N E W L A Y O U T

1,000,000,000 *CHF investment*

7,000,874 *hours of work*

6,587 *experiments*

423 *researchers*

1 *medicine*

With Prof Susan M Gasser
and Prof Olivier Michielin

THE MAKING OF AN INNOVATIVE MEDICINE

Introductory workshops on translational biomedical research and drug discovery and development

BIO-698 resumes Thursday September 21. 2023
4:15 PM @ AAC 108

EPFL

Sciences de la Vie -SV

Prof Roger G. Clerc

BIO 698 mid-term course evaluation FS2023

(your input is much valued thank you !)

MID TERM EVALUATION "THE MAKING OF AN INNOVATIVE MEDICINE"	HS 2022		
FOR EACH ITEM BELOW PLEASE CIRCLE ONLY A SINGLE RESPONSE	not at all	somewhat	very much
the course was sofar well organized overall			
I like the interactive part of the course (flipped classroom)			
the workshop sessions were relevant to the respective topics			
the presenters were well prepared overall			
the debates were receptive to participant's comment question			
the course enhanced my knowledge			
I realized how novel medicine development is a long complex journey			
I hope to be abe to use part of this knowledge and skills in future			
I would recommend to re/attend this course to a colleague, friends			
I am looking forward to the upccoming health hackathon			
	please tick accordingly X		
SELF ASSESSMENT LEARNING:EVALUATE KNOWLEDGE BEFORE/AFTER	before	after	
historical introduction to drug development	1 2 3	4 5 6	
therapeutic target identification _ patient need	1 2 3	4 5 6	
therapeutic modalities: SMW cpds, biologicals, RNA, DNA therapeutics	1 2 3	4 5 6	
MedChem, in silico/HTS screens/AI screen	1 2 3	4 5 6	
Personalized healthcare -precision medicine	1 2 3	4 5 6	
1= **NO** value/knowledge or skills			
3= **SOME** value/knowkedge or skills	please circle accordingly (see below)		
6= **LOT** of value/ knowledge or skills			
remarks: there are no right or wrong answers. no need to put your name (anonymous evaluation) !			
your comments :			

BIO 698 mid-term course evaluation FS2023 (your input was much valued thank you !)

MID TERM EVALUATION "THE MAKING OF AN INNOVATIVE MEDICINE"	HS 2022		
FOR EACH ITEM BELOW PLEASE CIRCLE ONLY A SINGLE RESPONSE	not at all	somewhat	very much
the course was sofar well organized overall	0%	7%	93%
I like the interactive part of the course (flipped classroom)	0%	14%	86%
the workshop sessions were relevant to the respective topics	0%	14%	86%
the presenters were well prepared overall	0%	14%	86%
the debates were receptive to participant's comment question	0%	14%	86%
the course enhanced my knowledge	0%	21%	79%
I realized how novel medicine development is a long complex journey	0%	28%	72%
I hope to be abe to use part of this knowledge and skills in future	0%	14%	86%
I would recommend to re/attend this course to a colleague, friends	0%	14%	86%
I am looking forward to the upccoming health hackathon	0%	28%	72%
	please tick accordingly X		
SELF ASSESSMENT LEARNING:EVALUATE KNOWLEDGE BEFORE/AFTER	before	after	
historical introduction to drug development	1 2 3	5 6	
therapeutic target identification _ patient need	1 2 3	5 6	
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MedChem, in silico/HTS screens/AI screen	1 2 3	5 6	
Personalized healthcare -precision medicine	1 2 3	5 6	
1= **NO** value/knowledge or skills			
3= **SOME** value/knowkedge or skills	please circle accordingly (see below)		
6= **LOT** of value/ knowledge or skills			
remarks: there are no right or wrong answers. no need to put your name (anonymous evaluation) !			
"the course was very informative thank you for the course materials lectures"			
"thank you so much for the meanignful and intersting course"			
"may be more careful to iming for presenters or start the course with pres. so then speakers don't have to worry about time"			

09 questionnaires back from
16 IS academia participants

The Making Of An Innovative Medicine – course schedule

Thursday's @ 4-6 PM except 14.12/21.12.23 @2-6 PM

Session 1: **Scope of the course _ general organization _ case study**
21.09.23 *Embracing a career at the heart of biomedical research !?*
AAC108

Session 2: **Historical perspective: the modern pharmacy**
28.09.23 *Advent of modern medicines - placebo controlled drug development*
AAC108

Session 3: **Introduction to translational research: crossing the bridge**
05.10.23 *A chasm has opened wide between biomedical research and patients in need*
AAC014

Session 4: **Therapeutic target identification I & II**
12-19.10.23 *"me too" vs a wealth of innovative targets _ small MW cpds vs biologicals*
AA014 AAC108 *Early front loading of biomarker identification for cohort stratification*

Session 5: **Structure based drug design _medicinal chemistry_low/high throughtput**
26.10.23 **screening assays_ multiple parallel parameters optimization MDO**
AAC108 *Setting up screening assays, the robotics, the million cpds librairies*

Session 6: **Therapeutic modalities peptides and biologicals: today's -**
02.11.23 **tomorrow's pharmacy NBEs**
AAC108 *Challengies (cost of goods - healthcare payers) and opportunities*

The Making Of An Innovative Medicine - course schedule

Thursday's @ 4-6 PM except 14.12/21.12.23 @2-6 PM

Session 7: **Personalized Healthcare PHC _ precision medicine**
09.11.23 *How PHC started: from a single case to a paradigm change*
AAC108

Session 8: **Pharmacogenetic polymorphisms, Pharmacogenomics**
16.11.23 *Interindivi[illegible]*
AAC[illegible]

Session 9: **In vivo pharmacology, investigative toxicology with Dr Nathalie Brandenberg PhD**
23.11.23 *Preclinical research ends up with IDB's, FDA guidelines for FIH*
[illegible]

Session 10: **[illegible] phase 0, phase I, II, III, IV**
30.11.23 *The long and complex experimental procedures with human patients*
AAC108

Session 11: **Intellectual property_ integrity in research_my genome vs our genomes**
07.12.23 *Why are patents essential to new medicine/biotech development*
AAC108

Session 12: **Health Hackathon – Hacking medicine I with Dr Greg Michielin MD PhD**
14.12.23 *Pitches –building teams – hacking problem - 5Ws – brainstorm*
starts @ 2PM ! MED21522

Session 13: **Health Hackathon – Hacking medicine II with Prof O. Michielin MD - Prof SM Gasser PhD judges**
21.12.23 *Building up solutions – make it better - final presentations*
starts @ 2PM ! AAC231

WORKSHOP LISTING - THE MAKING OF AN INNOVATIVE MEDICINE BIO698			
! NON EXHAUSTIVE LISTING - SUGGESTIONS WELCOME !			
sessions	**no**	**workshops**	**speaker/s**
S02 (28-09-23) ! AAC108 !			
historical medicines	1	vaccine discovery : E. Jenner and smallpox	Danica M
with Nobel laureates while	2	penicilin: impact, whose invention ?	
hopping on giant shoulders	3	prozac at the core of psychiatry	
	4	lipitor/statins at last a blockbuster	
	5	artemisinin and malaria	Umair
	6	cyclosporin from soil sample to blockbuster	Umair
S03 (5-10-23) ! AAC014 !			
translational research	7	expanding the scope of targeted therapies	
an emerging field	8	chronotherapy	Pitt
S04 (12-10-23) ! AAC014 !			
therapeutic target identification	9	rare diseases repurposing medicines	Adrien
S04b (19-10-23) ! AAC108 !	10	nocosomial inf/MRSA/phage antibacterials	Georges
therapeutic target identification	11	Crispr/Cas9 gene editing huntington disease	Pitt
	12	AI in drug discovery	Simon
S05 (26-10-23) ! AAC108 !			
structure based drug design	13	macrocycles and non druggable targets	Masota
	14	chemoproteomics - NMEs	Nico G
	30	AIDS HIV from deadly virus to chronic disease	Camilla
S06 (02-11-23) ! AAC108 !			
therapeutic modalities - NBEs	15	therapeutic peptides/incretins	Tim
	16	biologicals on the rise MABs medicines	Nico G
	16	RNA therapeutics, antisense medicines	
S07 (9-11-23) ! AAC108 !			
PHC personalized healthcare	17	BRCA1 preventive surgery/tumor board	Nikita
Human genomics	18	SOPHiA Genetics - GWAS	
	19	disease enabling biomarkers/micro RNAs	Isika
S08 (16-11-23) ! AAC014 !			
pharmacogenetic polymorphism	20	NextGenSequencing - precision medicine	Hien
	21	deCODE Inc pharmgenomic/iceland genealogy	
S09 (23-11-23) ! AAC108 !			
in vivo pharmacology	22	thalidomide repurposing mulitple myeloma	Ekatarina
toxicology	23	organoids come of age CFTR patients	Nathalie B
S10 (30-11-23) ! AAC108 !			
clinical research	24	AI medicine 2.0	Simon
	25	most common genetic defect : cystic fibrosis	
	26	sex bias in preclicnial and clinical research	Weilin
	27	placebo/nocibo effects	Tim
S11 (07-12-23) ! AAC108 !			
intellectual property/integrity	28	SMA gene therapy - pay for performance	Abtin
	29	biopatents - 23 and Me - my genome	Khosiyat
S12 (14-12-23) starts @ 2PM		Hacking medicine	all + invitees
! MED21522!			
S13 (21-12-23) start @ 2 PM		Hacking medicine	all + invitees
! AAC231 !			

Workshops _ The Making Of An Innovative Medicine

(today's class)

D O P P L Inc.

M E E T S W I T H

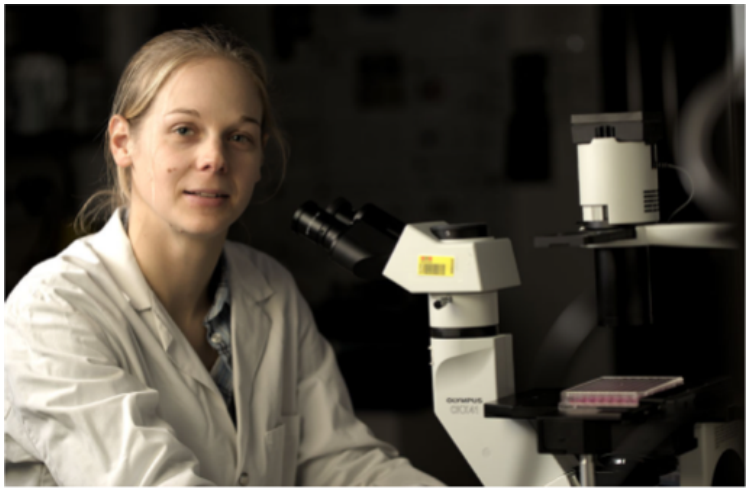
GUESTS WELCOMED !

THE MAKING OF
AN INNOVATIVE MEDICINE (BIO 698)

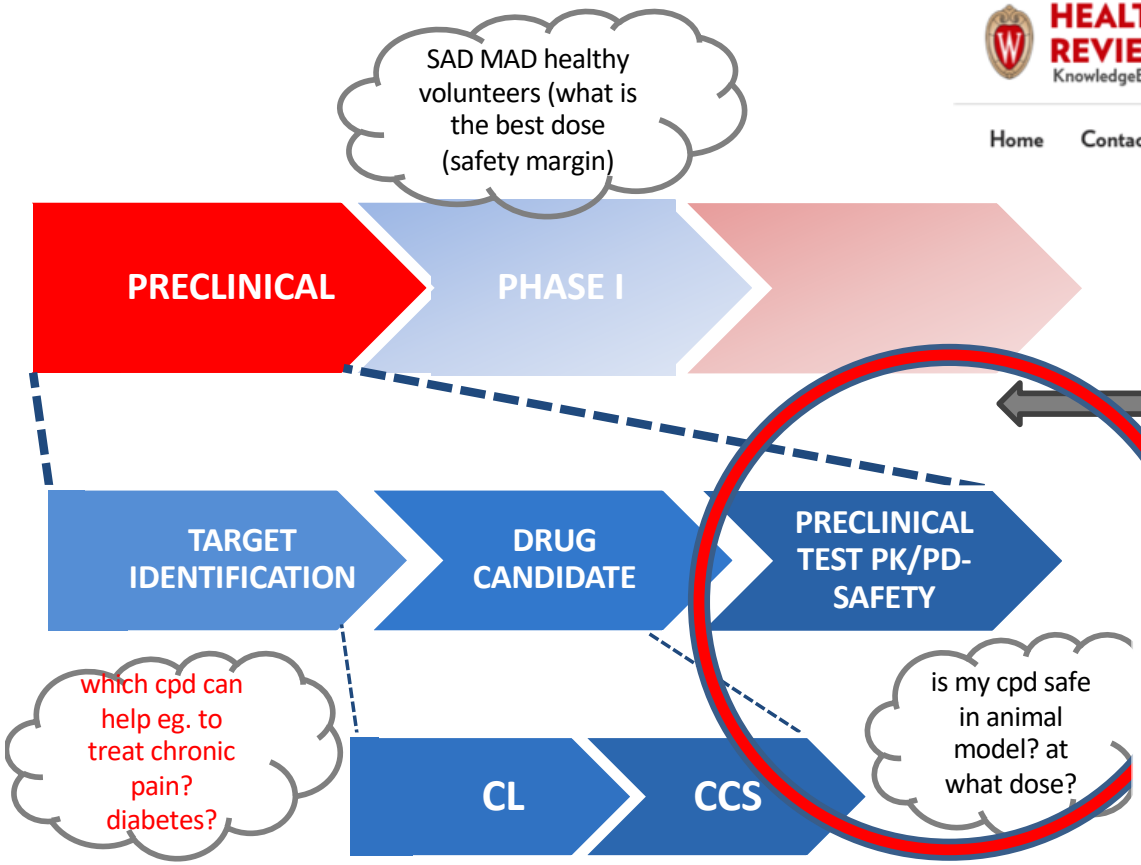
YOU ARE CORDIALLY INVITED TO A PRESENTATION GIVEN BY
Dr Nathalie Brandenberg , CEO DOPPL Inc.

Thursday November 23. 2023
5:15 PM EPFL ROOM AAC108
on

CFTR allosteric modulators in cystic fibrosis patients :
personalized assessment with rectal derived organoids



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



Closing preclinical tests – PK, PD, SAFETY

POC

IDB investigators' drug brochure

IND Investigational New Drug Application - FDA

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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.

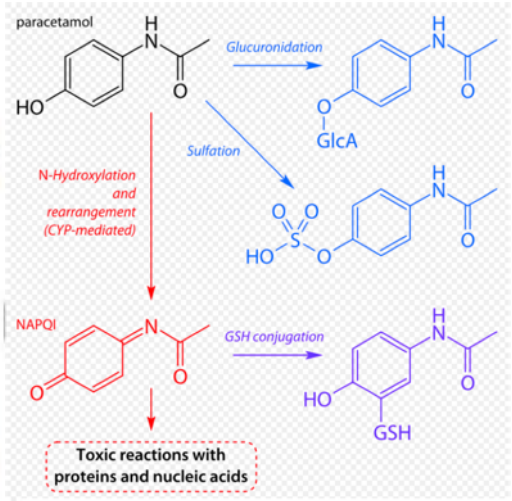
Note: Many studies involve using a combination of drugs, some of which may be covered by an IND and some of which may not be.

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

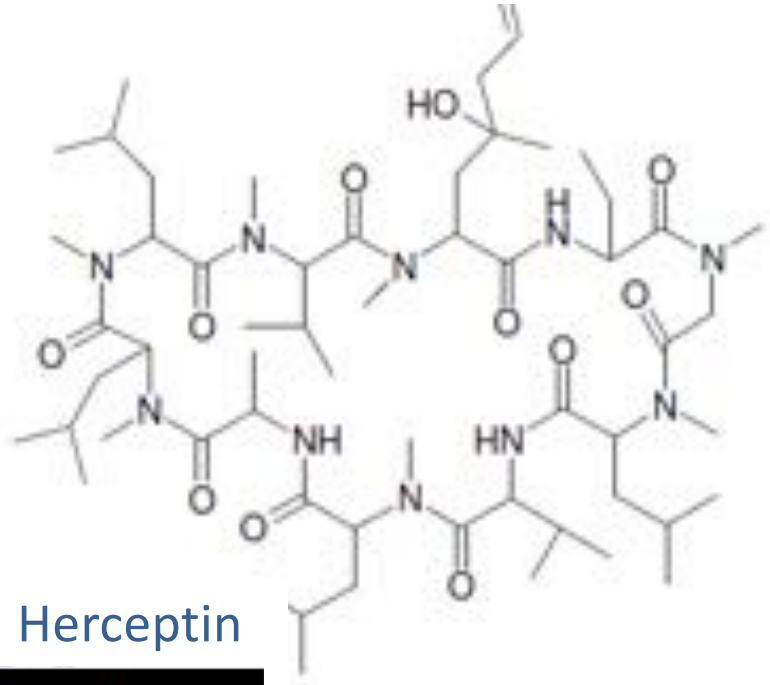
THE BIGGEST RISK FOR HUMAN BEEINGS IS NOT TO GET A MEDICINE !

PK PD ADME : making the real thing !

- Paracetamol

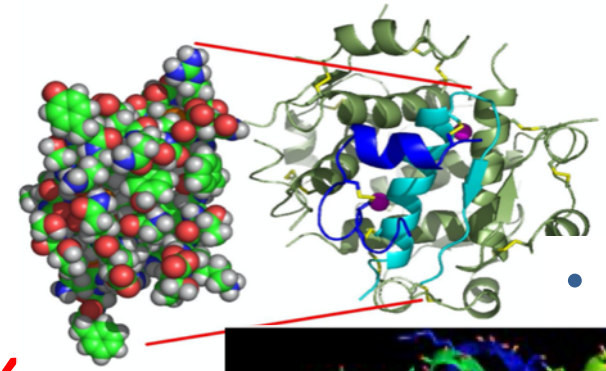


- Cyclosporin



- Sandimmun

- Insulin



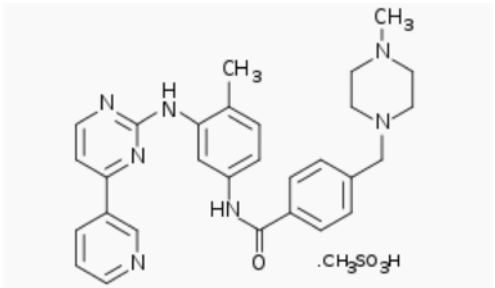
- MABs

- Herceptin

Modélisation de la molécule de trastuzumab

WILL IT WORK IN THE CONTEXT OF A LIVING ORGANISM ?

- Gleevec



Structure chimique du mésilate d'imatinib

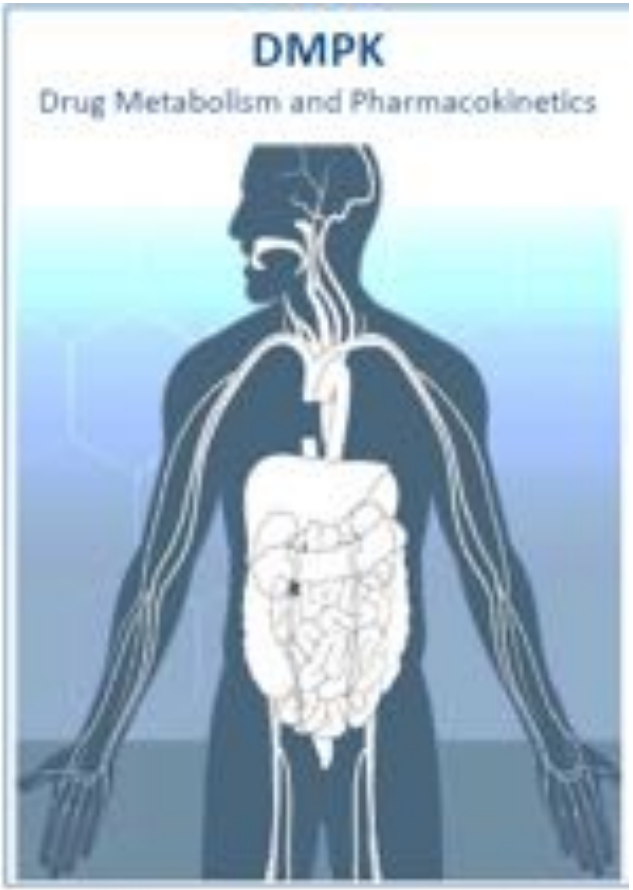
Pharmacology, DMPK, ADME

- **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.

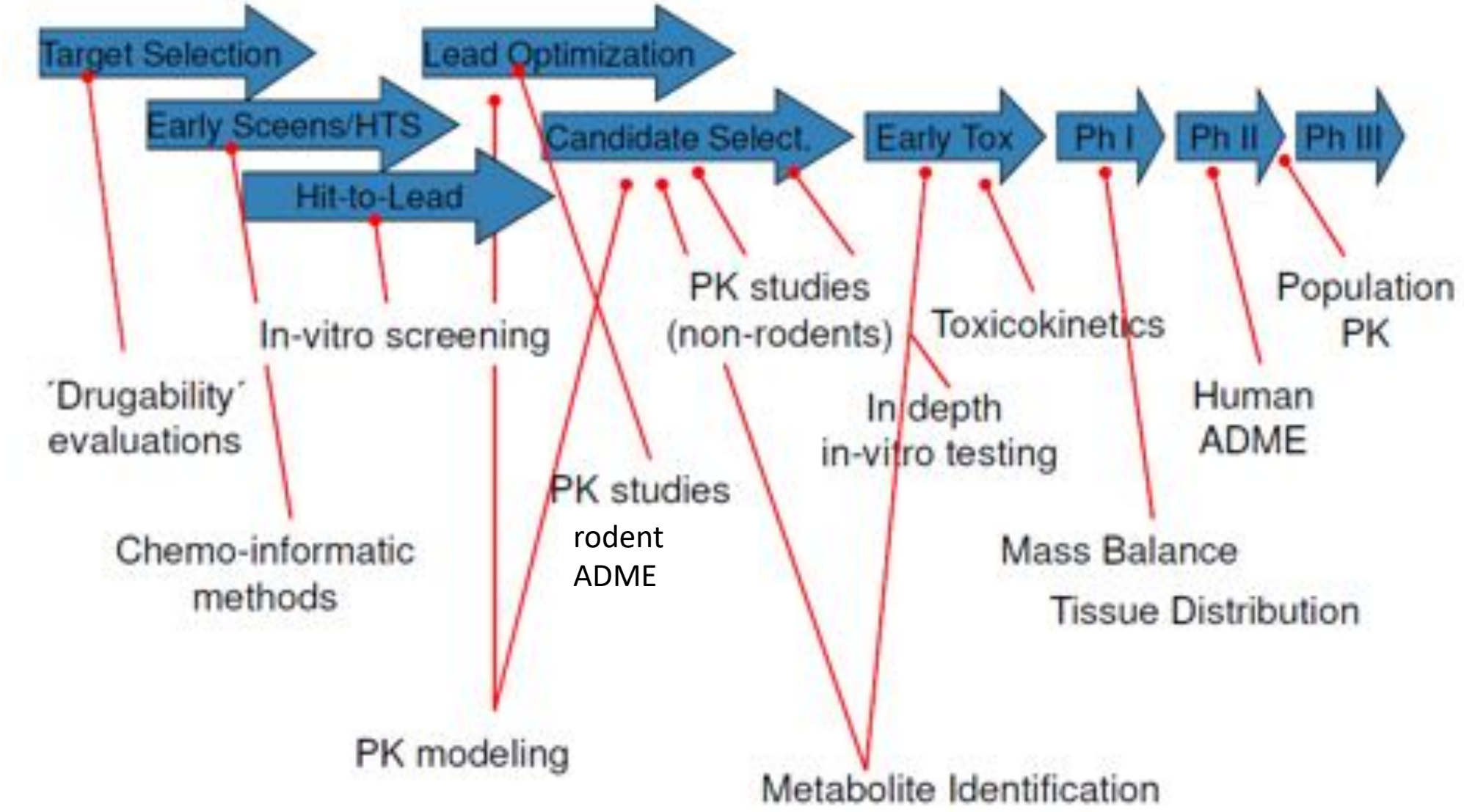
- **Pharmacodynamics (PD)** is the study of the relationships between the concentration of a drug and the effect site (where target enzymes or receptors are located) and the magnitude of its pharmacological efficacy (drug → body).

- **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.



Pharmacology during preclinical and clinical development



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

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.

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

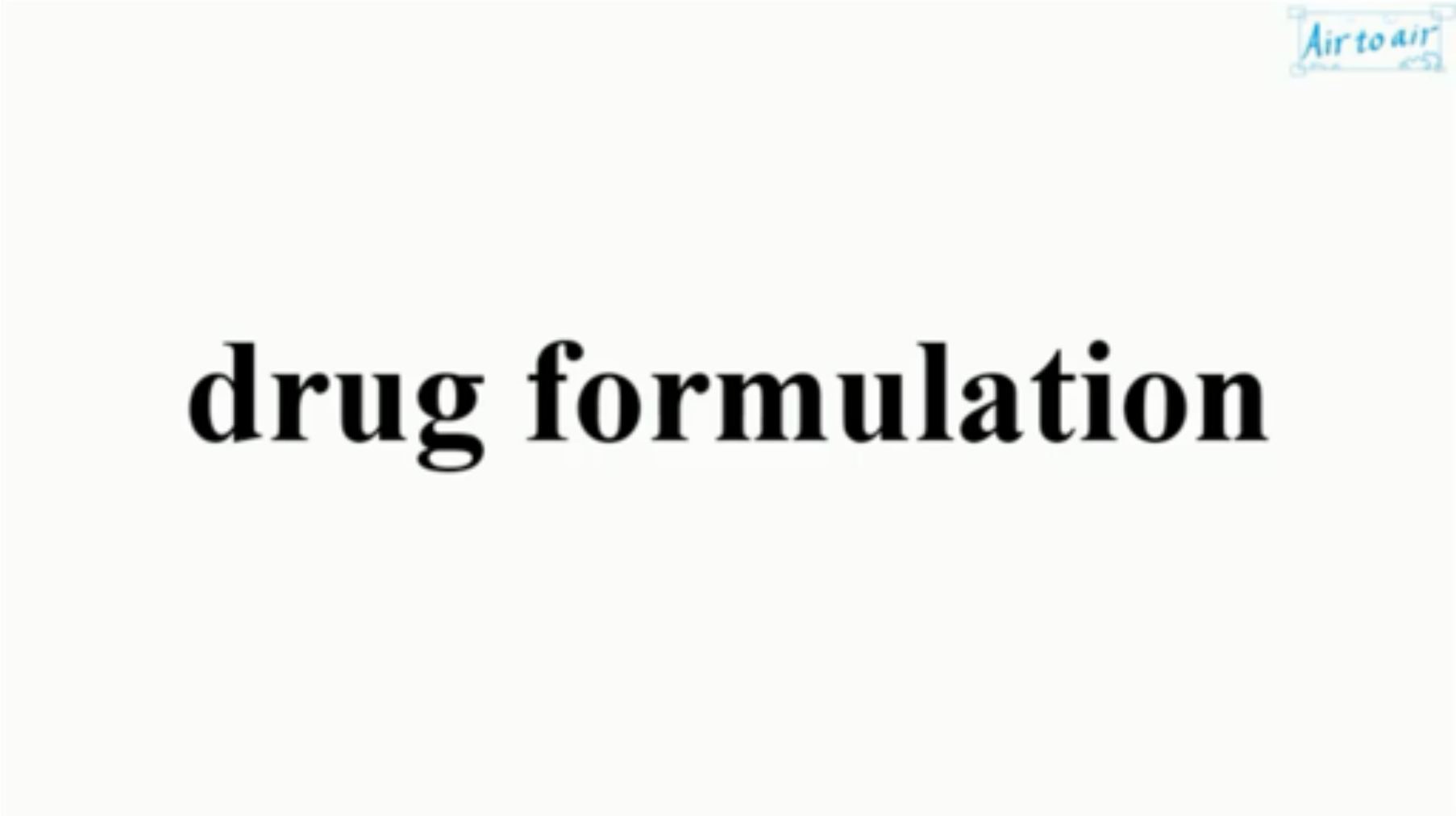
An active ingredient has to be incorporated into a suitable form of administration so that it can be transported to the part of the body where it is needed.

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 beeings is not to get a medicine : when benefits outweigh the known risks

Pharmacology : drug formulation (galenics) is key in PK

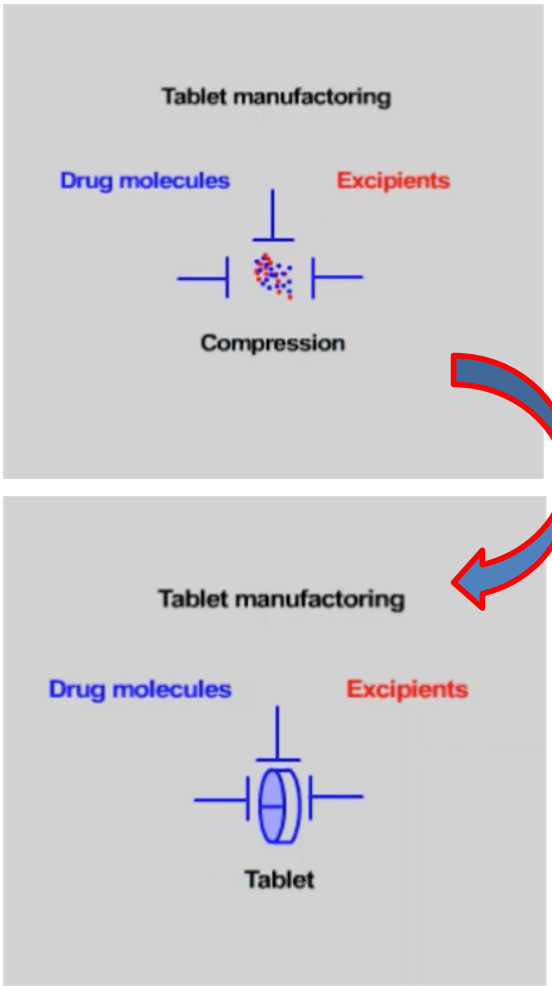


The biggest risk for human beeings is not to get a medicine :
when benefits outweigh the known risks

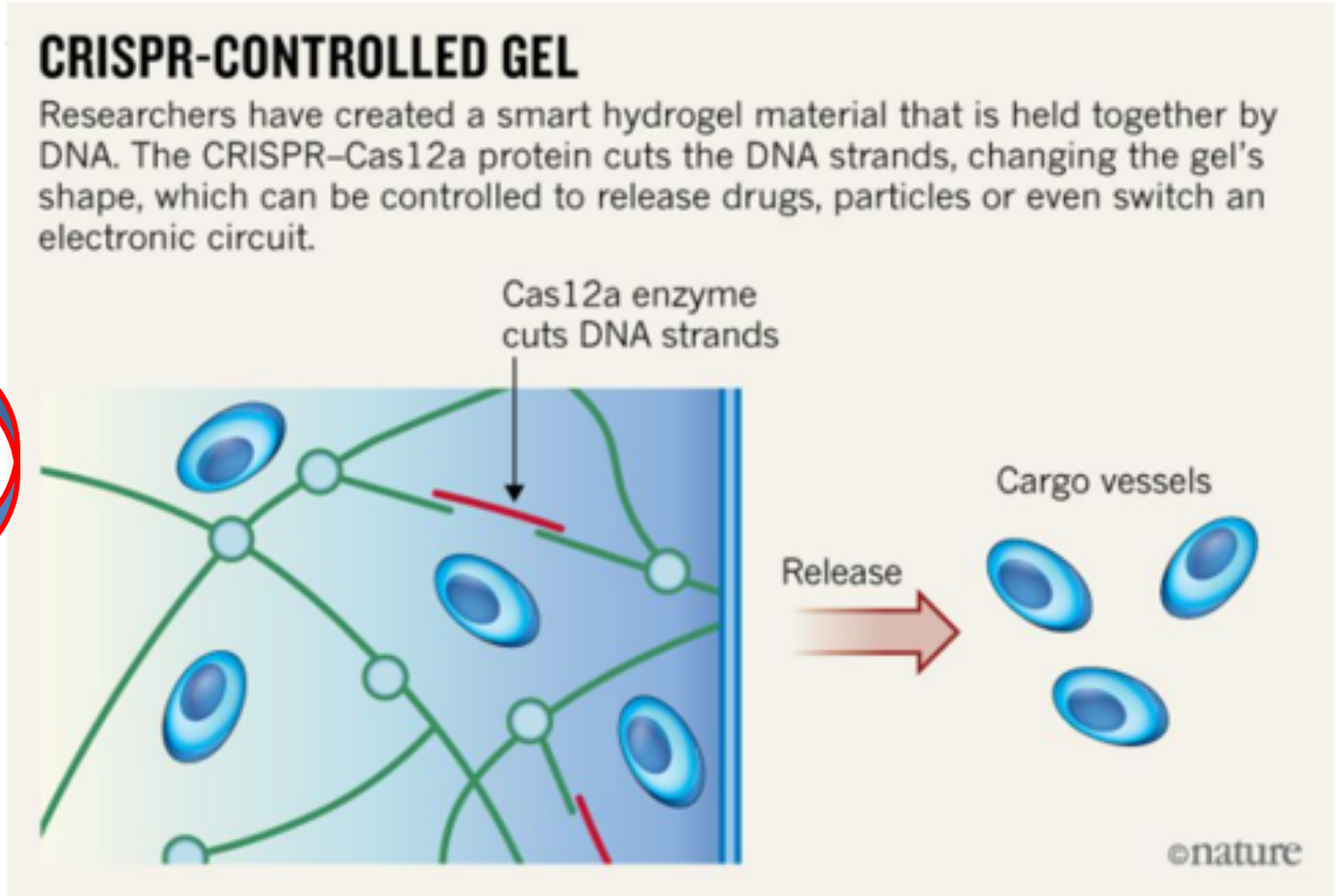
In vivo pharmacokinetics and galenics

tissue delivery/exposure, classical vs high tech galenic formulations

today's galenics



tomorrow's galenics



Han et al. 2019 Science 365:754-756

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

tissue delivery/exposure, prodrug overcome phamacokinetic barriers

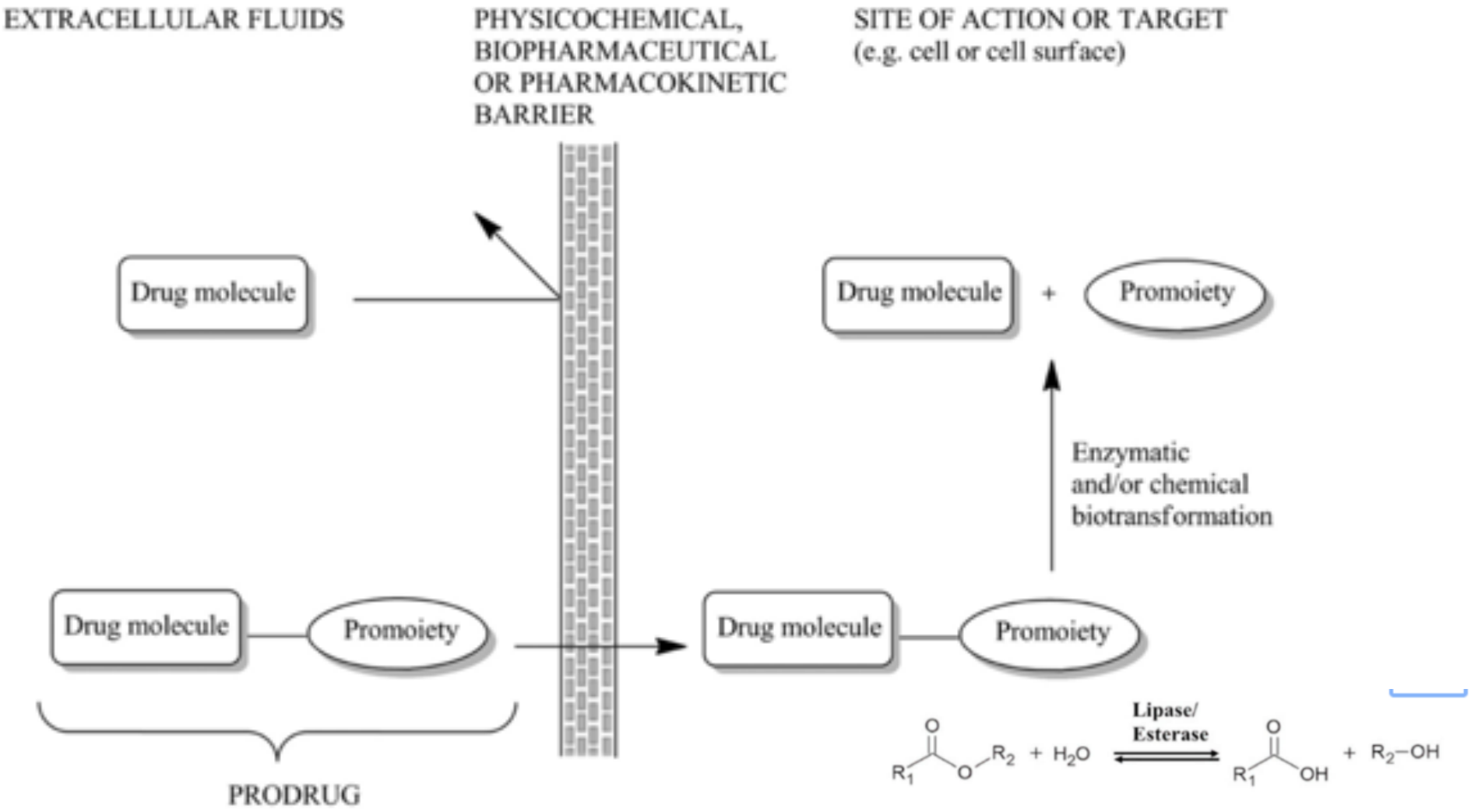


FIG. 1. A simplified illustration of the prodrug concept.

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

tissue delivery/exposure, prodrug overcome phamacokinetic barriers

TABLE 2

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-(isopropyloxy-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 guinee 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

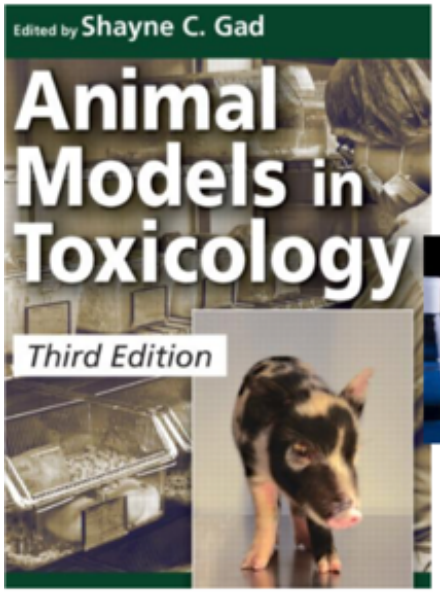

dbdb mouse


obob mouse

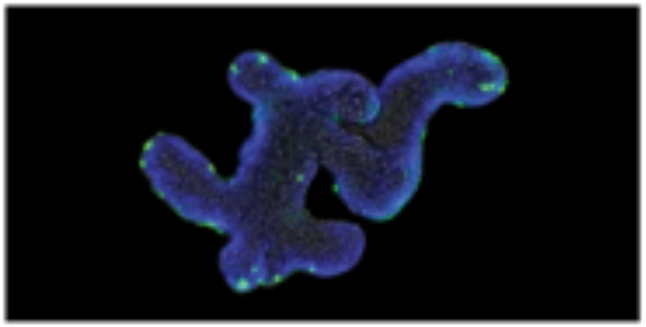

critecus mesocritecus
golden hamster


ZDF rat

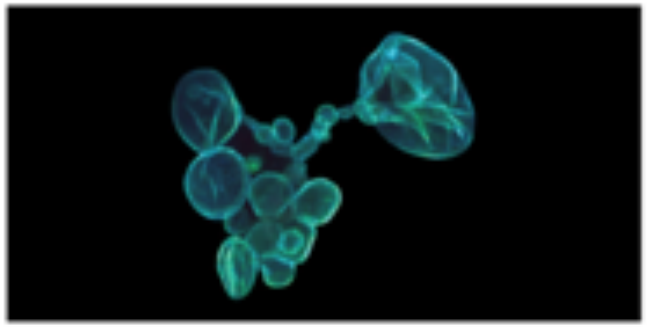
3R initiative in safety toxicology : can organoids help ?



