2014–2015 Activities and Accomplishments

Committee leaders:

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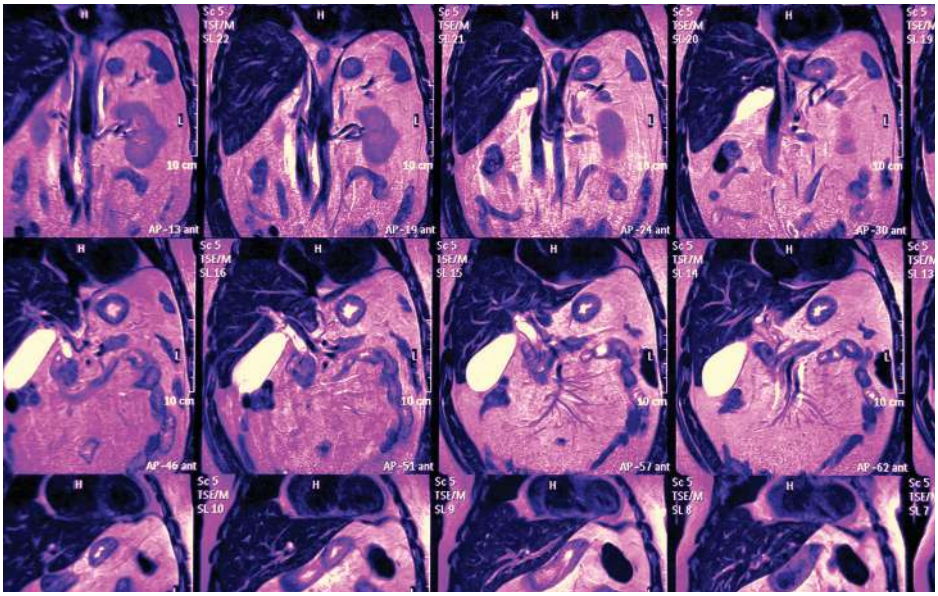
GlaxoSmithKline

HESI manager:

Dr. Connie Chen



This scientific program is committed to:

- Integrating imaging approaches into current safety assessment paradigms for drugs and/or hazard assessment approaches for chemicals.

Areas of scientific focus:

- Assessment of the sensitivity and specificity of different imaging modalities — such as magnetic resonance imaging (MRI), computed tomography (CT), and echocardiography (echo) — to identify organ-specific changes in function and/or structure in animal models and the potential for these changes to be translated as markers of relevance to human health.

Why get involved?

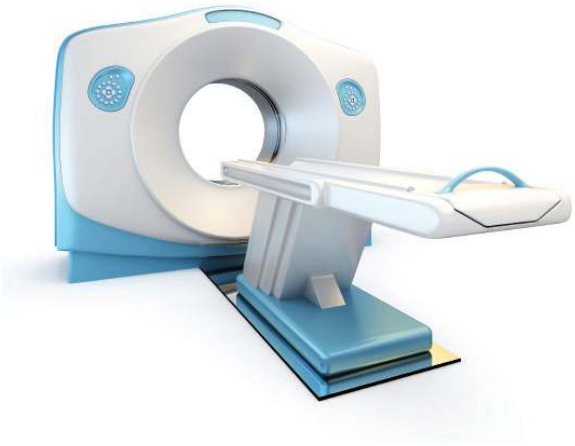
Engagement on the committee provides the opportunity to direct a first-of-its-kind initiative to develop and interpret robust data sets around the use of imaging for nonclinical safety assessment, environmental hazard identification, and translation to humans. Participants will also benefit from direct interactions with leading researchers in the field of small animal imaging, as well as their technological resources.

Key accomplishments:

- The liver subteam optimized the protocol for a multi-site study involving gadoxetate dynamic contrast-enhanced (DCE) MRI to detect cholestatic drug-induced liver injury in rat hepatobiliary transporters OATP1 and MRP2 using the target compound, rifampicin. The team also completed the modeling of the rifampicin study to determine *in vivo* inhibition of MRP2.
- Samples from the rat hepatocyte sandwich cell culture assay measuring the uptake and excretion kinetics of gadoxetate were analyzed.
- The results of the FDA-led *in vivo* MRI neurotoxicity and MRS study are being drafted for publication.

The Committee's focus for May 2015–May 2016:

- The results of the multi-site rodent echo cardiac imaging studies will be submitted for publication in the peer-reviewed literature. The group will also submit a series of additional manuscripts describing the sources of variability as well as learnings and recommendations for imaging centers for peer-review publication.
- The liver imaging sub-group will complete the multi-site rifampicin study to determine whether there is *in vivo* inhibition of MRP2. The sub-group will also select a new inhibitor compound that can be used to investigate additional mechanisms of drug-induced liver injury with the use of imaging modalities. Additional collaborations that would extend the work to human patients and volunteers are also being explored.
- A new scoping group will form to develop a new work stream on the use of non-invasive imaging of molecular biodistribution toward understanding molecule pharmacokinetics/pharmacodynamics as it relates to drug efficacy and toxicity.



2014–2015 Participating organizations:

Amgen Inc.
Astellas Pharma Inc.
AstraZeneca AB
Biogen Idec MA Inc.
Boehringer Ingelheim GmbH
Bristol-Myers Squibb Company
Duke University Center for *In Vivo* Microscopy
GlaxoSmithKline
Hoffman-La Roche Inc.
National Institutes of Health
Novartis Pharmaceuticals
Pfizer Inc.
Sanofi
Seoul National University
University of North Carolina, Chapel Hill
US Environmental Protection Agency
US Food and Drug Administration
VisualSonics

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