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Humanized Mouse Models: Using Human Cells to Conquer Disease

Rodent models provide significant insights into basic biology and underlying circuitry. But research on infectious diseases, viruses, and pathogenesis has been limited because animal models rely on the rodent's own immune system—a vastly different physiological system than a human's.

Our immune system is vital for resisting disease, but many unanswered questions remain about how immunity works. Humanized mouse models are developed from mice that have disabled immune systems. As shown in Figure 1, when human cells from fetal tissue are inserted in these animals, mice acquire human biological immunity and responses.

Humanized mouse models represent one of many ways fetal tissue contributes to life-saving research[1], combining the value of animal models with the accuracy of human immune responses, humanized mice are poised to revolutionize research by offering a way for scientists to directly study the human immune system.[2,3]

Scientists continue to create different techniques to produce these mouse models; each model has strengths and weaknesses. As in all fields of research, the model that is chosen depends on the research question and available resources. For a more in-depth look at the four primary ways scientists develop humanized mouse models, please refer to the table on p. 3.

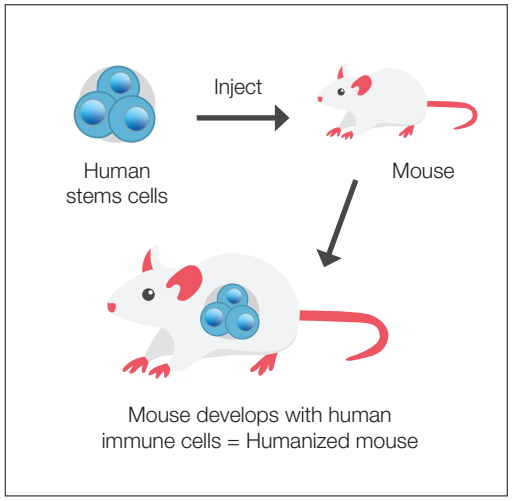
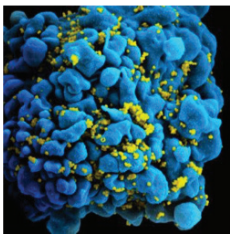


Figure 1: Development of Humanized Mouse Models. Schematic illustrating the overall experimental design used to establish humanized mouse models.



T cell infected with HIV: blue indicates T cell; yellow indicates HIV.
Credit: NIH, National Institute of Allergy and Infectious Diseases (NIAID)

Aedes mosquito that can transmit Zika virus.
Credit: NIH, NIAID

BREAKTHROUGHS AND DISCOVERY

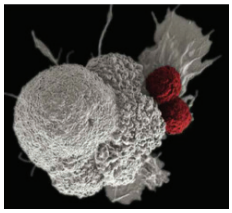
Humanized mice are a premier model for infectious disease research, serving as key pre-clinical tools for a wide variety of translational studies:

Human Immunodeficiency Virus (HIV): As of 2017, about 36.9 million individuals across the globe are HIV positive, 1.8 million of them under 15 years old. While antiretroviral therapy has helped prevent disease progression, there remains no cure for HIV.[4,5] Because the AIDS-causing virus is human-specific, researchers have relied upon humanized mice as one important model to study HIV.

- Researchers discovered that humanized Bone marrow, Liver, Thymus (BLT) mice are uniquely capable of acquiring HIV, and similarly to humans have rapid depletion of CD^4+ T cells.
- Humanized mice respond to antiretroviral drugs similarly to humans.[6]
- Humanized mice research holds significant promise if an HIV cure is discovered because the FDA requires potential therapies to be tested in animal models prior to clinical testing.[7]

Zika Virus: This virus was declared a public health emergency in 2016 and scientists accelerated efforts to develop a vaccine.[8]

Testing vaccine effectiveness requires human immune cells. In 2017, scientists tested a DNA vaccine with specific Zika proteins in humanized mice. They developed antibodies against Zika and showed no signs of viral infection.[9] While no vaccine has been approved, humanized mice studies have significantly increased knowledge about the disease's mechanism, and illuminate primary targets for a human Zika vaccine.