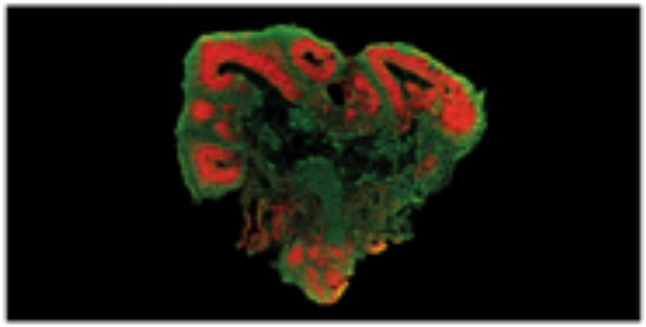
RRR



Intestinal Organoids



Liver Organoids



Neural Organoids

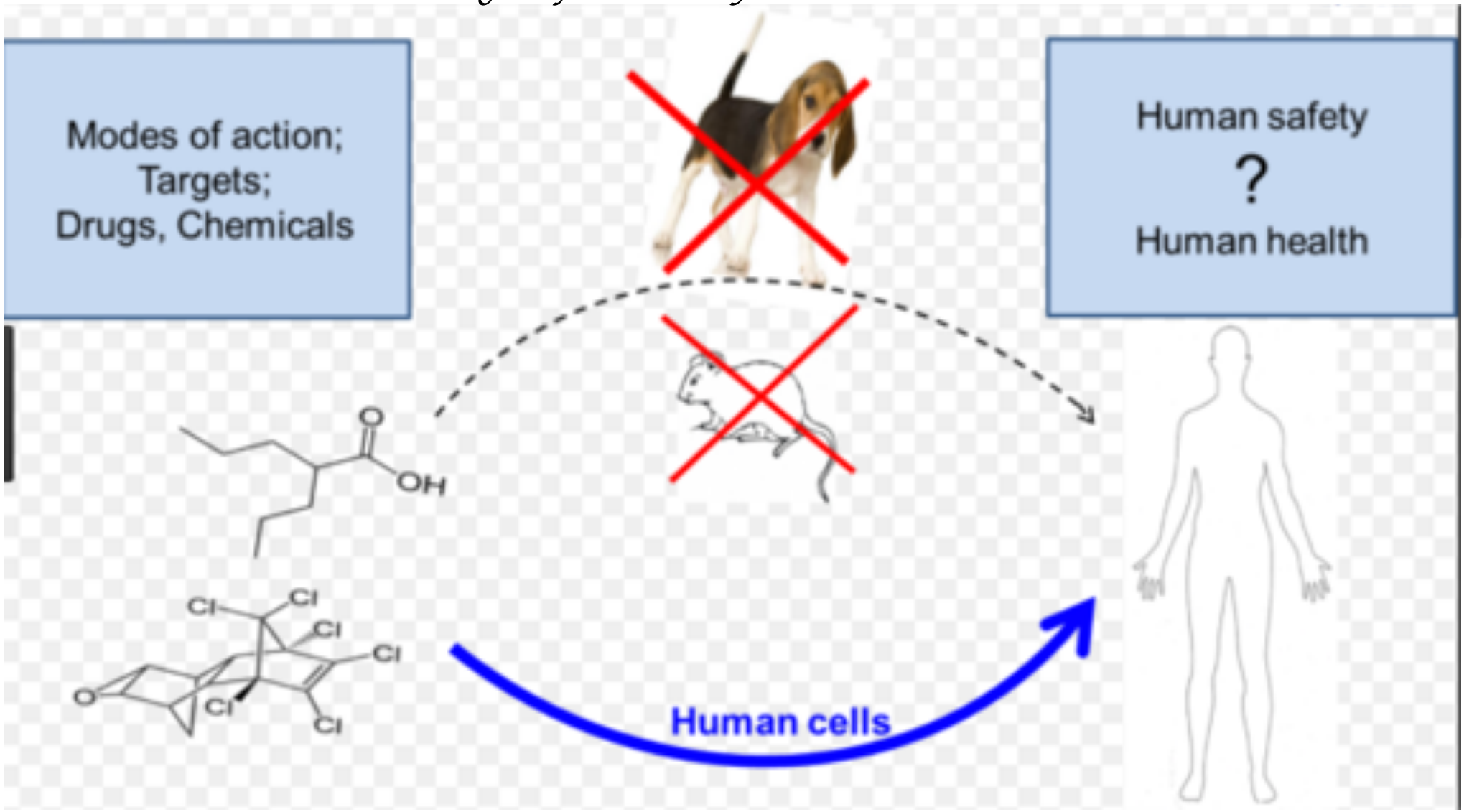
Strategic Focus on 3R Principles Reveals Major Reductions in the Use of Animals in Pharmaceutical Toxicity Testing

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

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

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 volonteer trial survivor



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 exterminted yearly by cats !
What about pets in custody, small appartments ? And over consumption of meat?
Against scientific process ? biomedical research

‹ Retour au sommaire

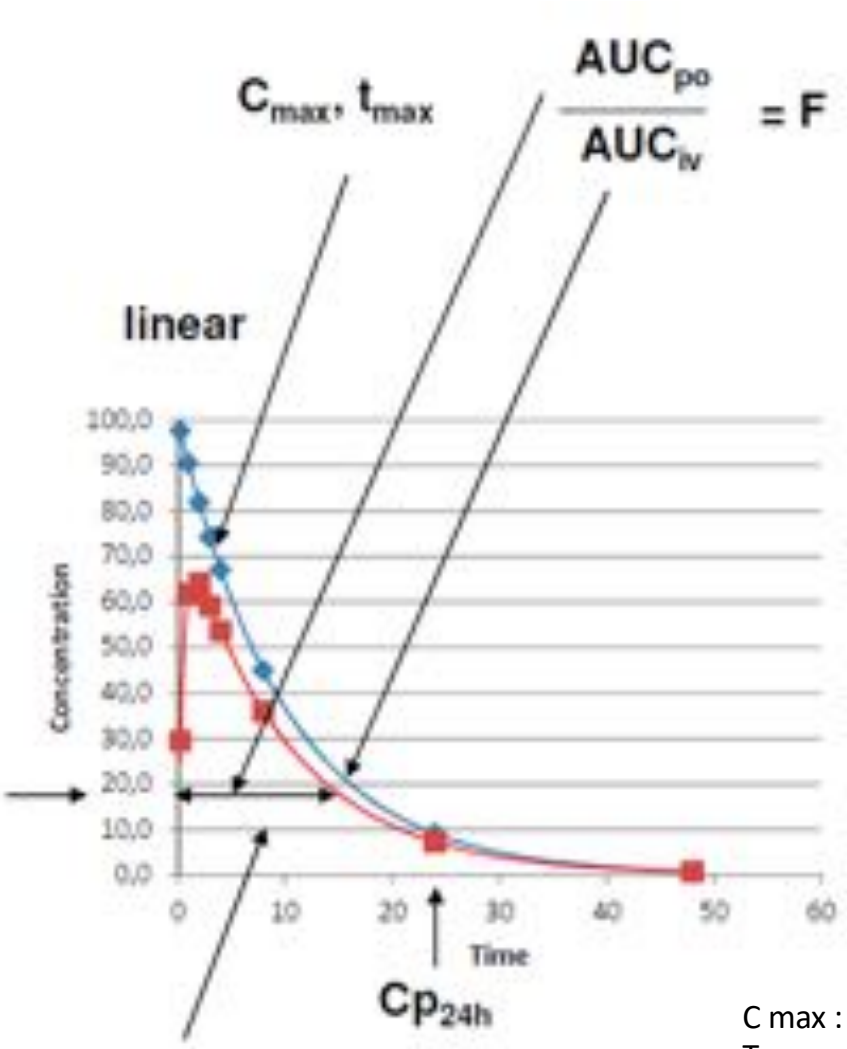
Lancement d'un programme national de recherche sur la thématique « animaux, recherche et société »

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

me national de recherche (PNR) 79 « Advancing 3R – animaux, t société » vise d'une part à faire diminuer le nombre ntations animales dans la recherche scientifique et, de ce fait, à siblement celui des animaux de laboratoire. Il a également pour but le plus possible les contraintes subies par les animaux de laboratoire ériences et de leur détention. D'autre part, ce PNR traitera des iques, juridiques, sociétaux, culturels et économiques de ntation animale.

ifient « remplacement », « réduction » et « raffinement ». Les R visent les objectifs suivants : remplacer autant que possible les

PK *in vivo – body on drug !*



iv
po

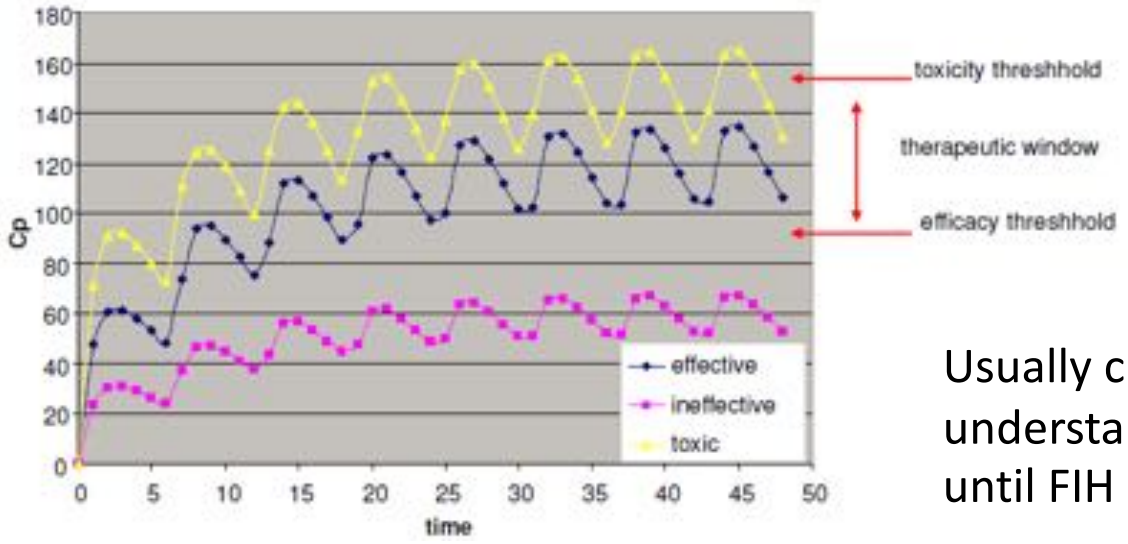
- AUC Area under the curve (from PK data analysis)
- C_{max} Peak Concentration (from PK data analysis)
- T_{max} Peak time (from PK data analysis)
- Elimination Rate Constant (λ_z, from PK data analysis)
- Elimination Half-live $t_{1/2} = \ln(2)/\lambda_z$
- F Bioavailability = AUC (po)/AUC (iv)
- Volume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

- In vitro/in silico
  - Microsomes, hepatcytes, enzymes, cell cultures
  - Computer models for in vitro-in vivo-correllation
- 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

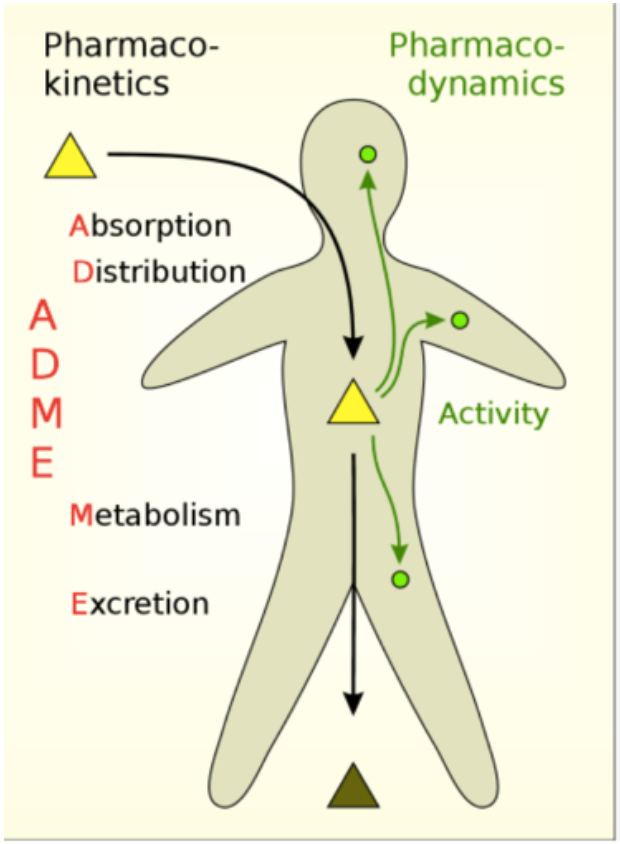


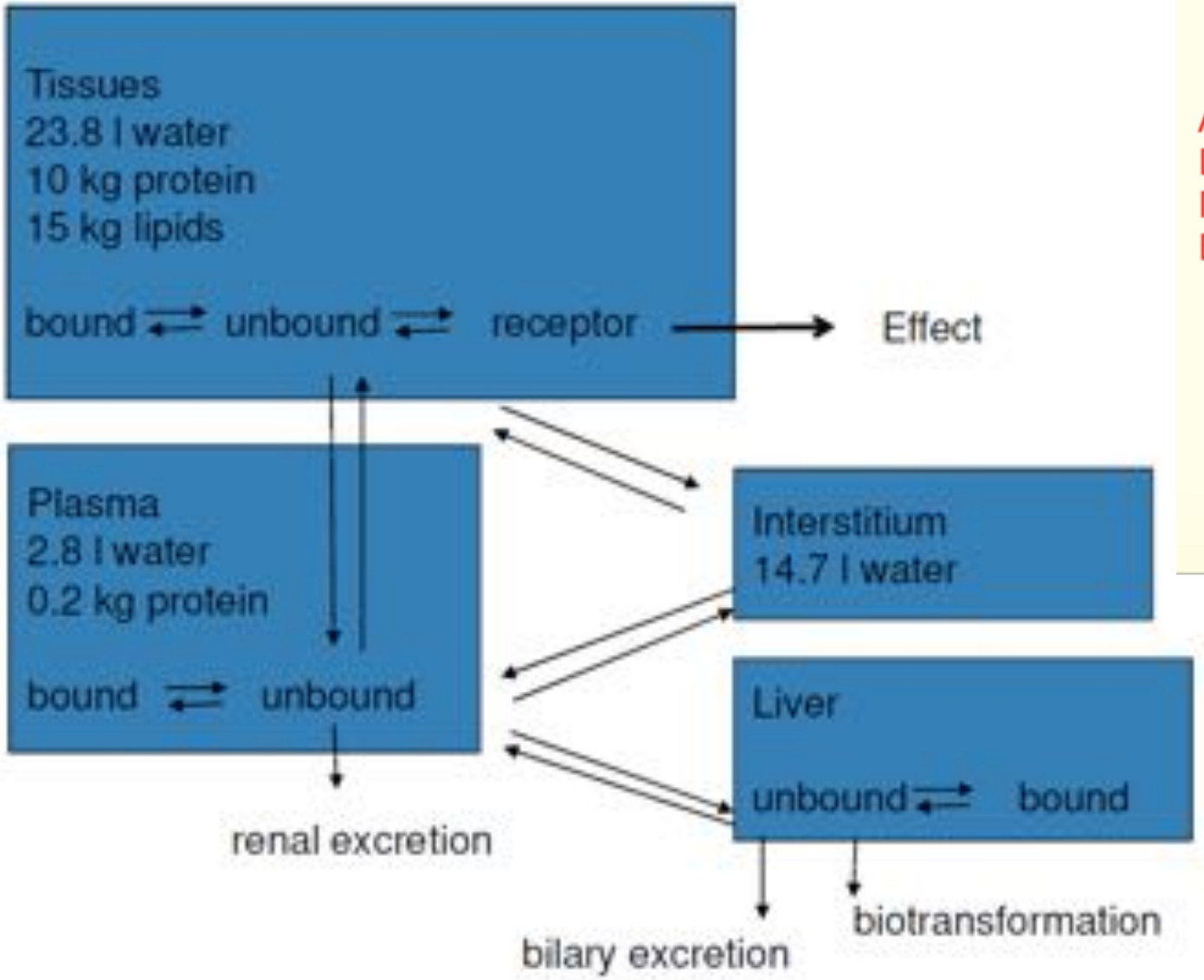
Usually clear understanding up until FIH

PK, ADME, PD - in silico simulation

Fraction unbound $fu = \frac{A_{unbound}}{A_{total}}$

A_ amount of drug
C=concentration of drug





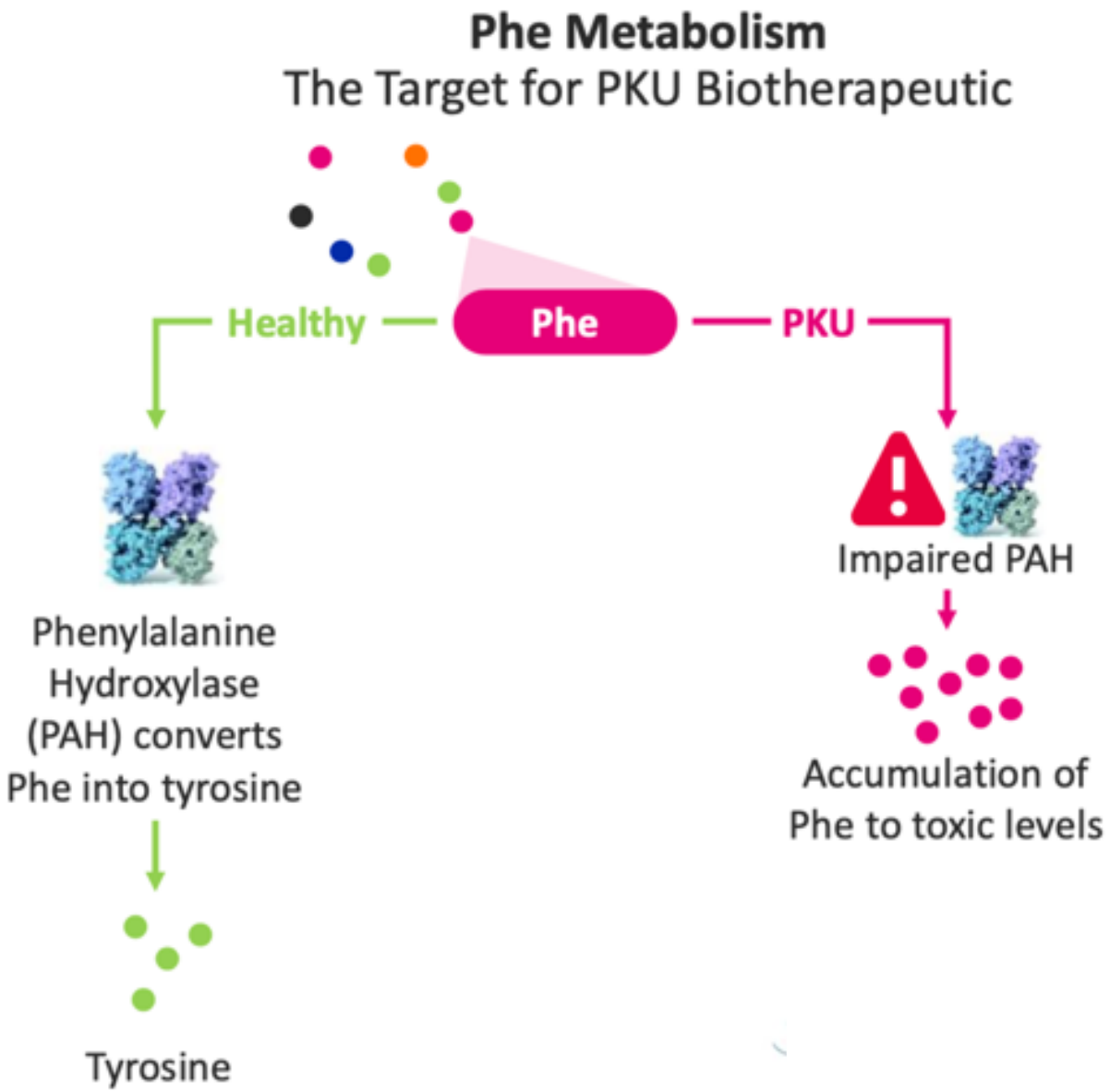
In vitro pharmacology, DMPK, ADME

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)



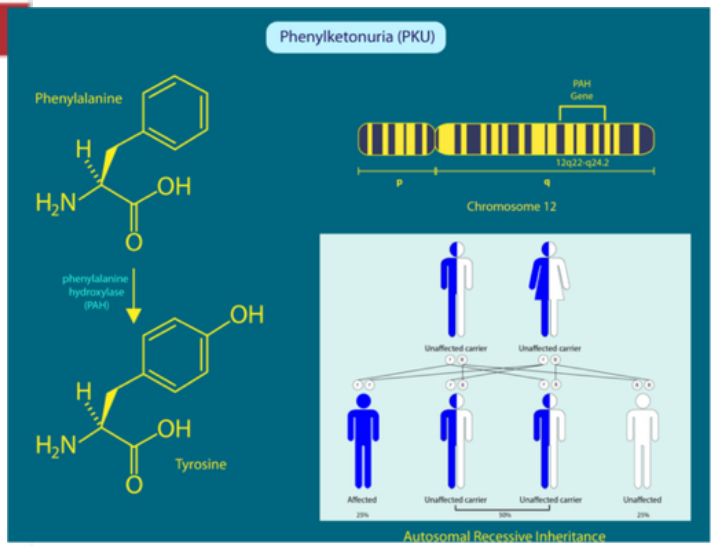
Phenylketonuria : facts and clinical figures

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.

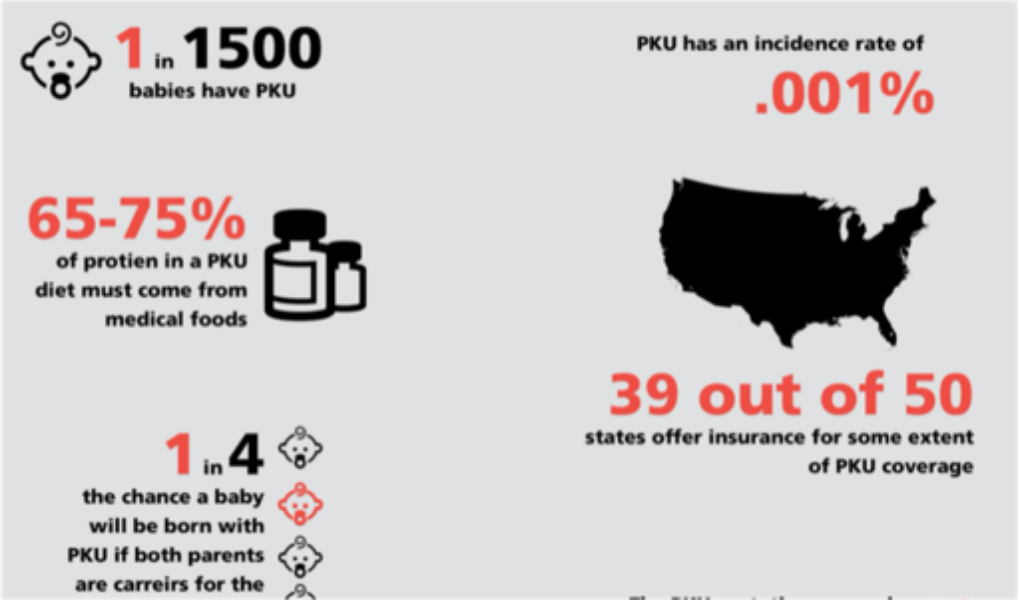


Diagnosis of PKU

- 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]).



Phenylketonuria : medical need

PKU: Significant Need Remains for New Treatment Options

US Population[1]

Pediatrics	Adults
~5,000 U.S.	~12,300 U.S.
25% out of Phe control[2]	**65% out of Phe control[2]**

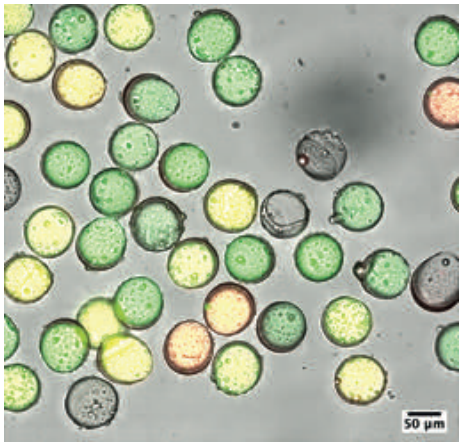
Challenges

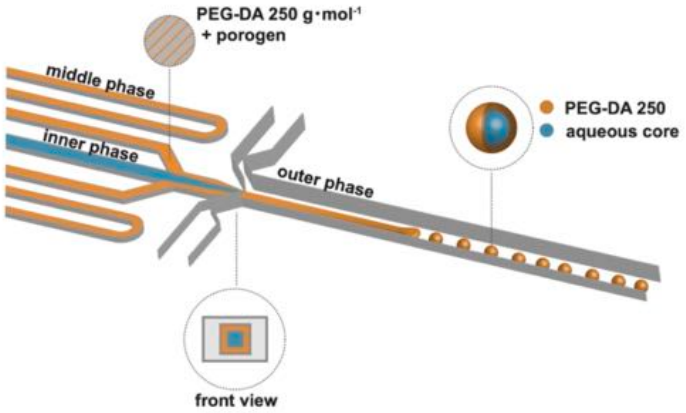
- Significant risk for **neurocognitive impairment** if untreated
- Extremely challenging diet with **low compliance**
- **Low response** to current oral therapies: 80% fail to respond[3]
- Most adult patients **out of Phe control** and difficulties in **executive function**
- Substantial need for increased intake of **natural protein**

Phenylketonuria : galenics 2.0

Fonds national suisse

CHUV Département femme-mère-enfant





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

Grégoire Michielin MD PhD

advisor:

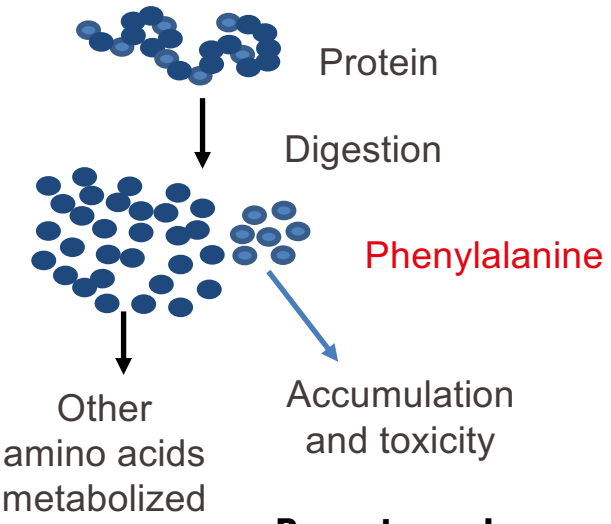
Professor S. Maerkl, LBNC, EPFL

Phenylketonuria : galenics 2.0

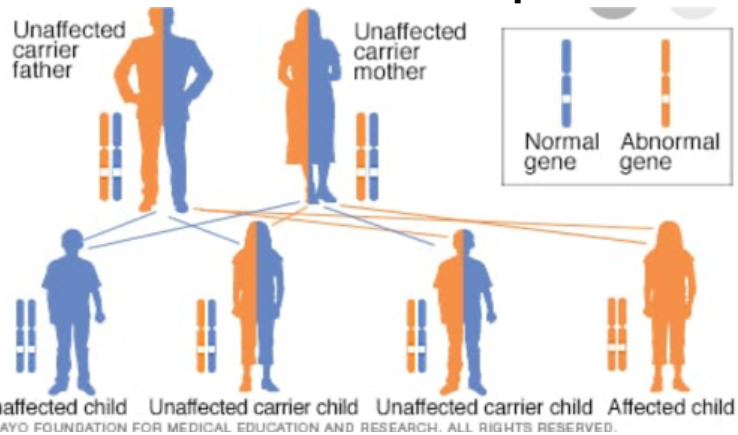
Fonds national suisse

Département femme-mère-enfant

Phenylketonuria

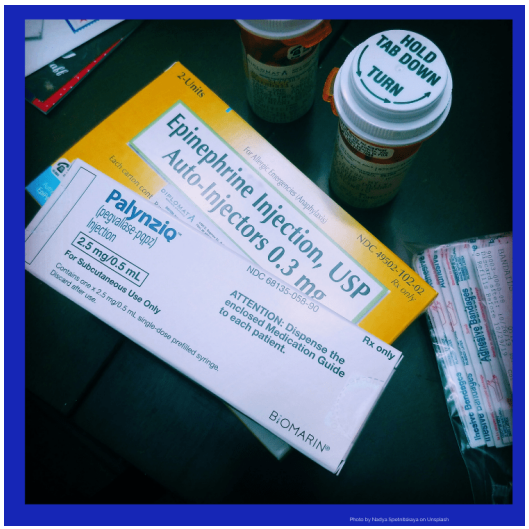


Rare autosomal recessive disorder
1:10'000 birth
0.5 millions patients ww



Context Grégoire Michielin

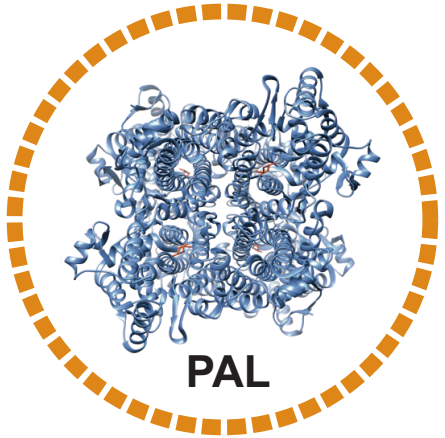
Enzyme replacement therapy by injection



https://prosperouspku.com/2021/04/01/dietary_transition_pku/

pegylated phenylalaninhydroxylase

This projet: Treatment by oral delivery !



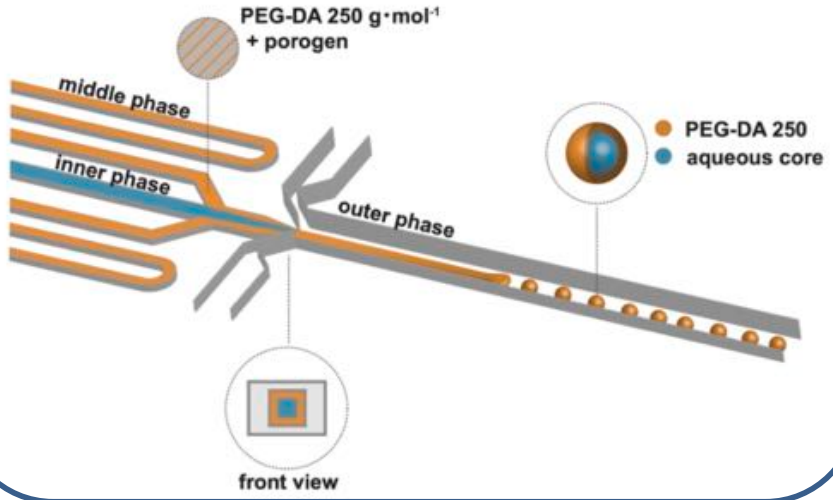
Phenylketonuria : galenics 2.0

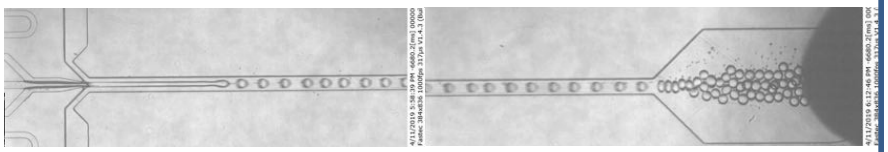
Fonds national suisse

Département femme-mère-enfant

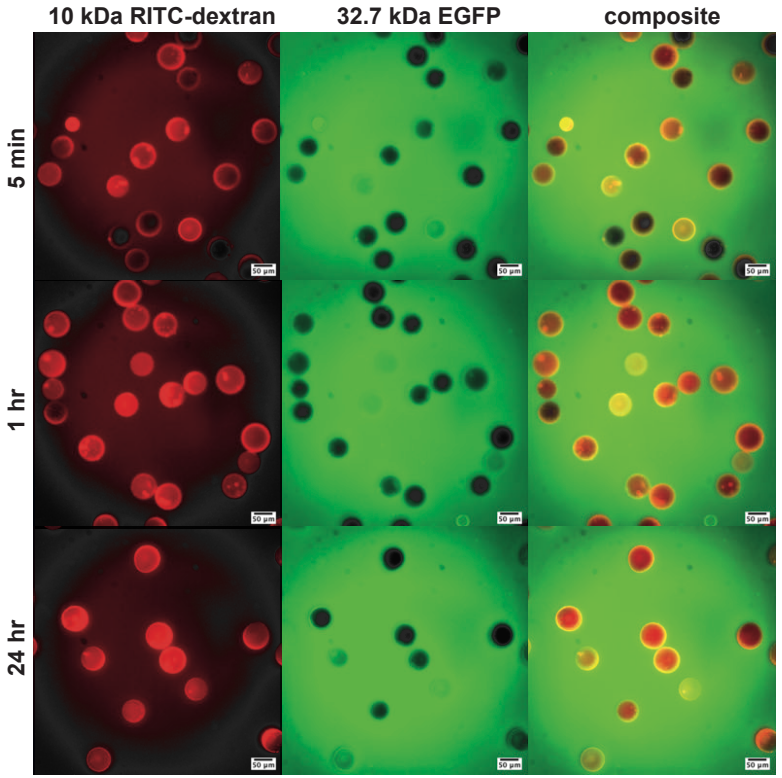
Results (1) Grégoire Michielin

Droplet microfluidics





Semi-permeable capsules



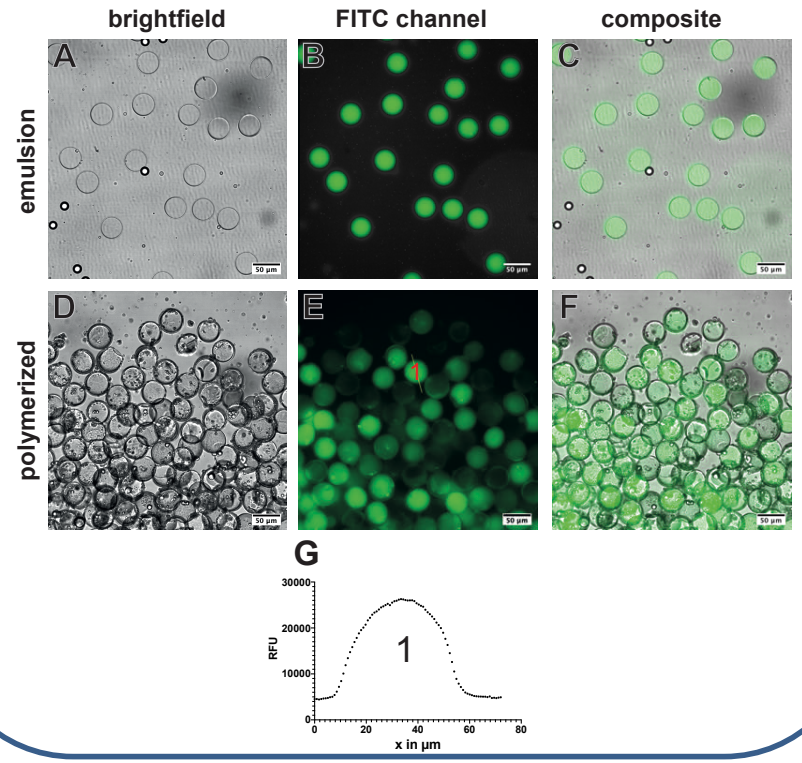
Phenylketonuria : galenics 2.0

Fonds national suisse

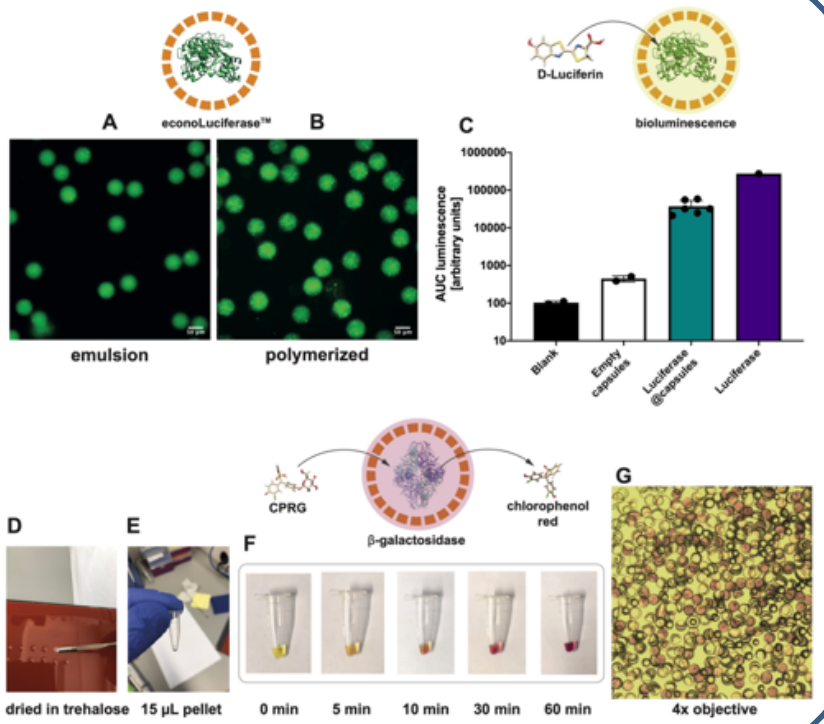
Département femme-mère-enfant

Results (2) Grégoire Michielin

Encapsulation of proteins



And active enzymes

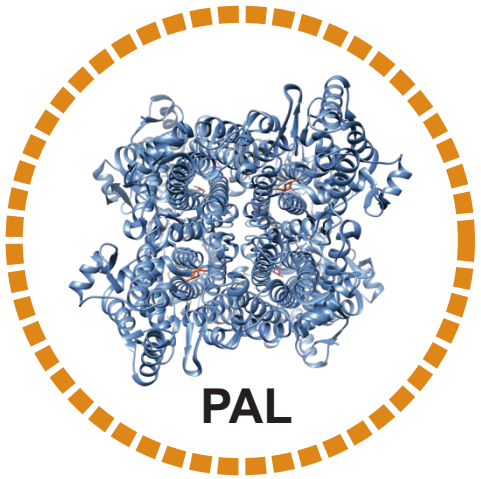


Phenylketonuria : galenics 2.0

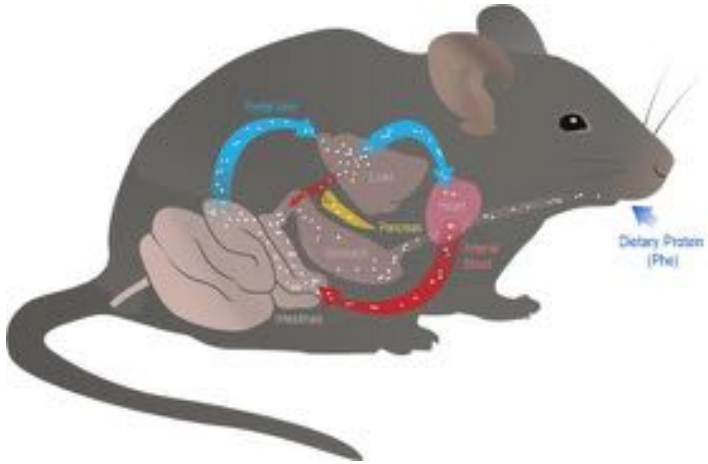
Fonds national suisse

CHUV Département femme-mère-enfant

Deliverables Grégoire Michielin



- Smaller pores
- Co-encapsulation of protease inhibitor

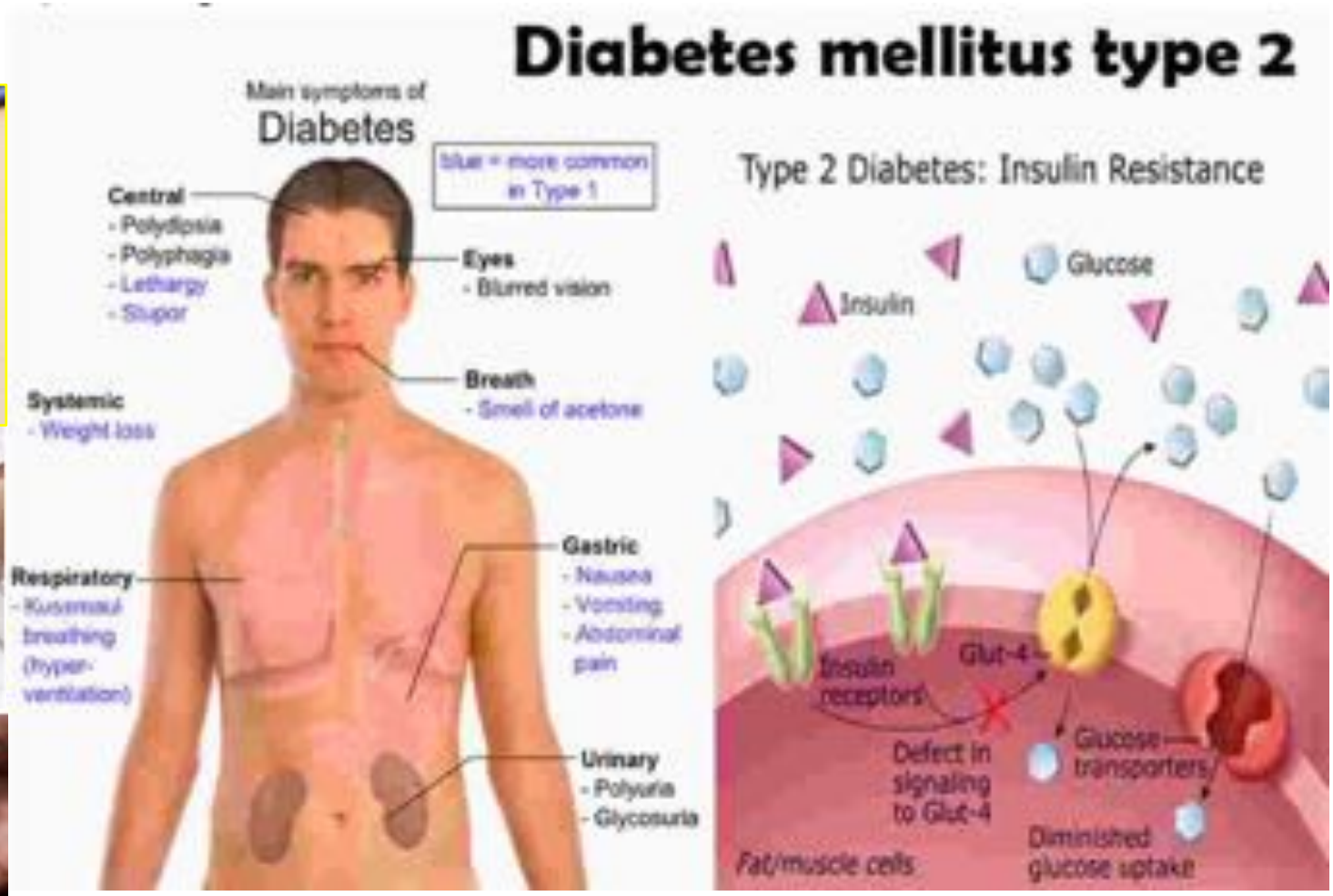


Isabella VM, Ha BN, Castillo MJ, Lubkowicz DJ, Rowe SE, Millet YA, et al. Nature Biotechnology. Nature Publishing Group; 2018 Aug 13;36(9):857–64.

