the activity of DRN neurons will be crucial, especially given that Castro and colleagues' results indicate that about half of DRN neurons in mice express μ-opioid receptors[4].

Inevitably, questions remain. For example, which mechanisms regulate the other half of the hunger-driven increase in eating? And what are the upstream signals that communicate the hunger state to the NAC? The authors speculate that neurons in a structure called the hypothalamus at the base of the brain, known to produce peptide signals that regulate feeding and project to the NAC, might be involved. If they are right, here comes another microcircuit that plays a feeding-related part in the big orchestra of the brain.

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Immunotherapy

Bacteria recycle tumour waste to fuel immune cells

Laurence C. Chen & Yvonne Y. Chen

Key nutrients that are needed by immune cells are scarce in tumours. Engineered cancer-invading bacteria can recycle tumour waste into metabolic fuel to boost anticancer immune responses in mice. **See p.662**

Harnessing a person's immune system to target a tumour — a type of treatment called cancer immunotherapy — has emerged as a promising treatment option for cancer. T cells are a type of immune cell that has a surveillance function and the capacity to kill foreign or infected cells that are perceived to pose a threat. These properties have cemented T cells as a central pillar of cancer immunotherapy. The generation of an effective antitumour T-cell response depends crucially on the availability of nutrients such as the amino acid L-arginine[1]. However, the tumour microenvironment poses a challenge because it is nutrient-poor[2]. Canale *et al.*[3] show on page 662 that the treatment of mice with metabolically engineered bacteria produces a local, continuous source of L-arginine in the tumour microenvironment that results in strong, long-lasting antitumour T-cell responses when combined with a form of immunotherapy called checkpoint blockade.

It was shown previously[1] that L-arginine supplementation prolongs T-cell survival, enhances the generation of a memory response, and improves tumour-killing efficacy in a mouse model of a skin cancer called melanoma. However, clinical treatment with L-arginine supplementation is not straightforward. Oral administration would require patients to consume impractically large quantities of the amino acid every day, whereas direct injection into a tumour would be possible only for tumours near the surface of the skin, and might be ineffective owing to leakage of the amino acid out of the tumour. Canale and colleagues hypothesized that a strategy to provide a local, continuous supply of L-arginine in the tumour microenvironment would aid T-cell immunotherapy (Fig. 1).

Ammonia is a waste product of metabolism of cancer cells that accumulates in the tumour microenvironment[4], and it can be converted enzymatically into L-arginine. The authors identified two key steps in the L-arginine biosynthesis pathway. These require the protein argR, which suppresses L-arginine biosynthesis, and the enzyme argA. High levels of intracellular L-arginine inhibit the amino acid's production by argA through negative feedback.

Canale and colleagues sought to capitalize on this knowledge when producing genetically engineered microbes. Bacteria can home to tumour microenvironments, colonize these sites and flourish there[5]. The bacterial strain *Escherichia coli* Nissle 1917 (ECN) is harmless and has a long history of medical use in therapeutics, vaccines and diagnostics[6]. The authors genetically manipulated these microbes, deleting the gene that encodes argR and introducing a mutant version of argA that is not inhibited by negative feedback. An ECN strain was thus generated that the authors called L-Arg bacteria, which converted ammonia into L-arginine both *in vitro* and in the tumour microenvironment.

The authors report that injecting L-Arg bacteria into tumour-bearing mice resulted in an increase in tumour-attacking T cells (a type known as conventional T cells) and a decrease in immunosuppressive T cells (a type termed regulatory T cells). This boost in tumour infiltration by conventional T cells complemented the therapeutic effects of checkpoint-blockade immunotherapy. The latter approach used antibodies that target the protein PD-L1, which is found on tumour

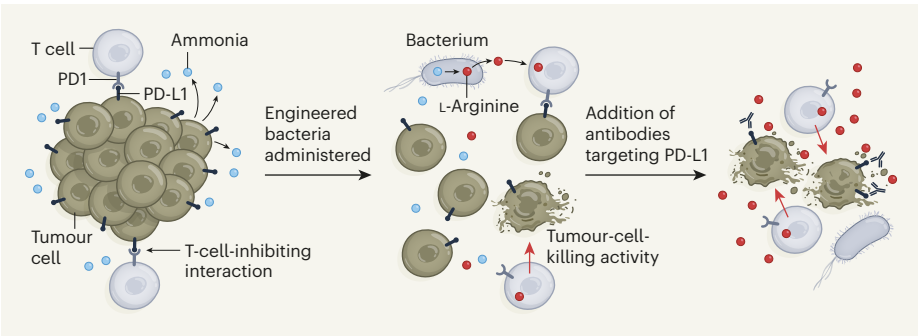

Figure 1 | An approach that boosts antitumour immune responses. Immune cells called T cells face various challenges that hinder their ability to kill tumour cells. The tumour microenvironment is poor in nutrients needed by immune cells, and high levels of metabolic waste products from the tumour cells, such as ammonia, are present. Moreover, T-cell activity can be suppressed as a result of interaction between the PD-1 protein on immune cells and the PD-L1 protein on tumour cells. Canale *et al.*[3] demonstrate that metabolically engineered bacteria that can convert ammonia to the amino acid L-arginine overcome the deficiency of L-arginine in the tumour microenvironment in mice, and thereby boost T-cell function and infiltration into the tumour. The authors report that, when this treatment is combined with a therapy that uses antibodies to block the activity of the PD-L1 protein, the antitumour response is further improved.

cells and on other immunosuppressive cells, thus preventing PD-L1 from suppressing the activity of tumour-targeting T cells. In a mouse model of colon cancer, treatment with L-Arg bacteria together with PD-L1-targeting antibodies had superior antitumour effects compared with effects seen in animals that received either therapy alone. Moreover, this combination therapy resulted in the formation of memory T cells. When T cells taken from treated animals were transferred to previously untreated tumour-bearing animals, tumour growth was suppressed.

