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

1,000,000,000 *CHF investment*

7,000,874 *hours of work*

6,587 *experiments*

423 *researchers*

1 *medicine*

Health Hackathon 4.12 & 11.12.2025

THE MAKING OF AN INNOVATIVE MEDICINE

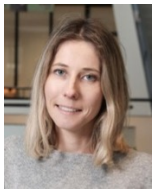
Introductory workshops on translational biomedical research, drug discovery and development

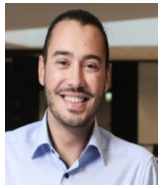
Judge Prof Dr med Olaia Naveiras

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

EPFL

Sciences de la Vie -SV





With Justine Epiney MD PhD cand Mehdi AliGadiri MD PhD cand Prof Roger G. Clerc

The Making Of An Innovative Medicine – class schedule

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

Session 1: **Scope of the course _ general organization _ case study**
11.09.25 *Embracing a career at the heart of biomedical research !?*
CM013

Session 2: **Historical perspective: the modern pharmacy**
18.09.25 *Advent of modern medicines - placebo controlled drug development*
CM013

Session 3: **Introduction to translational research: crossing the bridge**
25.09.25 *A chasm has opened wide between biomedical research and patients in need*
CM013

Sessions 4-5: **Therapeutic target identification I & II**
02-09.10.25 *"me too" vs a wealth of innovative targets _ small MW cpds vs biologicals*
CM013 *Early front loading of biomarker identification for cohort stratification*

Session 6: **Structure based drug design _medicinal chemistry_low/high throughput**
16.10.25 **screening assays_ multiple parallel optimization_ML-powered screens**
CM013 *Setting up screening assays, the robotics, the million cpds librairies*

Session 7: **Therapeutic modalities peptides and biologicals: today's -**
30.10.25 **tomorrow's pharmacy NBEs**
CM013 *Challengies (cost of goods - healthcare payers) and opportunities*

WORKSHOP LISTING - THE MAKING OF AN INNOVATIVE MEDICINE BIO 698-HS2025 in CM013

! NON EXHAUSTIVE LISTING - SUGGESTIONS WELCOME !

sessions		workshops	speaker/s
S02 (18-09-25)			
historical medicines		penicilin: impact, whose invention ?	
hopping on giant shoulders		prozac at the core of psychiatry	
		vaccine discovery:smallpoxJennerTodaymRNAvaccine	Eugenio
		artemisinin and malaria	
		insulin-Banting Best et al. beagle dog	
		slide51-X-ray image DNA--Rosalind Franklin	
		cyclosporin from soil sample to life saver	
S03 (25-09-25)			
translational research		expanding scope of translational therapies	
from bench to bedside and back		chronotherapy,circadian clock,sex,longevity	Solomon
		CAR-T, TCR-T cell therapies in "cold" tumors	
		Y chrom loss in immune cells drives cancer	
S04 (02-10-25)			
therapeutic target identification		th. target identification using a phenocopy screen	Justine
S05 (09-10-25)		rare diseases repurposing medicines ?	Jana postponed
therapeutic target identification		Crispr/Cas9 gene editing huntington disease	
		AI in drug discovery / ML-powered medicine	Lou
		AIDS - Lenacapavir : end of plague ?	
S06 (16-10-25)			
structure based drug design		macrocycles and non druggable targets	Benedikt
		chemoproteomics - NMEs	
		AIDS HIV from deadly virus to chronic disease	
S07 (30-10-25)			
therapeutic modalities - NBEs		therapeutic peptides/incretins et al	
		biologicals on the rise MABs medicines	Eleni
		RNA therapeutics, antisense medicines	
		Wnt pathway - PROTACs vs molecular GLUEs	
S08 (06-11-25)			
PHC personalized healthcare		BRCA1/2 preventive surgery/tumor board	
Human genomics		4P medicine - GWAS - CTCs PHC	Frederico
		disease enabling biomarkers/micro RNAs	
		AZ-biomarker BD-tau yet still no curative drug	
		centenarian host isoallo-LCA bile acid bacteria	

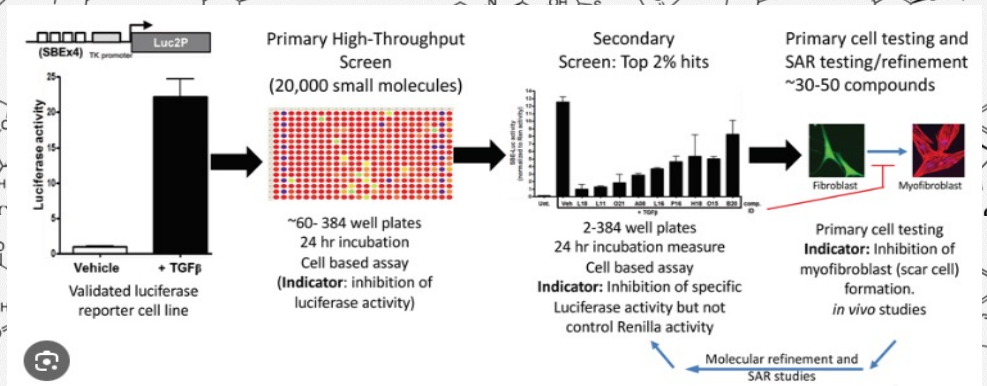
Workshops
The Making Of An Innovative Medicine
(today's class)

Prof O Naveiras

Prof J Shukry

Session 6 – Drug design : 90% of today's medicines are issued from medicinal chemistry

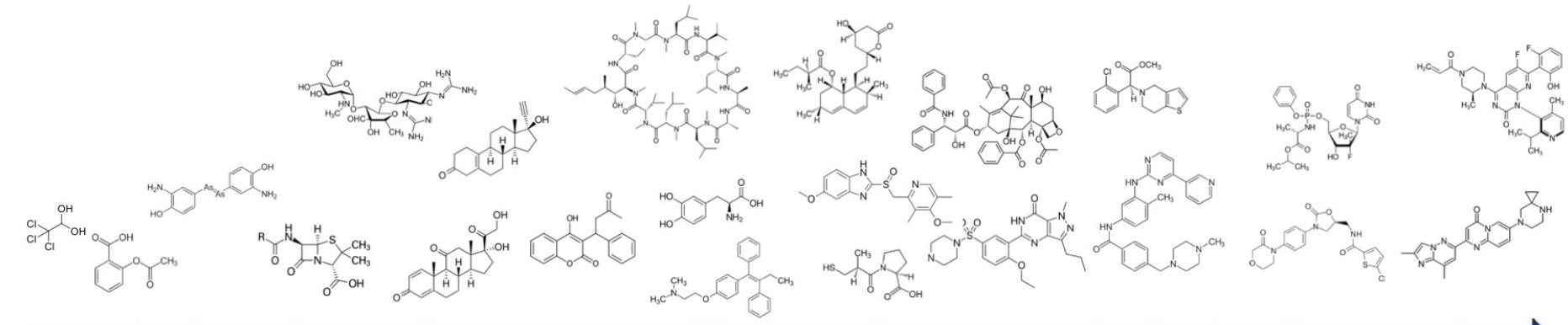
- High throughput cpd screens HTS : from hit to lead

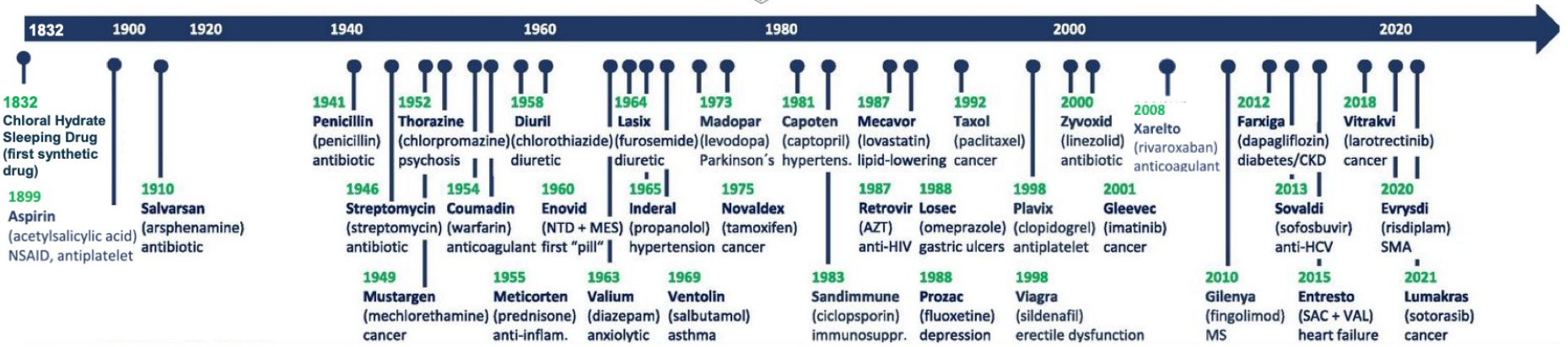


- Medicinal Chemistry : in silico screen, structure activity relationship (SAR – QSAR model) and drug design by MDO

- Protein:protein interactions

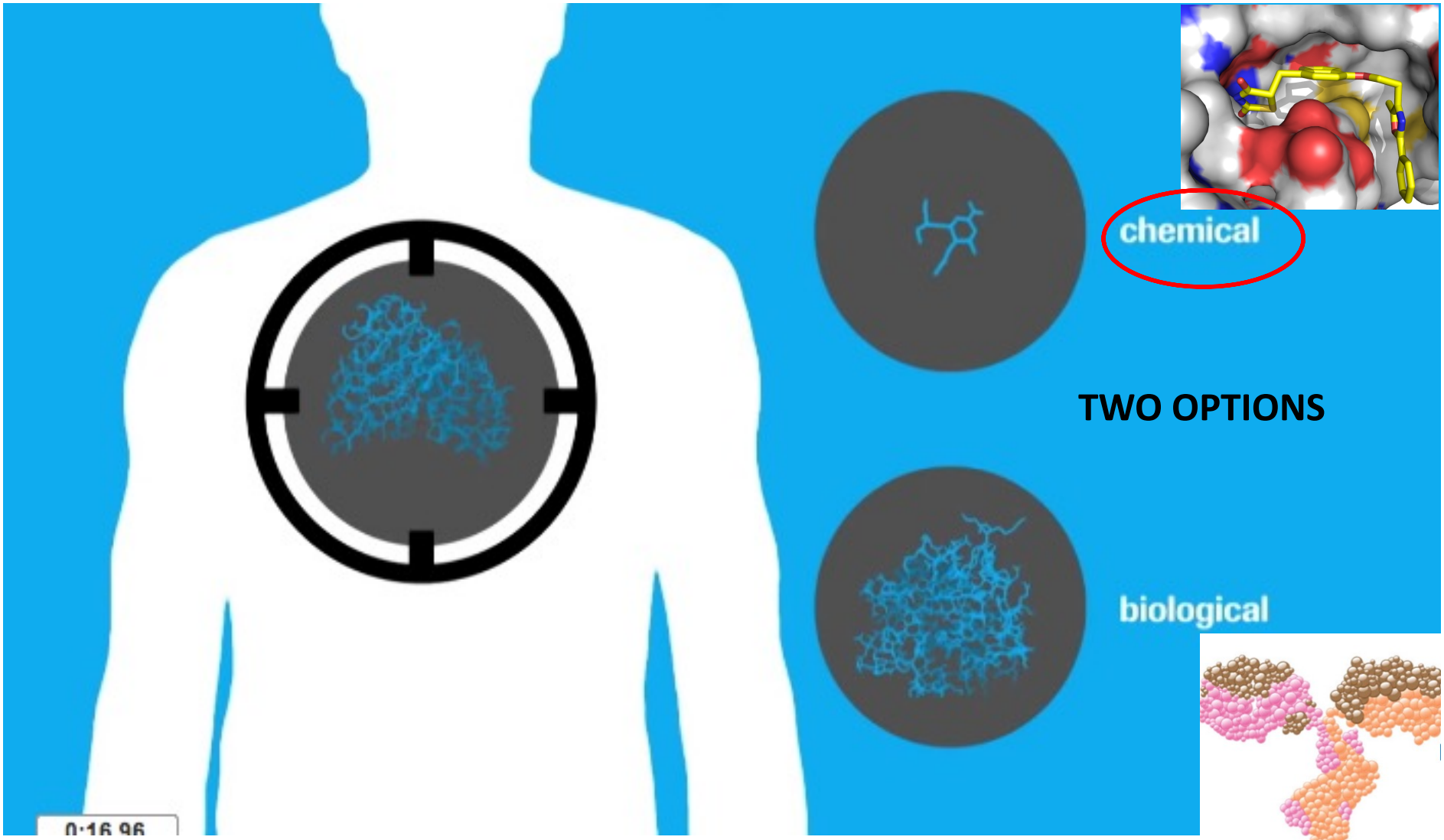
Medicinal chemistry : long and successful story from 20th century on





H. Beck, M. Härter, B. Haß, C. Schmeck, L. Baerfacker, *Drug Discov. Today* **2022**, *27*, 1560-1574.

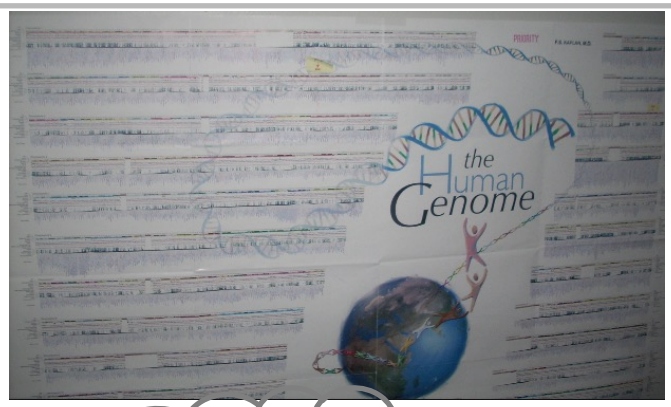
Adressing a novel therapeutic target : small MW chemical cpds versus large biological moieties : what's best ?



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

The Making Of An Innovative Medicine: From Idea to Medicine

HTS involvement



PRECLINICAL

POC

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

TARGET IDENTIFICATION

DRUG CANDIDATE

PRECLINICAL TEST PK/PD-SAFETY

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?

CL

CCS

Is the therapeutic target «druggable» ?

medicinal chemistry (med chem) involvement

~ 1'000'000'000 CHF

~ 10'000 animals

~ 10 years

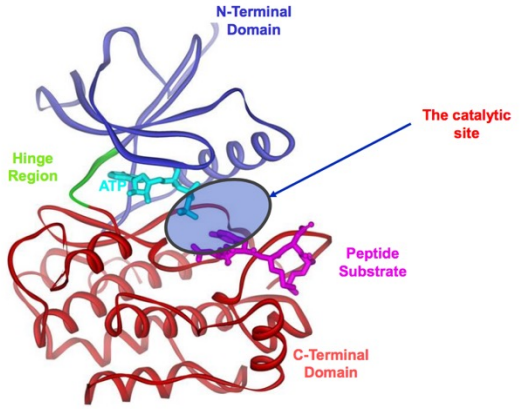
ONE DRUG

~ 1000 patients/ volunteers

~ 6500 expt

~ 450 scientists

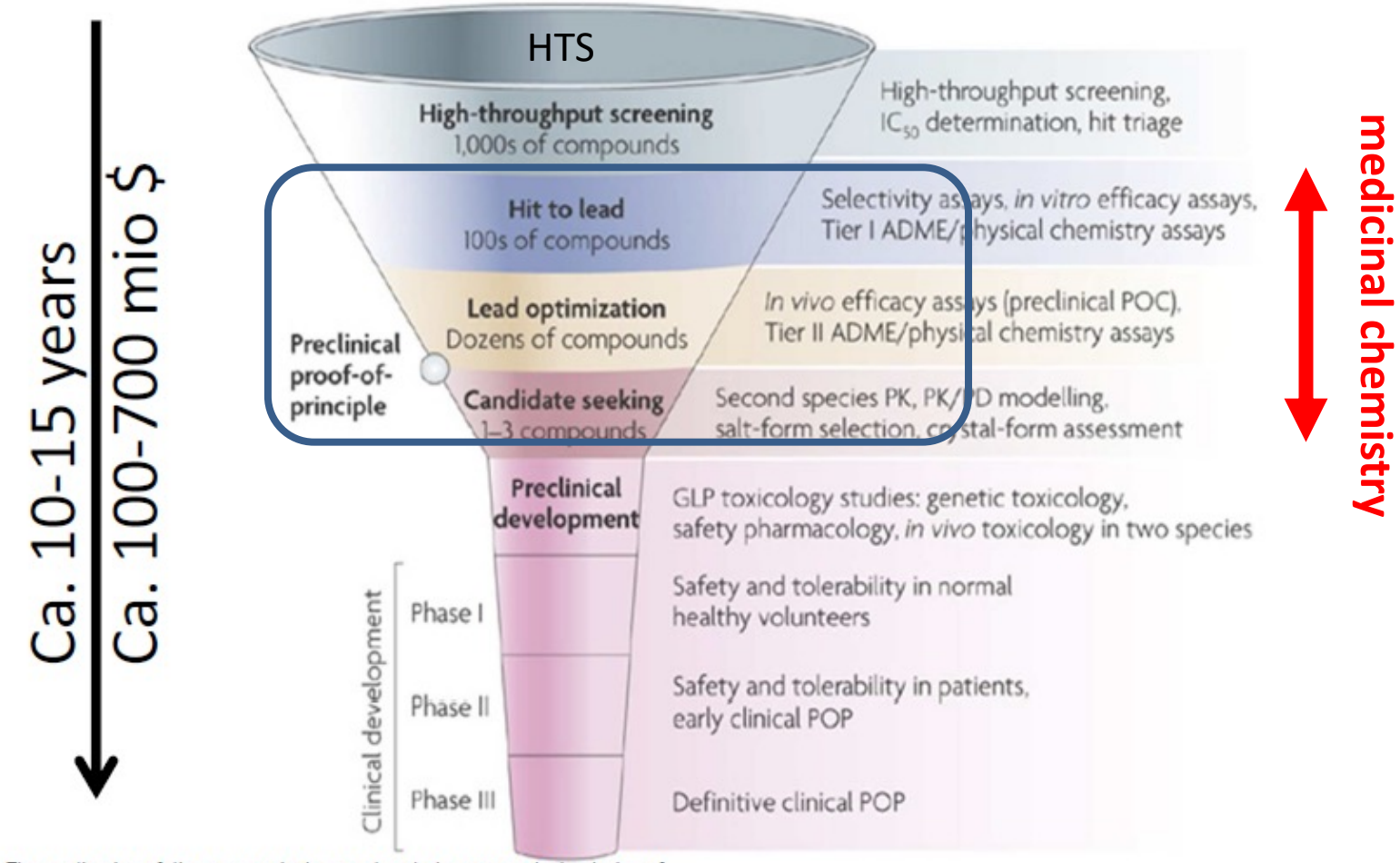
- **SMALL MW MOIETIES TYPICALLY POSSESS <100 ATOMS (MW <500Da) WHICH ENDOW A SMALL OVERALL SURFACE AREA AVAILABLE FOR INTERACTION AND PHARMACOLOGICAL INTERVENTION**



- **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

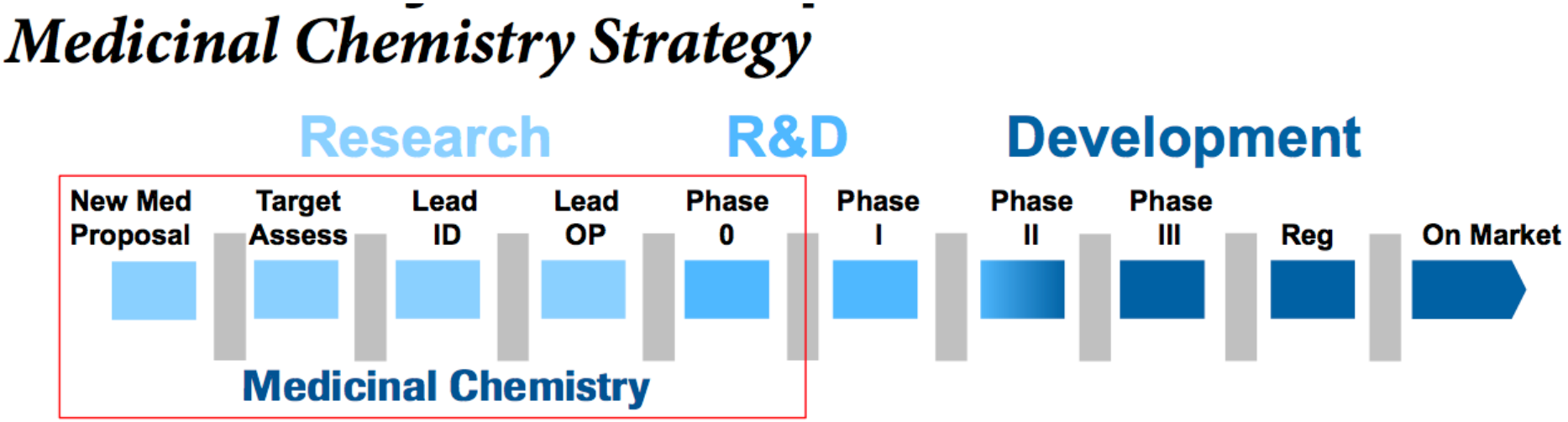
The screening cascade 1:10 000 makes it !



The application of discovery toxicology and pathology towards the design of safer pharmaceutical lead candidates
Jeffrey A. Kramer, John E. Sagartz & Dale L. Morris
Nature Reviews Drug Discovery 6, 636-649 (August 2007)

Nature Reviews | Drug Discovery

Medicinal chemistry step by step

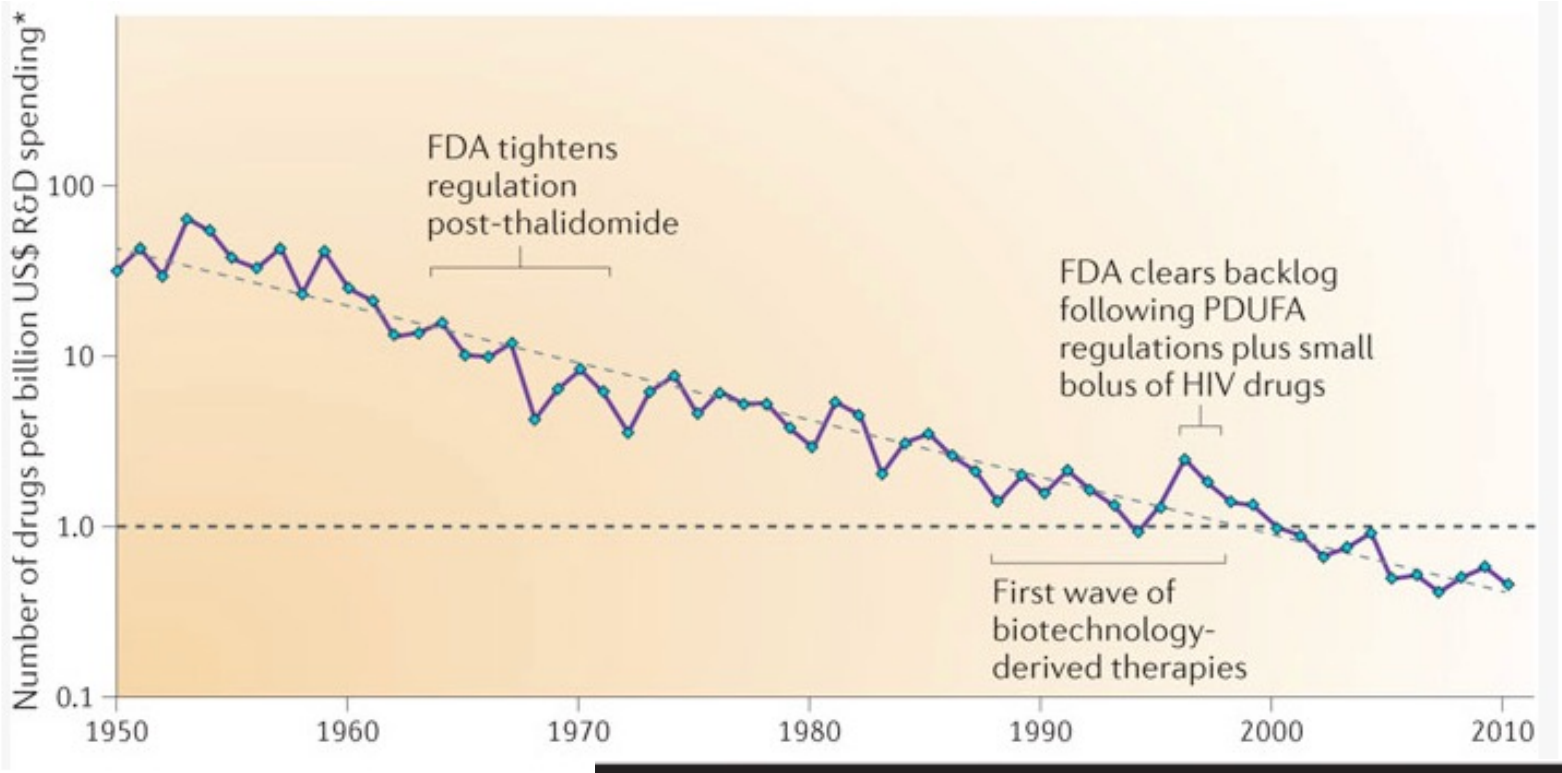


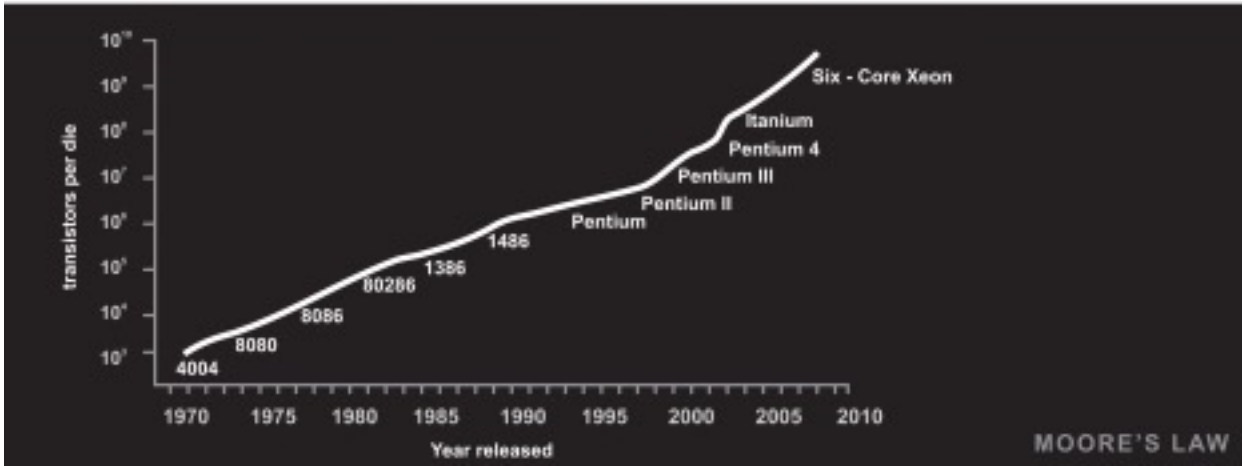
How to reduce pre-screening costs ? $$$

Bai XC. 2015

EROOM'S LAW
MOORE'S LAW

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

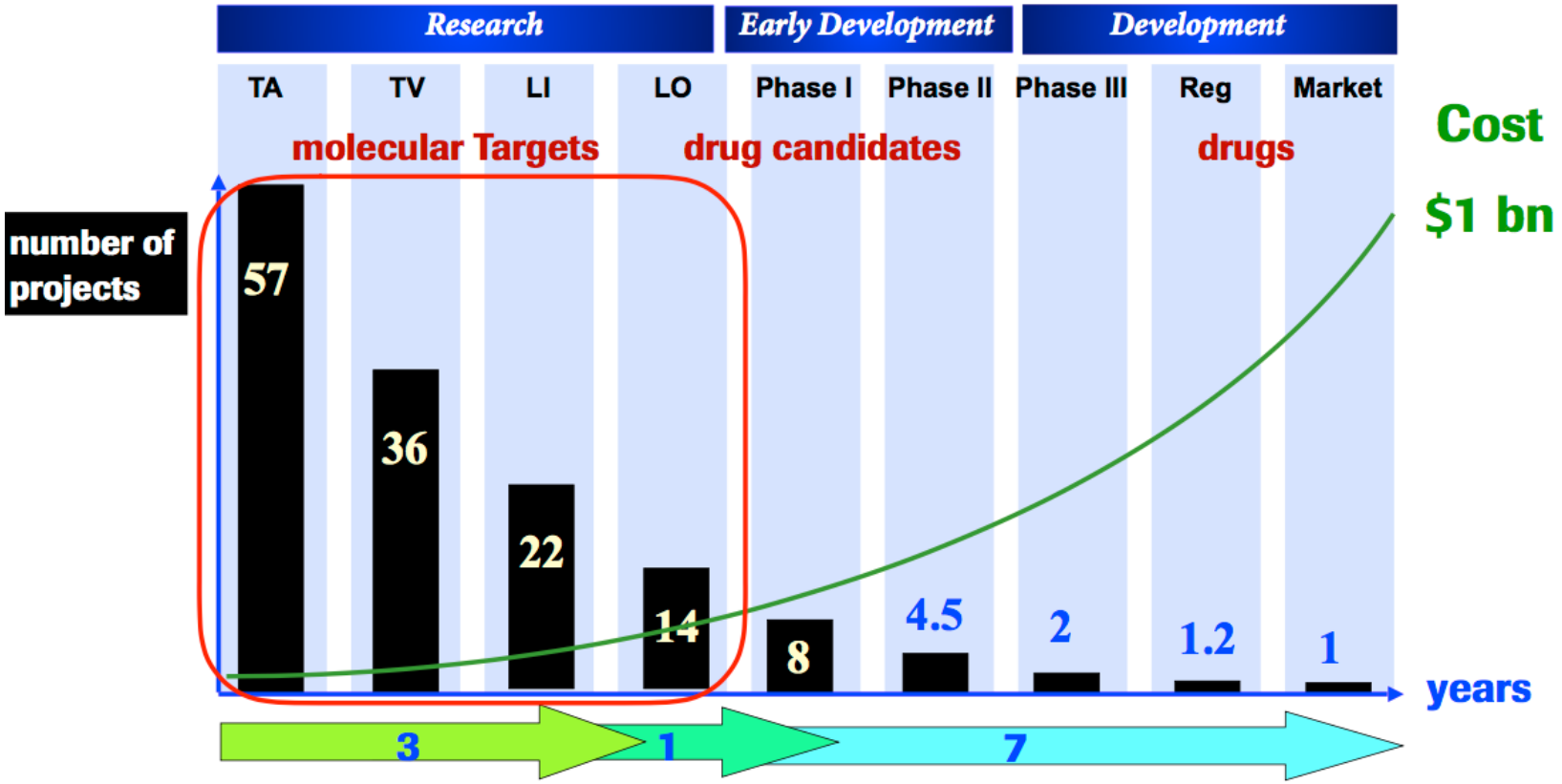




Medicinal chemistry : optimization of the target – a major challenge

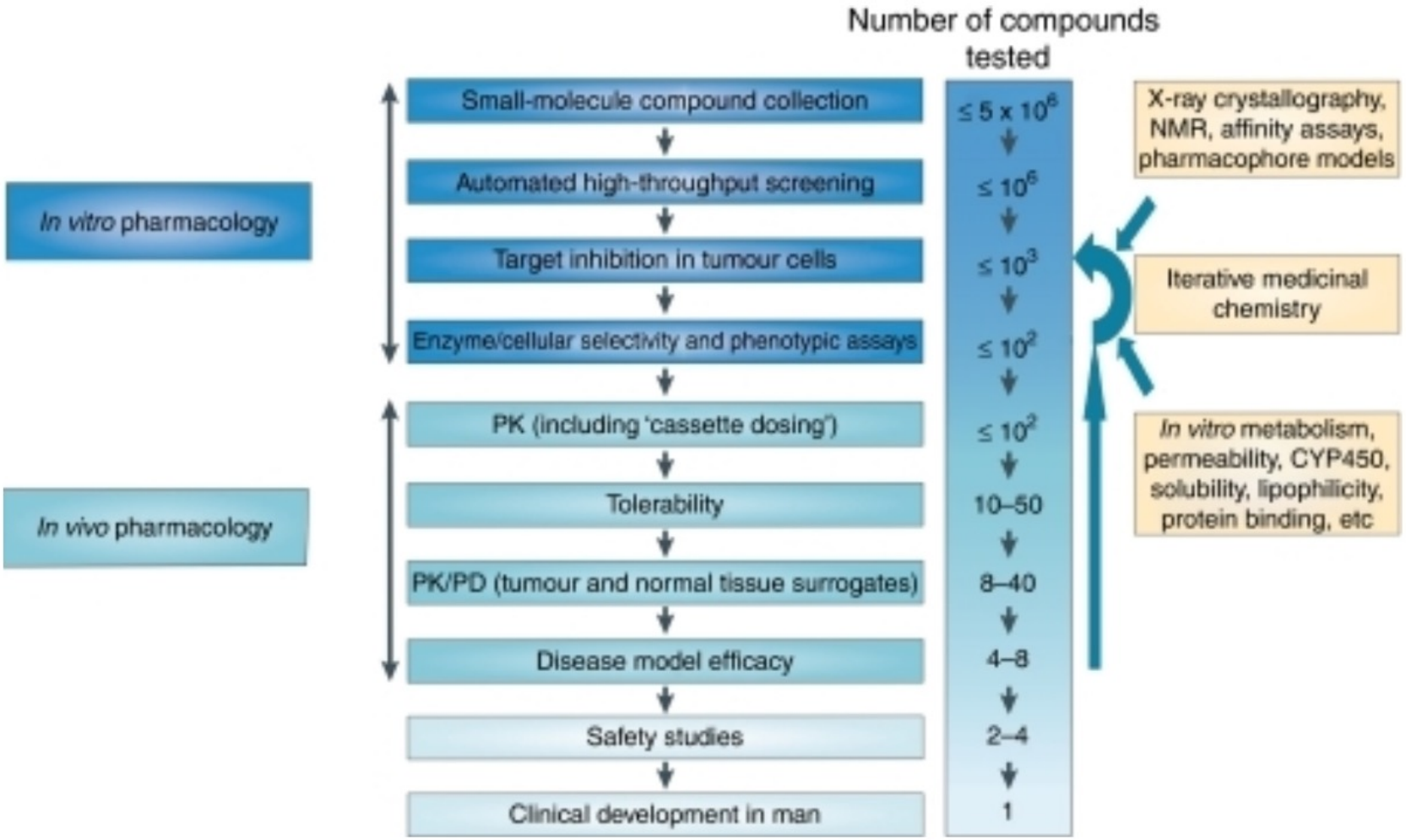
Drug discovery remains a very risky business : as a matter of fact the biggest risk in drug discovery is NOT to get a medicine

Compound optimisation is faced with attrition



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

The screening cascade



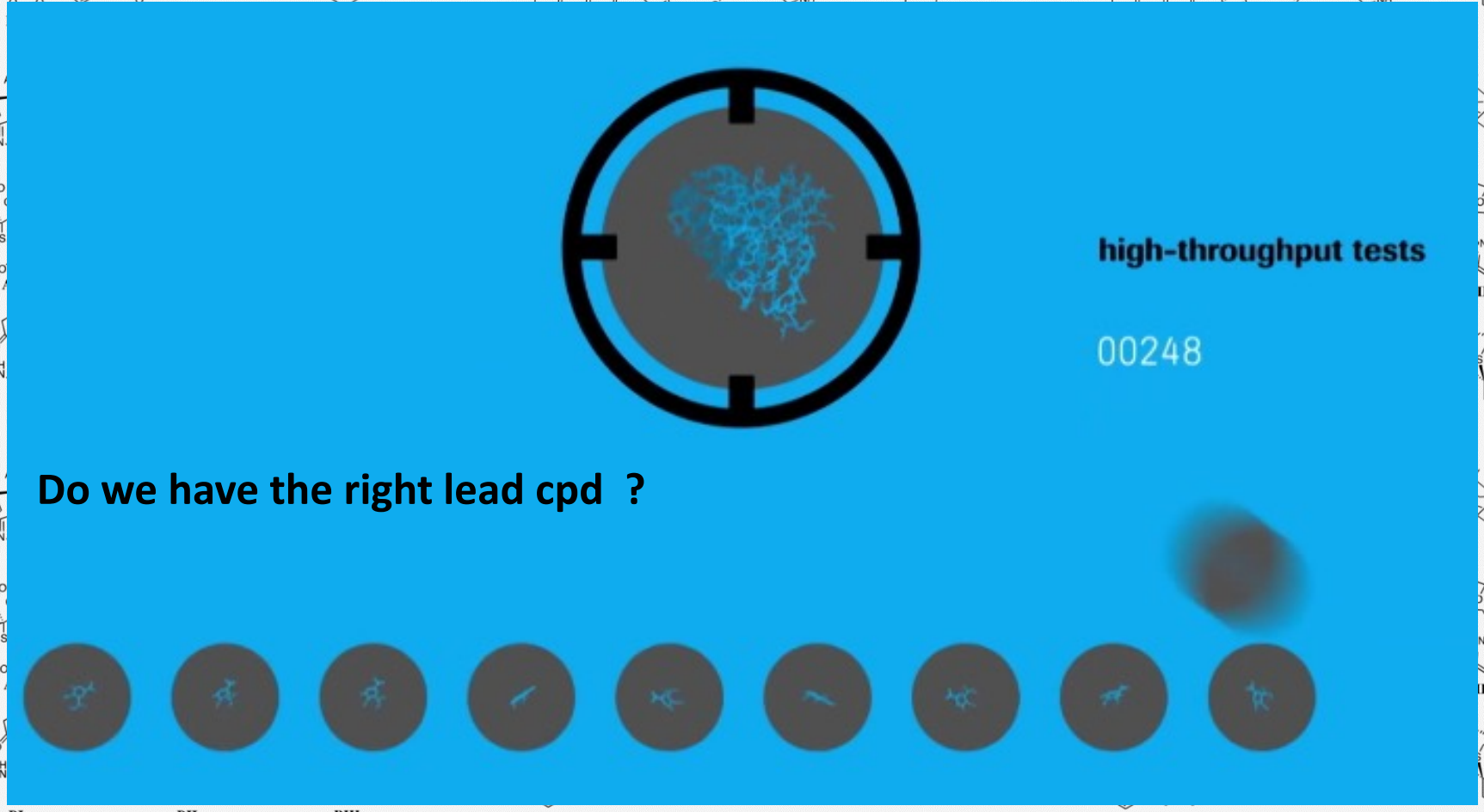
Each druggable therapeutic target class its drug type : SMCs, macrocycle, «glue» moiety, bIologics and more

- **Druggable proteins**
  - What kind of drug types / modality do you know?
    - Small molecules, macrocycles, biological drugs & antibodies
      - Small molecules (600 - 1'500 / 3000 disease modifying genes) [1]
      - Antibodies => restricted to extracellular targets
  - What kind of protein target classes do you know?
    - Receptors, ion channels, kinases, proteases, phosphatases, protein-protein interactions (PPI) [2]
    - Compact & expanded binding sites
    - PPI: 100'000 - 1'000'000 binary interactions [3]
    - Great opportunities for therapeutic intervention

High throughput screening SMCs : 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 ?



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

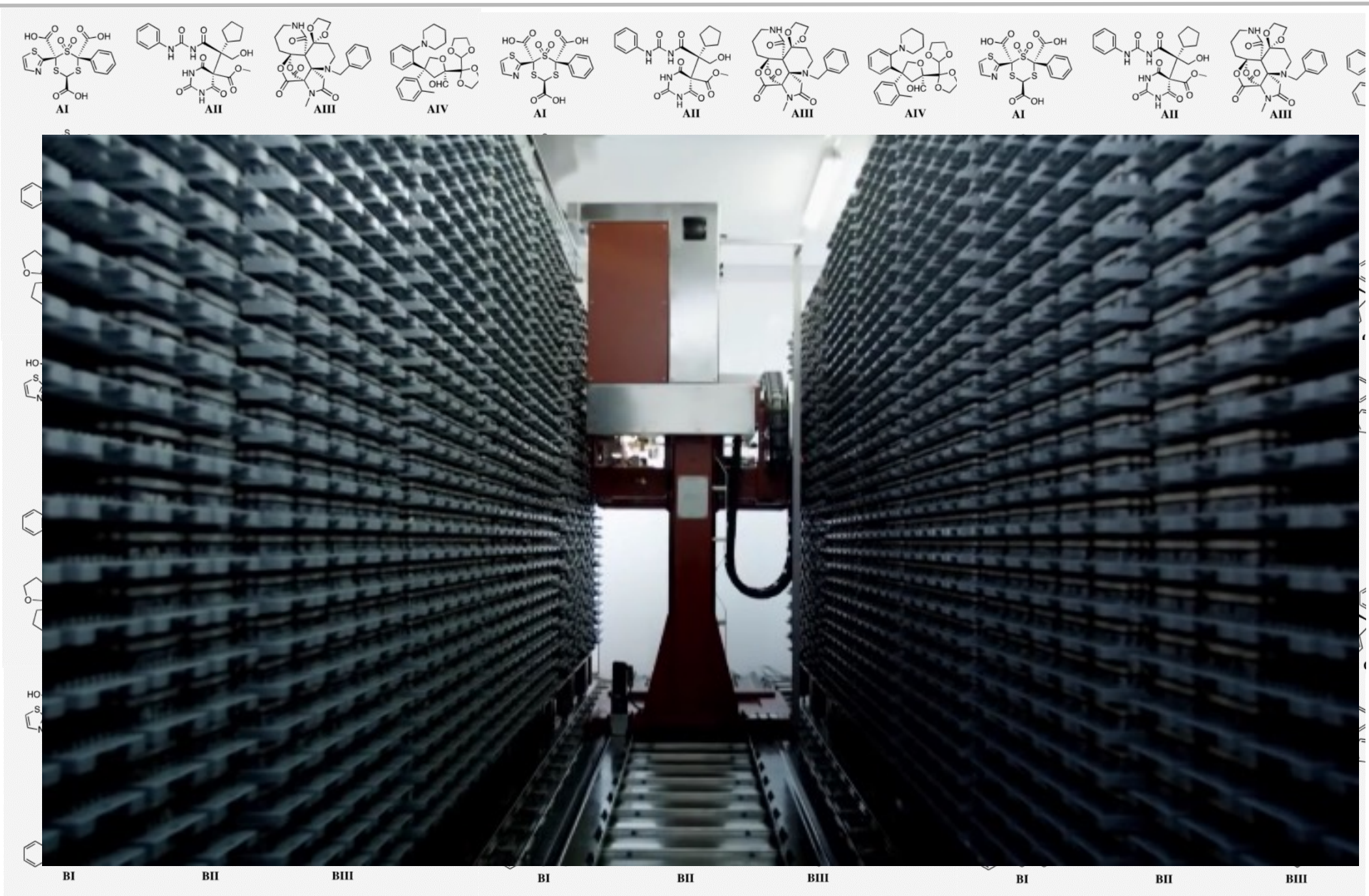
Every day thousands of novel cpds are synthesized and registered in cpd repositories

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 SEVERAL MILLIONS 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

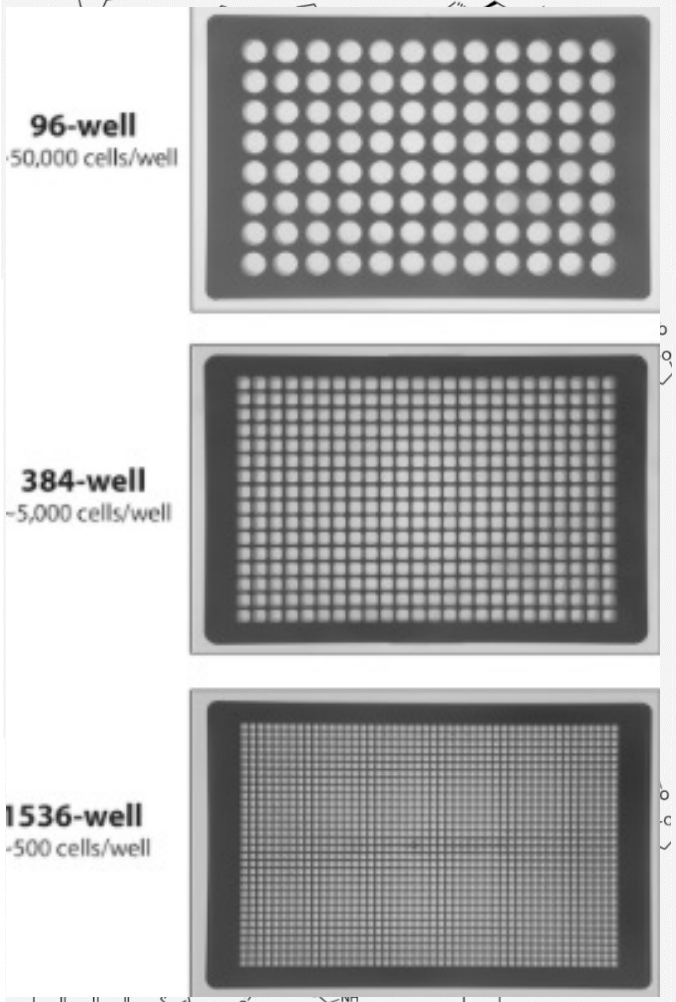
Hit confirmation at single dose, followed by DRC and potency

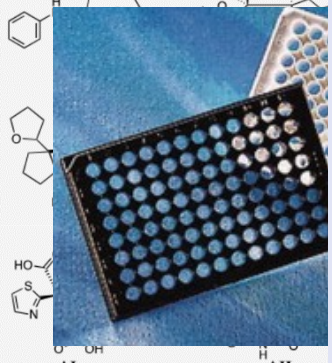
High throughput screening assays formats for all season : miniaturization (2-10 µl – 1536 wells) means cost effective HTS

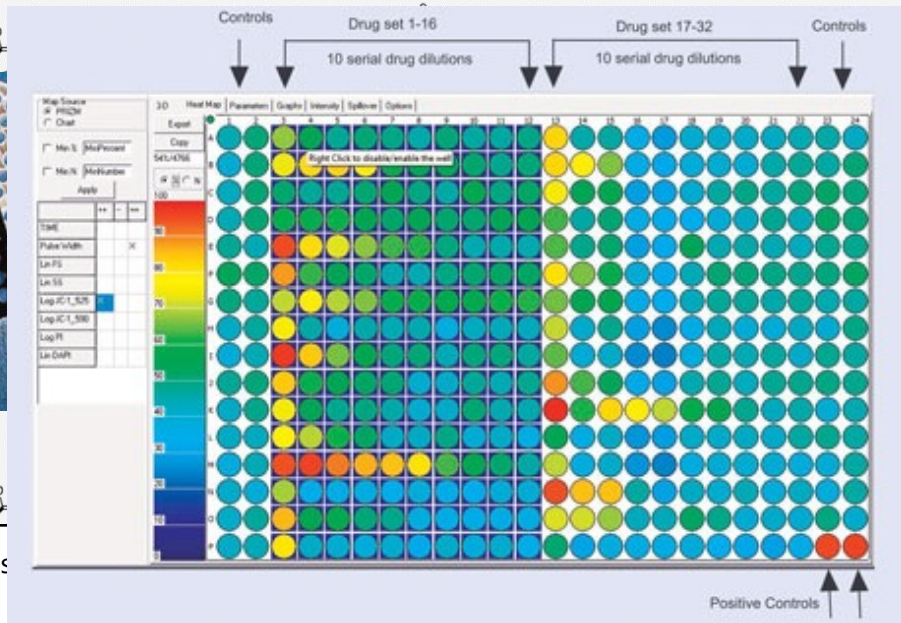
High throughput screen (HTS) : agonist/antagonist to the therapeutic target

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

Below layout of a 384 plate with controls !







