SJS/TEN Basic Research Gaps: Working Group Summary

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Areas considered

- Key gaps in research knowledge
- Barriers to execution
- Missing research perspectives
- What additional genetic studies are needed?
- Advances most ready for translation
- Needed resources and infrastructure
- Most promising research areas next 5 years

Key gaps in research knowledge

- Defining the cellular processes that lead to the development of drug neoantigens prior to MHC presentation
- Characterizing how specific culprit drugs activate immune responses outside of MHC restriction

Key gaps in research knowledge

- Characterization of co-factors that drive immunogenicity
- Validation of early diagnostic and prognostic markers at first onset of clinical signs
- Reliable confirmatory/safe *in vitro* challenge test(s)

Barriers to execution

- Need critical mass of well phenotyped patients
- Need expanded sentinel surveillance to catch patients early
- Need biobanked samples from early onset disease

Barriers to execution

- Animal models lacking but not the best lead approach
- Animals lack HLA restriction – can be used to test specific pathways but only after human phenotype is better understood

Missing research perspectives

- Are drugs being recognized in similar ways to viral antigens?
- Need to look beyond just T cells
  - NK cells, T regs, dendritic cells
  - Check-point blockade molecules
- Chemiinformatics of TEN drug culprits

Additional genetic studies

- Still need association studies for other drugs and in various ethnic groups
  - Oxicam-type NSAIDs
  - Lamotrigine
  - Ingredients in cough medications

Most ready for translation

- At this point, predictive genetic testing is the only thing ready for translation

Needed infrastructure

- An expanded consortium with international leadership
- Public-private funding model, with shared responsibility from pharma
  - “Not just death of patients but death of drugs”

Needed infrastructure

- Screening and biobanking patients in early onset phase
- International registry based on standardized phenotyping, including molecular signatures
  - Provides basis for adequately powered clinical trials

Promising over next 5 years

- Investigation of differences between maculopapular rash and SJS/TEN as therapeutic targets
- Biomarkers in acute phase to facilitate:
  - Diagnosis (define specific phenotypes)
  - Prognosis (who will progress?)
  - Treatment targets (such as cell death pathways)

Promising over next 5 years

- Massive parallel sequencing of HLAs linked to medical record outcomes
- Predictive tests in addition to HLAs
  - Pathway analyses of GWAS data
  - Role of metabolism and plasma drug/tissue concentrations

Comments and questions ?