natural bridge between machine learning and quantum theory. However, recognizing this bridge is only the beginning.

For instance, it remains to be seen whether the way in which Havlíček *et al.* represent data in quantum space is actually useful for real-world machine-learning applications. That is, it is not known whether the approach is associated with a meaningful measure of similarity that, for example, in classifying images of animals, places cat pictures close to cat pictures but not to dog pictures. Moreover, it is unclear whether there are other strategies that would work better. And would these techniques be good enough to beat almost 30 years of classical methods? If so, the desperate search for a 'killer application' for quantum computers would be over. But the answer to this question is probably more complicated. ■

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1. Havlíček, V. *et al. Nature* **567**, 209–212 (2019).
2. Schölkopf, B. & Smola, A. J. *Learning with Kernels: Support Vector Machines, Regularization, Optimization, and Beyond* (MIT Press, 2002).
3. Schuld, M. & Killoran, N. *Phys. Rev. Lett.* **122**, 040504 (2019).

MEDICAL RESEARCH

Molecular envoys aid cancer spread

Pancreatic cancer usually spreads to the liver. The identification of signals from cells adjacent to pancreatic tumours that boost liver colonization might suggest ways to block this deadly form of cancer invasion. SEE LETTER P.249

ANIRBAN MAITRA

Pancreatic cancer is rapidly lethal, and the five-year post-diagnosis survival rate in the United States is 8% (ref. 1). At diagnosis, the cancer has usually already spread beyond its primary pancreatic site to invade other parts of the body, most commonly the liver[2]. This renders futile the option of surgically removing the pancreatic tumour to prevent such lethal spread, or metastasis[3]. On page 249, Lee *et al.*[4] report their identification, in mice and humans, of molecules made in the pancreas that travel to the liver and alter its environment to create conditions that assist cancer-cell invasion.

Much remains to be uncovered about the signals and sequence of events that precede and facilitate establishment of the implantation site for tumour invasion — known as the pro-metastatic niche[5]. Alterations that enable niche formation include blood-vessel changes that create cancer-cell docking sites and modifications to the layer of endothelial cells that form an outer barrier around tissues and that must be crossed for tissue invasion[5].

Although metastasis is usually the main reason for the failure of cancer treatment and for eventual death, it is a remarkably inefficient process. Cancers release millions of cells into the bloodstream each day, yet studies of skin cancer in animal models indicate that fewer than 0.1% of tumour cells form metastases[6]. For metastasis to be successful, cancer cells must exit their primary site, enter the bloodstream and overcome challenges that include surviving physical stress in blood vessels, adapting to the unfamiliar cellular surroundings of a different host organ, and evading destruction by immune cells. Therefore, understanding the factors that create a pro-metastatic niche are of crucial importance for clarifying how cancer cells overcome such obstacles to become established at a distant site.

Lee and colleagues investigated how pancreatic-tumour cells generate the pro-metastatic niche. The authors demonstrate that, in mice, the protein interleukin 6 (IL-6), a type of immune-signalling molecule called a cytokine, is secreted from non-cancerous fibroblast cells[7] in the microenvironment of the pancreatic tumour cells (Fig. 1). Fibroblasts are the main cells of the connective tissue. The authors report that IL-6 binds to its receptor protein on liver cells and drives expression of the transcription-factor protein STAT3, which is then activated by undergoing phosphorylation (the addition of a phosphate group). Liver cells that express such activated STAT3 secrete the proteins SAA1 and SAA2, which prepare the liver for the influx of cancer cells. The SAA proteins attract myeloid cells, which dampen the body's immune-surveillance response by secreting cytokines that inhibit cancer-killing T cells. SAA1 and SAA2 also drive the activation of hepatic stellate cells, a type of liver cell that deposits extracellular-matrix material, thereby aiding the initial anchoring and

