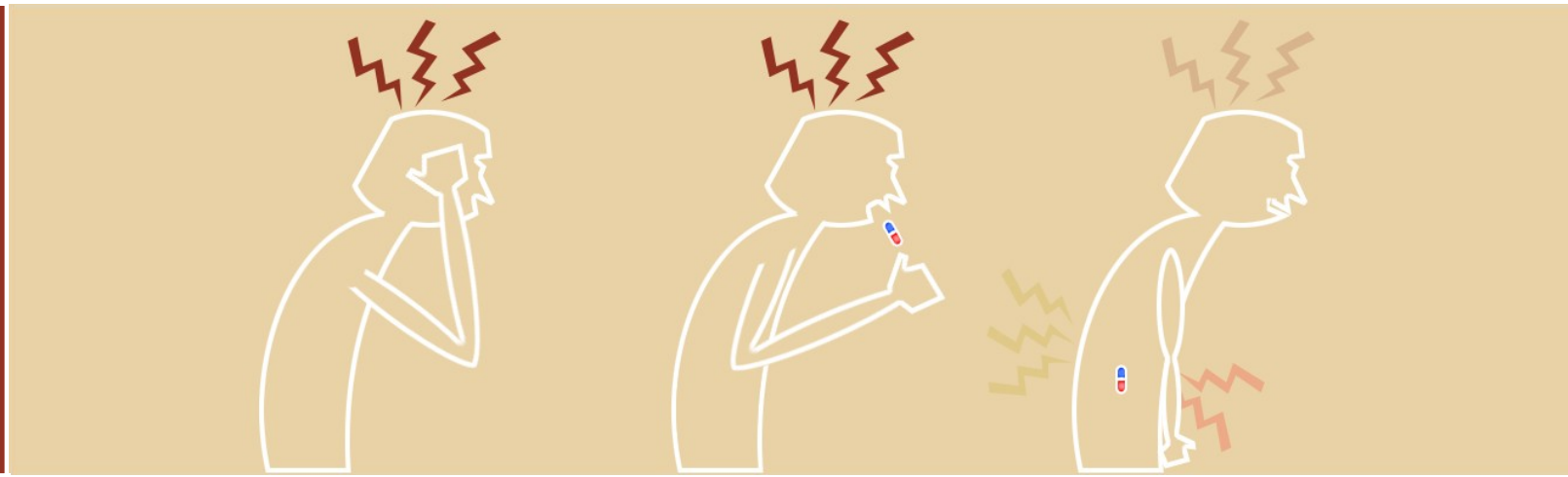

Side effect profile prediction

Tackling Big Pharma's worst nightmare at an early stage

Josef Scheiber, Lead Discovery Informatics

ACS meeting, Aug 19 2007

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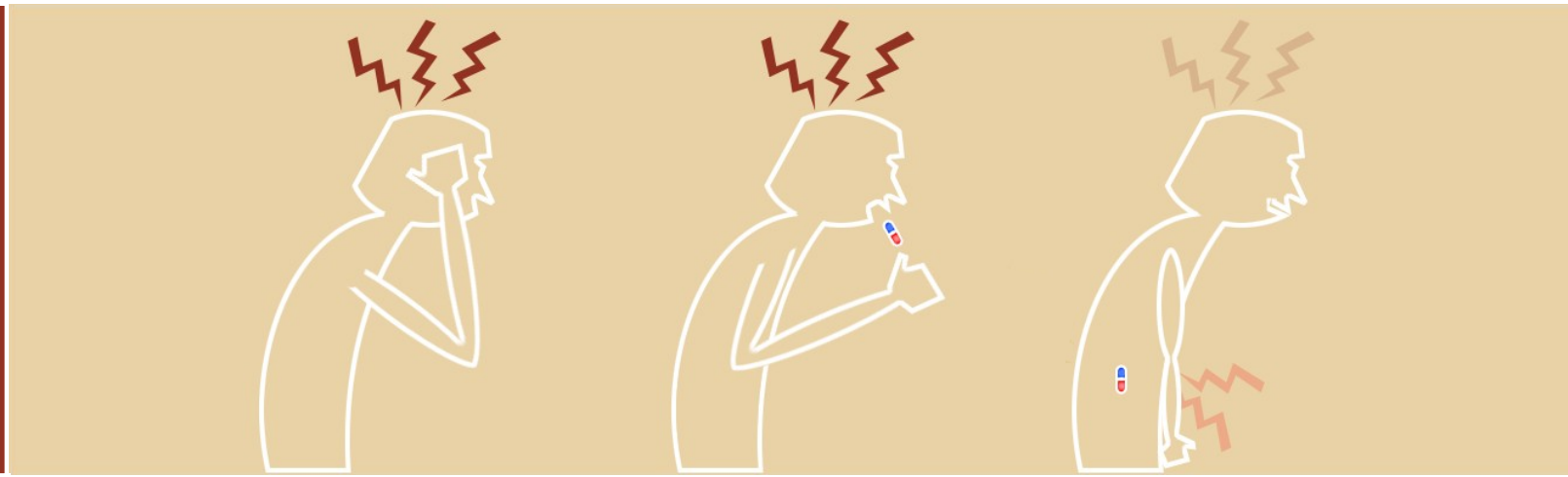

Side effect profile prediction

Tackling Big Pharma's worst nightmare at an early stage

Sepp Scheiber, Lead Discovery Informatics

ACS meeting, Aug 19 2007

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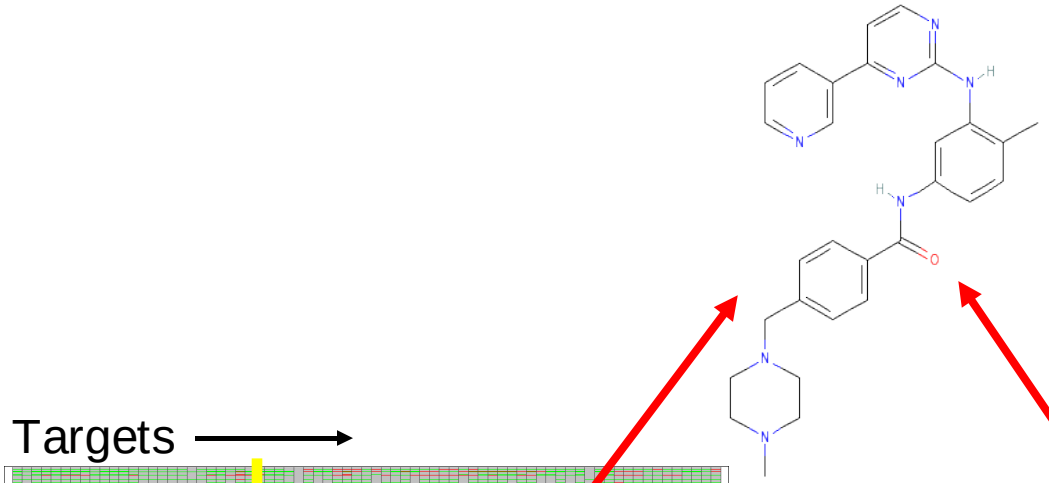
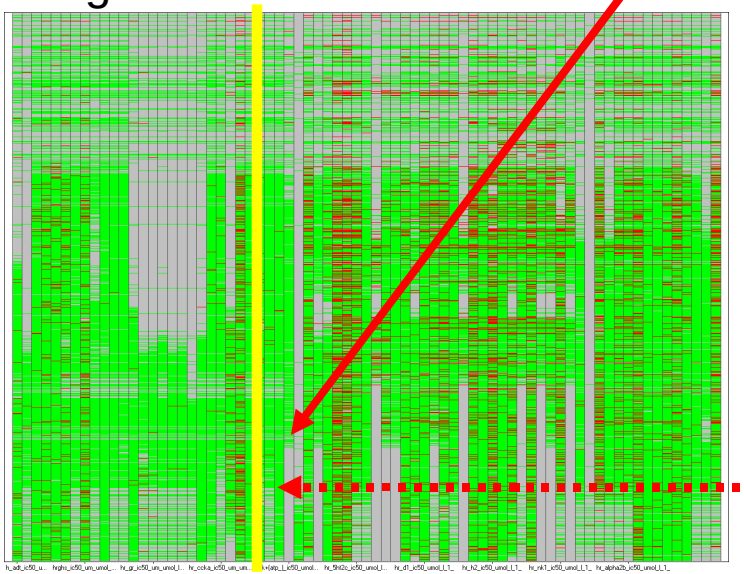
The idea

