Improve the Impact of Imaging Solutions on Drug Safety Evaluation

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SGG Translational Safety
Non-Clinical Development – Problem Statement

★ 43% concordance between clinical trial toxicities & rodent toxicity seen across 150 compounds; 63% in non-rodents
★ Clinical toxicity predictions vary by organ system as well as species dropping to as low as 36%

★ How can we guard against drug-induced injuries in the clinic but not in preclinical toxicological studies?
★ How can we advance development of good drugs showing toxicities in animals that are not expected to be present in humans?
★ How can we verify efficacy in preclinical and clinical settings?

Ohlsen et al., Reg Toxicol Pharmacol 2000, 32: 56-67
Challenge: Systematic translation of new imaging methods

Imaging “can”:

- DCE-MRI
- X-nucleus MRI
- Diffusion MRI
- MR-Spectroscopy
- Dual-Energy CT
- Perfusion CT
- ....

Currently used parameter in the Clinic:

- RECIST

Gap between available technology and clinical routine

Vision: Implement imaging biomarkers as integral part of clinical trials and clinical routine
MR Imaging of Brain Structure and Function

* Detection of changes in **anatomy** at high resolution (tissue size)
* Functional information on tissues (perfusion, oxygenation, diffusion, spectroscopy)
* Possibility to perform **longitudinal** studies (reduces animal number)

Rodent brain tissue MRI compared to histology

Calabrese et al. Neuroimage 2013, 67:375-384

Rodent brain spectroscopy in a huntington’s disease model

Journal of Neurochemistry 2006, 100 (5):1397-1406
MR Imaging of Kidney Function

- Detection of changes in contrast agent excretion kinetics
- Functional information: oxygenation
- Longitudinal study (reduces animal number)

CT of rodent kidney

Blood oxygenation level dependent (BOLD) MRI of rodent kidney

BOLD-MRI is considered one of the earliest biomarkers for kidney injury

Validation of Diagnostic Imaging Techniques for Their Use in Clinical Drug Development

- We need technically, biologically and clinically validated imaging biomarker techniques.

- What is needed for validation?
  - Technical standardization of imaging method & procedure
  - Technical standardization of image evaluation and read-out
  - Pre-clinical validation against currently accepted measures
  - Prove robustness and informative value in animal disease models
  - Translation to patients; confirm robustness and informative value

- Need for public private partnership to establish and extend the basis for imaging biomarker utilization in patients.
Value of Clinically Validated Imaging Biomarker

- **For patients:**
  - Improved basis for therapy decision

- **For pharmaceutical industry:**
  - Perform longitudinal studies: reduce number of animals used
  - Identify potential safety/efficacy issues earlier: enable earlier project decision (avoid respective late phase investments)

- **For imaging equipment vendors**
  - Intensified use of imaging in pharmaceutical development
  - Enable use of imaging biomarker as integral part of clinical routine

- **For software providers**
  - Novel qualified tools for data analysis and reporting
  - Image data analysis across patients for procedure refinement