Pharmacoinformatics Research Group
Department of Pharmaceutical Chemistry

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The OMICS Approach

The Buzz that makes the World go round

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Disclosure

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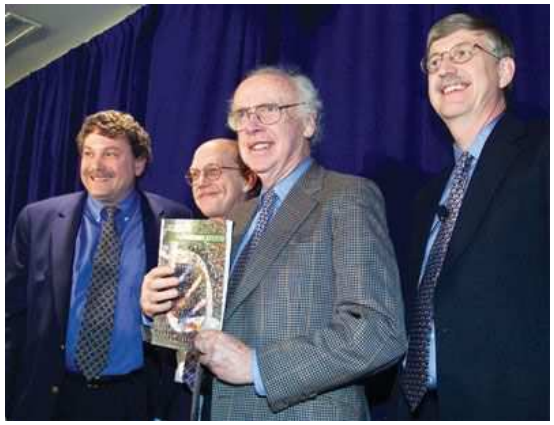
G. Ecker is co-founder of Phenaris GmbH

The Human Genome



2001: 10 Years, 2,7 bio USD
Now: a few days, a few 100 USD

2003: ENCODE Project (ENcyclopedia Of DNA Elements)

2008: 1.000 Genomes Project

2010: UK10K study; 4.000 healthy people, 6.000 with genetic disease

2012: 100.000 Genomes Project; status Aug 7, 2017: 32.642 genomes sequenced

2017: Chinese province is sequencing 1.000.000 genomes

100.000 Genomes Project

”Genomics has the potential to improve outcome through appropriate **stratification of medicines**, and pharmacists should be part of this exciting development”

“The sequencing part is relatively easy and fast. The challenge lies in data analysis and interpretation!”

May also **link genomic data** with **additional health data** from general practitioners, hospitals, national disease registries, but also other sources such as smart devices

Robinson, The Pharmaceutical Journal 2017

100.000 Genomes – Why?

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- Differences in our DNA determine our unique characteristics
- can also be the basis for certain diseases
- Sequencing the genomes of many individuals enables researchers
  - to gain better understanding of these diseases
  - to develop treatments
  - to make new diagnoses
- Variations in person's genome can affect their **individual response** to a drug
- Genome sequencing can
  - help match patients to the most appropriate drug
  - work out the best dose
  - predict whether they are likely to suffer adverse effects (pharmacogenomics)

Individual Genetic Profiles

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CYP2C19-Gen Chromosom 10q24

CYP2D6-Gen Chromosom 22q13.1

CYP3A4-Gen Chromosom 7q21.1

T

Tacrolimus | Talinolol | Tamoxifen | Tegafur | Telaprevir | Thioridazin

Tiotropium bromid | Tolterodin | Topiramat | Torasemid | Tramadol | Trimipramin

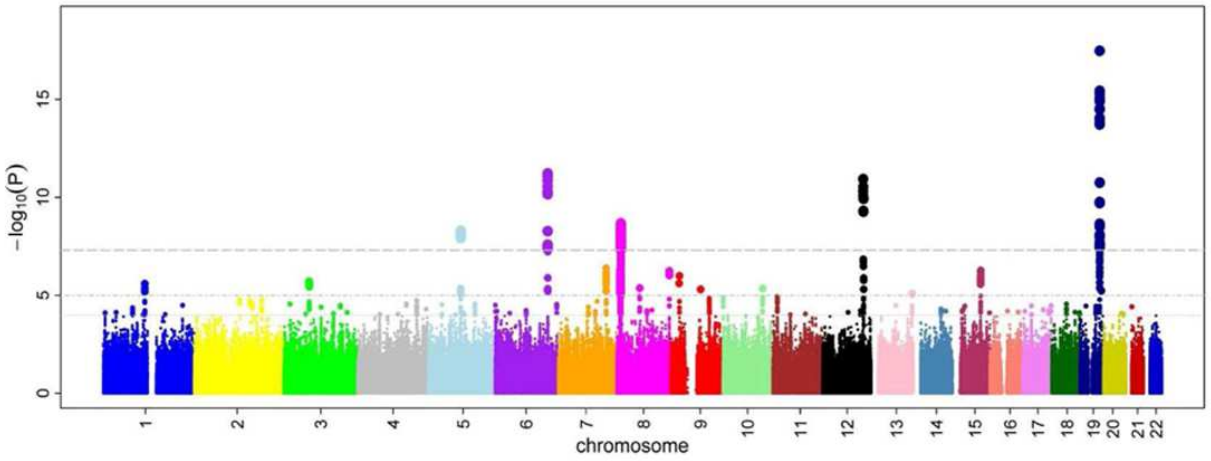
Thioridazin

Gefahr der Unverträglichkeit

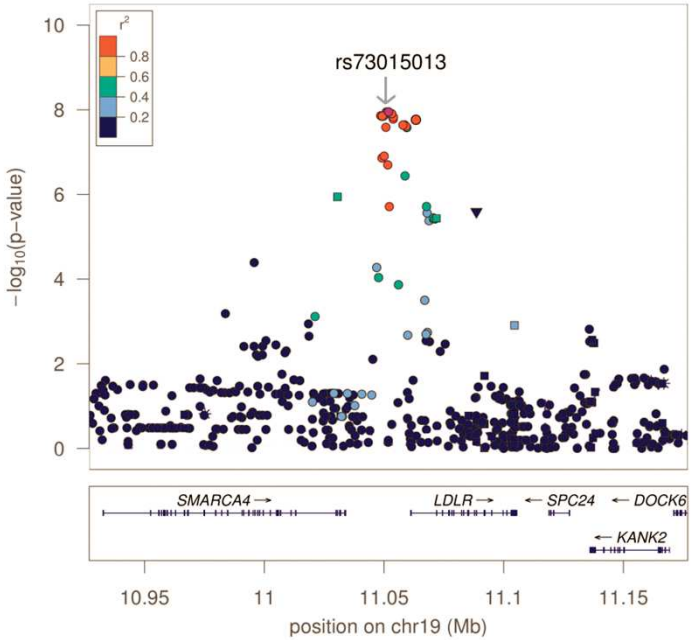
Aufgrund des genetischen Profils besteht ein erhöhtes Risiko für lebensbedrohliche Herzrhythmusstörungen.

Kontraindikation. Ausweichen auf Alternativwirkstoff dringend empfohlen.

Genome Wide Association (GWA)

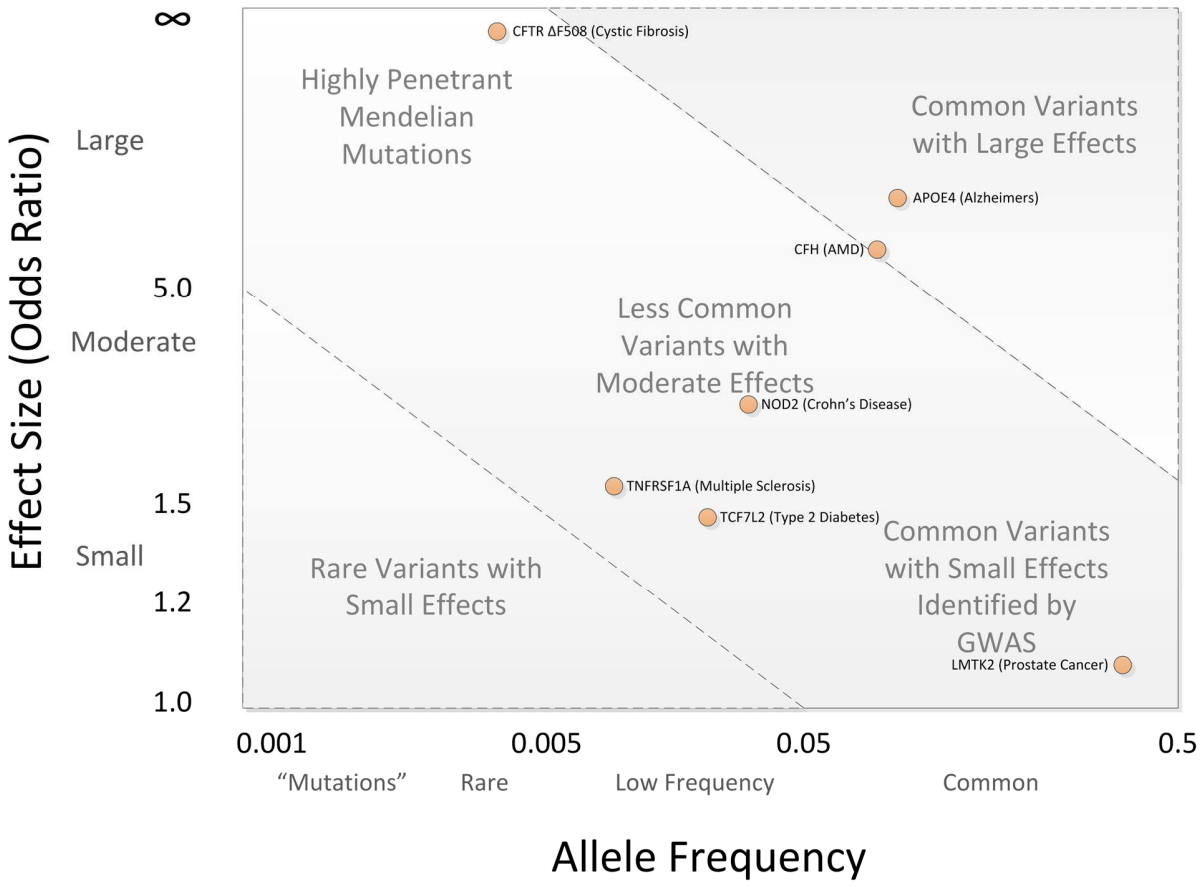


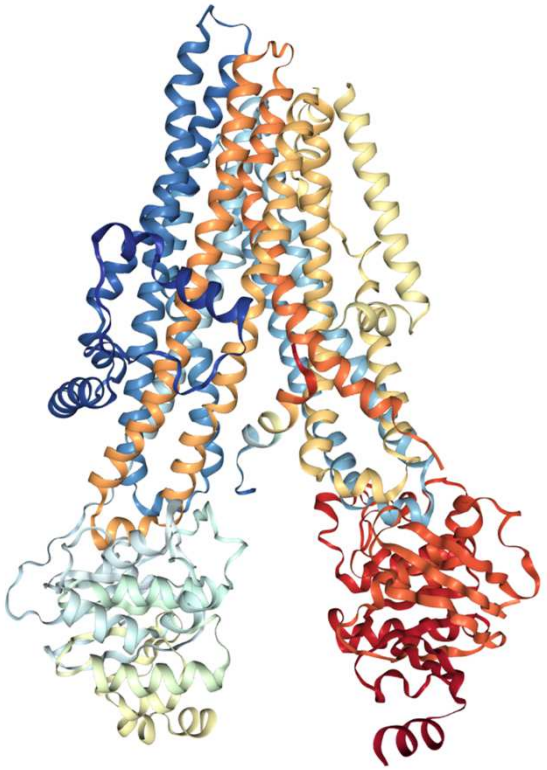
Ikram MK et al (2010) Four Novel Loci (19q13, 6q24, 12q24, and 5q14) Influence the Microcirculation In Vivo. PLoS Genet. 2010; https://commons.wikimedia.org



By Sanna S et al - Sanna S (2011) Fine mapping of five loci associated with low-density lipoprotein cholesterol detects variants that double the explained heritability. PLoS Genet. 2011 https://commons.wikimedia.org

GWAS and Causality





CFTR (pdb: 5UAK)

