to clonal haematopoiesis. Because increased cellular cholesterol and platelet activation promote inflammatory responses[11], these drugs might have anti-inflammatory properties that ameliorate the adverse effects of clonal haematopoiesis. ■

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QUANTUM PHYSICS

A solid more fluid than a fluid

A supersolid is a paradoxical and elusive state of matter that has been sought for more than 60 years. Two experiments have now observed its characteristic signatures in ultracold quantum matter. SEE LETTERS P.87 & P.91

KADEN R. A. HAZZARD

If you poke a solid object, the whole object moves rigidly. But if you poke your finger into a cup of water, some of the liquid is displaced. We learn this fundamental distinction as children: a solid is rigid and retains its shape, whereas a liquid conforms to its surroundings. On pages 87 and 91, Léonard *et al.*[1] and Li *et al.*[2] report results from experiments carried out at ultracold (nanokelvin-scale) temperatures. The authors observe characteristic signatures of a supersolid — a state of matter that marries solid and liquid properties in spectacular fashion.

Although a supersolid is rigid, it can flow like a liquid. Even more remarkably, it can behave like a liquid without viscosity — a superfluid (Fig. 1). For a different perspective, we can consider how the system organizes into patterns, known as its 'orders'. A supersolid has two orders: solid and superfluid. The former is a consequence of the system's spatially repeating pattern of particles. The latter arises from particles moving through the solid aided by the laws of quantum mechanics. This motion gives rise to a subtle quantum-mechanical order that characterizes how much quantum mechanics smears out the positions of the particles.

From the 1950s to the 1970s, theoretical physicists argued about whether a supersolid could exist. It was widely believed that the most promising candidate was pressurized helium cooled to temperatures of a few kelvin. Although fascinating features have been observed in helium in the past decade, it is unlikely that they are signs of supersolidity, at least of the conventional kind[3].

Over the past decade, physicists have pursued an alternative route to supersolidity, using the rapidly developing techniques for engineering ultracold quantum matter. Collections of atoms are now routinely cooled to just a few hundred nanokelvin. At these temperatures, thermal motion of the atoms gives way to the intrinsic fluctuations that are imposed by quantum mechanics. Such slowly moving atoms can be precisely controlled by minute forces from laser light, with which one can engineer an enormous variety of phenomena. However, although several groups have proposed methods to create supersolids[4–6] and experiments have revealed signs of related physics[7], the challenges of cooling these systems sufficiently and of reaching thermodynamic equilibrium have limited progress.

Li *et al.* and Léonard *et al.* now observe signatures of supersolidity in two radically different experimental platforms. Li and colleagues engineer variants of theoretically studied systems of two-state atoms[8–10]. In these systems, atoms can switch between states only if their momentum is changed by a specific amount — one implementation of a property called spin–orbit coupling. The authors prepare their system initially in a superfluid state using standard cooling techniques, and then turn on the spin–orbit coupling using a pair of lasers. The state-changing momentum kicks provided by these lasers shake the atoms in a regular way, causing them to line up in a spatially repeating pattern that manifests in addition to the previously observed superfluid order. Li *et al.* confirm this solid order by observing how laser light is reflected off the system at a specific angle, a technique known as Bragg diffraction.

Léonard and colleagues also start with an atomic superfluid, but they place these atoms between two mirrors, called an optical cavity. The authors then shine a 'pump' laser on the atoms, and the resulting excited atoms emit light into the cavity. The light forms a standing wave and exerts a force on the atoms, pushing them towards places where the light intensity is maximal. The atoms follow the standing wave and develop a spatially repeating pattern.

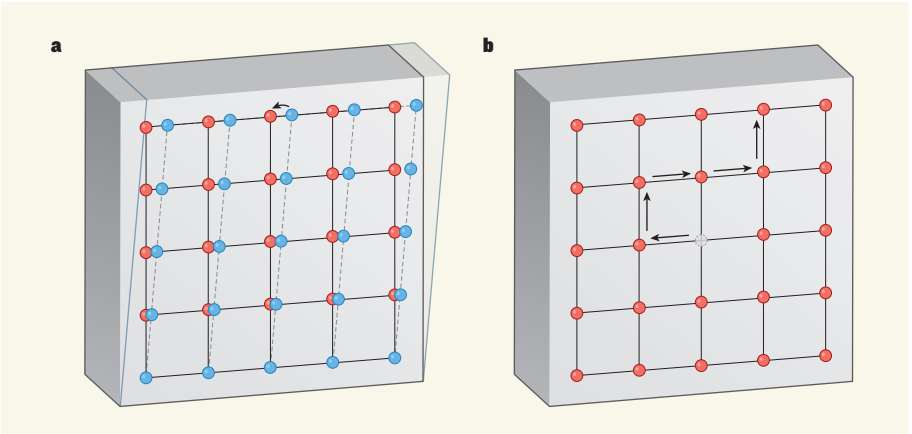

Figure 1 | Characteristics of a supersolid. Léonard *et al.*[1] and Li *et al.*[2] have observed experimental evidence of a supersolid, a state of matter that has two key characteristics. **a**, Like a solid, a supersolid is rigid and its atoms (red circles) snap back into place if displaced (blue circles), in contrast to a fluid, which is easily and permanently displaced. **b**, In a solid, a defect such as a missing atom (open circle) can flow through the atomic lattice, but, in a supersolid, quantum mechanics allows this motion to happen without viscosity.

