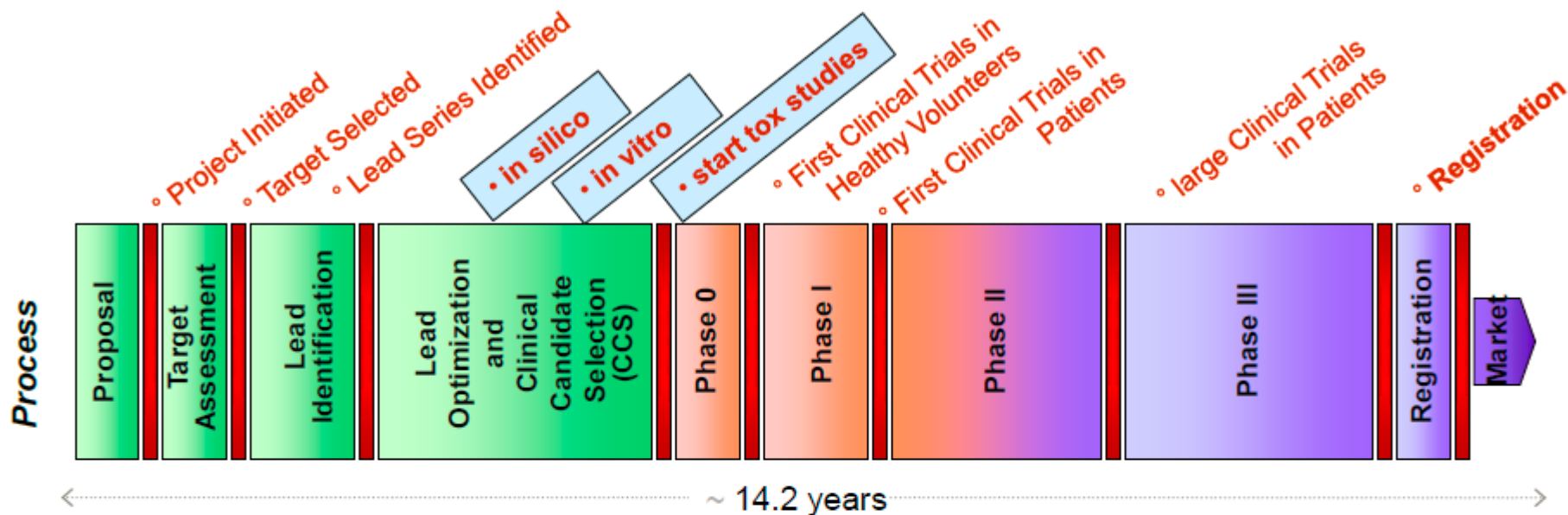
born 14 March 1854

“20th century turned poison into a medicine (the advent of chemotherapy) !
vindicating Paracelsus findings : “solely the dose determines that a medicine is a poison or not” (*sola dosis facit venenum*)

Safety assessment across the value chain



THE BIGGEST RISK IN DRUG DEVELOPMENT IS NOT TO GET A MEDICINE : “FAIL EARLY” STRATEGY



A central dogma in investigative toxicology _ ON vs OFF target



OFF target



ON target



WHAT HAPPENS WHEN A NEW MEDICINE INADVERTEDLY TARGETS UNWANTED PATHWAY/MOLECULES ? CONSEQUENCES CAN BE FATAL UNLESS YOU CAN PREDICT/DETECT OFF TARGETS BEFORE ENTERING CLINICAL DEVELOPMENT ! *cf Cerep® panel of th targets*



The High Price Of Failed Clinical Trials: Time To Rethink The Model

*By Ralf Huss, MD, Chief Medical Officer,
Definiens*

Back in 2014, a [study](#) in Nature Biotech showed that only 32% of drugs have a probability of making it to Phase 3 trials, and only one in 10 drugs overall actually makes it to market. Things haven't improved since then.

BIO recently [put out](#) a study reporting that the average overall likelihood of approval (LOA) by FDA from Phase I was 9.6 percent – a 1 in 10 chance. The rate is even lower for major disease areas like oncology. Phase II clinical programs continue to experience low success rates as well, with only 30.7 percent of candidates advancing to Phase III, a slightly worse rate than it was a few years ago.

The cost of failed clinical trials is high, and the industry needs to focus on ways to reduce the



WHAT HAPPENS WHEN A NEW MEDICINE INADVERTEDLY TARGETS UNWANTED PATHWAY/MOLECULES ? CONSEQUENCES CAN BE FATAL UNLESS YOU CAN PREDICT/DETECT OFF TARGETS BEFORE ENTERING CLINICAL DEVELOPMENT ! *cf Cerep® panel of th targets*

Safety assessment across the value chain eg Cerep Eurofins



THE BIGGEST RISK IN DRUG DEVELOPMENT IS NOT TO GET A MEDICINE : “FAIL EARLY” STRATEGY

Follow-up Required



Target	ADRs	Drugs
hERG inhibition	Ventricular arrhythmia	Terfenadine, astemizole, cisapride
5HT2B agonist	Cardiac valvulopathy	Fenfluramine, Pergolide
PDE4 inhibition	Emesis, vasculitis	-PDI 747
H1 antagonist	Sedation	Antihistamines
M2 antagonist	Bronchoconstriction	Rapacuronium
NMDA	Hallucinations	Phencyclidine
Dopamine D1 agonist	Dyskinesia	Levodopa
EGFR	Acneiform Rash	Gefitinib, Erlotinib, Lapatinib,

Compounds withdrawn from market

Lecture automatique activée

Early days of toxicology _ safety at its infancy _ turns into a tox scandal Contergan® forte anti emetikum (Grünenthal)



The thalidomide story...60 YEARS AGO

nausea with pregnant women !

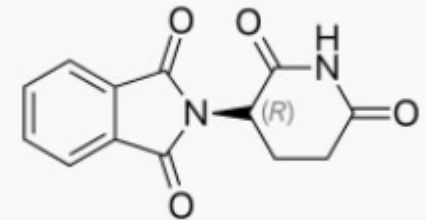
Sedative ! Anxiolytic !

NO TOXICITY IN ANIMAL M

Catalyzed a drastic GAME CHANGER in drug approval and monitoring by FDA/EMEA



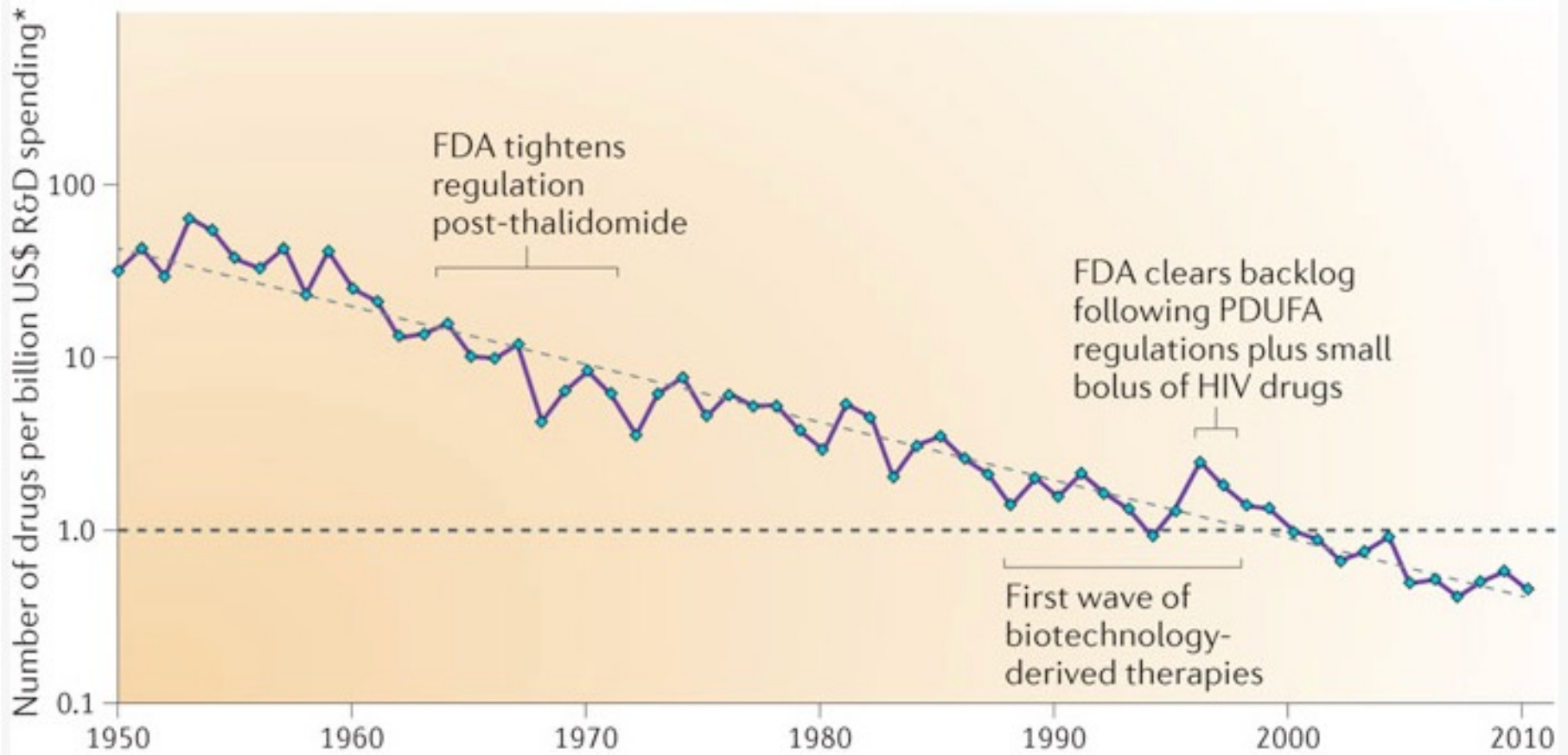
>10 000 patients world wide affected by birth defects such as *Phocomelia* (limb malformation), deafness etc



Contergan® from Grünenthal Chemie 1957 withdrawn in 1961

Many children in the 1960's, like the kindergartner pictured above, were born with phocomelia as a side effect of the drug thalidomide, resulting in the shortening or absence of limbs. (Photo by Leonard McCombe//Time Life)

The era «post thalidomide» : one of the biggest blow in productivity of modern drug development

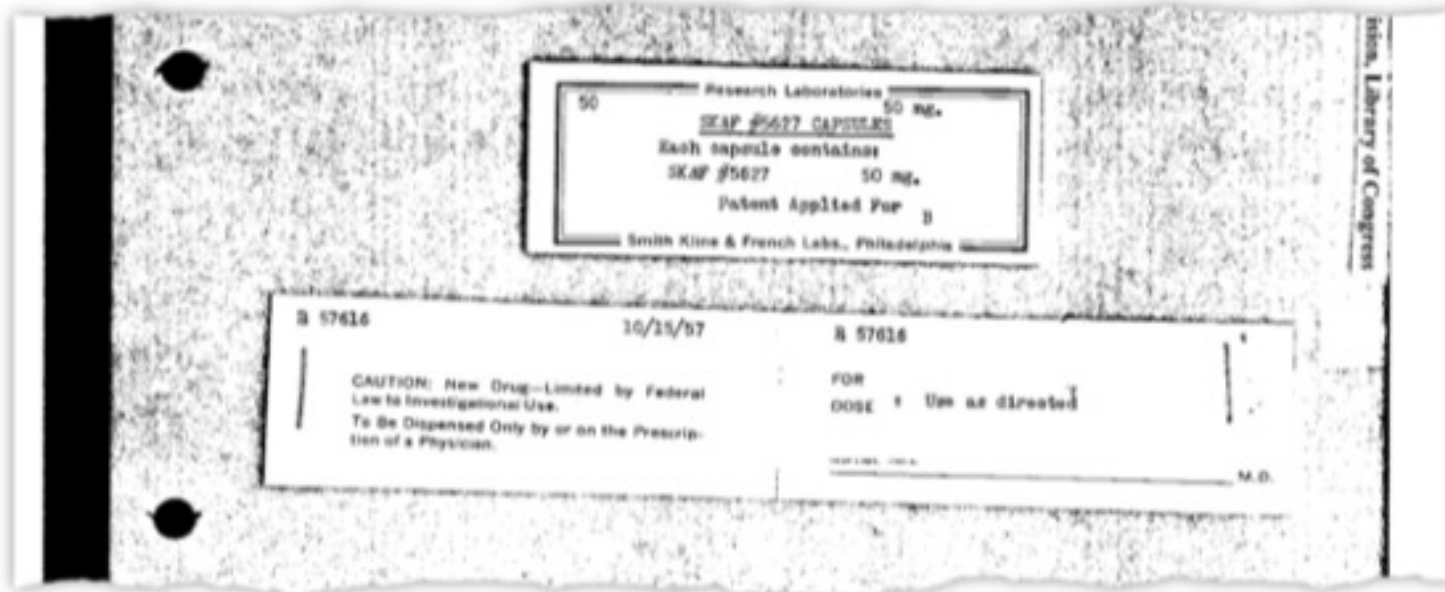


**The biggest risk is NOT to get a medicine !
productivity declines – why ?**

Thalidomide : 1960's a clinical trial in confusion with a pharma marketing campaign



A Marketing Campaign Disguised as a Clinical Trial



The drug company Smith, Kline & French did not identify the name of the drug, thalidomide, on packets distributed to patients, using only the code name SK&F #5627. Library of Congress



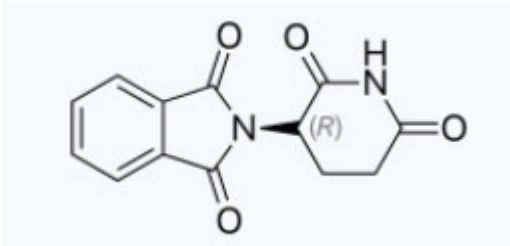
Early days of toxicology _ safety at its infancy _ turns into a tox scandal : the seminal involvement of drug regulatory bodies – FDA-EMEA-SWISSMEDIC



Catalyzed a drastic **GAME CHANGER** in drug approval and monitoring by FDA/EMA



Many children in the 1960's, like the kindergartner pictured above, were born with phocomelia as a side effect of the drug thalidomide, resulting in the shortening or absence of limbs. (Photo by Leonard McCombe/TimeLife)



Contergan® from Grünenthal Chemie 1957


The thalidomide story...60 YEARS AGO

>10'000 patients affected world wide

**Phocomelia (limb malformation), deafness, etc
(very few cases in USA - FDA push back –
by Dr Frances Kathleen Kelsey)**

**Today's patients are still working on a class action
against Grünenthal**



 National Women's History Museum
Frances Kathleen Oldham Kelsey
Frances Kathleen Oldham Kelsey ...
Frances "Frankie" Kathleen Oldham Kelsey. Kelsey was universally credited with sparing the US the damage inflicted by the drug ...

As a reviewer for the U.S. Food and Drug Administration (FDA), rejected authorize thalidomide for market because she had concerns about the lack of evidence regarding the drug's safety.





The thalidomide story REVISITED TODAY

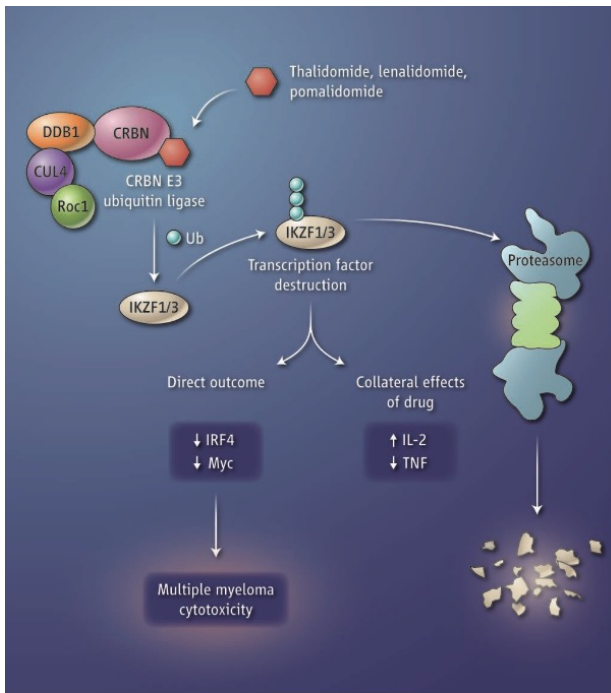
comes back with MOA and strict safety requirements (pregnancy test !)

multiple myeloma in B cell malignancies

IMiDs-Immunomodulatory drug

NK cells stimulation, cytokine IL6 production

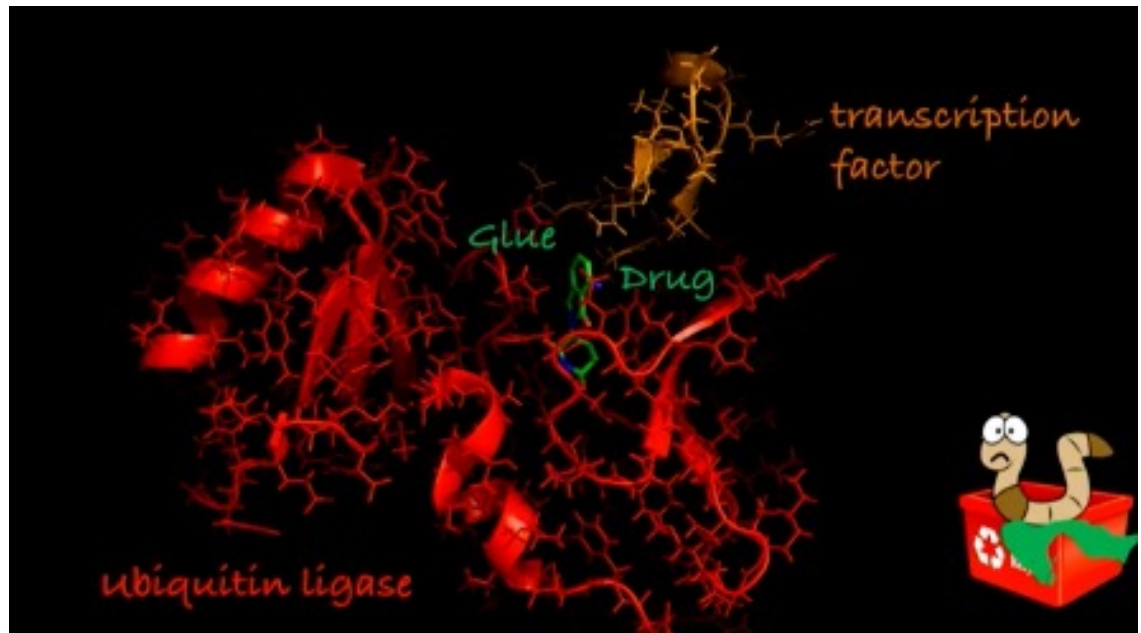
How thalidomide works against cancer



Immune modulators and myeloma. The small-molecule drugs thalidomide, lenalidomide, and pomalidomide bind to the protein cereblon (CRBN), which activates the enzymatic activity of the CRBN E3 ubiquitin ligase complex. The transcription factors Ikaros (IKZF1) and Aiolos (IKZF3) are modified with ubiquitin (Ub) molecules, targeting them for proteolysis. This alters the function of T cells and B cells, with a toxic outcome for multiple myeloma cells.

The surprising ability of thalidomide and its analogs to treat various hematologic malignancies is through the loss of two transcription factors.

MOLECULAR GLUE DEGRADER CONCEPT
(only when the cpd links the substrate and ubiquitin ligase the mutated/cancer activated protein is destroyed !)



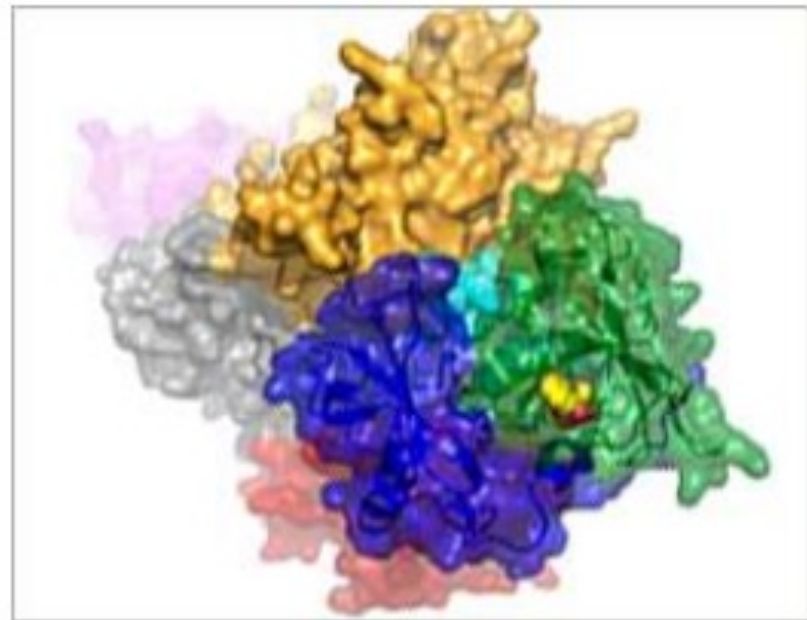
iMDs analogues are coined “molecular superglue degraders”



Mode of action (MOA) of thalidomide elucidated !

Crystal structure of thalidomide (yellow) bound to CRBN and DDB1.

Protein degradation complex (proteasome) which uses molecular tag ubiquitin to mark proteins for degradation (E3 ubiquitin ligases)



iMiDs prevent the CRBN cereblon receptor from engaging an endogenous substrate and are repurposed for “undruggable therapeutic targets” such as Zinc fingers and potentially any other therapeutic target

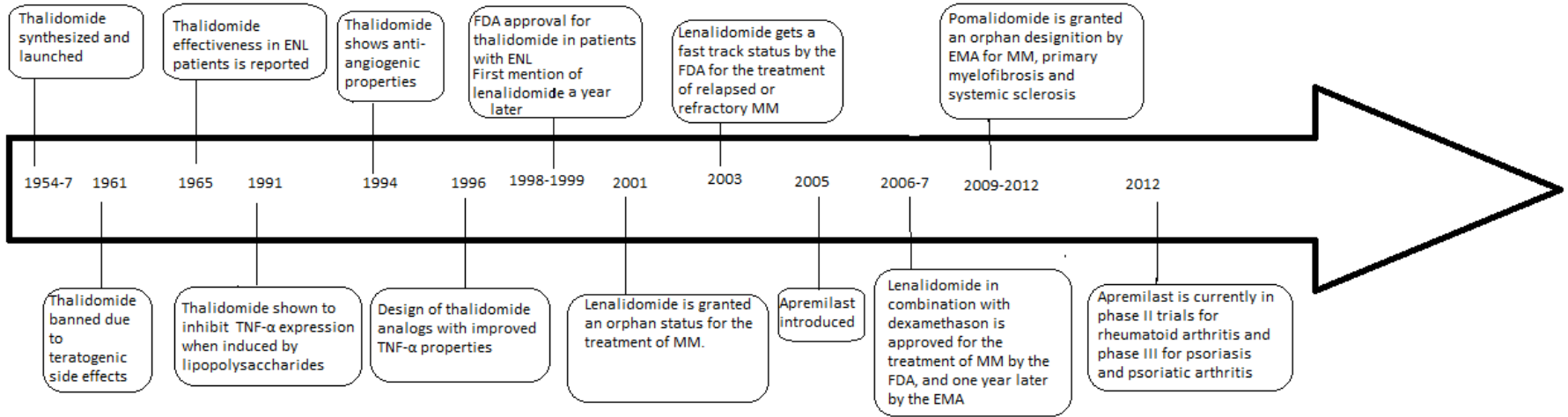


Transcription factor

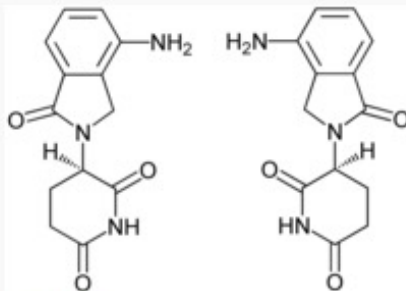


protein degradation

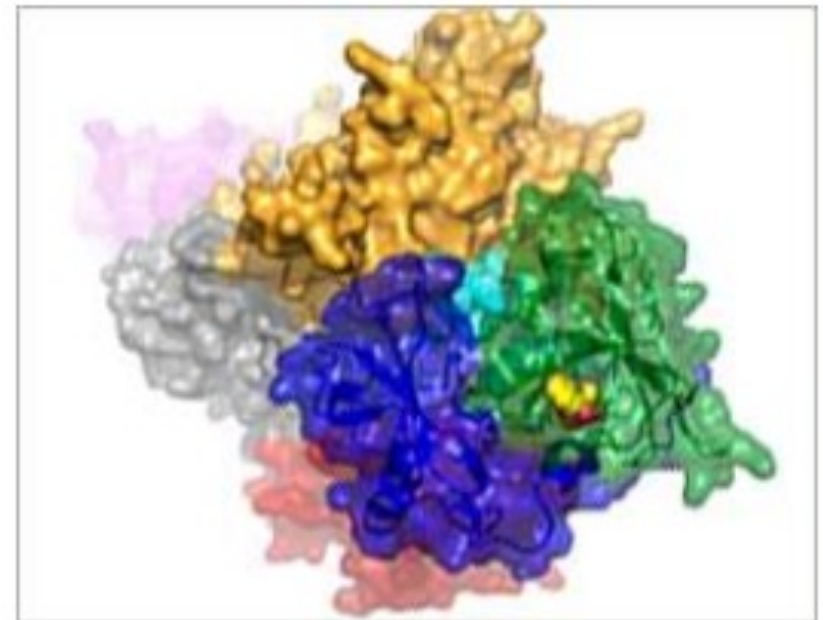
Chronological view of the history of thalidomide analogues as iMiDs (immunomodulatory imide drug eg lenalidomide as cancer therapeutics)



Fischer ES and Thomä N.(2014) Nature 512:49-53



Énantionère R du lénalidomide (à gauche) et S-lénalidomide (à droite)



Why we need to stop giving our kids codeine coughing sirup ASAP



Codeine coughing sirup overconsumption



RECALL: CHILDREN'S ROBITUSSIN, DIMETAPP COUGH MEDICINE

**RECALL
ALERT**

- POSSIBLE OVERDOSE RISK
- BOTTLES CAME WITH WRONG DOSING CUPS
- CHANCE PARENTS COULD ACCIDENTALLY GIVE TOO MUCH



The Dangers of
CODEINE
Syrup Addiction



The Cough Syrup Tragedy

By M. Sini
Professor of Pharmacology, Indian Institute of Science, Bangalore.

water-base printing table, but
varying compositions and other

How can loving parents ever dream that the sweet cough syrup commonly given to their children is nothing but a poison? Can the lives of these children be saved if the poisonous symptoms are detected early and appropriate treatment given immediately?

The public and practicing physicians should be informed of more detail of the nature of the disease for which the syrup was prescribed, the dose and the period during which the syrup was given, the development of symptoms and the course of the disease till the fatal end. It is also essential to know whether the development of toxic symptoms can be prevented.

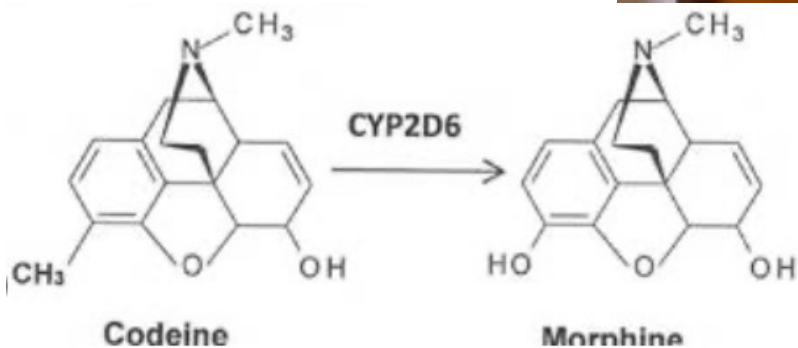
With industrialisation and advent of modern technology in all

HOW ?

COUGH SYRUP

LEADS TO

DEATH



Codeine overconsumption screening : avoiding kids fatal tragedy



Codeine is O-demethylated by cytochrome P450 2D6 (CYP2D6) to form the **more potent drug morphine**, accounting for much of codeine's analgesic and dependence-producing properties. CYP2D6 inhibition could be used to treat codeine dependence.

Codeine coughing sirup overconsumption



RECALL: CHILDREN'S ROBITUSSIN, DIMETAPP COUGH MEDICINE

**RECALL
ALERT**

- POSSIBLE OVERDOSE RISK
- BOTTLES CAME WITH WRONG DOSING CUPS
- CHANCE PARENTS COULD ACCIDENTALLY GIVE TOO MUCH



COLD SYRUP RECALL
CHILDREN'S MEDICINE POSES OVERDOSE RISK

HEADLINE
HEADLINES HEADL



Codeine coughing sirup overconsumption : 35 swiss adolescents do not survive the « party drug » cocktail



Press release on the judgment C-4125/2019, C-5006/2019

Cough medicine containing psychoactive substances not to be sold in drugstores

The Federal Administrative Court has issued two pilot judgments supporting Swissmedic's decision to classify certain cough medicines as prescription-only medications. Their active substances are classed as psychoactive and may only be dispensed by doctors and pharmacists in accordance with the revised legislation on therapeutic products.

28.04.2021

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Foto: Keystone

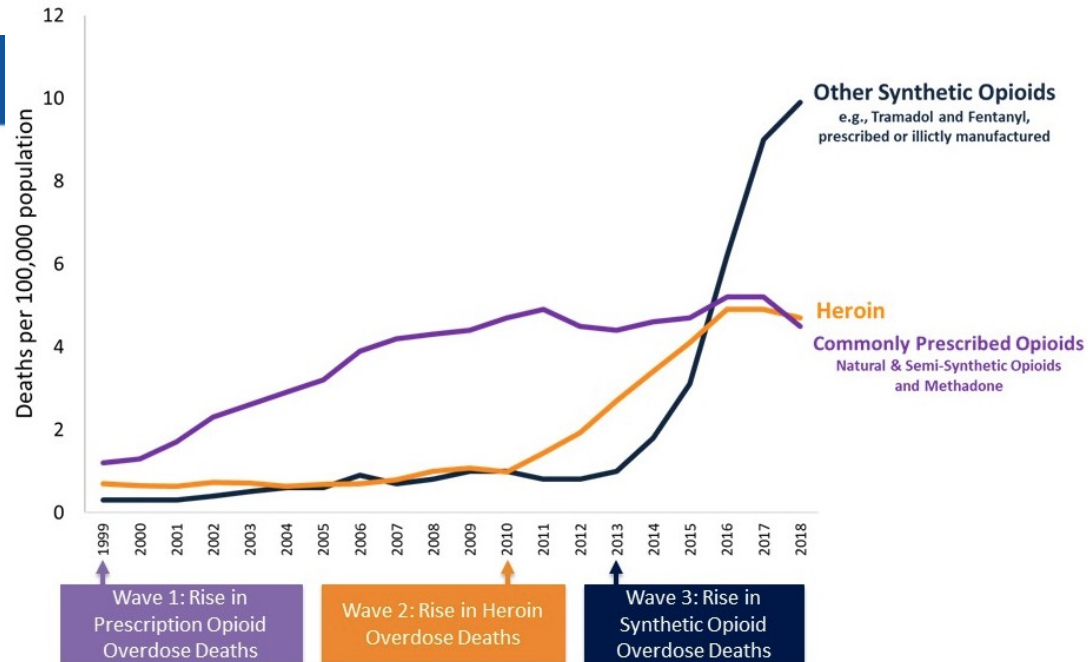
Neue Zürcher Zeitung 2023

35 Jugendliche sind in den letzten vier Jahren an Tablettenmissbrauch gestorben. Eine Forscherin spricht von einem «erschreckenden Ausmass»

opioid overprescription worldwide : how to manage chronic pain, eg. in palliative care ?



3 Waves of the Rise in Opioid Overdose Deaths



SOURCE: National Vital Statistics System Mortality File.



The Opioid Epidemic in the U.S.

In 2015...

