Translation of Safety Biomarkers in the Clinical Setting

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Outline

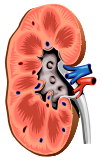
- IMI SAFE-T Consortium: brief overview
- Status 2012
- Clinical biomarker qualification program
- Focus drug-induced liver injury: biomarker candidates
- Initial experimental results
- Collaborations

The IMI SAFE-T* Consortium

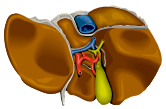
Scope

*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.

Vascular System: currently no biomarkers available for drug-induced vascular injury in human.

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

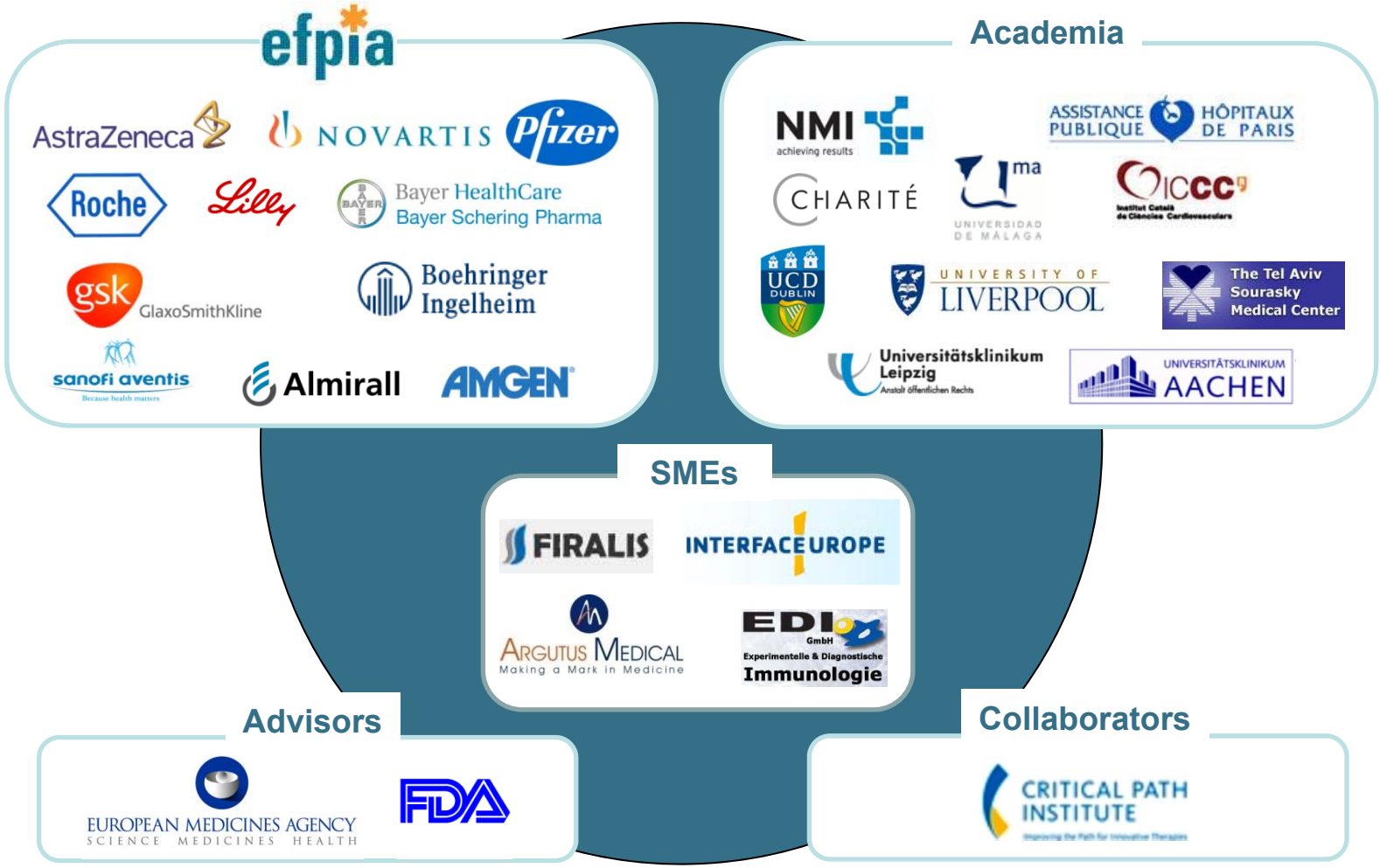
Key challenges for biomarker qualification