linking adverse side effects with target interaction



Targets



SOC_TXT
Gastrointestinal disorders
Pregnancy, puerperium and perinatal conditions
Infections and infestations
Congenital, familial and genetic disorders
Nervous system disorders
Skin and subcutaneous tissue disorders
Injury, poisoning and procedural complications
Eye disorders
Metabolism and nutrition disorders
Renal and urinary disorders
General disorders and administration site conditions
Reproductive system and breast disorders
Respiratory, thoracic and mediastinal disorders
Cardiac disorders
Endocrine disorders
Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Investigations
Psychiatric disorders
Blood and lymphatic system disorders
Immune system disorders
Surgical and medical procedures
Vascular disorders
Musculoskeletal and connective tissue disorders
Social circumstances
Hepatobiliary disorders
Ear and labyrinth disorders

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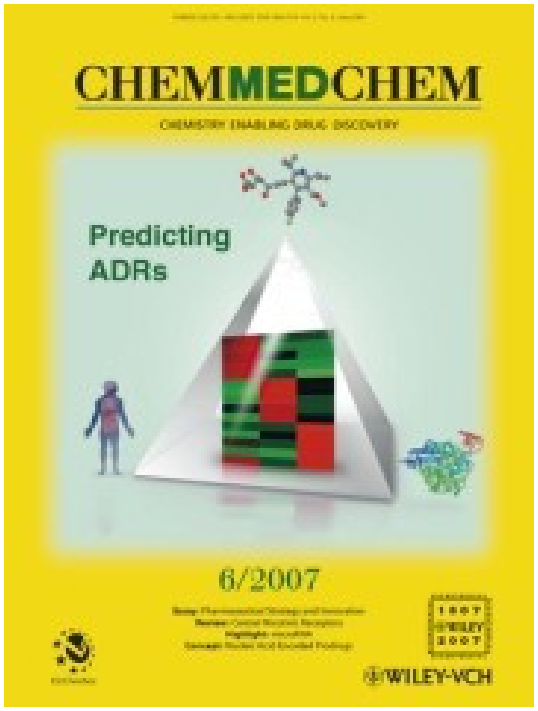
The predecessor technique



1 model based on World drug index as data pool

Hand-curated terminology

Predicted side effects

Analysis of Pharmacology Data and the Prediction of Adverse Drug Reactions and Off-Target Effect From Chemical Structure

