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

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*

WORKSHOP LISTING - THE MAKING OF AN INNOVATIVE MEDICINE BIO698

! NON EXHAUSTIVE LISTING - SUGGESTIONS WELCOME !

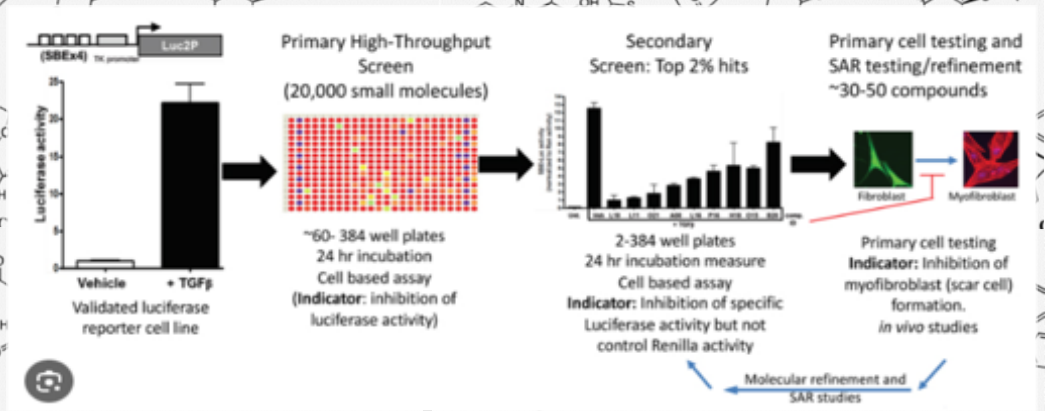
sessions	no	workshops	speaker/s
S02 (28-09-23) ! AAC108 !			
historical medicines	1	vaccine discovery : E. Jenner and smallpox	Danica M
with Nobel laureates while	2	penicillin: impact, whose invention ?	
hopping on giant shoulders	3	prozac at the core of psychiatry	
	4	lipitor/statins at last a blockbuster	
	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
S06 (02-11-23) ! AAC108 !			
therapeutic modalities - NBEs	15	Biologicals/biotech production/**incretins**	Tim
	16	armed monoclonal AB 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	organoids come of age	Nathalie B
toxicology	23	thalidomide repurposing	Ekaterina
S10 (30-11-23) ! AAC108 !			
clinical research	24	AI medicine 2.0	
	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 !			
other worshops opportunities	30	insulin-Banting Best et al. beagle dog	S02

Workshops _ The Making Of An Innovative Medicine

(today's class)

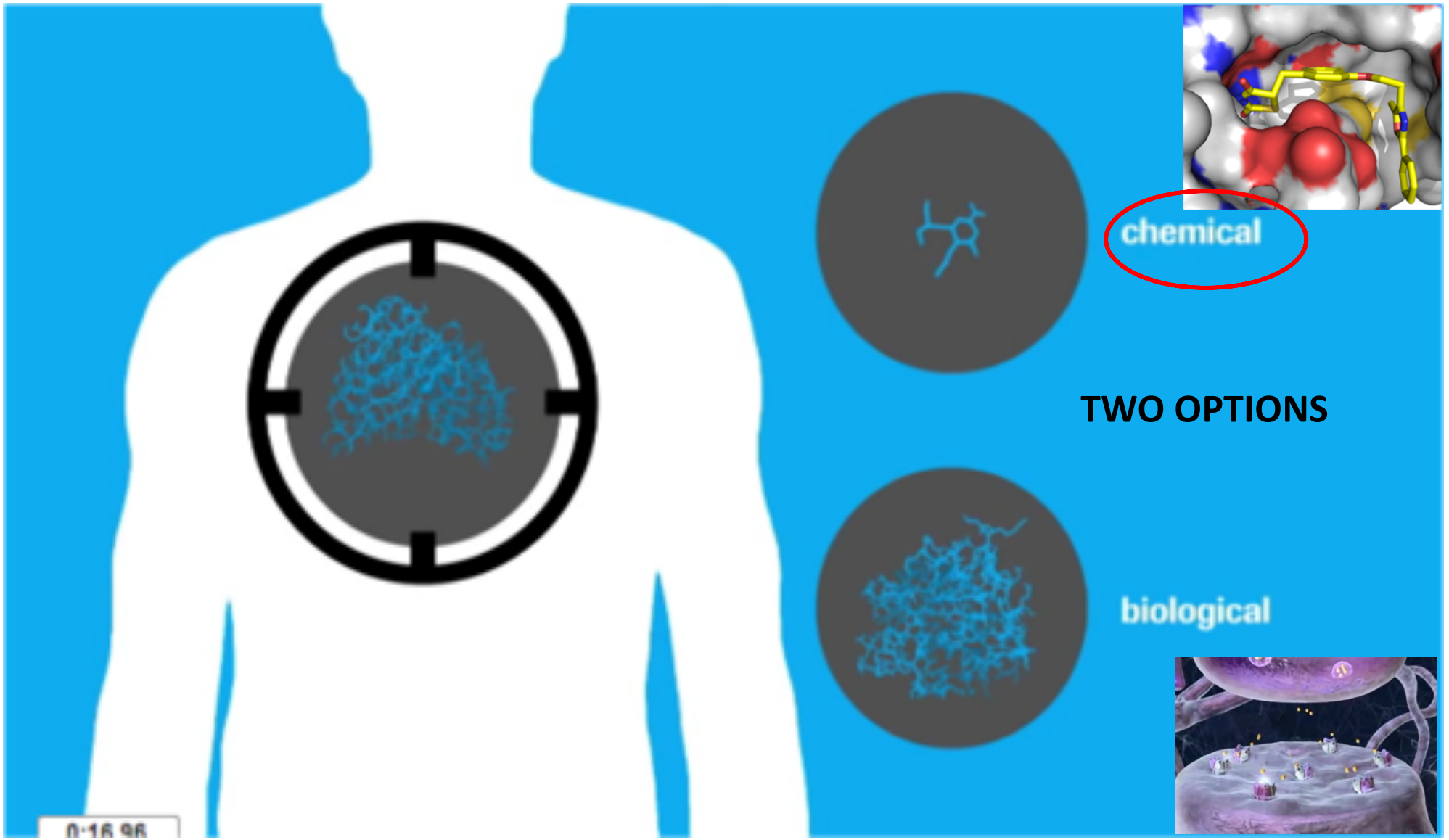
Session 5 – Drug design : 90% of today's medicines are issued from medicinal chemistry

- High throughput cpd screens HTS : from hit to lead



- Medicinal Chemistry : in silico screen, structure activity relationship (SAR) and drug design by MDO

Adressing a novel therapeutic target : small MW chemical cpds versus large biological moieties : what‘s best ?



On average you are likely to take 15,000 SMW pills during the course of your life time !

The Making Of An Innovative Medicine: From Idea to Medicine

HTS involvement

PRECLINICAL

TARGET IDENTIFICATION

DRUG CANDIDATE

PRECLINICAL TEST PK/PD-SAFETY

CL

CCS

which cpd, therapeutic modalities can help eg. to treat chronic pain? Diabetes? a rare disesase?

is my cpd safe in animal model? at what dose?

Is the therapeutic target «druggable»?

medicinal chemistry (med chem) involvement

POC

Do we have compelling genetic evidence underlying the symptoms/disease phenotype?

~ 1'000'000'000 CHF

~ 10'000 animals

~ 10 years

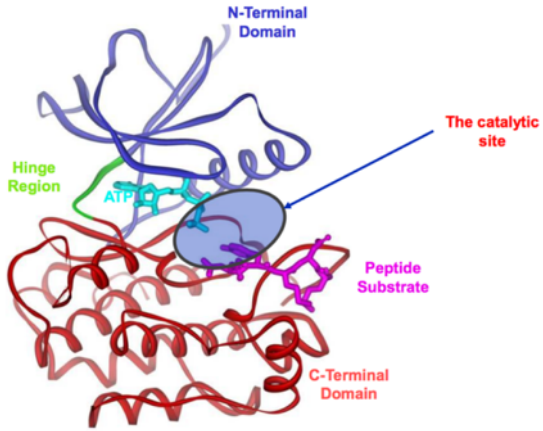
ONE DRUG

~ 1000 patients/ volunteers

~ 6500 expt

~ 450 scientists

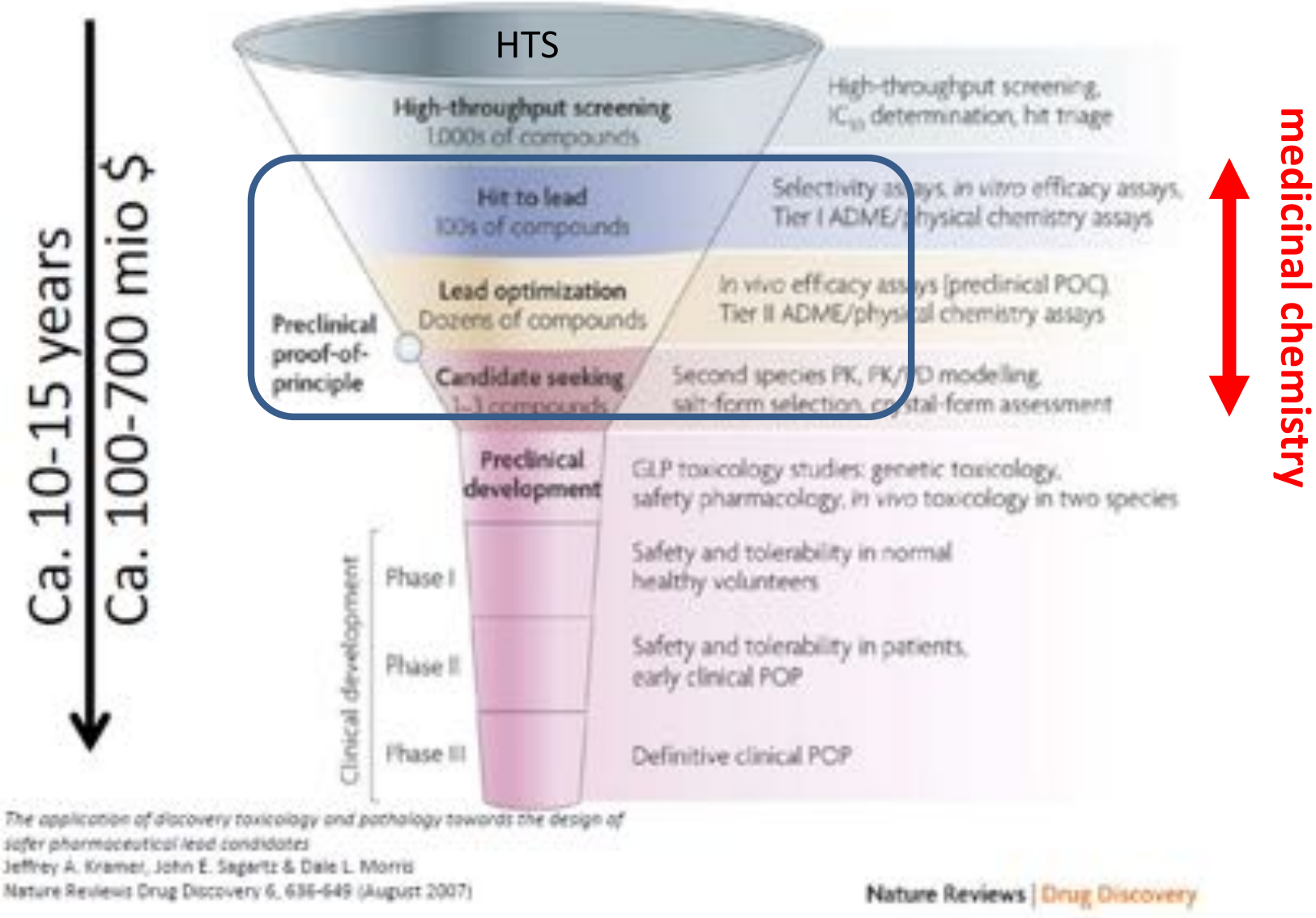
- **SMALL MW MOIETIES TYPICALLY POSSESS <100 ATOMS (MW <1000Da) WHICH ENDOW A SMALL OVERALL SURFACE AREA AVAILABLE FOR INTERACTION AND PHARMACOLOGICAL INTERVENTION**



- **A DRUGGABLE TARGET IS BEST KNOWN BY THE PRESENCE ON ITS SOLVENT ACCESSIBLE SURFACE OF AN HYDROPHOBIC "POCKET"**
- **(INVAGINATION LINED UP WITH HYDROPHOBIC AMINO ACID SIDE CHAINS)**

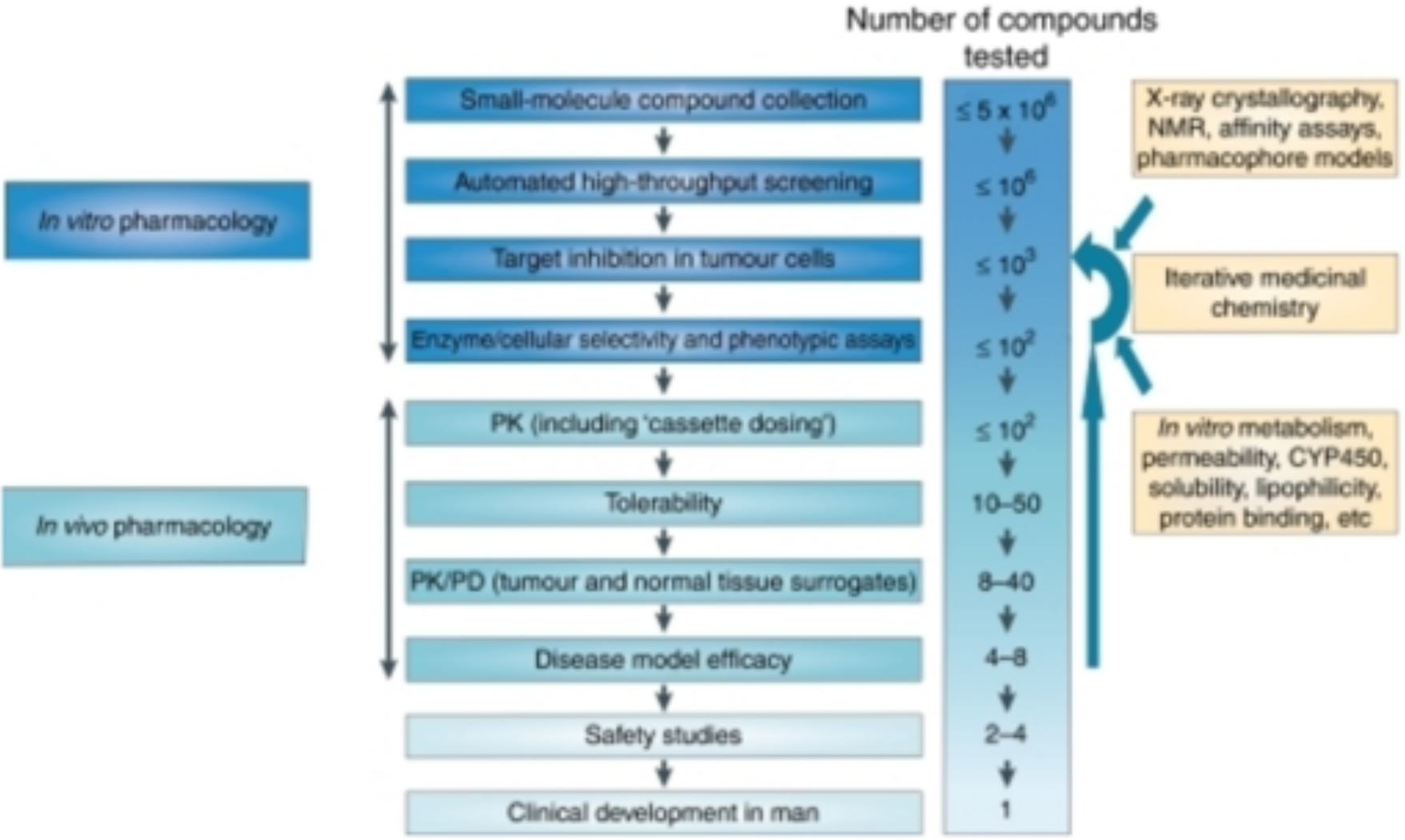
Moellering RE et al. 2002 Nature 462:182-188

The screening cascade 1:10 000 makes it !



HTS and MedChem : from milions cpd tested to a single medicine

The screening cascade



High throughput screening : from hits to lead cpds

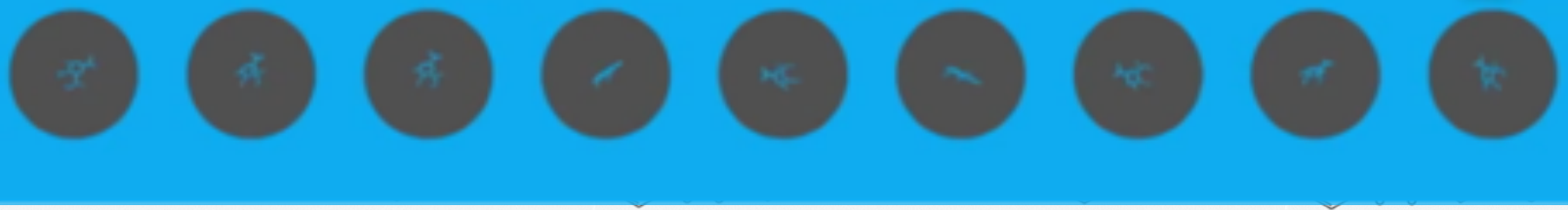
HIGH THROUGHPUT SCREEN (HTS) – HIGH CONTENT SCREENS (HCS) :

ARE YOU LOOKING FOR AN AGONIST/ANTAGONIST OR ALLOSTEROIC MODULATOR OF YOUR THERAPEUTIC TARGET ?

high-throughput tests

00248

Do we have the right lead cpd ?



The Making Of An Innovative Medicine: a look at the real world
eg. «big pharma» Roche Inc. campus Basel Switzerland – 04:39 on

https://www.youtube.com/watch?v=attNofZ7AnY

Robotics and medicinal chemistry : corner stone of HTS

High throughput screen (HTS) :

agonist/antagonist to the therapeutic target

Automated CPD repository

Every day thousands of novel cpds are synthesized and registered in cpd repositories

Do we have the right lead though ?

A million compounds selected on a specific therapeutic target in a few weeks time !

Clinical candidate selected ! Patent pending !

Roche Basel automatic cpd repository: millions of SMW awaiting HTS

AUTOMATED CPD REPOSITORY : CAN HOLD UP TO >1 MILLION OF PURIFIED MOLECULES IN THE RANGE OF FEW HUNDREDS kDa

CPD REPOSITORY : MOST VALUABLE ASSET OF A DRUG DISCOVERY FACILITY

CPD LOGISTIC : ALIQUOTS STORAGE IN 100% DMSO UNDER ARGON VAPOURS !

Every day MedChem synthesises thousands of novel cpds registered in cpd repositories

Hit confirmation at single dose, followed by DRC and potency

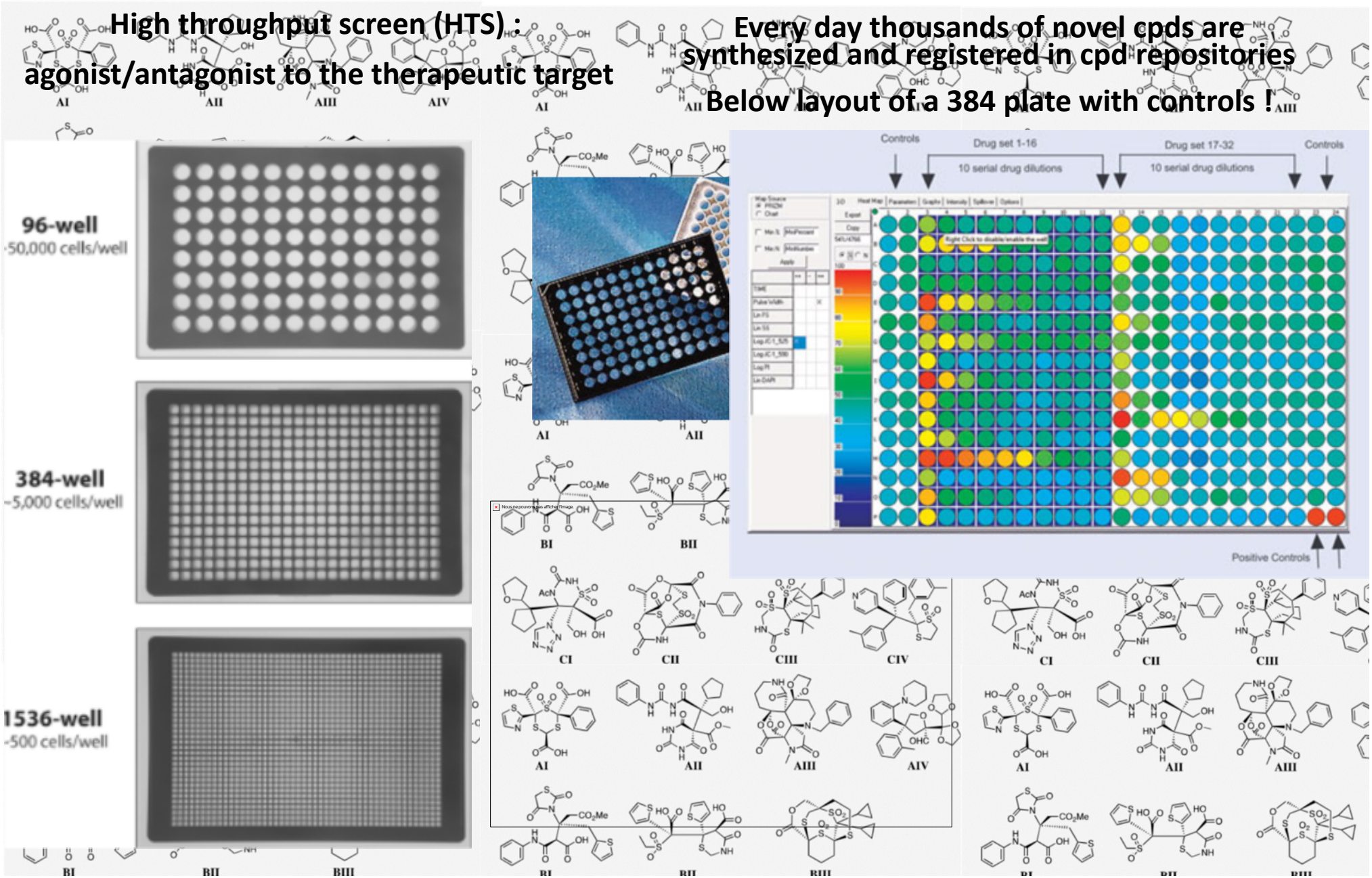
Often hit confirmation and potency assay need larger scale MedChem synthesis

High throughput screening assays formats for all season : miniaturization (2-10 µl – 1536 wells) means cost effective HTS

High throughput screen (HTS) : agonist/antagonist to the therapeutic target

Every day thousands of novel cpds are synthesized and registered in cpd repositories

Below layout of a 384 plate with controls !



Finding the perfect match: most novel medicine design starts with an HTS (eg TECAN «Freedom EVO platform») see video on robotics

Automation on a Freedom EVO platform enables cost-effective, high throughput HLA typing

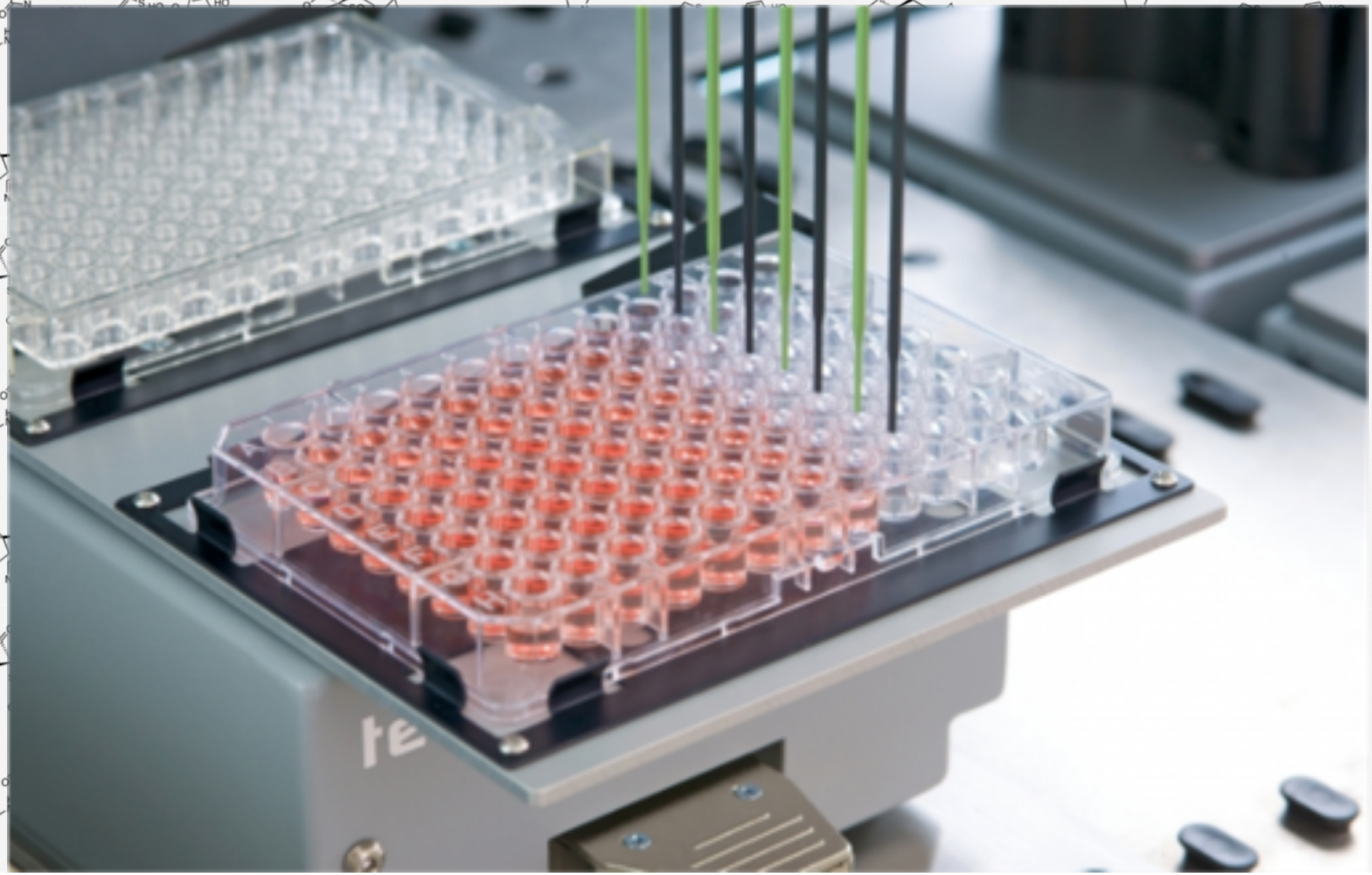
Automatic liquid handling device : data validation, robustness

High throughput screen (HTS) :

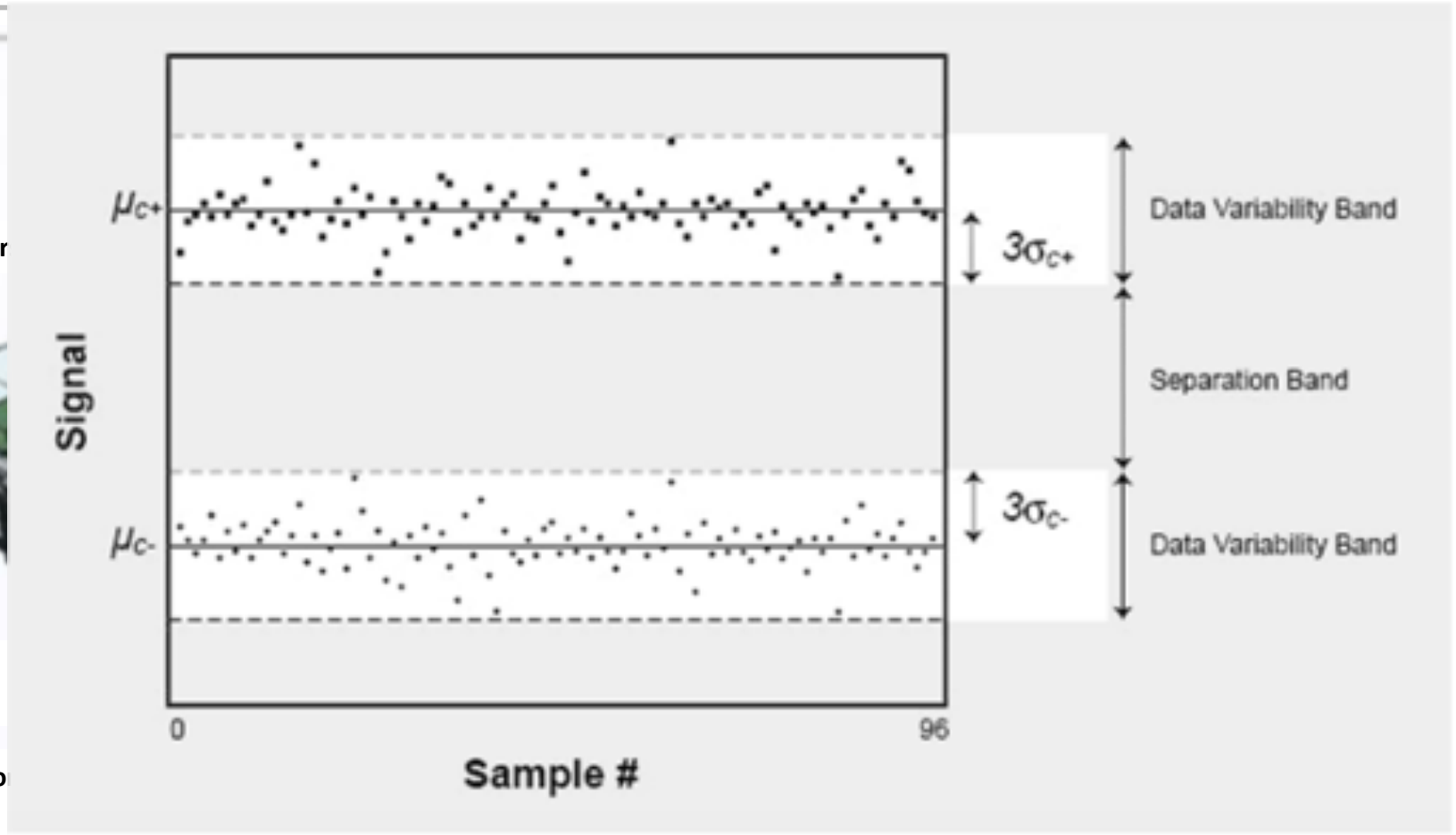
signal to background ratio (Z'value)

Data management, analysis

Do we have the right lead though ?



