

BREAKOUT SESSION 2 READOUT
Markers for AIHI

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PROPOSAL: CANDIDATE AIHI BIOMARKERS ARE BEST IDENTIFIED AND VALIDATED IN THREE RELEVANT HUMAN POPULATIONS

- ***Hy's Law Cases***—(elevation in both serum ALT and total bilirubin)
- ***Prospective, controlled clinical trials with established, well-characterized AIHI agent including INH***
- ***Clinical trial subjects receiving a drug known to cause ALT elevations but not yet known to cause AIHI –***

Priority Research Efforts

1. Define methods to overcome key barriers to accessing clinical information and biospecimens from Hy's law cases
 - Difficulty assigning phenotype (causality assessment). How can these rare cases be better accessed, characterized?
 - How can well-annotated appropriate specimens be obtained (including in matched controls)?
 - Can on-going initiatives (SAEC, DILN, other multinational efforts) and other partnerships be integrated more effectively?
 - How can electronic health records and large data bases (VA, Medco, Kaiser, etc) be better leveraged?
 - Can a data warehouse be established?

Priority Research Efforts, con't

2. Develop and implement protocol(s) for specimen and data collection in a prospective clinical trial of INH and potentially other drugs known to cause AIHI or known to cause ALT elevations but not cause AIHI .
 - For INH study: What subjects? (e.g. age range)
For other agents: how to control for concomitant tx/diseases
 - Are there markers that can enrich the population.
 - Can signals/markers for adaptation and severity of liver injury be differentiated/stratified? Markers that predict vs for effect.
 - What other agents should be considered for prospective trials (statin, heparin, tacrine, others?)
 - To what extent will the markers identified be “agent-specific”?
 - How can this be sponsored/funded? Can it be coupled with on-going studies?

Priority Research Efforts, con't

3. Develop and implement protocols for standardized data and biospecimen collection in clinical trials when an ALT signal is identified.
 - What should be the “trigger” for collection?
 - What specimens should be collected and how often (see #5)?
 - How can standardization (data, specimens) be achieved? (incl ascertainment and phenotype)
 - What should be the role of the regulators?
 - Should access to specimens/data be restricted (how can risk to sponsor be managed)?

Priority Research Efforts, con't

4. Conduct a thorough examination of existing FDA liver safety databases from Phase 3 clinical trials and the AERS database to test the hypothesis that the more frequent but benign ALT elevations occurring in patients receiving an AIH agent are mechanistically linked to AIH (*critical assumption the underpins study of clinical trial populations*).
 - How can these data be mined? (are current technologies available?)
 - How can privacy issues be addressed?
 - How can alignment among regulatory/pharma be achieved? What are the incentives?
 - What resources and oversight will be needed?
 - Can this research be decoupled from “regulatory decision making?”

Priority Research Efforts, con't

5. Prioritize biomarker discovery options using the data and biospecimens obtained from the three populations above.
 - How to achieve maximum biomarker discovery through appropriate specimen collection?
 - Should candidate biomarker domains be prioritized re established hypotheses (immune response, toxic metabolite, cumulative injury, adaptation features) or specific enabling technologies? Should this instruct what specimens are collected?

Priority Research Efforts, con't

6. Identify and prioritize non-clinical research options to generate biomarker hypotheses for testing in the clinical biospecimen banks.
 - Can animal models enable methods development?
 - If relevant models are identified, can they inform on progression factors, reversibility, kinetics of biomarker changes and other questions that tightly controlled conditions enable?
 - Can non-clinical studies be linked to the clinical studies to better inform biomarker identification?
 - Are there surrogate in vivo/in silico models that can suggest new candidate markers for the above human studies? What does the Entelos experience tell us?

RECOMMENDATION

There was consensus in the Breakout Group around this high level approach to finding biomarkers that can be applied to clinical trials to predict AIHI and the research priorities for achieving that.

The questions identified for each area attest to the complexity and challenges involved in implementing such a multidisciplinary and inter-institution effort.

Many questions regarding coordination, oversight and sponsorship remain, which the IOM is uniquely positioned to address.

The group recommended that working groups be convened for each of the above areas of research that could report back to the IOM.