The OMICS World

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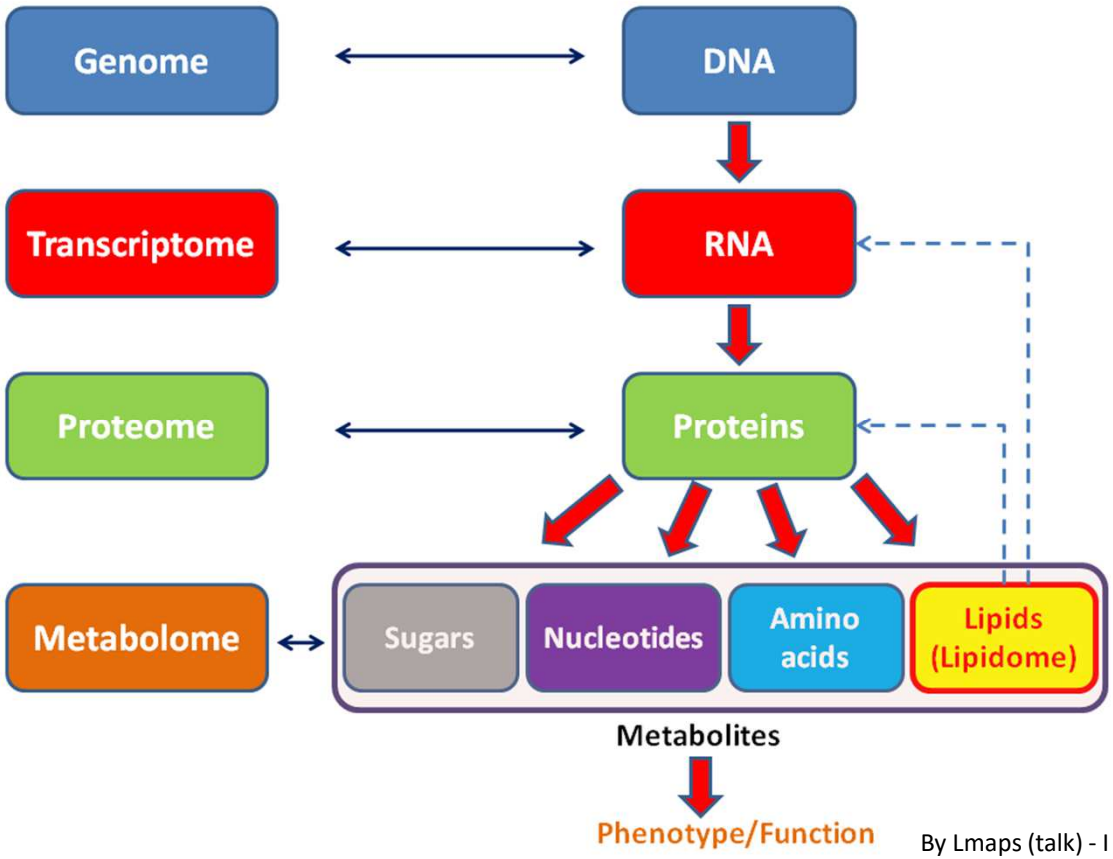
Definitions



Genomics is focusing on the structure, function, evolution, mapping, and editing of whole genomes. A genome is an organism's complete set of DNA, including all of its genes

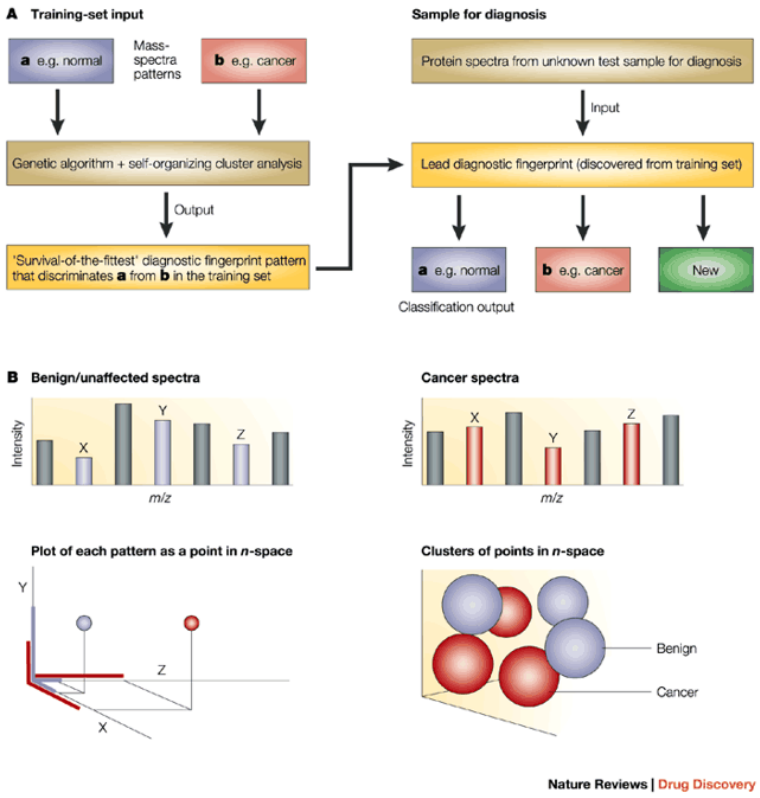
The **transcriptome** is the set of all RNA molecules in one cell or a population of cells

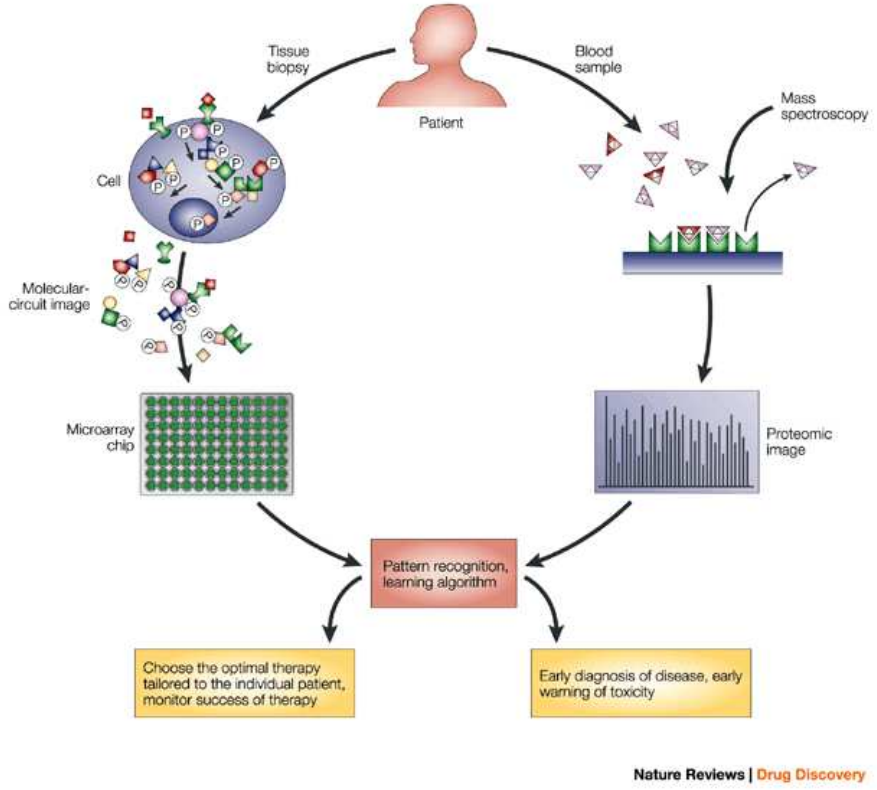
The **proteome** is the entire set of proteins that is produced or modified by an organism or system. This varies with time and distinct requirements, or stresses, that a cell or organism undergoes.

The **metabolome** refers to the complete set of small-molecule chemicals found within a biological sample. The biological sample can be a cell, a cellular organelle, an organ, a tissue, a tissue extract, a biofluid, or an entire organism

By Lmaps (talk) - I created this work entirely by myself., CC BY-SA 3.0, https://en.wikipedia.org/w/index.php?curid=21274382

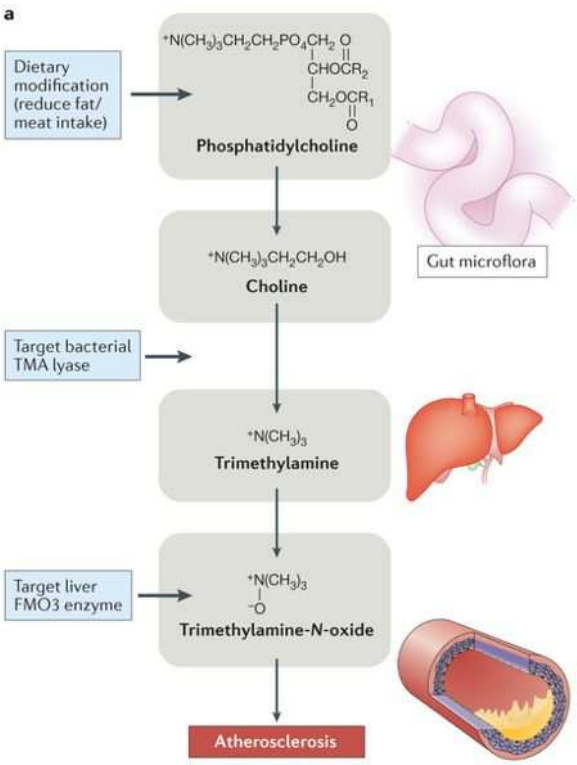
Proteomics

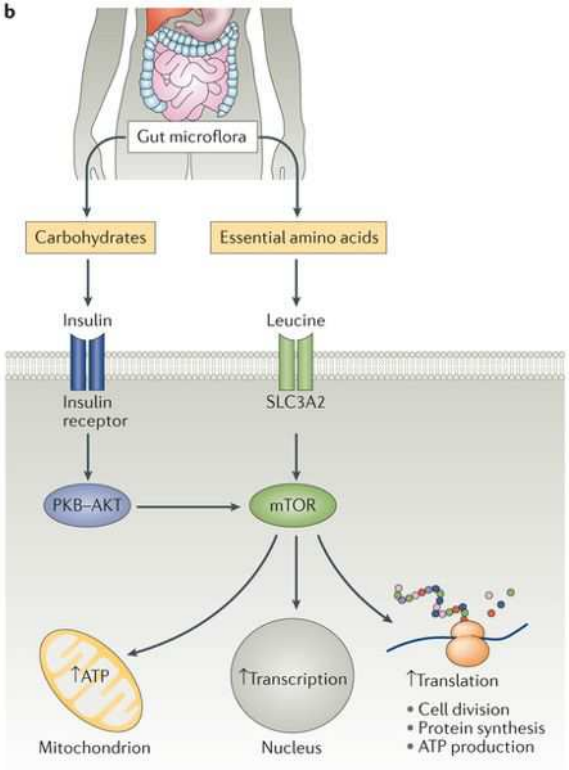




Petricoin, Nature Rev Drug Discov 2002

Metabolomics





Nature Reviews | Drug Discovery

Metabolomics is used to

- diagnose cancer
- understand disease mechanisms
- identify novel drug targets
- customize drug treatments
- monitor therapeutic outcomes

Wishart, Nature Rev Drug Discovery 2016

Personalized Medicine

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Norwegian Cancer Genomics Consortium

Norwegian Cancer Genomics Consortium: a platform for research on personalized cancer medicine in a public health system

