Many small steps: 'diversity outbred mice' open new pathways for researching human diseases

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from The Jackson Laboratory, a leader in translational science since its founding in Bar Harbor, Maine, in 1929. The presentation focused on work with new combinations of genetically diverse mice and human genomic profiles, which could reveal novel pathways for treating complex diseases.

Simply put, The Jackson Laboratory has greatly improved genetic diversity among

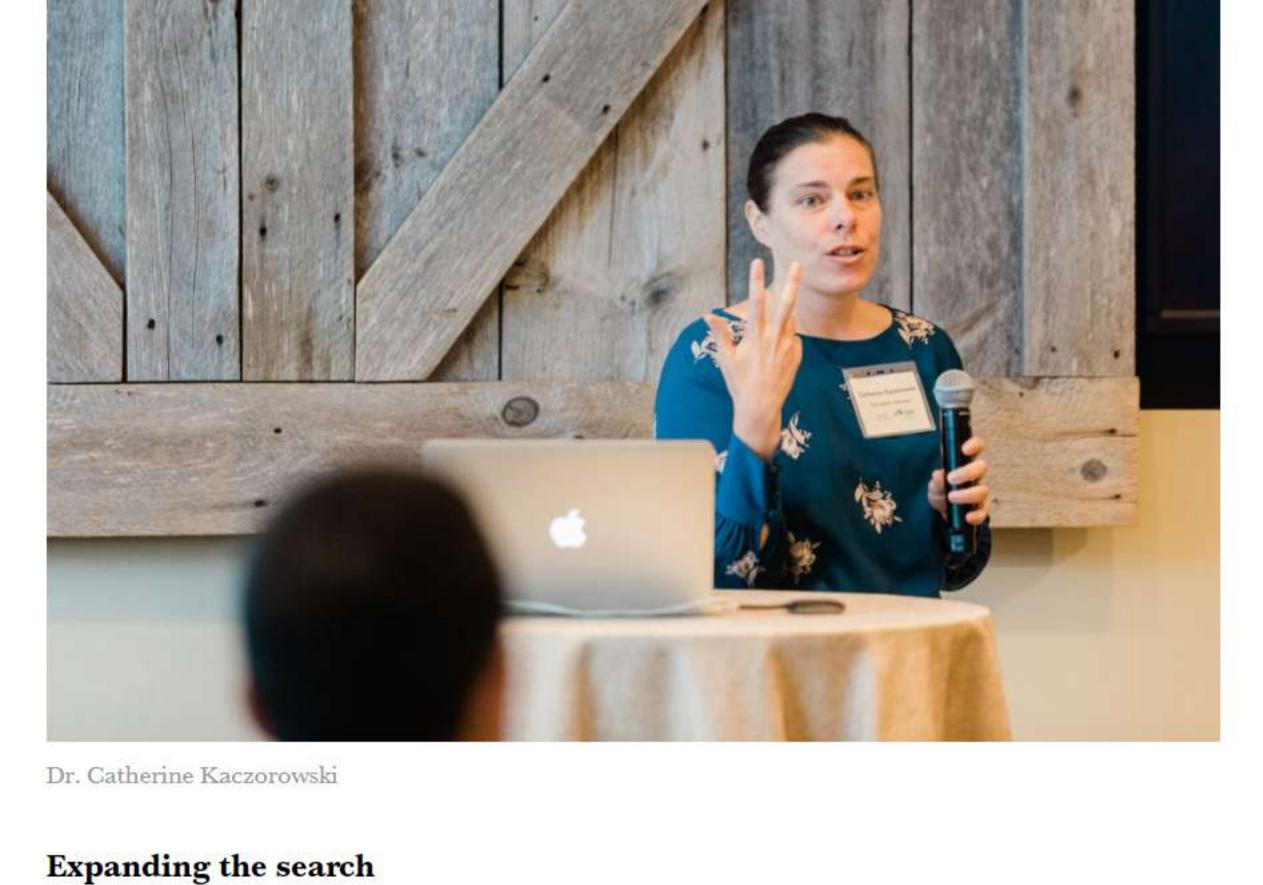
CAMBRIDGE, Mass. — A recent event in Technology Square featured researchers

mouse models. These new models yield data that translates to clinical trials in humans to a far greater degree than researchers previously thought possible.
"It's not that the mouse as a species was wrong," said Catherine Kaczorowski, PhD, associate professor, Evnin family chair in Alzheimer's research, in explaining the

limitations of earlier mouse models. "The problem was the selection of one and only one genetic background, which ended up being the worst one to pick, essentially. But the only way you know that is by doing complex genetics."

The implications are significant. For example, using "diversity outbred mice" to study disease could lead to the development of more effective and targeted therapies

It could also create novel pathways for approaching Alzheimer's disease. The goal, said Kaczorowski, "is not to identify things that put you at risk for Alzheimer's disease, but how you can escape Alzheimer's disease, even when you're faced with all of the challenges that should translate into developing cognitive symptoms."



relationship between amyloid beta protein (which can be a precursor to tau development and Alzheimer's onset) in the brain and the development of tau proteins

Kaczorowski said.

associated with the disease.

for cancer.

The Jackson Laboratory's genetically diverse mice have been bred specifically to explore that relationship. "We essentially leveraged the most aggressive thing we could identify to drive amyloid and even some tau pathology, and we bred it to a population of mice that are different in five million places across their genome,"

Next, researchers looked for signs of cognitive impairment in the mice. "They go in a

The key to understanding Alzheimer's disease lies in untangling the complex

'memory maze,'" Kaczorowski said. "A mouse that can remember where it is will look at new paths in the maze. Mice with memory impairment will enter the same area often and continue to make errors."

