NOVEL TARGETS AND PATHWAYS

VIEWPOINT

Optimal selection of tumor antigens

Sophie Papa

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CHALLENGES AND IMPERATIVES IN I-O DRUG DEVELOPMENT

Targeted I-O drug development requires antigens and we do not have enough of them. This limitation is both in number but also coverage of broad patient populations. Current targets were discovered as our understanding of cancer cell biology and the available tools for interrogation evolved which has resulted in multiple drug development efforts clustering around only a few suitable antigens.
We need new targets to continue to advance treatments and thankfully, recent advances in technologies underpinning antigen discovery are accelerating change.

The requirements of an immune therapy target vary depending on modality, from cell surface expression for antibody-based therapeutics, to robust presentation of a peptide in the human leucocyte antigen groove (pHLA) for T cell receptor (TCR) based therapies. There is much to be gained from stepping back from the antigens that we already have in hand to think about what a high-quality novel target would look like.

**OPTIMAL CHARACTERISTICS FOR ADVANCED THERAPEUTIC IMPACT**

At the tumor level, a target that is shared widely across patients will have the greatest potential for off-the-shelf drug development and resultant patient benefit. Ideally, this antigen will also be shared widely across tumor types. Tumor type matters as it contributes to risk as well as opportunity. We have seen significant success with immune therapies in certain diseases such as cutaneous melanoma, sub-sets of non-small cell lung cancer, and microsatellite unstable colorectal cancers with elusive impact in others, such as microsatellite stable colorectal cancer, pancreatic cancer, and ovarian cancers. Then there are the tantalizing exceptions, the preeminent of which is the impact of KIMMTRAK® in uveal melanoma [1]. A disease few would have singled out as likely to deliver such success with a T cell engager molecule. Having targets that enable a drug development plan that includes tumor types that are underserved and/or highly challenging with others where perhaps recruitment is a little easier and expectation of positive outcome higher would be optimal.

An ideal target should be found only in cancer and not in healthy tissue. For antibody-based therapeutics, where high cell surface density of the target is required for activity, a significant window of expression between cancer and normal can suffice to deliver safety and efficacy. For TCR therapeutics the unique ability of TCRs to recognize very low density of antigen emphasizes the need for clean cancer-specific presentation. Strategies are in development to try to overcome targeting non-cancer-restricted targets such as masking engineering and bivalency to enhance the impact on higher expressing tissues [2]. These approaches introduce complexity and are not yet proven to obtain their goals clinically.

**ADDRESSING EARLY RESISTANCE AND ENSURING TARGET STABILITY**

To mitigate the risk of early resistance having the greatest breadth of targetability through homogeneous expression is key. Linked to this is the stability of antigen expression across disease stages and after therapeutic intervention common to established treatment paradigms. This latter point is often overlooked in the initial validation of a promising new target, but it is vital for viable clinical impact.

For TCR-based therapies that target pHLA, resistance does not appear to be driven by loss of parent antigen in the clinical data we have seen to date, instead, it is mediated through abrogation of antigen presentation machinery [3–5]. This needs to be recognized as we discover new pHLA targets with an early eye to favoring novel targets that can be enhanced through rational therapeutic combination strategies and then testing these combinations early in clinical development.
REFERENCES


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SOPHIE PAPA is Chief Medical Officer at Enara Bio and a Clinical Reader in Immuno-oncology at King’s College London. Prior to joining Enara, she was a Consultant Medical Oncologist at Guy’s and St Thomas’ NHS Foundation Trust (GSTFT) in London specialising in skin cancers. She has extensive clinical trial experience as a principal investigator in the GSTFT early phase trials team. Central to this was Sophie’s leadership of the solid tumour cell therapy clinical trial portfolio at GSTFT as program lead for cell therapy. Sophie’s laboratory is focused on translational immune-therapy clinical trial portfolio at King’s College London. She was awarded an MRC Clinician Scientist Fellowship in 2014 and became a Fellow of The Royal College of Physicians (London) in 2019. She has published over 50 academic papers.

AUTHORSHIP & CONFLICT OF INTEREST

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