Finding the perfect match: layout of an automatic HTS platform : assessing whether the response in a particular assay is large enough



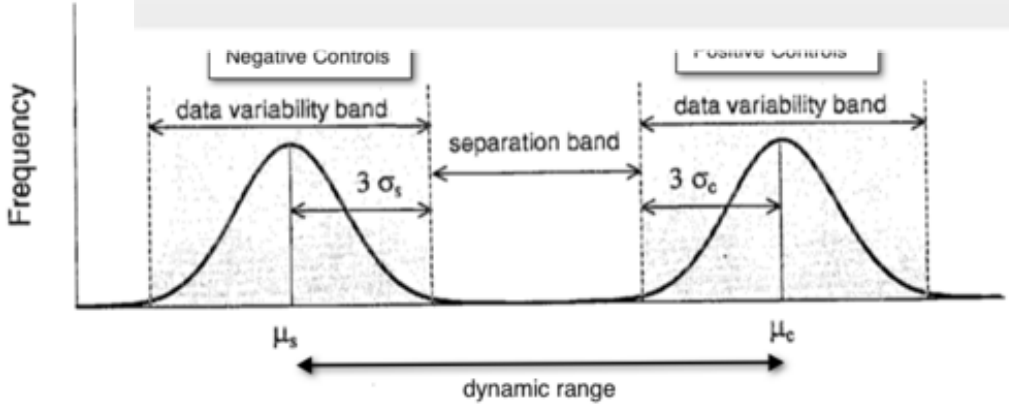
ntrol)

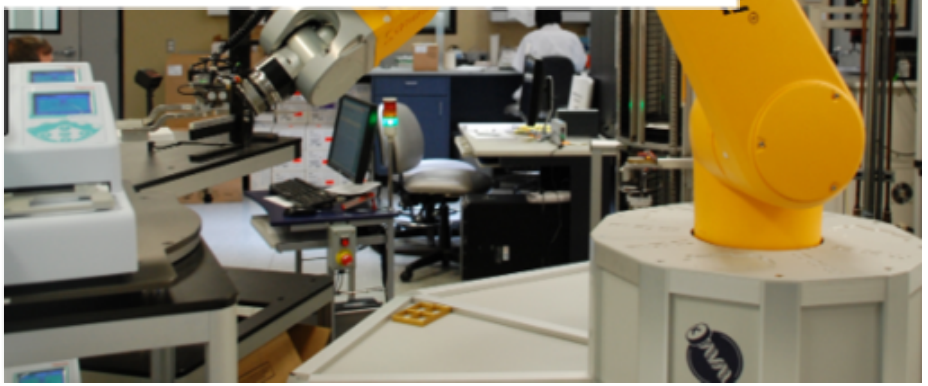
ntrol)

incubator

bulk reagent dispensers

plate co



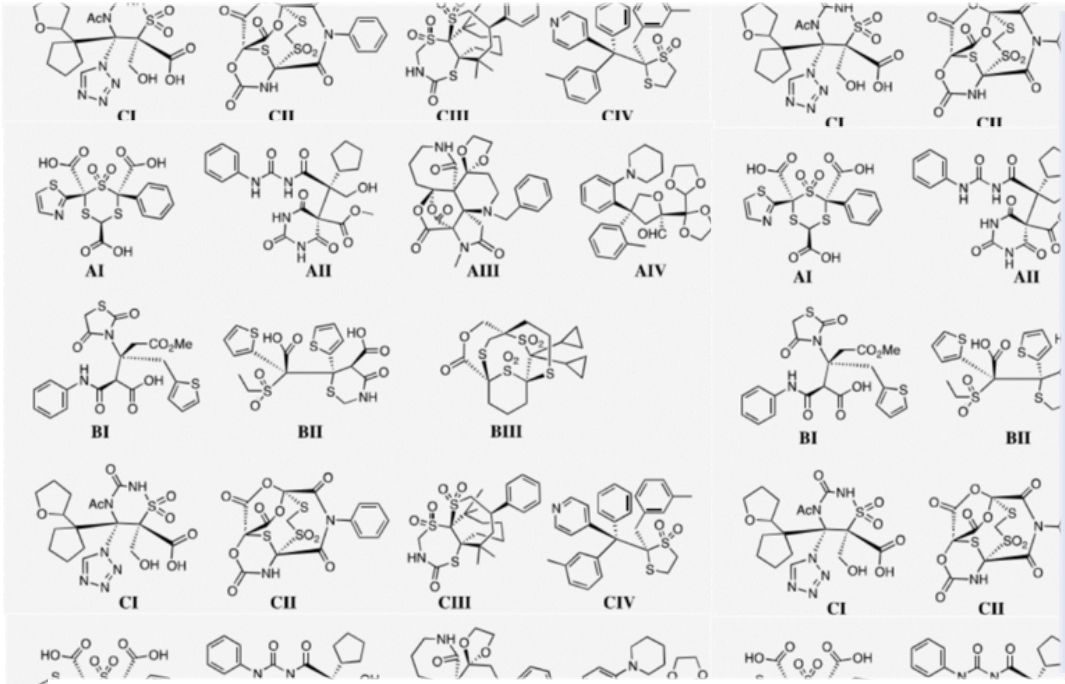


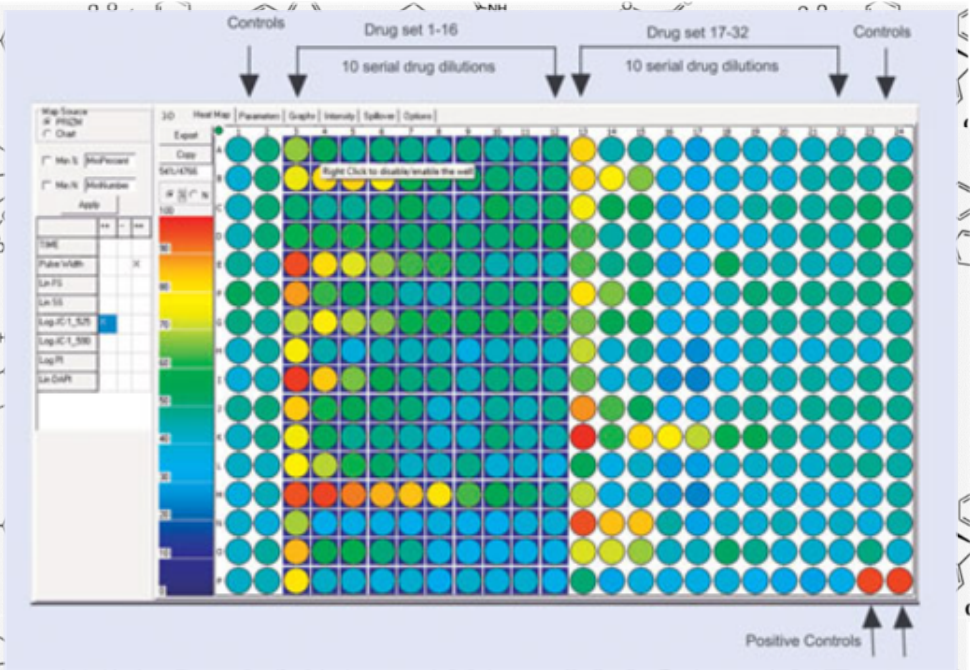
“Needle screens” of selected bioactive molecules: fast track to the clinical candidate

Bioactive Screening Libraries

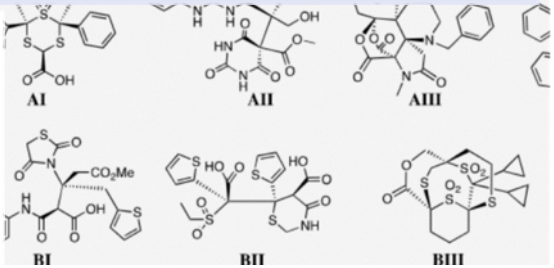
Our ready-to-use **MedChemExpress (MCE)** compound libraries consist of **over 4000** small molecules **with validated biological and pharmacological activities.** They are available for **high-throughput screening (HTS) and high-content screening (HCS).** Compound libraries are useful professional tools for **drug discovery and new indication research.**

- **Safety** and **effectiveness** have been confirmed by literature, patent reports and clinical research. Many products are **FDA-approved.**

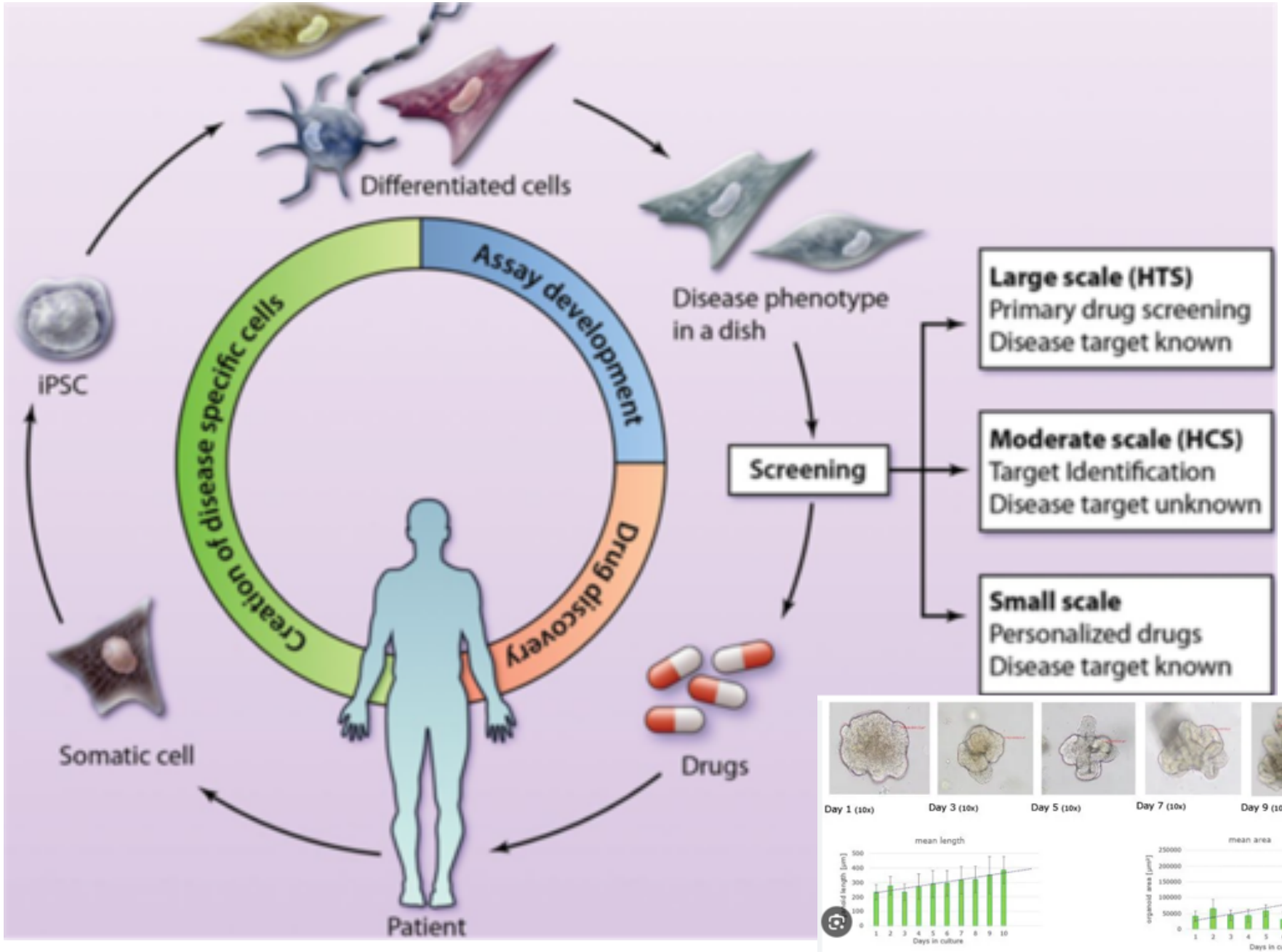




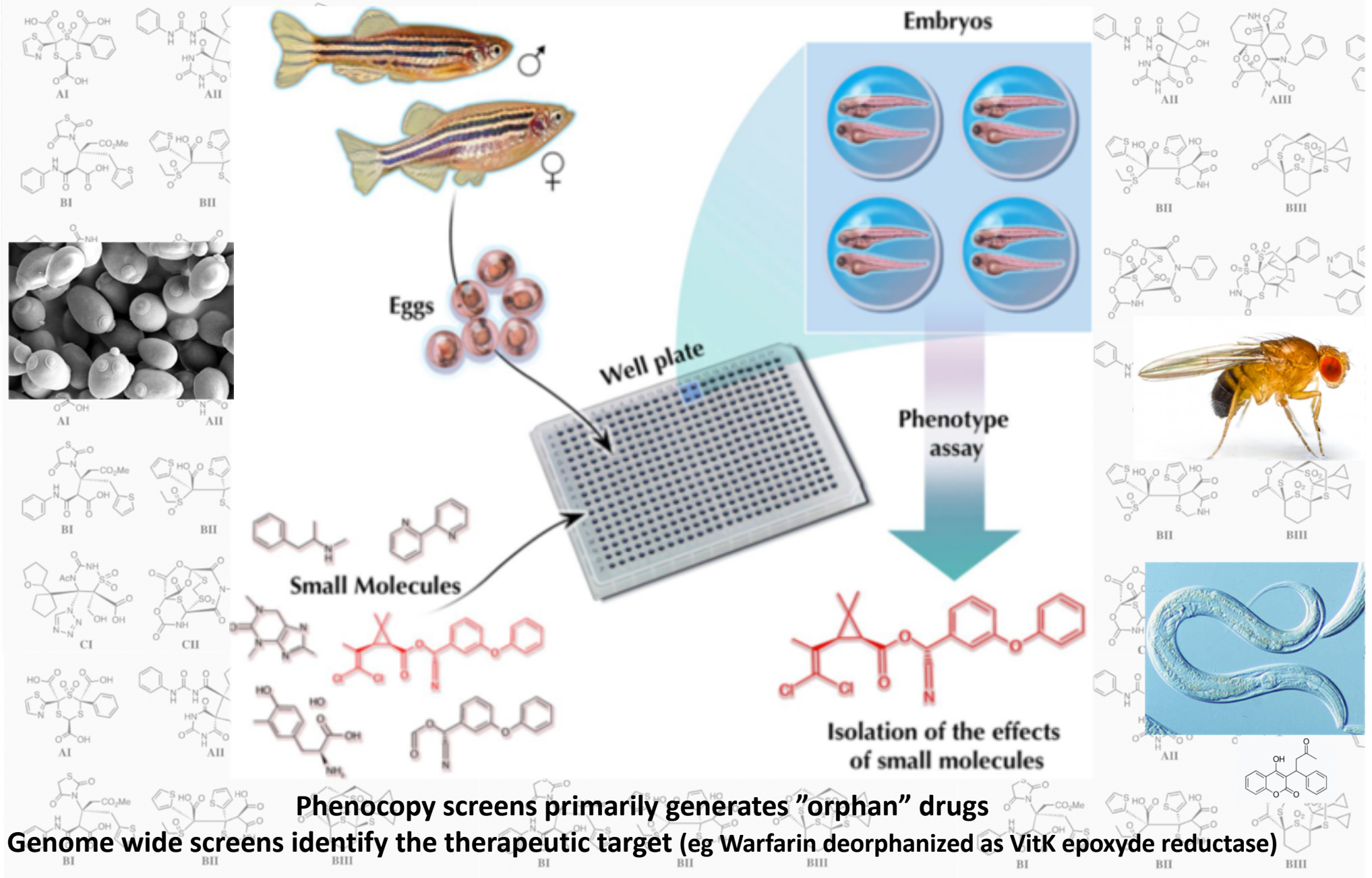
NIH National Institutes of Health — Turning Discovery Into Health
DANA-FARBER CANCER INSTITUTE
BROAD INSTITUTE
Karolinska Institutet
HARVARD UNIVERSITY
Northwestern University
Takeda
Tsinghua University
PEKING UNIVERSITY



The Making Of An Innovative Medicine: iPSC in translational research



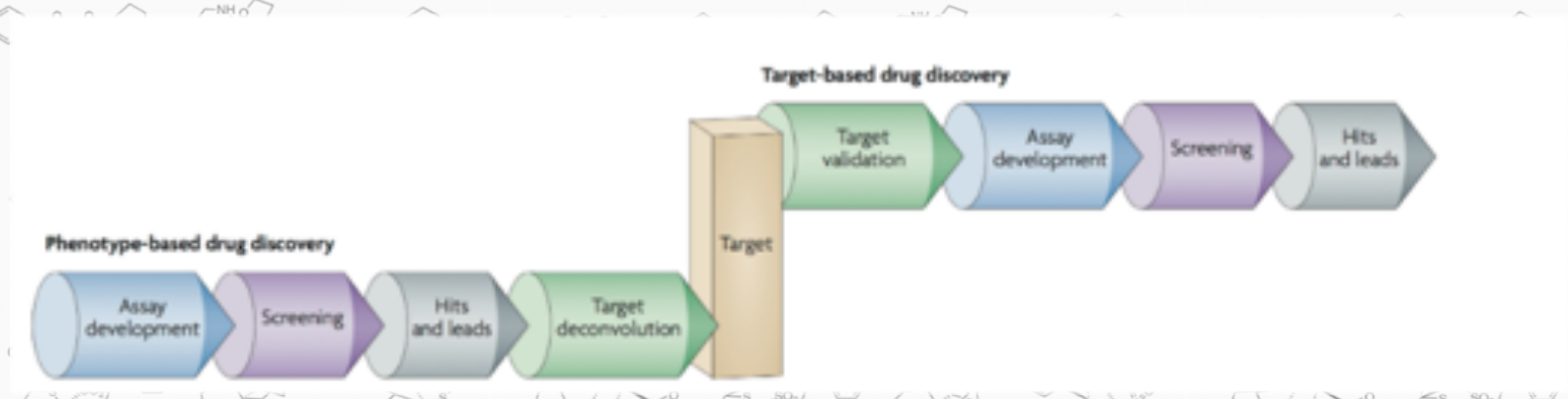
Any robust biological readout may serve as HTS :
PHENOCOPY SCREENS, eg Danio rerio, D. mel, C. elegans, S. cerevisiae etc

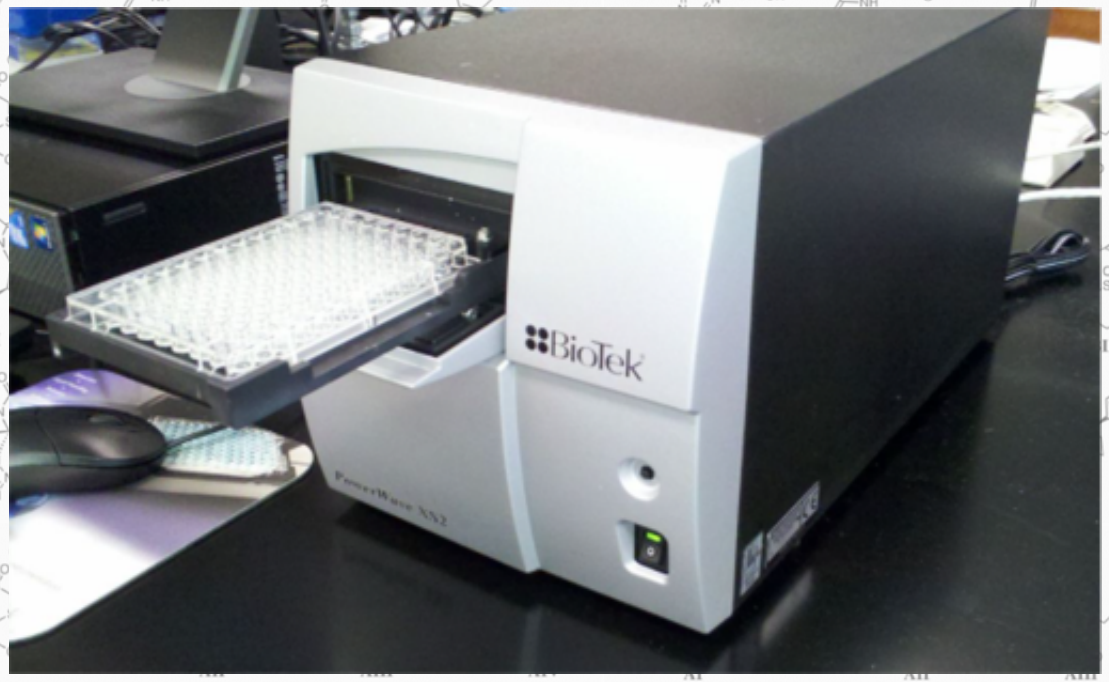


Phenocopy screens primarily generates ”orphan” drugs

Genome wide screens identify the therapeutic target (eg Warfarin deorphanized as VitK epoxyde reductase)

Phenocopy vs target based cpd screens

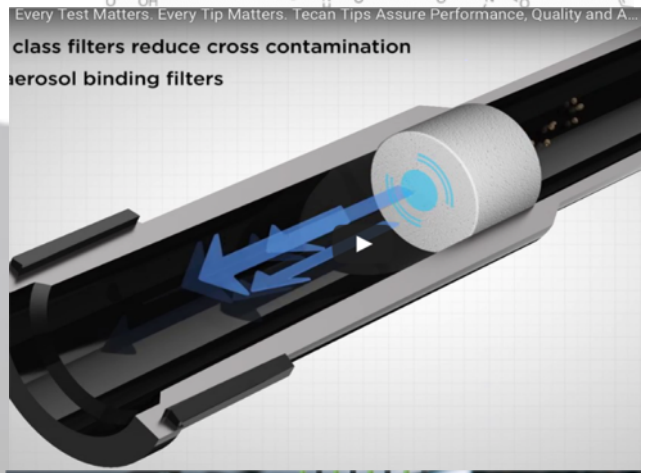




From hit to lead cpd : once a primary HTS screen has been performed, eg FRET secondary assays

Benchtop low throughput screening LTS assays: confirmation of first HTS hits (secondary assays)

Secondary lowthroughput screen : TECAN instruments leading



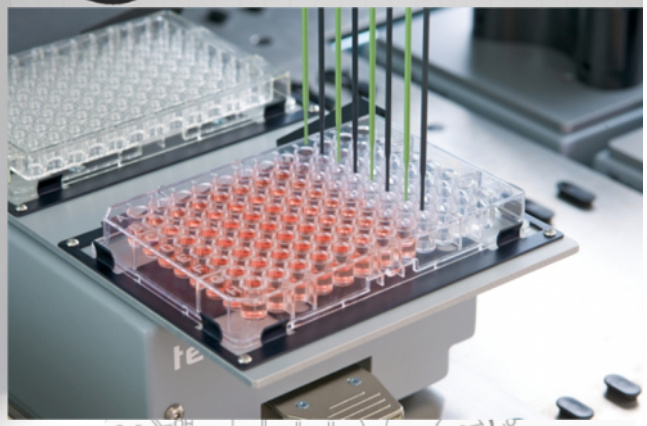
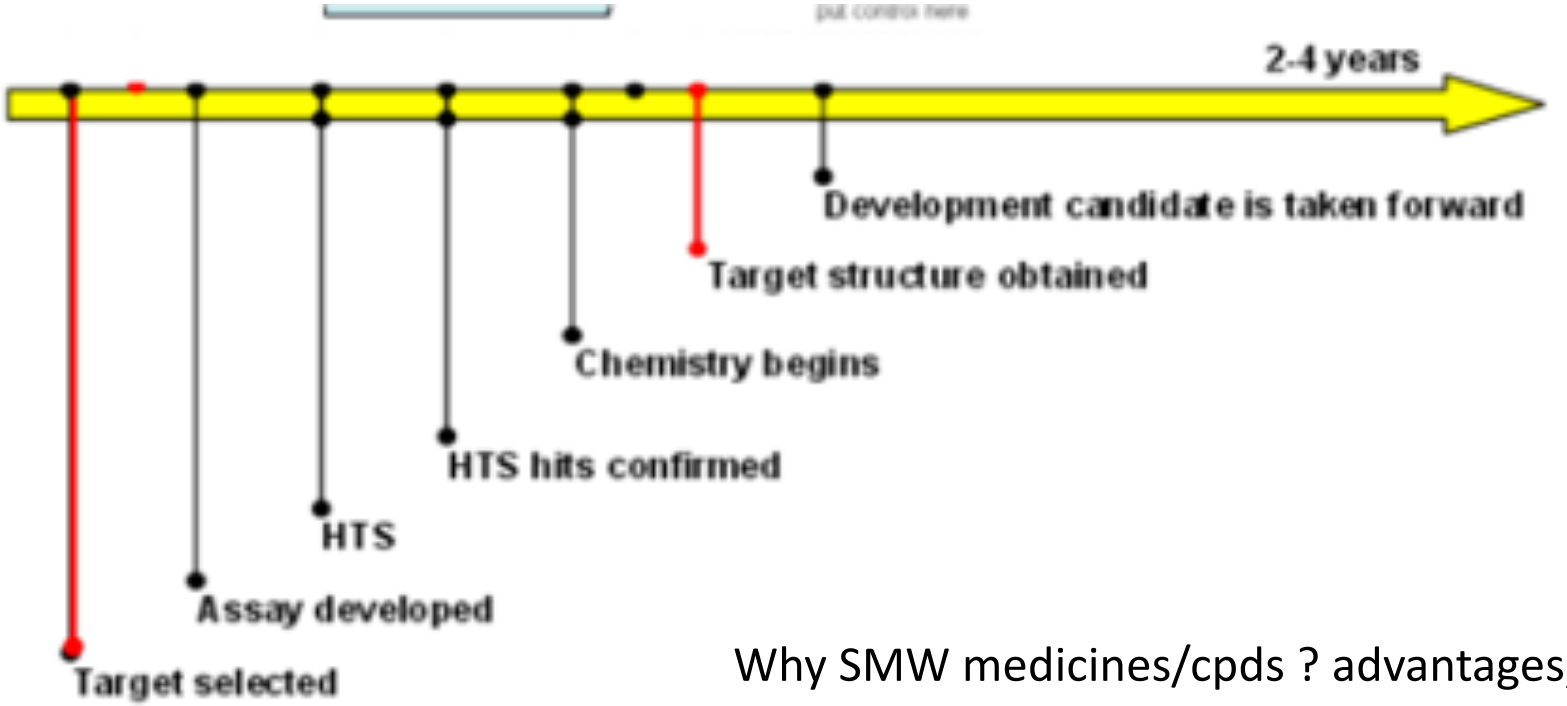


Table top precision liquid handling robotics once a primary “first hit” cpd has been selected

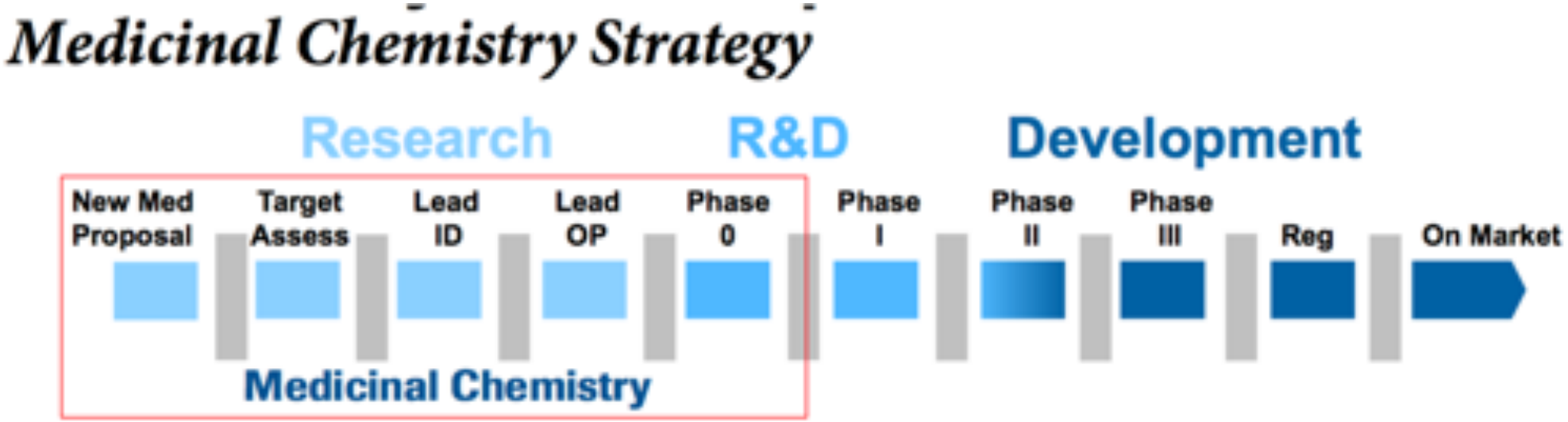
From HTS hits to lead cpd and clinical candidate identified

On average you are likely to take 15,000 SMW pills during the course of your life time !



