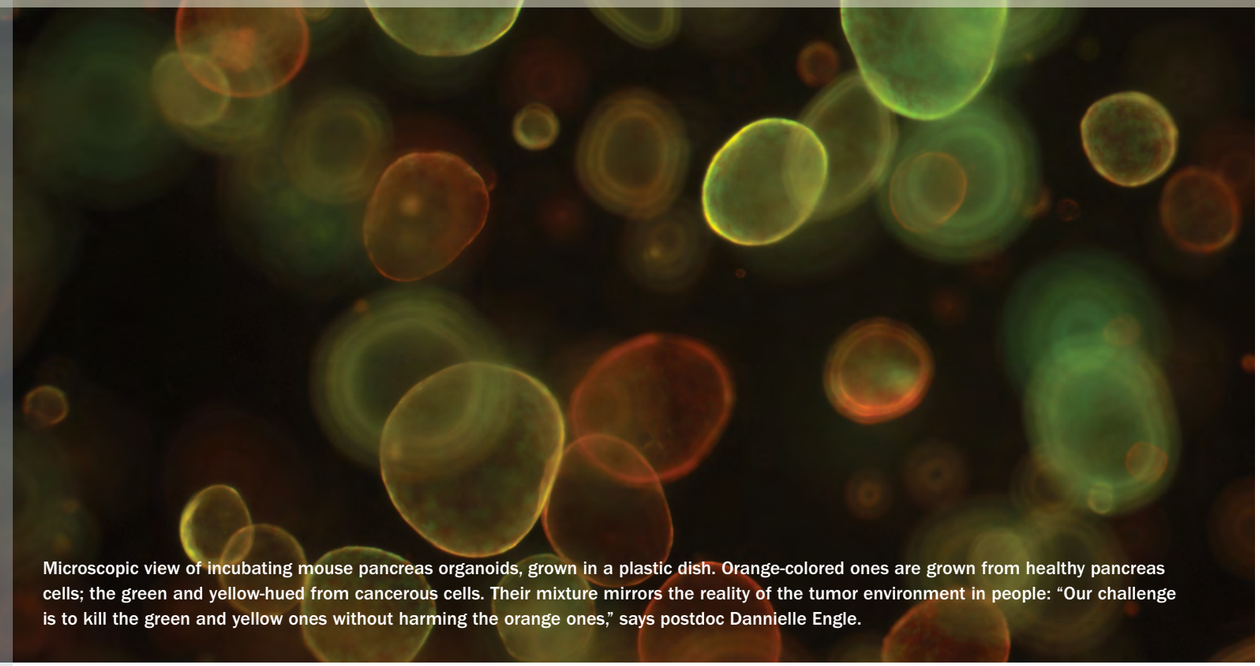
Cancer research in 3D



Microscopic view of incubating mouse pancreas organoids, grown in a plastic dish. Orange-colored ones are grown from healthy pancreas cells; the green and yellow-hued from cancerous cells. Their mixture mirrors the reality of the tumor environment in people: “Our challenge is to kill the green and yellow ones without harming the orange ones,” says postdoc Dannielle Engle.

Suspended in a gelatin infused with growth factors, small clusters of cells extracted from a cancer-stricken pancreas divide and grow, extending upward and outward. Slowly, shapes take form—spheres whose outer surface is composed of a single layer of cells, each filled with a slurry of all the protein building blocks and nutrients necessary for growth.

These three-dimensional balls of cells, called organoids, are providing researchers and clinicians with a desperately needed tool for creating personalized treatments against pancreatic cancer. They may also help diagnose the deadly disease years before current methods can.

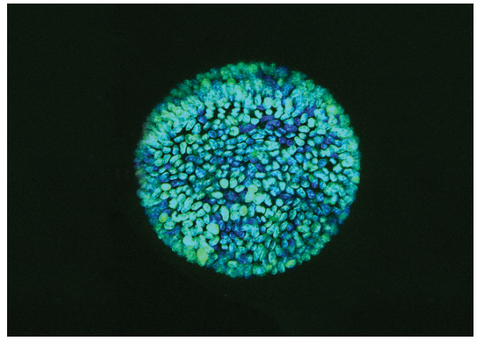
With only 6 percent of patients surviving 5 years beyond their diagnosis, pancreatic cancer is one of the deadliest cancer types. And because half of patients die within 6 months of diagnosis, it’s also one of the more challenging to research.

