

European Framework Programme 6 (2002-2006)

Innovative Medicines for Europe - InnoMed

Integrated Project: Predictive Toxicology – PredTox

EU FP6: Integrated Project “PredTox”



The EU FP6 PredTox (Predictive Toxicology) Project and Biomarker Identification Using an Integrative ‘omic Approach


Prof. Friedlieb Pfannkuch, MD
F. Hoffmann-La Roche Ltd. – for EFPIA

Timelines and Budget

EU FP6: Integrated Project "PredTox"

- Bid submitted: Nov-2004
- Official start: Oct-2005
- Contract signed: Dec-2005
- Official end: Jan-2009
- Budget: 8'000'000 €

CALL ID: FP6-2004-LIFESCIHEALTH-5 INTEGRATED PROJECT - INNO-MED



Proposal Full Title: **Innovative Medicines for Europe**

Proposal Acronym: **InnoMed**

DATE OF PREPARATION: 15 November 2004
 TYPE OF INSTRUMENT: INTEGRATED PROJECT
 THEMATIC PRIORITY: Life Sciences, genomics and biotechnology for health
 Call Identifier: FP6-2004-LIFESCIHEALTH-5
 Research area(s): LSH-2004-1.2.1-1 New approaches for accelerated development of new, safe and more effective medicines

LIST OF PARTICIPANTS: Summary (full list on page 2)

1	EFPIA	BE	16	JOP KCL	UK	31	NUID/UCD	IE
2	ROCHE	CH	17	UMJ	FI	32	PROTEOME	UK
3	ALTANA	DE	18	UnipG	IT	33	HU	TR
4	AVP	FR	19	GARCOA	GR	34	UCL	UK
5	BAYER	DE	20	Roskilde	DK	35	SOTON	UK
6	Boehringer	DE	21	AZ	SE	36	HFL	UK
7	EPB	NL	22	KTH	SE	37	AveD	DE
8	IRIS	FR	23	Ki	SE	38	AMERSHAM	NK
9	LELLY	UK	24	Novartis	CH	39	ART TIC	BE
10	MERCK	DE	25	Organon	NL	40	J&J	BE
11	Novo Nordisk	DK	26	Genentech	CH	41	Bowdler	UK
12	Pfizer	UK	27	KCL	UK	42	Carekron	FI
13	Schering	DE	28	RBM SpA	IT	43	MSD	UK
14	UNICLERZ	DE	29	CHU Toulouse	FR	44	EUFEPS	SE
15	CAPSANT	UK	30	GSK	UK			

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The 20 Partners of the PredTox Consortium

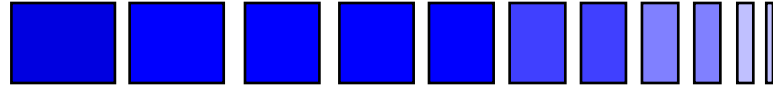
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Nycomed (former: Altana)
Bayer Schering Pharma (former: Bayer)
Boehringer-Ingelheim
Johnson & Johnson
Lilly (B) (Facility closed) - no EU funds
Merck-Serono (former: Merck KGaA)
Novartis
Novo-Nordisk
Schering-Plough (former: Organon)
Roche
Sanofi-Aventis (D)
Sanofi-Aventis (F)
Bayer Schering Pharma (former: Schering)
Merck-Serono (former: Serono)
Servier
University of Wuerzburg
Univ. College Dublin
University Hacettepe
Genedata
Bio-Rad (former: Ciphergen) - no EU funds

Ultimate Goal of the Project

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- **More informed decision making earlier in preclinical safety evaluation by combining results from**
 - ‘omics Technologies together with
 - Conventional toxicology methods
- **Development of scientists within Systems Toxicology**
- **Regulatory Authorities to review the approach**

Compound Selection

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- **14 'Failed' drug candidates from participating companies**
 - A major component of the failure was due to preclinical liver and / or kidney toxicity findings
- **2 Reference liver and kidney toxins**
 - Gentamicin
 - Troglitazon

