Report from Session 1

Chairs:

Dr. Marilyn Aardema (BioReliance, USA)

Dr. Stefan Pfuhler (Procter & Gamble, USA)

Speakers:

- **Overview of the use of 3-dimensional tissue constructs for genotoxicity testing**
- *Dr. Stefan Pfuhler (Procter & Gamble, USA)*
- **Development of in vitro toxicity testing using hepatocytes differentiated from human stem cells**

  Dr. Seiichi Ishida (NIHS, Japan)
- **Humanized models in toxicology and their applications to hazard characterization and risk assessment**

  Dr. Darrell Boverhof (Dow Chemical, USA)

Initial considerations (from discussion)

- Need to define for every assay what the expected use in risk assessment is
  - Which questions do we want these assays to answer?
  - Which current gaps do they fill?
- Physiological anchoring is important
  - Key to interpreting in vitro assays – are assay conditions reflective of in vivo physiological parameters?
- Genetox endpoint has to be model specific

Key findings:

Strengths

- Closer to ‘in vivo’ conditions
- Cells are of human origin and function more organ-like in terms of cell viability, proliferation, metabolism, differentiation, morphology, gene and protein expression
- Allows for better characterization of human hazard and risk potential
- Provides insights into mode/mechanism of action (humanized models) and helps to extrapolate from rodent to humans

Key findings:

Opportunities

- 3D constructs have the potential to serve as 2nd tear assays to follow up on positives from 1st tier
- Can be used where animal testing is impossible
- Humanized models: Allow for refinement in hazard and risk assessments and help decrease uncertainty, validate in vitro hypotheses
- Humanized models: Can be used to further define “toxicity pathways” thereby facilitating development of in vitro assays based on MoA

Key findings:

Weaknesses

- More expensive
- Low to medium throughput
- Cover specific questions rather than broad space – e.g. 3D skin models applicable for dermal exposure only
- Assays at various stage of development, and level of available supporting data varies also
- How reflect human vareabilty?

Key findings:

Threats

- Models availability
- Cost/timing/approach for validation
- Acceptance of regulatory use

General Discussion

- Use model specific approach – e.g, should not force proliferation if model does not proliferate naturally
- Model ‘validation’ needs to done on a case by case basis. Standard validation may not apply/ be necessary or practical
- For RA – go beyond guideline studies
    - Test battery locks us in
    - How do we achieve regulatory acceptance?

What can ILSI-HESI Do?

- Hold assay-specific meetings/workshops to boost development/acceptance
- IVGT could interface with Risk21
- Should ILSI make recommendations on whether a technology can replace previous assays?
  - Provide ‘white paper’?
- Cell bank – can cells (stem cells/ cells used to create 3D models) be made available for research?