„ Optimizing drug discovery through investigative toxicology: Current and future trends “

Think tank meeting organized by the Center for Alternatives to Animal Testing-Europe

Tentative time planning

July 10th (14:00) to July 12th (12:00) 2017

Venue

Hotel Belvedere Ranco (Lago Maggiore) Italy

Objective

"Investigative Toxicology" (INV TOX) within the safety assessment strategies focuses on mechanisms behind adverse outcomes, e.g. in the pharmaceutical sector on mechanisms behind adverse drug effects. In the course of product (e.g. drugs) development, aims also at early-stage identification of candidates toxic to human consumers (e.g. patients). Thus, the implementation of INV TOX implies the reduction of recruited animals, e.g. at different levels of drug development in the pharmaceutical industry.

The think tank on INV TOX hosted by CAAT-Europe and 14 Europe-based investigative toxicology experts from 14 multi-national pharmaceutical industries (Investigative Toxicology Leader (ITL) Forum), involves also experts from academia, other sectors and regulatory bodies. The think tank is to address regulatory perspectives, current gaps, shortcomings and pitfalls of INV TOX. Furthermore predictive features, validation criteria, transferability and quality criteria are to be discussed in this think tank.

Format:

Attendance is by invitation only (closed session face-to-face meeting), focusing on extensive exchange of knowledge. Participants are expected to prepare a short statement (1-2 slides) on the topics to be discussed or the questions raised ahead of the meeting. Starting in the early afternoon on day 1 and close with a wrap up in the morning of day 3 (2 overnight stays), currently planned in Ranco, Italy, July 10th to 12th, 2017. If group size does not allow lively discussion spread out sessions are used (5-8 people). The CAAT ThinkTank workshops are usually summarized in a position paper published in ALTEX (IF: 5,824).

Aims:

- To support relevant *in vitro* science, to foster innovative toxicological investigations and to promote culture of care (human consumers/patients and laboratory animals)
- Describe the present situation of Investigative Toxicology
    - Define Investigative Toxicology in general (applicable to all stakeholders)
    - Define Investigative Toxicology for your sector, e.g. pharmaceutical industry
- Describe what is needed for better non-animal safety translation (into clinic for instance)

Afternoon, 1st day:

- **Session:** Positioning and Definition of Investigative Toxicology (INV TOX)
    - Survey outcome of the European pharmaceutical industry (presentation)

1. **Questions (to be answered with a short statement by each participant):**

    - What is INV TOX?
        - Does the toxicology community have a common understanding of INV TOX?
        - What is the deliverable, what is the impact of INV TOX?
            - Is screening included?
    - Who is doing INV TOX and who is using its results, and for what purpose?
    - What are the differences & commonalities in INV TOX and how could the different groups benefit from each other to be most impactful?
        - academia
        - pharma industry
        - chemical and plant protection industry
        - cosmetics, food and other consumer products industries

- What is the regulatory perspective on INV TOX? Do risk assessors see a value and if so where are the shortcomings and pitfalls?
- What are the gaps which INV TOX could address (e.g. in pre-clinical safety)?
- How can INV TOX improve the safety prediction (clinical outcome), despite the lack of knowledge and uncertainties – quality of safety assessment
- INV TOX:
  - What are common validation criteria?
  - Are there KPIs (e.g. for translatability to clinics)?
  - What is the importance of QA/GLP?

2. **Task: Draft proposals for definitions**

3. **Next to definitions: Gaps, Needs, Deliverables – Mission of INV TOX**

Morning, 2nd day:

- **Session**: Investigative Toxicology for better safety translation to humans (e.g. from preclinical studies)

Short case examples (max 1-3 slides each)

Questions (to be answered with a short statement):

- What can be used now/ is needed now?
- What are regulatory agencies expecting from INV TOX and from industry use of INV TOX?
- Are NAMs (new assessment methods) an option also for the INV TOX in pharma?
- Discussion of current organ-focused toxicity assessment vs new concepts of adverse outcome pathways or integrated risk assessment (chances, challenges and limitations)
- What are next steps, e.g. towards safe medicines without animals?
- Has the ban of animal studies in the cosmetics arena advanced non-animal safety science? And can the lessons be extrapolated to other sectors, e.g. pharma?
- How can the different stakeholders support this today and in the long run?
- What is the value of precompetitive cooperation?

Afternoon, 2nd day:

- **Session:** Disruptive or breakthrough innovation

Three INV TOX challenges and the technologies to address these

1. Where do drug molecules "go" *in vivo*? How do we predict/assess drug distribution to specific organs/cell types? What are the emerging biophysical methods that could be game-changing?

2. What do cellular changes mean for the clinic? How do we translate phenotypic effects from systems biology approaches into a human relevant safety assessment? Is off-target profiling beyond classical Rc binding, i.e. omics technologies & high-content imaging required? If so, how? What are the bioinformatics / systems biology approaches that will make sense of these data? What are the limitations?

3. What will revolutionize the extrapolation of *in vitro* effects to *in vivo* and the clinic? What models can be applied to support quantitative clinical translation: what is the feasibility and relevance of conducting toxicology in cellular disease models? How can the therapeutic index (especially for human unique targets & drugs with no pre-clinical x-reactivity) be calculated? What is the role of MPS? Role of genetics?

The Challenges will be brainstormed in small groups:

Morning, 3rd day:

- **Session:** Wrap up of workshop

Summarize discussions and outcome

Fix definitions, align work plan and tasks for position paper, and agree on timelines.