New Translational Biomarkers for Drug Induced Organ Injury - The IMI SAFE-T Project

*Safer And Faster Evidence-based Translation*

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Outline

- Background
- SAFE-T objectives
- Structure and deliverables
- Biomarker qualification process
- Achievements
- Challenges
- Next steps
SAFE-T: because safety matters...

Between the **years 1900 and 2000**, average life expectancy has increased from **45 to 77 years of age**

*Part of this is due to innovative medicines*

*Lazarou J et al. (1998) JAMA; 279(15):1200-1205*
SAFE-T: because safety matters...

• However, making medicines safer is still one of the key challenges in pharmaceutical development

  ➢ In the US, fatal Adverse Drug Reactions (ADRs) are the 4th to 6th leading cause of death*
  ➢ Incidence has been stable for more than 30 years*
  ➢ Costs directly attributable to ADRs may lead to an additional $1.56 to $4 billion in direct hospital costs per year in the US*

SAFE-T: because safety matters...

• For many serious drug side effects, tools are lacking for adequate
  - prediction
  - detection
  - monitoring

• This is particularly the case for drug induced injury to the
  - kidney
  - liver
  - vascular system
Drug safety: room for improvement

The economic perspective

- Around 90% of compounds entering clinical development fail

- 30% of these failures are due to clinical safety and toxicology

Drug safety: need for improvement

The patient perspective

Drug induced liver injury (DILI)
Worst cases transplantation, death

Drug induced kidney injury (DIKI)
Worst cases hemodialysis, transplantation, death

Drug induced vascular injury (DIVI)
Worst cases multi-organ failure, death
IMI SAFE-T Consortium

Objectives

• To **evaluate utility** of safety biomarkers for detecting, assessing, and monitoring drug induced kidney, liver, and vascular injury **in humans**.

• To **develop assays** and devices for clinical application of safety biomarkers

• To compile enough evidence to qualify safety biomarkers for **regulatory decision making in clinical drug development** and in a **translational context**

• To gain evidence for how safety biomarkers may also be used in the **diagnosis of diseases** and in clinical practice
Biomarker attributes of interest

- **Patient level**
  - Lower injury threshold
  - Earlier time to onset
  - Larger extent of changes
  - Improved specificity
  - Better suited to monitor and predict clinical course
  - Better suited to assess causality

- **Population level**
  - Earlier and more specific signal detection in clinical development programs
  - Improved mechanistic insight
  - Superior in terms of identifying underlying pathology
  - Better suited to predict human risk from animal toxicity
Key challenges for biomarker qualification

- Substantial background variability in initial candidate markers
- Biomarker response varies across different populations
- Large initial number of biomarker candidates requires substantial sample volumes to be taken
- Key target responses, i.e. specific adverse drug reactions, suitable and accessible for qualification are overall very rare

- Large sample sizes are required
- Multitude of patient populations need to be included

Qualification cannot be achieved by one company alone
SAFE-T participants

EfpiA

Academia

NMI

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

CSIC

THE TEL AVIV SOURSKY MEDICAL CENTER

Universitätsklinikum Leipzig

Universitätsklinikum Aachen

SMEs

FIRALIS

INTERFACE EUROPE

Argutus Medical

IMMUNOLOGIE

Advisors

European Medicines Agency

FDA

Sponsors

Collaborators

Critical Path Institute
SAFE-T structure and deliverables

- Evidence-based decision making
- More reliable causality assessment
- Better mechanistic understanding
- Safer translation to clinical development
- Earlier and more specific signal detection
- Enhanced clinical monitoring

- Improved patient safety
- Reduced attrition rates
- Accelerated and safe approval of innovative medicines
Funding and timing

Financing

- IMI funding: 13.9 mio EUR
- EFPIA contribution, mainly in kind: 17.7 mio EUR
- Contribution academia/SME: 4.1 mio EUR
- Total project cost: 35.7 mio EUR

Timing:

- Starting date: June 15, 2009
- Duration: 5 years
Biomarker qualification process

Elements and process flow

- **DILI BM step 1 list**
  - Literature
  - Databases
  - SAFE-T sources

- **Select**
  - Healthy volunteers
  - Patients non-liver disease
  - Patients liver disease
  - Patients hepatotoxic drugs

- **Samples**

- **DILI BM step 2 list**
  - Evaluation
  - DILI BM step 2 list

- **Exploratory phase**
  - Regulatory advice
  - Assay availability / development
  - DILI BM step 3 list
  - Assay / stat analysis / select BMs
  - DILI BM step 4 list
  - Assay / stat analysis / select BMs

- **Background variability**
  - Thresholds

- **Confirmatory phase**
  - Regulatory advice
  - Assay / stat analysis / select BMs
  - DILI BM final list

- **Qualification**

- **Submit to health authorities**

- **Regulatory approval**

- **Q2 2009**
- **Q1 2010**
- **Q2 2011**
- **Q2 2014**
DILI biomarker candidates selected for qualification

