A critical breakthrough in the last two decades for I-O was the clinical demonstration that a patient’s immune system, specifically their T cells, can be manipulated as a powerful tool to overcome cancer and deplete malignant cells. The seminal evidence to support this came with the observation that the anti-CTLA4 antibody ipilimumab, conferred a significant survival benefit to a subset of patients with metastatic melanoma—a disease which at the time was considered a ‘graveyard’ of drug development [1]. Building on this, evidence quickly mounted that blocking checkpoints expressed on T cells such as PD-1, and their respective ligands on tumor cells, such as PD-L1, could provide striking clinical benefits to patients including durable complete responses in advanced disease [2].

Today, the historical perspective of 20 years ago is all but forgotten. T cell-focused...
immunotherapy is front and center in the treatment of I-O. It continues to be one of the most promising fields for delivering the hope of curative treatment for cancer patients. However, it has quickly become appreciated that despite the efficacious outcome of generally ‘releasing the brakes’ of T cells to restore and enable tumor cell targeting, significant challenges remain. Namely, only a minority of patients experience maximal benefit and there is often a trade-off with immune-related side effects, that in many cases can lead to treatment discontinuation and risk of significant harm [3]. As such, the field has recognized the need for targeted immunotherapies that harness the potency of a T cell.

Given the powerful capacity of T cells to destroy target cells, T cells have been exploited generally in two different ways to advance targeted immunotherapies. Firstly, T cells can be modified to express a targeting domain that recognizes a cancer-specific or over-expressed target. Secondly, a protein-based therapeutic can be generated that has specificity for both a cancer target and to engage the T cell to ‘re-direct’ its activity to the target, for example, bispecific T cell engagers. In both cases, the predominant challenge to address has been the target antigen itself. T cells are highly potent, thus the target must be either expressed exclusively on tumor cells or expressed on healthy tissues that are temporarily dispensable, for example, CD19 expressed on both malignant and healthy B-cells. One of the challenges with the latter approach to targets is that where antigen load is high, for example, tumor and B-cell compartment in the case of CD19, the T cell response is proportionate, leading to vast production of proinflammatory cytokines that can have other unwanted, and severe, side-effects such as cytokine release syndrome [4]. In addition, such targets to date have been restricted to hematological ‘liquid’ tumors. Given this and the paucity of targets, especially in the solid tumor setting, a significant challenge that remains for the field is the discovery of targets with an optimal expression profile for targeted immunotherapy.

In light of the challenges described for both general immunotherapy and targeted immunotherapy in cancer, there is a clear need for novel targets in the field. Thankfully, many academic groups and biopharma companies are pursuing this in earnest. This edition of Immuno-Oncology Insights seeks to address key considerations on antigens in I-O to provoke further progress in this area, by exploring the gaps, considerations for optimal targets and modalities for therapeutic application, and finally what the future could look like beyond novel targets in improving the patient benefit through overcoming escape mechanisms and maximizing efficacy.
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BIOGRAPHY

JOE DUKES is Chief Scientific Officer of Enara Bio, and joined the company in 2019 following leadership across research and early development of novel immunotherapies, having led molecules from early discovery and validation through to first-in-human clinical studies. Prior to joining Enara Bio, Joe spent eight years at Immunocore, developing novel T cell receptor (TCR)-based bispecific therapeutics. During this time, he established a bespoke, in vitro preclinical approach for generating safety data to de-risk TCR-based therapeutics. In his role as Head of Biology, Joe oversaw TCR discovery, characterisation, and preclinical screening of drug candidates. In addition, Joe was Program Leader for the second TCR-bispecific molecule to enter the clinic, candidates through preclinical and clinical development to successful IND/CTA submissions and first-in-human phase 1 studies. Joe also oversaw non-clinical studies and contributed authorship to the BLA for the first approved TCR-bispecific therapy, Kimmtrak (tebentafusp). Joe obtained a PhD in Cell Biology and a subsequent post-doctoral fellowship at the University of Bath, UK.

AUTHORSHIP & CONFLICT OF INTEREST

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