Published OnlineFirst August 23, 2019; DOI: 10.1158/2159-8290.CD-NB2019-099

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

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care analyst at William Blair & Company in Chicago, IL. He predicts, for instance, that the deal will not affect the price of Cologuard or Oncotype DX; the costs of the tests have already been negotiated with payers such as insurance companies. Nor will the deal reduce competition, because the target groups for the assays don't overlap. "These are two very different products," he says.

Uniting the companies' efforts will increase investment in R&D and likely lead to the development of innovative diagnostic products. The deal combines their experience and expertise, Weinstein says, and "provides a broader organization for Exact Sciences to draw from down the road."

Another upside, Weinstein says, is that the deal could help Exact Sciences expand internationally when its new products are available. Cologuard is sold only in the United States, whereas Oncotype DX assays are available in 90 countries.

Overall, he says, the acquisition will allow Exact Sciences to show that "it's not just the Cologuard company," but "a broad-based cancer diagnostic company." *–Mitch Leslie* ■

Fedratinib Becomes New Option in Myelofibrosis

The FDA recently greenlighted fedratinib (Inrebic; Celgene) for intermediate-2- or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis, making it just the second drug approved for the disease. The agency based its decision on a phase III trial in which the drug significantly reduced symptoms compared with a placebo. However, the drug comes with a Boxed Warning for encephalopathy.

Myelofibrosis is a rare blood cancer likely caused by abnormal blood stem cells in the bone marrow. Scar tissue then forms, impairing blood-cell production. This can cause the spleen to take over that task—and enlarge. Generally, patients at low risk require only surveillance, but those at intermediate and high risk of disease progression require treatment as symptoms—fatigue, weakness, shortness of breath, fever, and weight loss—worsen. The JAK1/2 inhibitor ruxolitinib (Jakafi; Incyte) has been the mainstay of treatment. Like ruxolitinib, fedratinib, a JAK2 inhibitor, disrupts JAK–STAT signaling, which becomes overactive in patients with myelofibrosis due to *JAK2*, *CALR*, or *MPL* mutations.

In the JAKARTA trial of 289 patients with newly diagnosed myelofibrosis, 37% of those treated with fedratinib had at least a 35% reduction in spleen volume, and 40% had at least a 50% improvement in symptoms, compared with 1% and 9%, respectively, of patients who received a placebo. In the phase II JAKARTA-2 trial, 55% of 83 patients resistant or intolerant to ruxolitinib had a splenic response.

However, side effects—namely encephalopathy—have been a concern: The FDA placed a clinical hold on fedratinib from 2013 to 2017 due to eight suspected cases of Wernicke's encephalopathy, a neurological disorder. The hold was lifted after a follow-up analysis confirmed only one case, but fedratinib now has a Boxed Warning for encephalopathy.

In JAKARTA, 21% of patients experienced serious side effects, most commonly cardiac failure and anemia, and 1% died from cardiogenic shock; 14% discontinued treatment due to side effects.

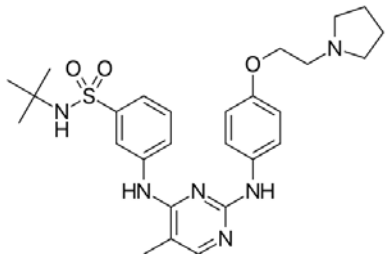
"Fedratinib has had a long road to get to this point, and I do think the approval is a positive development, particularly for patients who are resistant or intolerant to ruxolitinib," says Ann Mullally, MD, of Dana-Farber/Harvard Cancer Center in Boston, MA, who was not connected to the trials.

Naveen Pemmaraju, MD, of The University of Texas MD Anderson Cancer Center in Houston, who was also not involved in the trials, notes that fedratinib's broad approval means it can be given to patients with different types of myelofibrosis and at different times.

As for encephalopathy, "I think it's appropriate to be concerned about it, and like any post-FDA drug approval, we should be vigilantly watching this to see what a real-world cohort of patients with myelofibrosis does," Pemmaraju says.

Mullally agrees. "I think clinicians will be very aware of it, but I think it's a rare occurrence," she says.

Pemmaraju now wonders whether fedratinib can be combined with other drugs, particularly those that have been used with ruxolitinib, and how it should be sequenced with ruxolitinib.



Structural formula for the JAK2 inhibitor fedratinib.

Mullally also sees a need for drugs specific to the *JAK2* V617F mutation that leads to overactivity of the JAK–STAT pathway. "To have a big impact in this disease, we need potent selective drugs that can preferentially eradicate the cells that harbor the causative mutations, and then we'd have the potential to intervene earlier in the course of the disease," she says. *–Catherine Caruso* ■

Sylvester Cancer Center Receives NCI Designation

Sylvester Comprehensive Cancer Center at the University of Miami (UM) Leonard M. Miller School of Medicine in Florida has been named an NCI-Designated Cancer Center, becoming one of 71 U.S. centers to receive the recognition. The coveted distinction recognizes outstanding cancer programs committed to discovering innovative approaches to prevention, diagnosis, and treatment.

The Sylvester Center will receive $2.1 million annually for 5 years to continue building its programs, says Stephen D. Nimer, MD, the center's director.

To achieve NCI designation, institutions must complete a rigorous application process for a 5-year core grant from the NCI's cancer centers program to fund research infrastructure, advance scientific investigation, foster collaborative programs, and engage the community. Standard core grants—and the accompanying NCI designation—are awarded to institutions demonstrating superior organizational and scientific strengths.

Researchers at Sylvester have made significant strides in several key areas,

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CANCER DISCOVERY

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Cancer Discov 2019;9:1331-1332. Published OnlineFirst August 23, 2019.