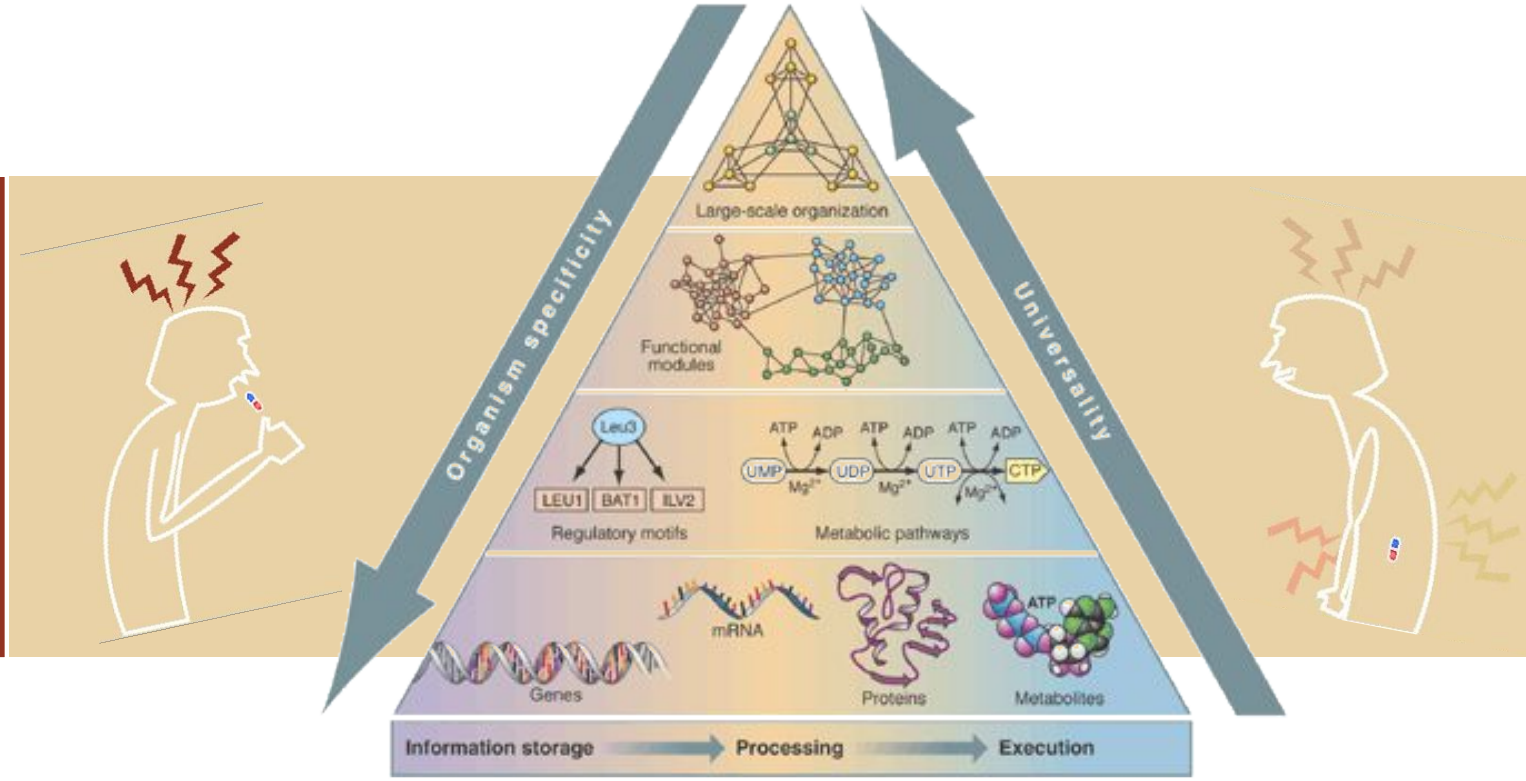

Exploiting systems chemical biology to predict and understand **unexpected** drug effects

Josef Scheiber

ICCS Noordwijkerhout, June 2008

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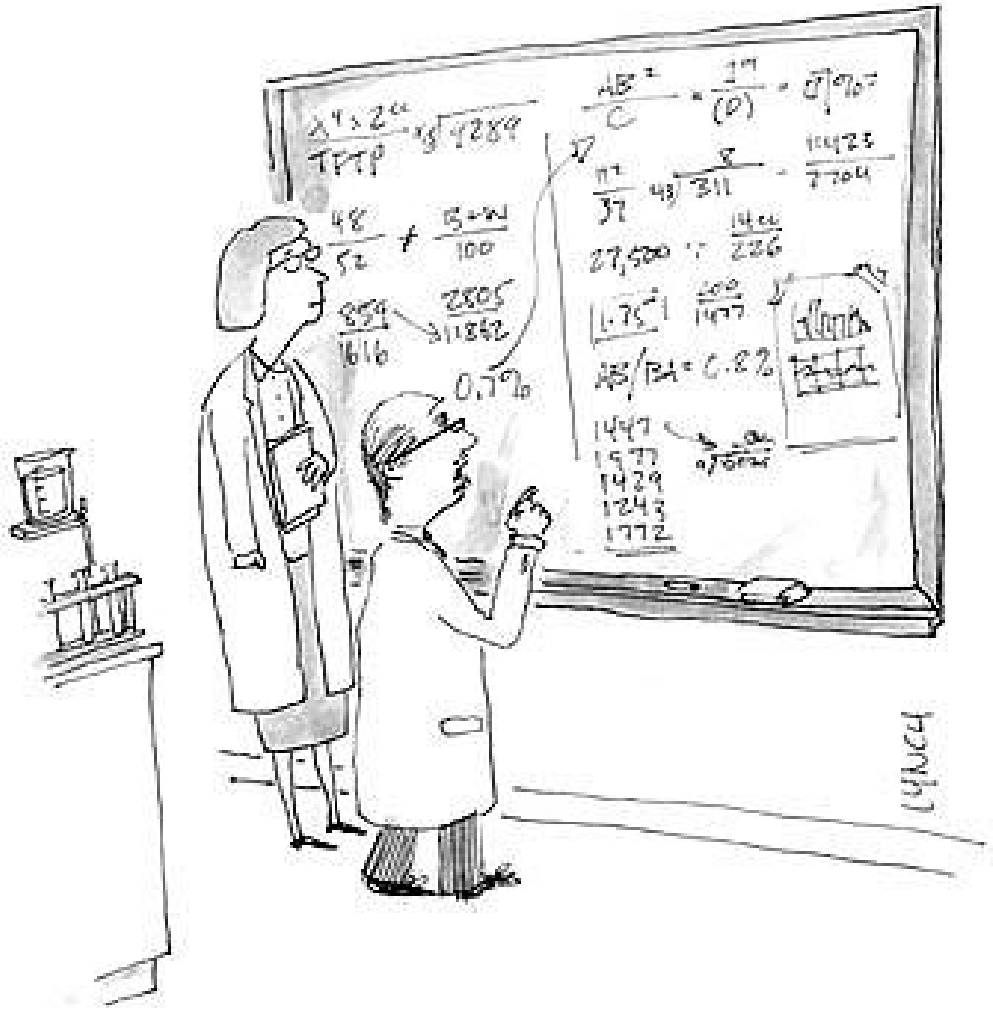

"Well, the drug's no good, but the side effects are bitchin'."