Why SMW medicines/cpds ? advantages, cost of goods etc ! from ancient herbal medicine to modern chemotherapies, HAART etc !

Medicinal chemistry step by step

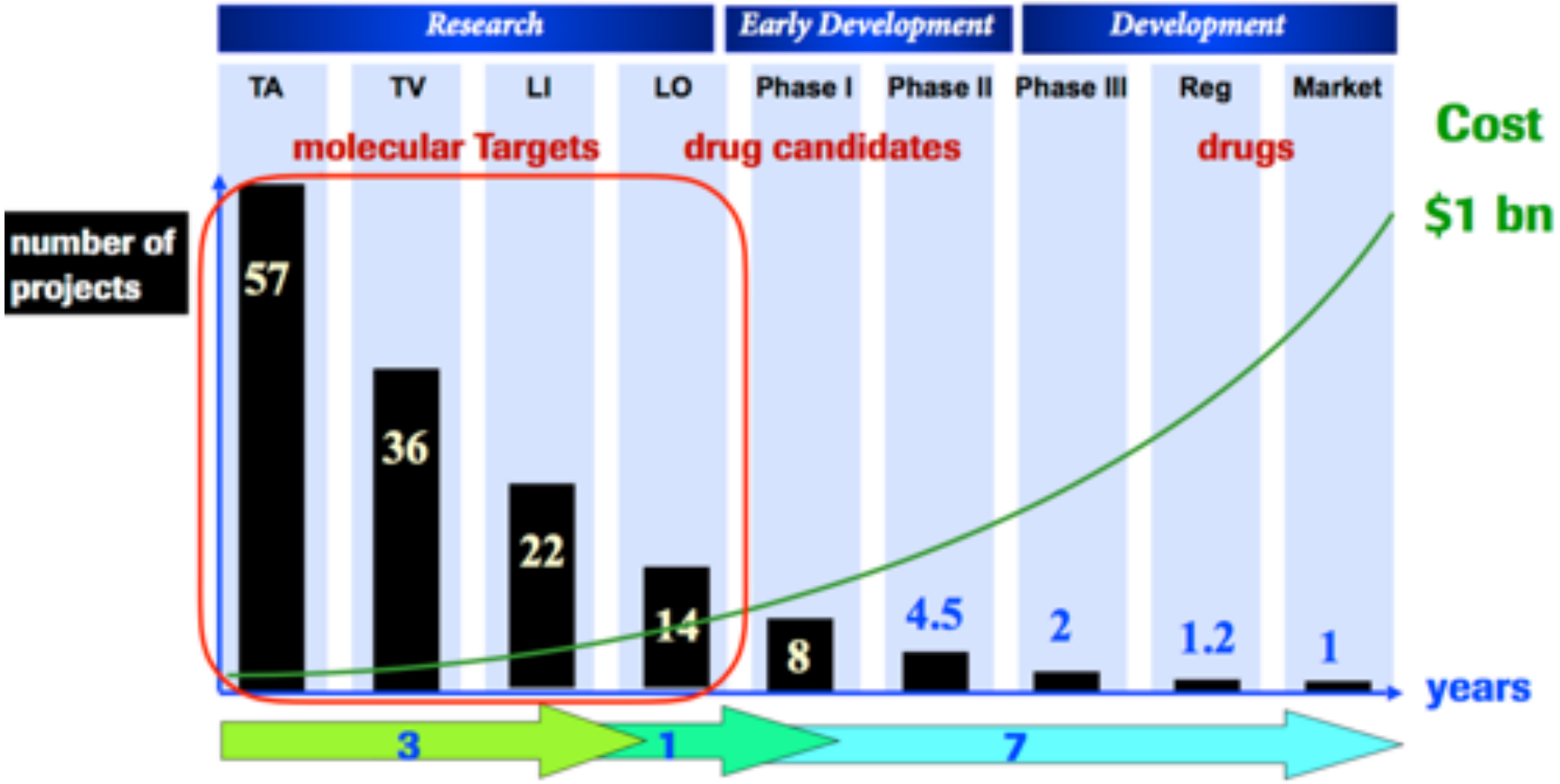


How to reduce pre-screening costs ? $$$

Bai XC. 2015

Medicinal chemistry : optimization of the target – a major challenge

Compound optimisation is faced with attrition



Medicinal chemistry has high attrition – fail fast, fail early, fail cheap!

medicinal chemistry driven drug design : which one is the good one ?

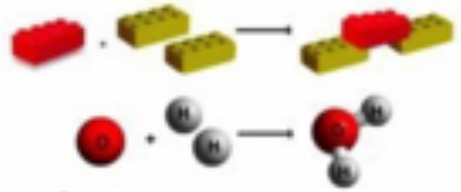
The '*chemistry*' in Medicinal Chemistry

Chemistry basics in 30 seconds:

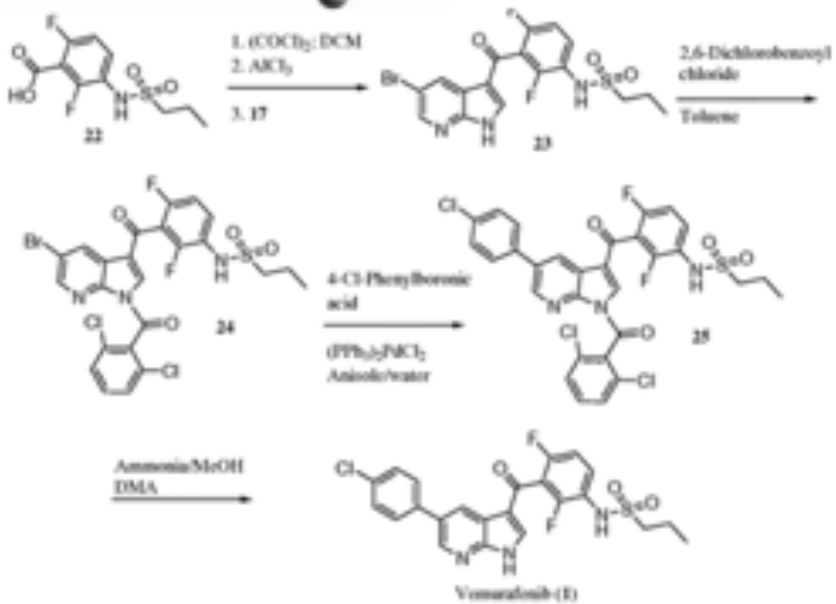
Atoms:

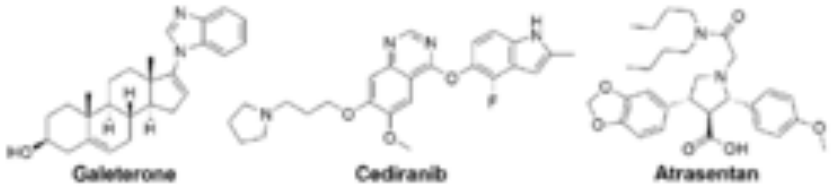
10^{60} theoretically possible molecules

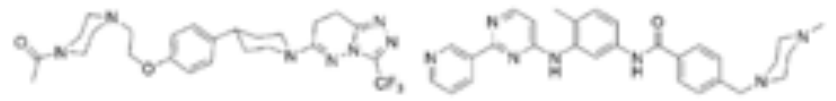
Atoms to molecules:

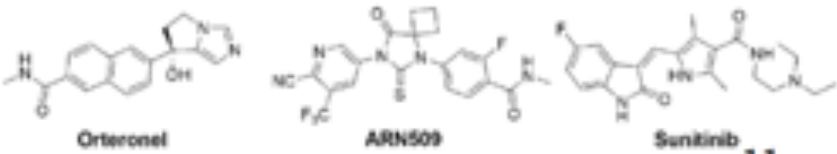


Smaller 'molecules' to bigger/complex 'molecules':









11

We would have to make lot of molecules – how do we know which one's to make and test?

MedChem : impact on clinical practice : HAART

1981 Discovery of HIV, shortly after monotherapy of AIDS patients on AZT

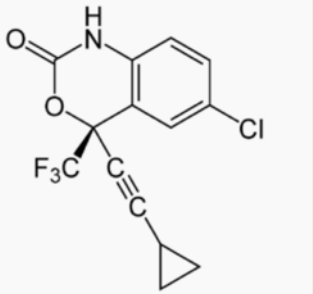
1982-1990 Monotherapies proved ineffective, due to HIV's ability to develop resistance to single drug treatments. death toll still massive

1995 Development of HIV drug cocktails was introduced and is known today as HAART for HIGHLY ACTIVE ANTI RETROVIRAL THERAPY

Diana shakes hands with an unidentified AIDS patient on April 19, 1987. John Redman/AP

AIDS patients experience a long life expectancy in seropositivity THANKS TO ESSENTIALLY only 3 PILLS A DAY (yesterday patients swallowed « the entire pharmacy »

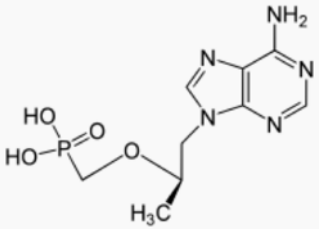
Éfavirenz



Identification

Nom UICPA	(*S*)-6-chloro-4-(cyclopropyléthynyl) -1,4-dihydro-4-(trifluorométhyl) -2H-3,1-benzoxazin-2-one

Ténofovir

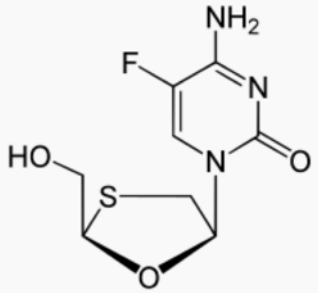


Structure chimique du ténofovir

Identification

Nom UICPA	L (*R*)-9-(2-phosphonylméthoxy-propyl)adénine

Emtricitabine

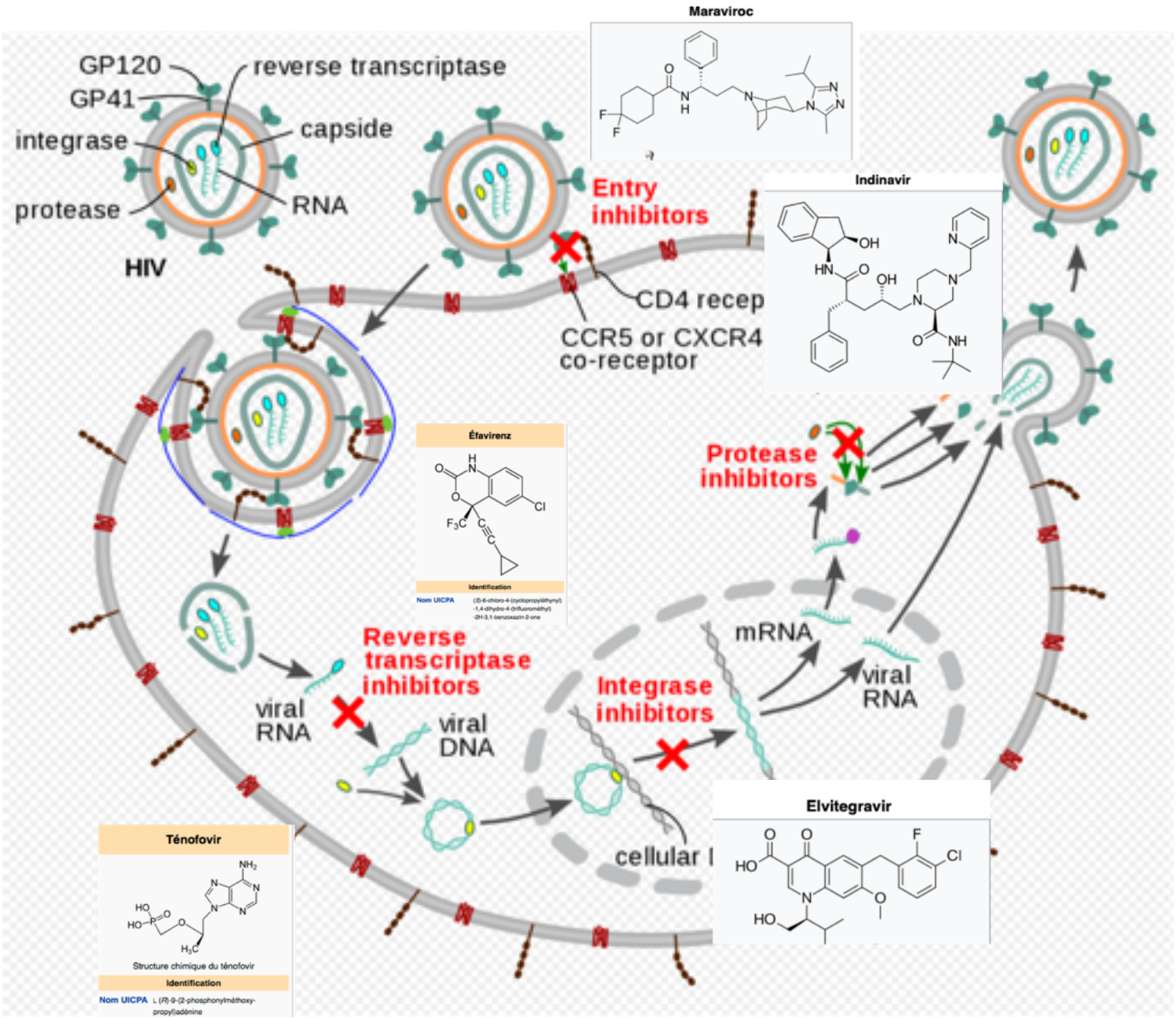


Structure chimique de l'emtricitabine

Identification

Nom UICPA	L-2',3'-didéoxy-5-fluoro-3'-thiacytidine

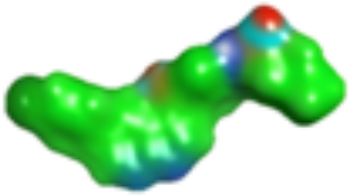
MedChem : impact on clinical practice : HAART



Medicinal chemistry : cryo EM allows prediction of enzyme function and medicinal chemistry driven drug design

How can we know which compounds to make?
The power of an optimal DSTA cycle!

10^{60} theoretically possible molecules



Small Molecule Clinical Candidate
MW ~ 500 Da

Med Chem Design Quality and Speed

"Overclocking the Design Cycle"

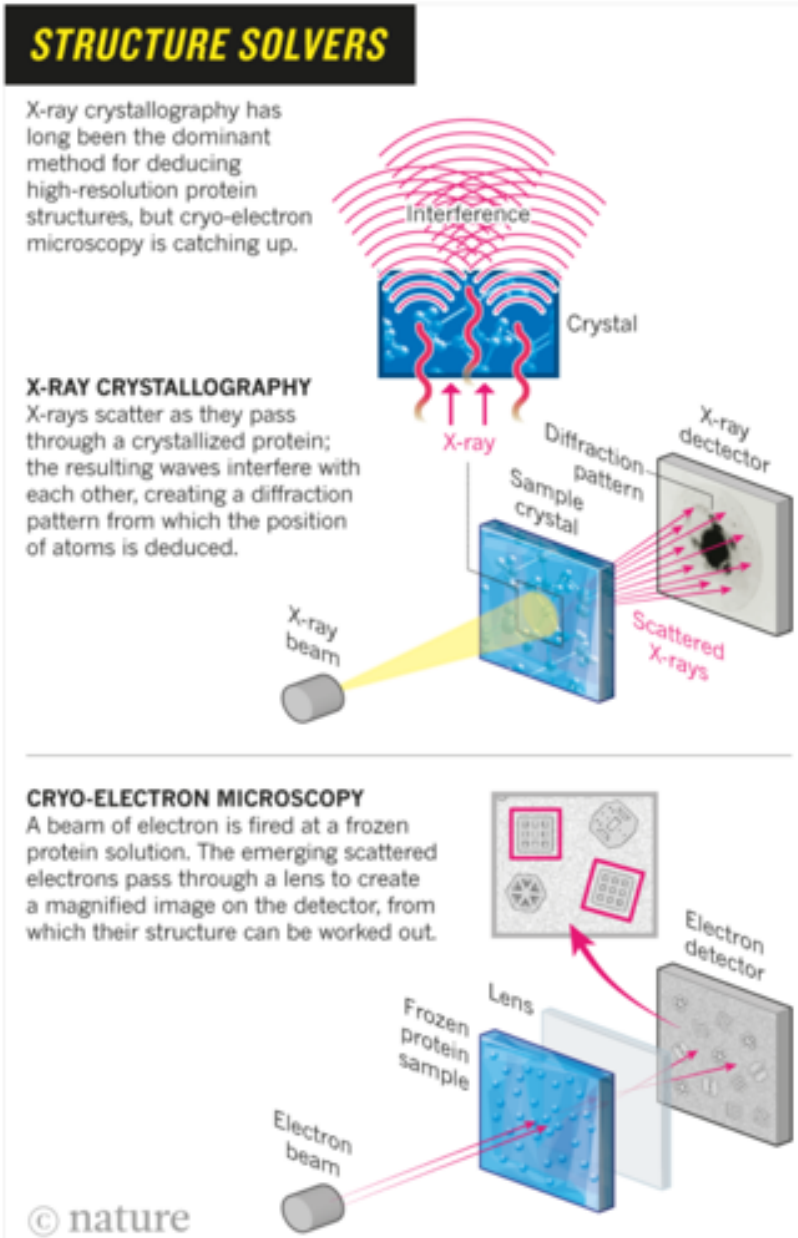
Data driven predictive drug design by medicinal chemist

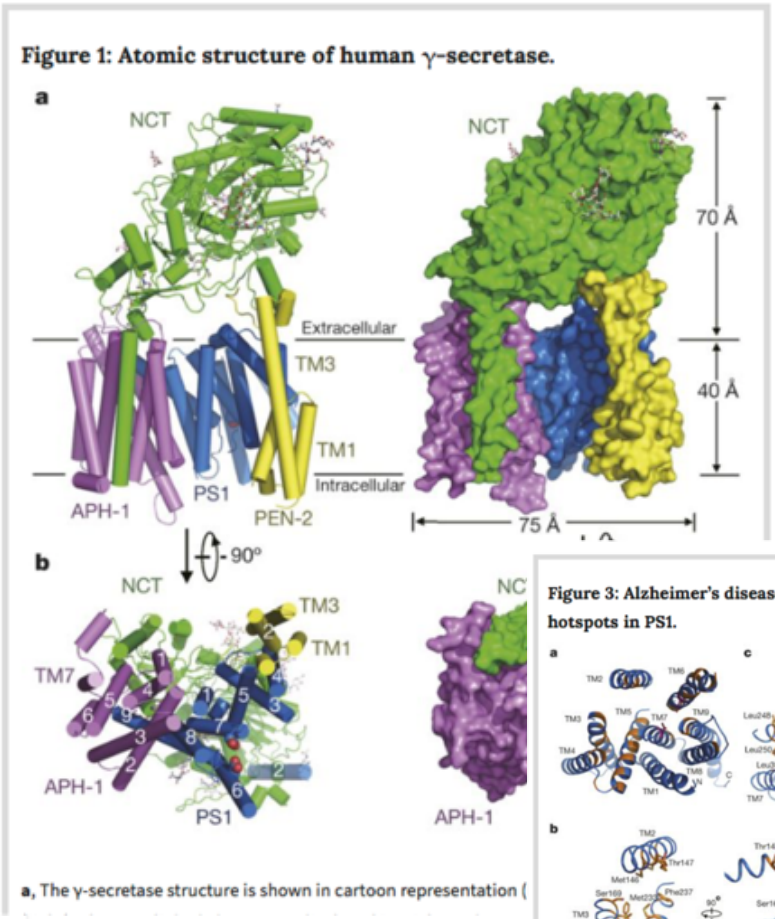
powered by

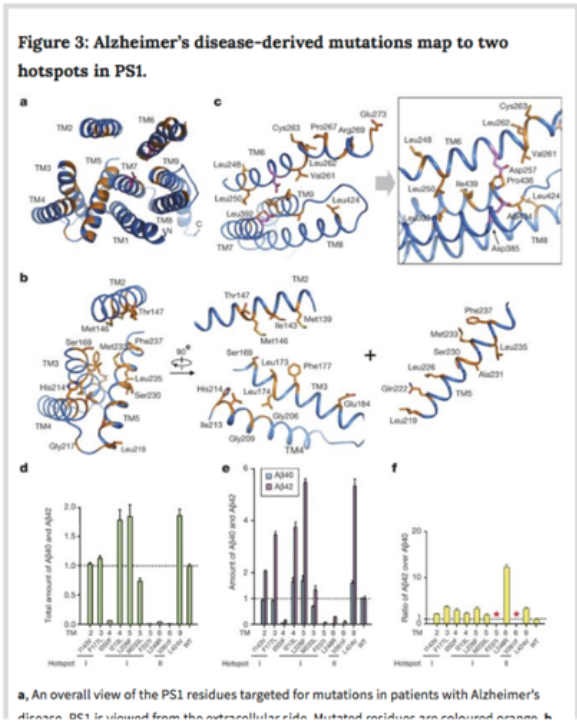
Med Chem CPU Clock speed

Iterative Design Cycle (DSTA cycle)

Medicinal chemistry : cryo EM allows prediction of enzyme function and medicinal chemistry driven drug design







Bai XC. 2015 Nature 535:212-217

MDO : parallel Multiple Drug Optimization

permeability

potency

binding kinetics

crystallinity

solubility

protein binding

chemical stability

CYP inhibition

clearance

pKa (acidity/basicity)

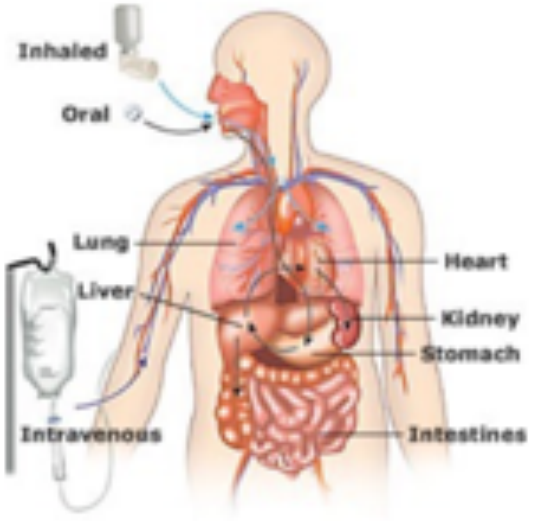
in vitro tox assays

Time dependent
CYP inhibition

efflux / P-gp

logD / lipophilicity

covalent binding



Potency

Selectivity

Absorption

Distribution

Metabolism

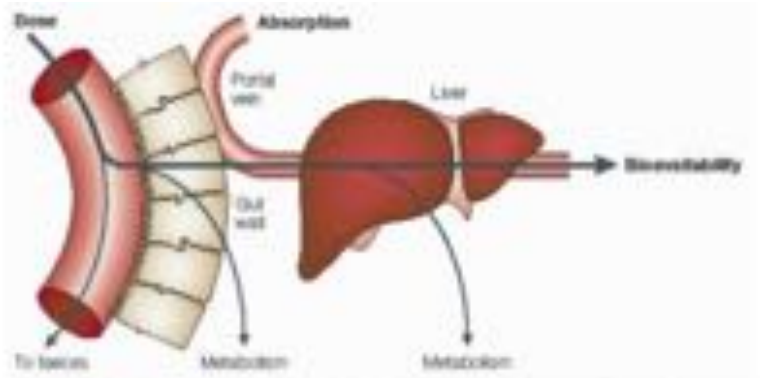
Excretion

Toxicity

MDO : Multiparameter Drug Optimization

MDO simplified (drug likeliness or Pfizer's rules)

- Solubility
- Lipophilicity (clogP) octanol water partition <5)
- Number of H donors (<5)
- Number of H acceptors (<10)
- Molecular weight (generally <500 Da
- Permeability (PAMPA assay)
- CYP450s screen (eg. adverse drug metabolites
- Metabolic stability (PK, PD, ADME)
- Cardiac ion channels (hERG, "torsade de pointes"
- CEREP screens, kinase panels, GPCR panels



C.A. Lipinski et al. *Adv. Drug. Delivery Reviews* **23** (1997) 3.

Why SMW cpd ? Practical dosage form, with a glass of water and more !

Medicinal chemistry : what properties a drug need to have ?

DRUG DISCOVERY

P. Leeson. 2012. Nature 481:455-456

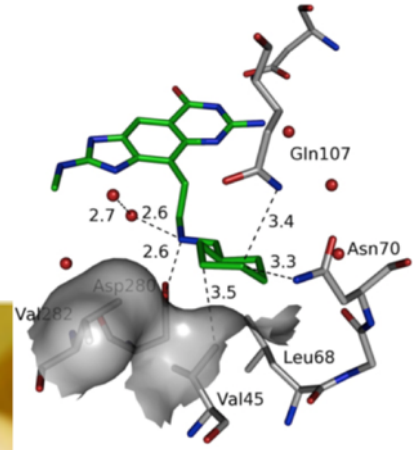
Chemical beauty contest

Most drug candidates fail clinical trials, in many cases because the compounds have less than optimal physico-chemical properties. A new method for assessing the 'drug-likeness' of compounds might help to remedy the situation.

- MedChem has still a bright future even with the advent of many other therapeutic modalities (MAB, RNA, DNA etc.
- Drug candidates are developed from the optimization of "lead" molecules (SAR) – selectivity versus off target (safety)– pharmacokinetics/pharmacodynamics – large production – cost of goods - manufacture
- Like all rules in biomedical research, Lipinski rules can be misleading (some cpd may pass through and dwell toxic in clinical trials, some excellent potential medicines may fail because of one criteria was not satisfied (eg high cLogP)

Medicinal chemistry : what properties a drug need to have ?

- **Activity on biological target & mechanism of action:** <10 nM
- **Selectivity versus off-targets:** highly selective or designed polypharmacology
- **Molecular Properties:** highly soluble & permeable, low MW, etc
- **Pharmacokinetics / ADME:** consistent with once a day dosing
- **Pharmacodynamics:** strong PD effect
- **Safety / Toxicities:** no serious adverse events
- **CMC/Chemistry, Manufacturing & Control:** short synthesis and low cost to produce



«Pfizer's» rules or «rule of five»

BOX 1

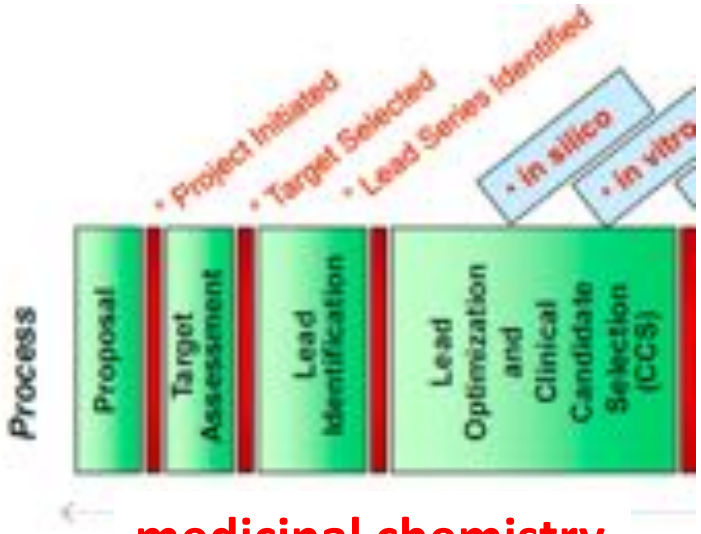
The Lipinski rule of five

The medicinal chemist Christopher Lipinski and his colleagues analysed[2] the physico-chemical properties of more than 2,000 drugs and candidate drugs in clinical trials, and concluded that a compound is more likely to be membrane permeable and easily absorbed by the body if it matches the following criteria:

- Its molecular weight is less than 500.
- The compound's lipophilicity, expressed as a quantity known as log*P* (the logarithm of the partition coefficient between water and 1-octanol), is less than 5.
- The number of groups in the molecule that can donate hydrogen atoms to hydrogen bonds (usually the sum of hydroxyl and amine groups in a drug molecule) is less than 5.
- The number of groups that can accept hydrogen atoms to form hydrogen bonds (estimated by the sum of oxygen and nitrogen atoms) is less than 10.