Ola Myklebost, ola.myklebost@imbv.uio.no

Drug Discovery Today 2015

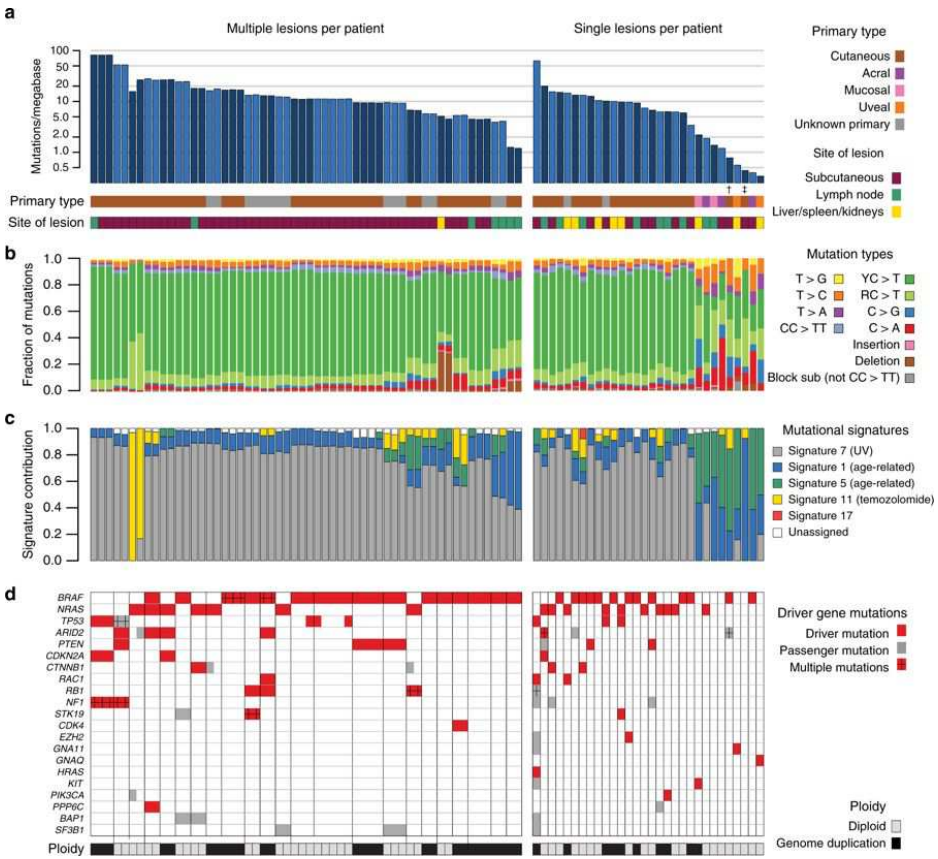
nature COMMUNICATIONS

ARTICLE

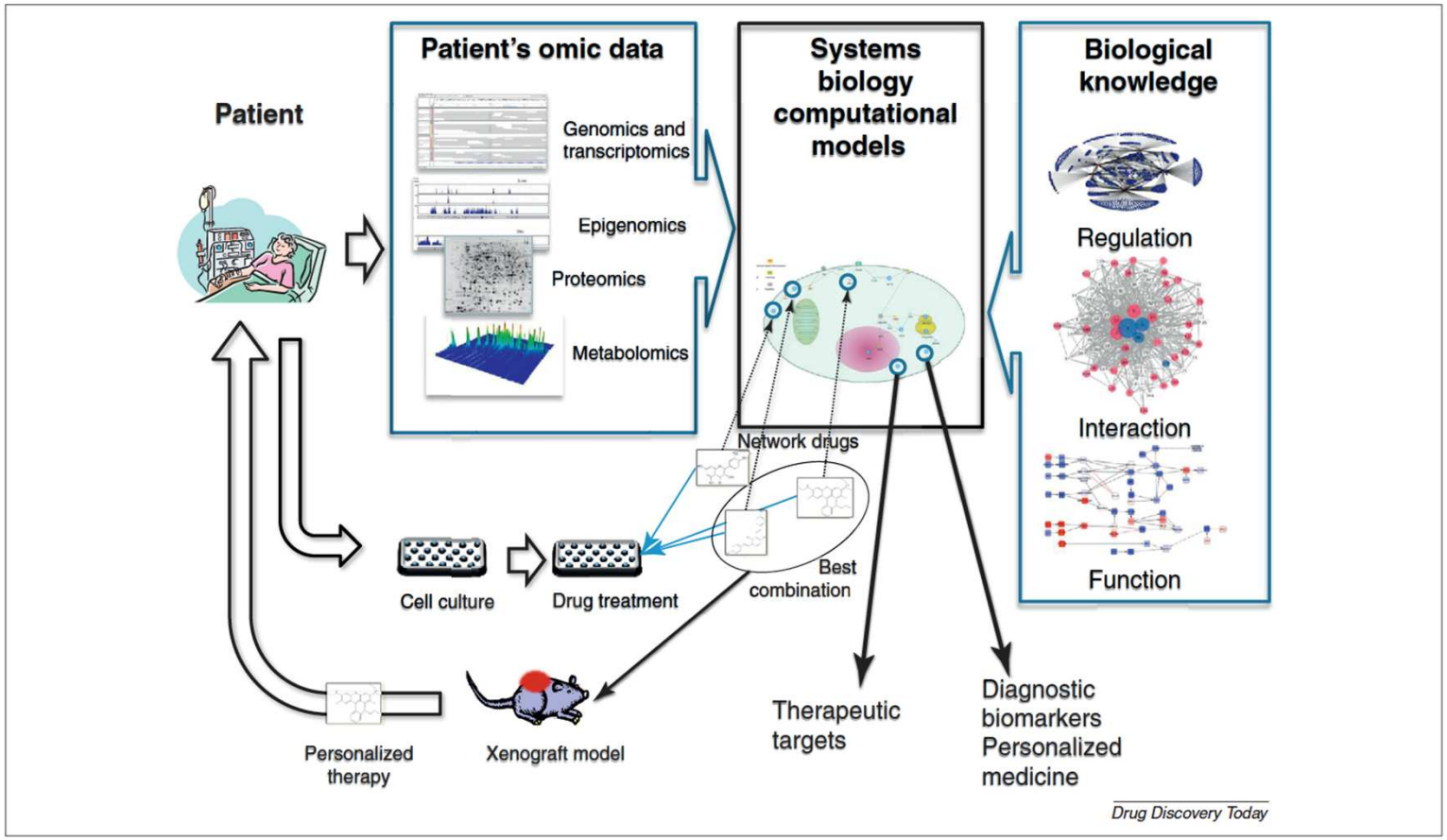
DOI: 10.1038/s41467-018-05063-1 OPEN

Patterns of genomic evolution in advanced melanoma

E. Birkeland[1,2], S. Zhang[1,2], D. Poduval[1,2], J. Geisler[3,4], S. Nakken[5,6], D. Vodak[5,6], L.A. Meza-Zepeda[5,6,7], E. Hovig[5,6,8,9], O. Myklebost[5,6], S. Knappskog[1,2] & P.E. Lønning[1,2]

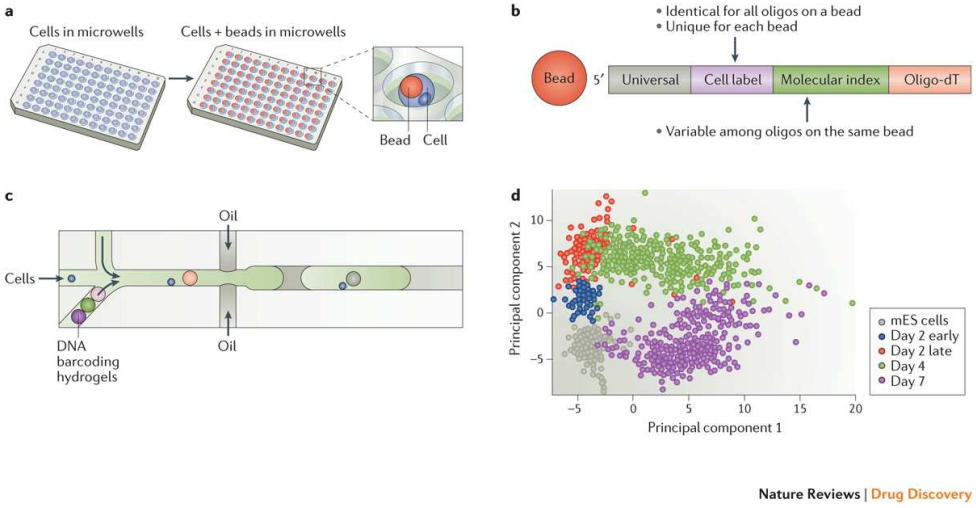


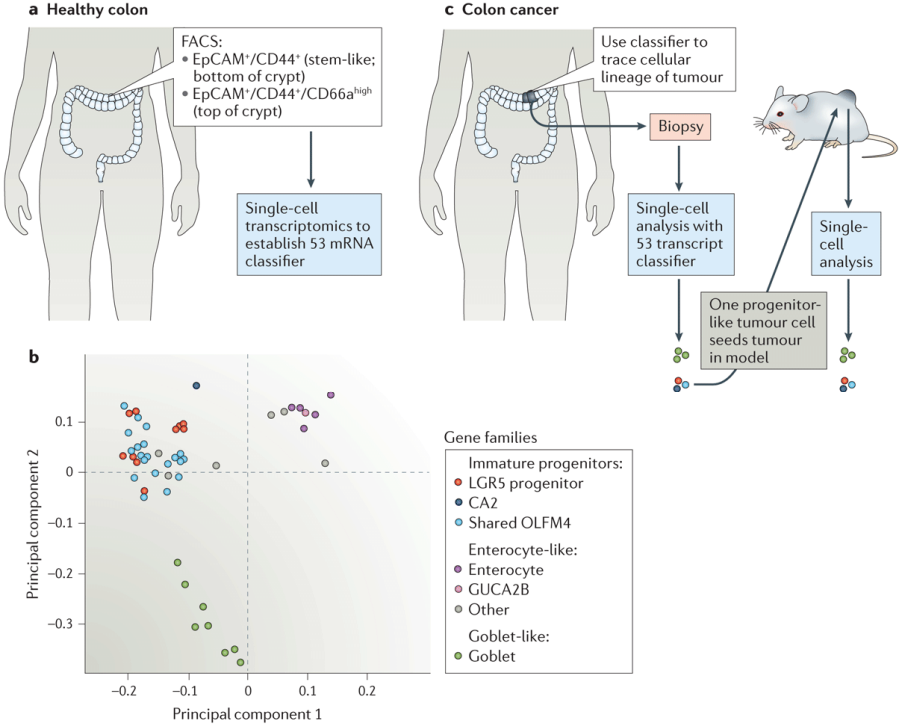
Personalized Therapies



Dopazo, DDT 2014

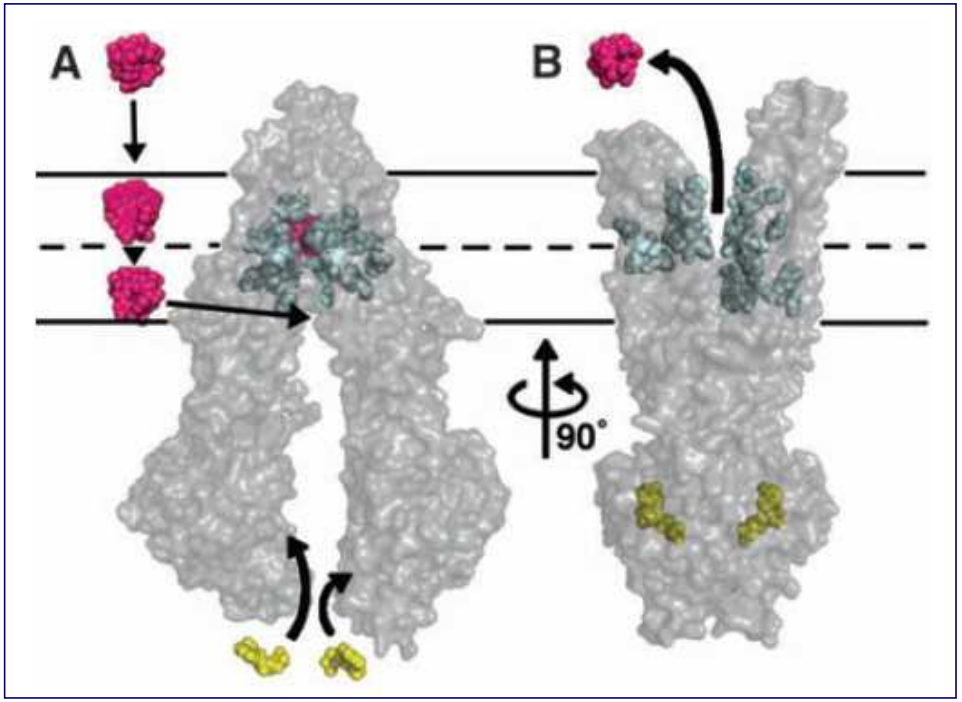
Single Cell Omics



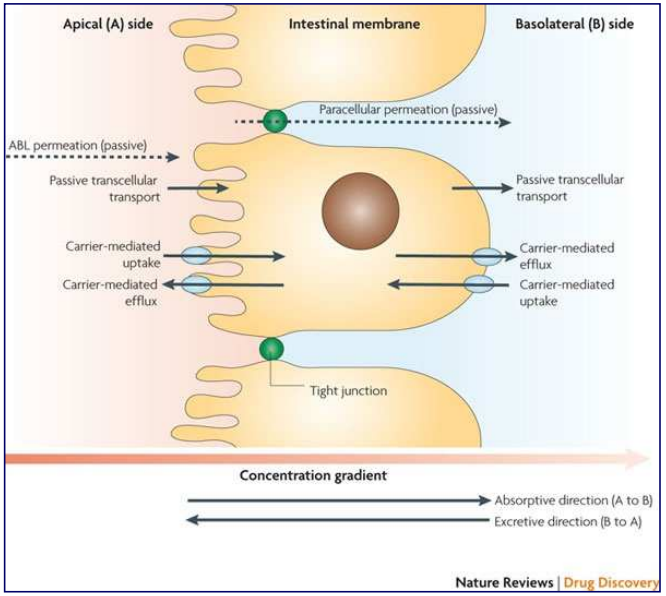


Heath, Nature Rev Drug Discov 2016

The Transportome (ABCs)



