



RESEARCH PROFILE

# David Tuveson

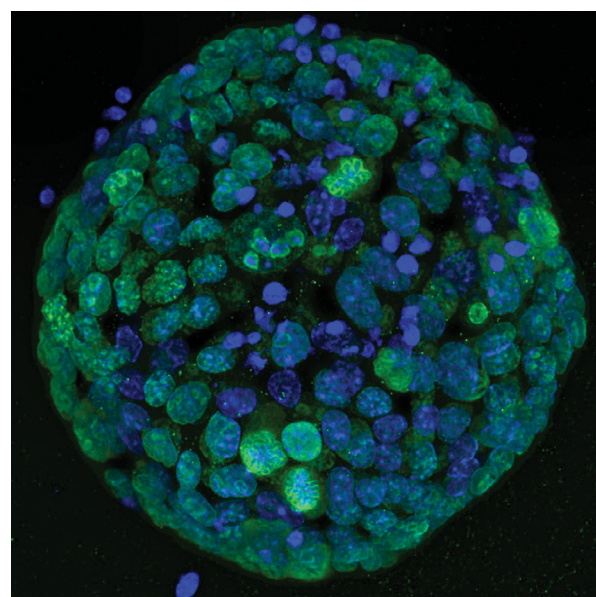
In his lab atop CSHL's Hillside campus, and in a sparkling new preclinical animal experimentation facility in nearby Woodbury, David Tuveson, M.D., Ph.D., and his large team are relentlessly testing new treatment approaches in mice and in three-dimensional cellular models of pancreatic cancer.

The 3D models, which take the form of tiny spheres called organoids, are derived from pancreatic tissue in mice and people. "Organoid technology provides us with the opportunity to learn what we were not previously able to learn about pancreatic cancer," Tuveson says. "These clumps of cells are telling us for the first time how the biology of the tumor is changing from its earliest beginnings through later stages of development, and this, in turn, is presenting new targets for therapy. Observations like this are what enable our science to move forward."

Tuveson, the Roy J. Zuckerberg Professor of Cancer Research at Cold Spring Harbor Laboratory and the recently appointed director of CSHL's National Cancer Institute-designated Cancer Center [see page 13], is also Research Director of the Long Island-based Lustgarten Foundation, the nation's largest philanthropic funder of pancreatic cancer research. He has spent his entire career fighting the illness, one of the few common cancers for which there is still no effective treatment. Half of newly diagnosed patients live only 6 months. Just 8 percent survive 5 years.

Pancreatic cancer is difficult for well-known reasons. Notorious for being "silent" in its initial (and presumably treatable) stages, it is usually diagnosed late—often at Stage 4, after it has begun to spread. Pancreas cancers are hard to see, sprouting in a part of the body that is not observed in routine physical exams. Worse, pancreas tumors are embedded in a mass of extraordinarily dense tissue called stroma, making them hard for chemotherapy to reach.

Tuveson compares pancreatic cancer to an oatmeal-raisin cookie, where the raisins are the cancer cells. Not only is the "oatmeal"—the stromal tissue surrounding the cancer cells—denser than in other cancer types; some of its non-cancerous component cells promote tumor survival



Organoids are hollow spheres that grow from samples of pancreatic tissue, enabling Tuveson's team to faithfully recapitulate the full course of pancreatic cancer and test new diagnostics and therapies in the lab.



Dr. Christine Chio, a postdoctoral investigator in the Tuveson lab, is working on a novel drug therapy that kills pancreatic cancer cells by reducing their antioxidant levels.

and growth. In important research published earlier this year, Tuveson's team demonstrated that a cell type in pancreatic stroma, called fibroblasts, comes in at least two varieties. One type seeds the stroma; the other secretes interleukin 6 (IL-6), an immune signaling molecule associated with cancer proliferation.

"This finding underscores that stroma is not homogeneous in pancreatic cancer," Tuveson notes, "and this provides an opportunity to develop therapeutic agents that target specific fibroblast populations." It's only one of several hopeful developments in the lab that could lead to new treatments and diagnostics.

Tuveson realized during his clinical training that "the disease nobody had any answers for was cancer—and the patients who seemed to have the worst luck of all were pancreatic cancer patients."

His postdoctoral project under Tyler Jacks at MIT was to develop the first animal model of the illness. He made good progress, and took the model with him to his first faculty job, at the University of Pennsylvania. He later moved to the University of Cambridge, in the U.K., where studies with the mouse model "made clear it was very difficult to get drugs into pancreas tumors," he recalls. This is when his focus began to turn to the "oatmeal-raisin cookie" problem.

After 6 years in England, Tuveson was persuaded by CSHL President Bruce Stillman and by the Lustgarten Foundation to come back to the U.S. "Cold Spring Harbor was perfect—someplace filled with brilliant basic scientists where I could think, as I was able to do in Cambridge," Tuveson says. He was particularly heartened by discussions with Stillman, Jim Watson and faculty about the Lab's evolving attitude toward translational cancer research. His interest in this branch of research—in which insights obtained in basic research are applied in experiments with clinical implications—stemmed from progress he was making with models of pancreatic cancer.

