Sun — on average, such disks exist for only a few million years[10]. Therefore, there is strong reason to think that gas in the disk would have diffused into the magma oceans on these embryos.

This diffusion process could help to answer some long-standing questions about, for example, the noble-gas content of Earth. Today, Earth releases noble gases that must have been implanted in the mantle at the time of the planet's formation. The origin of these gases has been unclear because the rocky material that built Earth contained only a small quantity of noble gases. The diffusion of noble gases from the gas disk directly into the magma ocean might solve the mystery.

Finally, Bouvier and co-workers' timeline allows the early histories of Earth and Mars to be compared directly. About 100 Myr after the formation of CAIs, Earth went through a magma-ocean phase that is thought to have been initiated by the collision of the planet with a Mars-sized body — a collision that led to the formation of the Moon[11]. Consequently, the authors' results suggest that Mars had clement conditions, and was possibly even hospitable to the formation of life, for as long as 100 Myr before such conditions existed on Earth. Mars had a head start on Earth in the planetary-evolution game. ■

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MEDICAL RESEARCH

Cancer drug tackles overgrowth syndrome

Abstract of the enzyme PI3K can drive cancer growth, and mutations in a PI3K subunit can sometimes lead to non-cancerous overgrowth. A cancer drug that inhibits PI3K dramatically reduces such overgrowth. SEE ARTICLE P.540

ROBERT K. SEMPLE
& BART VANHAESEBROECK

Researchers who investigate rare genetic conditions live in hope that the discovery of disease-causing mutations will lead swiftly to tailored treatments. Sadly, this is not often the case, because genetic defects usually cause impairments that are difficult or impossible to tackle using available medicines. In this issue, Venot *et al.*[1] (page 540) now provide a rare exception to this rule. In severe non-cancerous overgrowth syndromes caused by mutations in an enzyme called PI3K, they show the beneficial effects of a PI3K-inhibitor drug that was initially developed to treat cancer. Their results bring the possibility of a transformative therapy for people with overgrowth conditions one step closer.

The development of humans, from a single fertilized egg to an adult body that contains around 37 trillion cells[2] while maintaining symmetrical, paired body parts, is an astonishing feat that requires the lifelong coordination of cell division, survival and death. Growth-factor proteins can aid cellular coordination by acting on cell-surface receptors to stimulate intracellular signalling networks. These networks often include PI3K, which is essential for the regulation of growth and development by insulin and insulin-like growth-factor hormones.

Cancer arises from a flagrant breach of the rules of good cellular citizenship that are essential in multicellular organisms, and cancer cells acquire genetic abnormalities that subvert the checks and balances that constrain cell growth and migration. Mutations that activate PI3K signalling — mainly those in the gene *PIK3CA*, which encodes p110α, a catalytic subunit of PI3K — are among the most common mutations to drive solid cancers[3]. Such signalling can also be activated by mutations that inactivate the enzyme PTEN, which normally keeps PI3K activity in check. The link between overactive PI3K signalling and cancer motivated researchers to develop compounds known as PI3K inhibitors. However, the clinical impact of these drugs on cancer has been less impressive than hoped because of toxicity associated with high doses. And even when such drugs succeed in inhibiting activated PI3K, other proteins can compensate to provide alternative pathways that promote cancer[4].

In 2012, certain *PIK3CA* mutations, which had previously been linked to cancer, were reported to cause rare, non-cancerous forms of overgrowth in people[5–7]. A hallmark of these overgrowth syndromes is abnormal, excessive tissue growth that affects the body in a patchy and asymmetrical manner. This overgrowth is caused by *PIK3CA* mutations that occur after the start of embryonic development and

