RETRACTION

In view of the fact that the authors of 'A homing system targets therapeutic T cells to brain cancer' (H. Samaha *et al. Nature* **561**, 331–337; 2018) are retracting their report, Michael Platten wishes to retract the News & Views article 'T cells engineered to home in on brain cancer' (M. Patten *Nature* **561**, 319–320; 2018), which dealt with this study and was based on the accuracy and reproducibility of their data.

of the waves. Consequently, a stronger wakefield requires a shorter proton bunch.

The main innovation in Adli and colleagues' work was, therefore, to make the length of the proton bunch as short as possible so that the bunch resonates with the plasma's internal clock, maximizing the amplitude of the wakefield. The authors achieved this feat using a feature of the plasma known as collective force. Although the electric force produced by each particle in the plasma is small, the collective force generated from all of the particles can be large, and becomes larger as the plasma density is increased[2]. The authors used this force to chop a long proton bunch into a series of shorter bunches. Because proton bunches are stiff (difficult to deform) at the extremely high particle energies present in the AWAKE experiment, this chopping was possible and effective only by using the plasma's collective force.

Adli *et al.* found that the wakefield produced by the short proton bunches could accelerate electrons to energies of up to 2 gigaelectronvolts in a plasma that is only about 10 metres in length. For comparison, at the European X-ray free-electron laser facility (European XFEL) in Germany, electrons are accelerated to energies of up to 17.5 gigaelectronvolts in an accelerator that is about 2 km long (see go.nature.com/2n6857t). In addition to providing compact acceleration, the authors' approach has a key advantage over standard accelerators and other wakefield accelerators. Because the proton bunches are stiff, they maintain their structure and speed. As a result, high-energy electrons can be produced in a single acceleration stage, as opposed to the complex multi-stage process that is needed in other accelerators.

Usually, the higher the energy of a particle beam, the longer it takes to stop (dump) the beam after use. The dumping of high-energy beams has become a serious issue because of the requirement of longer dumping lengths, which in turn increases the production of unwanted radioactive isotopes in the dense materials used for the dumping. The authors show that their accelerated electrons can form a beam of short electron bunches, which would encounter a large collective force if injected into an appropriately prepared plasma. Such a beam could therefore be stopped over a much shorter distance than conventional beams, inducing little radioactivity[5]. Overall, the authors' work represents a major step towards the development of future high-energy particle accelerators that use collective force. ■

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CANCER

RETRACTED

T cells home in on brain tumours

Immunotherapies activate T cells to destroy tumours, but the approach has failed in some brain cancers. A strategy to improve migration of T cells across the blood–brain barrier could overcome this limitation. SEE ARTICLE P.331

MICHAEL PLATTEN

Therapies that activate immune cells called T cells to target tumours are an efficient way to combat many types of cancer[1]. But an aggressive brain cancer called glioblastoma has proved a particular challenge for immunotherapies[2]. The blood–brain barrier protects the brain against immune-cell infiltration to prevent the potentially life-threatening effects of brain inflammation. This phenomenon is beneficial in normal circumstances, but it prevents T cells from reaching glioblastomas, making the tumours immunologically 'cold'[3]. On page 331, Samaha and colleagues[4] report a way to trigger infiltration of T cells into the brains of mice, thus making glioblastomas vulnerable to immunotherapy.

In the disease encephalitis, brain inflammation occurs because T cells that are typically excluded from the brain migrate across the blood–brain barrier. This migration is a coordinated process that requires activated T cells circulating in the bloodstream to adhere to endothelial cells, which line blood vessels. Adhesion is mediated by the binding of ligand molecules on T cells to cell-adhesion molecules such as ALCAM, ICAM-1 and VCAM-1 on endothelial cells[5]. These cell-adhesion molecules are expressed at higher than normal levels in encephalitis[6]. Binding between ALCAM and the T-cell ligand CD6 halts the progress of activated T cells through blood vessels, allowing subsequent binding by ICAM-1 and VCAM-1.