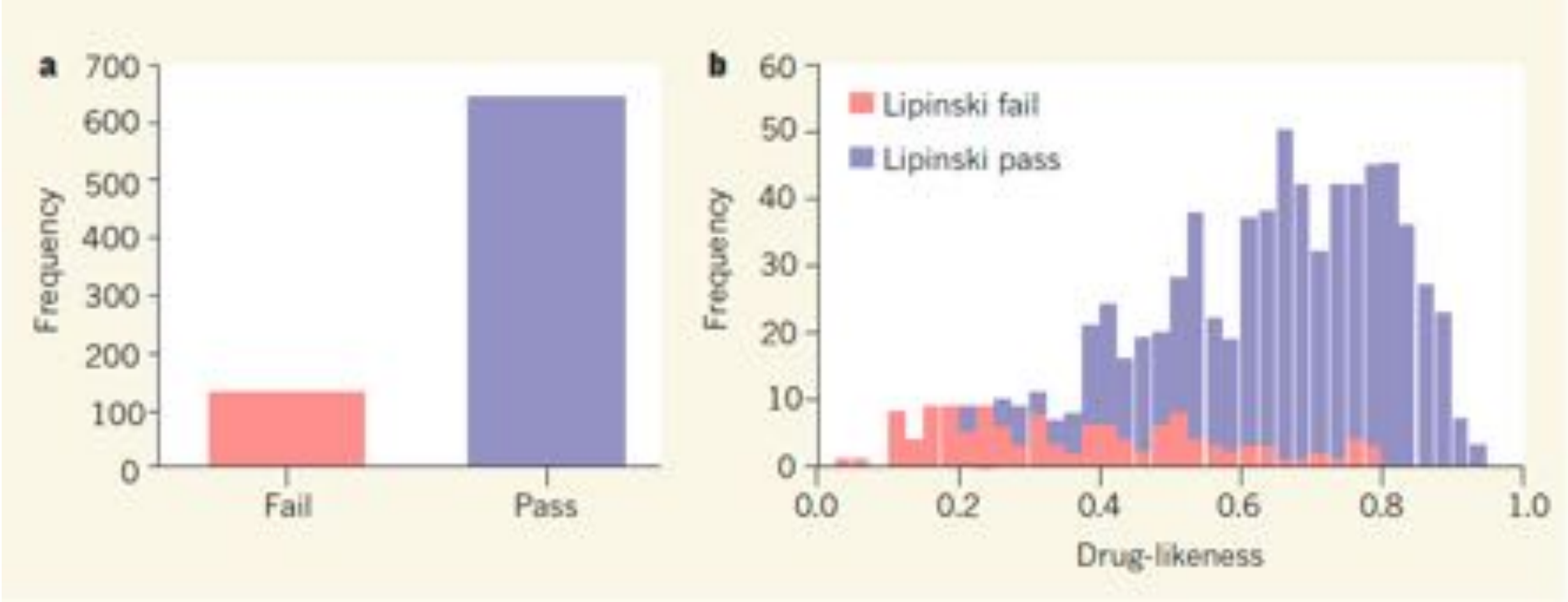
The rules, based on the 90-percentile values of the drugs' property distributions, apply only to absorption by passive diffusion of compounds through cell membranes; compounds that are actively transported through cell membranes by transporter proteins are exceptions to the rule. Due in no small part to their simplicity, the Lipinski criteria are widely used by medicinal chemists to predict not only the absorption of compounds, as Lipinski originally intended, but also overall drug-likeness.

«Pfizer's» rules or «rule of five»

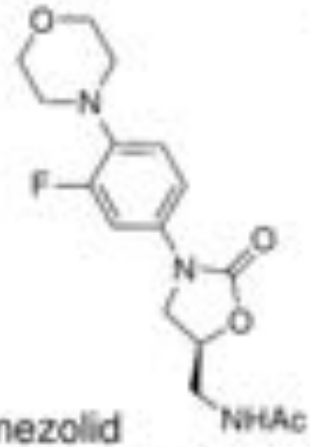


medicinal chemistry

Physico chemical criteria such as those defined by the "rule of five" are used to predict whether a cpd is drug like or not



Medicinal chemistry : drug like compounds



Linezolid
(PNU-100766)

Drug-like compounds (Lipinski's rule)

* Not more than 5 hydrogen bond donors :	1
* Not more than 10 hydrogen bond acceptors :	6 (8)
* A molecular weight under 500 daltons :	337
* A partition coefficient logP less than 5 :	0.9
* Number of atoms from 20 to 70 :	44
* Number of rotatable bonds less than 10 :	5
* Polar surface area (PSA) less than 140 :	91

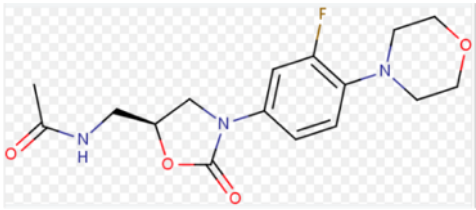
Computed Properties - Chem3D Properties Broker

Good solubility : 3.7 mg/mL in pH 7 phosphate buffer

The oral bioavailability : 100% (rapid and complete absorption)

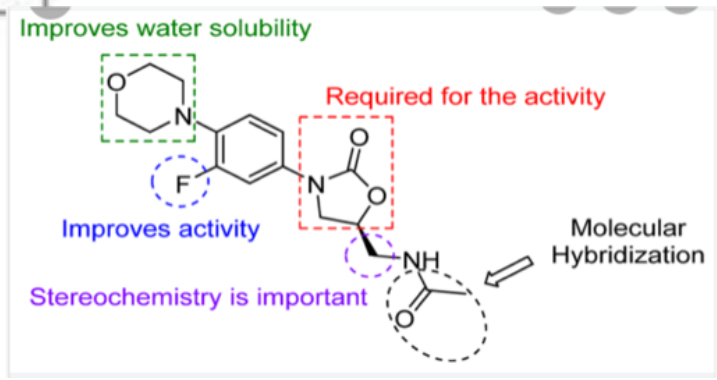
The excretion : 20–30% of the dose found in the urine as the parent drug

Has been approved by the FDA in 2000 under the trade name Zyvox

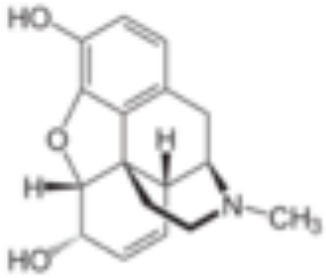
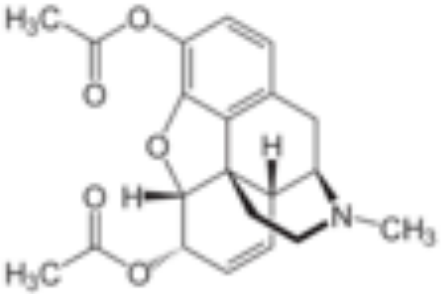
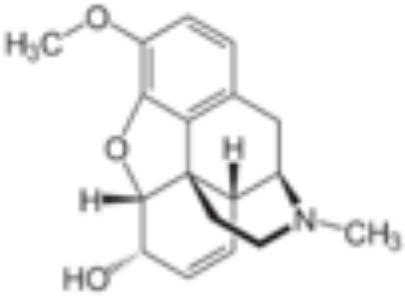
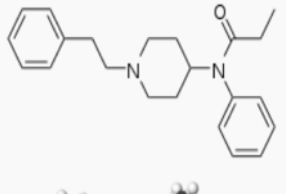


Ford, C. W.; Zurenko, G. E.; Barbachyn, M. R. *Cur. Drug Targets* **2001**, *1*, 181-199

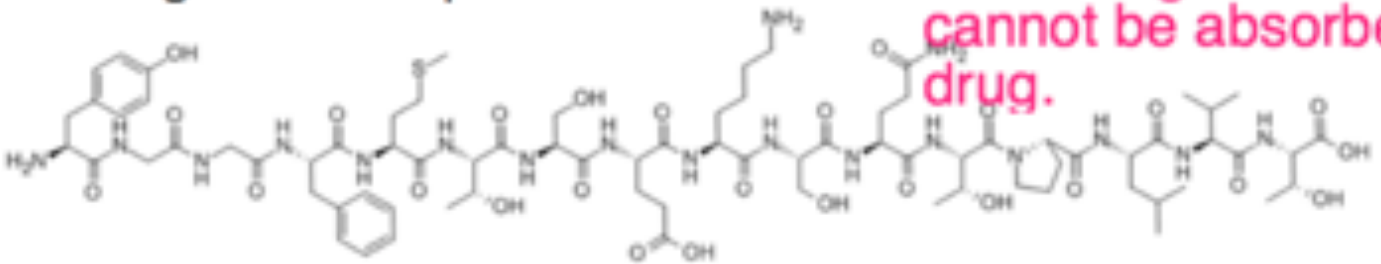
Used to be a “last resort” antibacterial
Oxazolidinone -Linezolid
(peptidyl transferase center (PTC) blocker)



SAR : eg. from poppy seeds to modern analgesics

Opium	Morphine	Heroin	Codeine	Fentanyl
				
	strong analgesic bioavailability 25%	2-4x potent vs **1** better brain penetrant	much less potent vs **1** metabolised to **1** by CYP2D6	more potent vs **1** longer half life bioavailability 87%
	logD=0.04	**logD=0.93**	**logD=0.46**	**logD=2.37**

Natural ligands: endorphins

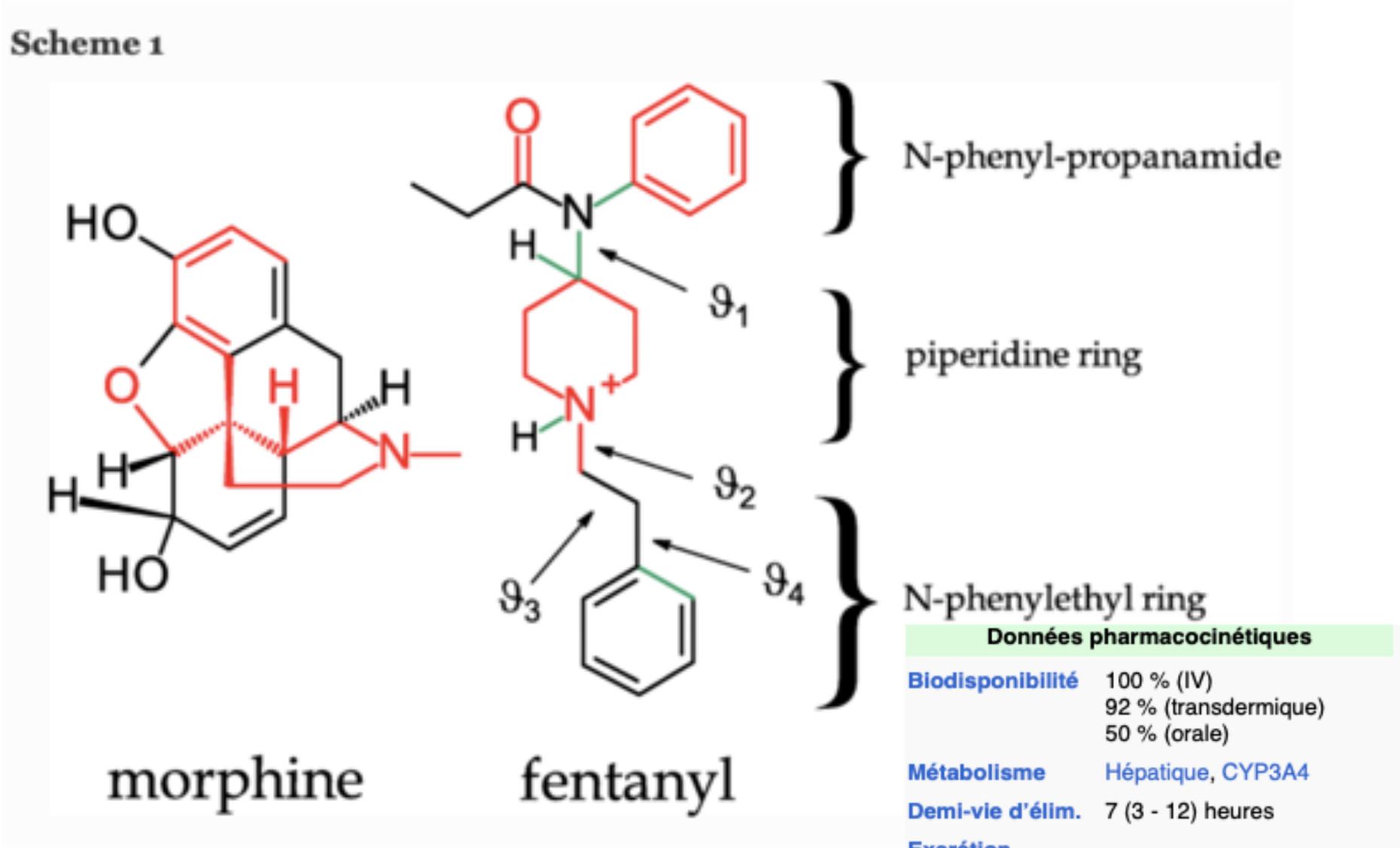


such a big molecule cannot be absorbed as a drug.

μ-opioid receptor (μOR) agonists are the most effective medicines in treatment of severe pain

Structure activity relationships (SAR) and structure property relationships (SPR)

SAR : eg. from poppy seeds to modern analgesics

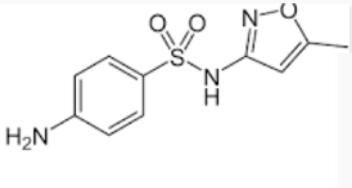


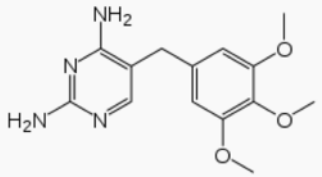
Données pharmacocinétiques	
Biodisponibilité	100 % (IV) 92 % (transdermique) 50 % (orale)
Métabolisme	Hépatique, CYP3A4
Demi-vie d'élim.	7 (3 - 12) heures
Excrétion	Rénale

μ-opioid receptor (μOR) agonists are the most effective medicines in treatment of severe pain

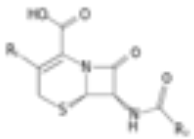
Medicinal chemistry : antibacterials

	Gram +	Gram -
Cocci	**Staphylocoque (coccis en amas) :** • à coagulase neg • aureus **Streptocoque (cocci en chainettes) :** • pyogenes du groupe A, pneumoniae • autres streptocoques : groupe D (bovis) .... **Enterocoques : (diplocoques)** enterococcus fecalis (ressemblent aux streptocoques)	Nesseria (2 principaux cocci gram -) • meningitidis (meningocoque) • gonorrhoeae Cocco-bacilles (germes en pédiatrie): • Moraxella • Branhamella catarrhalis
Bacilles	"Listeria monocytogenes (le seul BG+ a connaître)" "corynebacteirum diphteriae" Bacillus anthracis	**Enterobacteries :** E. Coli (ETEC, EPEC, EHEC), Klebsiella, enterobacter, serratia, proteus, salmonella, shigella, yersinia pestis / enterocolitica **Autres BGN :** campylobacter, helicobacter pilori et jejuni, vibrio cholerae, pasteurella, haemophilius influenzae HACEK (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella) bordetella pertussis, legionella (intracellulaire facultatives) morsures griffures : Bartonella henselae, Francisella tularensis (griffe du chat) pseudomonas (a part)

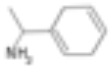
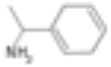
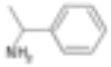
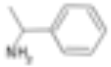
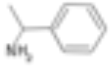
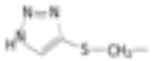
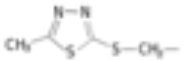
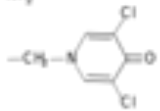
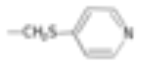
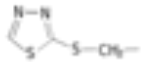
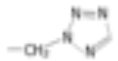
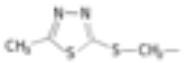
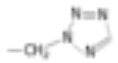
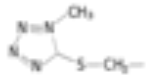
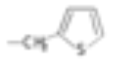
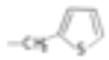
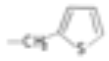


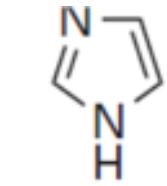


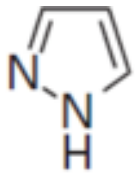
a combo winner :sulfammethoxasol/trimetoprim : nice charged groups, loves water : broad spectrum gram negative urinary tract infection

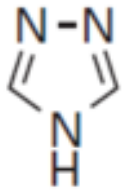


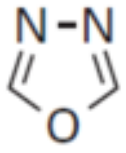
Medicinal chemistry : the cephalosporin example

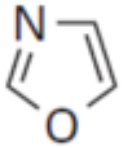
	R_1	R_2
Cefacetril	CH_3COOCH_2	CH_2CN
Cefradin	CH_3	
Cefroxadin	CH_3O	
Cefaloglycin	CH_3COOCH_2	
Cefaclor	Cl	
Cefalexin	CH_3	
Cefadroxil	CH_3	
Cefatrizin		
Cefazedon		
Cefapirin	CH_3COOCH_2	
Ceftezol		
Cefazolin		
Cefazaflur		$CH_2S{-}CF_3$
Cefalotin	CH_3COOCH_2	
Cefaloridin		
Cefalonium		

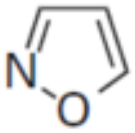

imidazole

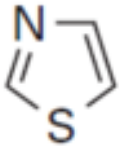

pyrazole

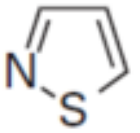

1,2,4-triazole


1,3,4-oxadizole


oxazole


isoxazole


thiazole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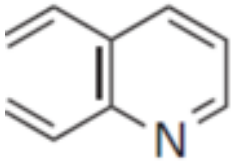
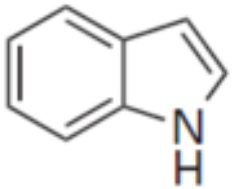
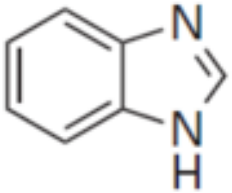
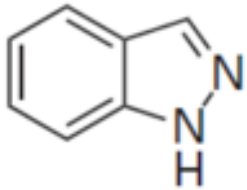
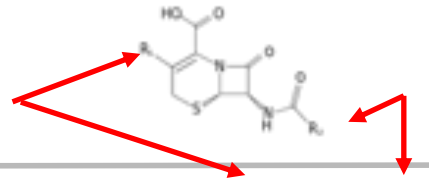

quinoline

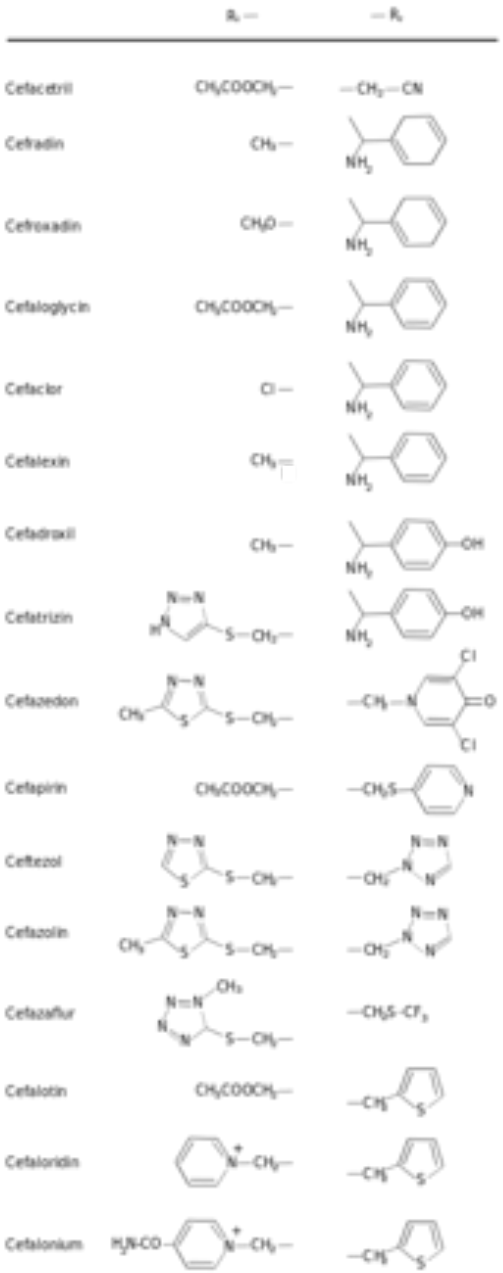

indole


benzimidazole

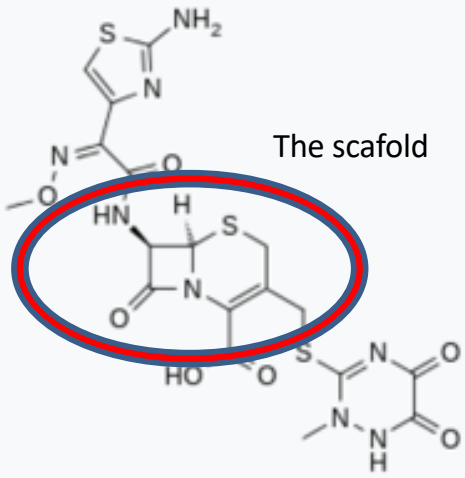

indazole

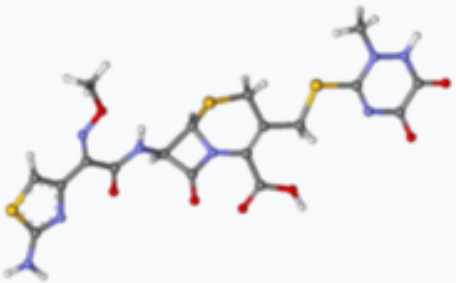


Ceftriaxone (Rocephin) : a cephalosporin third generation

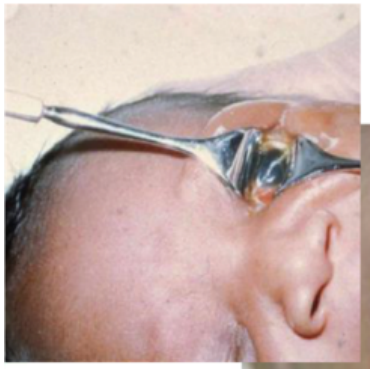


Ceftriaxone

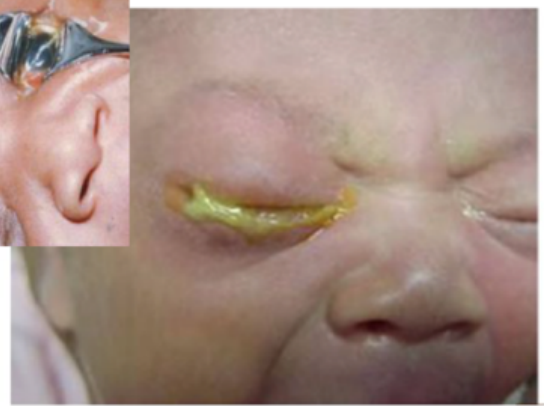


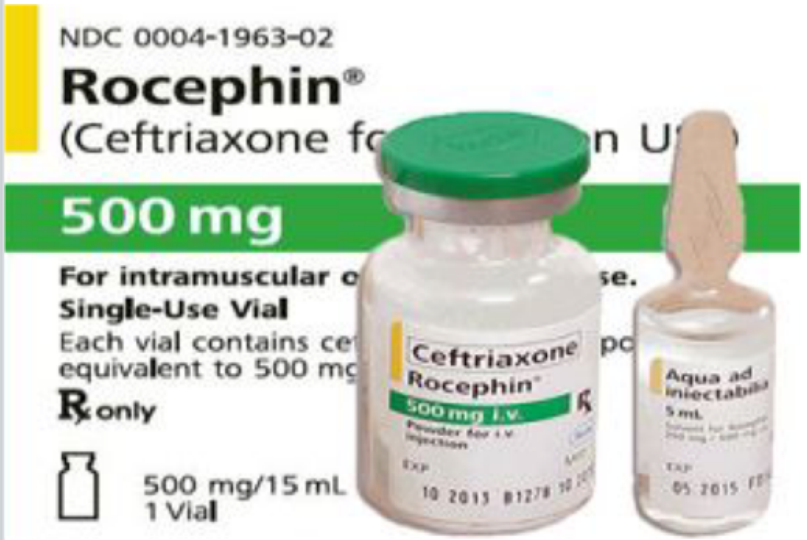


Clinical data	
Pronunciation	/ˌsɛftraɪˈæksoʊn/
Trade names	Rocephin, Epicephin, others
AHFS/Drugs.com	Monograph
Pregnancy category	AU: B1 US: B (No risk in non-human studies)
Routes of administration	Intravenous, intramuscular



Gonoccoccal ophtalmia neonatorum





Medicinal chemistry : covalent binding medicines time line

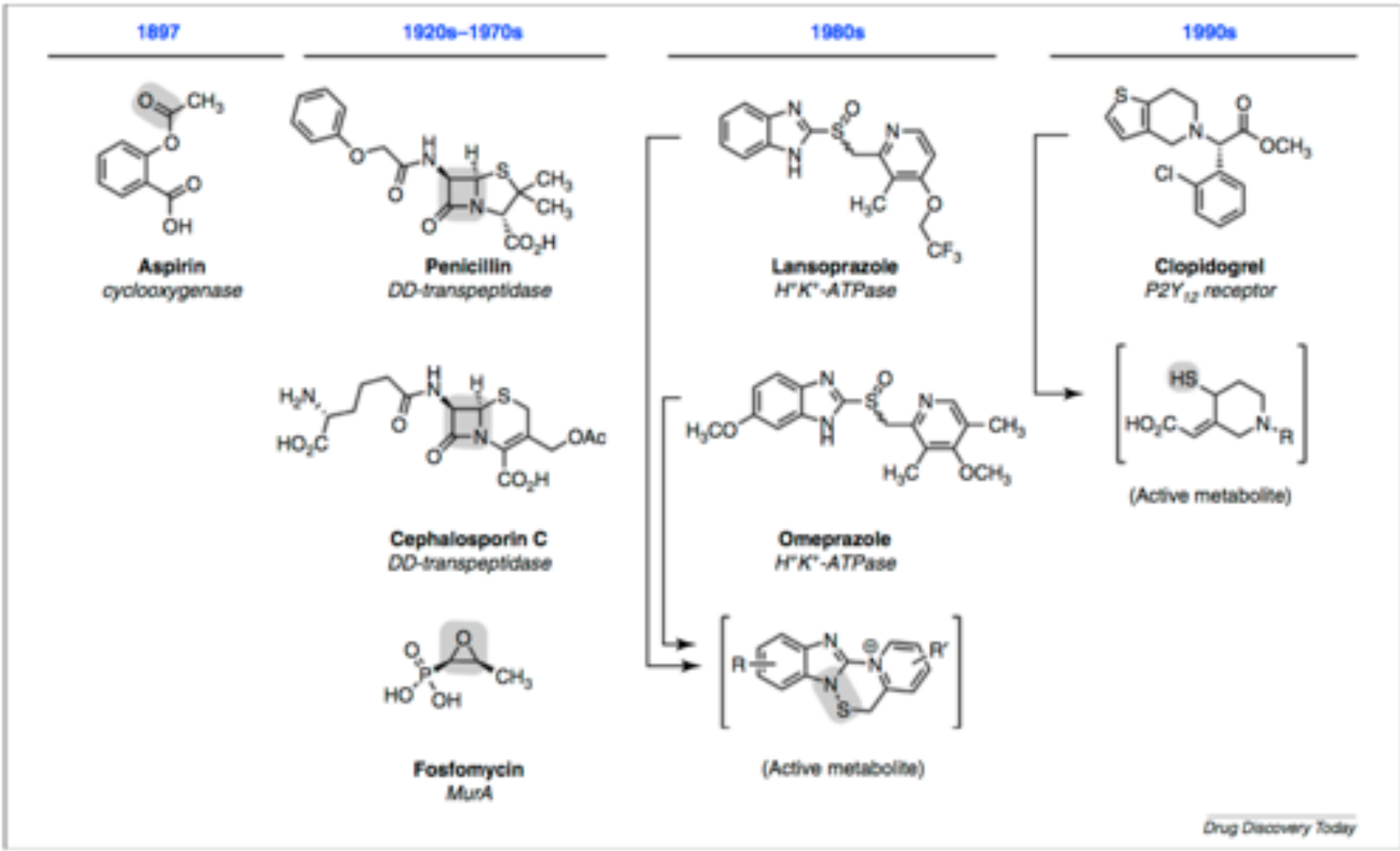


FIGURE 3

Historical examples of approved covalent drugs. Electrophiles are highlighted (sulfhydryl, SH, is a pre-electrophile).