- Preclinical studies
- Mouse/Pig model of PKU

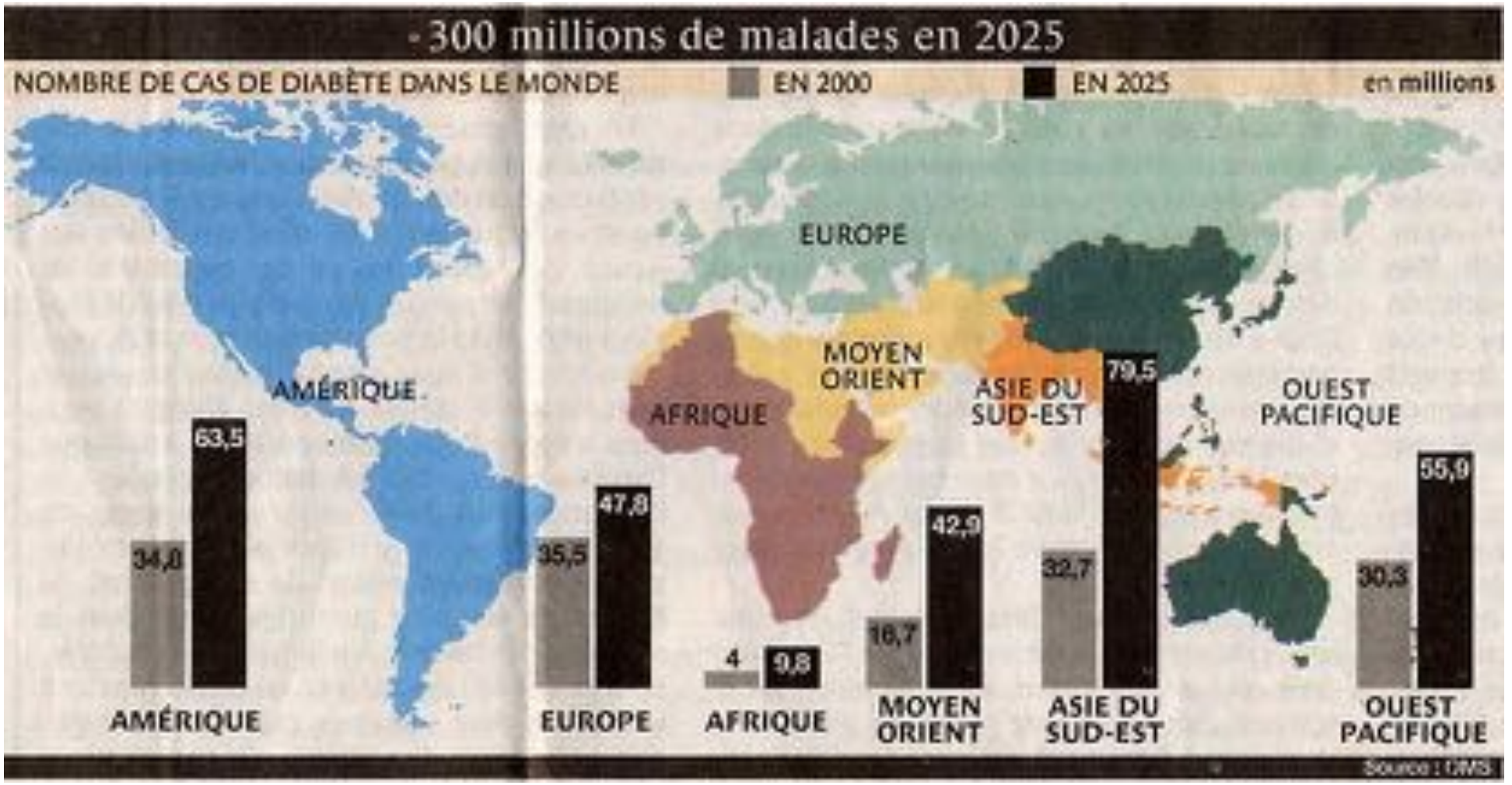
Case study : type 2 diabetes novel medicines : the impact of animal pharmacology and safety

elevated fasting blood glycemia > 1.3g/l



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**

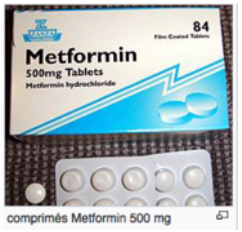
Type II diabetes and metabolic syndrome pandemia _ 2025 : WHO

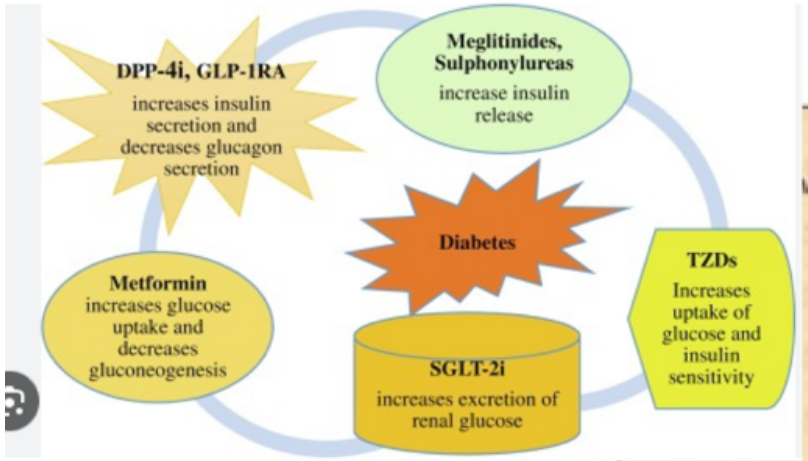


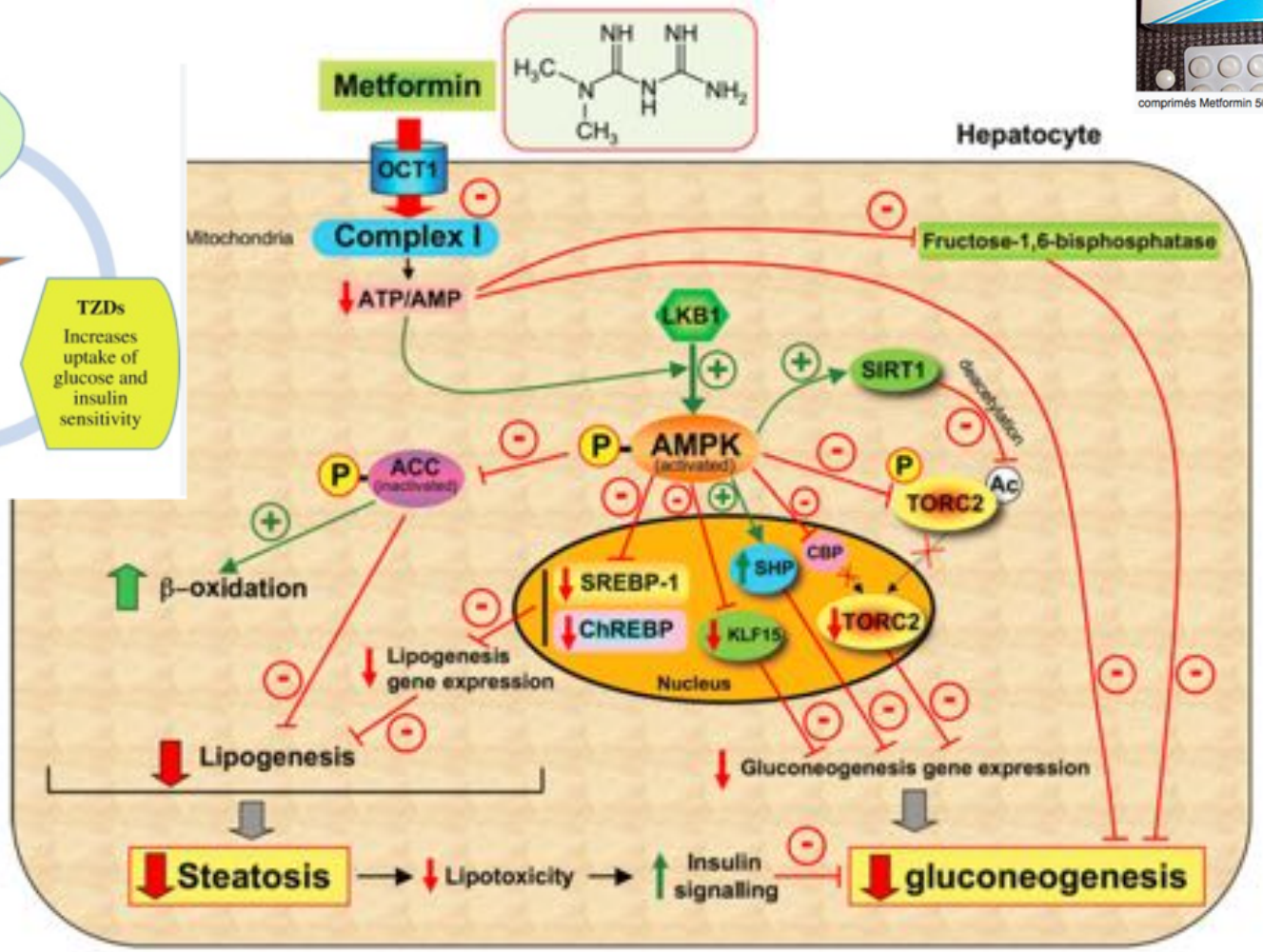
Le Monde

Type 2 diabetes current future therapies

Improve stadart of care : metformin



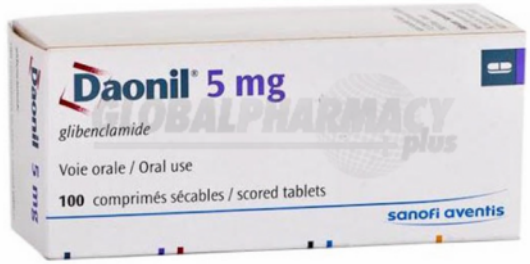




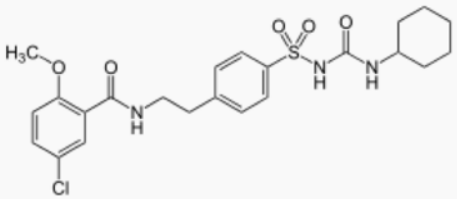
Viollet et al Clinical Sci.(2012) 122:253-270

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

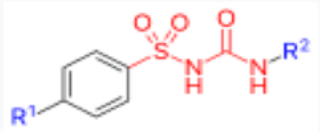
Type 2 diabetes current therapies



Glibenclamide

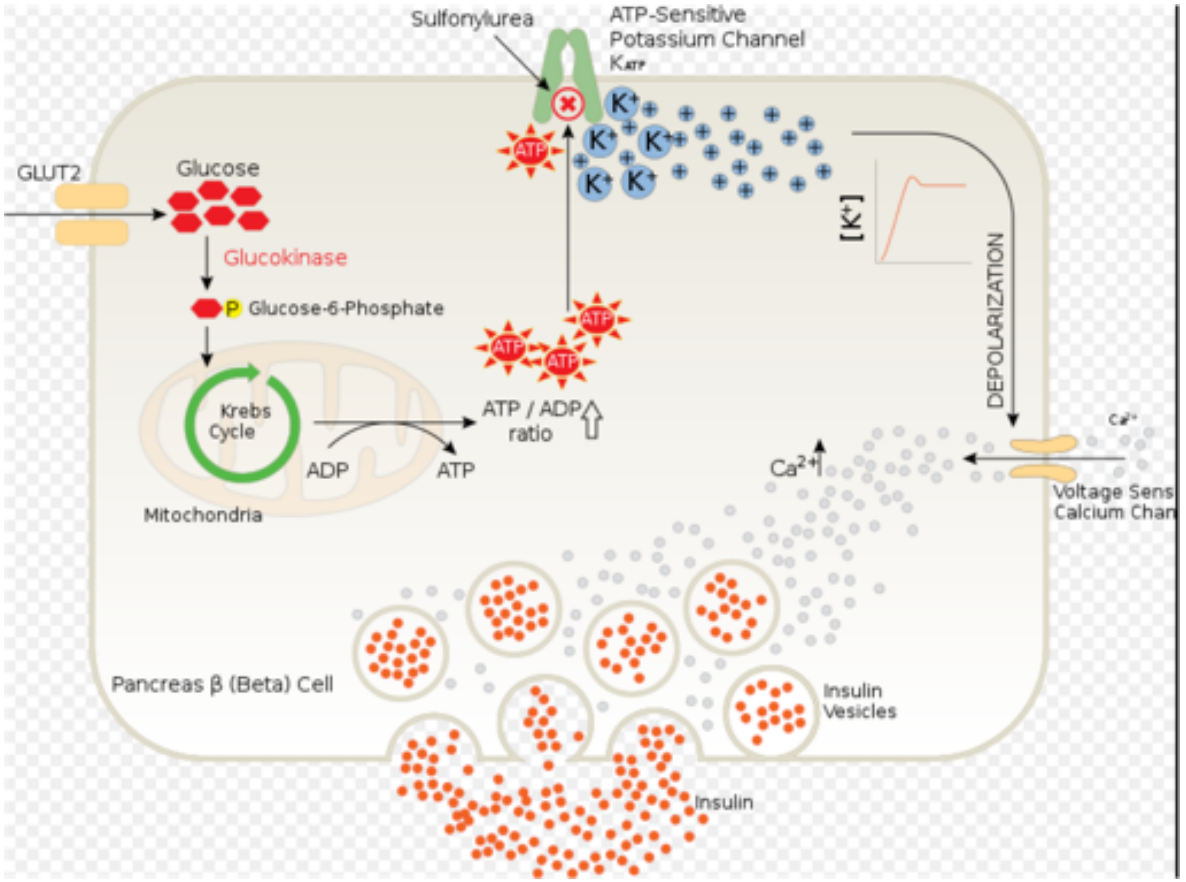


Structure du glibenclamide



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 βcells which in term depolarize voltage gated Ca2+ channels and increase degranulation of proinsulin vesicles

Case study: My story in the development of innovative medicine

The Aleglitazar Story

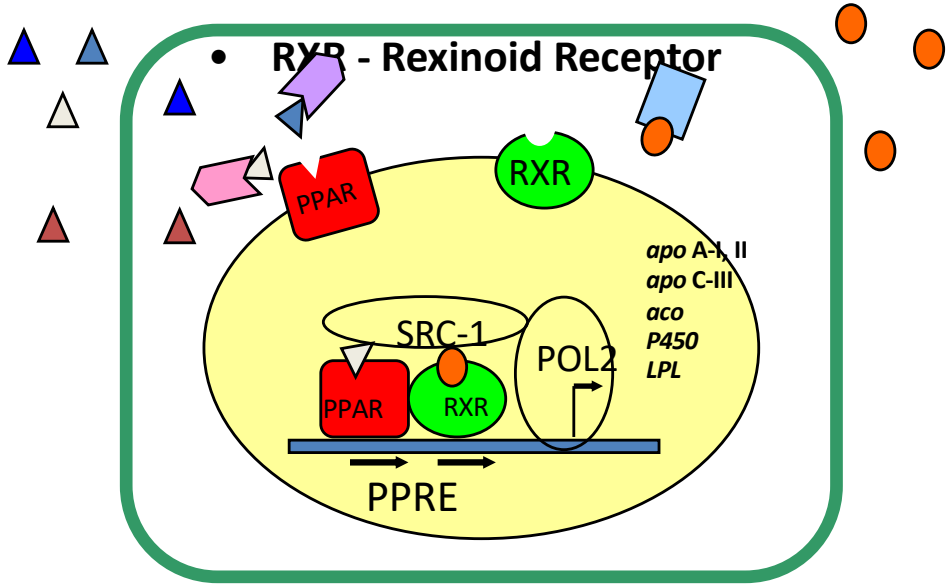
Challenged by developing

a balanced **non TZD PPARalpha PPARgamma** agonist

profiled in insulin resistant and cardiovascular patients

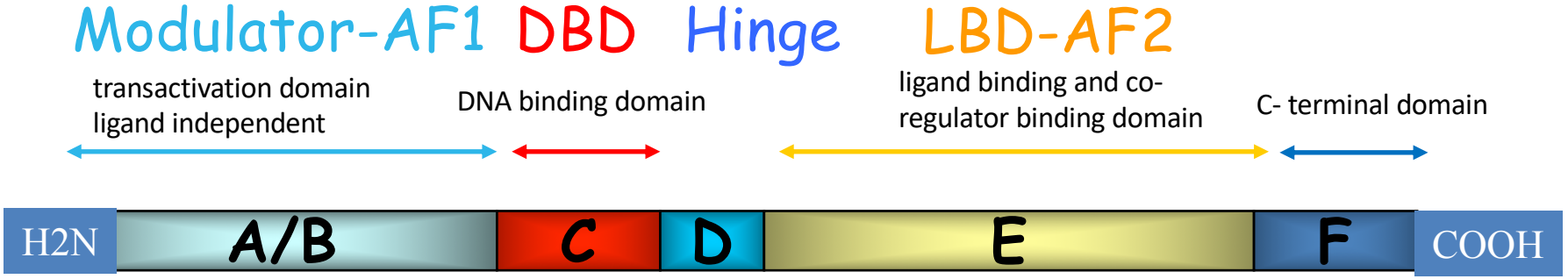
in clinical phase III

- **PPAR - Peroxisome Proliferator Activated Receptor**
- **RXR - Rexinoid 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

CPDs SCREENING CASCADE

PPAR$\alpha\gamma$ receptor binding assay (IC50)

RXR PPAR Heterodimer assay

Db/db mouse screening

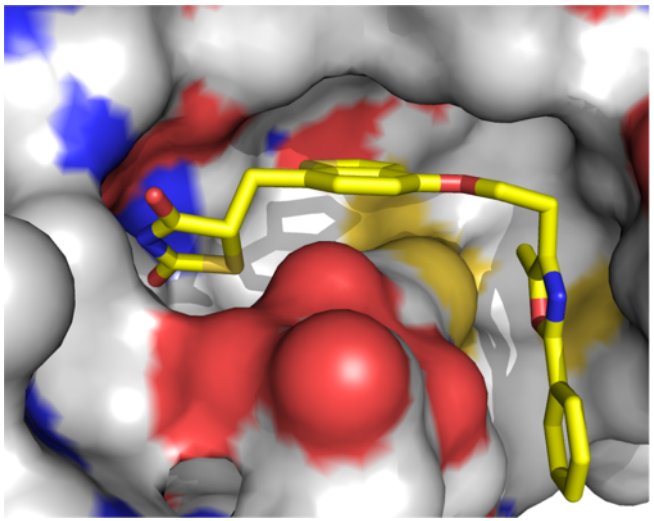
HDL assay in DIO mice and hamster

Safety margin IDB

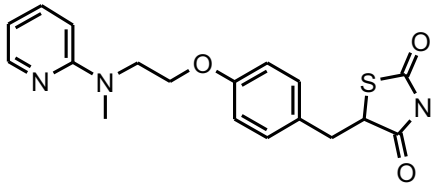
Non human primate monkey

First dose in man

Clinical trials

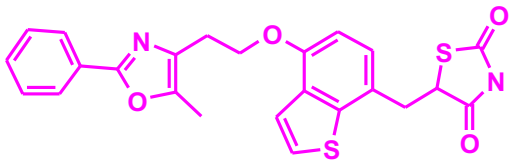


LBD = ligand binding domain



Rosiglitazone (Prototypical PPARgamma Agonist)

GSK-Tail (Phenyloxazole) ⇓ Benzothiophene Spacer (Boehringer "Invention")



Aleglitazar

Balanced PPAR's agonist - the thiazolidinedione class of cpds

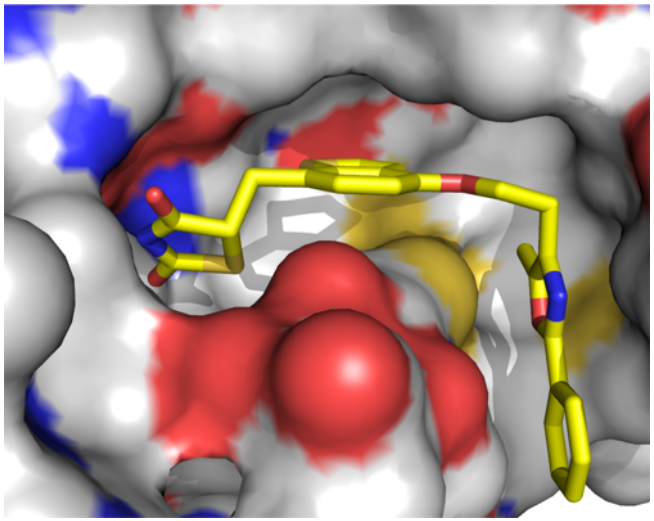
The Aleglitazar Story

Challenged by developing

a balanced **non TZD PPARalpha PPARgamma** agonist

Profiled in insulin resistant and cardiovascular patients

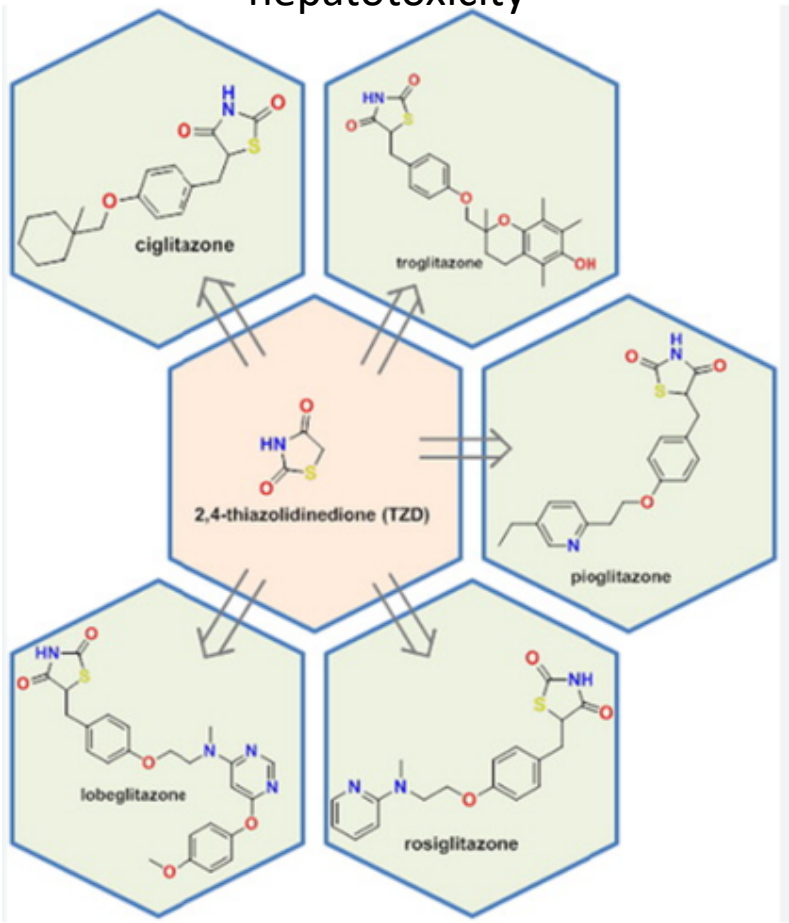
In clinical phase III



LBD = ligand binding domain

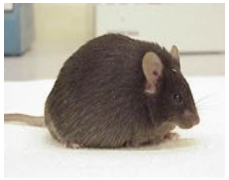
Adverse effects

- **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

4 day p.o
Glucose
Insulin

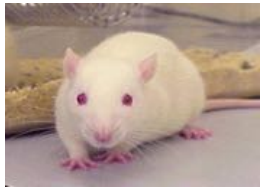


dbdb

> - 40%

† TG

4 day p.o
TG



SD Chol

> - 30%

† HDL

Cynomolgus monkey
Acute (3 hr.)
Glucose / Insulin

Dose-response

ZDF

>SUs

† Hypoglycemia
Rebound & duration

7-10 day p.o
Glucose, Ins, TG

OGTT

ZDF

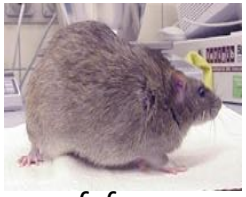
> -40%

† Efficacy
cf TZD/class best

ZDF

>-30%AUC

Clamp



fafa

GIR

† Insulin sensitivity

7-21 day p.o
Lipid profile

Hamster

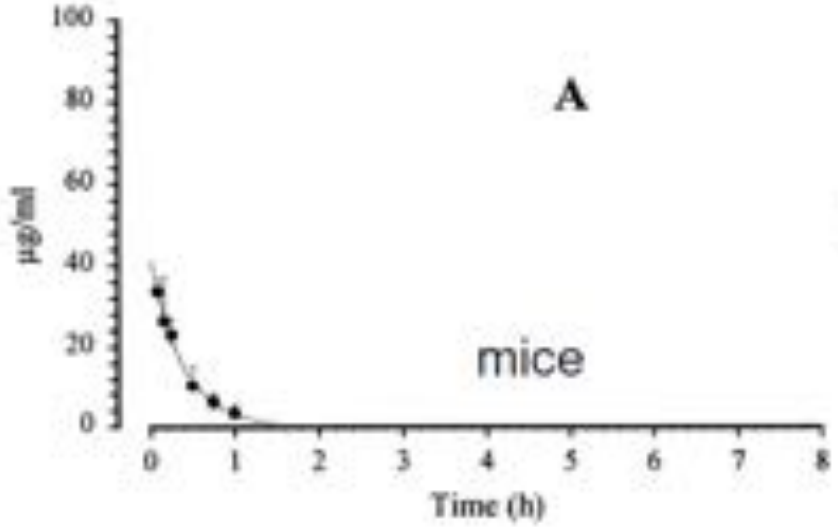
† LDL

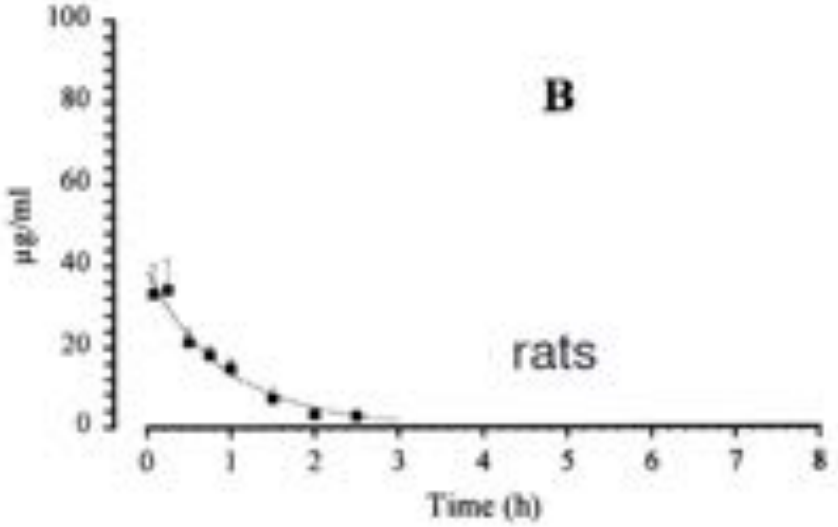
Only the combination of SEVERAL CRITICAL ANIMAL PHARMACOLOGICAL MODELS may predict the therapeutic value of an innovative medicine in future first-in-human clinical settings/trials

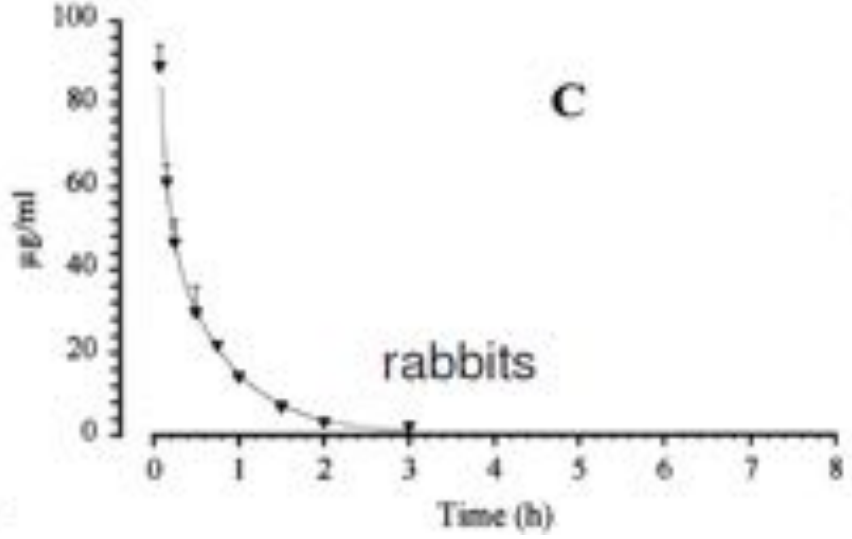
Case study: a balanced PPAR's agonist - the aleglitazar story

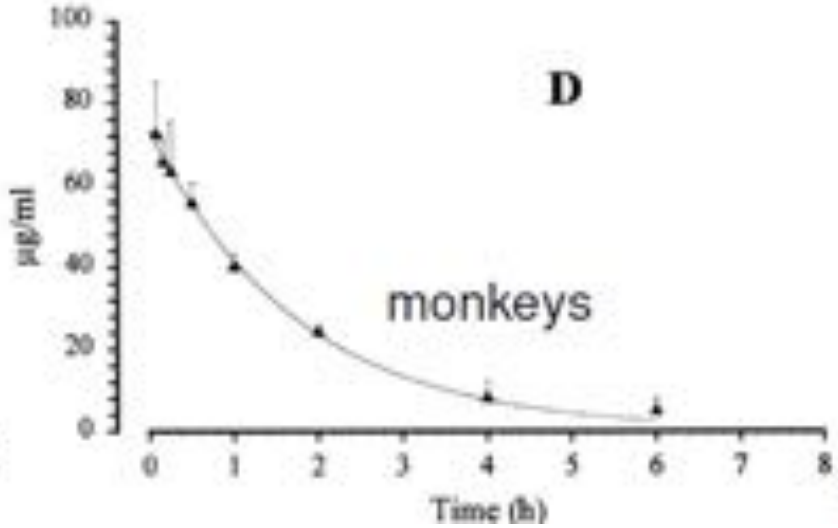
Pharmacokinetics	Total clearance	6.2 ml/min/kg	1.6 ml/min/kg
(Rat)	Vss	1.3 l/kg **(Cyno-monkey)**	0.4 l/kg
	Bioavailability	70 %	68 %
	T1/2	4 h	12.9 h
Safety (*in vitro*)	Cyp	3A4 19; 2C9 4.0; 1A2 >50	2D6 >50; 2C19 12 μM
	hERG	negative	
	Ames/MNT	negative	
	Phsopholipidosis	negative	
	Phototoxicity	negative	

PK PD *in vivo* different species tested



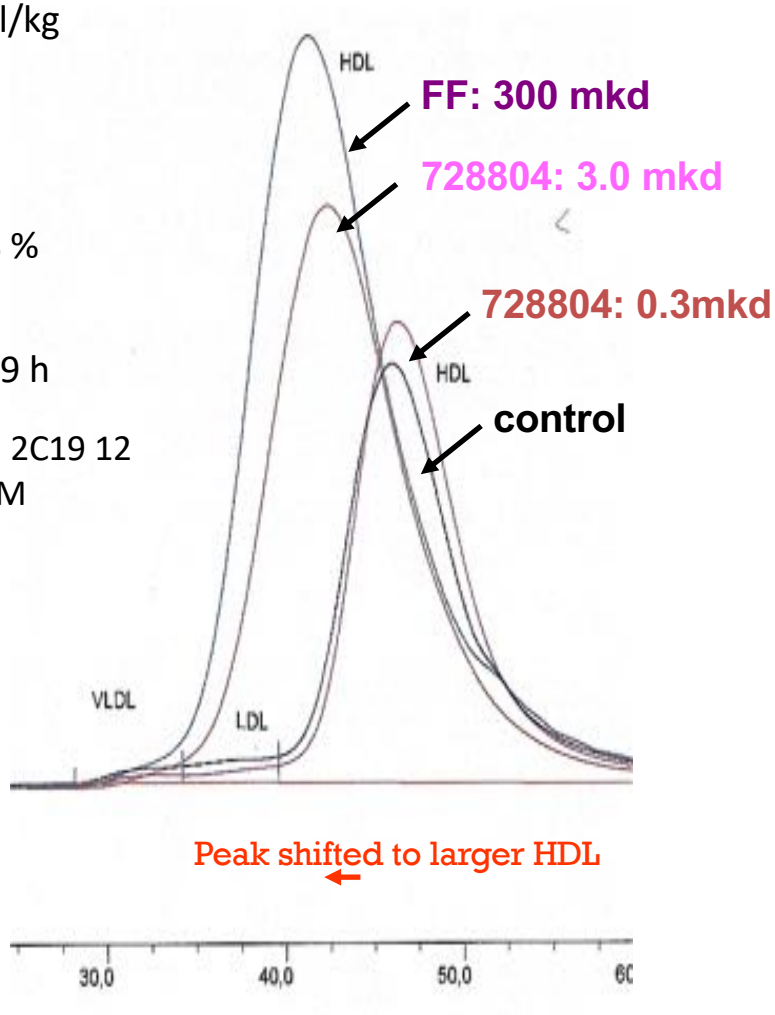






Case study: a balanced PPAR's agonist - the aleglitazar story

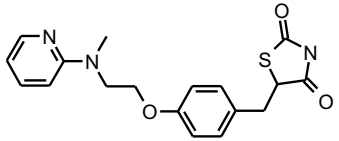
Pharmacokinetics	Total clearance	6.2 ml/min/kg	1.6 ml/min/kg	7-21 day p.o Lipid profile
(Rat)	Vss	1.3 l/kg **(Cyno-monkey)**	0.4 l/kg	
	Bioavailability	70 %	68 %	
	T1/2	4 h	12.9 h	
Safety (*in vitro*)	Cyp	3A4 19; 2C9 4.0; 1A2 >50	2D6 >50; 2C19 12 μM	
	hERG	negative		
	Ames/MNT	negative		
	Phospholipidosis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

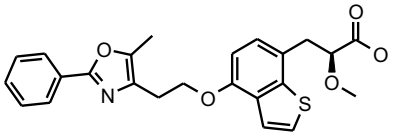


Case study: a balanced PPAR's agonist - the aleglitazar story

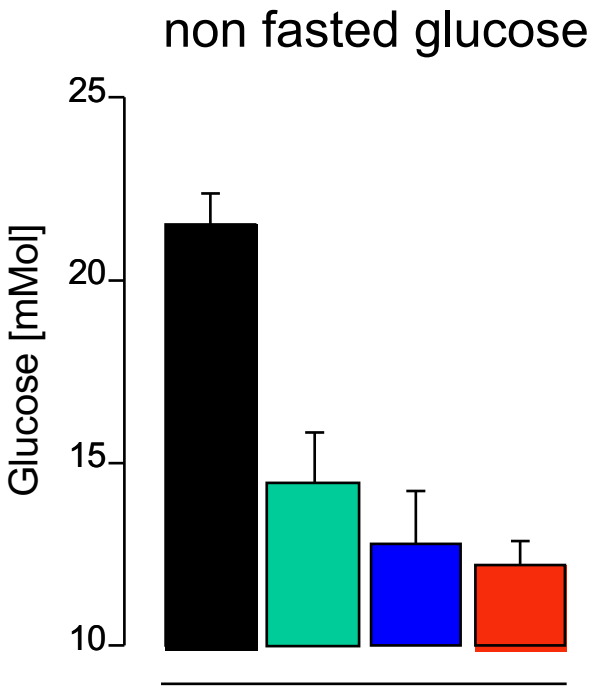
Treatment of db/db mice for 12 days

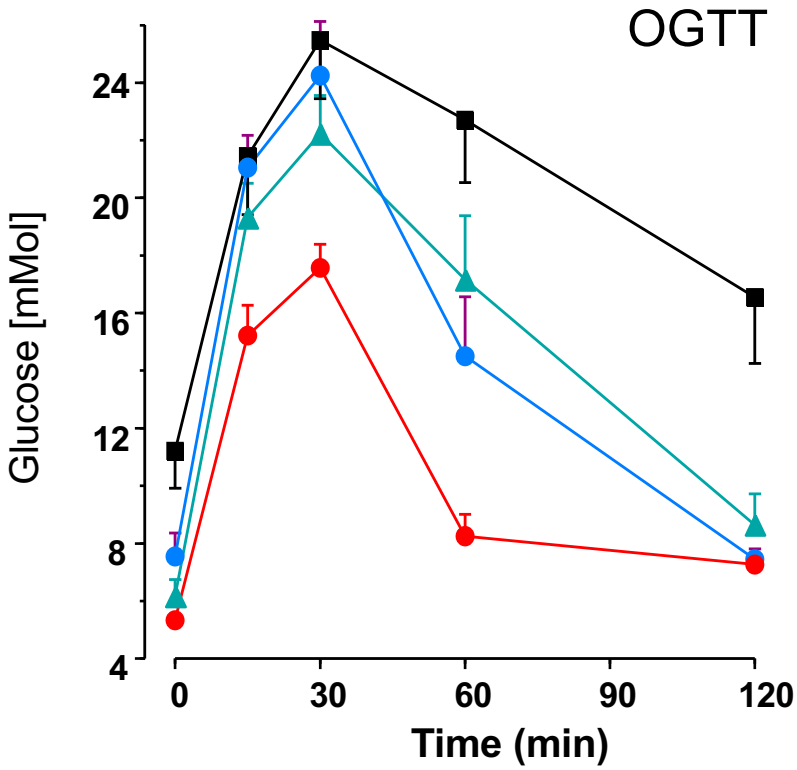
Rosiglitazone





Aleglitazar





Placebo

RSG
3 mkd

RO072000
0.3 mkd

RO072001
3.0 mkd

Efficacy and safety (adverse effects) is what patients care first !

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."

Kimmelmann 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 volonteer 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 pysician Paracelsus *:* the beginning of toxicology

«every medicine is a poison in disguise»

1493-1541

Paracelsus studied medicine at University of Basel Switzerland (founded April 4, 1460 !)

“solely the dose determines that a thing is a poison or not” *(sola dosis facit venenum)*

Swiss pysician Paracelsus *:* the beginning of toxicology

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Safety assessment : Paracelsius in the belgian comic strips !

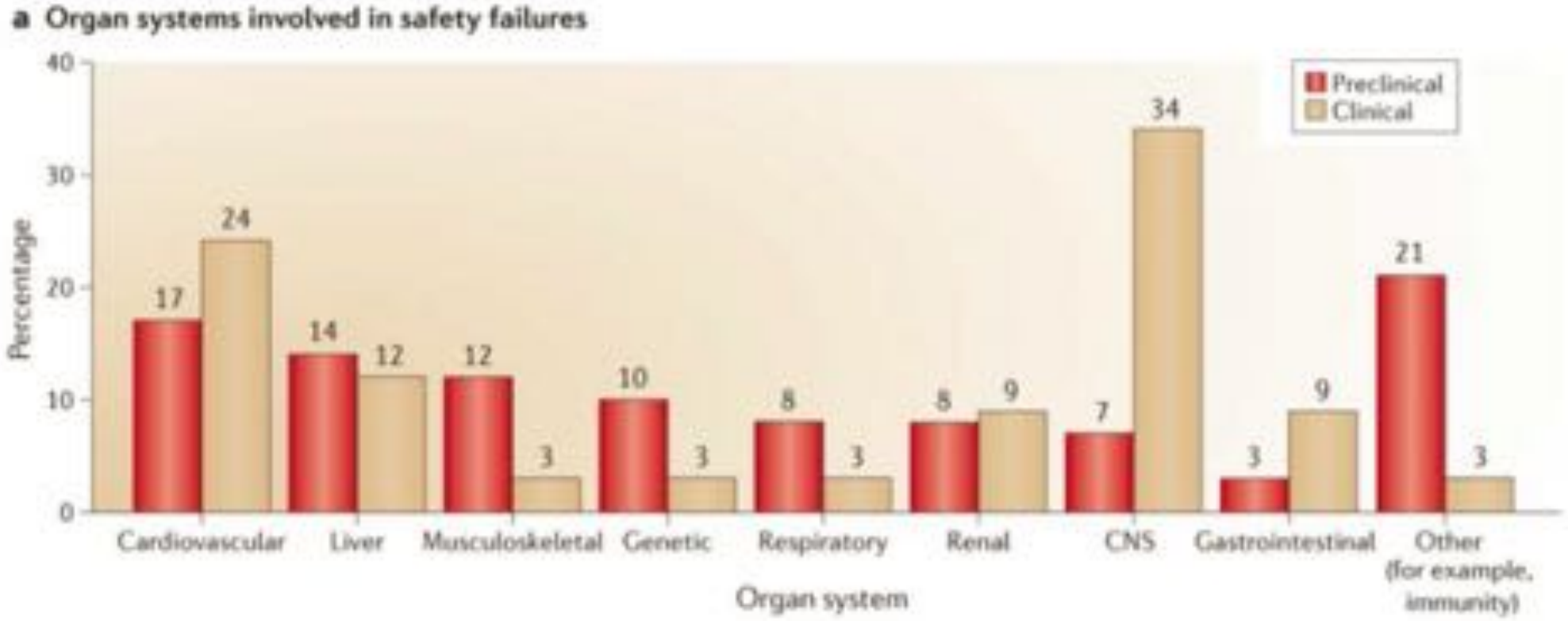
“solely the dose determines that a thing is a poison”
(dosis sola facit venenum)

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

- Depakine
- Opioid
- Thalidomide
- and more tox catastrophes

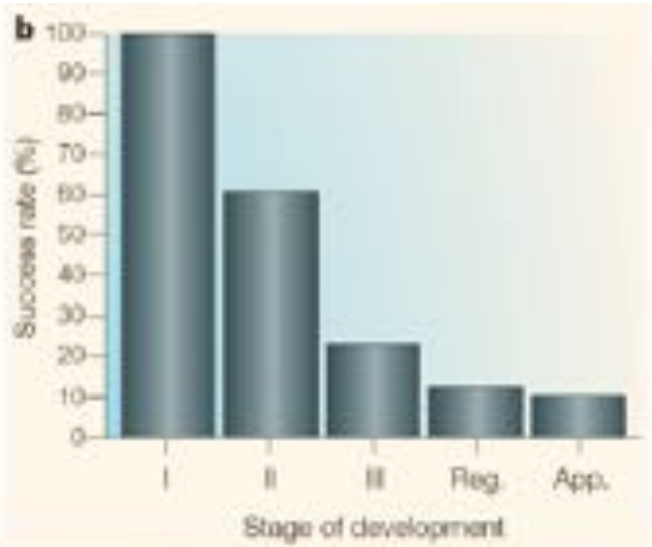
- A BALANCING ACT : NO THERAPIES WITHOUT ADVERSE EFFECTS !
- ANY THERAPEUTIC PHARMACOLOGICAL INTERVENTION SHOULD HOWEVER BE SAFE : TODAY'S INVESTIGATIVE TOXICOLOGY IS KEY !
- Paracelsius -16th cent : "every drug is a poison in disguise" *(sola dosis facit venenum)*

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

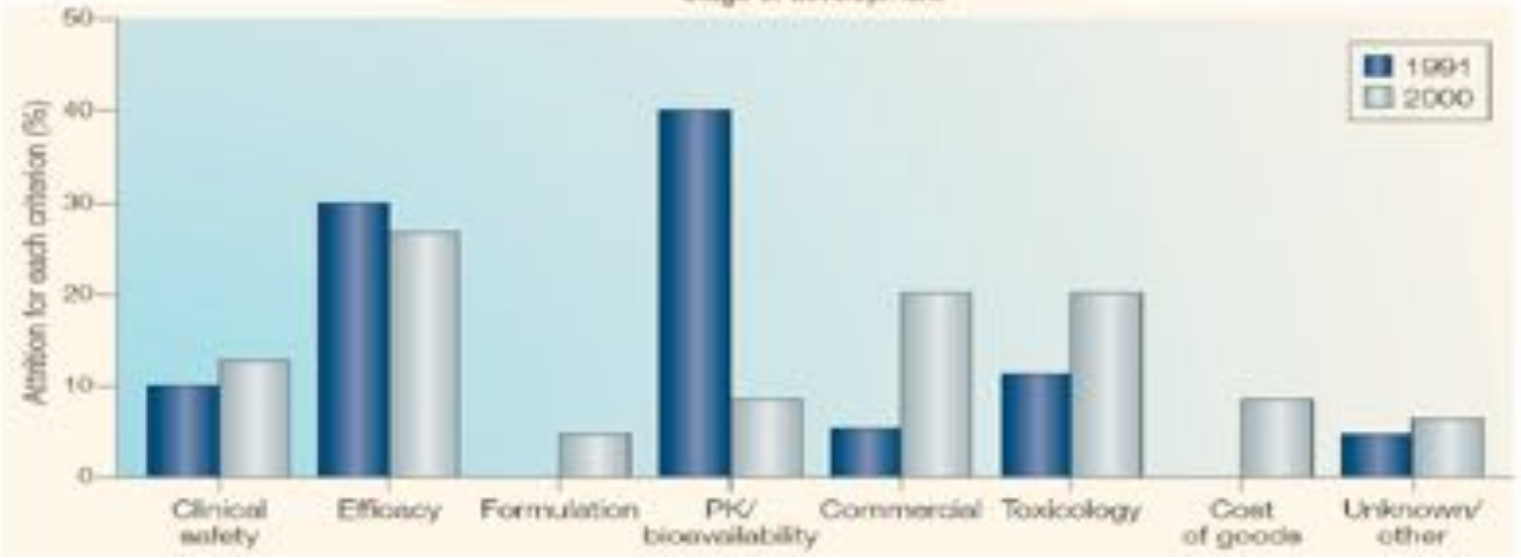


Food for thoughts : the biggest risk for human beings is not to get a safe and efficacious medicine !