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Agenda

- Introduction
- Our approach
- Results & Wrap-up

Agenda

- **Introduction**
- Our approach
- Results & Wrap-up

Why deal with this topic?

Troglitazone	1997	2000	Diabetes	Acute liver failure
Cerivastatin	1997	2001 (2002)*	Cholesterol lowering	Rhabdomyolysis Drug–drug interactions
Rapacuronium	1999	2001	Anaesthesia	Bronchospasm
Levomethadyl	1993	2003	Opiate dependence	Fatal arrhythmia
Rofecoxib	1999	2004	Pain relief	Heart attack; stroke
Valdecoxib	2001	2005	Pain relief	Skin reactions (SJS)
Natalizumab*	2004	2005 (2006)*	Multiple sclerosis	Brain infection
Technetium (99m Tc) fanolesomab	2004	2005	Diagnostic aid	Cardiopulmonary arrest
Pemoline	1975	2005	Attention-deficit hyperactivity disorder	Liver failure
Pergolide	1988	2007	Parkinson's disease	Valvulopathy
Tegaserod	2002	2007	Irritable bowel syndrome with constipation	Angina; heart attack; stroke

Kathleen M. Giacomini, et al. **When good drugs go bad**
Nature **446/2007**, 975-977

Why deal with this topic?

Unexpected side effect

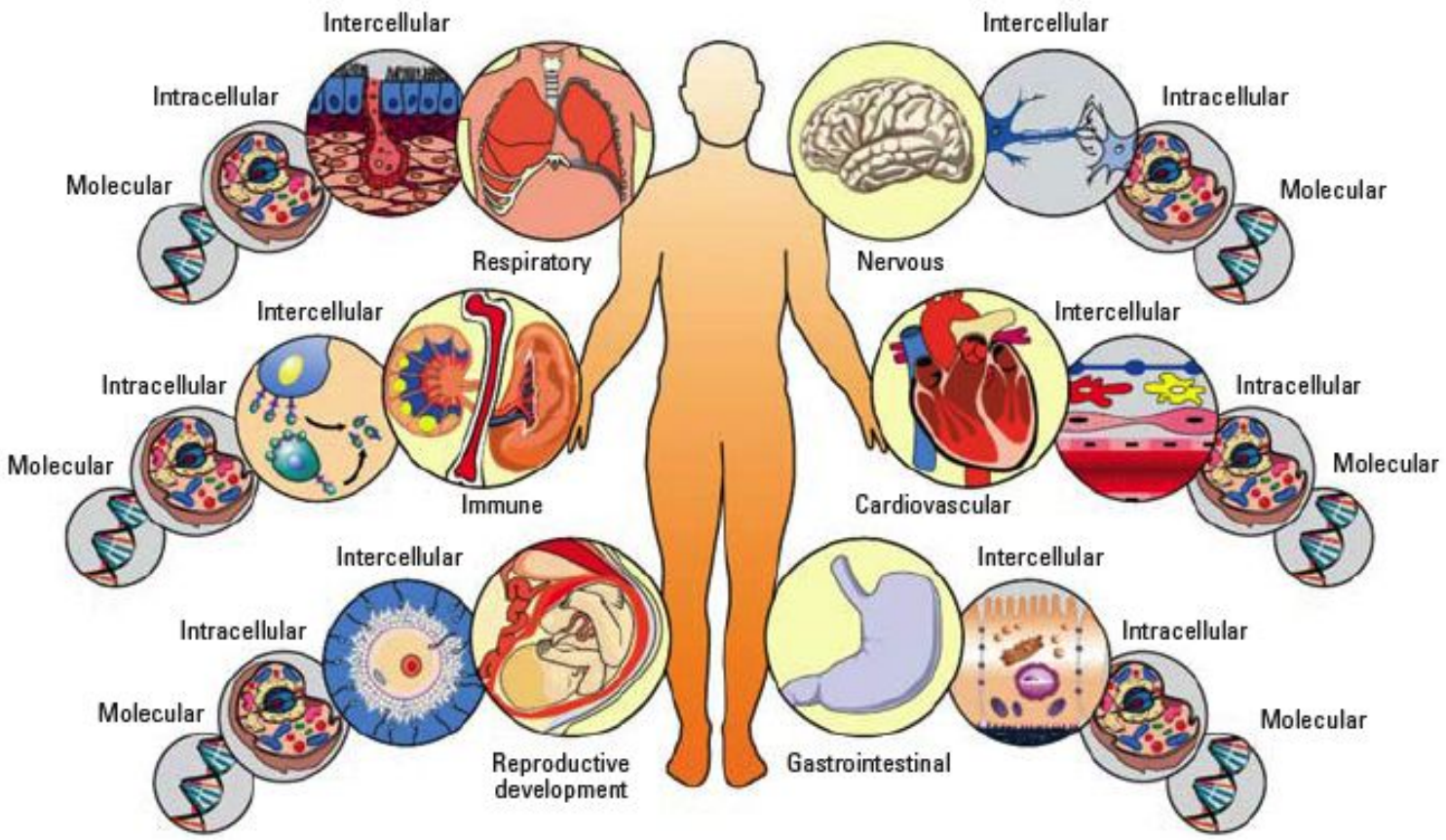
Detrimental

Beneficial

Table 2: Examples of reprofiled drugs that are marketed or in the late stages of development

Drug	Original indication	Reprofiled indication	Brand name
Apomorphine	Parkinson's disease	Erectile dysfunction	Uprima®
Bupropion	Depression	Smoking cessation (1)	Zyban®
Duluxetine	Depression	Stress urinary incontinence	Cymbalta®
Finasteride	Prostate hyperplasia	Male-pattern baldness	Propecia®
Imidapril	Hypertension	Cachexia (2)	Vitor®
Mycophenolate mofetil	Transplanted organ rejection,	Lupus nephritis (3) Pemphigus vulgaris (4)	CellCept®
Ropinirole	Hypertension	Parkinson's disease, primary restless legs syndrome	Requip®
Sildenafil	Hypertension, angina	Erectile dysfunction	Viagra®
Thalidomide	Emesis	Erythema nodosum leprosum (5) Multiple myeloma (6)	Thalomid®

A simplified overview – molecules in man



Adapted from Julia M. Gohlke and Christopher J. Portier
Environ Health Perspect 115:1261–1263 (2007)