Nous ne pouvons pas

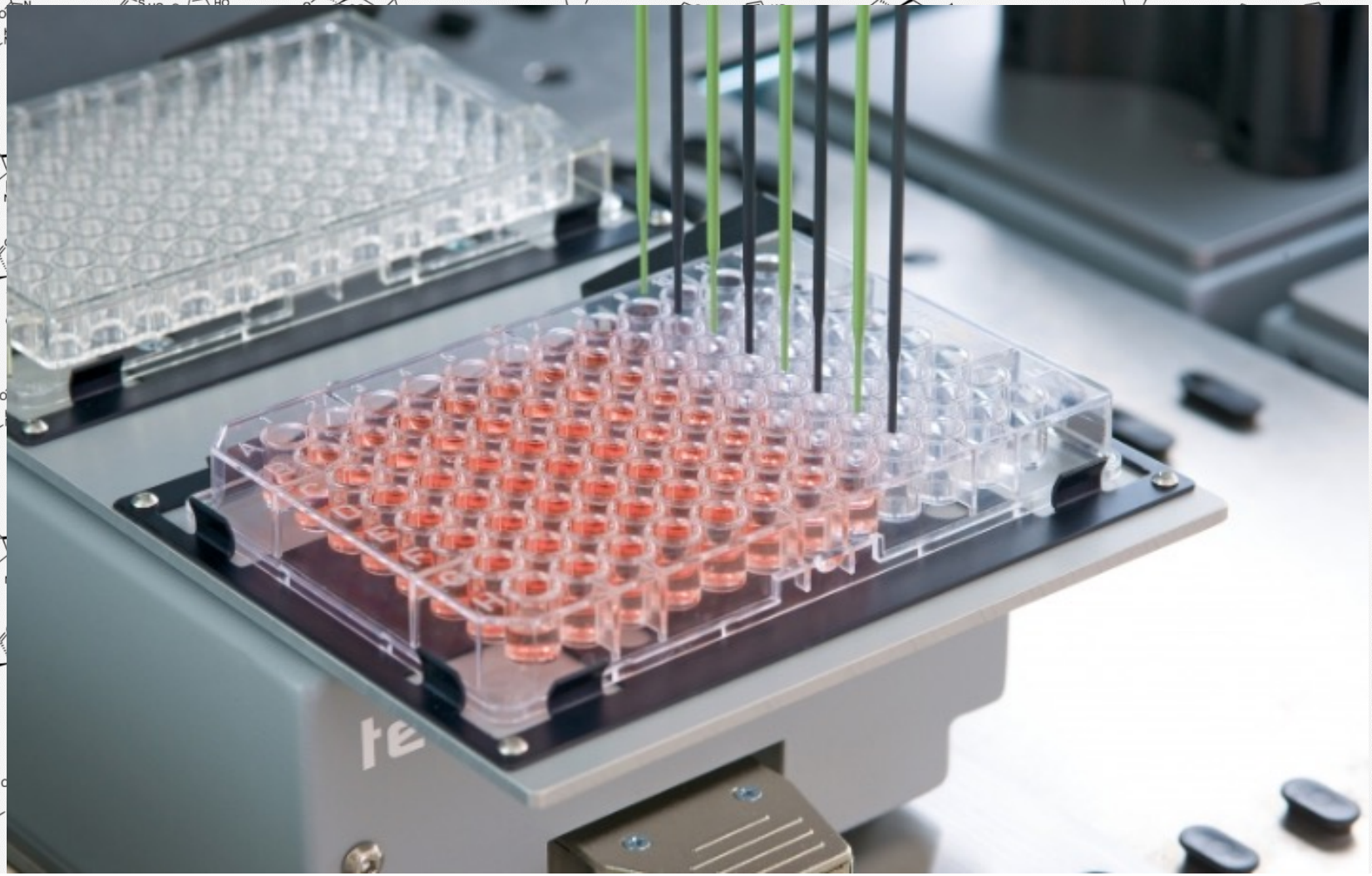
Finding the perfect match: most novel medicine design starts with an HTS (eg TECAN «Freedom EVO platform») see video on robotics

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

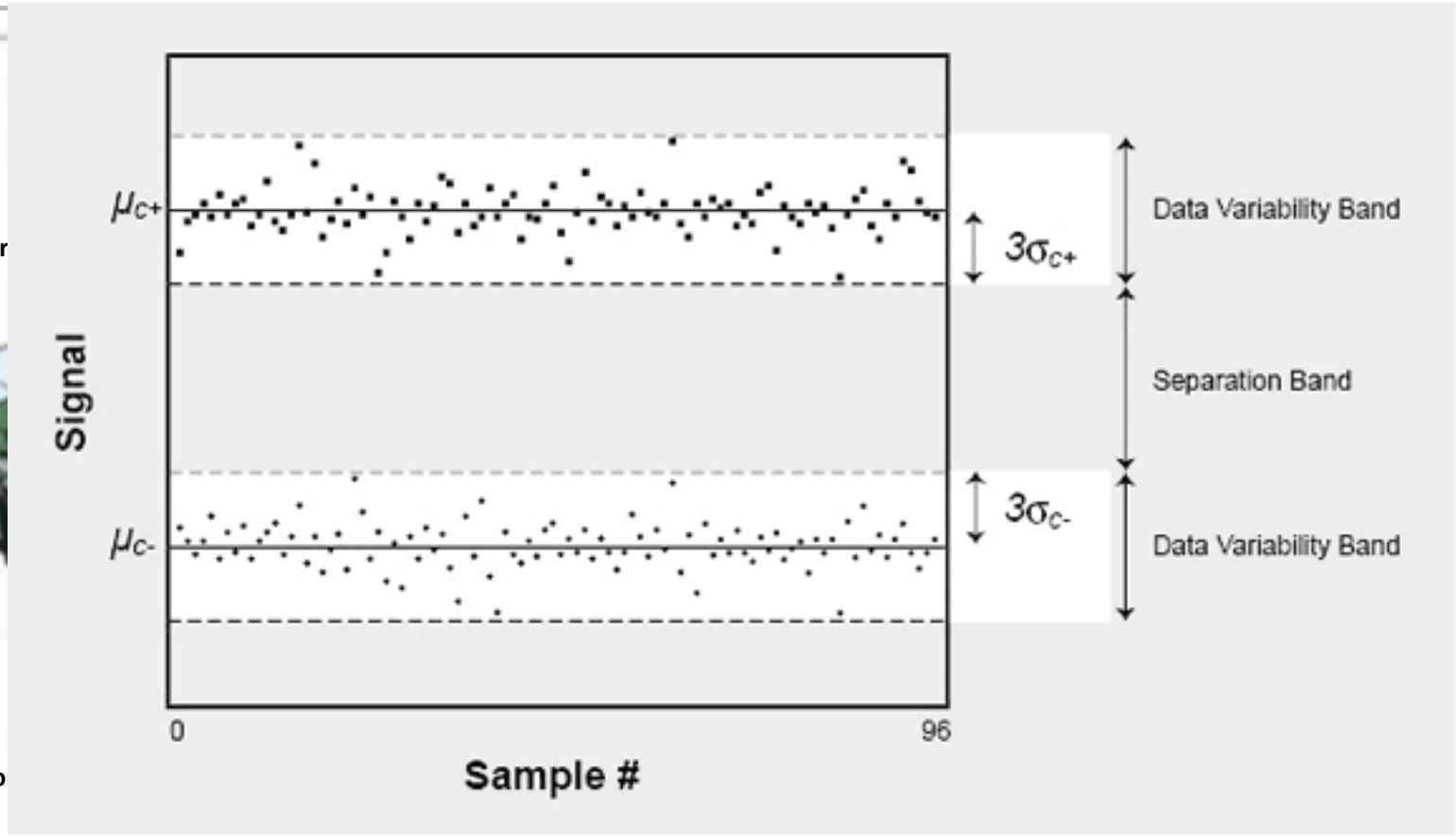
Automatic liquid handling device : data validation, robustness

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)

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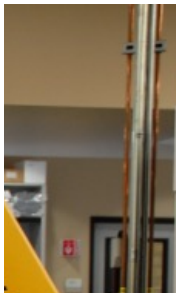
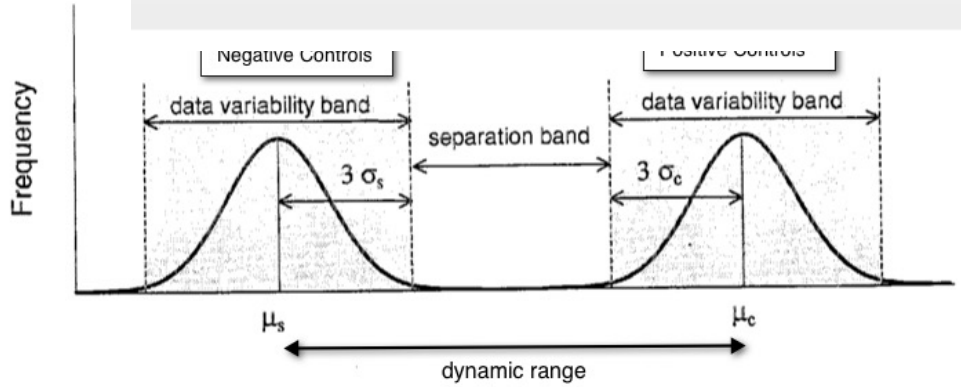
incubator

bulk reagent dispensers

plate co



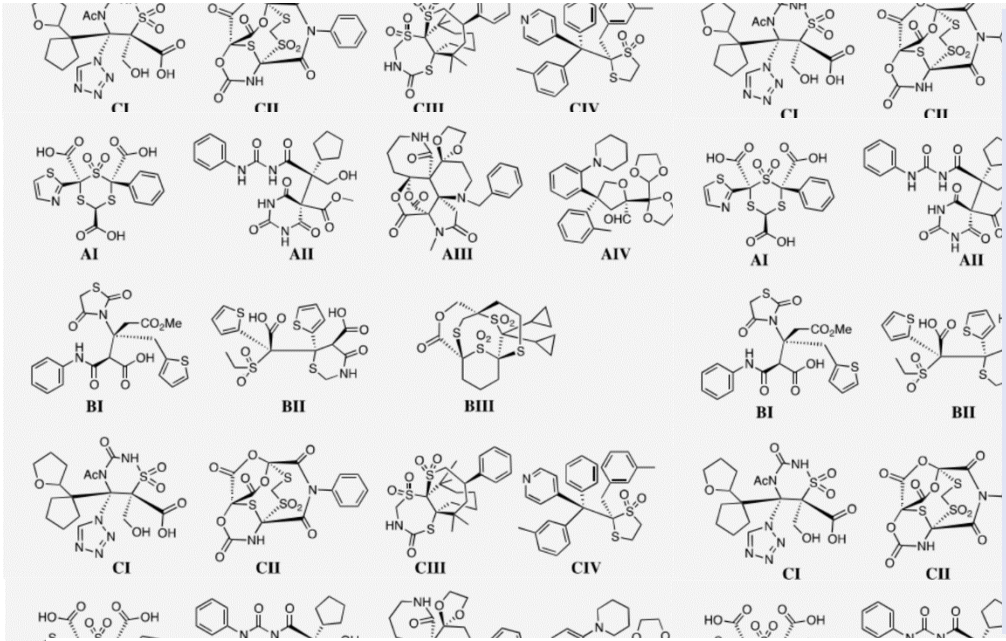


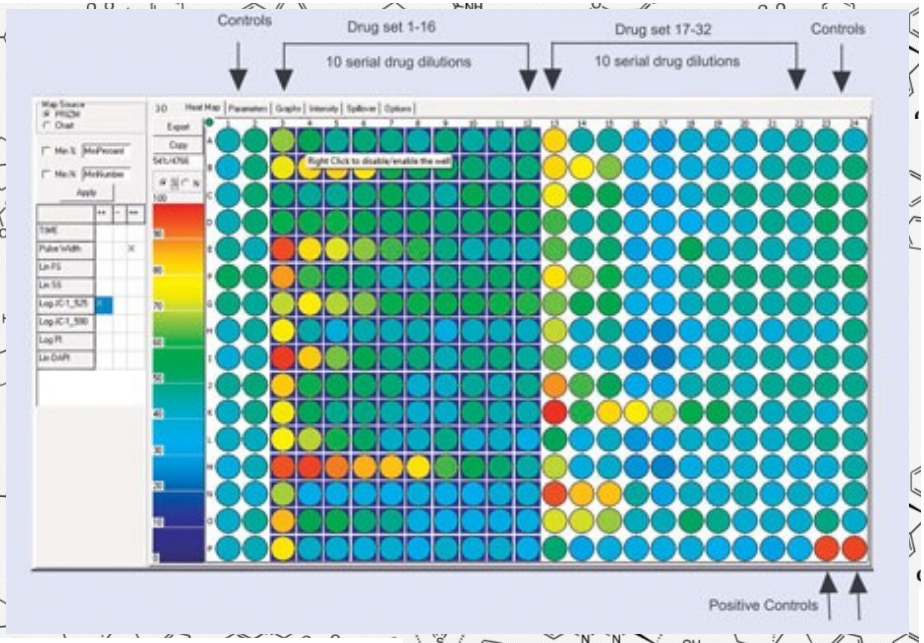
“Needle screens” of selected bioactive molecules: fast track to the clinical candidate

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

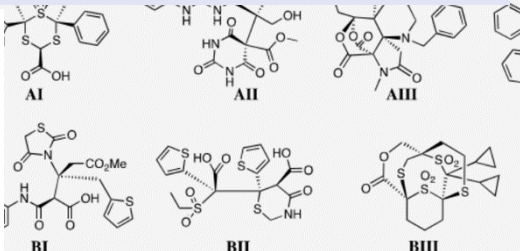
HARVARD UNIVERSITY

Northwestern University

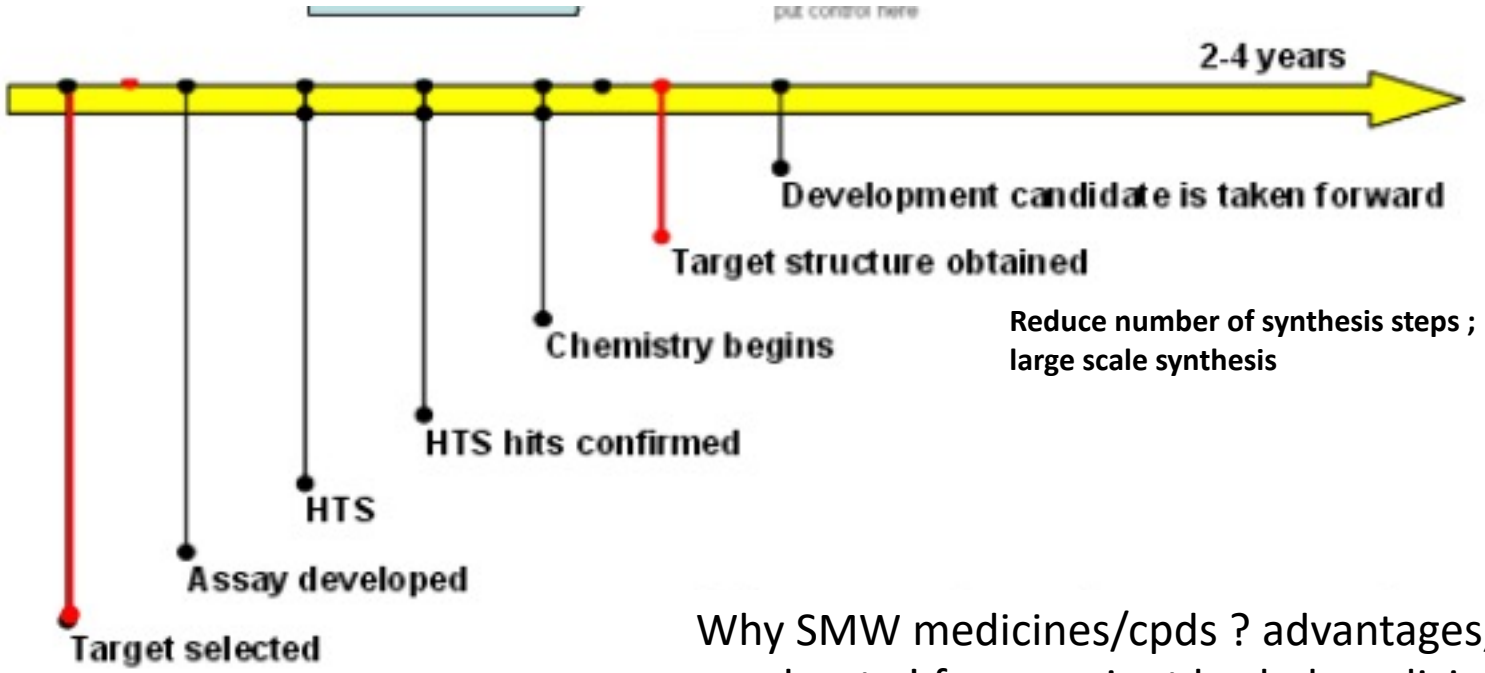
Takeda

清華大學 Tsinghua University

PEKING UNIVERSITY



From HTS hits to lead cpd and clinical candidate identified

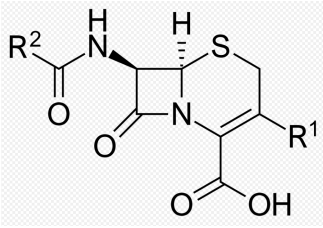


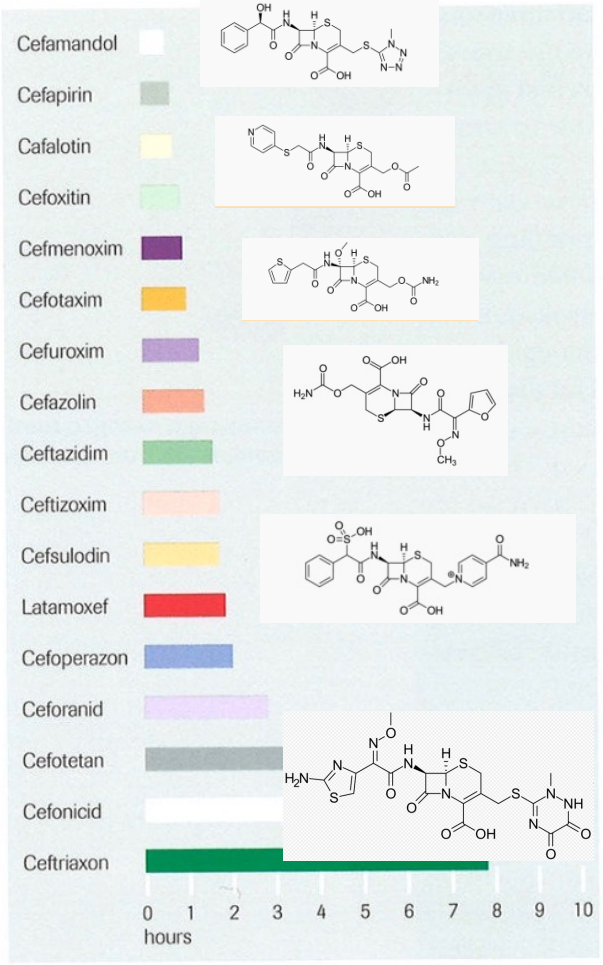
Reduce number of synthesis steps ; large scale synthesis

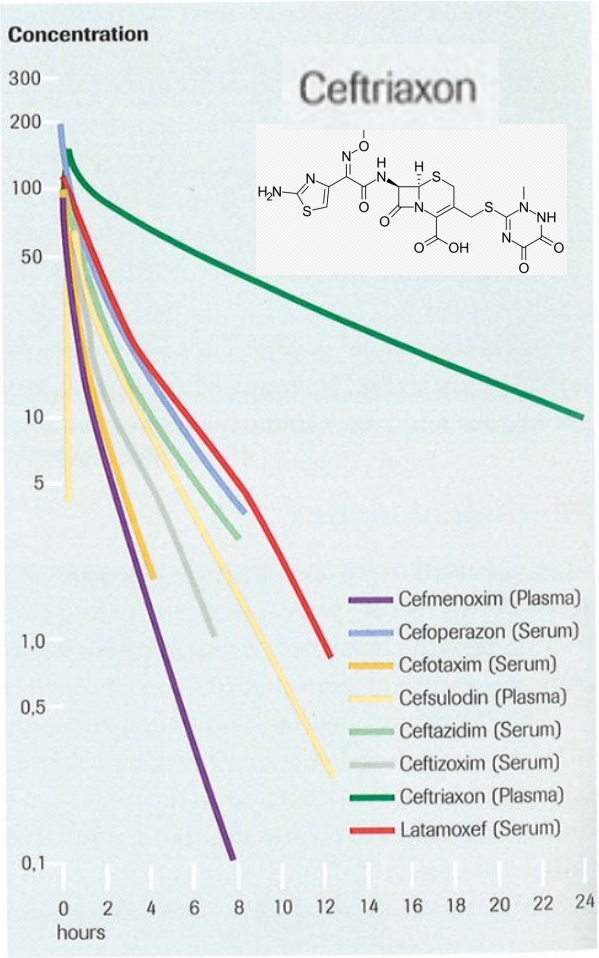
Why SMW medicines/cpds ? advantages, cost of goods etc ! from ancient herbal medicine to modern medicines, eg. HAART etc !

On average you are likely to take 15,000 SMC pills during the course of your life time !
Overall large proportion of current medicines derived from medChem !

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







R2 benzylalcohol
R1 thio-methyltetrazol

R2 mercaptopyridine
R1 methylester

R2 methylthiophen
R1 aminoester

R2 aminoester
R1 methoxyimine furane

R2 aminotriazol N-methoxyimine
R1 thiotriazindione

a remarkable example of mastering t ½ half life of an iv/im cpd

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

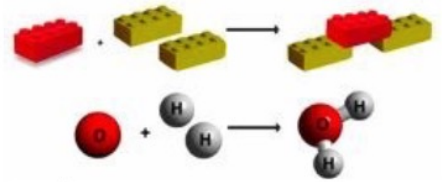
The '*chemistry*' in Medicinal Chemistry

Chemistry basics in 30 seconds:

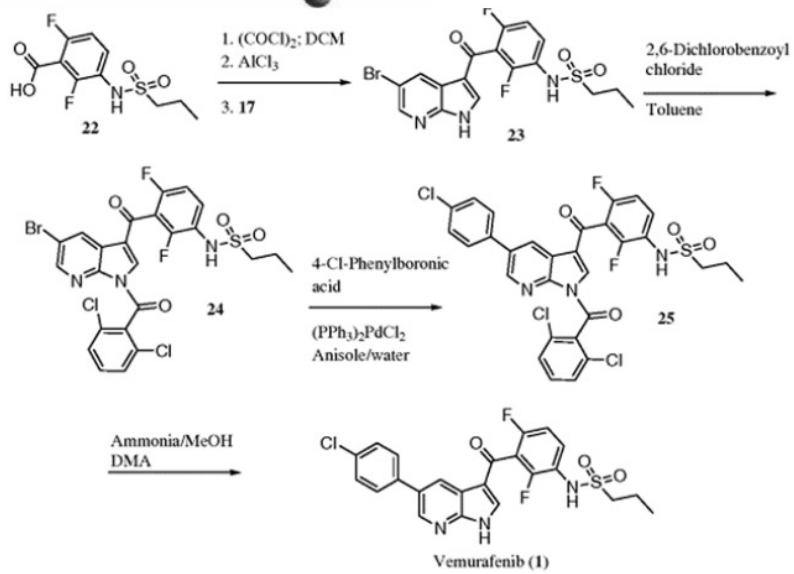
Atoms:

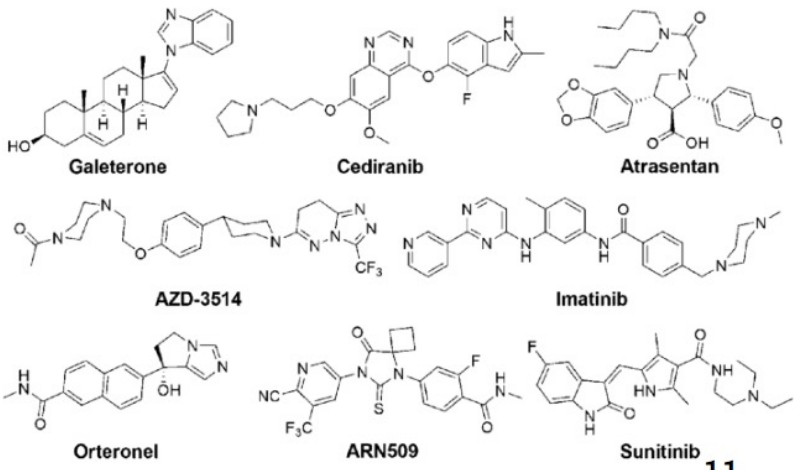
10^{60} theoretically possible molecules

Atoms to molecules:



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





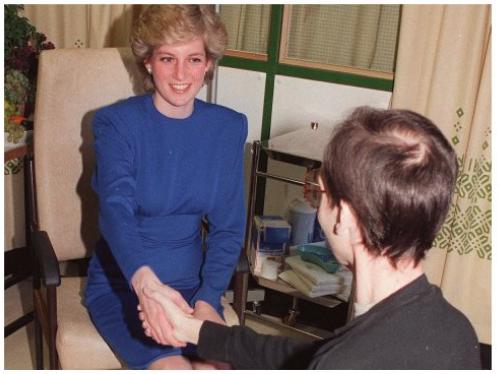
We would have to make lot of molecules – how do we know which one's to make and test?

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

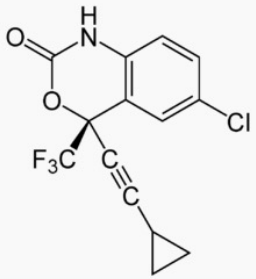
1995 Development of HIV drug cocktails was introduced and is known today as HAART for HIGHLY ACTIVE ANTI RETROVIRAL THERAPY



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 »

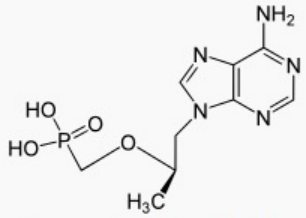
Éfavirenz



Identification

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

Ténofovir

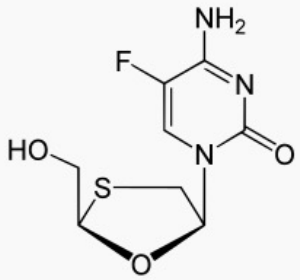


Structure chimique du ténofovir

Identification

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

Emtricitabine

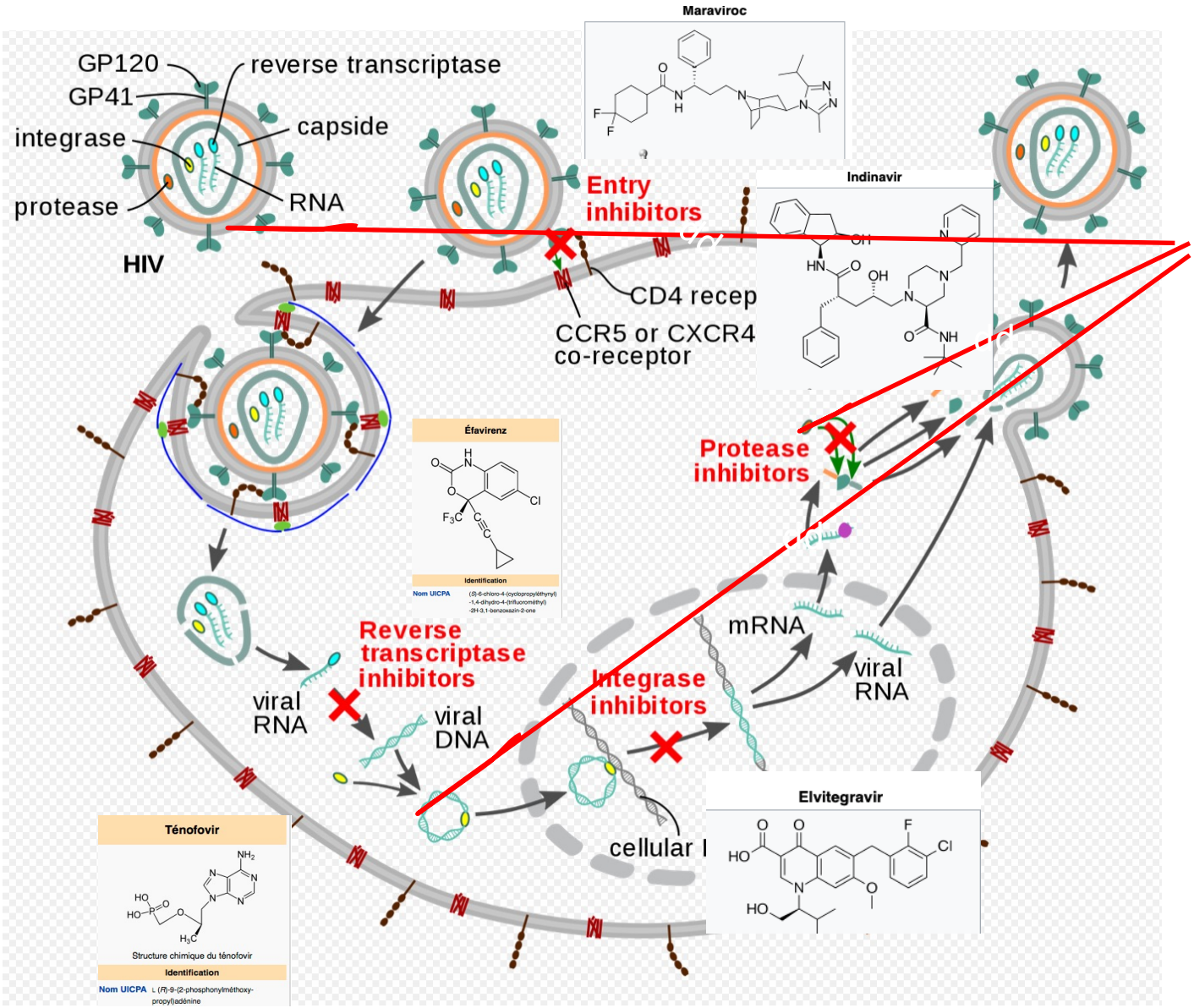


Structure chimique de l'emtricitabine

Identification

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

MedChem : impact on clinical practice : HAART
Breaking News : Lenacapavir® – end of HIV pandemia ?



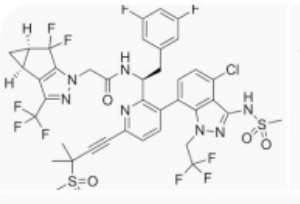
Breaking news 2025

LENACAPAVIR® : a multi step inhibitor, capsid replication inhibitor

PreP : sub cut slow release 8-12 weeks

issue : cost for high HIV incidence countries

$ 28’000.- year supply/Gilead



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)

«Pfizer's» rules or «Lipinski rule of five»

BOX 1

The Lipinski rule of five

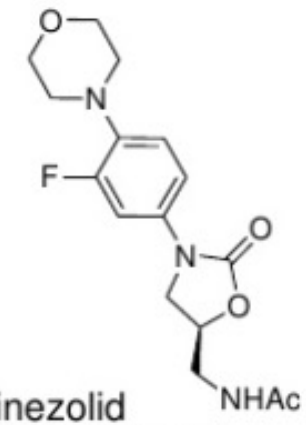
The medicinal chemist Christopher Lipinski and his colleagues analysed[2] the physico-chemical properties of more than 2,000 drugs and candidate drugs in clinical trials, and concluded that a compound is more likely to be membrane permeable and easily absorbed by the body if it matches the following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

In 1997, Christopher A. Lipinski and his colleagues published their guidelines for how to make drugs that are more easily absorbed by the body, and for several years their "rule of 5" has been and still is the guiding principle in drug research and new medicines design

Medicinal chemistry : Ro5 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

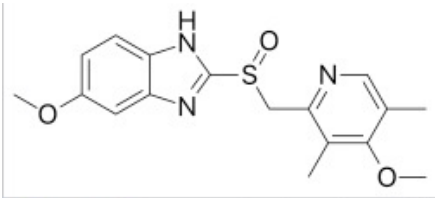
Good solubility : 3.7 mg/mL in pH 7 phosphate buffer

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

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

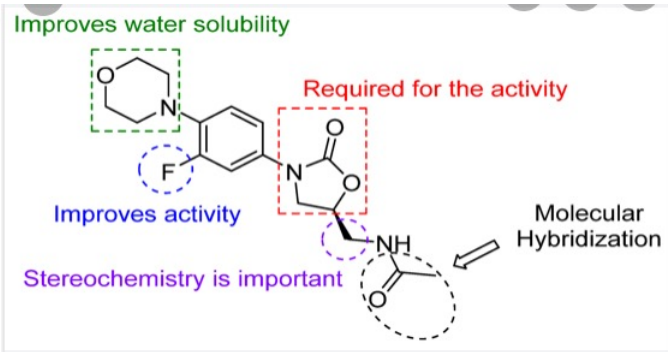
Has been approved by the FDA in 2000 under the trade name Zyvox

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



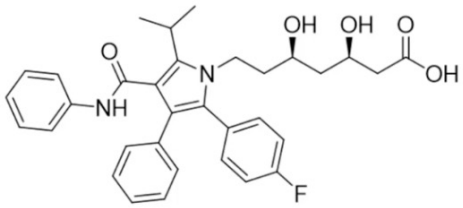
Omeprazole is a popular drug that conforms to Lipinski's rule of five.

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



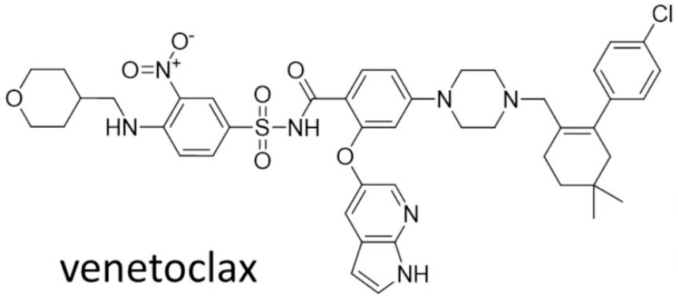
«Lipinski rule of five» violators, yet most commonly prescribed medicine !

ATORVASTATIN



- MW – 559 g/mol
- HBA – 6
- HBD – 4
- log P – 6.36
- F – 14%

BEYOND Ro5

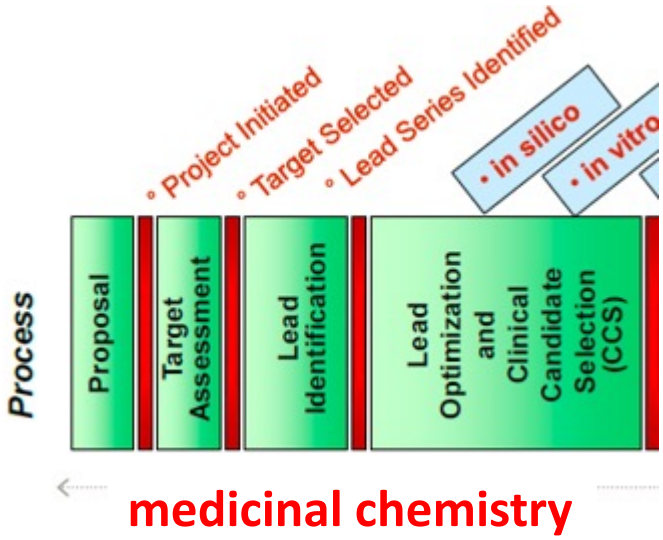


venetoclax

BCL2 inhibitor

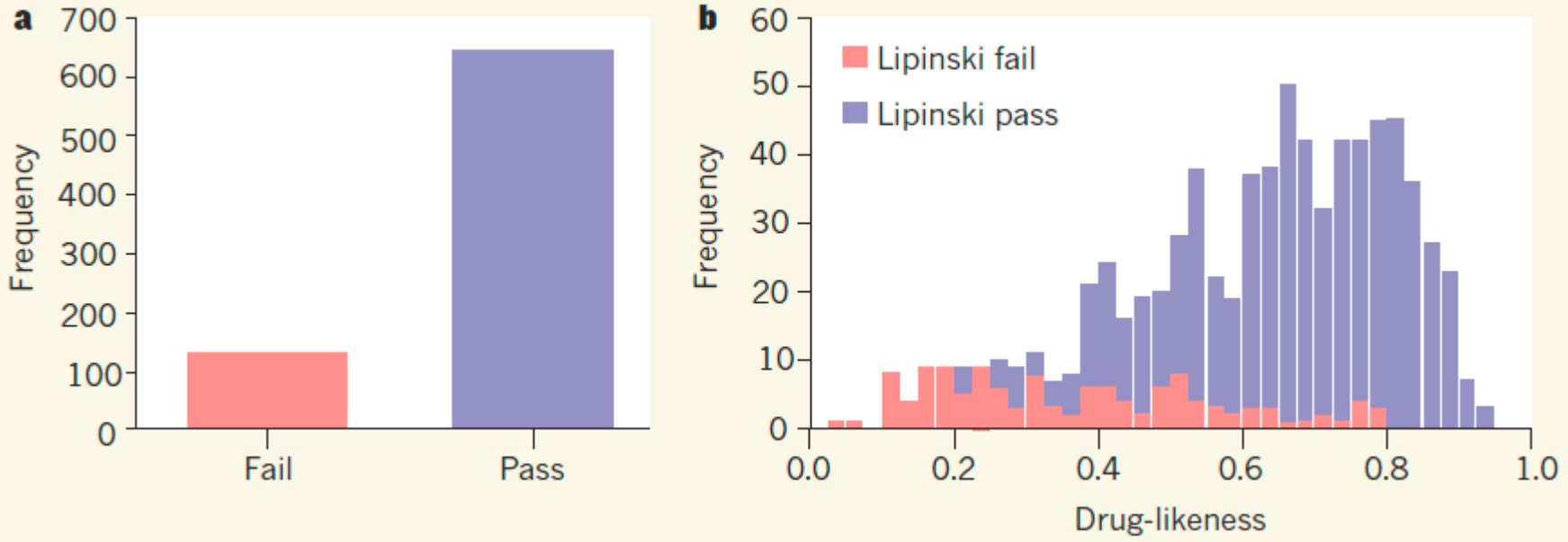
- MW – 868 g/mol
- HBA – 9
- HBD – 3
- clog P – 6.12
- F – 5.4%

«Pfizer's» rules or «rule of five»



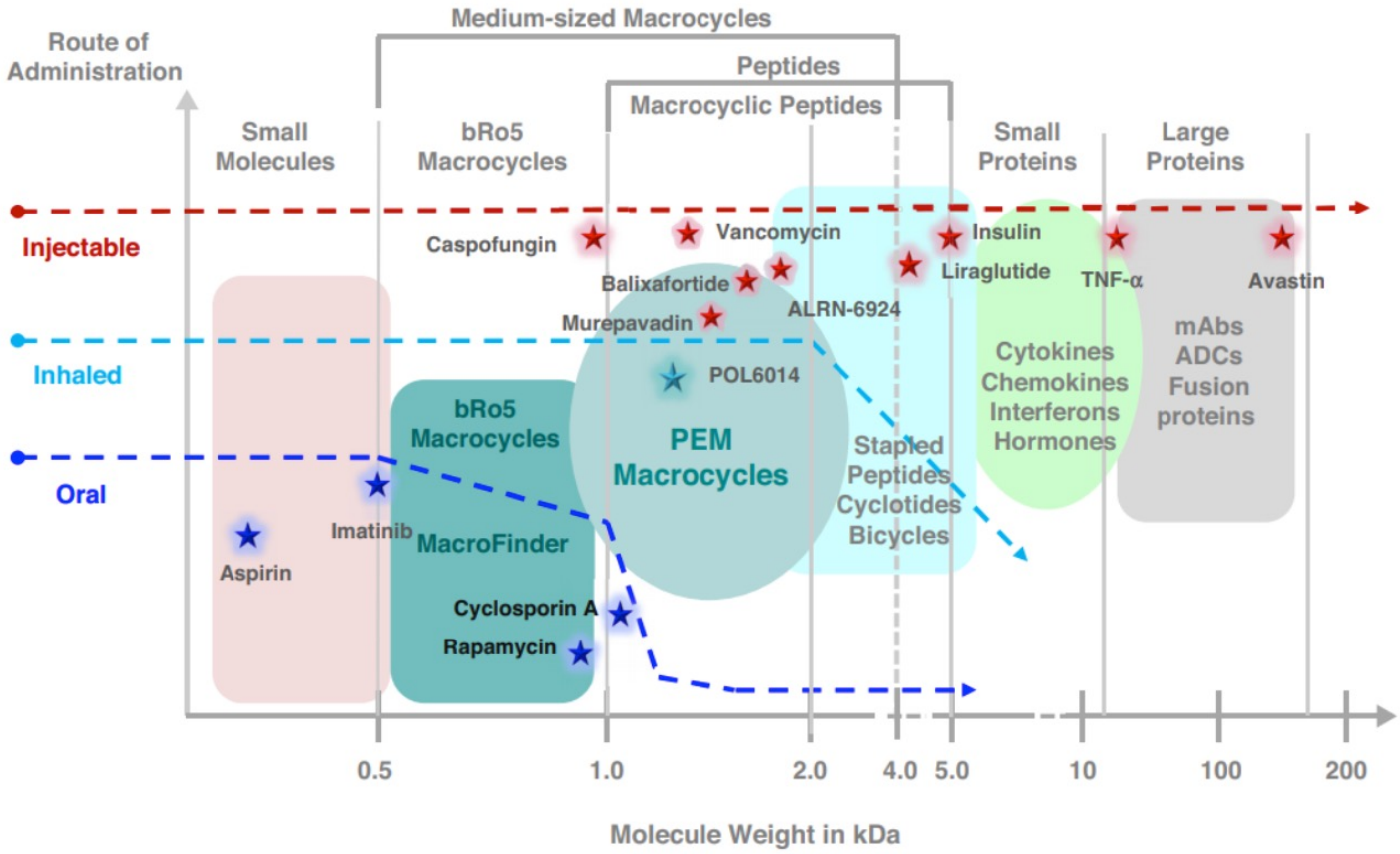
medicinal chemistry

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



«Pfizer's» rules or «Lipinski rule of five»
a medicinal chemistry «gold standart» for SMCs

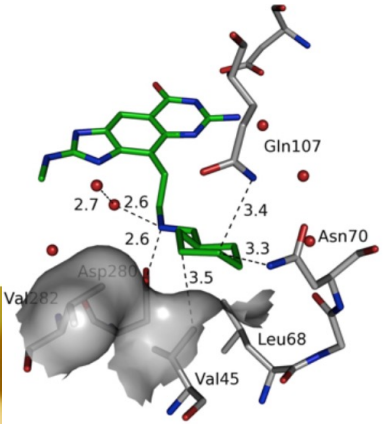
Guidelines for Oral Available Drugs



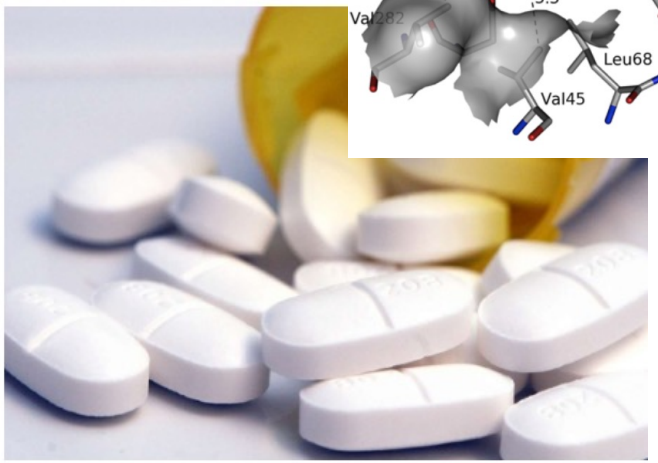
A. Luther et al., *Current Opinion in Chemical Biology*, **2017**, 38, 45-51

Medicinal chemistry : what properties a drug need to have ?

