Gone Wildling: Building a Better Lab Mouse

There is growing recognition that the microbiota helps shape the immune system—and thereby therapeutic responses. These complexities have been difficult to unravel using conventional laboratory mice, so researchers are turning to new models that, in terms of microbial makeup, better resemble their wild counterparts.

One such model is the "wildling" mouse, developed by Stephan Rosshart, MD, and Barbara Rehermann, MD, at the NIH (Science 2019;365:eaaw4361). Their strategy involved implanting C57BL/6 embryos into wild female mice. This produced a colony of wildlings with natural microbiota at key body sites, including the gut, skin, and genitals, but in which the highly tractable genetics of C57BL/6 mice were preserved.

Simply using wild mice for immunology studies would "remove the advantage of easy genetic modification, which has made the lab mouse a research mainstay," explains Rosshart, now at Universitätsklinikum Freiburg in Germany. Alternatively, although engrafting human microbiota into mice "sounds like a logical approach, it actually isn't." Doing so yielded mice that were practically immunodeficient, he notes. "Their gut immune system was so underdeveloped, it almost resembled that of a germ-free mouse."

Instead, the wildling model spotlights what Rosshart calls "the common link between free-living mammalian organisms"—constant exposure to microbes and pathogens, which influences immune development. "You could say we've first made the lab mouse more like a mouse, and this in turn may get us closer to reflecting the human immune system," he adds.

The bacterial, fungal, and viral repertoire of these wildlings was much like that of wild mice, the researchers reported. Stability was another feature; the animals' gut microbiota recovered quickly when challenged with antibiotics and modified diets. By contrast, gut microbiota in lab mice are considerably less resilient and prone to shifting with environmental changes, Rosshart observes. "If a commercial mouse was delivered to Freiburg and its sibling

to another institute, although they're from the same vendor and perhaps even shared a cage, within a short time they'd have very different microbiota. It does raise the question of data consistency and reproducibility in current research models."

To test the wildlings' translational value, his team revisited two therapies that failed in clinical trials. CD28SA, a monoclonal antibody, had shown efficacy in mouse models of autoimmune disease; in healthy volunteers, it unexpectedly triggered inflammatory T cells and life-threatening cytokine storms. Meanwhile, TNFα blockade rescued lab mice from septic shock, but increased mortality in patients. When both therapies were tested in wildlings, the results closely recapitulated human immune responses, not those of lab mice, Rosshart says.

That wildlings may better predict clinical outcomes "is very important for the researchers to have shown," says Marcel van den Brink, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York, NY. He notes that diversifying lab mice microbiota—for instance, through housing with pet store mice—"is catching on, and the wildling approach should spark even more interest among anyone using mouse models to understand human immunology" (Nature 2016;532:512–6).

For illuminating basic biology principles, conventional lab mice "will remain invaluable," van den Brink says. Pertinent to his own research, "it's how we learned that graft-versus-host disease [GVHD] involves donor T cells. Further GVHD studies haven't always translated well to humans, though, so wildlings may be very useful here."

Of late, "there's been this backlash against mouse models—that they can't teach us anything clinically useful," he adds. "It's almost a state of nihilism, which I hope wildlings and similar strategies help calibrate." –*Alissa Poh* ■

Exact Sciences Buys Genomic Health for $2.8 Billion

Exact Sciences' recent purchase of Genomic Health could speed the development of new cancer screening assays for a variety of tumor types—and build upon the success of the companies' Cologuard and Oncotype DX tests.

Madison, WI–based Exact Sciences, which has more than 2,200 employees, produces Cologuard, a colon cancer screening test. Approved by the FDA in 2014, Cologuard assesses stool samples for blood and 11 types of DNA alterations that may indicate colon cancer or advanced polyps, including mutations in *KRAS* and abnormal methylation of *BMP3*. In 2018, the company's revenue was $454.5 million.

Genomic Health, headquartered in Redwood City, CA, employs about 900 people. Its flagship products are the Oncotype DX assays that provide treatment guidance for patients with breast, colon, or prostate cancers. The breast cancer test, for example, uses expression levels of 21 genes, such as *KI67*, *ERBB2*, and *PGR*, to gauge the likelihood of a distant recurrence and predict whether a patient will benefit from chemotherapy. The company reported $394.1 million in total revenue last year.

Both companies are also working on new products, such as the blood biomarker assays that Exact Sciences is creating for other malignancies—including liver, lung, and pancreatic cancers—in collaboration with academic partners.

Exact Sciences and Genomic Health announced the $2.8 billion sale at the end of July. "Together, with our collective resources and broader platform, we will be able to provide our existing tests to more people, while also accelerating the development and launch of future cancer diagnostic tests," says Kevin Conroy, JD, chairman and CEO of Exact Sciences.

The purchase likely won't have any impact on the companies' current assays, says Brian Weinstein, a health