Aller et al. Science 2009

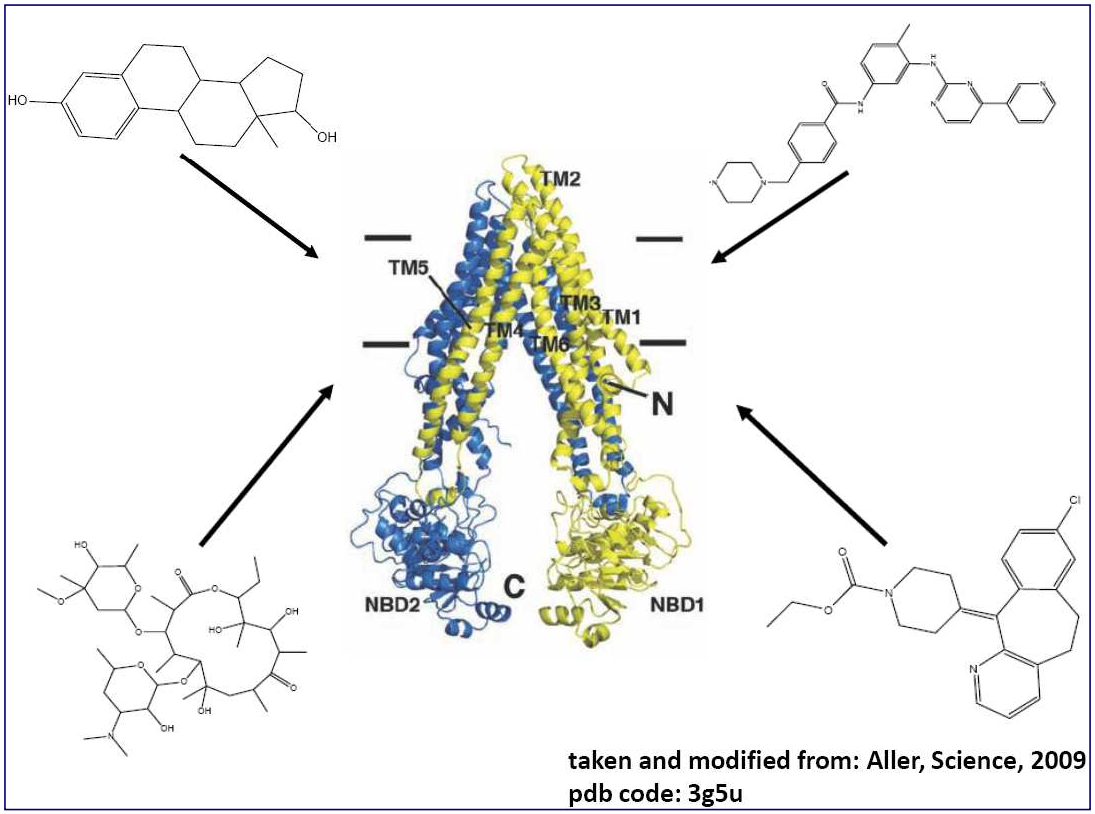


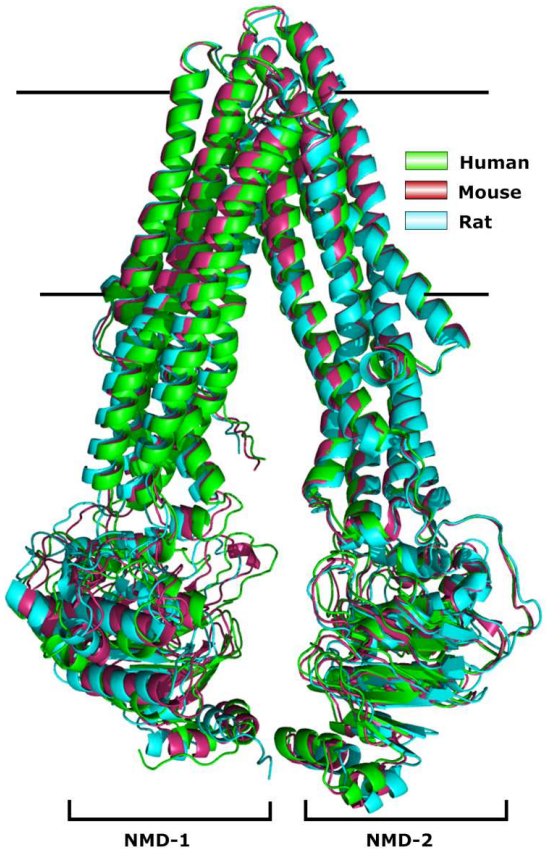
OPINION

Coexistence of passive and carrier-mediated processes in drug transport

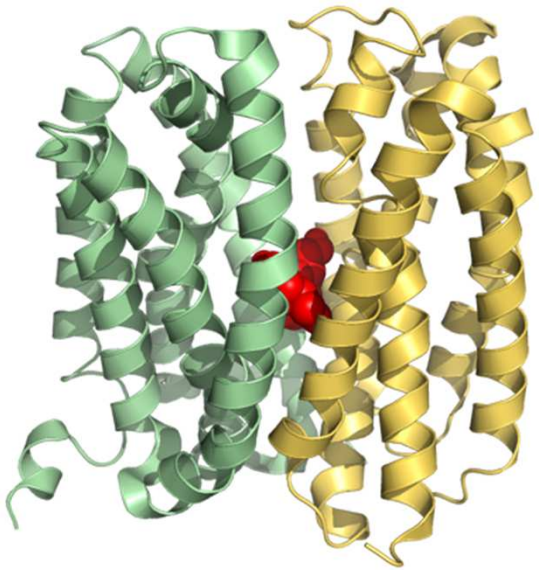
Kiyohiko Sugano, Manfred Kansy, Per Artursson, Alex Avdeef, Stefanie Bendels, Li Di, Gerhard F. Ecker, Bernard Faller, Holger Fischer, Grégori Gerebtzoff, Hans Lennernaes and Frank Senner

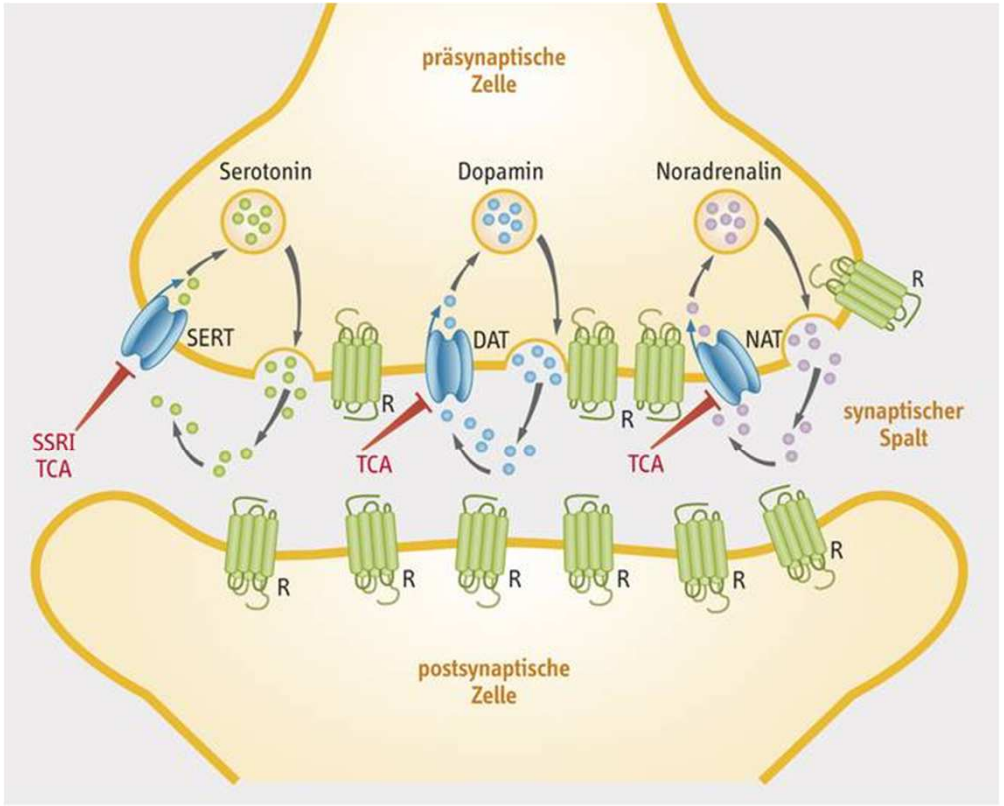
P-glycoprotein - Polyspecificity





The Transportome (SLCs)





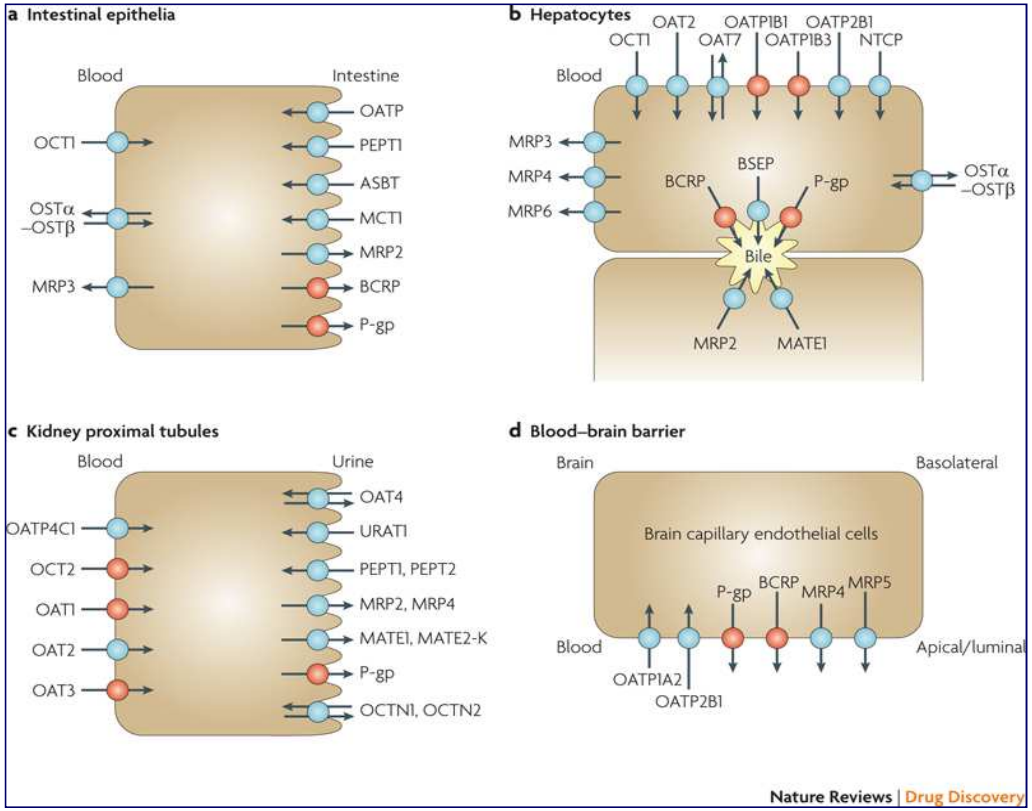
© Steinhilber / Schubert-Zsilavecz / Roth – Medizinische Chemie
2. Auflage, Deutscher Apotheker Verlag, 2010

Transporter and ADMET

48 ABC-Transporter
458 SLC-Transporter

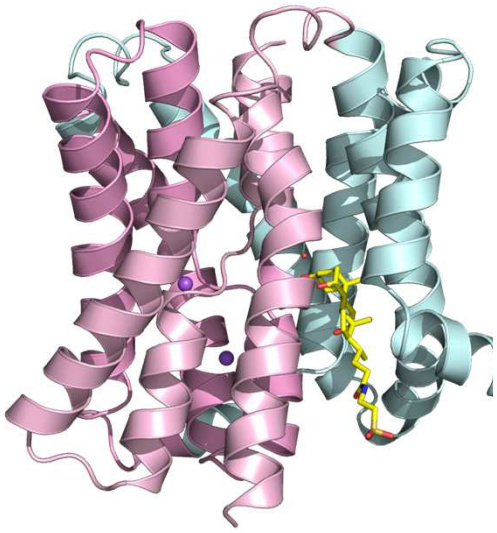
FDA asks for testing of the following transporter:

- MDR1 (P-glycoprotein)
- BCRP
- OATP (organic anion transporting polypeptide)
- OCT2 (organic cation transporter)
- OAT1/3 (Organic anion transporter)

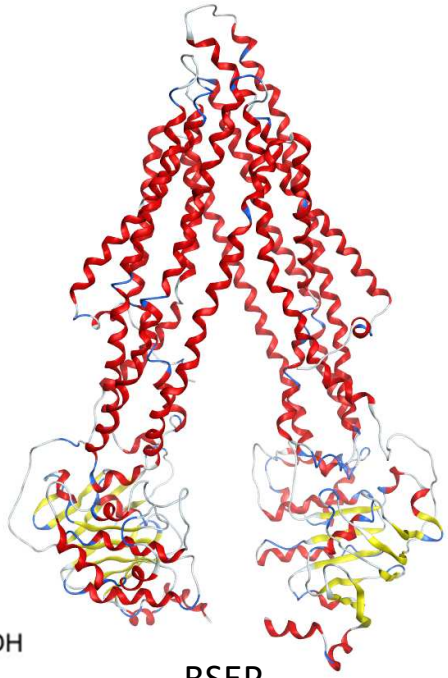


Nature Reviews Drug Discovery 9, 215-236 (March 2010)