The biggest risk in drug discovery is NOT to get a medicine
DO WHAT THE PATIENT NEEDS NEXT



- **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



MDO : parallel Multiple Drug Optimization - ADME

permeability

potency

binding kinetics

crystallinity

solubility

protein binding

chemical stability

CYP inhibition

pKa (acidity/basicity)

clearance

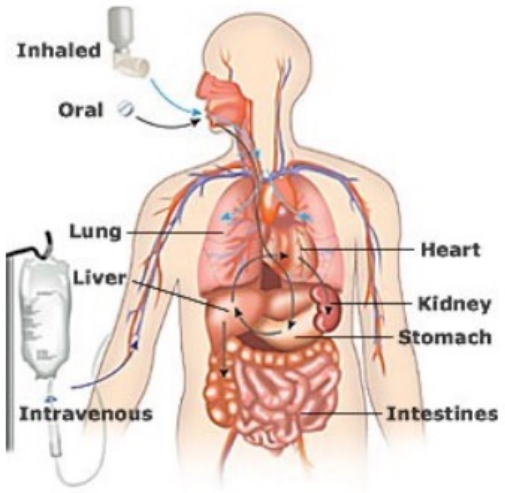
in vitro tox assays

Time dependent CYP inhibition

efflux / P-gp

logD / lipophilicity

covalent binding



Potency

Selectivity

Absorption

Distribution

Metabolism

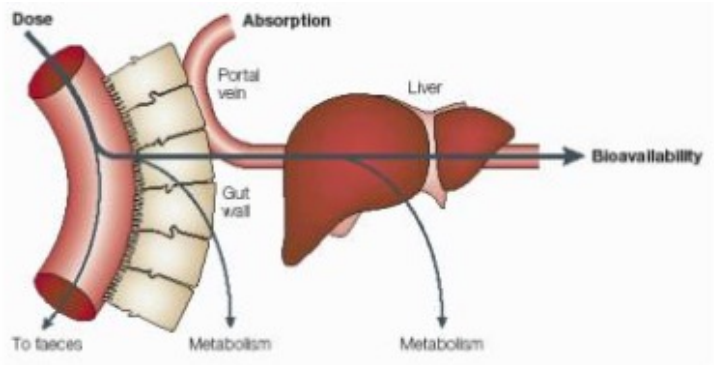
Excretion

Toxicity

MDO : Multiparameter Drug Optimization

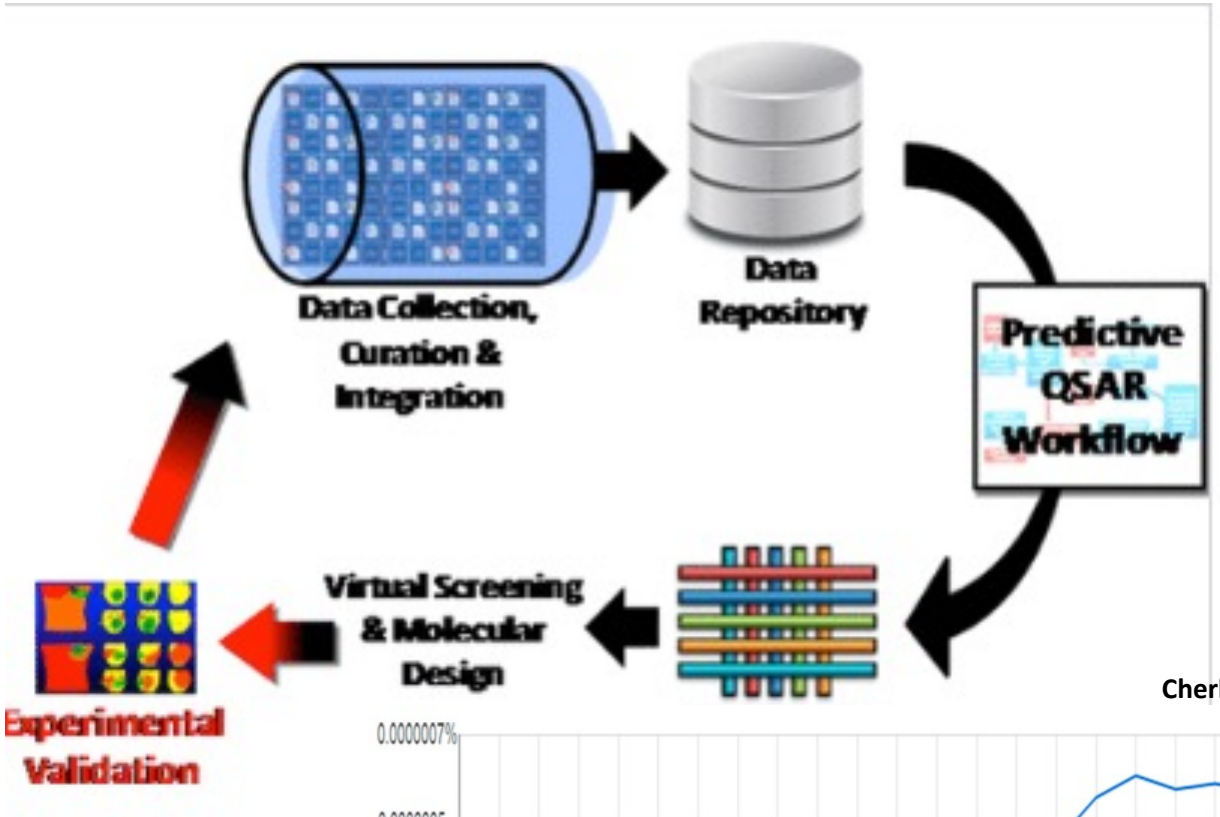
MDO simplified (drug likeliness or Pfizer's rules)

- 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

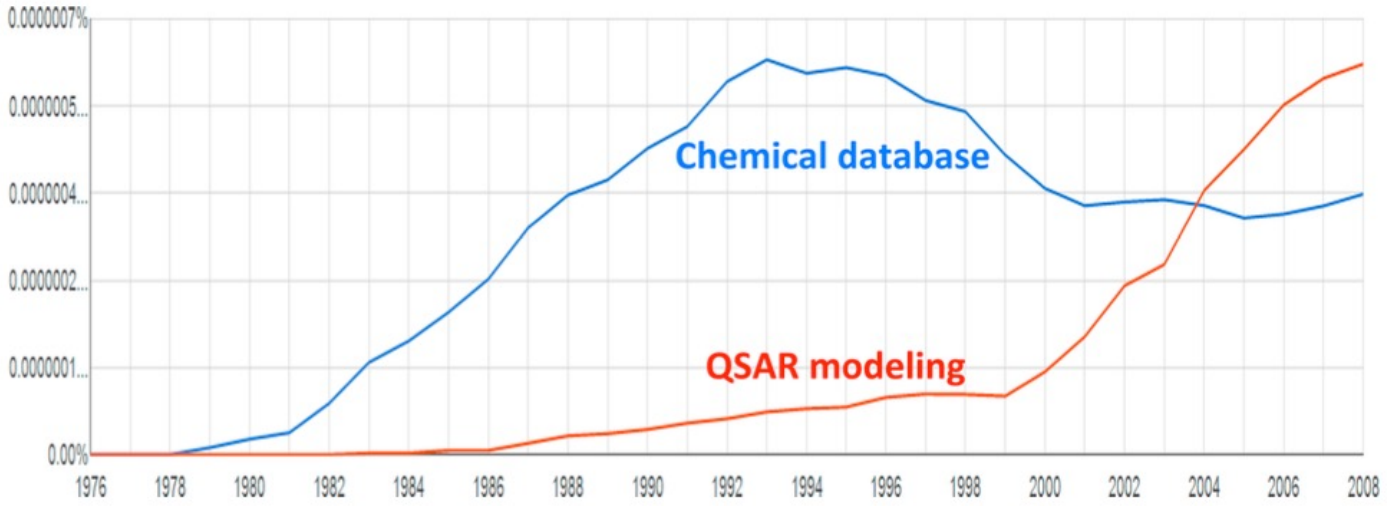


C.A. Lipinski et al. *Adv. Drug. Delivery Reviews* **23** (1997) 3.

Rule of five and the advent of QSAR (quantitative structure-activity relationship)

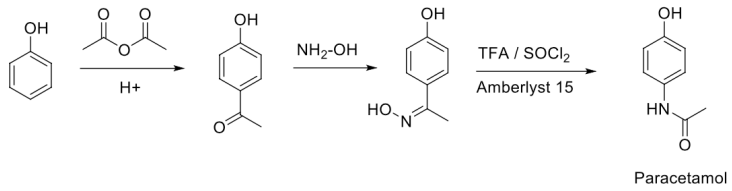


Cherkasov et al. 2014. J. Med. Chem. 57, 4977−5010



Med chem cost of goods : SMCs (eg paracetamol) vs macrocycle an important criteria in the life cycle of a medicine

Hoechst - Celanese Process:

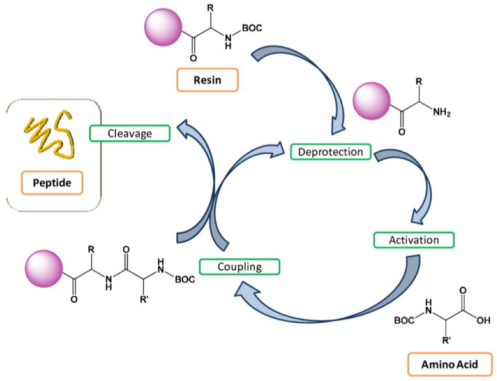


in US: $ 0.04 per dose
=> ~ $ 0.08 / g

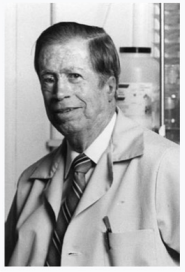
kilolab process !

- **Main cost driver:** Purification
- **Ideally:**
  - Starting material and reagents are cheap and available in bulk
  - Efficient process (atom economy)
  - High yields
  - Energy

US patent 452417; https://www.drugs.com/price-guide/acetaminophen (20.10.2019, 13:09 h)

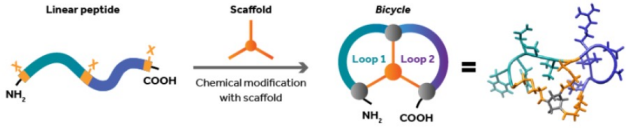


Robert Bruce Merrifield



1984 – Nobel prize

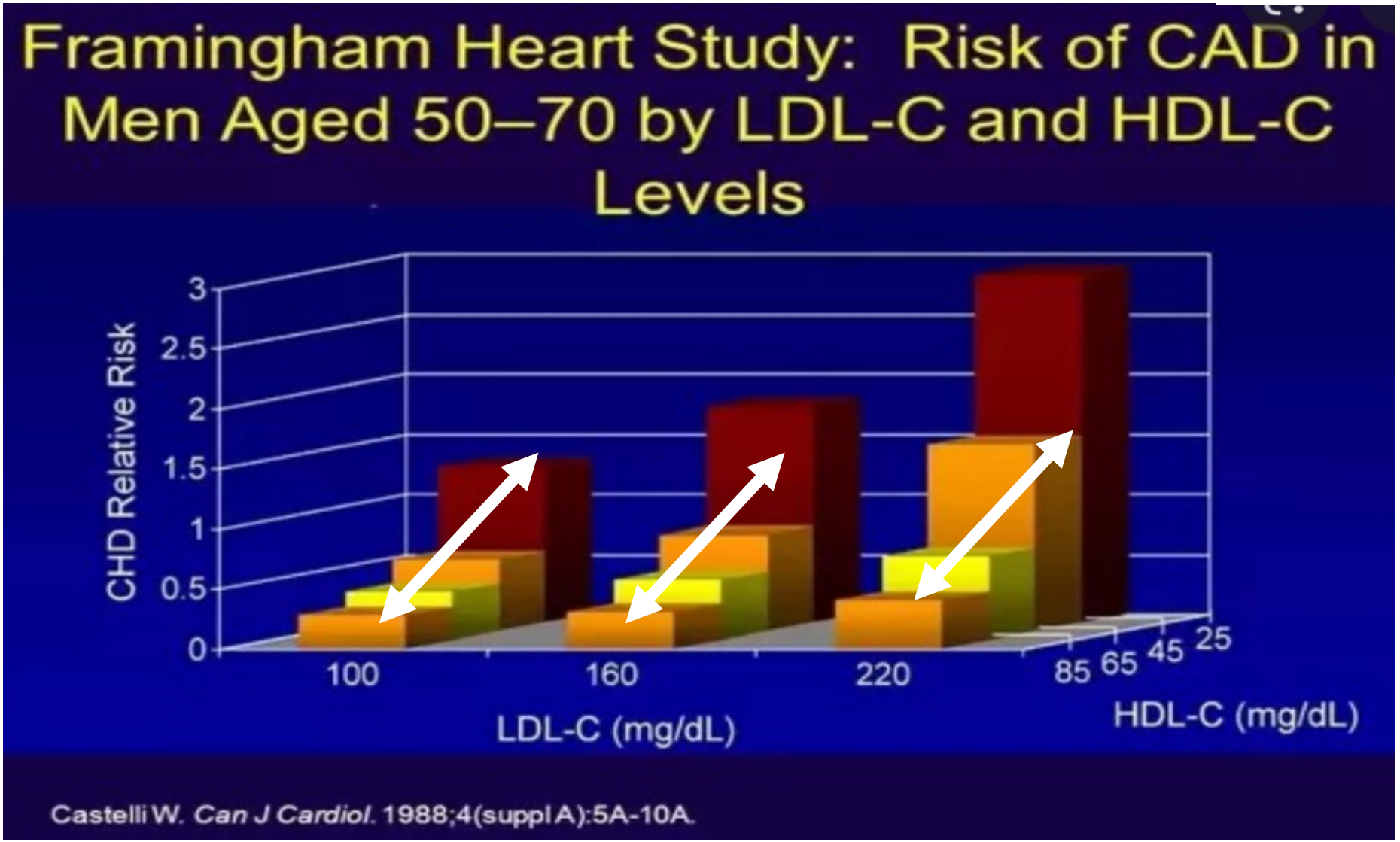
- **Main cost driver:**
  - Coupling reagents
  - Amino acids
  - Solvents
  - Lipholization (energy)
  - Purification
- **Advantages:**
  - High specificity
  - Binding activity
  - Automatization
- **Disadvantages:**
  - Bioavailability
  - Production
  - Stability



- **Good of costs:**
  - ~ $ 100 / g (100% bioavailability)

- A. Duro-Castano et al., *Poylmers*, **2014**, 6, 515-551; https://www.genengnews.com/magazine/252/peptides-new-processes-lower-costs/ (20.10.2019, 13:02 h); https://www.bicycletherapeutics.com/approach/ (22.10.2019, 11:02 h).

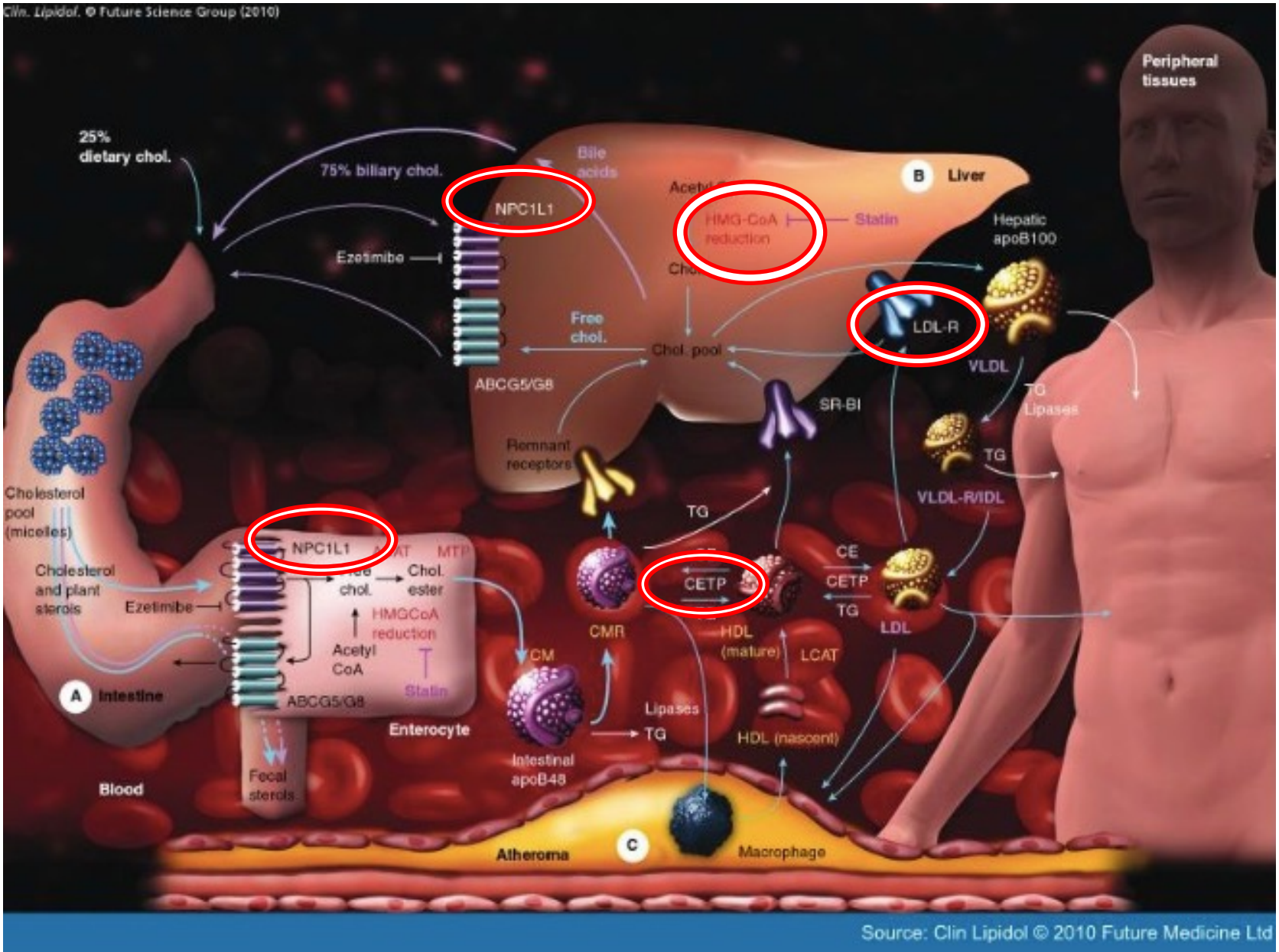
Large cohort studies on LDL vs HDL correlation : CVD are the first cause of mortality in westernized countries



Compelling epidemiological and genetical evidence : LDL-C is a strong risk factor while HDL-C reduces the risk of coronary heart disease CHD

The Framingham Heart Study over several generations of CHD patients

Atheroma as drug target - compelling epidemiological and genetic evidence in human – HDL's as target for CVD - number one killer in developed countries



Stroke and cardiac heart failure in the WHO radar scope : myocardial infarction is today still no 1 cause of death globally

World Health Organization

centre | Publications | Countries | Programmes | Governance | About WHO

Media centre

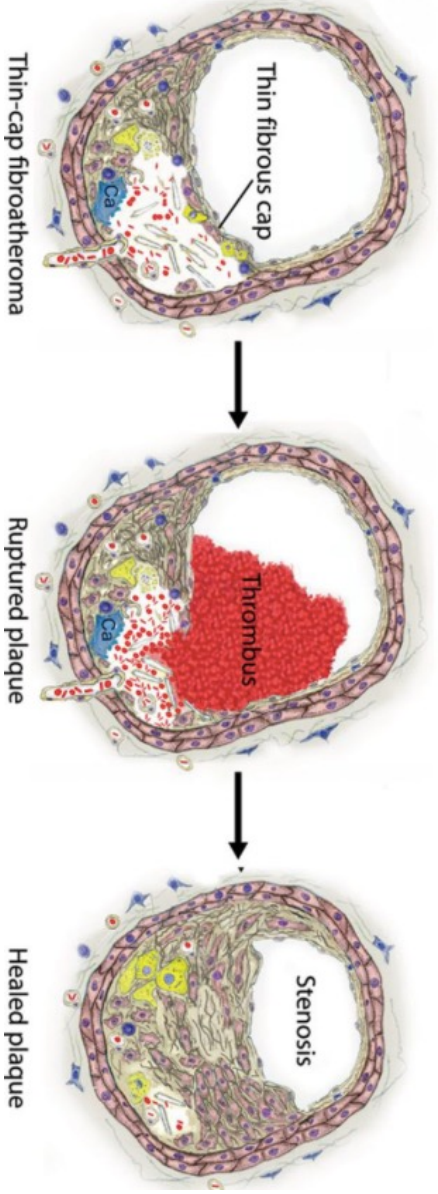
Cardiovascular diseases (CVDs)

Fact sheet
Updated May 2017

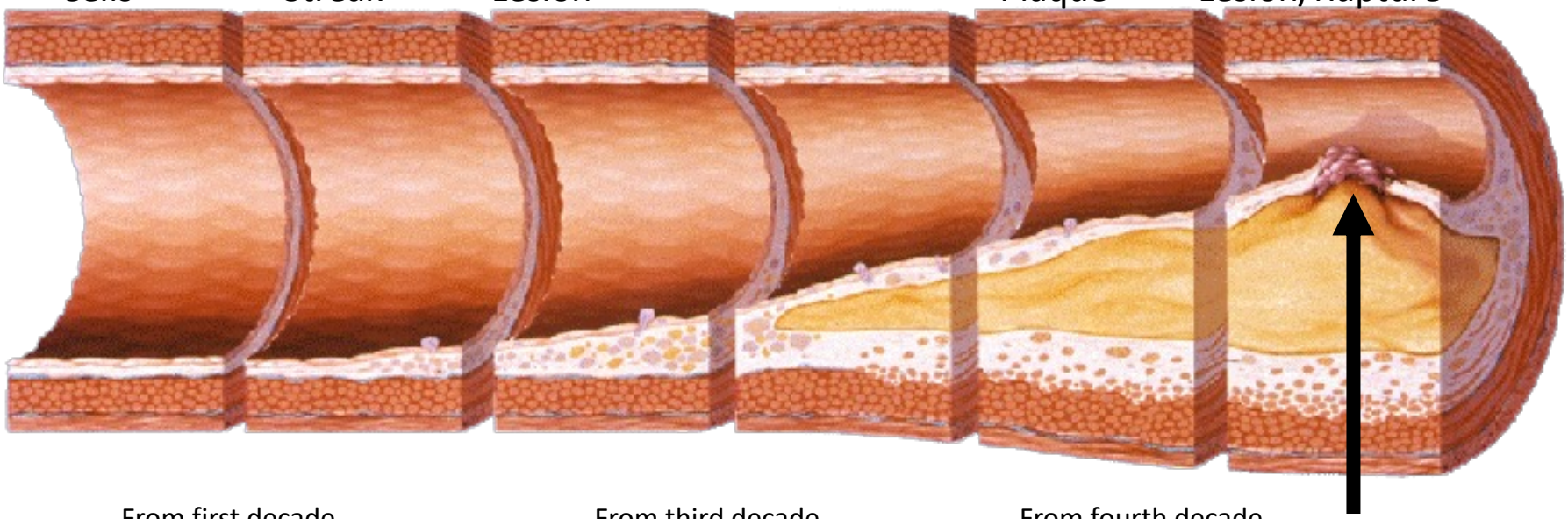
Key facts

- CVDs are the number 1 cause of death globally: more people die annually from CVDs than from any other cause.
- An estimated 17.7 million people died from CVDs in 2015, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke .

at histopathological level



Atherosclerosis – unstable plaque - a life threatening disease of the arteries



From first decade — From third decade — From fourth decade

Atherosclerosis → **Thrombosis**

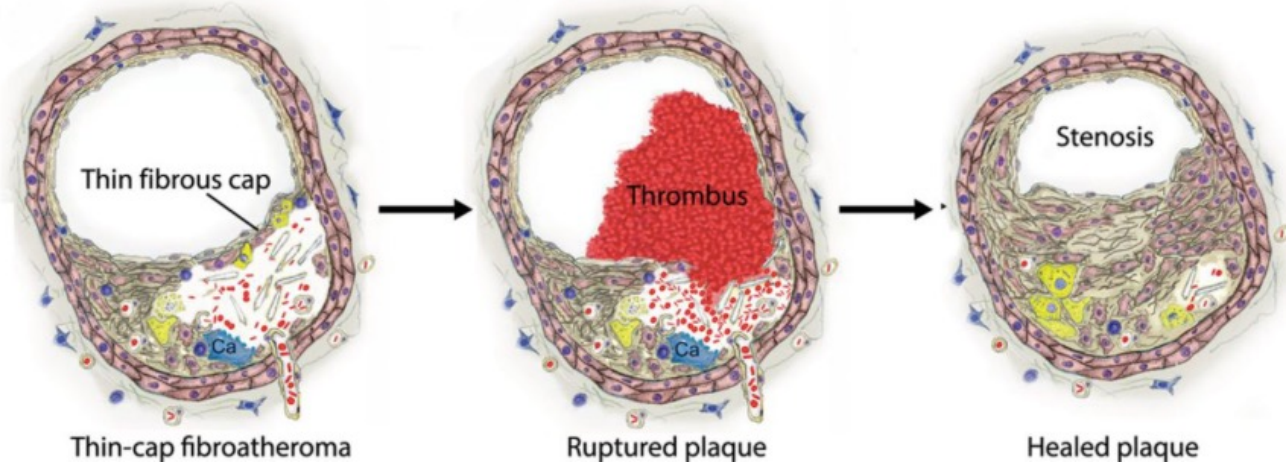
Stable angina

ACS/MI Stroke/TIA CV death

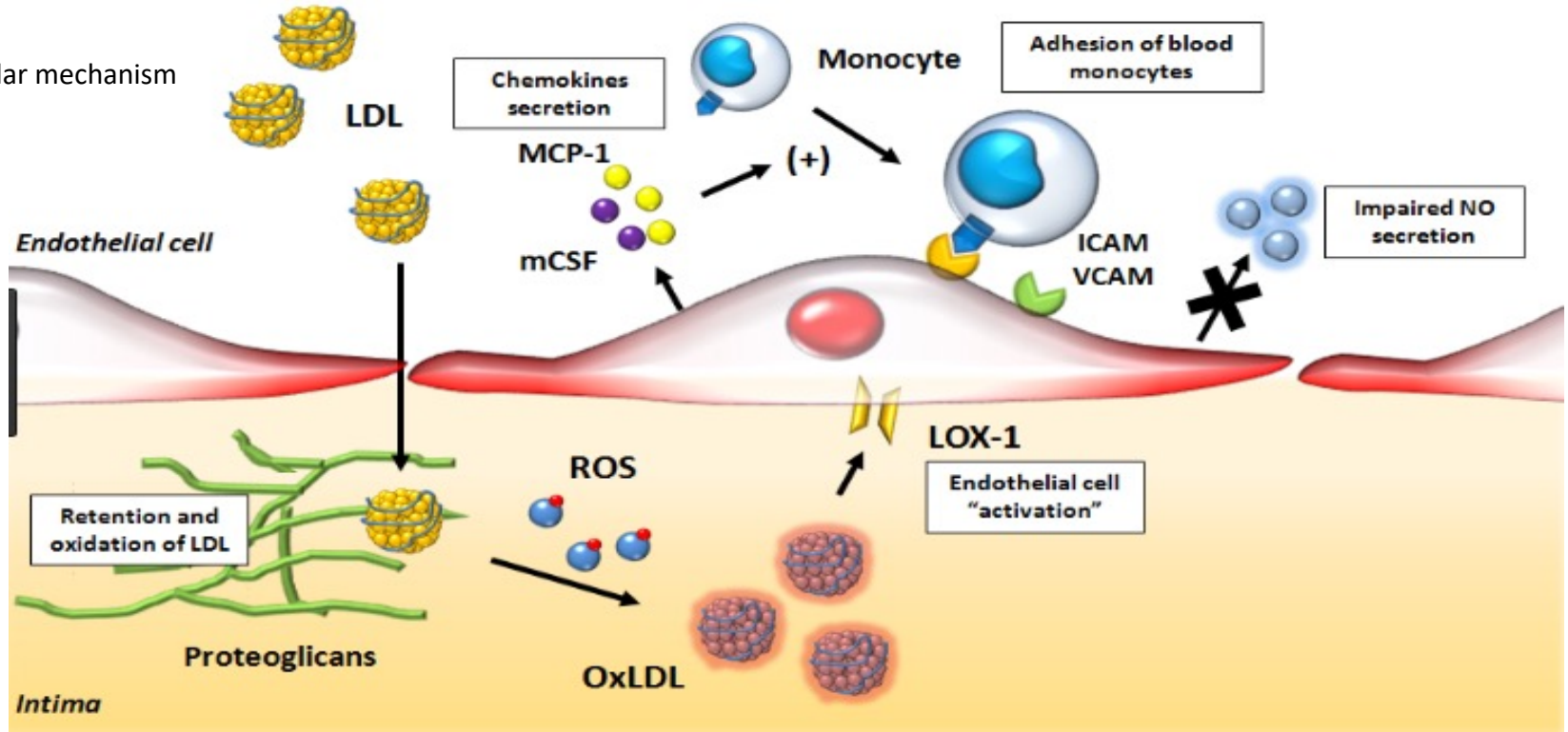
Adapted from Stary et al. *Circulation*. 1995;92:1355–1374.

Stroke and acute heart failure : the unstable atheroma plaque

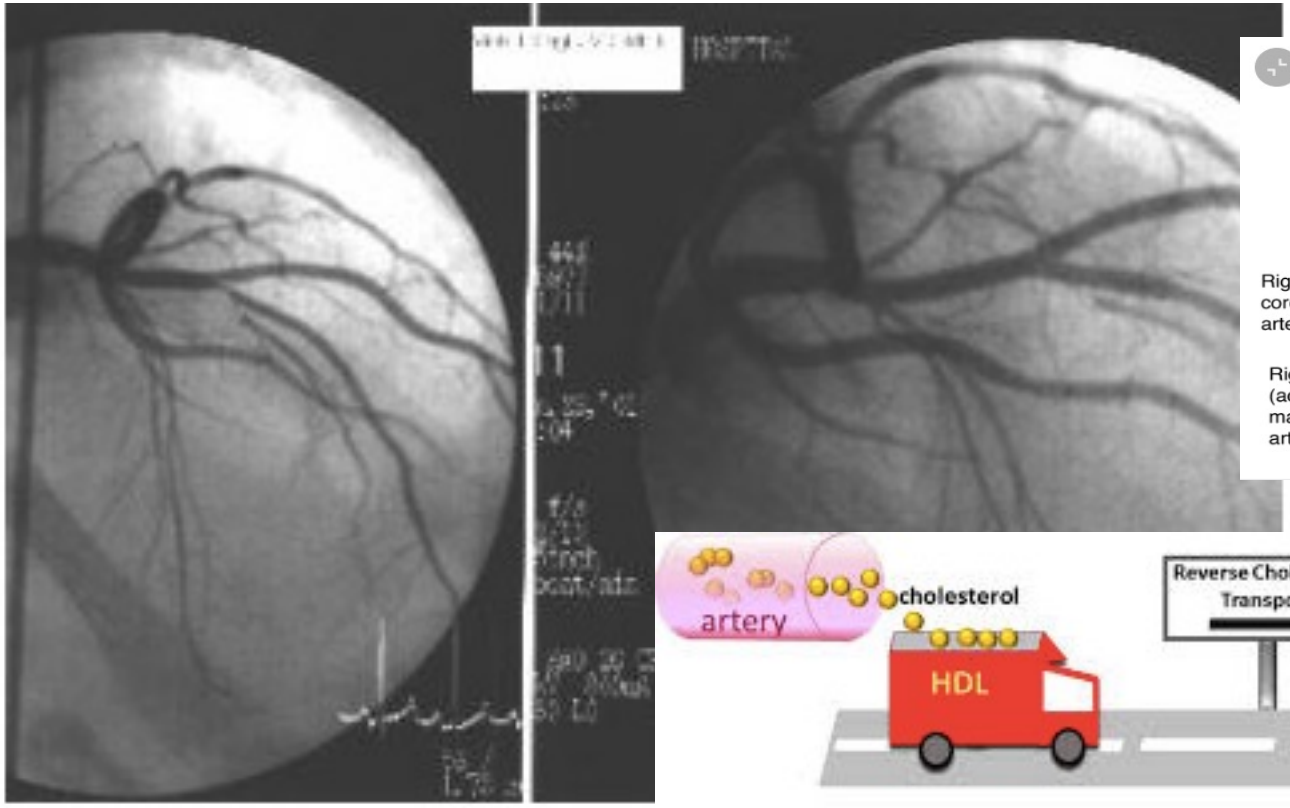
at histopathological level

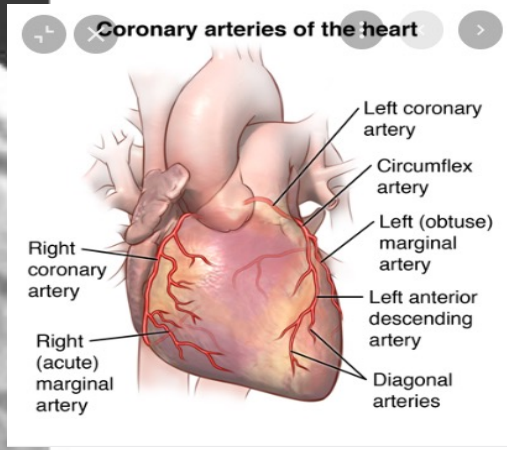


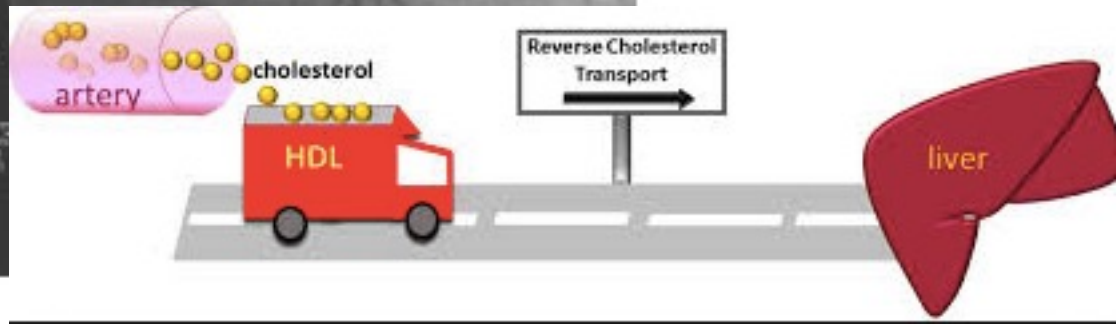
at molecular mechanism



IVUS/angiograhy diagnostic : coronary occlusion : at high heart failure risk !

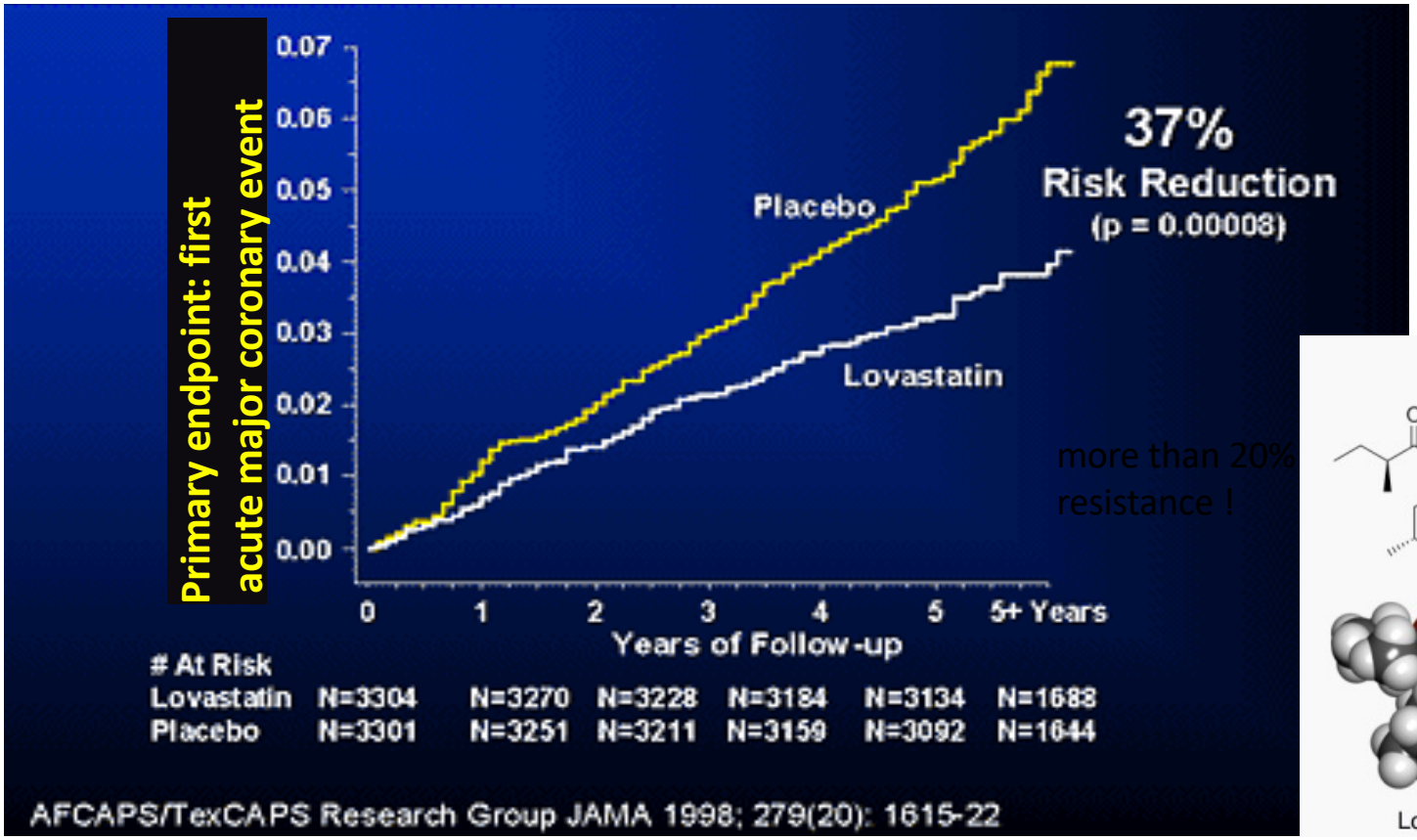




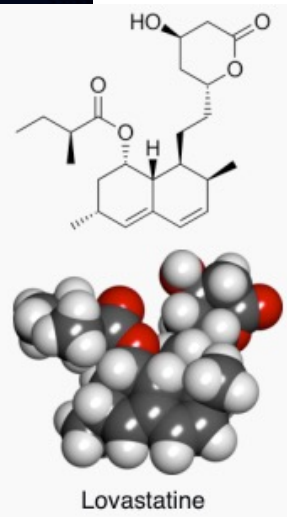


Cardiac catheterization and coronary angiography in the left panel shows severe left anterior descending coronary artery stenosis. This lesion was treated with stent placement in the left anterior descending coronary artery, as observed in the right panel.

CAD - standart-of-care: high level of residual risks: will HDL therapeutics revolutionize this ?



more than 20% resistance !

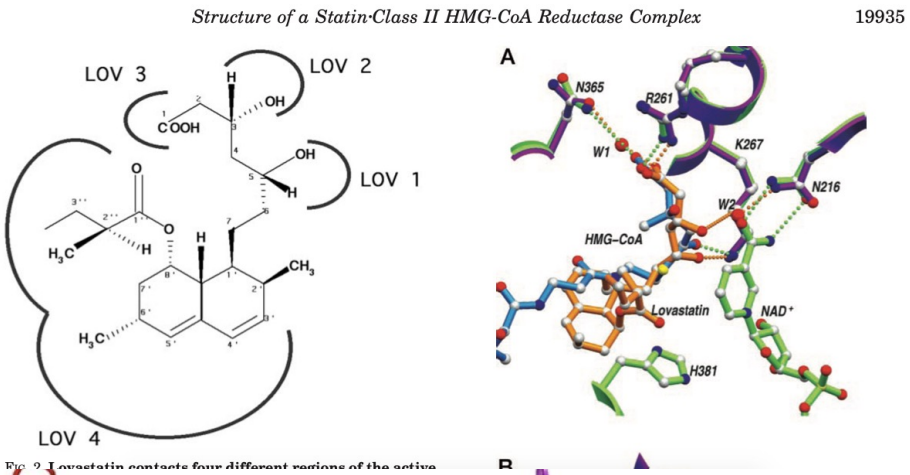


Lovastatine

study with a low HDL population, many of which had the metabolic syndrome 20 or 40 mg of lovastatin was compared with placebo. Over a 5-year period there was a 37% decrease in the risk of the first event. All of these participants had to have an LDL over 130 mg/dL and an HDL less than 50 mg/dL

Compelling epidemiological and genetical evidence : high LDL-C is a strong CVD risk factor while low HDL-C increases the risk of coronary heart disease CHD

Cholesterol synthesis : several versions of HMGoA reductase inhibitors : statins the ever most prescribed medicine as of today !

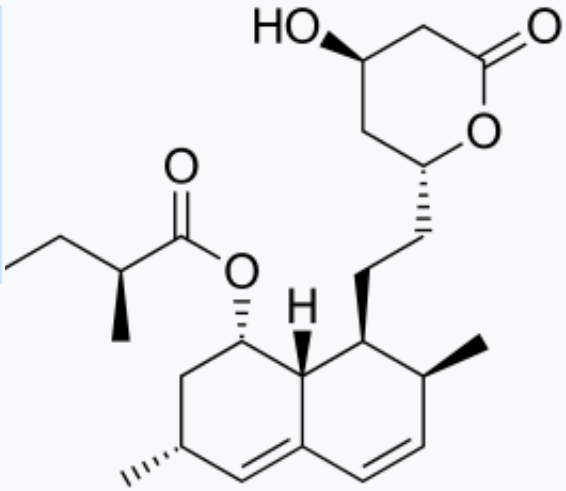


Three dimensional structure of homosapien hMg coa reductase downloaded from Protein Data Bank with PDB iD 1hWK bound to ligands.

Statin

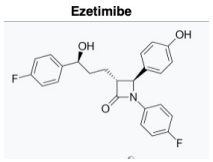
Drug class

Akira Endō



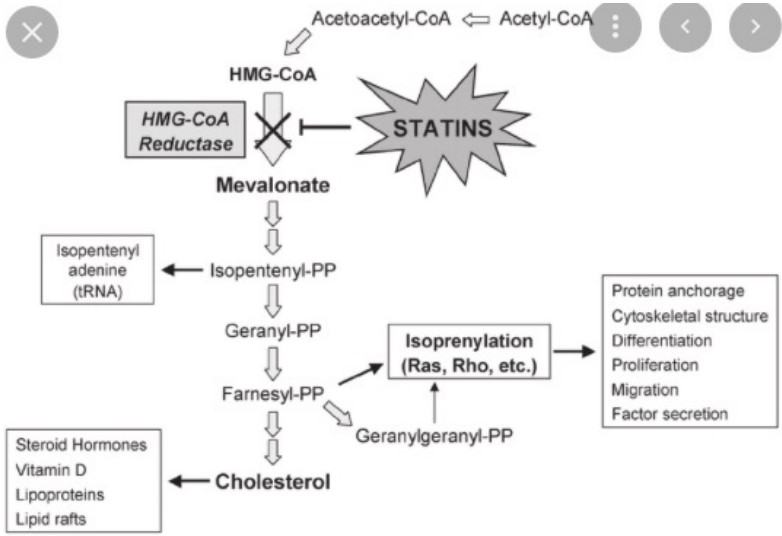
Lovastatin, a compound isolated from *Aspergillus terreus*, was the first statin to be marketed.

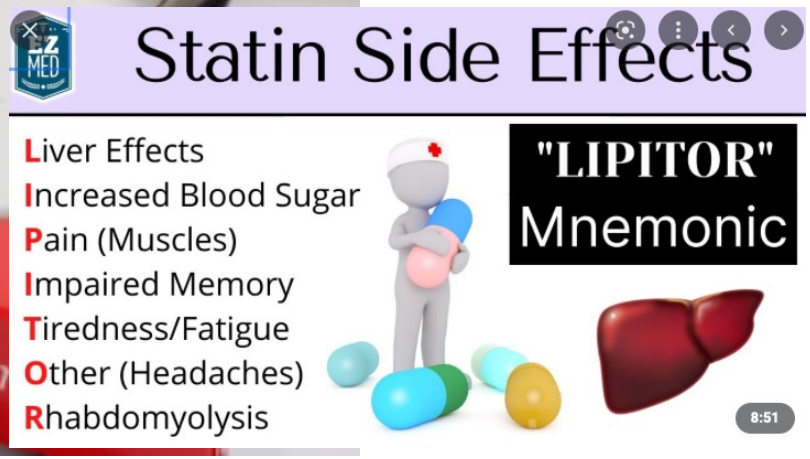
CVD standart of care : a glamorous perspective ?
HMGCoA reductase inhibitors are the ever most prescribed medicines



Global Statin Market

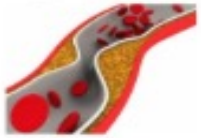
Base Year:	2020	2021-2027
Historical Data:	2016 to 2020	**US $ 14.1 Bn.**
Forecast Period 2021 to 2027 CAGR:	3%	US $ 17.34 Bn.
Segments Covered:	by Drug Class	• Astrovastatin • Fluvastatin • Lovastatin • Pravastatin • Simvastatin • Others

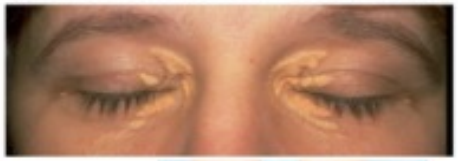


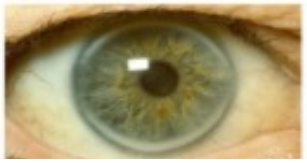


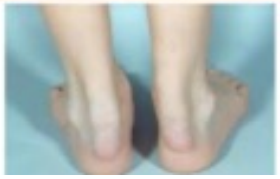
Target identification : clinical symptoms and compelling genetic evidence: LDL level and LDL R

Familial Hypercholesterolemia Autosomal dominant !

