**SAFE-T OBJECTIVES**

- **Primary objectives**
  1. To develop and qualify biomarkers that detect DIII earlier than the currently used standards (cCR & BUN) and with greater sensitivity.
  2. To gain scientific acceptance and regulatory endorsement for the use of these biomarkers in defined clinical and potentially translational contexts.

- **Secondary objectives**
  To characterize selected renal biomarkers with respect to their utility as follows:
  a. Assessment of sensitivity & specificity of biomarkers for injury in specific compartments of the kidney (e.g., glomerular, tubular, collecting ducts) and to different pathologies (e.g., fibrosis, necrosis, degeneration)
  b. Characterization of the effect on biomarkers of acute and chronic non-renal organ diseases, injuries and systemic conditions (e.g., diabetes, congestive heart failure, liver diseases)
  c. Determination of inter- and intra-individual variability of the candidate biomarkers in healthy individuals and patients with chronic kidney diseases, associated normal ranges and relevant covariates
  d. Evaluation of the potential of biomarkers to track not only the onset of kidney injury but also to monitor the resolution of kidney injury
  e. Exploration of the clinical utility when these biomarkers are used to trigger intervention (e.g., cessation of treatment or initiation of renal rescue therapy) in a narrow clinical context.

The principal objective of this new project is to collect and generate sufficient clinical data from a number of candidate kidney biomarkers, that will provide convincing evidence for the health authorities to endorse these biomarkers for the detection and monitoring of drug induced kidney injuries in specific clinical situations. To address this, a European-based partnership called the SAFE-T Consortium was formed from 20 participants from the pharmaceutical industry, small-medium enterprises, academic institutions and clinical units.

**SAFE-T PARTICIPANTS 2011**

- **Due to the high quality of the kidney biomarker candidates** the consortium expects to be able to select, within 2 years, a manageable number of kidney biomarker candidates for the clinical trial phase.

**RESULTS**

**CANDIDATE KIDNEY BIOMARKERS UNDER ASSESSMENT**

<table>
<thead>
<tr>
<th>Tissue Injury Response</th>
<th>Tissue Injury Mechanism</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney Injury</td>
<td>Kidney Injury</td>
<td>Functional</td>
</tr>
<tr>
<td>KM-1</td>
<td>Microalbumin</td>
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<tr>
<td>FGF-23</td>
<td>Osteopontin</td>
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<td>Cystatin</td>
<td>Podocin</td>
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<tr>
<td>TFF3</td>
<td>Collagen C3</td>
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<tr>
<td>TIMP-1</td>
<td>Lubricin</td>
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<td>CTGF</td>
<td>Renin</td>
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<tr>
<td>K-1</td>
<td>Angiotensin 2</td>
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<tr>
<td>MCP-1</td>
<td>CNTF</td>
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</tbody>
</table>

**ASSAY VALIDATION PROCESS**

SAFE-T are using commercially available assays for the candidate biomarkers selected where feasible. Through a series of low and high bar validation processes the markers will be assessed for their suitability for entry into the clinical sample assessment. For some of the markers that are available on multiple technologies (ELISA, Lumex, Mesoscale, etc.) the consortium has undertaken dual technology assessment in an attempt to cover any potential weaknesses left to a particular technology. The priority will be lent to the technology that has led to most publications in the literature.

**NPHROTOXIC DRUG SELECTION**

**ASSESSING PERFORMANCE OF NOVEL BIOMARKERS VS ???**

SAFE-T has adopted the AHRN criteria for the definition of acute kidney injury and its three stages. This classification is dependent on serum creatinine which has been described as a weak standard for AKI.

**How do you assess a novel biomarker against Scr reference test?**

SAFE-T has proposed an approach to novel biomarker assessment (which has been discussed with the regulatory authorities). The approach involves the establishment of adjudication committees to determine the relevance of increases of biomarkers in the absence of increases of serum creatinine and whether these are true positive or false positive signals (false positive signals of the patient assessments [control vs nephrotoxicant] on the basis of blinded review of:

1. Standard clinical parameters
2. Biomarker profiles
3. Biomarker profiles and clinical parameters?)

Further the adjudication committees will determine if changes of standard clinical parameters are due to:

1. Preclinical anomalies
2. Non-progressive renal disease
3. Acute kidney injury