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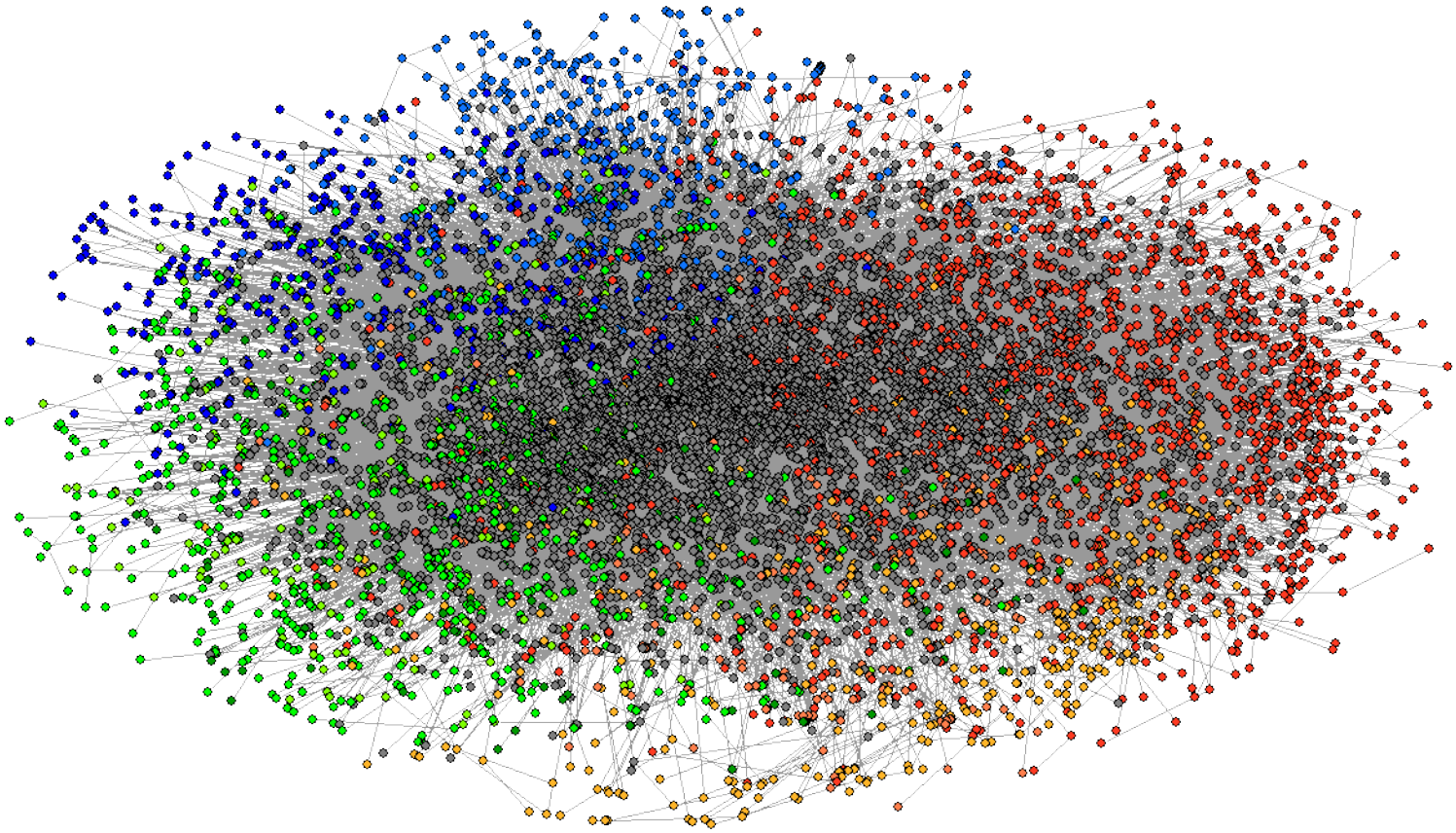
And “all of them” interact …



Chaurasia G, et al.
Nucleic Acids Res. 35 Database issue:D590-4, 2007.

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Agenda

- Introduction
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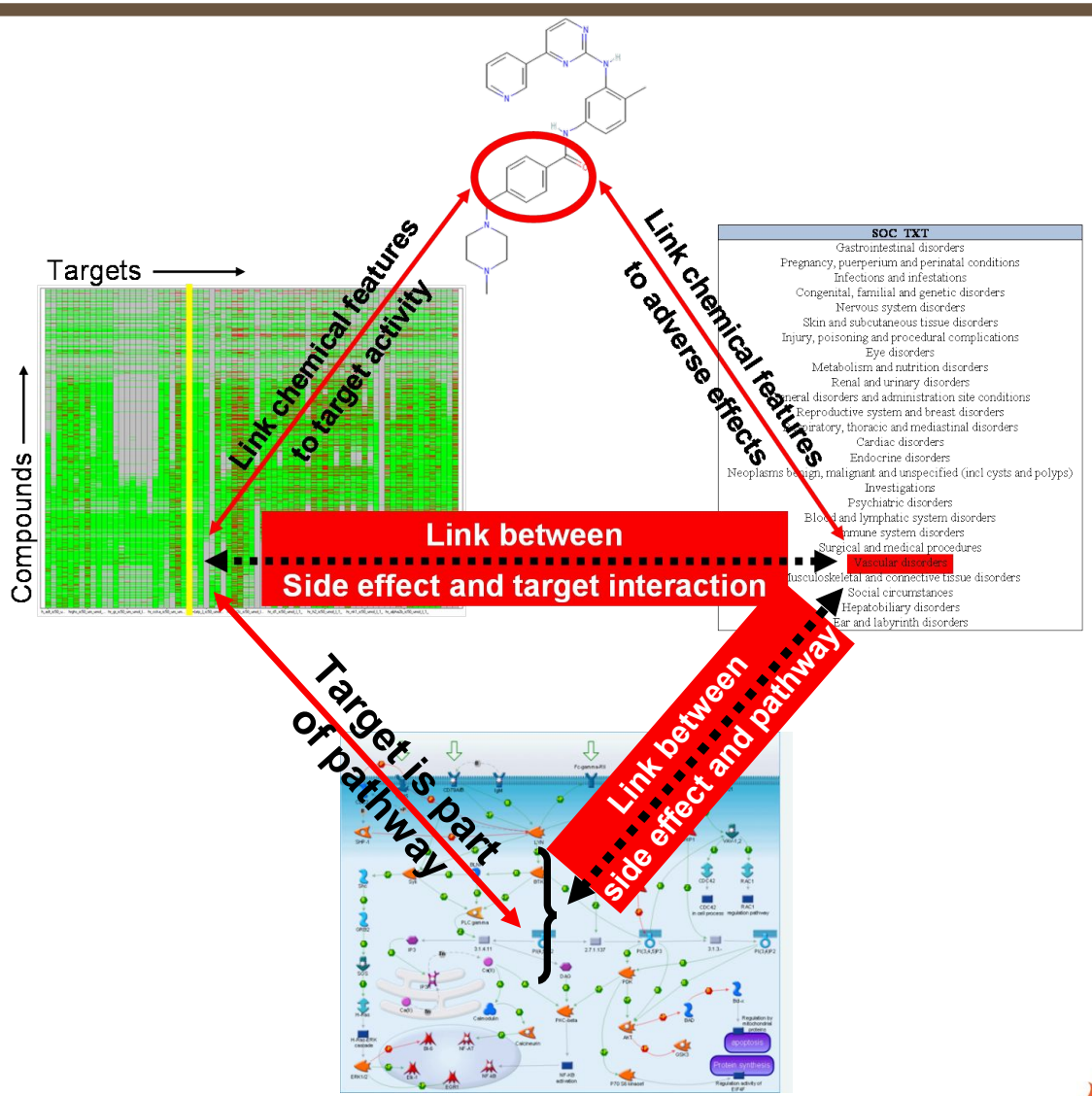
- Results & Wrap-up