Project Overview

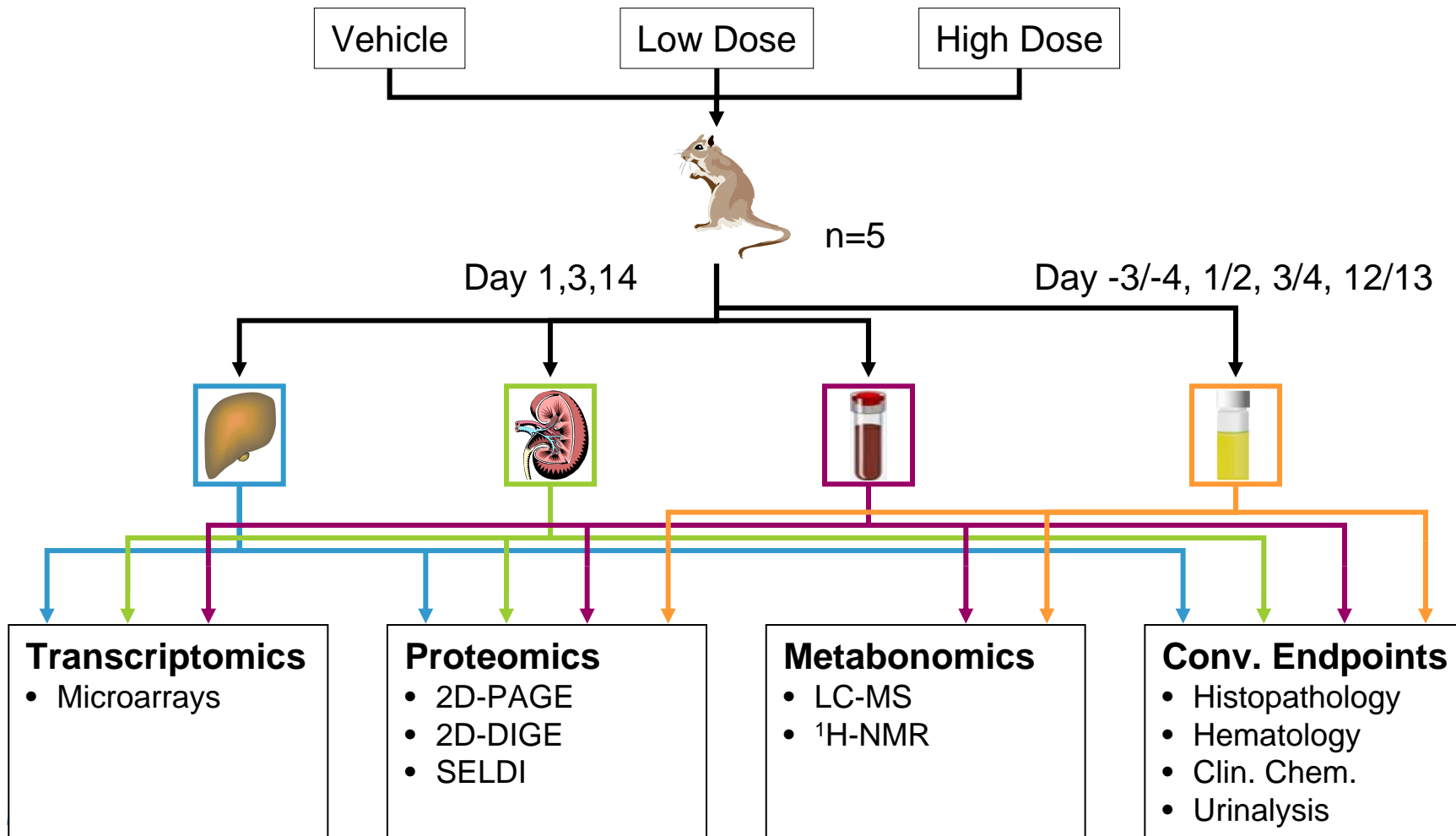
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- **In vivo animal studies in rats**
- **Investigations**
 - **Primary targets: liver, kidney, blood, urine**
 - **“Classical” endpoints**
 - Clinical chemistry, histopathology, including Peer Review
 - **“omics”-technologies**
 - Transcriptomics, proteomics, metabonomics
- **Data management**
 - Design, construction and management of a relational Database
 - Data processing, development of biostatistical models, data integration and biological interpretation
- **Mechanistic investigation and biomarker identification**

Study Design and Investigations

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Structure of the Database

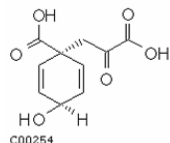
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Sample

Treatment and Compounds

- Compound
- Compound class
- Concentration
- Treatment time
- Dosing route
- Dosing frequency
- Vehicle
- Protocols
- ...



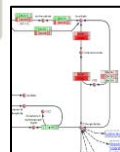
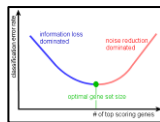
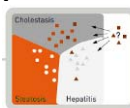
Animals

- Species
- Strain
- Sex
- Age
- Weight
- Husbandry
- Protocols
- ...



MOA, Tox Prediction

- MOA classification
- Biomarker candidates
- Tox Mechanism
- Tox Prediction
- ...

