Translation of Safety Biomarkers in the Clinical Setting

Michael Merz
Novartis Institutes for BioMedical Research

Ina Schuppe Koistinen
Global Safety Assessment, AstraZeneca R&D, Sweden

Coordinators IMI SAFE-T consortium

24th Annual EuroMeeting
26-28 March 2012
Copenhagen, Denmark
Disclaimer

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to Drug Information Association, Inc. (“DIA”), its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.

These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. Drug Information Association, DIA and DIA logo are registered trademarks or trademarks of Drug Information Association Inc. All other trademarks are the property of their respective owners.
Outline

• IMI SAFE-T Consortium: brief overview
• Status 2012
• Clinical biomarker qualification program
• Focus drug-induced liver injury: biomarker candidates
• Initial experimental results
• Collaborations
The IMI SAFE-T* Consortium

Scope

*Safer And Faster Evidence-based Translation

Three organs needing better clinical monitoring of drug-induced injuries:

- **Kidney**: current standards increase only once 50-60% of kidney function is lost.

- **Liver**: current standards are not sufficiently sensitive and specific and do not adequately discriminate adaptors from patients at high risk to develop liver failure.

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
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
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: Five years
Biomarker qualification process

*Initial challenges*

- Pathologies of interest
- Target populations
- Incidence of target disease
- Required sample sizes
- Biomarker identification
- Drug selection
- Sample matrices and volumes
- Sampling and shipment processes
- Number and design of clinical studies
- Prospective studies
- EFPIA studies with add-on sampling
- Retrospective samples
- Data capture, management, analysis
- Investigative sites
- Type of in-kind support required
- Capabilities
- Technology platform
- Extent of in-kind support required
- Database costs
- Data entry resources
- Recruitment rates
- Number of patients needed
- Number of study sites needed
- Assay identification
- Assay development
- Data management resources
- Investigative sites with add-on sampling
- Retrospective samples
- Capabilities
- Recruitment rates
- Number of patients needed
- Number of study sites needed
Key achievements at project half-time

- Biomarker candidates prioritised, assay development well advanced
- Central biobank for sample storage up and running
- Database and data capture system up and running
- Academic sites: **17 prospective clinical studies initiated**
- EFPIA partners:
  - Completed SAFE-T studies: 2
  - Retrospective samples: >6500 patients from 4 studies
  - Ongoing add-on sampling: 3 studies
  - Submitted or under preparation: 5 studies
- Initiated regulatory interactions via briefing meetings with EMA/FDA
- Established collaboration with Predictive Safety Testing Consortium (PSTC)
SAFE-T biobank: up and running

Clinical partners
- Patient / sample codes
- Guidelines for sample collection and processing, shipment instructions

Samples

Regulatory requirements group
- SOPs, informed consent
- Patient information

Data analysis group
- Approval of sample release

Sample approval team

Biomarker assay group
- Sample request

10 studies, >60,000 aliquots
- 29 studies planned
- 1538 aliquots

SAFE-T biobank: up and running

24th Annual EuroMeeting Copenhagen 2012
SAFE-T database: up and running
DILI biomarkers – status of assay development