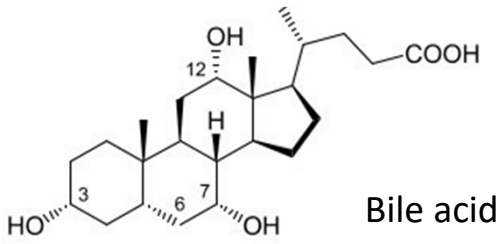
Enterohepatic Bile Acid Circuit



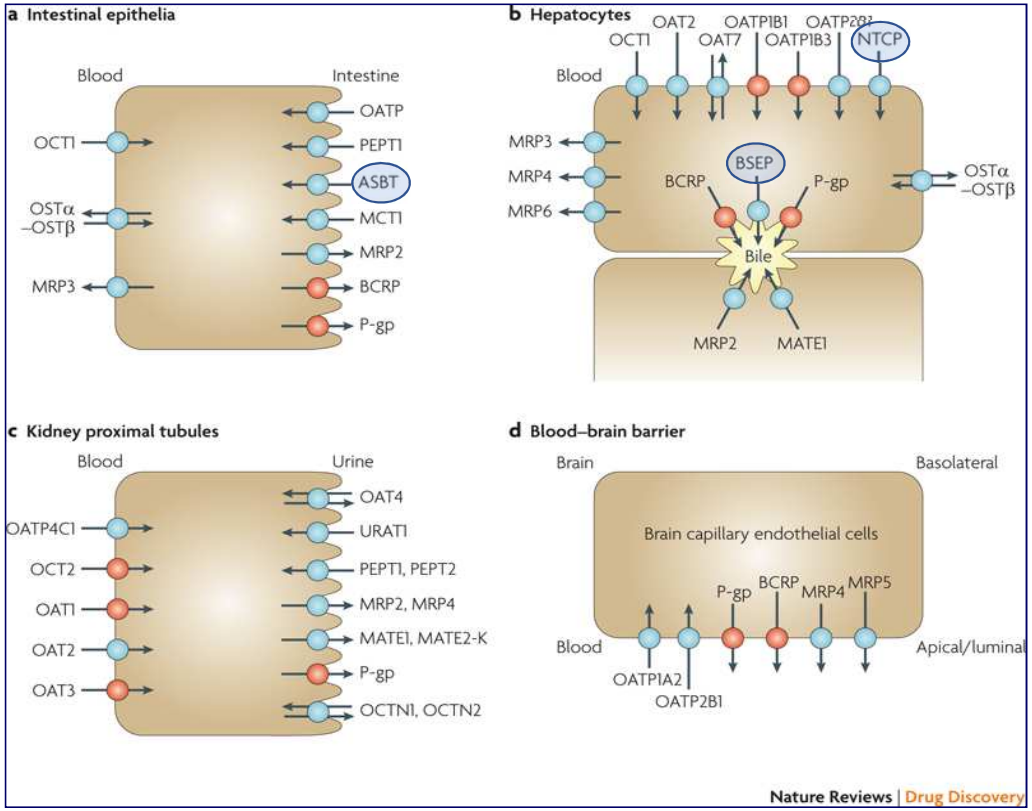
ASBT



BSEP



Bile acid (cholic acid)



Nature Reviews Drug Discovery 9, 215-236 (March 2010)

Prediction of Hepatotoxicity

Does hepatic transporters' information help to predict hepatotoxicity?

DILI	Hyperbilirubinemia	Cholestasis
Not really:	**Partially:**	**Substantially:**
➢ Complex system	➢Transporters ↑ ranked dscrs	➢Increase model's performance
➢ use of toxicity reports	➢MRP2 & UGT1A1 also involved	➢Synergistic effect- No predominant transporter identified
		➢More transporters most probably contribute

Kotsampasakou, Eur J Pharm Sci 2017; JCIM 2017; Toxicology 2017

Transporter mediated DDI

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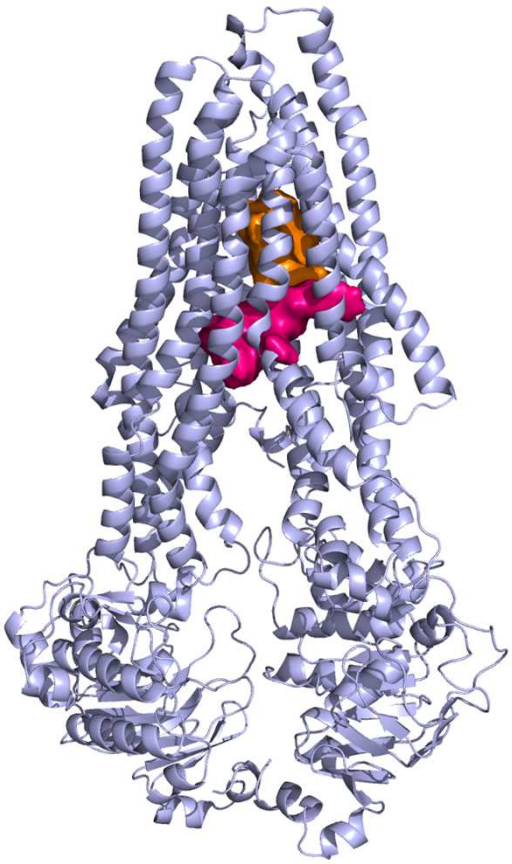
Interacting Drug	Affected Drug	Consequence	Fold Changes in Substrate Plasma AUC
Quinidine	Digoxin	Digoxin Exposure 1.7-fold ↑	P-glycoprotein (P-gp, MDR1) Inhibition
Rifampin	Digoxin	Digoxin Exposure 30% ↓	P-gp Induction
Dronedarone	Digoxin	Digoxin Exposure 2.6-fold ↑	P-gp Inhibition
Probenecid	Cephradine	Cephradine Exposure 3.6-fold ↑	Organic Anion Transporter (OAT) Inhibition
Cimetidine	Metformin	Metformin Exposure 1.4-fold ↑	Organic Cation Transporter (OCT) Inhibition
Cyclosporine	Rosuvastatin	Rosuvastatin Exposure 7-fold ↑	Organic Anion Transporting Polypeptide (OATP) Inhibition & Breast Cancer Resistance Protein (BCRP) Inhibition
Lopinavir/ Ritonavir	Rosuvastatin	Rosuvastatin Exposure 2-fold ↑	OATP Inhibition

Taken from Zhang, fda.gov

Transporter and Toxicity



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Vienna LiverTox Workspace

ABOUT | PREDICT | MODEL DOCUMENTATION | DISCLAIMER | SETTINGS

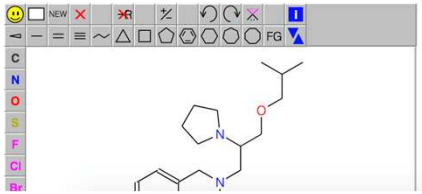
Select Models

SUBMIT

- SELECT ALL
- SELECT TRANSPORTER MODELS:
  - BSEP Inhibition
  - BSEP Transport
  - P-glycoprotein Inhibition
  - P-glycoprotein Transport
  - MRP4 Inhibition
  - MRP2 Transport
  - MRP3 Inhibition
  - MRP3 Transport
  - BCRP Inhibition
  - BCRP Transport
  - OATP1B1 Inhibition
  - OATP1B3 Inhibition
- SELECT TOXICITY MODELS:
  - Drug-induced liver injury
  - Hyperbilirubinemia
  - Cholestasis

Enter Compound

UPLOAD SDF FILE | EXAMPLE: BEPRIDIL



Results

DOWNLOAD AS SDF

#	BSEP Inhibition	BSEP Transport	P-glycoprotein Inhibition	P-glycoprotein Transport	MRP4 Inhibition	MRP2 Transport	MRP3 Inhibition	MRP3 Transport	BCRP Inhibition	BCRP Transport	OATP1B1 Inhibition	OATP1B3 Inhibition	Drug-induced liver injury	Hyperbilirubinemia	Cholestasis
1	1.0	0.0	0.6	0.3	1.0	0.6	1.0	0.4	0.2	0.4	1.0	1.0	0.7	0.9	0.3
2	1.0	0.0	0.5	0.2	1.0	0.8	1.0	0.2	0.2	0.6	0.0	0.0	0.6	1.0	0.9
3	1.0	0.0	0.7	0.2	1.0	0.8	1.0	0.2	0.5	0.6	0.0	0.0	0.6	0.3	0.9
4	0.0	0.0	0.3	0.3	1.0	0.6	0.0	0.2	0.2	0.6	0.0	0.0	0.6	0.3	0.9
5	0.0	0.0	0.3	0.1	0.8	0.4	0.0	0.2	0.2	0.4	0.0	0.0	0.7	0.7	0.7
6	0.0	1.0	0.3	0.1	1.0	0.0	0.0	0.2	0.2	0.6	0.0	0.0	0.6	0.3	0.0
7	0.0	0.0	0.2	0.1	0.0	0.4	0.0	0.4	0.4	0.4	0.0	0.0	0.7	0.2	0.9
8	1.0	1.0	0.5	0.3	0.0	0.0	1.0	0.4	0.1	0.6	1.0	0.0	0.5	0.9	0.0
9	1.0	0.0	0.8	0.3	1.0	0.0	1.0	0.2	0.3	0.2	1.0	1.0	0.6	1.0	0.0

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livertox.univie.ac.at

Folding Deficiencies & Diseases

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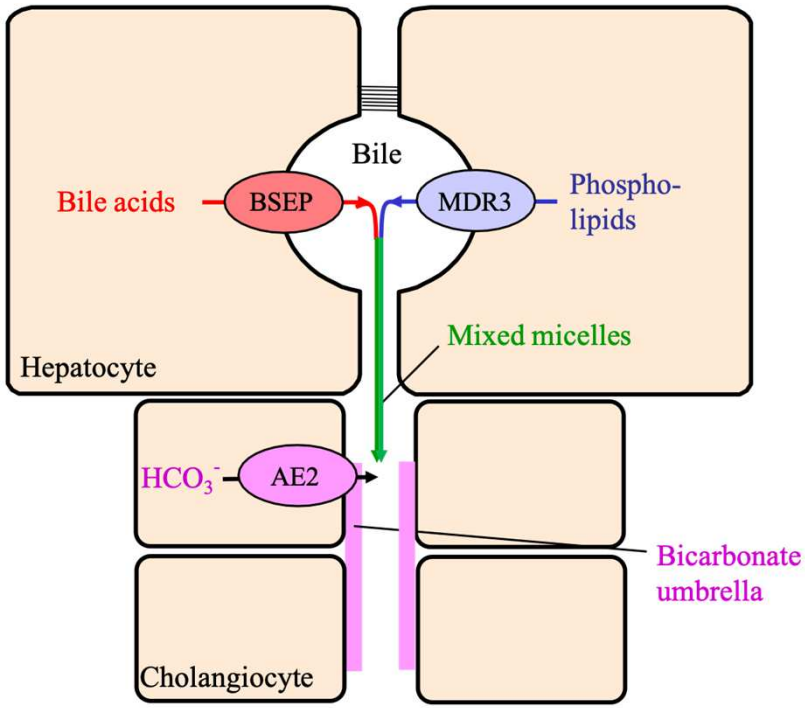
- ABCA1 Tangier disease
  ABCA3 Fatal surfactant deficiency
  ABCA4 Stargardt disease
- **ABCB1**
  ABCB4 **P**rogressive **F**amilial **I**ntrahepatic **C**holestasis type 3, PFIC3
  ABCB11 **P**rogressive **F**amilial **I**ntrahepatic **C**holestasis type 2, PFIC2
  Benign **R**ecurrent **I**ntrahepatic **C**holestasis type 2, BRIC2
- ABCC2 Dubin-Johnson
  ABCC4
  ABCC7 **C**ystic **F**ibrosis
  ABCC8
  ABCC11
- **ABCG2** gout