A. Bender, J. Scheiber, M. Glick, JW. Davies, K. Azzaoui, J. Hamon, L. Urban, S. Whitebread, JL. Jenkins.

ChemMedChem Volume 2, Issue 6, Date: June 11, 2007, Pages: 861-873

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Agenda

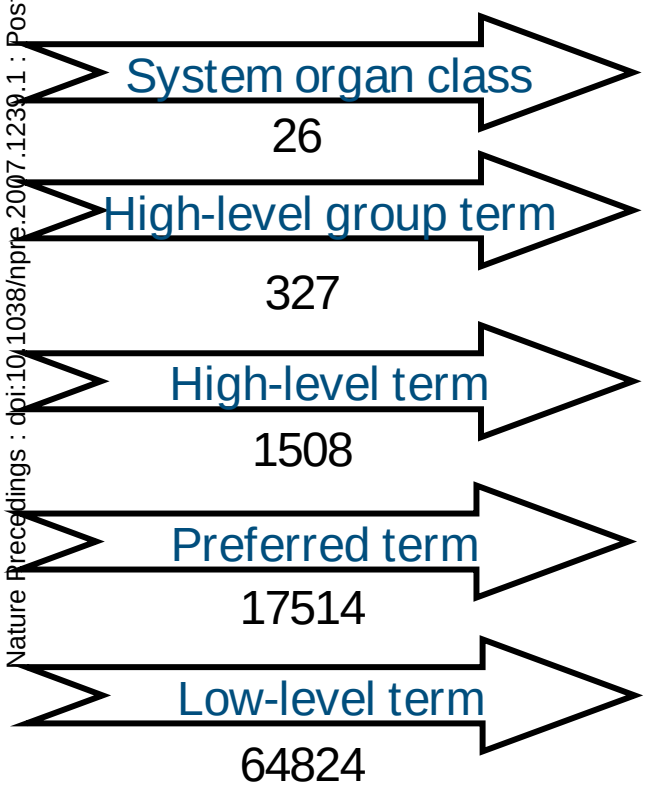
Key requirements

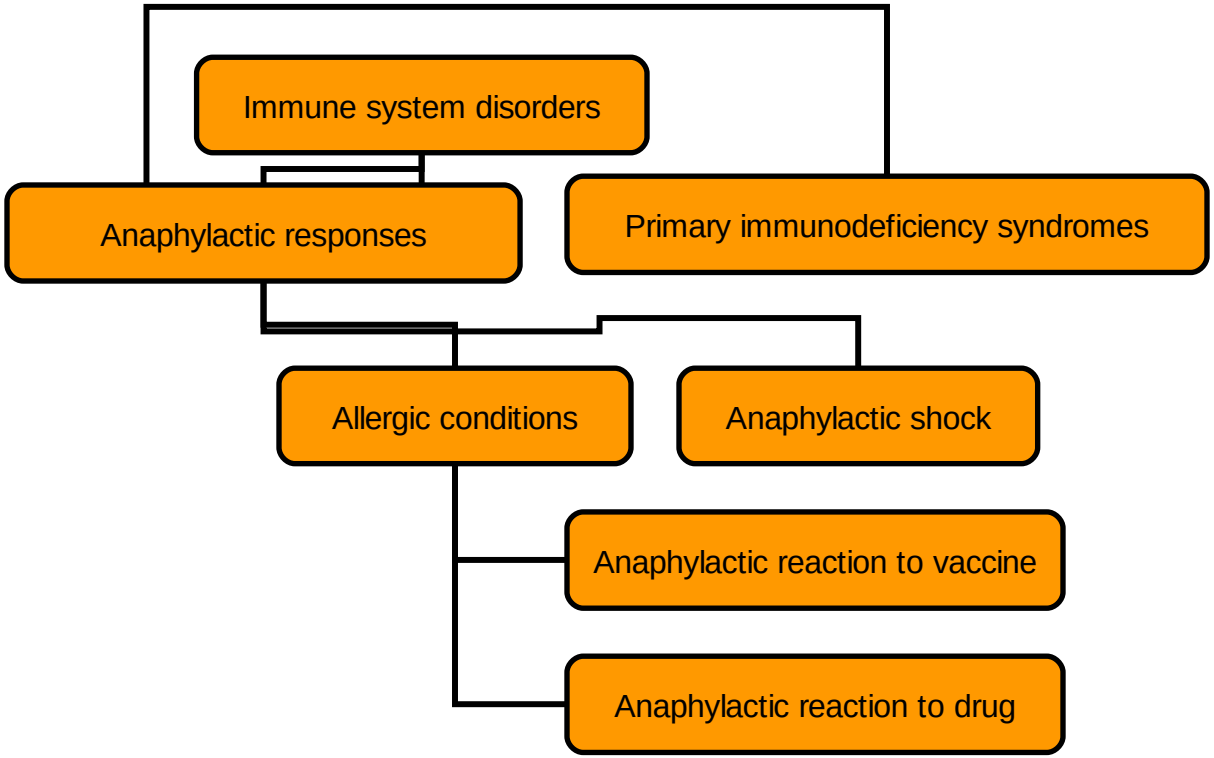
Analysis and modeling

Results

Key requirement 1: A curated terminology

MedDRA: the Medical Dictionary for Regulatory Activities





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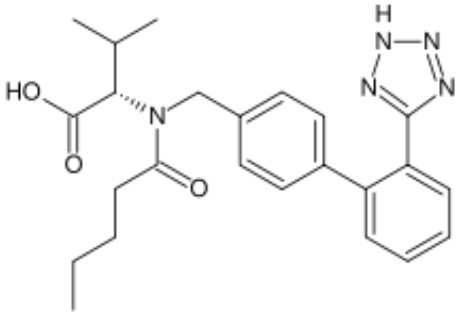
Key requirement 2:
Database of chemicals linked with terminology



stomach pain
joint pain
cough
diarrhea
dizziness
upper respiratory tract infection
fatigue
fluid retention
nausea/vomiting
headache
insomnia
pain
urinary tract infection
heartburn

Currently limited to compounds that made it to the market

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Data sources

Compound structures from DrugBank and PubChem

Side effects from Facts & Comparisons 4.0 (WoltersKluwer)

In total: 669 drugs

Agenda

Key requirements

Analysis and modeling

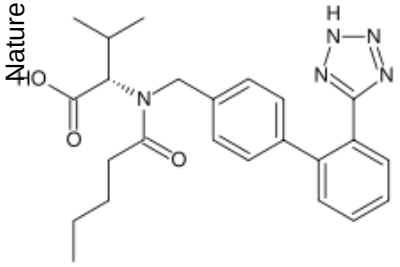
Results

Data preparation and modeling

Bayesian models

chemical descriptors (ECFP)

1	2	3	...	n-2	n-1	n



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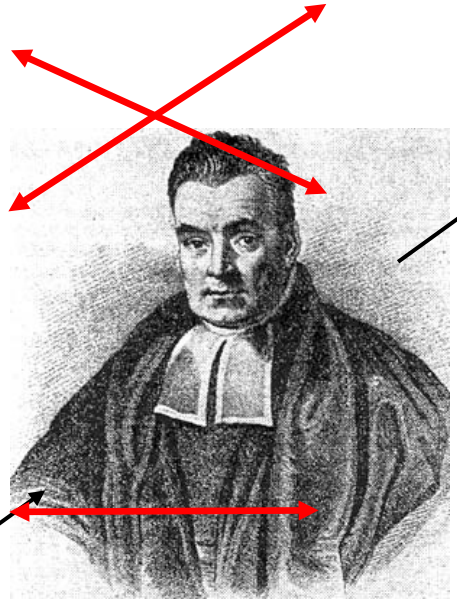
Data preparation and modeling

Rec. 1
Rec. 2
Rec. 3
Rec. 4
Rec. 5
Rec. 6
Rec. 7
Rec. 8
Rec. 9
Rec. 10
Rec. 11
Rec. 12
Rec. 13
Rec. 14



1	stomach pain
2	joint pain
3	cough
	diarrhea
	dizziness
	upper respiratory tract infection
.	fatigue
.	fluid retention
.	nausea/vomiting
	headache
	insomnia
n-2	pain
n-1	urinary tract infection
n	heartburn

ECFP descriptors

1	2	3	...	n-2	n-1	n

Agenda

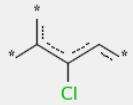
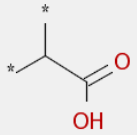
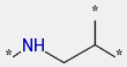
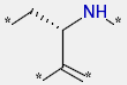
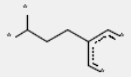
Key requirements

Analysis and modeling

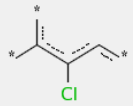
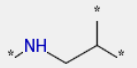
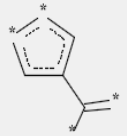
Results

The outcome: Features linked with AEs

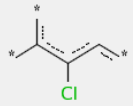
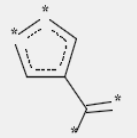
Category Nervous system disorders: good features from ECFP_4

 G6: 1335691903 13 out of 13 good Bayesian Score: 0.124	 G19: -1905455774 8 out of 8 good Bayesian Score: 0.119	 G27: -652986225 6 out of 6 good Bayesian Score: 0.114	 G28: 1336540477 6 out of 6 good Bayesian Score: 0.114	 G30: 1878498340 6 out of 6 good Bayesian Score: 0.114

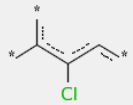
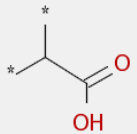
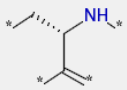
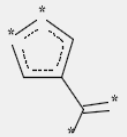
Category Skin and subcutaneous tissue disorders: good features from ECFP_4

 G8: 1335691903 13 out of 13 good Bayesian Score: 0.144	 G37: -652986225 6 out of 6 good Bayesian Score: 0.132	 G43: -175146122 6 out of 6 good Bayesian Score: 0.132		

Category Infections and infestations: good features from ECFP_4

 G3: 1335691903 13 out of 13 good Bayesian Score: 0.165	 G23: -175146122 6 out of 6 good Bayesian Score: 0.152			

Category Investigations: good features from ECFP_4

 G6: 1335691903 13 out of 13 good Bayesian Score: 0.095	 G26: -1905455774 8 out of 8 good Bayesian Score: 0.091	 G41: 1336540477 6 out of 6 good Bayesian Score: 0.087	 G43: -175146122 6 out of 6 good Bayesian Score: 0.087	

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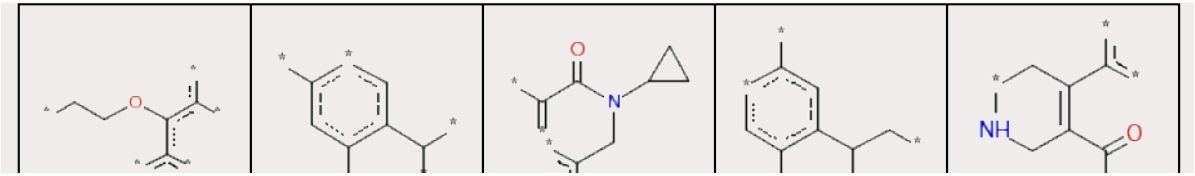
The outcome: Features linked with targets