- 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



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

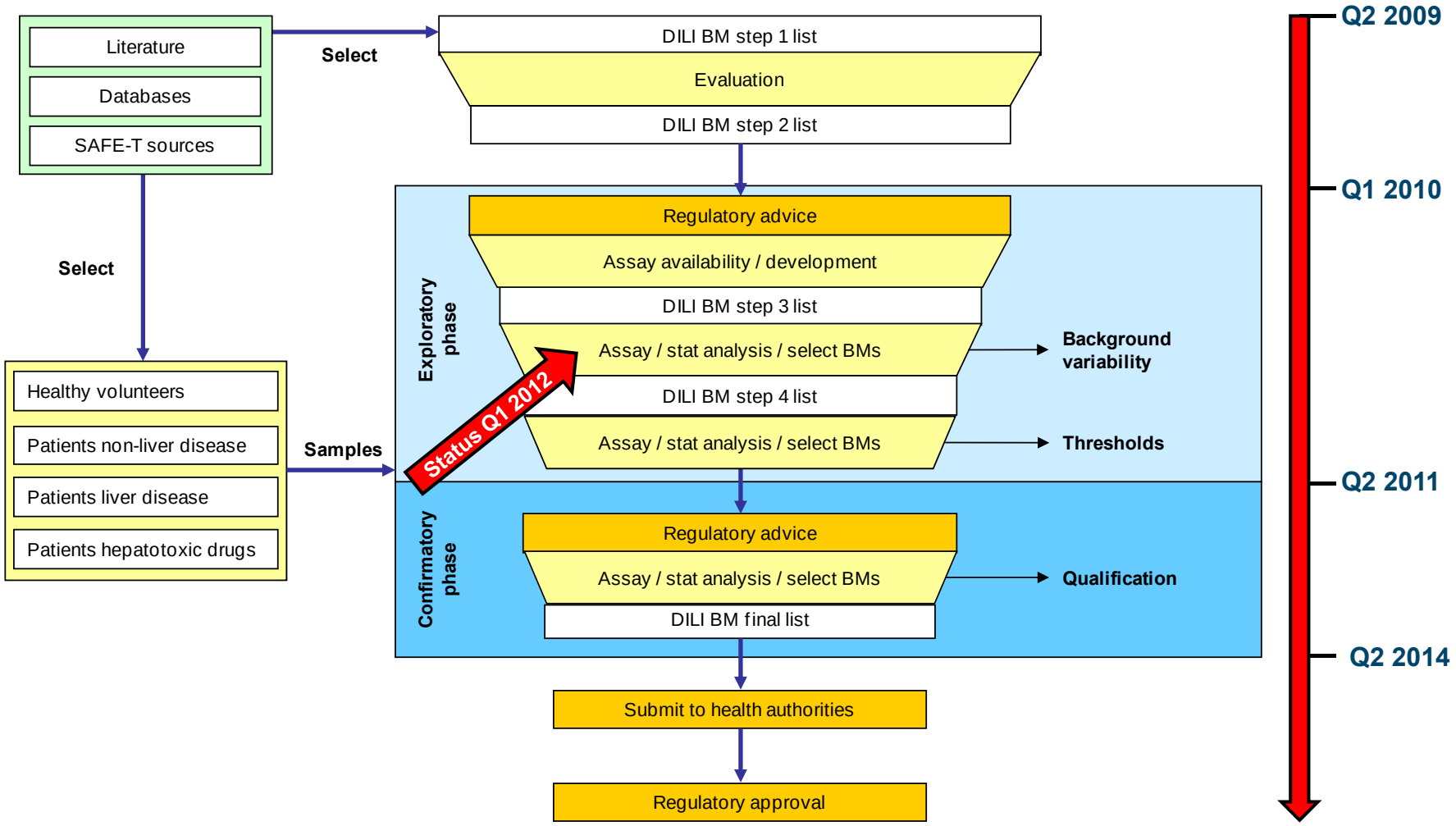
- Total project cost: 35.7 mio EUR

Timing:

- Starting date: June 15, 2009
- Duration: Five years

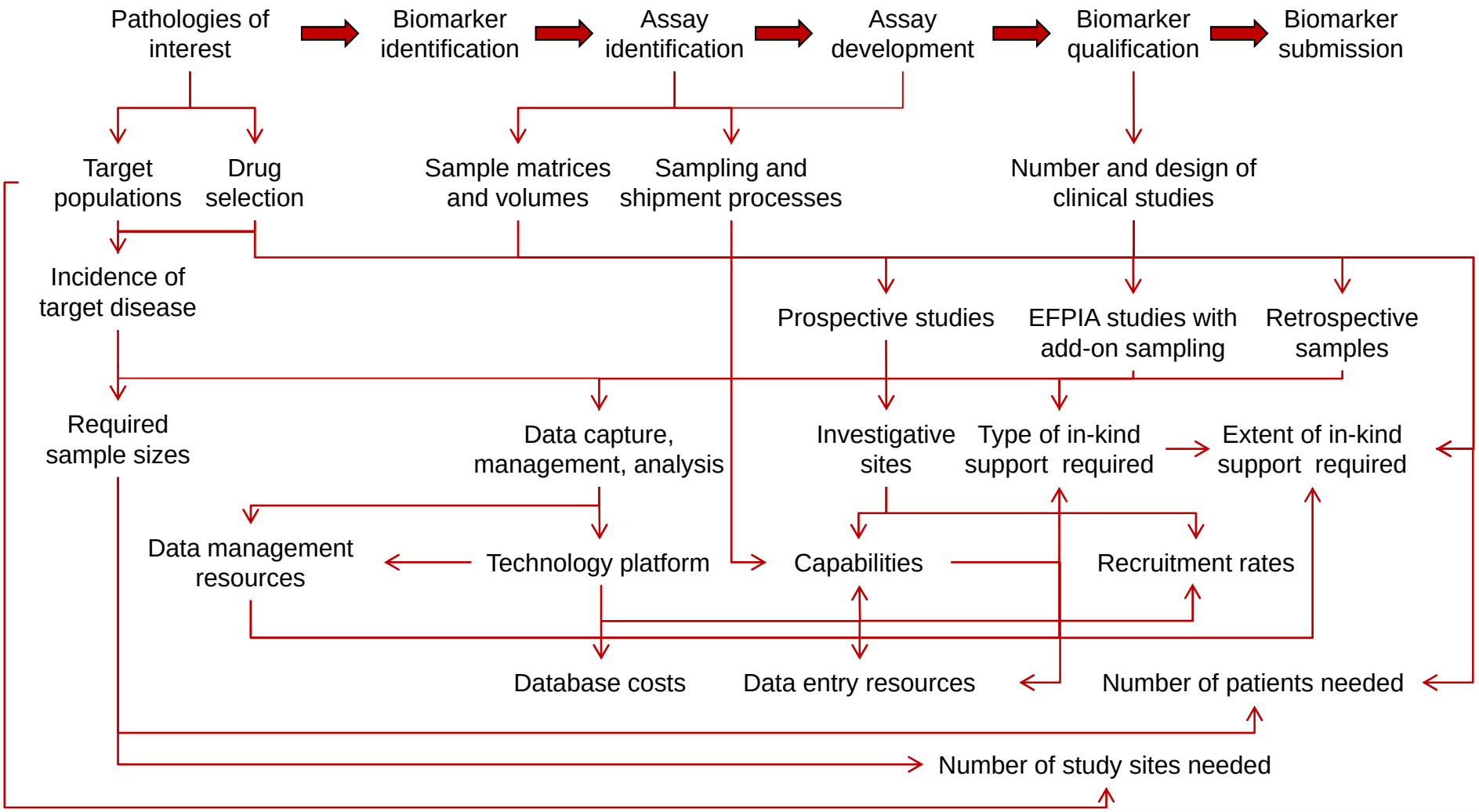
SAFE-T Biomarker qualification process

Elements and process flow



Biomarker qualification process

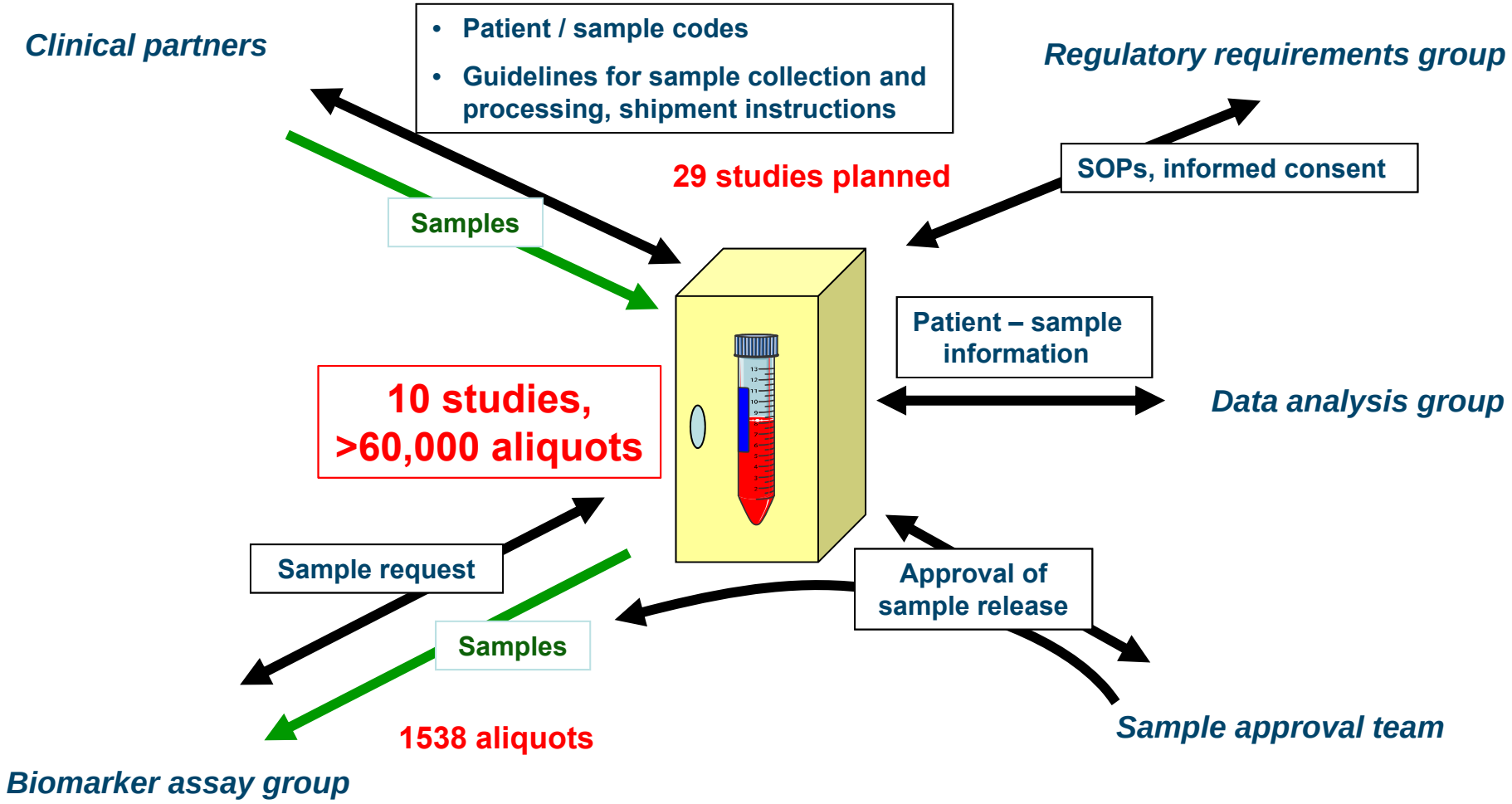
Initial challenges



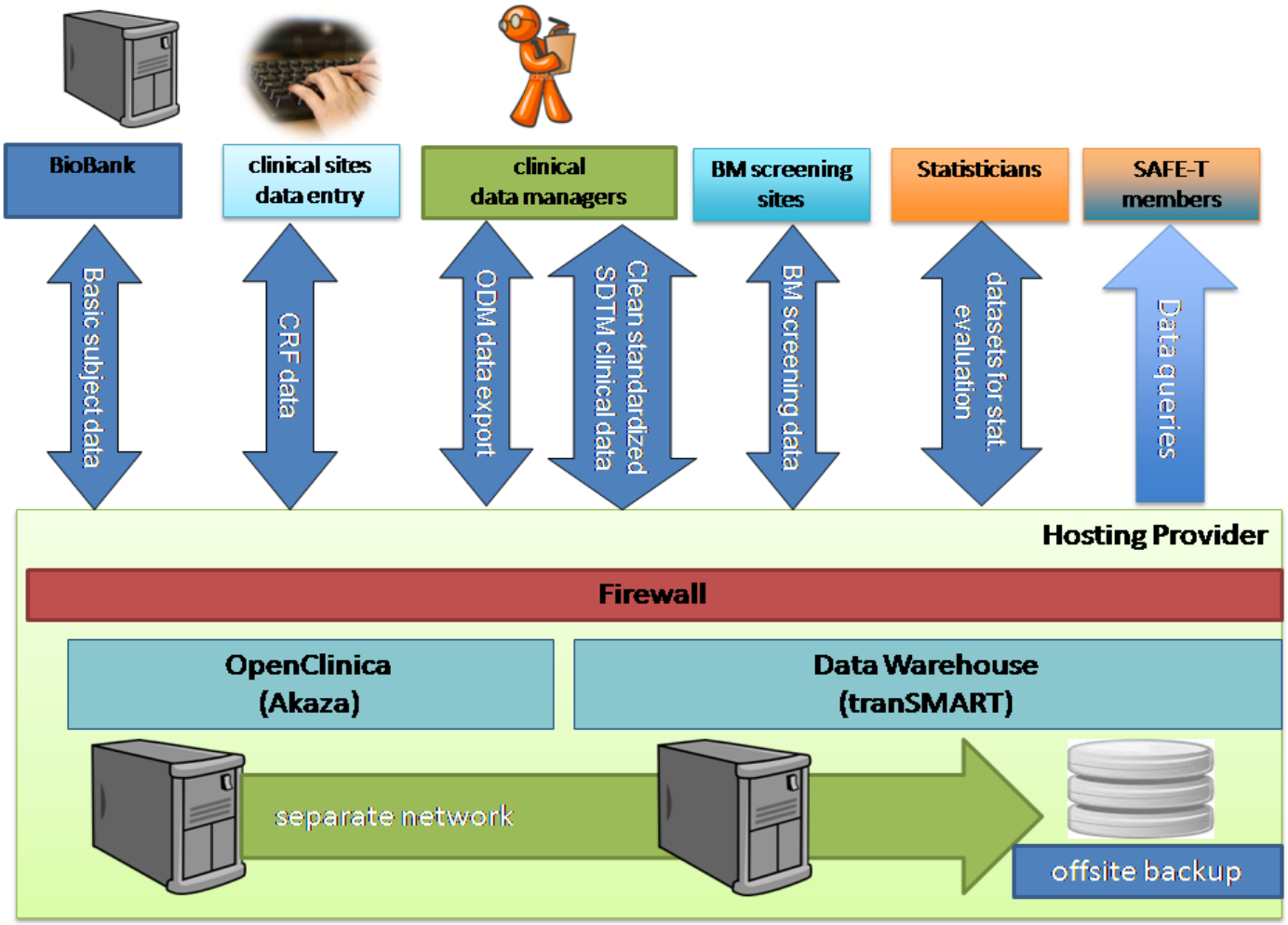
Key achievements at project half-time

- 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



SAFE-T database: up and running



DILI biomarkers – status of assay development

	Candidate biomarker	Status
RNA	miRNA 122	
	albumin mRNA	
	Microglobulin precursor (Ambp) mRNA	
LCMS	High mobility group box 1 (acetylated vs. non-acetylated)	
	Conjugated/unconjugated bile acids	
Immunoassay	High mobility group box 1 (acetylated vs. non-acetylated)	
	ALT 1 & 2, isoform specific	
	F-protein (HPPD)	
	Arginase 1	
	Keratin 18 (caspase cleaved & intact)	
	Alpha fetoprotein (AFP)	
	Regucalcin (RGN)	
	Glutathione S-Transferase (GST-alpha)	
	ST6gal I	
	Osteopontin	
	Colony stimulating factor receptor (CSF1R)	
	Paraoxonase 1 (PON1)	
	Prothrombin	
	LECT2	
Activity assay	Glutamate dehydrogenase (GLUD, GLDH)	
	Purine nucleoside phosphorylase (PNP)	
	Malate dehydrogenase (MDH)	
	Sorbitol dehydrogenase (SDH)	
	ALT1/2, isoform specific	

- Ready for sample screening
- Ready for small sample sizes
- Optimization phase
- In development
- Development necessary