Toxicogenomics

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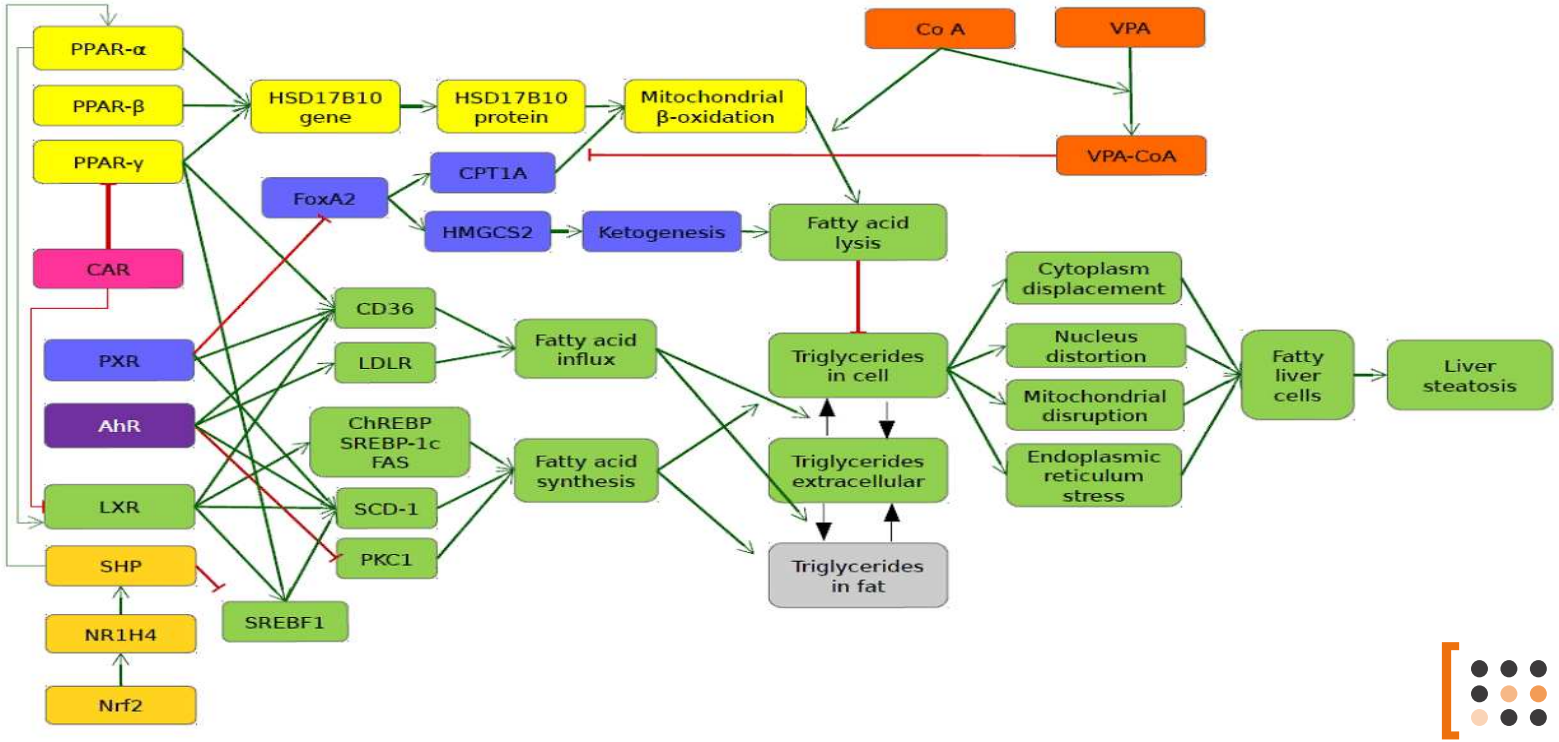
Hepatic Steatosis AOP Network (6 AOPs)



[:::] EUTOXRISK

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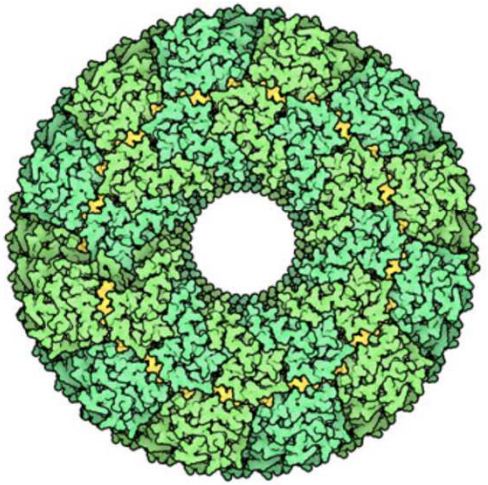
The RCSB PDB builds upon the data by creating tools and resources for research and education in molecular biology, structural biology, computational biology, and beyond.

Superbugs! How Bacteria Evolve Resistance to Antibiotics

March **Molecule of the Month**



Measles Virus Proteins

Structural Genomics

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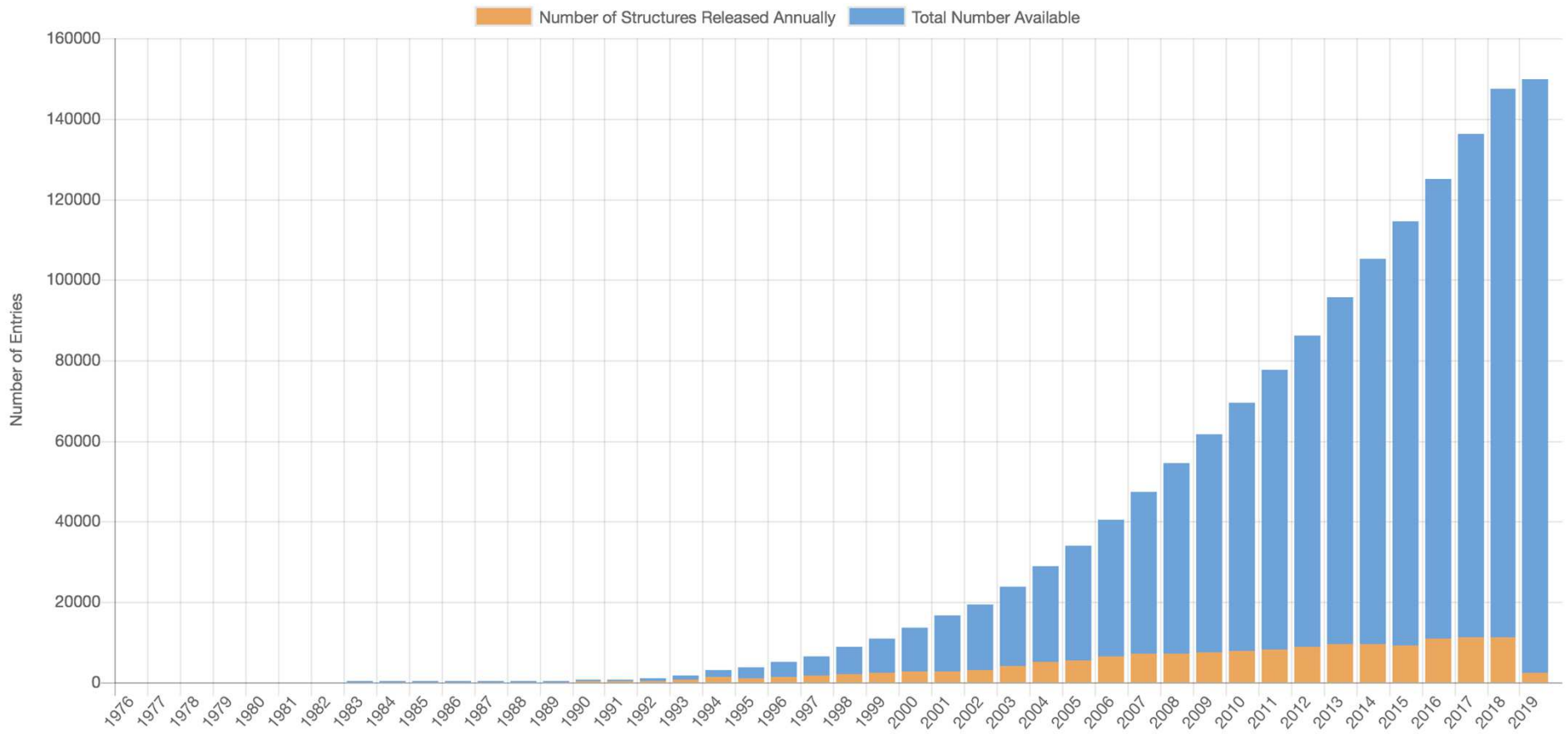

Structural Genomics Consortium

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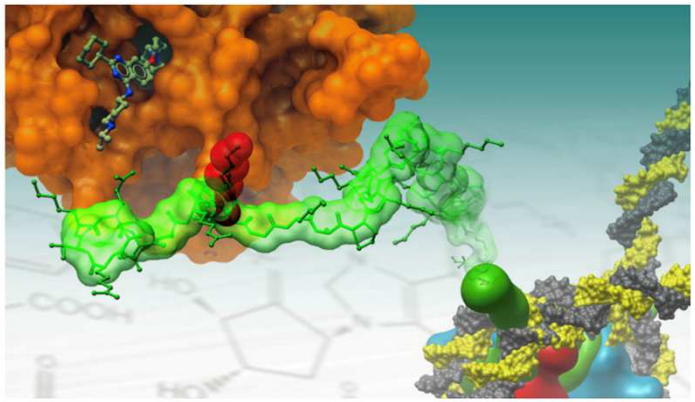
Pioneering Science to Inspire Pioneering Medicines



The SGC catalyses research in new areas of human biology and drug discovery by focusing explicitly on less well-studied areas of the human genome .

Structural Genomics

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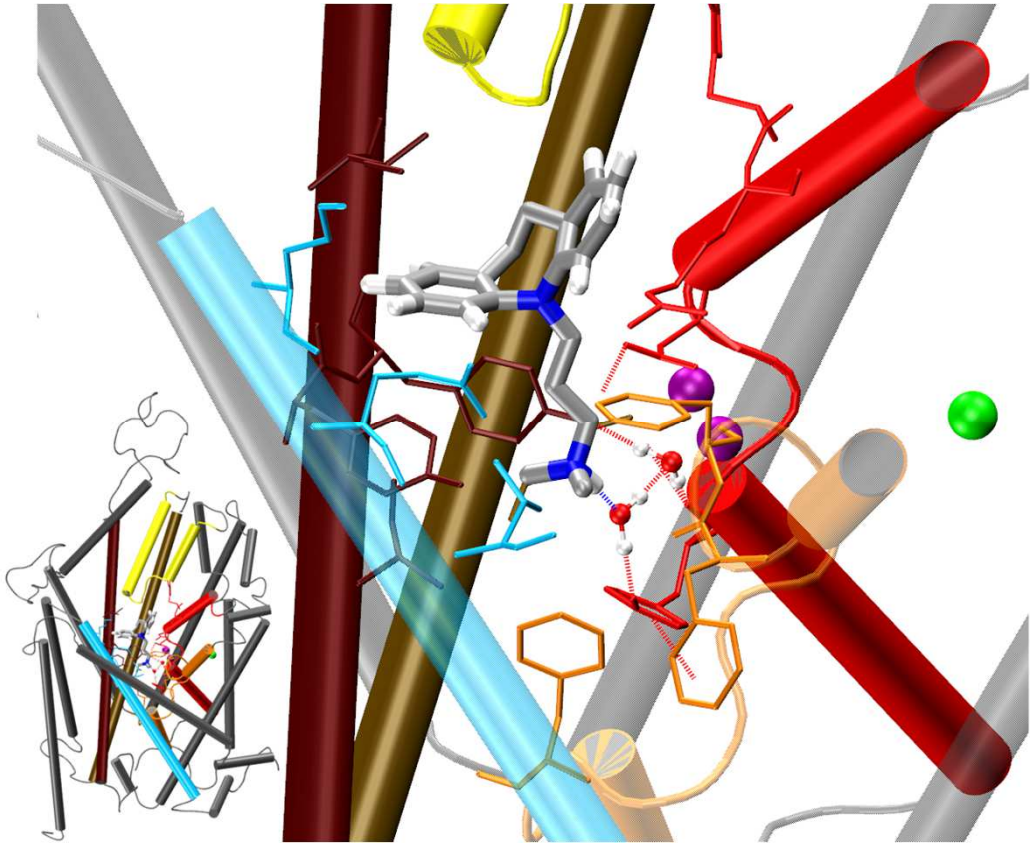