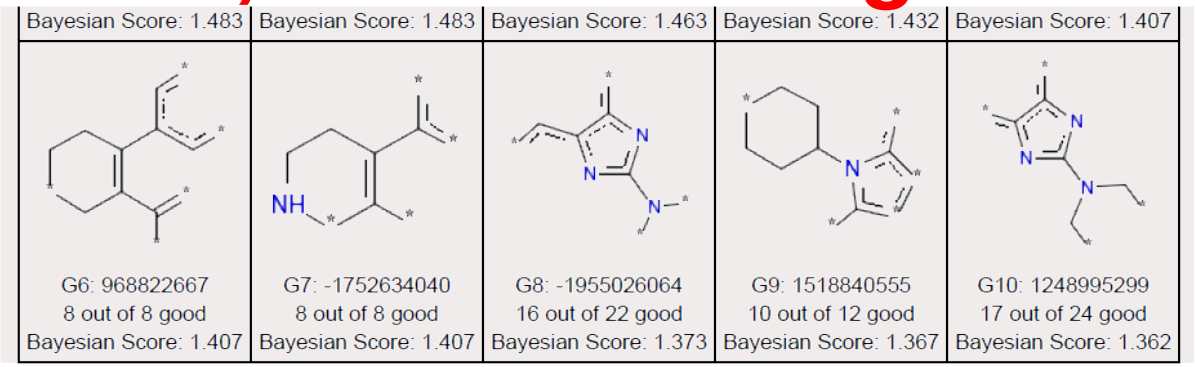
Features linked with AEs

Example:

Good features for the Growth Hormone Secretagogue receptor



Now, let’ s tie it together!



Showcase: Cerivastatin (Baycol®, Lipobay®)

Cerivastatin

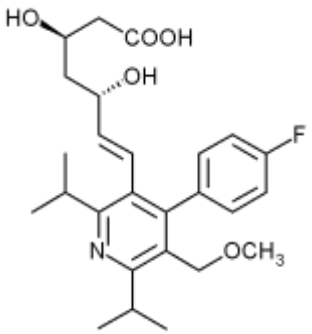
From Wikipedia, the free encyclopedia

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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Showcase: Cerivastatin (Baycol®, Lipobay®)

Targets correlated to color-blindness

HMG-CoA Reductase

JNK2alpha1

Cyt-p450-24

VDR

SkM1

ALK-5

Targets correlated to Muscle enzyme increased

HMG-CoA Reductase

Cyt-p450-24

ALK-5

JNK2alpha1

Cyt-P450-2D1

VDR

SkM1

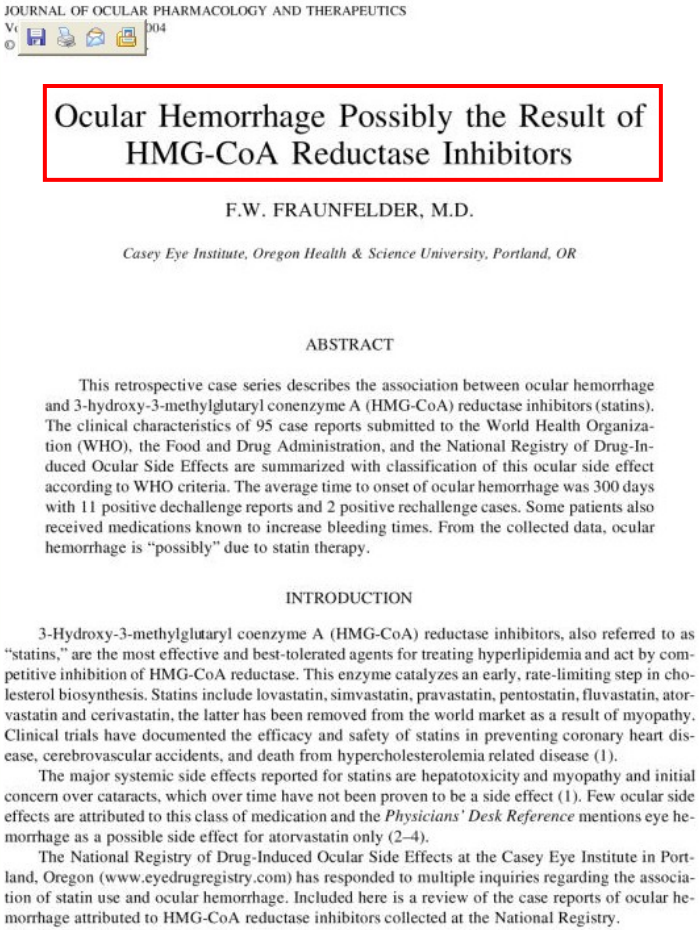
FXR

Showcase: Cerivastatin (Baycol®, Lipobay®)

Hypothesis based on prediction:

Cerivastatin hits JNK2alpha1
and causes thereby color-blindness

Showcase: Cerivastatin (Baycol®, Lipobay®)



JOURNAL OF OCULAR PHARMACOLOGY AND THERAPEUTICS
Vo 004

Ocular Hemorrhage Possibly the Result of HMG-CoA Reductase Inhibitors

F.W. FRAUNFELDER, M.D.

Casey Eye Institute, Oregon Health & Science University, Portland, OR

ABSTRACT

This retrospective case series describes the association between ocular hemorrhage and 3-hydroxy-3-methylglutaryl conenzyme A (HMG-CoA) reductase inhibitors (statins). The clinical characteristics of 95 case reports submitted to the World Health Organization (WHO), the Food and Drug Administration, and the National Registry of Drug-Induced Ocular Side Effects are summarized with classification of this ocular side effect according to WHO criteria. The average time to onset of ocular hemorrhage was 300 days with 11 positive dechallenge reports and 2 positive rechallenge cases. Some patients also received medications known to increase bleeding times. From the collected data, ocular hemorrhage is "possibly" due to statin therapy.

INTRODUCTION

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, also referred to as "statins," are the most effective and best-tolerated agents for treating hyperlipidemia and act by competitive inhibition of HMG-CoA reductase. This enzyme catalyzes an early, rate-limiting step in cholesterol biosynthesis. Statins include lovastatin, simvastatin, pravastatin, pentostatin, fluvastatin, atorvastatin and cerivastatin, the latter has been removed from the world market as a result of myopathy. Clinical trials have documented the efficacy and safety of statins in preventing coronary heart disease, cerebrovascular accidents, and death from hypercholesterolemia related disease (1).

The major systemic side effects reported for statins are hepatotoxicity and myopathy and initial concern over cataracts, which over time have not been proven to be a side effect (1). Few ocular side effects are attributed to this class of medication and the *Physicians' Desk Reference* mentions eye hemorrhage as a possible side effect for atorvastatin only (2–4).

The National Registry of Drug-Induced Ocular Side Effects at the Casey Eye Institute in Portland, Oregon (www.eyedrugregistry.com) has responded to multiple inquiries regarding the association of statin use and ocular hemorrhage. Included here is a review of the case reports of ocular hemorrhage attributed to HMG-CoA reductase inhibitors collected at the National Registry.

Bleeding in eyes causes distortion of color-vision!

