

**NHLBI Working Group
Use of Animal Models for Research in GVHD:
Knowledge Gaps and Future Directions
Rockledge II,
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I. Background. Animal models historically have proven to provide important preclinical data that has led to new clinical approaches to prevent GVHD. Both rodent and large animal models (canine; non-human primate) have contributed to such development.

Rodent animal models. General principles for developing new GVHD approaches.

1. Efficacy should be observed in more than one model with different pathophysiologies with uniformly high lethality in the the controls (eg. CD4, CD8, both; miH, MHC). Preferable if more than one lab has similar results in the same or different models
2. The degree of GVHD reduction can be estimated by T cell titration experiments
3. Consideration for assessment of efficacy in young vs older mice, TBI vs Cy/TBI
4. Due to differences/nuances in results between labs, it is important to understand responsible mechanisms and place data in that context with other studies
5. Ab or cellular therapy may be verified in xeno-GVHD or humanized mouse models

Large animal models (canine).

1. May better simulate human outcome data especially in the area of drug metabolism and drug interactions and when biological agents that have species cross-reactivity.

II. Challenges and recommendations. The Committee identified several areas in which gap support would greatly facilitate the development and clinical testing of new approaches to prevent and treat GVHD.

Challenge #1. Reagent access: At the current time, new reagent access awaits solid organ or autoimmunity approval, access from the pharmaceutical industry, or development within an individual investigator's laboratory. These would include antibodies and fusion proteins, small molecule inhibitors of signaling pathways, and new drugs that target the immune or the hematopoietic system. Consideration for NHLBI/NIH sponsored acquisition of materials at reduced cost and either access to the NCI RAID program or development of an ancillary NHLBI RAID program to piggyback onto the NCI RAID program for GVHD studies would be highly useful.

Challenge #2. National access to GVHD animal models. Not many investigators are able to do preclinical modeling in rodent or large animals followed by translation into the clinic. Moreover, typically an individual laboratory uses one or a limited number of models upon which sizable clinical trials are derived. The Committee found merit in developing the concept of a U19 mechanism to support 2-3 centers nationwide to perform contractual testing of new agents/approaches for GVHD prevention and therapy using agreed upon rodent model systems and conditions. An oversight committee would be needed to prioritize requests. Infrastructural support would be required to maintain such expertise. In addition, support was strong for a canine center to focus on pharmacological agent testing, including pharmacokinetics/pharmacodynamics and drug interactions.

Challenge #3. Clinical trial support for phase I/II studies. The Committee noted that the CTN has been very successful in phase III trial implementation. However, the infrastructure and resources as currently configured are not designed for early phase studies. Additional resources dedicated toward phase I/II studies are essential to move the field forward. A proposal was developed to consider an RFA mechanism for a clinical coordinating center for such studies along with resources that are dedicated for support of phase I/II studies as an open competition that would not compete with CTN but may leverage already existing infrastructures such as CTN, Emmes, etc.

Challenge #4. Junior investigator training and career development. The Committee agreed that few new faculty are being trained to utilize preclinical models to develop new GVHD prevention and therapeutic approaches. One solution to this work force shortage, which risks losing the capacity to utilize such valuable models that drive the field would be to support training of junior faculty (e.g that hold K08; K12; K22/23) for a period of 2-3 years at one of the national sites that are derived from challenge #2 above.

Challenge #5. GVHD pathophysiology and clinical translation. Although ASH, ASBMT and other meetings have components dedicated to preclinical models or clinical applications, there currently exists no forum for bringing together in a dialogue format junior and senior investigators to share overviews of the preclinical field of GVHD and discuss impediments and successes in the clinical arena. It is recommended that NHLBI sponsor a 2 day workshop every 2-3 years that uses a limited slide format and focuses on panel discussions and dialogues to overview advances in the field and to provide solutions that limit successful translation in the venue of GVHD.