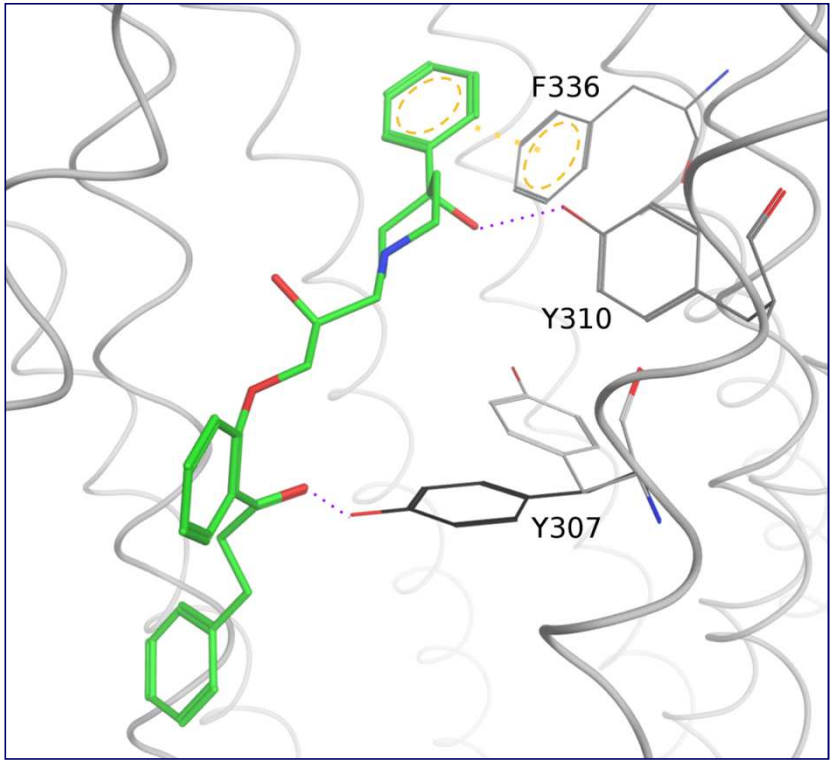

Klepsch, JCIM 2012

Data, data, data ……

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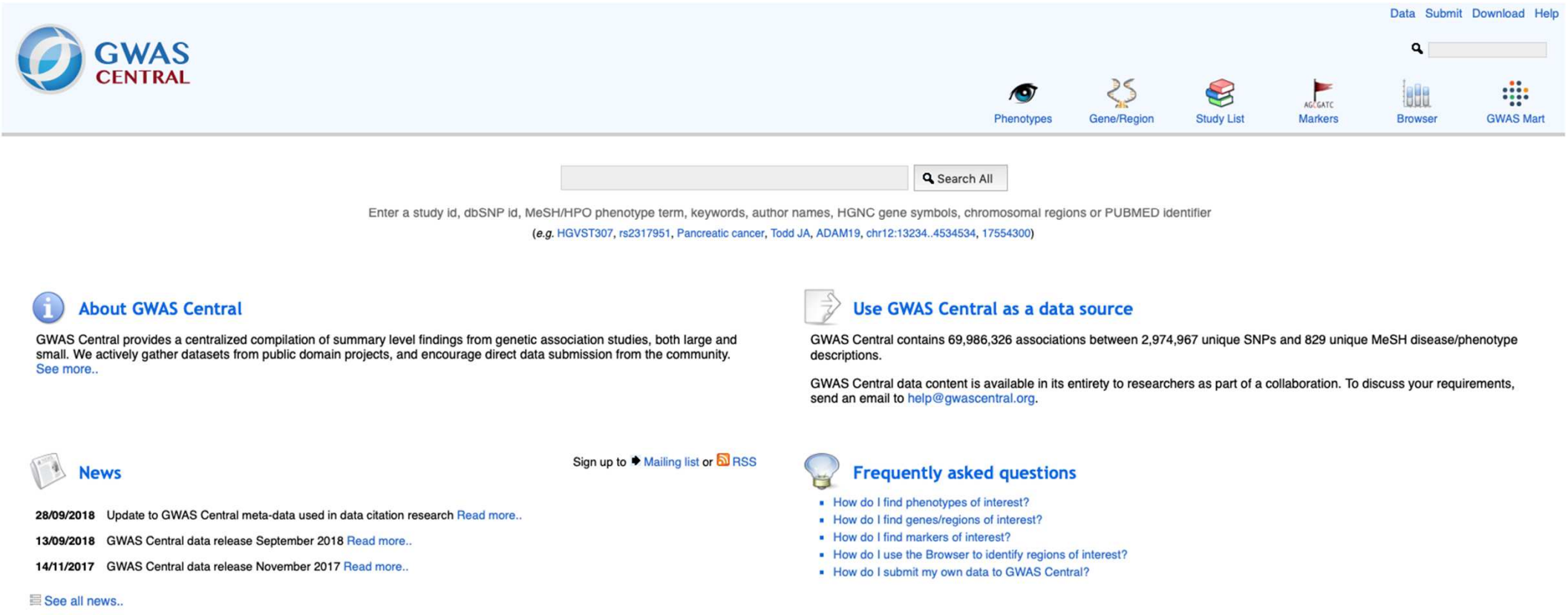

gwascentral.org

Data, data, data ……

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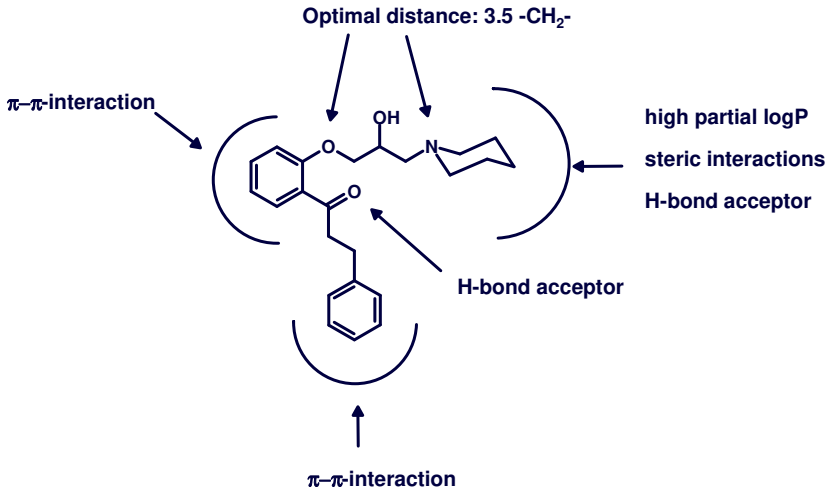
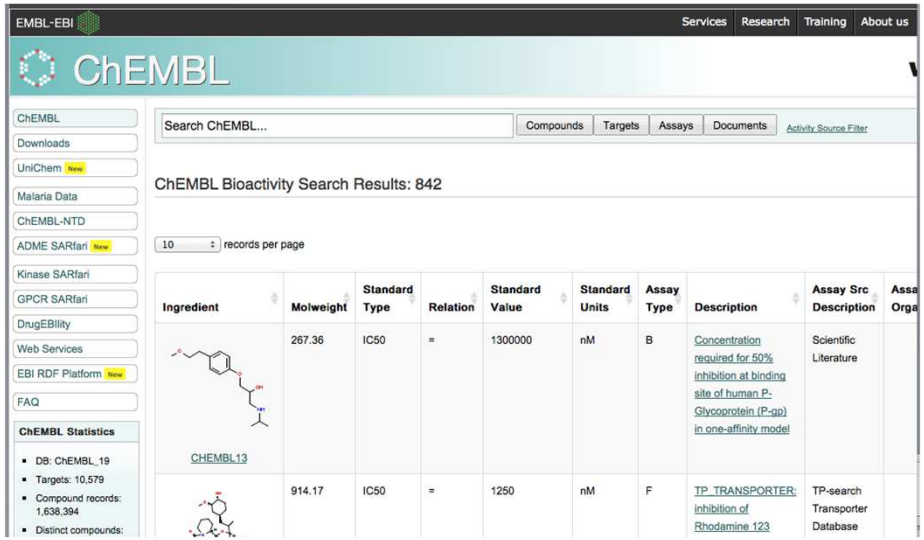




Open PHACTS
Open Pharmacological Space

"What is the selectivity profile of known p38 inhibitors?"

"Let me compare MW, logP and PSA for known oxidoreductase inhibitors"

"Find me compounds that inhibit targets in NFkB pathway assayed in only functional assays with a potency <1 µM"

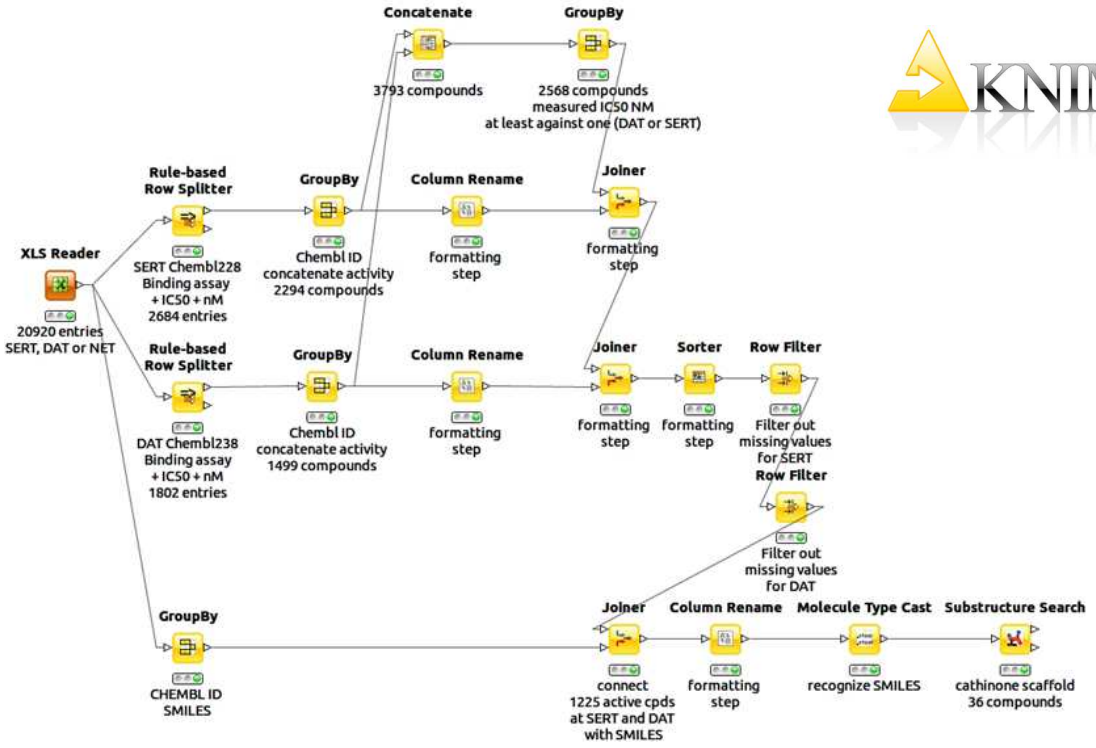
ChEMBL | DrugBank | Gene Ontology | Wikipathways | GeneGo