Linking side effects to targets in chemical space

A. Bender et al.
ChemMedChem,
Volume 2(6), 2007; 861-873



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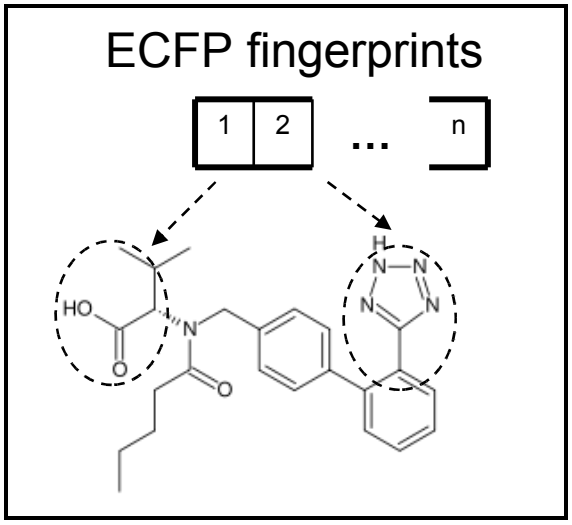
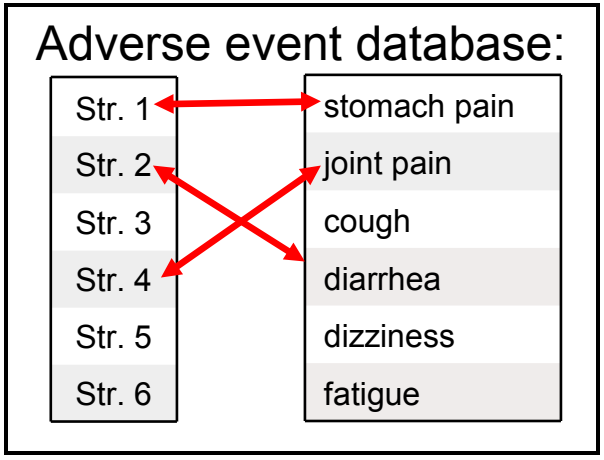
Data modeling: Naïve Bayesian (NB) with ECFP fingerprints for handling data

- **ECFP**: interpretable and can be linked with substructures
- **NB**: Naive Bayes is uniquely suited for AE modeling, as it treats features independently and thus can handle multiple MoAs and targets per AE
- **NB+ECFP**: strong track record from *in silico* HTS analyses



Bayesian models



Score	Predicted AEs
14.1	stomach pain
12.2	joint pain
9.4	cough
	diarrhea
--	dizziness
--	fluid retention
--	nausea/vomiting
	headache
	insomnia
5.8	pain
3.4	urinary tract infection
2.3	heartburn

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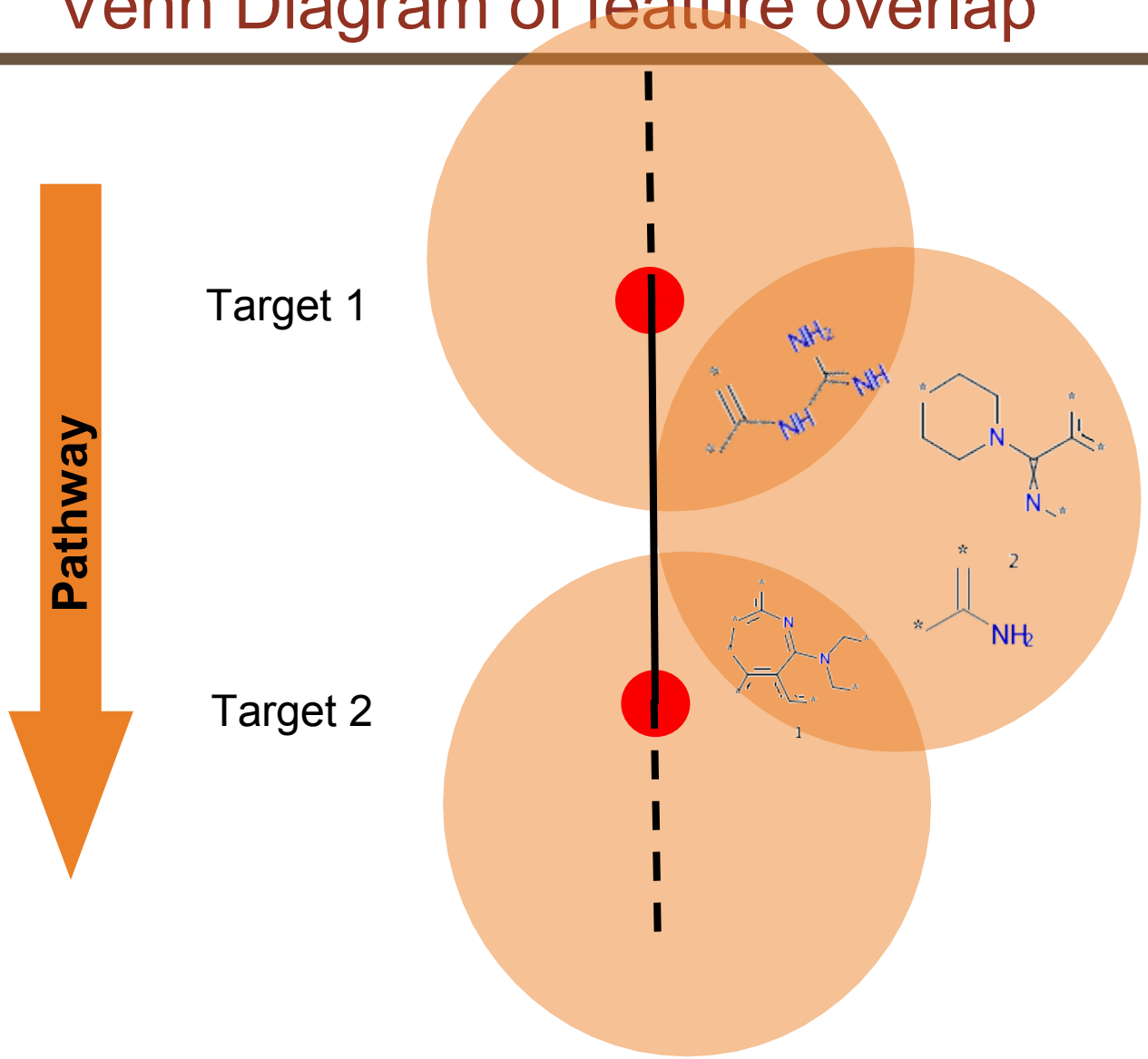
Venn Diagram of feature overlap



