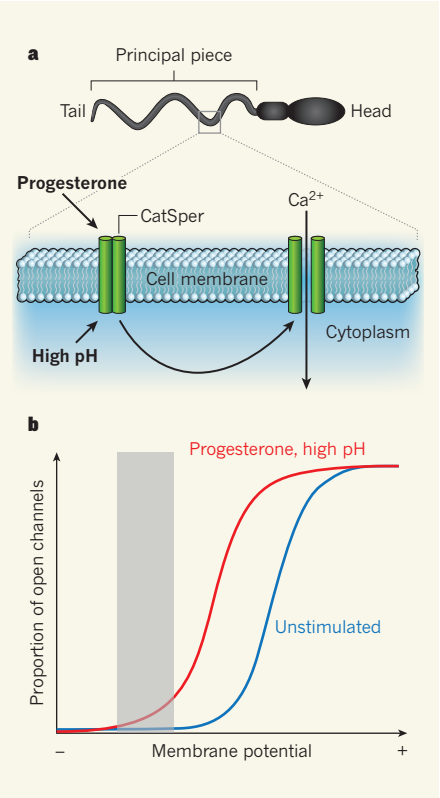

Figure 1 | CatSper and calcium-ion influx. **a**, The CatSper ion channel, which occurs in the plasma membrane of the principal-piece domain of the sperm tail, allows Ca^{2+} influx into these cells. New work[1,2] shows that progesterone leads to the opening of this channel, probably either by binding to it directly or through an associated protein; increased intracellular pH has the same effect. On opening, CatSper channels allow Ca^{2+} entry into the cell, which regulates events vital for fertilization. **b**, Opening of CatSper channels depends on the electrical difference across the cell membrane (the membrane potential) and occurs when the cell becomes electrically more positive inside. The normal membrane potential in sperm (grey bar) is such that nearly all CatSper channels are closed (blue line). Both progesterone and increased intracellular pH 'shift' the electrical sensitivity of CatSper so that the channel can open at more negative membrane potentials (red trace).

stringent buffering of this ion in the external medium abolishes the response to progesterone[1]. Intriguingly, the efficacy of progesterone is increased by *in vitro* manipulations designed to induce sperm capacitation (a crucial maturation process that naturally occurs in the female reproductive tract before fertilization).

The non-genomic action of progesterone is much more potent in human sperm than in mouse sperm[2]. But why? Lishko and colleagues show that, at the intracellular pH of 7.0 (a value within the physiological range), mouse spermatozoa show notable CatSper currents, whereas human sperm show a much smaller current. On applying progesterone to human sperm, the current increases to a level closely resembling that in mouse sperm, but in mouse sperm stimulation with this hormone leads to no further increase in current[2]. It seems, therefore, that in human sperm, progesterone induces a modulation of CatSper function that in mouse sperm is constitutive (at least under the conditions used in these experiments). This is potentially a crucial species difference in sperm regulation within the female reproductive tract.

The two papers also present a much clearer idea of how progesterone exerts its effect by modulating CatSper. Lishko *et al.*[2] could record progesterone-induced currents even in isolated sperm tails, which precludes indirect effects of progesterone exerted through receptors on the sperm head. Furthermore, Strünker *et al.*[1] provide compelling evidence that progesterone does not stimulate synthesis of the signalling molecule cyclic AMP, and they couldn't detect any effects of manipulating cAMP levels on Ca^{2+} influx through the sperm membrane. These observations rule out involvement of the cAMP–protein kinase A signalling cascade in the progesterone–CatSper response.

The new data also suggest that progesterone directly activates CatSper, by binding either to the channel itself or to an associated subunit(s). Whether CatSper activation is the only effect of progesterone on Ca^{2+}-signalling in human sperm remains to be seen. Several previous studies have attempted to identify progesterone receptors[6]. Both novel receptors and truncated versions of the classical (nuclear-type) receptors (some of these apparently localized to the sperm head) were proposed to mediate the effects of this hormone. Although such receptors almost certainly do not contribute to the modulation of CatSper reported here, it is noteworthy that completely blocking CatSper currents inhibits — but does not abolish — the effect of progesterone on intracellular Ca^{2+} levels[1,10].

Mobilization of intracellular Ca^{2+} stores, leading to complex Ca^{2+} signalling, occurs in progesterone-stimulated human sperm[5]. Is this purely a downstream effect of CatSper activation or does progesterone activate a separate pathway? Are store-controlled Ca^{2+} channels involved? These two studies[1,2] provide exciting insights, and there is more to come. ■

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HIGH-TEMPERATURE SUPERCONDUCTIVITY

The secret of the hourglass

The finding that a cobalt oxide insulator's magnetism is similar to that of cuprate superconductors lends support to the popular but contentious idea that stripe-like electronic order is present in the latter materials. SEE LETTER P.341

JAN ZAANEN

One hundred years after its discovery, superconductivity is still an active field of research. On page 341 of this issue, Boothroyd *et al.*[1] describe experimental results on an insulating material that offer insight into the physics of one of the most intriguing families of superconductors — the copper oxides, or cuprates.