<table>
<thead>
<tr>
<th>Serum or Plasma Marker</th>
<th>Assays</th>
<th>Liver specificity</th>
<th>Human data</th>
<th>Pathology</th>
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<tbody>
<tr>
<td>albumin mRNA</td>
<td>RT-PCR</td>
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<td>yes</td>
<td>hepatocellular damage</td>
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<td>Microglobulin precursor (Ambp) mRNA</td>
<td>RT-PCR</td>
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<td>Conjugated/unconjugated bile acids</td>
<td>LC-MS</td>
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<td>only in tissues</td>
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<td>high mobility group box 1 (HMGB1)</td>
<td>LC-MS</td>
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<td>Immuno</td>
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<td>alpha fetoprotein (AFP)</td>
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<td>yes</td>
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<td>Arginase 1</td>
<td>LMX</td>
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<td>yes</td>
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<td>Colony stimulating factor receptor (CSF1R)</td>
<td></td>
<td>not specific</td>
<td>yes</td>
<td>inflammation</td>
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<tr>
<td>F-protein (HPPD)</td>
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<td>highly specific</td>
<td>yes</td>
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<td>Glutathione S transferase alpha (GSTa)</td>
<td></td>
<td>specific</td>
<td>yes</td>
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<tr>
<td>Leukocyte cell-derived chemotaxin 2 (LECT2)</td>
<td></td>
<td>not specific</td>
<td>yes</td>
<td>inflammation</td>
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<tr>
<td>ST6Gal 1</td>
<td></td>
<td>specific</td>
<td>yes</td>
<td>inflammation</td>
</tr>
<tr>
<td>Osteopontin</td>
<td></td>
<td>not specific</td>
<td>yes</td>
<td>inflammation</td>
</tr>
<tr>
<td>Paraoxonase 1 (PON1)</td>
<td></td>
<td>not specific</td>
<td>yes</td>
<td>steatosis</td>
</tr>
<tr>
<td>Prothrombin</td>
<td></td>
<td>not specific</td>
<td>yes</td>
<td>steatosis</td>
</tr>
<tr>
<td>Regucalcin (RGN)</td>
<td></td>
<td>specific</td>
<td>only in tissues</td>
<td>hepatocellular damage</td>
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<tr>
<td>ALT1/2</td>
<td></td>
<td>highly specific</td>
<td>yes</td>
<td>hepatocellular damage</td>
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<tr>
<td>Glutamate dehydrogenase (GLUD, GLDH)</td>
<td>Enzyme</td>
<td>specific</td>
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<td>hepatocellular damage</td>
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<td>Purine nucleoside phosphorylase (PNP)</td>
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<td>specific</td>
<td>no</td>
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<td>Glutathione S transferase alpha (GSTa)</td>
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<td>specific</td>
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<tr>
<td>Malate dehydrogenase (MDH)</td>
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Composite disease markers to be assessed in addition: ActiTest™, Fibrotest™, SteatoTest™
DILI biomarker qualification:
The „population mosaic“
SAFE-T achievements

- Generic qualification strategy defined
- Biomarker candidates prioritised, assay development ongoing
- Study protocols for prospective DILI studies submitted for IRB review
- Completed HV study to assess within and between subject variability (Sanofi Aventis) and access to HV samples (AstraZeneca)
- Set up central biobank for sample storage
- Initiated regulatory interactions via briefing meetings with EMA/FDA
- Established collaboration with Predictive Safety Testing Consortium (PSTC)
### Key challenges for the consortium

<table>
<thead>
<tr>
<th>Biomarker candidates</th>
<th>How addressed?</th>
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<tbody>
<tr>
<td>• Out of scope:</td>
<td>• Covered by SAEC, DILIN, others</td>
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<tr>
<td>○ Genetic susceptibility markers</td>
<td></td>
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<tr>
<td>○ Preclinical assay validation</td>
<td></td>
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<tr>
<td>○ Preclinical biomarker discovery</td>
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<tr>
<td>• Close collaboration with PSTC</td>
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<tr>
<td>• Lack of functional and susceptibility marker candidates</td>
<td>• Biomarker discovery based on human cases from SAFE-T clinical studies, using mass spec and protein antibody array analyses of plasma samples</td>
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<tr>
<td>Methodology</td>
<td>• Identify suitable marker panels</td>
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<tr>
<td>• Due to low DILI prevalence, any new marker will have a low PPV.</td>
<td></td>
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<tr>
<td>○ Improvement is mainly needed in specificity rather than sensitivity.</td>
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<tr>
<td>○ Added value of new markers may be primarily as part of panels</td>
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<tr>
<td>• Use advanced statistical methods such as lasso regression and gradient boosted models</td>
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<tr>
<td>Logistics</td>
<td>• Add two studies in high risk patients</td>
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<tr>
<td>• Access to DILI cases</td>
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<tr>
<td>• Sampling requirements need to be aligned across different SAFE-T working groups</td>
<td></td>
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<tr>
<td>• Sampling to be seamlessly integrated into standard clinical trial workflows</td>
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<tr>
<td>• Dedicated cross-work package team to ensure alignment</td>
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<tr>
<td>• Provide standard protocol and ICF text sections</td>
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<tr>
<td>• Simplify sample collection, processing, and shipment</td>
<td></td>
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<tr>
<td>• Use samples available already</td>
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</table>
SAFE-T: next steps

- Set up consortium database
- Initiate prospective studies
- Include sampling into standard clinical trials
- Finalize agreement with PSTC
## Acknowledgements

(Incomplete) SAFE-T participant list, *team leaders*

<table>
<thead>
<tr>
<th>Name</th>
<th>Company</th>
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Thanks for your attention…

…I’m happy to take your questions

www.imi-safe-t.eu

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