12.5 million
People misused prescription opioids¹

2.1 million
People misused prescription opioids for the first time¹

33,091
People died from overdosing on opioids²

2 million
People had prescription opioid use disorder³

15,281
Deaths attributed to overdosing on commonly prescribed opioids^{2,3}

828,000
People used heroin⁴

9,580
Deaths attributed to overdosing on synthetic opioids^{2,3}

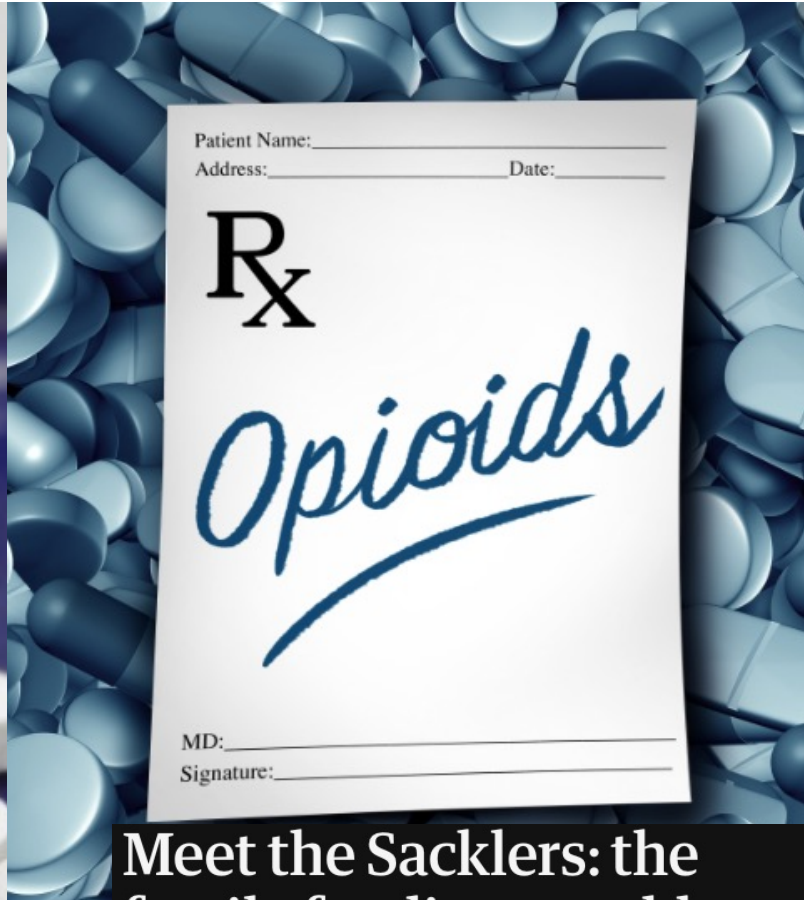
135,000
People used heroin for the first time⁴

12,989
Deaths attributed to overdosing on heroin^{2,4}

\$78.5 billion
In economic costs (2013 data)⁵

Sources: ¹ 2015 National Survey on Drug Use and Health (SAMHSA); ² MMWR, 2016; 65(10-51):1445-1452 (CDC); ³ Prescription Overdose Data (CDC); ⁴ Heroin Overdose Data (CDC); ⁵ Synthetic Opioid Data (CDC); ⁶ The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. Florence CS, Zhou C, Luo F, Xu L. Med Care. 2016 Oct;54(10):901-6

Opioid overconsumption : OxyContin pushed a worldwide addiction The Purdue Pharma and Sakler family found in corruption

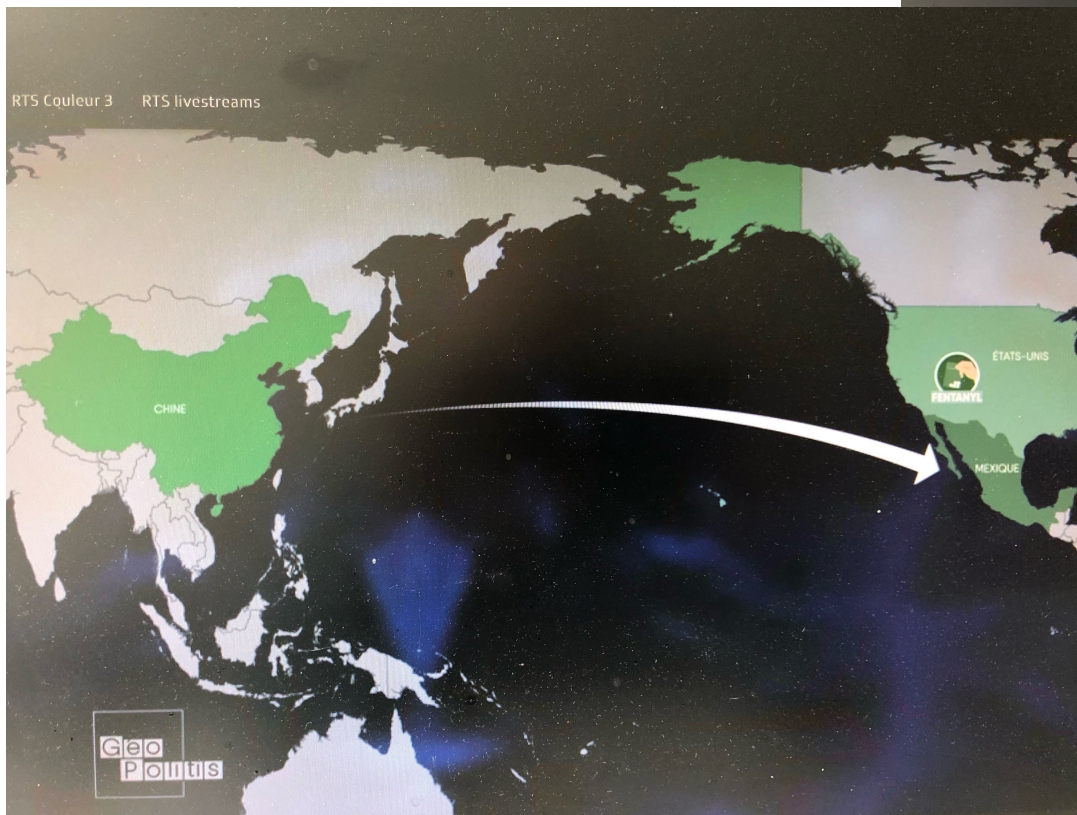


Meet the Sacklers: the family feuding over blame for the opioid crisis

Philanthropic heirs to OxyContin fortune have a 'moral duty to help make this right' says the widow of one of Purdue Pharma's founders

- **US drug companies accused of being 'cheerleaders' for opioids**

US : every 7 min a deathcase on fentanyl overdose (50x more potent over heroin)



mainly synthesized in China, then transited via Mexico etc.

US : every 7 min a deathcase on fentanyl overdose (50x more potent over heroin)

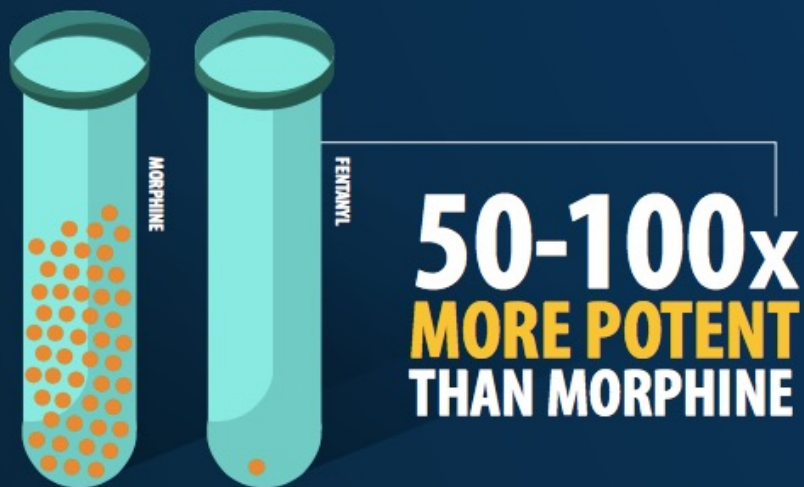


highly addictive, powder or pill for iv/po : 2mg – endstage fatal respiratory distress

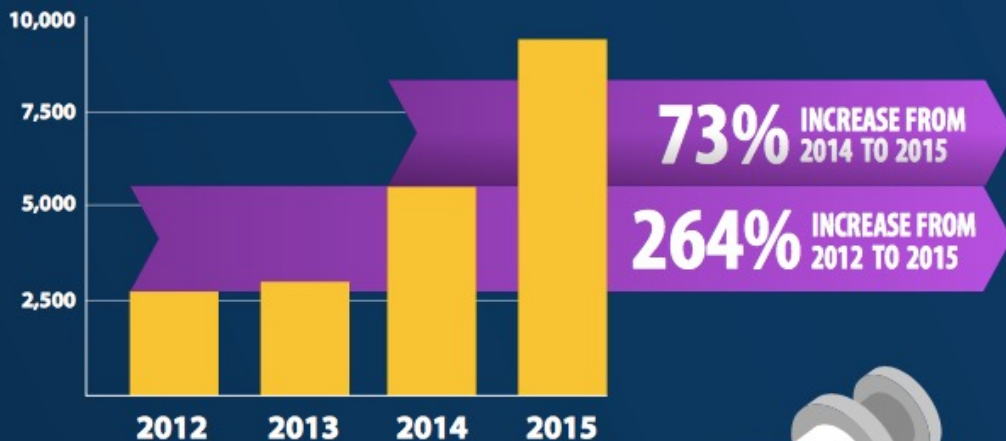


FENTANYL: Overdoses On The Rise

Fentanyl is a synthetic opioid approved for treating severe pain, such as advanced cancer pain. Illicitly manufactured fentanyl is the main driver of recent increases in synthetic opioid deaths.



SYNTHETIC OPIOID DEATHS ACROSS THE U.S.

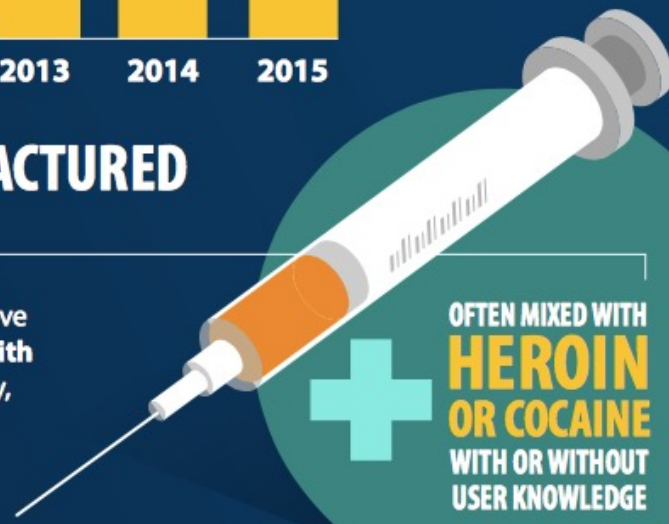


Ohio Drug Submissions Testing Positive for Illicitly Manufactured Fentanyl



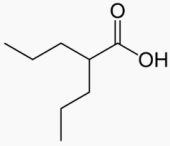
ILLICITLY MANUFACTURED FENTANYL

Although **prescription rates** have fallen, **overdoses associated with fentanyl** have risen dramatically, contributing to a sharp spike in synthetic opioid deaths.

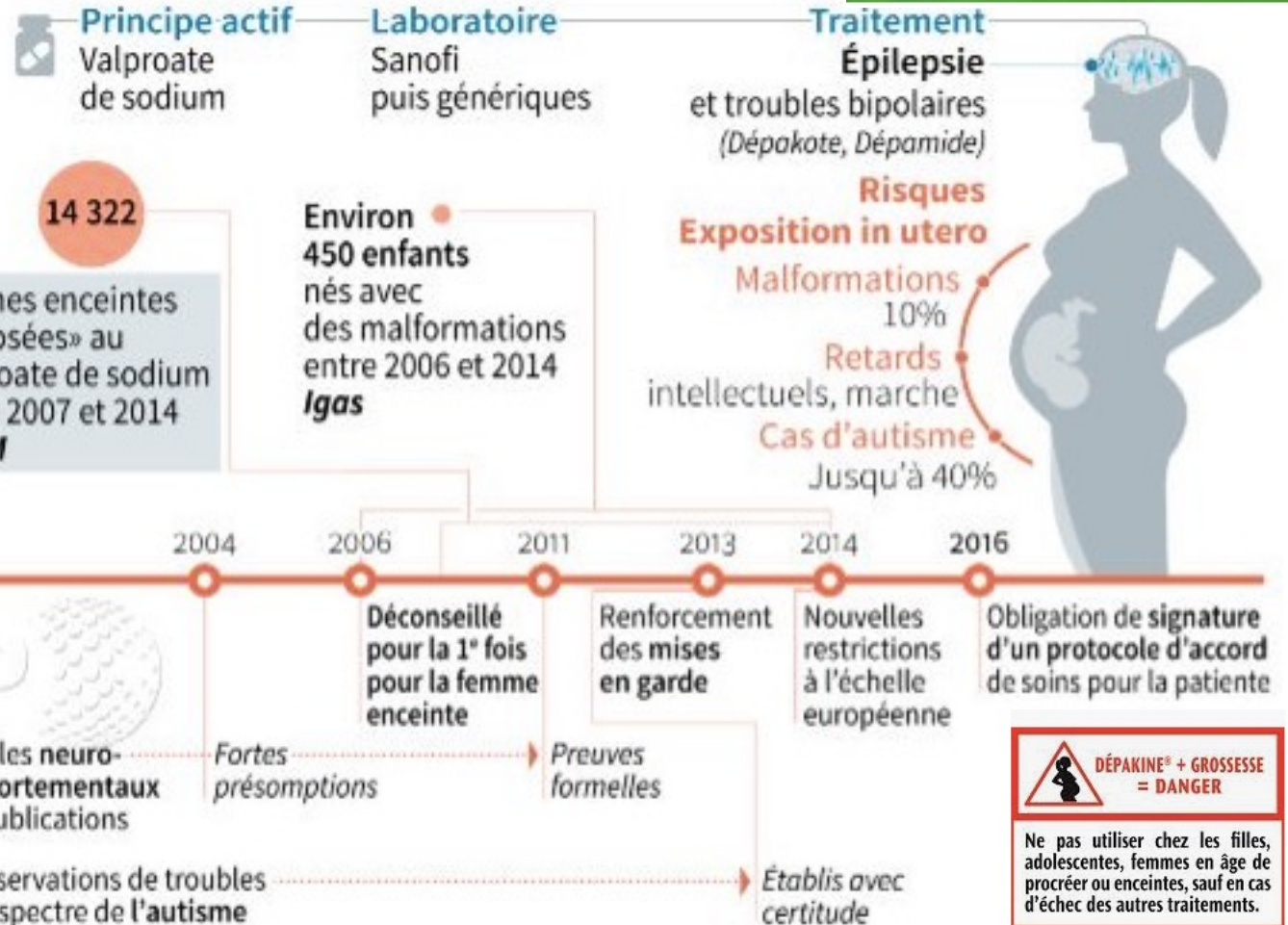


Valproic acid safety (adverse effects) : what child bearing women care first !

Acide valproïque

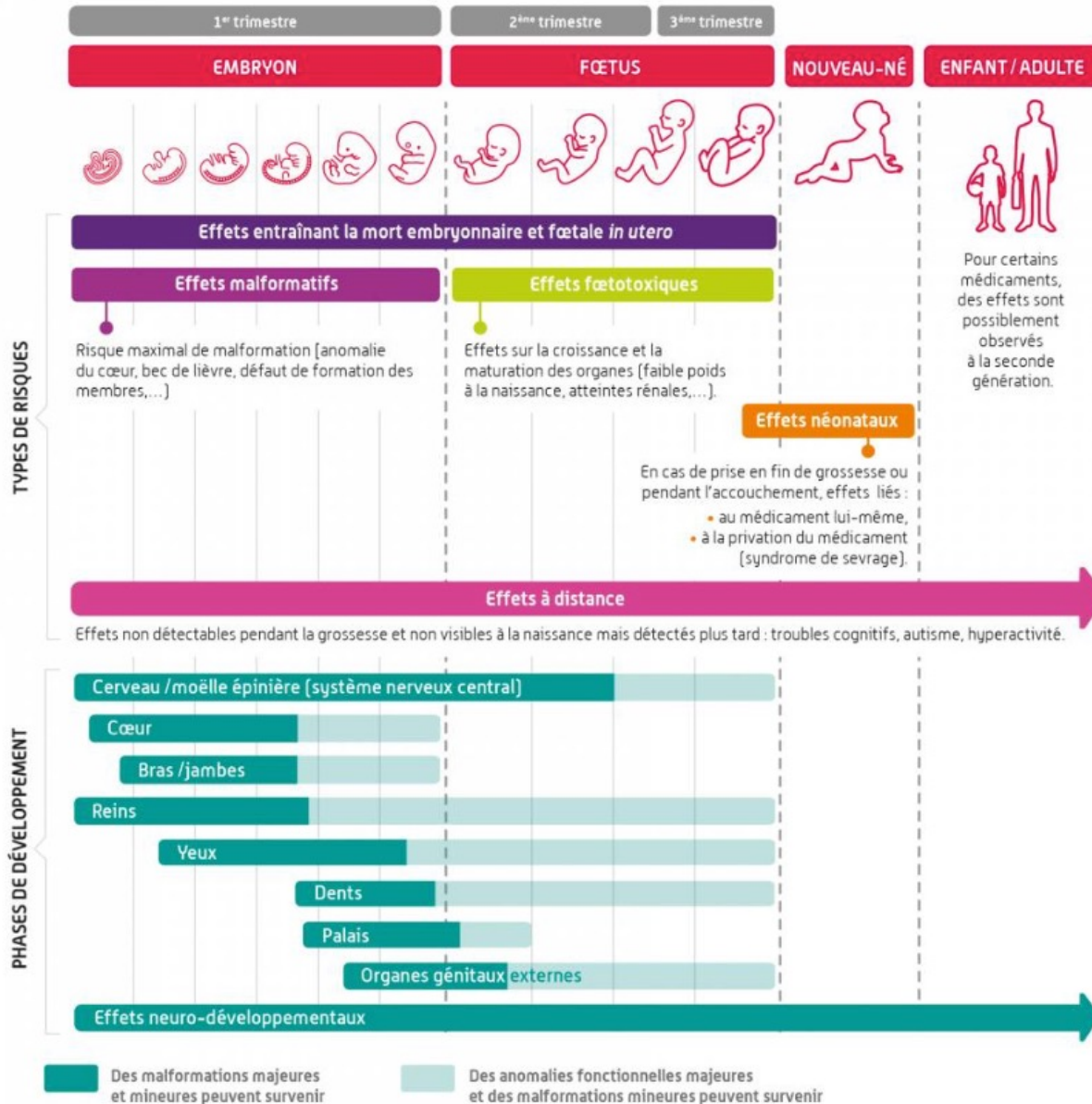


Prescribed in manic-depression, migraine, headache and epileptic convulsion



40 (!) years to introduce pregnancy and correlate **teratogenicity** with valproate salt prescription ! Nowadays mandatory pregnancy test before prescription ! Sanofi argues it had always communicated FDA their results ; it is FDA's job to warn patients and prescribing physicians. **Court decided the sponsors are responsible for the safety of their medicines like for any other products, eg. car safety.**

What child bearing women care first



① Swiss Federal Institute of Technology Lausanne does not subscribe to this content on ScienceOpen



The Journal of Pediatrics
 Volume 97, Issue 2, August 1980, Pages 332-333



Editorial correspondence

Teratogenicity of valproic acid

M.D. Bernard Dalens, M.D. Elie-Jean Raynaud, M.D. Jacqueline Gaulme

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[https://doi.org/10.1016/S0022-3476\(80\)80517-8](https://doi.org/10.1016/S0022-3476(80)80517-8)

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References (1)

Dickinson DG *et al.*
 Transmission of valproic acid (Depakene) across the placenta: Half life of the drug in mother and baby

Safety is first concern of patients and some lawyers...



HOW SAFETY IS
IMPORTANT TO
PHARMAS ?
HOW SERIOUS CAN
CLASS ACTION BE ?

SEVERAL PHARMA
SCANDALS IN COURT
TRIALS

Pharmakonzern Johnson & Johnson zu Milliardenstrafe verurteilt

13.07.18 15:48

Neue Zürcher Zeitung

Milliardenstrafe für Pharmakonzern Johnson & Johnson

22 an Eierstockkrebs leidende Frauen hatten gegen den amerikanischen Konzern geklagt. Sie machen Puderprodukte für ihre Erkrankungen verantwortlich und werfen dem Unternehmen vor, Gefahren verschwiegen zu haben.

13.7.2018, 04:14 Uhr

(Reuters/dpa) Der amerikanische Pharma- und Konsumgüterkonzern Johnson & Johnson (J&J) ist zu einer Milliardenstrafe verurteilt worden, weil bestimmte Körperpflegeprodukte Krebs verursacht haben sollen. Beim Prozess in St. Louis im amerikanischen Gliedstaat Missouri befand die Jury J&J einstimmig für schuldig und ordnete Schadenersatz- und Strafzahlungen in Höhe von insgesamt 4,7 Milliarden \$ (umgerechnet 4,0 Mrd. €) an.

Die Milliardensumme setzt sich aus 550 Mio. \$ Entschädigung und einer Strafe von 4,14 Mrd. \$ zusammen. Als Reaktion fielen die J&J-Aktien im nachbörslichen Handel um 1%. J&J äusserte sich über das Urteil enttäuscht und kündigte rechtliche Schritte an. Das Verfahren sei hochgradig unfair gewesen. Der Konzern bekräftigte, seine Produkte enthielten kein Asbest und lösten kein Krebs aus.

ENU

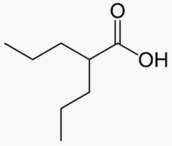
Le Parisien

Scandale de la Dépakine : Sanofi mis en examen pour «homicides involontaires»

Le laboratoire est déjà poursuivi pour « tromperie aggravée » et « blessures involontaires ».



Acide valproïque



Today's safety issues - improve on **pharmacovigilence** worldwide !

Prescribed in epilepsy, manic-depressive patients, chronic migraine and convulsions.

Lundi 6 janvier 2020 | Dernière mise à jour 17:01 | Petites annonces | Immo | Recherche

24heures

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Fédérales 2019 Suisse romande Faits divers Images

Dépakine: Swissmedic et industrie pharma épignlés

Santé Selon Brigitte Crottaz, présidente ad intérim de la Fédération suisse des patients, le fabricant de la Dépakine a fait preuve de négligence dans ses notices.



Brigitte Crottaz, présidente ad intérim de la Fédération suisse des patients et conseillère nationale (PS/VD).

Image: Keystone

Articles en relation

Les victimes de la Dépakine sont recensées

Suisse L'antiépileptique responsable de nombreuses malformations congénitales en France a fait une quarantaine de victimes en Suisse, selon une analyse de Swissmedic rendue publique. [Plus...](#)
06.12.2019

Berne va analyser les dégâts de la Depakine

Suisse Le Conseil fédéral établira un rapport sur le nombre de cas de femmes enceintes et d'enfants touchés par des malformations liées à la prise d'un anti-épileptique. [Plus...](#)
13.06.2018

Scandale de la Dépakine: malformations en nombre

Publicité

Programme de partenariat

Cartes de crédit et cartes prépayées personnalisées pour associations et entreprises.

[Plus](#)



January 2020 : Depakine® swiss patients class action on pharma, swissmedic (authority) and GPs Pregnant women were prescribed Depakine® up until 2015 while authorities have been warned on teratogenicity much earlier (2010)



40 years to introduce pregnancy and correlate with teratogenicity/mental retardation and valproate salt prescription ! Mandatory pregnancy test before prescription ! 4000 valproate affected kids registered in France in 2018.

January 2020 : Depakine® swiss patients suing pharma and swissmedic (authority)



Jeudi 13 février 2020 | Dernière mise à jour 11:28 ▶ Petites annonces ▶ Immo

24heures

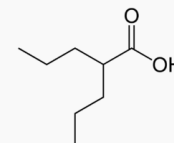
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Le Matin Dimanche Enquête E-paper Abonnements

Acide valproïque

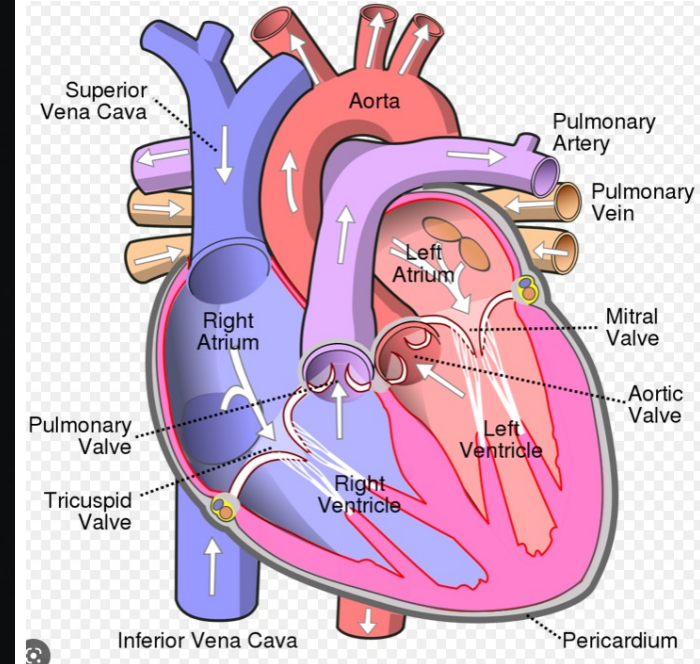


Dix enfants handicapés se battent contre les médecins et la pharma

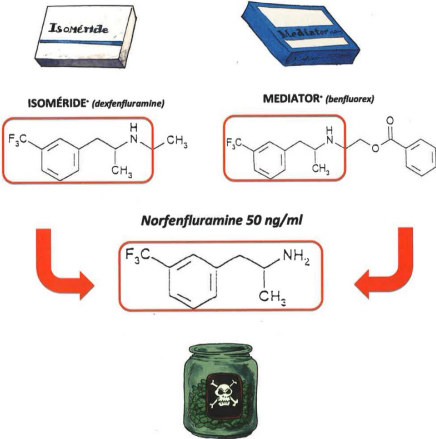
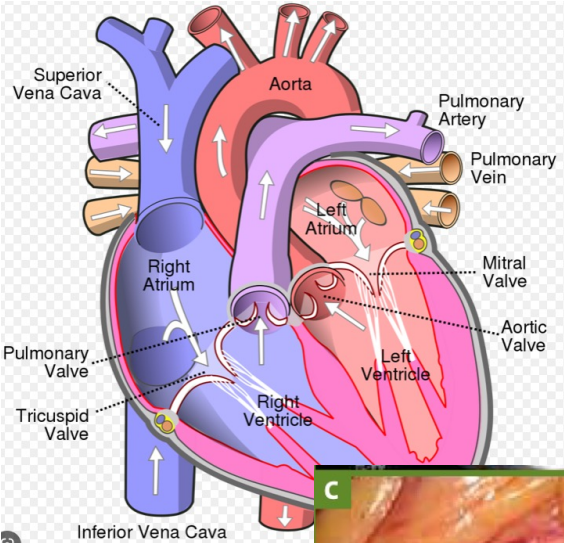
Ils sont tous nés en Suisse avec un retard mental. Leurs parents accusent un médicament, la Dépakine, d'en être responsable. Les autorités savaient, mais n'ont rien dit. Il y a beaucoup d'autres victimes.

- 40 years (!) to introduce pregnancy and correlate with teratogenicity/mental retardation and valproate salt prescription ! Mandatory pregnancy test before prescription ! Too bad it had been already prescribed !!
- Prescribed in manic-depressive patients, and helps prevent migraine headaches and convulsions.

Mediator® : a french pharma scandal : reported > 2000 death cases



Mediator[®] : cardiac valves calcification/replacement



Deaths associated with newly launched SARS-CoV-2 vaccination (Comirnaty®)

Carolin Edler^{*}, Anke Klein, Ann Sophie Schröder, Jan-Peter Sperhake, Benjamin Ondruschka

Institute of Legal Medicine, University Medical Center Hamburg-Eppendorf, Butenfeld 34, 22529 Hamburg, Germany

ARTICLE INFO

Keywords

Vaccination
Comirnaty®
SARS-CoV-2
COVID-19 vaccine
Autopsy

ABSTRACT

Since 27th December 2020, a mRNA vaccine from BioNTech / Pfizer (Comirnaty®) has been used across Germany. As of 12th March 2021, 286 fatalities of vaccinated German individuals were registered at the Paul Ehrlich-Institute with time intervals after vaccination between one hour to 40 days. From our catchment area in northern Germany, we have so far become aware of 22 deaths in connection with vaccination in a 5 week period (range: 0–28 days after vaccination). Three death cases after vaccination with Comirnaty®, which were autopsied at the Institute of Legal Medicine Hamburg, are presented in more detail. All three deceased had severe cardiovascular diseases, among other comorbidities, and died in the context of these pre-existing conditions, while one case developed a COVID-19 pneumonia as cause of death. Taking into account the results of the postmortem examination a causal relation between the vaccination and the death was not established in any case. If there are indications of an allergic reaction, histological and postmortem laboratory examinations should be performed subsequent to the autopsy (tryptase, total IgE, CRP, interleukin-6, complement activity C3/C5).

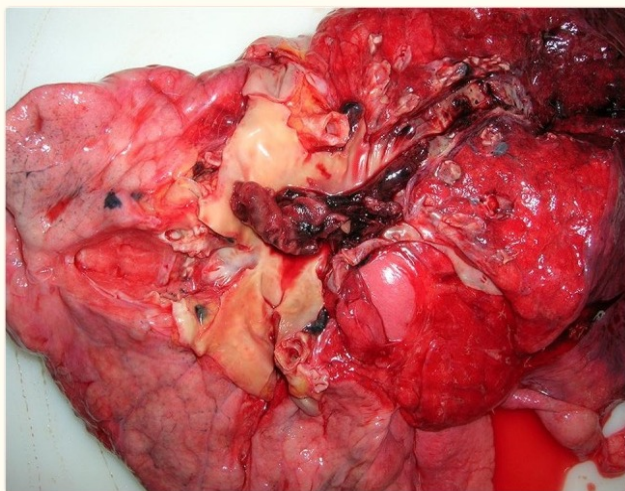


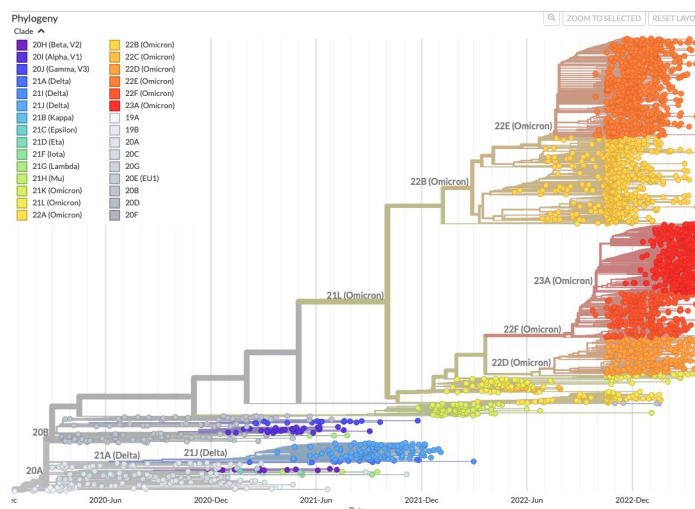
Fig. 1

Central pulmonary artery embolism in the right lung.

Genomic epidemiology of SARS-CoV-2 with subsampling focused globally over the past 6 month

Built with nextstrain/ncov. Maintained by the Nextstrain team. Enabled by data from [GISAI](https://gisaid.org/)

Showing 2799 of 2799 genomes sampled between Dec 2019 and Apr 2023.



Deaths associated with newly launched SARS-CoV-2 vaccination (Comirnaty®)

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ABSTRACT

Since 27th December 2020, a mRNA vaccine from BioNTech / Pfizer (Comirnaty®) has been used across Germany. As of 12th March 2021, 286 fatalities of vaccinated German individuals were registered at the Paul Ehrlich-Institut (PEI) in northern Germany. We report on a 40-year-old male patient who died of a central pulmonary artery embolism in northern Germany during a postmortem case. If there are more cases, a postmortem autopsy should be performed.