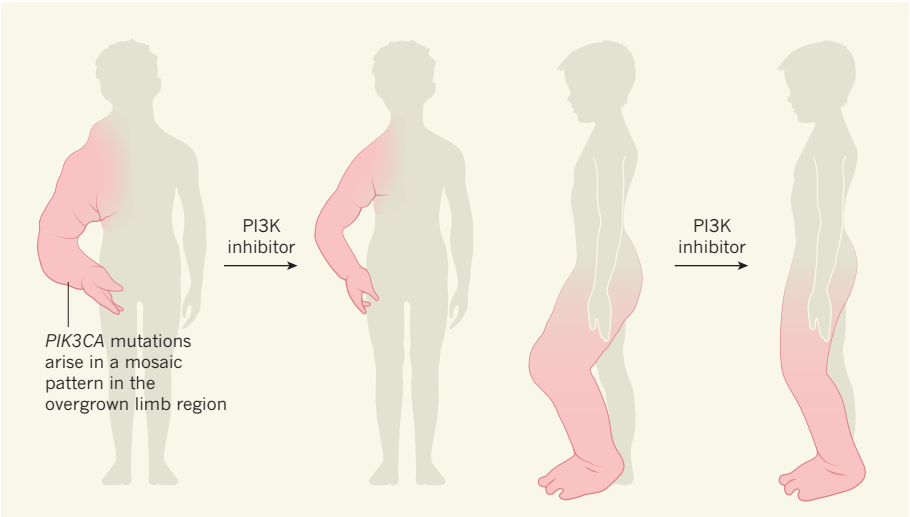

Figure 1 | People who have an overgrowth syndrome respond to treatment with a cancer drug. Venot *et al.*[1] investigated a syndrome linked to abnormal activation of the enzyme PI3K, which can result in the non-cancerous overgrowth of a variety of tissues. The authors tested whether a low dose of a PI3K inhibitor called alpelisib, developed previously as a cancer therapy, could treat people who have mutations in the gene *PIK3CA*, which encodes the catalytic subunit of PI3K. In overgrowth syndromes, these *PIK3CA* mutations arise in a mosaic patchwork pattern[5,6,8] in the region of the affected tissue (pink). Alpelisib treatment caused substantial improvements in the 19 recipients. Two examples of the decrease in overgrown tissue in patients after six months of drug treatment are shown.

only in some cells[5,6,8], which leads to cellular overgrowth in a mosaic-like pattern. The severity of the condition varies from person to person, and ranges from an isolated skin growth to a complex multisystem disorder called CLOVES syndrome[5], which comprises considerable and often widespread overgrowth that contains an abundance of fat cells and abnormal blood vessels. *PIK3CA* mutations are a common feature of many overgrowth syndromes and the term PROS (for *PIK3CA*-related overgrowth spectrum)[8] is used as a unifying description of such cases.

PROS disorders do not seem to be linked to an increase in the risk of forming the solid cancers in which *PIK3CA* mutations are most prevalent[9]. Although the reason for this is unclear, the *PIK3CA* mutations associated with such disorders usually occur in cell types of a different embryonic origin from those that develop cancer linked to *PIK3CA* mutations[9].

Severe PROS disorders can be debilitating or even life-threatening. Overgrown tissue causes compression that can lead to vascular problems or organ dysfunction. Treatments aim to reduce excess tissue by surgery or by the physical blockade of enlarged blood vessels, and other therapy options are needed urgently. The availability of targeted inhibitors of p110α that had already undergone clinical testing as treatments for cancer gave researchers hope that these might offer a new therapy for PROS disorders. Yet questions arise about the effect of prolonged patient exposure to these drugs. Would this cause side effects? Would their cells adapt to dull the effect of such treatment, as occurs in cancer[4]? And would the overgrowth be amenable to reversal by drug-based therapy?

Venot *et al.*[1] take an important step towards addressing these questions. Previous attempts to model PROS disorders in mice engineered to express *Pik3ca* containing disease-causing mutations produced excess growth in only some of the expected tissues[10]. Venot and colleagues engineered another mouse model of a PROS disorder, in which an artificial system was used to make the mice express constitutively active p110α in all tissues. These animals developed problems similar to those in people with PROS conditions, including the overgrowth of adipose, muscle and vascular tissue, and experienced a premature death caused by vascular complications. When the authors treated the mice with a PI3K inhibitor called alpelisib, an impressive, rapid and substantial decrease in the amount of overgrown tissue occurred, which prevented the premature death of the animals.