Conventional superconductivity — that which occurs in simple metals such as lead and aluminium — was explained back in 1957 by Bardeen, Cooper and Schrieffer, in what is known as the BCS theory[2]. But in 1986, a different, high-temperature form of superconductivity was discovered in complex cuprates[3]. This discovery rumbled like an earthquake through the physics community, because the superconducting transition temperatures (T_c), below which these materials conduct electricity without resistance, were much too high to be explained by BCS theory. What causes superconductivity in the cuprates is still much of a mystery, but intensive research has shown that the ground rules of

the quantum physics governing the electron systems in the cuprates are very different from those of conventional systems: in contrast to the featureless quantum gas formed by the electrons in conventional superconductors, the high-T_c electrons seem to form highly organized types of 'quantum matter', exhibiting a richness of electronic behaviour that challenges even the diversity found in classical complex fluids[4].

With their unique ability to measure how the magnetic properties of this 'electron stuff' fluctuate in time, experiments based on the scattering of neutrons have played a key part in discerning some of the signatures of the cuprates' electron quantum matter. Such measurements revealed that these magnetic fluctuations behave in a peculiarly organized manner, nicknamed the hourglass spectrum (Fig. 1). Boothroyd *et al.*[1] now demonstrate that the magnetic fluctuations in an insulating material, for which it is established that the electrons freeze out in a complex 'stripe' pattern, look very similar to those of the cuprates, thereby supporting the popular but controversial idea that such stripes are also present in superconducting cuprates — although in a quantum 'dynamical' form[5].

In conventional superconductors, electronic quantum zero-point motions dominate to such a degree that the electrons form a nearly featureless quantum gas, just leaving room for the formation of the electron pairs that, according to BCS theory, are responsible for superconductivity[2]. Such pairs are also formed in the cuprates, albeit in a mysteriously sturdy form. But there is much more going on in these materials. A large body of experimental work has shown that the cuprates' high-T_c superconducting state seems to coexist[4], to a greater or lesser degree, with a wealth of exotic quantum organizational phenomena, including static and dynamical stripes, spontaneous 'diamagnetic' currents, and quantum nematics (quantum versions of the liquid crystals used in liquid-crystal displays).

Among these exotic forms of electronic order, the stripes have a special status because they were the first to be identified — in fact as a surprising output[6] of computer simulations that I generated as a young postdoc in 1987. This story starts with the particulars of Cu ions[4], having the effect that the electrons in the copper oxide lattice repel each other much more strongly than in conventional superconductors. As a result, the cuprate electron world is more like traffic on a congested highway than like the 'quantum fog' of conventional metals. In the stoichiometric cuprates, the electron-traffic density is so high that the traffic jams completely, forming what is known as a Mott insulator. To get the electrons moving, some of them are removed by chemical doping, and one enters an 'underdoped' regime of quantum mechanical stop-and-go traffic — and here the exotic orders emerge.