In addition to using more genetically diverse mice, researchers at The Jackson Laboratory have begun actively studying other species. For instance, Ron Korstanje, PhD, FAHA, has been using mouse models to study Alport syndrome, a form of

"But somehow within a few weeks, they are able to completely recover," Korstanje said. "So we're trying to figure out what the mechanism is. Why can bears do that and humans can't?"

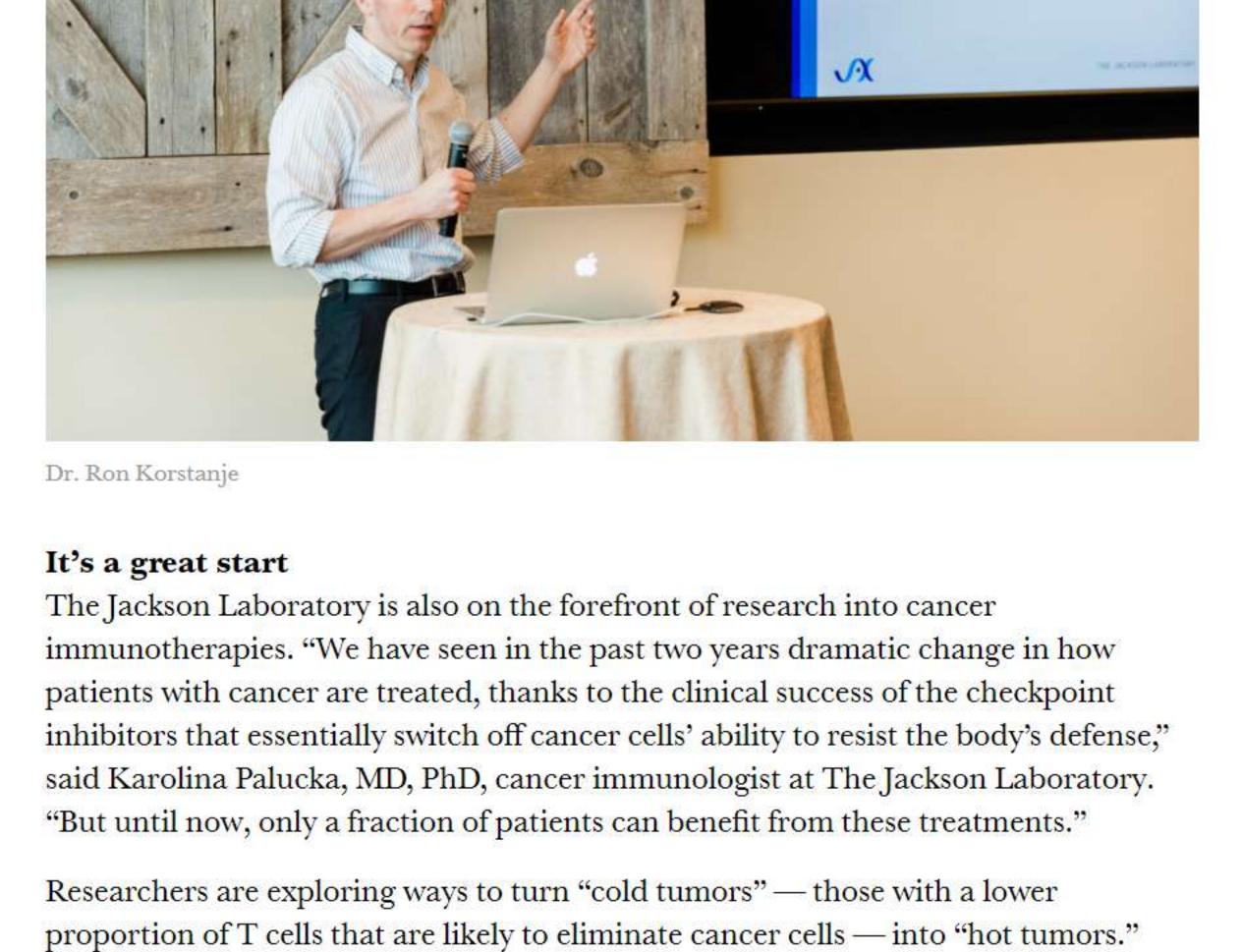
Candidate genes for albuminuria

Dighte Midallors are associated with respected systems below to produce the product of the

kidney disease. But he has also probed the genetic mechanism that black bears use to

reverse the kidney damage that occurs during hibernation, a level of harm that

Korstanje compared to that of a dialysis patient.



cells in patients' body via cancer vaccines.

"Cancer vaccines have gotten a bad rap," said Dr. Palucka. "Part of the reason is that we have not understood the mechanisms that regulate T-cell immunity." That's changing — again, in part due to the breeding of genetically diverse mice. Combined with checkpoint inhibitors, cancer vaccines are among the most promising

One way of doing this is adoptive transfer of CAR-T cells. Another way is to expand T

"Immunologists, and even oncologists, understand that immunology is the critical player," Dr. Palucka said.

developments in cancer immunotherapy.

B.J. Bormann, PhD, vice president of Translational Science and Network Alliances, concluded the breakfast with an optimistic summary of The Jackson Laboratory's ongoing development of diversity outbred mice. "This is the future of The Jackson Laboratory," she said. "Continuing to cycle between mouse and human, to validate gene signatures that we see in the patients, to prove what's causative and what's not. Together we're looking to create a roadmap for a truly disease-free life."

For more information on The Jackson Laboratory's cutting-edge research, visit www.jax.org.