Modeling Human Diseases and Treatment in Humanized Mice

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The major challenges of drug development are high failure rate at phase I (30%) and phase II (40%) clinical trials due to safety concerns and lack of efficacy, respectively. The significant level of toxicity and the lack of efficacy suggest that current models for preclinical toxicity and efficacy evaluation do not accurately reflect what is going on in human: the cell culture-based system *in vitro* lacks the physiological context and the animal models may not capture the nature of the human diseases. The recent development in humanized mouse technology may help to bridge the gap. Humanized mice refer to mice stably reconstituted or engrafted with human tissues/cells, such as immune and/or liver cells. For example, humanized mice with a reconstituted human immune system are constructed by engrafting immunodeficient mice with human hematopoietic stem cells (HSC), which then give rise to all human blood lineage cells throughout the lifetime of the mice. In humanized mice, diseases are mediated by human cells in the correct tissue context of the mouse and in the presence of human immune system and therefore may better predict toxicity and efficacy of candidate therapeutics in human. The potential of the humanized mouse technology in drug development will be illustrated using two examples: 1) de novo generation of human double-hit lymphoma, evaluation of alemtuzumab (anti-CD52) for treating double-hit lymphoma, and identification of synergistic combination therapy; 2) evaluation of cytokine storm induced by TGN1412 (anti-CD28). With further development, humanized mice will likely find significant applications in preclinical drug development for cancer, autoimmune and infectious diseases.