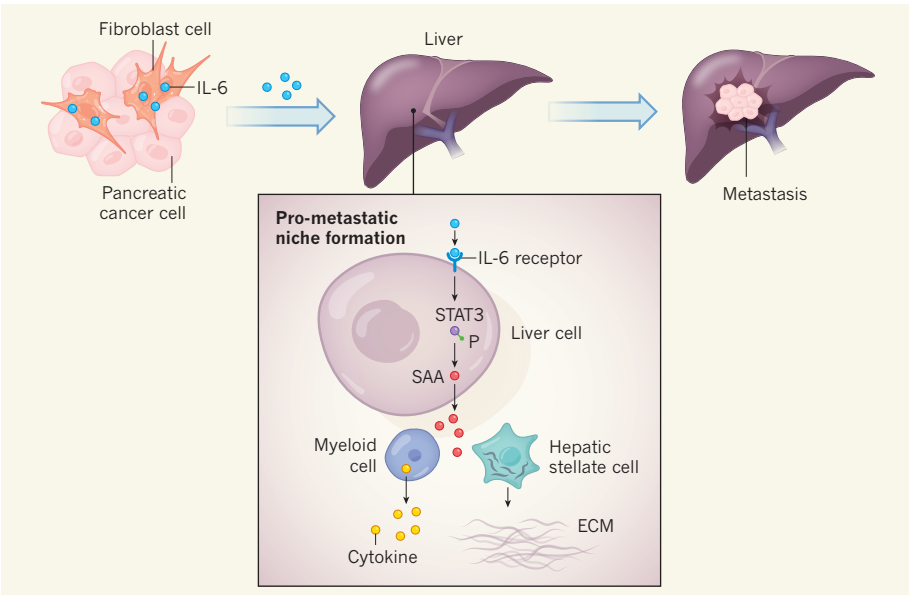

Figure 1 | A signal from the pancreas aids cancer invasion of the liver. Lee *et al.*[4] report studies in mice and humans that have uncovered a process driving the deadly step of cancer spread. The authors report that the protein IL-6, which is synthesized in non-cancerous fibroblast cells adjacent to a pancreatic cancer, is a key driver of tumour invasion of the liver. IL-6 travels through the bloodstream to the liver, where it binds to its receptor on liver cells. This drives expression of the protein STAT3, which is then phosphorylated (P denotes a phosphate group), and triggers the expression of SAA proteins (SAA1 and SAA2). These proteins are secreted from the cell and attract myeloid cells, which express cytokine molecules that dampen immune responses. SAA proteins also activate hepatic stellate cells, which deposit extracellular-matrix material (ECM). These changes create an environment, termed a pro-metastatic niche, that supports cancer colonization and growth. Once the pro-metastatic niche has formed, pancreatic cancer cells can invade the liver to form a secondary tumour site (metastasis).

sustenance of metastatic cancer cells.

When the authors blocked any of the signalling components that promote pro-metastatic-niche formation (IL-6 from fibroblasts, or STAT3, SAA1 or SAA2 from liver cells), the metastatic burden in animal models of pancreatic cancer was substantially reduced without affecting pancreatic-tumour growth, compared with the metastatic burden in animals in which the action of these signalling components wasn't interrupted. The disruption of these signalling components did not stop pancreatic cancer from invading the lung, confirming the idea that metastatic-site specificity can be driven by signalling cascades that are extrinsic to the cancer cell, and not just by intrinsic molecular changes in the tumour[8]. Lee and colleagues report that people who had pancreatic cancer and liver metastases, and those who had liver metastases arising from other types of primary tumour, such as lung or colorectal cancer, had higher than normal levels of SAA proteins in their bloodstream.

Lee and colleagues' work clearly demonstrates how a pro-metastatic niche is established in the liver, but it is also worth considering the role of other possible mediators of pancreatic cancer's 'advance team'. For example, vesicles called exosomes are released by these cancer cells and travel to the liver, where they release a protein called MIF that initiates pro-metastatic-niche formation[9]. Although Lee and colleagues did not measure exosome migration, they report that disruption of IL-6-mediated signalling did not affect the levels of MIF, suggesting that these two systems for driving pro-metastatic-niche formation might have non-overlapping roles. Indeed, a phenomenon as intricate as formation of the niche probably relies on a robustly regulated process that includes back-up mechanisms, and there are probably subtle differences in how the various pathways function. This is worth remembering, because it could explain why striking effects observed in animal models are often not replicated in humans.

What relevance do these findings have for the clinical treatment of pancreatic cancer? The disease stands out from other solid (non-blood cell) tumours in its tendency to form metastases early in the disease, when the tumour is small. This characteristic of early spread could explain why people in whom visible metastases are absent, and whose pancreatic tumour has been surgically removed, nevertheless soon develop liver metastases[10]. Could treatment that targets pro-metastatic-niche formation, such as the use of an inhibitor of STAT3 or an antibody that blocks IL-6 binding to its receptor, be effective? Blocking the signalling system that enables a pro-metastatic niche to develop would probably be most useful just after the surgery to remove the tumour, when visible metastases are absent but the foundations of a metastatic niche are probably being established. There might then be a small window of opportunity to effectively interrupt niche formation.