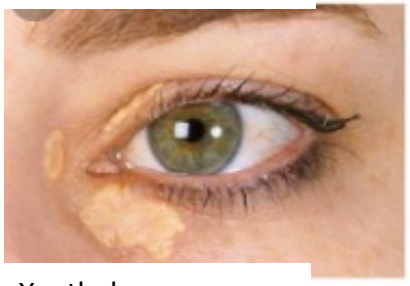




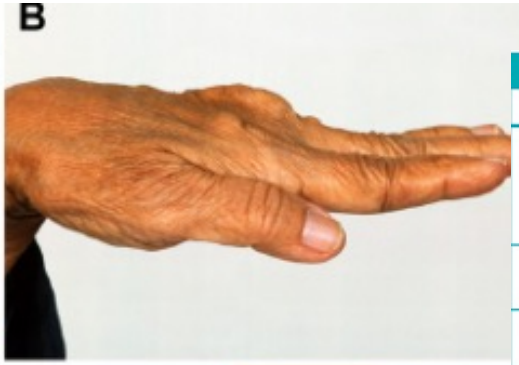


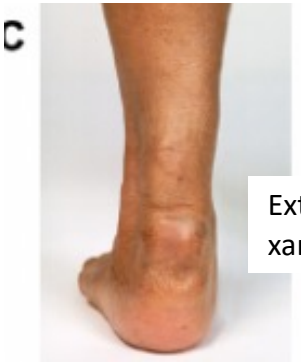


Corneal arcus

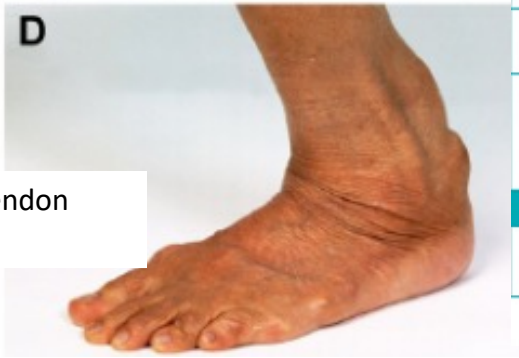


Xanthelasma





Extensor tendon xanthoma



Familial Hypercholesterolemia

A **genetic** condition leading to high cholesterols and higher risk for **early heart disease.**

FH affects **1 in 300** people

Patients with Familial Hypercholesterolemia have **20X** higher risk of Heart attack

If you have FH, each of your child has **50%** chance of getting FH

SIMON BROOME DIAGNOSTIC CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA[1]

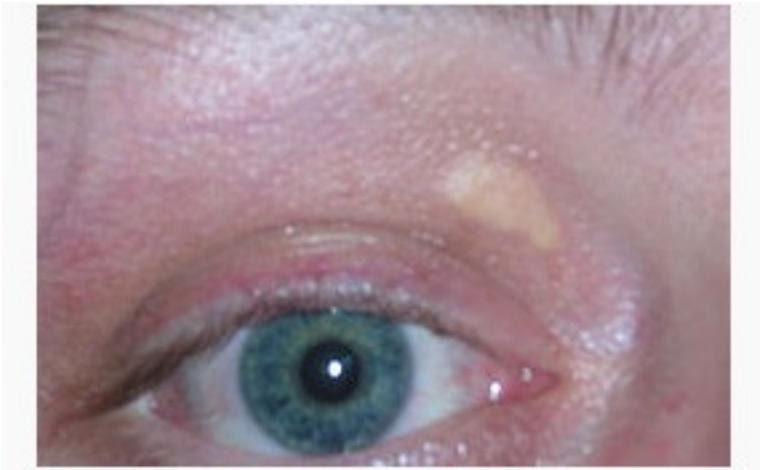
Point	Criteria
1	Total cholesterol levels > 290mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L) in adults. Total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L)
2	Tendon xanthomas in the patient or tendon xanthomas in a first or second degree relative.
3	DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.
4	Family history of myocardial infarction before age 50 years in a second degree relative or before age 60 years in a first degree relative.
5	Family history of elevated total cholesterol > 290 mg/dL (7.5 mmol/L) in an adult first or second-degree relative. Family history of elevated totacl cholesterol > 260 mg/dL (6.7 mmol/L) in a child, brother, or sister 16 years or younger.

DIAGNOSIS

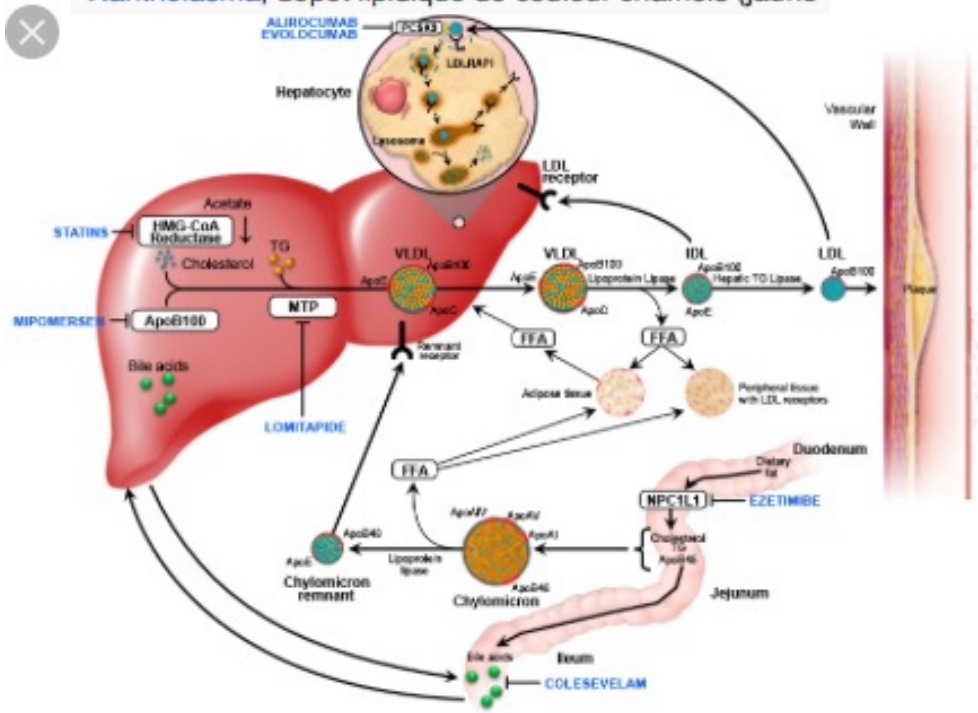
Definite familial hypercholesterolemia = 1+2 or 3
Possible familial hypercholesterolemia = 1+4 or 5

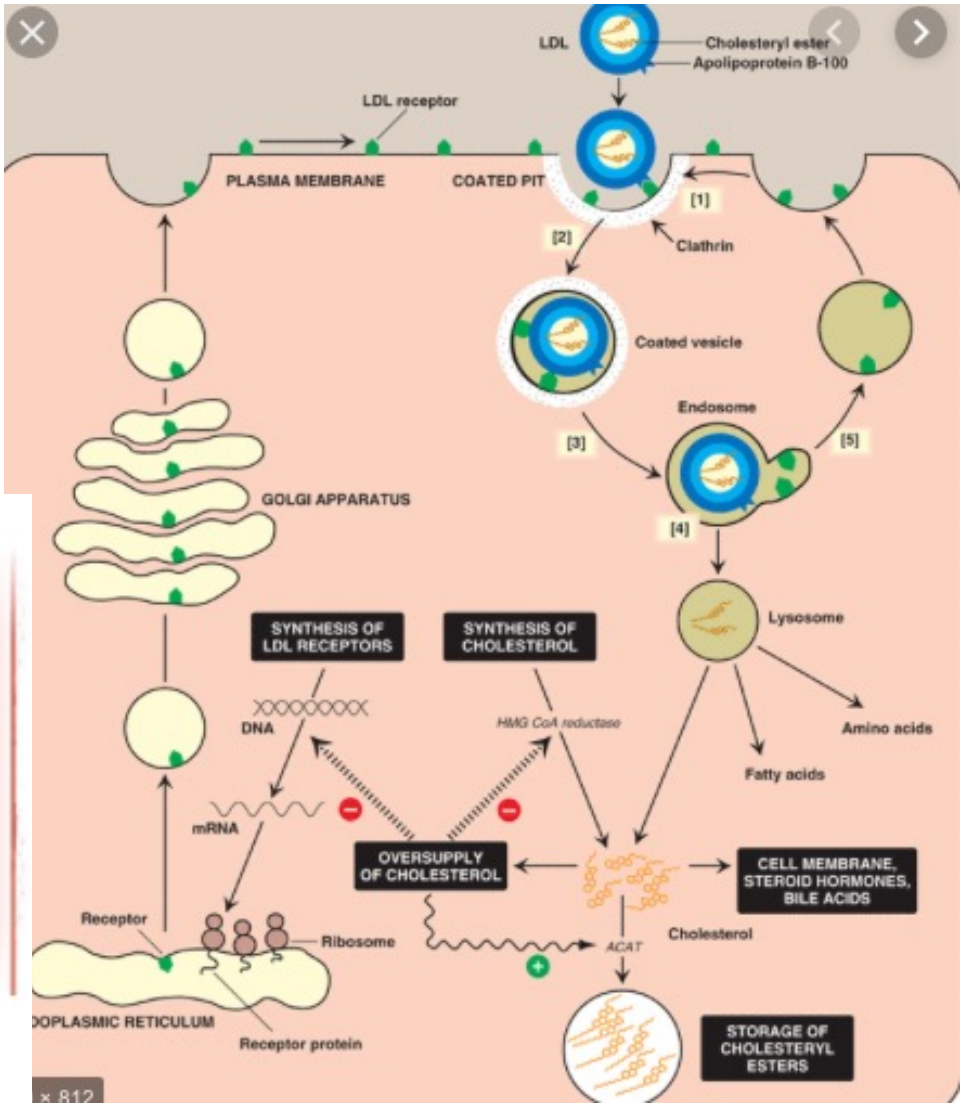
1. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *American journal of epidemiology*. 2004;160:407-420.

Familial hypercholesterolemia leads to revolution in CVD diseases



Xanthelasma, dépôt lipidique de couleur chamois (jaune





ABCA1 transporter mutations : Tangier Island USA

(ATP binding cassette transporter A1)

M.Teddy Laird (“tangier” patient)

Tangier Island

Chesapeak bay Virginia USA

ABCA1 transporter mutations : Tangier Island USA

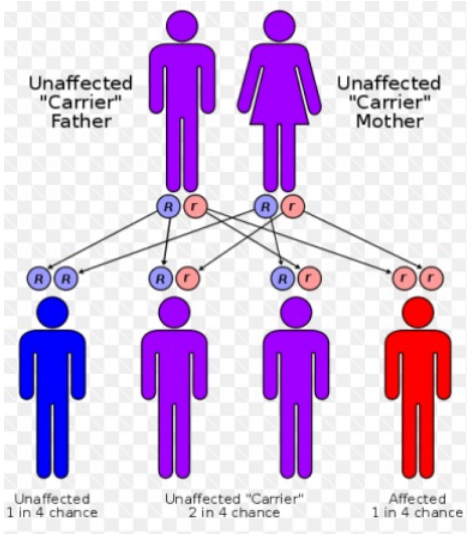
Tangier Disease (Familial High Density Lipoprotein Deficiency)*

Clinical and Genetic Features in Two Adults

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

Rochester, Minnesota *Bethesda, Maryland*

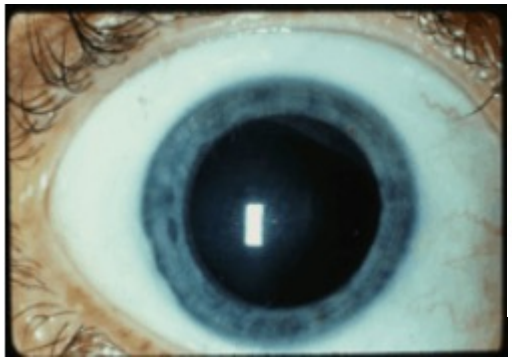
Donald S. Fredrickson, MD; photo courtesy of NIH.

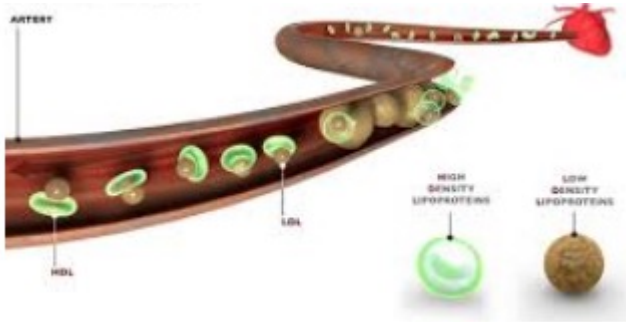


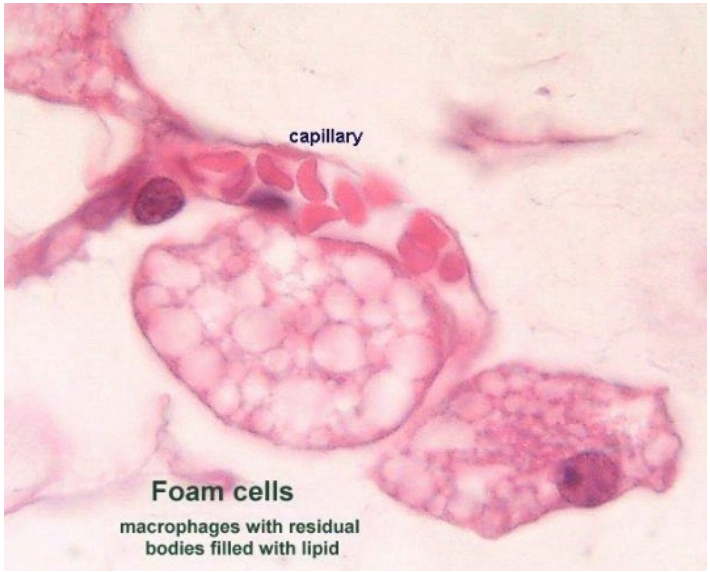
ABCA1 transporter mutations : a RARE disease (hundreds patients ww)

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 CVD disease. Each of the family member had fatalities due to the tangier disease (hypercholesterolaemia)

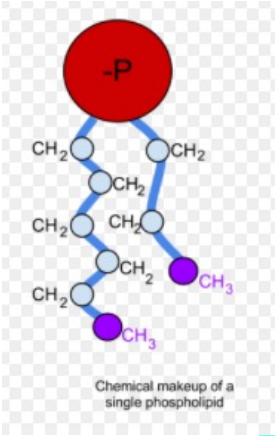
Teddy's sister and investigation revealing an extremely high number of foam cells in not only the tonsils but a wide range of tissues including the bone marrow and spleen, a second trip to the island was made and the discovery was made of **very low HDL cholesterol** in both the sister and parents of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



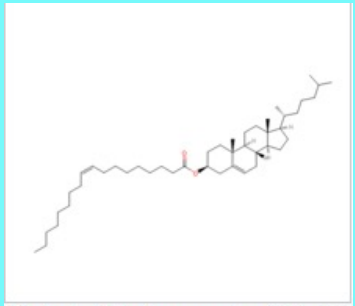




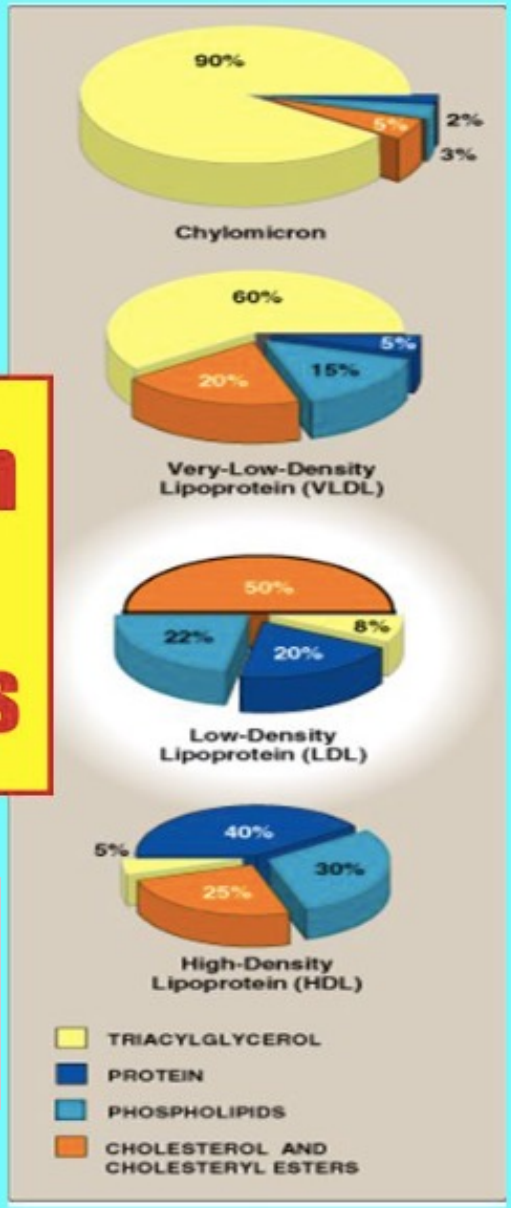
Lipid - protein composition of HDL, LDL and VLDV

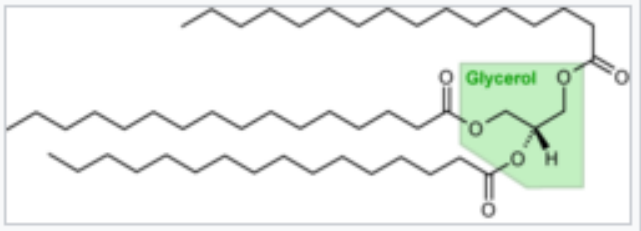


Chemical makeup of a single phospholipid


Cholesterol Oleate, a member of the cholesteryl ester family

Composition of Lipoproteins





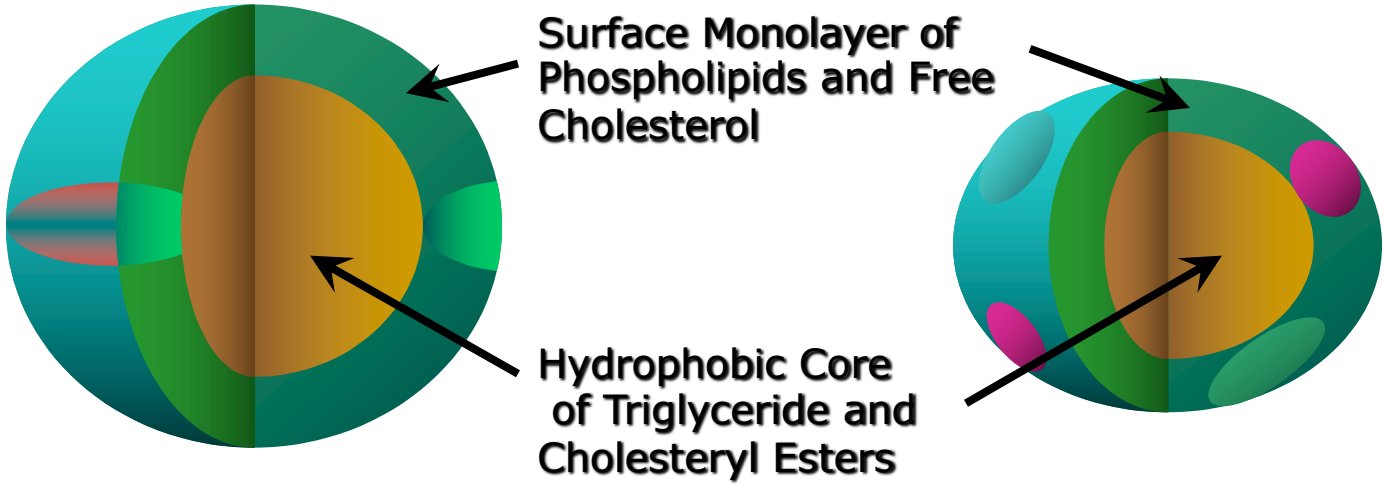
Chylomicrons

Very low density Lipoprotein (VLDL)
ApoB …

Low density Lipoprotein (LDL)

High density Lipoprotein (HDL)
ApoA1 …

THE „BAD“ AND THE „GOOD“



Low density lipoprotein

LDL

20–22 nm

Promote Atherosclerosis

High density lipoprotein

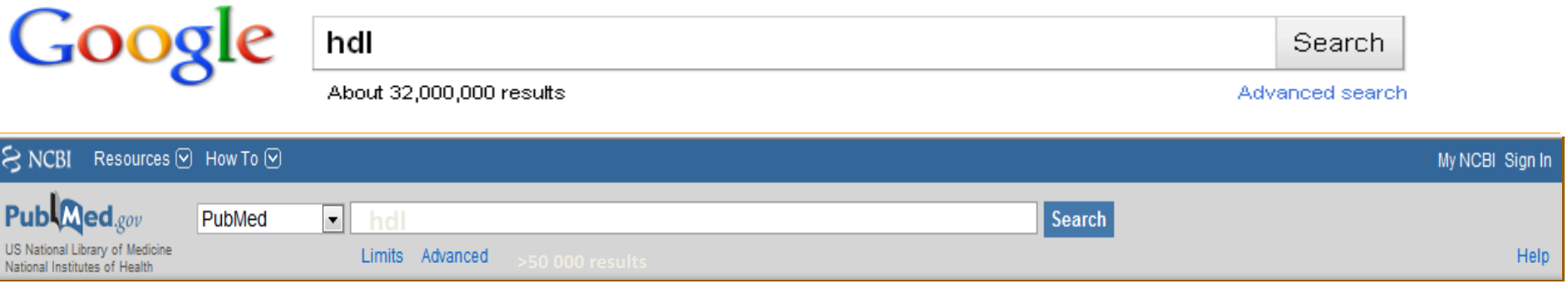
HDL

9–15 nm

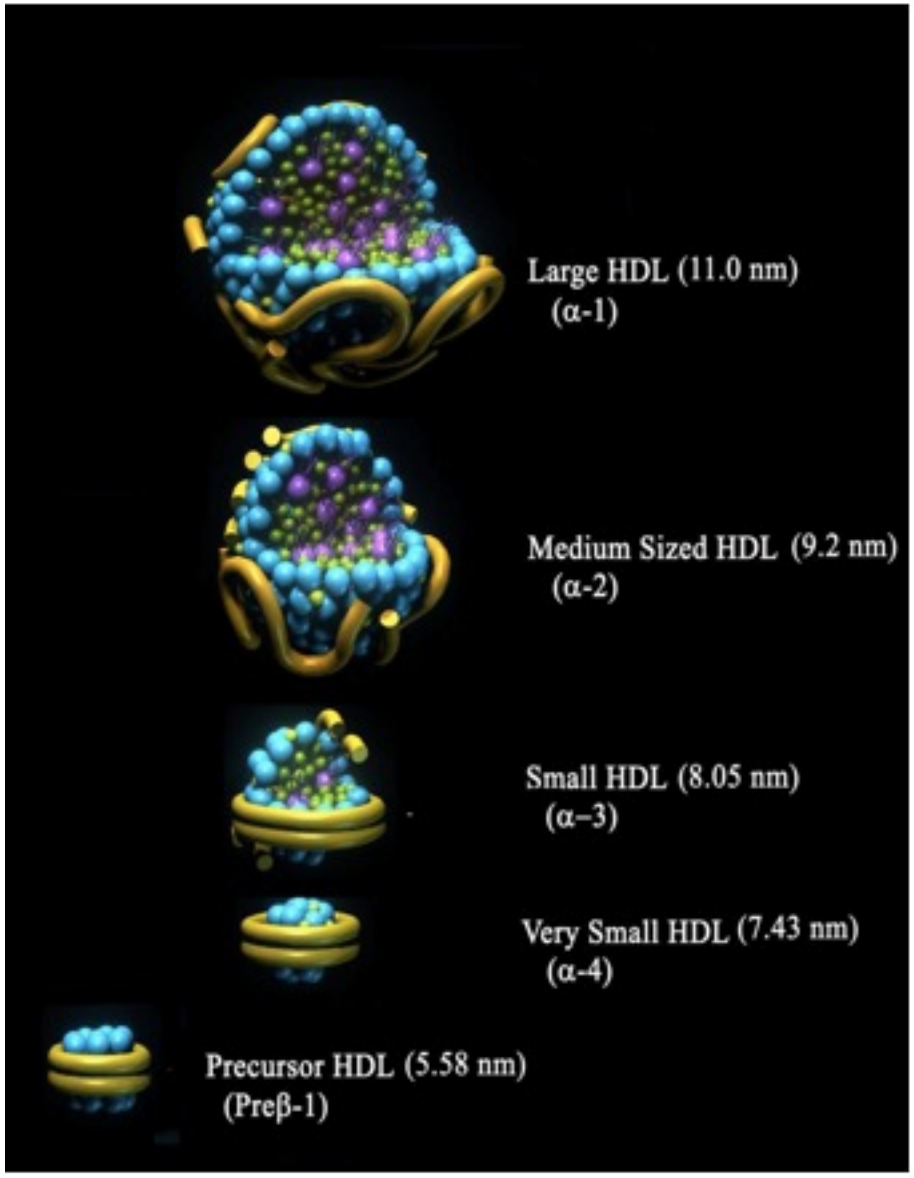
Inhibit Atherosclerosis

Asking Google …

TODAY 2025



Composition of different ApoA1 containing HDL lipoprotein particles



- Large Spherical Alpha 1 HDL, 400 kd, 6 ApoA-I, PL, FC, CE, TG

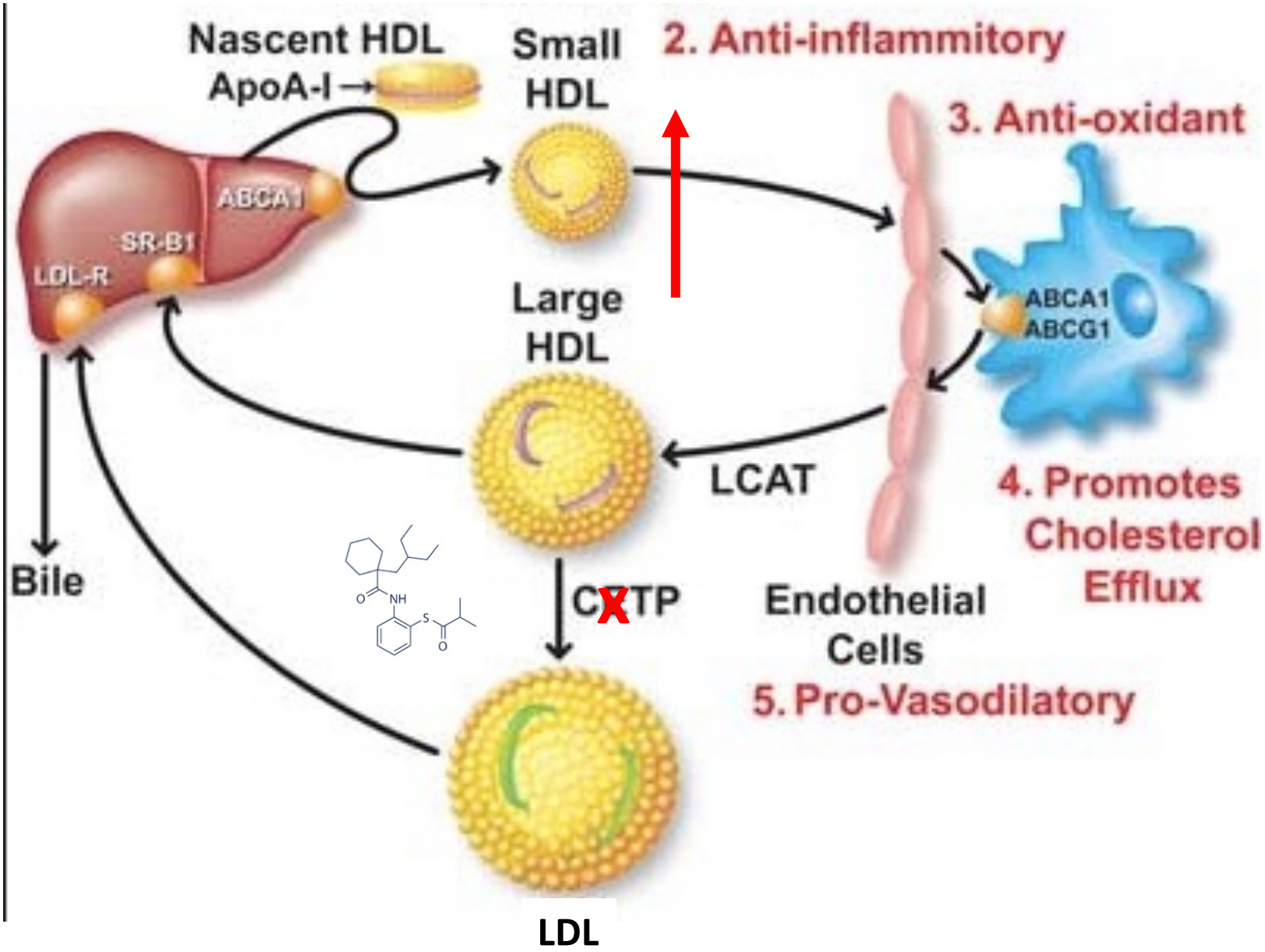
- Medium Spherical Alpha 2 HDL, 250 kd 4 ApoA-I, 2 ApoA-II, PL,FC,CE,TG

- Small Spherical Alpha 3 HDL, 100 kd, 2 ApoA-I, 1 ApoA-II, PL,FC, CE,TG

- Very Small Discoidal Alpha 4 HDL, 70 KD, 2 ApoA-I,PL,FC

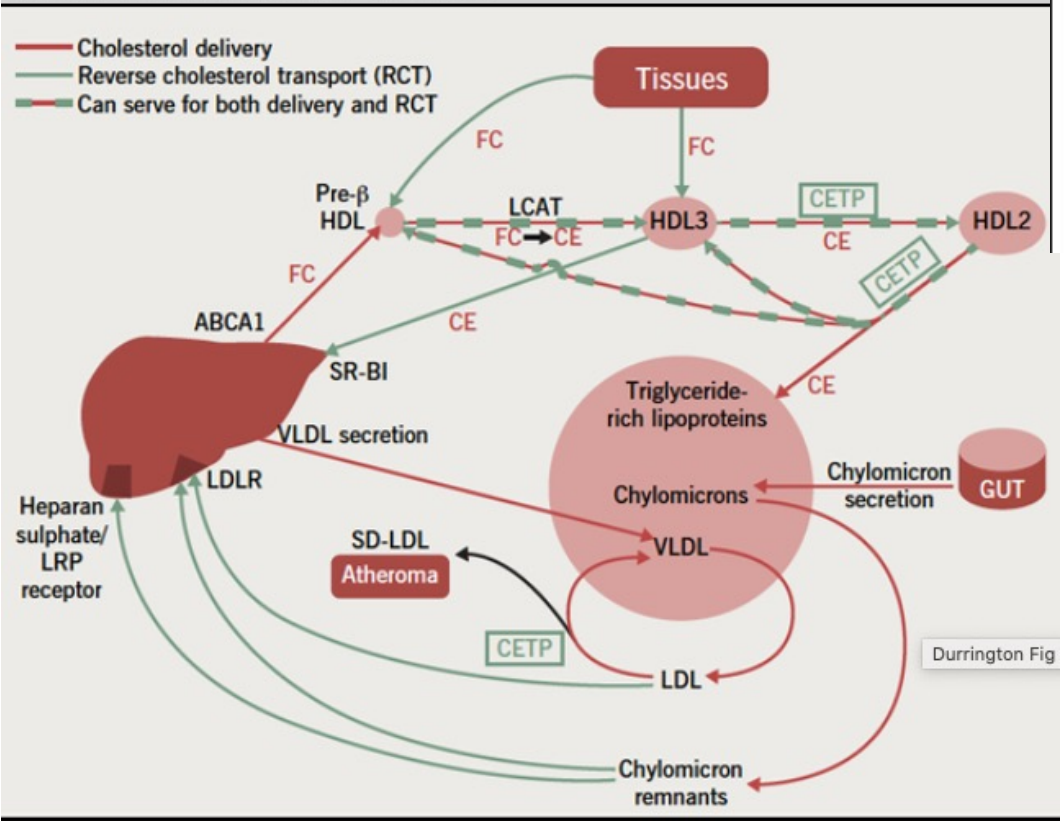
- Very Small Discoidal Pre-Beta 1 HDL, 60 KD, 2 ApoA-I,PL

Reverse cholesterol transport : from the periphery back to the liver
CETP inhibitor clinical candidate

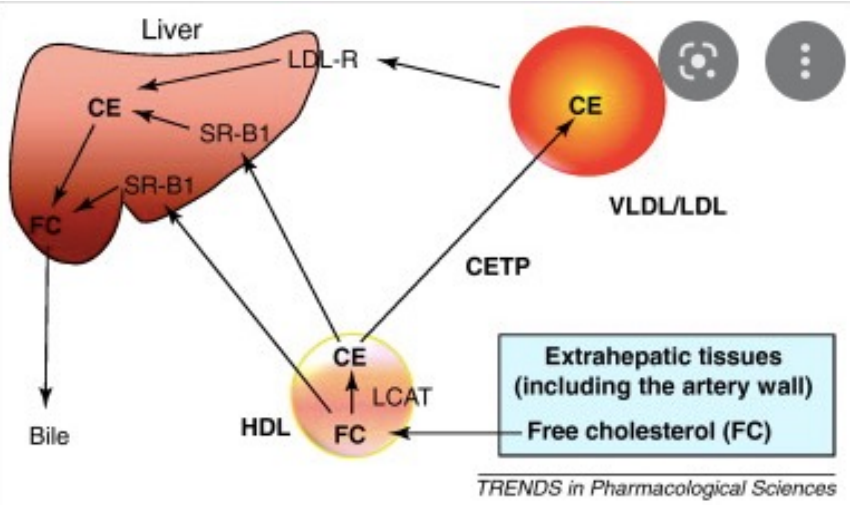


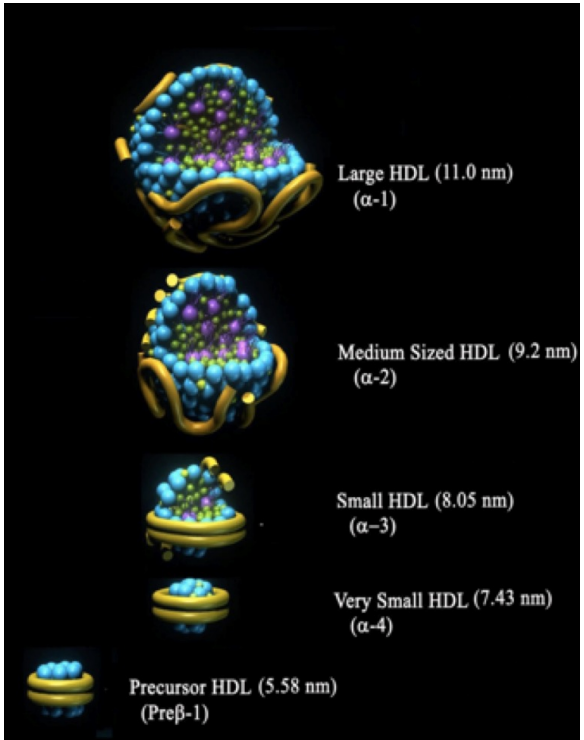
Reverse cholesterol transport : from the periphery back to the liver
CETP inhibitor clinical candidate

Figure 2. Reverse cholesterol transport. Cholesteryl ester transfer protein (CETP) reduces circulating high-density lipoprotein (HDL) levels by transferring cholesteryl ester (CE) from HDL to larger lipoproteins, such as chylomicrons, very low-density lipoprotein (VLDL) and LDL, in exchange for triglyceride. It creates a smaller, cholesterol-depleted HDL (remodelling), which is potentially beneficial in removing excess tissue cholesterol, but also a small, cholesterol-depleted LDL (SD-LDL), which is highly atherogenic. Inhibiting the latter without impairing HDL remodelling may be critical to the success of CETP inhibitors

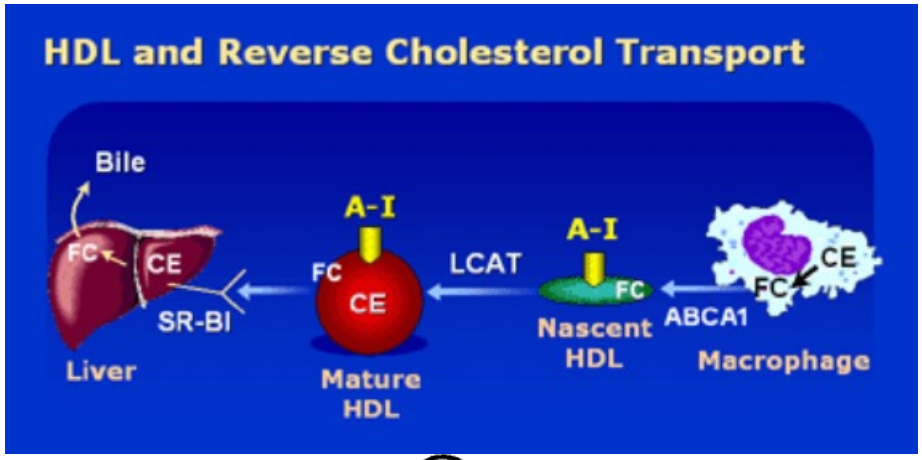


Key: ABCA1 = adenosine triphosphate (ATP) binding cassette A1; CE = cholesteryl ester; CETP = cholesteryl ester transfer protein; FC = free (non-esterified) cholesterol; HDL = high-density lipoprotein (in order of size: pre-β<HDL3<HDL2); heparan sulphate/LRP receptor = heparan sulphate/LDL receptor-like protein receptor; LCAT = lecithin:cholesteryl acyltransferase; LDL = low-density lipoprotein; LDLR = LDL-receptor; SD-LDL = small, dense LDL; SRB1 = scavenger receptor B1; VLDL = very low-density lipoprotein





THE FUTURE IS THE PAST , ONLY BETTER !
HDL and cholesterol homeostasis: still a new concept



From Glomset hypothesis to HDL driven reverse cholesterol transport (RCT)

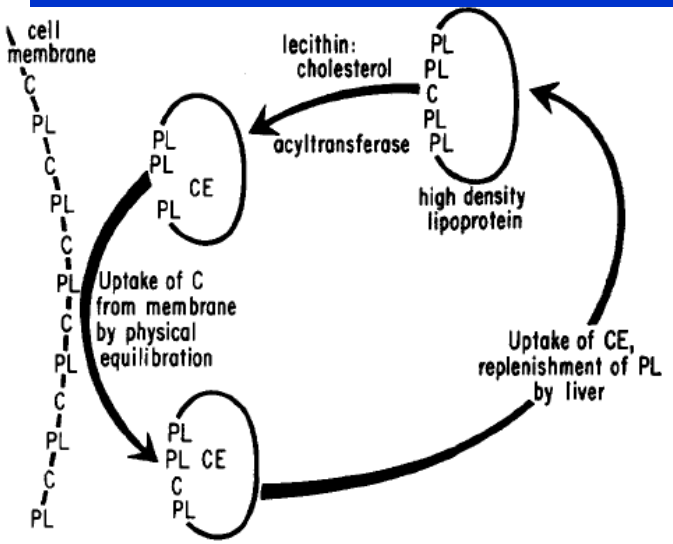
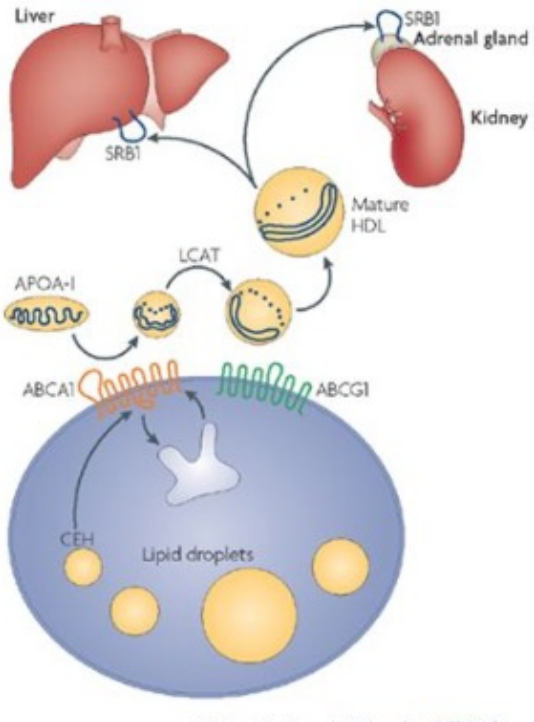
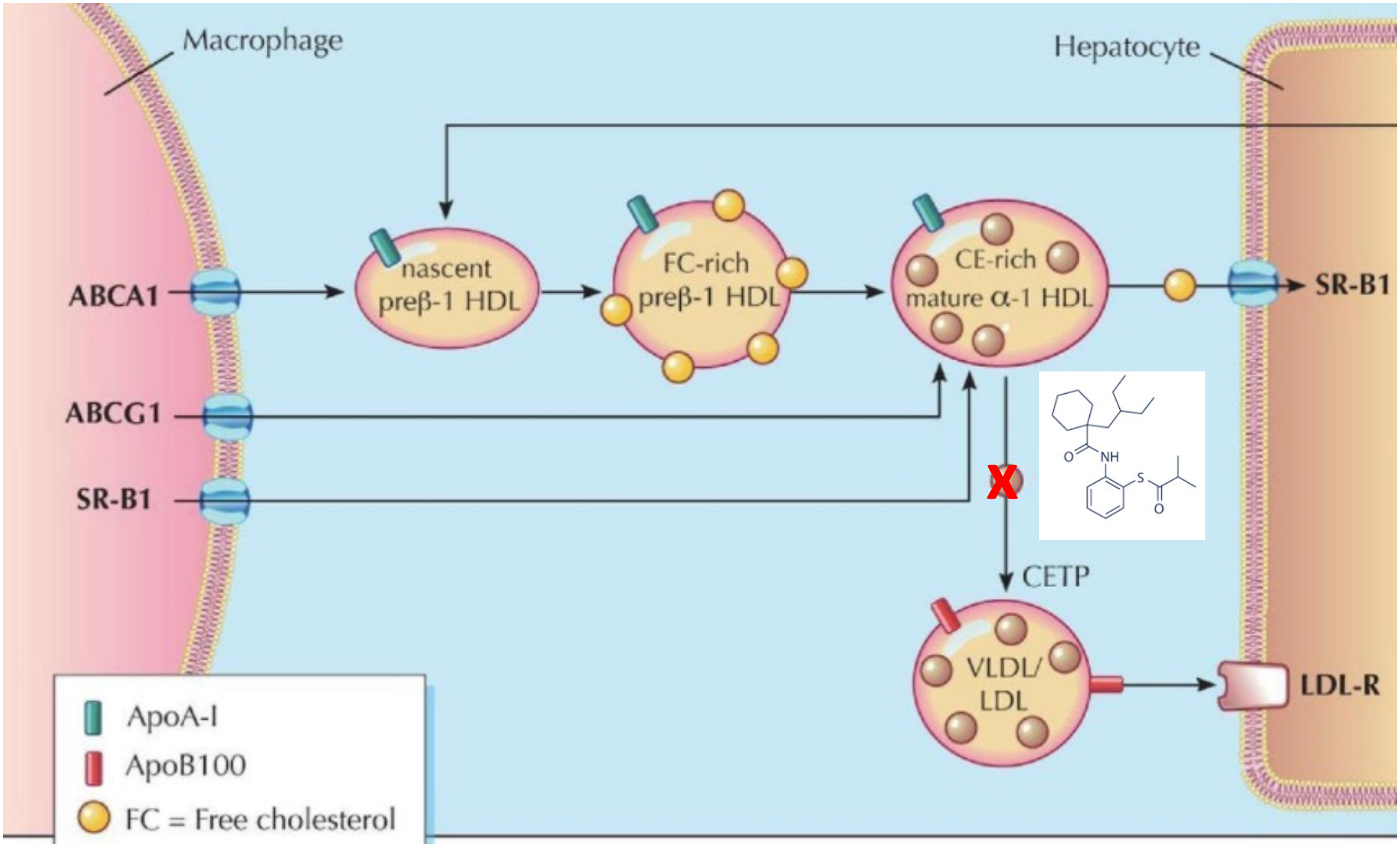


FIG. 1. Postulated mechanism for the transport of cholesterol from membranes of peripheral cells to the liver. Lecithin:cholesterol acyltransferase reacts with circulating lipoproteins to form cholesteryl esters from unesterified cholesterol and lecithin. The lipoproteins subsequently pick up unesterified cholesterol from cell membranes, circulate through the liver, and release esterified cholesterol. C, unesterified cholesterol; CE, cholesteryl ester; PL, phospholipid.

