Perhaps it is time to target abnormal signalling in cancer with a lighter touch, which could enable the use of combination therapies that are currently precluded for reasons of toxicity. After all, there is no need to use a hammer to kill a fly, and this principle might also apply to treating cancer. ■

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1. Venot, Q. *et al. Nature* **558**, 540–546 (2018).
2. Bianconi, E. *et al. Ann. Hum. Biol.* **40**, 463–471 (2013).
3. Samuels, Y. *et al. Science* **304**, 554 (2004).
4. Rozengurt, E., Soares, H. P. & Sinnet-Smith, J. *Mol. Cancer Ther.* **13**, 2477–2488 (2014).
5. Kurek, K. C. *et al. Am. J. Hum. Genet.* **90**, 1108–1115 (2012).
6. Lindhurst, M. J. *et al. Nature Genet.* **44**, 928–933 (2012).
7. Rivière, J.-B. *et al. Nature Genet.* **44**, 934–940 (2012).
8. Keppler-Noreuil, K. M. *et al. Am. J. Med. Genet. A* **167**, 287–295 (2015).
9. De Santis, M. C. *et al. Cancers* **9**, 30 (2016).
10. Castillo, S. D. *et al. Sci. Transl. Med.* **8**, 332ra43 (2016).
11. Gerstung, M. *et al.* Preprint at bioRxiv https://doi.org/10.1101/161562 (2017).
12. Jamal-Hanjani, M. *et al. N. Engl. J. Med.* **376**, 2109–2121 (2017).
13. Yehia, L. & Eng, C. *Endocr. Relat. Cancer* https://doi.org/10.1530/ERC-18-0162 (2018).
14. Sansregret, L., Vanhaesebroeck, B. & Swanton, C. *Nature Rev. Clin. Oncol.* **15**, 139–150 (2018).
15. Ortega-Molina, A. *et al. Cell Metab.* **21**, 558–570 (2015).
16. Bettedi, L. & Foukas, L. C. *Biogerontology* **18**, 913–929 (2017).

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QUANTUM NANOSCIENCE

Orbital insight from an upright molecule

A molecule standing on a metal surface has been found to emit electrons in the presence of an applied electric field. The emitted electrons produce an interference pattern reminiscent of a classic physics experiment. SEE LETTER P.573

THOMAS GREBER

Quantum systems are described by wavefunctions, which have an amplitude and a phase: the square of the amplitude describes the probability of finding a particle in a given region of space-time, whereas the phase describes the sign (plus or minus) of the wavefunction. The ability to control the phase of systems of electrons would open up opportunities for the development of quantum devices, and the first step in achieving such control is to ascertain what the phase is in the first place. Unfortunately, the phase of an object's wavefunction is not directly observable. It is, however, possible to work out the relative phase by observing interference patterns formed from the superposition (summation) of coherent electron waves (those between which there is a constant phase difference), by borrowing schemes from classic experiments that observed interference patterns in light, such as Thomas Young's 'double-slit' experiment[1] or Dennis Gabor's demonstration of holography[2]. Writing in this issue (page 573), Esat *et al.*[3] report a tabletop experiment that allows the phase of a molecular orbital to be determined from an interference pattern that arises as a result of electron emission from the molecule concerned.

Esat and colleagues began their investigation by assembling a molecule on a silver surface, using the tip of a scanning tunnelling microscope at cryogenic temperatures (5 kelvin) to manipulate atoms and molecules with sub-nanometre precision. More specifically, they attached two silver atoms to one end of a flat pigment molecule known as 3,4,9,10-perylene-tetracarboxylic dianhydride (PTCDA) that was lying on the surface. They then lifted up the metal–molecule complex using the tip of their microscope, so that it stood upright on the surface (Fig. 1).