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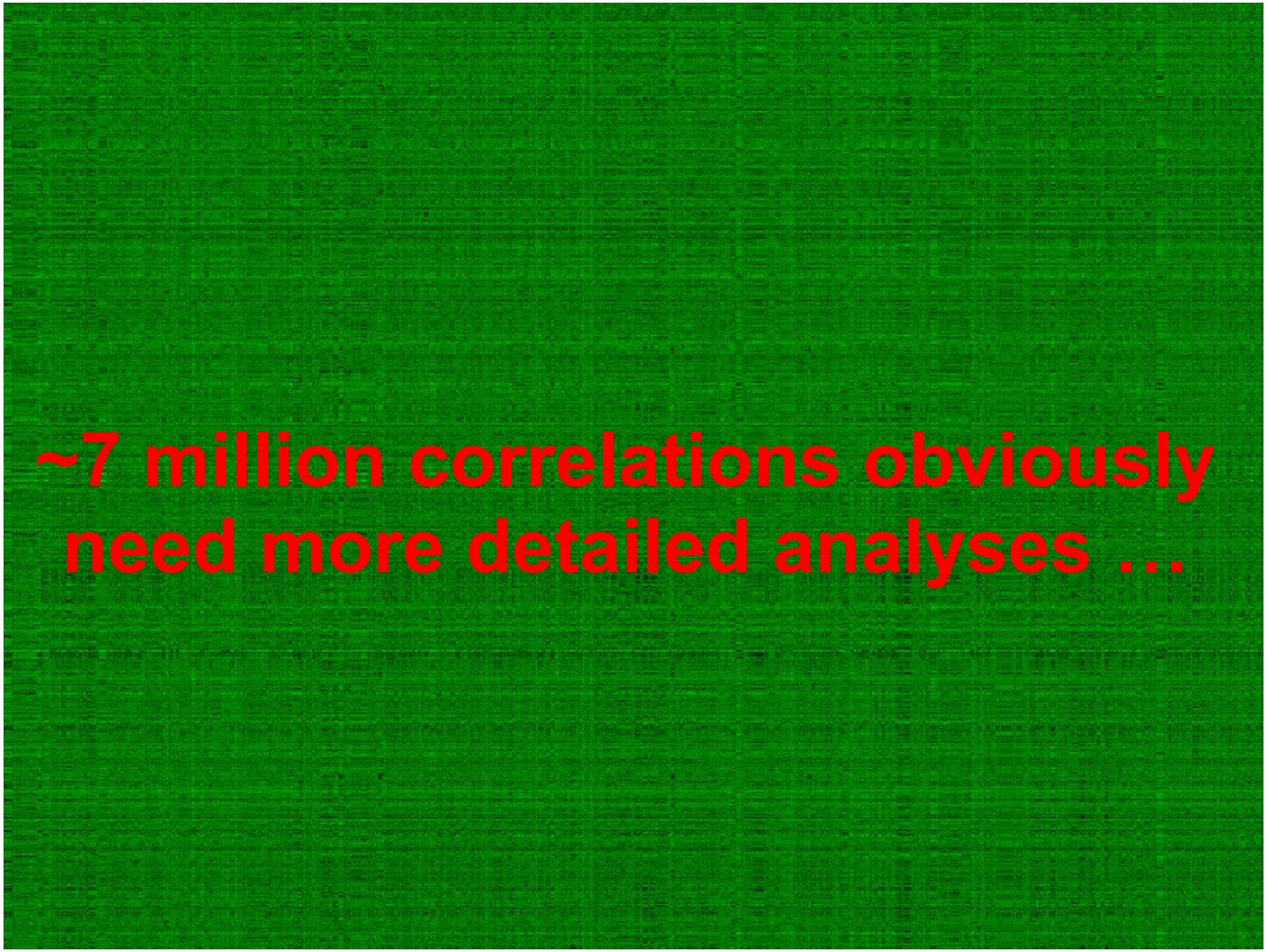
~2000 targets x 3300 side effects – The Pearson correlation matrix



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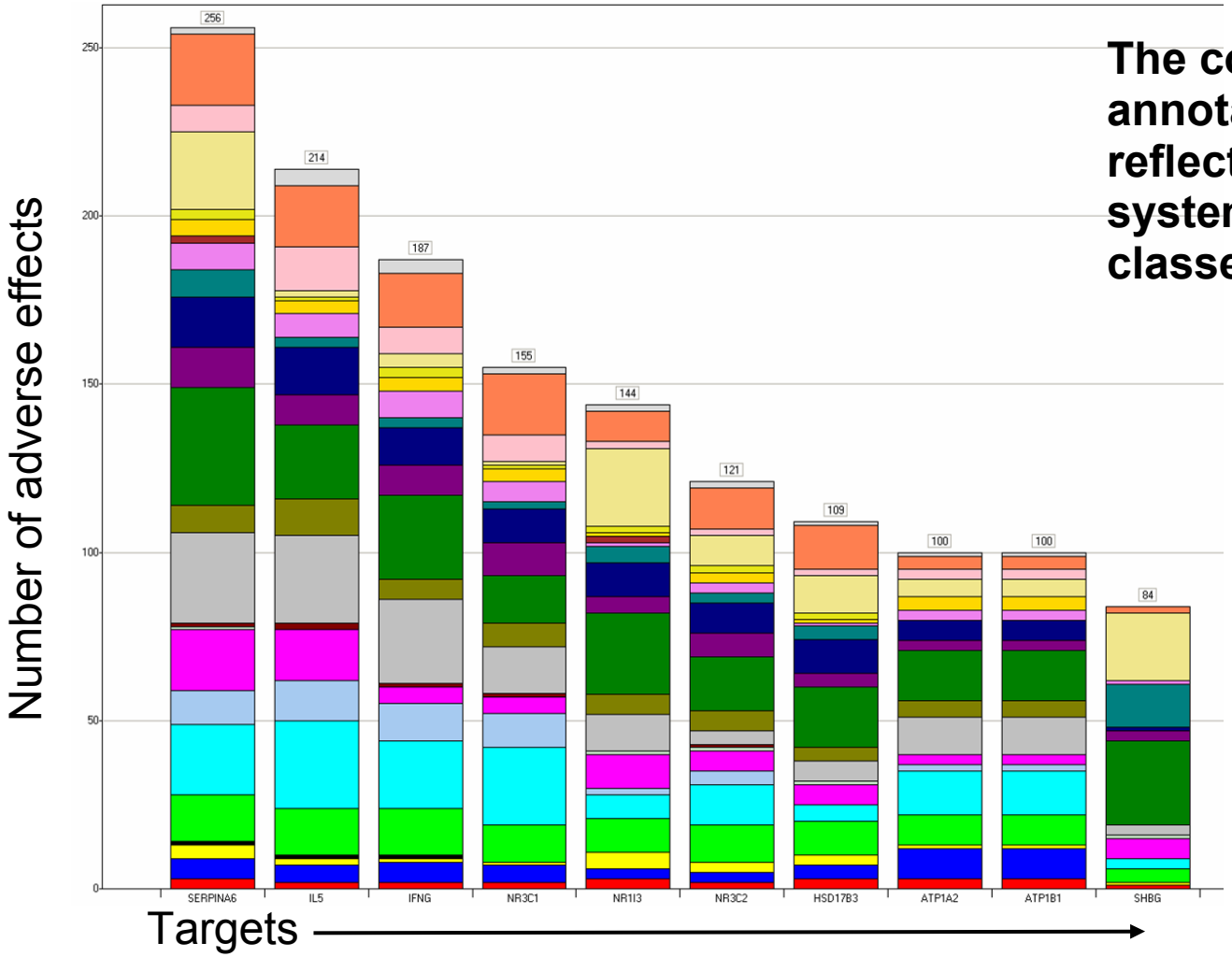
Agenda

- Introduction
- Our approach
- **Results & Wrap-up**
  - **Analyzing single targets (1 example)**
  - Analyzing pathways (2 examples)

Targets linked to most AEs with Pearson cutoff (not necessarily severe)



The colorful annotation reflects system organ classes

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SERPIN A6

- This is the target with most correlations to AEs in chemical space
- Serpin peptidase inhibitor, clade A, member 6 (antitrypsin)
- Alpha-globulin protein with corticosteroid-binding properties
- **major transport protein** for glucorticoids and progestins **in the blood** of most vertebrates