Reporting rates of myocarditis

Table 1. Rates of likely myocarditis cases following Comirnaty (Pfizer)*

Age (years)	All doses		Second doses	
	Rate* per 100,000 doses		Rate* per 100,000 doses	
	Male	Female	Male	Female
5-11	0.3	0.1	0.2	0
12-17	8.0	1.7	13.2	2.8
18-29	5.1	1.5	9.3	2.8
30-39	2.3	0.9	3.1	1.0
40-49	1.0	1.0	1.5	1.8
50-59	0.7	0.4	0.7	0.4
60-69	0.4	0.3	0.4	0.4
70+	0.1	0.3	0	0.4
All ages*	2.4	0.9	4.7	1.6

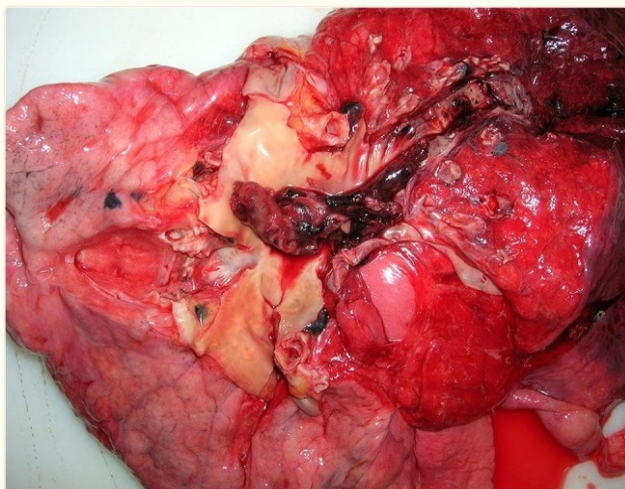


Fig. 1

Central pulmonary artery embolism in the right lung.



Small molecules



- chemical synthesis
- single molecule species
- well defined structure, stable, half life hours
- MW < 500-1000 Da
- standard models for safety testing (2 species: rodent and non-rodent)
- non-immunogenic
- Typically given oral
- distribution extra- and intracellular
- metabolised
- efficacy and toxicity from parent and metabolite(s)

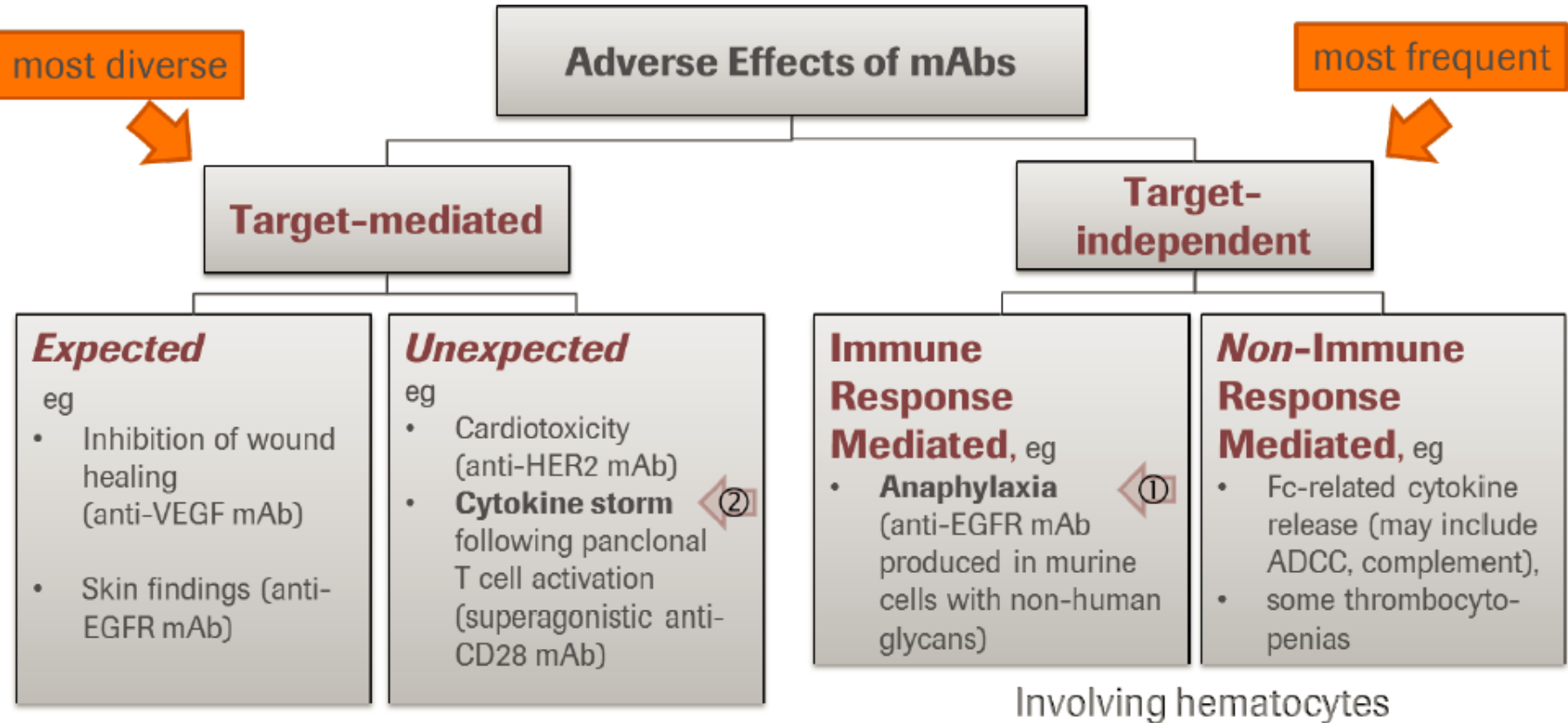
Antibodies



- **biotechnology** derived molecules
- Therapeutic mAb = mixture of molecule **variants**
- **complex** structure, heat sensitive, **long half life**
- **150'000 Da** for IgGs
- **high target selectivity** & **species specificity** (for safety testing often only monkey cross-reacts)
- may be **immunogenic**
- **Parenteral** administration (i.v., s.c.)
- distribution extracellular in blood (**low V_{ss}**)
- **catabolised** (proteolytic degradation)
- effects secondary to **MoA** and exaggerated pharmacology

Aspirin half life 1h ; mAB several weeks !

Mechanisms of adverse effects with mAbs



Trastuzumab subjected to scrutiny in drug safety and development

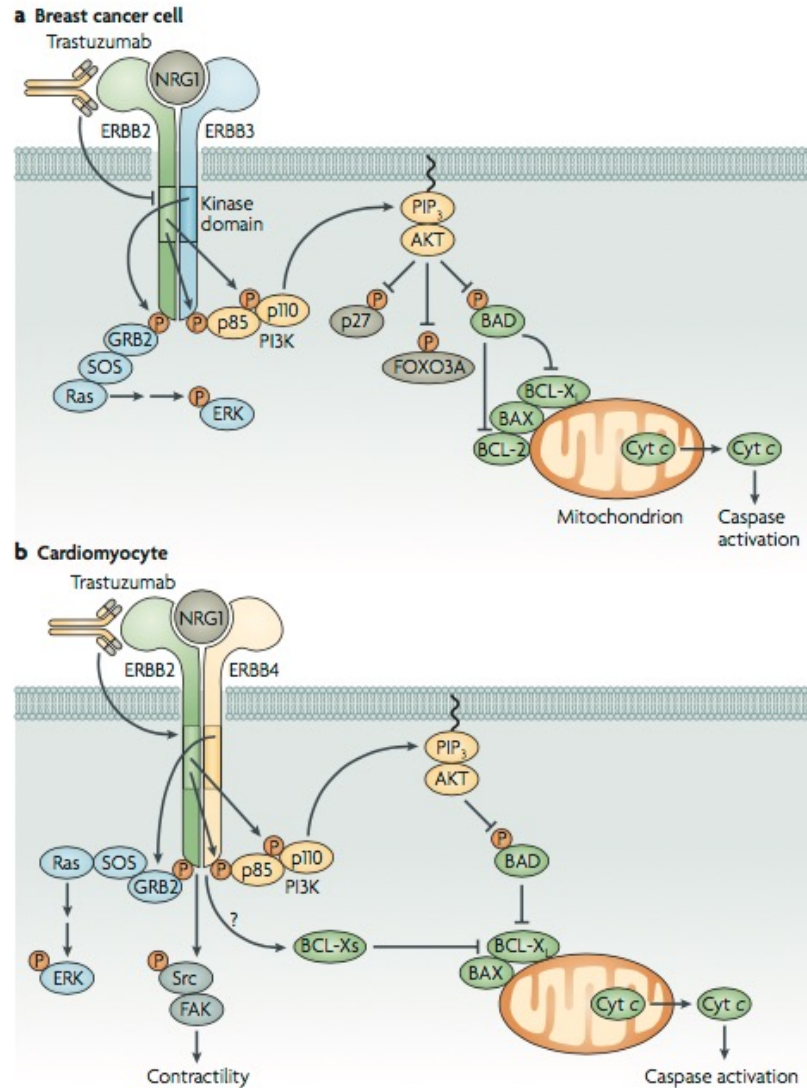
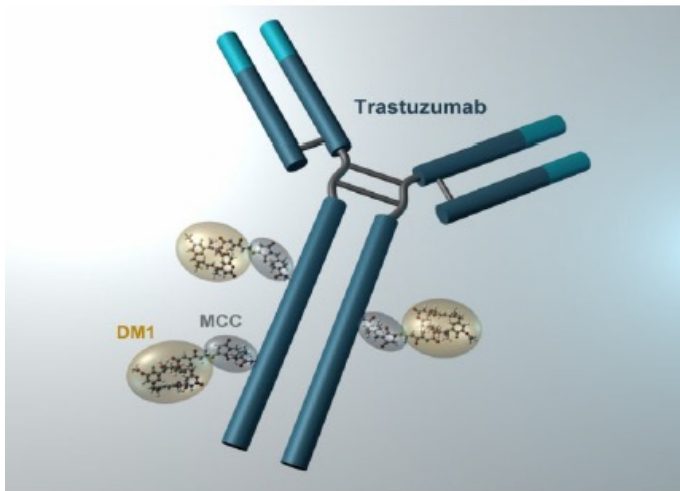
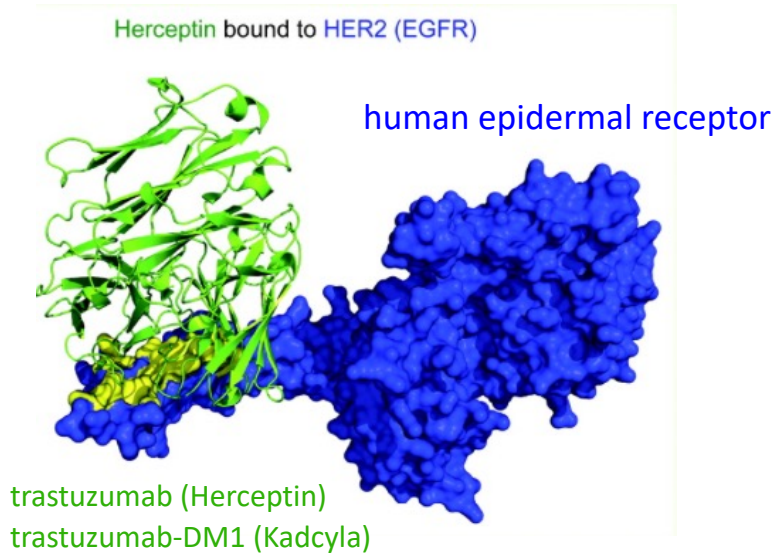


Figure 2 | Action of trastuzumab on breast cancer cells and on cardiomyocytes. Potential myocardium damages ; reduction in left ventricular systolic function

MABs are subjected to intense scrutiny in investigative toxicology



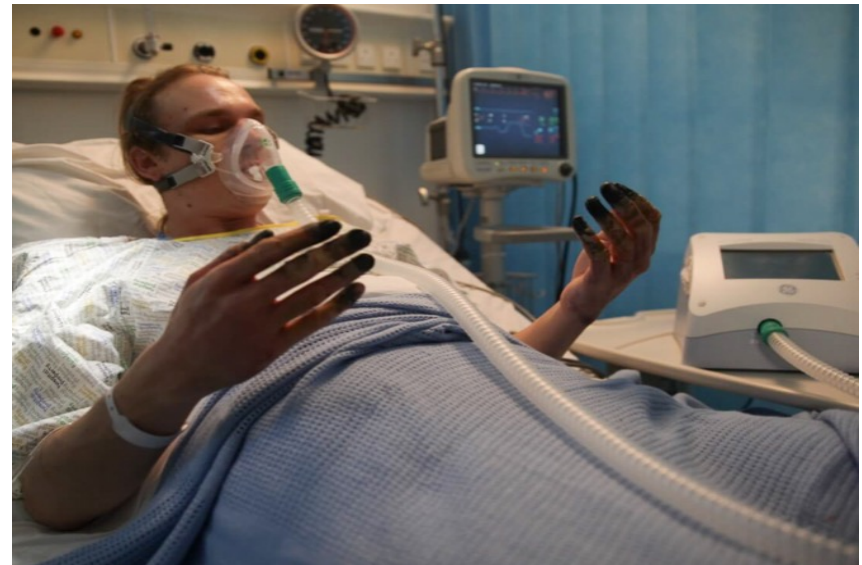
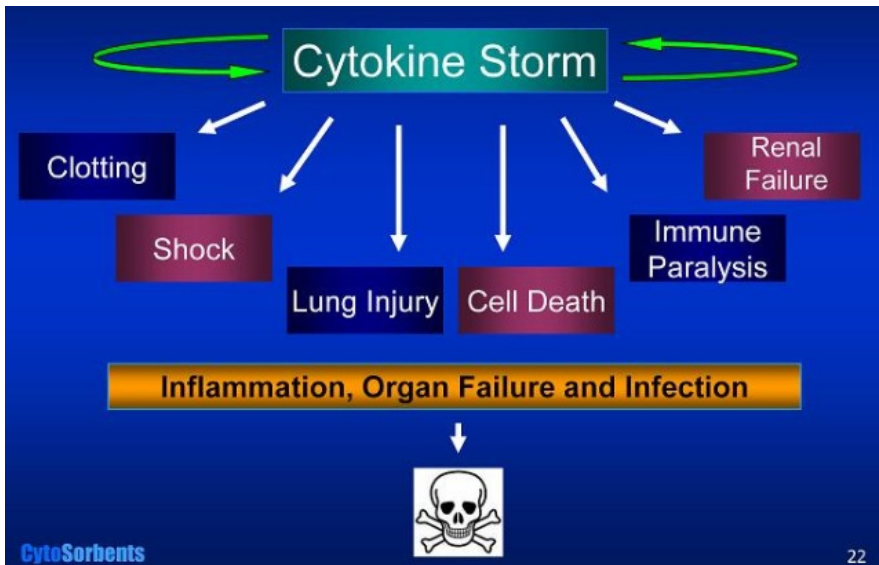
◆ Clinical signs of cytokine storm

- Early onset after 1st infusion with a mAb
- Signs and symptoms
 - Nausea, headache, fever, hypotension, hypoactivity, rash, shock, lower body temp., multiorgan failure
 - Neurological findings (encephalopathy, tremors, dizziness, seizures)
- Huge increases in cytokines and other mediators

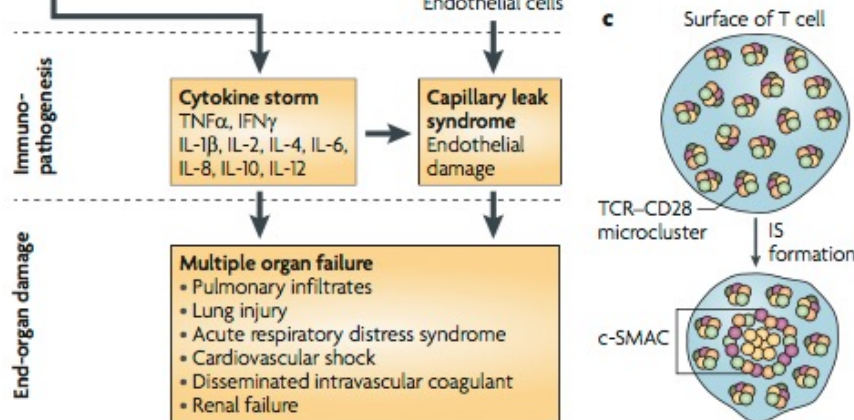
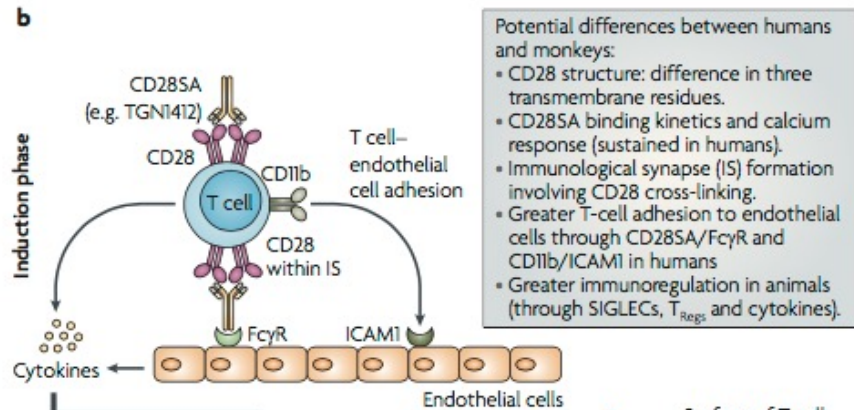
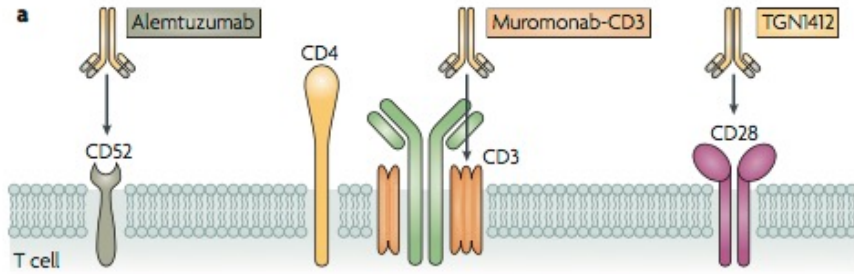
MOLECULAR BIOLOGY COMPLEX INCLUDING PATIENT HETEROGENEITY SAFETY HURDLE !

◆ Cytokine storm in patients first time treated with anti-CD28 mAb TGN1412

- Clinical signs: Severe symptoms, tissue damage, multiorgan failure
- Retrospectively, the mAb was shown to be a superagonist to CD28 with activation of all CD28⁺ immune cells



TGN1412 MAbs to CD28 ends with fatal in early clinical development (RA experimental medicine)



Mechanisms of adverse effects with mABs TGN1412 from discover to disaster

◆ Clinical signs of cytokine storm

- Early onset after 1st infusion with a mAb
- Signs and symptoms
 - Nausea, headache, fever, hypotension, hypoactivity, rash, shock, lower body temp., multiorgan failure
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◆ Cytokine storm in patients first time treated with anti-CD28 mAb TGN1412

- Clinical signs: Severe symptoms, tissue damage, multiorgan failure
- Retrospectively, the mAb was shown to be a superagonist to CD28 with activation of all CD28⁺ immune cells

After very first infusion of a **dose 500 times smaller** than that found safe in animal studies, all six human volunteers faced life-threatening conditions involving multiorgan failure for which most survived to ICU.



Figure 3 | Monoclonal antibodies and the cytokine storm. a | Surface receptors on

Therapeutic index : estimate the probability of success



Therapeutic index is given as follows :

Highest exposure without toxicity
Pharmacologically efficacious exposure

Consider free exposure rather than dose !

(use AUC, Cmax, IC50, not dose)

**Note: effective nor adverse dose/exposure is known for human at early stages
hence **extrapolation** with surrogate variants such as exposure data !**

Therapeutic index : why consider exposure rather than dose ?

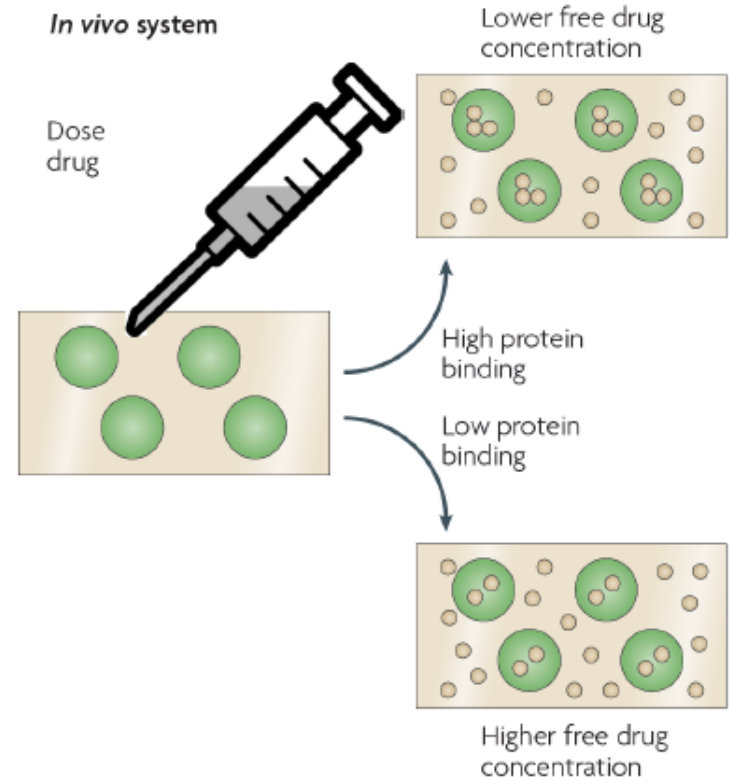


Dosage data is only comparable within same experimental setting:

- » Species (strain)
- » Genetics (gender, race)
- » Disease status / comorbidities
- » Route of administration
- » Formulation (eg suspension, tablet, capsule...)
- » *In vivo* vs *in vitro*

Free drug hypothesis:

- » The free drug concentration (ie. **drug NOT bound to plasma proteins**) at the site of action (tissue) exerts biological activity (pharmacology / toxicity)
- » In equilibrium, free tissue exposure *generally* reflects **free plasma exposure**



Smith DA, Di L, Kerns EH
The effect of plasma protein binding on *in vivo* efficacy: misconceptions in drug discovery.
Nature Reviews Drug Discovery. 2010;9:929-39 [\(LINK\)](#)

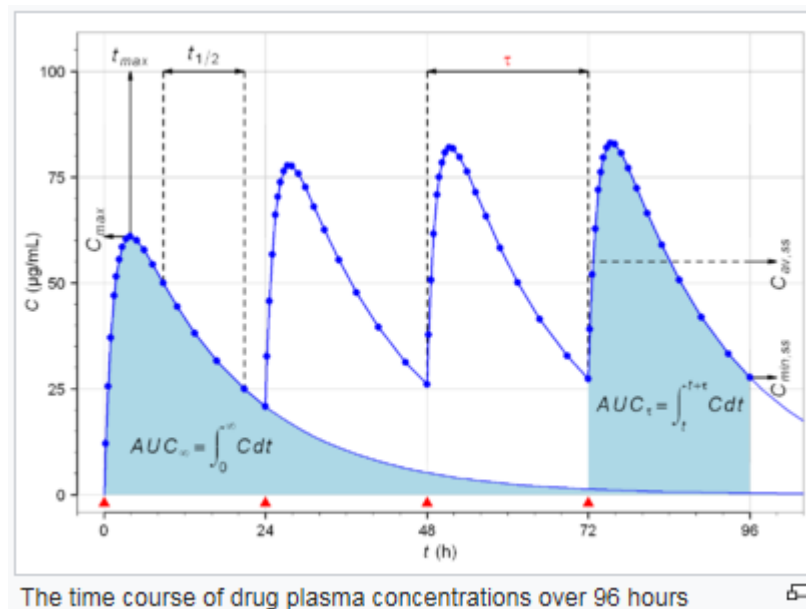
PPB : plasma protein binding

caveat: every drug is different ; BBB, organ penetration, highly active uptake and/or export etc.

Therapeutic index : estimate the probability of success

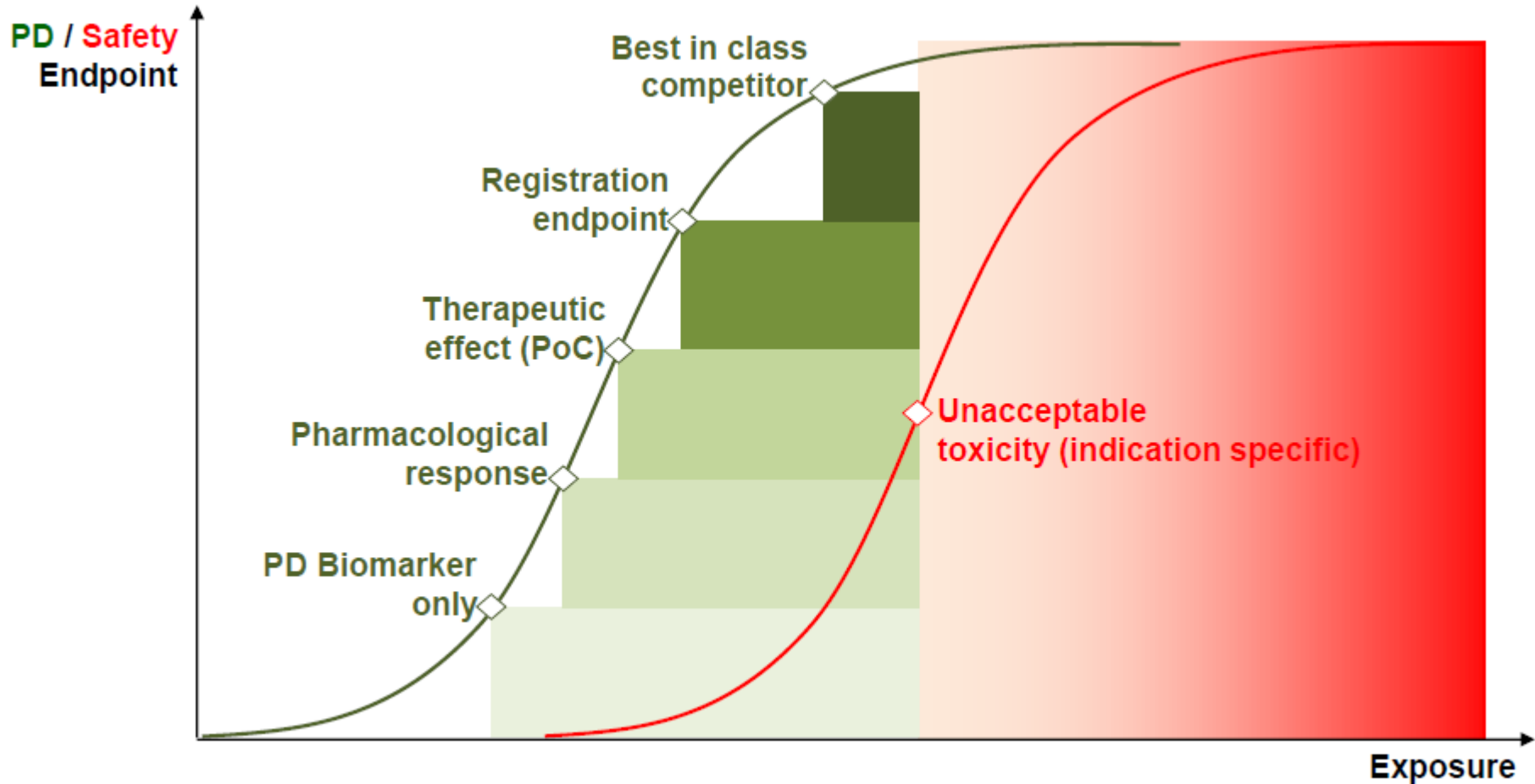


- » **Free drug hypothesis states** that the free drug concentration at the site of action exerts biological activity (pharmacology / toxicity)
- » In equilibrium, **free tissue exposure generally reflects free plasma exposure**
 - Free tissue exposure reflects plasma exposure
 - (for drugs with good membrane permeability, does not hold at BBB)
 - Free drug concentration reflects unbound drug to plasma proteins
 - (assess PPB plasma protein binding level → exposure → TI)



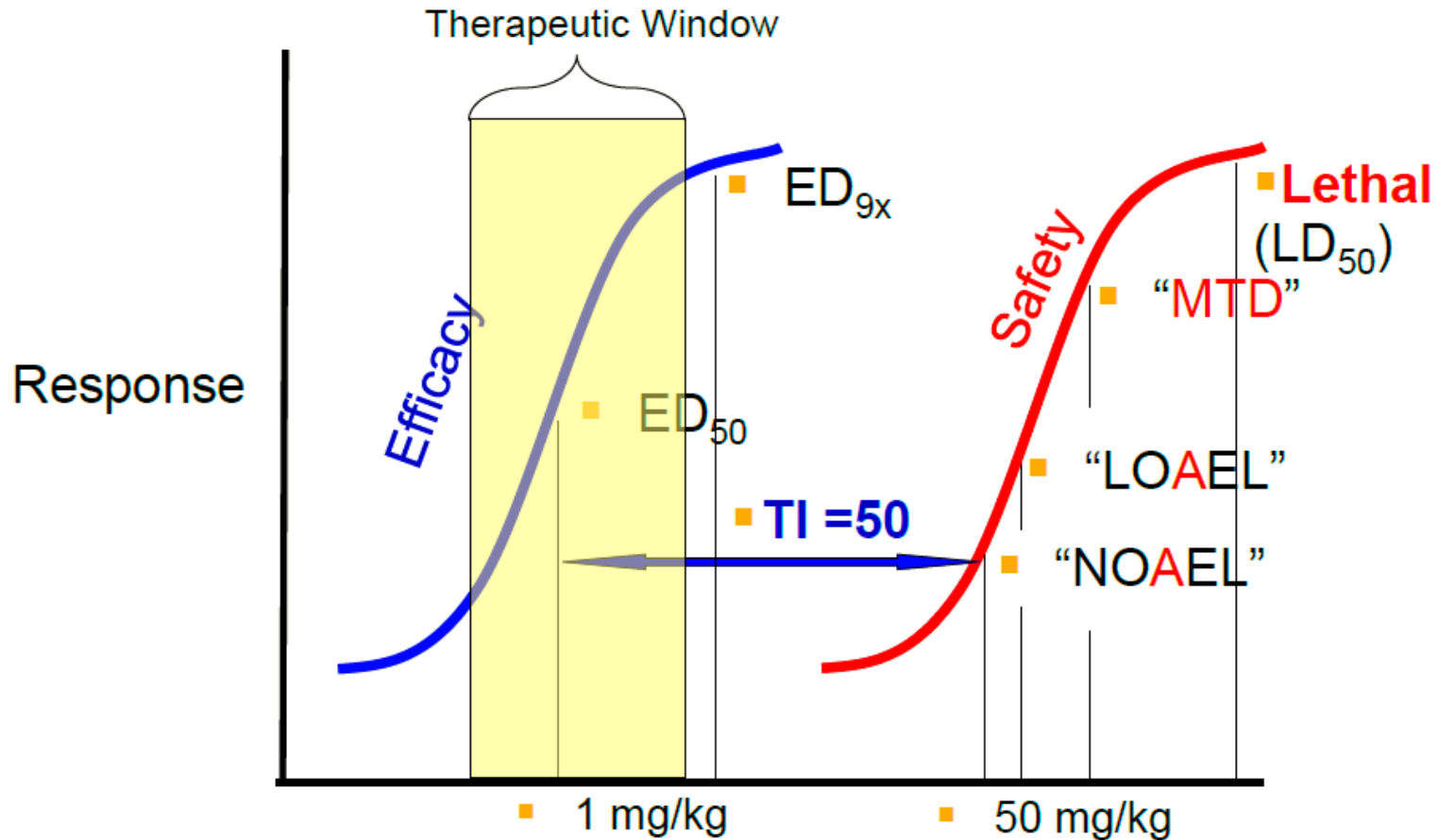
Therapeutic index : estimate the probability of success

Drugs are administered at a dosing schedule set by their therapeutic index, and termination of action is achieved by clearance and metabolism of the drug



Safety is key differentiation criteria in particular for chronic disease targets !