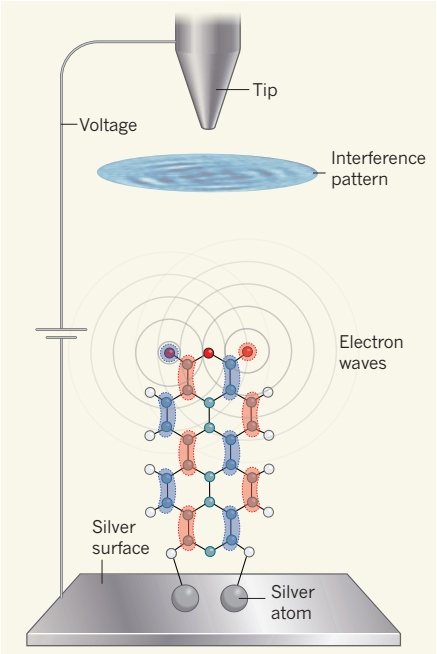

Figure 1 | A molecular electron emitter. Esat *et al.*[3] prepared a metal–molecule complex that stands upright on a silver surface. When the authors applied a voltage between the surface and the tip of a scanning tunnelling microscope, the molecule emitted electrons one at a time, producing electron waves. The spatial distribution of the resulting current contains patterns caused by interference between the electron waves. By analysing the patterns, the authors obtained information about the relative phase (plus or minus) of the region of the molecular orbital from which the electrons were emitted (the orbital is shown in blue and red; the colours represent the two relative phases).

The authors find that the complex is stable in this upright position — which might seem surprising to those in the know, because organic molecules preferentially lie flat on metallic surfaces. It is not known which conformation of Esat and colleagues' complex (flat or upright) is the more stable. However, their experimental finding casts light on how molecules such as PTCDA can be stacked on metal surfaces, knowledge of which is essential for constructing nanoscale devices in which molecules are in electrical contact with metals.

Erecting the molecule into this upright conformation allows it to perform a peculiar new function: it can emit electrons in the presence of an electric field. When the authors positioned the microscope tip 7 nanometres above the standing molecule and applied a voltage of about 25 volts, they detected an electron current of 100 picoamps (1 pA is 10^{-12} amps). Almost all of the electrons in the current pass across the sharp peak formed by the standing molecule. The electric field at the molecule's apexes is much greater than it would be between flat electrodes, because it is enhanced by the curvature of the molecule. Esat and co-workers show that the field enhancement is sufficiently high to allow electrons on the molecule to 'tunnel' into the surrounding vacuum, as measured in the field-emission current.

The authors report that the electrons undergo a two-step tunnelling process to pass from the silver metal surface to the vacuum. First, a single electron tunnels from the surface into the lowest unoccupied molecular orbital (LUMO), where it adopts the orbital's phase. In the second step, the electron is emitted at the edges of the molecule. The spatial distribution of the emitted current contains patterns caused by the interference of each electron with itself. The existence of these features indicates that the emitted electrons 'remember' the phase adopted from the part of the LUMO from which they were emitted — the

patterns wouldn't form unless the emissions had retained the orbital's phase.

Esat and colleagues' experiment is reminiscent of Young's double-slit experiment[1], in which the patterns formed by the interference of light proved that light is a wave. But, in contrast to Young's experiment, the emission patterns observed by Esat *et al.* can be explained only if the electron wavefunction has a different sign depending on whether it is emitted from the top right or top left corners of the molecule. The relative phases of the electrons emitted from different sites of the molecule can thus be worked out from the spatial distribution patterns of the emission current.

The authors used an established method for moving atoms and molecules[4] to produce their device. A complementary approach has previously been reported[5] in which electrons are coherently emitted from carbon nanotubes. The physics underpinning the emission process is the same in both systems, but the approaches used to realize it are completely different: Esat and colleagues' method can be thought of as a 'bottom-up' approach, in which the emitter is constructed from scratch, whereas the nanotube method was a 'top-down' approach in which nanotubes were painstakingly processed to allow the interference patterns to be observed and studied. The structures of Esat and colleagues' emitters are therefore much more precisely defined and reproducible.

The emission of electrons from a molecular device could, in principle, be triggered and steered using a laser, as was recently demonstrated for larger emitters[6]. This would require the stability of the molecular emitters to be improved, but would be another step towards the development of phase control. Molecular emitters might eventually find applications in devices such as electron microscopes, detectors that identify the phase or spin of electrons, or even quantum computers. ■

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1. Young, T. *Phil. Trans. R. Soc. Lond.* **92**, 12–48 (1802).
2. Gabor, D. *Nature* **161**, 777–778 (1948).
3. Esat, T., Friedrich, N., Tautz, F. S. & Temirov, R. *Nature* **558**, 573–576 (2018).
4. Eigler, D. M. & Schweizer, E. K. *Nature* **344**, 524–526 (1990).
5. Oshima, C. *et al. Rev. Lett.* **88**, 038301 (2002).
6. Yanagisawa, H. *et al. Sci. Rep.* **7**, 12661 (2017).

