In Vivo Imaging: Gaps and Opportunities

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HESI Annual Meeting

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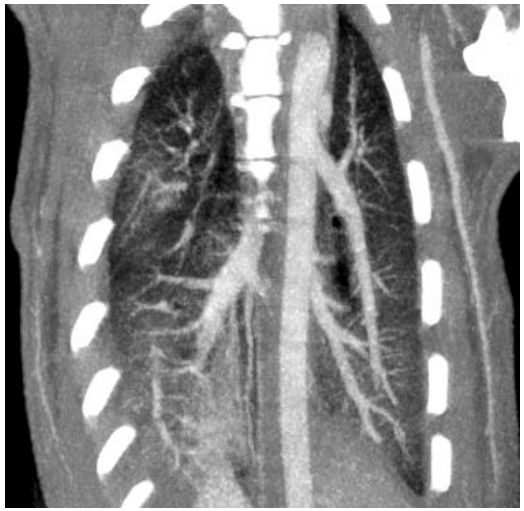
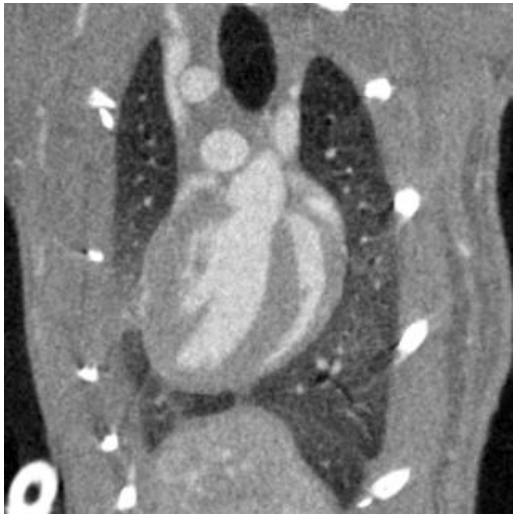
HESI Committee on Translational Imaging

Preclinical Safety Assessment and Environmental Hazard Identification

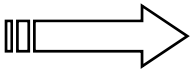




Background

- Significant advances have been made with *in vivo* imaging modalities in recent years
  - scaling- i.e. man to mouse
  - Resolution
  - Numbers of endpoints

- Advances have yet to significantly impact current paradigm of preclinical safety assessment leadership position



- Opportunities exist to engage these technologies to influence their development in ways that can be applied to and improve the way we do preclinical safety assessment and environmental hazard identification.
  - "improve" defined as
    - more predictive
    - more efficient
    - more translational

Opportunities…

1. …Utilization of *in vivo* imaging to address some of the challenges faced in preclinical development

2. …Development of *in vivo* imaging as an endpoint in safety studies to better understand and assess the safety of a potential therapeutic

3. …Advancements in the science of *in vivo* imaging to enhance understanding of the effects of potential therapeutics on organ function

Challenge…

Imaging historically used to monitor restoration of normalcy

- Efficacy models
- Examination of return to normal function or normal morphology
- Assess ability of drug to overcome insult

Use of imaging as safety marker? **Future?…**

- Assess drug effects on safety parameters
- Image pathology real time
- Look at loss of function in normal, healthy animal given drug
  - Understand mechanism
  - Assess toxicity

Current Toxicology Designs

- Drugs given to young healthy animals
- Dose, slice and dice designs with old technologies
- Single end point at end of treatment with objective of assessing toxicity

"...treatment related but of unknown toxicological relevance"