In vivo pharmacology : therapeutic index definition

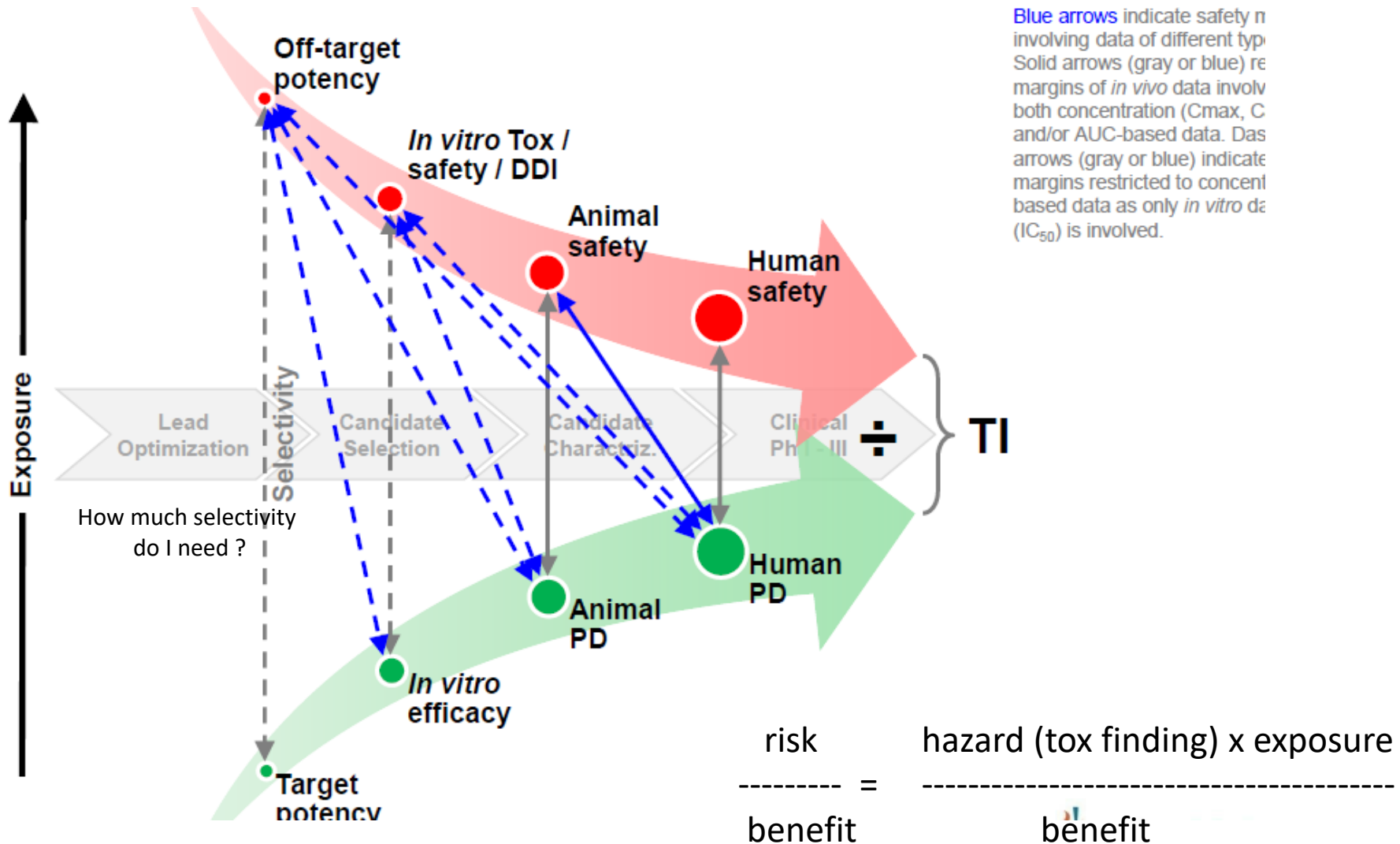


Safety is key differentiation criteria in particular for chronic disease targets !

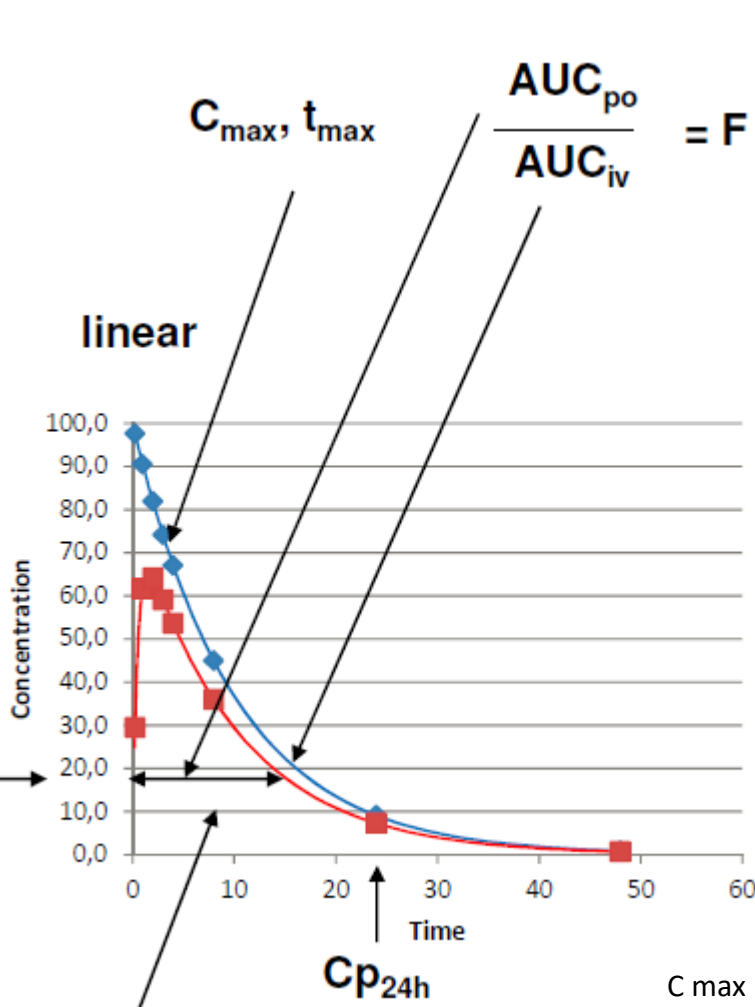
Therapeutic index TI : a critical milestone in drug development



Drugs are administered at a dosing schedule set by their **therapeutic index**, and termination of action is achieved by **clearance** and metabolism of the drug



PK in vivo – body on drug !



— iv
— po

- AUC Area under the curve (from PK data analysis)
- C_{max} Peak Concentration (from PK data analysis)
- T_{max} Peak time (from PK data analysis)
- Elimination Rate Constant (λ_z , from PK data analysis)
- Elimination Half-live $t_{1/2} = \ln(2)/\lambda_z$
- F Bioavailability = AUC (po)/AUC (iv)
- Volume of Distribution $V(t)$
 - $V_z = CL/\lambda_z$
 - $V_c = D/C(0)$
- CL: Total Body Clearance $D / F = AUC_{po} * CL = AUC_{iv} * CL$

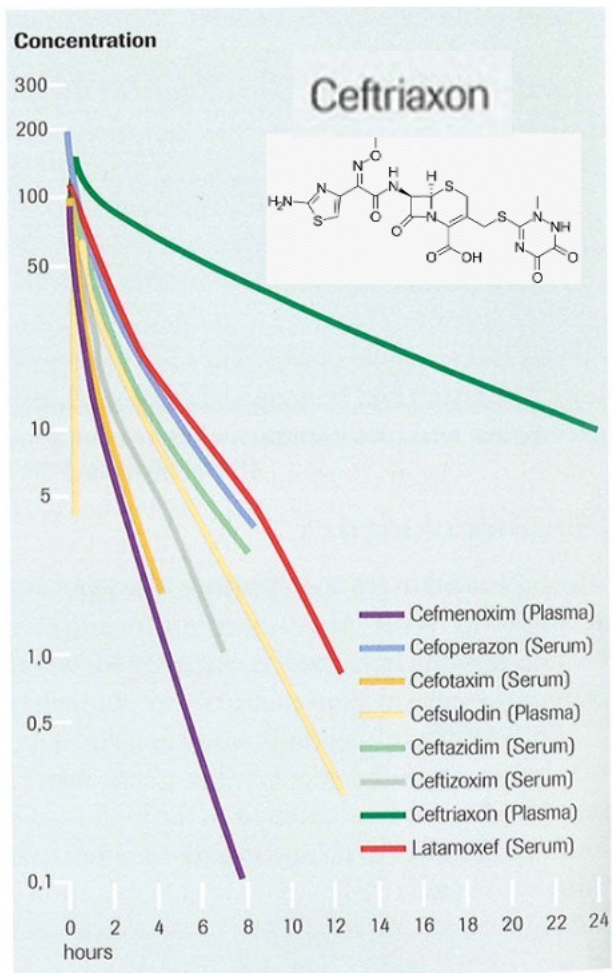
C_{max} : the peak serum concentration of a therapeutic drug

T_{max} : The amount of time that a drug is present at the maximum concentration in serum.

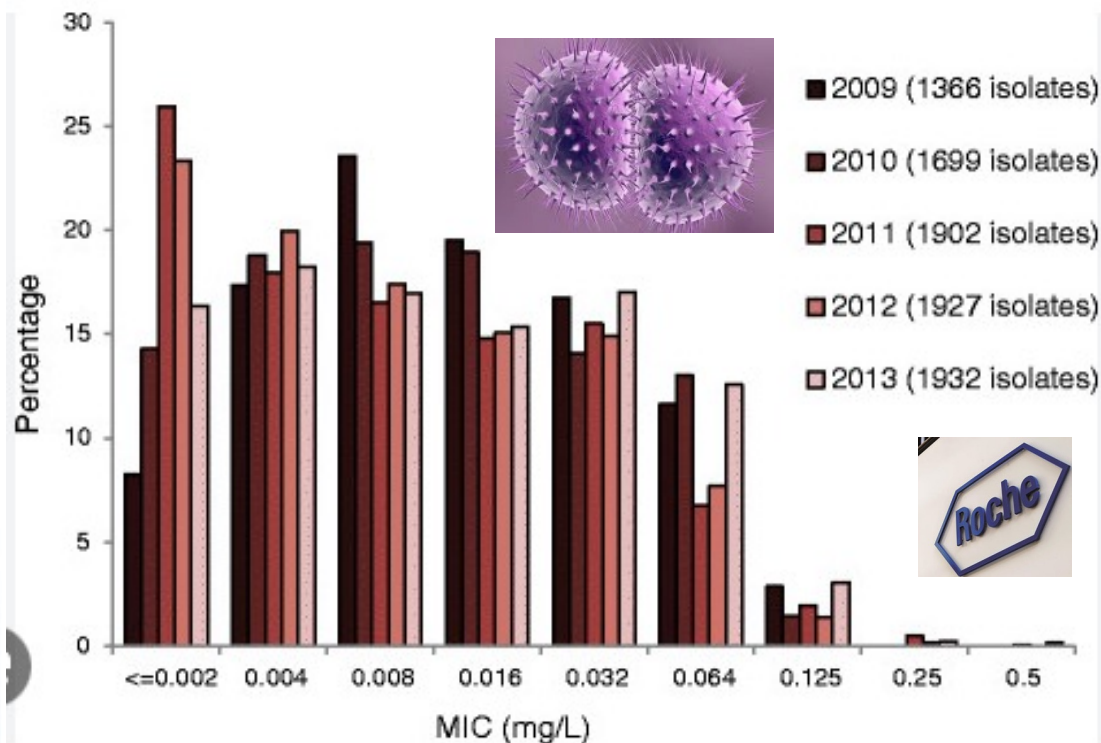
Therapeutic index : early stage assessment



Drugs are administered at a dosing schedule set by their **therapeutic index**, and termination of action is achieved by **clearance** and metabolism of the drug



Ceftriaxon MIC -minimum inhibitory concentration-
distribution for *Neisseria gonorrhoea* upon iv
1mg/L susceptible, 2mg/L intermediate, >4mg/L resistant



risk = hazard (tox finding) x exposure

benefit = benefit

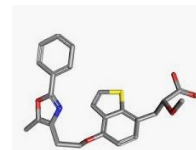
Metabolic clearance varies dramatically from one residue to the other even with the same scaffold !

FIH : SAD, MAD oral dosing in human healthy volunteers: exemplary pharmacokinetics PPAR α / γ co-agonist in T2D

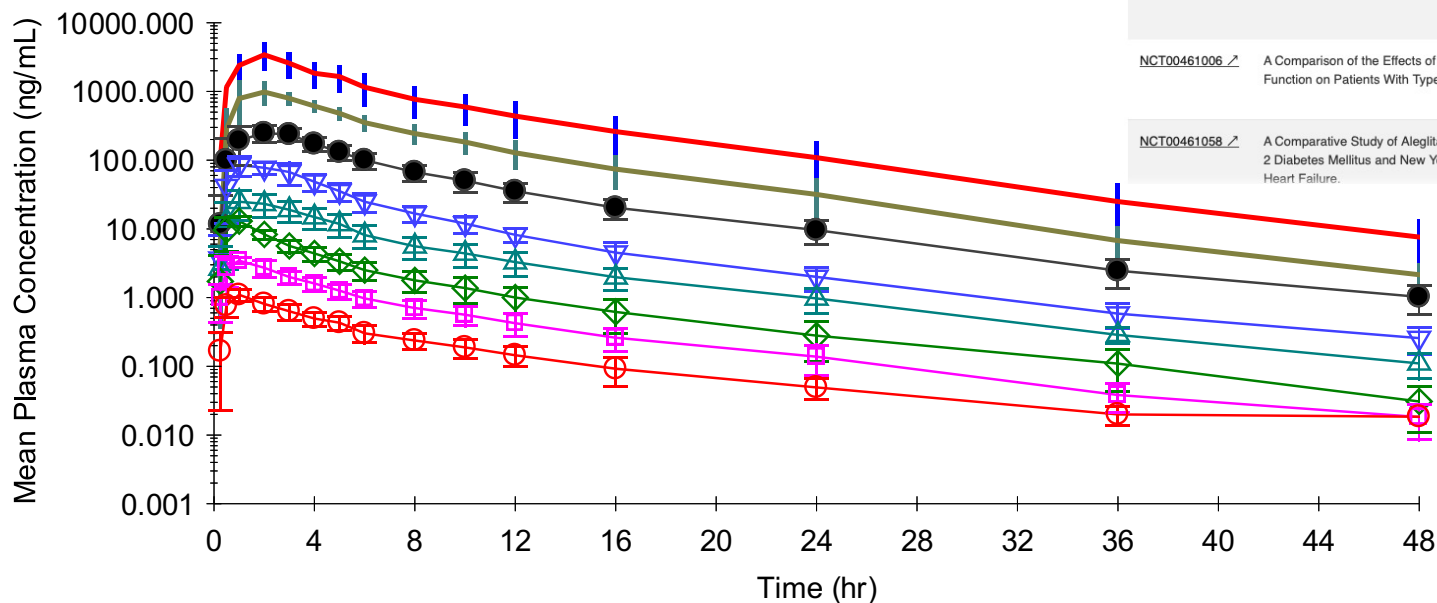


Mean (n=6) Plasma Concentration Time Profiles of RO0728804 (preliminary) by dose (0.01, 0.03, 0.1, 0.3, 1, 3, 10 and 30 mg)

PPAR α agonists in insulin sensitizing for T2D



Analyte=RO0728804

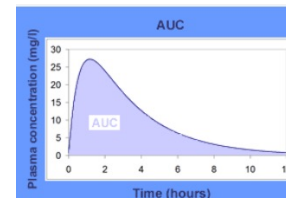


Show 10 entries

TRIAL ID	TITLE	STATUS	SPONSOR
NCT00388518	A Study of Alogliptaz in Patients With Type 2 Diabetes	Completed	Hoffmann-La Roche
NCT00461006	A Comparison of the Effects of Alogliptaz and Actos on Renal Function on Patients With Type 2 Diabetes.	Completed	Hoffmann-La Roche
NCT00461058	A Comparative Study of Alogliptaz and Actos in Patients With Type 2 Diabetes Mellitus and New York Heart Association (NYHA) Class II Heart Failure.	Completed	Hoffmann-La Roche



- No relevant deviation from oral dosing proportionality was evident for the exposure to **RO0728804** for doses ranging from 0.01 to 30 mg
- The inter-subject variability on C_{max} and AUC of analyte was low
- Best case scenario : NO ADR ! C_{max} and T_{max} dependent on clearance

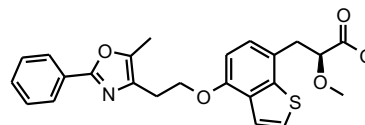
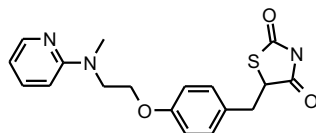


Case study: a balanced PPAR's agonist - the aleglitazar story



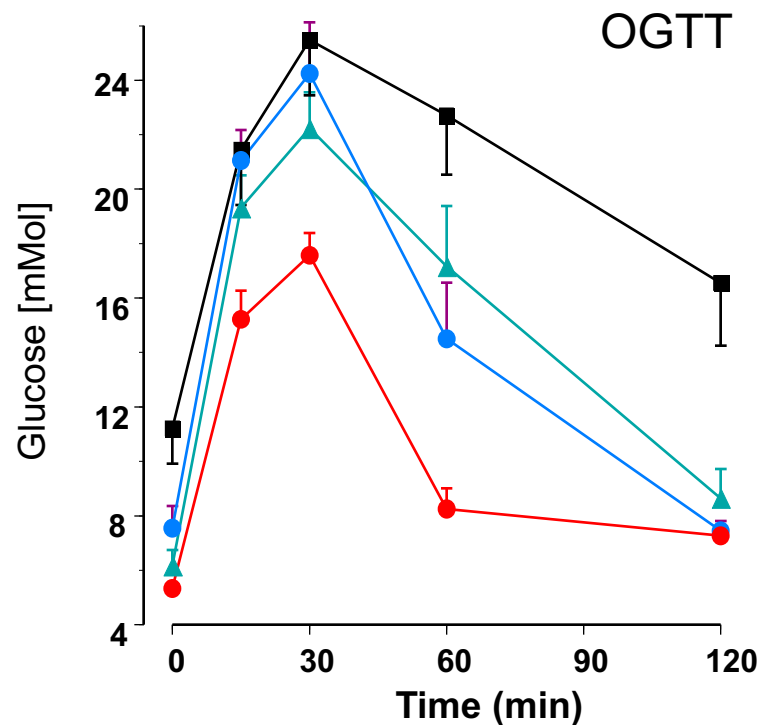
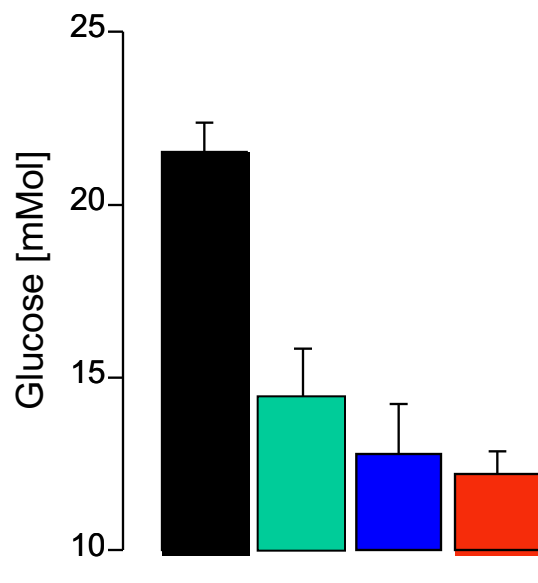
Treatment of db/db mice for 12 days

Rosiglitazone



Aleglitazar

non fasted glucose

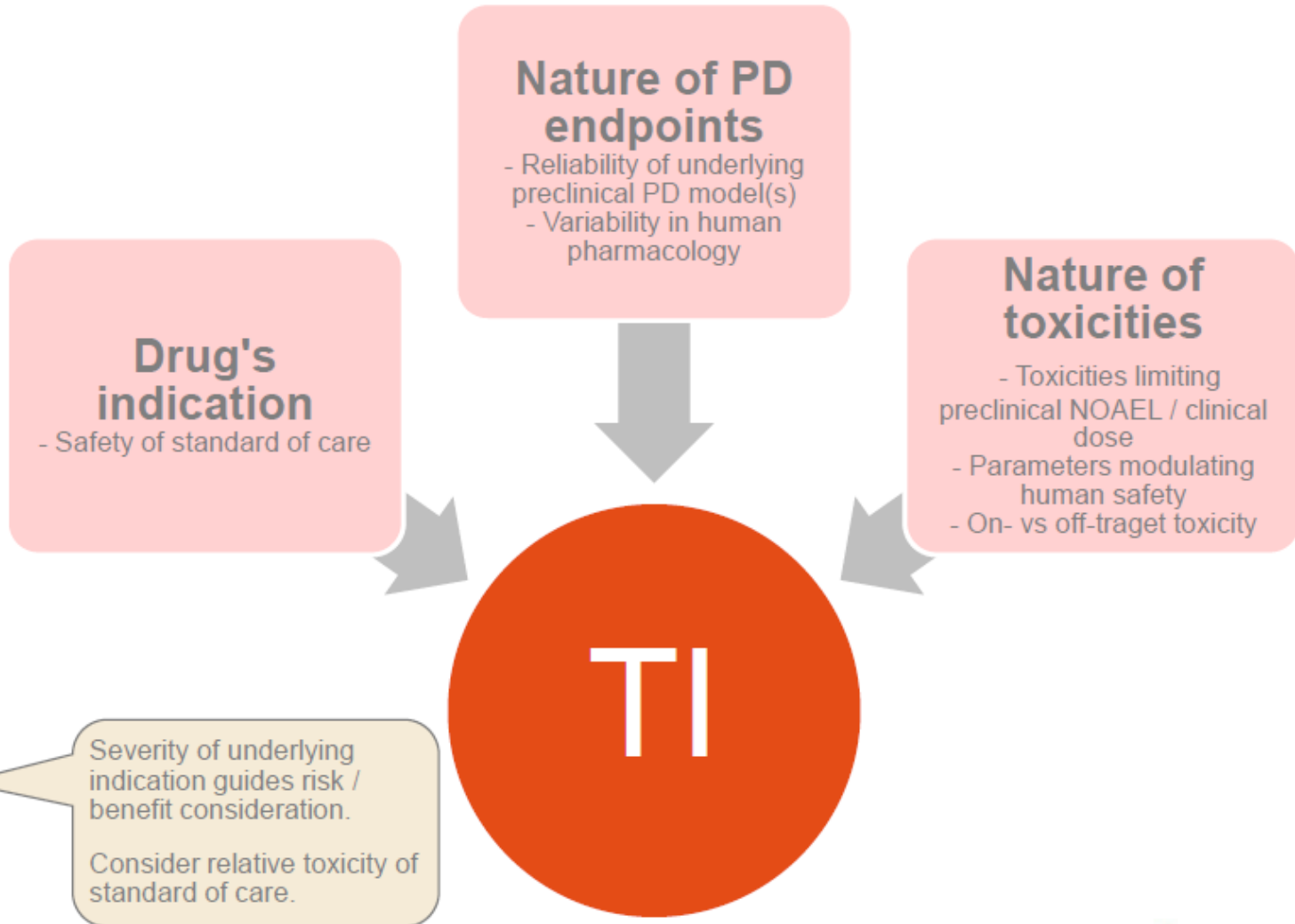


■ Placebo ■ RSG 3 mkd

■ RO072000 0.3 mkd

■ RO072001 3.0 mkd

Therapeutic index



Severity of underlying indication guides risk / benefit consideration.
Consider relative toxicity of standard of care.

Therapeutic index : numerical example



	Species	AUC _{total} [ng*hrs/mL]	TI _{tot}
Safety (NOAEL Exposure)	Dog	300	3
Efficacy (PD Exposure)	Rat	100	

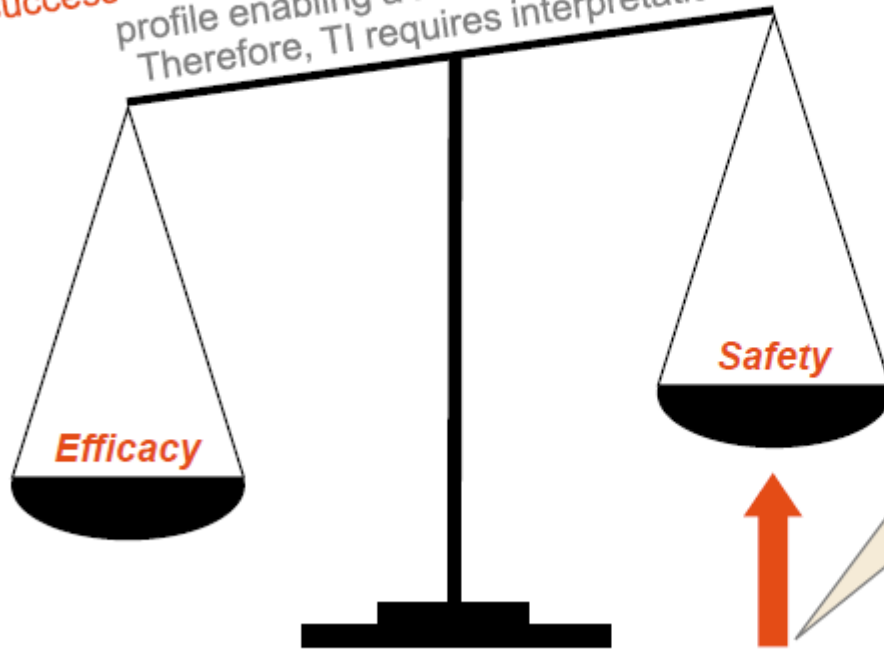
» 'Lower' TIs may be impacted considerably based on PPB

Low TI acceptable only for life threatening indication, TI highly depending on PBP !

Therapeutic index : paradigm in drug development



TI is an important parameter to estimate **probability of success** of a molecule re. its indication-specific safety profile enabling a risk benefit analysis. Therefore, TI requires interpretation !



Safety as success factor of a drug is a key differentiation criterion and competitive advantage based on changing societal, legal and regulatory expectations.



Therapeutic index is a concept in which you combine the early stage risk:benefit values of a medicine as early as possible in development, before late clinical trials as you do not want to wait for an expensive phase II/III.

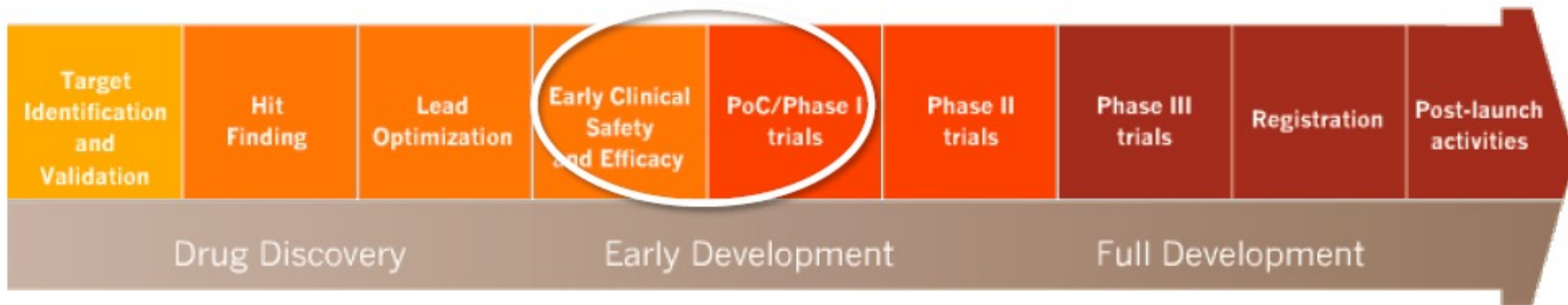
PHARMACOLOGY MEETS WITH TOXICOLOGY !



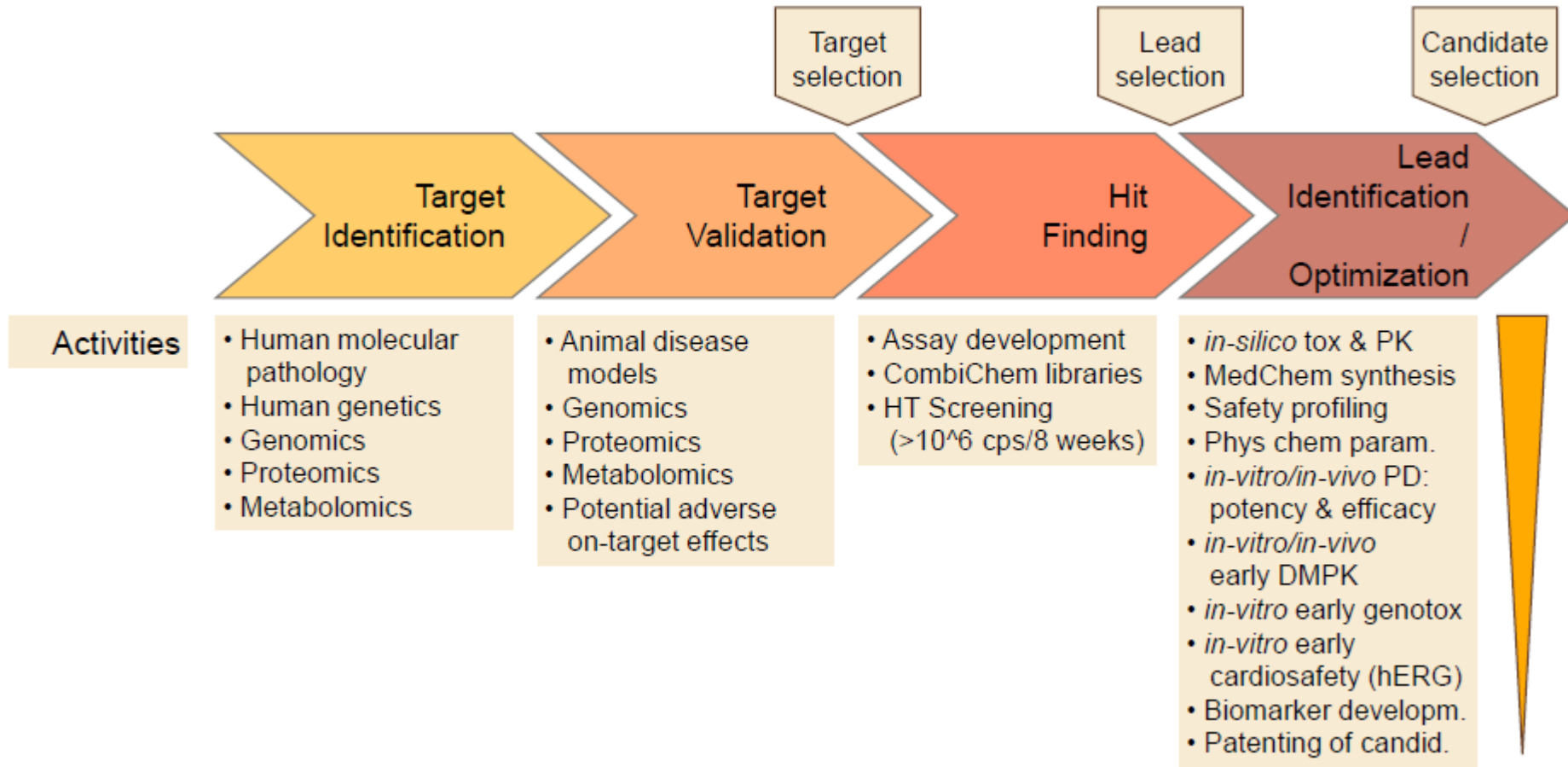
**ESTABLISHING THE INITIAL
SAFETY PROFILE FOR A
NOVEL MEDICINE
REQUIRES EXTENSIVE TOX
AND SAFETY
PHARMACOLOGY STUDIES
PERFORMED *IN SILICO*, *IN
VITRO* AND IN
PHARMACOLOGICAL
APPROPRIATE MODELS**

What makes FIH “first-in-human” clinical trials special ? first time ever !

- No human exposure data ! (PK, PD, safety, tolerability)
- Which dose ? Safety margin ? NOAEL !
- Which formulation ?
- Which go no go criteria to set further clinical trials ?