MedChem: covalent binding medicines pros and cons

BOX 1

Summary of pros and cons for covalent inhibitors

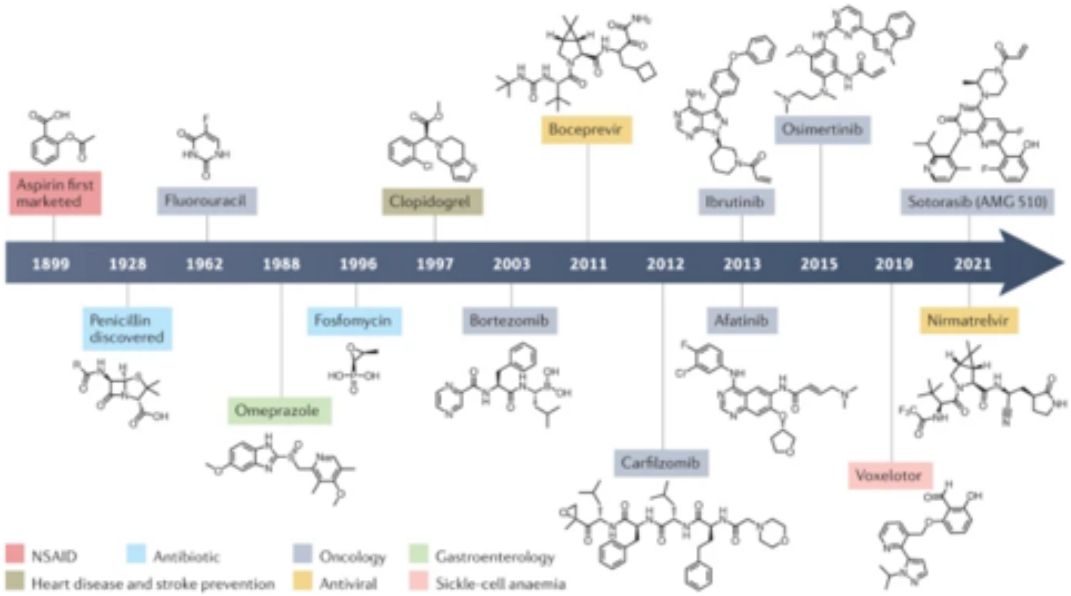
Pros

- High biochemical efficiency may translate to lower doses and reduced off-target effects
- Nonequilibrium binding might help to overcome competing endogenous substrate concentrations that bind to the same target site
- Covalent binding might mitigate the development of drug resistance resulting from mutation of a binding site.
- Uncoupled PK/PD and prolonged duration of action can result in less-frequent drug dosing
- Can potentially address targets with shallow, undruggable binding sites

Cons

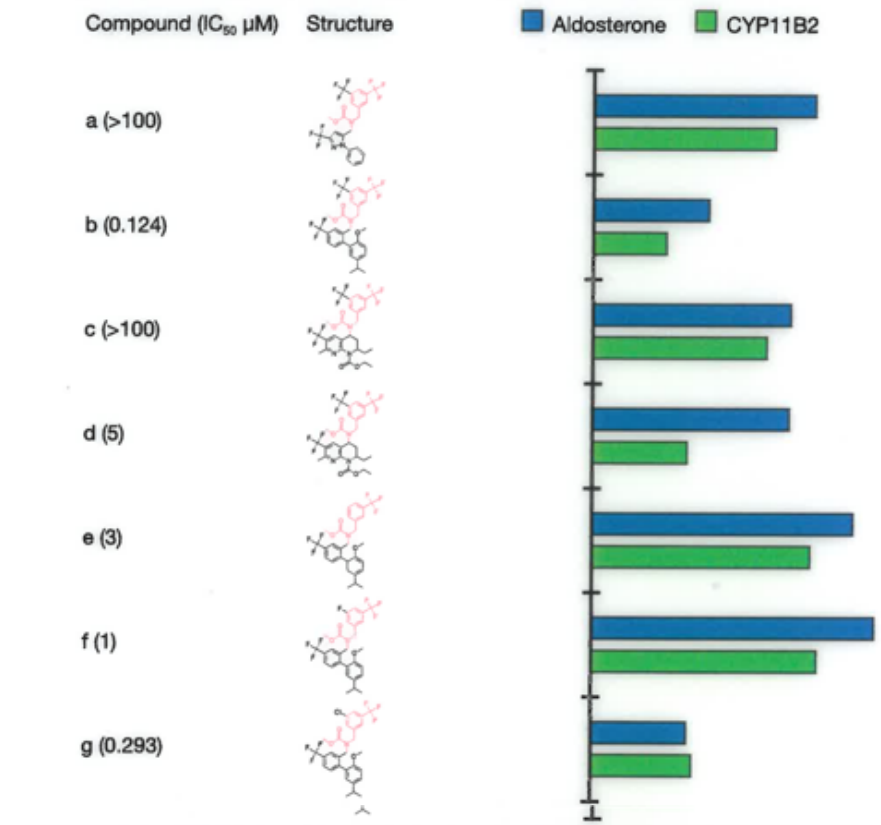
- Potential risk of idiosyncratic toxicity and/or immune-mediated drug hypersensitivity
- Hyper-reactive warheads might lead to other drug-induced toxicity (e.g., hepatotoxicity, mutagenicity, or carcinogenicity)
- Not suitable for mechanisms requiring short residence time, transient or partial inhibition
- Little advantage for biological targets that are rapidly turned over by protein synthesis

Fig. 1: Timeline of the development of major covalent drugs.

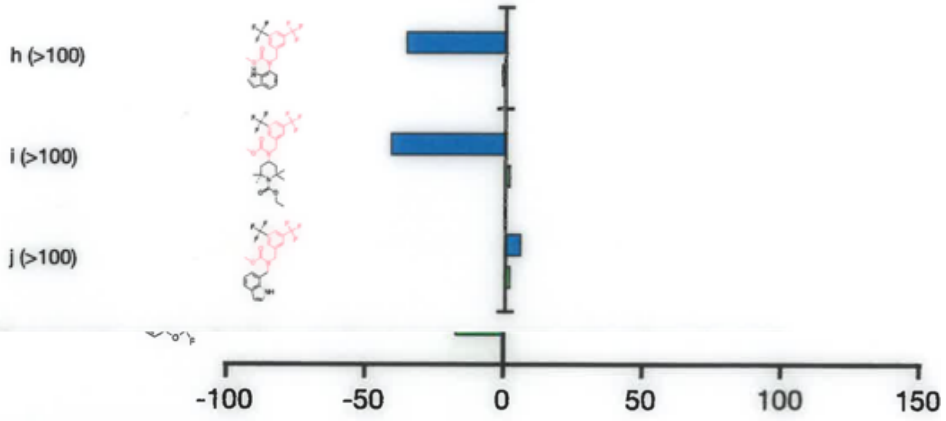


Each covalent drug is classified according to the drug type or type of disease it treats. Unless

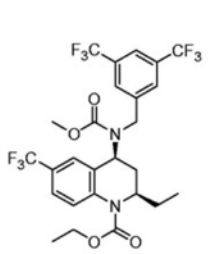
1a. Compounds with methyl-(3-trifluoromethyl-benzyl)-carbamic acid methyl ester motif of torcetrapib (IN RED COLOUR) attached to a suitable THQ-replacement

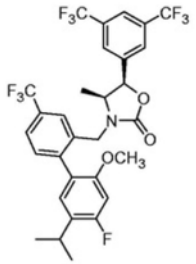


1b. Compounds with methyl-(3-trifluoromethyl-benzyl)-carbamic acid methyl ester motif of torcetrapib (IN RED COLOUR) but no suitable THQ-replacement

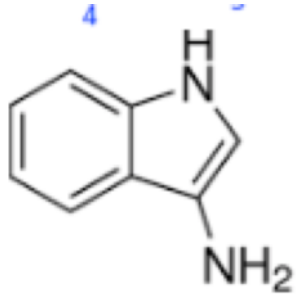


IC_{60} of CETP activity determined using a scintillation proximity assay.
nd, not determined (benzoic acid derivative).


Torcetrapib

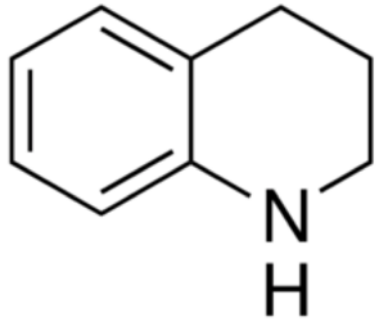

Anacetrapib

An example of assay read out and medicinal chemistry MDO



Indole

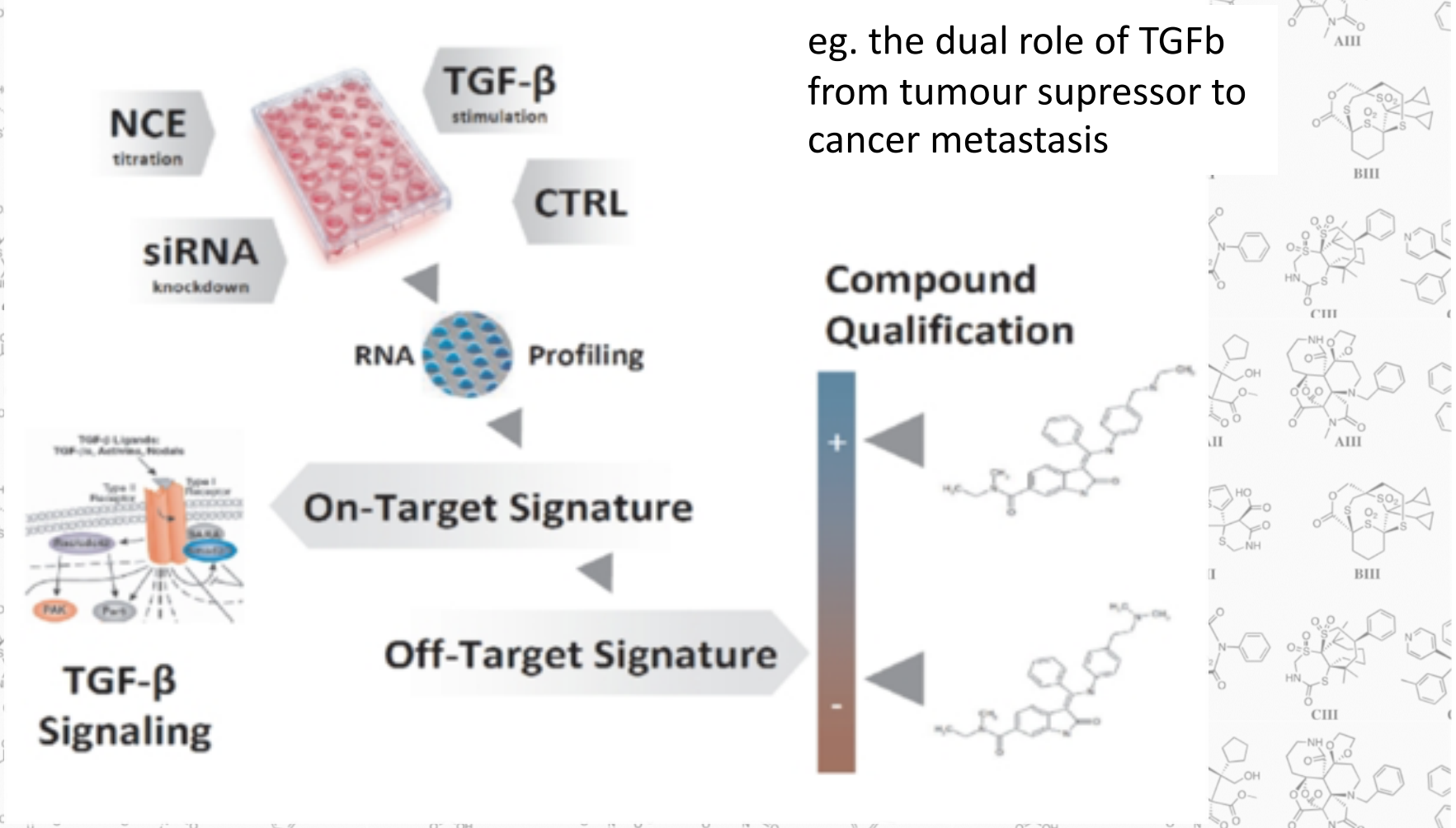
Composé organi



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

Clerc RG. and Niesor EJ. American Heart Association Washington DC. USA

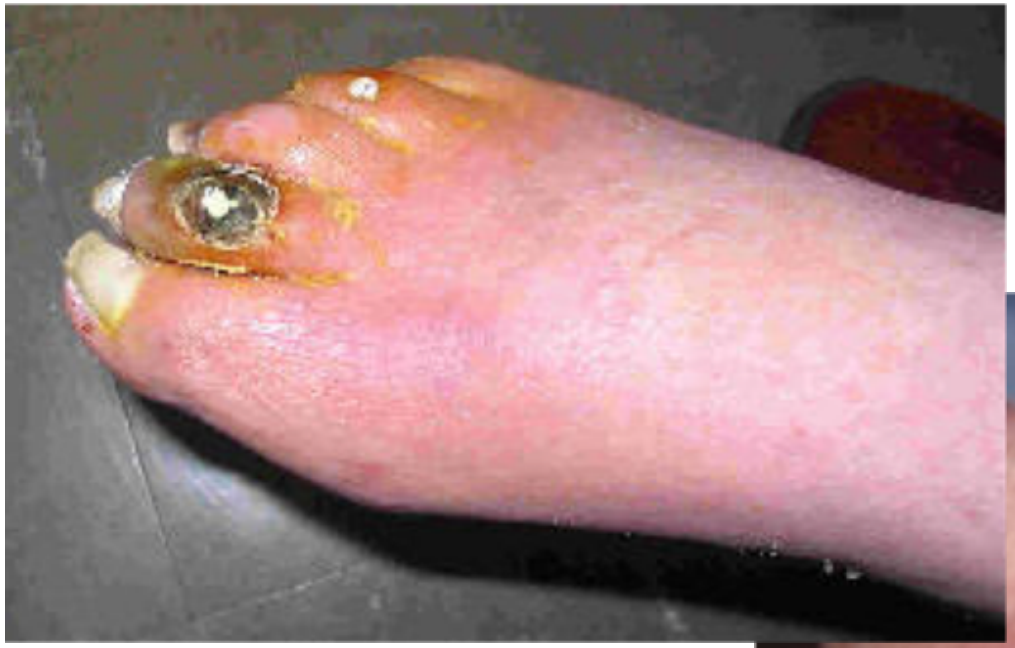
Secondary assays to validate on/off therapeutic target



eg. the dual role of TGFb from tumour supressor to cancer metastasis

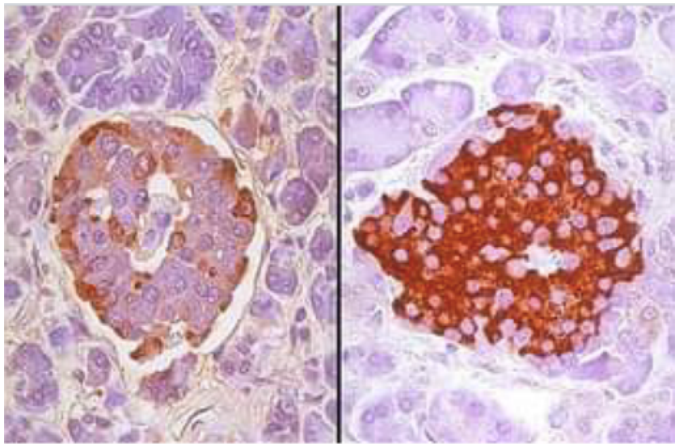
From hit to lead cpd : on- resp. off-target validation (undesired pharmacological adverse effects !)

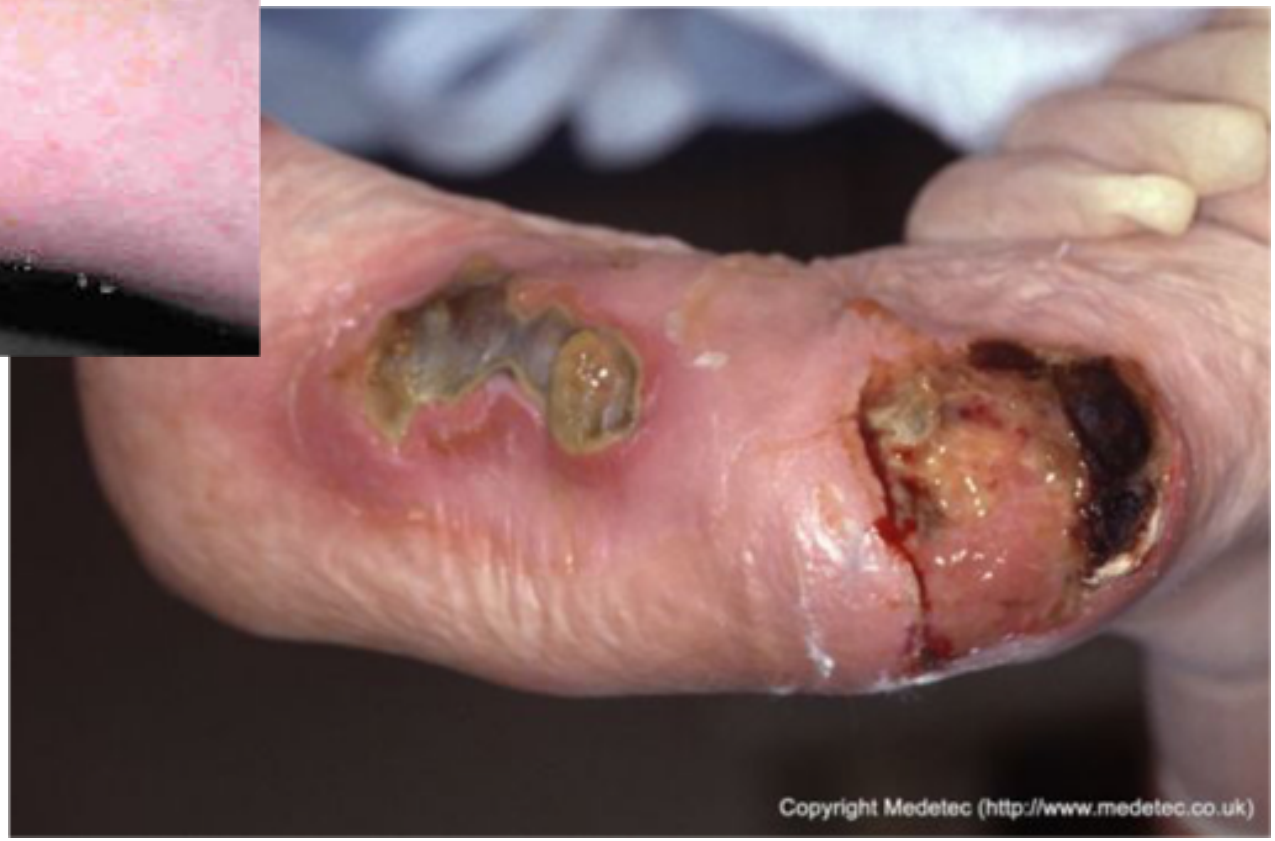
Advanced ……. : peripheral ischaemia-necrosis



MEDICAL NEED : IMPROVE

…… **USING A MEDICINAL CHEMISTRY DESIGN**



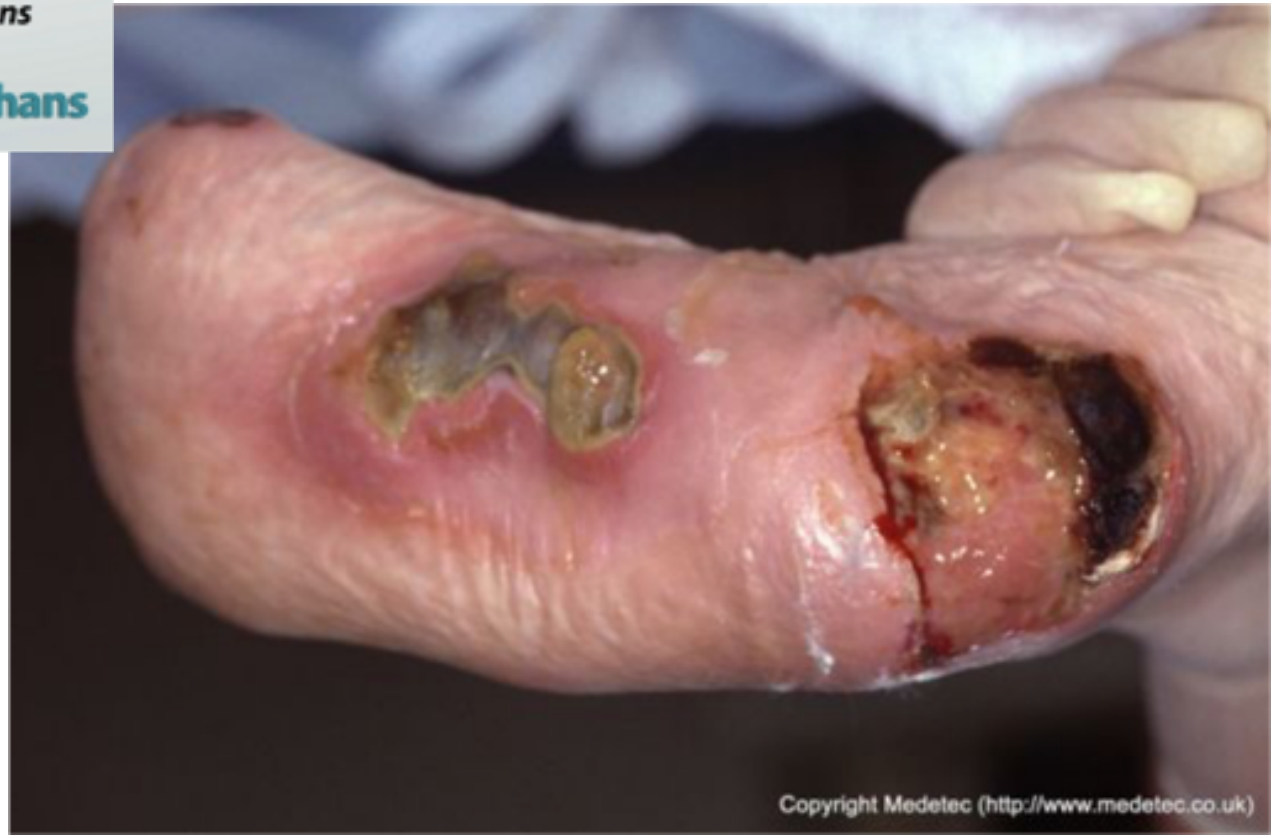


MACRO- AND MICROVASCULARIZATION IMPAIREMENTS

Advanced ……. : peripheral ischaemia-necrosis

MEDICAL NEED : IMPROVE

……. **USING A MEDICINAL CHEMISTRY DESIGN**



INAUGURAL-DISSERTATION.

ZUR

ERLANGUNG DER DOCTORWÜRDE

IN DER

MEDICIN UND CHIRURGIE

VORGELEGT DER

MEDICINISCHEN FACULTÄT

DER FRIEDRICH-WILHELMS-UNIVERSITÄT

ZU BERLIN

UND ÖFFENTLICH ZU VERTHEIDIGEN

am 18. Februar 1869

VON

Paul Langerhans

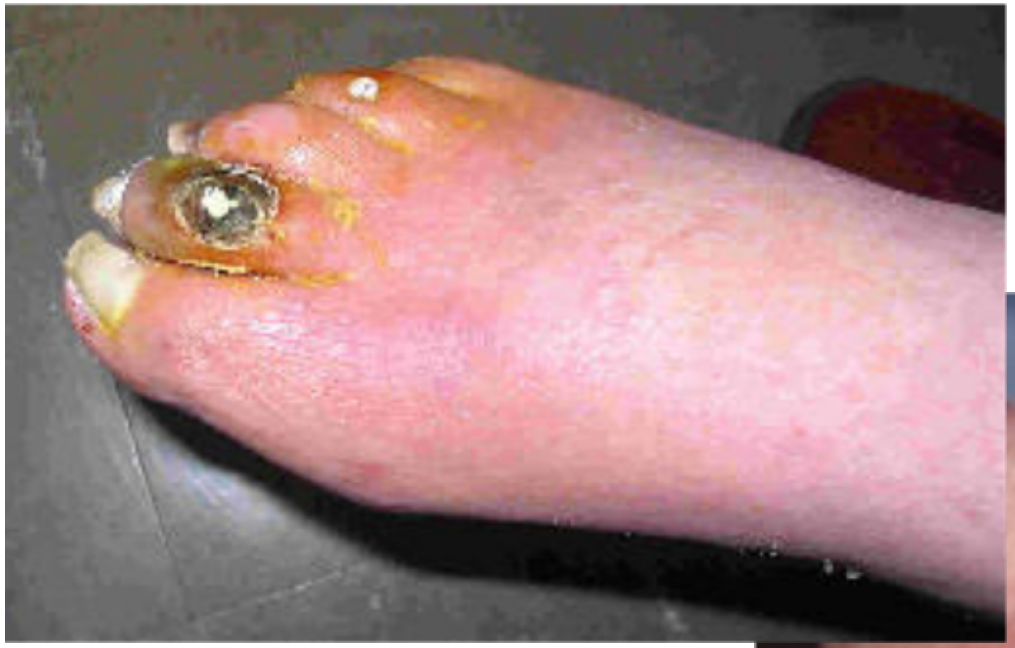
aus Berlin.

OPPONENTEN:

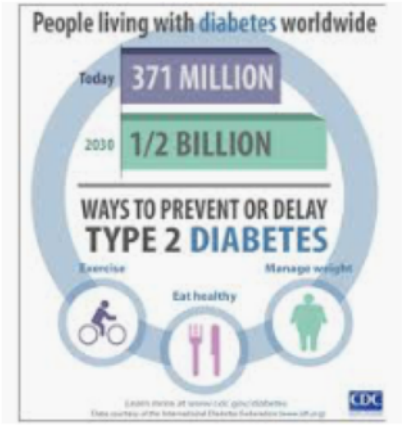
O. Loeillet de Mars, Dd. med.
O. Soltmann, Dd. med.
Paul Ruge, Stud. med.

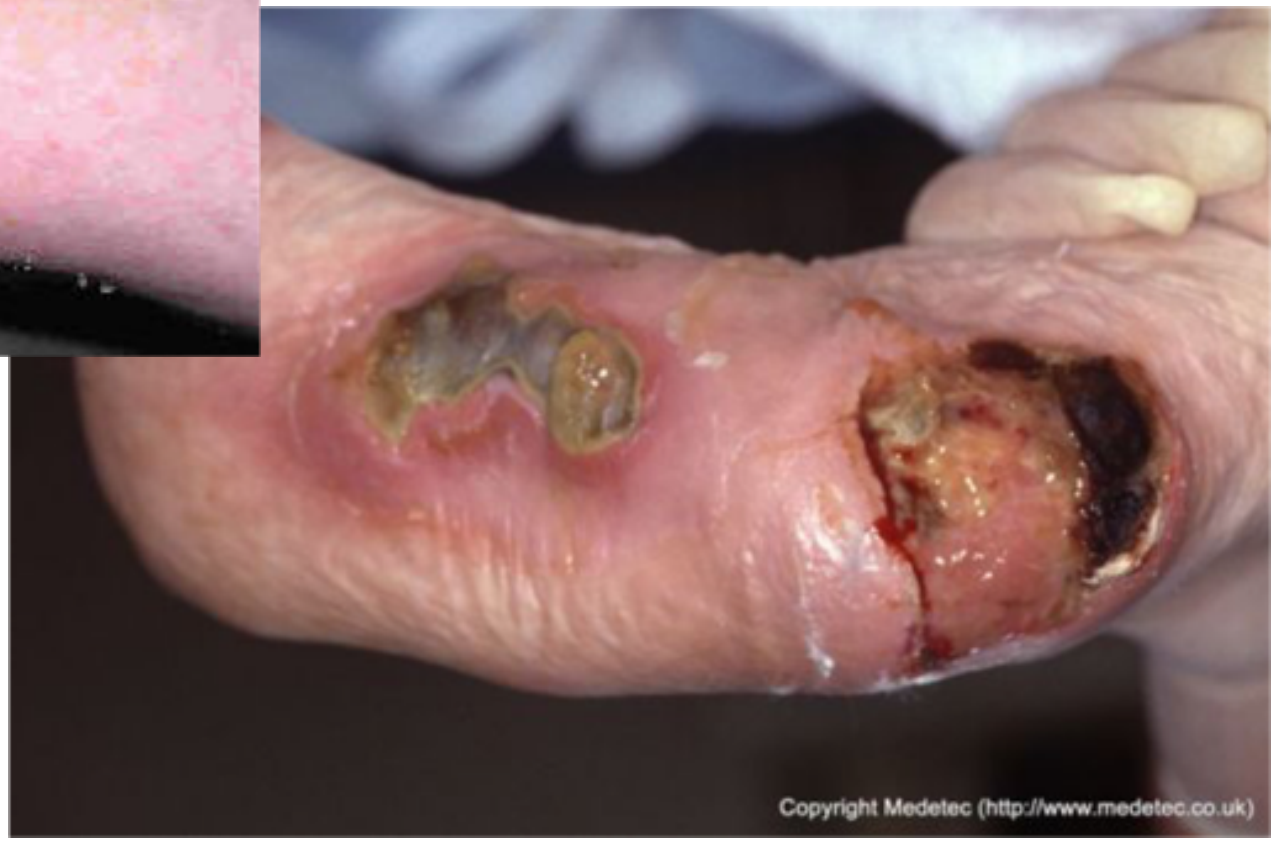
BERLIN.

