

## Session 2: Emerging Alternative Methodologies with Potential Applicable to a Broad Spectrum of Toxicity Evaluation Strategies

Session Chair: William Stott (Dow Chemicals)

### Panel Discussion and Audience Dialogue

- The panel had been asked to consider what the likely 1 and 5 year accomplishments would be and what barriers will lay in the path in their respective areas.
  - Dr. Li stated that there is a lot of effort devoted to predicting human toxicity. The human-based in vitro assay system is on the horizon with the most prominent barrier the acceptance of the system by classical toxicologists.
  - Dr. Janzen believes that the development of public databases of toxicological information for comparison and data pairing will be a near future accomplishment. The barriers to this are creating a common database structure and insuring quality data.
  - Dr. Muntendam stated that a very real near term opportunity is the development of organ specific damage biomarkers for use in toxicity testing. Funding is a large barrier.
  - Dr. Richard stated that the biggest limitations (other than the lack of data) are the lack of imagination and familiarity with the power of relational searching and capabilities for data exploration to yield new insights, and the lack of data accessibility (privileged or non-electronic format).
- After an alternative technique is developed, validated, and recommended for use, what are the incentives for industry to implement those techniques? Should monetary incentives be given, such as additional exclusivity or a reduction in the FDA user fees? The panel agrees that incentives are needed; however the use of alternative methods in drug development is done to reduce costs for research and development. The panel held the belief that an alternative method will be adopted if it provides more, or better, information than the animal testing method. The adoption of new methods in industry safety testing will largely depend on the adoption of those methods at the regulatory level as industry will not want to hold the legal liability of relying only on the data generated from alternative methods.
- In an in vitro system, how is human pharmacokinetics accounted for, *i.e.* is a solution bath an adequate substitute in the IdMOC assay? IdMOC mimics metabolism and distribution of a drug in human tissues. It does tell you if a drug or drug metabolite is active in a certain cell or tissue type. It does not model blood flow/perfusion, but a PB/PK model could be used in conjunction.
- After exposure to a substance the human body can produce not only toxic responses, but also adaptive/compensatory responses. How would measurement of a biomarker in vitro account for these types of responses? Dr. Muntendam explained that it is difficult to predict adaptive responses and that in vitro responses should be compared to those seen in an intact animal. Additionally, the response fingerprint can change over time and changes in the genome do not necessarily result in morphological changes. It is a judgment call as to where to draw the line as a toxic response.

- In pesticide research, clinical trials are not done and there is a difference between testing the product for efficacy or for safety, which is very different from drug development. How would safety testing be possible without 'old school' animal or human testing? In an ideal world, in vitro test results could be extrapolated to provide human relevant safety information. However, industry does not want to generate human-related in vitro data on pesticide effects that would generate a regulatory nightmare. Data gathered on chemical manufacturing employees may provide a good place to start. Broader classes of biomarkers are needed for characterizing ecotoxicology. To keep in mind is the different level of exposure and desired effects between drugs (high dose resulting in therapeutic response) and pesticides (low environmental exposure resulting in toxicity).
- From a classical toxicologist's point of view – the ground rules of toxicology have not changed, *i.e.* dose response, target organ, molecular target, etc., and still apply to new toxicological methods such as high-throughput screening.
- Is there a role for stem (or somatic) cells in the new technologies discussed today? Yes, and many drug development companies are currently looking into the use of stem cells for drug discovery and monitoring.
- For some of the assays discussed, their use in toxicity testing and current application is obvious. But for other more complicated systems or databases, their use is less obvious and not easy to explain to the public or even to potential funding sources. The panel was asked to describe a way to make the method and potential uses of these new technologies more clear.
  - In systems toxicology, a clear example of the usefulness of biomarkers is rat liver toxicity. More detailed information is generated out of a 28-day study when biomarker information is collected. These data can then be used to develop organ-specific biomarkers of toxicity which can find their way in the regulatory arena. In general, complicated scientific issues are difficult to explain and need to be popularized to get broader support.
  - Anything that can be boiled down to a plain language paragraph from an authoritative figure would be more widely accepted.
  - For relational databases, demonstrations of their capability often opens researcher's eyes to how they work and how various data are related.
  - There is a wealth of data being compiled or generated, especially through the NIH initiative. The data generated through the NIH initiative is purely for academic purposes; however, it is being used for regulatory purposes which can be dangerous. It would be beneficial to introduce the rigor of the regulatory environment into the academic research so that the data may be used in both capacities.
  - Need to avoid hype or over-promising what these new technologies can do, as was the case for the Human Genome Project.
- There is no current effort to standardizing the in vitro 'metabolizing' systems. Dr. Li explained that the 'organ on a chip' assays were developed using a democratic process that identified the need, not because the FDA mandated them. The standardization of these types of protocols would lead to less innovation and refinement of the assay's capacity.