devices, based either on SiC or on gallium nitride grown epitaxially on SiC, have become practical for use in advanced communications and radar systems. In addition, SiC wafers have been shown to be an effective vehicle for realizing large-area graphene films that may find application in terahertz devices and next-generation microprocessors.

The elimination of micropipes, when accompanied by reductions in BPDs and TSDs, suggests that high-voltage, high-current SiC electronic switches with increased efficiencies may be on the horizon. These types of devices will have a direct impact on energy conversion and distribution systems, as well as on electromechanical conversion processes that now rely on less efficient technologies.

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10.1126/science.1168704

CANCER

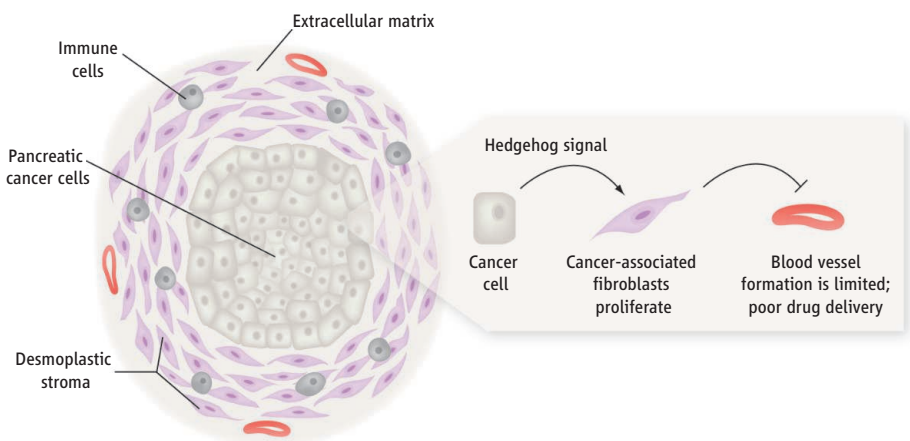
Breaching the Cancer Fortress

Pancreatic tumors are poorly vascularized, suggesting that new therapeutic strategies are needed.

Peter Olson and Douglas Hanahan

The predominant and invariably lethal form of pancreatic cancer—ductal adenocarcinoma—is characterized by an enveloping fibrotic stroma of excessive connective tissue and cells that forges rock-hard tumors. These tumors are refractory to essentially all therapies; gemcitabine, the standard-of-care chemotherapeutic drug, extends survival by only a few weeks. It has long been surmised that these pathological and clinical features are interconnected. On page 1457 in this issue, Olive *et al.* (*1*) confirm this notion, showing that cancer-associated fibroblasts in pancreatic ductal adenocarcinoma are responsible for a poorly vascularized architecture that imposes a barrier to drug delivery. Removing these fibroblasts stimulated the formation of new blood vessels (angiogenesis), improved drug delivery, and extended life span in a de novo mouse model of the disease. This study defines biophysical properties endowed by the tumor microenvironment that contribute to its therapeutic intractability and raises new questions about the role of the microenvironment in the development of this uncontrollable cancer.

Olive *et al.* noted that tumors from a de novo mouse model of pancreatic ductal adenocarcinoma responded poorly to gemcitabine, mimicking the clinical experience. However, transplanted tumors that were generated from cell lines derived from these tumors were remarkably sensitive to the drug. Transplanted tumors lacked the abundant fibrotic response present in human and de novo mouse tumors, in which epithelial cancer cells are surrounded by large swathes of activated fibroblasts, immune cells, blood vessels, and extracellular matrix components—a "fortress" collectively referred to as the desmoplastic stroma (see the figure) (*2*). The tumor microenvironment is thought to promote an ample vasculature to fuel tumor growth. However, in the de novo mouse model, blood vessels were sparse, only partially functional, and were physically separated from the epithelia by stroma. Two imaging techniques confirmed that blood flow was low in these tumors, and delivery of the naturally autofluorescent anticancer drug doxorubicin was decreased compared with delivery to transplanted tumors or normal tissue.



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Barrier to drug delivery. In pancreatic ductal adenocarcinoma, cancer cells are surrounded by a fortress of desmoplastic stroma composed of cancer-associated fibroblasts and inflammatory cells along with copious amounts of extracellular matrix components. This assemblage impedes angiogenesis, limiting drug delivery. **(Inset)** The secreted factor Hedgehog sustains this stromal environment. Inhibition of Hedgehog signaling eliminates cancer-associated fibroblasts, thus increasing angiogenesis and vascular delivery of chemotherapeutic drugs.

Cancer-associated fibroblasts promote tumor growth and angiogenesis in other tumor types (*3*–*5*). Surprisingly, cancer-associated fibroblasts in pancreatic ductal adenocarcinoma were responsible for the sparse vasculature and poor drug delivery. These cancer cells signal in a paracrine fashion to fibroblasts via the secreted factor Hedgehog. Olive *et al*. treated mice with de novo tumors with a pharmacological Hedgehog inhibitor alone and in combination with gemcitabine. There was equivocal survival benefit with Hedgehog inhibitor therapy, and only a few weeks of added survival with the combination. Nevertheless, the Hedgehog inhibitor largely eliminated fibroblasts, while vascular endothelial and other cell types proliferated. The results suggest that cancer-associated fibroblasts in pancreatic ductal adenocarcinoma limit the formation of new blood vessels, with

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Published by AAAS

poor drug delivery an unfortunate but incidental consequence.