50 Years Ago

A campaign was opened last week for funds to refloat the Great Britain, one of the three major ships designed by Brunel. The object is to tow her back from the Falkland Islands to the Bristol shipyard … The Great Britain was the first ocean-going iron ship and the first to be driven by propeller … Brunel intended the ship to carry passengers of the Great Western Railway … to New York, but the Great Britain made only a few transatlantic voyages before running aground … Brunel managed to refloat the ship, which for the next 20 years carried emigrants to Australia … In 1875, the Great Britain's engines were removed and she was converted to sail, plying between Liverpool and San Francisco until put out of service by a fire near the Falkland Islands … Despite the ship's age, her structure is still sound enough to survive the journey back to Britain.
From *Nature* 21 September 1968

100 Years Ago

On the afternoon of Saturday, August 24 last, the allotment-holders of a small area in Hendon … were sheltering in their sheds during a heavy thundershower, when they observed that small fish were being rained to the ground. The fish were precipitated on three adjoining roads and on the allotment-gardens enclosed by the roads; the rain swept them from the roads into the gutters and from the roofs of the sheds … It is not easy to say how many fish fell, but … they were numerous … All the examples which came into my hands … prove to be the lesser sand-eel (*Ammodytes tobianus*) … The place where the sand-eels in question were deposited lies about one-quarter of a mile from the seashore … The only explanation … is that a shoal of sand-eels was drawn up by a waterspout.
From *Nature* 19 September 1918

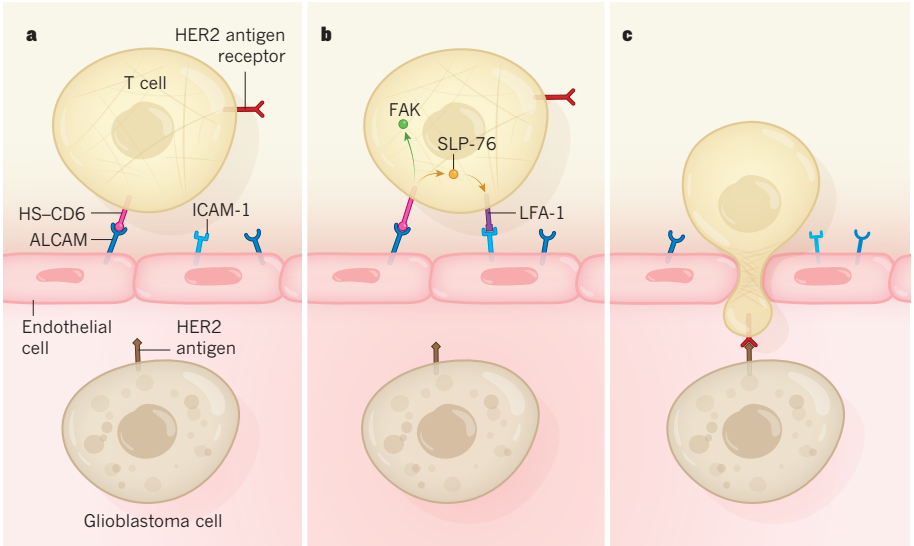

Figure 1 | Targeting of tumour-specific T cells. Immune cells called T cells harbour ligand molecules that bind to the receptor molecules ALCAM and ICAM-1 on endothelial cells, which line blood-vessel walls in the brain. Samaha *et al.*[4] have developed a strategy to enhance this binding, enabling T cells to cross the blood–brain barrier and infiltrate brain tumours such as glioblastoma. **a**, The authors engineered T cells to express both a synthetic ALCAM-specific ligand, HS–CD6, and an antigen-receptor protein designed to bind to the antigen molecule HER2 on glioblastoma cells. HS–CD6 bound ALCAM with high affinity. **b**, This binding resulted in activation of the protein SLP-76, which induced the ligand LFA-1 to move to the cell surface and bind ICAM-1, strengthening endothelial-cell binding. Binding also led to activation of the protein FAK. **c**, FAK remodelled the actin-protein network that gives the cell its shape (faint lines), enabling the T cell to squeeze between endothelial cells. The HER2 antigen receptor then bound HER2 on glioblastoma cells, triggering an immune response against the tumour.