<table>
<thead>
<tr>
<th>Candidate biomarker</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>miRNA 122</td>
<td></td>
</tr>
<tr>
<td>albumin mRNA</td>
<td></td>
</tr>
<tr>
<td>Microglobulin precursor (Ambp) mRNA</td>
<td></td>
</tr>
<tr>
<td><strong>High mobility group box 1 (acetylated vs. non-acetylated)</strong></td>
<td><strong>Ready for sample screening</strong></td>
</tr>
<tr>
<td>Conjugated/unconjugated bile acids</td>
<td></td>
</tr>
<tr>
<td>High mobility group box 1 (acetylated vs. non-acetylated)</td>
<td></td>
</tr>
<tr>
<td>ALT 1 &amp; 2, isoform specific</td>
<td></td>
</tr>
<tr>
<td>F-protein (HPPD)</td>
<td></td>
</tr>
<tr>
<td>Arginase 1</td>
<td></td>
</tr>
<tr>
<td>Keratin 18 (caspase cleaved &amp; intact)</td>
<td><strong>Optimization phase</strong></td>
</tr>
<tr>
<td>Alpha fetoprotein (AFP)</td>
<td></td>
</tr>
<tr>
<td>Regucalcin (RGN)</td>
<td></td>
</tr>
<tr>
<td>Glutathione S-Transferase (GST-alpha)</td>
<td></td>
</tr>
<tr>
<td>ST6gal I</td>
<td></td>
</tr>
<tr>
<td>Osteopontin</td>
<td></td>
</tr>
<tr>
<td>Colony stimulating factor receptor (CSF1R)</td>
<td></td>
</tr>
<tr>
<td>Paraoxonase 1 (PON1)</td>
<td></td>
</tr>
<tr>
<td>Prothrombin</td>
<td></td>
</tr>
<tr>
<td>LECT2</td>
<td></td>
</tr>
<tr>
<td>Glutamate dehydrogenase (GLUD, GLDH)</td>
<td><strong>Ready for small sample sizes</strong></td>
</tr>
<tr>
<td>Purine nucleoside phosphorylase (PNP)</td>
<td></td>
</tr>
<tr>
<td>Malate dehydrogenase (MDH)</td>
<td></td>
</tr>
<tr>
<td>Sorbitol dehydrogenase (SDH)</td>
<td></td>
</tr>
<tr>
<td>ALT1/2, isoform specific</td>
<td></td>
</tr>
</tbody>
</table>

Legend:
- Green: Ready for sample screening
- Yellow: Ready for small sample sizes
- Orange: Optimization phase
- Red: In development
- Dark Red: Development necessary
HMGB1 and Cytokeratin 18

Mechanism based biomarkers

Apoptosis:
- Keratin-18 – intermediate filament protein / structural integrity
- Is cleared by caspases
- Fragment released into blood
- Full length K18 passively released during necrosis

Necrosis and Inflammation:
- HMGB1 – chromatin binding protein
- Passive released by necrotic cells
- Active released by activated immune cells (hyper-acetylated (Lys NLS))
- Cytokine activity (TLR/RAGE)

Antoine DJ et al., 2010 Mol Med
Antoine DJ et al., 2009 Toxicol Sci
Patients post acetaminophen overdose

Markers for inflammation, necrosis, and apoptosis

Association with King‘s College Criteria

Based on Antoine DJ et al., 2012 J Hepat

- Acetylated HMGB1 may be a prognostic DILI marker, indicating extent of inflammation
- Caspase cleaved cytokeratin 18 may have value as a prognostic DILI marker, indicating involvement of apoptosis as protective mechanism
Parallel to *qualification*: DILI biomarker *discovery*

**Why?**
- Biomarker candidates do not cover all objectives of SAFE-T DILI WP
  - Lack of susceptibility markers
  - Lack of sensitive functional markers, some pathologies poorly represented
  - Most markers identified in pre-clinical models

**How?**
- Based on human DILI cases from SAFE-T clinical studies
- Characteristic changes in serum proteome and metabolome expected
  - Mass spec and protein antibody array analyses of plasma samples planned
- Genetic analysis not planned, but possible collaboration with iDILIC
Collaboration

Key to success

• SAFE-T is collaborating closely with C-Path’s Predictive Safety Testing Consortium (PSTC), utilizing synergies and preventing overlaps

• There may be more opportunities to expand collaboration, helping to increase efficiency and maximize output
Conclusions

- Qualification of new safety biomarkers can best be done in a setting of large scale pre-competitive collaborations such as the IMI-SAFE-T consortium, PSTC, and others alike.
- The IMI SAFE-T consortium has made significant progress during the past 2.5 years.
- Consortium systems and processes for sample collection, processing, storage, shipment, and analysis have been set up and are running well.
- Data capture, storage, management, and analysis tools are in place.
- Seventeen prospective clinical studies have been initiated, but need to increase recruitment.
- SAFE-T may serve as an encouraging example to establish further precompetitive collaborations focusing on drug safety.
Acknowledgements

SAFE-T consortium

Kevin Park
Neil French
Daniel Antoine

Hannes Planatscher
Jens Goepfert
Nicole Schneiderhan-Marra

Thomas Joos

Teresa Padro
Lina Badimon

24th Annual EuroMeeting Copenhagen 2012