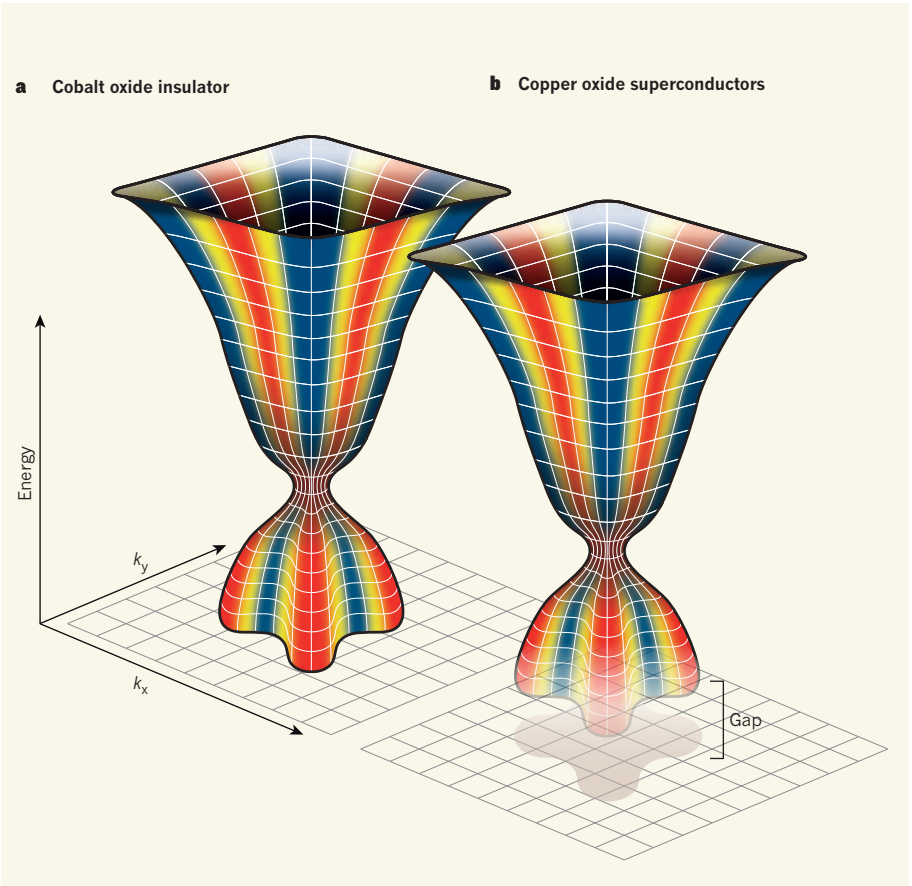

Figure 1 | The hourglass magnetic spectrum. **a**, Boothroyd *et al.*[1] find that the collective magnetic 'vibrations' (spin waves) in a cobalt oxide insulator have an hourglass shape when plotted as a function of their energy and inverse wavelengths (k_x, k_y); the colours indicate the intensity of the spin waves as measured from neutron scattering. **b**, In the superconducting copper oxides, the neutron-scattering results display a very similar shape, except that at low energies a gap appears that is indicative of a collective quantum melting of stripe-like electronic order[5]. (Graphic based on a sketch by A. Boothroyd.)

By dismissing all collective electronic quantum fluctuations, the physics of such dense quantum traffic can be computed, and my calculations[6] showed that the electron traffic spontaneously forms complex patterns, which we nicknamed stripes. These consist of 'rivers', in which the electron motions are relatively free, separated by domains in which the traffic continues to be completely jammed. The electron spins in this stripe phase interact through short-range quantum fluctuations, which cause the spins to freeze out in a special 'incommensurate' antiferromagnetic order: within the insulating domains, the orientation of the spin of each electron is opposite to those of its neighbours, and the rivers act as 'domain walls' in this antiferromagnet. Disappointingly, in the cuprates, my computations insisted that this static stripe phase should insulate instead of superconduct. But this turned out to have been a blessing in disguise when it became gradually clear in the 1990s that the static stripes explain why doped Mott insulating oxides that do not contain copper as a rule form insulators: invariably, their electrons freeze in the sturdy stripes of my computer code.

Starting from the mid-1990s, evidence accumulated that stripes might also have a role in the cuprates, albeit in a 'dynamical' way that is not that well understood: in underdoped superconducting cuprates, stripes would be present in the form of strong correlations at short timescales, but at longer timescales they would fall prey to a quantum melting driven by collective quantum fluctuations[4,5]. Consistent with this hypothesis, it was found that stripes become static only in some special cases[7], and that static stripes have a detrimental effect on superconductivity. Neutron-scattering experiments were pivotal in collecting that evidence. These experiments measure spin fluctuations in the materials as a function of their energy and of their wavenumber (inverse wavelength), and in this energy–wavenumber space the spin-fluctuation spectrum of the underdoped cuprates is shaped like an hourglass (Fig. 1). It was argued[5] that this could be explained in terms of collective 'vibrations' (spin waves) of the stripe-phase incommensurate antiferromagnetic order, except that at low energies a gap appears in this spectrum that was interpreted as the signature of the collective quantum

melting of the stripe phase as a whole.

However, an equally credible case was made[8] that the hourglass spectrum could instead be explained in terms of spin excitations in a rather weakly interacting gas of itinerant electrons, and a debate regarding the interpretation of the hourglass spectrum evolved that rages up to the present day. All along, the problem for the dynamical-stripe interpretation was that the modelling of the spin waves involved a lot of assumptions. In this regard, Boothroyd and colleagues' study[1] makes a big difference. The authors perform a neutron-scattering experiment on a material that falls outside the family of cuprate superconductors — a cobalt oxide insulator — and that is known to display stripes[9] in a simple static form[6]. They show that the material exhibits an hourglass spin-fluctuation spectrum (Fig. 1a) strikingly similar to that of the cuprates (Fig. 1b); the only difference is seen at low energies, where the cuprate 'quantum gap' is absent in the cobalt oxide. This similarity lends support to the hypothesis that the hourglass spin-fluctuation spectrum in the cuprate superconductors arises from dynamical stripes[4,5].