### 'I hated disease'

A native Chicagoan, Tuveson grew up outside Ann Arbor, Michigan, where, he says, "I was always interested in life—things that flew in the air, crawled on the ground, swam in the water. I just loved looking at nature and touching it."

He attended MIT, where he majored in chemistry, and turned to biology as a postgraduate because "I just hated disease—and not because members of my family were sick. It was just the dismay that the beautiful intricacy of biology could collapse with the snap of your fingers. Disease seemed to me counter to the care that was taken by nature to create life in the first place."

He earned a medical degree at Johns Hopkins, then studied for a Ph.D. under physician-researcher Douglas Fearon, who "pretty much taught me the scientific method." Now that Fearon has also joined the CSHL faculty, the two are actively collaborating in pancreatic cancer research.



Members of the Tuveson lab help increase public awareness at the Lustgarten Foundation's annual Long Island Pancreatic Cancer Research Walk.





World Pancreatic Cancer Day provides another occasion for Lab members to educate the public about one of the most lethal cancers.

Not just animal models. While still in Cambridge, then continuing in his new lab at CSHL, Tuveson and collaborator Hans Clevers, president of the Royal Netherlands Academy of Arts and Sciences, developed a method to grow pancreatic tissue in the form of hollow spheres called organoids.

Pancreatic cancer cells had always been hard to grow in culture, slowing research. Until the advent of organoids, scientists had to rely on cells grown in flat culture dishes and depended on samples from genetically engineered mice, which take a year to generate. Organoids, which grow in a 3D medium, develop in days.

In addition to enabling researchers to observe pancreatic cancer from its beginnings, pancreatic organoids have

in people. Extrapolating from the new knowledge gained in organoids to preclinical experiments “is really the foundation of our laboratory,” Tuveson says.

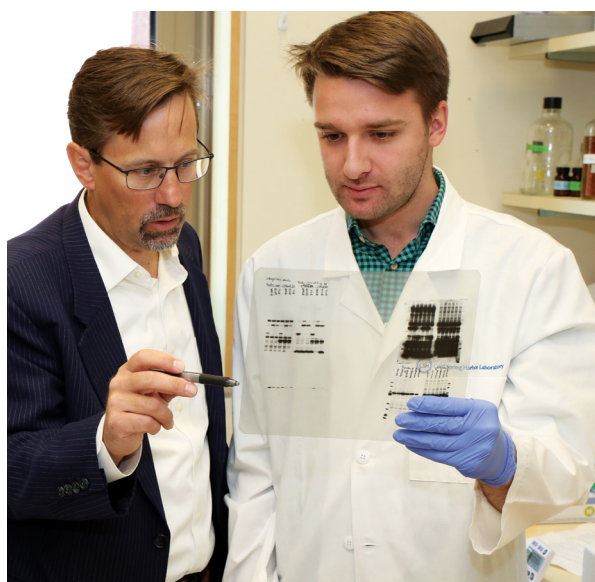
One of Tuveson’s insights while still at Cambridge centered on the role of antioxidants in pancreatic cancer. This work, taken up by postdoc Christine Chio in his CSHL lab, has led to another new therapeutic idea. Chio has led experiments showing how reducing antioxidant levels in cancer cells provides a powerful way to get the cancer, in her words, “to burn itself out.”

This work stems from Tuveson’s research on Nrf2, a master regulator of the delicate oxidant-antioxidant balance in cells. Chio is testing combination therapies to reduce antioxidants in cancer cells while leaving healthy cells unharmed. Her team is learning that some of these combinations work better than others and is trying to optimize the approach.

Another team, led by Tuveson lab postdoc Danielle Engle, is finding ways to detect pancreas tumors while they’re still small and treatable. “Current technology shows us tumors that are golf ball-sized,” says Tuveson. “I would love to have a way of seeing them when they’re the size of blueberries or grapes.” Tuveson hopes Engle and her team will devise “a dipstick test,” *i.e.*, one that can be given routinely at trivial cost to people at their annual physical exam. Early signs of abnormality would call for a more expensive and detailed anatomical examination of the pancreas with functional MRI scans.

“Our lab has a remarkable amount of freedom to find answers,” Tuveson reflects. “Strong support from Bruce Stillman and the very generous contributions made by Lustgarten allow us to be fearless as we pursue things we think important. Waking up every morning, I can’t wait to get to the lab to see the results of the previous day’s experiments. The science we’re doing is so exciting. This is the best time I’ve ever had as a scientist!”

**Peter Tarr**



Dr. Tuveson conferring with Georgi Yordanov, a Watson School grad student in his lab.

special value in “in vivo” experiments. Once the spheres grow to a certain size, they can be transplanted into mice, where they faithfully recapitulate the course of the illness