Is it possible being poorly vascularized is advantageous for tumor growth? Though it is not obvious why a tumor would prefer to be starved for oxygen and nutrients, clues are emerging that this environment can promote malignant phenotypes. Hypoxia can drive genomic instability and lead to a more aggressive tumor phenotype (*6*, *7*), which may explain the highly metastatic nature of pancreatic ductal adenocarcinoma. Additionally, low blood-vessel density and high interstitial pressure may prevent host-derived factors (e.g., cells and/or molecules, akin, in principle to anticancer drugs) from reaching the tumor in sufficient quantities to exert an antitumor effect (*8*, *9*). Notably, the effects of the Hedgehog inhibitor proved transitory, followed by restoration of the hypovascular state, suggesting that the hypovascular, stromal-rich microenvironment is functionally important for the biology of pancreatic ductal adenocarcinoma.

Stimulating angiogenesis to treat pancreatic cancer, in the context of disrupting the desmoplastic fortress, is seemingly counterintuitive. Targeting tumor vasculature to improve blood flow and drug delivery is not new (*10*). However, previous theories posited that angiogenesis inhibitors can "normalize" tumor vasculature by pruning back immature vessels, thereby improving delivery of anticancer drugs to the tumor. By contrast, Olive *et al.* show that Hedgehog inhibition actually induced angiogenesis to improve drug delivery.

The predominant stroma and sparse vasculature in pancreatic ductal adenocarcinoma could be envisioned as a barrier to metastasis; hence the increased vascularization consequent to Hedgehog inhibitor therapy might be expected to spur metastasis. On the contrary, however, Hedgehog inhibition decreased metastatic frequency (*11*). Notably, a minority of pancreatic cancer cells express much higher amounts of Hedgehog and are 100 times more tumorigenic than the majority population (*12*–*14*). Perhaps these rare pancreatic cancer cells engage Hedgehog signaling as part of a metastatic program and, thus, are impaired by Hedgehog inhibition.

A somber lesson from this study is the eventual failure of the combined gemcitabine plus Hedgehog inhibitor therapy, which extended life span by only 2 weeks. The hypovascular state was restored upon relapse, although the effects on the stroma are unclear. Multiple cell signaling pathways have been implicated in orchestrating the desmoplastic stroma, including transforming growth factor–β, platelet-derived growth factor, and various cytokines (*13*, *15*). Thus, Hedgehog inhibition may transiently eliminate pancreatic cancer–associated fibroblasts until alternative signaling pathways are activated to restore the desmoplastic stroma, reflecting another form of adaptive resistance to targeted therapies (*16*).

Numerous conventional clinical trials with a variety of anticancer drugs have failed to make substantial inroads in treating pancreatic ductal adenocarcinoma. There is reason to hope that authentic mouse models of this cancer could provide a more effective means to define mechanisms and flight test new therapeutic strategies involving mechanism-based drugs in different sequences, and layered combinations. The approach taken by Olive *et al*. represents a step in the right direction.

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10.1126/science.1175940

MATERIALS SCIENCE

Yield Stress Fluids Slowly Yield to Analysis

The behavior of a type of complex fluid (exemplified by mayonnaise and concrete) can depend on the sample's flow history.

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We are surrounded in everyday life by yield stress fluids: materials that behave as solids under small stresses but flow like liquids beyond a critical stress. For example, paint must flow under the brush, but remain fixed in a vertical film despite the force of gravity. Food products (such as mayonnaise), other consumer products (such as toothpaste), concrete, and even radioactive nuclear waste sludge exhibit yield stresses. The yield stress may serve to keep particulate fillers from settling, as in many consumer products and gelled propellants, or determine whether bubbles remain trapped in cement. For handling and using these materials, it is paramount to know the stress at which the material starts to flow, but a consensus on the mechanical behavior of these materials is only slowly emerging.

Yield stress materials have been studied for nearly a century (*1*). In the classical description, initiated by Bingham, there is no flow (infinite viscosity) if the shear stress is less than a critical value (the yield stress), and the stress is a monotonically increasing function of the shear rate above that value. In practice, however, measurement of the shear stress as a function of shear rate is fraught with difficulty (*2*, *3*). Apparent wall slip due to heterogeneity and the contribution of nondissipative elastic stresses are obvious and well-known experimental problems (although the latter is rarely considered), but they do not explain why different measurements often give very different yield stresses for the same material. Despite the practical importance, there is no reliable way at present to predict the onset of flow. Indeed, there has been a discussion in the rheological literature for two decades as to whether a "true" yield stress even exists.

Perhaps the main difficulty with much of the literature on yield stress fluids is the prevail-

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Science **324**, 1400 (2009);
DOI: 10.1126/science.1175940

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.