Key milestones in early development



Case study : cardio safety assessment



hERG test (arrhythmia, torsade de pointe / ECG)

<http://onlinelibrary.wiley.com/doi/10.1002/med.20019/abstract;jsessionid=040FBD5912CB94D08E4F006C161CDBB8.f03t01>

DESCRIBE HOW CARDIO SAFETY ASSESSMENTS ARE PERFORMED IN ORDER TO AVOID A CARDIAC DEATH OF A PATIENT

WORKSHOP

QT Prolongation Through hERG K⁺ Channel Blockade: Current Knowledge and Strategies for the Early Prediction During Drug Development

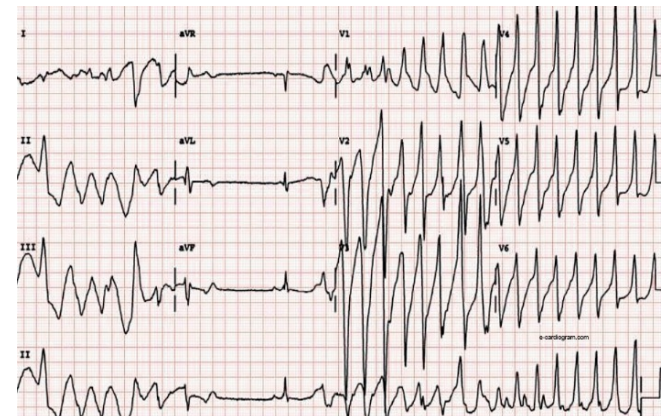
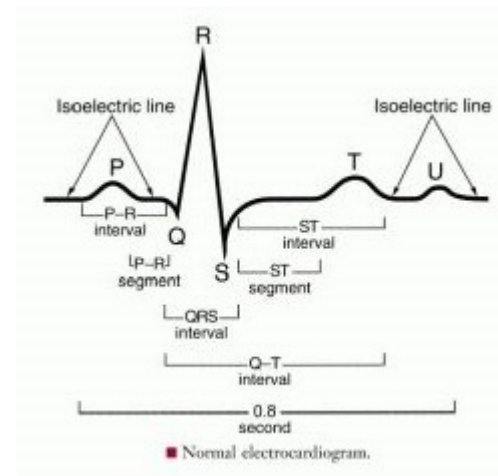
Maurizio Recanatini,¹ Elisabetta Poluzzi,² Matteo Masetti,¹
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¹Department of Pharmaceutical Sciences, Via Belmeloro 6, University of Bologna,
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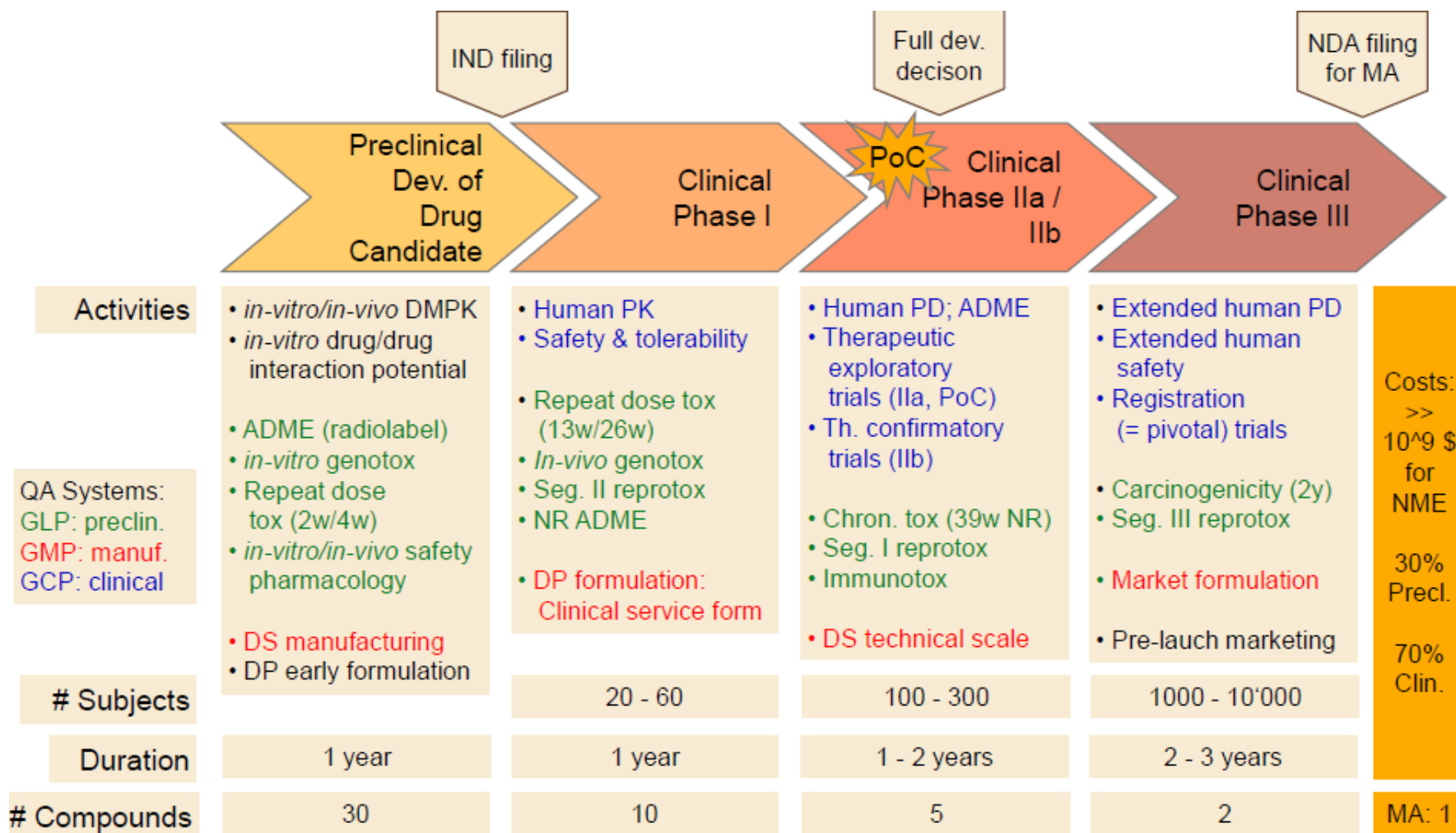
²Department of Pharmacology, Via Imerio 48, University of Bologna,
I-40126 Bologna, Italy

Published online 16 August 2004 in Wiley InterScience (www.interscience.wiley.com).
DOI 10.1002/med.20019

Abstract: Prolongation of the QT interval of the electrocardiogram is a typical effect of Class III antiarrhythmic drugs, achieved through blockade of potassium channels. In the past decade, evidence has accrued that several classes of drugs used for non-cardiovascular indications may prolong the QT interval with the same mechanism (namely, human ether-à-go-go-related gene



Preclinical Clinical pharmacology and drug selection in vitro and in vivo models





What is an IND? (investigational new drug application)

- Application to FDA to seek permission to test a new drug (or biologic) in human
- Notice of Claimed Investigational Exemption for a New Drug
- Usually starts with Phase I Study
- 21 CFR 312

CFR - Code of Federal Regulations Title 21

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U.S. FOOD & DRUG
ADMINISTRATION

INDs (investigational new drug application) : your ticket for first-entry-in human



U.S. Department of Health and Human Services

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Investigational New Drug (IND) Application

Emergency Investigational New Drug (EIND) Applications for Antiviral Products

IND Forms and Instructions

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Pre-IND Consultation Program

Regulatory Information for INDs

Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs)

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An Investigational New Drug Application (IND) is a request for Food and Drug Administration (FDA) authorization to administer an investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug that is not the subject of an approved new drug application.

IND regulations are contained in Title 21, Code of Federal Regulations, Part 312. Copies of the regulations, further guidance regarding IND procedures, and additional forms are available from the FDA Center for Drug Evaluation and Research, Drug Information Branch (HFD-210), 5600 Fishers Lane, Rockville, Maryland 20857, telephone (301) 827-4573 or toll free at 1-888-INFOFDA. In addition, forms, regulations, guidances, and a wide variety of additional information are available online on the FDA Web site.

The following instructions address only the administrative aspects of preparing and submitting an IND and are intended primarily to provide assistance to individual Sponsor-Investigator applicants, not pharmaceutical companies.

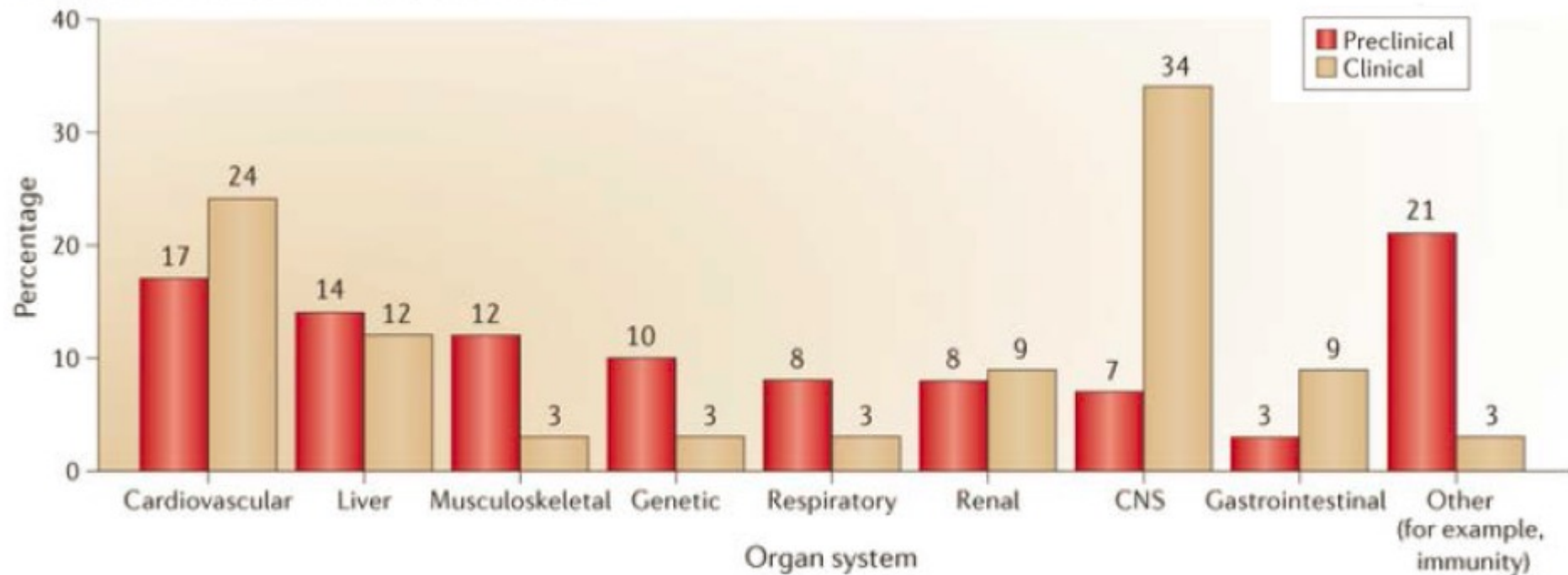
Form 1571: Investigational New Drug Application

- [Form FDA 1571 \(PDF - 221KB\)](#) [Form FDA 1571 Instructions](#)

Attrition rate at eg. Astra Zeneka portfolio 2005-2015



a Organ systems involved in safety failures





Drugs suspended from most but not all markets in the European Union and the United States

Drug name	Indication	Important ADRs
Alosetron (Lotronex)	Irritable bowel syndrome	Serious gastrointestinal events, especially ischemic colitis and constipation
Cisapride (Propulsid)	Gastroesophageal reflux disease	<u>Cardiovascular</u> (QT-interval prolongation, arrhythmias)
Phenylpropylamine (Proin)	Nasal decongestant, weight control	<u>Hemorrhagic stroke</u>
Sertindole (Serdolect)	Schizophrenia	<u>Cardiovascular</u> (QT-interval prolongation, potentially fatal arrhythmias)
Tolcapone (Tasmar)	Parkinson's disease	<u>Hepatic toxicity</u>
Trovafloxacin (Trovan)	Antibiotic	<u>Hepatic toxicity</u>



OFF target



ON target



WHAT HAPPENS WHEN A NEW MEDICINE INADVERTEDLY TARGETS UNWANTED PATHWAY/MOLECULES? CONSEQUENCES CAN BE FATAL UNLESS YOU CAN PREDICT/DETECT OFF TARGETS BEFORE ENTERING CLINICAL DEVELOPMENT !

“Cerep Eurofins” in vitro pharmacology_ ON vs OFF target



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Cell Based Phenotypic ▼

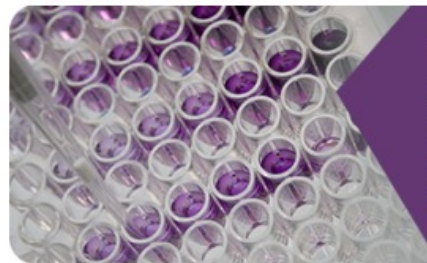
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Together with our customers, we're evolving the science of safety and liability testing, **providing thought leadership that advances adverse drug reaction research.**

Providing critical early assessment across a range of targets, our safety and liability service panels use a combination of functional and binding assays to empower you to make better decisions. When you know everything you can about your drug candidates, including potential off-target liabilities, you'll avoid costly setbacks and develop more promising compounds, faster.

Each of our safety and liabilities panels were specifically chosen for their relevance to critical diseases and biological processes, including neurotoxicity, cytotoxicity, cardiac function, immunoprotection, diabetes, inflammation, and gastrointestinal functions. These panels can provide early identification of potential adverse activity in order to help you optimize your drug's safety margins.

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Work with our partner lab, Pharmacology Discovery Services, for non-GLP safety and efficacy in vivo studies.



“Cerep Eurofins” comprehensive collection of in vitro pharmacology assays



FAMILY	ASSAY	Agonist radioligand ▼	REF.
■ GPCR			
ADENOSINE	A _{2A}	● 🧑	0004
ADRENERGIC	alpha _{1A}	🧑	2338
	alpha _{2A}	🧑	0013
	beta ₁	● 🧑	0018
	beta ₂	● 🧑	0020
CANNABINOID	CB ₁	● 🧑	0036
	CB ₂	● 🧑	0037
CHOLECYSTOKININ	CCK ₁ (CCK _A)	● 🧑	0039
DOPAMINE	D ₁	🧑	0044
	D _{2S}	● 🧑	1322
ENDOTHELIN	ET _A	● 🧑	0054
HISTAMINE	H ₁	🧑	0870
	H ₂	🧑	1208
MUSCARINIC	M ₁	🧑	0091
	M ₂	🧑	0093
	M ₃	🧑	0095
OPIOID & OPIOID-LIKE	delta ₂ (DOP)	● 🧑	0114
	kappa (KOP)	●	1971
	mu (MOP)	● 🧑	0118
SEROTONIN	5-HT _{1A}	● 🧑	0131
	5-HT _{1B}		0132
	5-HT _{2A}	● 🧑	0471
	5-HT _{2B}	● 🧑	1333
VASOPRESSIN	V _{1a}	● 🧑	0159
■ TRANSPORTERS			
DOPAMINE	dopamine transporter	🧑	0052

🧑 human 🕒 standard turnaround time

FAMILY	ASSAY	Agonist radioligand ▼	REF.
NOREPINEPHRINE	norepinephrine transporter	🧑	0355
SEROTONIN	5-HT transporter	🧑	0439
■ ION CHANNELS			
GABA CHANNELS	BZD (central)	●	0028
GLUTAMATE CHANNELS	NMDA		0066
NICOTINIC CHANNELS	N neuronal α4β2	● 🧑	3029
SEROTONIN CHANNELS	5-HT ₃	🧑	0411
Ca ²⁺ CHANNELS	Ca ²⁺ channel (L, dihydropyridine site)		0161
K ⁺ CHANNELS	hERG (membrane preparation)	🧑	1868
	K _v channel		0166
Na ⁺ CHANNELS	Na ⁺ channel (site 2)		0169
■ NUCLEAR RECEPTORS			
STEROID NUCLEAR RECEPTORS	AR	● 🧑	0933
	GR	● 🧑	0469
■ KINASES			
CTK	Lck kinase	🧑	2906
■ OTHER NON-KINASE ENZYMES			
AA METABOLISM	COX ₁	🧑	0726
	COX ₂	🧑	0727
MONOAMINE & NEUROTRANSMITTER	acetylcholinesterase	🧑	0363
	MAO-A		0443
PHOSPHODIESTERASES	PDE3A	🧑	2432
	PDE4D2	🧑	2434

TABLE 4

Broad Cerep screen undertaken to determine the pharmacological activity of fenobam

Target	% Control (10 μ M)	Target	% Control (10 μ M)
A ₁ (h)	89.9	Opiate (nonsel)	114.8
A _{2A} (h)	96.7	ORL1 (h)	101.4
A ₃ (h)	35.3	PCP	95.3
α_1 (nonsel)	103.3	P2X	108.5
α_2 (nonsel)	102.1	P2Y	95.8
β_1 (h)	95.9	5-HT (nonsel)	94.1
β_2 (h)	79.0	σ_1	88.2
AT ₁ (h)	91.2	σ_2	79.2
AT ₂ (h)	109.6	Glucocorticoid (h)	96.7
GABA _A -BZD	97.6	Estrogen (h)	100.2
B ₁	108.5	Progesterone (h)	105.8
B ₂ (h)	102.1	Androgen (h)	108.0
CB ₁ (h)	95.0	TRH	90.6
CB ₂ (h)	100.5	V ₁	103.7
CCK _A (h)	112.8	V ₂ (h)	109.4
CCK _B (h)	84.8	Ca ²⁺ L channel (DHP)	96.7
CRF ₁	106.9	Ca ²⁺ L channel (dilt)	104.6
D ₁ (h)	100.0	Ca ²⁺ L channel (verap)	150.9
D ₂ (h)	95.3	K ⁺ ATP channel	136
D ₃ (h)	100.6	K ⁺ V channel	103.6
D ₄ (h)	86.7	SK ⁺ Ca ²⁺ channel	97.9
ET _A (h)	93.3	Na ⁺ channel	88.9
ET _B (h)	85.1	Cl ⁻ channel	103.7
GABA (nonsel)	107.5	ADO transporter	99.6
AMPA	93.1	NE transporter (h)	99.9
Kainate	103.2	DA transporter (h)	98.2
NMDA	91.9	GABA transporter	104.7
Glycine (strych-sens)	126.2	Choline transporter	81.4
Glycine (strych-insens)	104.1	5-HT transporter (h)	101.2
H ₁	89.9	PDE I	100.3
H ₂	97.6	PDE II (h)	99.1
H ₃	89.8	PDE III (h)	95.9
I ₁	83.2	PDE IV (h)	93.4
I ₂	66.3	PDE V (h)	106.3
LTB ₄ (h)	99.0	PKC	96.0
LTD ₄ (h)	106.2	COMT	98.9
MC ₄ (h)	92.2	GABA transaminase	94.6
M (nonsel)	94.6	Glu. decarboxylase	105.7
NK ₁ (h)	102.2	MAO-A (h)	70.5
NK ₂ (h)	89.7	PNMT	88.9
NK ₃ (h)	104.1	TH	122.6
NPY (nonsel)	102.5	ATPase	97.4
N (neuronal)	119.4	Acetylcholinesterase (h)	98.5

h, human; nonsele, nonselective; NMDA, *N*-methyl-D-aspartate; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; PDE, phosphodiesterase; PKC, protein kinase C; PNMT, phenylethanolamine-*N*-methyltransferase; MAO-A, monoamine oxidase-A; COMT, catechol-*O*-methyl transferase; LTB, leukotriene B; LTD, leukotriene D; NPY, neuropeptide Y; ET, endothelin; CRF, corticotrophin-releasing factor; CCK, cholecystokinin; CB, cannabinoid; 5-HT, serotonin; TRH, thyrotrophin-releasing factor; DHP, dihydropyridine; ADO, adenosine; NE, norepinephrine; DA, dopamine; TH, tyrosine hydroxylase; Dilt, diltiazem; Verap, verapamil; PCP, phenylcyclidine; P2X, purinergic 2X; P2Y, purinergic 2Y; BZD, benzodiazepine.

OFF TARGET : EROFINS CEREP ! eg mGluR5 selective antagonist (anxiolytic)

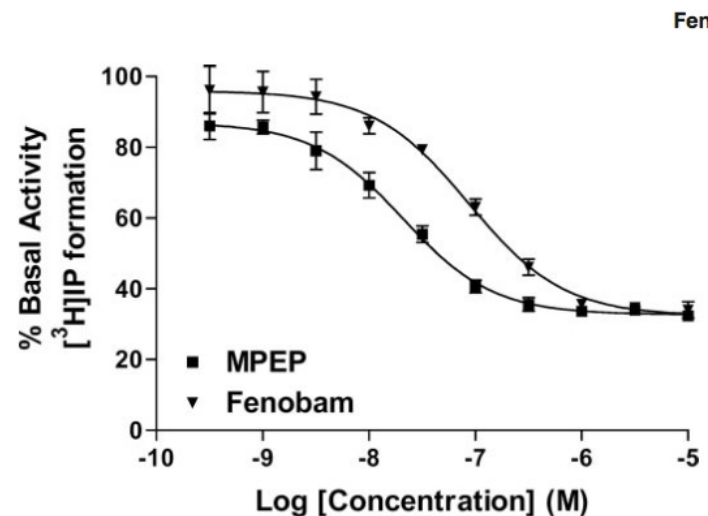
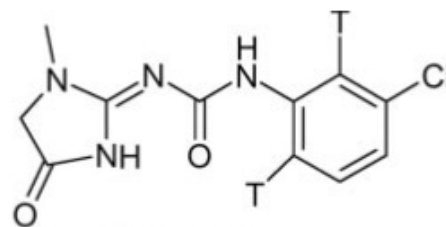


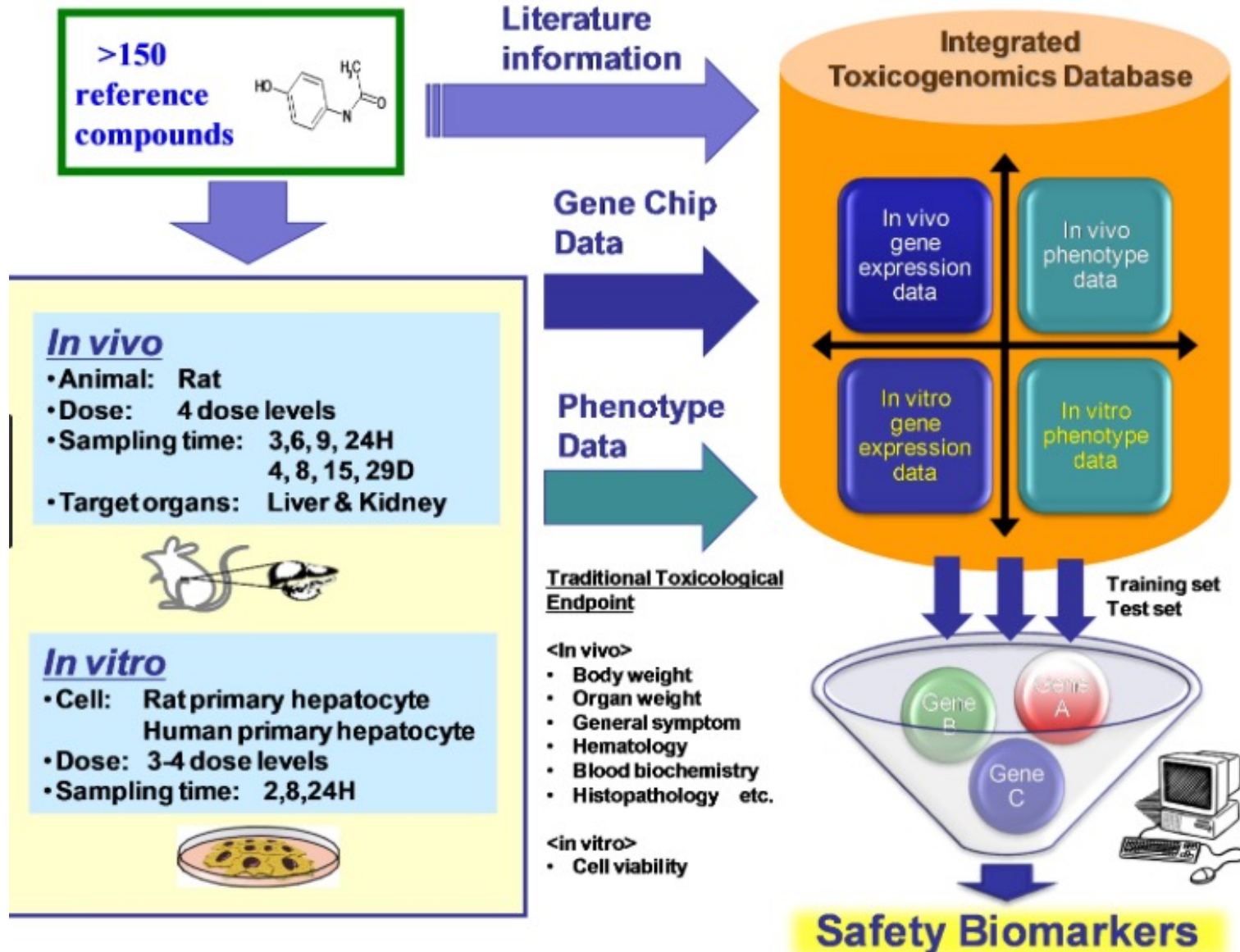
Fig. 5. Inhibition of mGlu5 basal activity by fenobam and MPEP. The



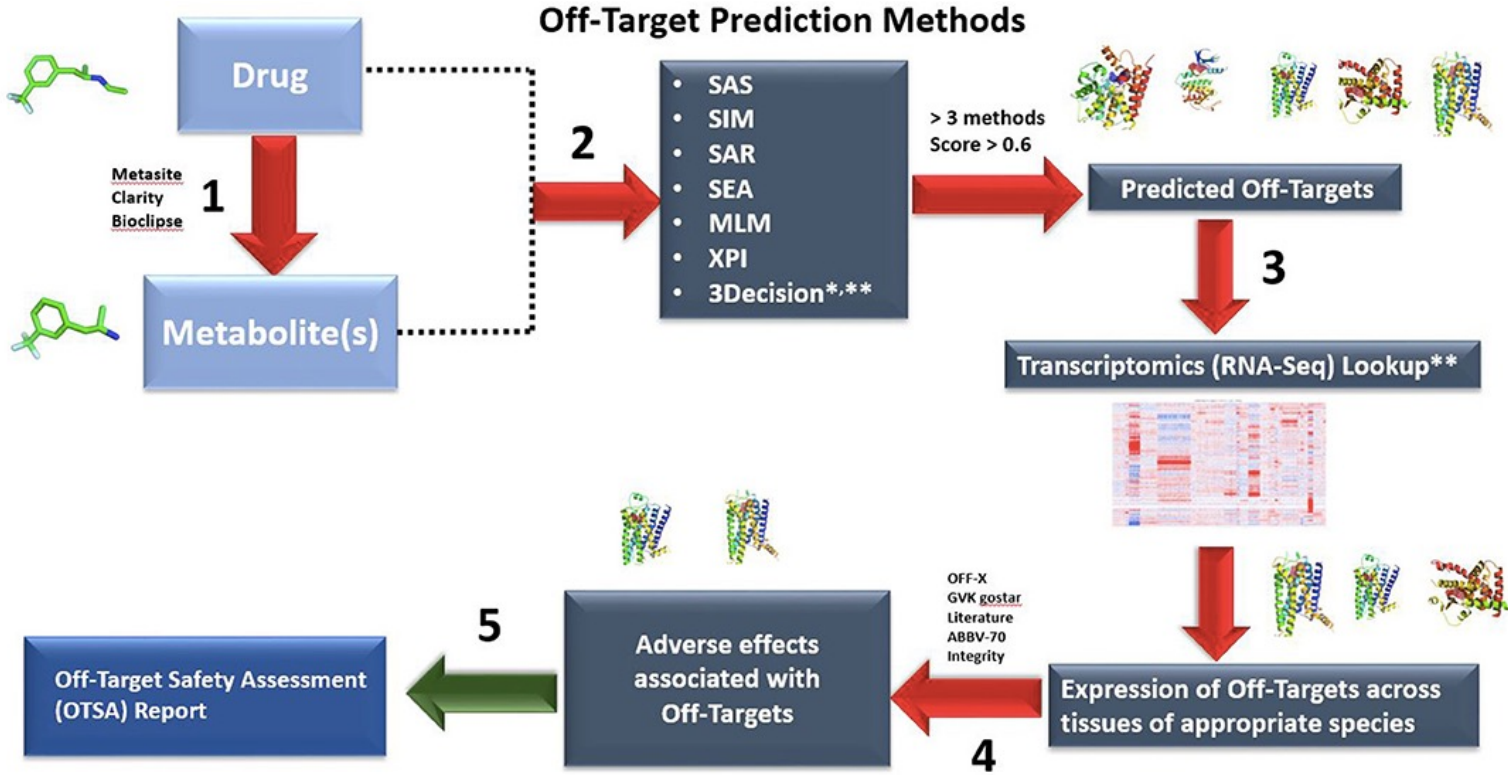
[³H]Fenobam

profile at Cerep (Paris, France) (www.cerep.fr). Fenobam was considered inactive (<50% activity at 10 μ M) at all targets tested with the exception of the adenosine A₃ receptor, where it caused a 65% displacement of specific binding at 10 μ M (Table 4).

The Making Of An Innovative Medicine: toxicogenomics



OFF TARGET : EROFINS CEREP !



* Not considered for scoring, ** Not used for assessing very large data sets such as approved and discontinued drug databases.

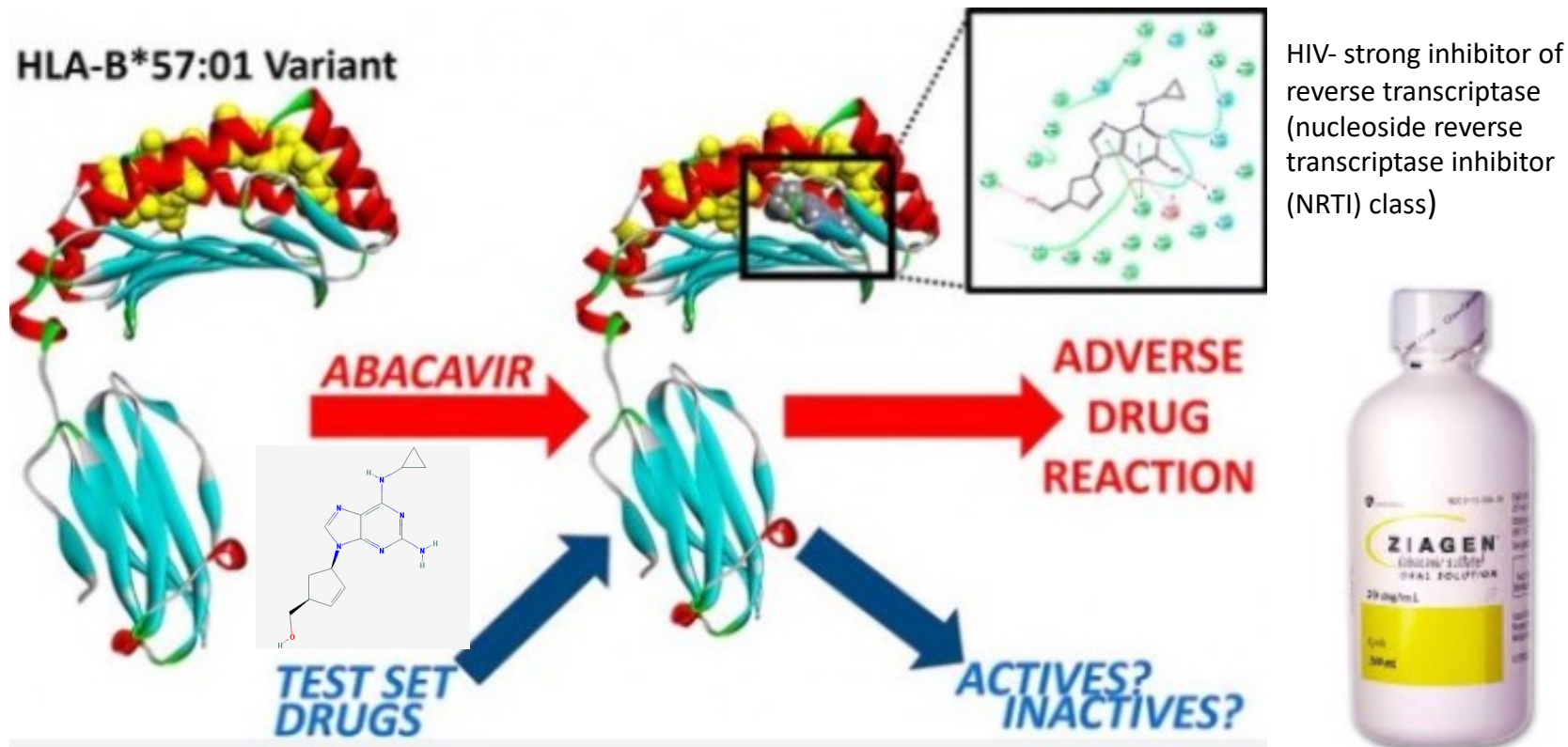


Modeling of drug adverse effects : *in silico* model of idiosyncratic reactions



HLAs (human leukocyte antigens) encode the MHC class I, II and III (major histocompatibility complex)

HLAs surface proteins are directly involved in idiosyncratic adverse drug reactions



NC State University researchers looked at what happens at the molecular level when abacavir interacts with a variant of a human leukocyte antigen known as HLA-B*57:01.