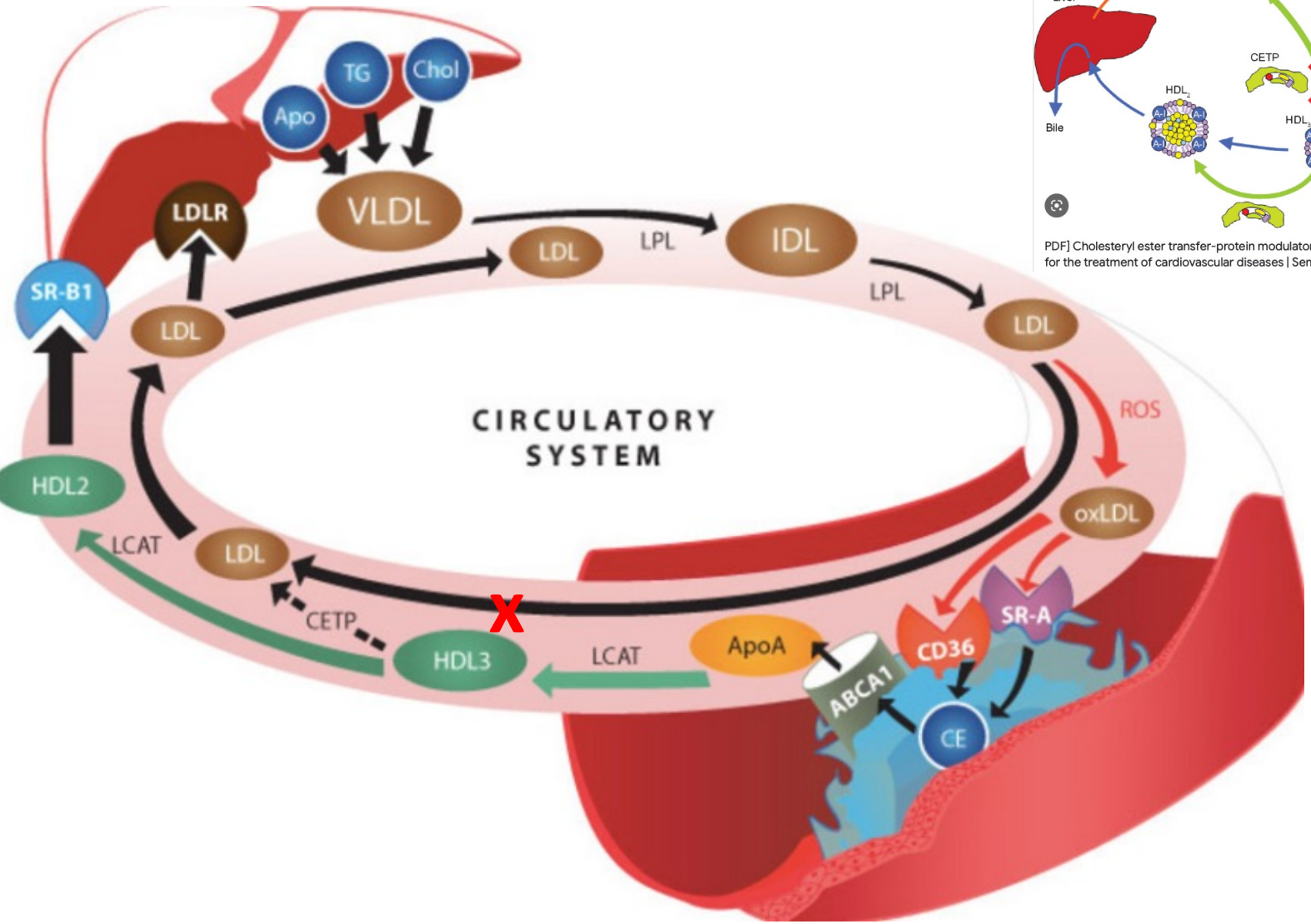
Glomset JA. J. Lipid Res (1968) 9:155-167

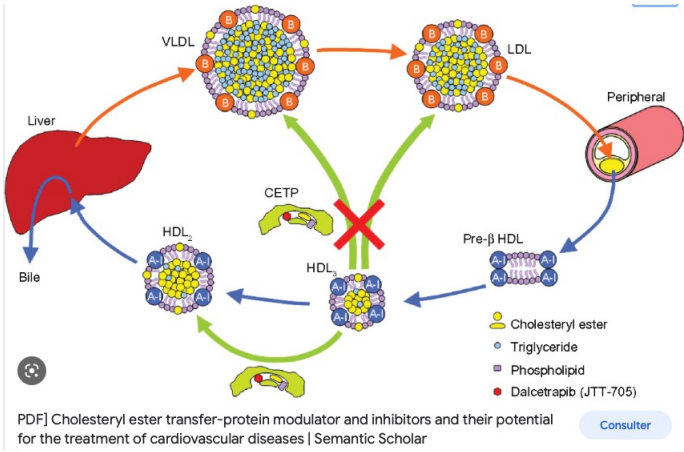


Reverse cholesterol transport : from the periphery back to the liver
The future is the past only better : HDL breakthrough in cardiology ?



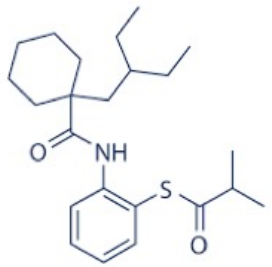
Reverse cholesterol transport : from the periphery back to the liver





PDF] Cholesteryl ester transfer-protein modulator and inhibitors and their potential for the treatment of cardiovascular diseases | Semantic Scholar

Consulter



dalcetrapib

CETP deficiency increases HDL's levels and lowers LDL-C levels with potential decrease of coronary heart diseases CHD : genetic evidence

Research Article

Human plasma CETP deficiency: identification of a novel mutation in exon 9 of the CETP gene in a Caucasian subject from North America

Evelyn M. Teh, Peter J. Dolphin, W. Carl Breckenridge, Meng-Hee Tan

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https://doi.org/10.1016/S0022-2275(20)33905-5

Abstract

Human plasma cholesteryl ester transfer protein (CETP) is a 476-residue hydrophobic glycoprotein that catalyzes the heterotransfer of cholesteryl esters and triacylglycerols among lipoproteins: Mutations in the CETP gene have been identified, mostly in the Japanese population. These mutations result in hypercholesterolemia due to the presence of large cholesteryl ester-rich HDL particles, elevated plasma apoA-I and apoE, and reduced apoB levels. Here we

Korean J Intern Med. 2002 Jun; 17(2): 83–87.
doi: 10.3904/kjim.2002.17.2.83

PMCID: PMC4531667
PMID: 12164095

A common mutation in cholesteryl ester transfer protein gene and plasma HDL cholesterol level before and after hormone replacement therapy in Korean postmenopausal women

Hyun Suk Choi, M.D., Jeong Bae Park, M.D., Ki Ok Han, M.D., Chang Hoon Yim, M.D., Ho Yeon Jung, M.D., Hak Chul Jang, M.D., Hyun Ku Yoon, M.D., Dong Hee Cho, M.D.,* Hyun Ho Shin, M.D., and In Kwon Han, M.D.

Author information Copyright and License information Disclaimer

Abstract

Go to:

Background

Plasma cholesteryl ester transfer protein (CETP) functions to transfer cholesteryl ester from HDL to trigiyceride-rich lipoproteins and regulates plasma HDL cholesterol level. A common mutation, the exon 15 A to G substitution at codon 442 (D442G) results in reduced plasma CETP activity and increased plasma HDL cholesterol level. Meanwhile, hormone replacement therapy (HRT) in postmenopausal women increases plasma HDL cholesterol level.

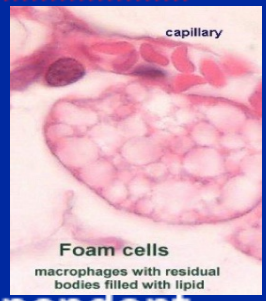
CETP deficiency increases HDL's levels and lowers LDL-C levels with potential decrease of coronary heart diseases CHD

Roche

Functionality of HDL raised in CETP deficient subjects

- Large and cholesteryl ester rich high density lipoprotein in cholesteryl ester protein (CETP) deficiency cannot protect macrophages from cholesterol accumulation induced by acetylated low-density lipoproteins.

  Ishigami, M. et al J Biochem 116, 257-262, 1994



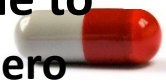
- HDL from CETP-deficient subjects shows enhanced ability to promote cholesterol efflux from macrophages in an apoE and ABCA-1 dependent pathway.

  Matsuura, F. et al J Clin Invest 116, 1435, 2006

- Cholesterol efflux from J774 macrophages and Fu5AH hepatoma cells to serum is preserved in CETP-deficient patients.

  Miwa, K. et al Clinica Chemica Acta (in press 2009)

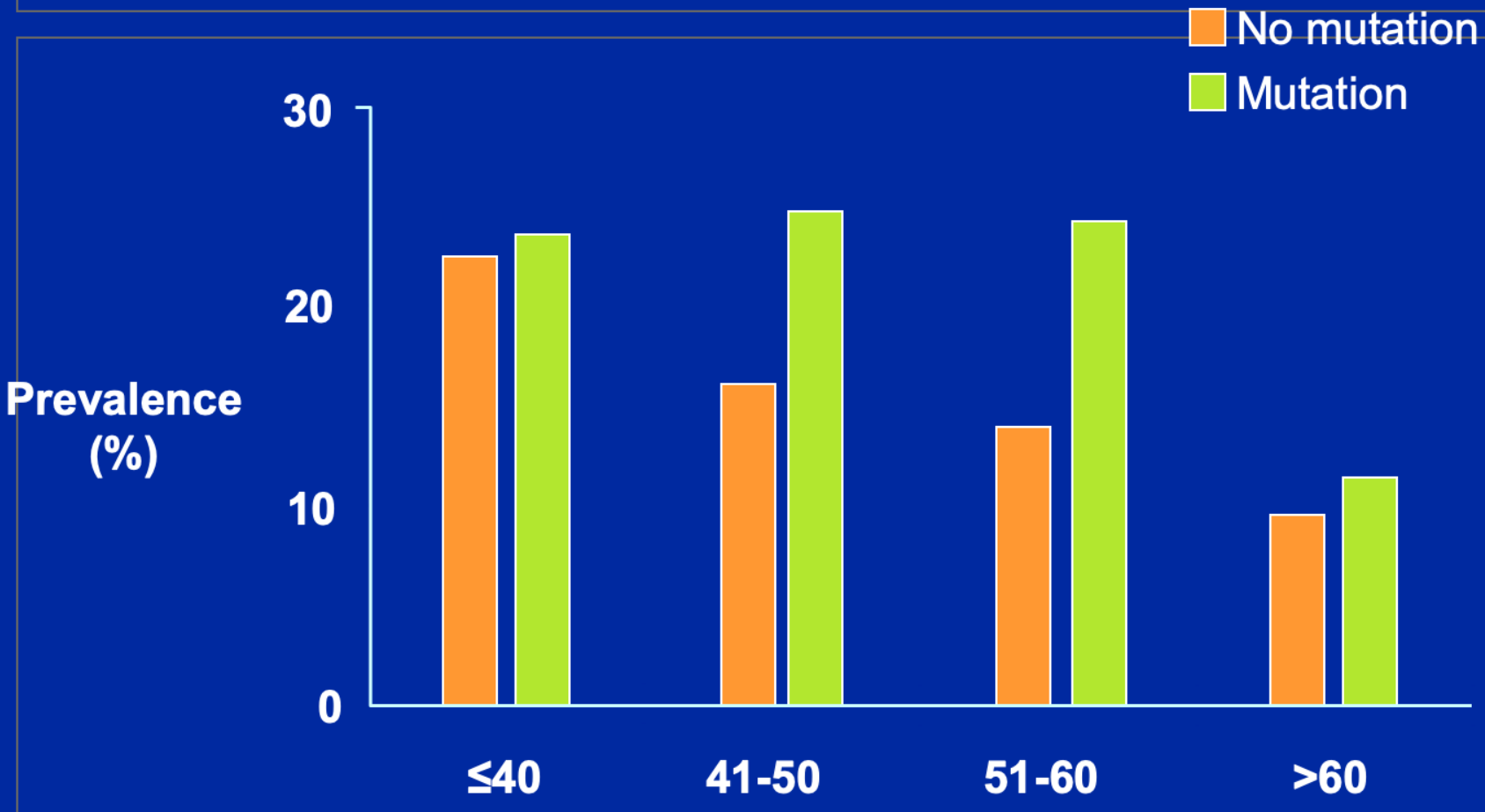
Rabbits like humans have high level of activity of CETP -highly susceptible to atherosclerosis - inhibiting CETP in rabbits and hamsters consistently anti athero



CETP Activity and HDL-C/TC Ratio in Laboratory Animals

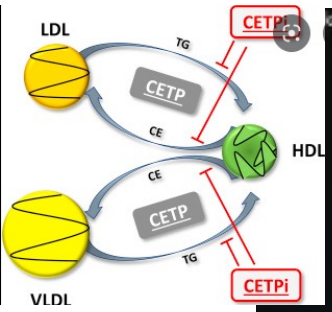
Tsutsumi K et al. *Biol Pharm Bull* 2001;24:579-581

The Honolulu Heart Program: Increased CHD in Men with CETP Mutations

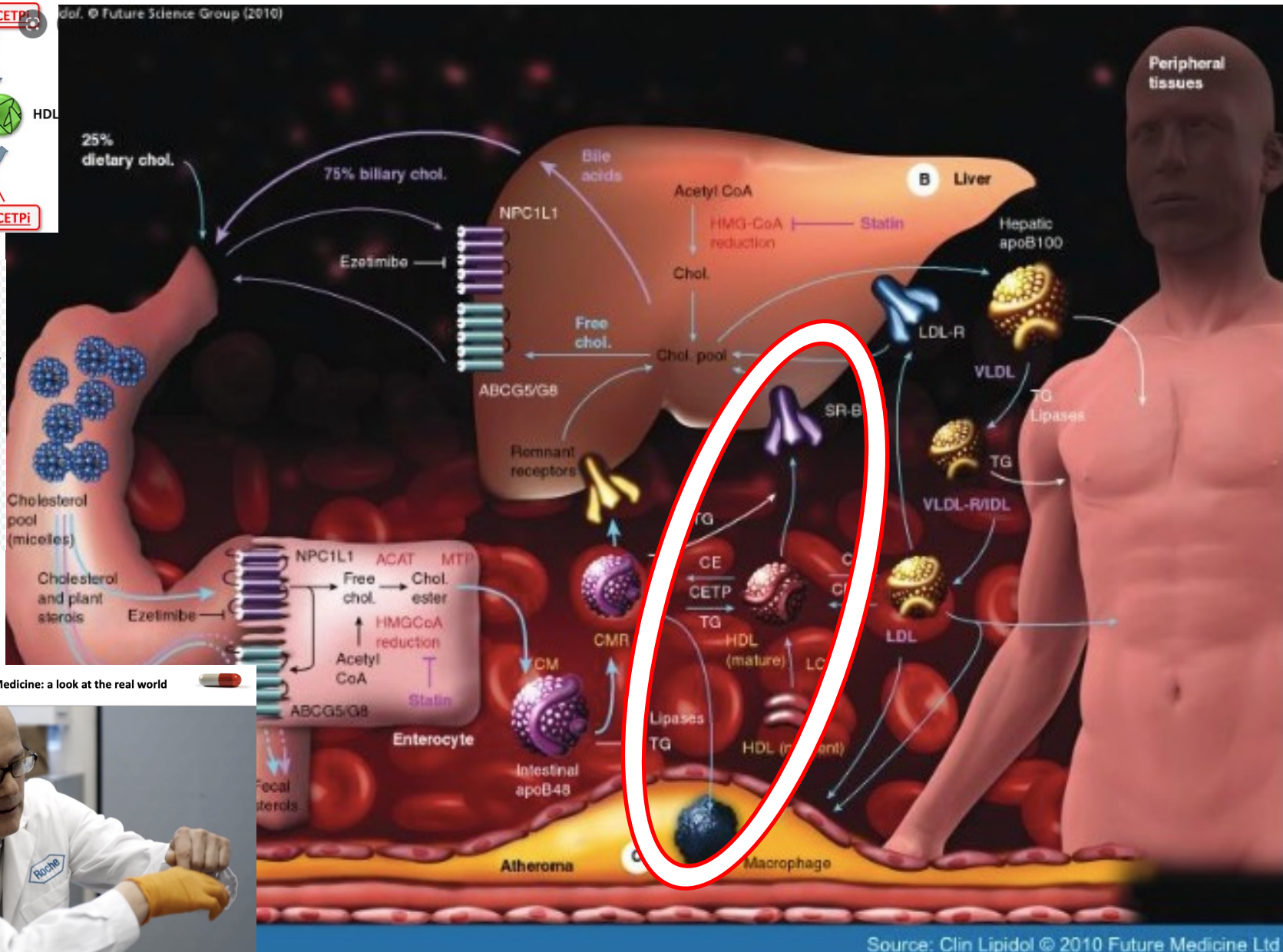


Zhong S et al. *J Clin Invest* 1996;97:2917-2923.

Atheroma as drug target - compelling genetic evidence in human HDL's for CHD – CETP inhibitors

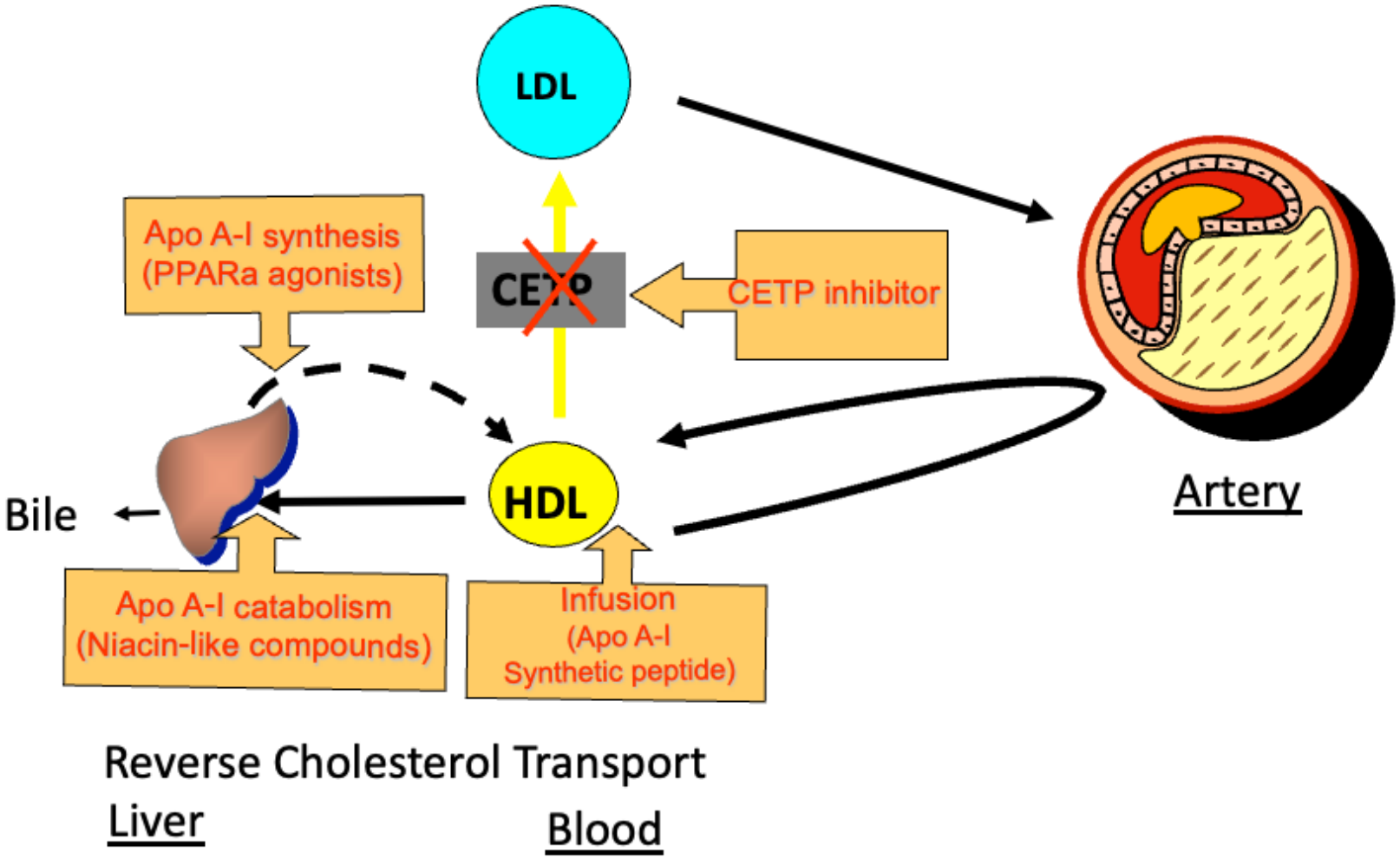


dalcetrapib

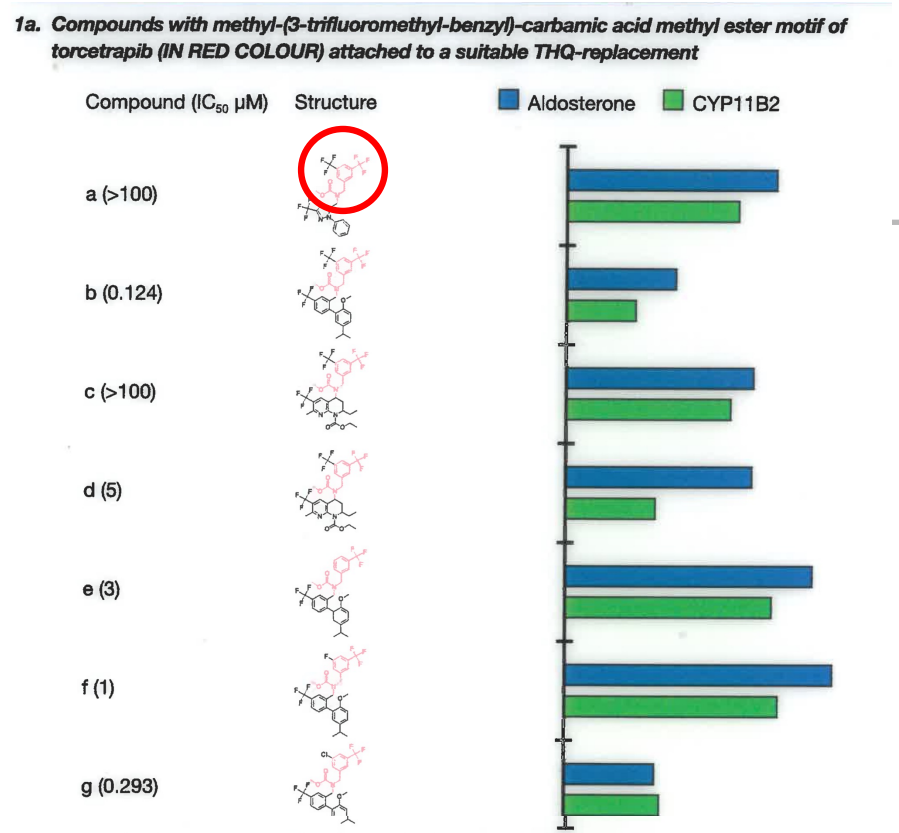


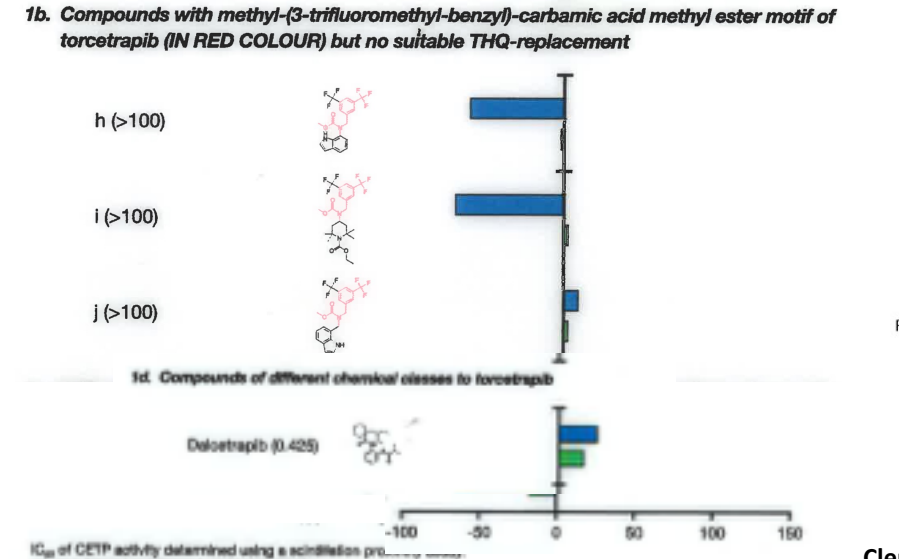
The Making Of An Innovative Medicine: a look at the real world

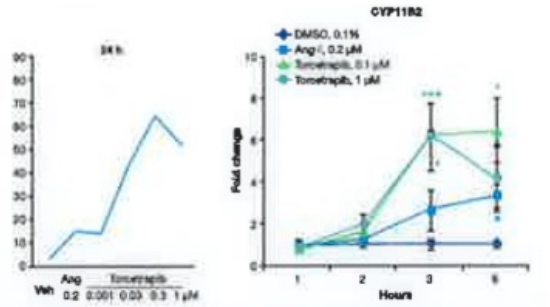
Atheroma as drug target - compelling genetic evidence in human HDL's for CHD – CETP inhibitors



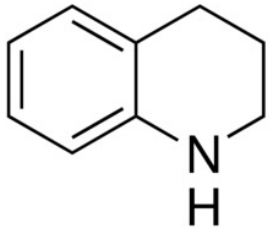
An example of assay read out and medicinal chemistry MDO SAR

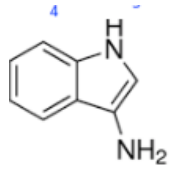






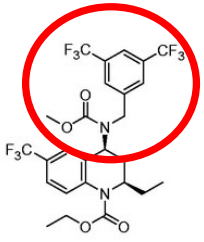
THQ backbone is not a prerequisite for induction of aldosterone /blood pressure



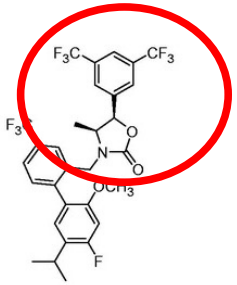


Indole

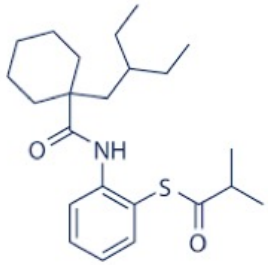
T15504 ALDRICH
1,2,3,4-Tetrahydroquinoline
98%
Synonym: THQ



Torcetrapib



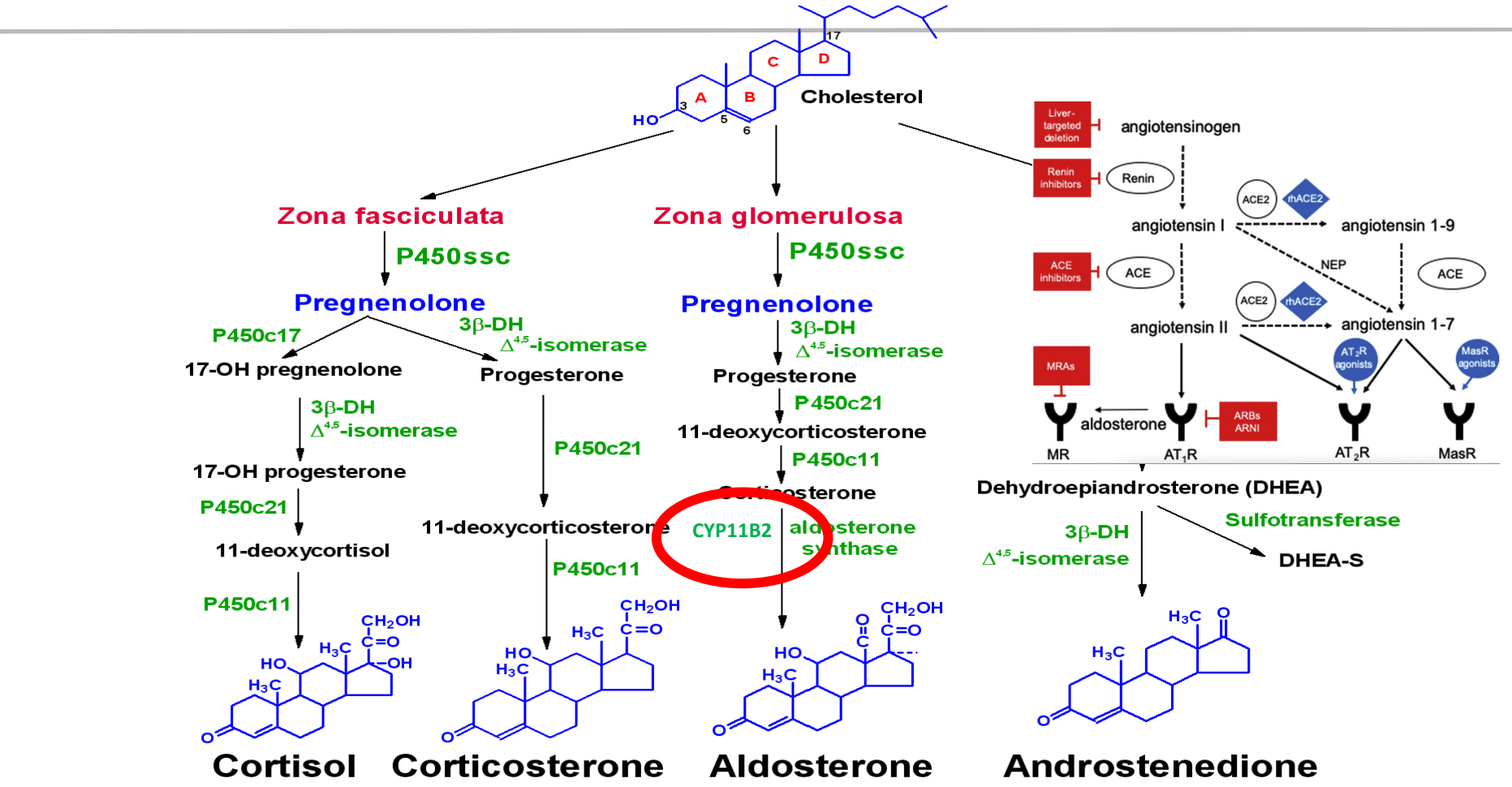
Anacetrapib



dalcetrapib

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

Adrenal Cortex and RAAS pathway



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

CETP deficiency increases HDL's levels and lowers LDL-C levels with potential decrease of coronary heart diseases CHD

Mechanisms underlying off-target effects of the cholesteryl ester transfer protein inhibitor torcetrapib involve L-type calcium channels

Roger G. Clerc[a], Andrea Stauffer[a], Franziska Weibel[a], Emmanuelle Hainaut[a], Anne Perez[a], Jean-Christophe Hoflack[a], Agnès Bénardeau[a], Philippe Pflieger[a], Jose M.R. Garriz[b], John W. Funder[c], Alessandro M. Capponi[b] and Eric J. Niesor[a]

Objective The increased mortality observed with the cholesteryl ester transfer protein inhibitor torcetrapib is partly due to increased aldosterone production and blood pressure. The mechanisms underlying these effects were investigated.

Methods Cytochrome P450 subunit 11B2 (aldosterone synthase), extracellular signal-regulated kinase (p44/42) and voltage-gated Ca^{2+} channel alpha subunit mRNA profiling, aldosterone production, cytosolic calcium and RNA interference were assessed in adrenocarcinoma human cells (H295R). Telemetry was conducted in spontaneously hypertensive rats.

alpha 1C subunit. In spontaneously hypertensive rat, torcetrapib had a potent hypertensive effect mediated by the L-type Ca^{2+} channel.

Conclusion The unique steroidogenic and hypertensive side effects of torcetrapib may be linked and involve voltage-gated L-type Ca^{2+} channels. Structurally unrelated cholesteryl ester transfer protein inhibitors such as dalcetrapib do not share this effect. *J Hypertens* 28:1676–1686 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Journal of Hypertension 2010, 28:1676–1686

✤ *Author's Choice*

BJP BRITISH JOURNAL OF PHARMACOLOGY

BPS BRITISH PHARMACOLOGICAL SOCIETY

British Journal of Pharmacology (2009), 158, 1763–1770

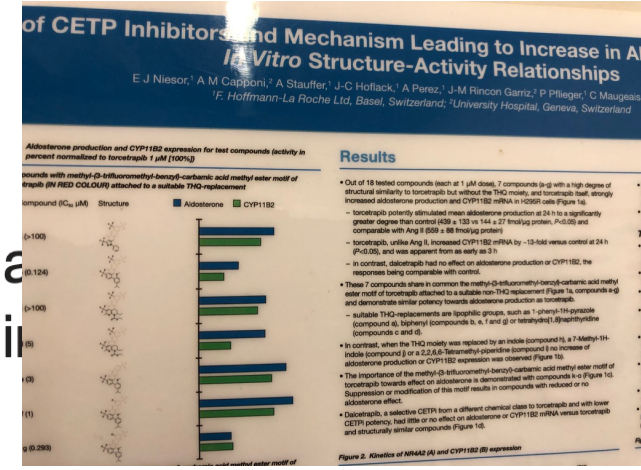
0007-1188/09
www.brjpharmacol.org

RESEARCH PAPER

Dalcetrapib: no off-target toxicity on blood pressure or on genes related to the renin-angiotensin-aldosterone system in rats

ESG Stroes[1], JJP Kastelein[1], A Bénardeau[2], O Kuhlmann[2], D Blum[2], LA Campos[2,3], RG Clerc[2] and EJ Niesor[2]

[1]*Academic Medical Center, Amsterdam, The Netherlands,* [2]*F. Hoffmann-La Roche Ltd, Basel, Switzerland, and* [3]*Faculty of Medicine, Aalborg University, Denmark*


of CETP Inhibitors and Mechanism Leading to Increase in A
In Vitro Structure-Activity Relationships
E J Niesor,[1] A M Capponi,[2] A Stauffer,[1] J-C Hoflack,[1] A Perez,[1] J-M Rincon Garriz,[2] P Pflieger,[1] C Maugeais
[1]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [2]University Hospital, Geneva, Switzerland
Aldosterone production and CYP11B2 expression for test compounds (activity in percent normalized to torcetrapib 1 µM (100%))
Aldosterone
CYP11B2
Results

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

Eric J. Niesor,[1,]* Christine Magg,[2,]* Naoto Ogawa,[†] Hiroshi Okamoto,[†] Elisabeth von der Mark,* Hugues Matile,* Georg Schmid,* Roger G. Clerc,* Evelyne Chaput,* Denise Blum-Kaelin,* Walter Huber,* Ralf Thoma,* Philippe Pflieger,* Makoto Kakutani,[†] Daisuke Takahashi,[†] Gregor Dernick,* and Cyrille Maugeais*

Pharmaceuticals Division,* F. Hoffmann-La Roche Ltd, Basel, Switzerland; and Central Pharmaceutical

CETP deficiency increases HDL's levels and lowers LDL-C levels with potential decrease of coronary heart diseases CHD

Roche

Roche Pharma
CEO Awards

for Innovation and Excellence

OVERALL WINNER

08

Roger Clerc, PhD

Differentiation of CETP inhibitors according to their potential off-target adverse effects

Menschen & Meinungen 13

Roche Nachrichten · Ausgabe 2/2009

Wissenschaft ist sein Leben

Roger G. Clerc kennt die Höhen und Tiefen des Forscheralltags. Auch als kaum noch einer an den einst viel gepriesenen Herz-Kreislauf-Wirkstoff glaubte, forschte er unermüdlich weiter. Mit Erfolg: Kürzlich erhielten er und seine Mitstreiter den Roche Pharma CEO Award.

Helden des Alltags (19)

Es ist einer der bewegendsten Momente im Leben des Roger G. Clerc: 180 General Manager klatschen minutenlang, während der Molekularbiologe und seine Mitstreiter den Roche Pharma CEO Award entgegennehmen. Lobende Worte von Pharma-Chef Bill Burns: «Ich habe viele exzellente Gewinner-Projekte geprüft und zwei Gesamtsieger ausgewählt, die unsere Kriterien nicht nur erfüllt haben, sondern viel mehr als das», sagt er beim Pharma-Management-Forum in Buonas.

Es war ein denkwürdiger Abend. Und doch ist der Molekularbiologe froh, jetzt wieder in seinem bescheidenen Büro zu sitzen. «Ich tauge nicht als Popstar», sagt der Laborleiter in der präklinischen Forschung mit Spezialgebiet Genomik (Gesamtheit aller Gene). «Die Wissenschaft ist mein Leben.» Clerc hat schon manche Auszeichnung erhalten. Doch diesmal war es anders. Anerkannt wurde ein Projekt, an das kaum noch einer glauben wollte. Der Senior Scientist arbeitete trotz erheblichen Widerstands unermüdlich weiter. Nach einreinhalb Jahren konnte er seine These beweisen.

Querdenker

Roger Clerc und Eric Nieser waren die treibenden Kräfte bei einem Projekt um einen Herz-Kreislauf-Wirkstoff – aus der Klasse der sogenannten CETP-Hemmer. Clerc hatte gezeigt, dass Dalcetrapib, ein Cholesterylester-Transferprotein-(CETP)-Hemmer, den Roche von Japan Tobacco einlizenziert hatte, nicht die gravierenden Nebenwirkungen hatte wie die Substanz eines grossen Mitbewerbers. Dieser Pharmakonzern hatte die Entwicklung in Phase III abgebrochen, da der Wirkstoff mit einer erhöhten Sterberate in Verbindung gebracht wurde. Dabei hatte man zuvor grosse Hoffnungen in diese Wirkstoffklasse gesetzt. Im Gegensatz zu den Fettsenkern sollen CETP-Hemmer die Konzentration des sogenannten 'guten' HDL-Cholesterins gezielt ansteigen lassen. Dies wiederum soll eine schützende Wirkung auf das Herz haben.

Roche hatte den Wirkstoff damals in Phase-II-Studien und bereits viele Millionen investiert. Doch auch hier dachte man ans Aufgeben. Nicht so Clerc. «Ich war überzeugt, dass die hohe Sterblichkeit nicht spezifisch ist für die ganze Wirkstoffklasse.» Also machte er sich auf die Suche nach einer Erklärung für den Wirkmechanismus der Konkurrenzsubstanz und die Todesursache. Sein Fazit: Diese spezielle Substanz kurbelt die Produktion des Hormons Aldosteron an, was in hoher Konzentration zu hohem Blutdruck führt und bei einigen Patienten schliesslich zum Tod. Das Roche-Produkt hat diese Nebenwirkungen nicht, da es eine andere, einzigartige chemische Struktur besitzt. «Dies zeigten wir in Tiermodellen und liessen die Ergebnisse von externen Experten überprüfen.»

Milliardenmarkt

Seit April 2008 testet Roche die Substanz jetzt in Phase III an 15'000 Patienten und plant, das Produkt 2013 oder 2014 auf den Markt zu bringen. Sollten sich die Beobachtungen aus Tiermodellen bestätigen und keine weiteren Komplikationen auftreten, dann wartet ein Milliardenmarkt auf die neue Medikamentenklasse. «In Versuchen mit Goldhamstern wurde gezeigt, dass durch die erhöhte HDL-Konzentration Cholesterinablagerungen an den Arterienwänden sogar wieder abgebaut werden können», berichtet Clerc und macht sich auf den Weg zu einem Meeting.

Fortsetzung auf Seite 14

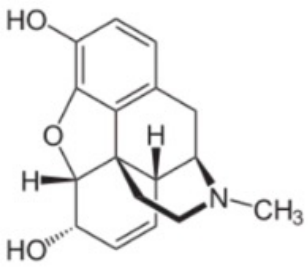
Forschen

Kaum einer glaubte an sein Forschungsprojekt. Jetzt erhielten Roger G. Clerc und seine Mitstreiter den Pharma CEO Award. Seite 13

SAR : eg. from poppy seeds to modern analgesics

Opium

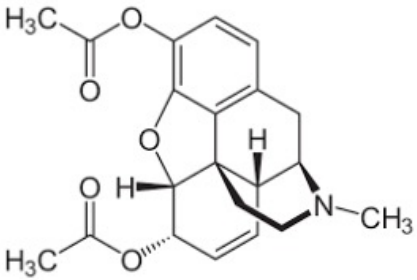
Morphine



strong analgesic
bioavailability 25%

logD=0.04

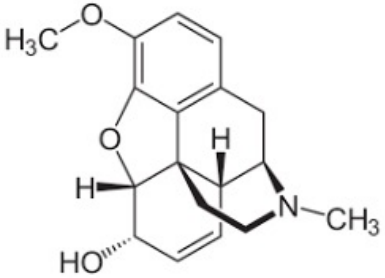
Heroin



2-4x potent vs **1**
better brain penetrant

logD=0.93

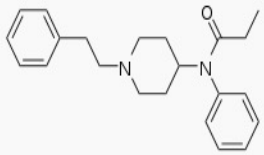
Codeine

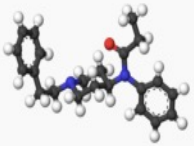


much less potent vs **1**
metabolised to **1**
by CYP2D6

logD=0.46

Fentanyl

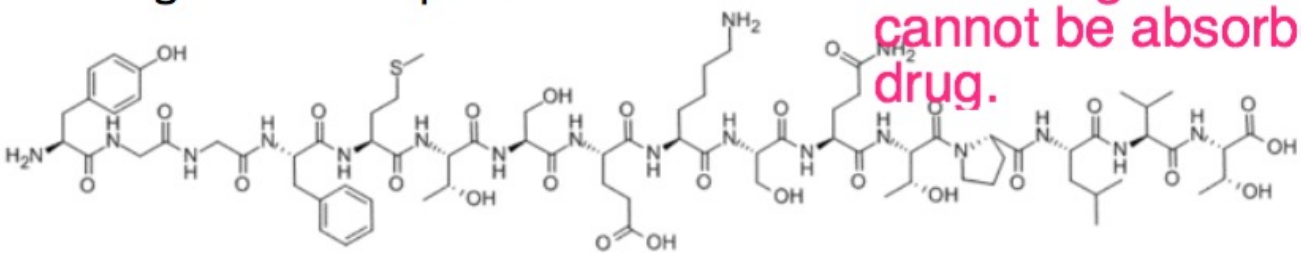




more potent vs **1**
longer half life
bioavailability 87%

logD=2.37

Natural ligands: endorphins

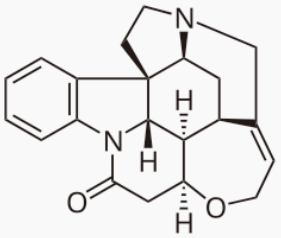


such a big molecule cannot be absorbed as a drug.