See e.g. http://www.psych.ucalgary.ca/pace/va-lab/Brian/acquired.htm

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Showcase: Cerivastatin (Baycol®, Lipobay®)

Human Molecular Genetics

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Institution: Novartis Pharmaceuticals Sign In as Personal Subscriber

Oxford Journals › Life Sciences › Human Molecular Genetics › Volume 14, Number 19 › Pp. 2945-2958

Human Molecular Genetics Advance Access originally published online on August 26, 2005
Human Molecular Genetics 2005 14(19):2945-2958; doi:10.1093/hmg/ddi325

Distinct gene expression profiles and reduced JNK signaling in retinitis pigmentosa caused by RP1 mutations

Jiewu Liu[1], Qian Huang[1], Jason Higdon[1], Wei Liu[2], Tao Xie[3], Tetsuji Yamashita[1], Kyeogmi Cheon[1], Cheng Cheng[2] and Jian Zuo[1,*]

[1]Department of Developmental Neurobiology, [2]Department of Biostatistics and [3]Hartwell Centre, St Jude Children's Research Hospital, Memphis, TN 38105-2794, USA

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Received July 18, 2005; Accepted August 23, 2005

Showcase: Cerivastatin (Baycol®, Lipobay®)

Research Article

Suppressive Effects of Statins on Acute Promyelocytic Leukemia Cells

Antonella Sassano,[1] Efstratios Katsoulidis,[1] Giovanni Antico,[1] Jessica K. Altman,[1] Amanda J. Redig,[1] Saverio Minucci,[2] Martin S. Tallman,[1] and Leonidas C. Platanias[1]

[1]Robert H. Lurie Comprehensive Cancer Center and Division of Hematology/Oncology, Northwestern University Medical School and Lakeside VA Medical Center, Chicago, Illinois and [2]Department of Experimental Oncology, European Institute of Oncology, Milan, Italy

Abstract

In addition to reducing cholesterol levels, statins have potent

MAPK cascade is not engaged by statins (Fig. 1*B*). On the other hand, treatment of NB4 cells with atorvastatin or fluvastatin induced phosphorylation of JNK (JNK1 and JNK2/3), although such phosphorylation/activation was less intense than chemical stress–induced activation (Fig. 1*C*). Moreover, treatment of the cells with

downstream engagement of the c-Jun NH_2-terminal kinase kinase pathway, whose function was found to be essential for the generation of proapoptotic responses. Importantly, different statins were found to enhance all-*trans*-retinoic acid (ATRA)–dependent differentiation of APL blasts and reverse resistance to the antileukemic effects of ATRA. In addition, fluvastatin exhibited growth-inhibitory properties on primary bone marrow–derived leukemic progenitors from patients with AML and enhanced the suppressive effects of ATRA on leukemic progenitor colony formation. Altogether, these

protein geranylation is essential for lovastatin-induced apoptosis of human AML cells (22).

Although the effects of statins on cell cycle regulation and induction of apoptosis are well described, very little is known on the ability of these agents to induce leukemic cell differentiation. There has been some previous evidence that simvastatin (23) and lovastatin (24) promote osteoblastic differentiation while they inhibit adipocytic differentiation, but their effects on differentiation of acute leukemia cells remain to be established. In the present

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Finally …

Laboratory Investigation (2006) 86, 106–115

www.laboratoryinvestigation.org

TGFβ pathobiology in the eye

Shizuya Saika

JNK phosphorylates SMAD 2/3 which also interacts with TGFβ

Disturbance of the system causes fibrosis

Fibrosis causes bleeding

Laboratory Investigation (2006) **86**, 106–115. doi:10.1038/labinvest.3700375; published online 5 December 2005

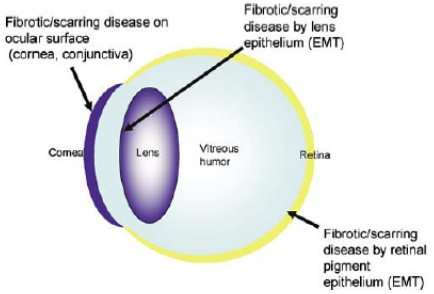

Figure 1 Typical fibrotic diseases or surgical complications that may occur in cornea, conjunctiva, lens, and retina.

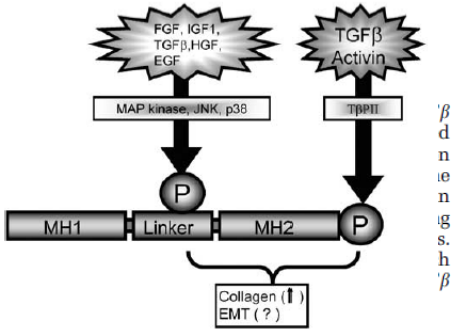

Figure 2 Smad2/3 can be activated by non-TGFβ growth factors at the middle linker region.

cular endothelial growth factor (VEGF), as well as

humor of the eye

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Ok …

Hypothesis based on prediction:

Cerivastatin hits JNK2alpha1
and causes thereby color-blindness

But: There' s no color-blindness with statins

ORIGINAL INVESTIGATION

Risk of Cataract in Patients Treated With Statins

Raymond G. Schlienger, PhD; Walter E. Haefeli, MD; Hershel Jick, MD; Christoph R. Meier, PhD, MSc

Background: Studies in
droxymethylglutaryl coer
(statins) are associated v
tered in excessive doses. C
garding cataract developn
limited value so far.

Objective: To determine
ins is associated with an i

Methods: We conducted a
from the United Kingdon
search Database. The main
nosis of cataract and/or cata
40 to 79 years. Controls we
practice, calendar time, and
the database. Use of statins, fibrates, or other lipid-lowering drugs was compared with nonuse of any lipid-lowering drug, stratified by exposure duration and dose.

5 cases and 28 327 controls.
≥30 prescriptions) was not
cataract risk (adjusted odds
ence interval [CI], 0.5-1.6),
other lipid-lowering drugs
.3-1.1; and OR, 0.7; 95% CI,
und evidence that concomi-
erythromycin, a potent in-
olism, is associated with an
ted odds ratio, 2.2; 95% con-

rovides evidence that long-
n doses does not increase the
Concomitant use of eryth-
y increase the cataract risk.

Arch Intern Med. 2001;161:2021-2026

Only when given in combination with erythromycin, a potent inhibitor of statin metabolism !

Bioavailability in eye is low, therefore no bigger problems

Showcase: Rofecoxib (Vioxx®)

Rofecoxib

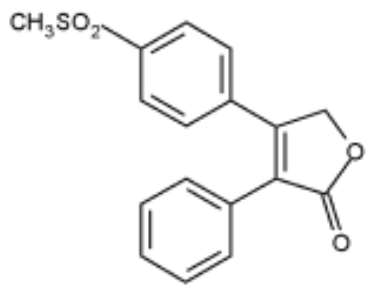
From Wikipedia, the free encyclopedia
(Redirected from Vioxx)

Rofecoxib (IPA: [rofa'kɒksɪb]) is a nonsteroidal anti-inflammatory drug (NSAID) developed by Merck & Co. to treat osteoarthritis, acute pain conditions, and dysmenorrhoea. Rofecoxib was approved as safe and effective by the Food and Drug Administration (FDA) on May 20, 1999 and was subsequently marketed under the brand name **Vioxx**, **Ceoxx** and **Ceeoxx**.

Rofecoxib gained widespread acceptance among physicians treating patients with arthritis and other conditions causing chronic or acute pain. Worldwide, over 80 million people were prescribed rofecoxib at some time.

On September 30, 2004, Merck voluntarily withdrew rofecoxib from the market because of concerns about increased risk of heart attack and stroke associated with long-term, high-dosage use. Rofecoxib was one of the most widely used drugs ever to be withdrawn from the market. In the year before withdrawal, Merck had sales revenue of US$2.5 billion from Vioxx.[1]

Rofecoxib was available on prescription as tablets and as an oral suspension.