“When patients get the diagnosis, it’s usually very late in the course of the illness,” says Dr. David Tuveson, CSHL Professor and Director of Research for the Lustgarten Foundation. “It’s hard to study because patients don’t live long enough to participate in clinical trials.”

All cancer research relies on a steady supply of cells—both normal and cancerous. By comparing normal cells to cancer cells, scientists can identify the changes that lead to disease—information useful in developing effective therapies. In many cancer types, researchers obtain cells during surgery or autopsy. But since 85 percent of pancreas cancer patients are ineligible for surgery at the time of diagnosis, there are few opportunities to obtain tissue to study in the lab.

When researchers do get their hands on pancreatic cancer cells, growing them in plastic Petri dishes and testing potential drugs against them has provided flashes of hope, but the results have ultimately disappointed. “We’re very good at killing those cells in culture dishes, but once we try to kill those same cells in the patients, we find that their tumors are much more complicated,” says Dannielle Engle, a postdoctoral researcher in Tuveson’s lab.

Pancreatic tumors are comparatively complex. Only 10 percent is composed of cancer cells; the rest is a combination of fibroblasts (cells that give structure to tissue), blood vessels, and immune cells. This mix forms a “stromal shell” that can be hard for drugs to penetrate. Looking to test therapies on a more representative model of pancreatic tumors, including the confounding stromal shell, Tuveson turned to organoids.



This organoid mimics a very aggressive form of pancreas cancer. The blue-green color in virtually every cell signals cell division—a hallmark of cancer.

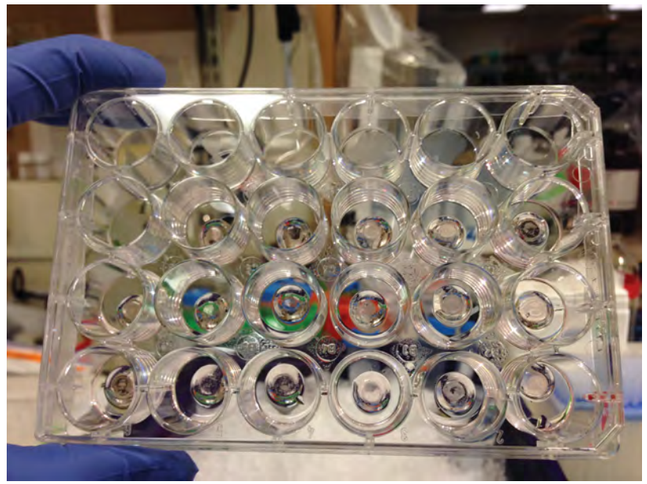
In his former position at Cambridge University in the UK, Tuveson struck up a friendship with Dutch researcher Hans Clevers, who developed a general technique for creating organoids. “I take care of patients with pancreatic cancer,” explains Tuveson, “and I was just sick and tired of watching everything going so slowly towards helping individual patients.” He collaborated with Clevers to perfect a method of fabricating organoids from pancreatic cells.

Creating enough organoids to test a variety of drugs for an individual patient takes about two weeks. Tuveson and his team obtain cell samples from patients—either during surgery or a needle biopsy. Then they cultivate the cells into dozens of the spherical 3D tumor facsimiles. Once developed, the organoids are transferred into the pancreas of several mice and allowed to form tumors, providing the team with a chance to simultaneously test different therapies. They probe the organoids to identify molecular pathways contributing to their growth and try to target those pathways with various drugs to see if survival rates improve.

In addition to deriving personalized therapies for patients, organoids can be used to identify biomarkers—molecular signatures of disease that can aid diagnosis. “Before, when you grew these cells in a dish, you could only grow fully cancerous cells,” says Engle. But with organoids, each stage of the cancer can be grown. Studying differences across organoids from many patients could help identify reliable biomarkers. “This would give us a way of finding pancreatic cancer early enough that more patients would be eligible for surgery,” says Engle.

Because patients live on average only 6 months past their diagnosis, pancreatic cancer has been viewed as an incredibly fast-moving disease. However, two recent studies suggest that the progression from the cancer’s initiating events to an overt malignancy can take more than 10 years. After that, spread throughout the body can take another 5–7 years. “That means we have at least a decade to find these tumors before they spread,” says Lindsey Baker, a postdoc who has worked closely with Tuveson, Engle and others to make organoids a tool that might help change the prognosis for pancreas cancer patients.

Chris Palmer



A plate with 24 “wells” in which pancreas organoids are grown. The tiny spheres can be discerned within the dome-like gels at the center of each well.