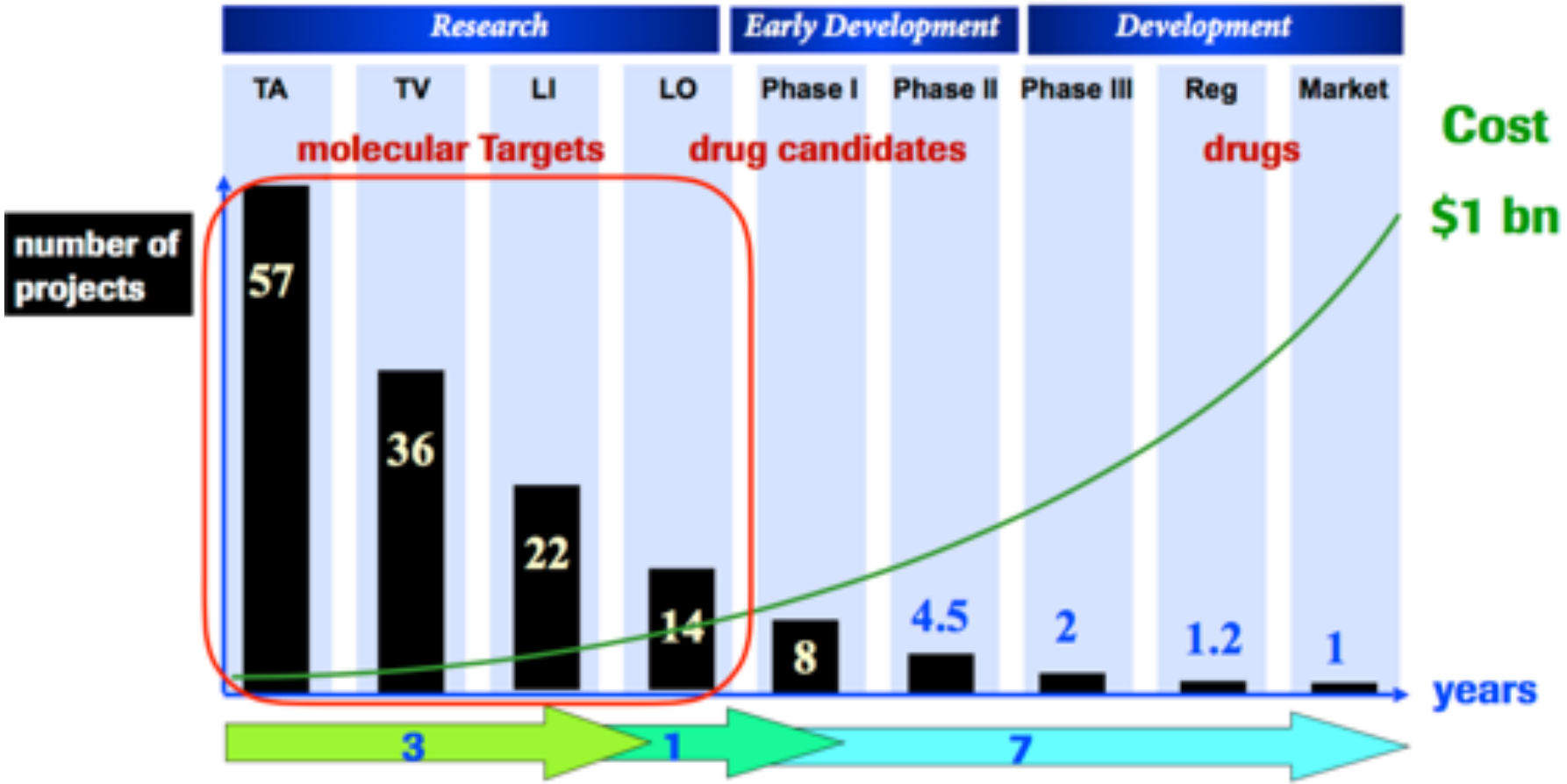
Safety vs Efficacy : drug development success rate overall and by criteria



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



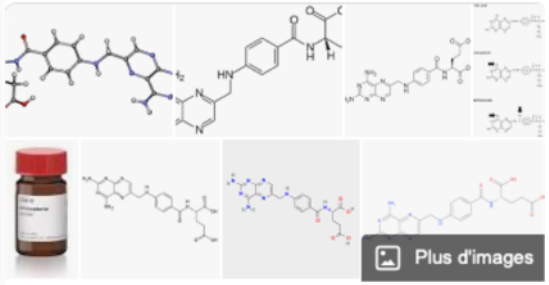
High attrition rate : only very few experimental medicine makes it to the clinical practice



>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

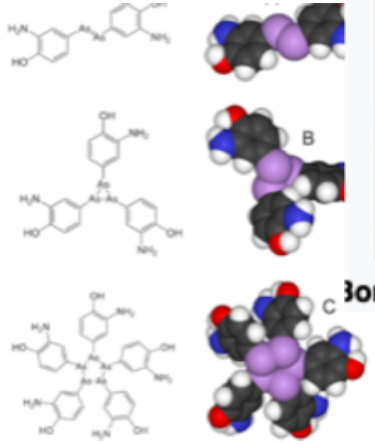


Aminoptérine (Aminopterin)

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

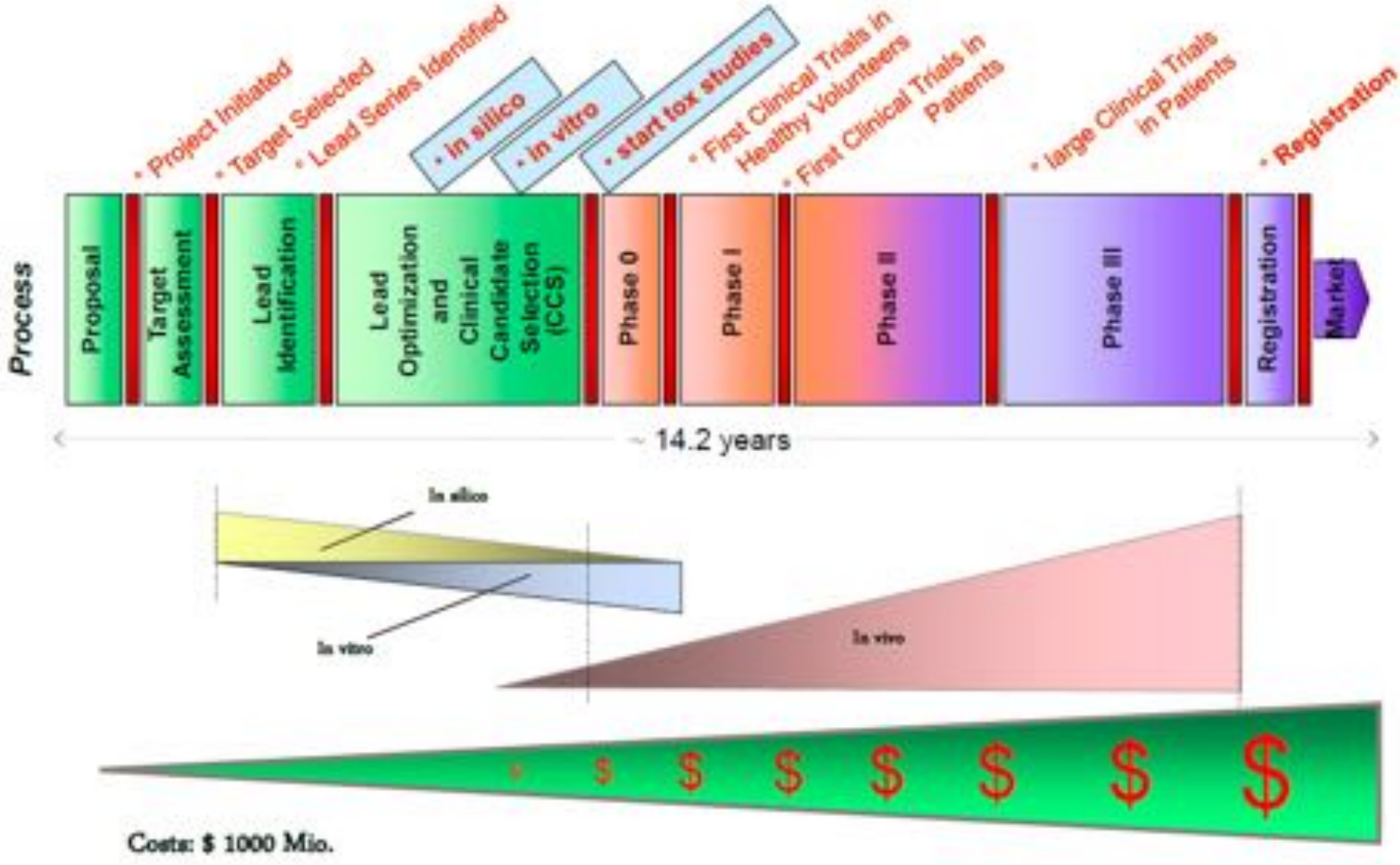
Born 14 March 1854

"20th century turned poison into a medicine (the advent of chemotherapy) !

vindicating Paracelsus findings :"solely the dose determines that a thing 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



Early days of toxicology _ safety at its infancy _turns into a tox scandal

The thalidomide story…60 YEARS AGO

nausea with pregnant women !

Sedativ

NO TOXICITY IN AN

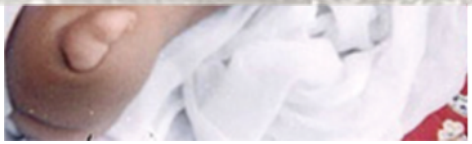
(today ant

10 000 cases world wide

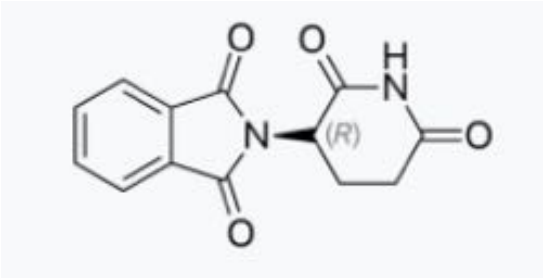
birthde

Phocomelia (limb ma

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



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



Contergan® from Grünental Chemie 1957
wthdrawn in 1961

Early days of toxicology _ safety at its infancy _turns into a tox scandal : the critical involvement of drug regulatory bodies FDA EMEA SWISSMEDIC

The thalidomide story…60 YEARS AGO

nausea with pregnant women !

Sedative ! Anxiolytic !

NO TOXICITY IN ANIMAL MODELS, NO MOA !

Catalyzed a drasti
approval and m

10 000 cases world wide patients (fewer in USA thanks to Frances Kathleen Kelsey) affected by birth defects such as
Phocomelia (limb malformation), deafness,

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

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

Contergan® from Grünental Chemie 1957

Investigative toxicology : thalidomide reloaded

The thalidomide story TODAY

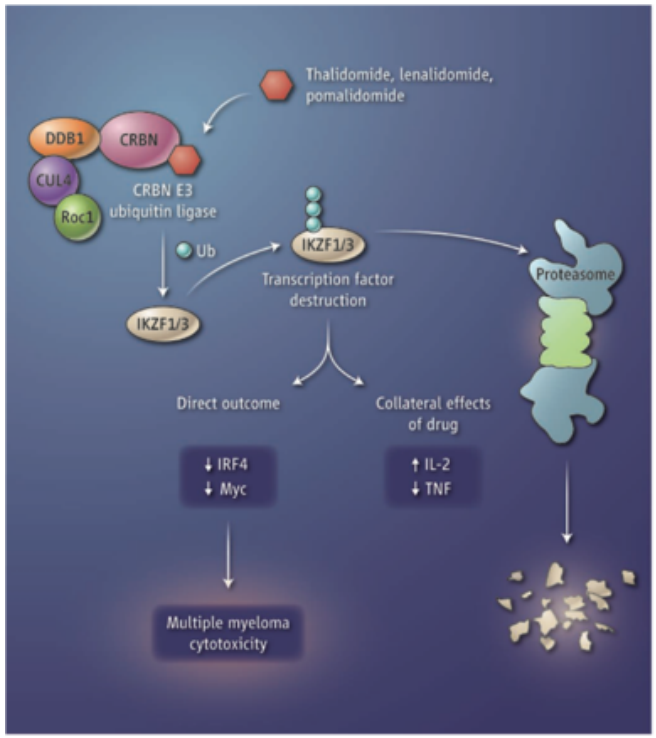
comes back with MOA and strict safety requirements (pregancy test !)

multiple myeloma in B cell malignancies

IMiDs-Immunomodulatory drug

NK cells stimulation, cytokine IL6 production

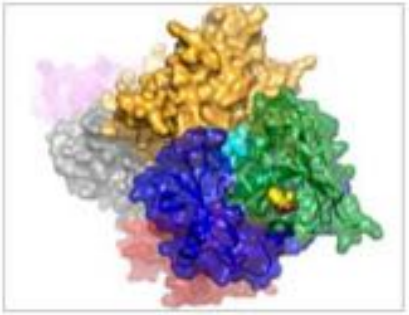
How thalidomide works against cancer



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.

Stewart KA et al (2014) Science 343:256-258

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



Mode of action (MOA) of thalidomide recently elucidated !

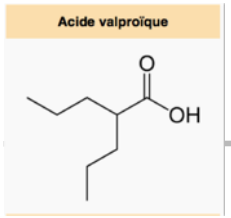
Crystal structure of thalidomide (yellow) bound to CRBN and DDB1.

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 on "undruggable therapeutic targets" such as Zinc fingers

"molecular glue between protein:protein interaction"

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



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

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

Principe actif
Valproate de sodium

Laboratoire
Sanofi puis génériques

Traitement
Épilepsie
et troubles bipolaires
(Dépakote, Dépamide)

Risques
Exposition in utero
Malformations 10%
Retards intellectuels, marche
Cas d'autisme Jusqu'à 40%

50 000 à 70 000
victimes possibles
depuis 1967
Apesac

14 322
femmes enceintes «exposées» au valproate de sodium entre 2007 et 2014
ANSM

Environ **450 enfants** nés avec des malformations entre 2006 et 2014
Igas

1967 **Mise sur le marché**

1982 1er cas de **malformations congénitales** documentés

2000 Troubles **neuro-comportementaux** 1ères publications

2004 *Fortes présomptions*

2006 **Déconseillé pour la 1re fois pour la femme enceinte**

2011 *Preuves formelles*

2013 Renforcement des **mises en garde**

2014 Nouvelles restrictions à l'échelle européenne

2016 Obligation de **signature** d'un protocole d'accord de soins pour la patiente

Études scientifiques

Observations de troubles du spectre de **l'autisme** → *Établis avec certitude*

DÉPAKINE® + GROSSESSE = DANGER

Ne pas utiliser chez les filles, adolescentes, femmes en âge de procréer ou enceintes, sauf en cas d'échec des autres traitements.

40 (!) years to introduce pregnancy and correlate **teratogenicity** with valproate salt prescription ! Nowadays mandatory pregnancy test before prescription ! Sanofy 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.**

Safety is first concern of patients and some lawyers…

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.

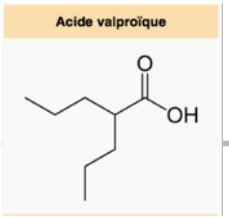
HOW SAFETY IS IMPORTANT TO PHARMAS ?
HOW SERIOUS CAN CLASS ACTION BE ?

SEVERAL PHARMA SCANDALS IN COURT TRIALS

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 ».



Today's safety issues - improve on pharmacoviligence worldwide !

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

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

24heures SIGNÉ LAUSANNE

Vaud&Régions Suisse Monde Économie Sports Savoirs Culture High-Tech People Vivre Auto Plus

Fédérales 2019 Suisse romande Faits divers Images

Publicité

Programme de partenariat

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

▸ Plus

Dépakine: Swissmedic et industrie pharma épinglés

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

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.

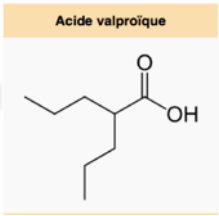
January 2020 : Depakine® swiss patients suing pharma and swissmedic (authority)

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

24heures SIGNÉ LAUSANNE

Vaud&Régions Suisse Monde Économie Sports Savoirs Culture High-Tech People Vivre Auto Plus

Le Matin Dimanche Enquête E-paper Abonnements

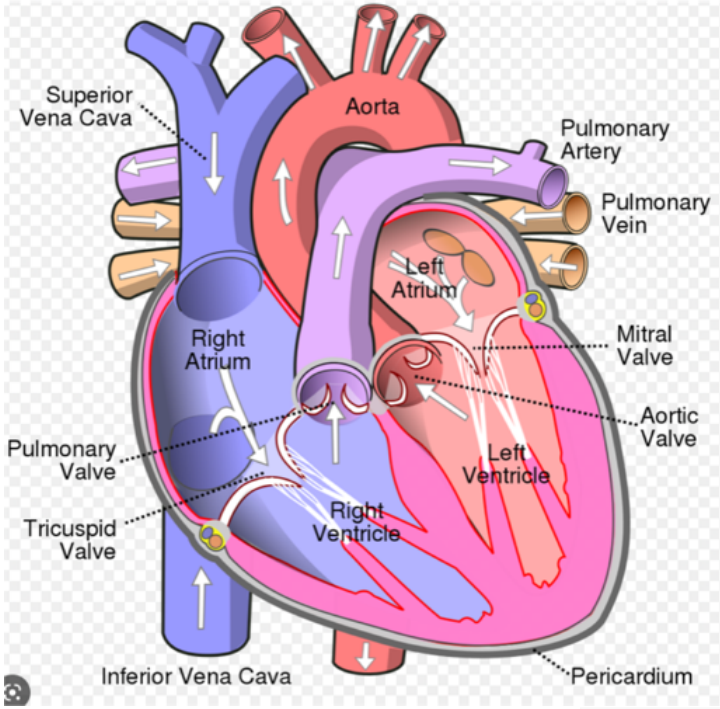


Dix enfants handicapés se battent contre les médecins et la pharma

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.

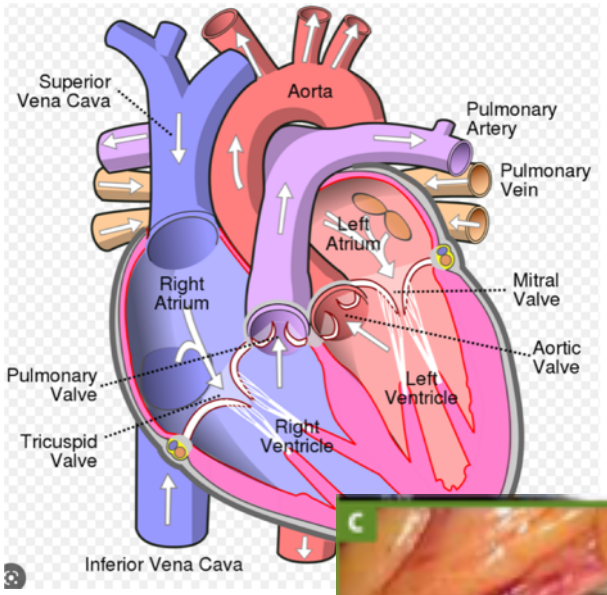
- **40 years (!) to introduce pregnancy and correlate with teratogenicity/mental retardation and valproate salt prescription ! Mandatory pregnancy test before prescription ! Too bad it had been already prescribed !!**
- Prescribed in manic-depressive patients, and helps prevent migraine headaches and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

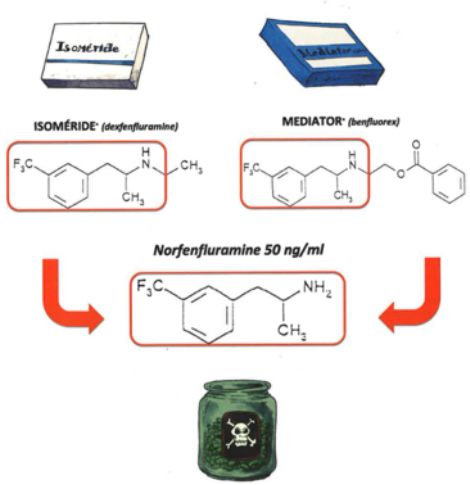
Mediator ® : a french pharma scandal : reported > 2000 death cases

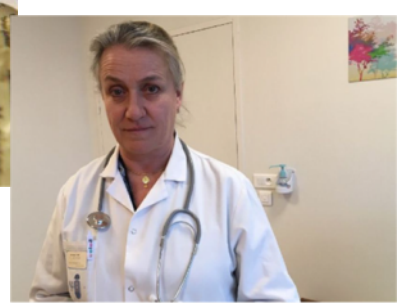


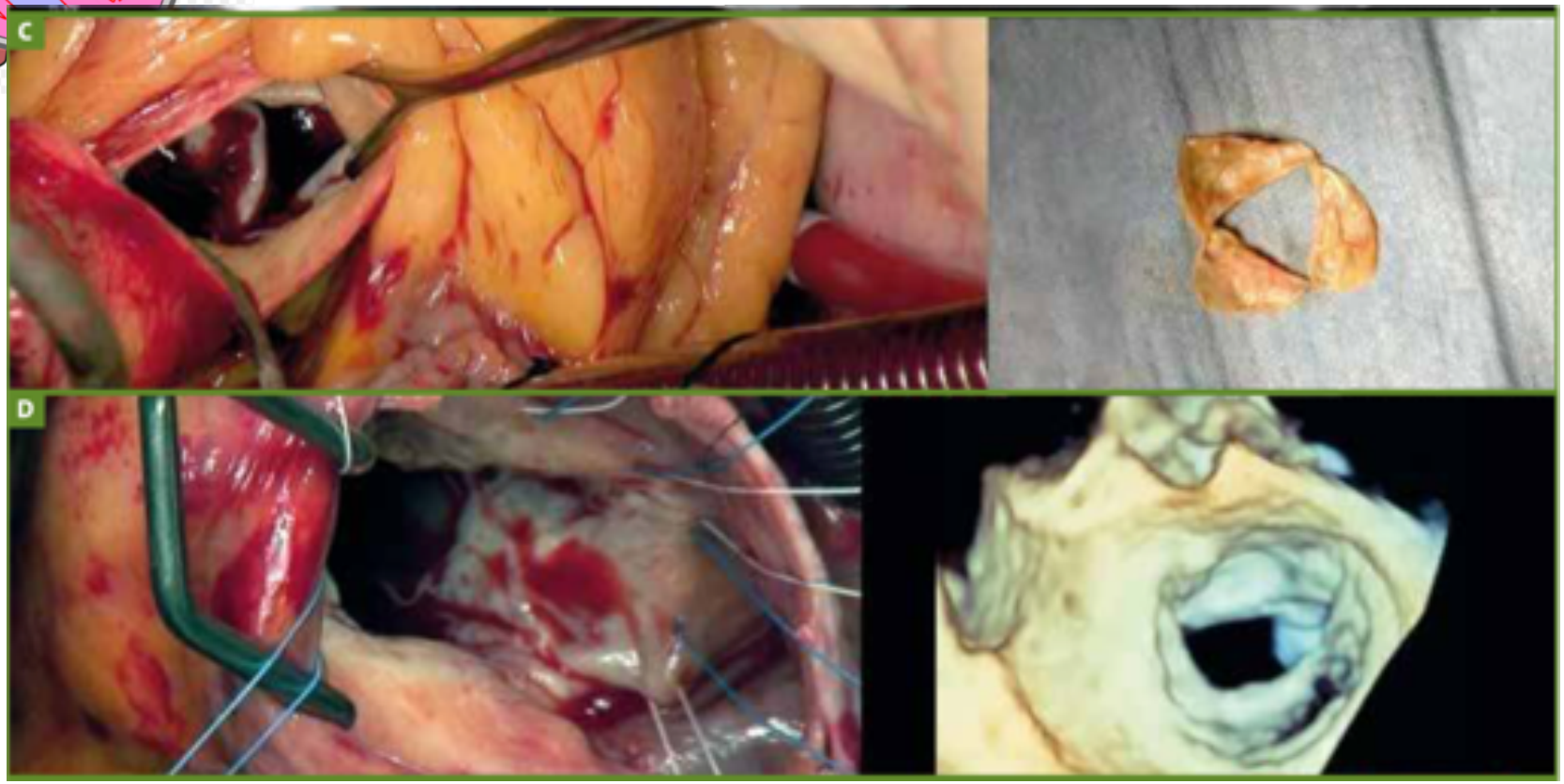
SERVIER

Mediator ® : cardiac valves calcification/replacement

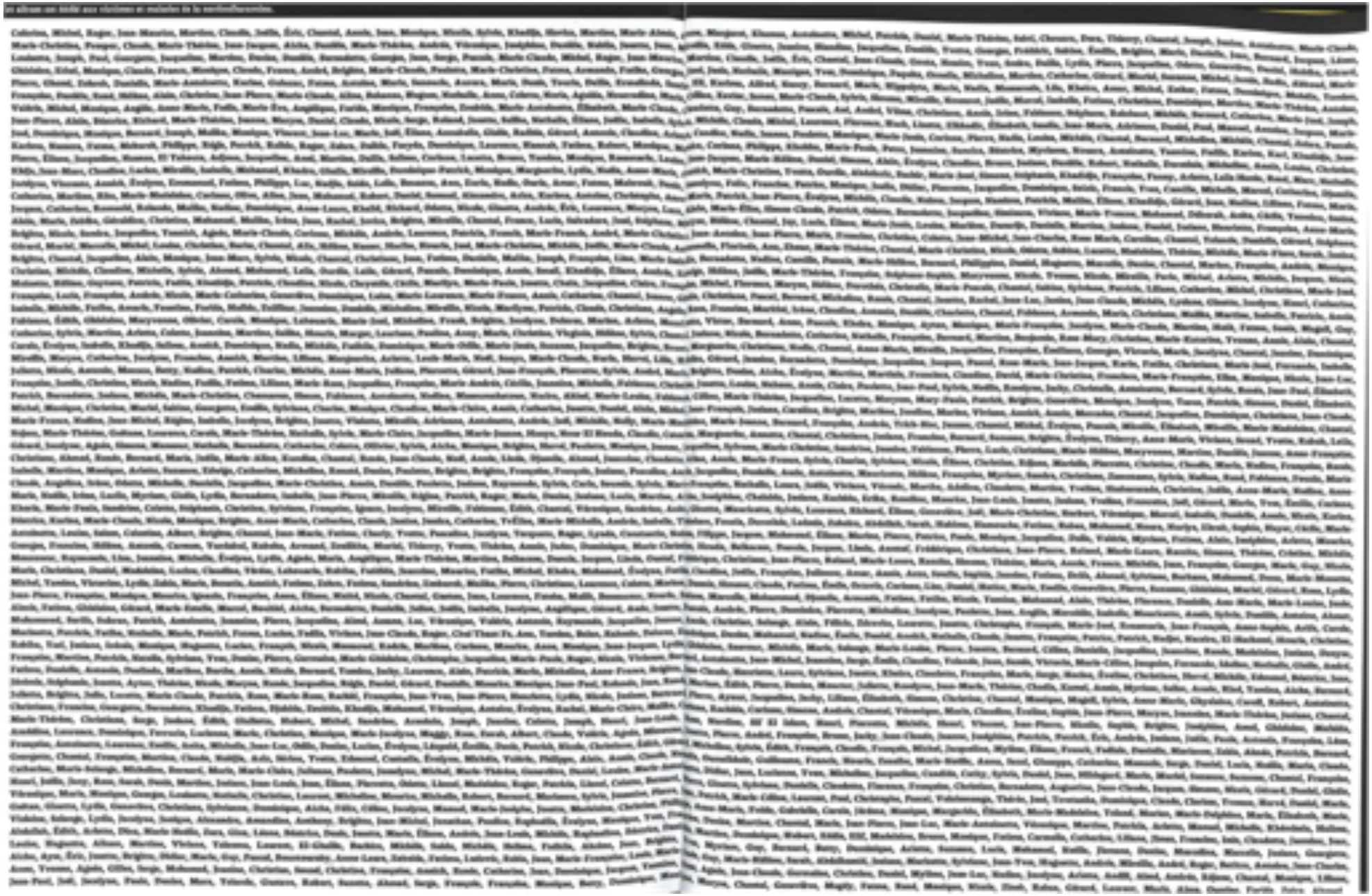






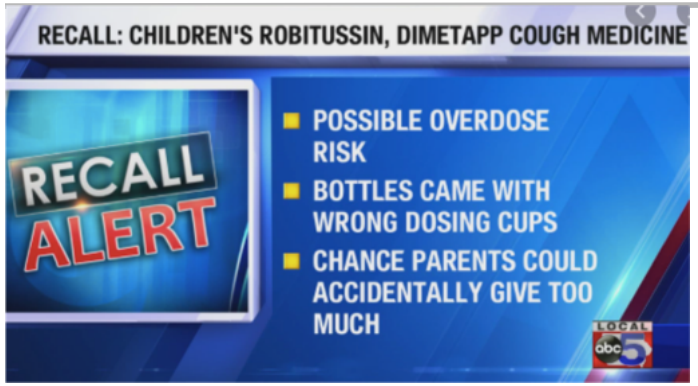


Mediator ® : cardiac valves calcification/in memoriam



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

Codeine coughing sirup overconsumption

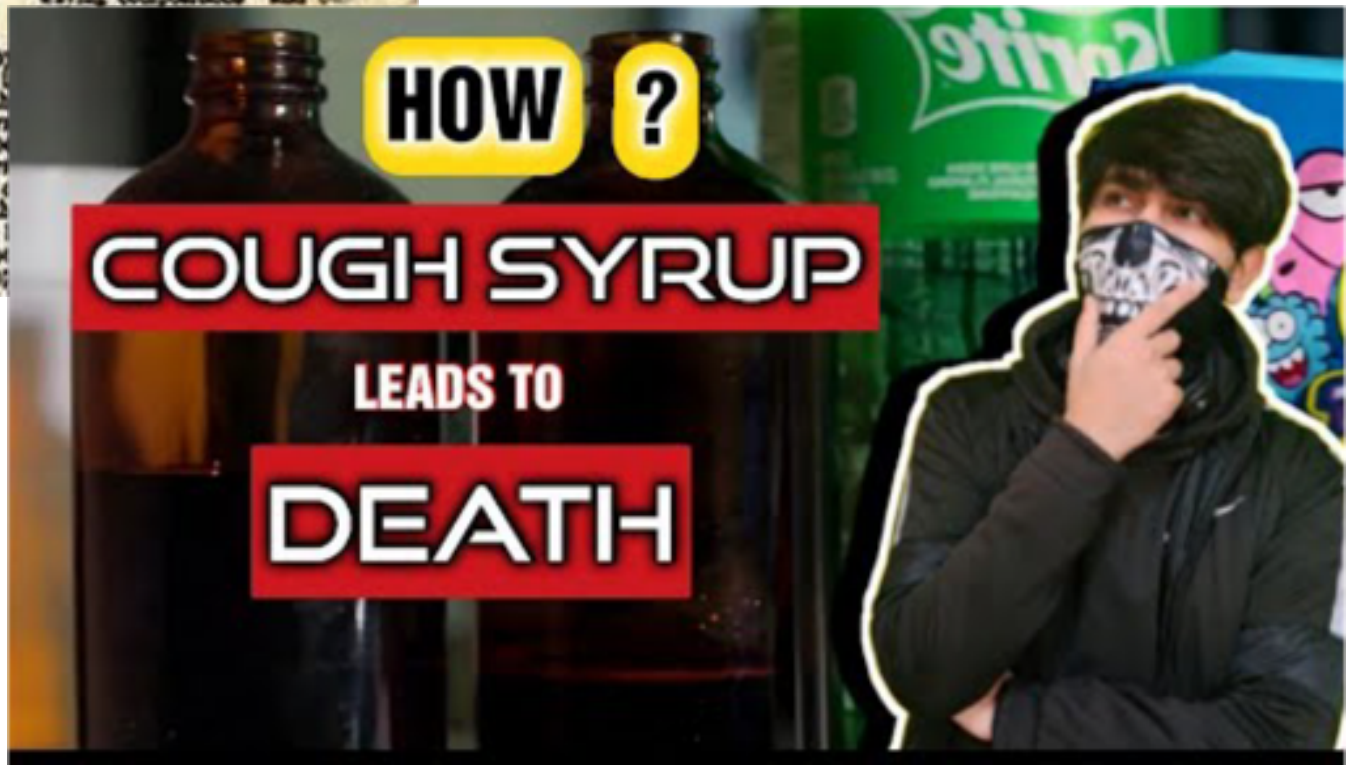


The Cough Syrup Tragedy

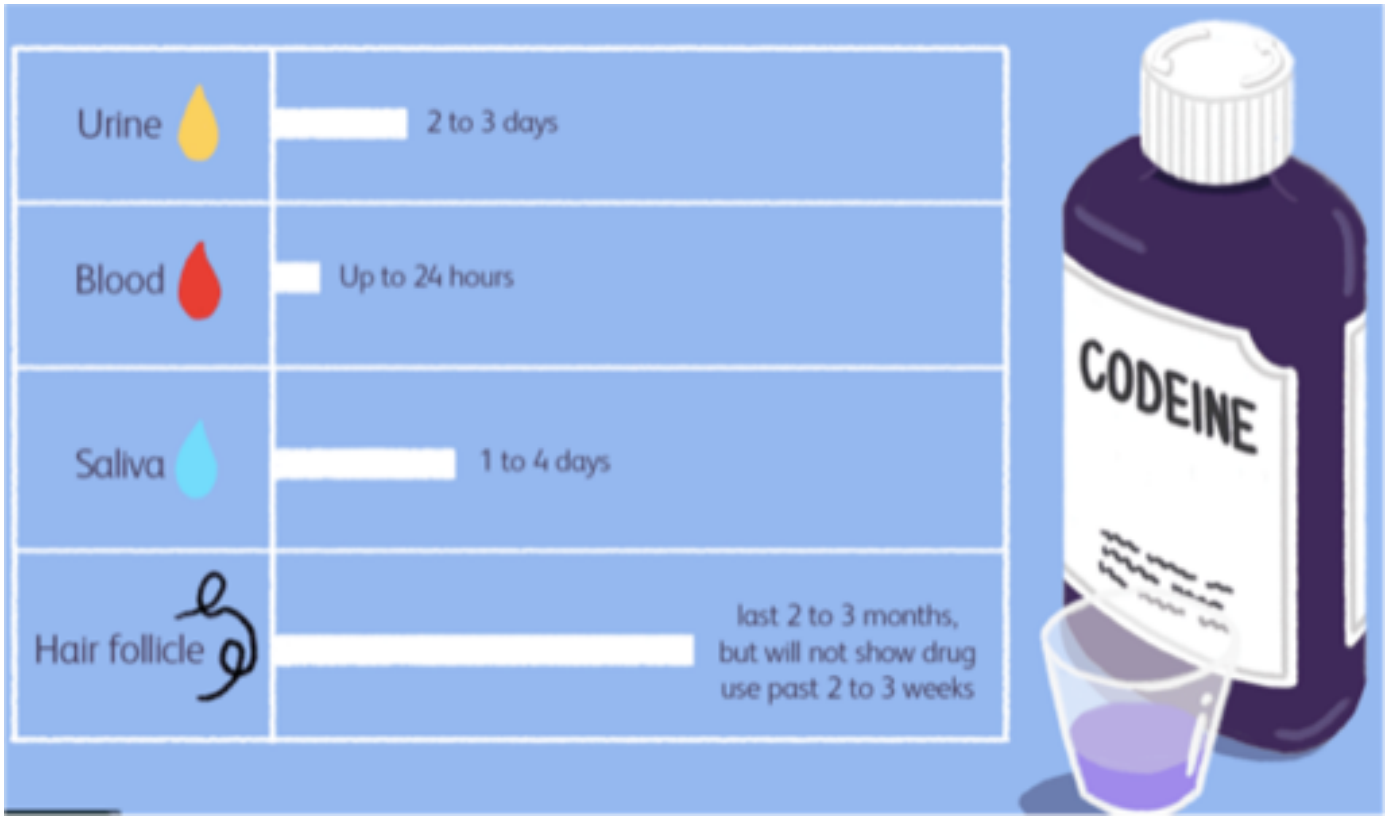
By M. Sirsi

Professor of Pharmacology, Indian Institute of Science, Bangalore.

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?



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

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

Neue Zürcher Zeitung 2023

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

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

Cough medicine containing psychoactive substances not to be sold in drugstores

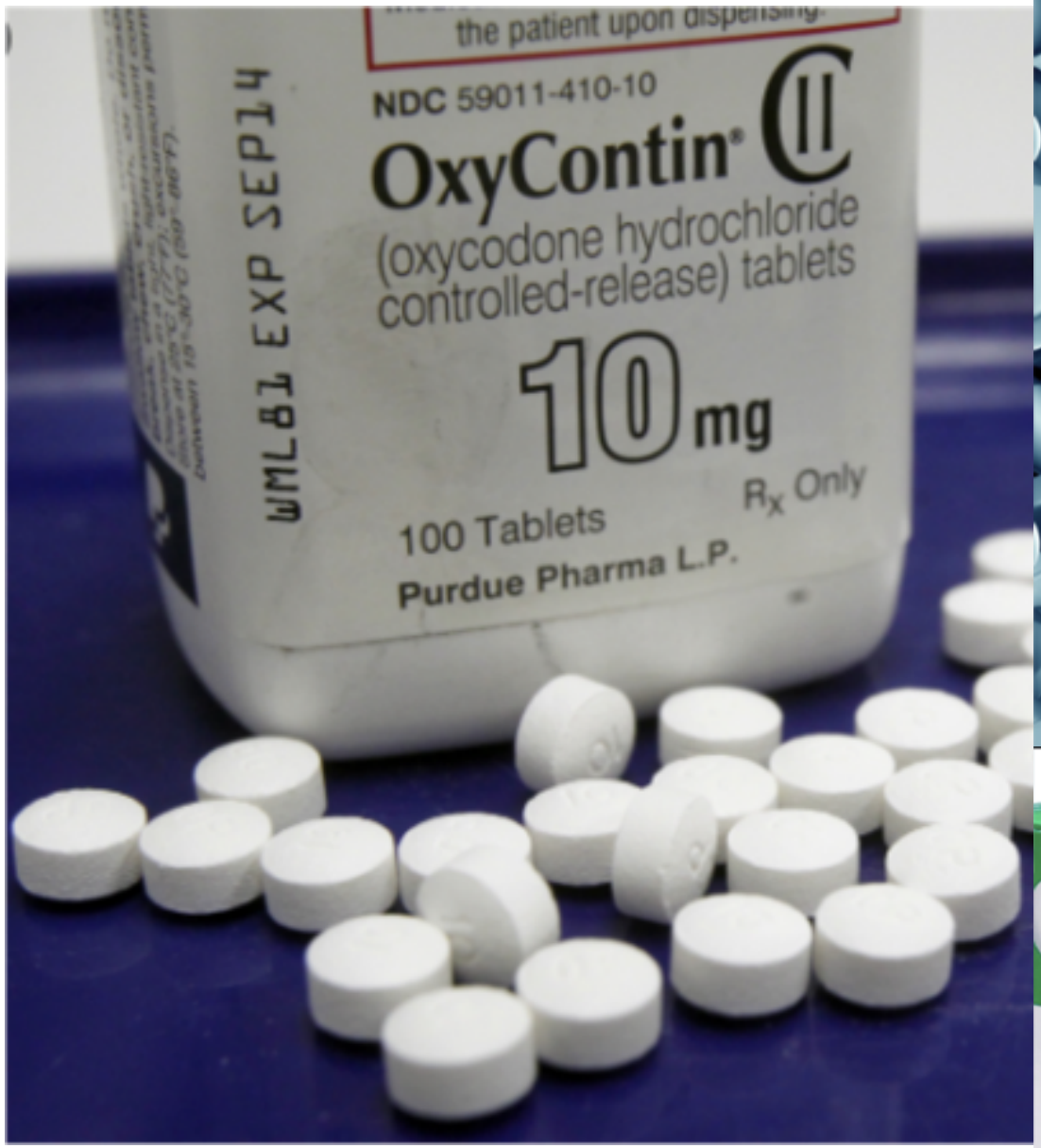
The Federal Administrative Court has issued two pilot judgments supporting Swissmedic's decision to classify certain cough medicines as prescription-only medications. Their active substances are classed as psychoactive and may only be dispensed by doctors and pharmacists in accordance with the revised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

28.04.2021

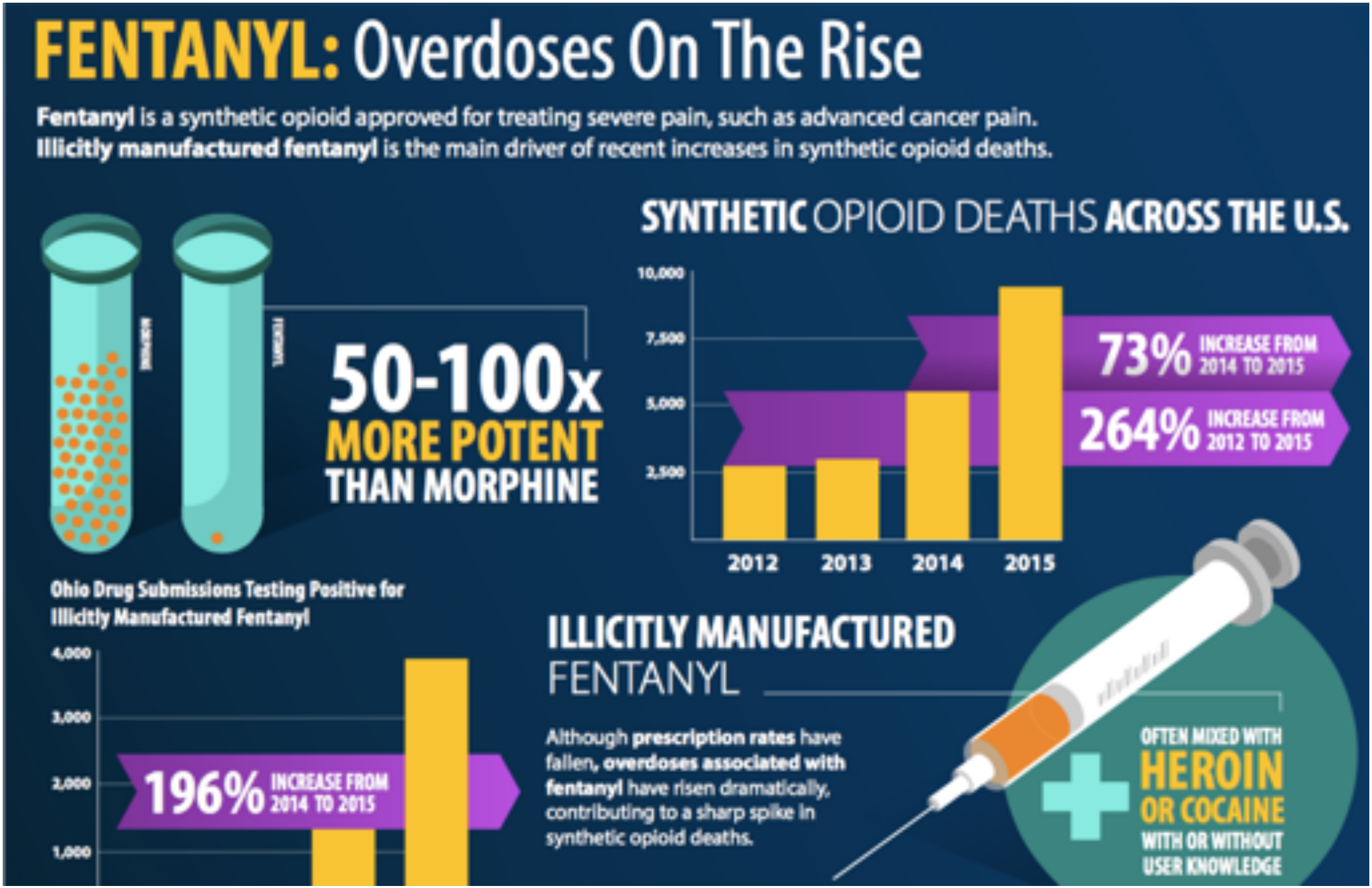
Share

Foto: Keystone

Opioid overprescription/overconsumption : worldwide addiction



Addiction and Overdose : opioid overprescription for chronic pain symptoms



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

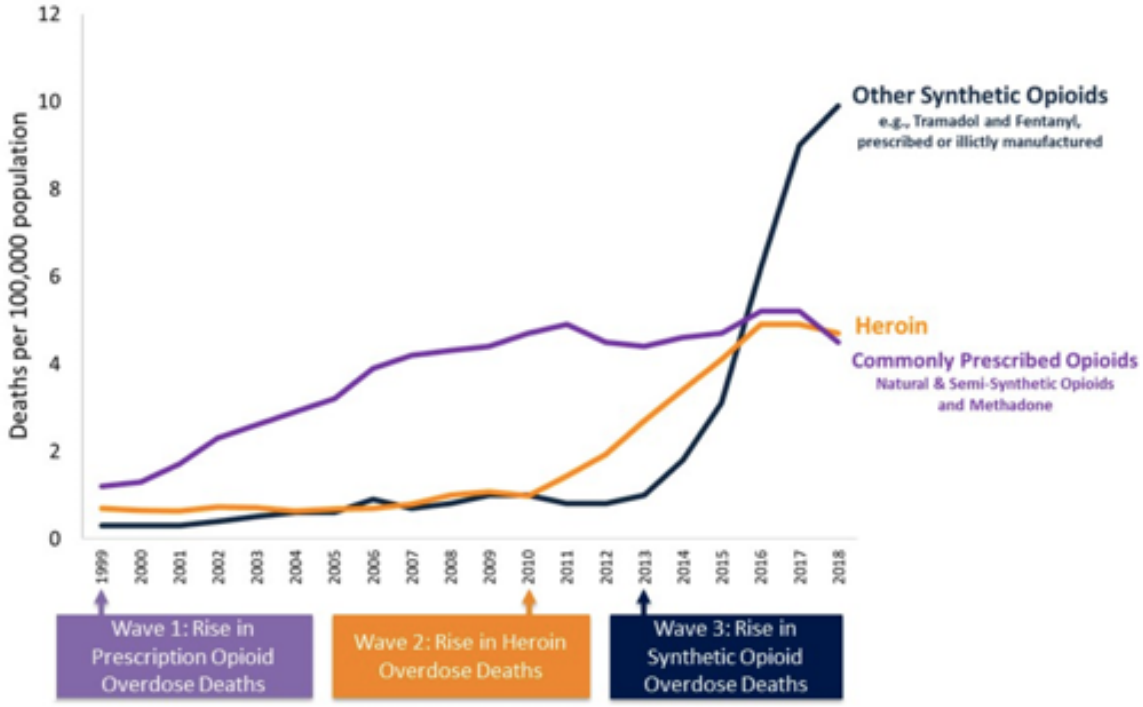
The Opioid Epidemic in the U.S.

In 2015...

