# ADRIS

A New in silico Approach to Collect, Store, Mine, Simulate, and Visualize Pharmaco- and Toxicogenetic Information Related to Severe Adverse Drug Reactions (ADRs)

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# Today:

- **1. Introduction to ADRs**
- 2. Knowledge & Data Management: Focus on ADRs

- 3. ADRIS
- 4. Examples from ADRs Library

# TheraSTrat: Vision and Mission

### Vision

Bring the right drug to the right patient: Essentially free of serious ADRs.

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 Identify individual patients with predispositions for serious ADRs and withhold them from therapy with (a) offending drug(s).

### **Mission**

 Develop tools that help to make individualized drug safety a reality, in order to reduce the impact of ADRs on patients and on companies.

## **ADRs:** Traumatic for Affected Individuals



Drug-induced Hypersensitivity



Drug-induced Lyell- Syndrome



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Drug-induced Hepatitis

# **ADRs:** Predisposition of Individuals



#### • Why me?

Abacavir: Hypersensitivity	~	1:	20
Thiopurine: Myelotoxicity	~	1:	150
Rezulin: Liver toxicity	~	1:	15'000
Halothane: Liver toxicity	~	1:	35'000

- Am I the wrong patient?
- Do I have a predisposition?
- Can I avoid ADRs?
- Are there therapeutic alternatives?

Number of ADRs:	<ul> <li>Up to 7% hospitalized patienes</li> <li>Up to 2'200'000 patients per</li> <li>Up to 106'000 deaths per y</li> </ul>	ents er year ⁄ear
The big killers:	Cardiovascular	743'46(
	Cancer	529'904
	Stroke	150'508
	ADRs	106'000
	Pulmonary diseases 🛛 🗖	101'077
	Accidents	90'523
	Pneumonia	75'71
	Diabetes 🔹	53'894
Serious ADRs are	Diabetes	53'8

### **ADRs:** Lead to Market Withdrawals

Cerivastatin Rapacuronium Raplon Alosetron Astemizole Rezulin **Troglitazone** Cisapride Pemoline Cylert Tolcapone Tasmar Grepafloxacin Raxar Bromfenac Duract Mibefradil **Fenfluramine Dexfenfluramine Redux** Terfenadine

Lipobay Lotronex Hismanal Propulsid Posicor Pondimin Seldane

**Rhabdomyolysis Bronchospasm Ischemic Colitis Cardiac Arrhythmia Liver Toxicity Cardiac Arrhythmia Liver Toxicity Liver Toxicity** Long QT-Interval **Liver Toxicity Drug/Drug Interact.** Heart Valve Disease Heart Valve Disease **Cardiac Arrhythmia** 

Bayer Organon Glaxo-SK Jansen Warn.-Lamb. Jansen Abbott Roche Glaxo Wyeth Roche Wyeth Wyeth Hoechst M-R. Aug-2001/WW Mar-2001/US Nov-2000/US Jun-2002/US Mar-2000/US Mar-2000/US Sep-1999/US Nov-1998/EU Oct-1998/US Jul-1998/US Jun-1998/US Sep-1997/US Sep-1997/US Jan-1997/US

Financial I	osses due to mai	rket withdrawals	
Drug	Company	Clinical endpoint	Loss on return/year
Rezulin®	Warner-Lambert	Liver toxicity	US\$ ~ 2.0 Bill
Lipobay®	Bayer	Rhabdomyolysis	US\$ ~ 1.5 Bill
Duract®	Wyeth- Ayerst	Liver toxicity	US\$ ~1.0 Bill.
Discontinu	ed clinical develop	ment in phase III	US\$ Mio 500 - 800





#### Predispositions Multitude of possible risk factors: "Fingerprints"



# Knowledge / Data Management:

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# Focus on ADRs (Drug Safety)

Simulation?

# Knowledge Space (1/3)

### Function (amount) means everything

Function	DNA	RNA	Proteome	Drugs/ Metabolites/ End. Comp.	Confounding Factors
	Gene Variation	Gene Expression	Proteins Expression Modification	Interactions	Diet Environm. Disease
Normal	None	None	None	Normal	Pheno- copying
Increase	Duplications	Up	Up	Activation	Pheno copying
Decrease	SNP's Splicing Frameshifts	Down	Down Inactivation	Inhibition	Pheno copying
New	New Sequence Motifs	Expression of silent genes	New Motifs Altered Motifs	Haptens	Pheno copying

# Knowledge Space (2/3)

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### Very heterogeneous knowledge & data on ADRs

#### Chemical **Structures**

- Intermediates
- Metabolites
- Metabolic pathways
- Adducts
- Structural mimics
- 2D-Structures
- 3D-Structures
- Similarities

#### Targets

- Proteins
- DNA
- RNA
- Biomolecules
- Complexes
- Neo-Antigenes
- Functional mimics

 Genetics • Genes Alleles • SNP's Splice variants Amplifications Allele frequencies • Genotypes Haplotypes  $\overline{\langle}$  $\widehat{1}$  $\widehat{}$  $\widehat{1}$  Numeric values • Individuals • Future Endpoint • Km Clinical Patients data & • Vmax Toxicological Populations knowledge • T1/2 Functional Cohortes • AUC's Biochemical • ? • Ethnic groups Odd's Ratios • ? Mechanistical Controls Selectivities • ? • Kinetic

Sensitivities

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• ?







# ADRIS: Ontology (2/3)

#### Nodes contain: - node-specific data

- meta-data
- organized in properties
- live links to the original source data via internet or intranet.



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## ADRIS: Ontology (3/3)



Example 1: **Patient (Cohort) Individual Patient Patient Genotype** Alleles **Coded for Protein Catalyzed Process** Substrate Metabolite **Kinetics** 

# ADRIS: Ontology (3/3)

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Example 2: Compound Oxidation **Reactive Intermediate** Inactivation **Adduct Formation Adducted Protein** Autoantigenicity **Autoantibodies Target Protein: Autoantigen Clinical Endpoint** 



### **Ontology:** Examples from ADRs Library (1/5)

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### Troglitazone: Ontological analysis of knowledge space surrounding parent troglitazone

Views:

Simple



### **Ontology:** Examples from ADRs Library (1/5)

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### Troglitazone: Ontological analysis of knowledge space surrounding parent troglitazone

Views:

Medium



### **Ontology:** Examples from ADRs Library (1/5)

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### Troglitazone: Ontological analysis of knowledge space surrounding parent troglitazone

Views:

Complex







# **Ontology:** Examples from ADRs Library (4/5)

### **Troglitazone-dependent signal transduction**



### **Ontology:** Examples from ADRs Library (5/5)

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#### Single Patient & Primary Biliary Cirrhosis: Risk Profile



