Qualification of Translational Safety Biomarkers

IMI SAFE-T Consortium

Joe Keenan – Argutus Medical Ltd
What is the IMI

✓ Innovative Medicines Initiative
Aims and Objectives

European Innovative Medicines Initiative

- **Aim**
  
  To remove **major bottlenecks** in drug development, acting where research is the key

- **Long-term objectives**
  
  To *increase competitiveness of European pharmaceutical sector* and foster Europe as the most attractive place for pharmaceutical R&D, thereby **enhancing access to innovative medicines for patients**
IMI
Core Activities and Goals

• IMI will foster the development of a new **toolbox** (toxicology tests, biomarkers, clinical trials protocols etc.) for drug developers to reduce the risk of failure of new medicines.

• IMI will provide the opportunity for **validation of the new tools** in view of rapid **uptake into regulatory and industry practice**.

• IMI will set up a ‘**knowledge platform**’ by pooling **data** from toxicology testing and biomarker validation that will be available to all researchers (industry and academic).

• IMI will **not develop new medicines** or new vaccines!
IMI Funds 2008-2017

2 Billion EURO

1 Billion Euro
Public Partnership

1 Billion Euro
Private
IMI Finance Model

EU FP7 Budget

Cash €1 billion

IMI RESEARCH PROJECTS

Regulators

Pharmaceutical Companies

Patients

Academia

Small Medium Enterprises

In kind €1 billion

Funding:

€ Funding

Funding

Funding

Funding

Funding
IMI Call & Evaluation Process

Based on Research Agenda

**IMI Annual Implementation Plan**

EFPIA Companies

Topics + pre-established « EFPIA Consortiums »

Executive Office

**STAGE I**

Submit Expression of Interest

“Applicant Consortia” Academic, SMEs, & Patients

Q1 2009

**1st Peer Review**
Selection by indep. experts + EFPIA Consortium

**STAGE 2**
Submit Full Proposal

**2nd Peer Review**
Evaluate by indep. experts No EFPIA Consortium

“Full Consortium”:
EFPIA + Public Consortium

IMI Board

**Approval**
<table>
<thead>
<tr>
<th>#</th>
<th>Title</th>
<th>Companies</th>
<th>Budget Mio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Improve Predictivity of Immunogenicity</td>
<td>12</td>
<td>€22</td>
</tr>
<tr>
<td>2</td>
<td>Non-genotoxic Carcinogenesis</td>
<td>8</td>
<td>€21.5</td>
</tr>
<tr>
<td>3</td>
<td>Expert Systems for in silico Toxicity Prediction</td>
<td>10</td>
<td>€9</td>
</tr>
<tr>
<td>4</td>
<td>Improved Predictivity of non-clinical Safety Evaluation</td>
<td>11</td>
<td>€17</td>
</tr>
<tr>
<td>5</td>
<td>Qualification of Translational Safety Biomarkers</td>
<td>12</td>
<td>€36</td>
</tr>
<tr>
<td>6</td>
<td>Strengthening the Monitoring of Benefit/Risk</td>
<td>15</td>
<td>€26</td>
</tr>
<tr>
<td>7</td>
<td>Islet Cell Research</td>
<td>11</td>
<td>€17</td>
</tr>
<tr>
<td>8</td>
<td>Surrogate Markers for Vascular Endpoints</td>
<td>7</td>
<td>€34</td>
</tr>
<tr>
<td>9</td>
<td>Pain Research</td>
<td>12</td>
<td>€12.5</td>
</tr>
<tr>
<td>11</td>
<td>Neurodegenerative Disorders</td>
<td>14</td>
<td>€12.5</td>
</tr>
<tr>
<td>12</td>
<td>Understanding Severe Asthma</td>
<td>10</td>
<td>€21.5</td>
</tr>
<tr>
<td>13</td>
<td>COPD Patient Reported Outcomes</td>
<td>9</td>
<td>€17</td>
</tr>
<tr>
<td>14</td>
<td>European Medicines Research Training Network</td>
<td>24</td>
<td>€9</td>
</tr>
<tr>
<td>15</td>
<td>Safety Sciences for Medicines Training Programme</td>
<td>24</td>
<td>€5</td>
</tr>
<tr>
<td>16</td>
<td>Pharmaceutical Medicine Training Programme</td>
<td>24</td>
<td>€8</td>
</tr>
<tr>
<td>17</td>
<td>Integrated Medicines Development Programme</td>
<td>24</td>
<td>€5</td>
</tr>
<tr>
<td>18</td>
<td>Pharmacovigilance Training Programme</td>
<td>24</td>
<td>€6.5</td>
</tr>
</tbody>
</table>
The IMI SAFE-T consortium
Qualification of translational safety biomarkers