Predicted AE	Bayes Score
Endocrine. Changes in spleen weight	39.73
Duodenal perforation	39.64
Faecal occult blood	39.58
Labile hypertension	39.35
Endocrine. Changes in adrenal weight	38.64
Haemorrhoidal haemorrhage	38.51
Blood pressure diastolic	38.51
Gastric ulcer haemorrhage	38.46
Bladder injury	38.26
Gastric outlet obstruction	38.26
Renal failure chronic	38.03
Blood pressure	37.99
Endocrine pancreatic disorder	37.98
Menopausal symptoms	37.84
Behavioral. Alteration of classical conditioning	37.63
Coronary artery thrombosis	37.63
Arterial rupture	37.55
Gastrointestinal erosion	37.55
Gastrointestinal ulcer perforation	37.55
Allergy to arthropod bite	37.51
Median nerve lesion	37.51
Wrist fracture	37.51
Gastroduodenal haemorrhage	37.51
Lower gastrointestinal haemorrhage	37.51
Tonsillar disorder	37.51
Breast cancer female	37.51
Oral infection	37.51
Sense organs and special senses (nose, eye, ear, and taste). Eye Tumors	37.51
Purpura senile	37.51
Cartilage injury	37.51
Calcium ionised decreased	37.24
Haemarthrosis	37.16
Liver. Changes in liver weight	37.06
Venous occlusion	36.85
Small intestinal haemorrhage	36.81
Diaphragmatic hernia	36.78
Upper gastrointestinal haemorrhage	36.77
Colon cancer	36.71
Painful respiration	36.68
Body temperature decreased	36.55
Large intestinal ulcer	36.52
Microalbuminuria	36.52
Gastrointestinal obstruction	36.44
Biochemical. Metabolism (intermediary). Plasma proteins not involving coagulation	36.42
Erosive duodenitis	36.39
Systolic hypertension	36.33
Red blood cell count abnormal	36.29
Nephrotic syndrome	35.96
Tubulointerstitial nephritis	35.92
Coronary artery occlusion	35.9

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Just last week: Rosiglitazone (Avandia®)

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Warning label urged for Avandia

FDA panel: Greater risk of heart attack

By Bruce Japsen | Tribune staff reporter
July 31, 2007

GAITHERSBURG, Md. - A Food and Drug Administration advisory panel on Monday found that people who use the popular diabetes pill Avandia face a greater risk of heart attack and urged the FDA to slap its strictest warning on its label.

The panel, however, did not go as far as to suggest pulling the drug off the market as one high-profile FDA safety reviewer had urged in his testimony Monday. The agency typically follows the recommendations of its panels but is not bound to do so.

Still, the committee's recommendation is a blow to Avandia's maker, GlaxoSmithKline PLC, which submitted its own studies that showed the drug had no greater risk of heart attack than other drugs

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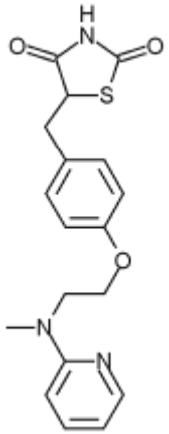

Predicted AE	Bayes Score
Weight	88.73
Blood glucose decreased	62.35
Fluid retention	56.84
Pitting oedema	56.73
Biochemical. Enzyme inhibition, induction, or change in blood or tissue levels: Transaminases	56.49
Superovulation	56.35
Hypoglycaemia	54.67
Hepatitis viral	53.66
Endocrine pancreatic disorder	53.35
Haematocrit decreased	53.29
Haemoglobin decreased	52.75
Low density lipoprotein abnormal	52.51
Weight increased	52.15
Myelodysplastic syndrome	51.49
Blood cholesterol abnormal	50.87
Generalised oedema	50.82
Haematocrit abnormal	49.82
Blood triglycerides abnormal	49.79
Lung disorder	49.32
Drug effect increased	48.86
Hepatitis granulomatous	48.70
Lipids abnormal	48.66
Cardiomyopathy	47.95
High density lipoprotein increased	47.91
Haematology test abnormal	47.51
Upper respiratory tract infection	47.39
Blood triglycerides increased	45.55
Ischaemia	45.29
Alanine aminotransferase abnormal	44.99
Macular oedema	44.96
Hepatocellular damage	44.71
Low density lipoprotein increased	43.99
Weight abnormal	43.77
Coronary artery disease	41.20
Blood cholesterol increased	40.53
Visual acuity reduced	39.31
Blood sodium decreased	38.39
Blood albumin increased	38.24
Electrocardiogram QT corrected interval prolonged	38.23
Pulmonary oedema	37.95
Blood pressure decreased	37.71
Hepatic failure	37.40
Cardiac failure	37.17
Conduction disorder	36.64
Pharyngolaryngeal pain	36.36
Electrocardiogram abnormal	35.90
White blood cell count abnormal	35.45
Heart rate abnormal	34.96
Influenza	34.65
White blood cell count decreased	34.20

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Summary

Prediction of AEs and link to targets is established

Model quality can be analyzed and utilized in future work

Results give a very good match with reality

Future plans

Incorporate gene expression data to better localize AEs

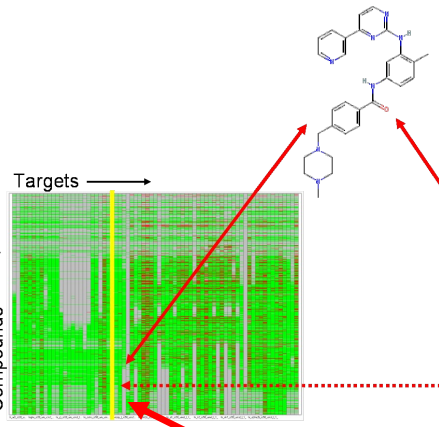
Identify pathway combinations that cause AEs

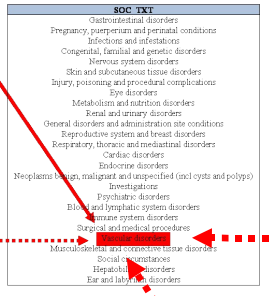
Find AE/AE correlations

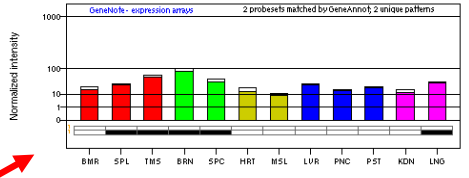
In general: **A better understanding of side effects**

The vision: Expanding the knowledge

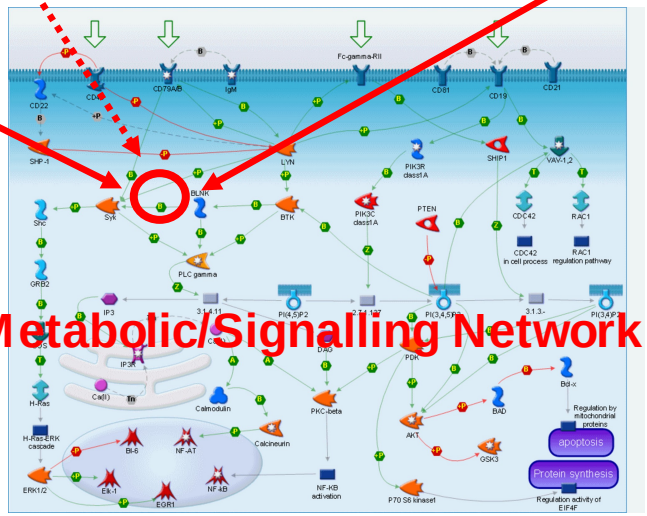
A better understanding of side effects







Gene Expression Profile



Metabolic/Signalling Network

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Acknowledgement

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Steven Whitebread

Thank you for your attention !

