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FOUND IN TRANSLATION

Personalized cancer T-cell therapy takes the stage, mirroring vaccine success

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Personalized T-cell therapy is emerging as a pivotal treatment of cancer care by tailoring cellular therapies to individual genetic and antigenic profiles, echoing the exciting success of personalized vaccines. We describe here the parallel evolution and analogies of cancer vaccines and T-cell therapies.

In cancer research, antigens have long been recognized as pivotal triggers of immune responses and potential therapeutic targets. Antigens are commonly categorized into tumor-associated antigens (TAAs) or canonical neoantigens (Peri et al., 2023). TAAs are self-antigens, showing varied expression patterns within tumors. They comprise tissue-specific antigens found exclusively in particular healthy tissues and in tumors, along with cancer germline antigens, which are typically silenced in most healthy tissues but become active again in cancerous cells (Peri et al., 2023). Due to their presence in healthy tissues, TAAs encounter central immune tolerance mechanisms and lack the specificity required for effective cancer treatment. On the contrary, canonical neoantigens, arising from genomic alterations, are unique to tumor cells and their offspring, evading central tolerance, and are being recognized as prototypic tumor rejection antigens. Recently, a new category of tumor antigens referred to as the "dark matter" of the genome has emerged (Peri et al., 2023). These encompass antigens resulting from non-canonical transcriptional and posttranscriptional aberrations in tumor cells, as well as those originating from intratumoral pathogens such as viruses, bacteria, or fungi. Antigens stemming from pathogens associated with cancer, such as *Helicobacter pylori* or human papillomavirus, represent promising targets for cancer immunotherapy, while the role of other bacteria-derived antigens remains to be clarified (Peri et al., 2023).

Unlike canonical neoantigens, which are mostly private, TAAs are shared across various patients and cancer types, making them initially attractive but ultimately limited in their precision and effectiveness, leading to significant side effects (Peri et al., 2023). Lately, the greater clinical significance of neoantigens, when compared to TAAs, is attributed not only to their tumor-specific nature but also to the stronger T-cell responses they induce, owing to their superior avidity (Schmidt et al., 2023; Oliveira et al., 2021).

In the cancer vaccine field, the initial strategy involving whole tumor lysate, including all private antigens, led to limited clinical efficacy due to low expression levels of variable and undefined antigenic specificity. By analogy, adoptive transfer of bulk tumor-infiltrating lymphocyte (TIL) products generated from individual patients offers complete patient specificity, although concomitant with an unpredictable and uncertain prevalence of tumor-specific clones (Chiffelle et al., 2023, *Preprint*) (Fig. 1 a). In response to the latter limitations, more refined strategies have emerged. In the pursuit of personalized therapy, a fundamental objective is to enrich treatment for tumor-specific responses, achieved by incorporating specific antigens into vaccines (Tanyi et al., 2018), mirroring the concept of enriched or selected TILs (Arnaud et al., 2022) (Fig. 1 b). Alternatively, the approach may focus exclusively on well-identified antigens (Hu et al., 2018), aligning with the core objective of T-cell receptor (TCR)-T/chimeric antigen receptor-T-cell therapy (Chandran and Klebanoff, 2019) (Fig. 1 c). The success of this approach hinges heavily on the precise identification of tumor antigens and cognate TCRs, often centered around extensively studied shared TAAs. Nonetheless, even with the potential to benefit a large group of patients, vaccines and T-cell therapies targeting these antigens face similar challenges, characterized by low immunogenicity (Harari et al., 2020) or suboptimal TCR affinities, resulting in limited efficacy, in addition to off-target toxicities (Chandran and Klebanoff, 2019; Leko and Rosenberg, 2020). Enhancing TCR affinity through molecular engineering is a solution pertaining to cellular therapy. Another option to make vaccines and cellular therapies more potent and specific to tumors is to transition to neoantigens, which are, in general, associated with heightened specificity and higher avidity (Peri et al., 2023; Schmidt et al., 2023; Oliveira et al., 2021; Hu et al., 2018).

Targeting shared neoantigens is a prospect that beckons with the promise of swift and cost-effective therapies benefiting a