Advanced type II diabetes : peripheral ischaemia-necrosis



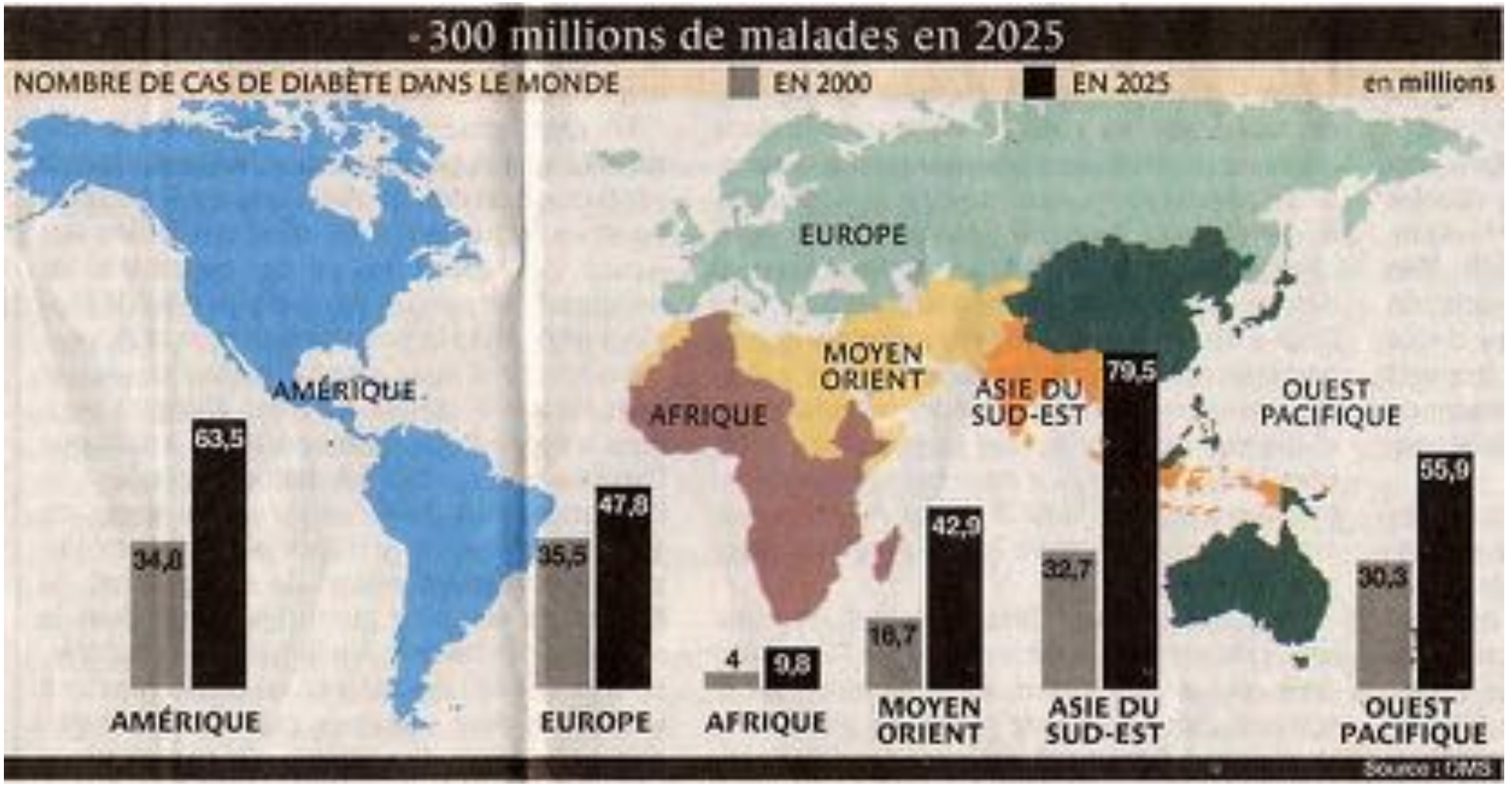
MEDICAL NEED : IMPROVE INSULIN SENSITIVITY **USING A MEDICINAL CHEMISTRY DESIGN**





Metabolic syndrome – when patients become insulin resistant
MACRO- AND MICROVASCULARIZATION IMPAIREMENTS

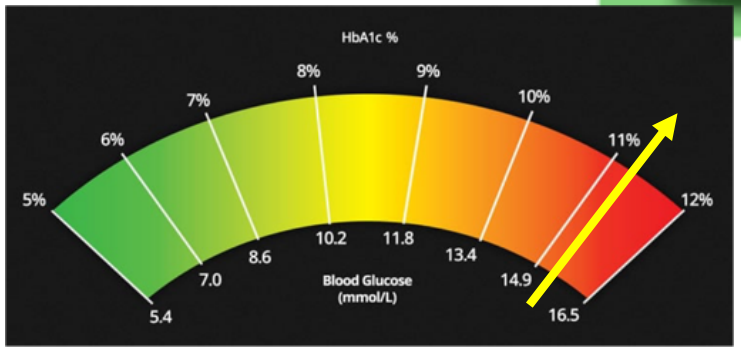
Type II diabetes and metabolic syndrome global pandemia _ 2025 : WHO



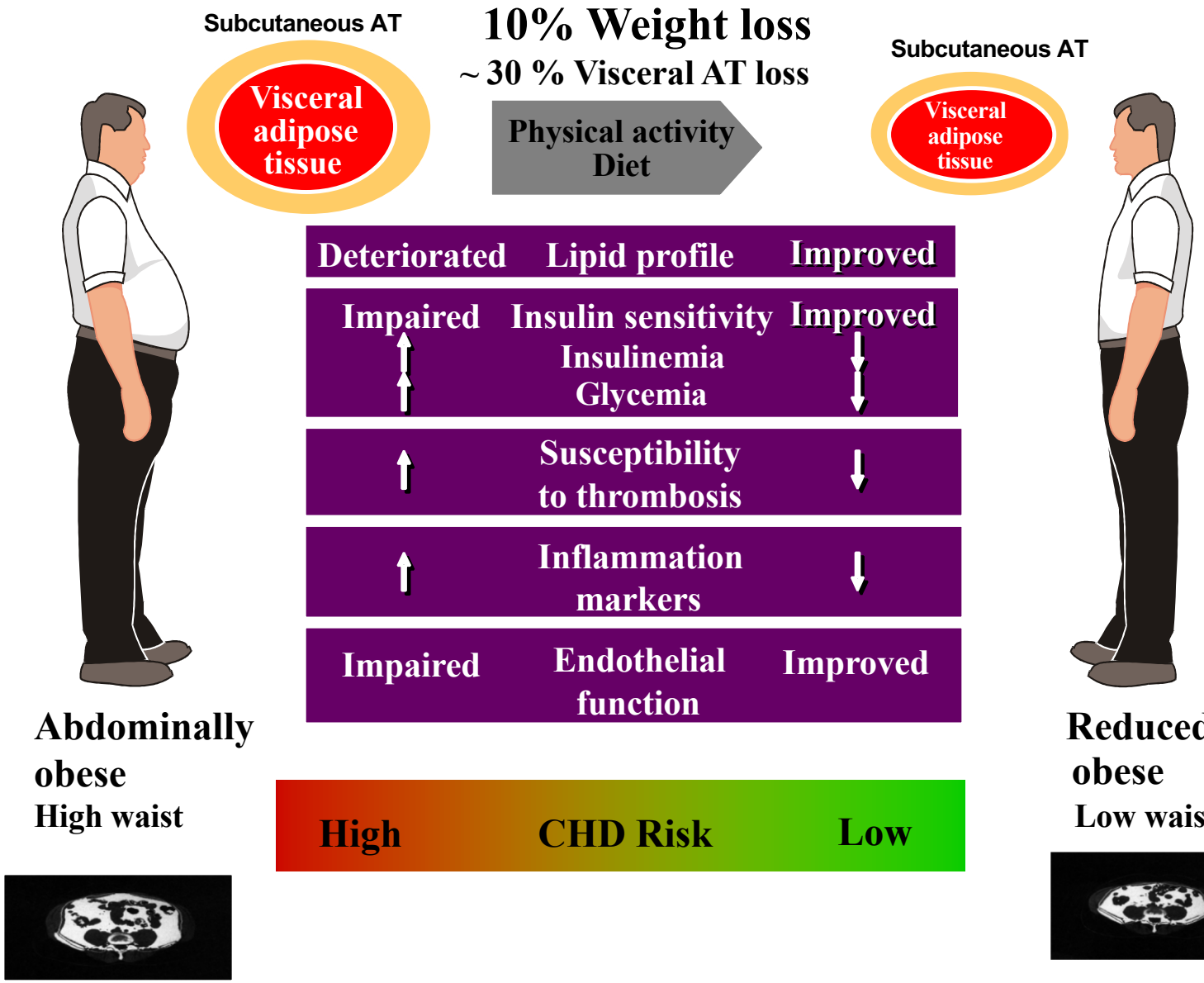
Le Monde

Metabolic syndrome pandemia and short cuts:
BMI body mass index, WHR waist hip ratio, viceral fat content

$$BMI = \frac{weight}{(height)^2}$$

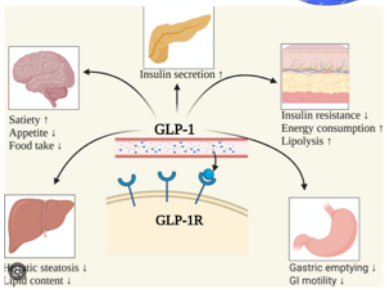


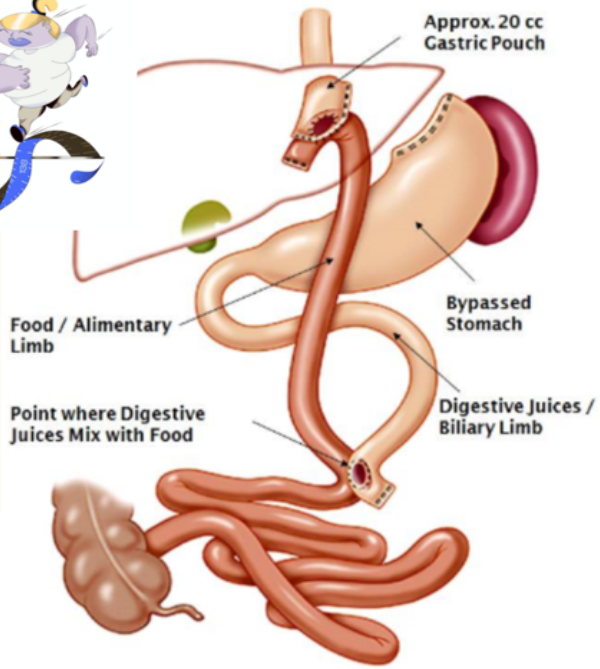
Clinical Endpoint: Metabolic Syndrome



Adapted from Després et al. BMJ (2001) 322:716-720

Type II diabetes and metabolic syndrome pandemia : a cartoonist view of a threat or towards the end of obesity ?



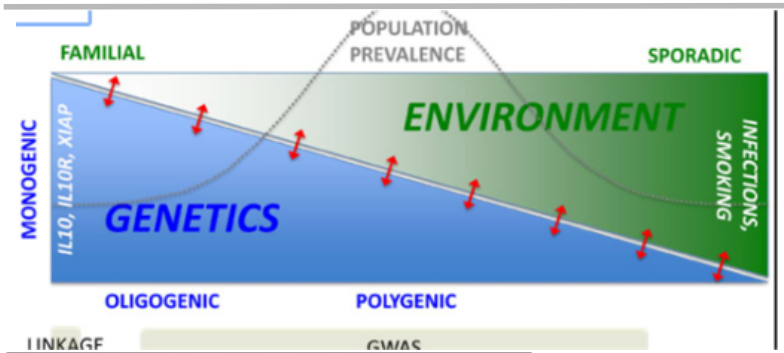


Type 2 diabetes develops as a consequence of the metabolic syndrome diabetes is also known key risk factor for developing severe/fatal COVID-19

Diabetes itself is pandemic just like COVID-19 is pandemic :
two pandemia that did clashed - looking at the underlying molecular mechanisms
overactivity of the immune system - cytokine storm and more

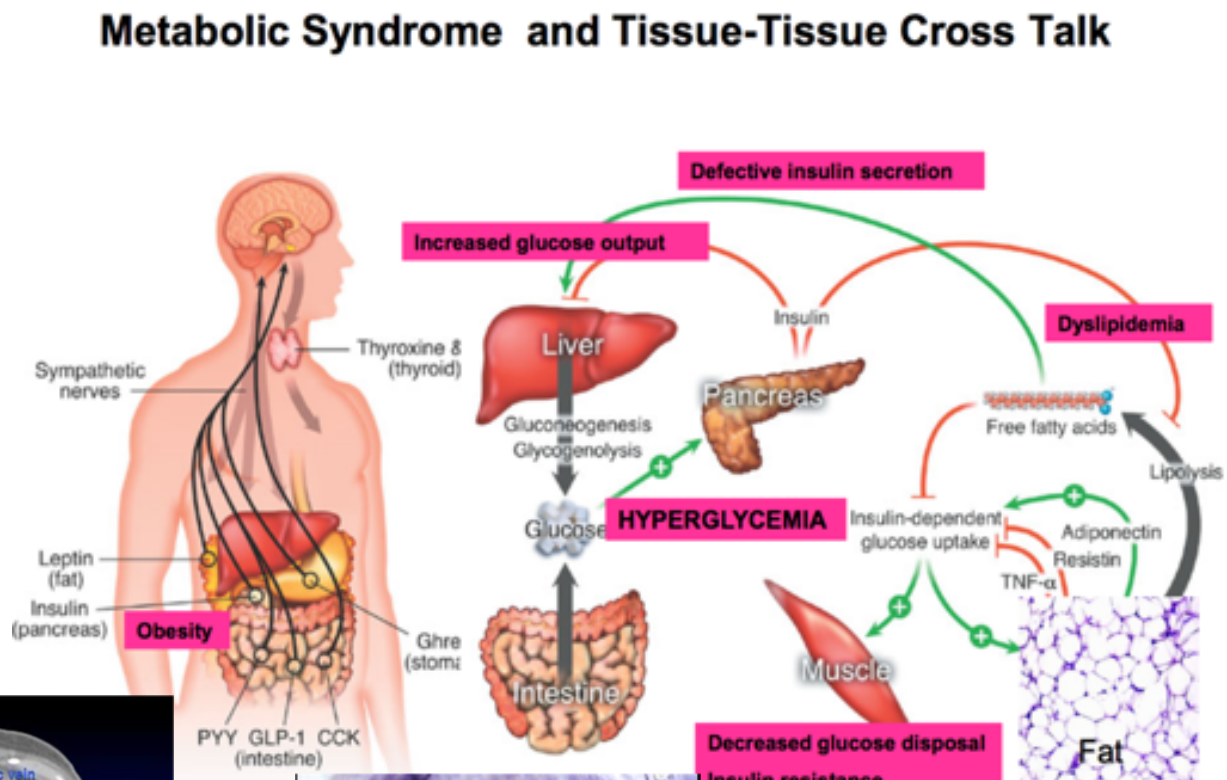
Cases of type 1 diabetes, which is caused by the body's own immune system attacking pancreatic cells, rose in young people during the COVID pandemic Credit: BSIP/Universal Images Group via Getty Nature News July 21. 2023

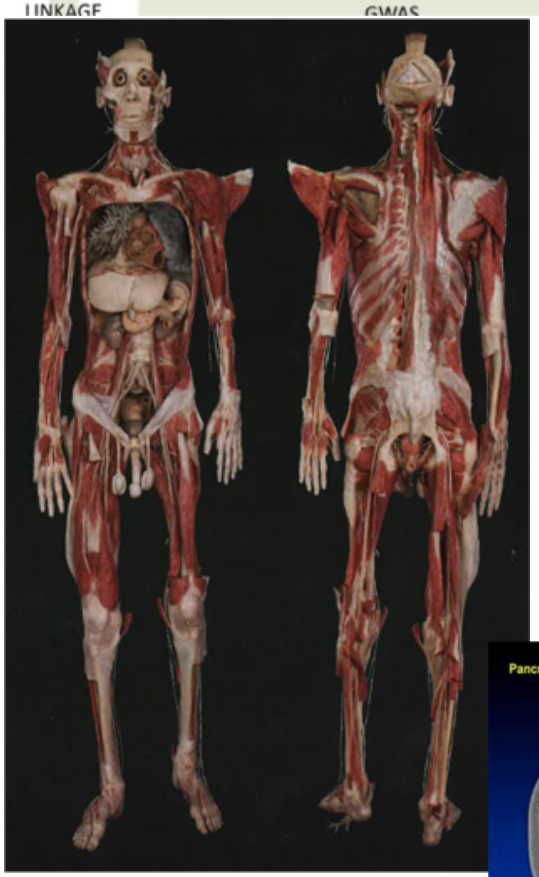
Metabolic syndrome : when patients become insulin resistant



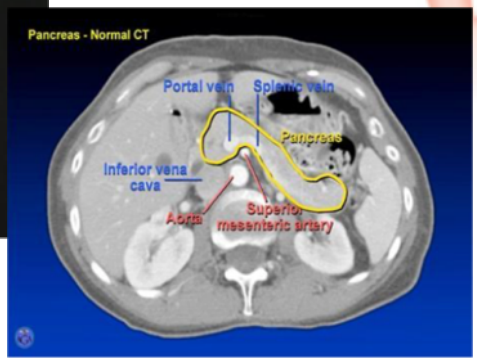
Metabolic Sydrome and Tissue-Tissue Cross Talk

MEDICAL CHALLENGE : COMPLEX TRAITS DISEASE :
GENETICS AND ENVIRONEMENT PLAY A COMBINED ROLE



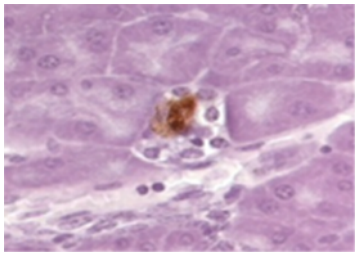


Gubener Plastinate GmbH
Guben Germany



Progression to type II diabetes : pathophysiology of pancreatic beta cells exhaustion

Stage I II III IV



Obese
Peripheral insulin resistance

Pre-diabetic/obese
Impaired glucose tolerance

β-cell failure and insulin resistance

Early diabetes

Late diabetes
hyperglycaemia

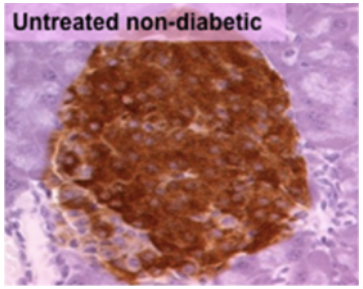
Vascular complications

diet

Prevention
- insulin sensitization
- organoprotection ?
- decrease vascular risk?

Intervention
- Normalize glucose
- Preserve β-cell insulin?
- decrease vascular risk?

insulin



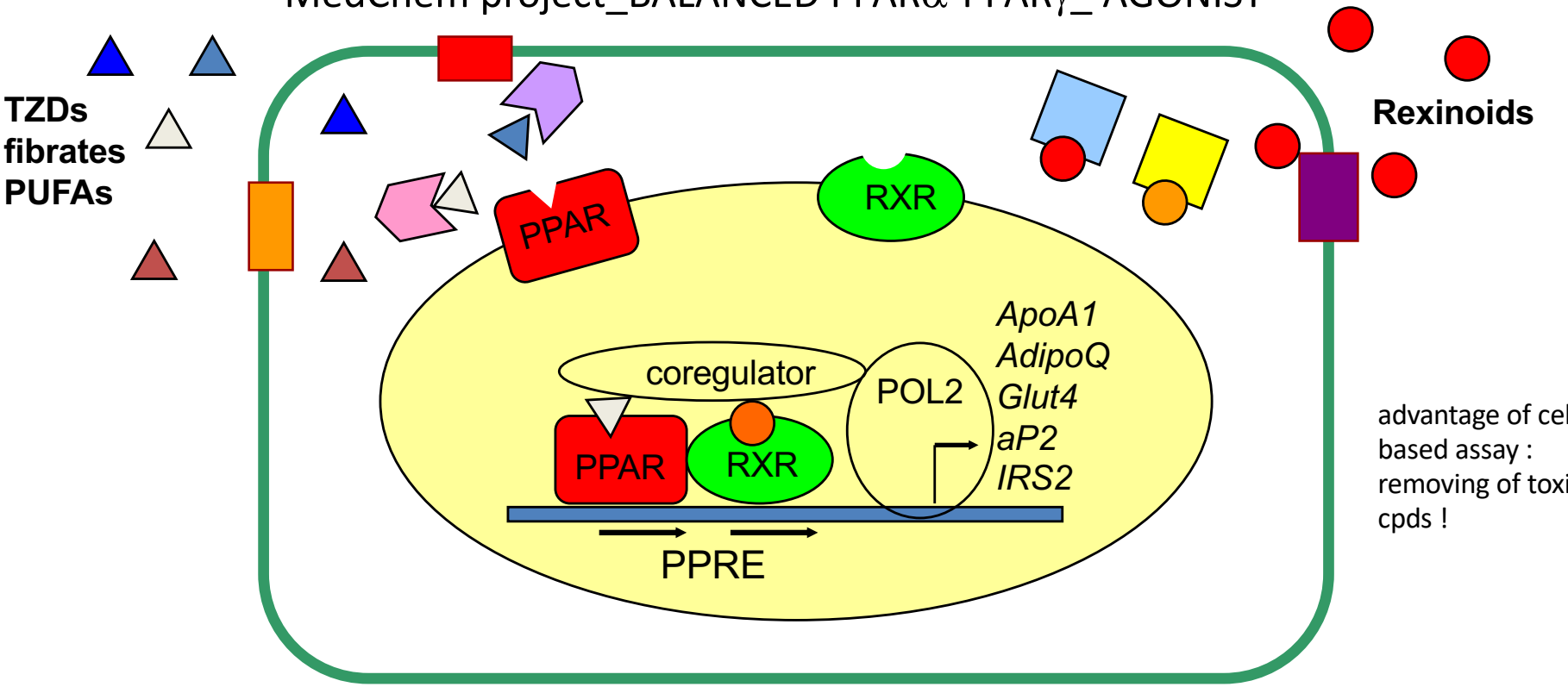
← Environment + "obesigenes" →

← "+diabetogenes" →

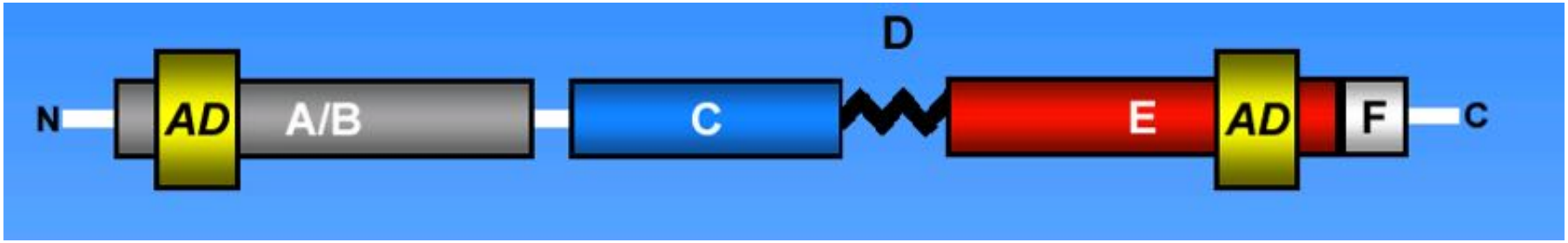
Cell based assay: type II diabetes and insulin resistance

PPAR/RXR-dependent cellular signaling

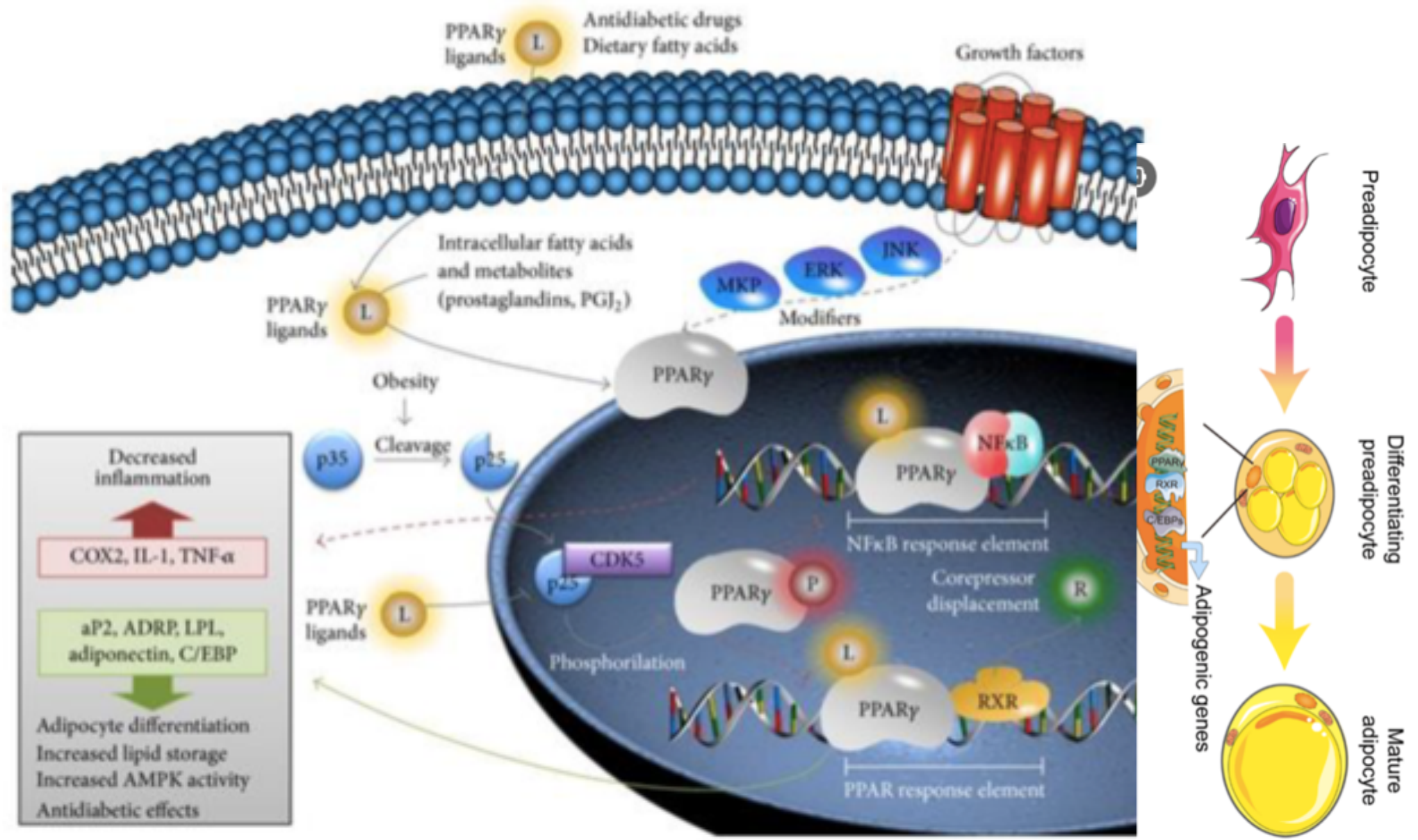
MedChem project_BALANCED PPARα-PPARγ_ AGONIST



advantage of cell based assay : removing of toxic cpds !