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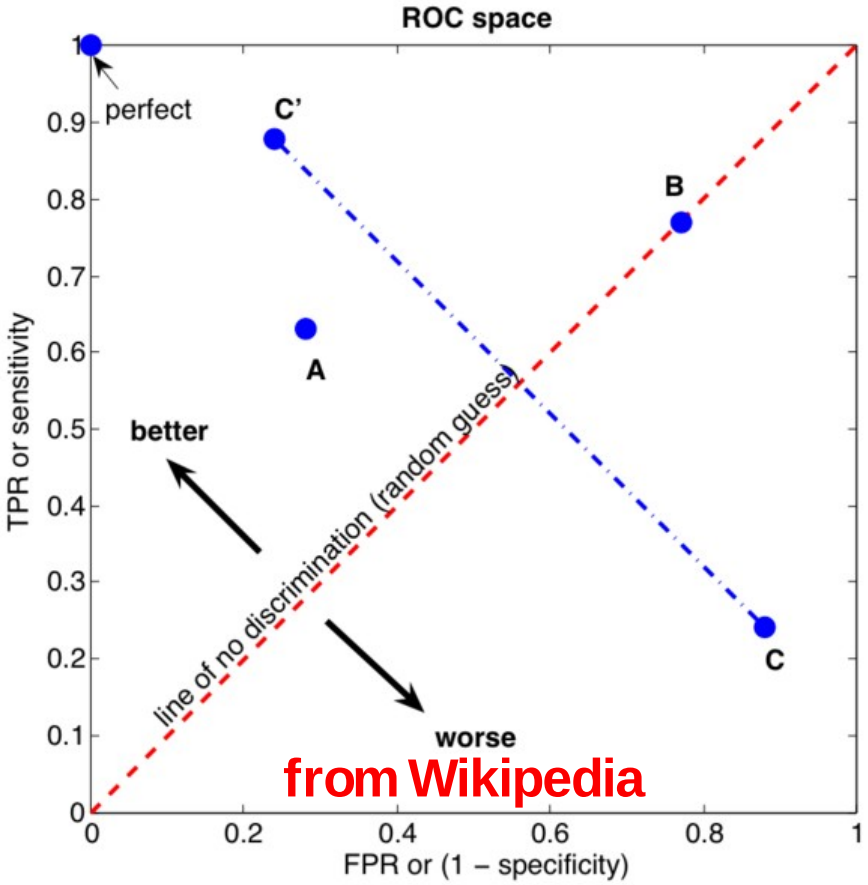
How to visualize the quality of many models ? *ROC plot*



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But …

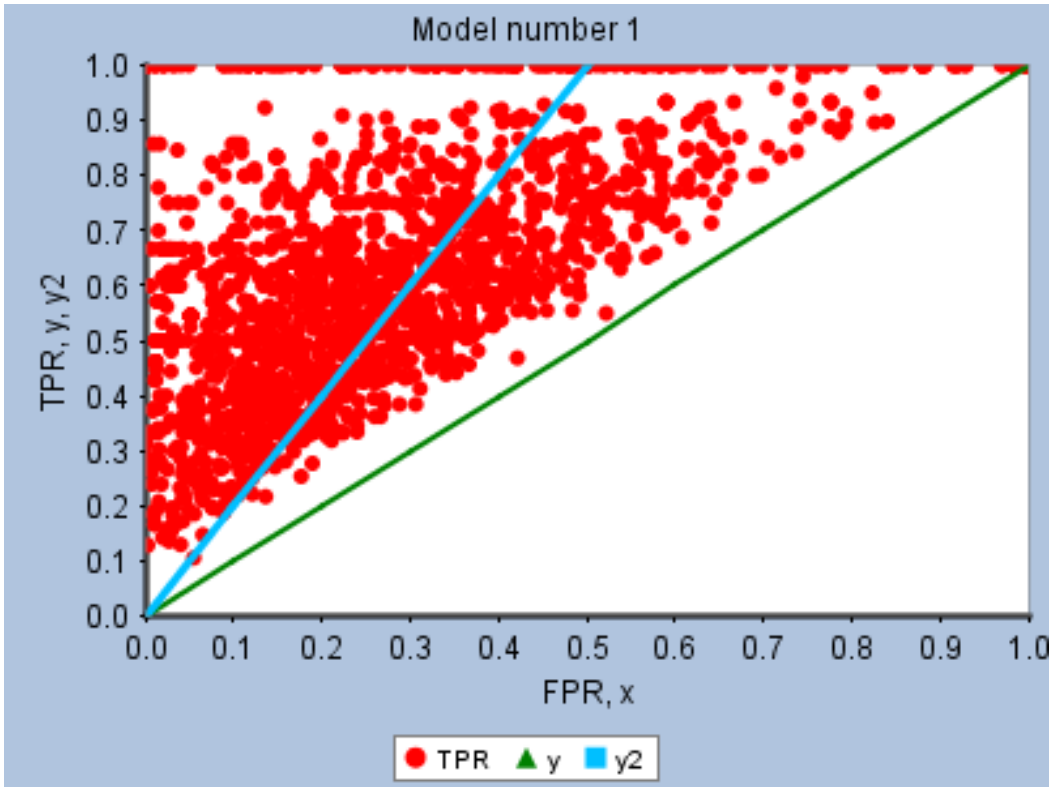
How reliable are the models ?

Modeling the DrugBank data

Or: Testing Bayes' fitness

Multicategory Bayesian modeling in Pipeline Pilot **Preferred term** level

100 different MCM models (each ~ 1700 categories)



Model quality is consistent, BUT:

What does that mean for single categories ?

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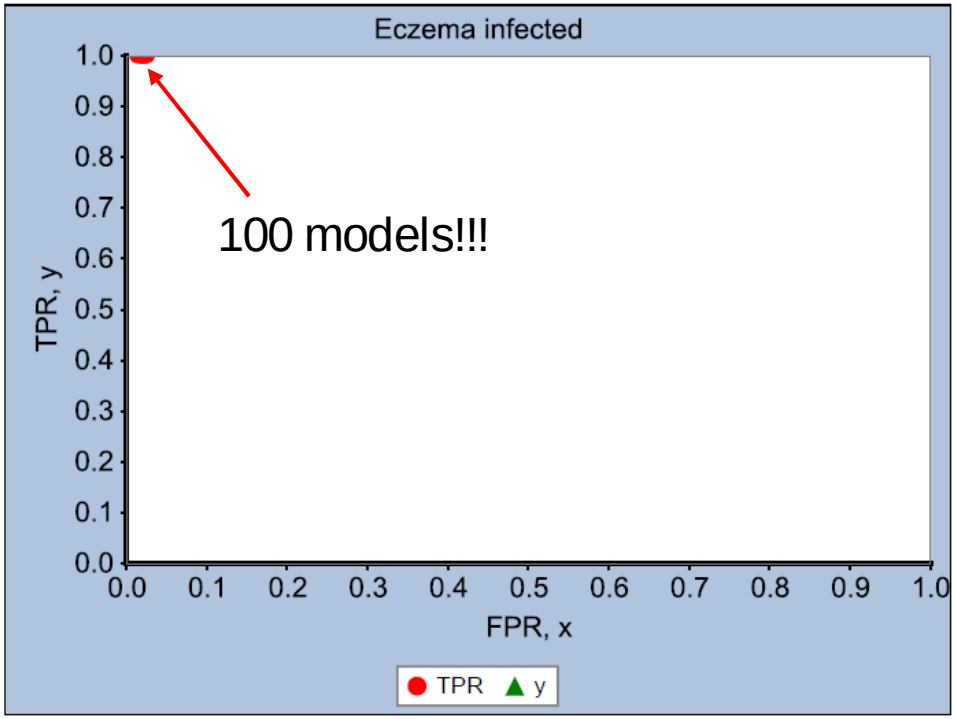
Analyzing the categories