MEDICAL RESEARCH

Weighing in on weight loss linked to cancer

Weight loss and tissue wasting often occur in pancreatic cancer. Analyses of human and mouse data reveal a mechanism behind these events, and raise the question of whether tissue wasting affects cancer survival rates. SEE LETTER P.600

J. MATTHIAS LÖHR

An early symptom of pancreatic cancer is a profound loss in weight that can precede disease diagnosis by months[1]. Weight loss also occurs in other types of cancer, and is often associated with severe illness and a reduced quality of life. On page 600, Danai *et al.*[2] report an analysis of pancreatic cancer, using mouse models and clinical data, that illuminates the consequences of weight loss for cancer outcomes.

Cachexia, the term used to describe the cancer-linked symptom of severe weight loss, has been recognized since at least the time of the ancient Greek physician Hippocrates. It is often a hallmark of cancers originating in the gut system[3], and might manifest in changes such as loss of fat (adipose) tissue or skeletal-muscle wasting, which could arise if the body is using up the nutrient stores in such tissues. Cachexia is particularly common in people who have a type of cancer called pancreatic ductal adenocarcinoma. The mechanisms driving cachexia are not the same in all tumours[4], but whether there are different types of cachexia depending on the tumour type or the stage of the cancer at which weight loss occurs remains to be determined.

Two key mechanisms[4] thought to drive cachexia are the breakdown of molecules in a process called catabolism, and inflammation, which is controlled by the body's immune system. The pancreas secretes digestive enzymes that break down complex, calorie-rich food to provide the components needed for tissue growth and maintenance[5]; this catabolism-supporting function is known as its exocrine role. Exocrine-system impairment causes malnutrition that can lead to life-threatening tissue wasting. However, the degree to which pancreatic exocrine-system abnormalities contribute to human cachexia was unknown.

Human pancreatic cancer often occurs in a region of the organ that can obstruct the main pancreatic duct, hampering enzyme release. This can lead to a situation termed pancreatic exocrine insufficiency, which results in nutrient-absorption deficiencies and weight loss[6]. Cachexia in humans can be exacerbated if deficiencies occur in essential nutrients[7,8], for example long-chain fatty acids and vitamin D, whose uptake is facilitated by pancreatic enzymes such as lipase. The administration of fatty acids increases skeletal-muscle mass in people with pancreatic cancer, particularly when this supplementation is combined with pancreatic enzymes[9].

"This striking result indicates that cachexia does not drive cancer-associated mortality."

The research group that conducted the current study had previously[10] observed that tissue breakdown occurs before pancreatic-cancer diagnosis in humans and before the development of early-stage pancreatic cancer in mice. To continue their investigation, Danai and colleagues studied pancreatic cancer using genetically engineered mouse models of the condition[11,12], and they used transplantation experiments to test whether tumour location affects wasting. They found that if pancreatic-tumour cells were transplanted into mice beneath the skin surface, adipose-tissue wasting did not occur, whereas wasting did occur if the cells were transplanted into the pancreas. This finding indicates that some aspect of the pancreatic environment has a key role in this phenomenon, and is consistent with the results of a previous study[11]. However, that study also found that tissue wasting was promoted when tumour cells were introduced into the body cavity, suggesting that tumour presence at a non-pancreatic site can also trigger this phenomenon.

Danai and colleagues' metabolic investigations revealed that mice with pancreatic tumours used less oxygen and produced less carbon dioxide than did control mice lacking tumours. This suggested that the presence of the cancer might be linked to a decrease in the processes involved in food breakdown and nutrient adsorption. To investigate how the pancreatic-tumour environment might cause this early metabolic change and weight loss, the authors tested whether pancreatic exocrine insufficiency was responsible, given that this can occur in human pancreatic cancer[6]. When Danai and colleagues gave the mice pancreatic enzymes, the level of adipose-tissue wasting decreased, suggesting that pancreatic exocrine insufficiency has a causal role in cachexia (Fig. 1).

Danai and colleagues found that, although pancreatic-enzyme supplementation could limit the tissue wasting, the animals' survival rate did not improve. This striking