Speciation Knowledge Gaps

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Conflicts of Interest

Scientific Advisory Boards of Bracco Diagnostics Inc, Archeus LLC, Empirion LLC, and Enlyton LLC, and has advisory roles at Reveal LLC and Molecular Theranostics LLC. Co-investigator on a grant from Geurbet. Invented the marketed GBCA, gadoteridol.

Speciation Knowledge Gaps

- ADME (Absorption, Distribution, Metabolism, Excretion) is insufficiently described for GBCA (class), GBCA subclasses (ionicity, structure, protein binding), and individual GBCA in humans and in animals.

Quantitative speciation knowledge is essential to acquiring a sufficient mechanistic understanding of ADME to guide design and interpretation of toxicologic and pharmacologic studies that can then guide design and monitoring of efficient outcome studies.

- Comprehensive tissue analyses using combined multiple methods (to mitigate individual method weaknesses) are lacking.
- Interaction of GBCA and Gd at the cellular level is largely unknown.
- Very few studies include all available GBCA or even all classes of GBCA.
- Animal species and animal : Human crossover is poorly explored.
- The speciation problem is complex in chemistry, instrumental analytics, separation science, and biology, implying a need for multidisciplinary teams.

Speciation-Relevant Breakout Session Questions (GBCA class, GBCA subclass, and individual GBCA)

- How much Gd, GBCA and GdX remains residual, and for how long, after administration, per dose?

- By what pathway(s) does the last 1 -2% of injected GBCA traffic through the body to excretion, over what time period? How does it scale and change with commonly studied species?

- What chemical form of Gd could / does cause elevated signal measurable by MRI in tissues (not just the DN)? (This might be clinically relevant aside from toxicology concerns?)

- Under what conditions, and by what mechanism does GBCA metabolize in vivo, into what, where, over what time period, and is it accelerated by any known physiologic or biochemical condition?
  - Requires study of the individual Gd-metabolites in isolation, once they are known.
  - Furthered by studies in simple to complex solutions, living ex vivo tissue, animals, and human crossover studies.

- How can we accelerate the above studies to provide the earliest data that are fundamental to guiding and interpreting further downstream studies, like toxicology and imaging.