Side effects linked to SERPINA6 in chemical space

Abnormal clotting factor
Accelerated idioventricular rhythm
Acne
Adrenal cortical insufficiency
Adrenal insufficiency
Adrenocortical insufficiency chronic
Application site abscess
Application site anaesthesia
Application site atrophy
Application site dermatitis
Application site discolouration
Application site erythema
Application site inflammation
Application site paraesthesia
Application site scar
Application site vesicles
Arachnoiditis
Benign intracranial hypertension
Benign prostatic hyperplasia
Biopsy endometrium
Biopsy ovary abnormal
Blood cholesterol decreased
Blood cortisol decreased
Blood fibrinogen increased
Blood growth hormone decreased
Blood luteinising hormone abnormal
Blood oestrogen increased
Blood triglycerides decreased
Bradycardia neonatal
Breast discharge
Breast disorder male
Breast mass
Cardiomegaly
Cervical discharge
Cervical polyp
Cervix carcinoma
Cervix disorder
Chloasma
Cold agglutinins positive
Colitis ulcerative
Conjunctival bleb
Conjunctivitis allergic
Corneal perforation
Corneal thinning
Cortisol free urine decreased
Crepitations
Cryptococcosis
Cushing's syndrome
Dermatitis acneiform
Disorder of globe
Dyslipidaemia
Emotional disorder
Encephalitis herpes
Endocrine. Changes in adrenal weight
Endometrial hyperplasia
Endometritis
Eosinophil count decreased
Epiphyses premature fusion
Equivocal Tumorigenic

Eye infection
Eye infection bacterial
Fat embolism
Fat tissue increased
Feminisation acquired
Femur fracture
Fluid retention
Folliculitis
Gardnerella infection
Gastrointestinal perforation
General symptom
Genital disorder male
Genitourinary tract neoplasm
Global amnesia
Glucocorticoids increased
Glucose tolerance decreased
Glucose urine present
Haemorrhage subcutaneous
Hair growth abnormal
Heat rash
Hepatic neoplasm
Hirsutism
Hypertonic bladder
Hypertrichosis
Hypertrophy of tongue papillae
Hypervolaemia
Hypotrichosis
Inadequate lubrication
Increased upper airway secretion
Infertility female
Infertility tests abnormal
Injection site atrophy
Injection site discolouration
Instillation site burning
Insulin resistance
Intestinal functional disorder
Intracranial pressure increased
Intraocular pressure increased
Iridocyclitis
Kaposi's sarcoma
Keratitis interstitial
Learning disorder
Leukocyturia
Meningitis viral
Menometrorrhagia
Menstruation irregular
Mood swings
Muscle disorder
Musculoskeletal. Tumors
Mutagenic: DNA Inhibition liver cells
Mutagenic: Morphological Transformation embryonic cells
Mutagenic: Other mutation test system
Mutagenic: Sperm Morphology
Mutagenic: Unscheduled DNA Synthesis
Mycobacterial infection
Nail growth cessation
Nasal candidiasis
Nasal discomfort
Nasal septum disorder
Nasal septum perforation
Nipple exudate bloody

Ocular hypertension
Odynophagia
Ophthalmoplegia
Optic nerve disorder
Optic nerve injury
Oral fungal infection
Oral mucosa atrophy
Oral neoplasm
Oropharyngeal candidiasis
Oropharyngitis fungal
Osteitis deformans
Osteochondrosis
Osteomyelitis
Osteonecrosis
Osteoporosis
Osteoporotic fracture
Ovarian disorder
Parametritis
Pathological fracture
Personality change
Pharyngitis streptococcal
Pierre Robin syndrome
Pneumocystis carinii pneumonia
Pneumothorax
Postpartum disorder
Prostate cancer
Prostatic specific antigen increased
Related to chronic data. Changes in testicular weight
Retinal haemorrhage
Ruptured ectopic pregnancy
Skin chapped
Skin malformation
Smear cervix
Smear cervix abnormal
Sodium retention
Sperm count decreased
Spermatogenesis abnormal
Testicular failure
Tetany
Throat irritation
Total cholesterol/HDL ratio increased
Toxoplasmosis
Trichomoniasis
Trigeminal nerve disorder
Trigeminal neuralgia
Trigger finger
Tuberculosis of eye
Tympanic membrane disorder
Uveitis
Vaginal cyst
Varicella
Very low density lipoprotein decreased
Viral upper respiratory tract infection
Withdrawal bleed

Drugs known to interact with SERPINA6

Accession No	Common Name	Chemical Formula	Molecular Weight
DB00180	Flunisolide	C24H31FO6	434.4977
	SERPINA6		
DB00240	Alclometasone	C28H37ClO7	521.0422
	SERPINA6		
DB00253	Medrysone	C22H32O3	344.4877
	SERPINA6		
DB00324	Fluorometholone	C22H29FO4	376.4617
	SERPINA6		
DB00394	Beclomethasone	C22H29ClO5	408.9157
	SERPINA6		
DB00588	Fluticasone Propionate	C25H31F3O5S	500.5709
	SERPINA6		
DB00591	Fluocinolone Acetonide	C24H30F2O6	452.4882
	SERPINA6		
DB00596	Halobetasol Propionate	C25H31ClF2O5	484.9604
	SERPINA6		
DB00620	Triamcinolone	C21H27FO6	394.4339
	SERPINA6		
DB00648	Mitotane	C14H10Cl4	320.0412
	SERPINA6		
DB00663	Flumethasone Pivalate	C27H36F2O6	494.5679
	SERPINA6		
DB00846	Flurandrenolide	C24H33FO6	436.5136
	SERPINA6		
DB00860	Prednisolone	C21H28O5	360.4440
	SERPINA6		
DB00896	Rimexolone	C24H34O3	370.5250
	SERPINA6		
DB01047	Fluocinonide	C26H32F2O7	494.5249
	SERPINA6		
DB01384	Paramethasone	C22H29FO5	392.4611
	SERPINA6		
DB01410	Ciclesonide	C32H44O7	540.6876
	SERPINA6		

Source: DrugBank

- Mostly Corticosteroids

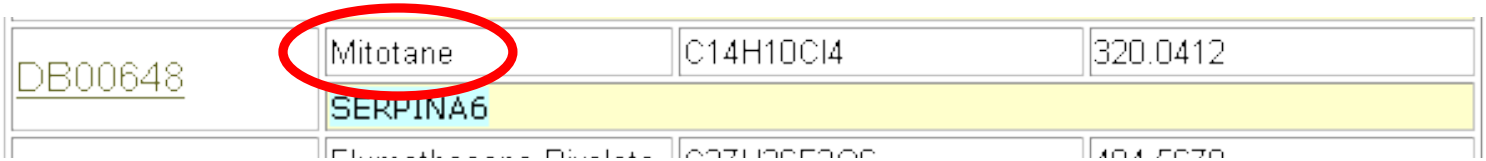
- PharmaPendium: The side effects related to SERPINA6 are the common Corticosteroid side effects

- Reason: drug-induced Cushing's disease (see e.g. http://en.wikipedia.org/wiki/Corticosteroid)

SERPINA6 as drug target

- This means inducing Cushing's disease
- Where is this helpful?