Léonard *et al.* experimentally confirm both solid and superfluid orders by the appearance of characteristic peaks in the distribution of the atoms' momenta. In contrast to previous work[11,12], the clever use of two cavities oriented along different axes allows the solid formed by the atoms to be uniformly and continuously displaced along one direction — in a similar way to familiar, conventional solids.

Besides advancing our understanding of supersolidity, the experimental techniques developed in these papers open other frontiers. Li and colleagues' work will help researchers to create other states of matter in which spin–orbit coupling is essential, including exotic topological states[13]. Léonard and colleagues advance the techniques for coupling an atomic superfluid to multiple optical cavities. One can view such a cavity as producing a long-range interaction between the atoms. Using multiple cavities allows greater flexibility to control these interactions, enabling the study of poorly understood phenomena, such as the forms of matter called quantum spin glasses[14].

Despite this progress, challenges remain for future studies of supersolidity. The heating rate of the lasers used by Li *et al.* is large, and it is possible that effects associated with this are a major factor in the authors' observations. In both experiments, it will be valuable to learn to what extent the supersolids are in thermodynamic equilibrium, and what new physics results if they are not.

Going forward, it would also be useful to complement the measurements of the supersolids' characteristic orders with measurements of their response to external stimuli. Are they rigid? Do they support zero-viscosity flow, and, if so, under what conditions? Léonard and colleagues' system lacks low-energy excitations that arise when systems that have short-range interactions become ordered — what features does this lend to the authors' supersolid?

Supersolids are of particular interest because they manifest two intertwined orders, one of which is associated with zero-viscosity flow. Every zero-viscosity state of matter that has so far been discovered — for example, helium superfluids, superconductors and ultracold Bose–Einstein condensates — has been pivotal in expanding physicists' theoretical concepts and experimental techniques. The supersolid is sure to be another on this list. ■

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IMMUNOLOGY

T-cell tweaks to target tumours

Immune cells known as T cells can destroy tumour cells, but their clinical use requires complex preparation and the cells can lose effectiveness over time. A new approach might improve the efficiency of T-cell therapy. SEE LETTER P.113

MARCELA V. MAUS

The T cells of the immune system can kill cells that express a molecule known as an antigen, if the antigen is specifically recognized by a T-cell receptor protein (TCR). T cells can be removed from the body and genetically modified *in vitro* to insert the sequence encoding an engineered TCR known as a chimaeric antigen receptor (CAR). A CAR can be designed to recognize an antigen expressed in a cancer cell, such as the CD19 antigen. These genetically engineered cells, called CAR T cells, are returned to the patient's body, and this approach has successfully treated some cancers[1]. As they report on page 113, Eyquem *et al.*[2] have developed an approach to integrating DNA sequences encoding CARs into T cells that offers several advantages over the strategies currently used.

During T-cell development, T cells rearrange gene sequences that encode the TCR so that each T cell expresses a unique TCR that binds a specific antigen. T cells with TCRs that have a high affinity for antigens expressed by the body's own cells (self antigens) are destroyed to avoid autoimmunity. Attacks on tumours by T cells are usually weak because tumours express self antigens. Most current approaches to making CAR T cells insert the CAR-encoding gene into T cells without disrupting the resident TCR gene. This means that the patients' own T cells have to be used to avoid the risk of rejection or graft-versus-host disease when the T cells are transplanted back into the body. However, a recent study has explored disrupting the resident TCR α-chain constant region (TRAC) sequence when creating CAR T cells, thereby disabling the TCR and enabling a patient to be treated with CAR T cells made from another person's cells[3].

To create a consistent way to introduce CAR sequences into T cells, Eyquem and colleagues decided to integrate a CAR sequence directly into the TRAC. A direct-insertion strategy to genetically modify DNA sequences in human T cells has been used to target the *CCR5* gene using zinc-finger nuclease enzymes[4,5], and RNA-based nuclease enzymes have integrated CAR sequences into the *CCR5* locus[6].

The direct-insertion strategy for CAR sequences chosen by Eyquem and co-workers used CRISPR–Cas9 gene-editing tools. The authors introduced RNA encoding the DNA-cleaving nuclease enzyme Cas9 into T cells along with an RNA 'guide' sequence that targets the TRAC sequence. The Cas9 protein used the RNA guide sequence to create a targeted double-stranded break in the TRAC DNA sequence. A viral vector with a CAR sequence flanked by sequences homologous to the TRAC sequence was introduced into the T cells. The double-stranded break in the TRAC sequence was repaired using the viral vector sequence as a template, resulting in the original TRAC sequences being replaced by the introduced CAR sequences (Fig. 1).

In genetic engineering approaches, viral promoter sequences can be used to drive gene expression, which can result in high expression. However, expression often drops off over time. Constitutively active promoters offer another way to drive gene expression. Both types of promoter approach have been shown to drive constitutive CAR signalling in T cells[7,8], and this can affect the ability of CAR T cells to control tumours. Constitutive T-cell activation might cause T-cell exhaustion, a dysfunctional T-cell state characterized by the inability to exert antitumour effects and the expression of some inhibitory receptor proteins such as PD-1 (ref. 9). Constitutive signalling might also result in toxicity because of