Like any other promising observation in an animal model, these discoveries should be investigated further. Although there have been steady improvements in survival for people who have this type of tumour[11], the opportunity is ripe for a clinical trial to investigate the effects of targeting the pro-metastatic niche in pancreatic cancer. ■

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1. Siegel, R. L., Miller, K. D. & Jemal, A. *Cancer J. Clin.* **68**, 7–30 (2018).
2. Yachida, S. & Iacobuzio-Donahue, C. A. *Arch. Pathol. Lab. Med.* **133**, 413–422 (2009).
3. Massagué, J. & Obenauf, A. C. *Nature* **529**, 298–306 (2016).
4. Lee, J. W. *et al. Nature* **567**, 249–252 (2019).
5. Peinado, H. *et al. Nature Rev. Cancer* **17**, 302–317 (2017).
6. Luzzi, K. J. *et al. Am. J. Pathol.* **153**, 865–873 (1998).
7. Feig, C. *et al. Clin. Cancer Res.* **18**, 4266–4276 (2012).
8. Vanharanta, S. & Massagué, J. *Cancer Cell* **24**, 410–421 (2013).
9. Costa-Silva B. *et al. Nature Cell Biol.* **17**, 816–826 (2015).
10. Groot, V. *et al. Ann. Surg.* **267**, 936–945 (2018).
11. Conroy, T. *et al. N. Engl. J. Med.* **379**, 2395–2406 (2018).

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In Retrospect

Forty years of fathoming life in the ocean depths

Ocean-floor hot springs teeming with animal life were reported 40 years ago. How has knowledge of life thriving in such extreme conditions grown since then, and what challenges remain for exploration and conservation down there?

CINDY LEE VAN DOVER

Four decades have passed since vibrant clusters of giant, metre-long tubeworms, discovered at hot springs on the ocean floor by Corliss *et al.*[1], were reported in *Science*. Until then, the ocean floor was considered to be more like a desert than an oasis.

Corliss and colleagues didn't discover underwater hot springs by accident; rather, they were trying to discover whether the hypothesis that such sites existed was correct. Theories on the movements of tectonic plates had set the course for this discovery with the idea that the mountain ranges that girdle the globe on the ocean floor, called spreading centres, are volcanic sites at the boundaries of tectonic plates. A key clue to the existence of underwater hot springs was the unexpectedly low conductive heat flux in the ocean's crust[2]. Convective heat flow through hot springs could solve the riddle of this missing heat. Warm-water anomalies documented above a spreading centre called Galapagos Ridge guided Corliss *et al.* to the site at which they discovered underwater hot springs (also called hydrothermal vents).

Finding these hot springs was in itself an incredible breakthrough. But what really turned deep-sea science upside down were the unexpected oases of life bathed by those warm waters. During the discovery dive in the submersible vehicle *Alvin*, geologist Jack Corliss called up to the crew on the surface ship from his position 2.5 kilometres below to ask, "Isn't the deep ocean supposed to be like a desert?" "Yes," was the reply. "Well, there's all these animals down here", he responded (see go.nature.com/2tdoubx).

This brief interchange marked what is arguably the greatest discovery in biological oceanography so far, and it was made by a team of geologists and geochemists. The authors noted presciently in their paper that these "fragile communities provide a unique opportunity for a wide range of zoological, bacteriological, ecological, and biochemical studies". What has come of those studies?

It didn't take biologists long to discover just how exquisitely giant tubeworms are adapted to their environment. In that profound darkness, generating cellular energy by photosynthesis is not an option. And because organic material produced at the ocean's surface loses much of its nutritional value by the time it reaches the deep sea bed, it doesn't provide a suitable energy source to sustain dense populations of large organisms. Instead, hot-spring inhabitants living in warm water enriched in hydrogen sulfide and other chemically reduced inorganic compounds (such as methane) benefit from symbiotic or free-living bacteria that generate energy through chemosynthesis — chemical oxidation of those reduced compounds[3].

Soon after the initial discoveries at the Galapagos site, a different type of hot spring called a black smoker — which emits metal-rich hydrothermal fluids — was found at another ocean-floor site[4]. Hot-spring ecosystems (Fig. 1) have now been found on sea-floor spreading centres throughout the world. They exist as 1,000 or more submarine oases,