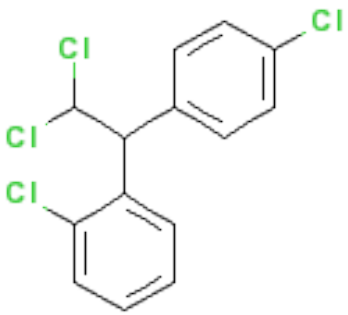
There's one non-corticosteroid in the list of compounds interacting with SERPINA6:



DB00648	Mitotane	C14H10Cl4	320.0412
	SERPINA6		

Adrenocortical carcinoma

- Mitotane – Chemotherapy for tumors that cannot be treated with surgery
- Toxic to cells in adrenal cortex, inhibits steroid synthesis
- SERPINA6 “transport capabilities” are taken advantage of



Agenda

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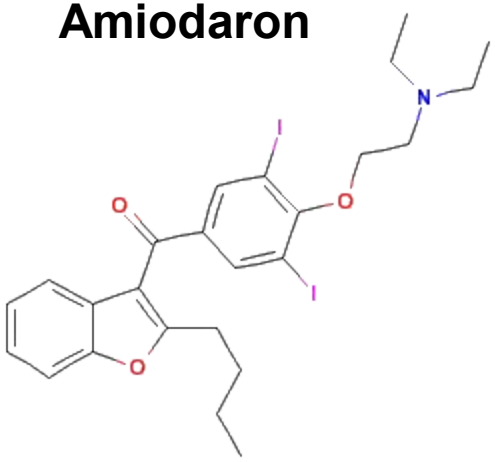
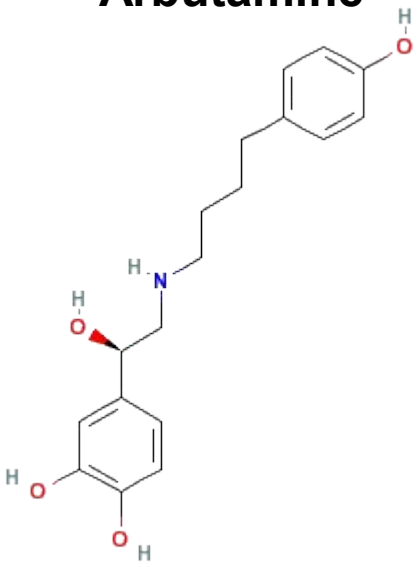
  - Analyzing single targets (1 example)
  - **Analyzing pathways (2 examples)**

Leveraging pathways – An example

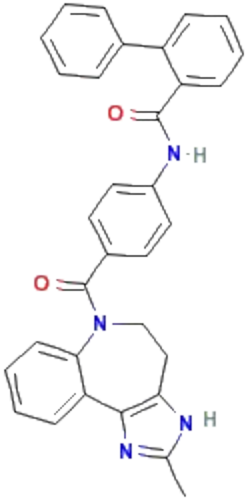
Amiodaron



Arbutamine



Conivaptan



They do not have a single common target predicted

Ok, can we still find something?

Top 5 pathways for **Hypotension as AE (predicted targets linked to pathways in Novartis Pathway DB)**:

(1) Glutamate receptor signalling ? (✔)

(2) ACE-system ✔

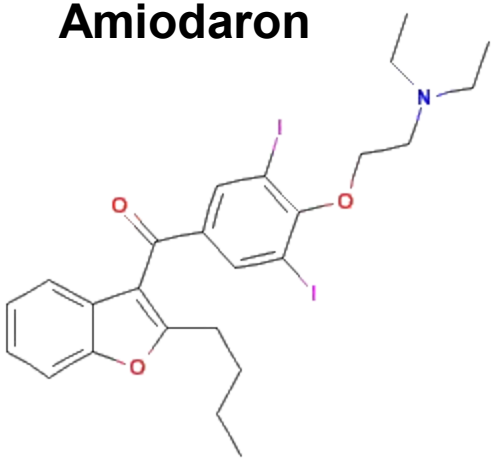
(3) FAS signaling ✔

(4) Nitrogen metabolism ✔

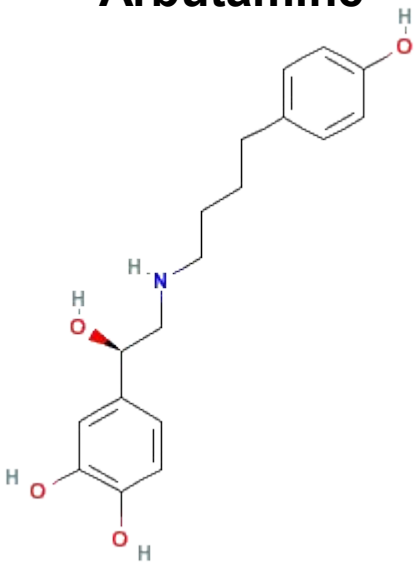
(5) “Gap junctions” ?

An example

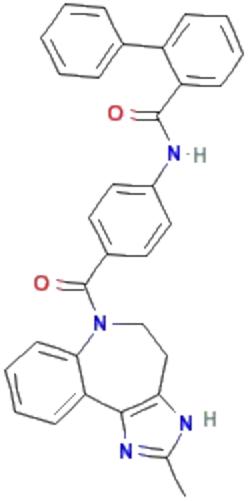
Amiodaron



Arbutamine



Conivaptan



They all have at least one target in the Top 3 pathways predicted

Another example

Cerivastatin

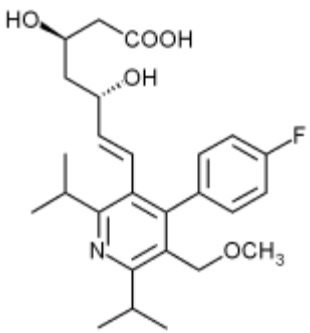
From Wikipedia, the free encyclopedia

In pharmacology, **cerivastatin** (Baycol®, Lipobay®) is a synthetic member of the class of statins, used to lower cholesterol and prevent cardiovascular disease. It was withdrawn from the market in 2001 because of the high rate of serious side-effects.

Cerivastatin was marketed by the pharmaceutical company Bayer A.G. in the late 1990s as a new synthetic statin, to compete with Pfizer's highly successful Lipitor®.

During post-marketing surveillance, 52 deaths were reported in patients using cerivastatin, mainly from rhabdomyolysis and its resultant renal failure.[1] Risks were higher in patients using fibrates (mainly gemfibrozil/Lopid®) and in patients using the high (0.8 mg/day) dose of cerivastatin. Another 385 nonfatal cases of rhabdomyolysis were reported. This put the risk of this (rare) complication at 5-10 times that of the other statins.

In 2001, Bayer announced the voluntary withdrawal of the drug from the market.