- **12.5 million** People misused prescription opioids[1]
- **2.1 million** People misused prescription opioids for the first time[1]
- **2 million** People had prescription opioid use disorder[1]
- **828,000** People used heroin[1]
- **135,000** People used heroin for the first time[1]
- **33,091** People died from overdosing on opioids[2]
- **15,281** Deaths attributed to overdosing on commonly prescribed opioids[2,3]
- **9,580** Deaths attributed to overdosing on synthetic opioids[2,5]
- **12,989** Deaths attributed to overdosing on heroin[2,4]
- **$78.5 billion** In economic costs (2013 data)[6]

Sources: [1] 2015 National Survey on Drug Use and Health (SAMHSA). [2] MMWR. 2016; 65(50-51):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.

3 Waves of the Rise in Opioid Overdose Deaths



SOURCE: National Vital Statistics System Mortality File

Case Report

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).

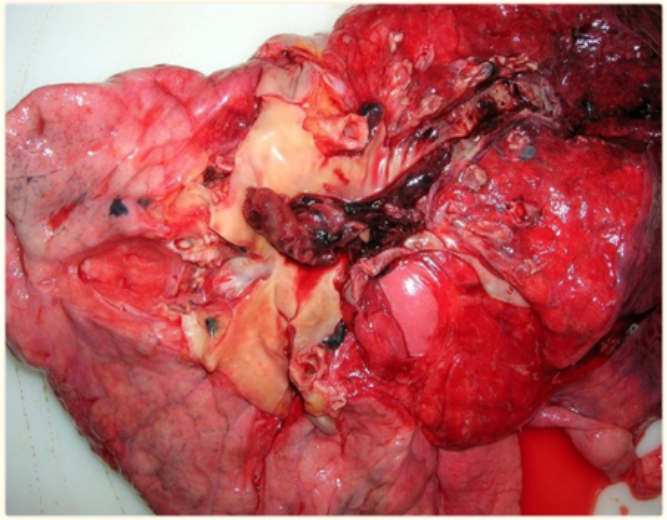
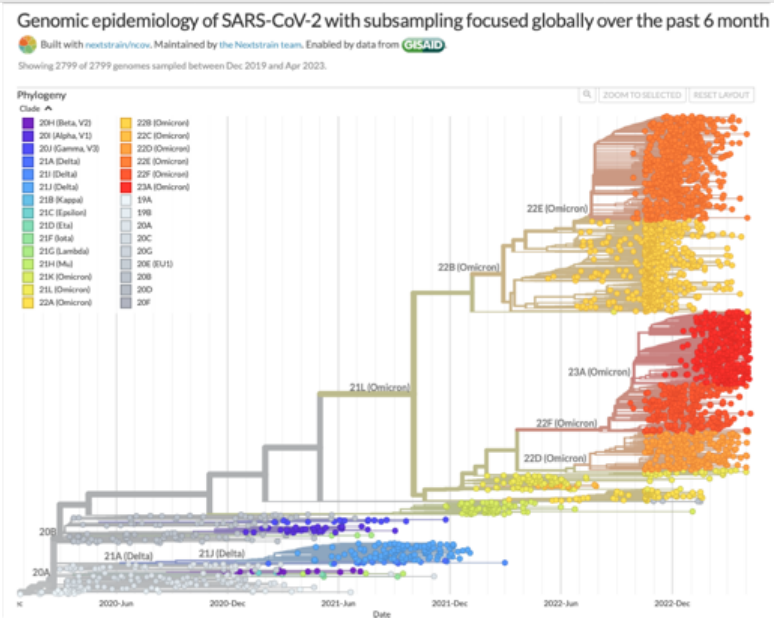


Fig. 1

Central pulmonary artery embolism in the right lung.



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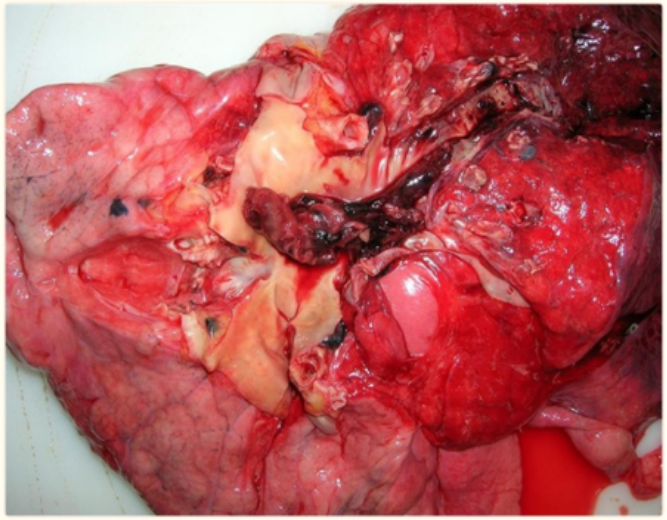


Fig. 1

Central pulmonary artery embolism in the right lung.

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**

Biotherapeutics and safety

Small molecules

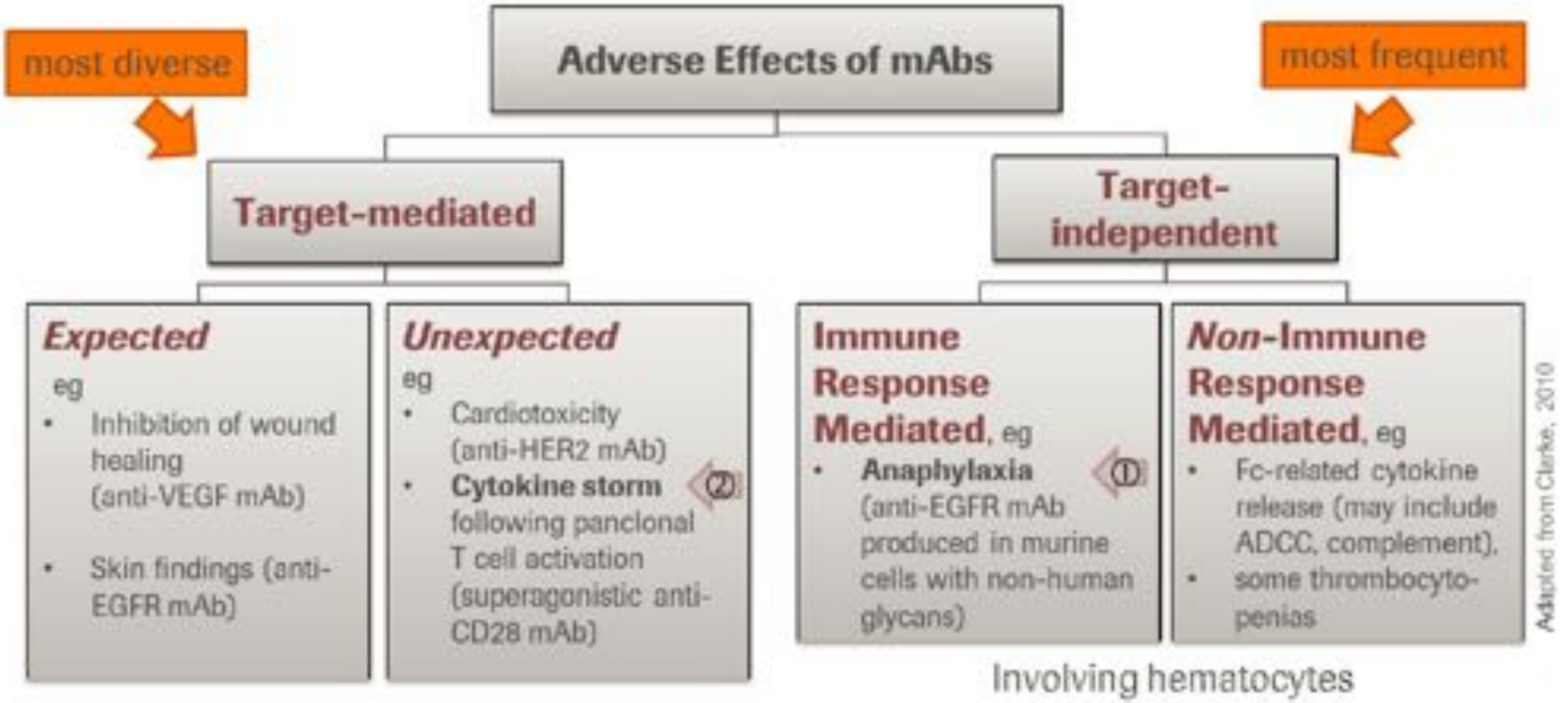
- chemical synthesis
- single molecule species
- well defined structure, stable, half life hours
- MW < 500-1000 Da
- standard models for safety testing (2 species: rodent and non-rodent)
- non-immunogenic
- Typically given oral
- distribution extra- and intracellular
- metabolised
- efficacy and toxicity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

Antibodies

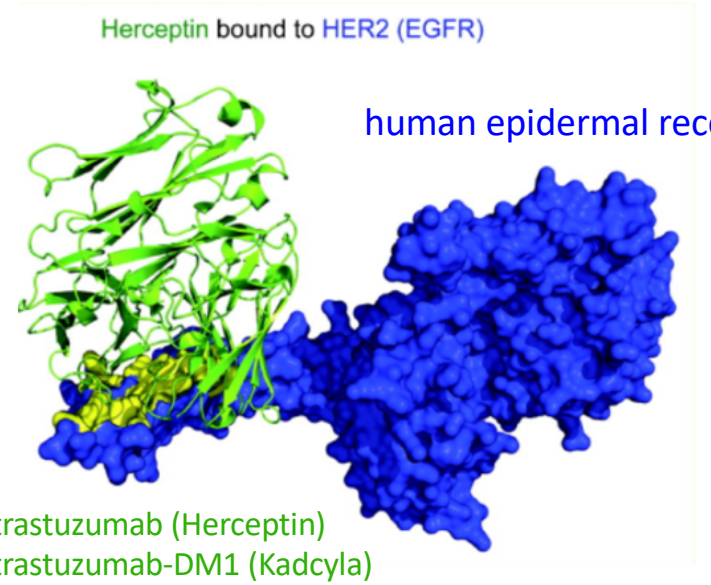
- biotechnology derived molecules
- Therapeutic mAb = mixture of molecule variants
- complex structure, heat sensitive, long half life
- 150'000 Da for IgGs
- high target selectivity & species specificity (for safety testing often only monkey cross-reacts)
- may be immunogenic
- Parenteral administration (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 !

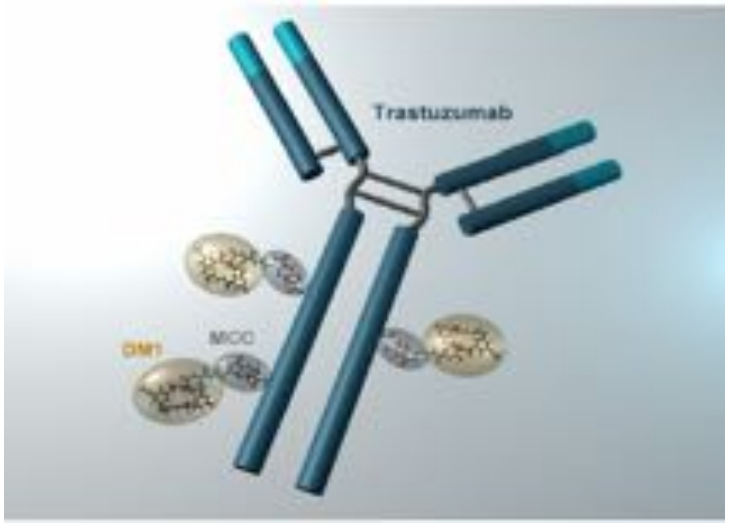
Mechanisms of adverse effects with mABs



Trastuzumab subjected to scrutiny in drug safety and development



trastuzumab (Herceptin)
trastuzumab-DM1 (Kadcyla)



Hansel TT, Singer T. et al. 2010 The safety and side effects of monoclonal antibodies Nature Reviews 9: 325-338

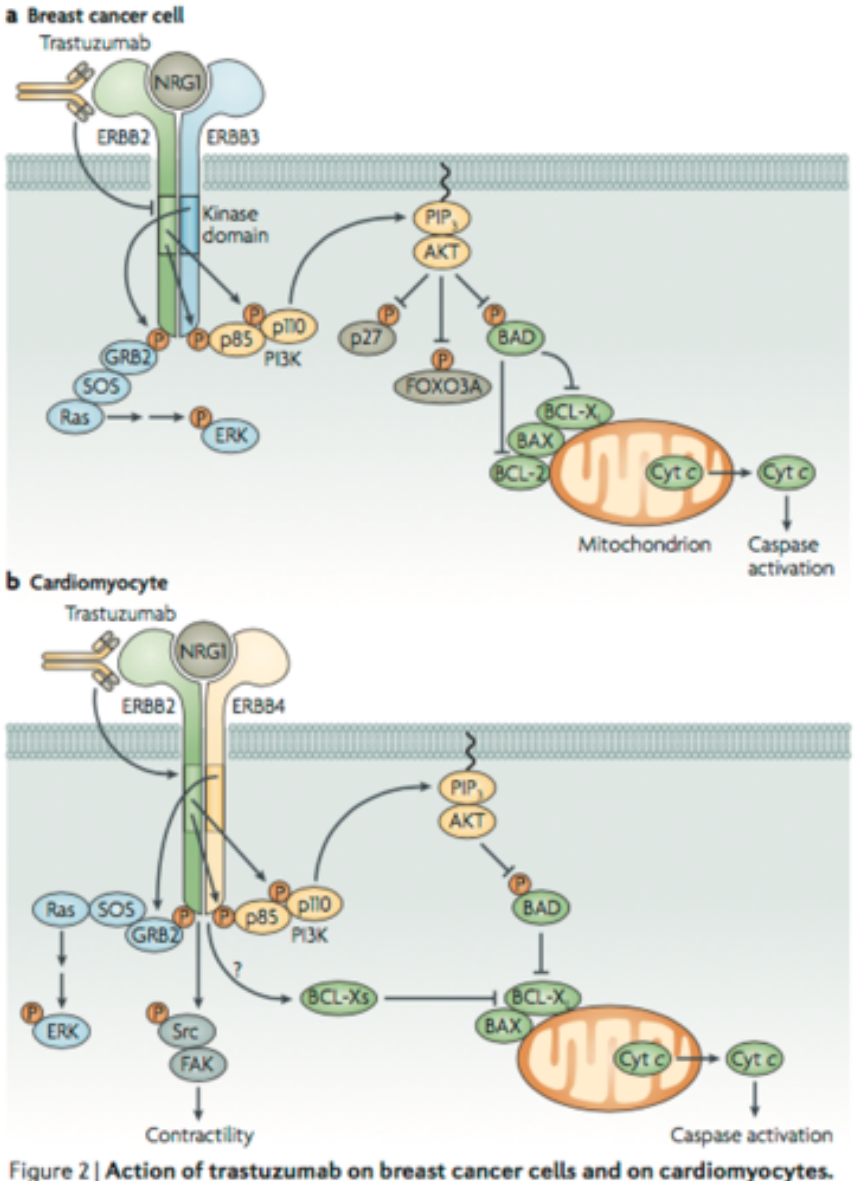


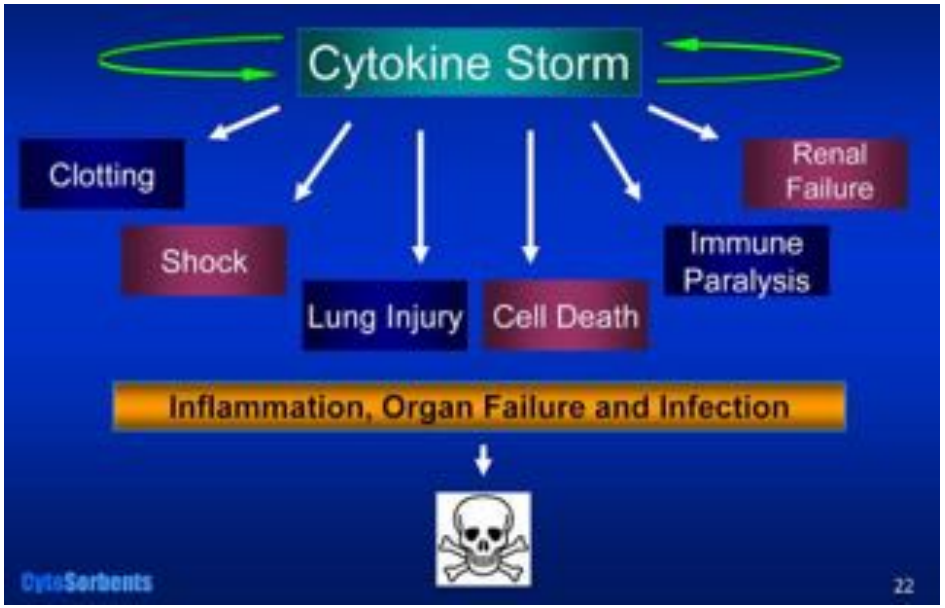
Figure 2 | **Action of trastuzumab on breast cancer cells and on cardiomyocytes.**

Potential myocardium damages ; reduction in left ventricular systolic function

MABs are subjected to intense scrutiny in investigative toxicology

MOLECULAR BIOLOGY COMPLEX INCLUDING PATIENT HETEROGENEITY SAFETY HURDLE !

- **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
- **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



mAbs to CD28 fatal in early clinical development

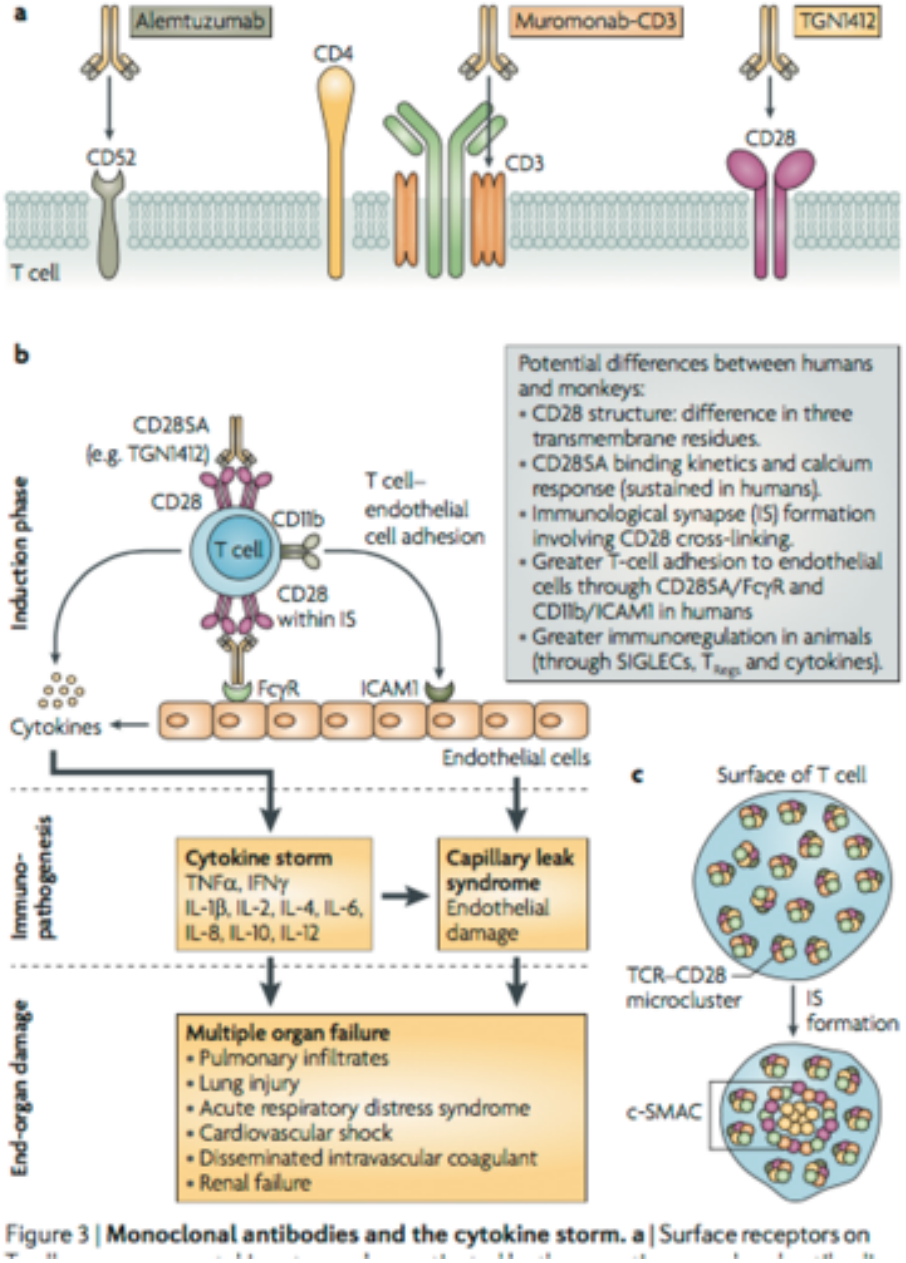


Figure 3 | **Monoclonal antibodies and the cytokine storm. a** | Surface receptors on

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
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  - 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.

Therapeutic index : estimate the probability of success

Therapeutic index is given as follows :

$$\frac{\text{Highest exposure without toxicity}}{\text{Pharmacologically efficacious exposure}}$$

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 !

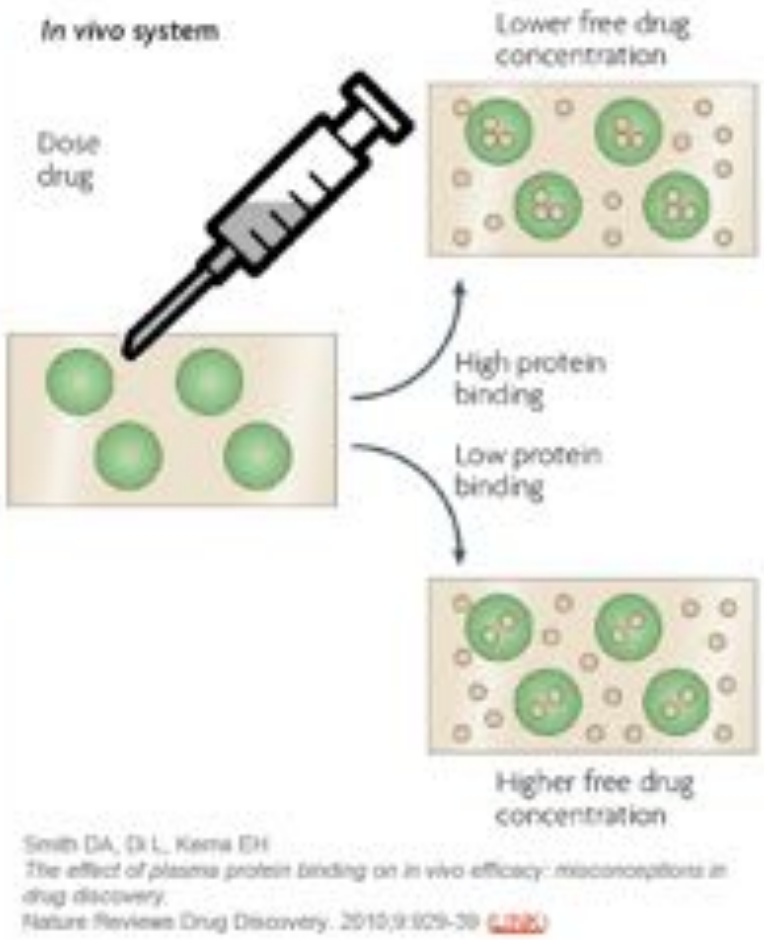
Therapeutic index : why consider exposure rather than dose ?

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



PPB : plasma protein binding

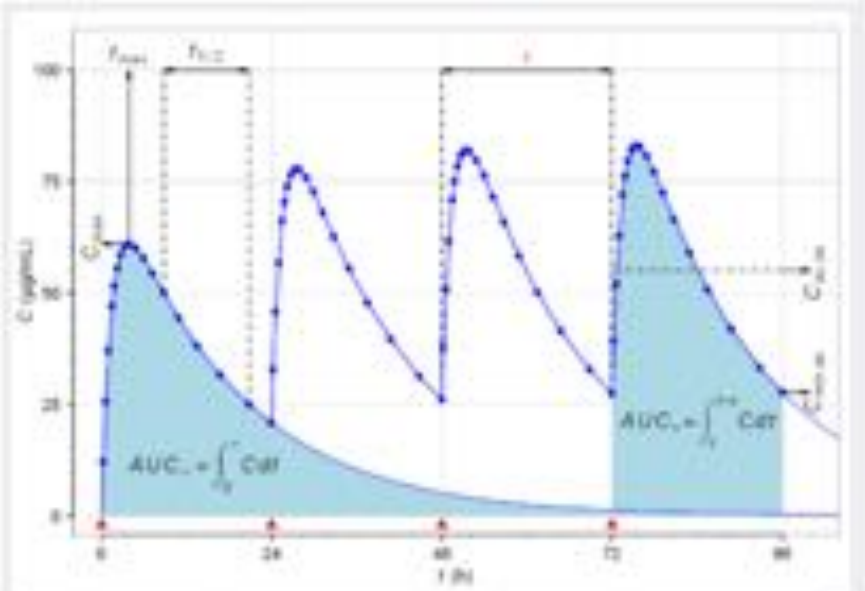
caveat: every drug is different ; BBB, organ penetration, highly active uptake and/or export etc.

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)

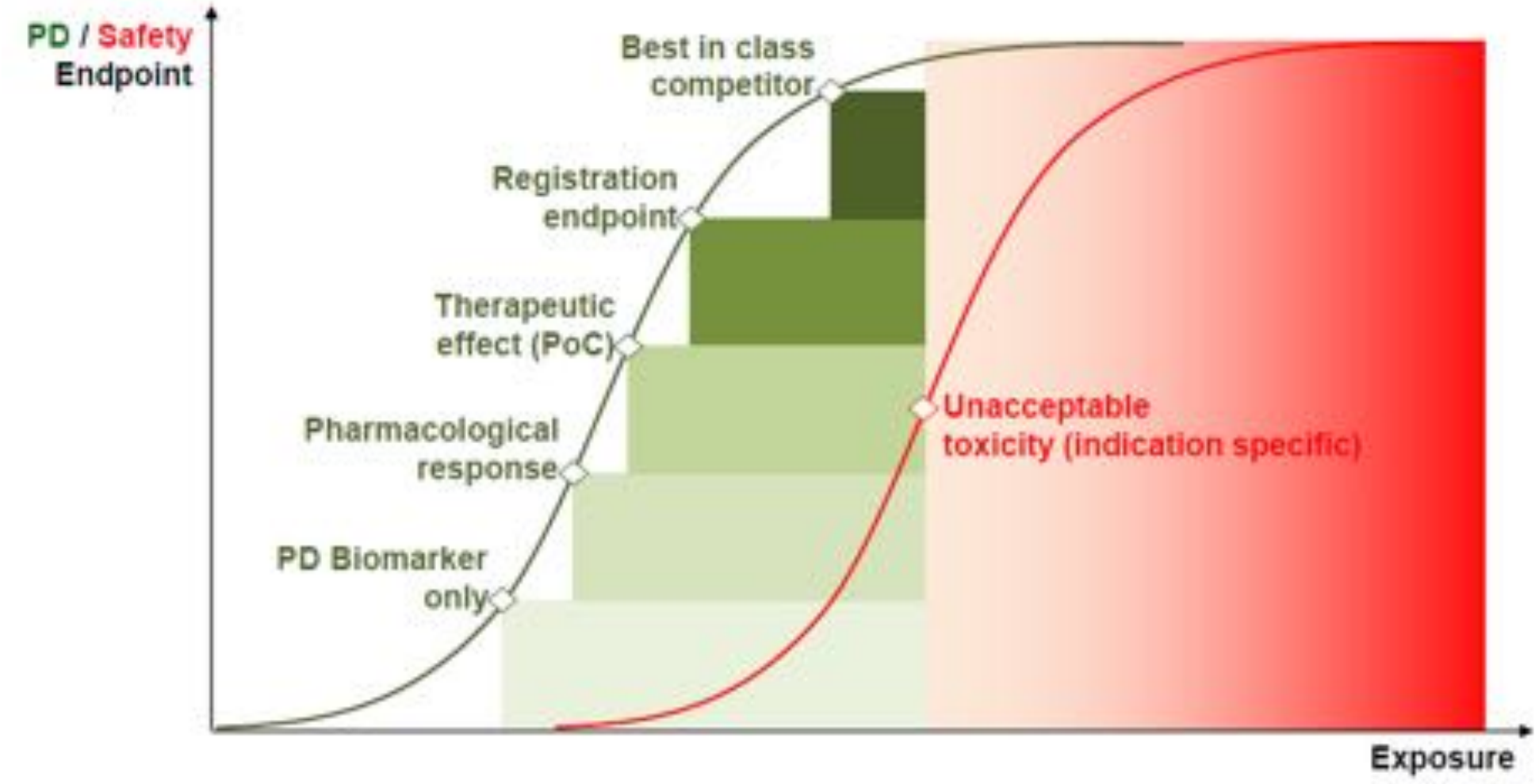
» In equilibrium, free tissue exposure generally reflects free plasma exposure

- 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



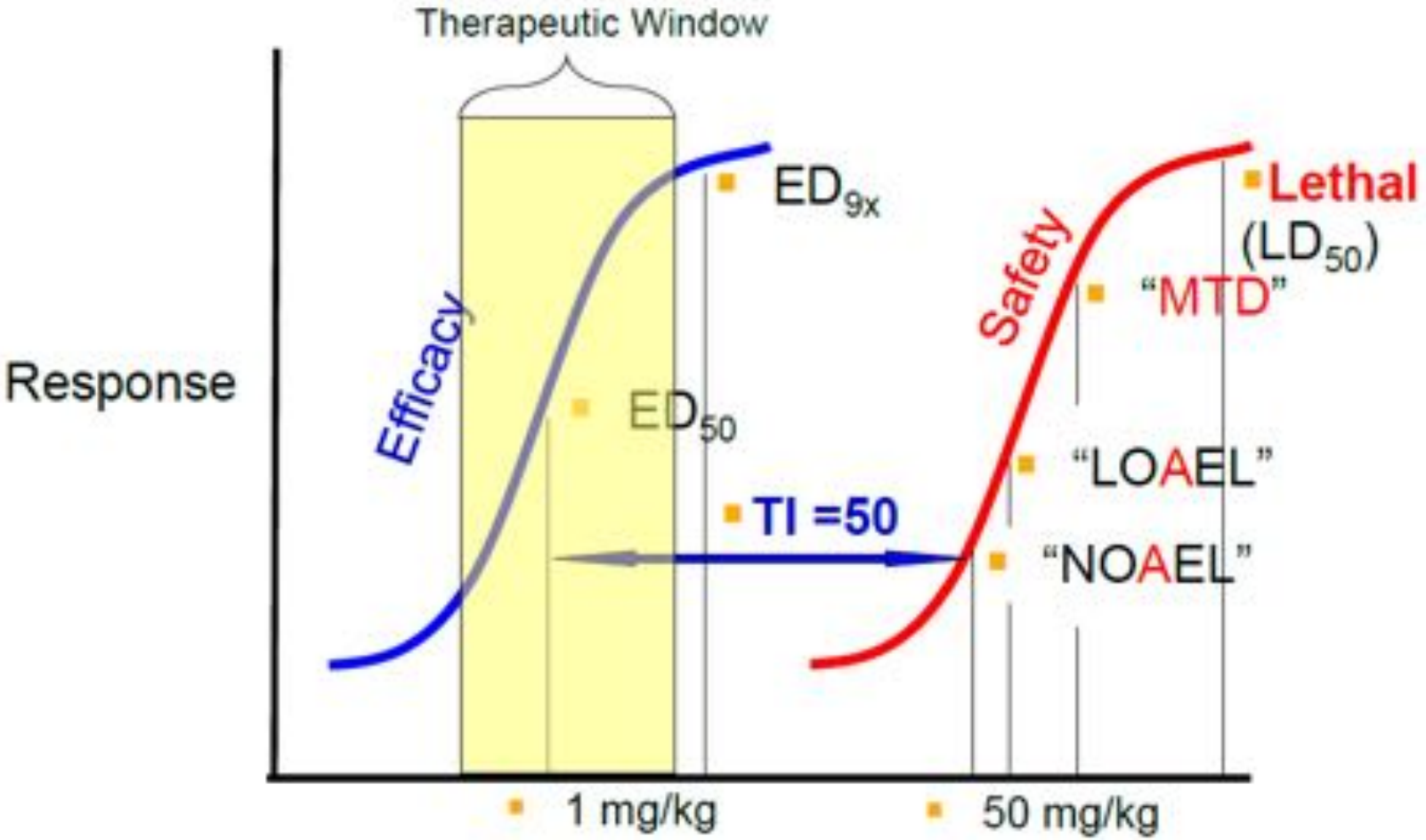
The time course of drug plasma concentrations over 96 hours

Therapeutic index : estimate the probability of success



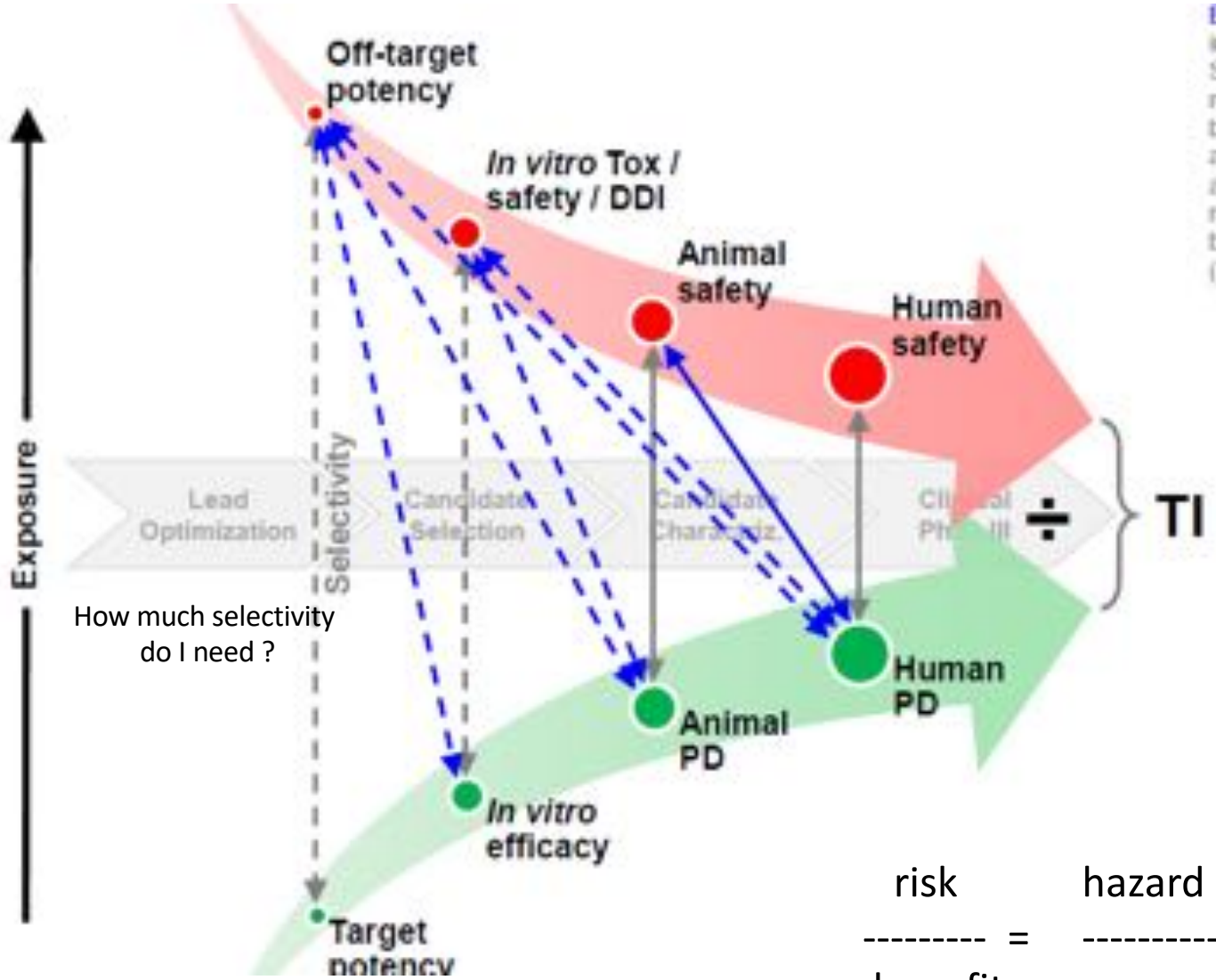
Safety is key differentiation criteria in particular for chronic disease targets !

In vivo pharmacology : therapeutic index definition



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

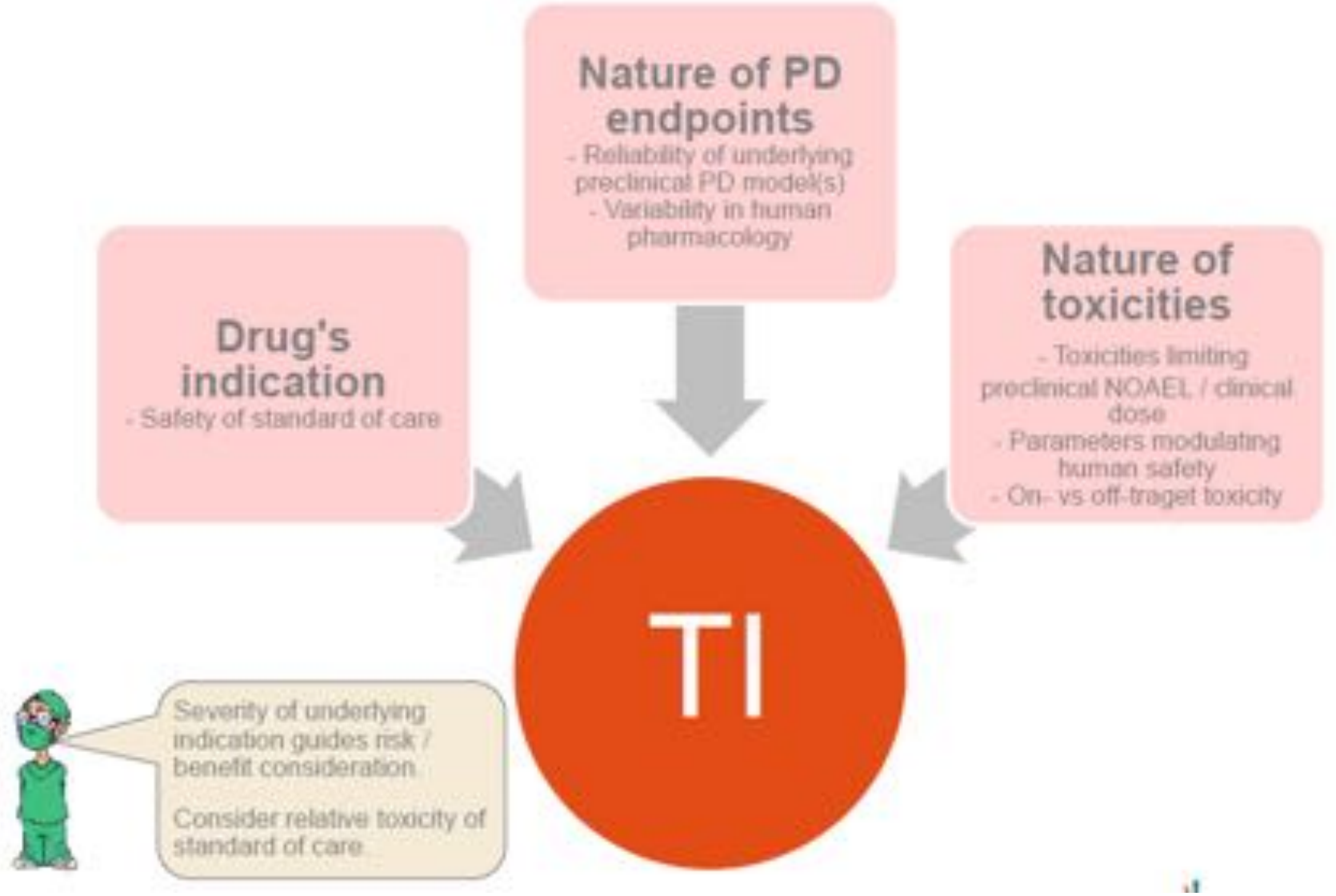
Therapeutic index : early stage assessment



Blue arrows indicate safety m
involving data of different typ
Solid arrows (gray or blue) re
margins of *in vivo* data involv
both concentration (Cmax, C
and/or AUC-based data. Das
arrows (gray or blue) indicate
margins restricted to concent
based data as only *in vitro* da
(IC_{50}) is involved.

$$\frac{\text{risk}}{\text{benefit}} = \frac{\text{hazard (tox finding) x exposure}}{\text{benefit}}$$

Therapeutic index



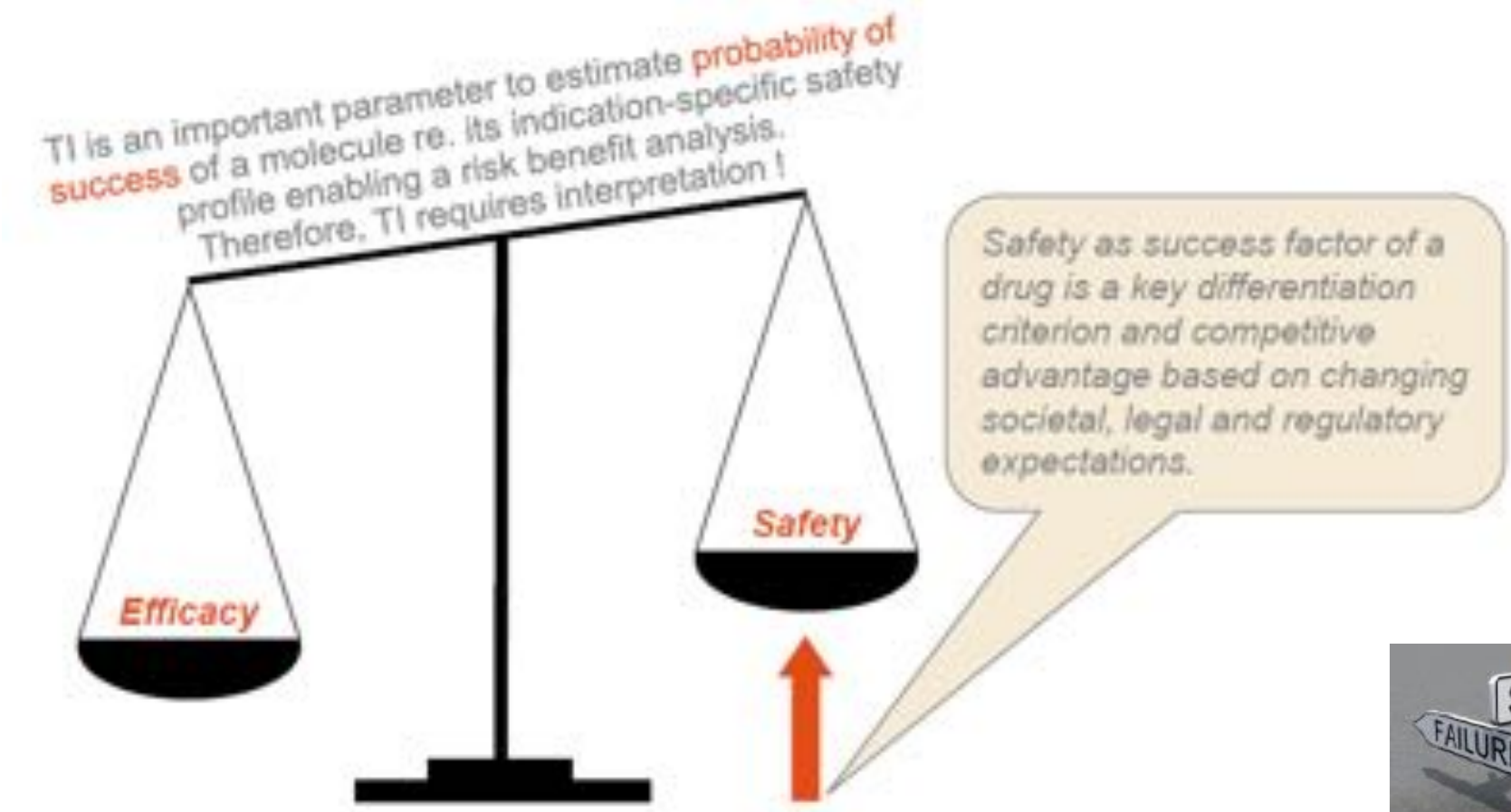
Therapeutic index : numerical example

	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



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.