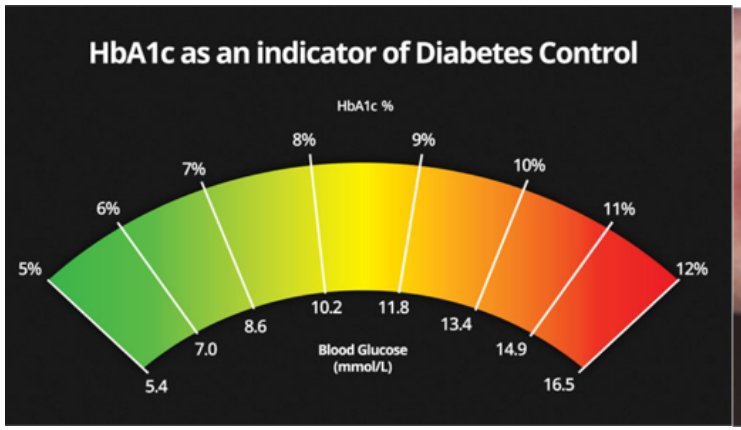
Type II diabetes and insulin resistance : The underlying molecular mecanism

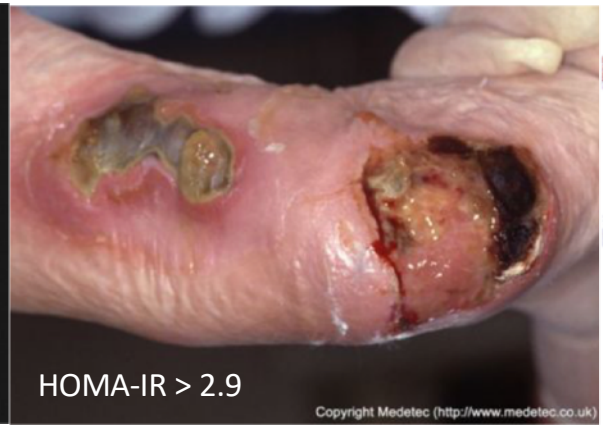


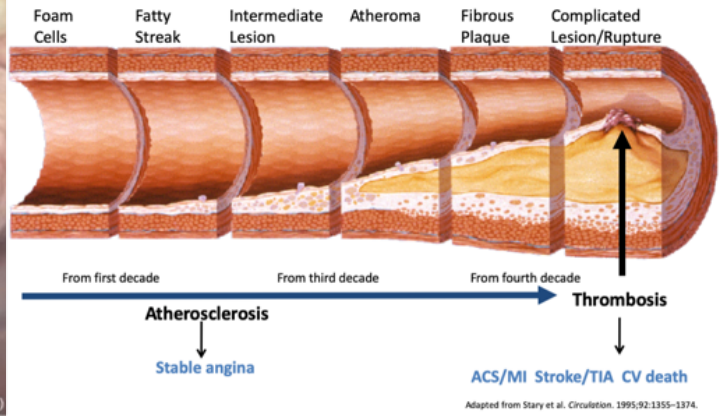
Medical need : improve insulin sensitivity and dislipidaemia : assay development

Goal: balanced pharmacological activation of PPAR alpha-gamma receptors

A medicinal chemistry approach to treatment of type II diabetes

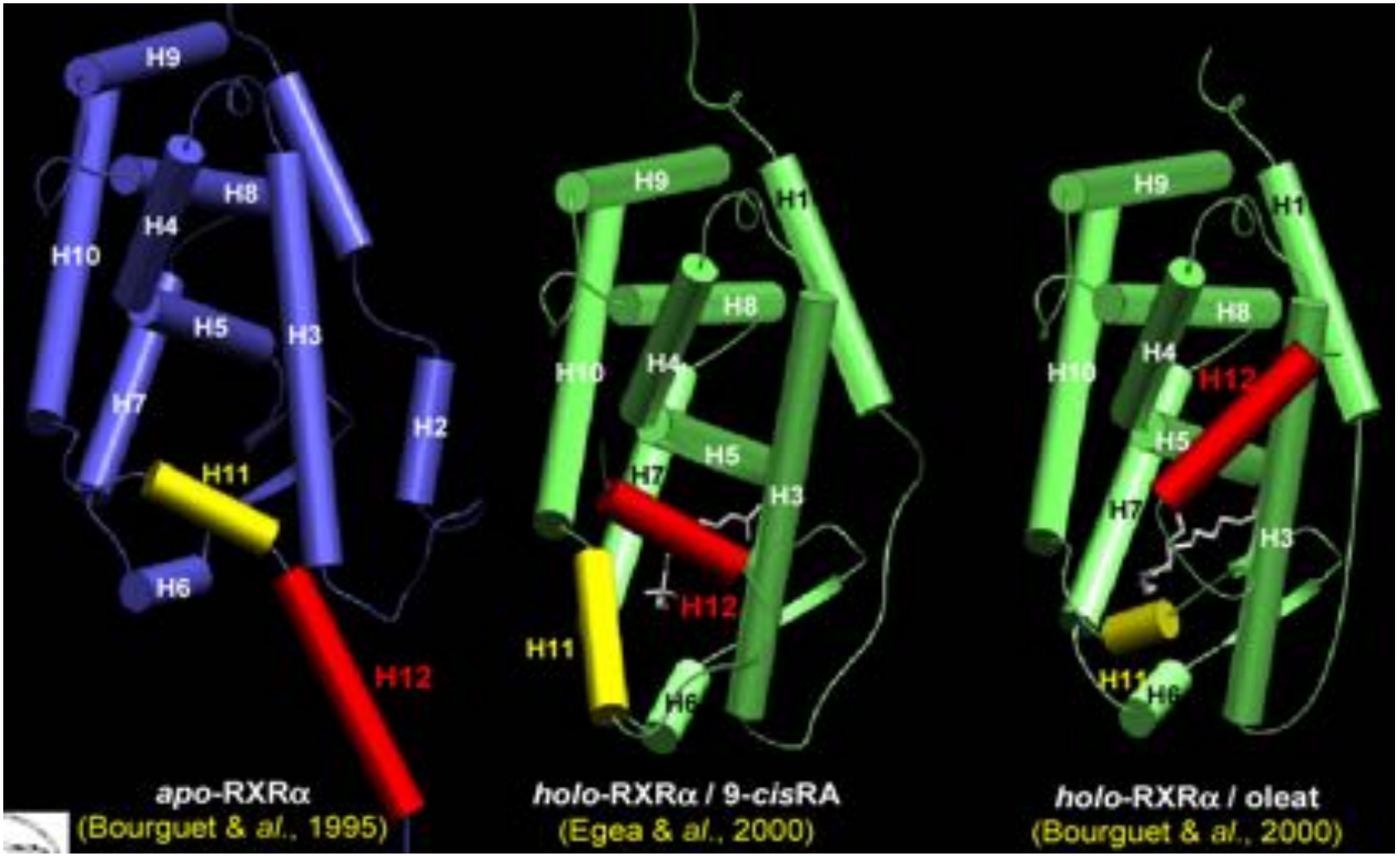






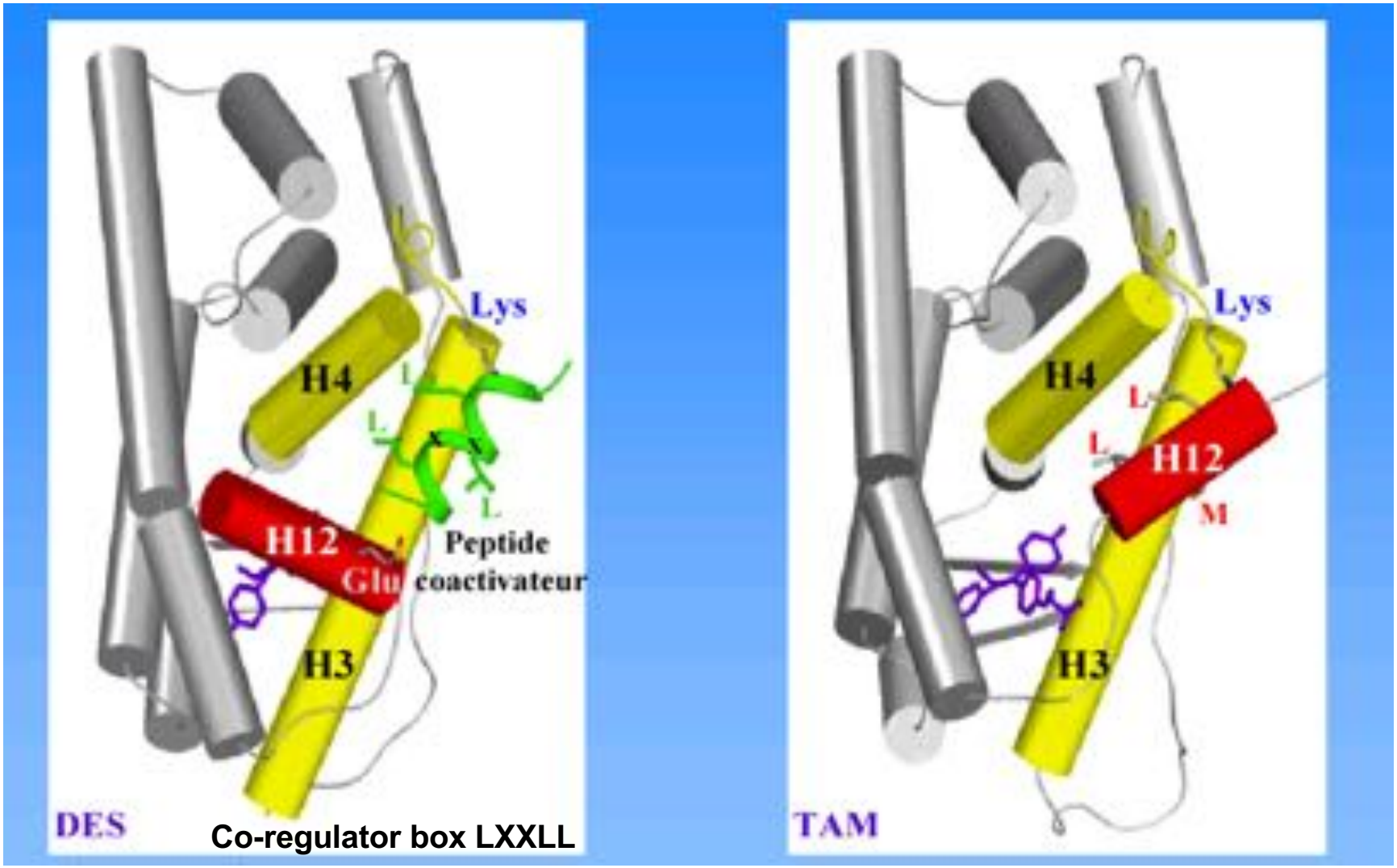
RXRα co-crystal structure assisted modeling

NHRs-dependent cellular-nuclear signaling



unliganded liganded liganded

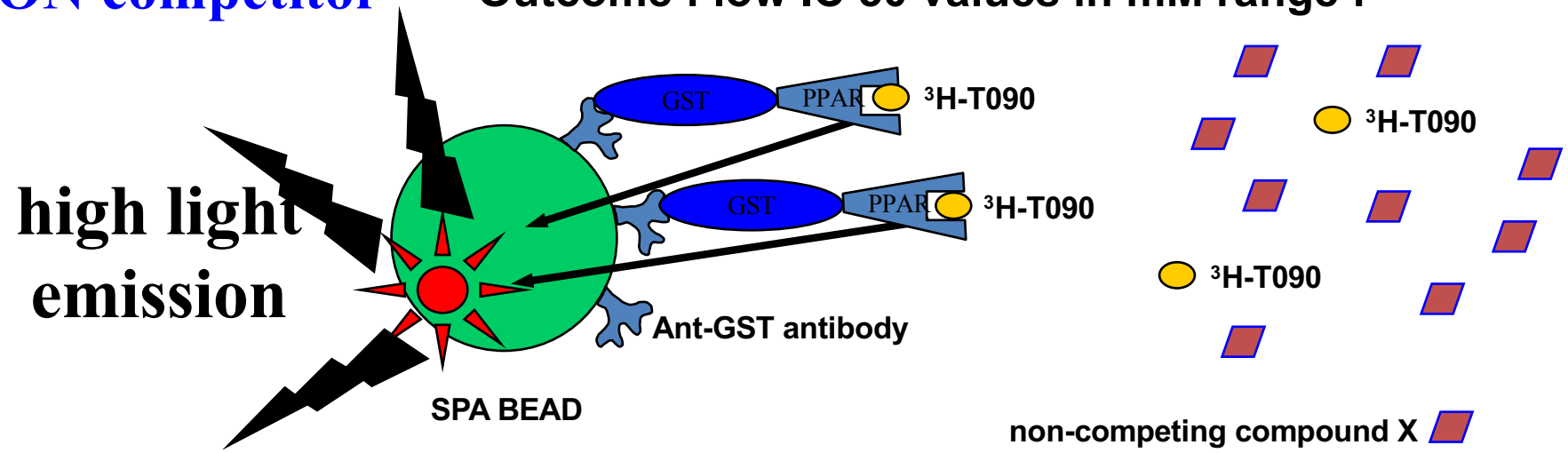
Molecular Bases for Agonism vs, partial agonism vs antagonist: ERα co-crystals



Primary biochemical HTS screen : cell free nuclear hormone receptor ligand affinity assay

NON competitor

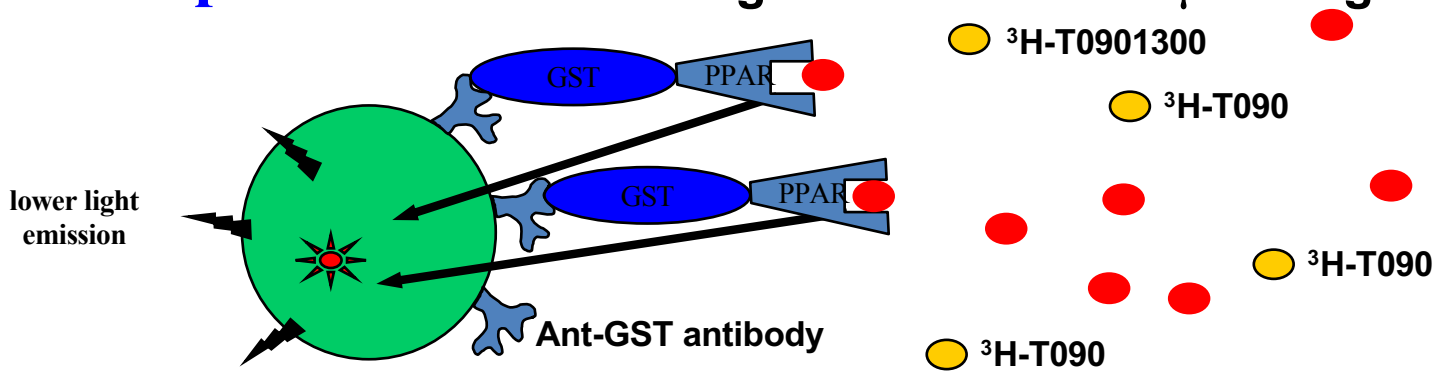
Outcome : low IC 50 values in mM range !



COMPETITION RADIOLIGAND BINDING SCREENING BY SCINTILLATION PROXIMITY DETECTION

GOOD competitor

Outcome : high IC 50 values in μM range !



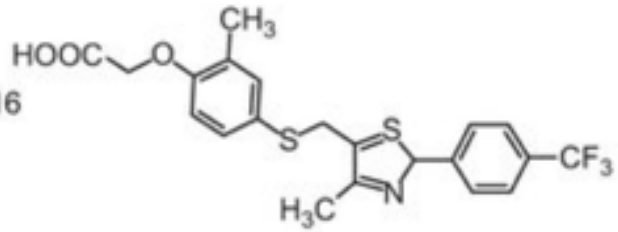
PerkinElmer For the Better

SPA BEAD scintillation proximity assay beads – (release β–particles)

competing compound Y

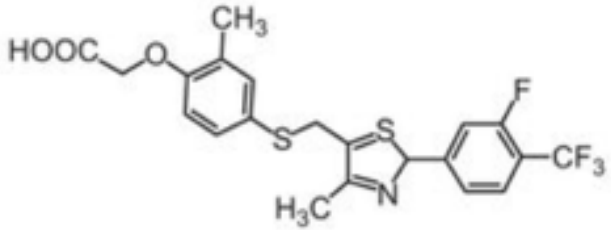
Primary biochemical HTS screen : cell free nuclear hormone receptor ligand affinity assay

GW501516



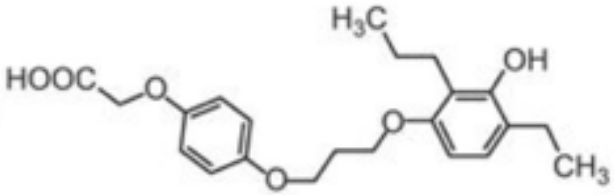
EC_{50} (μM)		
PPARα	PPARβ	PPARγ
1.1	0.001	0.85

GW0742



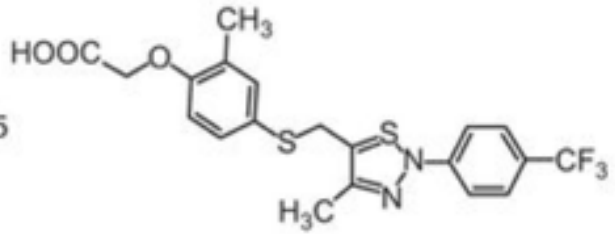
EC_{50} (μM)		
PPARα	PPARβ	PPARγ
1.1	0.001	2

L-165041



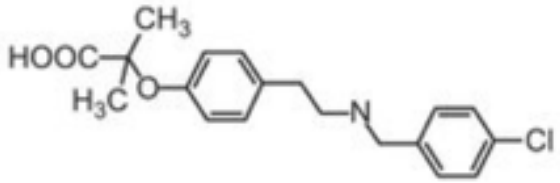
EC_{50} (μM)		
PPARα	PPARβ	PPARγ
10	0.002	>10

MBX-8025



EC_{50} (μM)		
PPARα	PPARβ	PPARγ
>10	0.002	>10

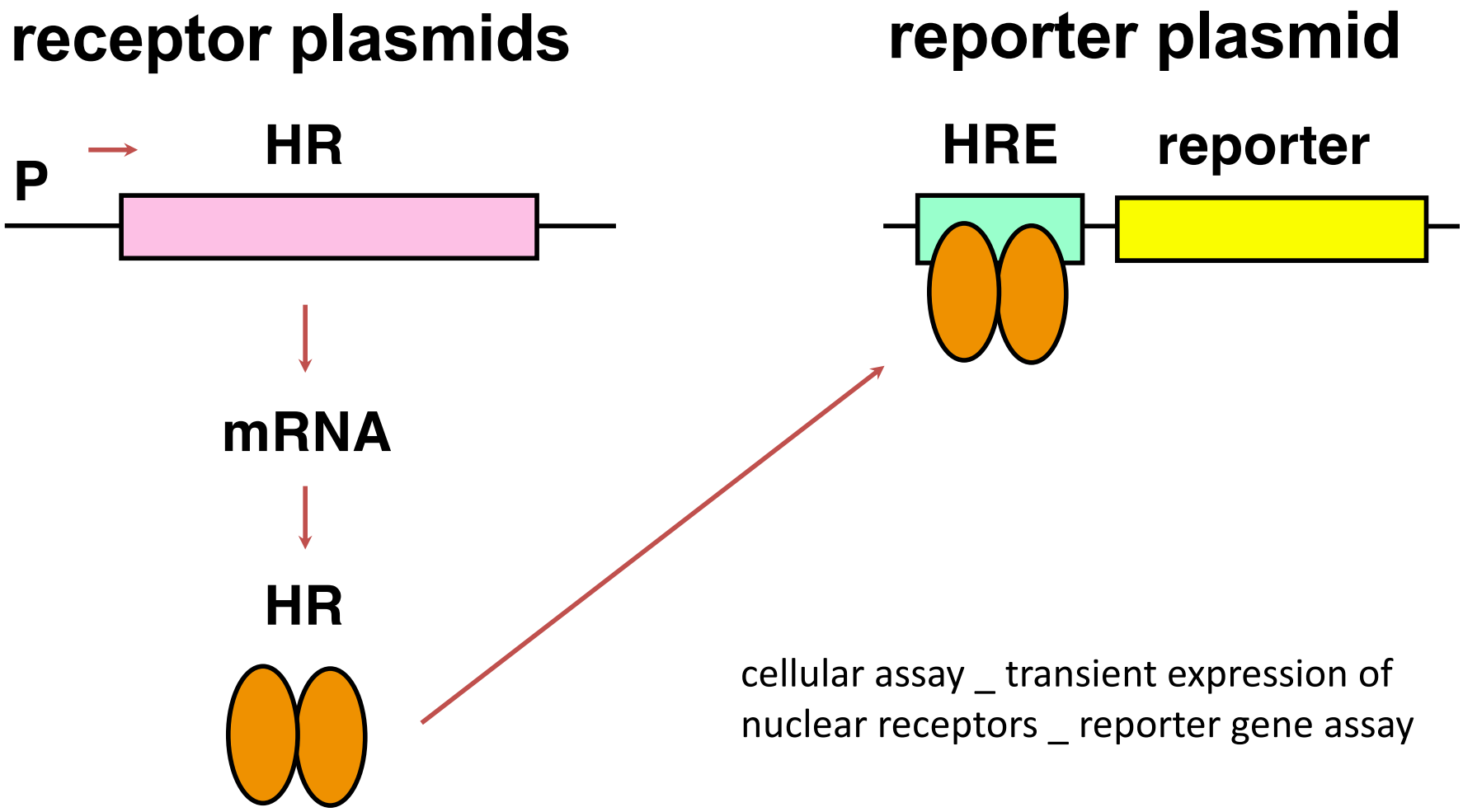
Bezafibrate



EC_{50} (μM)		
PPARα	PPARβ	PPARγ
50	20	60

Secondary LTS screen : cell based NHRs screening assay

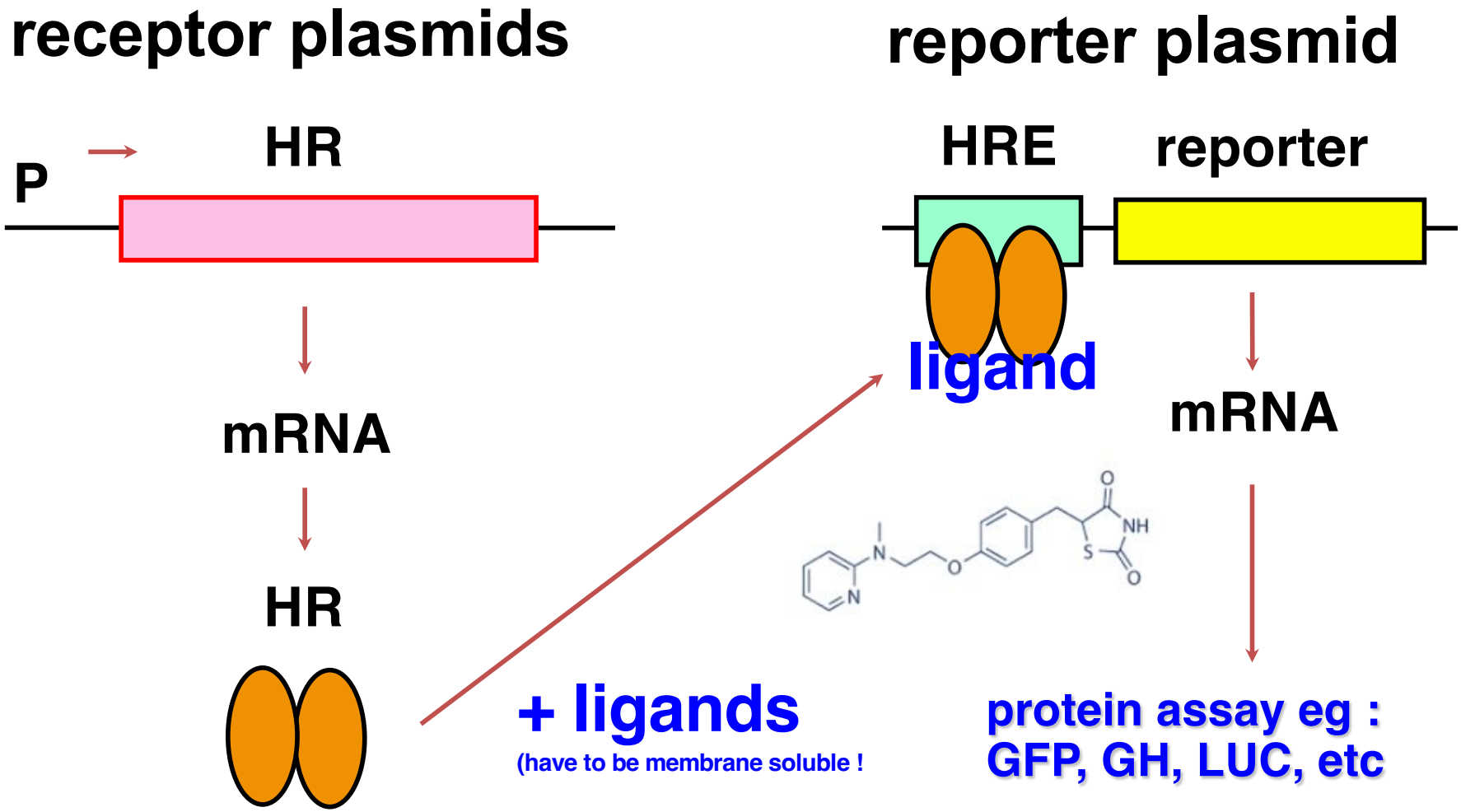
Principle of Transactivation Assay
(nuclear proteins)



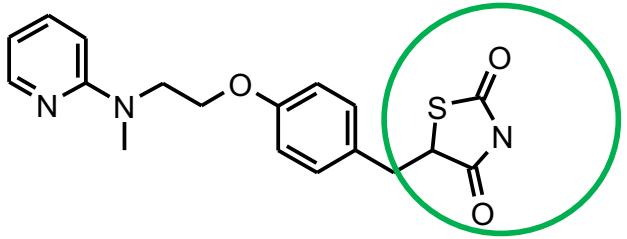
cellular assay _ transient expression of nuclear receptors _ reporter gene assay

Secondary screen : cell based NHRs screening assay

Principle of Transactivation Assay II (EC50 values)
(nuclear proteins !)



Competitive medicinal chemistry : «me too» compounds - time to market

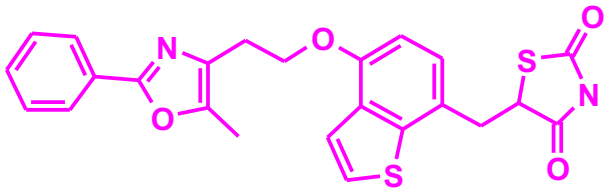


2-4 Thiazolidinedione controversial head piece in PPARγ

Rosiglitazone (Prototypical PPARgamma Agonist)

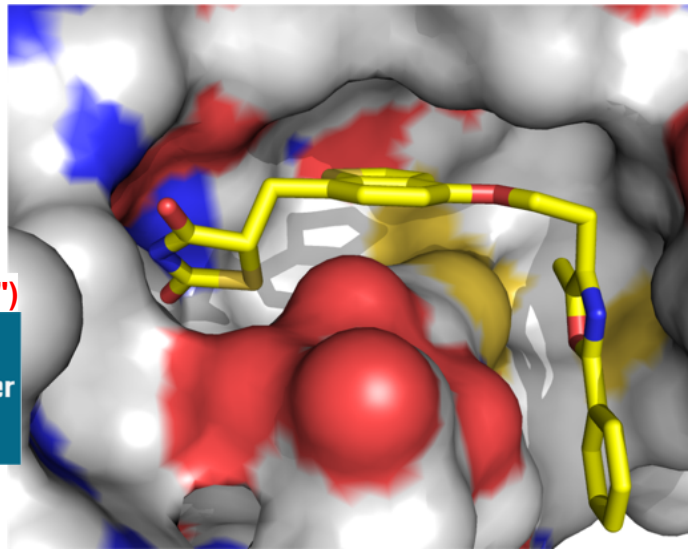
GSK

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



Edaglitazar

Boehringer Inc

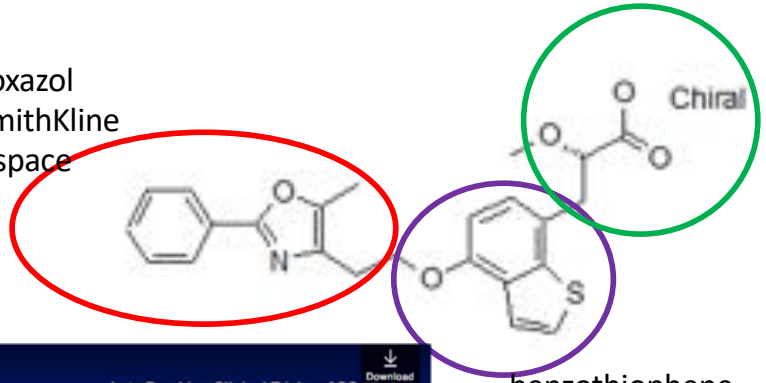


Replacement of thiazolidinedione controversial head piece in PPARγ

IC_{50} α/γ/δ [nM]	35 / 66 / 21
EC_{50} α/γ/δ [nM]	53 / 32 / 444 (22%)

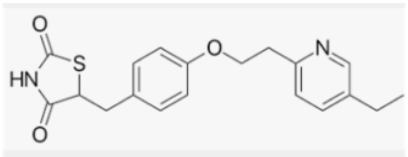
***In vitro* Activity**

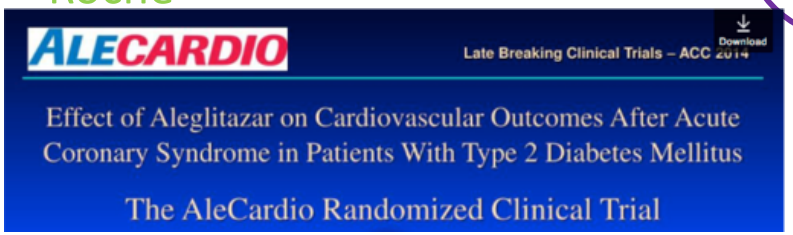
Phenyloxazol GlaxoSmithKline patent space



Aleglitazar

Roche

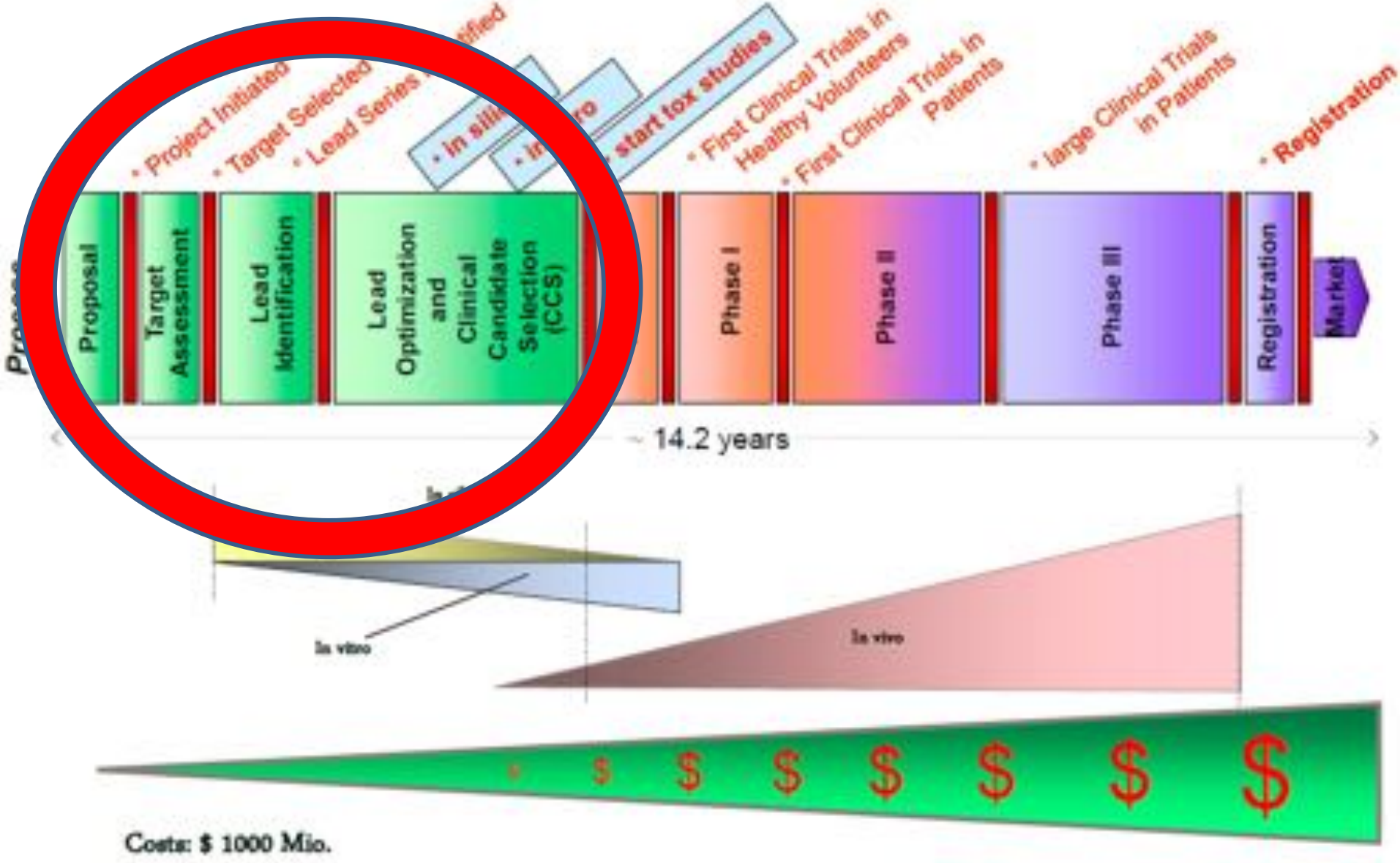




benzothiophene Boehringer Manheim patent space

Early steps/assessment across the value chain : from „hits“ to lead compounds

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



A pharmacological model of insulin resistance

-/- wt

obese (ob/ob) leptin mice pharmacological model are obese, hyperphagic, hyperglycemic and hyperinsulinemic (insulin resistant). They are commonly used as animal pharmacological models for developing diabetes medicines

