

Lustgarten-Funded Study in *Cancer Discovery* Reveals Possible New Targets for Therapeutics

Characteristics of Fibroblasts in the Stroma of Pancreatic Cancer Have Been Identified

Woodbury, NY (10/26/18) - Pancreatic cancer has shown to have limited effective treatment strategies. Researchers in the Lustgarten Foundation Pancreatic Cancer Research Laboratory at Cold Spring Harbor Laboratory (CSHL) have made a discovery that could lead to a different, more effective kind of treatment.

Part of the problem is that cancer cells in the pancreas are protected by the dense matrix that surrounds them, a mixture of extracellular components and noncancerous cells known as the stroma. All solid tumors contain stroma, but the fibrous material is particularly abundant in pancreatic cancers, making up as much as 90 percent of a tumor's mass. Stroma impedes anticancer drugs' access to their targets and stromal cells secrete factors that support tumor growth. Overcoming the stroma's protective influence has been challenging. But, David Tuveson, M.D., Ph.D., Lustgarten Foundation's Chief Scientist and Director of CSHL Cancer Center and his team have found new information which points toward a promising strategy as reported on in today's *Cancer Discovery*.

The new findings suggest that drugs that target the right cellular pathways can do more than just thwart tumor-supporting cells in the stroma: they may recruit them to the anticancer fight. Ultimately, patients may benefit most from combination therapies that target both cancer cells and the components of their microenvironment that support their growth, explains Giulia Biffi, Ph.D., leader of the new study.

A key element of the stroma is a type of cell called a fibroblast. Fibroblasts manufacture the stroma's connective tissue. Some also generate factors that promote cancer cell growth and prevent the immune system from attacking the cancerous cells. Last year, Dr. Tuveson's team discovered that the stroma of pancreatic tumors contains at least two types of fibroblasts. And while one type show features known to support tumor growth, the other type appears to have the opposite effect. The good news is that the fibroblasts' identities are not fixed. With the right cues, tumor-promoting fibroblasts can become tumor-restricters.

"These cells can convert into one another, depending on the cues they get from the microenvironment and from the cancer cells," explains Dr. Biffi. "This is potentially useful, because in theory, you can shift the tumor-promoting to tumor-restraining, rather than just depleting the tumor-promoting cells."

In the new work, Dr. Biffi and her colleagues have identified specific molecular signals released by cancer cells that determine fibroblasts' character within pancreatic tumors. They have discovered that one such molecule, IL-1, drives fibroblasts to take on a tumor-promoting identity. They have also shown how another molecule, TGF-beta, overrides that signal, keeping fibroblasts in a potentially anticancer state even when IL-1 is present.

Now, the team is exploring in laboratory models what happens to pancreatic tumors when they manipulate IL-1 and TGF-beta signaling to convert tumor-promoting fibroblasts to a more

beneficial state. They will also investigate what happens when they target these pathways in combination with chemotherapy or cancer immunotherapies.

About the Lustgarten Foundation

The Lustgarten Foundation is America's largest private funder of pancreatic cancer research. Based in Woodbury, N.Y., the Foundation supports research to find a cure for pancreatic cancer, facilitates dialogue within the medical and scientific community, and educates the public about the disease through awareness campaigns and fundraising events. Since its inception, the Lustgarten Foundation has directed \$165 million to research and assembled the best scientific minds with the hope that one day, a cure can be found. Thanks to private funding, 100 percent of every dollar donated to the Foundation goes directly to pancreatic cancer research. For more information, please visit www.lustgarten.org