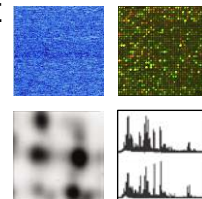


Measurements and Observations

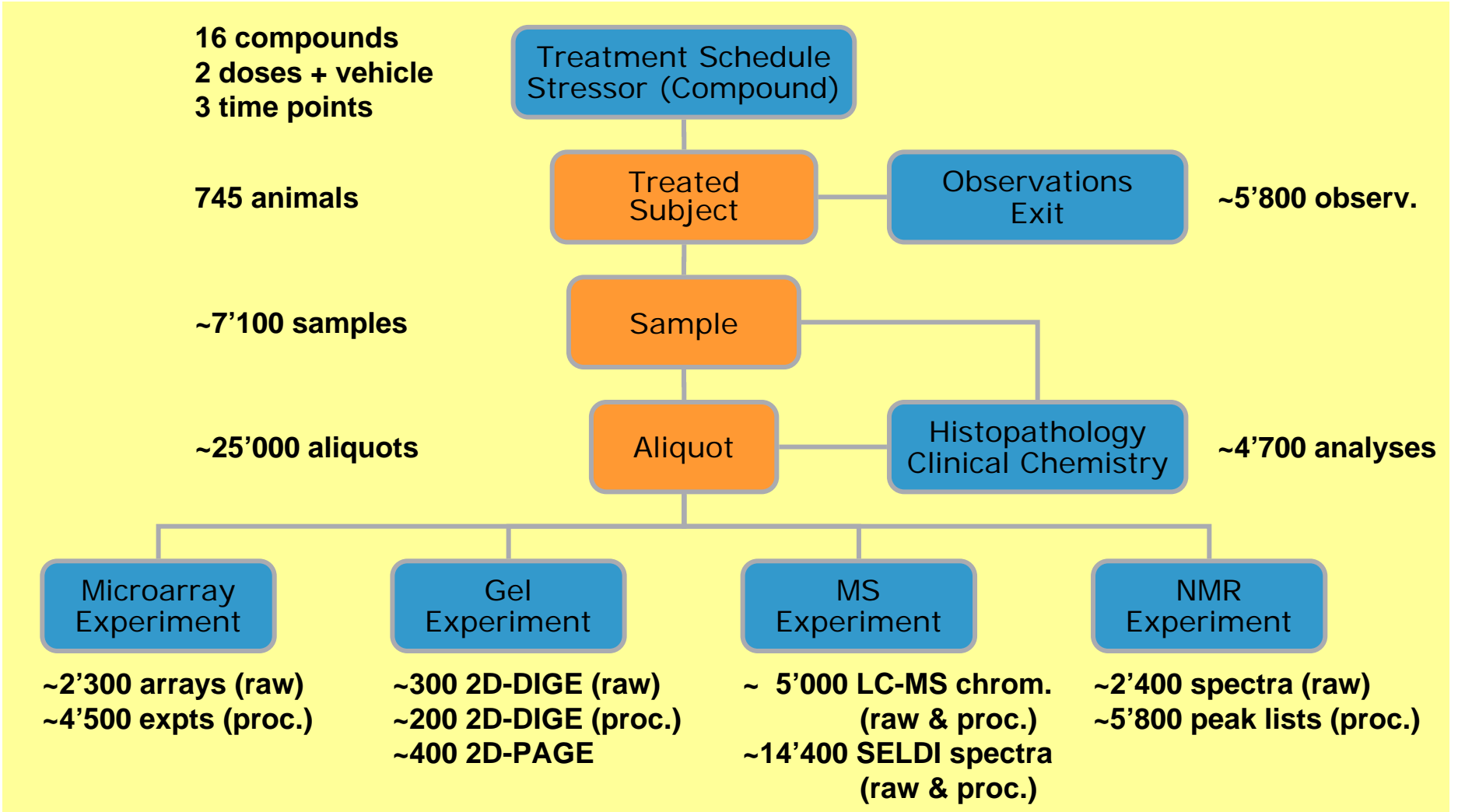
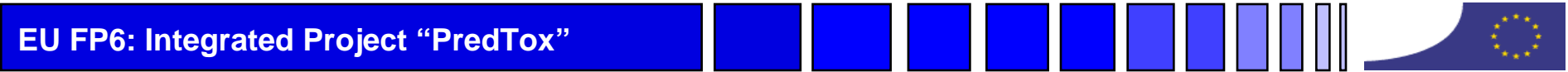
- Live animal observations
- Sample handling
- Clinical endpoints
- Histopathology
- Serum chemistry
- Urine chemistry
- Hematology
- Protocols
- ...