Traditional safety studies

Endpoints of organ toxicity

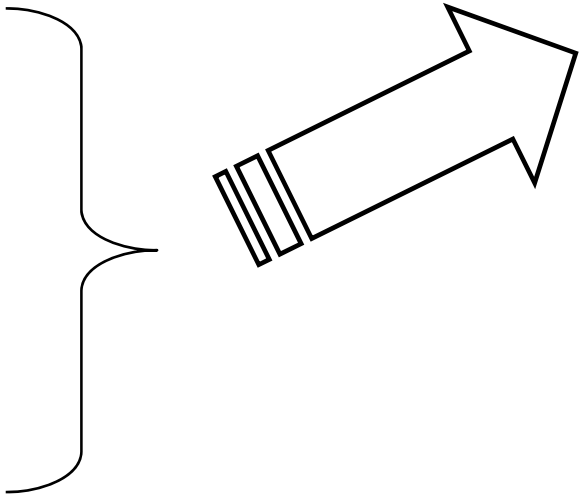
- Clinical Observations
- Exposure
- Morphological change
- Biomarkers

Snap shot at end of study

- Sometimes difficult/impossible to understand what occurred over length of study
- Dose limitations set upon parameters which may or may not be important/relevant

Technology Today…

- **Technology continues to advance, throughput increased**
  - Able to image up to 12 rodents simultaneously
- **Numerous modalities available**
  - MRI
  - PET
  - CT
  - Optical
  - Ultrasound
  - …



Many different endpoints

- Anatomy
- Biochemistry
- Surface Receptors/Alterations
- Macrophage infiltration
- Cardiac function
- Glucose utilization
- …….

Examples of Functional Imaging

- **Cardiac Function** – Ultrasound, CT, MR
- **Quantification of chemical species in selected tissue** - Localized MR spectroscopy
- **Renal flow** - CT
- **Intermediary metabolism** - CT PET / fluorinated labels
- **Brain (neurotransmitters)** - CT PET / carbon labels

As we discuss further…

Critical to Remember…

- Functional Imaging used in synergy with pathology
- Challenges to use of imaging (cost, timing, availability)
- Interesting questions will arise for which we may have no answer or a myriad of opinions about an answer

These questions and more…

- Considered by small team of scientists (industry, academic, and gov't) – need for broader forum for consensus and research identified.

- HESI contacted as part of 'Resources at Initiation' Process in June 2009 to help meet this need.

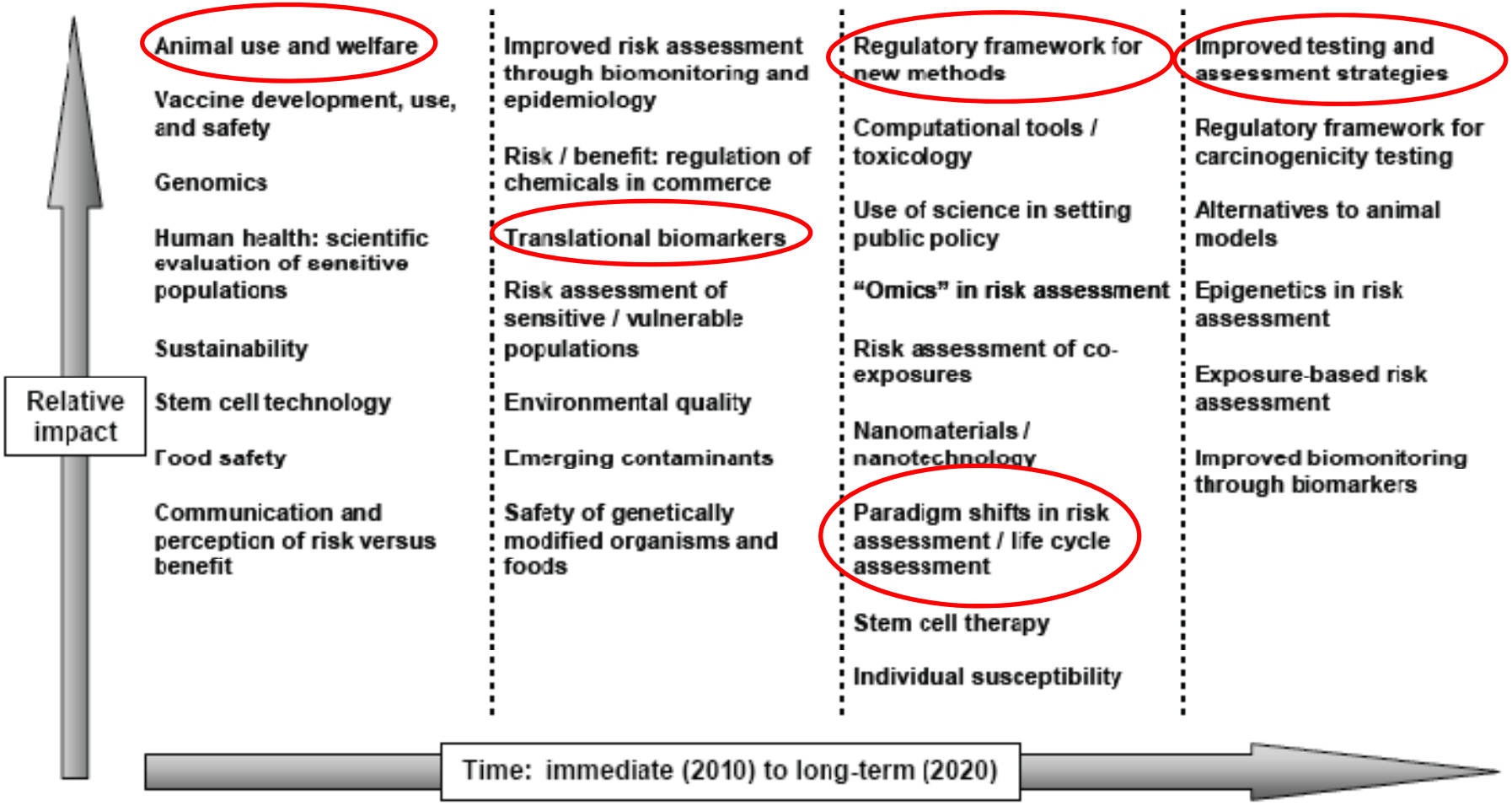
- Workshop held at HESI in December 2009.