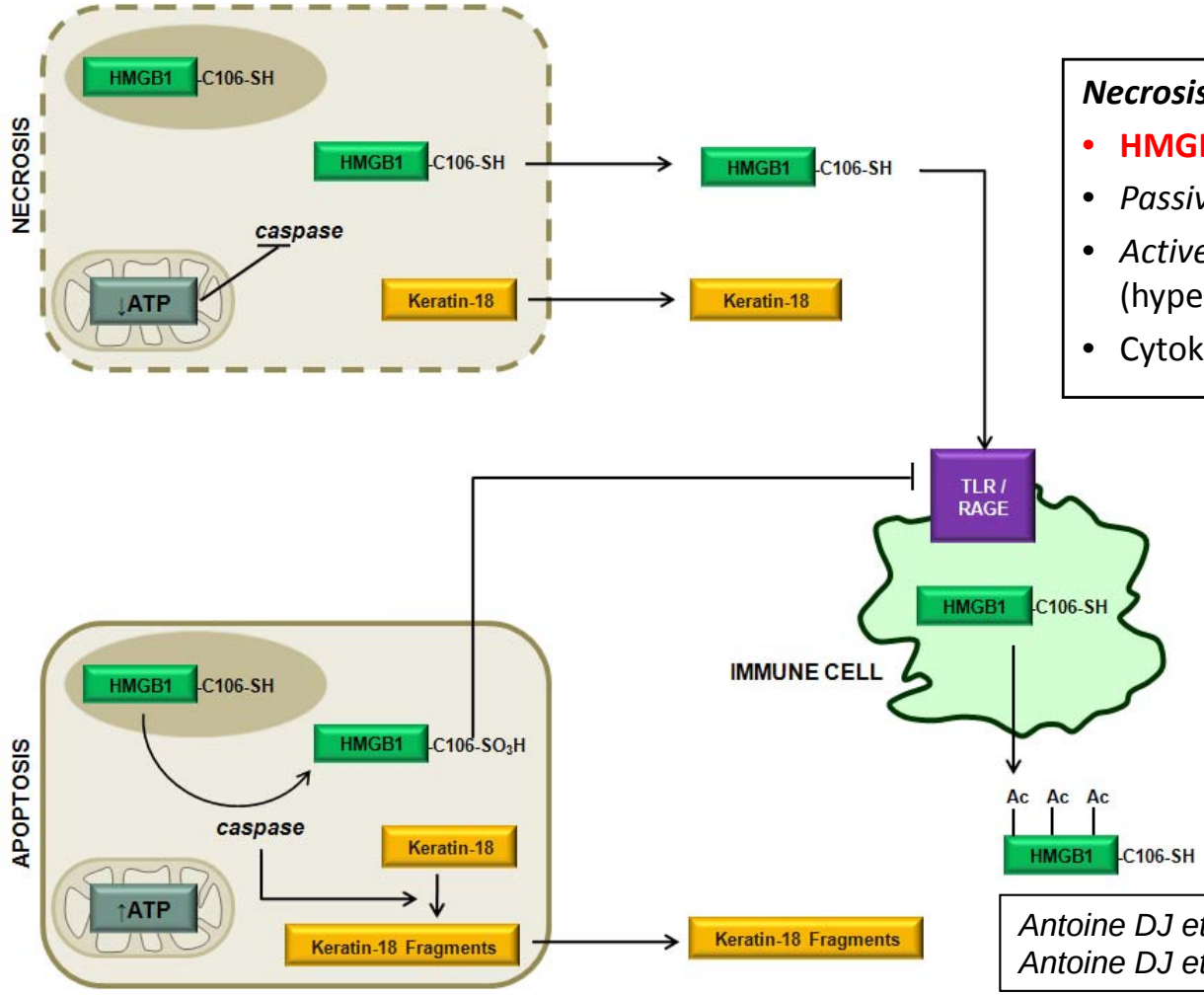
HMGB1 and Cytokeratin 18

Mechanism based biomarkers

UNIVERSITY OF LIVERPOOL

MRC Centre for Drug Safety Science

Slide courtesy Neil French, MRC CDSS