-omics data

- 1 channel data
- 2D-PAGE, 2D-DIGE
- LC/MS, GC/MS, SELDI
- NMR
- Raw data
- Processed data
- Expression values
- Quality parameters
- Protocols and algorithms
- Annotations
- ...



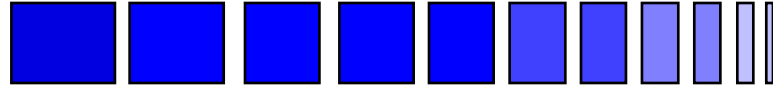
Database – Data Collection Has Been Completed



Data Analysis ... Within Individual Study

(within and across technologies)

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- **Is there a concordance between technologies and sample types?**
- **Can a potential of toxicity be identified earlier or at lower dose than from traditional endpoints?**
- **What is the mechanistic understanding of the changes?**

Data Analysis ... Across Studies

(within and across technologies)

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- **Do the compounds profiles cluster according to their observed pathologies?**
- **Which part of the data is the most determining for these separations and might contain ...**
- **Potential biomarkers?**
- **What combination of methods / technologies delivers best predictive results?**

Approach of Project Evaluation

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- **Compounds of similar *histopathological* effects grouped in order to**
 - assist identification of potential biomarkers and
 - allow mechanistic hypotheses to be generated
- **Expert Working Groups (EWGs) established**
 - Liver Hypertrophy
 - Bile Duct Damage / Necrosis (BDN)
 - Nephrotoxicity

Mechanistic Investigations - 1

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- **Hepatotoxicity**

- **Potential markers for hepatotoxic endpoints identified**

- to be analyzed in samples from *in vivo* studies
 - Further experiments depending on results from transcriptomics' cross-study comparison

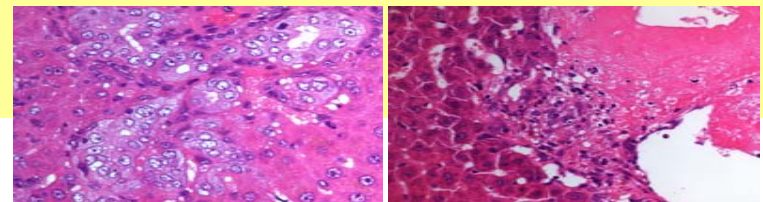
- **Nephrotoxicity**

- **Set of promising gene-based biomarkers identified**

- Currently analyzed in tissues obtained from *in vivo* studies

- **ELISA for urinary kidney biomarkers**

- Analysis of urine samples from *in vivo* studies



H_d14 (42)

H_d14 (45)

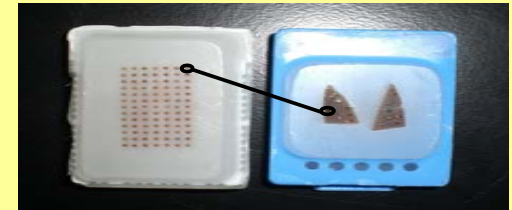
Mechanistic Investigations - 2

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- **Tissue microarrays**

- Established to make best use of the limited amount of tissue available
- to confirm gene-based markers
 - by immunohistochemistry and / or
 - *in situ* hybridization



- **Ultimate aim: Design of sensitive multiplex assays for nephro- and hepatotoxicity**

- Low density custom arrays
- Multiplex ELISA

Experiences with the Project

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- **Strengths**

- **Sharing of**

- Expertise
- Methods and know-how
- Costs

- **Closer co-operation of Industry and Academia**

- **Inclusion of Small- and Mid-size Enterprises - SME's**

- Better solutions faster

- **Weaknesses**

- **IP issues**

- **Hidden competition – No frank data sharing**

- **Small groups do not participate due to economical reasons**

Threats Mastered so far ...

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- **Industry specifics**
 - **Merger & Acquisitions – Internal reorganizations**
 - e.g. Changing the research focus
 - **Decision taking and internal prioritization**
 - **Project is driven by individual people not their organizations**
 - Two-front battle with project and company goals
 - Personal development / change of personal interest
- **Result driven approach vs. Freedom of research**
 - Adopting new scientific approaches is hardly feasible
 - Though project management puts pressure on academics
- **The role of the public partner**
 - **Requirements of the European Commission and of many stakeholders within the European Union are to be considered**
 - **Inherent bureaucracy**

Summary

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- **in vivo Studies and 'omics investigations accomplished and in major parts reported**
- **Bioinformatics evaluation in progress**
- **Confirmatory experiments and subsequent activities by the academic partners initiated**
- **All consortium members committed**
- **Project is on schedule**

www.innomed-predtox.com

The PredTox Consortium

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