Crucially, Venot *et al.* then assessed the effects of alpelisib in 19 people with PROS disorders who had severe or life-threatening complications. In adults, the team administered the lowest dose that had been tested in trials on people with cancer (250 milligrams a day), and in children they used a dose of 50 milligrams a day. Dramatic anatomical and functional improvements occurred in all patients across many types of affected organ (Fig. 1), with some benefits noted within days of the treatment starting. The study was not randomized, blinded or subject to placebo control, yet these striking initial results suggest that this outcome is likely to have clinical importance. Resistance to alpelisib was not observed, and the drug was well tolerated by the recipients.

A predicted side effect of PI3K inhibition is a high blood glucose level, caused by interference with the PI3K-mediated metabolic effects of insulin. However, blood-glucose elevation occurred in only three people, in whom the elevation was modest. In children, the drug did not have an effect on normal growth, which suggests that overgrown tissue can be targeted without harmfully blocking PI3K-dependent childhood growth. Further systematic clinical studies are now needed, and ethics committees will have to assess whether it could be justified to include a placebo in trials on patients who are severely affected.

The study of PI3K inhibition as a treatment for PROS disorders might also offer something in return towards the design of cancer therapies. The aim of PI3K-inhibitor therapy in PROS conditions would be to suppress disease-causing levels of PI3K signalling, while minimizing any side effects during the long-term, and probably lifelong, treatment. By contrast, the conventional approach of cancer therapy involves identifying differences between healthy and cancerous cells, and then hitting the cancer-specific characteristics as hard as possible to induce the death of cancer cells. In clinical trials for cancer, PI3K inhibitors are usually studied at the maximum tolerated dose. Yet whether this makes sense is unclear, given that the activity level of mutated p110α in cancer, which is low, is probably similar to the activity level of the same subunit in PROS disorders. Could a low dose of PI3K inhibitor be beneficial in treating a cancer linked to a *PIK3CA* mutation? This might abolish any PI3K activity that is above the usual level without completely blocking PI3K signalling, as would occur with a high dose of inhibitor. This could be tested, for example, as a strategy for preventing types of cancer in which PI3K activation or PTEN inactivation is an early event[11,12], or for preventing PTEN hamartoma tumour syndrome in people who carry a mutation in PTEN and are therefore prone to cancer[13].

Low-dose PI3K inhibition might also be used as an option, following conventional treatments such as chemotherapy or surgery, for slowing the evolution of cancer and its adaptation to selective pressures[14]. And long-term, low-dose PI3K inhibition could offer further benefits — for example, it increases the metabolic health of obese mice and rhesus monkeys[15], and sustained blockade of the PI3K pathway can slow ageing in animal models[16].

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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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).

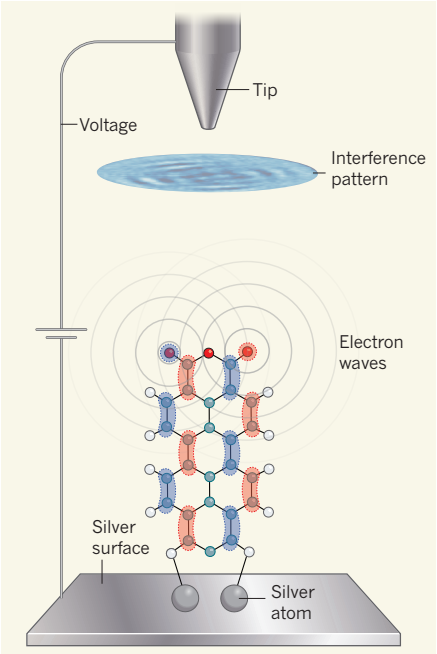

Figure 1 | A molecular electron emitter. Esat *et al.*[3] prepared a metal–molecule complex that stands upright on a silver surface. When the authors applied a voltage between the surface and the tip of a scanning tunnelling microscope, the molecule emitted electrons one at a time, producing electron 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