Striking a balance between T-cell activation and inhibition is crucial for the proper functioning of the immune system. Among the expanding list of molecules referred to as immune checkpoints and involved in the inhibition of T-cell function, the two most validated to date are the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4; ref. 1), expressed on activated T cells, and the programmed cell death protein-1 (PD-1; ref. 2), which binds to its ligands (the PD-L1 and PD-L2 proteins expressed on many cell types) and interrupts signalling mediated by the T-cell antigen receptor. The ability to modulate the activity of these checkpoints has given rise to the field of immune-checkpoint therapy, now considered a pillar of cancer therapy. On the basis of the most validated immune checkpoints identified to date (CTLA-4, PD-1 and PD-L1), four antibodies have been approved for clinical use: ipilimumab, nivolumab, pembrolizumab and atezolizumab. Durable patient responses have been documented, and in the case of ipilimumab, which has the longest clinical history, survival of 10 years or more has

**Figure 1** | Clinically approved immune checkpoint inhibitors. a, Developed human or humanized monoclonal antibodies (i), FDA approvals (ii), and examples of ongoing clinical trials (iii) for the clinically approved inhibitors CTLA-4, PD-1 and PD-L1. b, Most common side effects. Detailed demographic data and medication dosages can be found in ref. 3. Graph adapted from ref. 3, Macmillan Publishers Ltd.
Platelet-mediated delivery of anti-PD-L1 to surgical wound sites. Platelets are modified by covalent attachment of anti-PD-L1 to surface proteins through a bifunctional linker. The engineered platelets are deployed to the surgical wound site, become activated, and produce both inflammatory mediators and platelet-derived microparticles (PMPs) with anti-PD-L1 on their surfaces. The release of PMPs and inflammatory mediators results in the activation of CD8+ T cells and hence antitumour activity mediated by the interaction between T-cell receptors (TCR) and the major histocompatibility complex (MHC).
to mimic circulating tumour cells only anti-PD-L1 immunoplatelet conjugates prevented the formation of a recurrent tumour at the site of the surgical wound and conferred a marked survival benefit. Interestingly, given the unique mechanism of the engineered immunoplatelet conjugates to home to and become activated at the surgical site, the potential reduction in blood-plasma exposure of the engineered immunoplatelet conjugates in humans (because of the shorter circulating half-life of human platelets with respect to that for atezolizumab) may actually translate into an improvement in the anti-PD-L1 therapeutic window.

Gu and colleagues’ conjugation strategy for the targeted delivery of immune checkpoint inhibitors to the surgical wound may pave the way for safer and more effective checkpoint therapy in an adjuvant setting while ameliorating some of the adverse effects of systemic administration. Although the system is complex and the scalability, regulatory and manufacturing hurdles are considerable, it is tantalizing to imagine that the efficacy of the authors’ approach may be further improved by attachment of anti-CTLA-4, which has a mechanism of action distinct from, but synergistic with, that of PD-L1. In fact, clinical experience to date has shown that combination therapy with anti-CTLA-4 and anti-PD-1 confers additional clinical benefits. But the application of such therapy is limited by a higher incidence of toxicities and their broader spectrum. Gu and co-authors’ approach could thus facilitate such combination therapy and mitigate its adverse effects. Additionally, the authors’ conjugate approach could be combined with recently developed nanotechnologies that make use of platelet biology, such as nanoparticle-coating platelet membranes isolated from human blood that enhance the nanoparticles’ circulation time and their ability to target injured vasculature. The combination of both methods might eventually lead to the in situ synthesis of anti-PD-L1-conjugated platelet-membrane-coated nanoparticles that can simultaneously carry other agonists to augment T-cell responses. To accelerate the clinical translation of such strategies, proper regulatory standards must be established to overcome any issues associated with the development of biologically modified platelets and to ensure robust and reproducible conjugation chemistry in combination with analytical methods to support the manufacturing of the final biologic product.

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