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

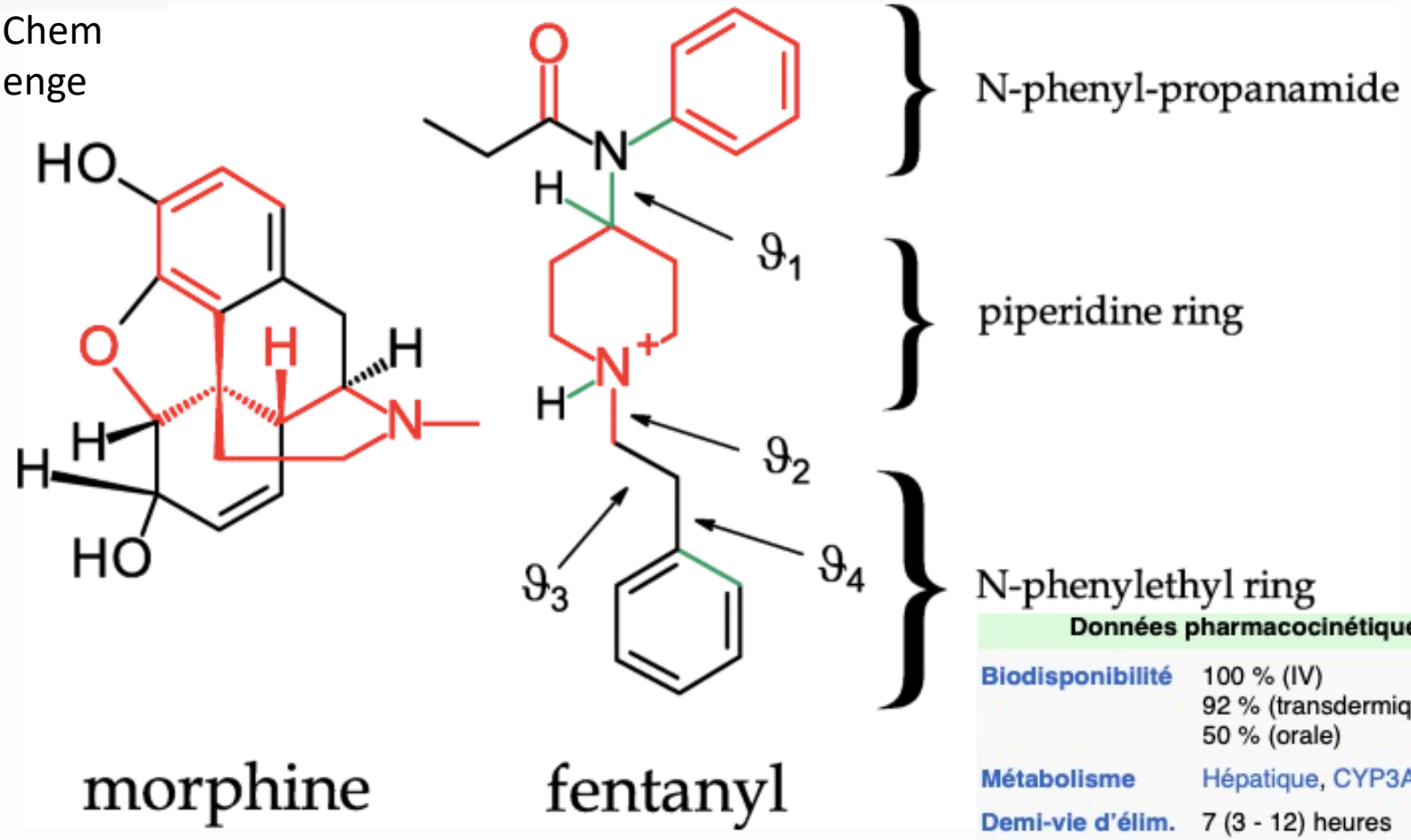
Structure activity relationships (SAR) and structure property relationships (SPR)

Strychnine



SAR : eg. from poppy seeds to modern analgesics

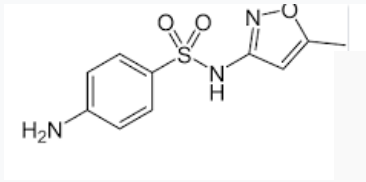
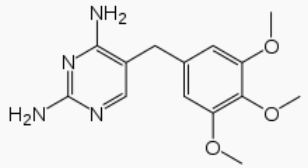
MedChem challenge

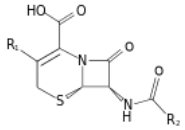


Données pharmacocinétiques	
Biodisponibilité	100 % (IV) 92 % (transdermique) 50 % (orale)
Métabolisme	Hépatique, CYP3A4
Demi-vie d'élim.	7 (3 - 12) heures
Excrétion	Rénale

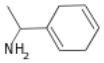
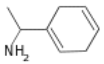
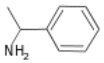
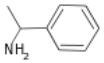
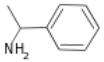
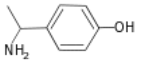
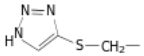
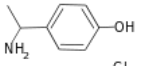
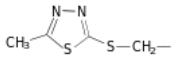
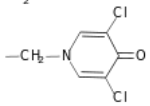
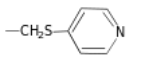
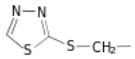
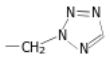
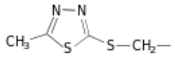
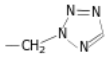
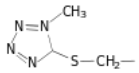
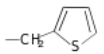
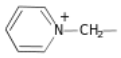
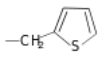
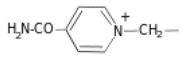
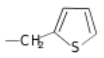
μ-opioid receptor (μOR) agonists are the most effective medicines in treatment of severe pain

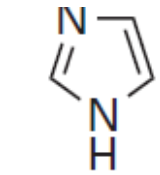
Medicinal chemistry : antibacterials

	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-baciles (germes en pédiatrie): • Moraxella • Branhamella catarrhalis   a combo winner :sulfammethoxasol/trimetoprim : nice charged groups, loves water : broad spectrum gram negative urinary tract infection
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, heliicobacter 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)**



Medicinal chemistry : the cephalosporin example

	R_1 —	— R_2
Cefacetril	CH_3COOCH_2—	—CH_2—CN
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		



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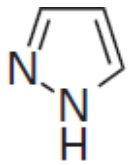
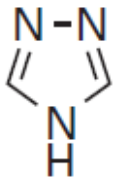


pyrazole



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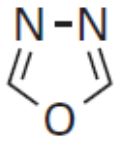
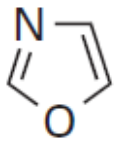


1,3,4-oxadizole



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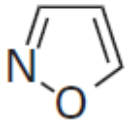

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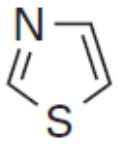

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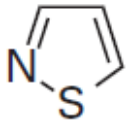
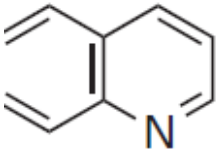


isothiazole



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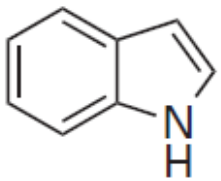
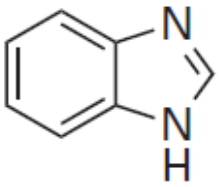
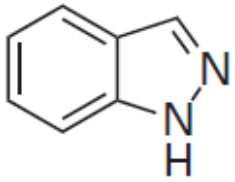


indole

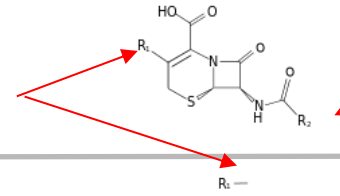


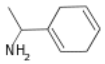
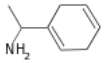
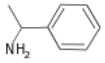
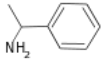
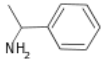
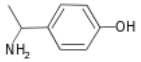
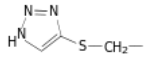
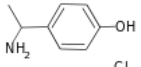
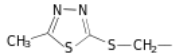
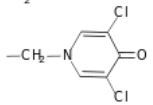
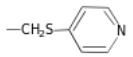
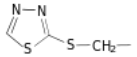
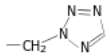
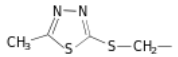
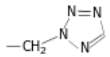
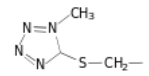
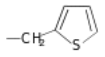
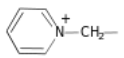
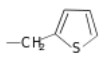
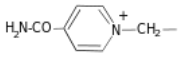
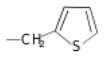
benzimidazole



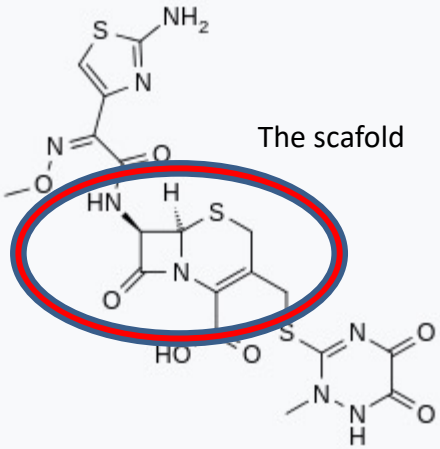
indazole

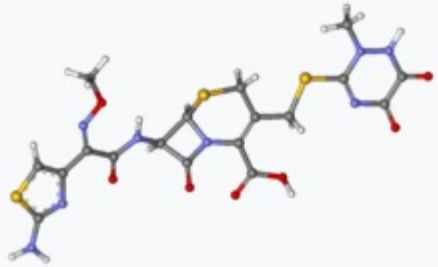
Ceftriaxone (Rocephin®) : a cephalosporin third generation
Rp meningitis, endocarditis, nephritis etc



	R_1	R_2
Cefacetril	CH_3COOCH_2—	—CH_2—CN
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		

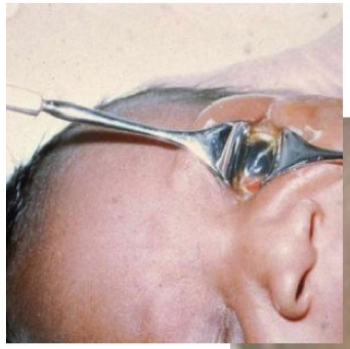
Ceftriaxone



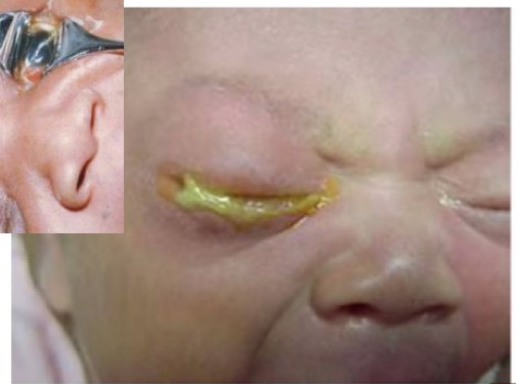


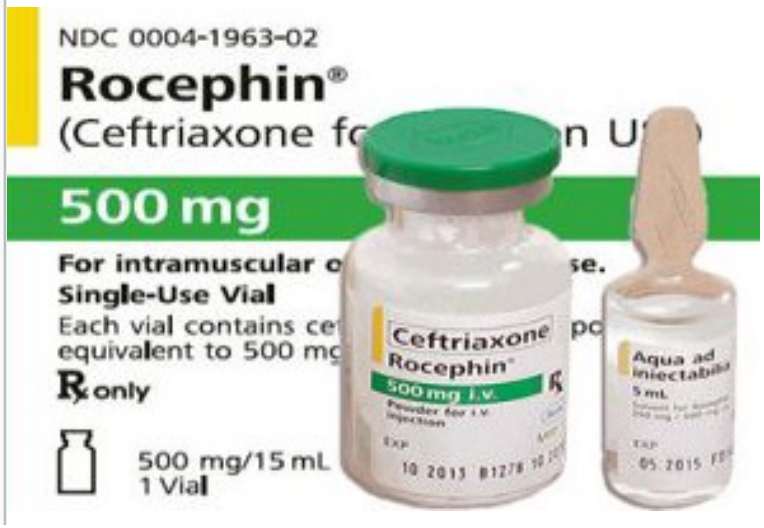
Clinical data

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

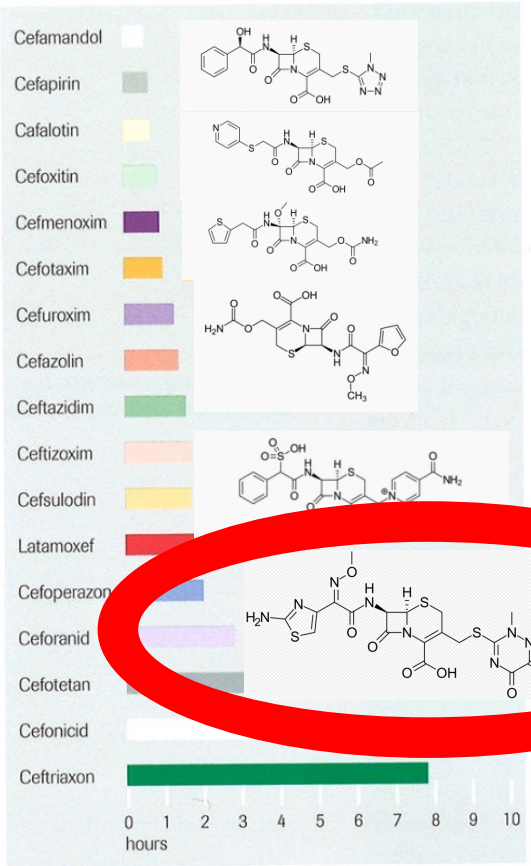


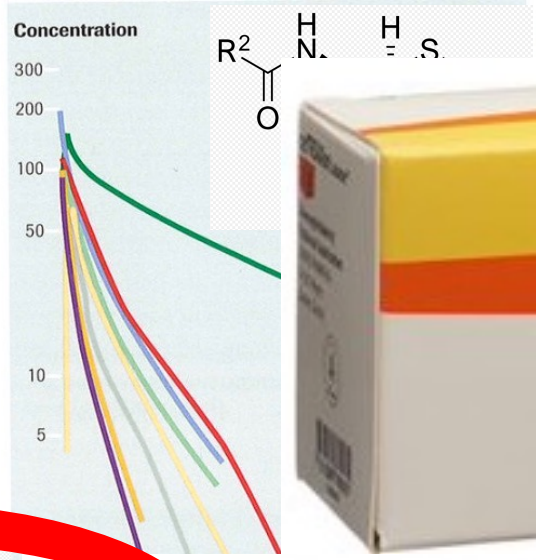
Gonoccoccal ophtalmia neonatorum





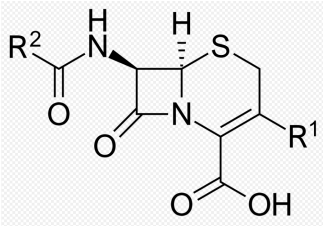
World most prescribed injectable cephalosporin Rocephin® becomes Ceftriaxon, a generic blockbuster

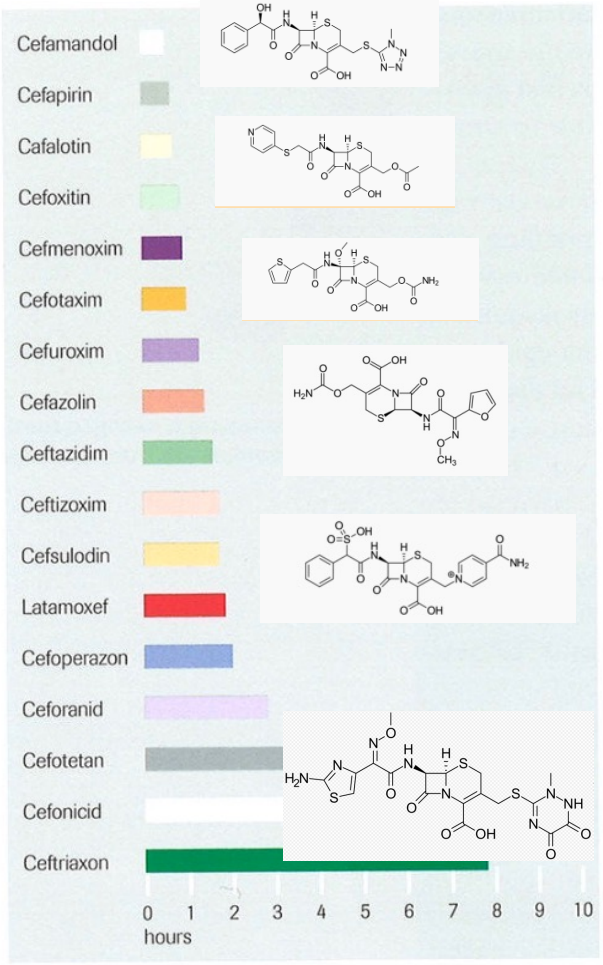


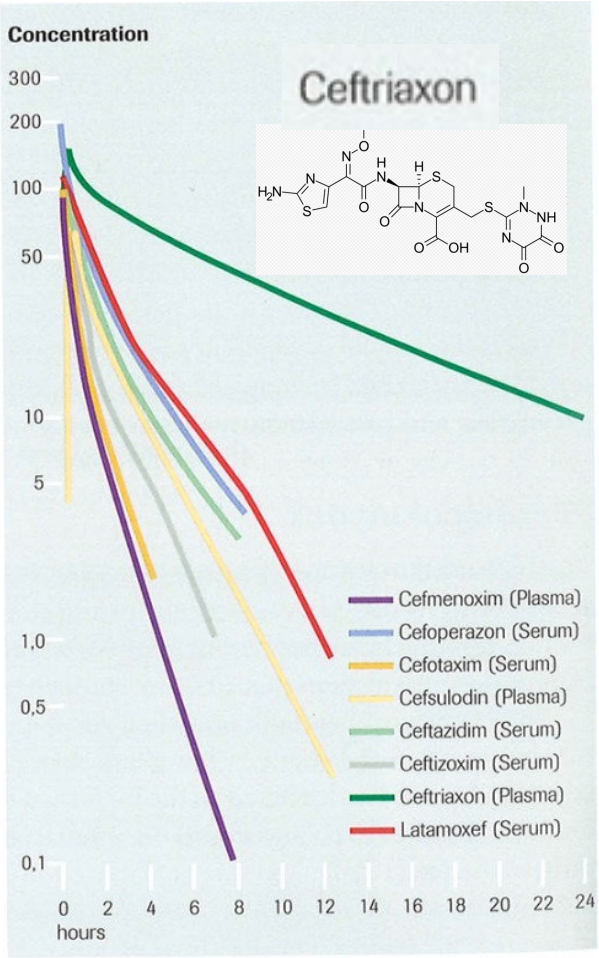


Ceftriaxone (green) PK profile
(vs other cephalosporins)

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







R2 benzylalcohol
R1 thio-methyltetrazol

R2 mercaptopyridine
R1 methylester

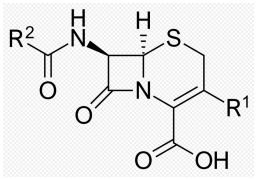
R2 methylthiophen
R1 aminoester

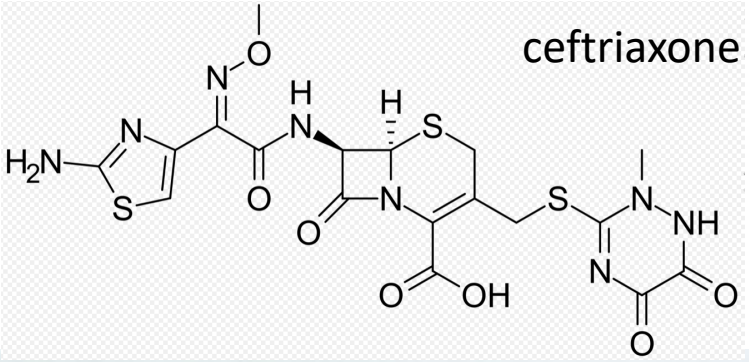
R2 aminoester
R1 methoxyimine furane

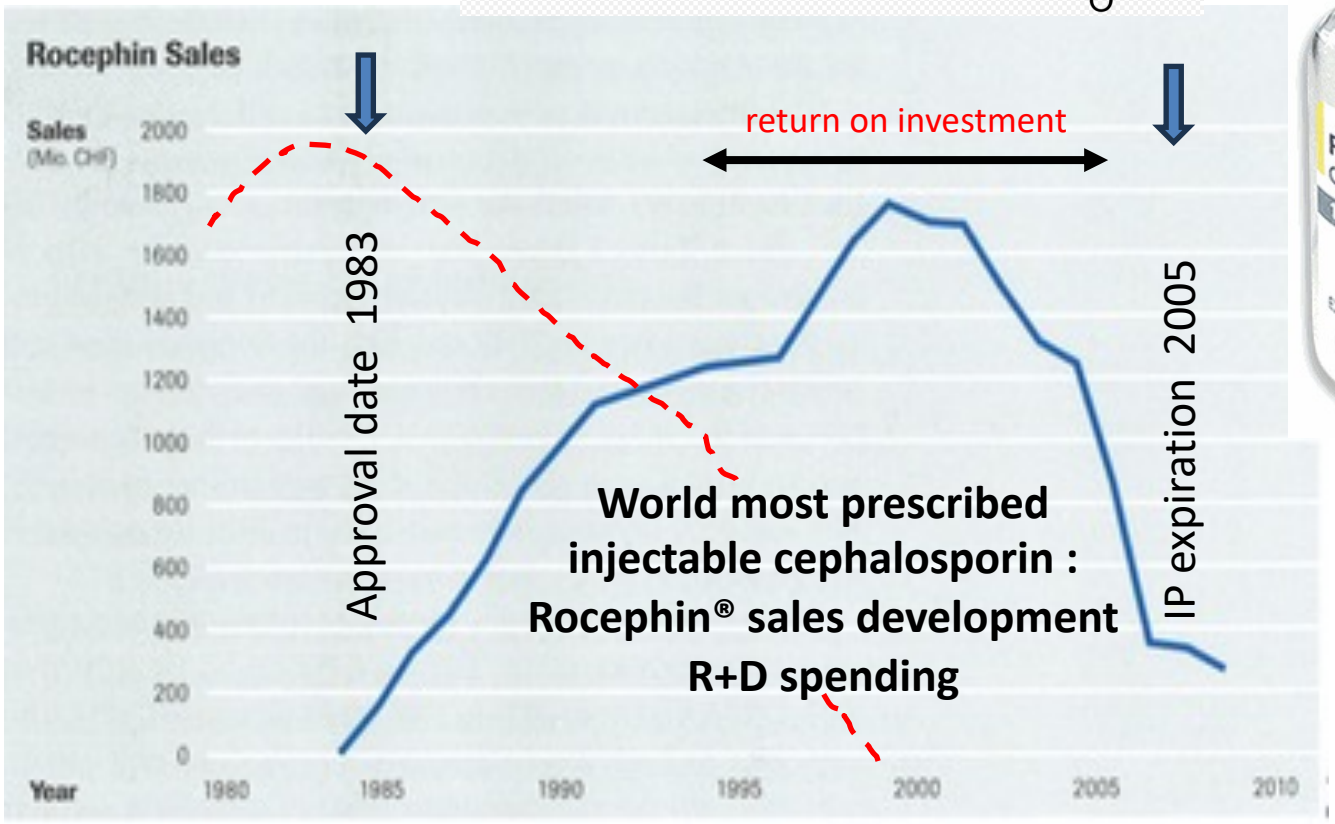
R2 aminotriazol N-methoxyimine
R1 thiotriazindione

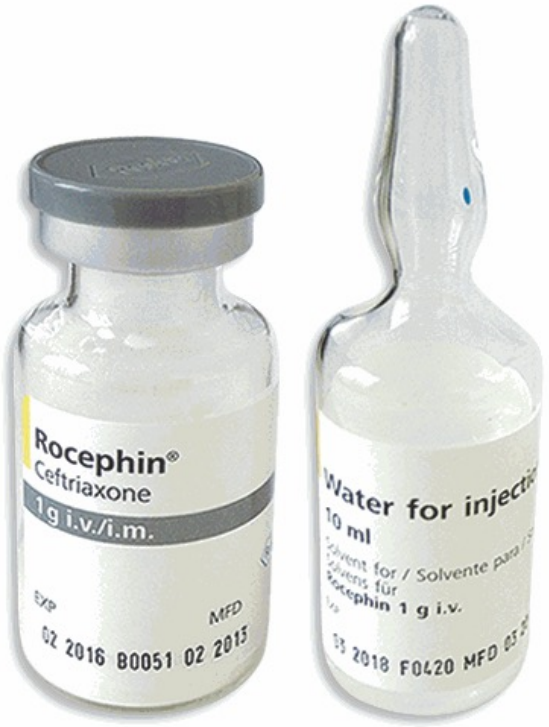
a remarkable example of mastering t ½ half life of an iv/im cpd

World most prescribed injectable cephalosporin : rise and fall of Rocephin® sales development & R+D spending

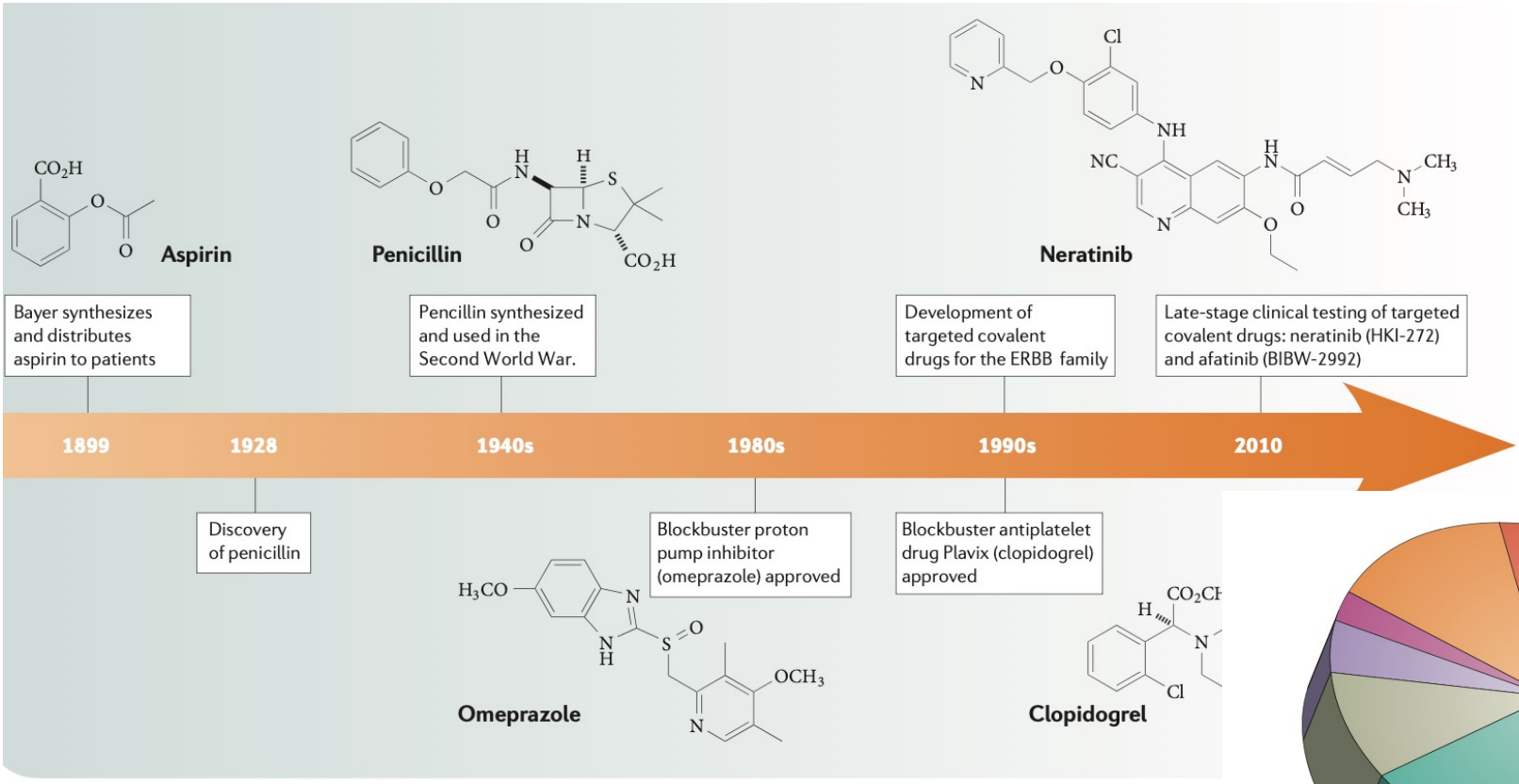








Covalent medicines have proved successful : safety concerns have limited their popularity



Random, covalent binding of highly reactive drug metabolites to cellular macromolecules can sometimes result in acute tissue injury, or it can activate the immune system through haptenization of proteins. This

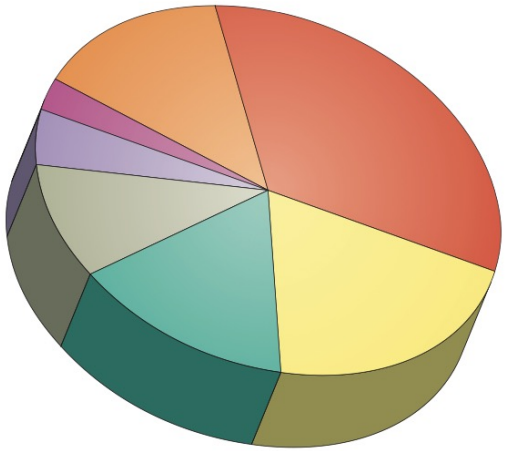


Figure 1 | **Prevalence of approved covalent drugs by therapeutic indication (*n* = 39).** Pie chart of 39 covalent

Singh et al 2011 Nature Drug Disc 10:307-317

Medicinal chemistry : covalent binding medicines time line

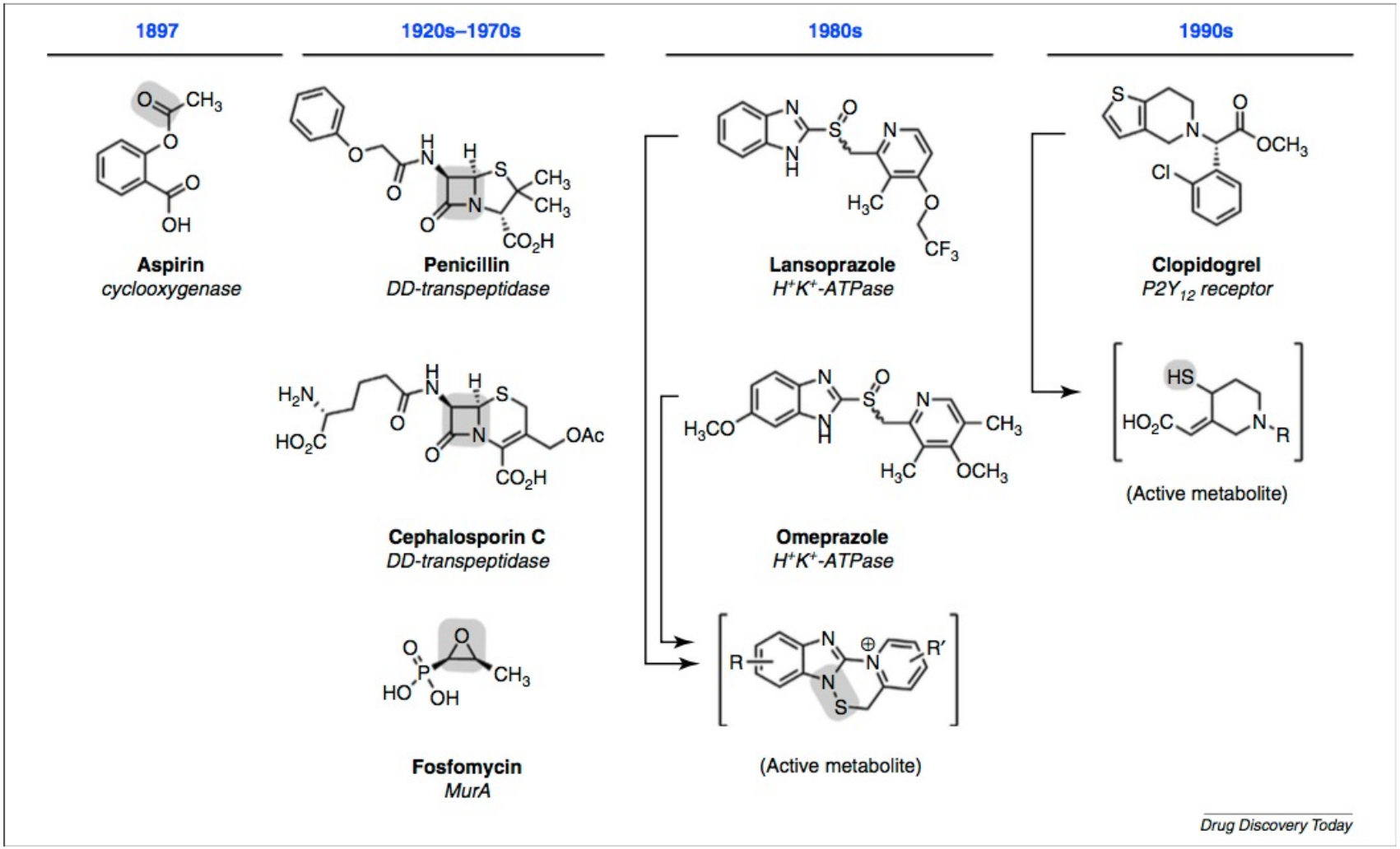


FIGURE 3

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

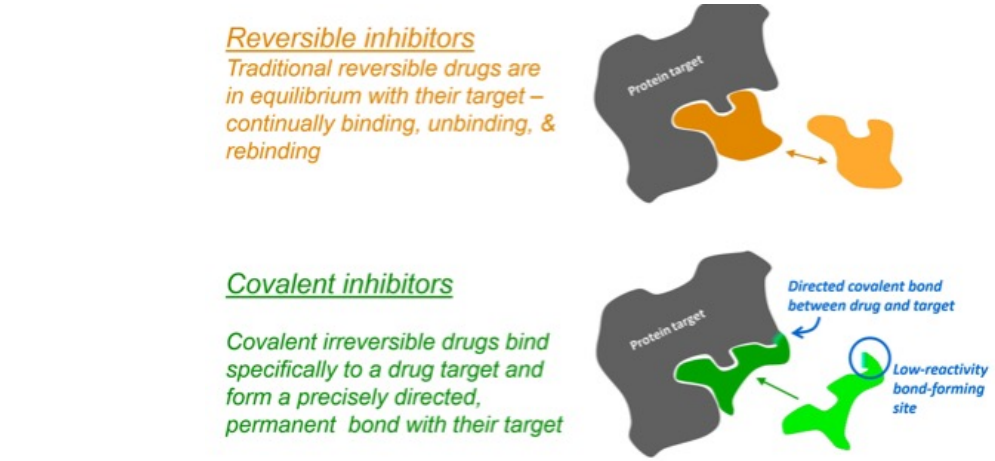
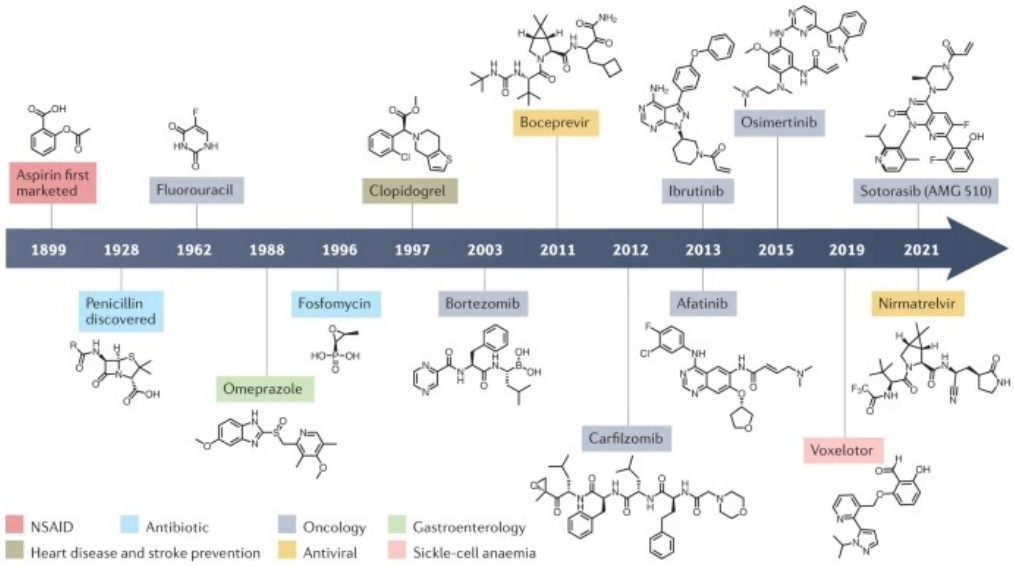


Fig. 1: Timeline of the development of major covalent drugs.



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

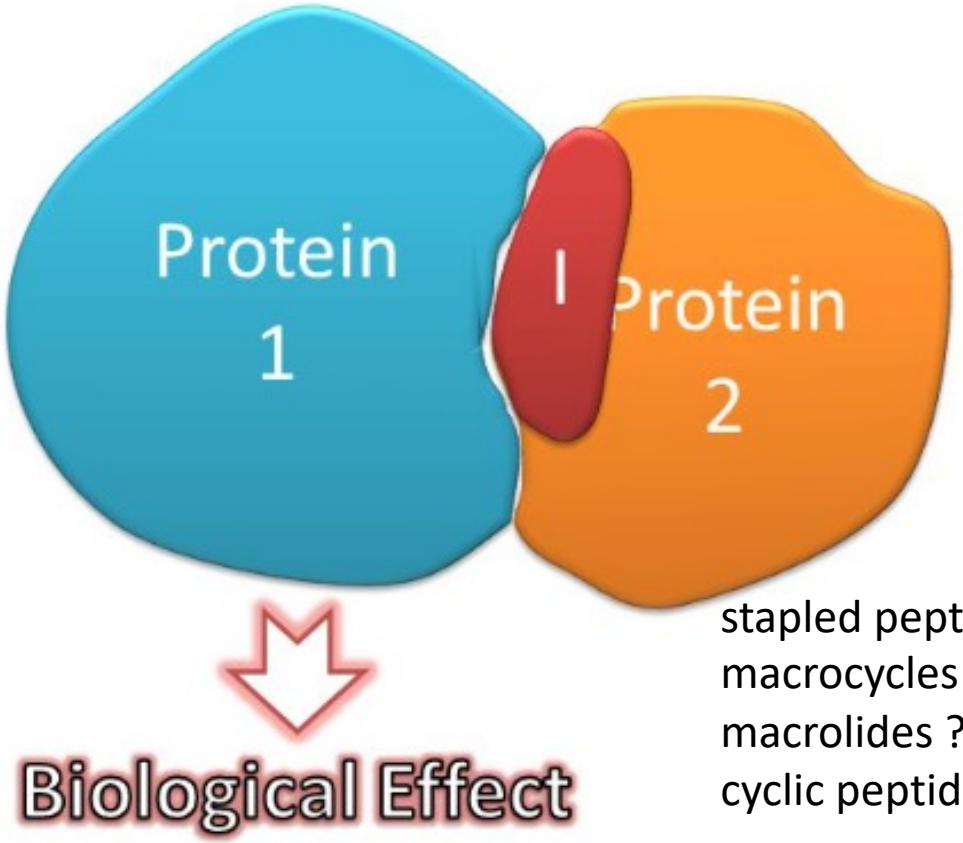
Why protein : protein interactions as drug target ? …

The 'Undruggable?': Inhibiting Protein-Protein Interactions

Protein responsible for biological effect

Effect modulated by protein-protein interaction

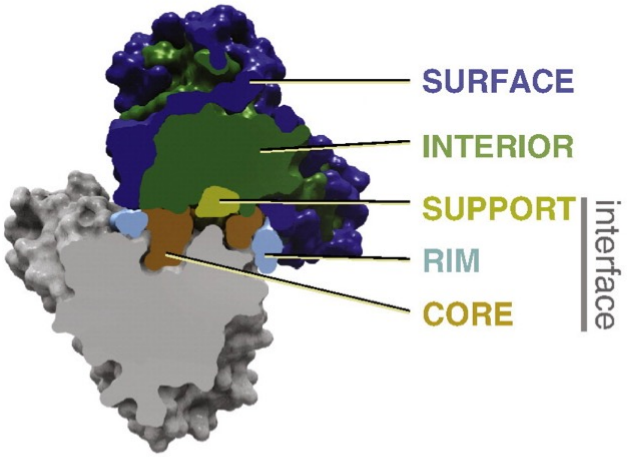
Inhibitor regulates effect by blocking protein-protein interaction



stapled peptides ?
macrocycles ?
macrolides ?
cyclic peptides ?

Why is it hard to drug PPIs?

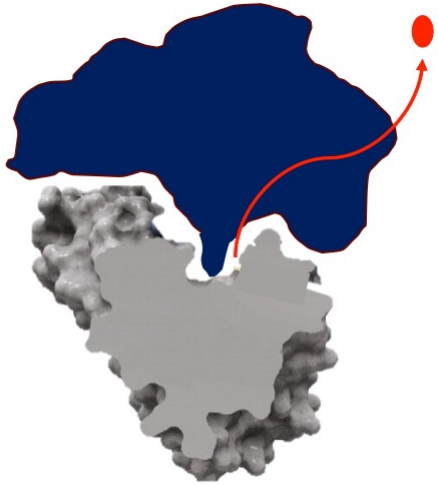
Cross-section of a protein complex



Levy, J Mol Biol 2010

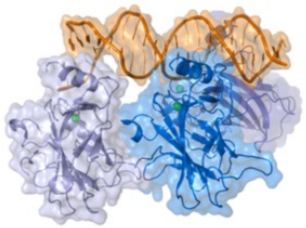
PROTEINS ARE PLASTIC
AND ACCOMMODATE THE INHIBITOR

THE INHIBITOR CAN NOT COMPETE WITH THE PROTEIN FOR BINDING

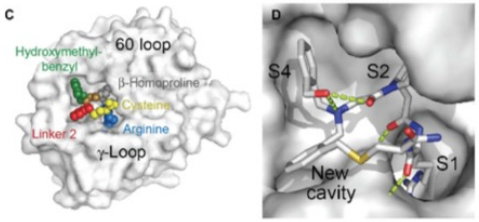


Cyclic peptide therapeutics and macrocycles for undruggable targets

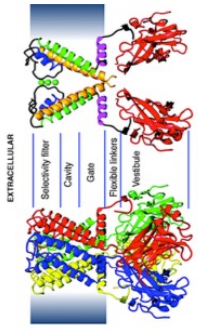
Introduction – Druggable Proteins & Macrocycles



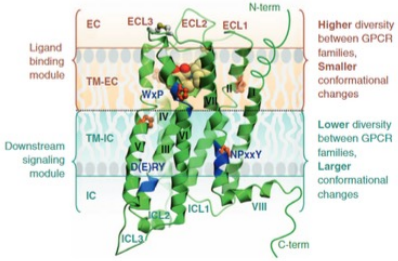
p53



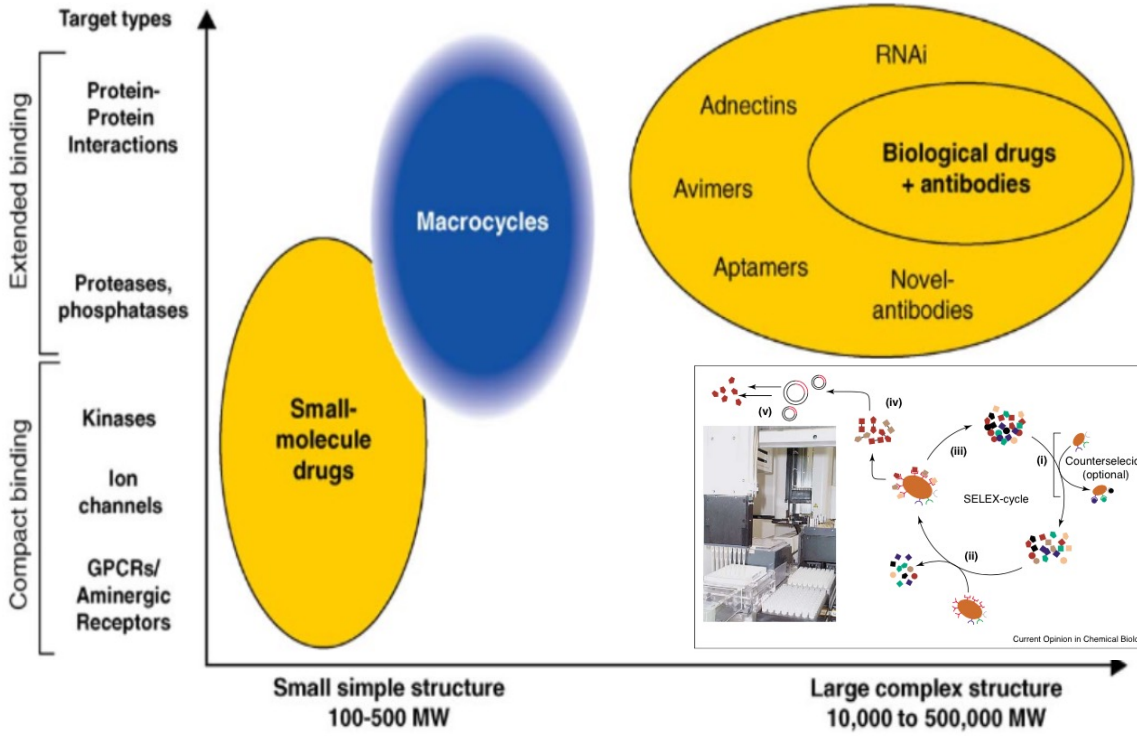
thrombin



KirBac1.1



GPCR



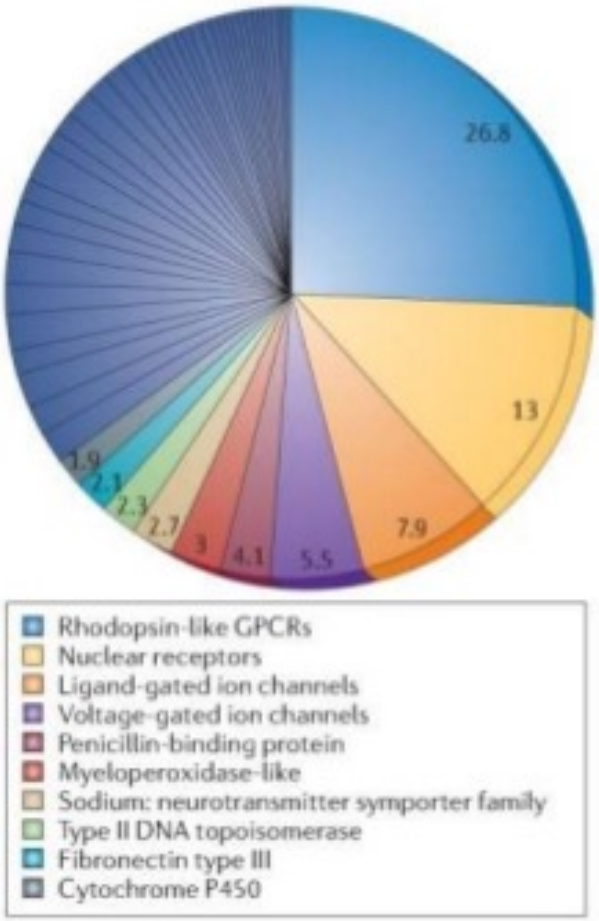
N. K. Terrett, *Drug Disco. Today: Techno.* **2010**, 7 (2), 97-104; N.London et al., *Current Opinion in Chemical Biol*ogy, **2013**, 17, 952-959; S. Kale et al., *Science Advances*, **2019**, eaaw2851; A. I et al., *Science*, **2003**, 300 (5627), 1922-1926; V. Katritch et al., *Trends in Pharmacological Sciences*, **2012**, 33 (1), 17-27i

… they are found throughout cellular signaling cascades !