Boothroyd and colleagues' results arrive at a time when the reality of complex quantum matter in underdoped cuprates is becoming mainstream wisdom. Perhaps we already know so much about these materials that research should be refocused on the greatest mystery of all[4]: that increased levels of doping make the complex quantum stuff gradually fade away, and that the best superconductors are found at the point where the electron traffic starts to resemble the quantum fog of the simple metals. ■

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TRANSLATIONAL MEDICINE

Cancer lessons from mice to humans

New clinical trials report the efficacy of two mechanism-based therapies for treating human pancreatic neuroendocrine tumours. Studies in mouse models have contributed to these success stories, and continue to do so.

DAVID TUVESON & DOUGLAS HANAHAN

Advances in cancer medicine have reset our clinical and social expectations: the aim now is to effectively combat formidable tumours — an effort that was previously deemed improbable. Writing in *The New England Journal of Medicine*, Raymond *et al.*[1] and Yao *et al.*[2] report phase III clinical trials of two drugs that target distinctive cancer-associated signalling pathways. The results suggest an impressive efficacy of both drugs (sunitinib and everolimus) for treating pancreatic neuroendocrine tumours. It is therefore likely that these drugs, which are already standard treatments for other cancers, will become the first new approvals in 25 years by the US Food and Drug Administration (FDA) for treating these cancers, a remarkable milestone.

Pancreatic neuroendocrine tumours (PNET) are uncommon, but difficult to diagnose and treat. These cancers, which originate from the hormone-producing pancreatic islet cells, stand in stark contrast to another type of pancreatic cancer, pancreatic ductal adenocarcinoma, which is much more prevalent and deadly: a larger proportion of patients with PNET undergo surgical excision, and the clinical course of the disease is highly variable. Nonetheless, patients with advanced PNET who are not candidates for surgery have a terminal illness, and their tumours are difficult to manage; the FDA-approved chemotherapeutic agent streptozotocin shows only modest activity in these patients.

A vast number of potential anticancer drugs are currently in the pipelines of biopharmaceutical companies. Indeed, the scope of mechanism-based targeting is broad, often with several potential drugs affecting the same target. Consequently, it is challenging to decide which targets and candidate drugs might be of value in particular forms of human cancer, especially those that are rare but deadly like PNET. There is growing optimism that genetically engineered mouse models, which can mimic the progression of specific types of human cancer at the genomic and tissue levels, can contribute to this prioritization[3]. The hope is that preclinical trials of candidate drugs in representative mouse models could help to motivate and guide clinical trials of targeted therapies in the related human tumours (Fig. 1). The two new papers[1,2] reflect proof of this concept.

The mouse model of PNET, called RIP-Tag2, shows similar tissue-level features to the human tumours[4]. However, the cancer in the animal does not follow the same — currently obscure[5] — initiating events that lead to human PNET; it is instead driven by a viral oncogene that abrogates the function of two generic tumour-suppressor pathways commonly lost in human tumours.

Preclinical trials in this model had predicted that both sunitinib, a pan-specific inhibitor of tyrosine-kinase enzymes, and everolimus,

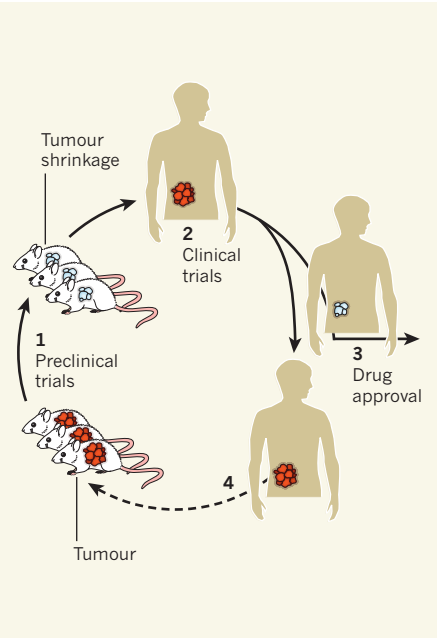

Figure 1 | Linking preclinical and clinical trials. (**1**) Preclinical trials on cohorts of mice engineered to develop a particular type of cancer are a good starting point for evaluating mechanism-based drugs. (**2**) If the mice show detectable therapeutic benefits, such as increased survival and/or tumour shrinkage, the preclinical trials can motivate and guide the design of clinical trials in the same type of cancer. (**3**) Clinical benefit, such as tumour shrinkage, increased progression-free-survival and overall survival, can justify drug approval for clinical use. (**4**) Relapses and clinical failures, however, can be translated back into refined preclinical trials aiming to understand and circumvent the limitation.