A cancer cell (white) under attack by two T cells (red) during an immune response.
Credit: NIH, National Cancer Institute

Cancer Immunotherapy: Cancer immunotherapy has made noteworthy strides with the help of rodent models. Scientists are just beginning to unravel the possibilities of this new category of treatment, and humanized mice serve as a valuable resource to help bridge outstanding gaps in the field. For example, although immunotherapies offer relief, patients do not experience significant improvement until months into treatment. Humanized mice allow researchers to investigate and evaluate different cellular and antibody-based immunotherapies in real time, and with more precision.[10]

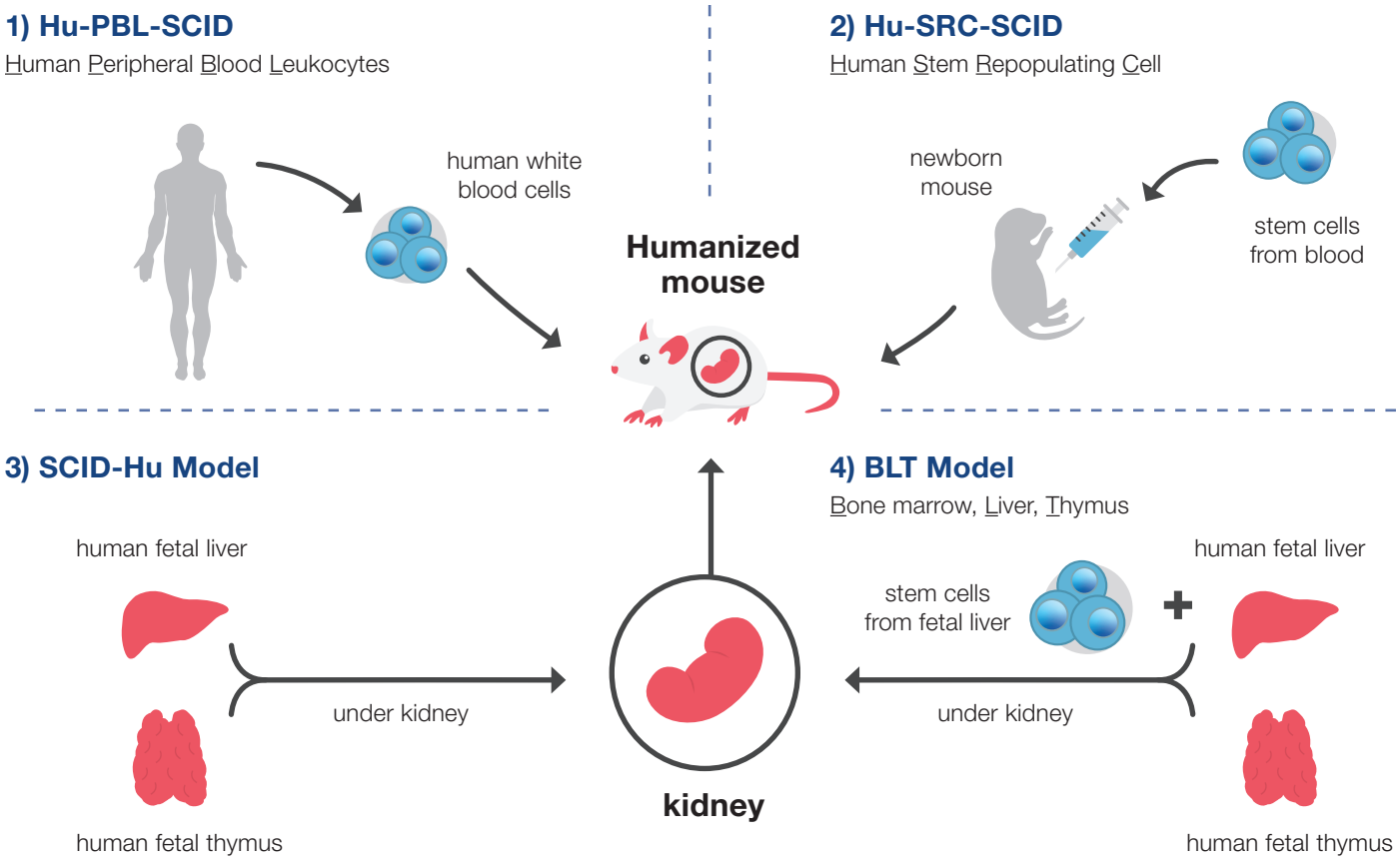
- Researchers utilized humanized mice to create a human pancreatic cancer model. Mice with established pancreatic tumors were injected with chimeric-antigen-receptor (CAR) human T-cells,[11] specifically targeting a protein called PSCA that is overexpressed in this cancer.
- These CAR-engineered human T-cells exerted significant anti-tumor activity, suggesting PSCA is a potential target for developing immunotherapies.[12]

The Bottom Line: Federal Support is Necessary

Understanding the causes of and developing new treatments for the world's most debilitating diseases requires sustained, predictable funding for basic science research from the National Institutes of Health (NIH), including fetal tissue projects. In fiscal year 2019, about 517 projects across 20 Institutes and Centers support humanized mouse model experiments. Over 200 of them are sponsored by the National Institute of Allergy and Infectious Diseases, the leading institution in the fight against HIV.

