Humanized mice created at Yale, are opening new avenues of research into cancers caused by disorders in the production of blood, such as acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS). Until recently, such research was hindered because human blood stem cells are difficult to grow in cell cultures or to engraft in mice.

Richard Flavell, PhD, FRS, Sterling Professor of Immunobiology, solved that by designing a new mouse. He genetically modified the murine immune system to make it more human-like. The mice even express human cytokines, growth factors secreted by the liver and other cells in the body that are important regulators of stem cell proliferation and maturation. These humanized "MISTRG" mice accept and nourish human cells, especially bone marrow stem cells, without destroying them and allow them to make mature blood cells.

MISTRG mice have transformed the research of Stephanie Halene, MD, PhD, Associate Professor and Interim Chief of Hematology, who studies AML and MDS. "Now we can model the disease and maintain it in mice for many months," she said, "which allows us to replicate the complexity and changes that can occur in patients over time."

Using MISTRG mice, researchers can track the initiation and progress of these blood cancers—how and when mutations occur, how they alter the production of blood, and how they cause AML and MDS. In 2019, Dr. Halene and her colleagues published a paper in *Nature Communications* describing this process in MISTRG mice. The paper excited MDS researchers all over the world and has led to many collaborations, with scientists traveling to Yale to test new ideas in the mice.

Dr. Halene's work also prompted a translational spinoff closer to home, a collaboration with Ranjit Bindra, MD, PhD, Associate Professor of Therapeutic Radiology. They used MISTRG mice to test PARP inhibitors in combination with other drugs against abnormal isocitrate dehydrogenase (IDH).

Their project is a good example of how breakthroughs are distributed at Yale and applied to different cancers. Since IDH is also a driver of MDS, Dr. Halene noticed Dr. Bindra's research and their collaboration was born.

"These IDH mutations very commonly co-recur in MDS and AML with splicing factor mutations, one of the primary subjects in my lab," said Dr. Halene. "So now we can put Ranjit's expertise in DNA damage repair and mine in RNA biology together and ask, 'how do these two different mutations collaborate to form MDS?'"

When they tested the PARP inhibitor olaparib against IDH-mutant cells in MISTRG mice engrafted with MDS and AML, olaparib showed the same deadly effects as it had in prior research in IDH-mutant gliomas. "We can see exactly the same mechanism," said Dr. Halene, "but we're even more interested in how we can exploit it for new options for MDS and AML patients."

Next, they plan to look at the synergy of PARP inhibitors with other drugs and pathways. "The nice thing," said Dr. Halene, "is that we can figure out optimal combinations in our mouse models and then translate that into a clinical trial." A trial is already planned to launch this year in collaboration with clinician Thomas Prebet, MD, PhD, Associate Professor and Medical Director for Hematology and Cell Therapy.

Dr. Halene is now working with the next generation of MISTRG mice, in which Dr. Flavell solved another research dilemma. MISTRG mice have a humanized immune system, but their red blood cells are murine. When researchers attempt to introduce human red blood cells or platelets, they quickly disappear, eliminated by the mouse's innate immune system.

Dr. Flavell's lab used fluorescence to track introduced human blood cells and found that most of them ended up in the mouse's liver, where they were destroyed. The Flavell lab knocked out a gene, fumarylacetoacetate hydrolase (FAH), in the MISTRG mice, an absence that leads to a buildup of toxic metabolites and eventual liver failure. Next, after the scientists damaged the mice's liver cells, they used injected human liver cells to regenerate the mice livers.

"In the end," said Dr. Halene, "we got a mouse that has human cytokines and 80 to 90 percent human liver cells. Now we can put in human bone marrow stem cells that make human immune cells and red blood and other mature cells, and we can see human red blood cells circulating. That's very attractive, because we can study anemia, MDS, and other diseases of the red blood cell and test new therapies.

She hopes that these scientific breakthroughs will become new therapies that target MDS and AML, slowing progression or inducing remission. Someday it might even be possible to detect these cancers early enough to prevent them. "It's a longshot," she said, "but that's where all fantastic science aims."

Stephanie Halene, MD, PhD

Humanized Mice Lead to Breakthroughs in Blood Cancers