Type II diabetes animal pharmacological screening cascade

Cynomolgus monkey
Acute (3 hr.)
Glucose / Insulin

4 day p.o
Glucose
Insulin

4 day p.o
TG

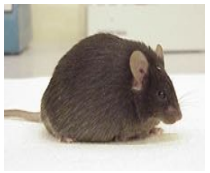
7-10 day p.o
Glucose, Ins, TG

7-21 day p.o
Lipid profile

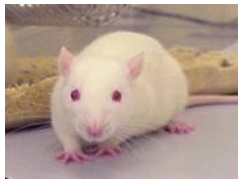
Dose-response

OGTT

Clamp



dbdb

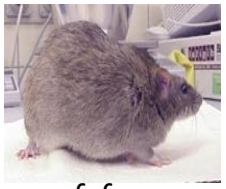


SD Chol

ZDF

ZDF

ZDF



fafa

Hamster

> - 40%

† TG

> - 30%

† HDL

>SUs

† Hypoglycemia
Rebound & duration

> -40%

† Efficacy
cf TZD/class best

>-30%AUC

GIR

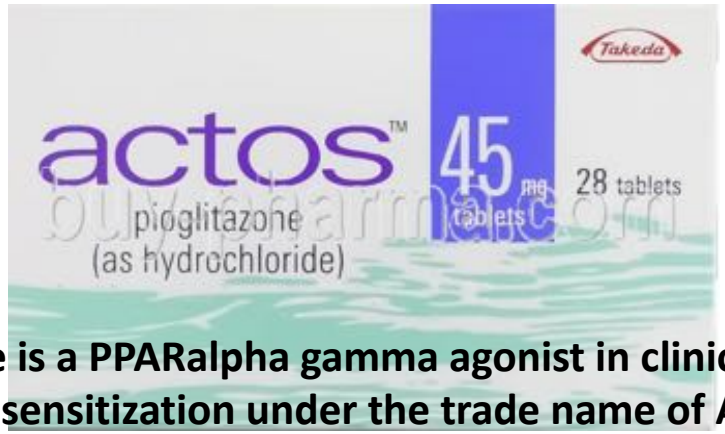
† Insulin sensitivity

† LDL

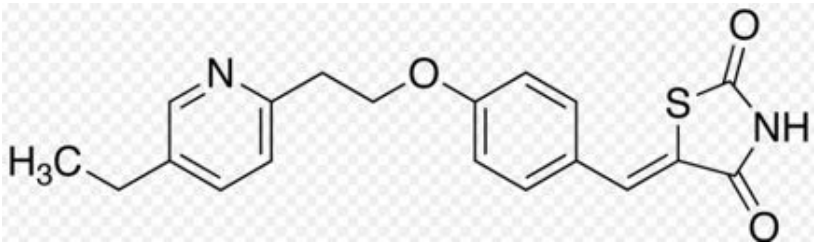
Only the combination of several critical animal pharmacological models may predict the therapeutic value of an innovative medicine in future first-in-human clinical settings/trials

Knock out, Knock in, TG animal models to reduce the amount of protein/RNA in the disease animal pharmacological model

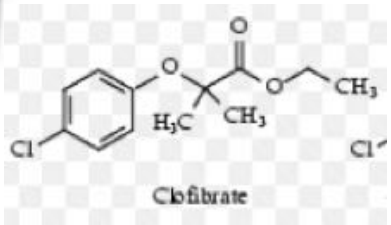
PPARs and insulin sensitization and lipid disorder

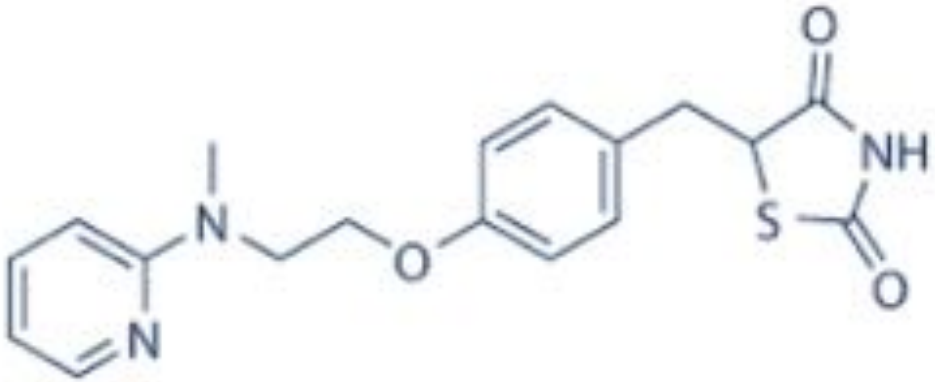


pioglitazone is a PPARalpha gamma agonist in clinical use for insulin sensitization under the trade name of Actos



rosiglitazone is a PPARgamma agonist in clinical use f insulin sensitization under the trade name of Avand





Type 2 diabetes develops as a consequence of the metabolic syndrome diabetes is also known key risk factor for developing severe/fatal COVID-19

Diabetes itself is pandemic just like COVID-19 is pandemic :
two pandemia that did clashed - looking at the underlying molecular mechanisms
overactivity of the immune system - cytokine storm and more

Nature News July 21. 2023

Is PPARγ polymorphisms associated with an «unthrifty allele» ?

« A DAY WITHOUT UNI SPORT IS NOT A SUCCESSFUL DAY ! «

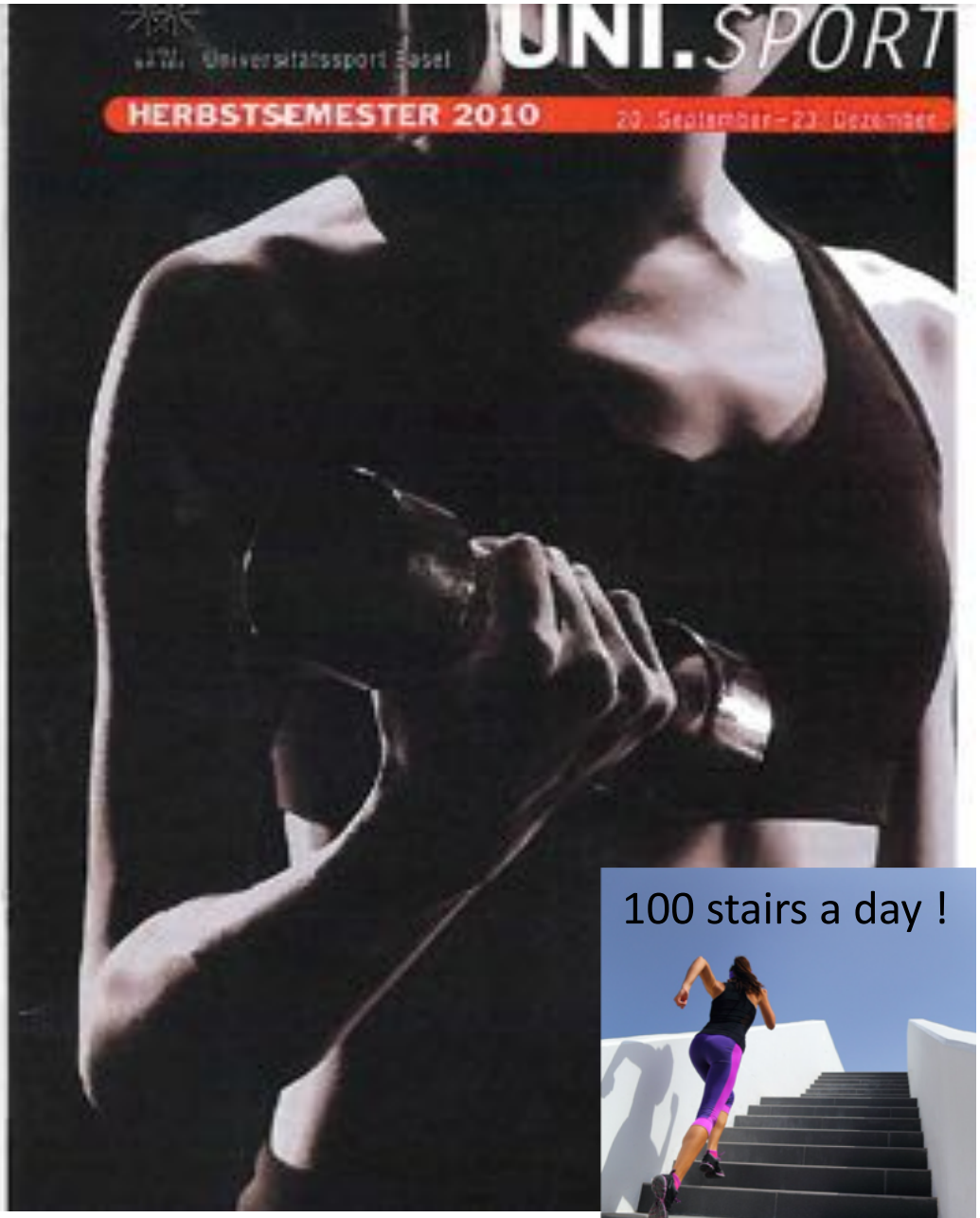
«Sparsame Gene»: Trainiere jeden Tag beim Unisport!

Das Universitätsstudium und insbesondere seine Prüfungen innerhalb bestimmter Fristen sind stressig. Wir sind so mit einem Lebensstil konfrontiert, welcher uns - nicht nur an der Universität - immer mehr geistige Leistungen in immer kurzfristigeren Zeithorizonten abverlangt, wobei wir uns oft nicht mehr ausreichend körperlich aktiv bewegen. Zu dieser Bewegungsarmut gesellt sich oft eine ungesunde Ernährung. Viele Menschen sind daher übergewichtig und entwickeln metabolisches Syndrom mit u.a. erhöhtem Blutzucker, Bluthochdruck und erhöhten Blutfettwerten.

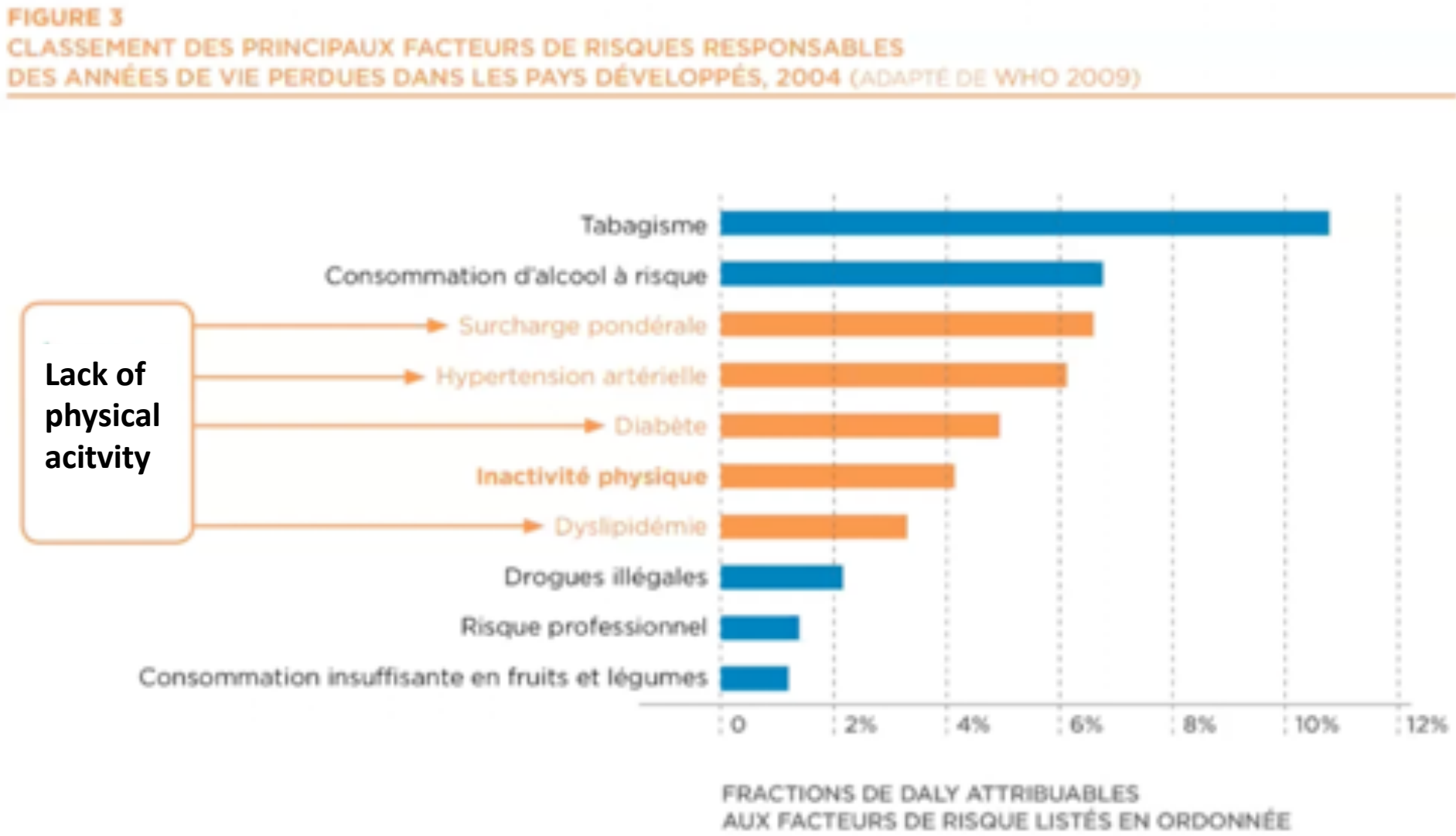
Unser Genom hat sich in Millionen von Jahren entwickelt, in denen Nahrungsmangel herrschte. Der Mensch der Urzeit war ein hoch beweglicher Jäger, der nur selten etwas zum Essen fand. Sein Körper passte sich evolutiv daran an, diese rare kostbare Energie in seinen Geweben dank der "sparsamen Gene" zu speichern. An den erst seit wenigen Jahrzehnten herrschenden „plötzlichen" Überschuss an sehr kalorienreicher Nahrung und die mangelnde körperliche Bewegung heutzutage, konnte sich unser Genom noch nicht anpassen. Um das empfindliche Gleichgewicht unserer körperlichen und geistigen Gesundheit zu erhalten, ist es deshalb notwendig, regelmässig sportliche Aktivitäten, die Spass machen, zu betreiben. Auch eine intelligente Ernährung, mit wenig Zucker und gesättigten Fetten, dafür aber reich an Ballaststoffen und Eiweiss, und ein nur moderater Alkoholkonsum, sind notwendig, um unsere "sparsamen Gene" so zu trainieren, dass wir kein metabolisches Syndrom entwickeln. Deswegen gibt es Unisport: um die Balance zwischen Körper und Geheim während dem Studium beizubehalten

Buchen Sie daher jeden Tag einen Sport-Termin im Kalender und profitieren Sie das aussergewöhnliche Sportangebot der Universität! Über 80 verschiedene Sportarten werden im neuen Unisport Programm angeboten. Beteiligen Sie sich aktiv am Unisport. „A day without sport is not a successful day!"

Prof. Dr. Roger G. Clerc
Dozent für Molekularbiologie an der Universität Basel
und Teilnehmer am Universitätssport



Type II diabetes and metabolic syndrome pandemia : best preventive medicine : exercise every day !



Risk factors involved in life expectation reduction in developed countries (loss of lived years) (adapted from WHO 2009)

GLOBAL HEALTH METRICS | VOLUME 396, ISSUE 10258, P1223-1249, OCTOBER 17, 2020

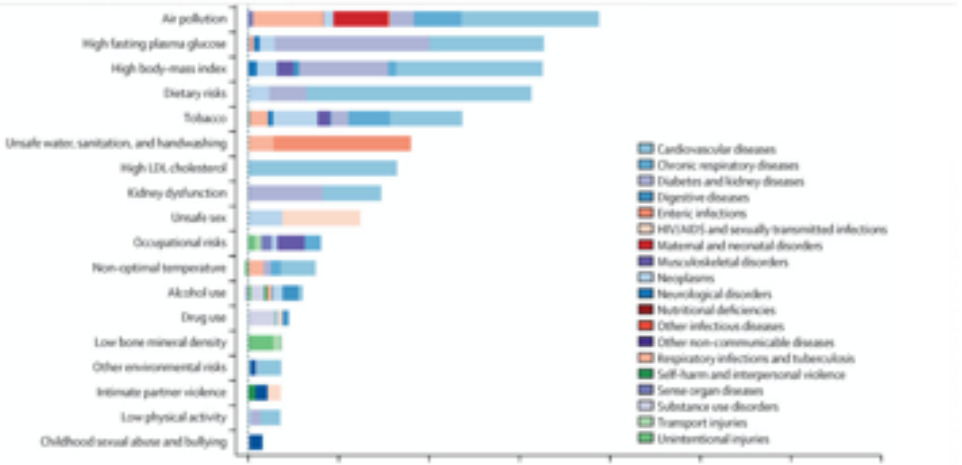
Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019

GBD 2019 Risk Factors Collaborators † • Show footnotes

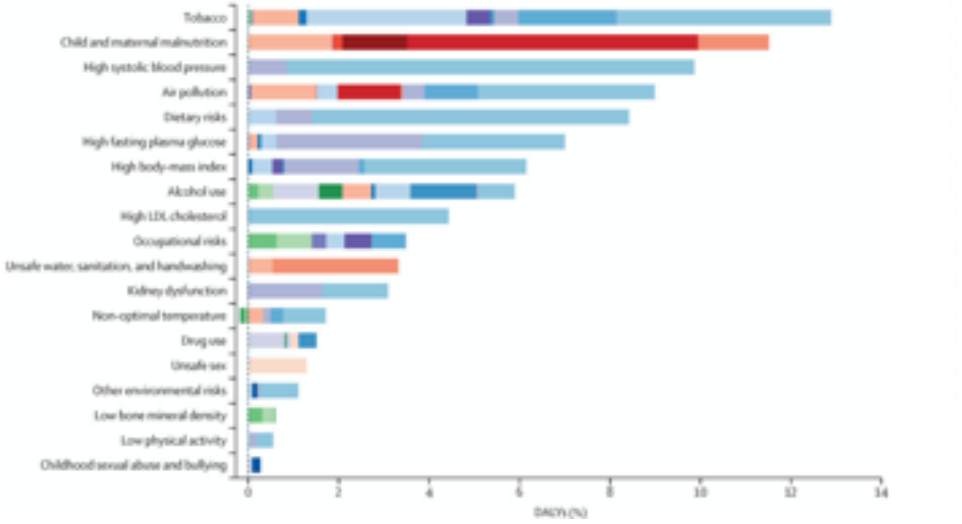
Open Access • Published: October 17, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)30752-2 •

THE LANCET

Global burden of 87 risk factors in 204 countries and territorie...



D Global attributable DALYs from Level 2 risk factors for males in 2019



BENEFITS OF PHYSICAL ACTIVITY : THE SEDENTARITY DISEASES

	ADULTES, TOUS ÂGES
MORTALITÉ, TOUTE CAUSE	Diminution du risque
SANTÉ CARDIOMÉTABOLIQUE	Diminution du risque de maladie cardiovasculaire et de mortalité cardiovasculaire Diminution du risque d'hypertension Diminution du risque de diabète de type 2
CANCER	Diminution du risque de cancer de la vessie, du sein, du colon, de l'endomètre, de l'œsophage, du rein, de l'estomac et du poumon
SANTÉ MENTALE	Réduction du risque de démence Amélioration des fonctions cognitives Amélioration de la qualité de vie Amélioration du sommeil Réduction du risque de dépression
STATUT PONDÉRAL	Effet supplémentaire sur la perte de poids lorsque l'activité physique est combinée avec une restriction alimentaire modérée Perte de poids et prévention de la reprise de poids lorsqu'une quantité suffisante d'activité physique d'intensité modérée à élevée est atteinte.
	PERSONNES ÂGÉES
CHUTES	Réduction du risque de chute Réduction du risque de blessure liée à une chute
CAPACITÉ PHYSIQUE	Amélioration de la capacité physique chez la personne âgée avec et sans fragilités.
	FEMMES ENCEINTES OU EN POST-PARTUM
DURANT LA GROSSESSE	Réduction du risque d'une prise de poids excessive Réduction du risque de diabète gestationnel Aucun risque pour le fœtus lié à une activité physique d'intensité modérée
DURANT LA PÉRIODE DU POST-PARTUM	Réduction du risque de dépression post-partum

Metabolic syndrome : a public health challenge

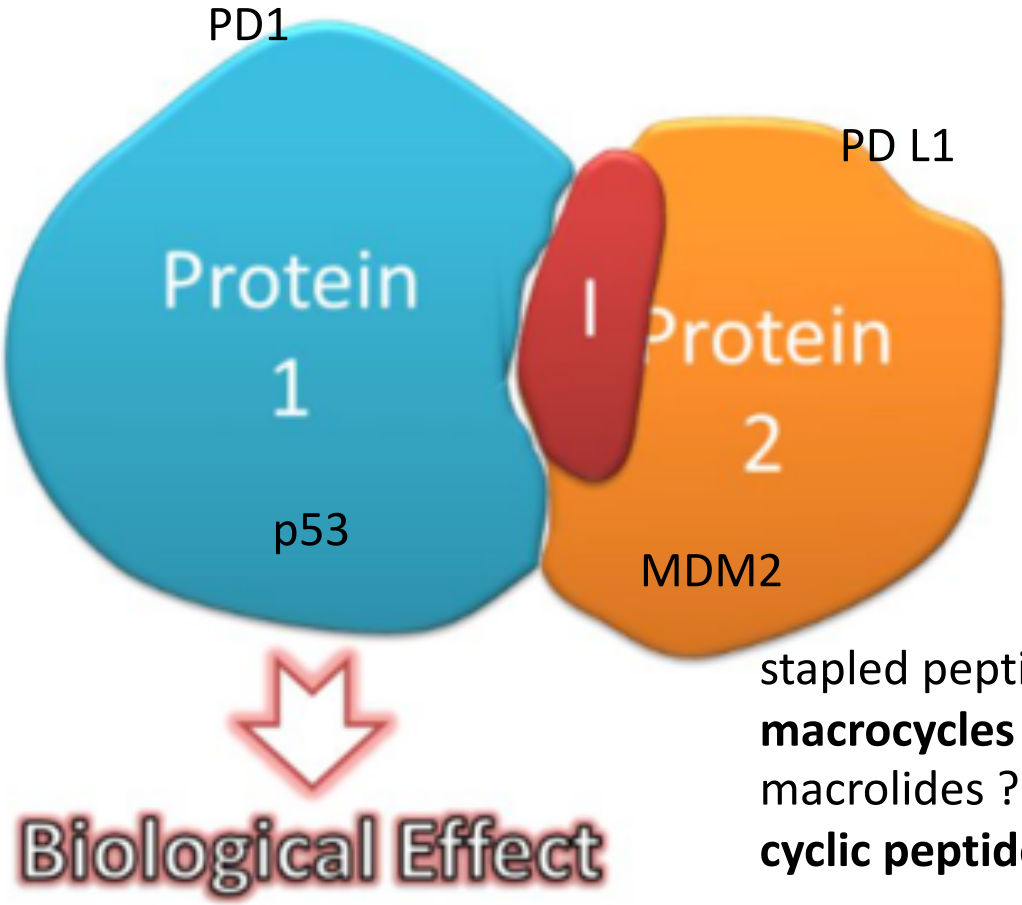
Protein : protein interactions as drug target : flat contact surface with lack of surface groove/pockets

The 'Undruggable?': Inhibiting Protein-Protein Interactions

Protein responsible for biological effect

Effect modulated by protein-protein interaction

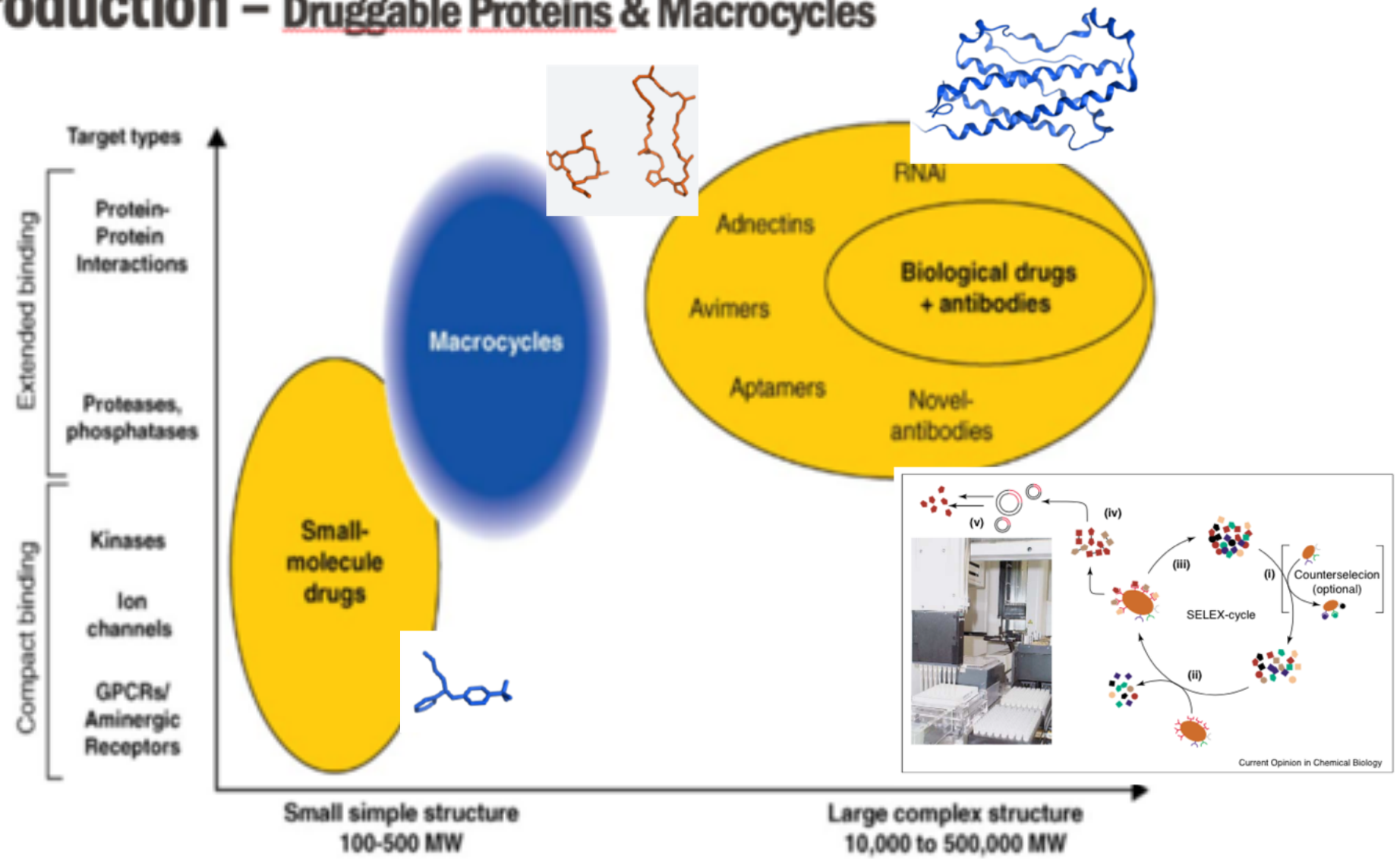
Inhibitor regulates effect by blocking protein-protein interaction



stapled peptides ?
macrocycles ?
macrolides ?
cyclic peptides ?

The druggable space : cyclic peptide therapeutics and macrocycles (medium sized molecules) covers undruggable targets between SMW cpds and biologicals

Introduction – Druggable Proteins & Macrocycles



THANK YOU.....

DO YOU HAVE ANY QUESTİONS ?