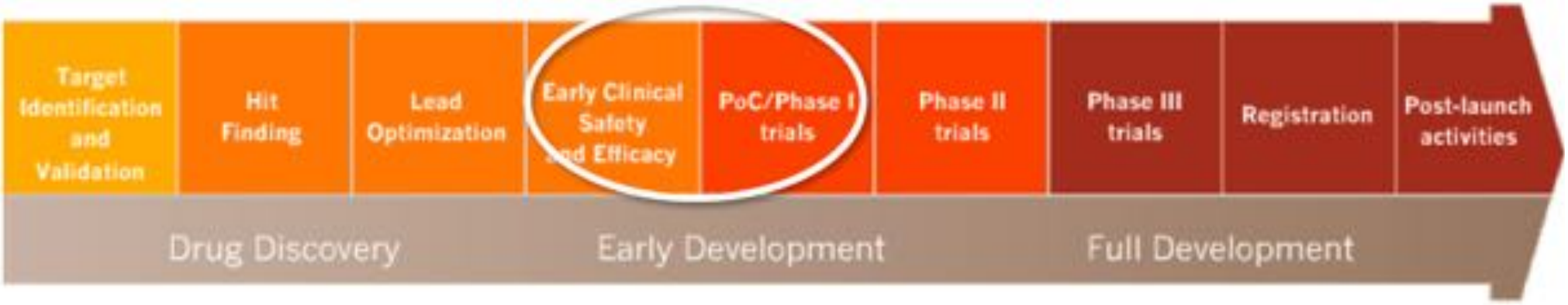
PHARMACOLOGY MEETS WITH TOXICOLOGY !

Clinical pharmacology and early safety toxicology

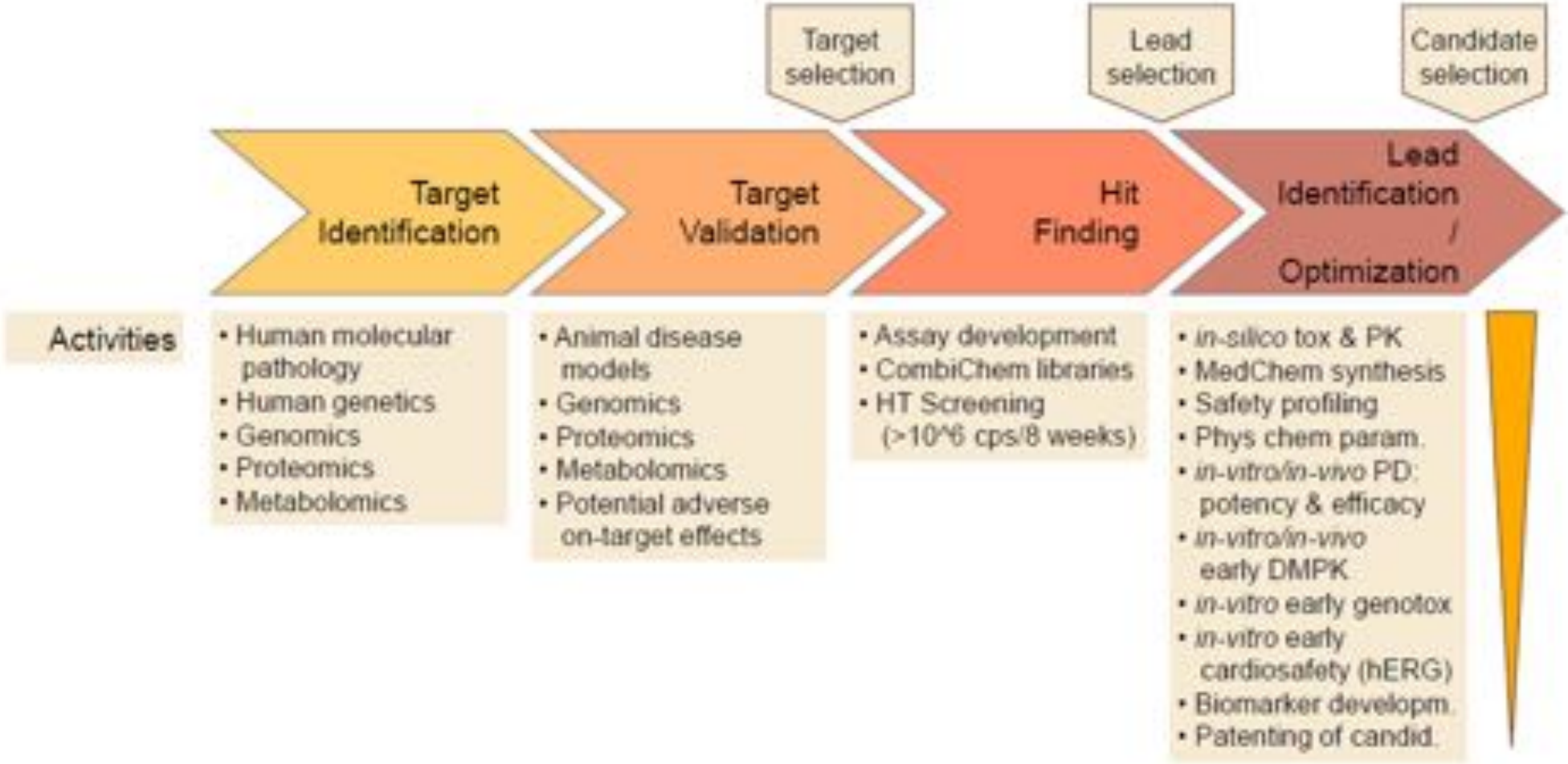
ESTABLISHING THE INITIAL SAFETY PROFILE FOR A NOVEL MEDICINE REQUIRES EXTENSIVE TOX AND SAFETY PHARMACOLOGY STUDIES PERFORMED *IN SILICO, IN VITRO* AND IN PHARMACOLOGICAL APPROPRIATE MODELS

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

WORKSHOP

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

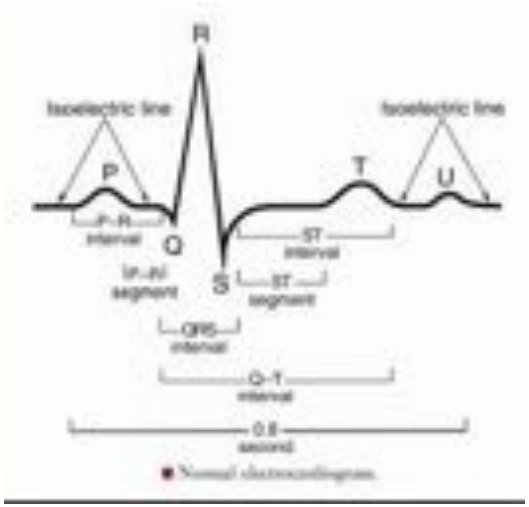
QT Prolongation Through hERG K^+ Channel Blockade: Current Knowledge and Strategies for the Early Prediction During Drug Development

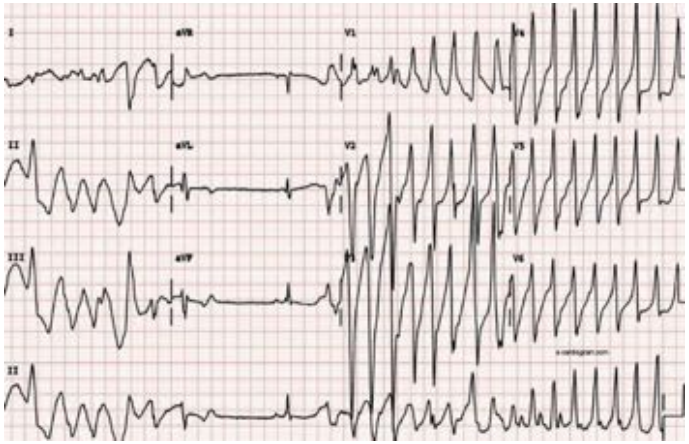
Maurizio Recanatini,[1] Elisabetta Poluzzi,[2] Matteo Masetti,[1] Andrea Cavalli,[1] Fabrizio De Ponti[2]

[1]Department of Pharmaceutical Sciences, Via Belmeloro 6, University of Bologna, I-40126 Bologna, Italy
[2]Department of Pharmacology, Via Irnerio 48, University of Bologna, I-40126 Bologna, Italy

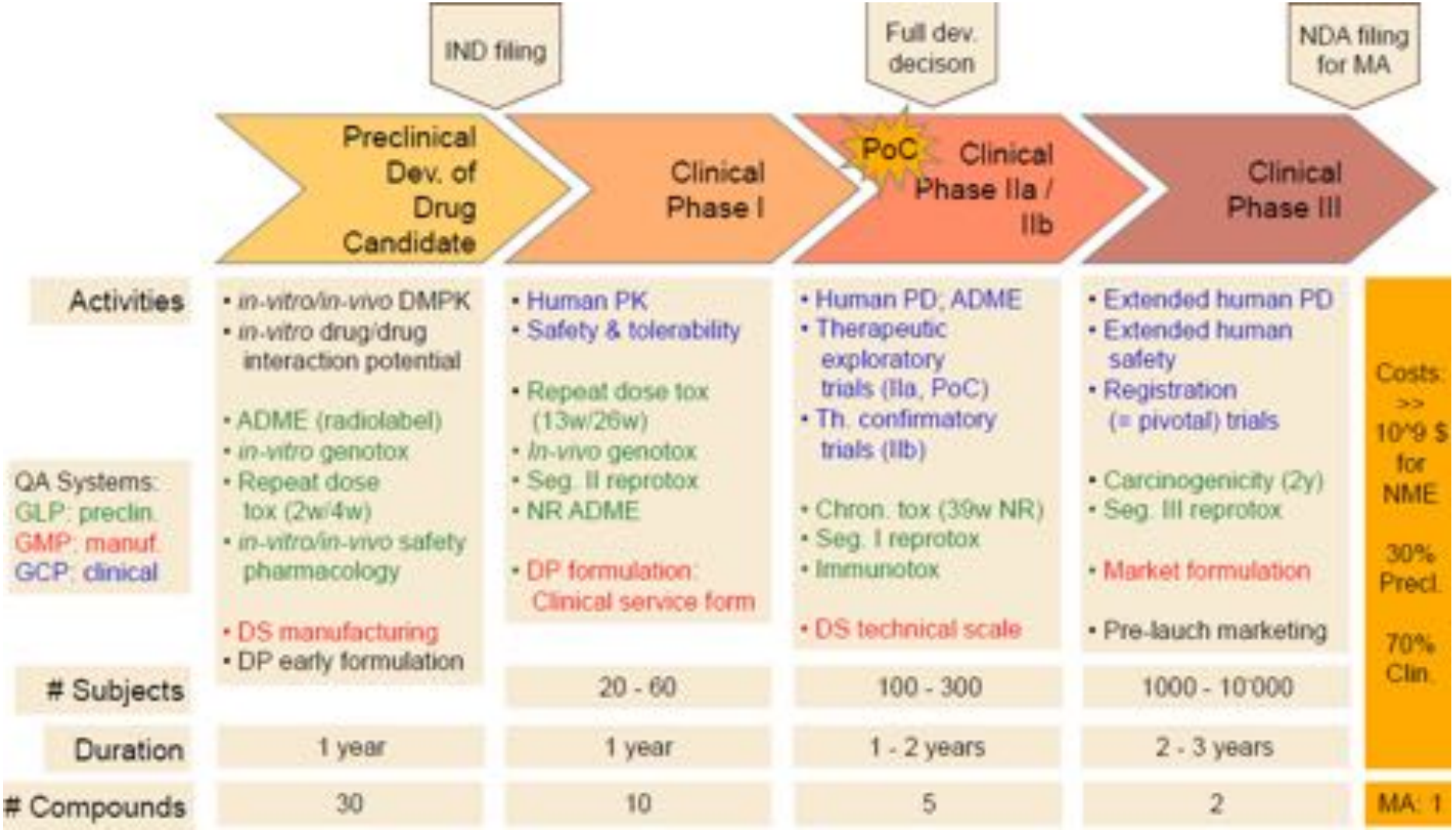
Published online 16 August 2004 in Wiley InterScience (www.interscience.wiley.com)
DOI 10.1002/med.20019

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



INDs (investigational new drug application)

What is an IND?

(**i**nvestigational **n**ew **d**rug **a**pplication)

- 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

FDA Home › Medical Devices › Databases

FDA 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

FDA U.S. FOOD & DRUG ADMINISTRATION

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Drugs

Home > Drugs > Development & Approval Process (Drugs) > How Drugs are Developed and Approved > Types of Applications > Investigational New Drug (IND) Application

- Investigational New Drug (IND) Application
- Emergency Investigational New Drug (EIND) Applications for Antiviral Products
- IND Forms and Instructions
- Investigator-Initiated Investigational New Drug (IND) Applications
- 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.

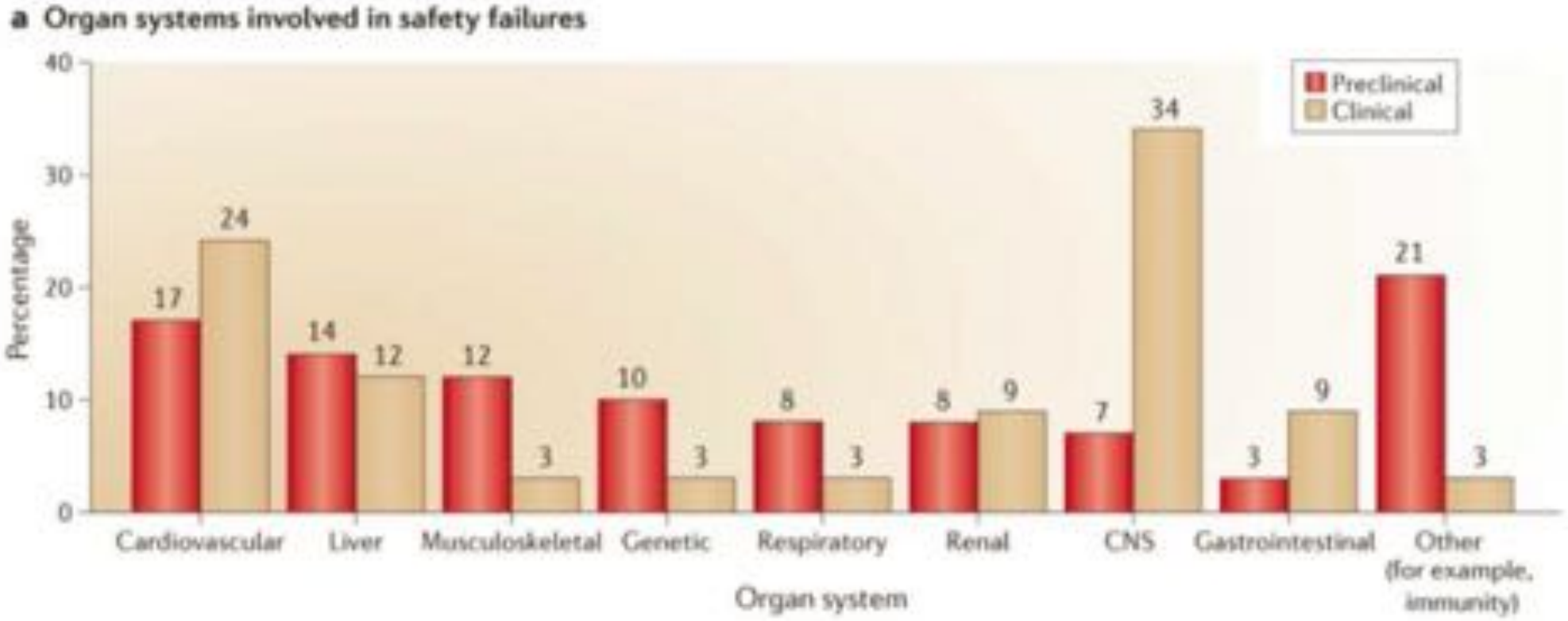
IND regulations are contained in Title 21, Code of Federal Regulations, Part 312. Copies of the regulations, further guidance regarding IND procedures, and additional forms are available from the FDA Center for Drug Evaluation and Research, Drug Information Branch (HFD-210), 5600 Fishers Lane, Rockville, 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



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)	Gastroesophagal reflux disease	Cardiovascular (QT-interval prolongation, arrhythmias)
Phenylpropylamine (Proin)	Nasal decongestant, weight control	Hemorrhagic stroke
Sertindole (Serdolect)	Schizophrenia	Cardiovascular (QT-interval prolongation, potentially fatal arrhythmias)
Tolcapone (Tasmar)	Parkinson's disease	Hepatic toxicity
Trovafloxacin (Trovan)	Antibiotic	Hepatic toxicity

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 !

“Cerep Eurofins” in vitro pharmacology_ ON vs OFF target

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OFF TARGET : EROFINS CEREP !

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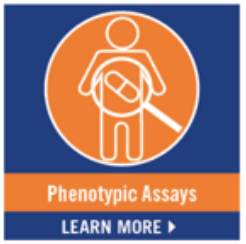

A systems-based approach to screen for compound potency & liability as well as related predictive biomarkers using human cell models of oncology, immunology, and cellular toxicity.

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

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“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
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

human standard turnaround time

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

TABLE 4

Broad Cerep screen undertaken to determine the pharmacological activity of fenobam

Target	% Control (10 μM)	Target	% Control (10 μM)
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
$D_{4.4}$ (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; nonsel, 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, monoamineoxidase-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, phencyclidine; P2X, purinergic 2X; P2Y, purinergic 2Y; BZD, benzodiazepine.

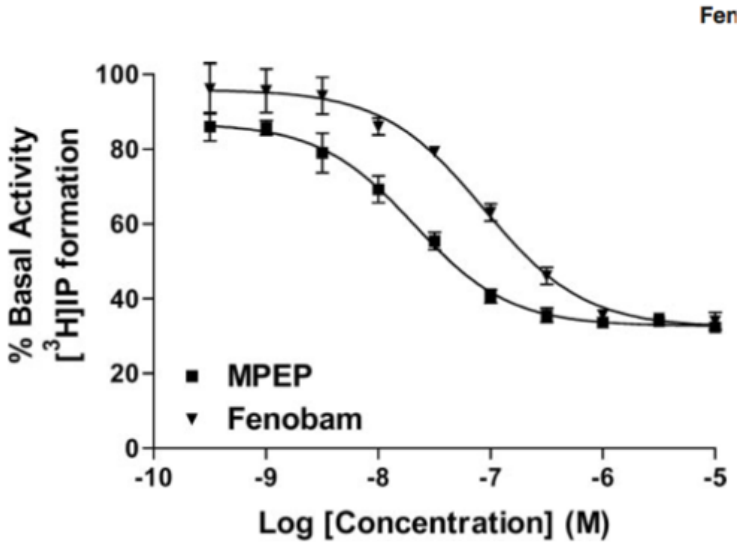
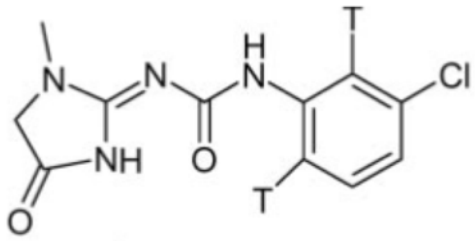


Fig. 5. Inhibition of mGlu5 basal activity by fenobam and MPEP. The



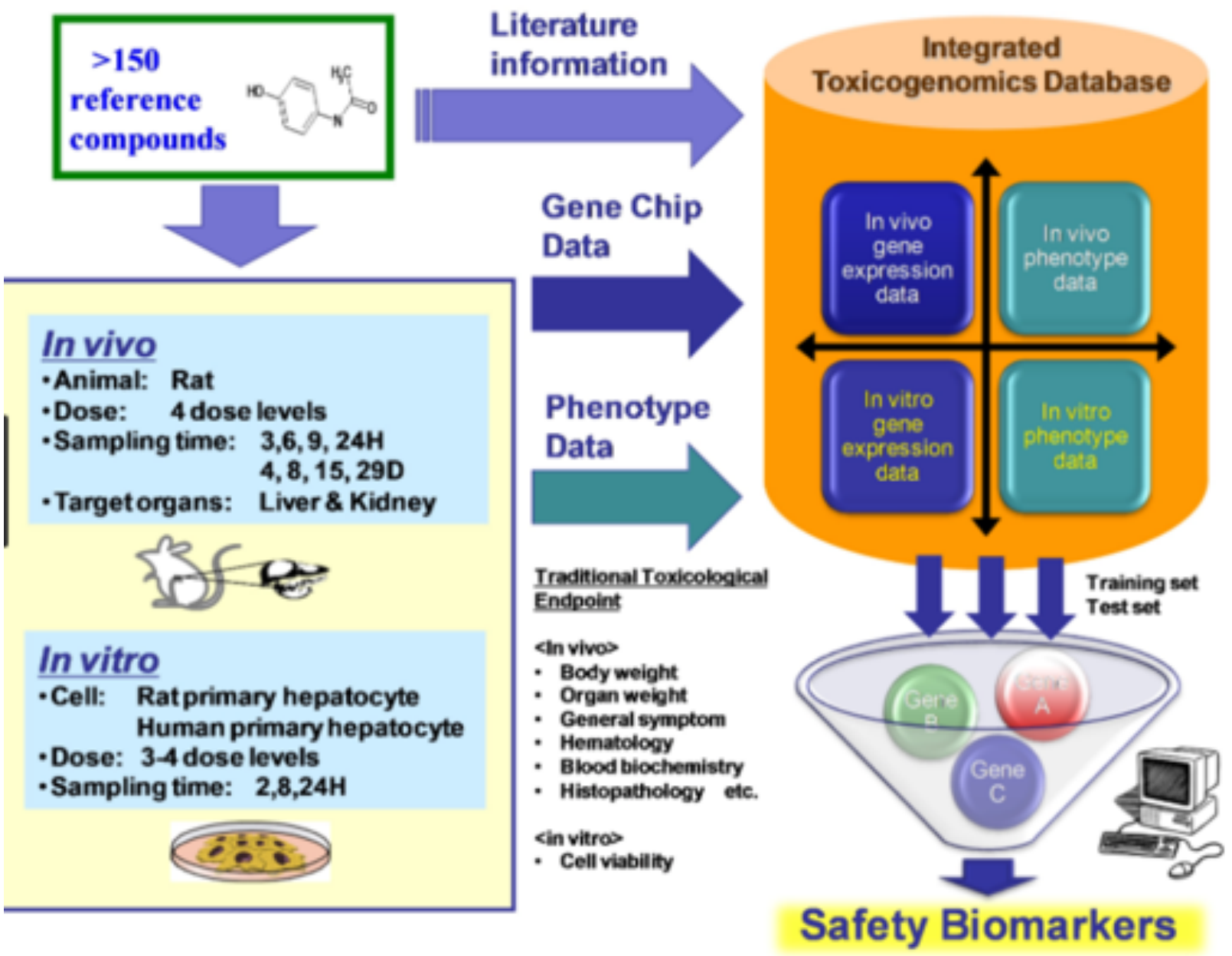
[3H]Fenobam

profile at Cerep (Paris, France) (www.cerep.fr). Fenobam was considered inactive (<50% activity at 10 μM) at all targets tested with the exception of the adenosine A_3 receptor, where it caused a 65% displacement of specific binding at 10 μM (Table 4).

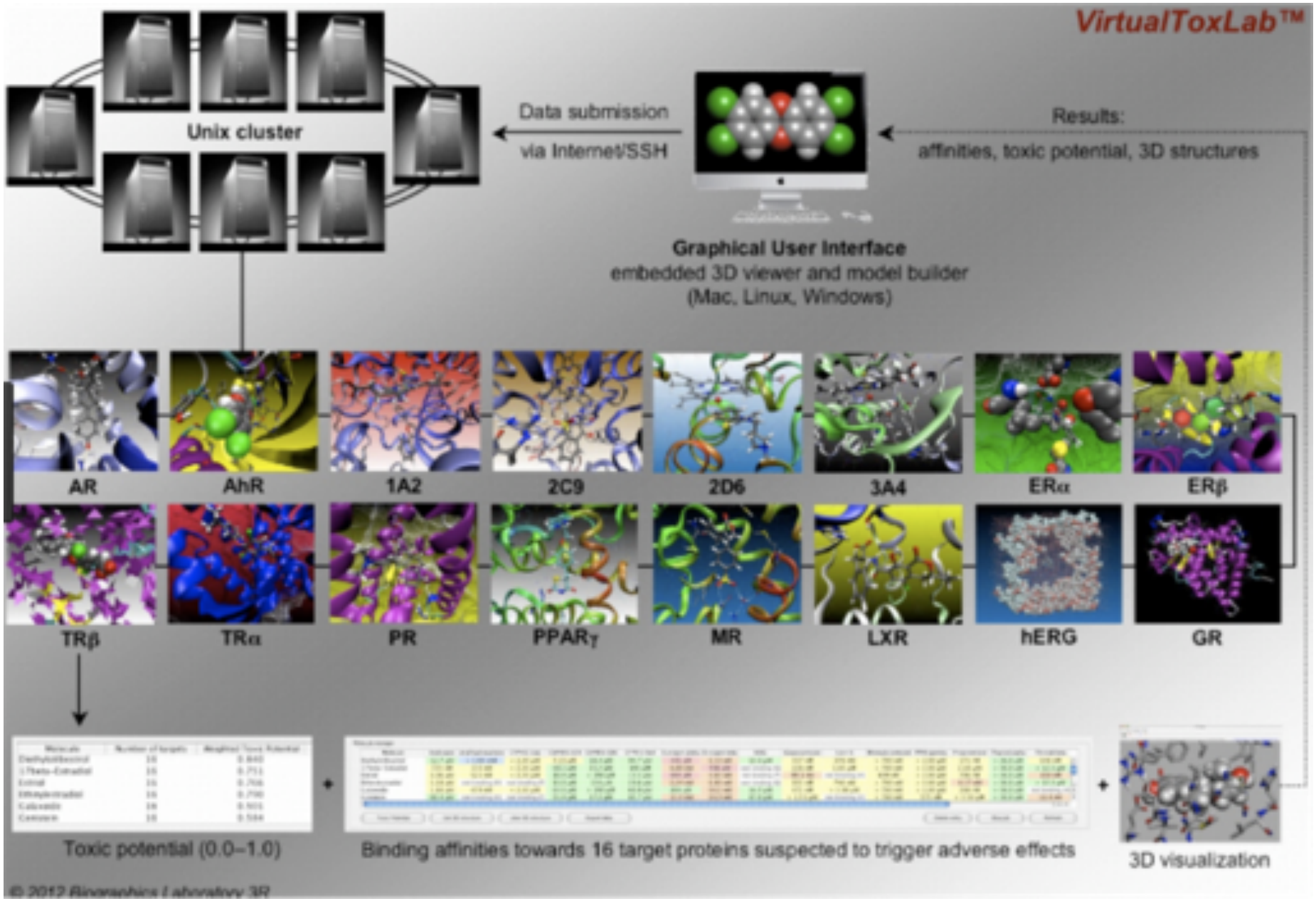
Porter R. et al. 2005 J. Pharmacology 315:711-721

Cerep

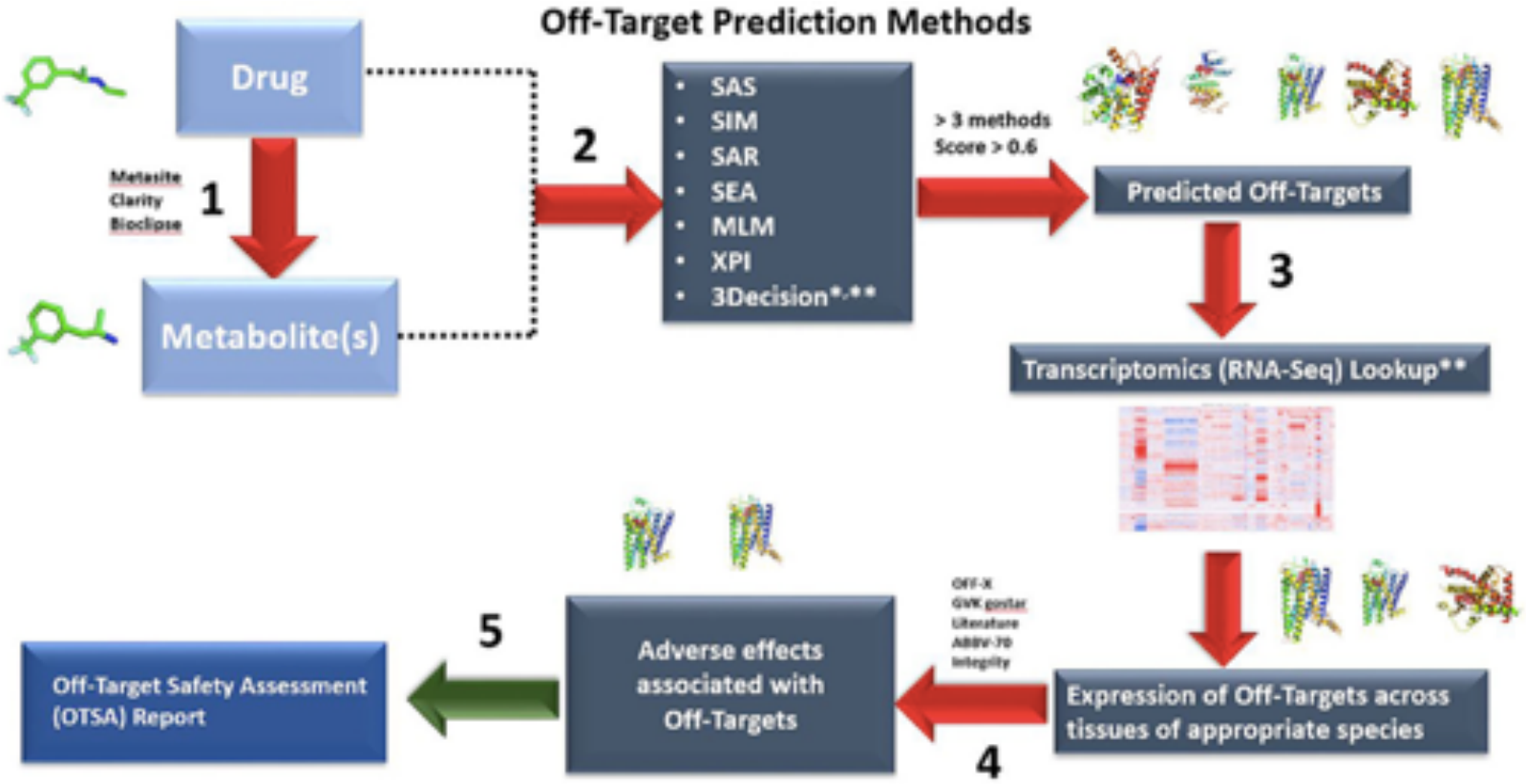
The Making Of An Innovative Medicine: toxicogenomics



In silico toxicology : how close to patients safety ?



OFF TARGET : EROFINS CEREP !



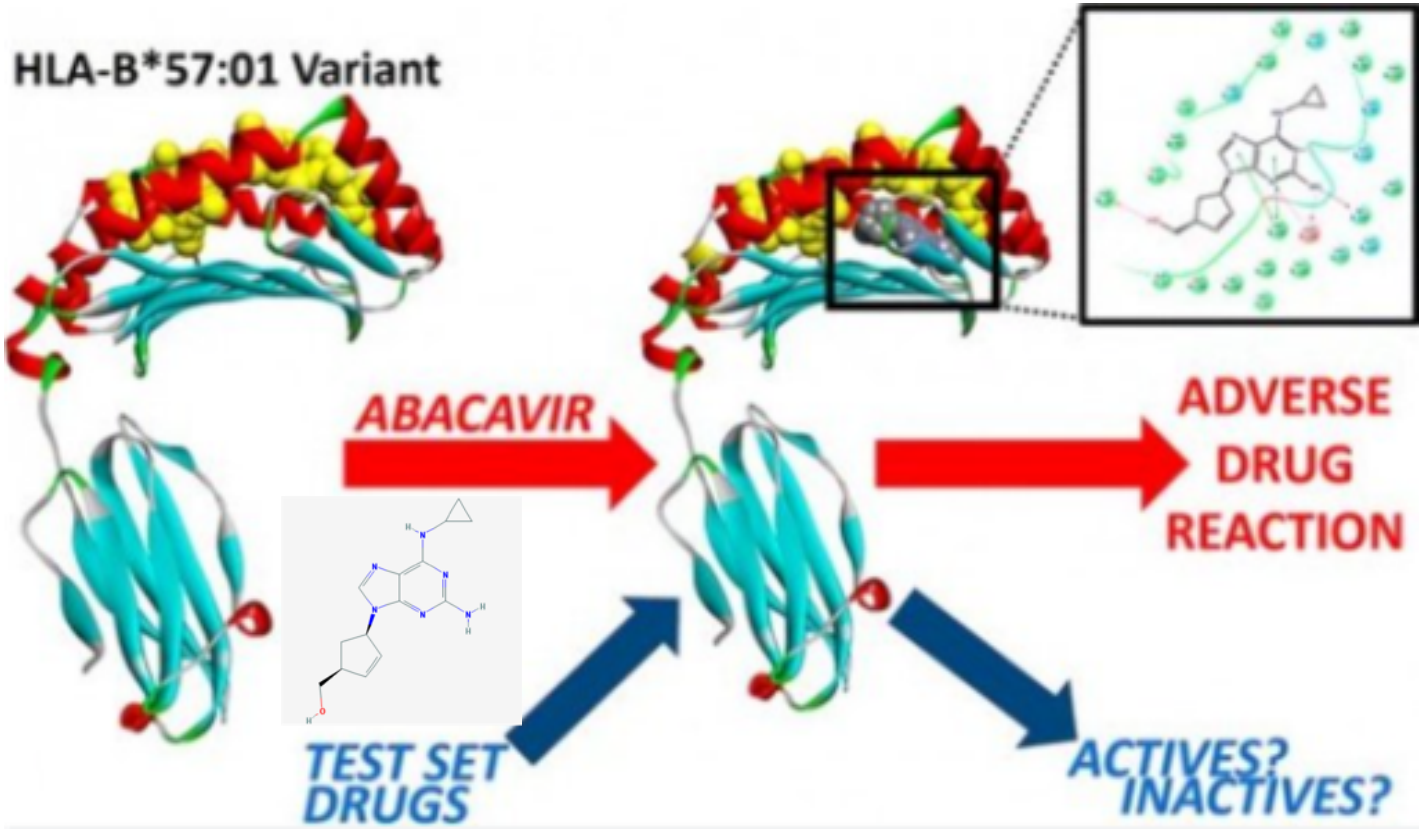
* Not considered for scoring, ** Not used for assessing very large data sets such as approved and discontinued drug databases.

Cerep

Modeling of drug adverse effets : *in sillico* 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.

Credit: North Carolina State University

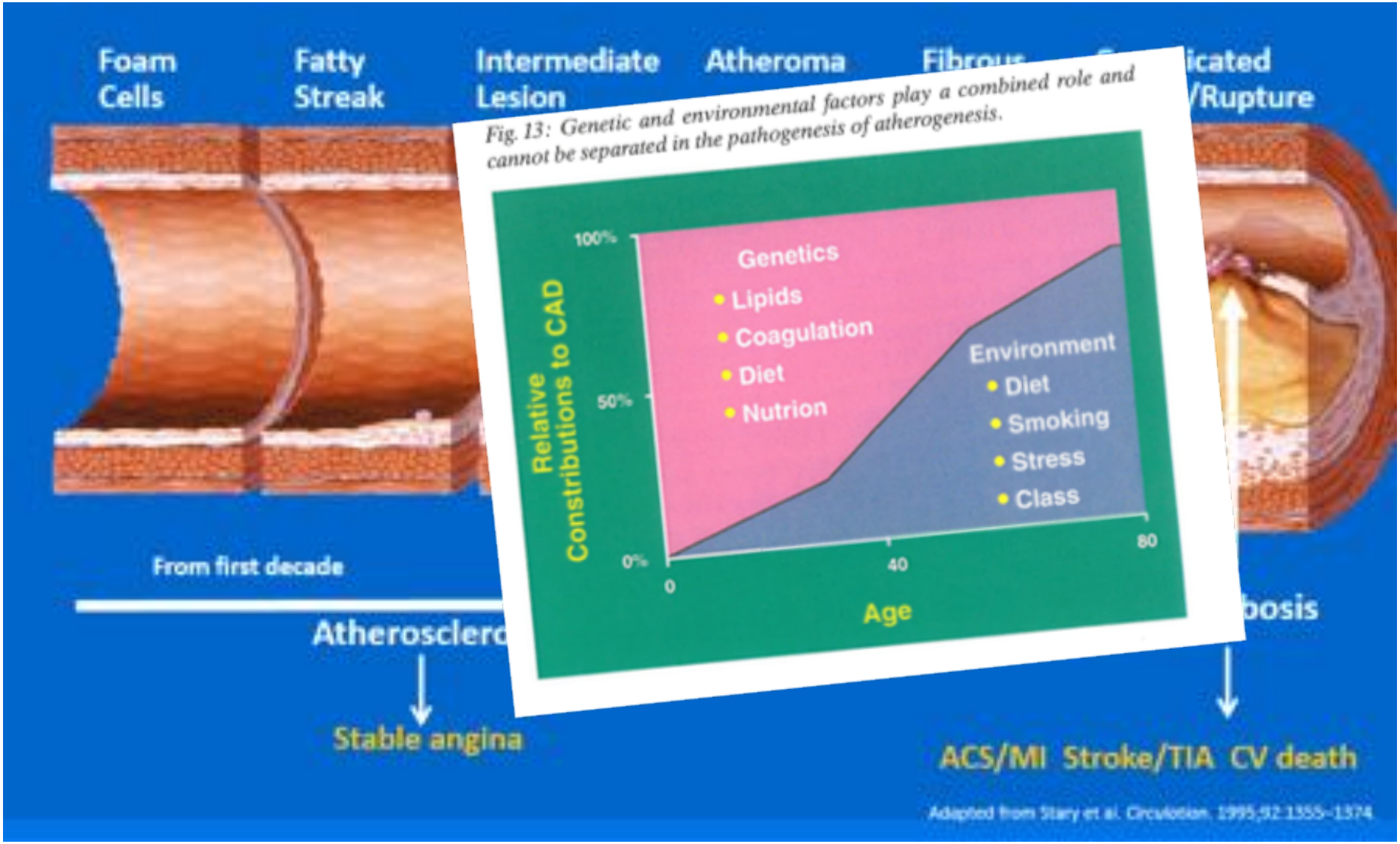
HIV- strong inhibitor of reverse transcriptase (nucleoside reverse transcriptase inhibitor (NRTI) class)

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

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

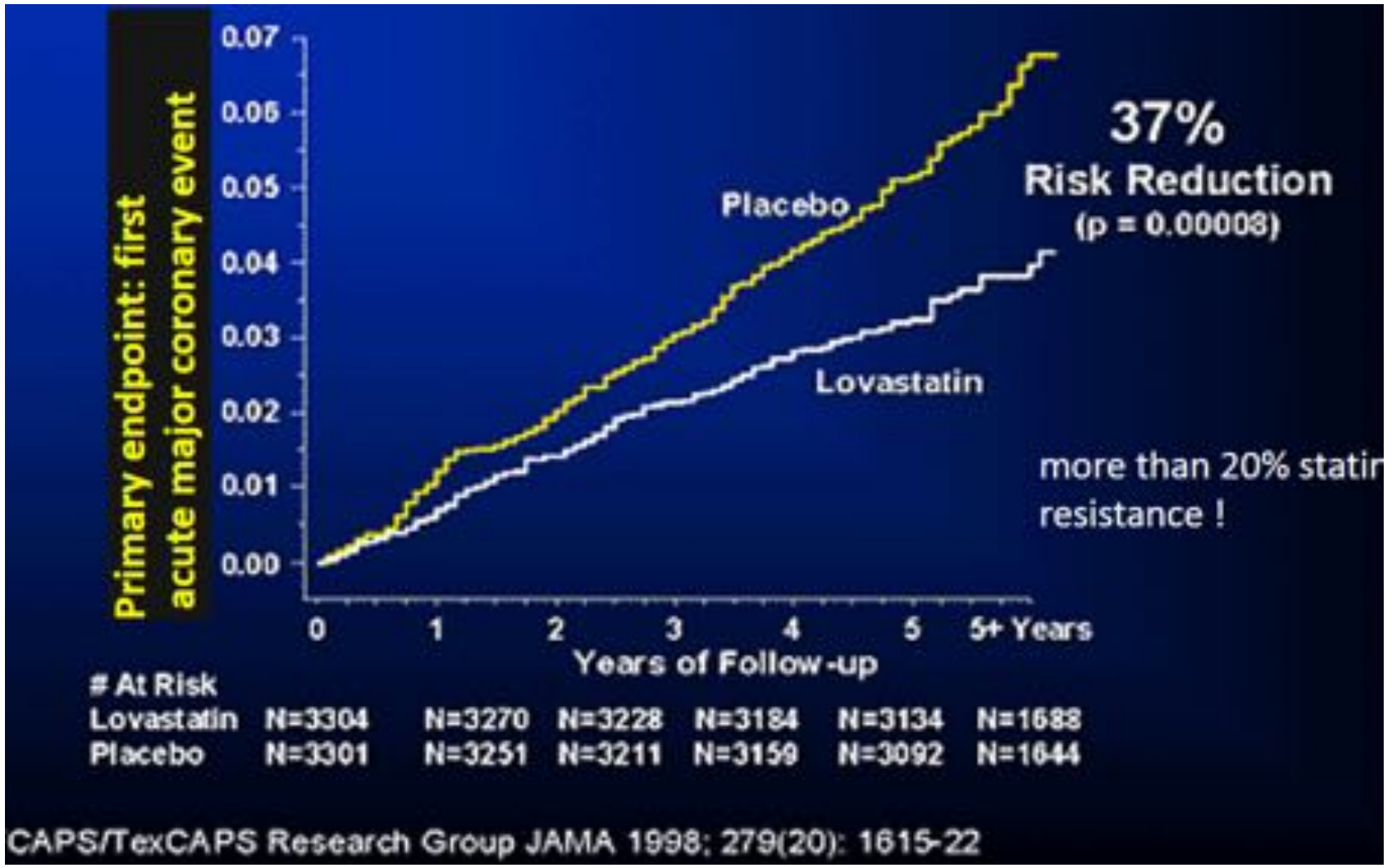
Atheroma, thrombosis and acute coronary syndrome

The CYP11B2 story and Torcetrapib



Reduction of LDL levels improves ACS enpoints

The CYP11B2 story and Torcetrapib



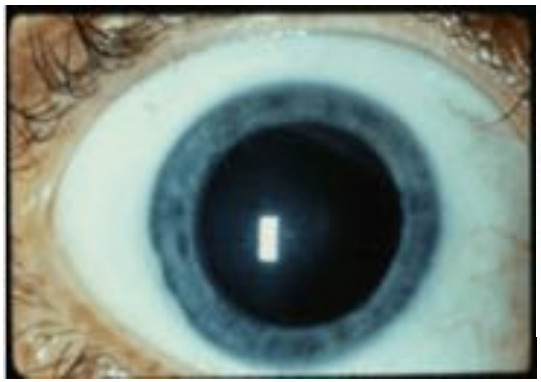
ABCA1 transporter mutations : Tangier Island USA

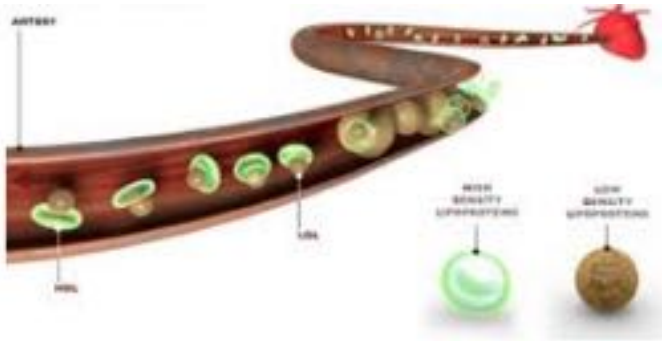
M.Teddy Laird Tangier USA

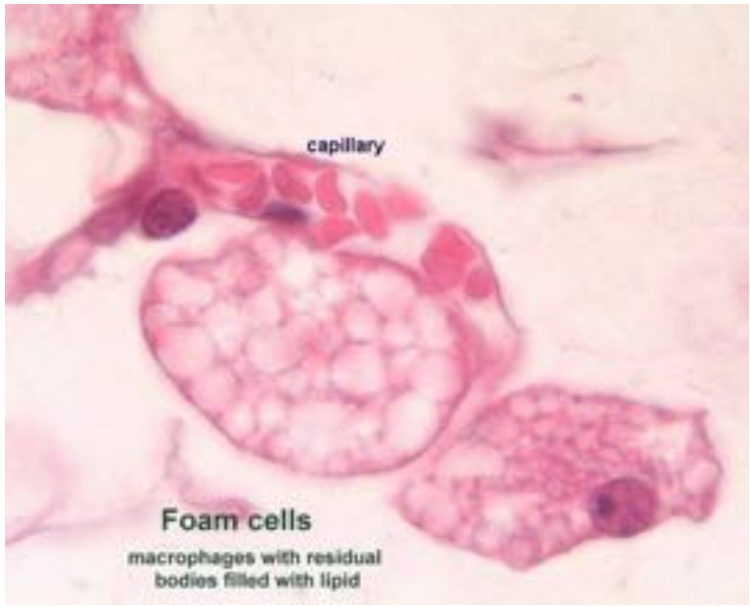
ABCA1 transporter mutations : Tangier Island MD USA

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.