Protein-Protein Interactions as a Classically "Difficult" Target

It has been proposed that no class of interaction rivals the complexity of protein-protein interactions, and targeting these interactions has been regarded as "difficult."

- Contact surface area is typically very large at approximately 1500-3000 Å^2
- Binding pockets are often flat, featureless, and lack well-defined grooves
- Lack a natural small-molecule partner, so difficult to find a suitable starting lead
- Often a HTS is dominated by compounds that have been used for classic drug targets, and each protein-protein interaction may require a different starting compound
- Protein-protein interactions are key to intracellular signaling pathways



Wells, J.A.; McClendon, C.L. *Nature* **2007**, *450*, 1001.
Bauer, R.A.; Wurst, J.M.; Tan, D.S. *Curr. Opin. Chem. Biol.* **2010**, *14*, 308.

Drugging the undruggable : cyclic peptide therapeutics

Table 1

Cyclic peptide drugs approved in the last t

Approved[a]	Generic name	Indication	Company
2006	Anidulafungin	Fungal infecti	Vicuron/Pfizer
2007	Lanreotide	Acromegaly, r tumors	Ipsen
2009	Telavancin	Complicated s structure infec nosocomial pr	Theravance
2009	Romidepsin	Cutaneous T-c (CTCL), periph lymphomas (P	Gloucester Pharmaceuticals/ Celgene
2012	Peginesatide	Anemia assoc chronic kidney	Affymax/Takeda
2012	Linaclotide	Constipation-p irritable bowel (IBS-C) and ch constipation (	Forest Labs/ Ironwood Pharmaceuticals
2012	Pasireotide	Cushing's dise acromegaly, n tumors	Novartis
2014	Dalbavancin	Complicated s structure infec	Durata Therapeutics/Teva
2014	Oritavancin	Complicated s structure infec	The Medicines Company

[a] Year of first approval by FDA or EMA for at
[b] Administration route: IV, intravenous, SC, s

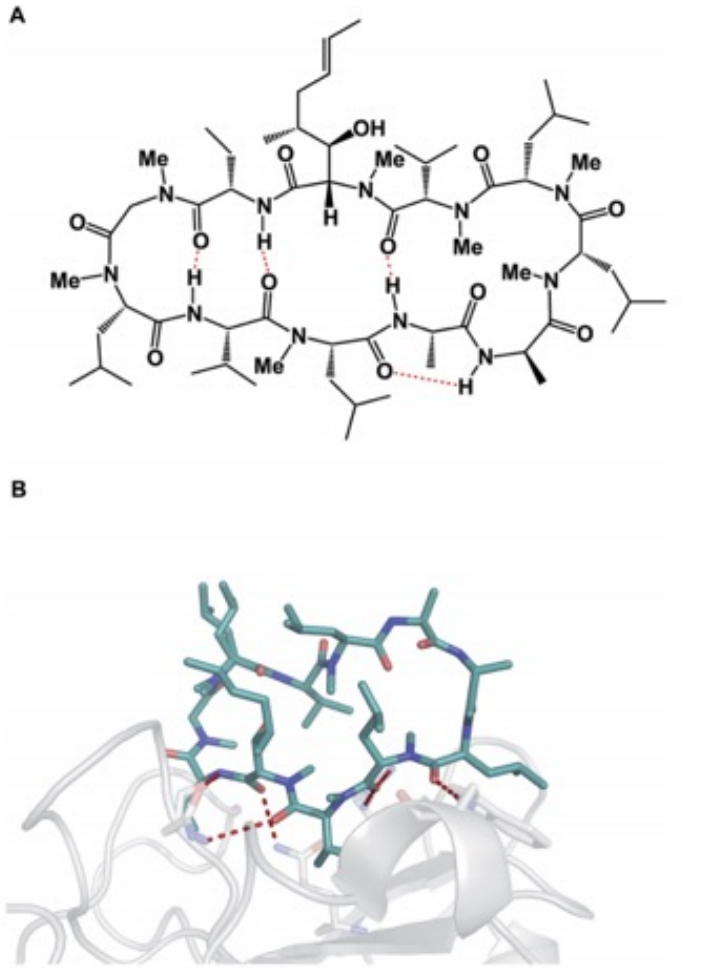
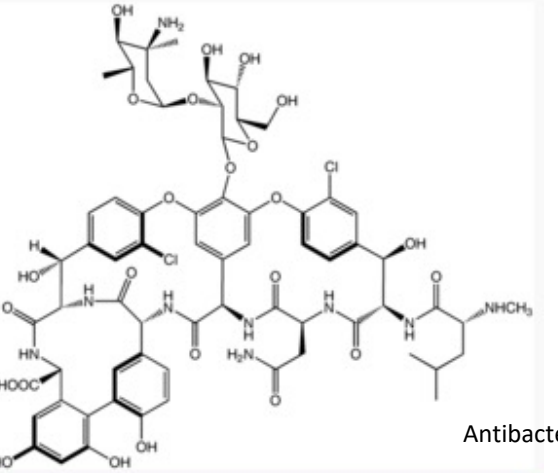


Fig. 3 Cyclosporine A: membrane conformation (A) and conformation during target engagement (B, pdb id: 2z6w).

Chemical Biology 38: 24-29

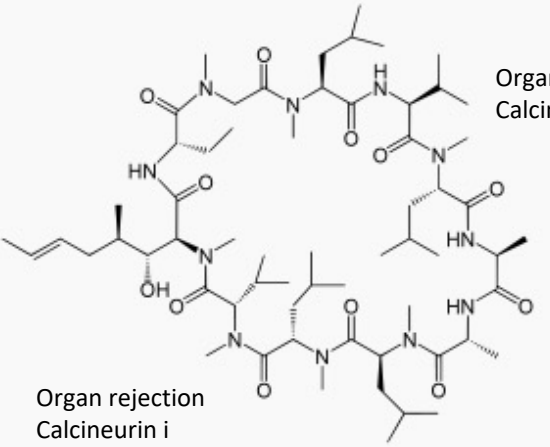
Cyclic peptide therapeutics from natural products and synthetic

Vancomycine

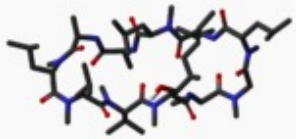


Antibacterial MRSA

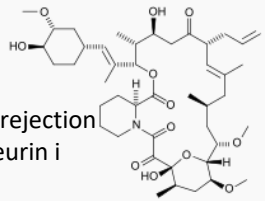
Ciclosporine



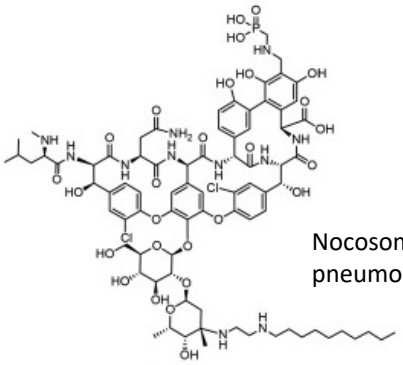
Organ rejection
Calcineurin i



Tacrolimus

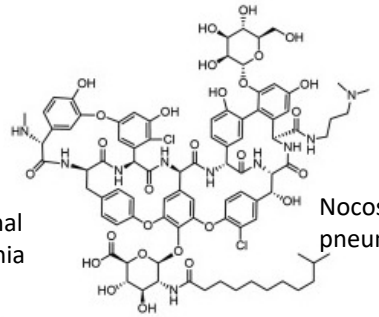


Organ rejection
Calcineurin i



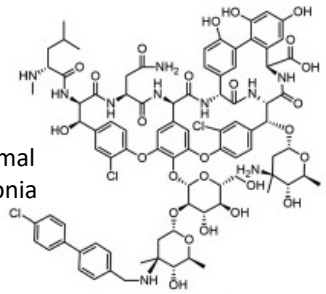
Telavancin

Nocosomal pneumonia

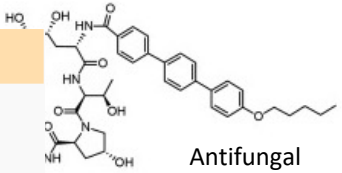


Dalbavancin

Nocosomal pneumonia

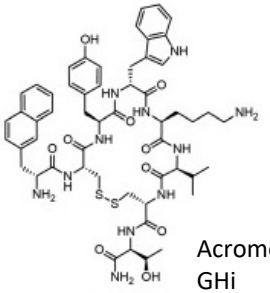


Oritavancin



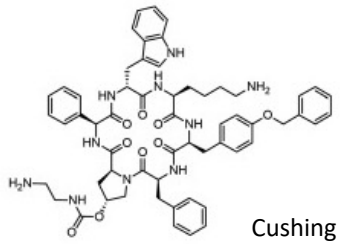
Anidulafungin

Antifungal



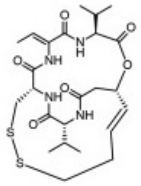
Lanreotide

Acromegaly
GHi



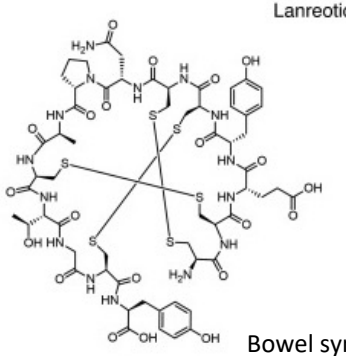
Pasireotide

Cushing
GHi



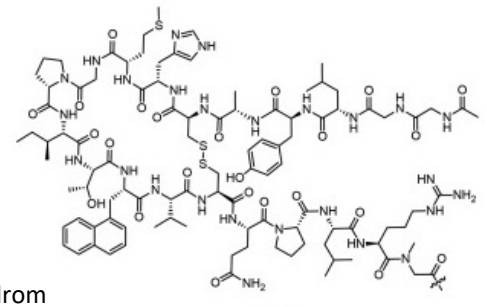
Romidepsin

Lymphoma
HDACi



Linaclotide

Bowel syndrom
chronic constipation
GMP cyclase agonist



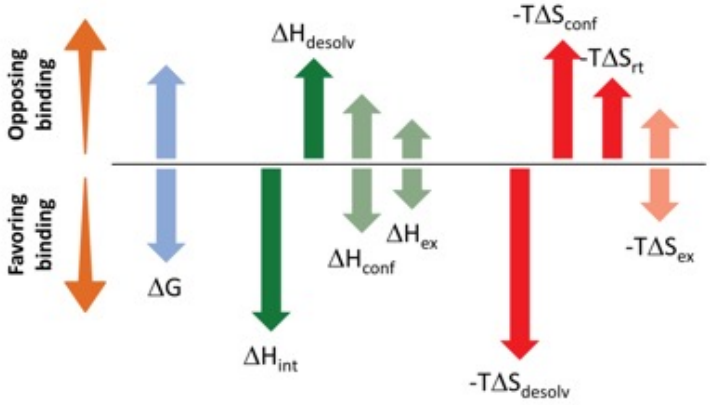
Peginesatide

Anemia
EPOr agonist

Definitions & Features

- **Macrocycles** [2]
  - Ring size (size ≥ 12 atoms)
  - Suitable PPI drug modality
  - Expanded binding surface
  - Pre-organization
  - Increases proteolytic stability
  - Higher specificity
  - Permeability
  - Molecular size (~1 kDa)

- 1) Desolvation of the binding partner
- 2) Conformational adaptation of binding partners
- 3) Formation of drug-target interactions



$$\Delta G = \Delta H - T\Delta S$$

Appendix - Macrocycle Library Technologies

- **Individually synthesized & purified macrocycles** [4]
  - Enormous effort
  - Size limitations
- **DNA encoded cyclic library (DECL)** [5]
  - Library size limited by base pairs
  - Arsenal of DNA compatible reactions
  - Overall efficiency after many consecutive synthesis steps
  - High synthetic effort
- **Phage or mRNA display** [6]
  - Larger macrocyclic peptides
  - Low diversity for small peptide macrocycles
- **Combinatorial Chemistry**
  - Very large chemical diversity (building blocks)
  - Liquid phase

POLYPHOR

Best macrocycle small size pharma in Basel CH

Proprietary macrocycle technology platform for pharma companies

Polyphor offers its macrocycle library to interested parties for screening on their biological targets.

Explore pharma collaborations

We aim to become a leading pharma company focused on oncology and antibiotics

We are a clinical stage biopharmaceutical company based in Allschwil, Switzerland, and are focused on the discovery and development of immuno-oncology compounds and a new class of antibiotics.

Protein : protein interactions : stapled peptides, bicyclic peptides etc

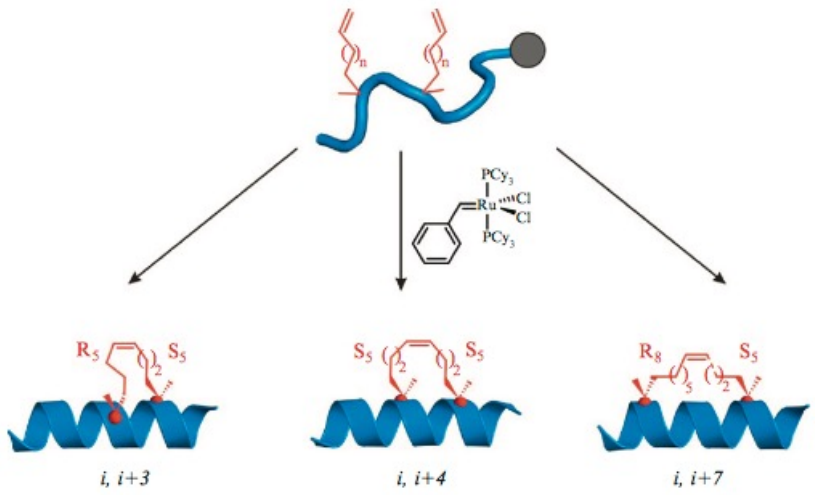
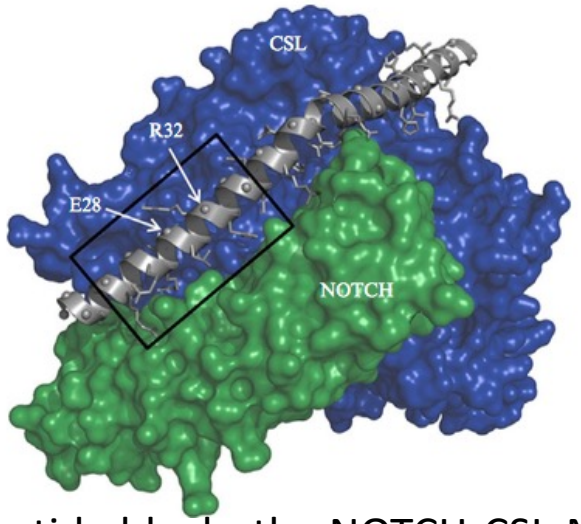
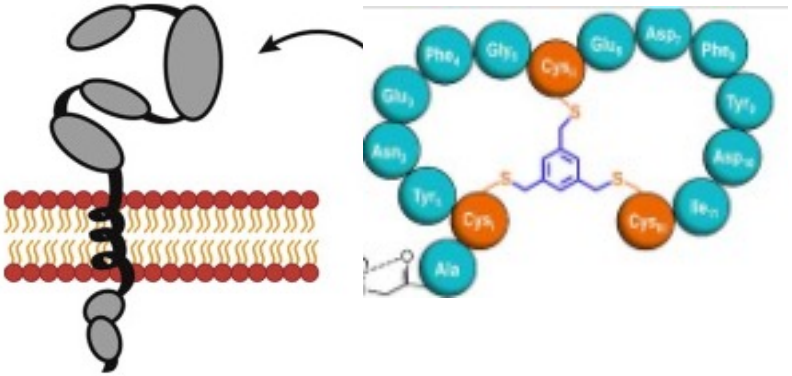


Figure 1.1 The three types of all-hydrocarbon stapled peptides. α-Methyl, α-alkenyl-

Verdine G. et al. (2012) Method in Enzymology Vol 503



stapled peptide blocks the NOTCH-CSL-MAML ternary complex aberrent expression and activation of Notch is linked to a variety of different pathologies (cancer, CVD etc



Bicyclic peptide blocks Her2 Tyr k receptor from oligomerization in aberrent expression and activation (15% breast cancer)

Diderich P and Heinis C. 2014. Tetrahedron 70:7733-39

Table 1.1 A list of bioactive all-hydrocarbon stapled peptides

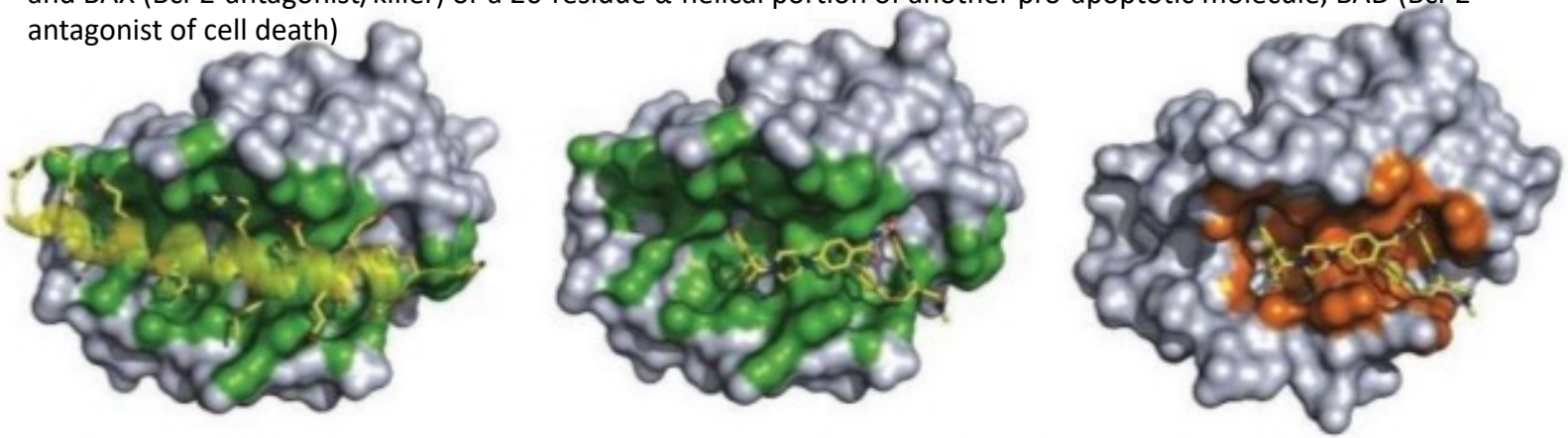
Stapled peptide	Sequence	Source protein	Target protein(s)	Reference(s)
BID SAHB$_A$	EDIIRNIARHLA**S$_5$**VGD**S$_5$**N$_L$DRSIW	BID	BCL-2, BCL-X$_L$, BAX	Walensky *et al.* (2004), Walensky *et al.* (2006)
BAD SAHB$_A$	NLWAAQRYGRELR**S$_5$**N$_L$SD**S$_5$**FVDSFKK	BAD	BCL-X$_L$	Walensky *et al.* (2006)
BIM SAHB$_A$	IWIAQELR**S$_5$**IGD**S$_5$**FNAYYARR	BIM	BCL-X$_L$, BAX	Walensky *et al.* (2006), Gavathiotis *et al.* (2008)
SAH-p53-8	QSQQTF**R$_8$**NLWRLL**S$_5$**QN	p53	hDM2, hDMX	Bernal *et al.* (2007), Bernal *et al.* (2010)
NYAD-1	ITF**S$_5$**DLL**S$_5$**YYGP	(Phage display)	HIV-1 CA	Zhang *et al.* (2008)
SAHM1	ERLRRRI**S$_5$**LCR**S$_5$**HHST	MAML	NOTCH/CSL	Moellering *et al.* (2009)
SAH-gp41$_{(626-662)}$	N$_L$TW**S$_5$**EWD**S$_5$**EINNYTSLIHSLIEESQNQ **S$_5$**EKN**S$_5$**QELLE	HIV-1 gp41	HIV-1 gp41	Bird *et al.* (2010)
MCL-1 SAHB$_A$	KALETLR**S$_5$**VGD**S$_5$**VQRNHETAF	MCL-1	MCL-1	Stewart *et al.* (2010)
SAH-apoA-I	VLESFKVS**R$_8$**LSALEE**S$_5$**TKKLNTQ	apoA-I	ABCA1	Sviridov *et al.* (2011)

S$_5$ and R$_8$ are abbreviations for α-methyl, α-alkenylglycine cross-linking amino acids. N$_L$ is an abbreviation for norleucine.

Protein:protein interaction blockade: an enourmous challenge towards promoting apoptosis in cancer targets

Bcl-X_L Bound to Natural Peptide Partner and Inhibitor

B-cell lymphoma Bcl-2 and Bcl-XL inhibit apoptosis by binding a 16-residue α-helical portion of pro-apoptotic molecule BAK and BAX (Bcl-2-antagonist/killer) or a 26-residue α-helical portion of another pro-apoptotic molecule, BAD (Bcl-2 antagonist of cell death)



Protein-peptide interaction
Bcl-X_L and 26-residue of BAD

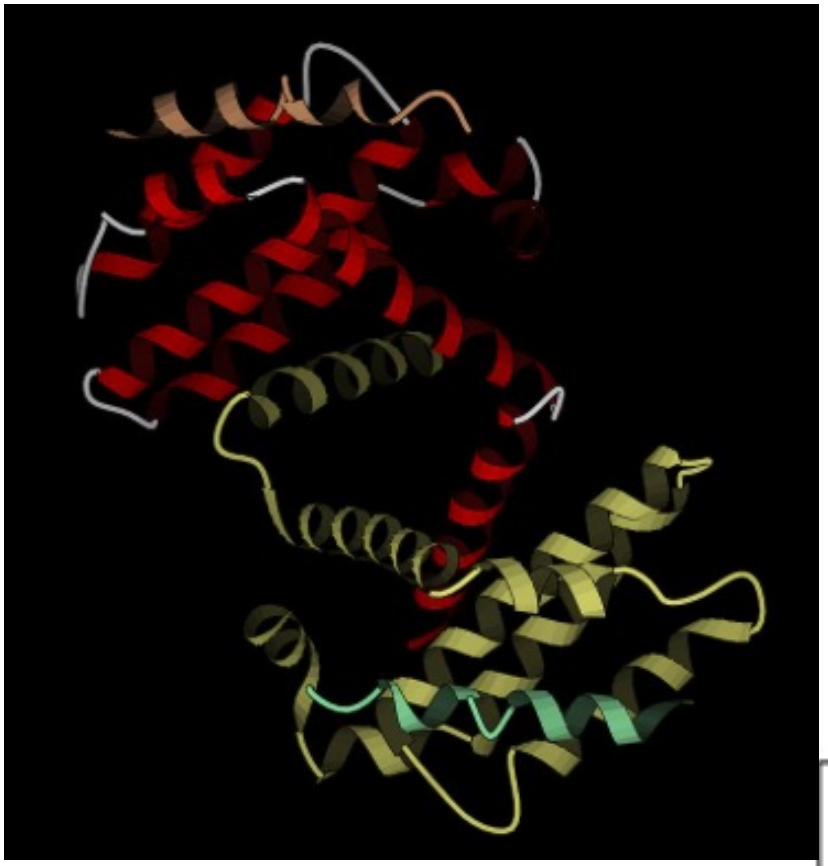
Protein-small molecule interaction
Bcl-X_L and ABT-737

Bcl2 that fail to complex with Bax (Bcl2-Bax complex is anti-apototic) can no longer inhibit apoptosis

	Molecular Mass (Da)	Bcl-x_L K_i (nM)	LE (kcal/mol/HAC)
BAD-derived peptide	3,110	0.6	0.16
ABT-737	813	0.6	0.23

Wells, J.A.; McClendon, C.L. *Nature* **2007**, *450*, 1001.

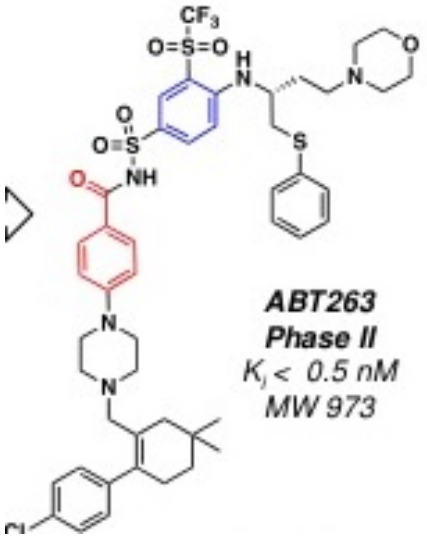
Drugging the undruggable : blocking Bcl-Xl ANTI apoptotic mitochondrial protein as antitumor agent

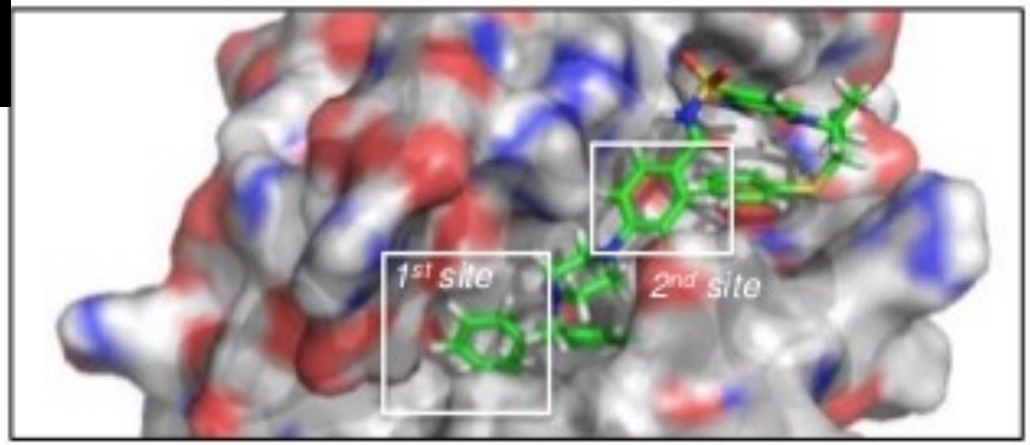


Bcl-Xl at 1.7 A atomic resolution

Mimicking Bcl-l : BH3 domain protein:protein interaction

Bcl-Xl one of the first successful example of SMWs cpd inhibiting protein:protein interactions !

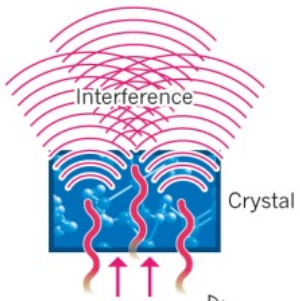




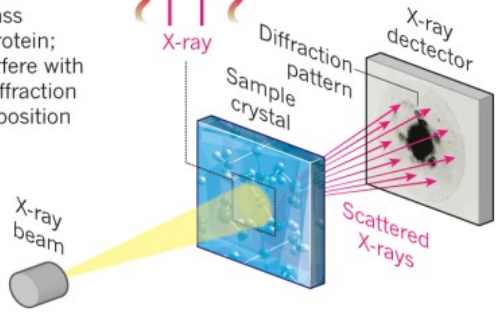
Medicinal chemistry : cryo EM allows prediction of enzyme function and medicinal chemistry driven drug design

STRUCTURE SOLVERS

X-ray crystallography has long been the dominant method for deducing high-resolution protein structures, but cryo-electron microscopy is catching up.



X-RAY CRYSTALLOGRAPHY
X-rays scatter as they pass through a crystallized protein; the resulting waves interfere with each other, creating a diffraction pattern from which the position of atoms is deduced.



CRYO-ELECTRON MICROSCOPY
A beam of electron is fired at a frozen protein solution. The emerging scattered electrons pass through a lens to create a magnified image on the detector, from which their structure can be worked out.

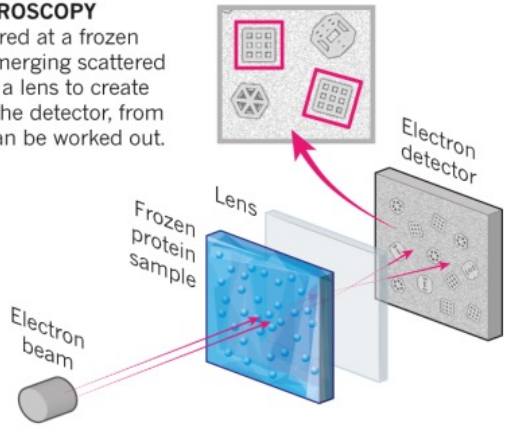
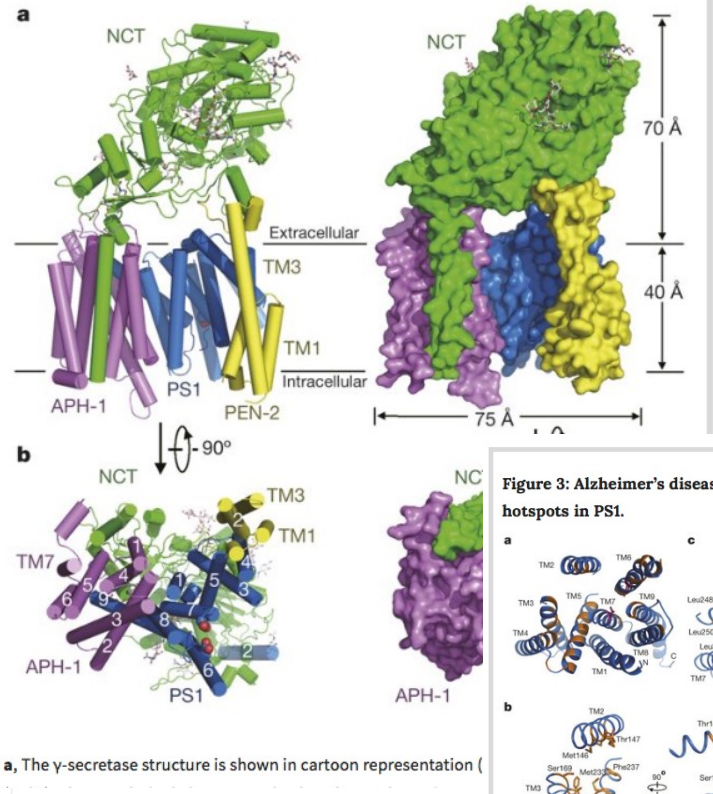


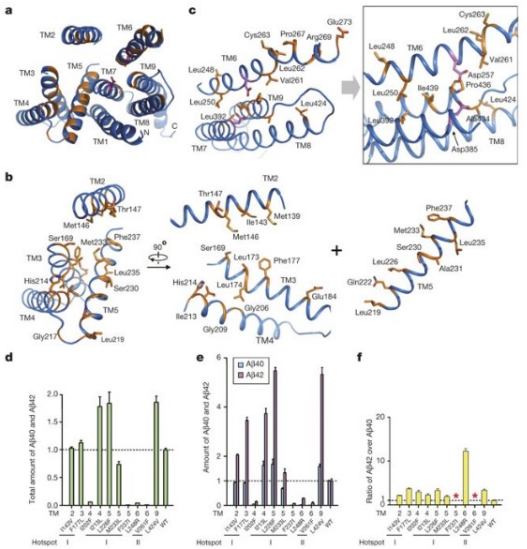
Figure 1: Atomic structure of human γ-secretase.



a, The γ-secretase structure is shown in cartoon representation (

Bai XC. 2015 Nature 535:212-217

Figure 3: Alzheimer's disease-derived mutations map to two hotspots in PS1.

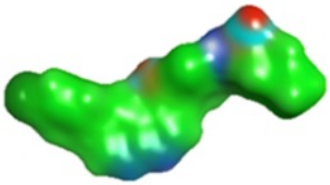


a, An overall view of the PS1 residues targeted for mutations in patients with Alzheimer's

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



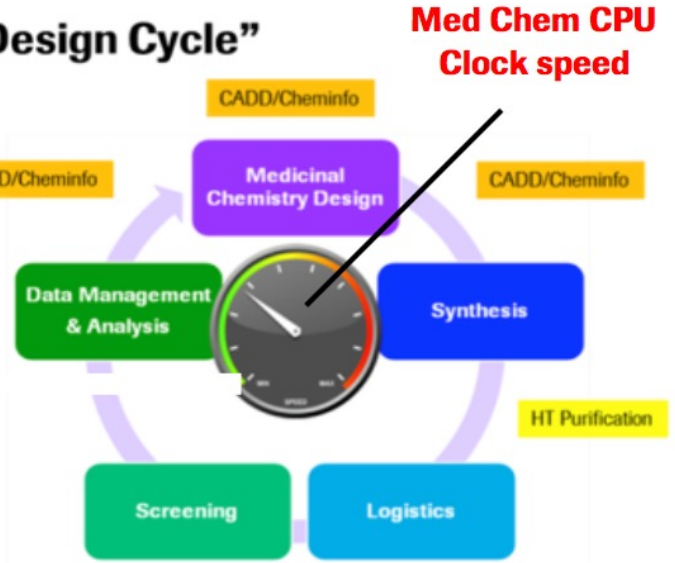
Small Molecule Clinical Candidate
MW ~ 500 Da

Med Chem Design Quality and Speed

"Overclocking the Design Cycle"

Data driven predictive drug design by medicinal chemist

powered by



Iterative Design Cycle (DSTA cycle)

Thalidomide (iMiDs) : a drug repurposing paradigm

The thalidomide story REVISITED TODAY

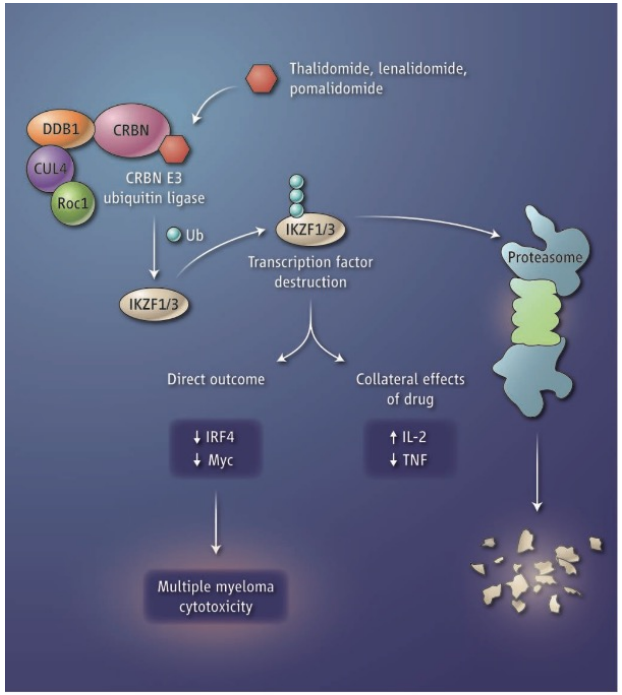
comes back with MOA and strict safety requirements (pregancy test !)

multiple myeloma in B cell malignancies

IMiDs-Immunomodulatory drug

NK cells stimulation, cytokine IL6 production

How thalidomide works against cancer



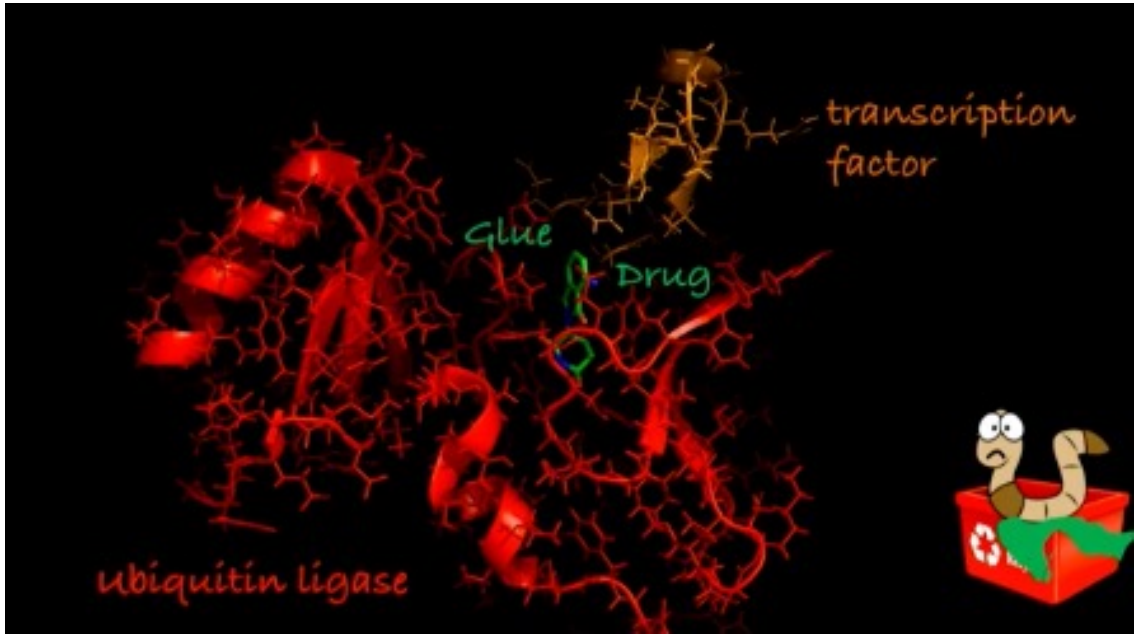
Immune modulators and myeloma. The small-molecule drugs thalidomide, lenalidomide, and pomalidomide bind to the protein cereblon (CRBN), which activates the enzymatic activity of the CRBN E3 ubiquitin ligase complex. The transcription factors Ikaros (IKZF1) and Aiolos (IKZF3) are modified with ubiquitin (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.

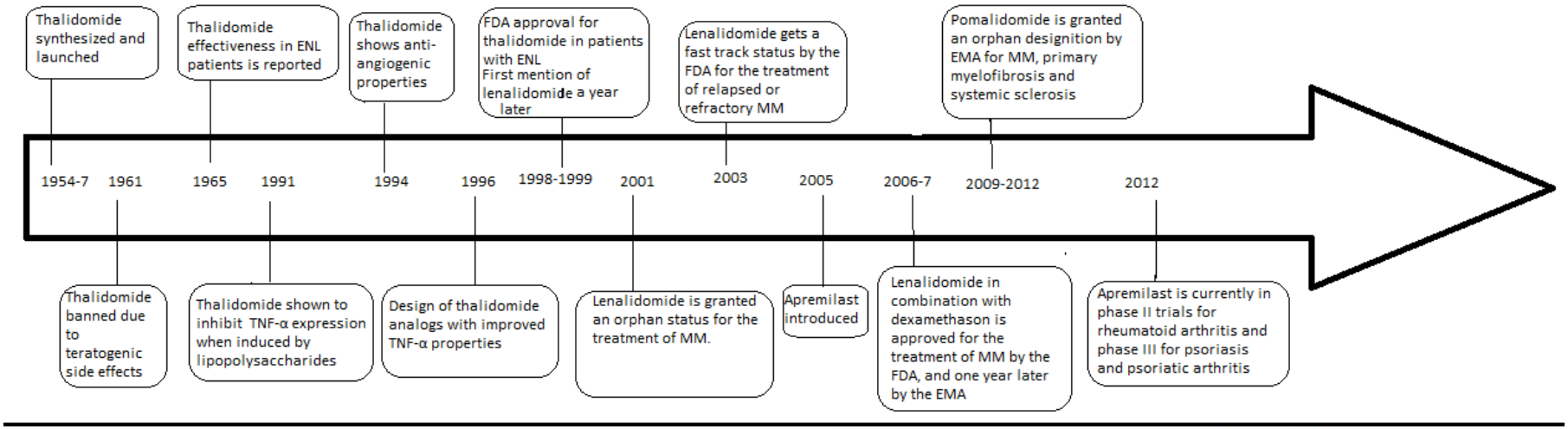
MOLECULAR GLUE DEGRADER CONCEPT

(only when the cpd links the substrate and ubiquitn ligase the mutated/cancer activated protein is destroyed !)

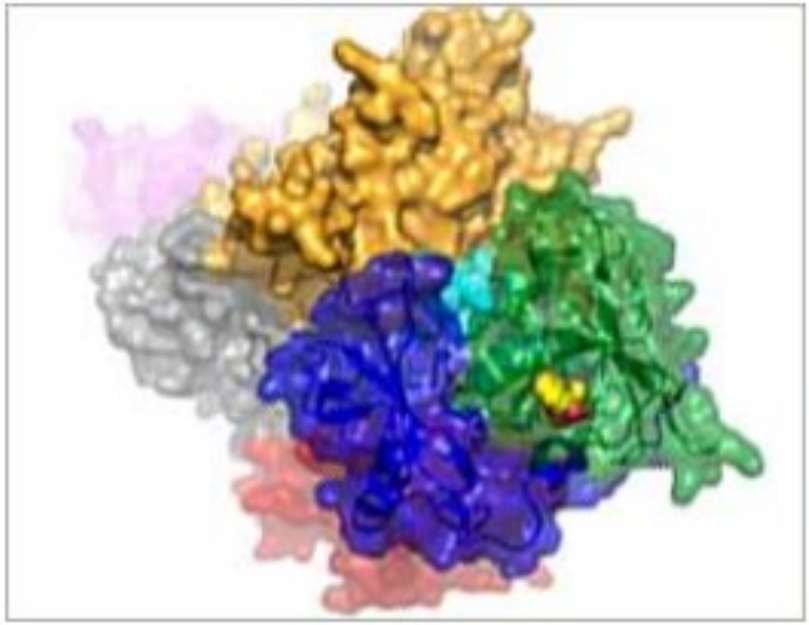


Fischer ES and Thomä N.(2014) Nature 512:49-53

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



Patient compliance :
Revlimid is sold by BMS formerly Celgen.
The US list price of Revlimid is $ 18'723 per cycle when given as 25mg once a day on days 1-21 of a 28 day cycle of multiple myeloma (plasmocyte cancer, often >50 y old patients, production of non sense kappa and lambda light IgG chains in the bone marrow.
Early symptoms : fatique due to low Hb reduced count of erythrocytes
Diagnostic only thru bone marrow puncture !



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

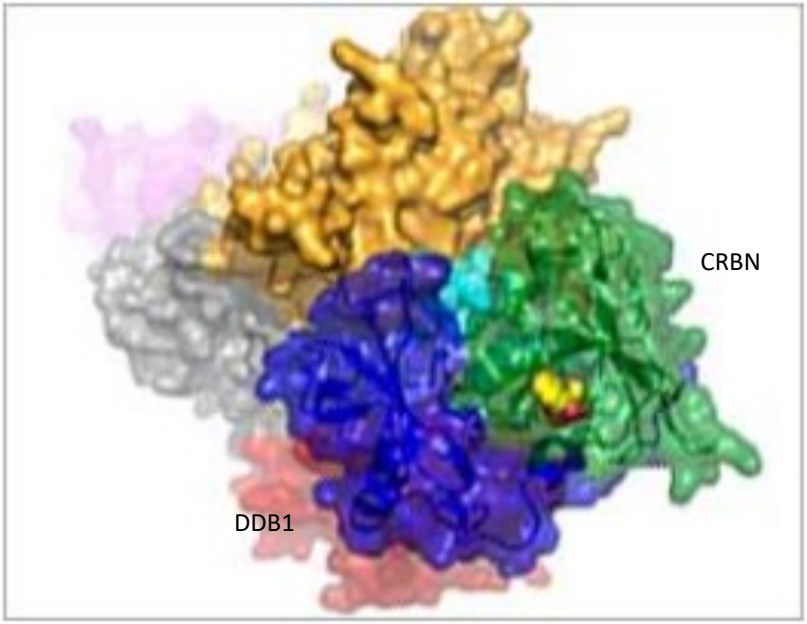
iMiDs analogues are coined “molecular superglue degraders”

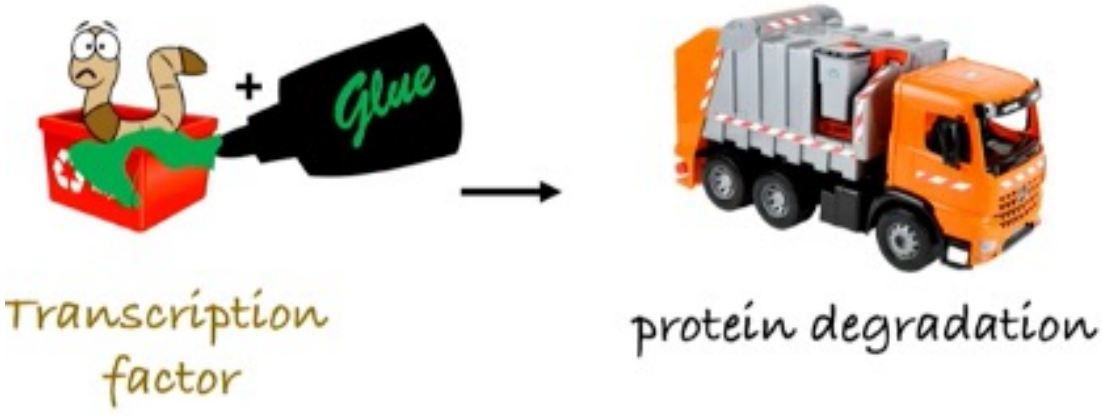
Mode of action (MOA) of thalidomide elucidated !