Consistent NIH support is crucial for the advancement of promising models such as humanized mice along the research pipeline, supporting efforts from bench to bedside.

Four Methods to Develop Humanized Mouse Models[1, 13]



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Mouse Model Name	Description	Advantages	Disadvantages
1) Hu-PBL-SCID: Human Peripheral Blood Leukocytes	Human peripheral blood leukocytes (Hu-PBL) are injected into mice with a genetic defect known as severe combined immunodeficiency defect (SCID)	• Rapid uptake of human T-cells by first week • T-cell function can be evaluated in real time	Because two species are crossed, animals frequently develop lethal graft-versus-host disease (GVHD) within 4-8 weeks
2) Hu-SRC-SCID: Human Stem Repopulating Cell	Human stem cells derived from bone marrow, umbilical cord blood, or fetal liver are injected into newborn mice, which subsequently develop all blood cell types	Complete immune system develops	• Uptake levels of human cells are low • T-cells mature within the mouse rather than human thymus, preventing T-cells from recognizing human-derived foreign agents
3) SCID-Hu	Human fetal liver and thymus segments are implanted beneath the mouse kidney capsule	Fully functioning human thymus and immune system develops	Peripheral immune system (e.g., spleen, lymph nodes, tonsils, etc.) remain under-developed
4) BLT: Bone marrow, Liver, Thymus	Human fetal liver and thymus segments are implanted beneath the kidney capsule, plus injection of fetal liver human stem cells	• Mouse develops complete immune system • Mouse develops all blood cell types • T-cells mature in human thymus, allowing cells to recognize and attack human-derived molecules	Mouse often develops lethal GVHD

REFERENCES

1) Use of fetal tissue is subject to strict government regulation and review -- National Institutes of Health, Office of Extramural Research. NIH Grants Policy Statement. Available at: https://grants.nih.gov/grants/policy/nihgps/html5/section_4/4.1.14_human_fetal_tissue_research.htm
2) Walsh NC, Kenney LL, Jangalwe S, Aryee KE, Greiner DL, Brehm MA, Shultz LD (2017) Humanized Mouse Models of Clinical Disease. Annu Rev Pathol 12:187-215.
3) Skelton JK, Ortega-Prieto AM, Dorner M (2018) A Hitchhiker's guide to humanized mice: new pathways to studying viral infections. Immunology 154:50-61.
4) Global Statistics, HIV.gov. Available at: https://www.hiv.gov/hiv-basics/overview/data-and-trends/global-statistics
5) Marsden MD, Zack JA (2017) Humanized mouse models for human immunodeficiency virus infection. Annu Rev Virol 4:393-412.
6) Denton PW, Estes JD, Sun Z, Othieno FA, Wei BL, Wege AK, Powell DA, Payne D, Haase, AT, Garcia JV (2008) Antiretroviral pre-exposure prophylaxis prevents vaginal transmission of HIV-1 in humanized BLT mice. PloS Med 5:e16.
7) U.S. Food & Drug Administration, Development & Approval Process (Drugs) (2018). Available at: https://www.fda.gov/drugs/developmentapprovalprocess/default.htm
8) World Health Organization (WHO) (2016). "Zika virus and complications: 2016 Public Health Emergency of International Concern." Available at: https://www.who.int/emergencies/zika-virus/en/
9) Yi G, Xu X, Abraham S, Petersen S, Guo H, Ortega N, Shankar P, Manjunath N (2017). A DNA Vaccines Protects Human Immune Cells against Zika Virus Infection in Humanized Mice. EbioMedicine 25:87-94.
10) De La Rochere P, Guil-Luna S, Decaudin D, Azar G, Sidhu SS, Piaggio E (2018). Humanized Mice for the Study of Immuno-Oncology. Trends Immunol 39: 748-763
11) FASEB, Breakthroughs in Bioscience Report (Spring 2018). Cancer Immunotherapies: From Magic Bullets to Super T Cells
12) Abate-Daga D, Lagisetty KH, Tran E, Zheng Z, Gattinoni L, Yu Z, Burns WR, Miermont AM, Teper Y, Rudloff U, Restifo NP, Feldman SA, Rosenberg SA, Morgan RA (2014) A novel chimeric antigen receptor against prostate stem cell antigen mediates tumor destruction in a humanized mouse model of pancreatic cancer. Hum Gene Ther 25:1003-1012
13) Shultz L (2017) Next Generation Humanized Mouse Models for Human Infectious Diseases. The Jackson Laboratory.