ABCA1 transporter mutations : Tangier Island USA

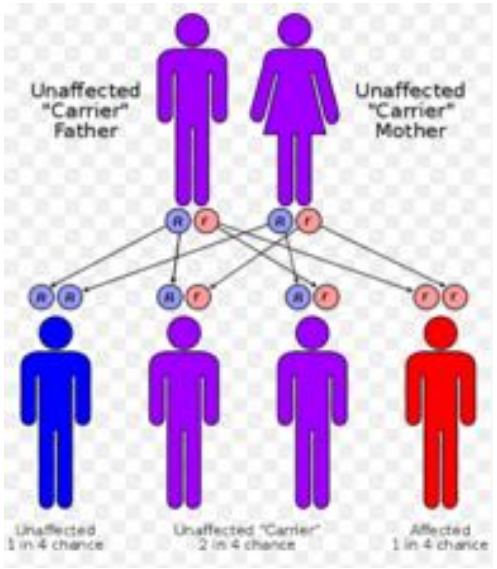
Tangier Disease (Familial High Density Lipoprotein Deficiency)*

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.



ABCA1 transporter polymorphisms : cholesterol efflux

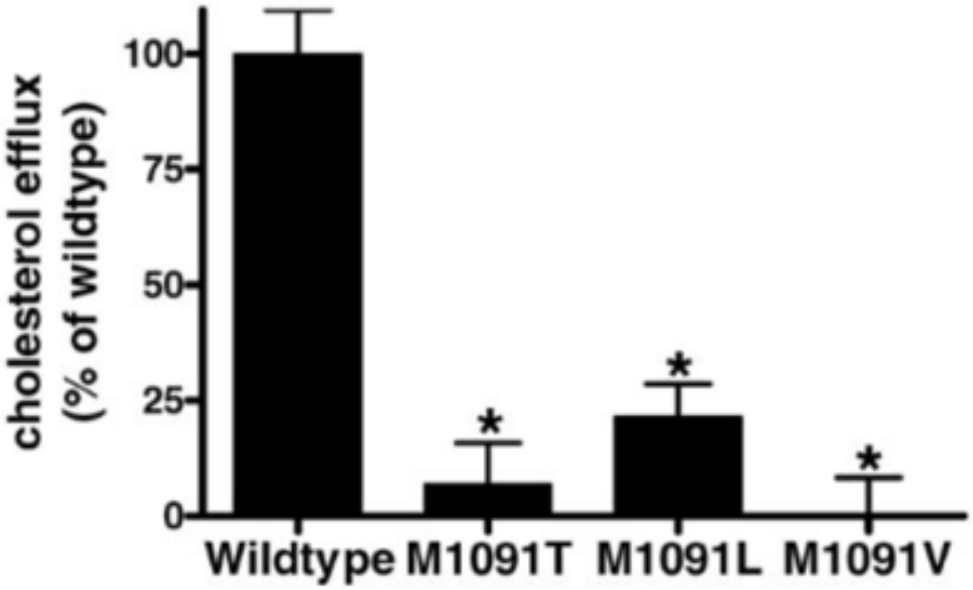
OPEN ACCESS Freely available online

PLoS GENETICS

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

Liam R. Brunham[1], Roshni R. Singaraja[1], Terry D. Pape[1], Anish Kejariwal[2], Paul D. Thomas[2], Michael R. Hayden[1*]

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



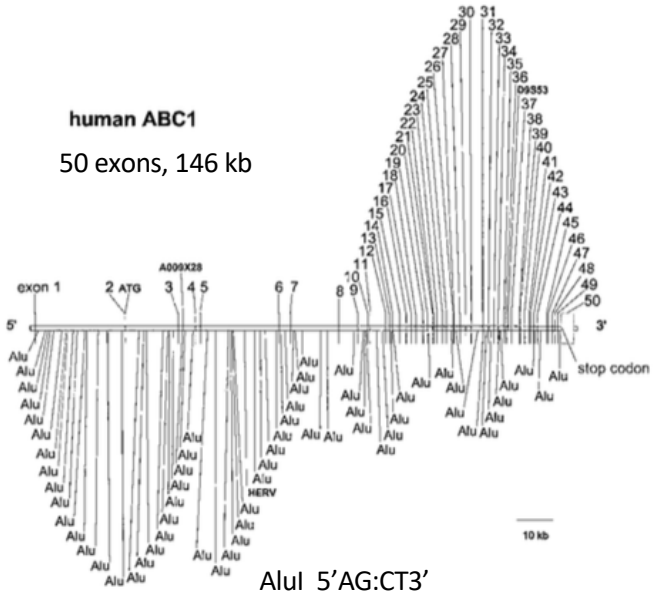
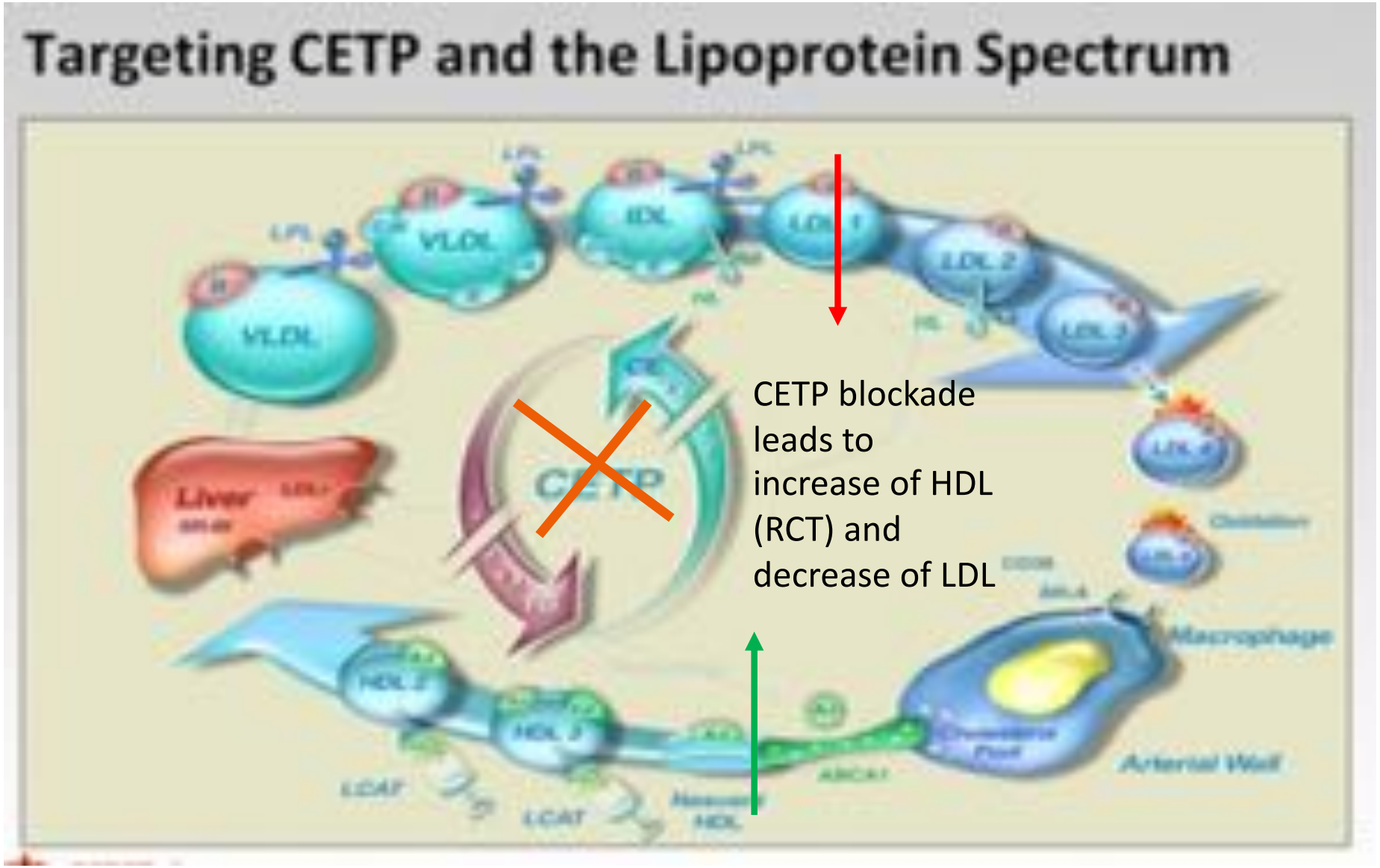


Fig. 1. The genomic organization of the human *ABCA1* gene is illustrated. The

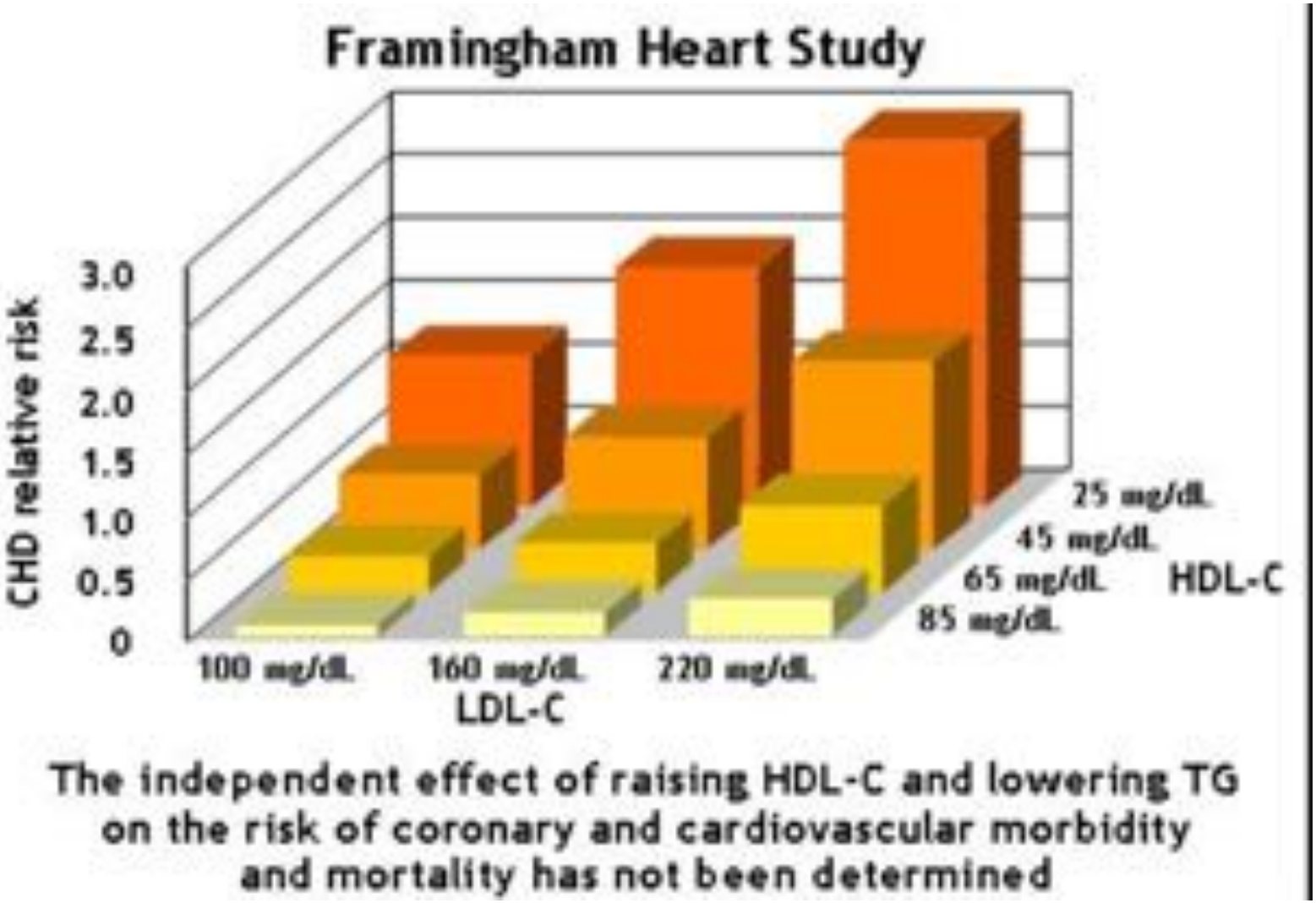
Screening cascade of cpds

The CYP11B2 story and Torcetrapib

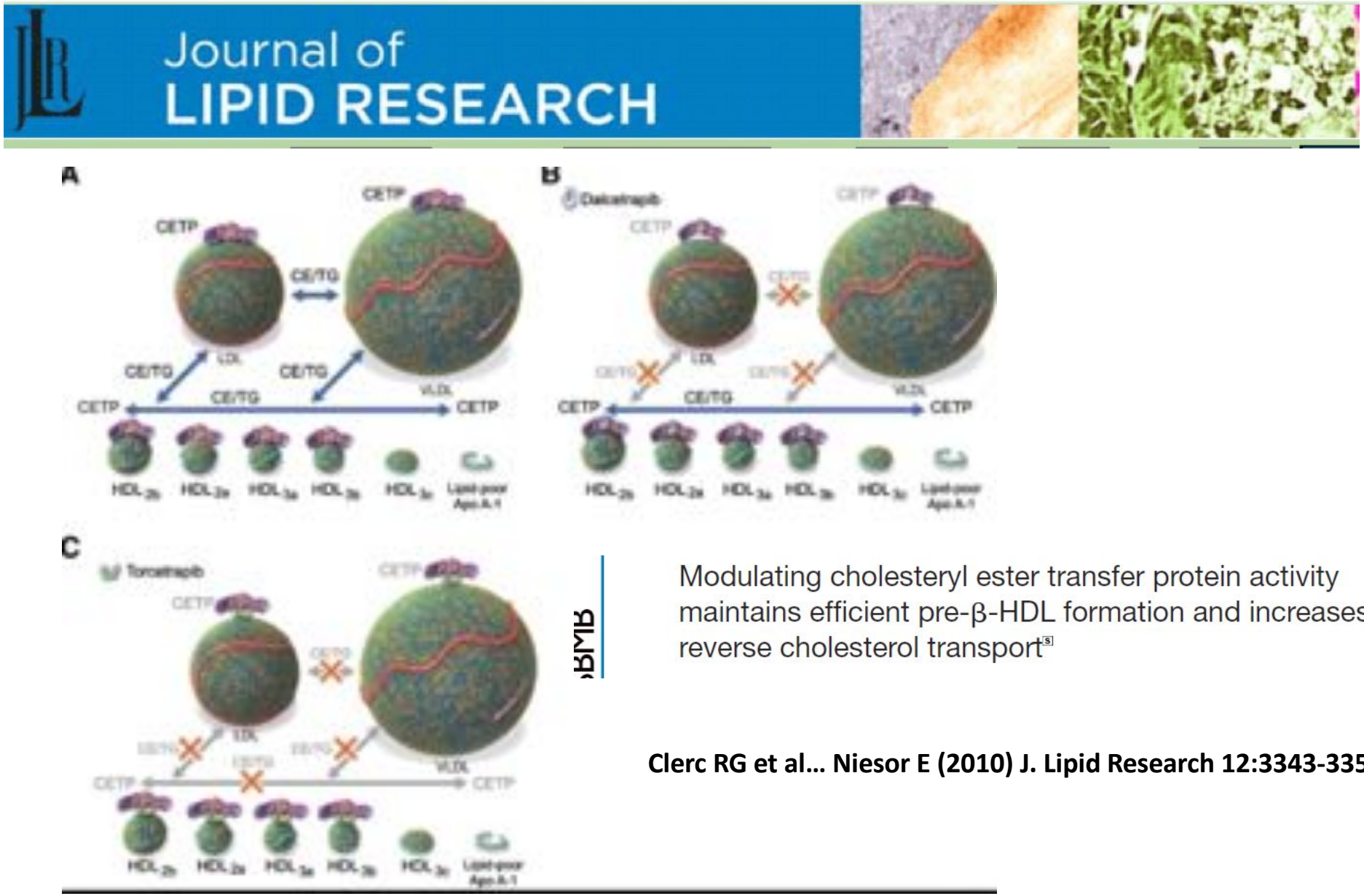


High HDL levels correlate with good CVD prognostics

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



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

Clerc RG et al… Niesor 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

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.

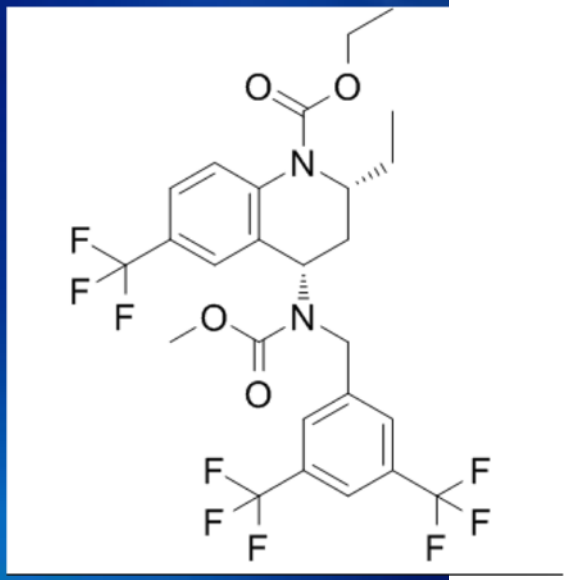
Pfizer said that "in the interests of patient safety" it was stopping the clinical trials of torcetrapib (called Illuminate) because the independent data safety monitoring board found more deaths and cardiovascular events in patients taking the drug. The trials included 7500 patients who were taking 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

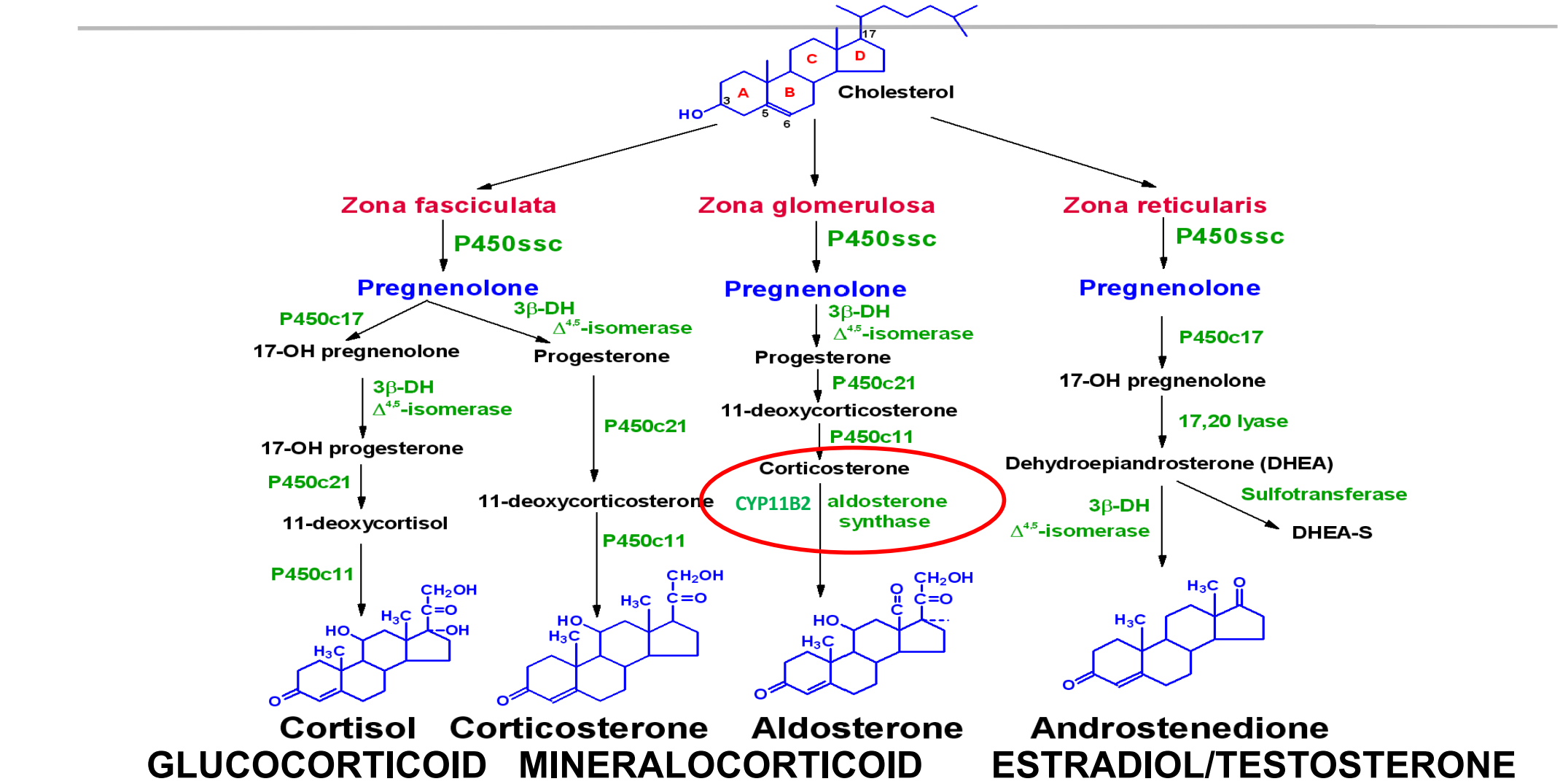
- reduces eNOS,
- increases ET-1
  →induces endothelial dysfunction



Other CETP inhibitors do not have these off-target effects

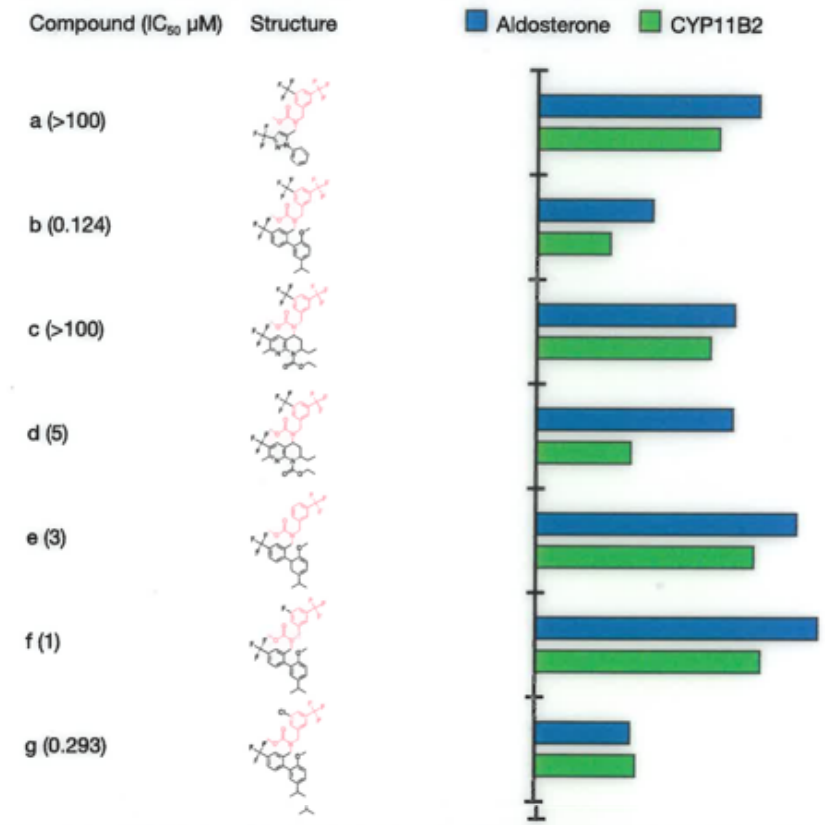
IS THIS ADVERSE TOXIC EFFECT A CETPi CLASS OR A CPD –SPECIFIC OFF TARGET EFFECT??

Steroids and the Adrenal Cortex

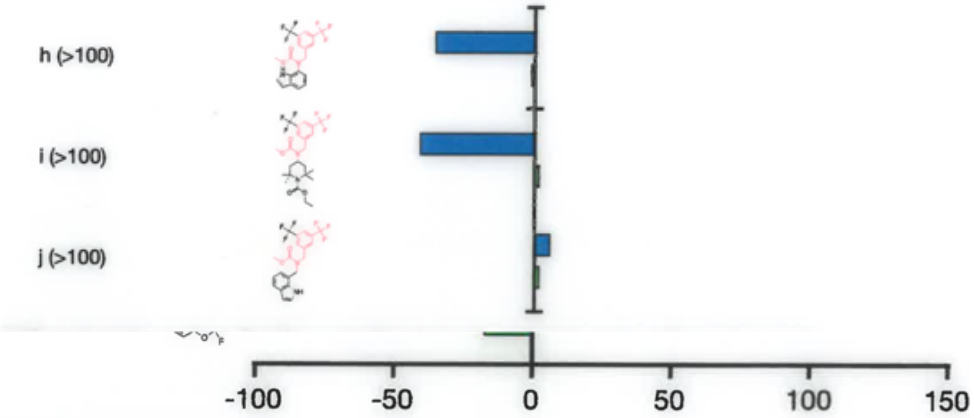


The adrenal cortex is responsible for production of 3 major classes of steroid hormones: glucocorticoids, which regulate carbohydrate metabolism; mineralocorticoids, which regulate the body levels of sodium and potassium; and androgens, whose actions are similar to that of steroids produced by the male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

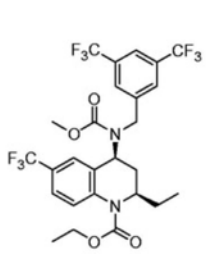
1a. Compounds with methyl-(3-trifluoromethyl-benzyl)-carbamic acid methyl ester motif of torcetrapib (IN RED COLOUR) attached to a suitable THQ-replacement

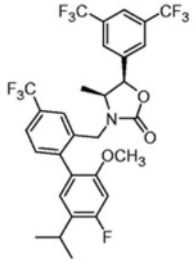


1b. Compounds with methyl-(3-trifluoromethyl-benzyl)-carbamic acid methyl ester motif of torcetrapib (IN RED COLOUR) but no suitable THQ-replacement

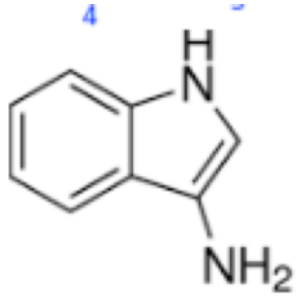


IC_{60} of CETP activity determined using a scintillation proximity assay.
nd, not determined (benzoic acid derivative).



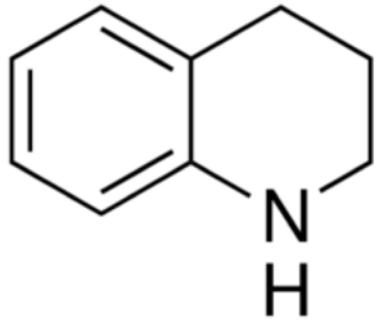


An example of assay read out and medicinal chemistry MDO



Indole

Composé organi



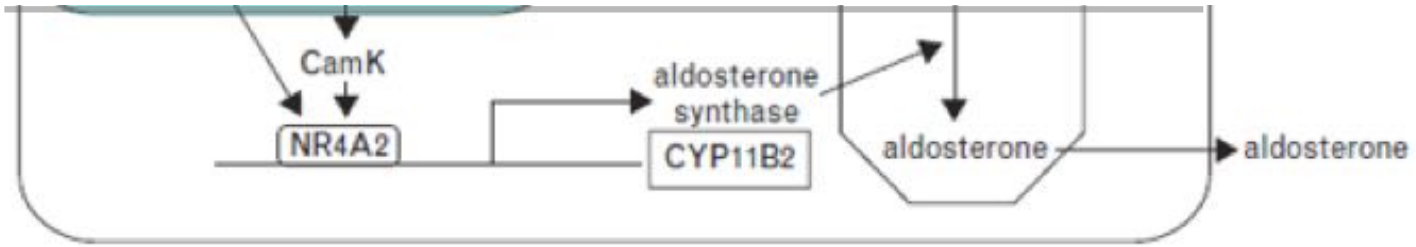
T15504 ALDRICH
1,2,3,4-Tetrahydroquinoline
98%
Synonym: THQ

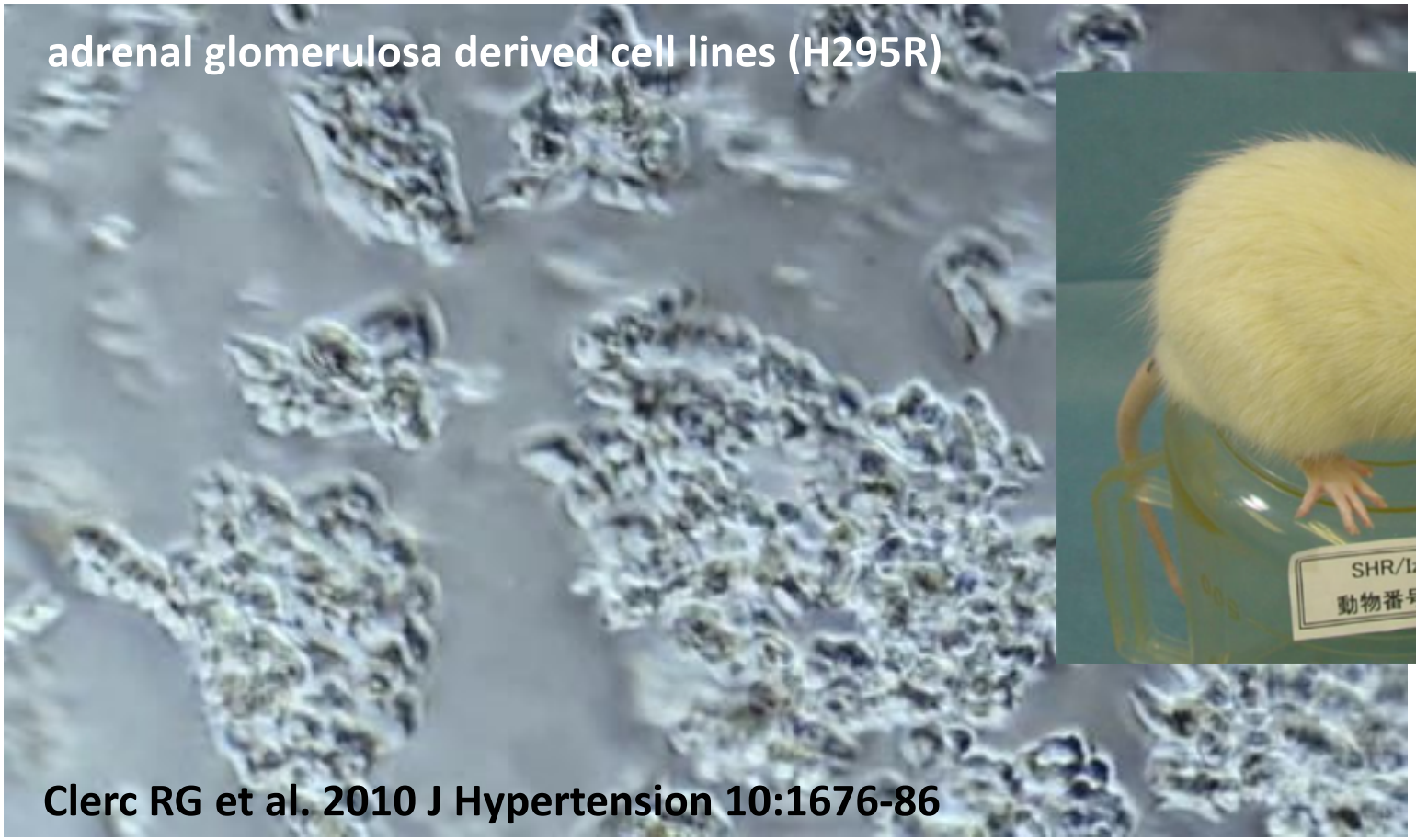
Clerc RG. and Niesor EJ. (2012) American Heart Association Washington DC

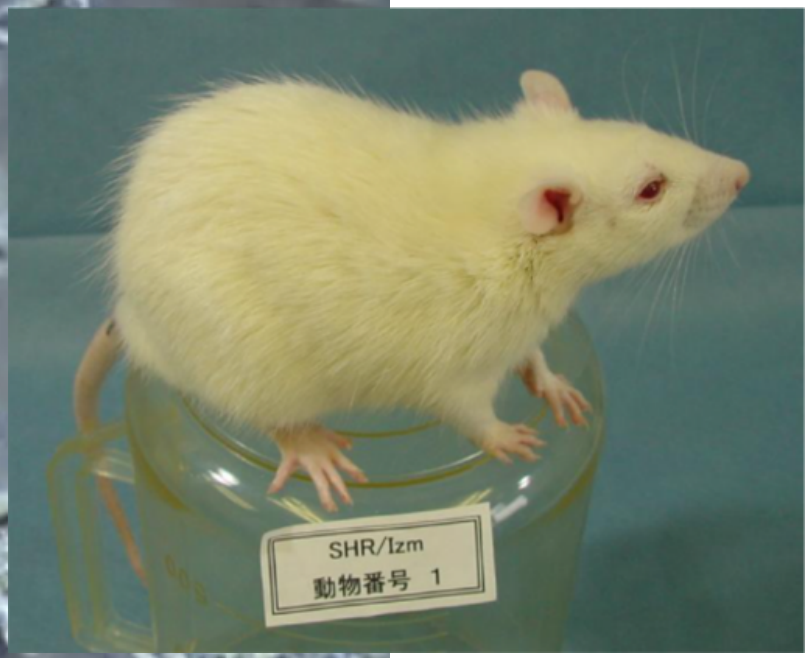
Investigative toxicology _CETPi Torcetrapib but not Dalcetrapib did increase aldosterone synthesis CYP11B2 synthase and blood pressure in SHR

Screening cascade of cpds targeting the aldosterone synthase

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



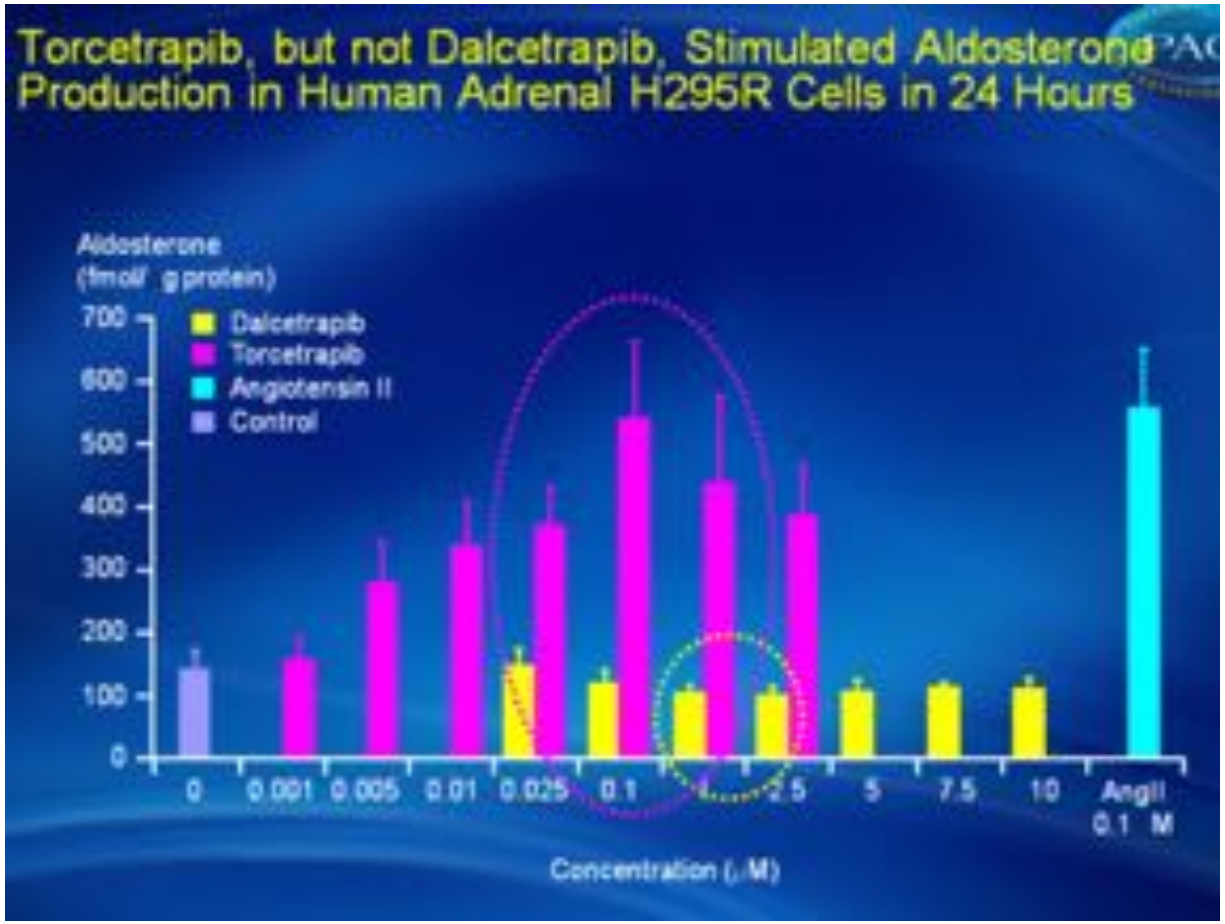




Clerc RG et al. 2010 J Hypertension 10:1676-86

Screening cascade of cpds

The CYP11B2 dramatically activated byTorcetrapib but not Dalcetrapib



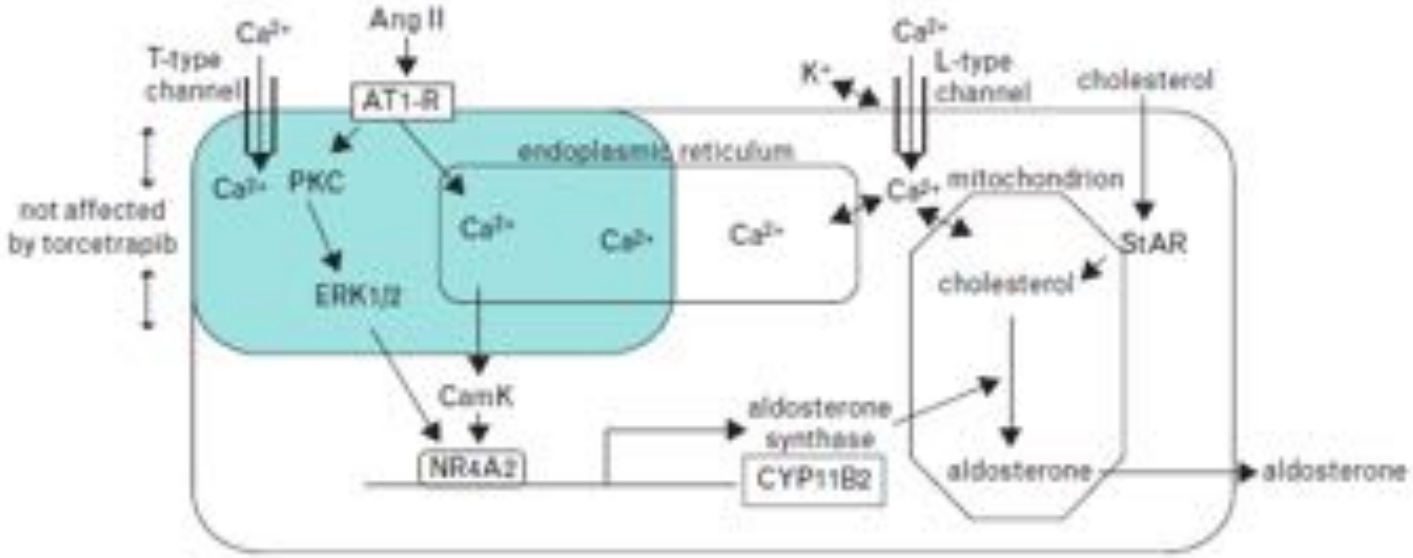
Stroes and Clerc RG et al. 2010 Br J Pharmacol. 2009 Dec;158(7):1763-70. doi

Screening cascade of cpds

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.

Clerc RG et al. 2010 J Hypertension 10:1676-86

Intellectual property _ patents

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 ?