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)

Apoptosis:

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

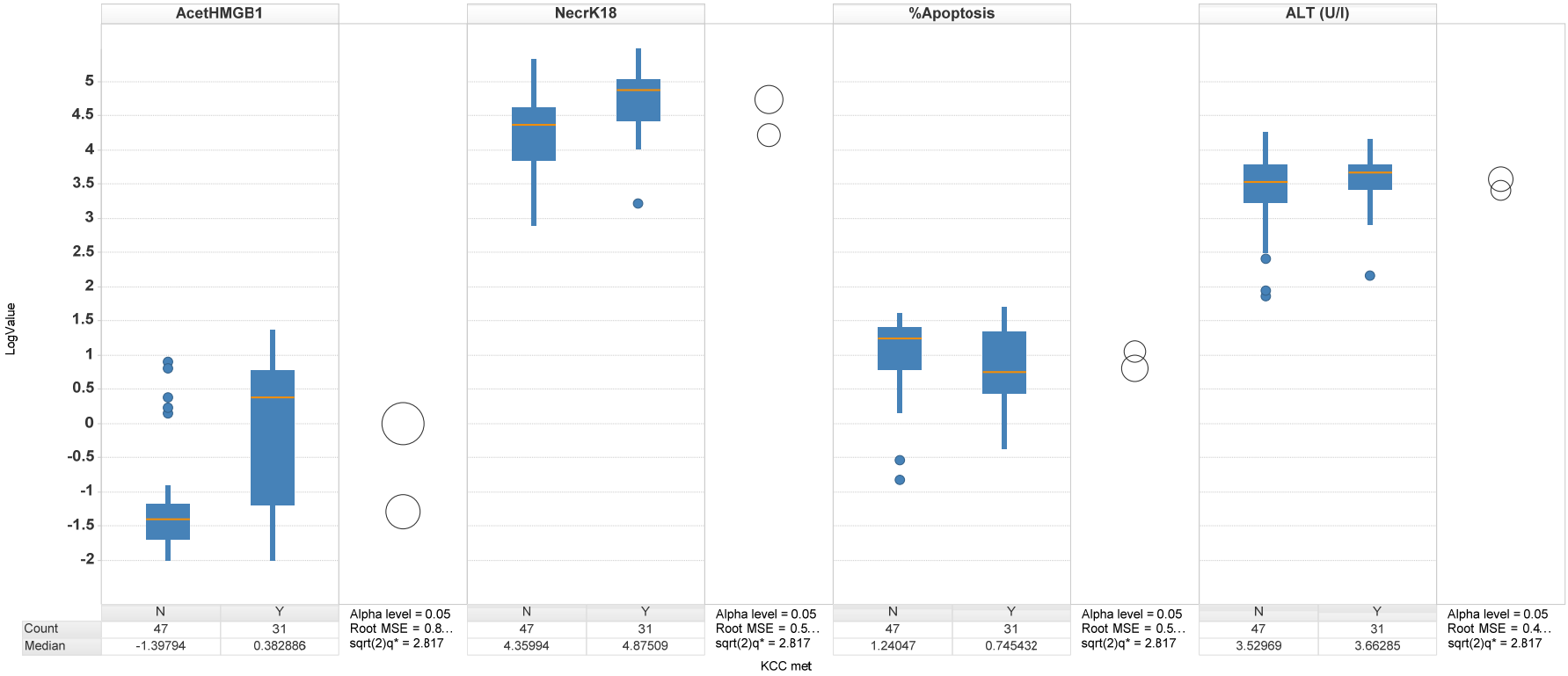
Antoine DJ et al., 2010 Mol Med
Antoine DJ et al., 2009 Toxicol Sci