Abacavir (Ziagen): AIDS patients suffer from hypersensitivity reactions (off target)

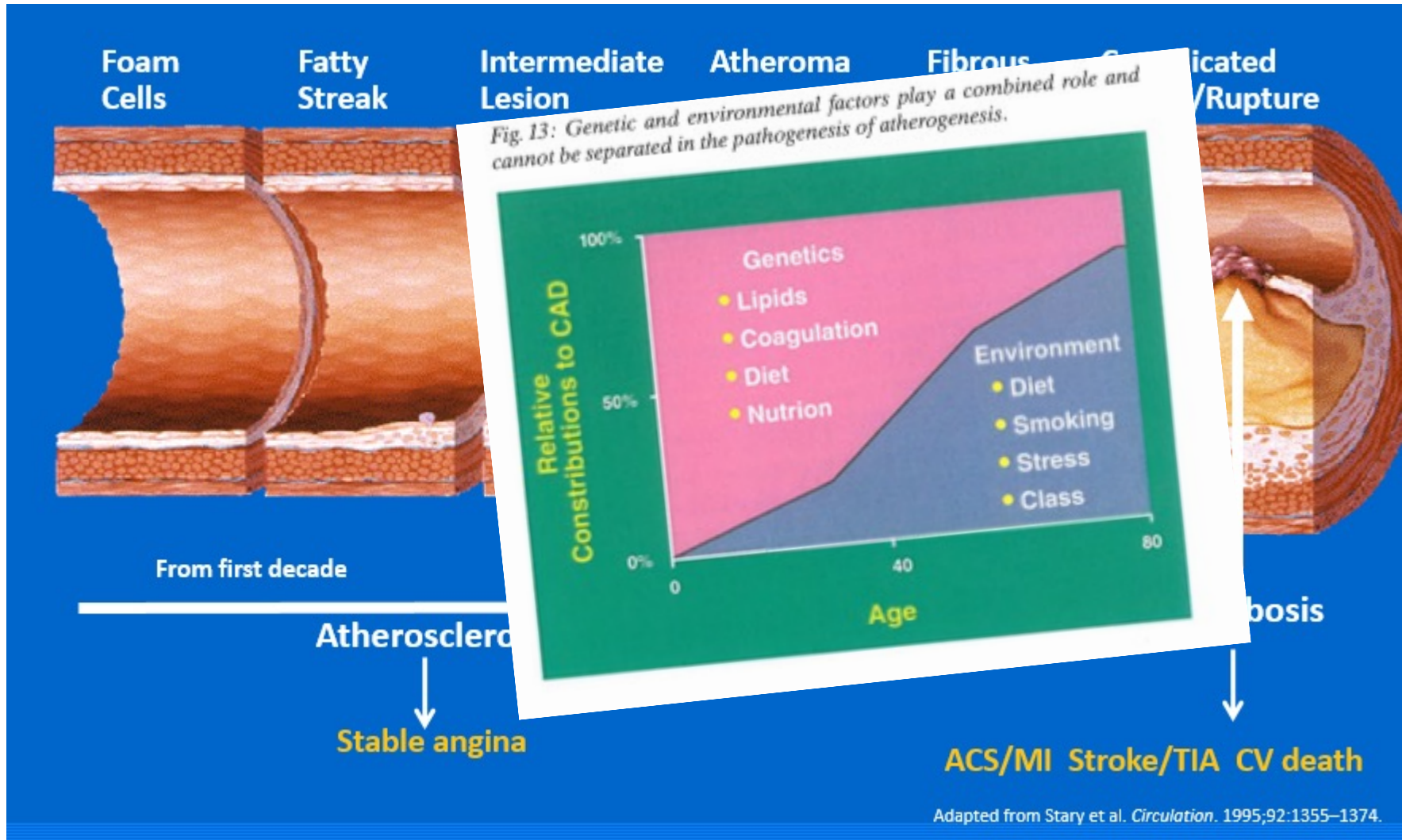
Credit: North Carolina State University

Van Den Driessche G, Fourches D (2017) J Cheminformatics 9: 1-17

Atheroma, thrombosis and acute coronary syndrome



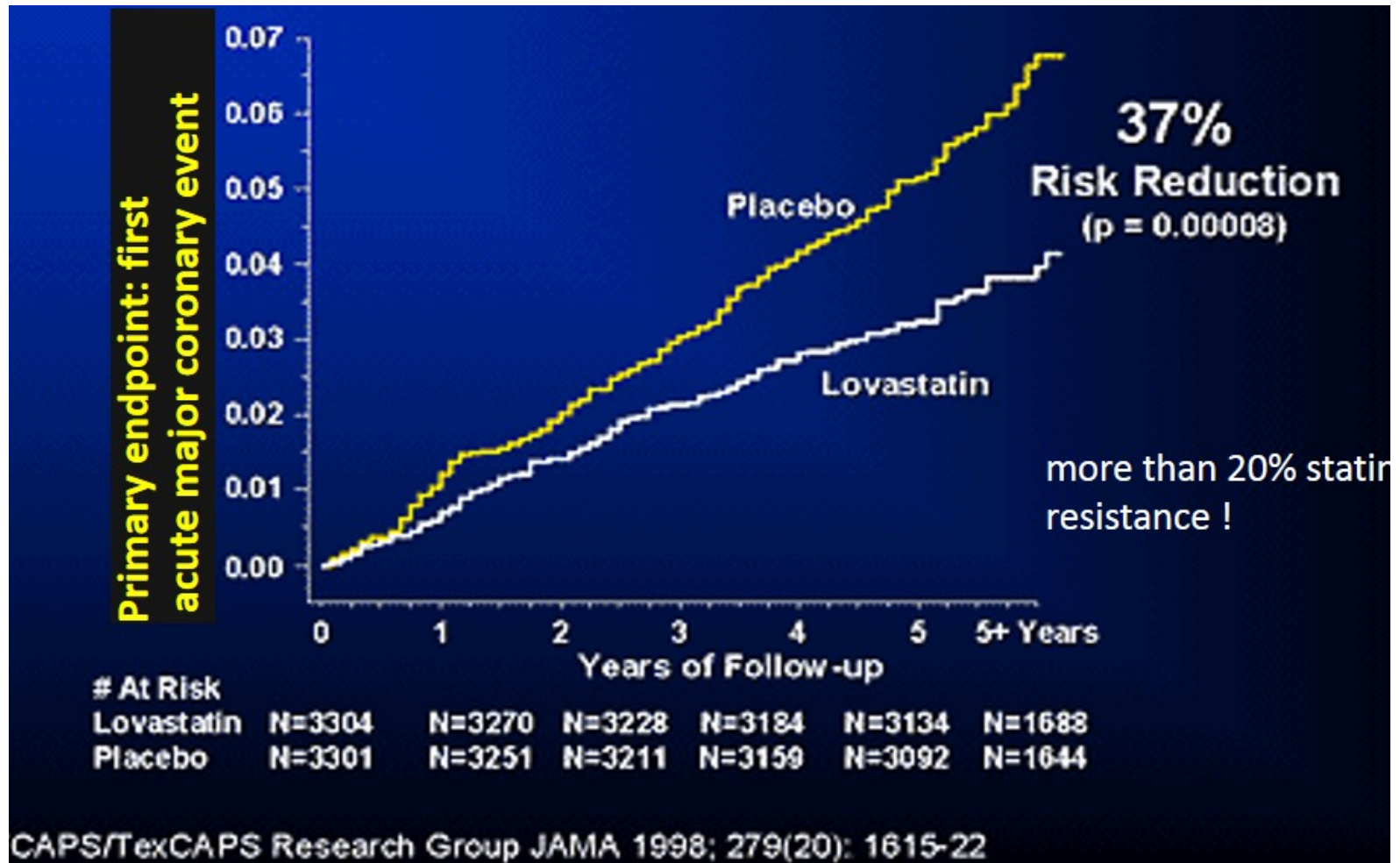
The CYP11B2 story and Torcetrapib



Reduction of LDL levels improves ACS endpoints



The CYP11B2 story and Torcetrapib



ABCA1 transporter mutations : Tangier Island USA



Tangier Island Maryland - USA



M. Teddy Laird Tangier USA

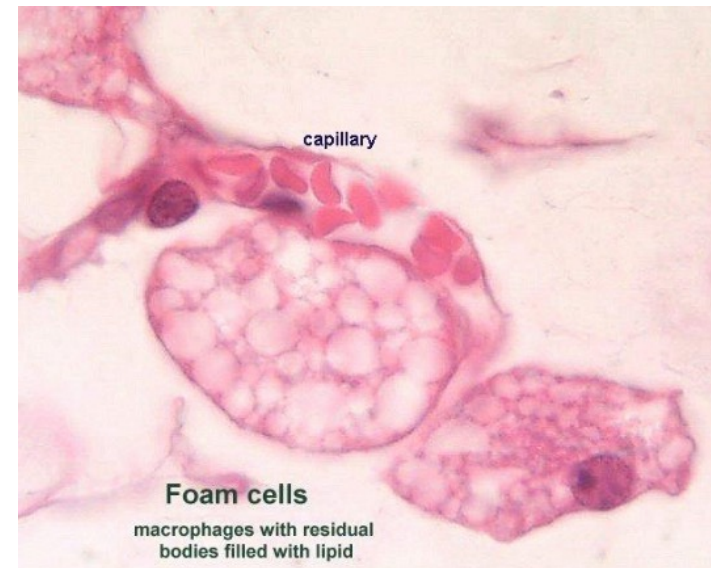
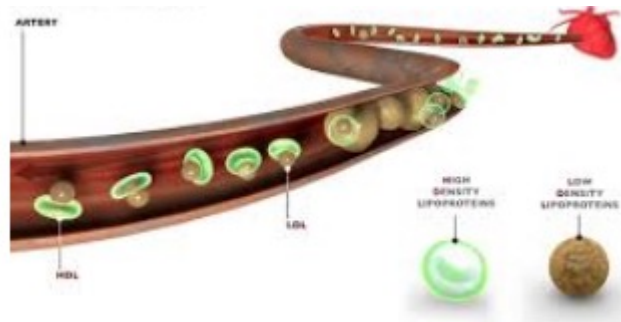
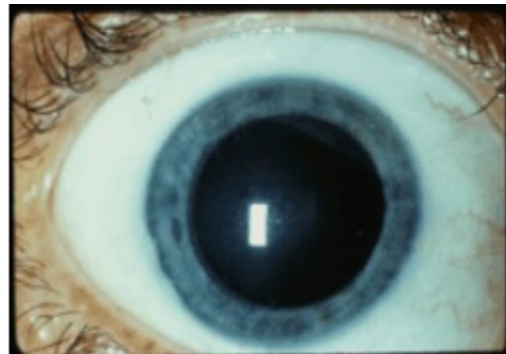
The CYP11B2 story

ABCA1 transporter mutations : Tangier Island MD USA



Mr Teddy Laird, origin from Tangier Island is in his 50's now. His health is deteriorating from "Tangier" disease; HIS DAD PASSED AWAY FROM TANGIER disease; his sister passed away from the disease. Each of the family member had issues due to the "Tangier" disease (hypercholesterolaemia)

Teddy's sister and investigation revealing an extremely high number of [foam cells](#) in not only the tonsils but a wide range of tissues including the bone marrow and spleen, a second trip to the island was made and the discovery was made of **very low HDL cholesterol** in both the sister and parents of Teddy, evidence for a genetic basis of the disease.





Tangier Disease (Familial High Density Lipoprotein Deficiency)*

Clinical and Genetic Features in Two Adults

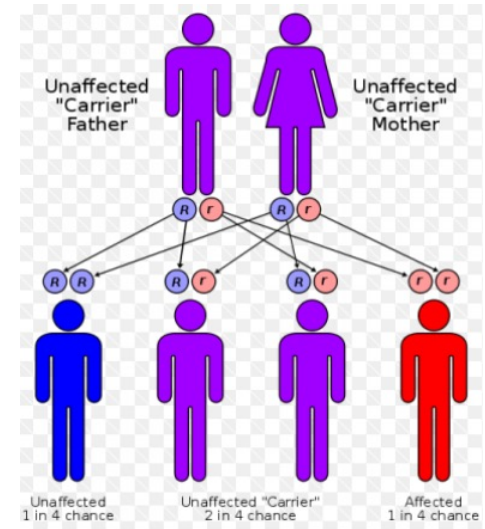
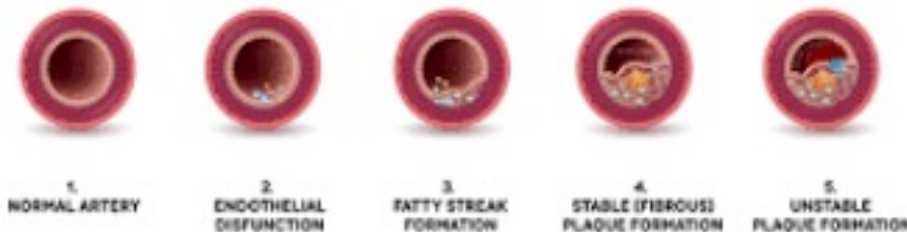
HARRY N. HOFFMAN, II, M.D. *and* DONALD S. FREDRICKSON, M.D.

Rochester, Minnesota

Bethesda, Maryland



Donald S. Fredrickson, MD;
photo courtesy of NIH.





Accurate Prediction of the Functional Significance of Single Nucleotide Polymorphisms and Mutations in the *ABCA1* Gene

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¹ Centre for Molecular Medicine and Therapeutics, Department of Medical Genetics, Child and Family Research Institute, University of British Columbia, Vancouver, British Columbia, ² Computational Biology, Applied Biosystems, Foster City, California, United States of America

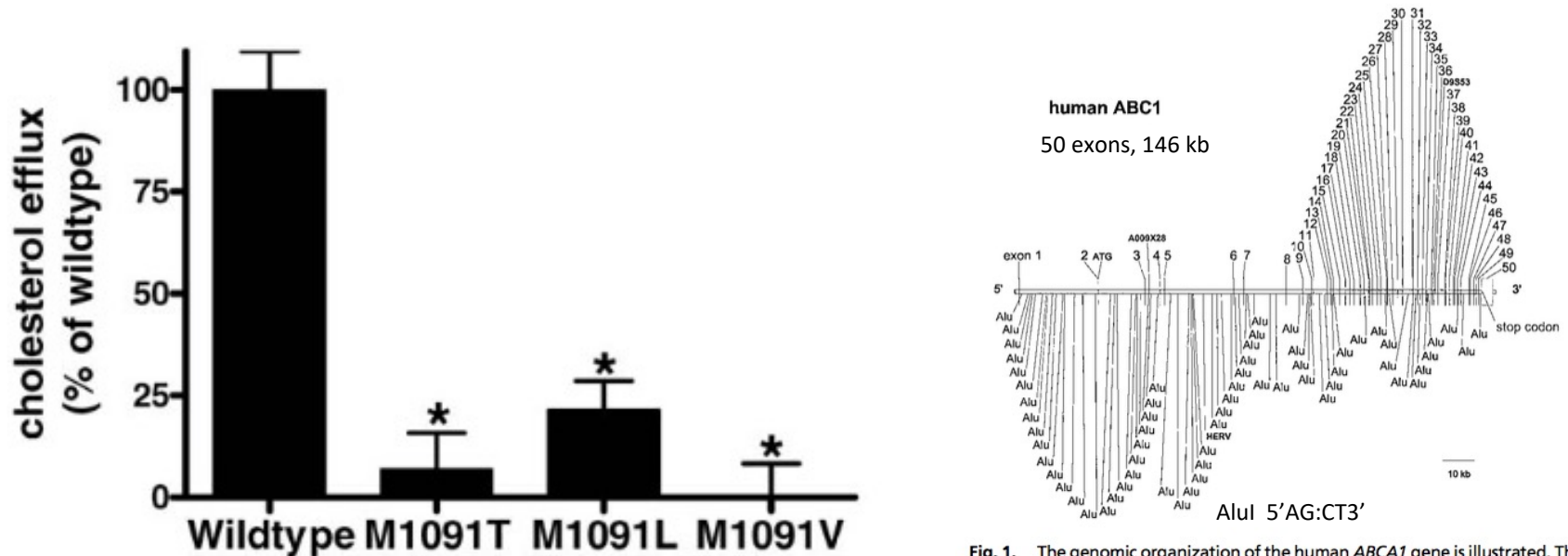
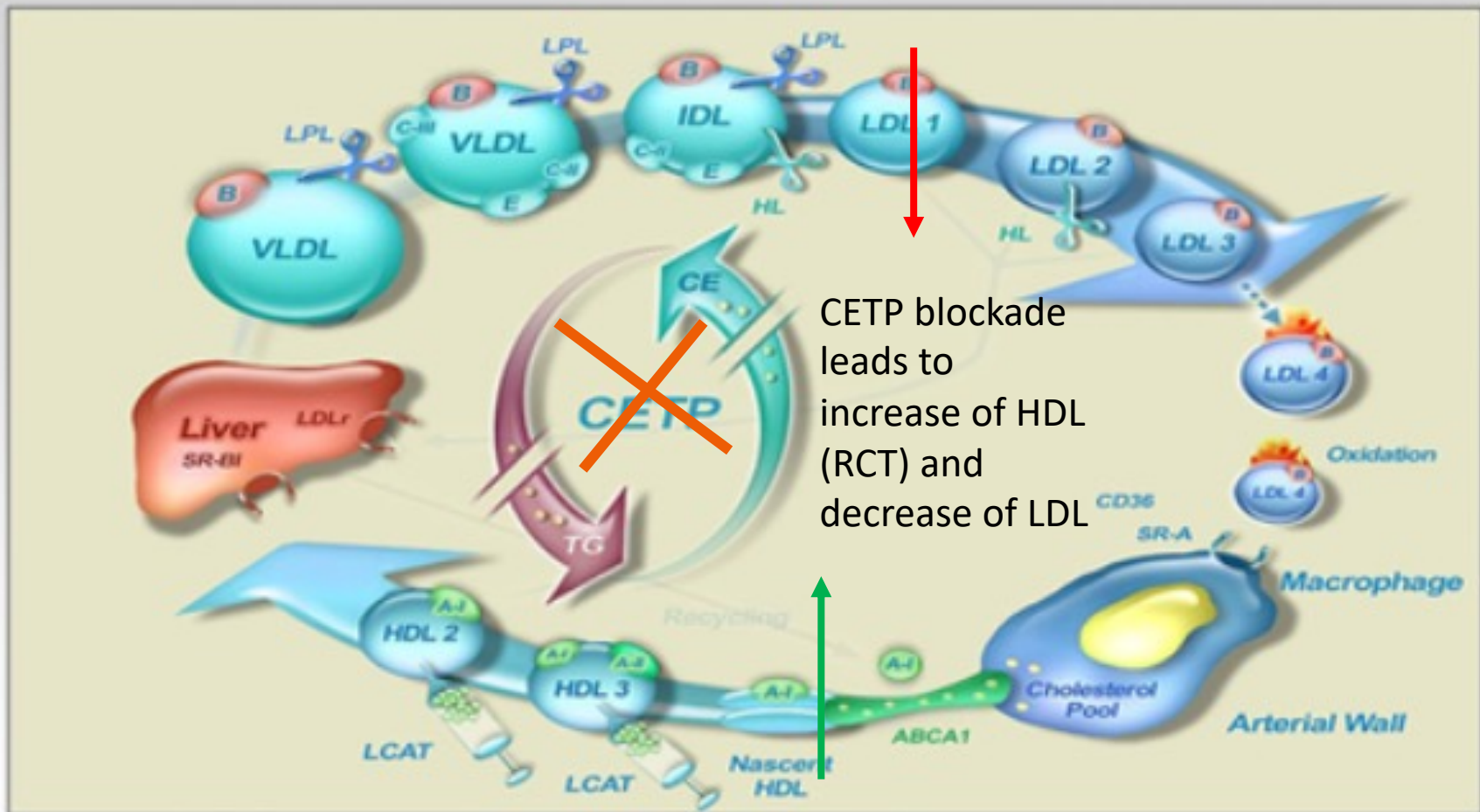


Fig. 1. The genomic organization of the human *ABCA1* gene is illustrated. The



The CYP11B2 story and Torcetrapib

Targeting CETP and the Lipoprotein Spectrum

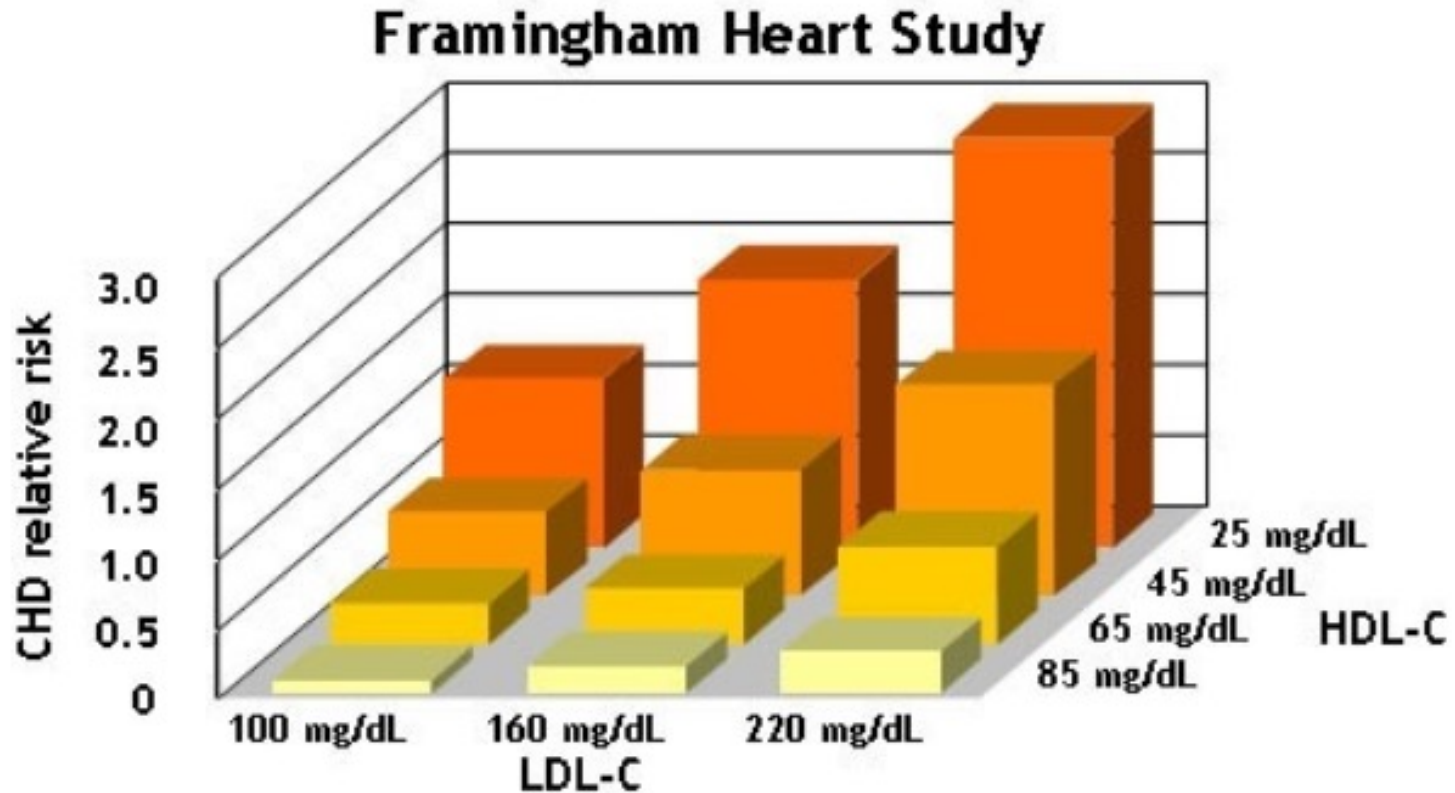


High HDL levels correlate with good CVD prognostics

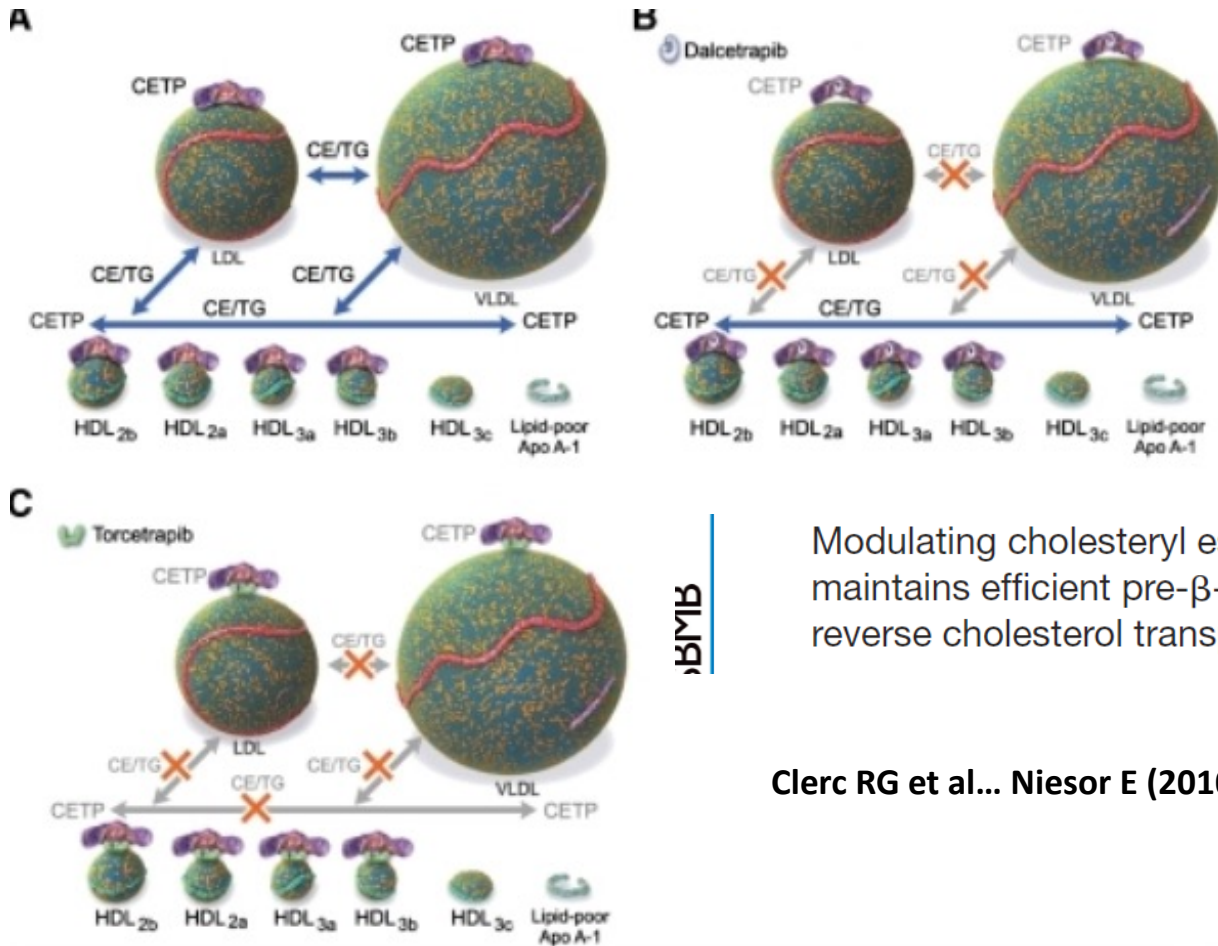


Screening cascade of cpds

The CYP11B2 story and Torcetrapib



The independent effect of raising HDL-C and lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined



BMB

Modulating cholesteryl ester transfer protein activity maintains efficient pre- β -HDL formation and increases reverse cholesterol transport^[3]

Clerc RG et al... Nisor E (2010) J. Lipid Research 12:3343-3354

Investigative toxicology _ a personal view

BMJ. 2006 Dec 16; 333(7581): 1237.


doi: [10.1136/bmj.39059.438044.DB](https://doi.org/10.1136/bmj.39059.438044.DB)

Pfizer stops clinical trials of heart

[Janice Hopkins Tanne](#)

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In December 2006, Pfizer announced that data from the ILLUMINATE trial showed that the combination of Lipitor plus torcetrapib was linked to a **60% increase in mortality rate and cardiovascular events** compared to Lipitor alone. Pfizer subsequently discontinued the development of the drug following recommendations from the Data Safety Monitoring Board which was supervising the study. Since December, Pfizer eliminated 10,000 jobs (10% of its work force) and faced a corporate shakeup with the ouster

Pfizer, the world's largest drug company, suddenly halted phase III clinical trials of torcetrapib on 2 December. Torcetrapib is a new agent that increases concentrations of “good” high density lipoprotein (HDL) cholesterol.

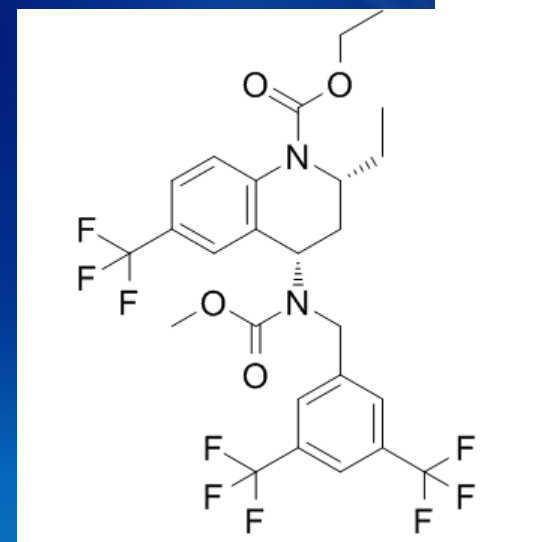
Pfizer said that “in the interests of patient safety” it was stopping the clinical trials of torcetrapib (called Illuminate) because the independent data safety monitoring board found more deaths and cardiovascular events in patients taking the drug. The trials included 7500 patients who were taking a combination of torcetrapib and atorvastatin (marketed as Lipitor) and 7500 patients who were taking atorvastatin alone. There were 82 deaths in the group taking the combination, compared with 51 in the group taking atorvastatin.

The trial investigators were instructed to tell patients to stop taking the combination, and Pfizer also notified the FDA.