- Interest in technical area so high that self-funding Committee initiated in January 2010.

Committee Participants 2010

- AstraZeneca
- Bayer HealthCare
- Bristol-Myers Squibb
- Boehringer Ingelheim
- Charles River Laboratories
- Covance
- GE Healthcare
- GlaxoSmithKline
- Hoffman-La Roche
- Merck
- Pfizer
- sanofi-aventis
- Quintiles
- Duke University Center for In Vivo Microscopy
- FDA
- EPA
- NIH

2010-2020 HESI COMBINED CHALLENGES MAP



Source: HESI Newsletter Spring 2010

Committee Mission

- Identify and pursue opportunities to efficiently and beneficially integrate imaging approaches into current safety assessment paradigms for drugs and/or hazard assessment approaches for chemicals.

Committee Focus and Workstreams

- Several Potential Areas for Project Work were Identified
  - Developmental and reproductive toxicity
  - Cardiovascular function in repeat-dose studies
  - Carcinogenicity (tumor number, onset, growth rates, etc.)
  - Developmental neurotoxicity

Anticipated Deliverables

- Survey on current practice
- Data and experience sharing on best-practices
- Novel experimental work conducted in collaboration with Duke CIVM – data used as basis for discussion on application to 'routine' safety evaluation;
- Possible FDA-NIH grant (research, committee discussion on data applications, etc.)

In Summary....

- ...Utilization of *in vivo* imaging will help to address some of the challenges faced in preclinical development
  - Mechanism of effect
  - Onset and progression of reversal of effect or pathology real time
- ...Development of *in vivo* imaging as an endpoint in safety studies may help to better understand and assess the safety of a potential therapeutic
  - Retrospective, based upon target, indication, critical physiological functions
- ...Enhancement of *in vivo* imaging will lead to better understanding of effects of potential therapeutics on organ function
  - Heart, bone, kidney, Others?.

Today's Speakers

- Dr. Allan Johnson – Duke, CIVM, Use of Imaging for Small Animals
- Dr. William Slikker, Director, NCTR – Imaging as a Resource for Drug Safety Evaluation