Assessing model stability



Optimal case

Very stable model

Many true positives

Almost no false positives

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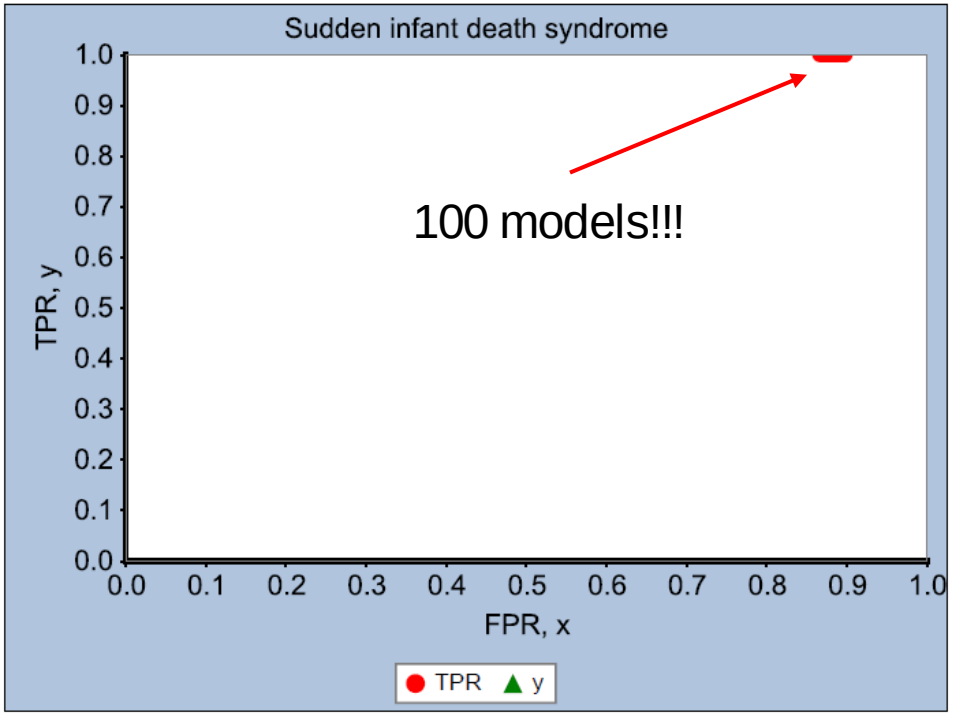
Analyzing the categories

Assessing model stability



Very stable model

Many true positives

Too many false positives

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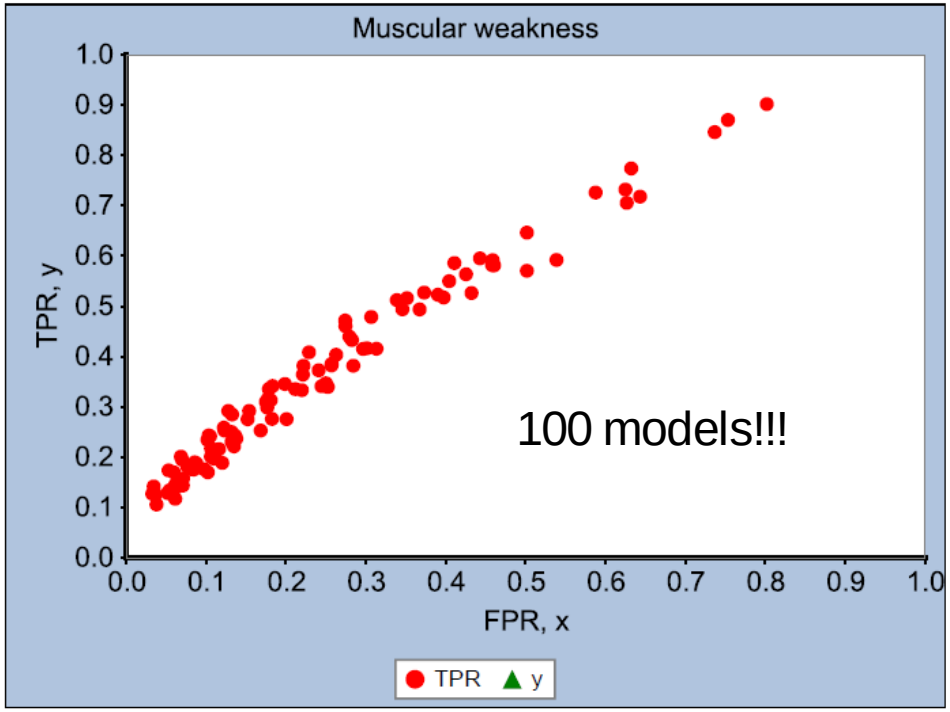
Analyzing the categories

Assessing model stability



Instable model

Direct correlation between true and false positives

This is an unwanted case

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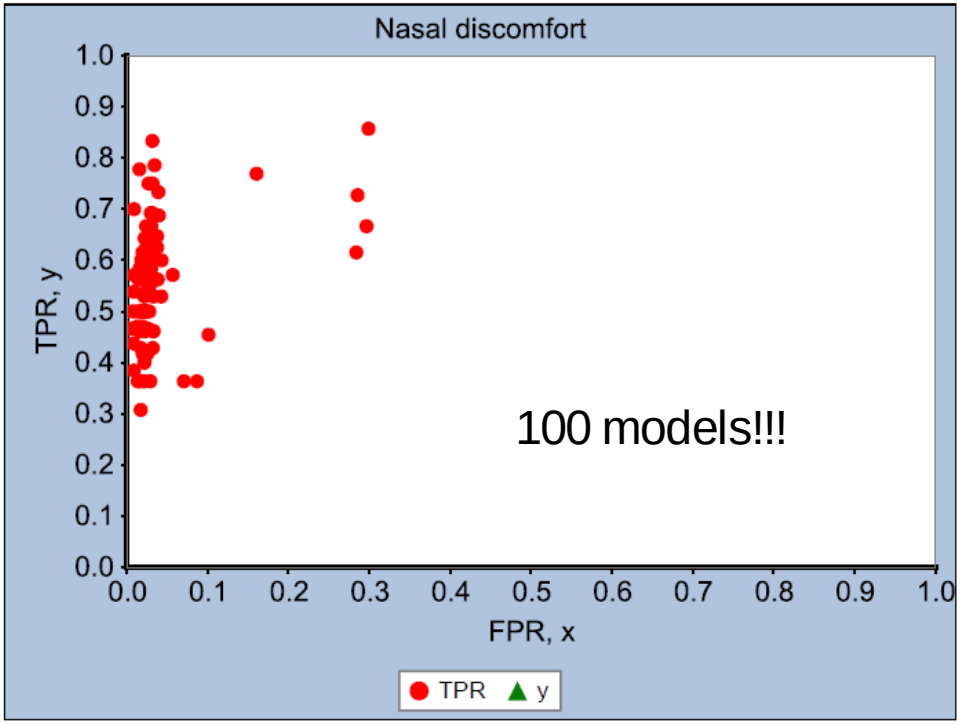
Analyzing the categories

Assessing model stability



Instable model

No correlation between true and false positives

This is fine

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The consequence

Prefer models with at least a 2:1 TP/FP-rate

Rank models based on their stability