Academia

External Advisors

SME

Collaborators
IMI SAFE-T Consortium
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 adapters from patients at high risk to develop liver failure.
  – **Vascular System**: there are currently no biomarkers available to monitor drug-induced vascular injury in human.

• Consortium goals:
  – To evaluate **utility** of safety BMs for monitoring DIKI, DILI and DIVI in humans.
  – To **develop assays** and devices for clinical application of safety BMs.
  – To compile enough evidence to qualify safety BMs for **regulatory decision making in clinical drug development** and in a **translational context**.
  – To gain evidence for how safety BMs may also be used in the **diagnosis of diseases** and in clinical practice.
Key Milestones and Deliverables

• Define scientific clinical qualification processes for safety biomarker qualification in clinical development with health authorities.
• Define the needs for new clinical biomarkers compared to current standards and criteria to be met (e.g. pathologies)
• Assay development: fit for purpose for exploratory phase (several), multiplexed and GLP-validated for confirmatory phase (selected)
• Establish baseline values and their variability in healthy subjects and various patient populations.
• Evaluate performance of these biomarkers against current standards to detect organ injuries and diseases in clinical studies and hospital units (exploratory and confirmatory phase)
• Establish a common database and biosample repository
• Qualify appropriate markers for regulatory decision making in clinical contexts together with health authorities.
• Gain mechanistic understanding when needed (pre-clinical studies)
The IMI SAFE-T consortium

Work packages and process flow

WP1 - Development of generic scientific qualification strategy for translational safety biomarkers (BMs)

WP2 – DIKI BMs
WP3 – DILI BMs
WP4 – DIVI BMs

Selection of candidate BMs and injuries/injury models to study

TWO STEP FORWARD BM QUALIFICATION APPROACH

BM Proof of Translation (PoT) Studies
BM Proof of Performance (PoP) Studies
Biologic/mechanistic studies to support BM qualification

WP5 - BM Assay Development, Validation & Testing of Clinical Samples

Assay availability for selected candidate BMs
BM assay development and validation
Sample testing - BM PoT, PoP & mech. studies

WP6 - Integrative Data Analysis & Project Database

Project Database including human BM profiles

Integrative data analysis of BM PoT, BM PoP and mechanistic studies Meta-analysis

WP7 - Biobank for Qualification of Translational Biomarkers

Establishing guidelines
IT infrastructure
Sample management
Maintenance
Management

WP9 – SAFE-T Consortium Management

WP8 - Dissemination / Communication / Training Plan

VALIDATED BM QUALIFICATION STRATEGY
DATABASE OF HUMAN BIOMARKER PROFILES
QUALIFIED BMS & VALIDATED ASSAYS for DILI, DIKI & DIVI
BIOBANK
COMMUNICATION, DISSEMINATION TRAINING EXPLOITATION
Research Plan

Milestones and Deliverables-Based

Submission Forms

IMI Joint Undertaking

Full Project Proposal

Description of Work

Proposal full title: Safer And Faster Evidence-Based Translation
Proposal acronym: SAFET
IMI Cell topic: IMICell_2008_1.05

Name of the coordinating person: Frank DIETERLE
Novartis Pharma
Phone: +41 01 800 1000
Fax: +41 01 800 1212
Email: Frank.Dieteler@Novartis.com

List of participants:

<table>
<thead>
<tr>
<th>Participant No.</th>
<th>Participant organisation name</th>
<th>Participant organisation head name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Coordinator)</td>
<td>Novartis Pharma</td>
<td>NOVARTIS</td>
</tr>
<tr>
<td>2 (Managing entity)</td>
<td>Natural and Medical Sciences Institute</td>
<td>MNI</td>
</tr>
<tr>
<td>3</td>
<td>Friesis SAS</td>
<td>FIRALIS</td>
</tr>
<tr>
<td>4</td>
<td>Almirall</td>
<td>ALMIRALL</td>
</tr>
<tr>
<td>5</td>
<td>Aigen</td>
<td>AIGEBN</td>
</tr>
<tr>
<td>6</td>
<td>Alqubes Medical Limited</td>
<td>ARGUTUS</td>
</tr>
<tr>
<td>7</td>
<td>AstaPharma</td>
<td>A2</td>
</tr>
<tr>
<td>8</td>
<td>Bayer Schering Pharma AG</td>
<td>BSP</td>
</tr>
<tr>
<td>9</td>
<td>Boehringer Ingelheim</td>
<td>B</td>
</tr>
<tr>
<td>10</td>
<td>Charite Hospital</td>
<td>CHARITE</td>
</tr>
<tr>
<td>12</td>
<td>Experimental &amp; Diagnostic Immunology GmbH</td>
<td>EDI</td>
</tr>
<tr>
<td>13</td>
<td>Eli Lily</td>
<td>ELI</td>
</tr>
<tr>
<td>14</td>
<td>Groupe Hospitalier Pitié Salpêtrière, Paris (APHP-1)</td>
<td>APHP-1</td>
</tr>
<tr>
<td>15</td>
<td>Groupe Hospitalier Pitié Salpêtrière, Paris (APHP-2)</td>
<td>APHP-2</td>
</tr>
<tr>
<td>16</td>
<td>Globocentrics</td>
<td>QSK</td>
</tr>
<tr>
<td>17</td>
<td>Barcelona Cardiovascular Research Center</td>
<td>ISCC</td>
</tr>
<tr>
<td>18</td>
<td>Interface Europe</td>
<td>IE</td>
</tr>
<tr>
<td>19</td>
<td>Pfenzer</td>
<td>PFRZER</td>
</tr>
<tr>
<td>21</td>
<td>Hoffmann-La Roche</td>
<td>ROCHE</td>
</tr>
<tr>
<td>22</td>
<td>Televiro (Slovakia) Medical Center</td>
<td>TARMAC</td>
</tr>
<tr>
<td>23</td>
<td>Sanofi-Aventis Research and Development</td>
<td>SARD</td>
</tr>
</tbody>
</table>

1 units in the Project Agreement APHP-1 is based on one partner in the Cell it is divided into two units – APHP-1 and APHP-2 to better determine the tasks and roles of each partner in grade of APHP in the project
Joining efforts
SAFE-T’s links (existing/planned) to other groups and consortia
Objectives / Deliverables

1. Collection of candidate biomarkers
2. Collection of drug-induced pathologies of interests
3. Identification of relevant co-factors, diseases, renal diseases, target populations
4. Exploratory studies to select biomarkers and establish thresholds / diagnostic performance characteristics
5. Confirmatory studies to validate thresholds / performance
6. Potentially: Intervention studies
Status: Biomarkers Selected

- **Key results**
  - Extensive questionnaire (50 questions) for biomarker candidates characteristics and report (178 pages)
  - Pathologies of interest identified
  - List of nephrotoxic drugs to be investigated
• Key results
  – Pathologies of interest identified
  – List of nephrotoxic drugs to be investigated
Variability in healthy subjects

Response to DIKI

Response to non-kidney disease

Response to non-DIKI Kidney disease

Exploratory phase

Confirmatory phase

Drop

High

Low

Bad

Good

Yes

No

Information on...

Pathology?

Mechanism?

Disease severity?

Drug-relatedness?

Clinical outcome?
Key results

- DILI Book submitted
- DIKI and DIVI submitted 5th May 2010
WP2 Needs from WP5 (Assay Development)

- Development of three assays
- Assay Validation
- Assay measurements
- Mitigation for key biomarkers with limited assay performance
- High-throughput (multiplexing)
Next steps

Clinical exploratory studies and clinical biomarker assay validation

• Design the exploratory studies and protocol and interact health authorities
• Studies in healthy volunteers
• Studies in patients receiving nephrotoxic drugs
• Studies in patients with chronic kidney disease
• Studies in patients with chronic systemic non-renal diseases
• Data Management
• Bio-Banking
Conclusion

**IMI Safe-T consortium will deliver**

- A panel of qualified kidney / Liver and Vascular injury biomarkers
- A bio-bank of samples and data points
- A dissemination plan to share the knowledge
- A true consortium effort to improve drug development and clinical patient management