Importantly, the effects of L-Arg bacteria were observed when the bacteria were injected either directly into the tumour or into the bloodstream. The therapeutic effects of combined L-Arg bacteria and PD-L1-targeting antibodies depended on T cells. The authors observed similar results when they carried out the same type of experiment in another mouse model of melanoma (B16-OVA), in which the animals were treated with T cells that specifically target the ovalbumin protein associated with this type of tumour.

Canale and colleagues' pioneering work provides substantial support for the use of bacterium-induced modulation of the tumour microenvironment. Further investigation to answer some key questions could help pave the way to clinical implementation.

First, although the tumour-homing behaviour of bacteria such as ECN is well documented, the exact mechanism underlying this process is unclear. As a result, questions linger about both its effectiveness and its safety in humans. Although mice treated with L-Arg bacteria showed no overt signs of toxicity, a transient reduction in body weight occurred. Whether the effects of treatment would be more subtle or amplified in humans remains to be explored. The increasing numbers of clinical trials that are evaluating bacterial therapy[7] might provide a clearer picture of the anatomical distribution of bacteria harnessed for treatment, as well as their effects on longevity and any resulting potential toxicity.

Second, the effectiveness of metabolically oriented strategies, such as the conversion of ammonia to L-arginine, might depend on the specific tumour type. Further investigation of the intrinsic properties of tumours and their microenvironments that render particular cancer types more susceptible or resistant to such a therapeutic strategy could be crucial for effective selection and treatment of patients.

Finally, as with all genetically modified cell-based therapeutics, consideration must be given to the genetic stability of the modified organism. In-depth analysis is needed to determine whether other features, such as the use of 'suicide' genes to enable the controlled destruction of the engineered bacteria, would be necessary to ensure short- and long-term safety for patients.

Canale *et al.* have highlighted a new approach using engineered microbes to address the metabolic challenges presented by the tumour microenvironment. By converting a tumour-derived waste product into metabolic fuel for tumour-reactive T cells, L-Arg bacteria potentiate stronger and more-durable antitumour responses. Although the safety of the treatment should be explored more extensively before it can be moved towards clinical use, Canale and colleagues' work provides a much-needed step forward for cancer immunotherapy.

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Condensed-matter physics

A compact device sustains a fluid of bosons

Denis Golež & Zhiyuan Sun

A device that generates exotic fluids of particles at equilibrium conditions and high temperatures could have applications ranging from low-loss electrical cables to memory storage. **See p.585**

Imagine that your favourite cinema has just installed a single VIP seat that everybody wants to sit in. If cinema-goers were bosons, a type of elementary particle, they could all fit in this seat at the same time. This is the physics behind Bose–Einstein condensation, a phenomenon that involves a large fraction of the bosons in a gas simultaneously occupying the quantum state with the lowest energy. Bose–Einstein condensates have been achieved in cold atomic gases, a type of gas comprising atoms held at a temperature near absolute zero. But sustaining microkelvin temperatures is far from trivial because of the size of the machinery required. On page 585, Ma *et al.*[1] report a fluid of bosons in equilibrium, generated in a compact solid-state device at temperatures as high as 100 K — well within the reach of an ordinary physics laboratory. However, it remains to be confirmed whether it is indeed a Bose–Einstein condensate.

When a Bose–Einstein condensate forms, the resulting state is known as a superfluid, which behaves like a zero-viscosity fluid. The temperature at which it forms can be raised either by reducing the mass of the bosons or by increasing their density. Both approaches have been used in semiconducting devices[2] in which electrons and holes (their positively charged counterparts) pair up to form particles called excitons — bosons that are much lighter than atoms. The exciton mass can be reduced further using light-trapping systems called optical cavities, in which the excitons mix with light to form even lighter bosons[3]. Attempts to increase the bosonic density are limited by the fact that adding particles tends to destroy the excitons by weakening the electron–hole binding. Still, the excitonic densities achievable in atomically thin semiconductors are high enough to allow high-temperature condensates[4].

Raising the temperature is not the only challenge in creating a Bose–Einstein condensate. To generate excitons, lasers are needed — an impractical and expensive component for a compact device. Furthermore, excitons can be short-lived, lasting as little as a few picoseconds (one picosecond is 10^{-12} s) before being destroyed when the electron and hole recombine. Confining electrons and holes to separate semiconductor layers creates interlayer excitons, which have a substantially lower recombination rate. But the condensate that forms is still transient, and accompanied by heat generation, making the system difficult to control. Persistent condensates have previously been sustained without