Off-target effects of Torcetrapib

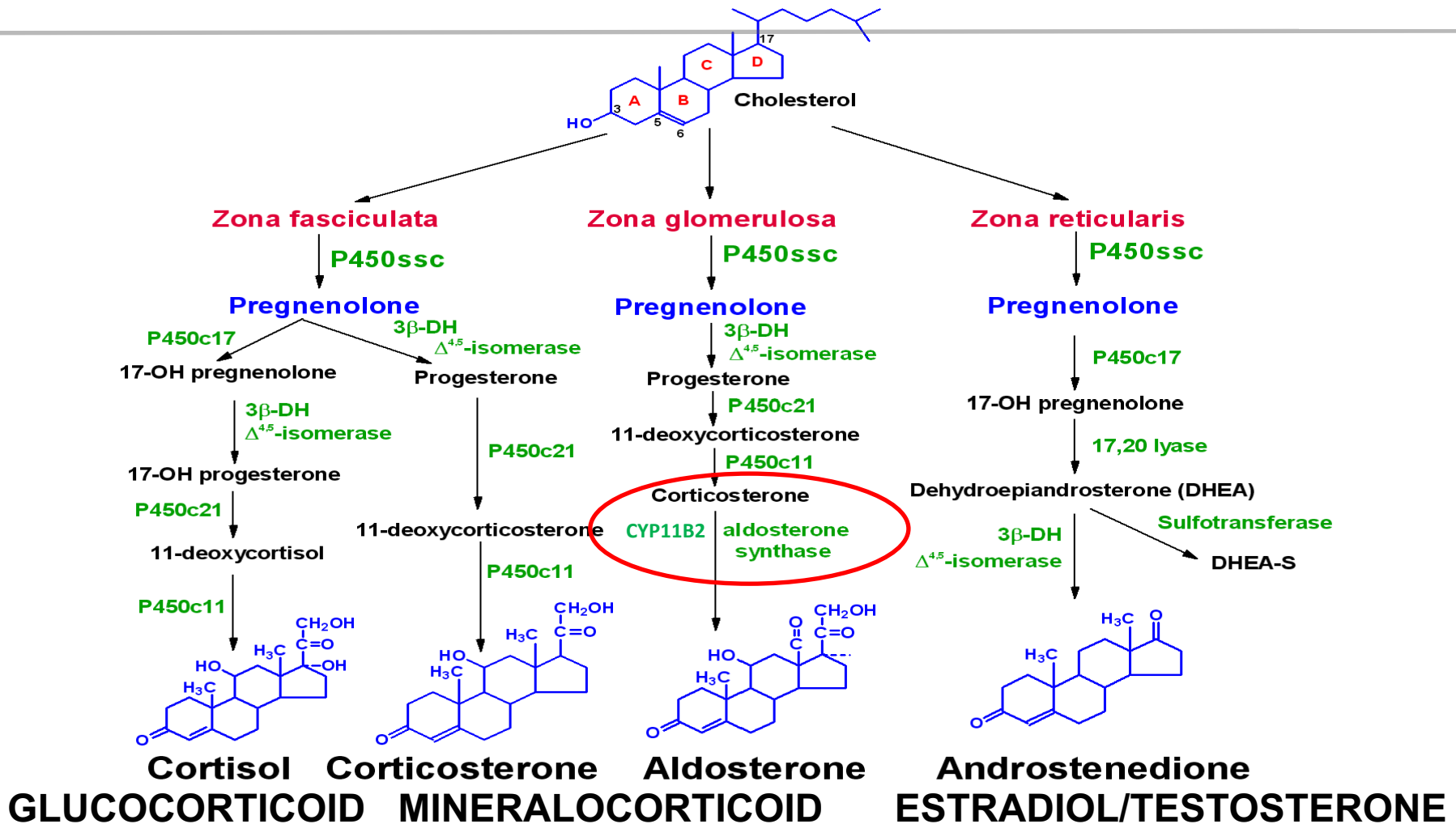
- increases aldosterone / cortisol
→ increases blood pressure
- reduces eNOS,
- increases ET-1
→ induces endothelial dysfunction



Other CETP inhibitors do not have these off-target effects

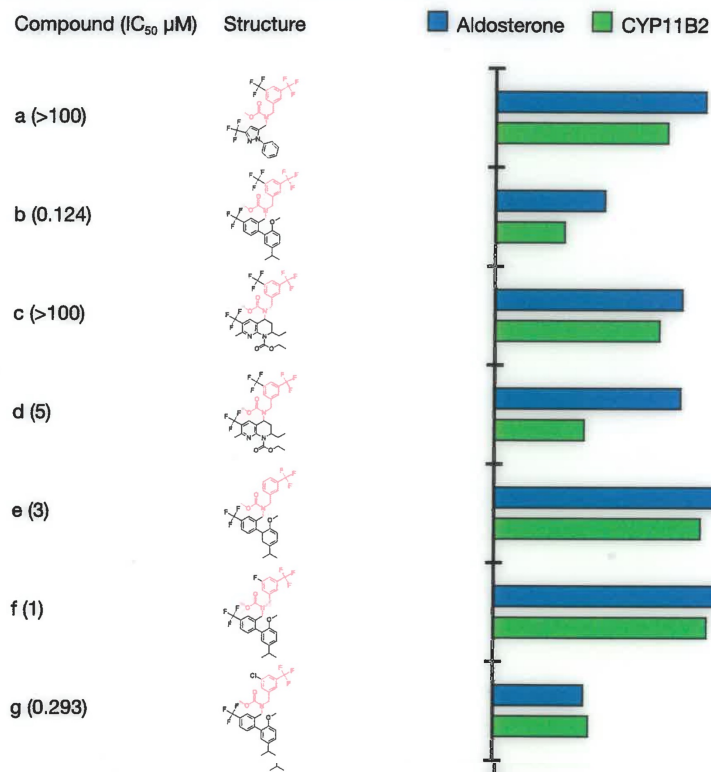
IS THIS ADVERSE TOXIC EFFECT A CETPi CLASS OR A CPD –SPECIFIC OFF TARGET EFFECT??

Steroids and the Adrenal Cortex

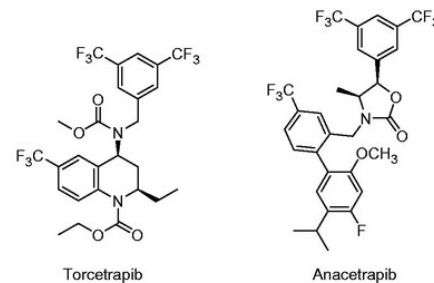
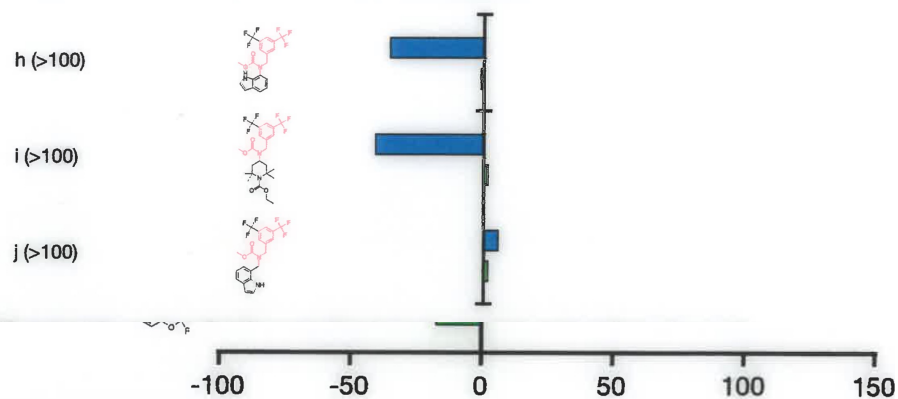


The adrenal cortex is responsible for production of 3 major classes of steroid hormones: glucocorticoids, which regulate carbohydrate metabolism; mineralocorticoids, which regulate the body levels of sodium and potassium; and androgens, whose actions are similar to that of steroids produced by the male gonads

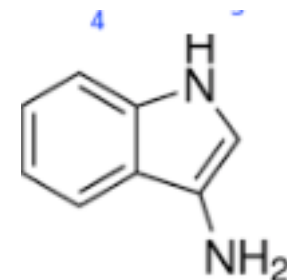
1a. Compounds with methyl-(3-trifluoromethyl-benzyl)-carbamic acid methyl ester motif of torcetrapib (IN RED COLOUR) attached to a suitable THQ-replacement



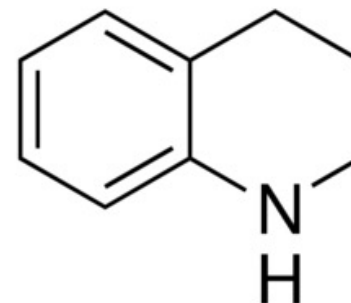
1b. Compounds with methyl-(3-trifluoromethyl-benzyl)-carbamic acid methyl ester motif of torcetrapib (IN RED COLOUR) but no suitable THQ-replacement



An example of assay read out and medicinal chemistry MDO



Composé organique



T15504 ALDRICH
1,2,3,4-Tetrahydroquinoline
98%
Synonym: THQ

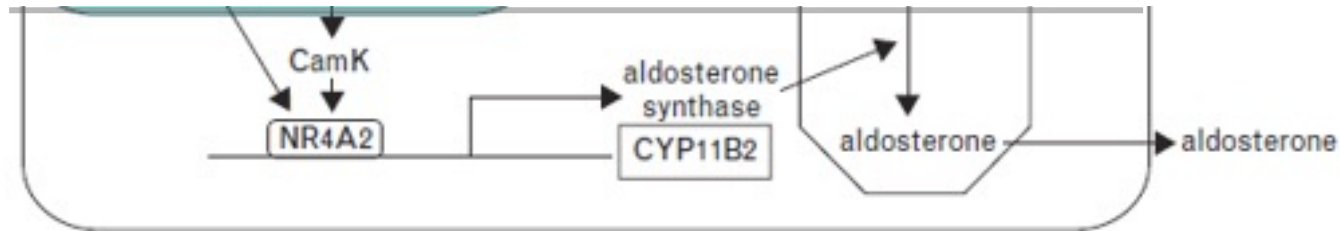
IC₅₀ of CETP activity determined using a scintillation proximity assay. nd, not determined (benzoic acid derivative).

Clerc RG. and Niesor EJ. (2012) American Heart Association Washington, DC

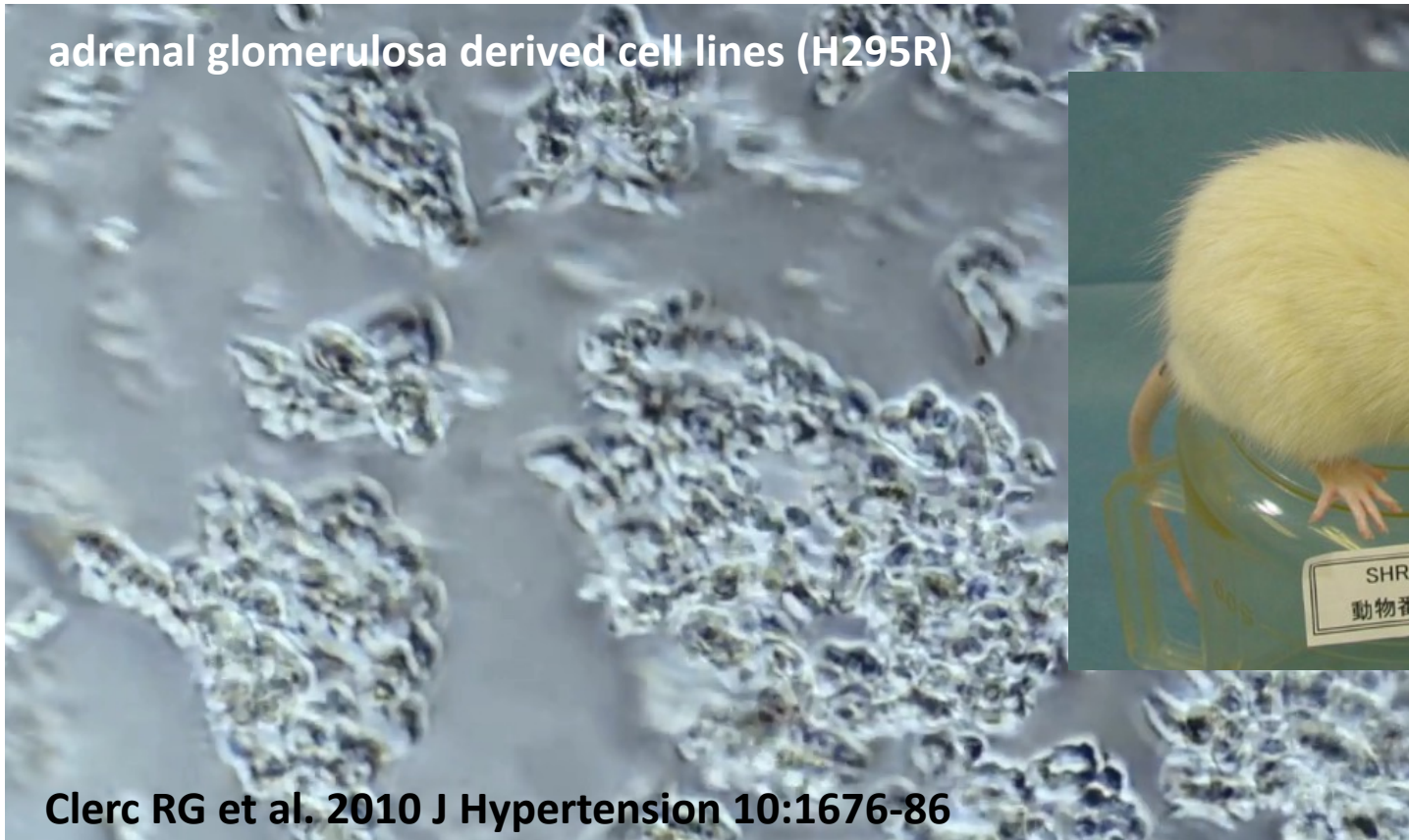
Investigative toxicology _CETPi Torcetrapib but not Dalcetrapib did increase aldosterone synthesis CYP11B2 synthase and blood pressure in SHR

Screening cascade of cpds targeting the aldosterone synthase

eg. H295R adrenal glomerulosa derived cell line and SHR hypertensive rats

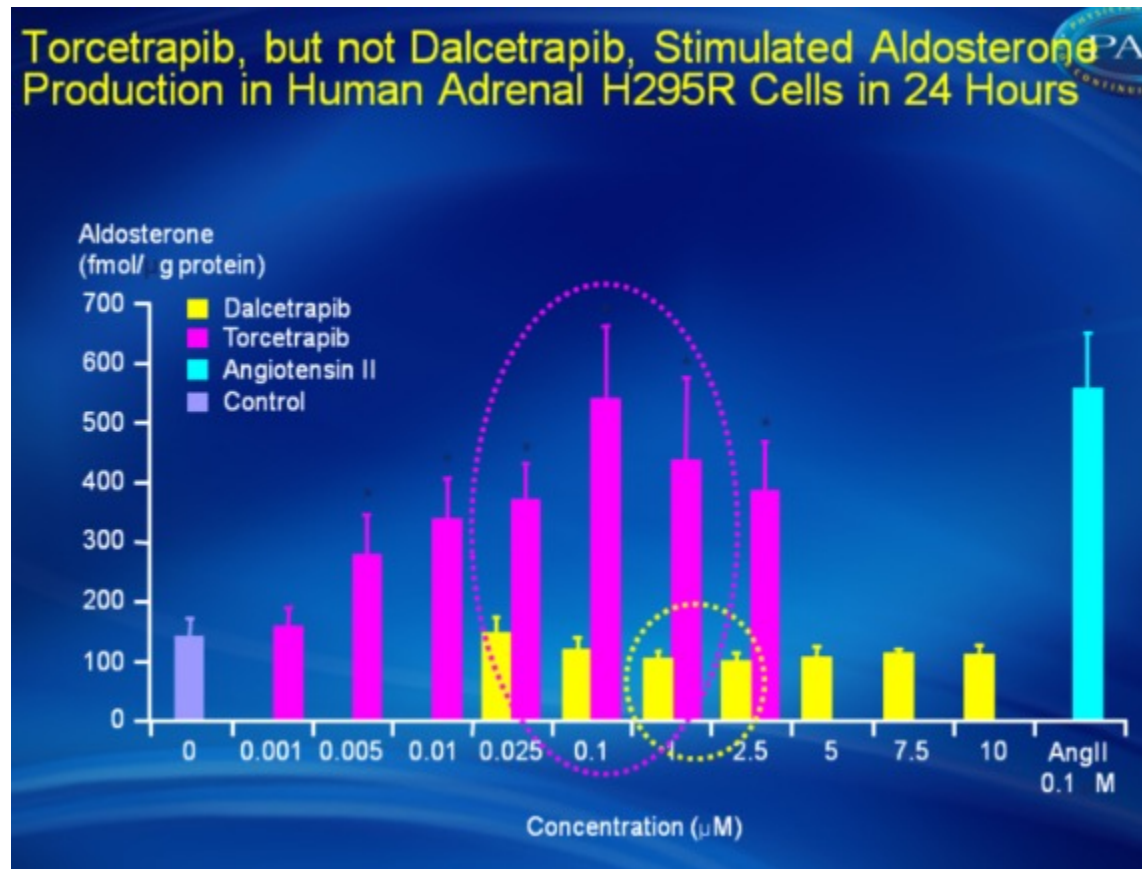


adrenal glomerulosa derived cell lines (H295R)





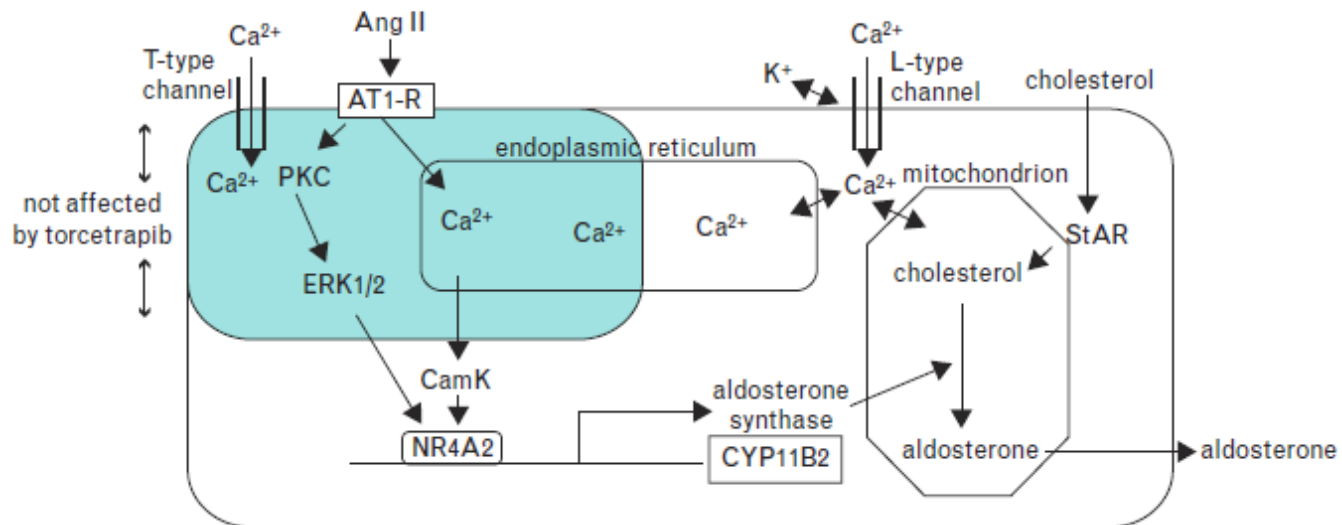
The CYP11B2 dramatically activated by Torcetrapib but not Dalcetrapib





The CYP11B2 story and Torcetrapib Adrenal hormone biosynthesis

Fig. 7



Flow diagram to indicate putative site of action of torcetrapib on the angiotensin II/aldosterone pathway. Ang II, angiotensin II; AT1-R, Ang II type 1 receptor; CYP11B2, cytochrome P450 subunit 11B2; ERK, extracellular signal-regulated kinase; NR4A2, orphan nuclear hormone receptor; PKC, protein kinase C; StAR, steroidogenic acute regulatory protein.



Pharmakonzern Johnson & Johnson zu Milliardenstrafe verurteilt

13.07.18 15:48

Neue Zürcher Zeitung

Milliardenstrafe für Pharmakonzern Johnson & Johnson

22 an Eierstockkrebs leidende Frauen hatten gegen den amerikanischen Konzern geklagt. Sie machen Puderprodukte für ihre Erkrankungen verantwortlich und werfen dem Unternehmen vor, Gefahren verschwiegen zu haben.

13.7.2018, 04:14 Uhr

(Reuters/dpa) Der amerikanische Pharma- und Konsumgüterkonzern Johnson & Johnson (J&J) ist zu einer Milliardenstrafe verurteilt worden, weil bestimmte Körperpflegeprodukte Krebs verursacht haben sollen. Beim Prozess in St. Louis im amerikanischen Gliedstaat Missouri befand die Jury J&J einstimmig für schuldig und ordnete Schadenersatz- und Strafzahlungen in Höhe von insgesamt 4,7 Milliarden \$ (umgerechnet 4,0 Mrd. €) an.

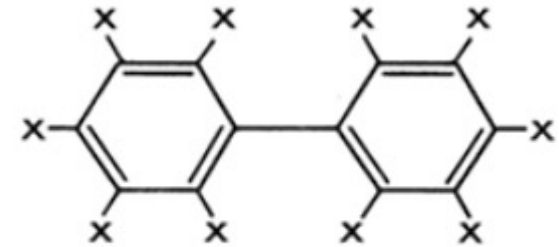
Die Milliardensumme setzt sich aus 550 Mio. \$ Entschädigung und einer Strafe von 4,14 Mrd. \$ zusammen. Als Reaktion fielen die J&J-Aktien im nachbörslichen Handel um 1%. J&J äusserte sich über das Urteil enttäuscht und kündigte rechtliche Schritte an. Das Verfahren sei hochgradig unfair gewesen. Der Konzern bekräftigte, seine Produkte enthielten kein Asbest und lösten kein Krebs aus.

**WHY SAFETY IS
IMPORTANT IN
PHARMA ?
HOW SERIOUS CAN
CLASS ACTION BE ?**



Endocrine disruptors and the CYP11B2 nanomolar affinities Adrenal hormone biosynthesis

PCBs, Dioxins are very stable chemical entities hence invading the entire food chain



POLYCHLORINATED BIPHENYLS (PCB's)

Phthalates mainly used as plastic softener are very stable chemical entities hence invading the entire food chain

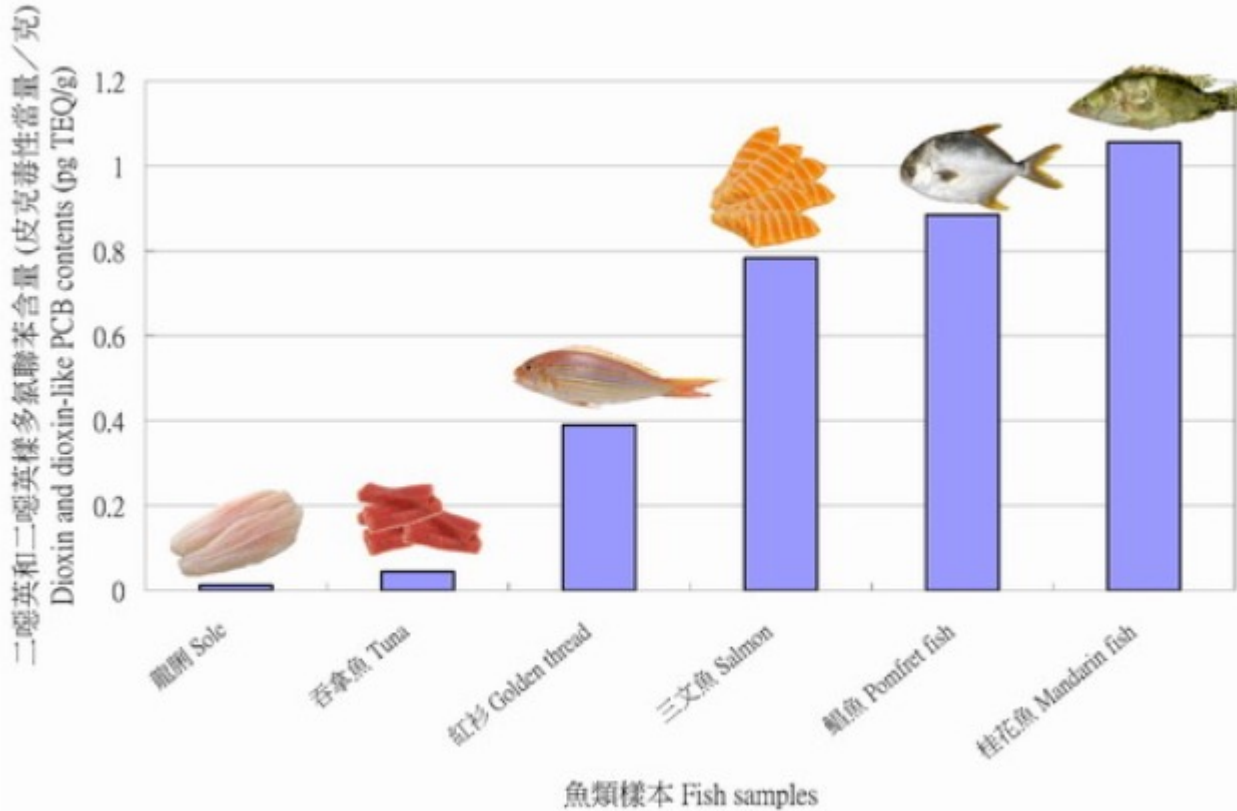
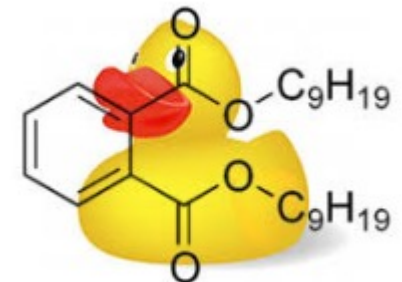


Figure 1. Dioxin and dioxin-like PCB contents among various fish

Reproductive investigative toxicology _ endocrine disruptors : decrease in ano genital distance in boys exposed prenatal to PCBs



**Endocrine disruptors and the
CYP11B2 nanomolar affinities
Adrenal hormone biosynthesis**



Phthalates are very stable chemical entities hence invading the entire food chain (PLASTIC SOFTENER)

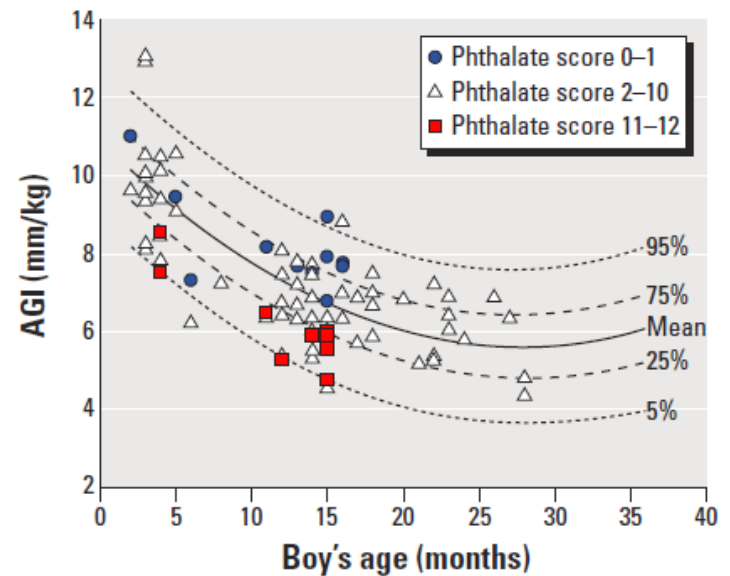
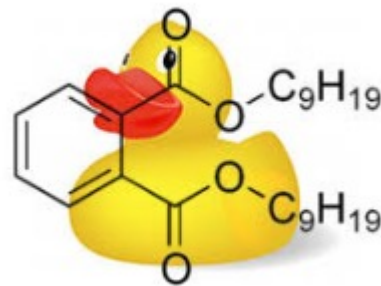
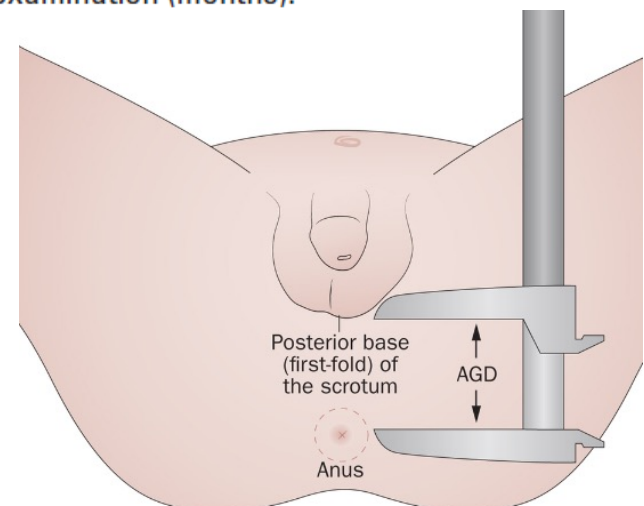
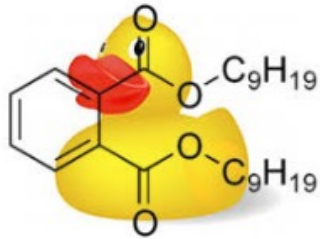


Figure 1. Mean AGI (mm/kg) in relation to boys' age at examination (months).

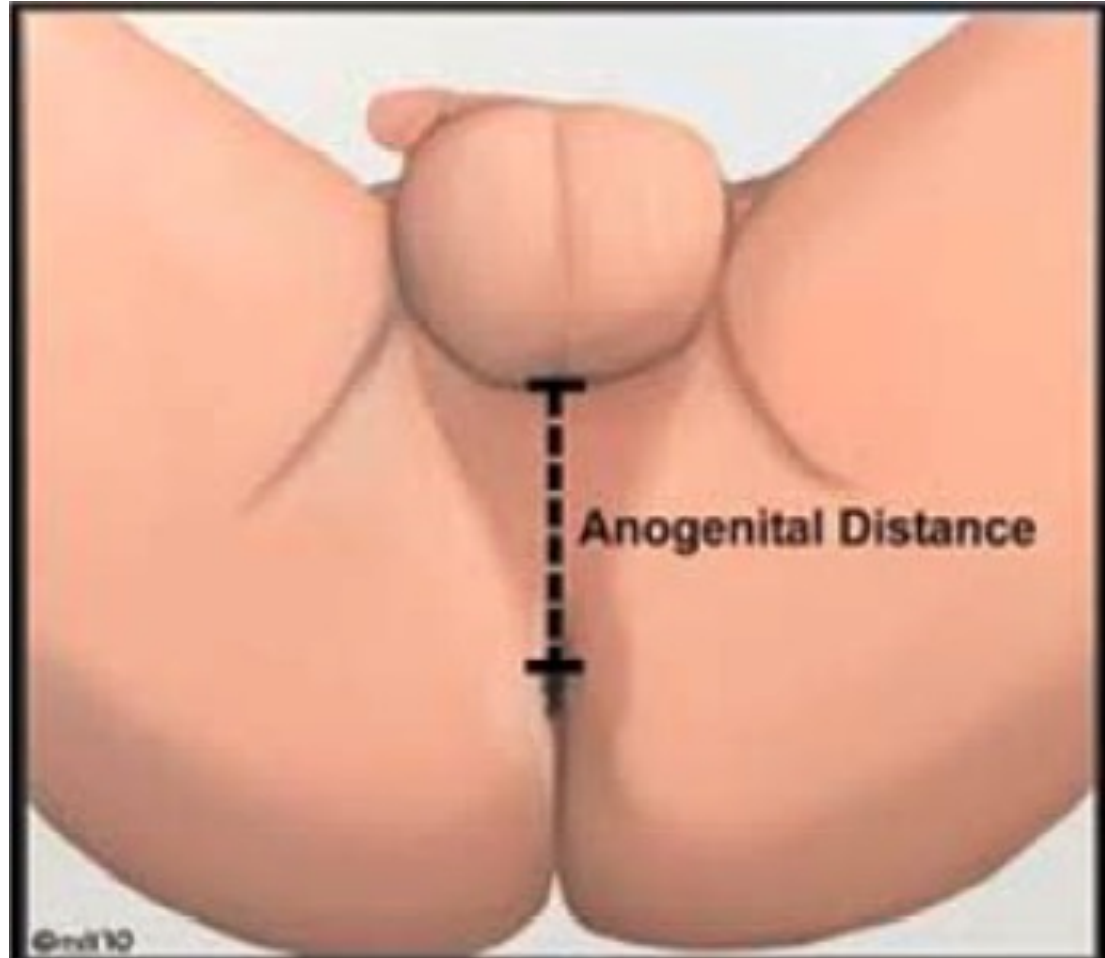




Endocrine disruptors /reproductive clinical toxicology / pregnancy post partum caution / low sperm counts / infertility



PHTHALATES



Clinical toxicology : the drug_drug interactions : explosive cocktails !