Investigative toxicology _ PCBs, endocrine disruptors

Endocrine disruptors and the CYP11B2 nanomolar affinities

Adrenal hormone biosynthesis

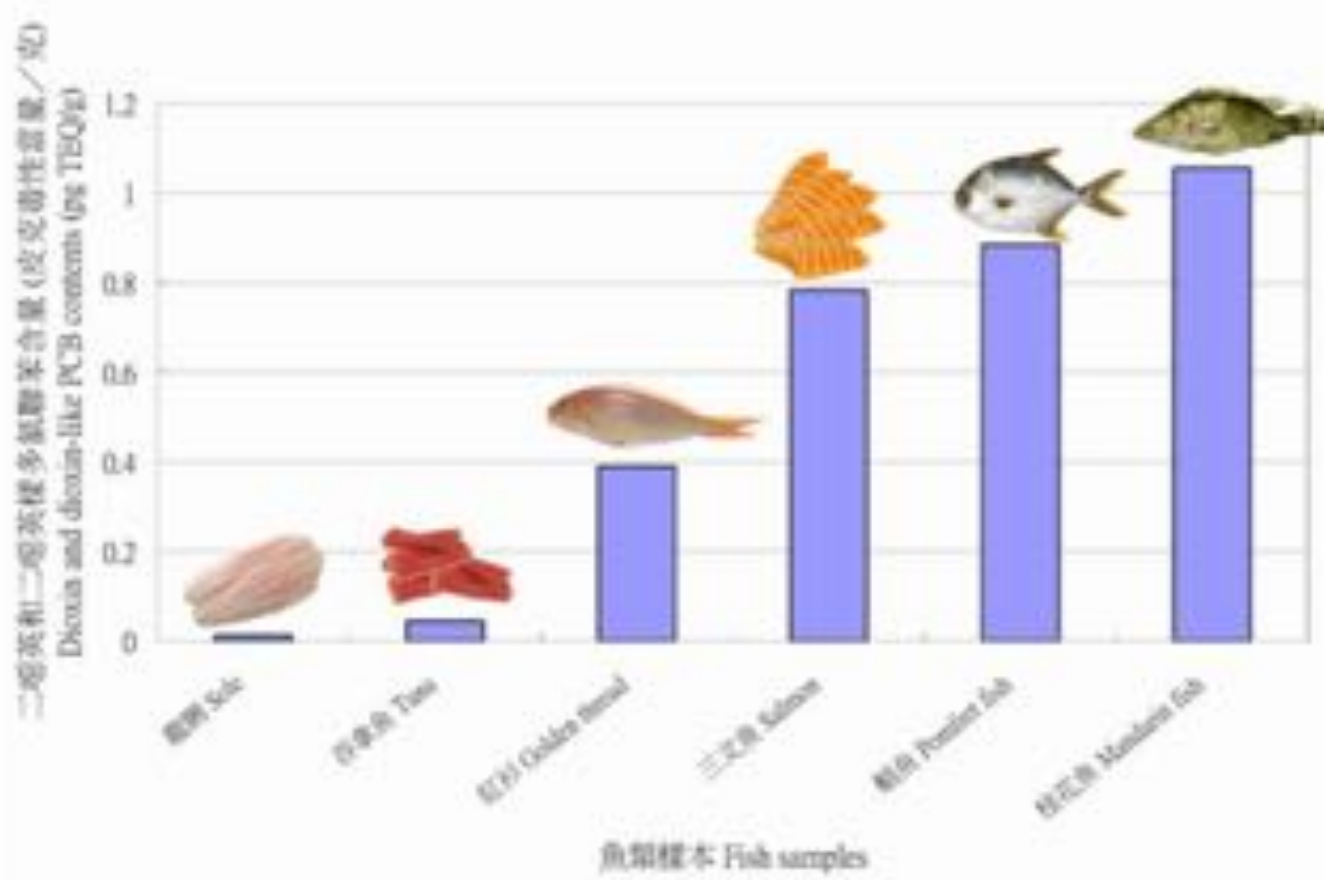
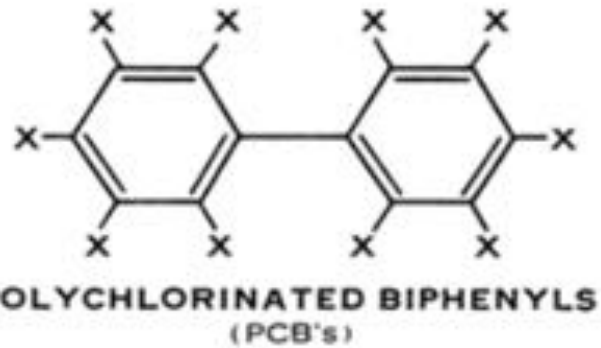


Figure 1. Dioxin and dioxin-like PCB contents among various fish

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



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

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

Endocrine disruptors and the CYP11B2 nanomoloar affinities

Adrenal hormone biosynthesis

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

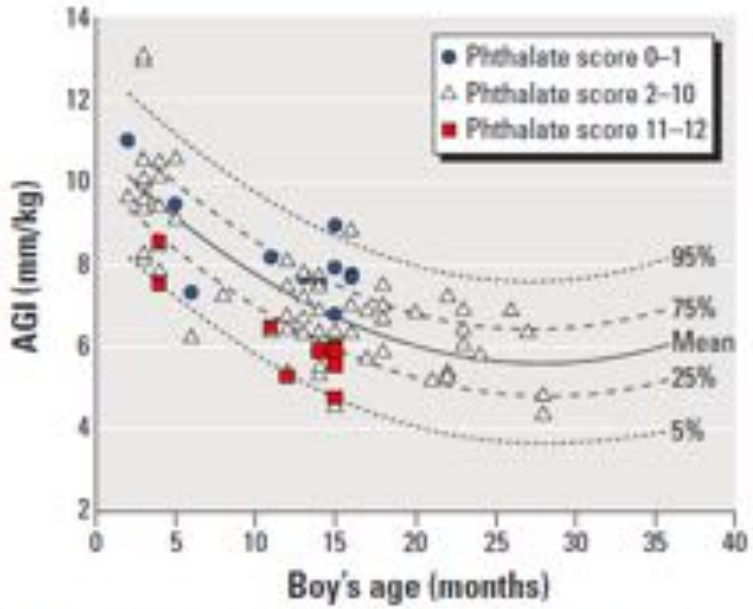
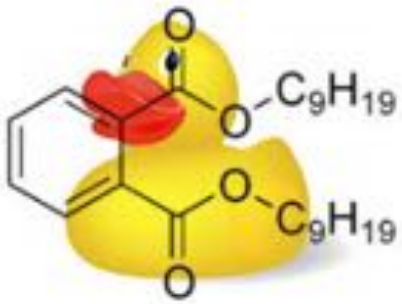
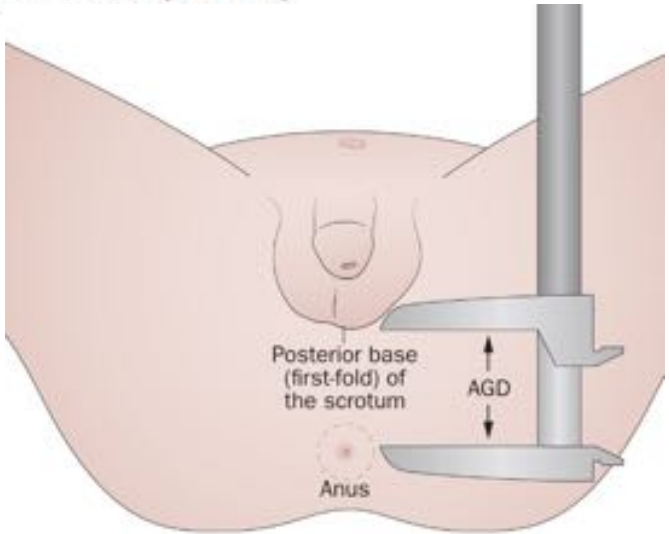


Figure 1. Mean AGI (mm/kg) in relation to boys' age at examination (months).

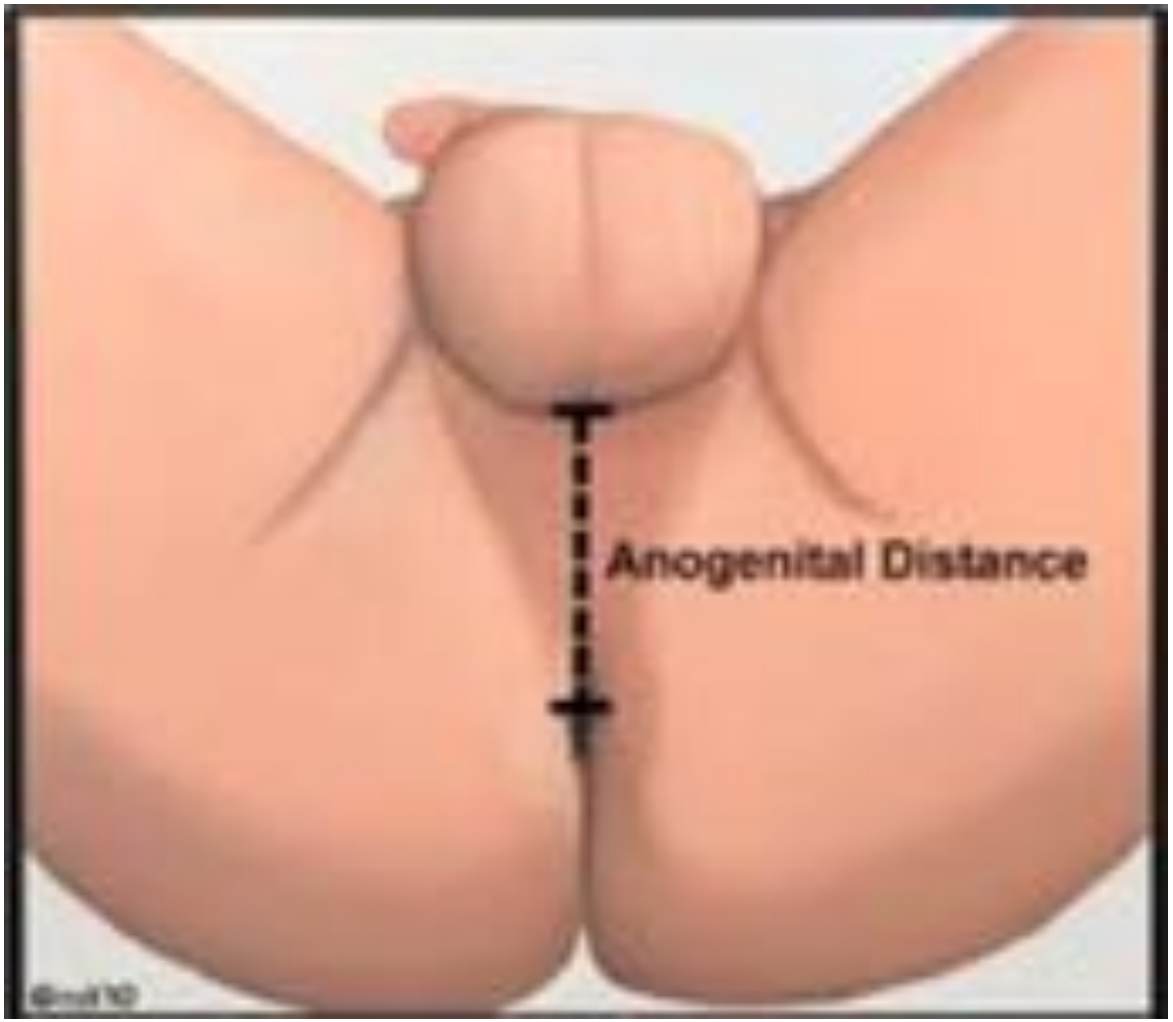




Environmental Health Perspectives • VOLUME 113 | NUMBER 8 | August 2005

Reproductive clinical toxicology

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

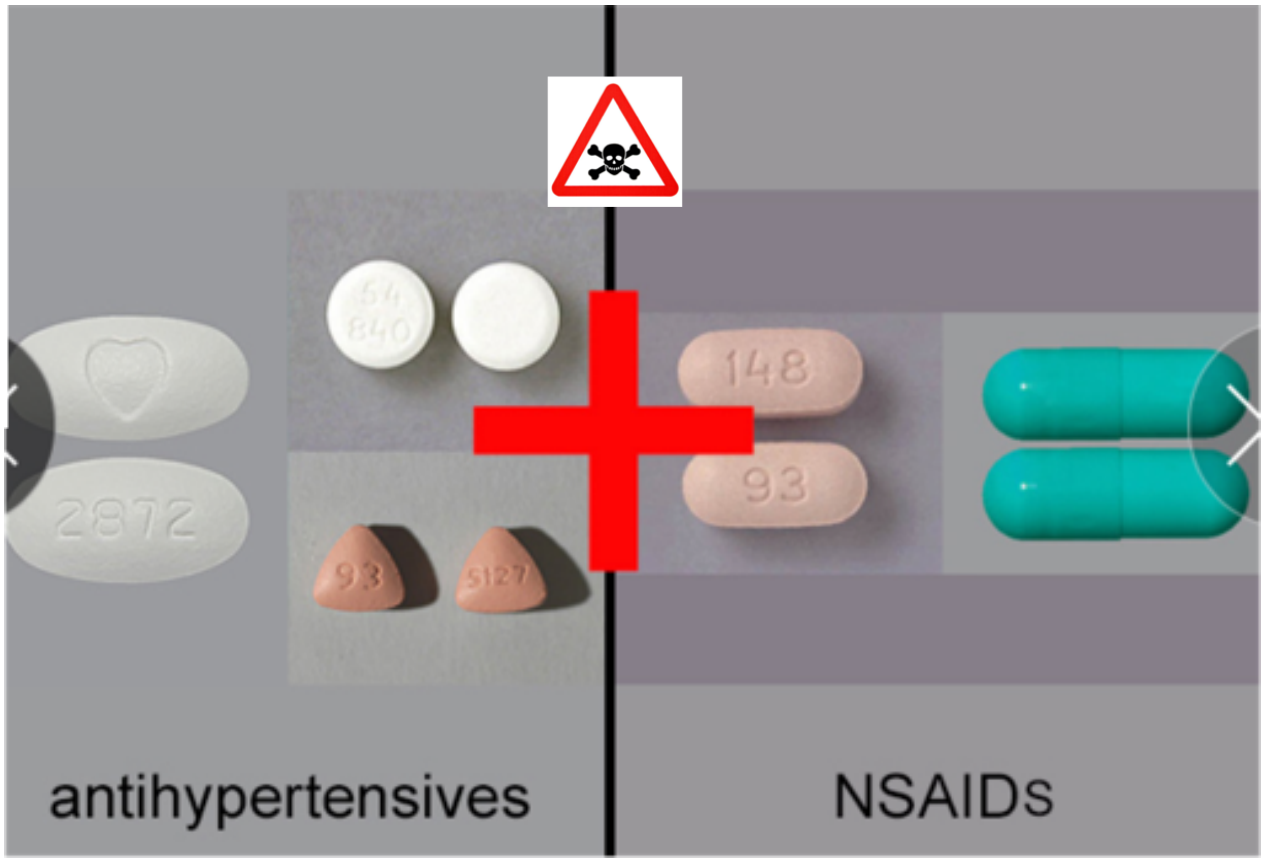


Environmental Health Perspectives • VOLUME 113 | NUMBER 8 | August 2005

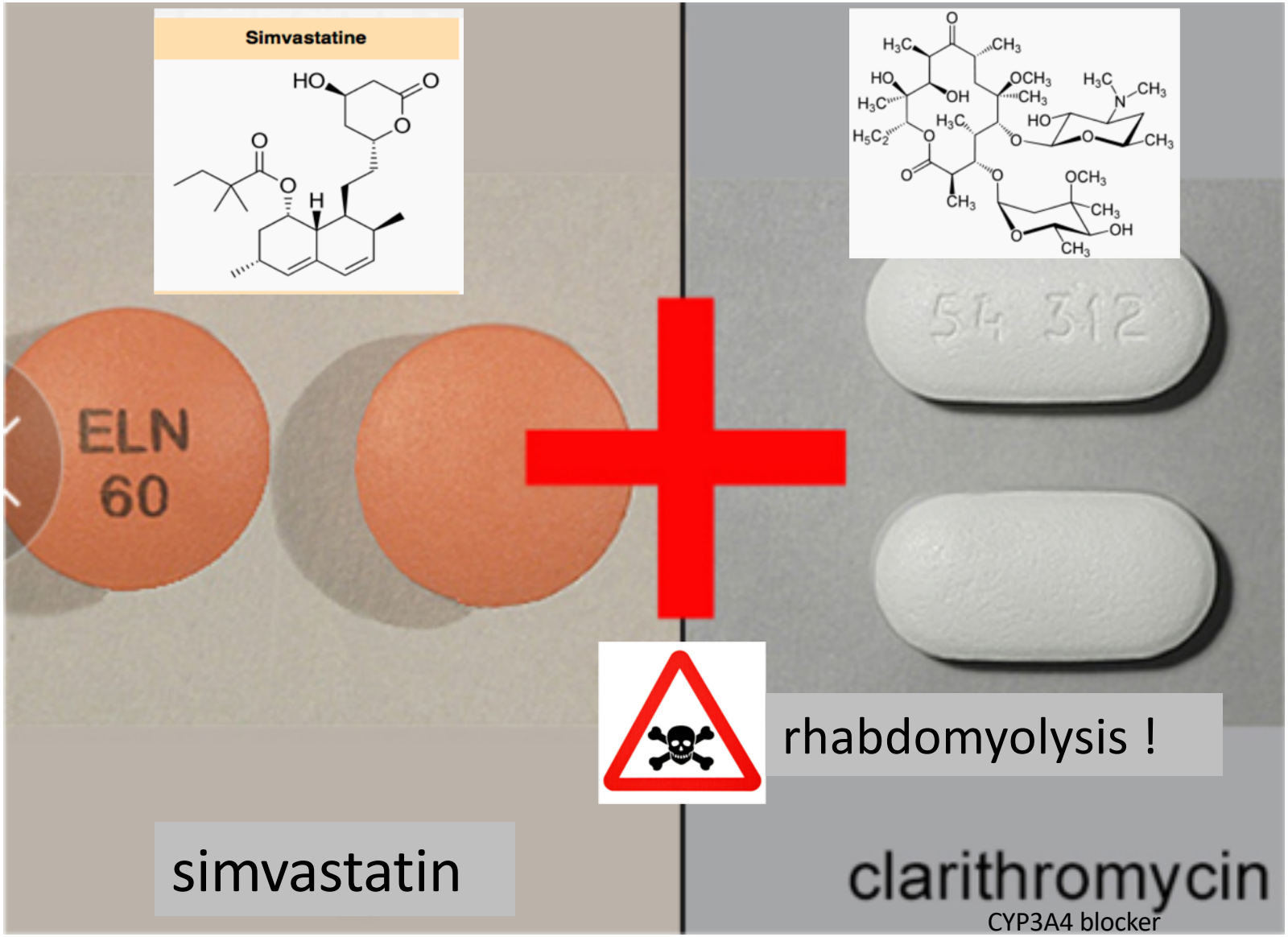
Clinical toxicology : the drug_drug interactions : explosive cocktails !

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.



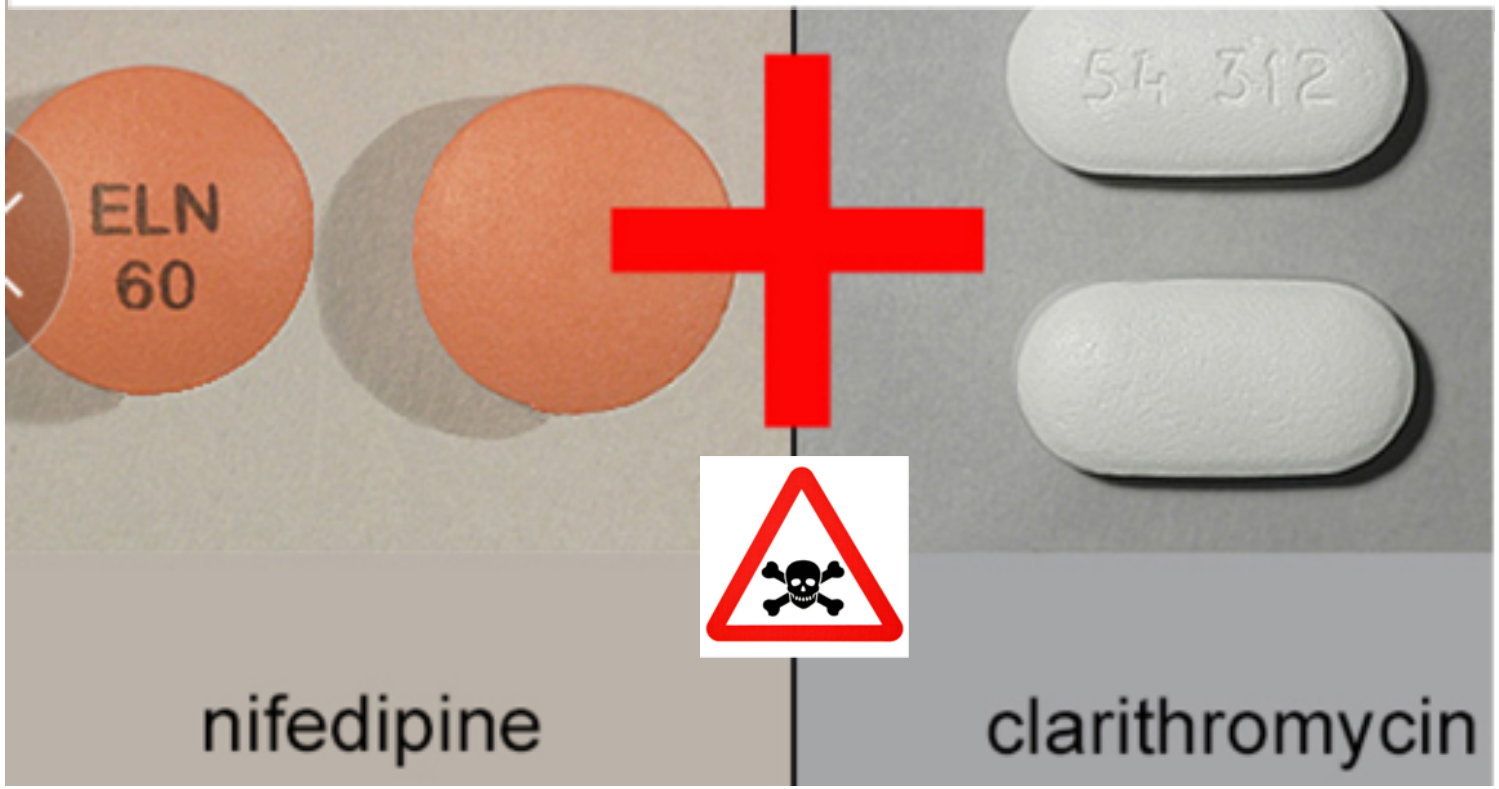
*Case study : a patient on statin suffers from pharyngitis (ORL Othorhinolaryngology **symptoms) What do you do ?***

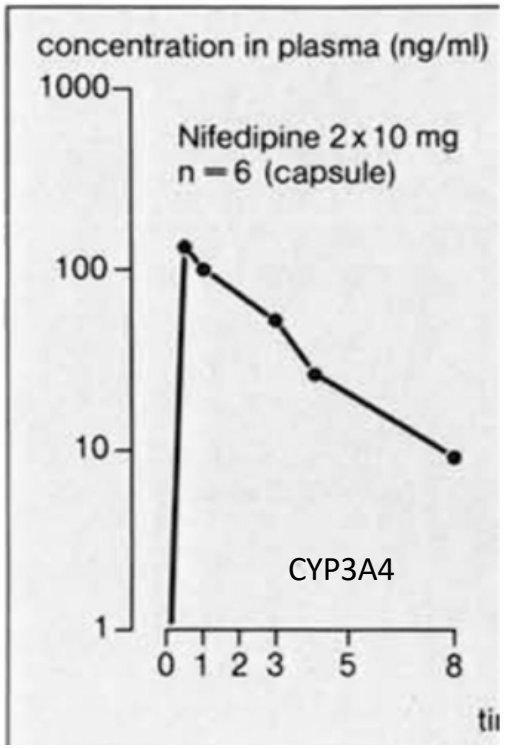


Case study: a patient on calcium channel blocker suffers from pharyngitis (ORL** Otorhinolaryngology **symptoms) What do you do ?

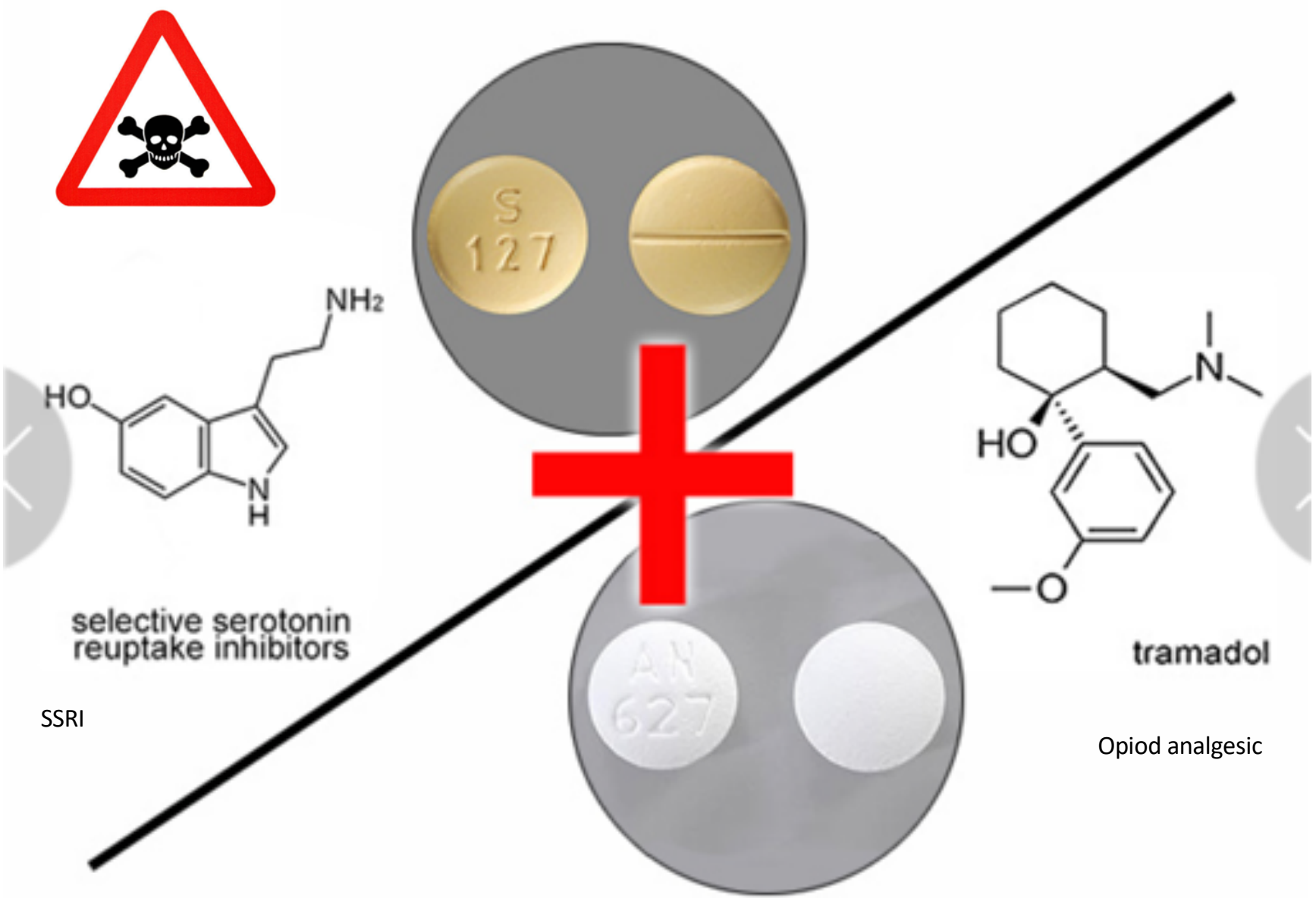
Figure 1. Clarithromycin With Each Type of Calcium-Channel Blocker and the Risk of Acute Kidney Injury

	Clarithromycin		Azithromycin					
	Events, No.	No. at Risk (%)	Events, No.	No. at Risk (%)	OR (95% CI)	Risk Lower With Clarithromycin	Risk Higher With Clarithromycin	*P* Value for Interaction	NNH (95% CI)
Amlodipine	202	50 706 (0.40)	126	50 944 (0.25)	1.61 (1.29-2.02)			[Reference]	663 (451-1223)
Diltiazem	63	21 403 (0.29)	46	21 207 (0.22)	1.36 (0.93-1.99)			.36	NS[b]
Felodipine[a]	17	3665 (0.46)	≤5	3191 (≤0.16)	2.97 (1.09-8.06)			.19	NR
Nifedipine	129	16 644 (0.78)	22	15 038 (0.15)	5.33 (3.39-8.38)			<.001	160 (128-205)
Verapamil	9	3808 (0.24)	9	3703 (0.24)	0.97 (0.39-2.45)			.29	NS[b]

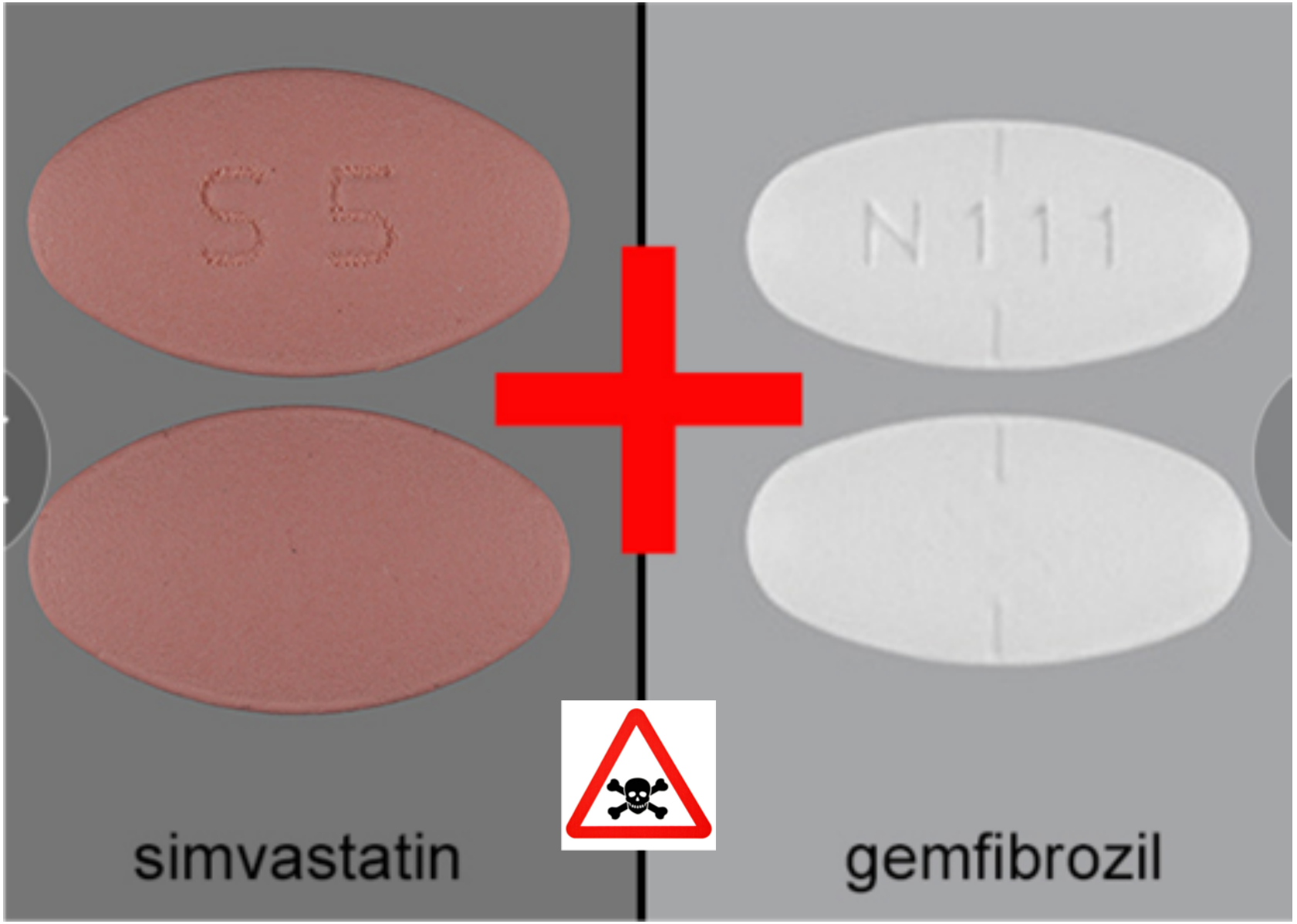




Dangerous pharmacological cocktails : the drug_drug interactions and the serotonin syndrome



Careful : dangerous cocktails : the drug_drug interactions
CYP450 3A4 blockade



Careful : dangerous grapefruit drink : the drug_drug interactions

~70% of drug-drug interactions can be avoided by computer program assisted 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 *credible* 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 *precipitant* 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 *credible* 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 *precipitant* 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?*	−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

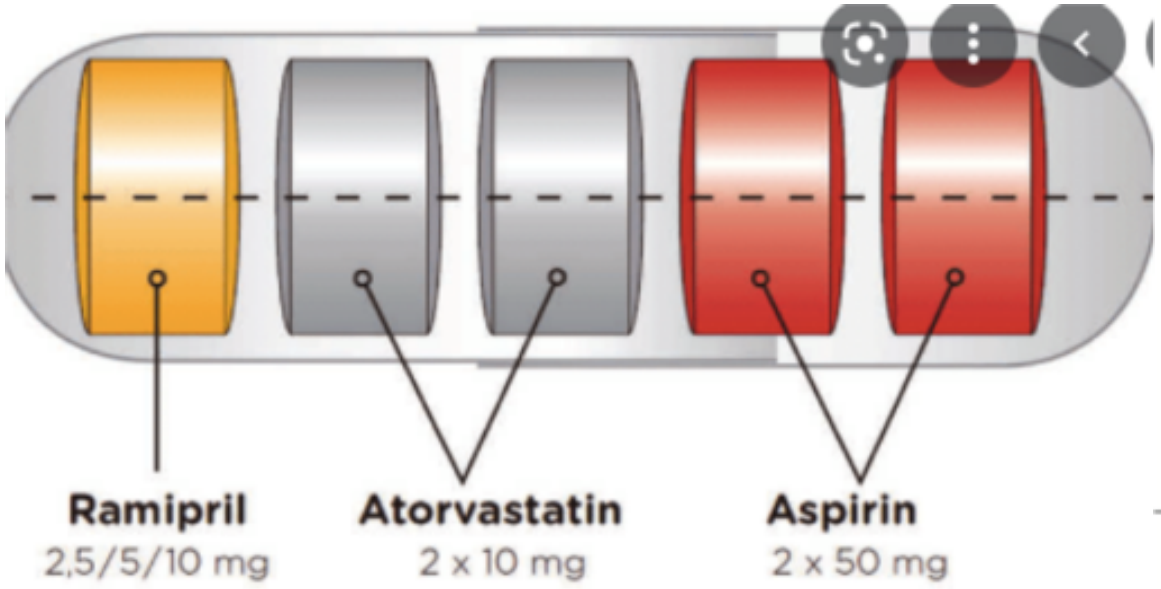
*Consider clinical conditions, other interacting drugs, lack of adherence, risk factors (eg, age, inappropriate doses of object drug). A NO answer presumes that enough information was presented so that one would expect any alternative causes to be mentioned. When in doubt, use Unknown or NA designation.

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

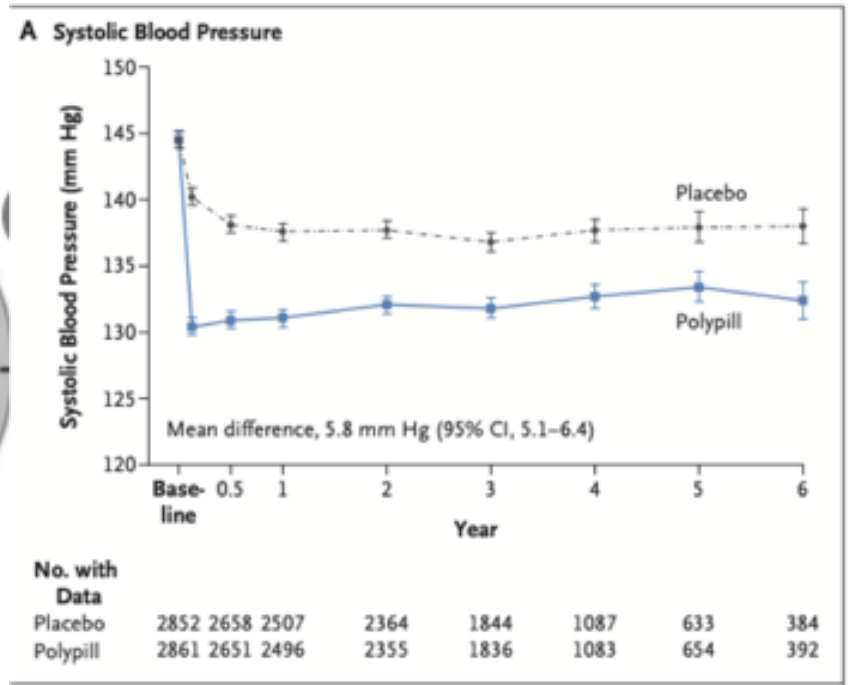


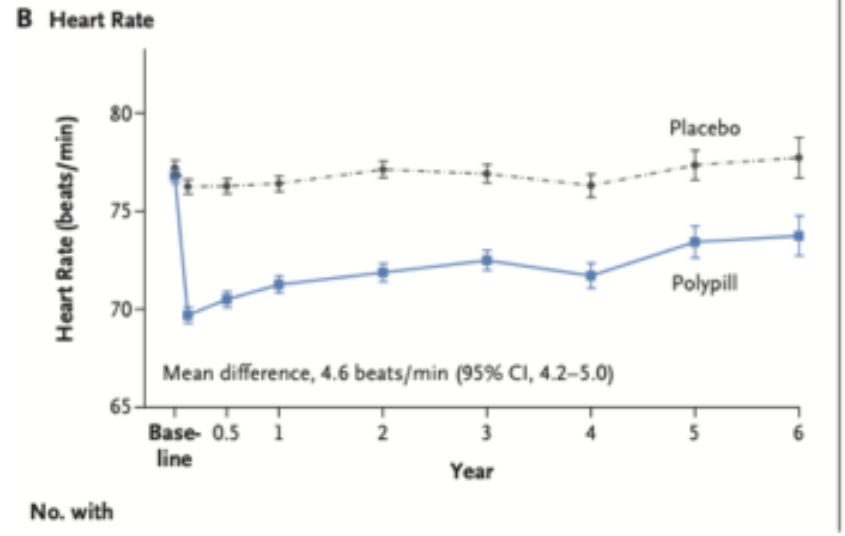
ACE i

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. McCready, J. Tyrwhitt, J. Bosch, and P. Pais, for the International Polycap Study 3 Investigators*





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

Ezetimibe Drug Interactions

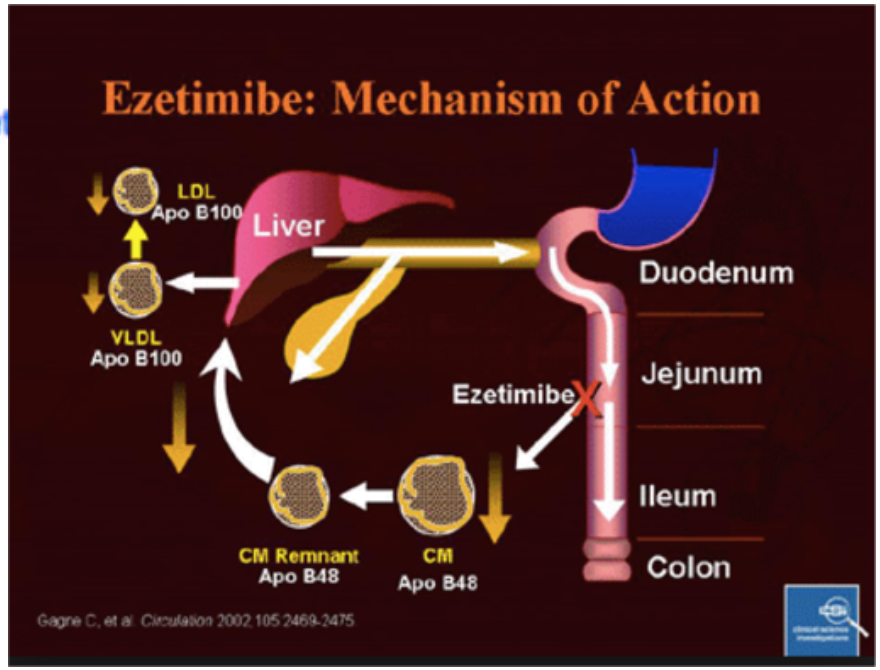
Overview | Side Effects | Dosage | Professional | **Interactions** | Pregnancy

Drug Interactions (34) | Disease Interactions (3)

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

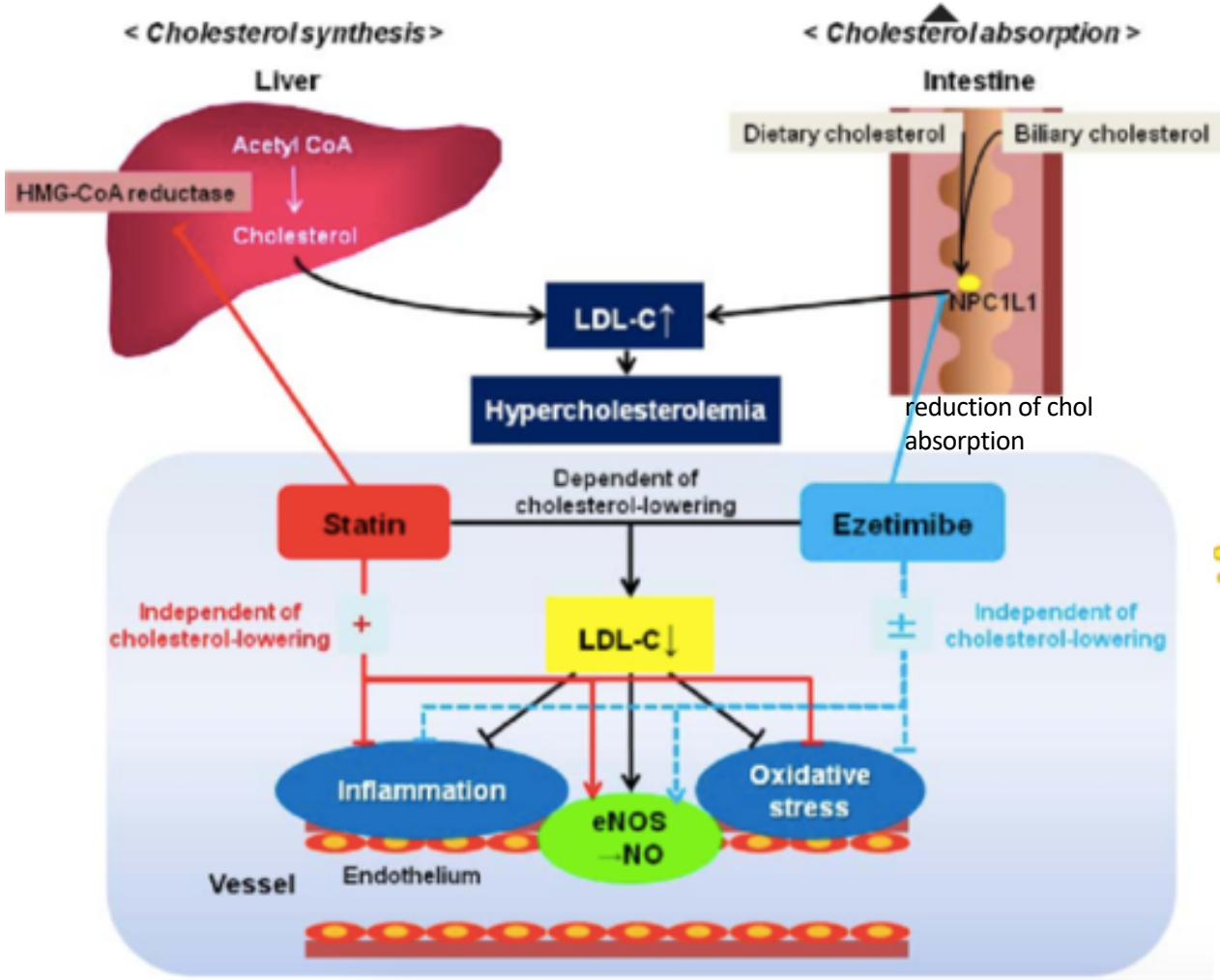
- **30 moderate** drug interactions (81 brand and generic names)
- **4 minor** drug interactions (8 brand and generic names)

Show all medications in the database that may interact with ezet

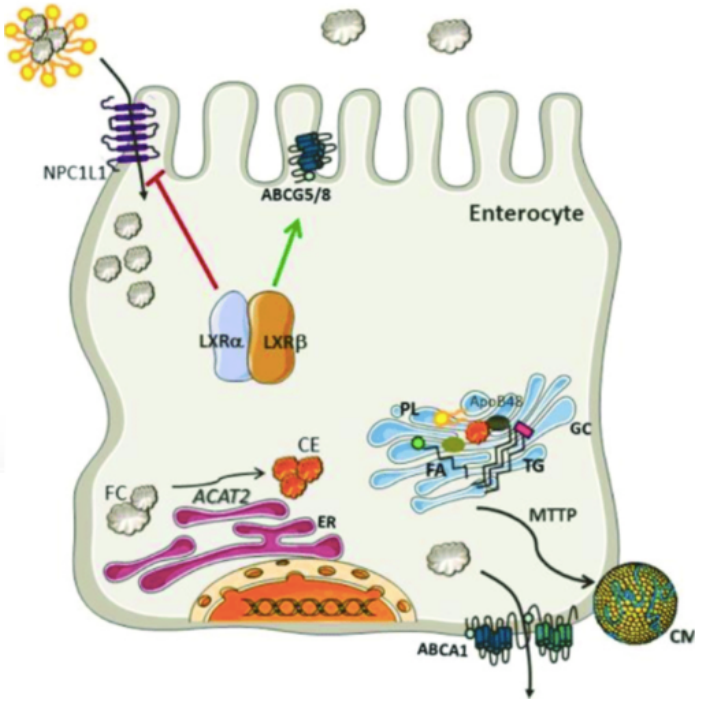


Ezetimibe originally screened as ACAT inhibitor..

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 QUESTİONS ?

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