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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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,

CHARLES FISHER/WOODS HOLE OCEANOGRAPHIC INST.

Figure 1 | Animal life on the floor of the Pacific Ocean in hot springs at the East Lau Spreading Centre.

strung like minute pearls along the spreading centres. Although numerous, they are a rare habitat in terms of their total area — together, they might all fit on the island of Manhattan, with room to spare[5]. They are ephemeral habitats, too, lasting for years to decades, or possibly centuries, depending on the geological setting[6]. This raises the question of how the invertebrate populations are maintained, and the nature of the biogeographic barriers between populations at hot springs. The life cycles of nearly all invertebrates living in underwater hot springs includes a larval stage that disperses in the water column. Larval ecology, population connectivity, and oceanographic barriers and transport routes are key topics of current research.

Different types of species are found at hot springs on different spreading centres[7]. Some spreading centres in the Southern Hemisphere and the Arctic remain to be explored, raising the possibility that previously unknown types of invertebrate–bacterial relationship and adaptation will be found there.

Surprising species and astonishing biological adaptations continue to come to light. Pompeii worms (*Alvinella pompejana*) live at temperatures as high as 42 °C. These are among the most extreme temperatures endured by any multicellular animal on Earth[8]. The worms challenge us to understand how the proteins in the animals' bodies are protected from melting. Microorganisms termed Archaea can grow at 121 °C, which is the hottest life known on Earth[9]. 'Blind' shrimp (*Rimicaris exoculata*) sport highly derived 'eyes' that are inferred to detect gradients of dim light emitted by the 350 °C fluids of black smokers, which might help the shrimp to avoid being 'cooked' by the heat[10]. Yeti crabs (*Kiwa tyleri*) have hairy claws and legs that might aid them in farming bacteria for nourishment[11]. Scaly-foot snails (*Chrysomallon squamiferum*) creep on 'feet' protected by metal scales of a type not found in other living or fossil molluscs, and offer an inspiration for the design of material for armour[12].

The importance of microbial chemosynthesis at hot springs also presses us to rethink our ideas about the extremes to which life can adapt, the origin of life on this planet, and even the potential for life elsewhere in the Universe. NASA's missions to Mars in the 1970s were searching for evidence of life based on energy from sunlight; now, planetary missions also consider the potential for life fuelled by chemical energy. Astrobiologists study submarine hot springs as a way of glimpsing conditions that might reflect those of primordial Earth[13], and consider oceanic hot springs as possible analogues of alien submarine environments on oceanic worlds beyond our planet[14].

Together with scholarly incentives to explore hot springs come engineering incentives to design and build ever-more-capable vehicles to enable precise and reliable access to the sea bed[15]. Remotely operated tethered vehicles came first, and autonomous underwater vehicles soon followed, pre-programmed to glide over the sea-bed like drones, carrying instruments that map the sea floor and sense the properties of the water. The development of cables that transmit video data allows such live feeds from the sea bed to be beamed around the world on freely available websites (see, for example, go.nature.com/2xrxsuh and go.nature.com/2vhrmcs).

The latest generation of deep-sea vehicles under development is turning a sharp corner from use for discovery and scientific research towards having a commercial role. Gigantic grinders, cutters and collectors are being designed, built and tested for open-pit mining of sea-bed sulfide deposits formed by hydrothermal activity[16]. One Canadian company has secured a lease to mine copper-, gold- and silver-rich hot springs in the Bismarck Sea, although so far there is no commercial mining of sea-bed sulfide deposits.

Many nations have placed the hot-spring ecosystems in their territories under protection, but the fate of such ecosystems in areas beyond national boundaries lies in the hands of the International Seabed Authority, which is currently revising its mining code. Attention might be shifting from the mining of active hot springs, which risks destroying their associated species, to exploiting sulfides at locations without visible signs of hydrothermal-fluid flux or vent-dependent organisms[5], but such an outcome is not yet guaranteed. Actions in the near future will determine whether the frontier of discovery at hot springs opened by Corliss and colleagues 40 years ago moves from exploration to exploitation. ■

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ORGANIC CHEMISTRY

Decoration of molecules made easy

The ability to attach a variety of chemical groups to one position in a molecule facilitates the search for compounds that have useful properties. Reactions have been reported that could transform how chemists do this. SEE LETTER P.223

ERIC M. FERREIRA

Chemists have spent decades developing and refining the tools for constructing bonds in complex organic molecules — especially carbon–carbon (C–C) bonds, which form the framework of such molecules. Metal-catalysed cross-coupling reactions generate C–C bonds from carbon–halogen bonds, and have long been go-to reactions for synthesis. In an exciting report on page 223, Berger *et al.*[1] describe an alternative cross-coupling strategy that uses a special type of carbon–sulfur (C–S) bond as a proxy for carbon–halogen bonds. Notably, this C–S bond is activated so that it becomes the most reactive site in a molecule for cross-coupling, and it can be installed directly at individual molecular positions with unprecedented levels of selectivity. The authors' work could therefore reshape the strategic use of cross-coupling reactions for organic synthesis.

The aim of synthetic chemistry is generally to make molecules that have a desired function — such as binding to an enzyme or emitting light of a specific colour. This, in turn, requires the chemical groups in the molecules to be connected in a particular way, or to have a specific spatial arrangement. Chemists would ideally like to have the tools to set up desired connectivities and spatial arrangements in any molecule. Great strides have been made towards this goal, but difficulties remain.

The problems are analogous to the challenge of hanging pictures on plaster walls. The optimum situation is to be able to place a picture at any desired position. But in the days when nails were the only option for hanging artwork, one was restricted to positions at which the wall plaster was backed by wooden studs — which raised the problem of finding the studs. Mistakes could be made that would damage the walls. New technology has simplified the problem: electronic stud finders make detection simple, and hooks that stick to walls using damage-free adhesives offer more-flexible alternatives to nails. With these better tools, we can now hang pictures in nearly any arrangement we desire, with minimum fuss.

Molecules can be thought of as blank walls: we need to be able to decorate them with chemical groups in specific arrangements, but the reactions available have restricted the positions that can be accessed, and/or have been difficult to target to specific positions. Metal-catalysed cross-couplings[2] have been tremendously valuable for molecular decoration. This family of reactions allows a remarkably wide range of groups to be attached to molecules through the formation of a C–C bond, but the carbon atoms to be decorated must already have a halogen atom attached. Methods for installing halogens predominantly at specific carbons in a molecule exist, but have varying degrees of site selectivity. More-selective means of making carbon–halogen bonds (or equivalent motifs that can also take part in cross-couplings) would be greatly enabling.

Reactions known as metal-catalysed C–H bond functionalizations[3], which can convert carbon–hydrogen (C–H) bonds to C–C bonds, were developed in part to circumvent the limitations of cross-couplings — why bother installing a halogen if you can instead convert one of the many C–H bonds found in all organic molecules selectively and directly to the C–C bond of your desired product?