Dangerous clinical pharmacological cocktails : the drug_drug interactions



In the **POLYPHARMACY ERA**, it is not unusual for patients with eg chronic diseases to be taking half a dozen or more different medicines. Hence, drug-drug interactions have increased than ever before in clinical practice.

antihypertensives

NSAIDs

Careful : dangerous cocktails : the drug_drug interactions CYP450 3A4 blockade – the best known cases of fatalities

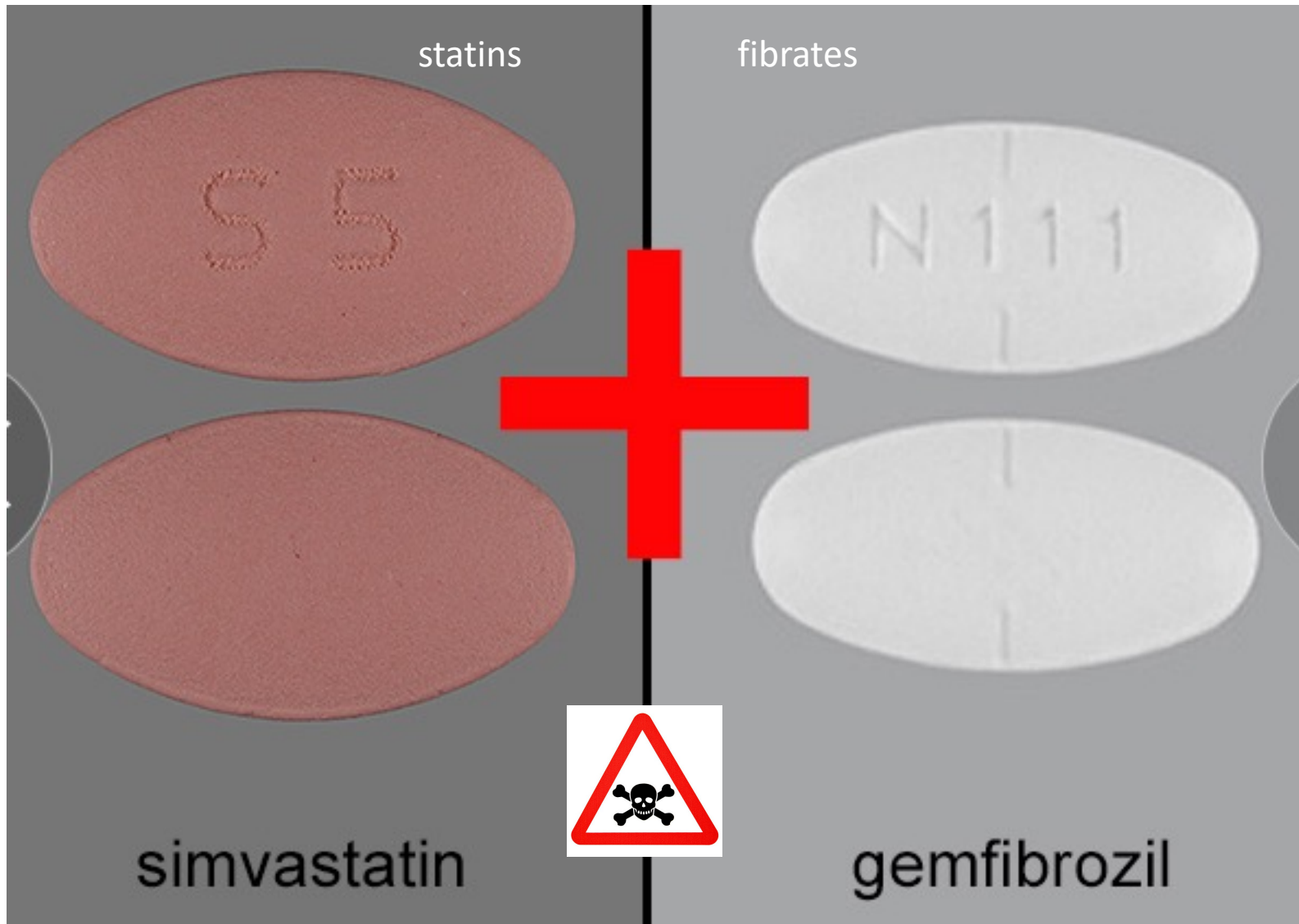


statins

fibrates

simvastatin

gemfibrozil



Careful : dangerous cocktails : the drug_drug interactions CYP450 3A4 blockade – the best known cases of fatalities



sildenafil

nitroglycerin

structure du trinitrate de glycérine.

CN1C=NC2=C1C=CC2[N+](=O)[O-]

**Case study : a patient on statin suffers from pharyngitis
(ORL Othorhinolaryngology symptoms) What do you do ?**



Simvastatine

CC(C)C(C)C(=O)O[C@@H]1C[C@@H](C[C@@H](C)C[C@H]1C)C[C@@H](C)C

clarithromycin
CYP3A4 blocker

ELN 60

54 312

simvastatin

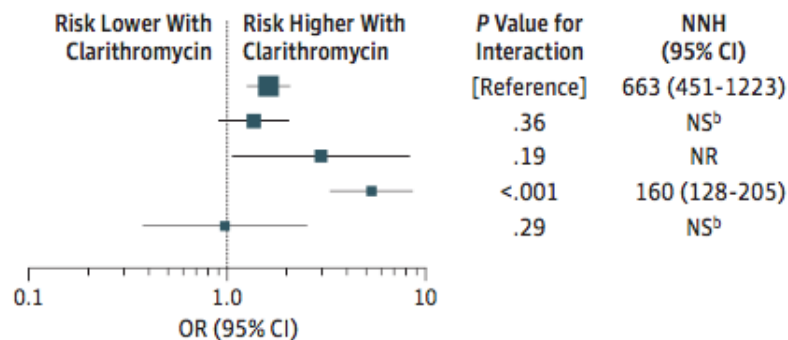
rhabdomyolysis !

Case study: a patient on calcium channel blocker suffers from pharyngitis (ORL Otorhinolaryngology symptoms) What do you do ?

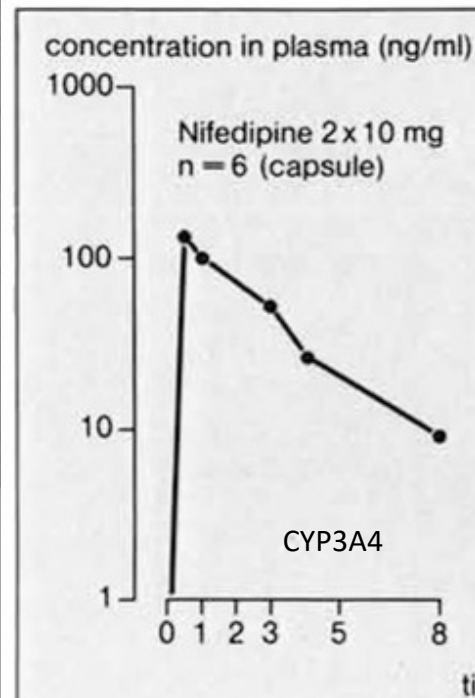


Figure 1. Clarithromycin With Each Type of Calcium-Channel Blocker and the Risk of Acute Kidney Injury

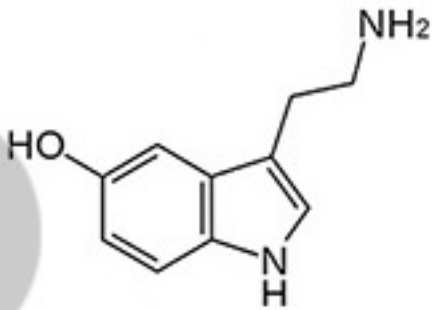
	Clarithromycin		Azithromycin		OR (95% CI)
	Events, No.	No. at Risk (%)	Events, No.	No. at Risk (%)	
Amlodipine	202	50 706 (0.40)	126	50 944 (0.25)	1.61 (1.29-2.02)
Diltiazem	63	21 403 (0.29)	46	21 207 (0.22)	1.36 (0.93-1.99)
Felodipine ^a	17	3 665 (0.46)	≤5	3 191 (≤0.16)	2.97 (1.09-8.06)
Nifedipine	129	16 644 (0.78)	22	15 038 (0.15)	5.33 (3.39-8.38)
Verapamil	9	3 808 (0.24)	9	3 703 (0.24)	0.97 (0.39-2.45)



nifedipine + clarithromycin

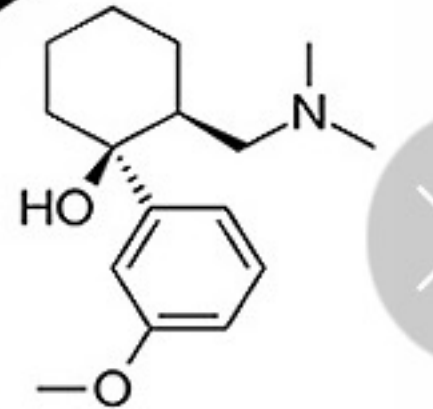


Dangerous pharmacological cocktails : the drug_drug interactions and the serotonin syndrome



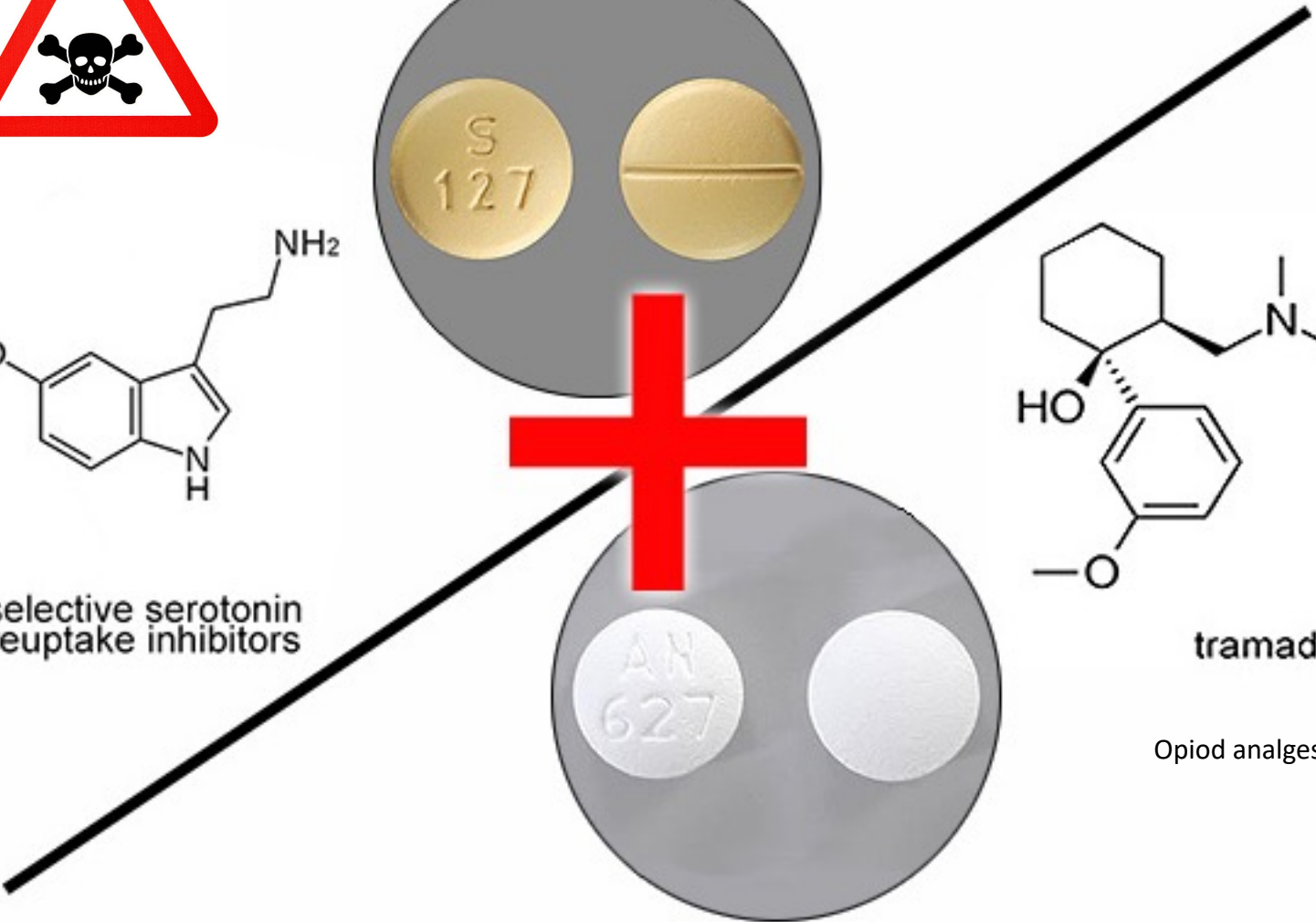
selective serotonin reuptake inhibitors

SSRI



tramadol

Opioid analgesic



Dangerous clinical pharmacological cocktails : the drug_drug interactions



At the onset of the **COVID PANDEMIA**, it was not unusual for patients in life threatening conditions– respiratory distress, cytokine storms etc. to be prescribed medicines such as azithromycin and hydroxychloroquine: this drug-drug interaction has caused of over 17'000 death cases in EU during first SarsCoV2 wave in 2020 (acute heart failure)



Azithromycine Sandoz® 500 mg
Antibiotique
3 comprimés pelliculés
SANDOZ

Plaquenil® 200 mg
Hydroxychloroquine sulfas
30 Filmtabletten / comprimés pelliculés
SANOFI

MACOLIDE AZITHROMYCIN

HYDROXYCHOLOQUINE

Careful : dangerous grapefruit drink : the drug_drug interactions



CYP 3A4
blockade !

~70% of drug-drug interactions should be avoided by AI powered algorithms assisting pharmacists and prescribing MDs; what about the residual risk ?



Table 1. Example of Completed DIPS Form

DIPS QUESTIONS	Answer/ Score	Comments
1. Are there previous <i>credible</i> reports of this interaction in humans?	NA / 0	At the time of the report, 1 case report purporting an interaction and 1 report of 6 cases without an interaction had been published. ^{12,13} Neither report met the criteria for a credible report; both are disregarded as evidence in this case.
2. Is the observed interaction consistent with the known interactive properties of precipitant drug?	no / -1	Cyclosporine is a substrate for CYP3A4 and P-glycoprotein. Azithromycin is not known to inhibit CYP3A4 or P-glycoprotein.
3. Is the observed interaction consistent with the known interactive properties of object drug?	NA / 0	Since no known properties of azithromycin affect cyclosporine, the answer is NA.
4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	yes / 1	The time course of the change in cyclosporine concentrations would be consistent with a change in its elimination.
5. Did the interaction remit upon dechallenge of the <i>precipitant</i> drug with no change in the object drug? (If no dechallenge, use "Unknown or NA" and skip Question 6).	yes / 1	Stopping azithromycin did coincide with a fall in the concentration of cyclosporine.
6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	no / 0	No rechallenge was attempted.
7. Are there reasonable alternative causes for the event?	yes / -1	As noted by the authors, alternative reasons existed (eg, cytokine-induced inhibition of CYP3A4 metabolism) that could lead to reduced cyclosporine metabolism.
8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	yes / 1	Cyclosporine concentrations were measured and varied appropriately with the administration and discontinuation of azithromycin.
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	NA / 0	There was no other evidence of the interaction except elevated cyclosporine concentrations.
10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	NA / 0	There was no change in the precipitant drug dose.

DIPS = Drug Interaction Probability Scale; NA = not applicable.

Drug interactions probability



Questions	Yes	No	Unk or NA
1. Are there previous <i>credible</i> reports of this interaction in humans?	+1	-1	0
2. Is the observed interaction consistent with the known interactive properties of precipitant drug?	+1	-1	0
3. Is the observed interaction consistent with the known interactive properties of object drug?	+1	-1	0
4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	+1	-1	0
5. Did the interaction remit upon dechallenge of the <i>precipitant</i> drug with no change in the object drug? (if no dechallenge, use Unknown or NA and skip Question 6)	+1	-2	0
6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	+2	-1	0
7. Are there reasonable alternative causes for the event? ^a	-1	+1	0
8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	+1	0	0
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	+1	0	0
10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	+1	-1	0

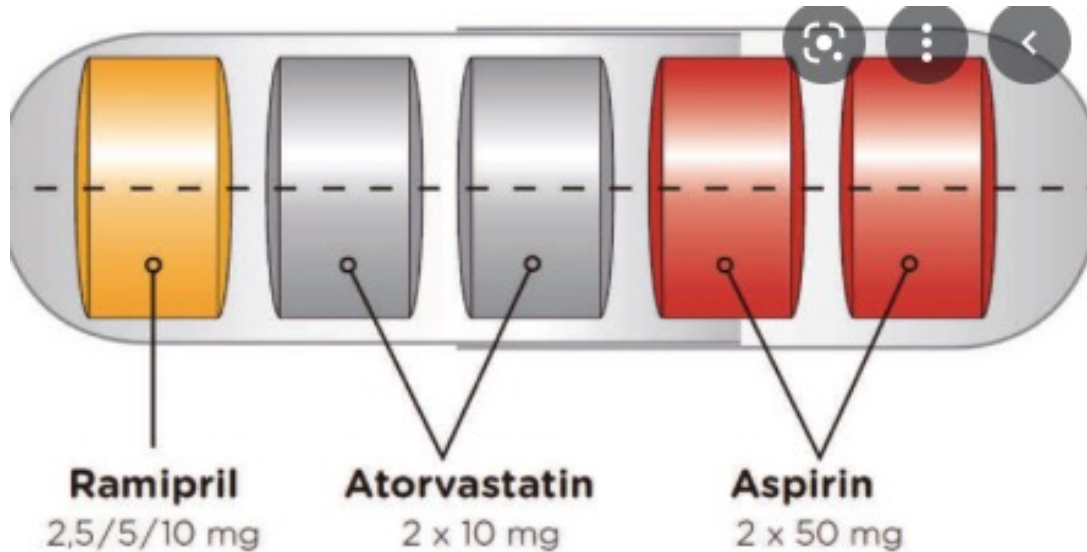
^aConsider clinical conditions, other interacting drugs, lack of adherence, risk factors (eg, age, inappropriate doses of object drug). A NO answer presumes that enough information was presented so that one would expect any alternative causes to be mentioned. When in doubt, use Unknown or NA designation.

Total Score ____

Highly Probable:	>8
Probable:	5-8
Possible:	2-4
Doubtful:	<2

Better compliance, lower medical costs with efficacious and safe polypill : a nightmare in experimental safety pharmacology !

explore safe combinations in cardiovascular prevention CVD:
eg. combo statin, ACE inhibitor, Ca²⁺ L channel blocker (amlodipine),
diuretic (dihydrochlorothiazide), etc

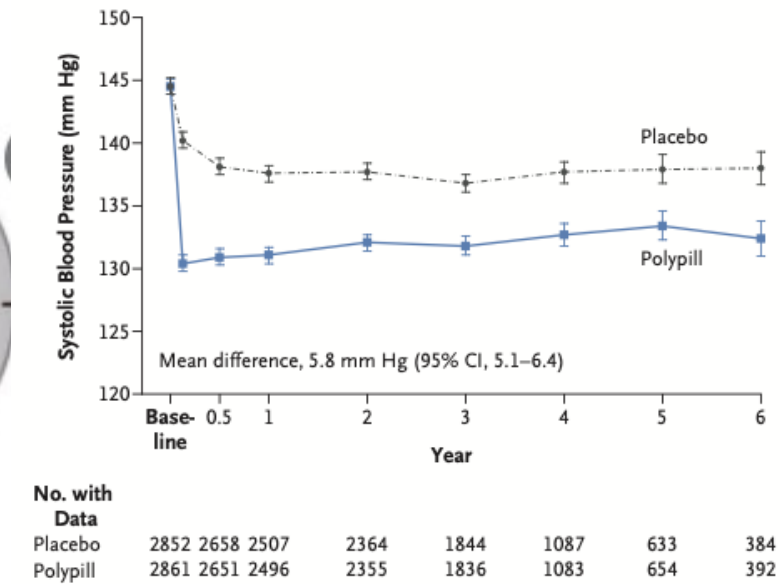


ORIGINAL ARTICLE

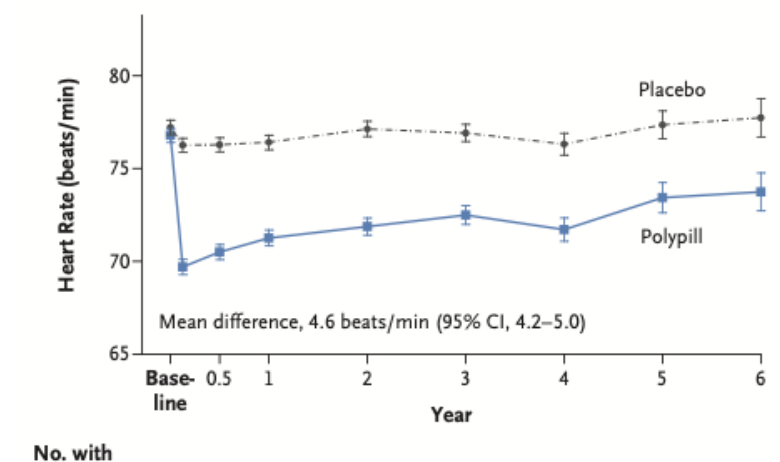
Polypill with or without Aspirin in Persons without Cardiovascular Disease

S. Yusuf, P. Joseph, A. Dans, P. Gao, K. Teo, D. Xavier, P. López-Jaramillo, K. Yusoff, A. Santoso, H. Gamra, S. Talukder, C. Christou, P. Girish, K. Yeates, F. Xavier, G. Dagenais, C. Rocha, T. McCreedy, J. Tyrwhitt, J. Bosch, and P. Pais, for the International Polycap Study 3 Investigators*

A Systolic Blood Pressure



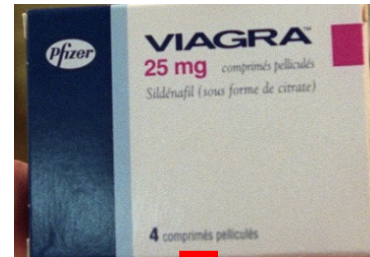
B Heart Rate



Drug Drug combination with fatal consequences !



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Methods

Results

Discussion

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eLetters

Effects of Sildenafil Citrate (Viagra) Combined With Nitrate on the Heart

Fuminobu Ishikura, Shintaro Beppu, Toshiaki Hamada, Bijoy K. Khandheria, James B. Seward and Ajay Nehra

Originally published 14 Nov 2000 | <https://doi.org/10.1161/01.CIR.102.20.2516> | Circulation. 2000;102:2516–2521

Abstract

Background—Sildenafil citrate (viagra) is indicated for the treatment of erectile dysfunction. Large and sudden decreases in systemic blood pressure were reported in a substantial number of patients taking sildenafil citrate combined with nitroglycerin. We studied the effect of sildenafil citrate on the relationship between changes in systemic blood pressure and coronary blood flow.

Methods and Results—Healthy male beagles were used to assess systemic blood pressure, pulmonary arterial pressure, and flow in the left circumflex artery (in which a critical stenosis was established) and left anterior descending coronary artery. After measurement of the hemodynamic variables, 2 mg/kg sildenafil citrate was administered via a nasogastric tube. Hemodynamic changes were monitored for 1 hour. Subsequently, the acute effect of nitrate combined with sildenafil citrate was studied by the bolus injection of 0.2 mg isosorbide dinitrate before and after sildenafil citrate. Systemic blood and pulmonary arterial pressures and circumflex flow did not change during this study; however, left anterior descending coronary arterial flow increased from 16.0 ± 5.8 to 24.6 ± 8.7 mL/min 1 hour after administration of sildenafil citrate. The prolongation of systemic blood pressure decrease and the circumflex flow decrement induced by isosorbide dinitrate after sildenafil citrate were significantly larger and longer than those before sildenafil citrate.

Conclusions—Sildenafil citrate had the effect of vasodilation in a normal coronary artery; however, a combined effect with nitrate resulted in large and protracted decreases in systemic blood pressure and coronary blood flow in vessels with critical stenosis.

Many Drug Drug interactions with ezetimibe ! No rational drug design !



Ezetimibe Drug Interactions

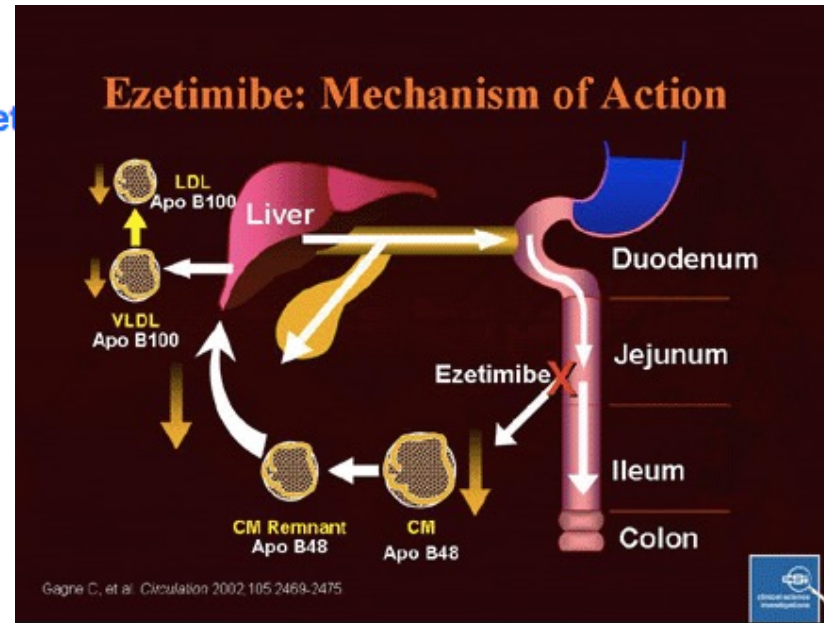
[Overview](#)[Side Effects](#)[Dosage](#)[Professional](#)[Interactions](#)[Pregnancy](#)

[Drug Interactions \(34\)](#) | [Disease Interactions \(3\)](#)

A total of **34 drugs** (89 brand and generic names) are known to interact with **ezetimibe**.

- **30 moderate** drug interactions (81 brand and generic names)
- **4 minor** drug interactions (8 brand and generic names)

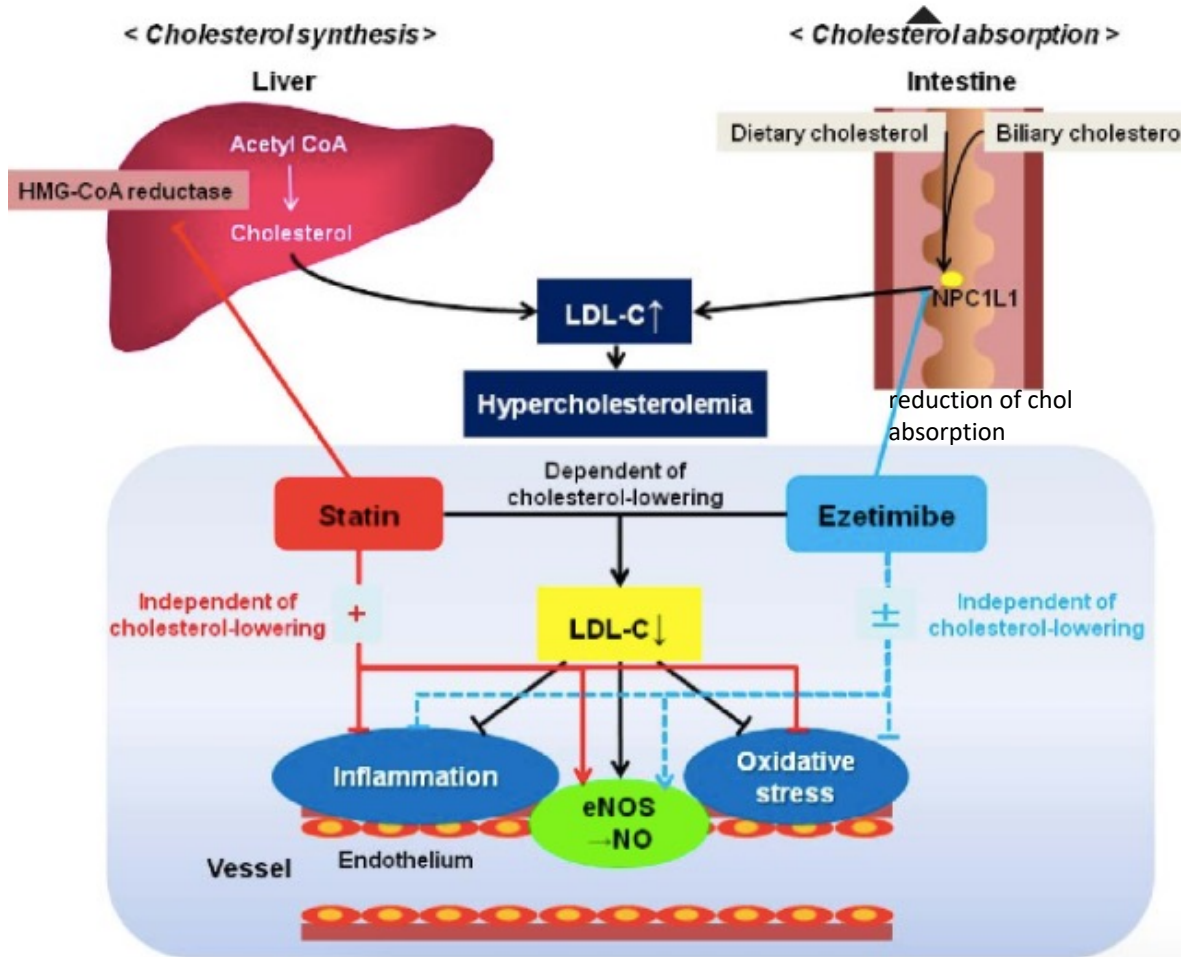
[Show all medications in the database that may interact with ezetimibe](#)



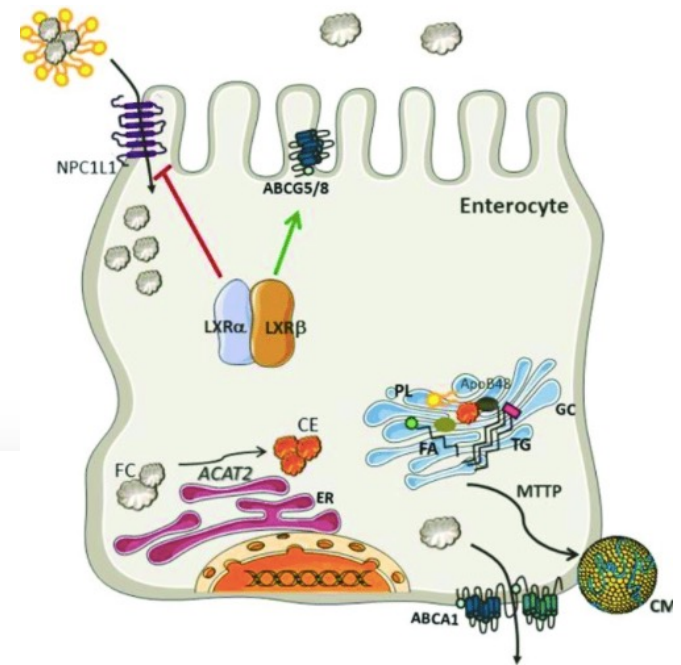
Ezetimibe originally screened as ACAT inhibitor..



cholesterol acyltransferases (ACATs) utilize long-chain fatty acyl-CoA and cholesterol as substrates to form cholesteryl esters.



...NPC1L1 gut receptor identified eventually many years later !





THANK YOU.....



DO YOU HAVE ANY QUESTIONS ?

It is not because things are difficult that we do not dare, it is because we do not dare that they are difficult.

Lucius Annaeus Seneca