Once binding of T cells by cell-adhesion molecules reaches a critical threshold, the T cells can migrate between endothelial cells and so out of the vessel into the brain.

In glioblastoma, however, the brain vasculature is reprogrammed such that endothelial cells produce little or no ICAM-1 and VCAM-1 (ref. 7). If researchers could increase adhesion between T cells and endothelial cells in people with glioblastoma, as occurs in encephalitis, it might be possible to enable transendothelial migration of T cells.

Samaha and colleagues found that endothelial cells in glioblastoma overexpress ALCAM. They reasoned that, by engineering T cells to bind to ALCAM more firmly, they could enhance T-cell anchoring in the endothelium and subsequently improve transendothelial migration. To this end, the authors generated a synthetic ligand for ALCAM, derived from CD6. They engineered their molecule, which they named homing-system CD6 (HS–CD6) such that individual ligands interacted with one another to produce a multimeric protein. The researchers introduced the synthetic ligands into T cells using a retrovirus construct. They found that the presence of multimeric HS-CD6 on T cells enhanced adhesiveness between these cells and ALCAM-expressing endothelial cells and, as predicted, enabled transendothelial migration in *in vitro* models.

Samaha and colleagues also uncovered details of the molecular program by which HS–CD6 triggers transendothelial migration. On binding by ALCAM, HS–CD6 activates the protein SLP-76 in T cells. SLP-76 mobilizes the protein LFA-1, which moves to the cell surface and binds the few ICAM-1 molecules present on endothelial cells, further enhancing binding between T cells and endothelial cells. These changes also activate FAK, a protein that modulates the network of actin proteins that confer T-cell shape, enabling T cells to squeeze between endothelial cells, crossing the blood–brain barrier (Fig. 1).

The next step for the authors was to ensure that T cells entering the brain would home in on tumour cells. T cells harbour antigen-receptor proteins on their surfaces that bind to specific protein fragments called antigens on target cells, enabling T cells to pick out foreign cells for destruction. Samaha *et al.* engineered T cells to express an antigen receptor that was designed to bind to human epidermal growth factor receptor 2 (HER2) — an antigen produced by glioblastoma cells. They then introduced these cells into mice in whose brains human glioblastomas had been surgically implanted. T cells that expressed both HS–CD6 and the HER2-specific antigen receptor infiltrated the glioblastomas, leading to complete remission and long-term survival in most of the treated animals. By contrast, T cells harbouring only the antigen receptor (which are typically used for cancer immunotherapy) did not infiltrate the tumour.

"This study lays out a viable strategy for immunotherapy in glioblastoma."

This study lays out a viable strategy for immunotherapy in glioblastoma. But key challenges must be overcome before we can translate the discovery from mice to patients. For instance, ALCAM is expressed by a variety of cell types, including bone-marrow cells[8]. More studies will be required to assess whether the integrity and functions of these non-endothelial cells are affected by the approach. In addition, toxicity could be an issue if T-cell targeting damages healthy brain tissue, either directly or indirectly. Strategies to limit T-cell activation and lifespan using genetic 'off' switches have already been developed[9], and could potentially be used to combat such toxicity. Encouragingly, the fact that the authors' mice survived long-term suggests that the treatment did not cause severe toxicity in the animals. However, the group did not investigate the persistence and activity of the HER2-targeting T cells in the body, or examine whether the cells targeted non-glioblastoma cell types.

Finally, targeting T cells to brain tumours is only a first, albeit crucial, step in triggering an effective antitumour T-cell response against glioblastoma. T cells entering a glioblastoma will encounter a profoundly immunosuppressive microenvironment created by low oxygen and pH levels and immunosuppressive molecules. This did not harm T cells in the glioblastoma-harbouring mice, but these animals do not mimic many key features of true human glioblastoma — and immunosuppression will certainly pose a challenge in humans. A successful immunotherapy strategy for glioblastoma will ultimately consist of a combinatorial therapy that allows enough active tumour-specific T cells to enter and persist in an immune-permissive tumour microenvironment[10]. Such an approach would transform this deadly disease from an immunologically cold target to a hot one. ■

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