Mice injected with human genes may transform research into cancers of the immune system, multiple myeloma, and other hematologic cancers. Yale scientists designed this groundbreaking mouse model by removing six genes from mice and inserting key genes found in human bone marrow, where myeloma develops. This revolutionary mouse model is providing researchers and clinicians at Yale and beyond with multiple possibilities to advance both research and treatment.

To build this mighty mouse took more than a decade, says Richard Flavell, PhD, Sterling Professor of Immunobiology. Previous researchers had succeeded in putting human cells into mice, but unless the immune system of the mouse was disabled, it attacked the human cells and impeded their ability to develop. But even when the immune system was knocked out, the human immune cells did not populate the mouse well. Dr. Flavell attributed this to chemical differences in the growth factors (proteins that bind to receptors on cell surfaces) found in the immune systems of mice and humans. He set out to design a mouse model that mimicked the human immune system so that researchers could use mice to study that system and its responses to infections and cancer.

“He identified the growth factors we thought were important for immune cell development,” says Madhav V. Dhodapkar, MBBS, Arthur H. Bunker and Isabel Bunker Professor of Medicine (Hematology), Chief of Hematology, and Professor of Immunobiology. The injected myeloma cells behaved in the mice much as they do in humans. “So now we can grow patients’ tumor cells, we can study them, we can look at their genetic evolution and the way they behave hematologically,” Dr. Dhodapkar notes. That work has started at Yale.

Myeloma may be foreshadowed by a precursor stage called MGUS (monoclonal gammopathy of undetermined significance). But MGUS cells had never been grown successfully, so their development and link to myeloma remained unclear. But MGUS grows in MISTRG6, a scientific first.

“This was really wonderful,” says Dr. Flavell. “Because it’s a general paradigm for other hematologic malignancies. We’re very excited. These humanized mice can be a useful intermediate point between people doing mouse studies and people working with patients in the clinic.”

Imagines, he adds, that you are considering four experimental drugs to treat human myeloma. You could test them on an individual patient’s tumor cells to see if they work. “That’s a lot slower and more expensive than doing a Phase I clinical trial, and it’s also less burdensome for the patient. Or you could take a patient’s tumor cells and put them into 20 mice to test which one is best for that patient. It’s an additional kind of translational research.”

The mice are already serving Yale researchers studying bone marrow cancers such as myeloma and myelodysplastic syndromes. Another researcher has started using the mice to study lung cancer. Because the mice replicate both malignant and normal human cells, they are useful for Yale scientists trying ways to trigger the immune system to attack tumor cells.

Interest in the mice is also strong outside of Yale at both academic centers and pharmaceutical companies who plan to do their own research using the mice. “Right now, created at Yale, will benefit cancer patients everywhere.”