Predicted AE	Bayes Score
Colour blindness	87.15
Muscle enzyme increased	87.15
Systemic lupus erythematosus	75.26
Myopathy	68.30
Neuropathy	64.17
Diplopia	63.31
Rhabdomyolysis	62.21
Neuropathy peripheral	60.54
Myositis	60.03
Sleep disorder	58.94
Thyroid function test abnormal	58.30
Myasthenic syndrome	54.41
Nodule	53.31
Hepatic enzyme increased	52.51
Peripheral nerve palsy	52.51
Facial paresis	51.13
Polymyalgia rheumatica	51.01
Cranial nerve disorder	50.58
Dermatomyositis	50.51
Biliary cirrhosis	50.30
Ophthalmoplegia	50.07
Extraocular muscle disorder	49.74
Neuralgia	49.29
Renal impairment	48.77
Loss of libido	48.71
Arthritis	48.47
Mucosal dryness	48.45
Erectile dysfunction	48.32
Antinuclear antibody positive	46.92
Duodenal ulcer	46.30
Alanine aminotransferase increased	46.02
Blood creatine phosphokinase increased	45.42
Laboratory test abnormal	45.36
Hepatic neoplasm malignant	45.12
Red blood cell sedimentation rate increased	44.75
Carcinoma	44.70
Myoglobinuria	44.38
Hypertonia	44.31
Gastroenteritis	43.84

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Another example

Rhabdomyolysis per 10000 Person-Years of Therapy With Lipid-Lowering Drugs Used as Monotherapy or as Combination Therapy With Another Drug

Table 3. Rhabdomyolysis per 10000 Person-Years of Therapy With Lipid-Lowering Drugs Used as Monotherapy or as Combination Therapy With Another Drug

		Combination Therapy	
Drug	Monotherapy, Incidence Rates (95% CI)	Combination	Incidence Rates (95% CI)
Atorvastatin	0.54 (0.22-1.12)	Atorvastatin + fenofibrate	22.45 (0.57-125)
Cerivastatin	5.34 (1.46-13.68)	Cerivastatin + gemfibrozil	1035 (389-2117)
Pravastatin	0 (0-1.11)	No cases	0 (0-67.71)
Simvastatin	0.49 (0.06-1.76)	Simvastatin + gemfibrozil	18.73 (0.47-104)
Fenofibrate	0 (0-14.58)	Fenofibrate + atorvastatin	16.86 (0.43-93.60)
Gemfibrozil	3.70 (0.76-10.82)	Gemfibrozil + cerivastatin	789 (166-2138)

Abbreviation: CI, confidence interval.

Graham, D. J. et al. JAMA 2004;292:2585-2590.

Rhabdomyolysis

Causes

Anything that destroys muscle tissue can cause rhabdomyolysis. The causes of rhabdomyolysis can be classified as either physical or non-physical. Physical rhabdomyolysis is in some situations confined to a particular area of the body, while rhabdomyolysis due to other causes tends to affect all muscles simultaneously.[1]

Physical causes

[edit]

Recognized physical causes for rhabdomyolysis are:[1]

- Traumatic compression of muscles: crush syndrome (e.g. in earthquakes), car accident, confinement in a fixed position (e.g. after a stroke, due to drunkenness or in prolonged surgery), physical torture or abuse
- Obstruction of blood supply to mus… gery, generally reduced blood supply in shock or …
- Excessive muscle strain or activity: extreme physical exercise (particularly when poorly hydrated), delirium tremens (alcohol withdrawal), tetanus, prolonged seizures or status epilepticus
- Electrical: lightning, high-voltage electric shock, including electroshock weapon injuries[4].

various defects in the mitochondrial respiratory chain

Non-physical causes

[edit]

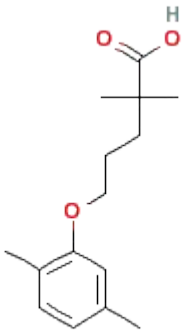
Non-physical causes reported to cause rhabdomyolysis include:[1]

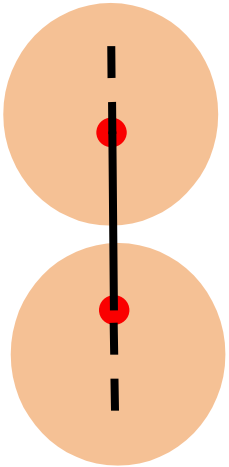
- Disorders of muscle energy supply (usually hereditary enzyme problems): carnitine deficiency, CPT type I or type II deficiency, McArdle's disease, various defects in the mitochondrial respiratory chain, phosphofructokinase deficiency, VLCAD deficiency.[5]
- Poisons such as heavy metals and venom from insects or snakes
- Foodborne toxins, e.g. coniine from quail that have consumed hemlock (coturnism),[6] *Tricholoma equestre* mushrooms in France and Poland,[7] and an unidentified toxin in fish (Haff disease)[8]
- Drugs of abuse,[9] including: ethanol,[10] methamphetamines,[11] cocaine,[12] heroin,[13] phencyclidine (PCP),[14] ketamine,[15] 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy),[16][17]
- Medications:
  - statins, especially when prescribed in combinations with fibrates. Cerivastatin (Baycol) was withdrawn in 2001 after numerous reports of rhabdomyolysis. Other statins have a small risk of 0.44 cases per 10,000 patients annually, which increases to 5.98 if a fibrate is added.[18] However, other studies detected no increased risk from statins.[19]
  - anti-psychotic medications may cause neuroleptic malignant syndrome, which can cause severe muscle rigidity, with rhabdomyolysis and hyperpyrexia.
  - neuromuscular blocking agents, used in anasthesia may cause malignant hyperthermia, also associated with rhabdomyolysis.
  - medications that interfere with potassium levels (e.g. diuretics)
- Infections: Coxsackie virus, *Plasmodium falciparum* (malaria), herpes viruses, *Legionella pneumophila*, Salmonella and *Francisella tularensis* (tularemia)
- Electrolyte and metabolic disturbances: increased plasma osmolality, hyper- and hyponatremia (elevated or reduced blood sodium levels), hypokalemia (low potassium levels), hypocalcemia (low calcium leve… phosphate levels), ketoacidosis (e.g. in diabetes) or hypothyroidism (abnormally low thyroid function)
- Autoimmune muscle damage: polymyositis, dermatomyositis

Source: http://en.wikipedia.org/wiki/Rhabdomyolysis

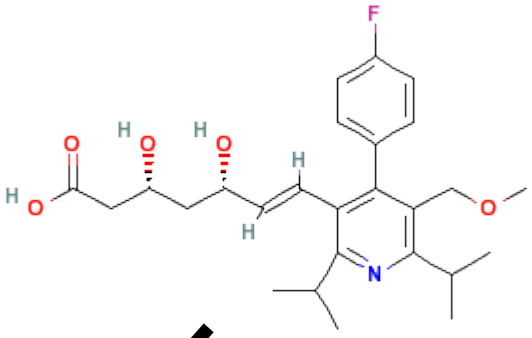
Another example

Gemfibrozil





Cerivastatin



They do not have a single common target predicted (but CYPs linked back to back)

Pathways for Cerivastatin and Gemfibrozil

(1) Steroid metabolism

(2) Xenobiotic metabolism

(3) Inflammation_Neutrophil activation

(4) Muscle contraction

One of numerous literature examples

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GEMFIBROZIL INHIBITS CYP2C8-MEDIATED CERIVASTATIN METABOLISM IN HUMAN LIVER MICROSOMES

JUN-SHENG WANG, MIKKO NEUVONEN, XIA WEN, JANNE T. BACKMAN, AND PERTTI J. NEUVONEN

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1/3 of Cerivastatin-related deaths were related to co-treatment with Gemfibrozil!

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Summary

- Linking side effects to biological cause by chemical space
- Targets and pathways can be identified as most likely reasons (we deal with structural dissimilarity)
- Biological data can be used to validate predictions

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Thank you for your attention !

… many others!

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