The demand for targeted and efficacious anticancer therapies has driven researchers to strive for a greater understanding of the immune system and its potential for tumor eradication. These efforts are now beginning to bear fruit as new knowledge brings about new methods and new reagents that are designed to stimulate the defense mechanisms of the host and block the loopholes exploited by tumors. Strategies with arguably the greatest potential for success exploit the inherent ability of the adaptive arm of the immune system to distinguish the antigenic markers which form the signature of tumor cells. Monoclonal antibodies were the first agents to come to prominence. However, despite considerable success, antibodies are generally restricted to targeting membrane-bound cell surface proteins, limiting the number of potential targets. Attention has now refocused on T cells and, in particular, the unique properties of the T-cell receptor (TCR).

**T Cells and Tolerance**

The isolation of cancer-specific T cells from patients first indicated a central role for T cells in mediating antitumor responses in vivo. TCRs expressed by CD8+ T cells specialize in recognizing peptides derived from intracellular proteins and presented on the cell surface in complex with MHC molecules. Since the majority of tumor antigens are of intracellular origin, T cells are ideally placed to drive an antitumor response to a wide range of targets. Nevertheless, tumors can and do evade T-cell attacks, often by exploiting low-affinity antigen recognition. The natural affinity of TCRs for their cognate antigen is much weaker than that of antibodies, typically in the low micromolar range, and for tumor-specific TCRs antigen binding appears to be especially weak. In our recent work published in *The European Journal of Immunology,* we compared the binding affinity of 24 isolated TCRs to their cognate virus- or cancer-specific antigen. This work represents the largest study of its type and provides clear evidence for the comparatively weak affinity of cancer-specific TCRs. The reason for such weak affinity lies with the mechanism of central tolerance and T-cell selection in the thymus. Since many tumor-associated antigens are derived from self-proteins, T cells bearing the corresponding high affinity TCRs are deleted from the circulating repertoire. Low affinity for antigen is often further compounded by the low numbers of antigens typically presented on the surface of tumor cells (our unpublished observations).

**High Affinity TCRs and ImmTACs**

To overcome the inherent recognition problems of the natural T-cell repertoire, our new immune mobilizing monoclonal T-cell receptors against cancer (ImmTAC) are based on engineered, soluble, affinity-enhanced monoclonal TCRs (mTCRs). A relatively small number of mutations is required to improve affinity down to the picomolar range. In addition, the removal of the transmembrane domain and the addition of a non-native disulphide bond generate a readily soluble protein with exceptional stability. Altogether, these properties make mTCRs potentially useful diagnostic tools. ImmTACs are engineered by fusing an mTCR to a humanized anti-CD3 single chain antibody fragment, to potently redirect T-cell killing to tumor cells.
antigens with the simultaneous redirection and activation of non-tumor-specific T cells (Fig. 1).

**ImmTACs Mediate Potent Killing of Tumor Cells**

Our initial investigations with ImmTACs have been recently published in *Nature Medicine.* Each of the four ImmTACs studied generated a potent redirected T-cell response to tumor cell lines presenting the corresponding tumor-associated peptide antigen. The enhanced affinity of the interaction means that very little reagent is required to produce a response (in the region of 100 pM), and, within this range, stringent specificity is maintained. The affinity of the mTCR component correlates closely with enhanced T-cell activation and, importantly, provides greater sensitivity to low numbers of antigens.

The success of immunotherapeutic agents in the clinic depends on a large extent on their ability to drive a polyfunctional T-cell response. Our data show that ImmTACredirected T cells generate multiple effector functions including the production of various cytokines and ImmTAC-activated CD8+ T cells are found throughout the various subsets of memory cells. Moreover, we have recently found evidence for an ImmTAC-mediated cross presentation by dendritic cells (manuscript in preparation). All these observations point toward the potential for inducing a durable and self-sustaining antitumor immune response in vivo.

**ImmTACs in Vivo**

For a therapeutic reagent to be successful, in vitro functionality must translate into in vivo efficacy. We tested the effects of ImmTACs in vivo using mouse xenograft models and observed an ImmTAC-dependent reduction in tumor burden over a 40-day period, even with low doses of the reagent. Importantly, in the absence of specific target cells, the anti-CD3 component did not lead to any adverse effects. Increased survival and reduced tumor burden were associated with T-cell localization at the tumor site. These results supported the entry of ImmTACs in early Phase clinical trials and preliminary results are promising.

**Outlook**

The ability to generate ImmTAC reagents to any one of a vast number of cancer epitopes provides a novel opportunity to produce tailored off-the-shelf therapeutics possessing exceptionally high specificity and efficiently mediating cancer-cell killing.

**Disclosure of Potential Conflicts of Interest**

J.O. and B.K.J. are employees of Immunocore Ltd. The ImmTAC reagents discussed in this manuscript were developed by Immunocore Ltd.

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