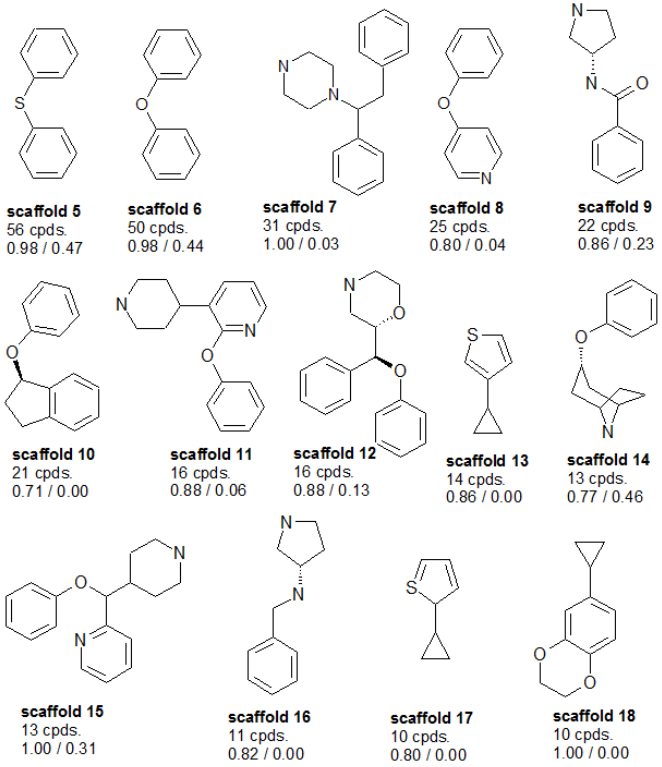
ChEBI | Uniprot | UMLS | GVKBio

ConceptWiki | ChemSpider | TrialTrove | TR Integrity

Approaching complex research questions needs integration of data sources

The Power of Workflows





Zdrazil, MedChemComm 2016

Phenotypic Screening

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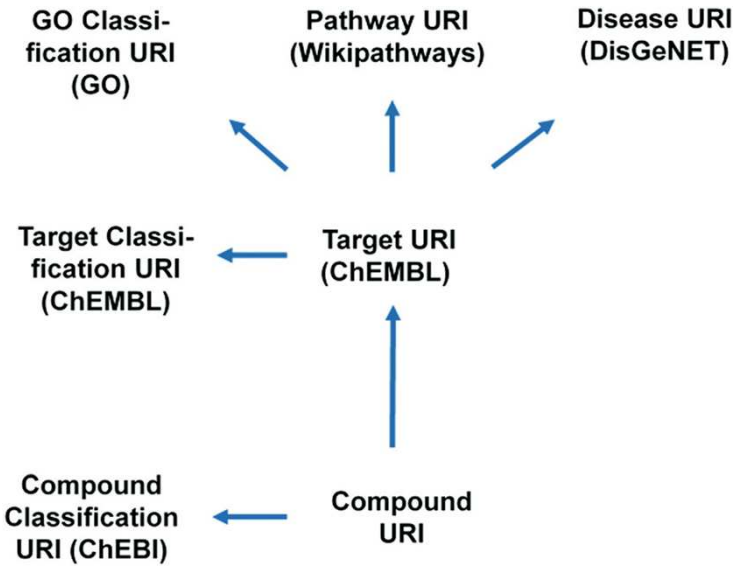
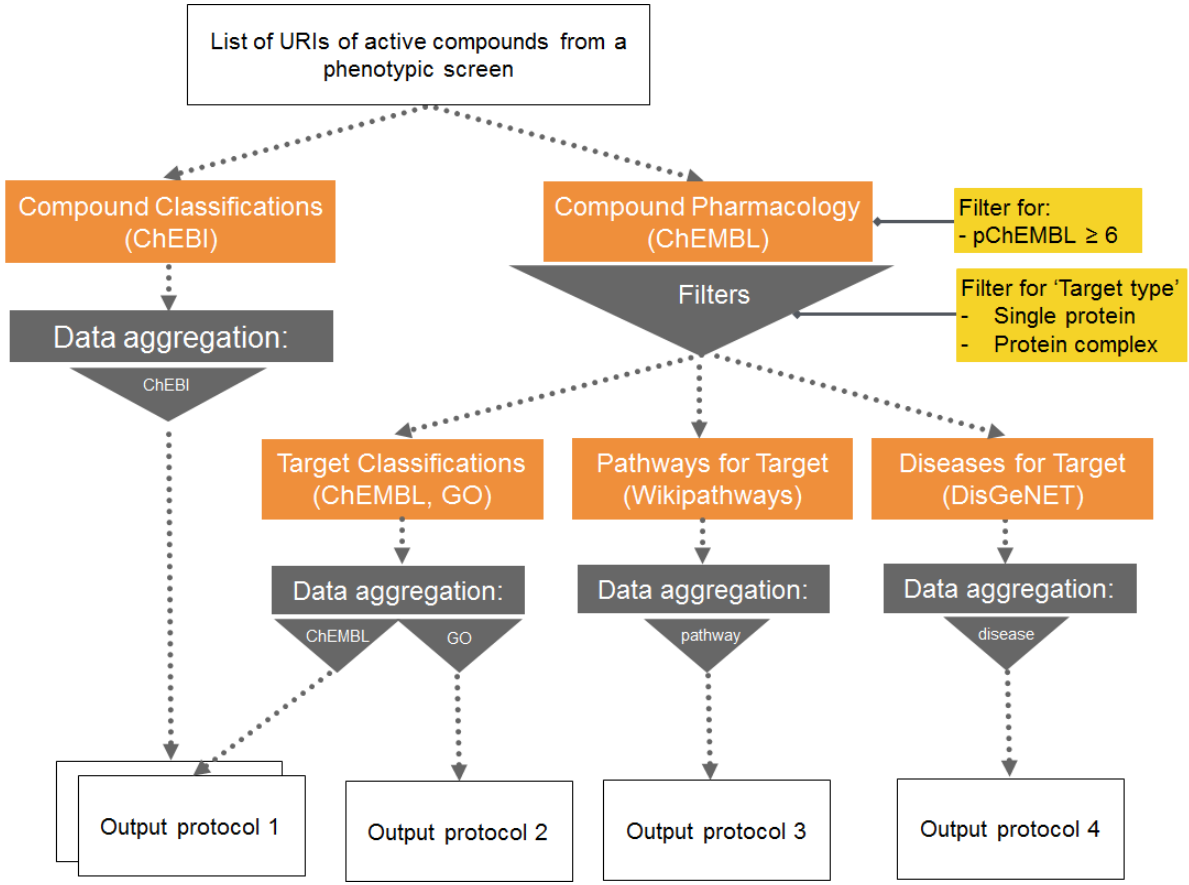
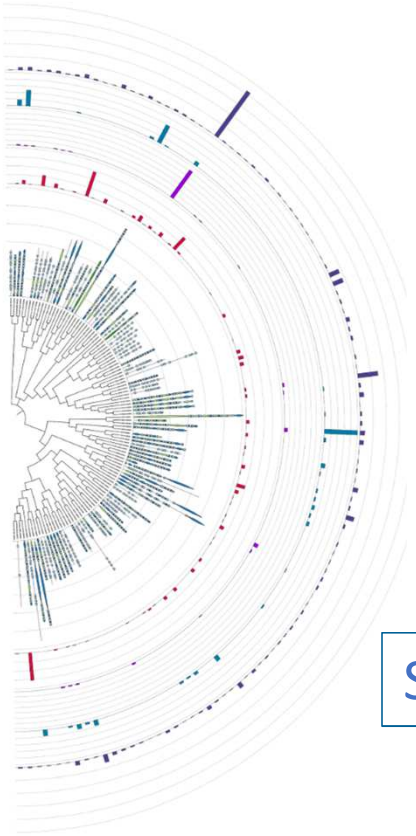
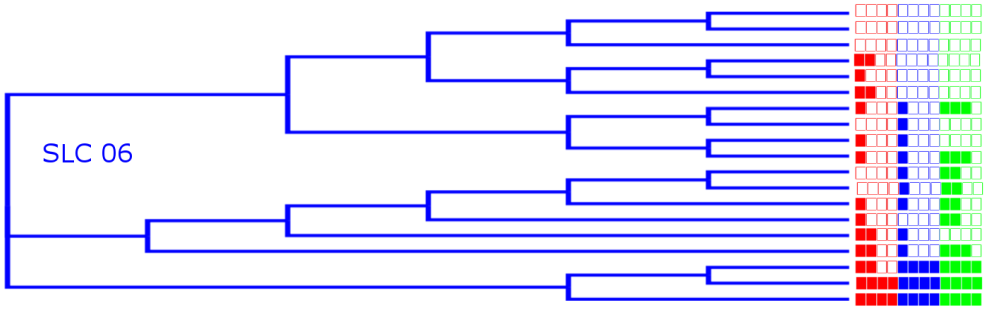


Digles, Med Chem Commun 2016



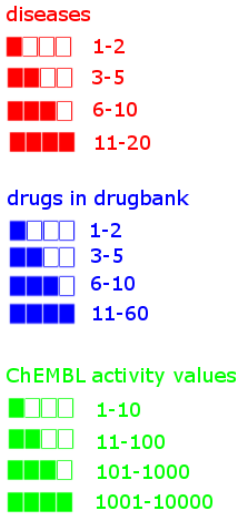
SLC data analysis





Diseases: Type 2-Diabetes Mellitus, Fanconi-Bickel Syndrome, Carcinoma, Gout, …

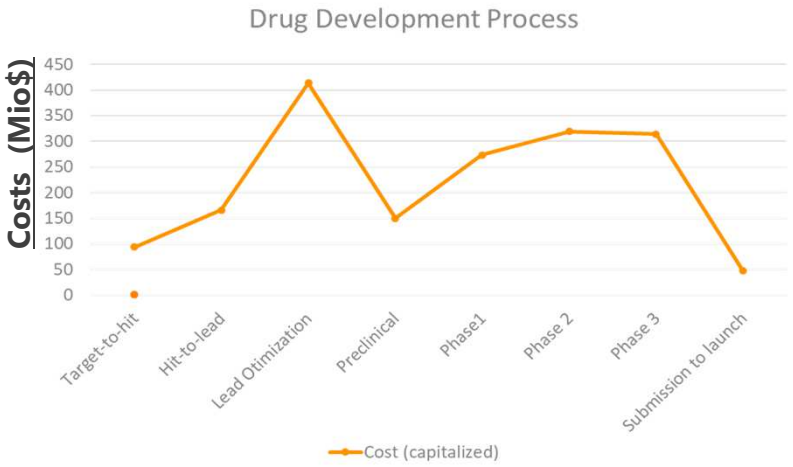
SLC02: GLUT1, GLUT2, GLUT9, …

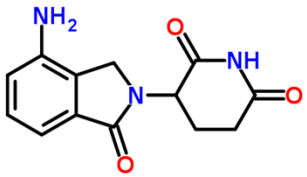


- Priorisation of SLCs
- Chemical space analysis of ligands
- Proposal for assay type
- Automatic generation of SCL dossiers in ppt format
- Domain analysis across families

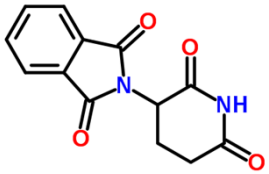
Toxicological Read Across

ToxPHACTS





Compound 1



Thalidomide

Similarity Search

AI-driven read across using various similarity algorithms and bioisostery

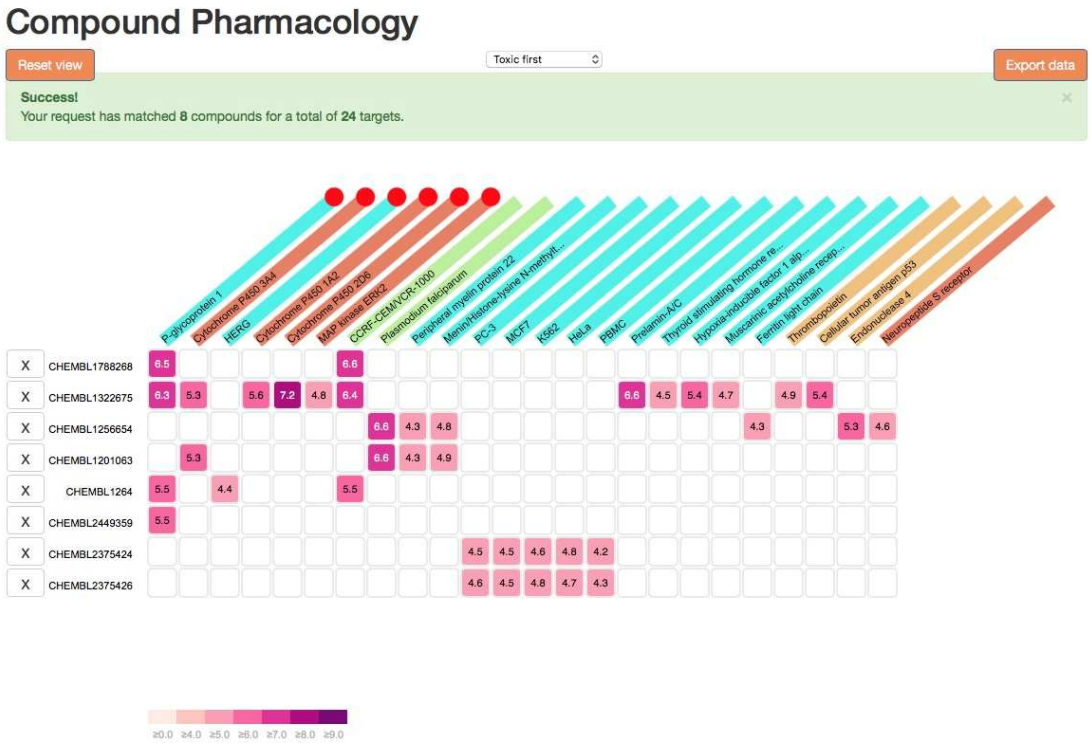
Data Extraction

Simultaneously search across various data sources including in-house data bases

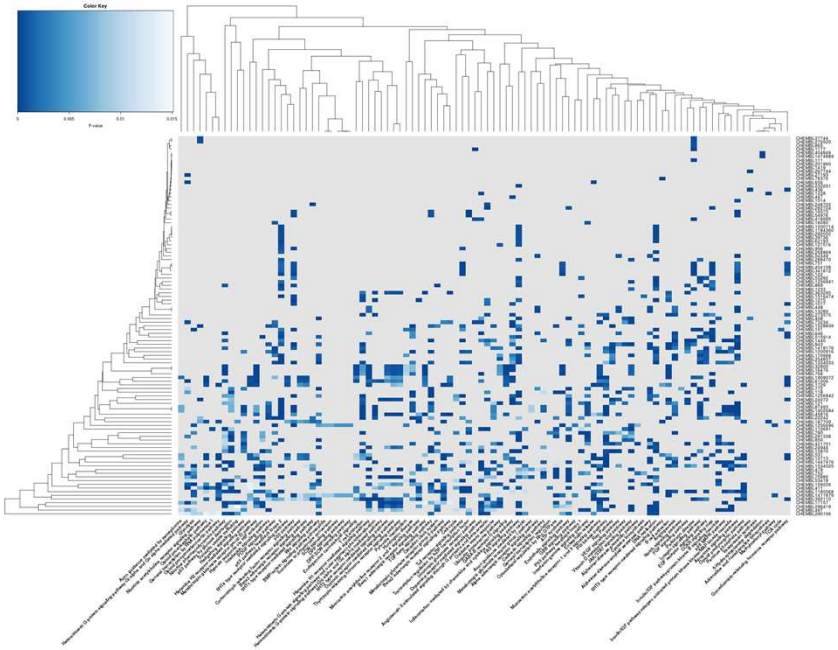
Data Analysis

Results in a standardised and aggregated form and state of the art data visualisation

Toxicological Read Across



Toxphacts.com



Withdrawn compounds from ChEMBL

Take Home Messages

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OMICS technologies open the way to personalized diagnosis and treatment

Data integration and big data analytics is key to fully exploit the potential of OMICS – use workflows

Watch out for microbiomics

Pharmacoinformatics Research Group

Department of Pharmaceutical Chemistry

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Innovative Medicines Initiative

FWF

SFB 35

MDT

eTOX

Open PHACTS
Open Pharmacological Space

eTRANSAFE

EUTOXRISK

RESOLUTE