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?

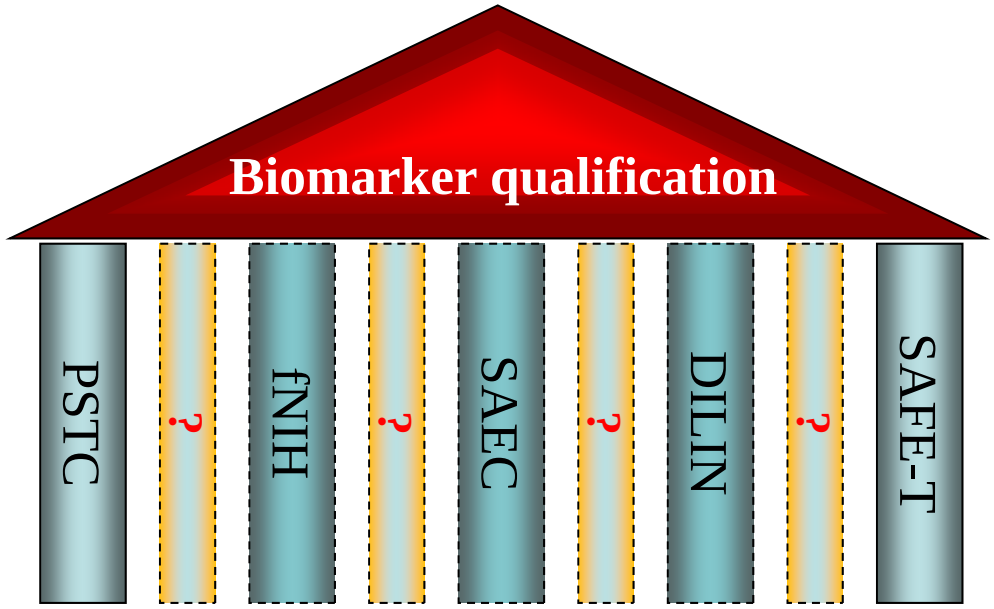
- Biomarker candidates do not cover all objectives of SAFE-T DILI WP
  - Lack of susceptibility markers
  - Lack of sensitive functional markers, some pathologies poorly represented
  - Most markers identified in pre-clinical models

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

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