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

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

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



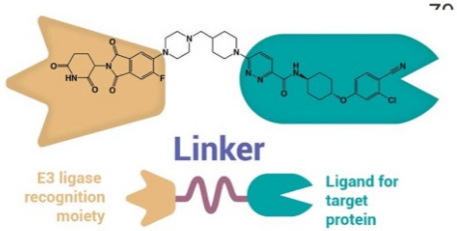


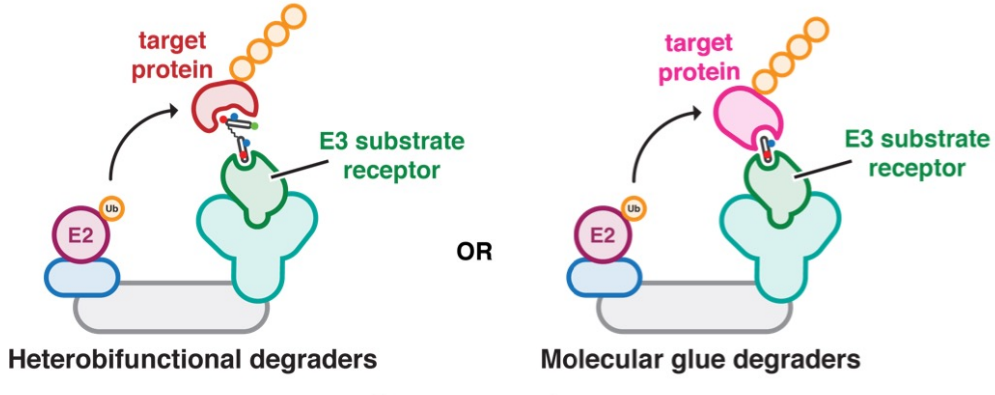
Fischer ES and Thomä N.(2014) Nature 512:49-53

PROTACs (proteolysis targeting chimeras) vs “molecular glue” degraders

PROTACs:

THE TWO EXTREMES OF THE TARGETED PROTEIN DEGRADATION CONTINUUM





Rational design
Dependent on ligand availability
High(er) M_W

Serendipitous discovery
Less reliant on ligands/pockets
Small(er) and intrinsically more drug-like

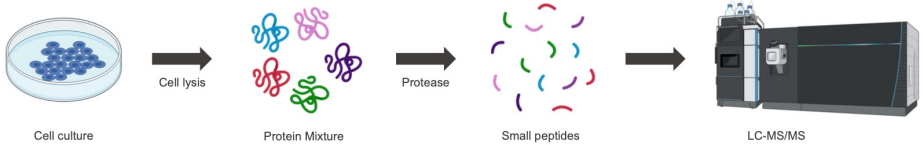
Nicolas Thomä

Druggable proteome discovery : target identification, specificity profiling
Repurposing – screening known drug on proteome

Key challenge in drug discovery is to understand the mode of action of eg. small molecule candidates

Understanding the targets of small molecules is essential in drug discovery

Chemoproteomics allows for a broad characterization of the targets of small molecules, target deconvolution

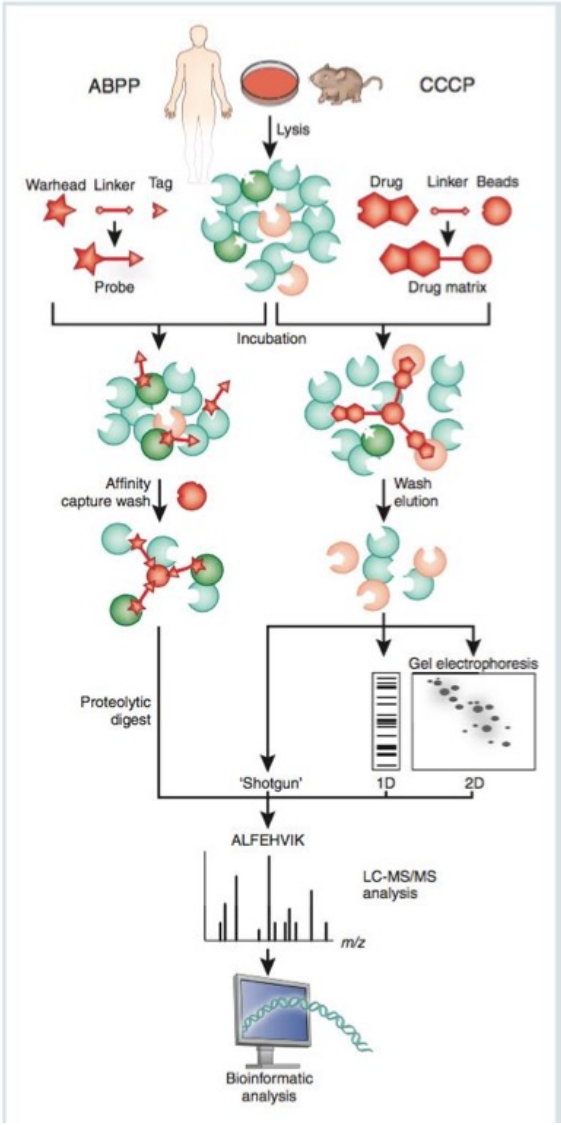


Biological sample

Small Molecule

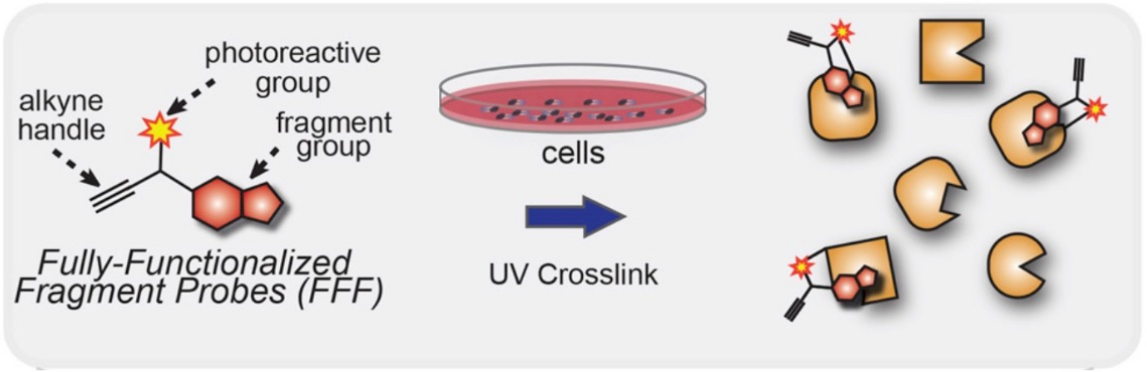
Biochemical processing

Protein Identification



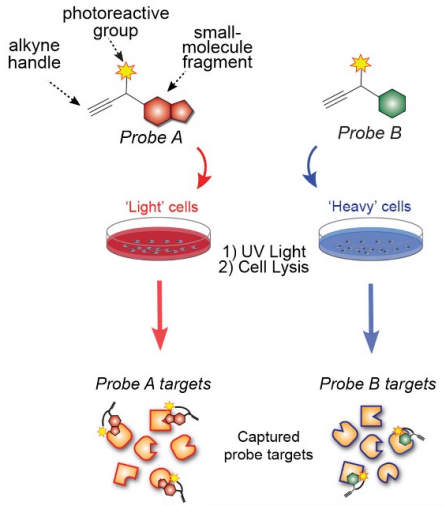
Proteome-wide covalent ligand discovery in native biological systems.**Backus KM**, **Correia BE**, Lum KM, Forli S, Horning BD, González-Páez GE, Chatterjee S, Lanning BR, Teijaro JR, Olson AJ, Wolan DW, Cravatt BF.Nature. 2016 Jun 23;534(7608):570-4. doi: 10.1038/nature18002. Epub 2016 Jun 15.

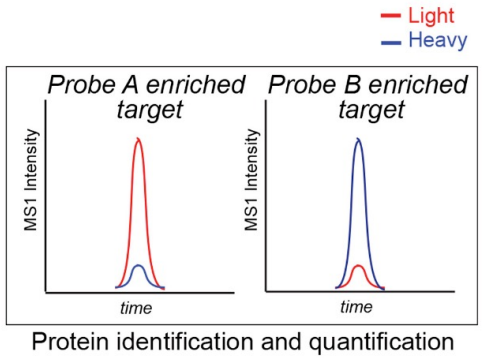
Chemoproteomics : the needle in the haystack



SILAC

stable isotope labeling by/with amino acids in cell culture

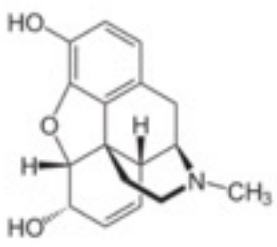


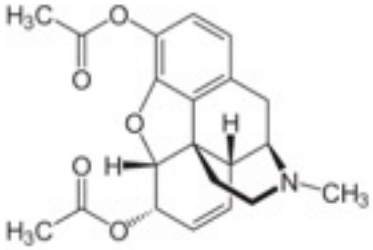


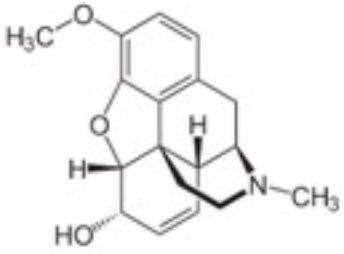
Protein identification and quantification

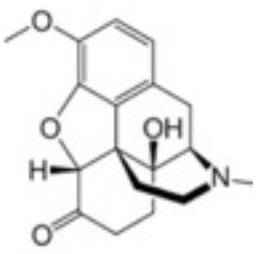
Molecular therapeutic target validation in preclinical drug discovery

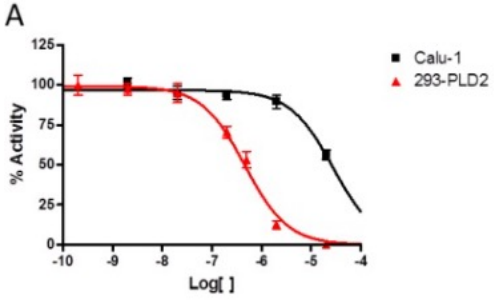
- **Increase confidence in a particular drug target, ligand-target interaction**
- **Ki, Kd, on target efficacy, potential off target, lack of specificity**
- **50 % clinical trial phase II-III have been shown to fail because of insufficient efficacy**

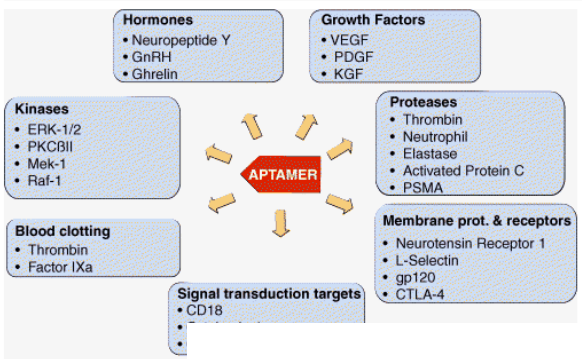






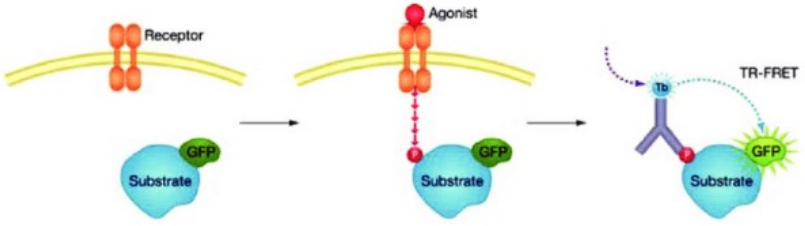




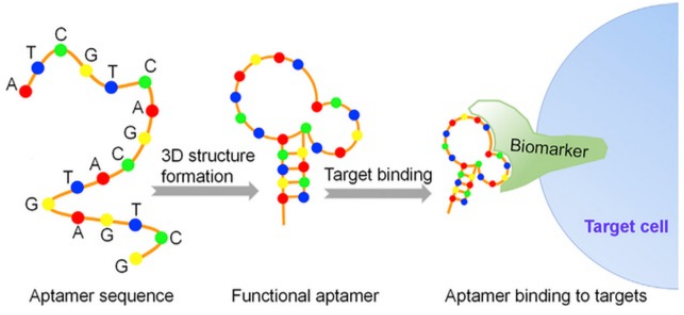


Aptamers in contrary to SMW cpds function by binding to a specific site of an endogenous protein and blocking its activity.

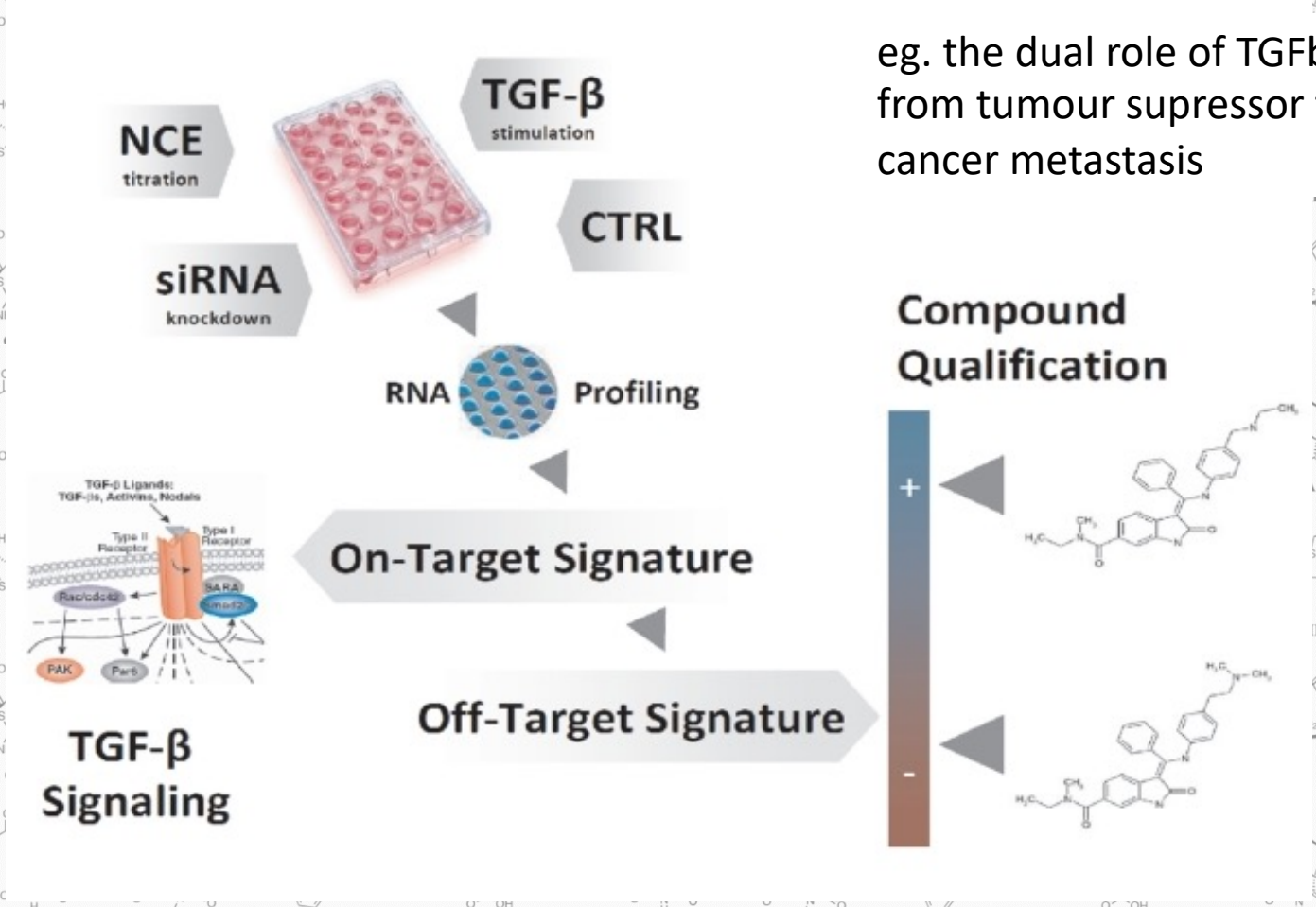
They prove to be efficient inhibitors of a wide variety of druggable protein classes



aScreen™ cellular assay schematic. Stable cell lines are generated that express the kinase substrate of



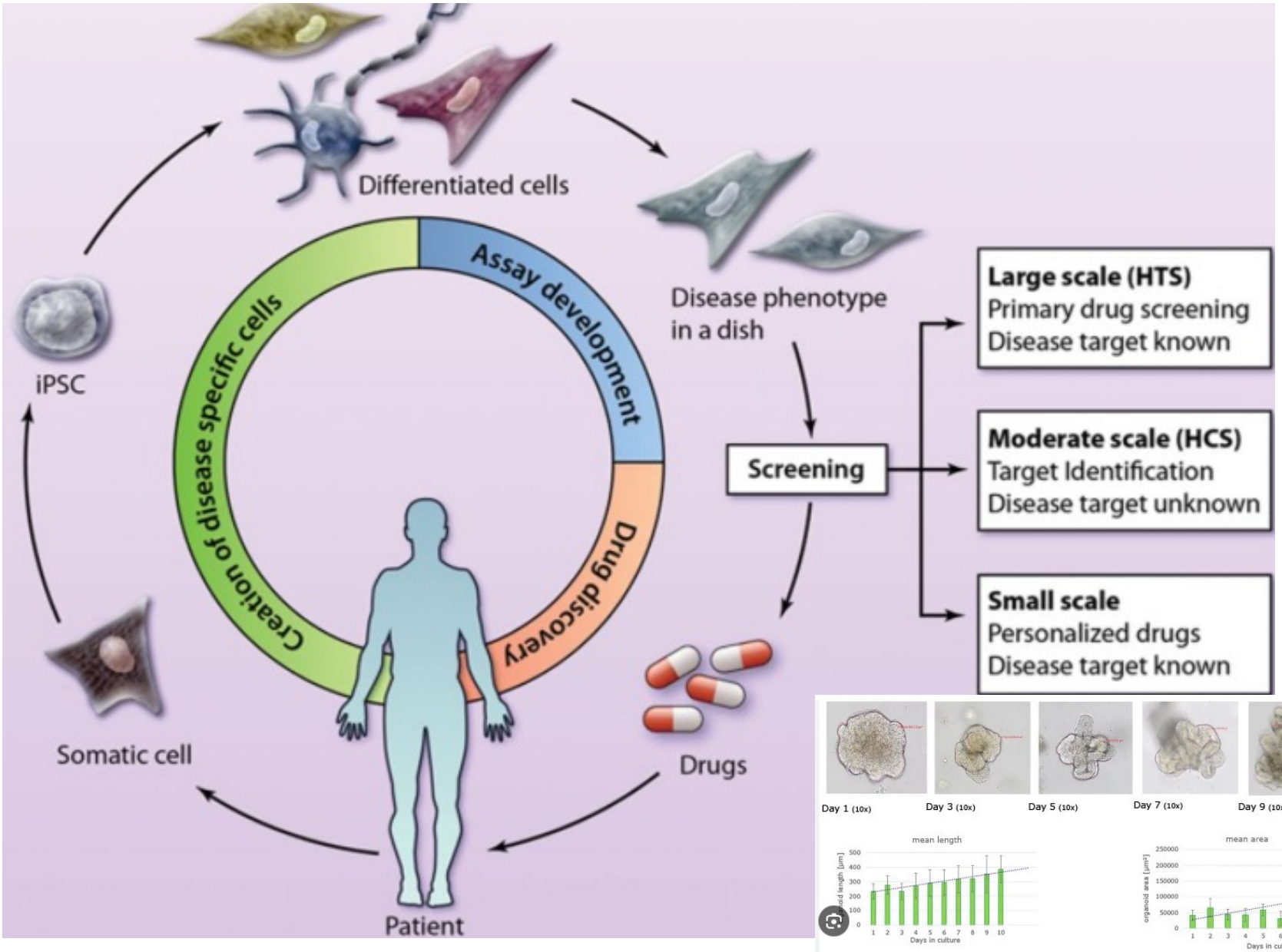
Secondary assays to validate on/off therapeutic target



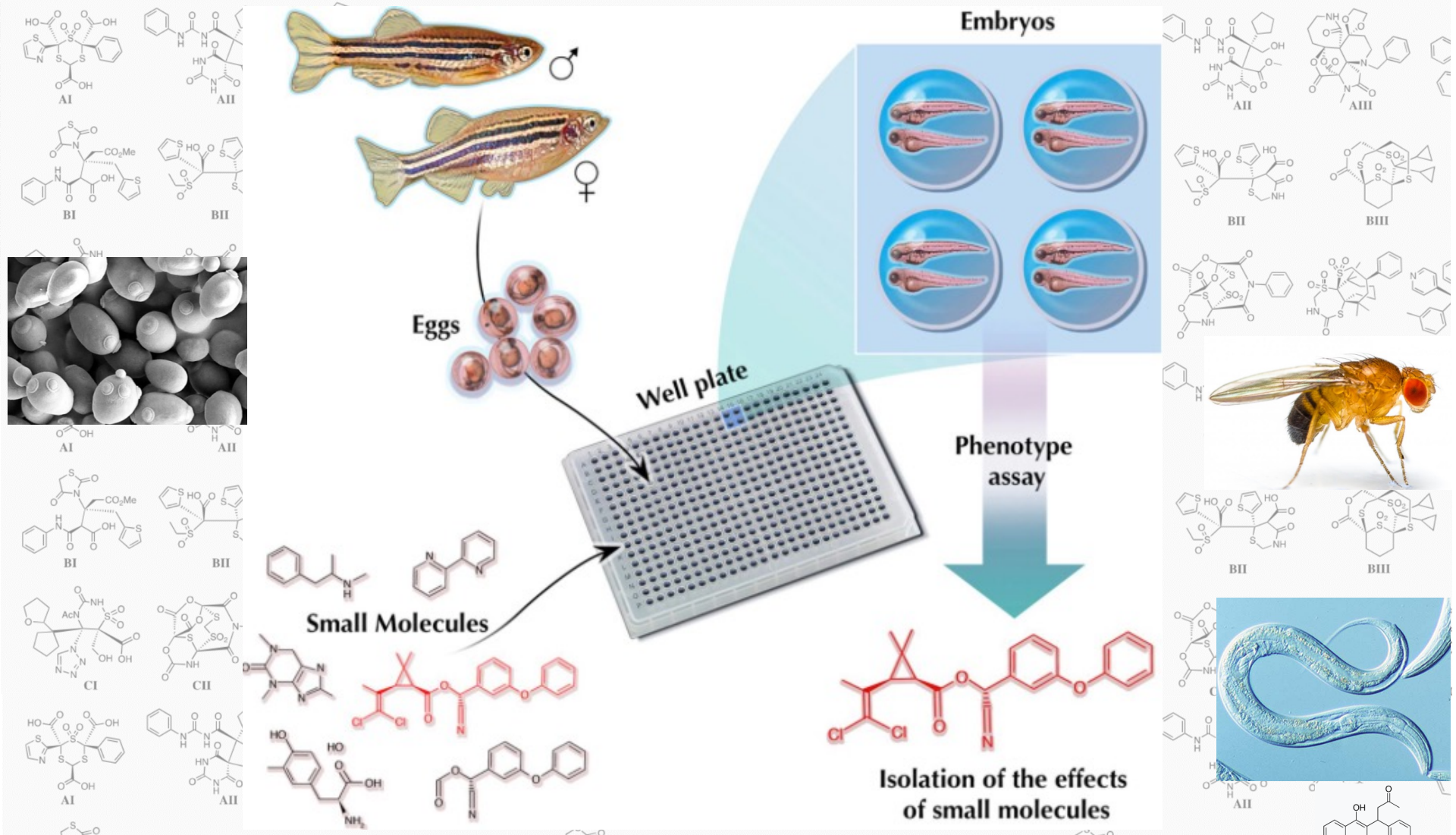
eg. the dual role of TGFb from tumour supressor to cancer metastasis

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

The Making Of An Innovative Medicine: iPSC in translational research



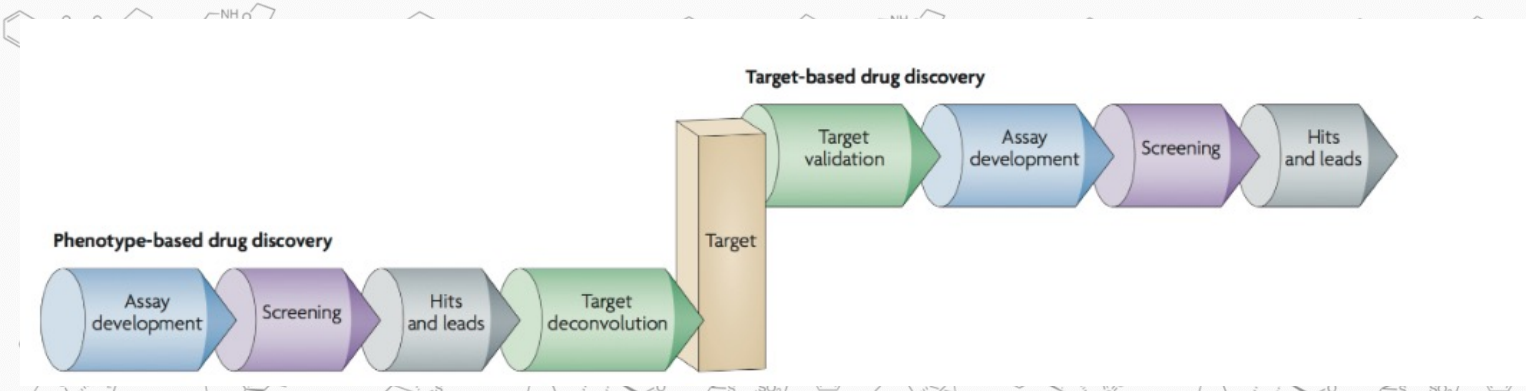
Any robust biological readout may serve as HTS :
PHENOCOPY SCREENS, eg Danio rerio, D. mel, C. elegans, S. cerevisiae etc

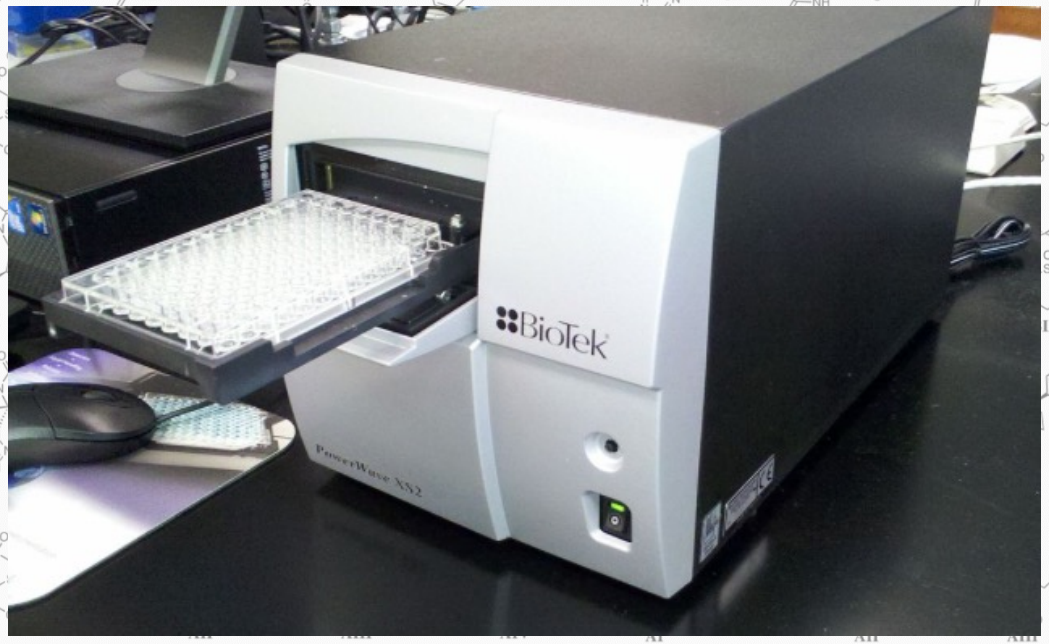


Phenocopy screens primarily generates ”orphan” drugs

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

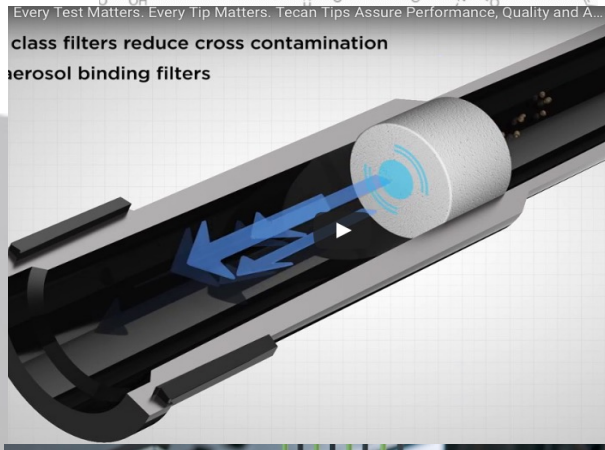
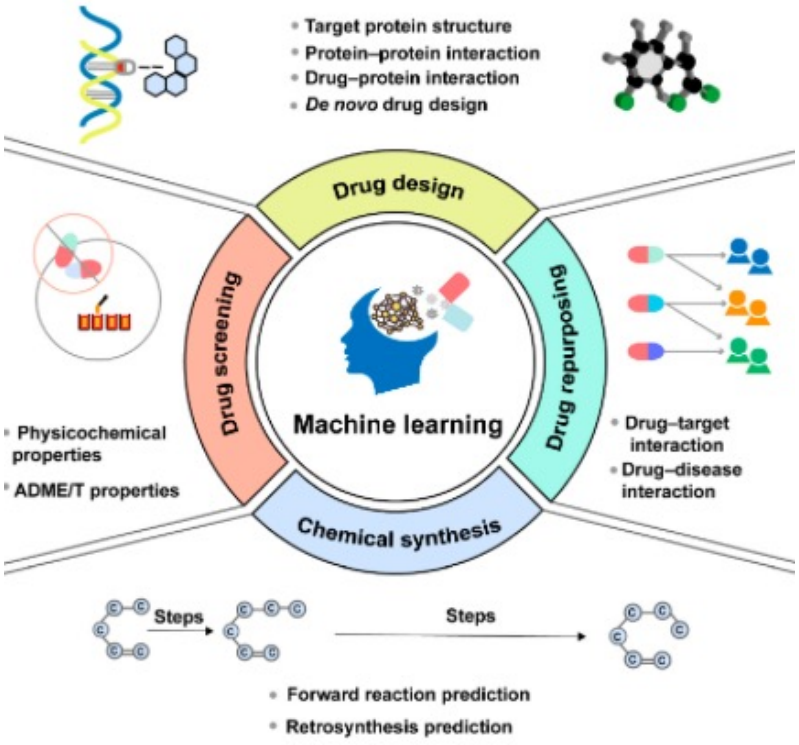
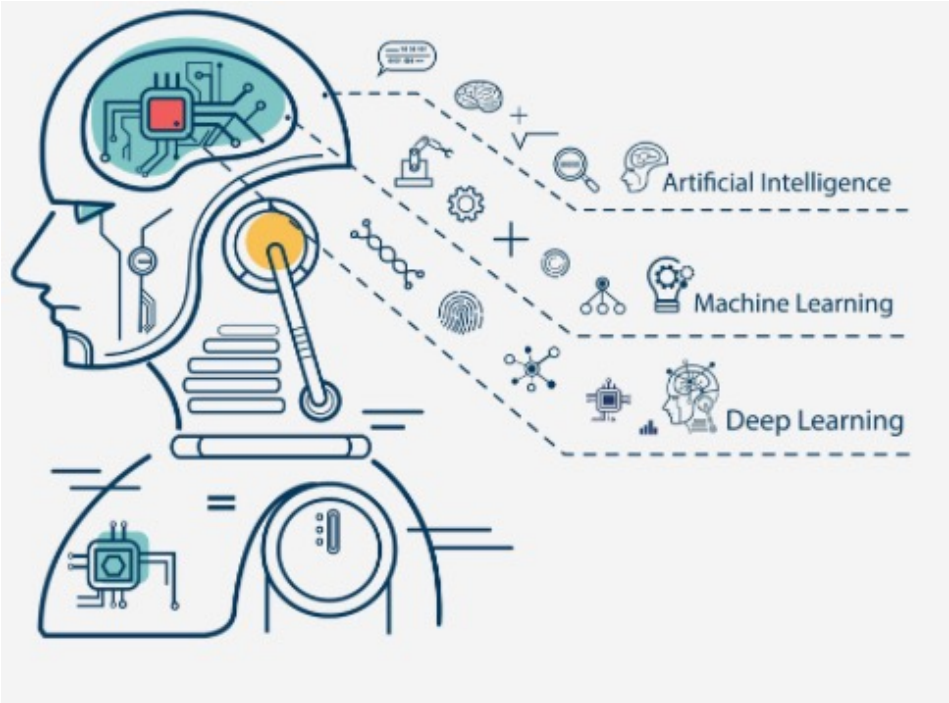


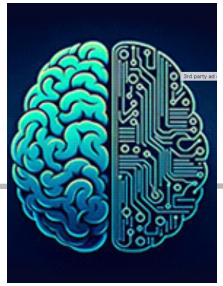
Table top precision liquid handling robotics once a primary “first hit” cpd has been selected

Machine learning/AI approaches to drug discovery and start up entreprises in the quest for effective therapeutics - from Venture capital and non profit organization dependent POC to pharma clinical development





A deep learning approach to antibiotic discovery : a paradigm shift

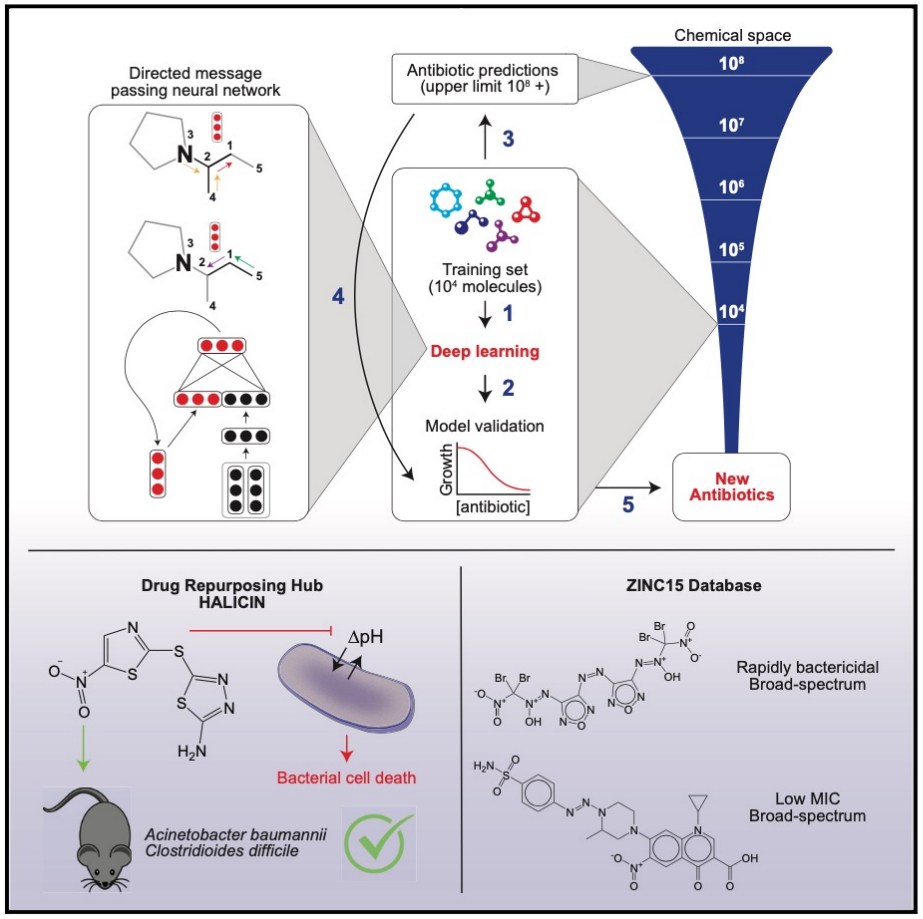


Article

Cell

A Deep Learning Approach to Antibiotic Discovery

Graphical Abstract



Authors

Jonathan M. Stokes, Kevin Yang, Kyle Swanson, ..., Tommi S. Jaakkola, Regina Barzilay, James J. Collins

Correspondence

regina@csail.mit.edu (R.B.), jimjc@mit.edu (J.J.C.)

Highlights

- A deep learning model is trained to predict antibiotics based on structure
- Halicin is predicted as an antibacterial molecule from the Drug Repurposing Hub
- Halicin shows broad-spectrum antibiotic activities in mice
- More antibiotics with distinct structures are predicted from the ZINC15 database

Stokes JM et al. 2020. Cell *180*, 688–702

Machine learning in antibiotic in multiple chemical librairy screen

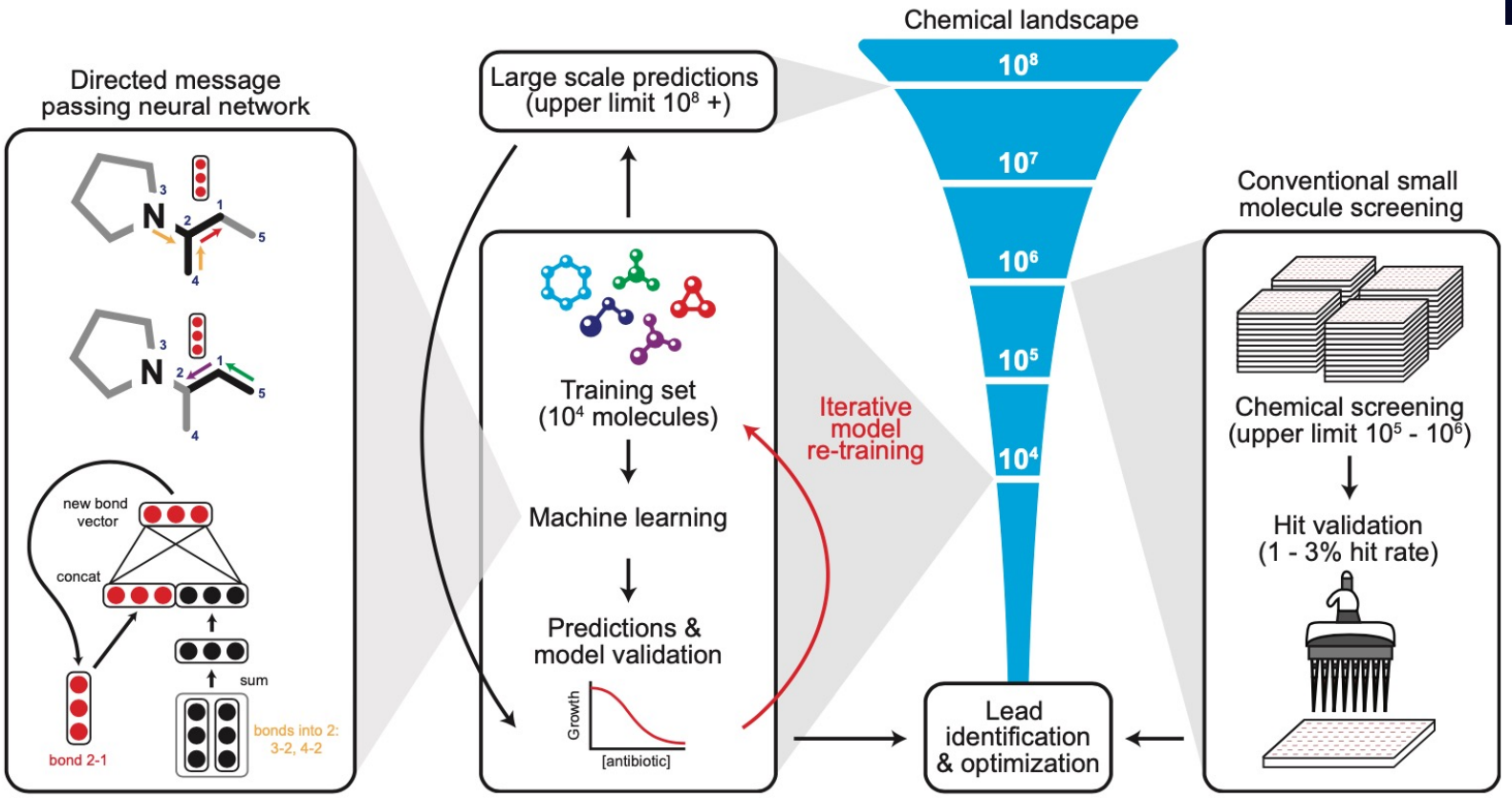
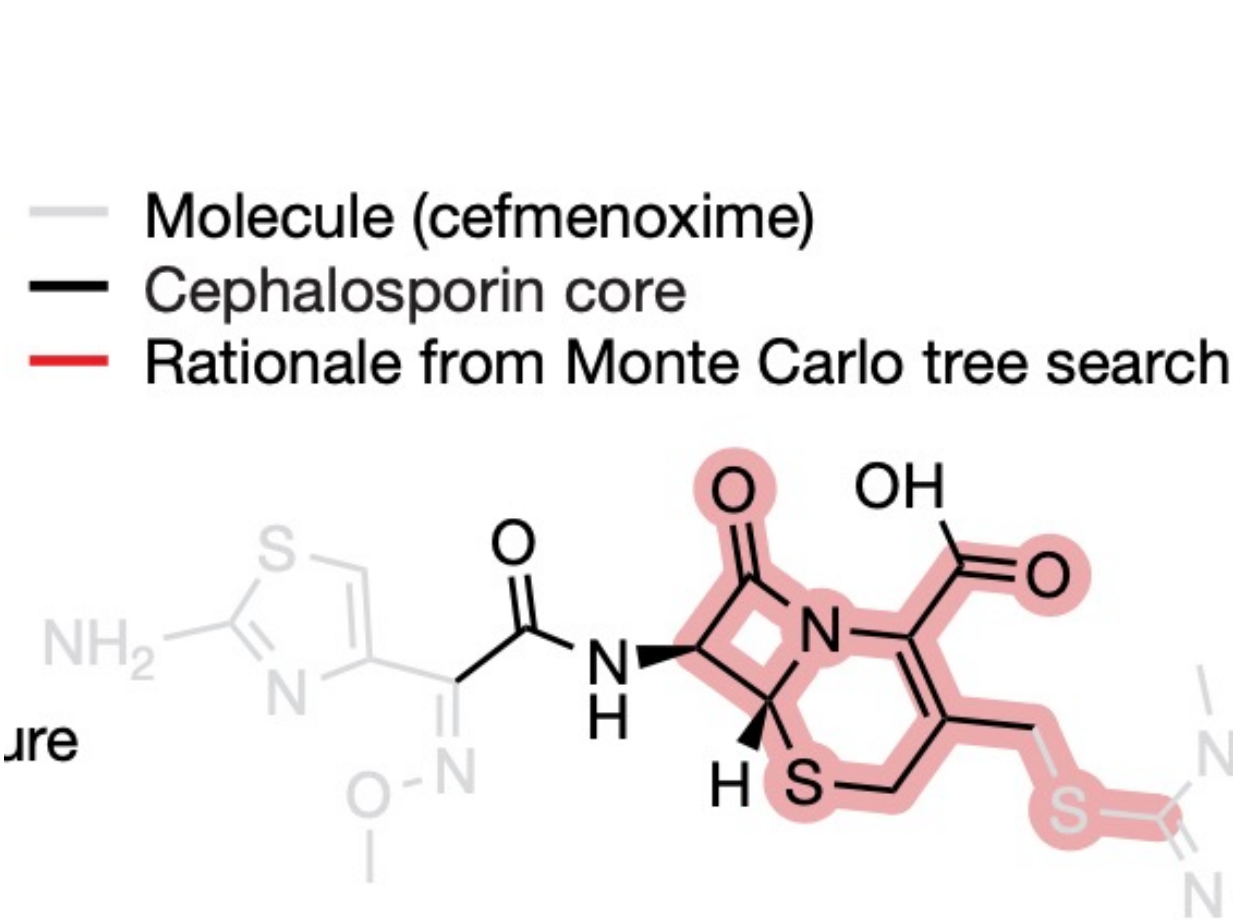
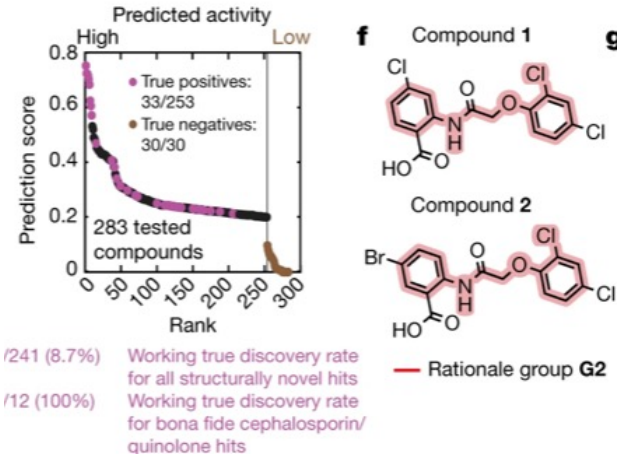


Figure 1. Machine Learning in Antibiotic Discovery

Modern approaches to antibiotic discovery often include screening large chemical libraries for those that elicit a phenotype of interest. These screens, which are upper bound by hundreds of thousands to a few million molecules, are expensive, time consuming, and can fail to capture an expansive breadth of chemical space. In contrast, machine learning approaches afford the opportunity to rapidly and inexpensively explore vast chemical spaces *in silico*. Our deep neural network model works by building a molecular representation based on a specific property, in our case the inhibition of the growth of *E. coli*, using a directed message passing approach. We first trained our neural network model using a collection of 2,335 diverse molecules for those that inhibited the growth of *E. coli*, augmenting the model with a set of molecular features, hyperparameter optimization, and ensembling. Next, we applied the model to multiple chemical libraries, comprising >107 million molecules, to identify potential lead compounds with activity against *E. coli*. After ranking the candidates according to the model's

Neural network models to predict structural classes of antibacterial cephalosporins





Wong et al… J. Collins. Nature published online December 20. 2023

THANK YOU.....

DO YOU HAVE ANY QUESTIONS ?