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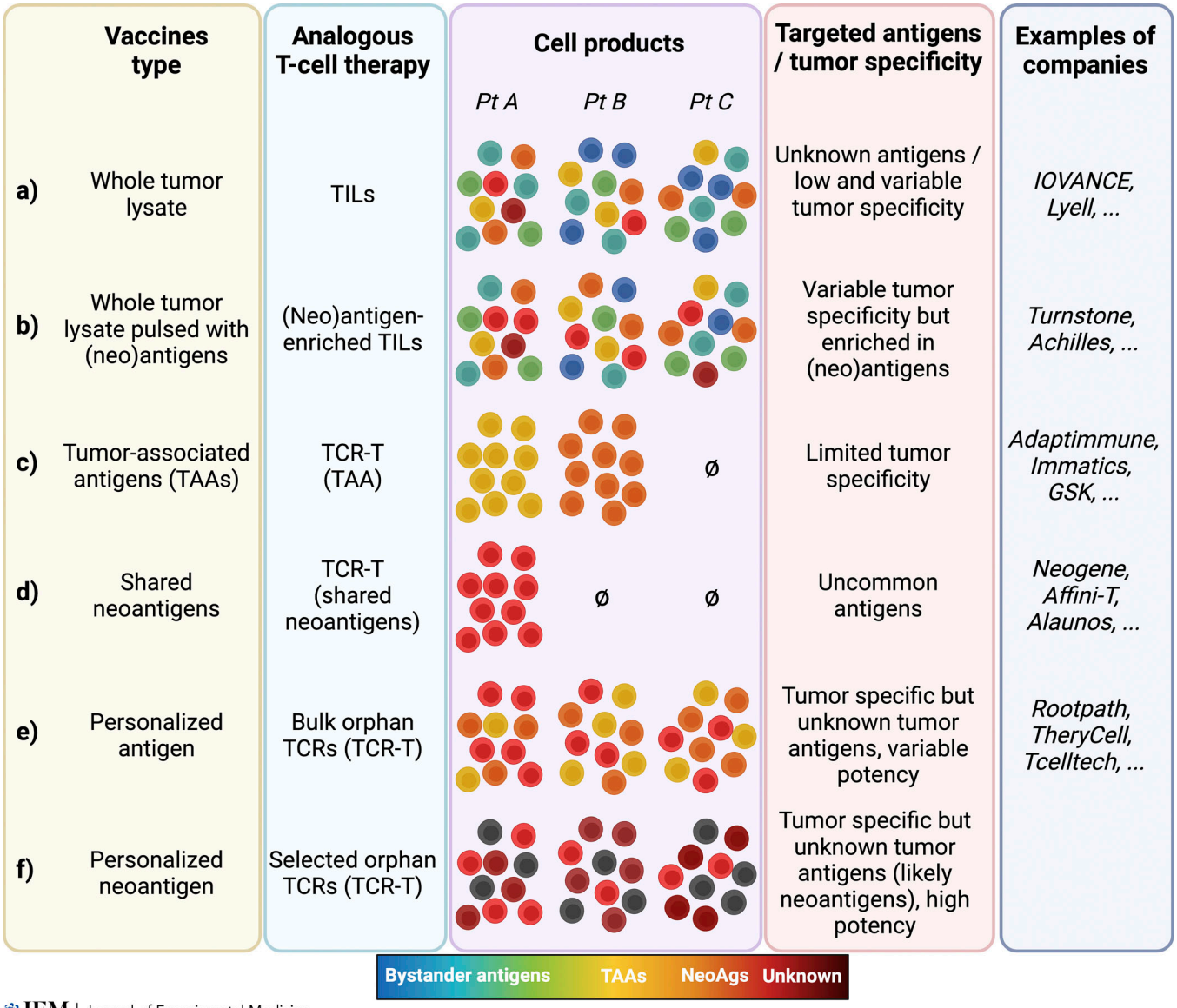

Figure 1. **Illustration of the analogy between the different types of cancer vaccines and T-cell therapy strategies. (a–f)** The different types of cognate cell products are schematically represented for three illustrative patients (i.e., Pt A–C). The listed companies are derived from a random and non-exhaustive sampling among all existing companies focusing on cell-based immunotherapies for cancer treatment. Created with https://BioRender.com.

subset of patients whose tumors share identical mutations. While shared neoantigens are compelling targets for both vaccines and cellular therapies (Chandran et al., 2022), challenge lies in their scarcity (Fig. 1 d). The low prevalence of these mutations exacerbated by variable patients' human leukocyte antigen restrictions significantly narrows the number of patients with potential benefits.

To circumvent the limitations of the paucity of shared neoantigens, and to democratize these treatments to virtually all patients, attention has pivoted toward personalized approaches. In this parallel journey, the cancer vaccine field uses personalized tumor antigens (Blass and Ott, 2021) while the T-cell therapy field is moving toward personalized TCRs (Chandran and Klebanoff, 2019) (Fig. 1 e). Simultaneously, orphan (i.e., of unknown antigenic specificity) tumor–reactive TILs were shown to display distinct transcriptomic signatures relative to bystander TILs (Oliveira et al., 2021). This discovery has promoted the recent development of in silico predictors for specific TCR profiles (Tan et al., 2024; Pétremand et al., 2024), paving the way for personalized T-cell products predominantly composed of cells engineered with orphan tumor–reactive TCRs (Fig. 1 e). Still, whether these TCRs target the broader category of TAAs or the exclusive realm of neoantigens remains a concern since most of the former and a significant proportion of the latter are of low avidity (Schmidt et al., 2023; Oliveira et al., 2021).

The solution lies in a multifaceted approach aiming at selecting TCRs that are both tumor reactive and of high avidity (Fig. 1 f). This can be achieved by using in silico predictors of high-avidity TCRs, which will deplete the list of candidate TCRs of low-avidity ones and enrich for high-avidity (i.e., prototypical neoantigen specific) TCRs (Schmidt et al., 2023; Oliveira

et al., 2021), thus mirroring, again, the cancer vaccine's evolution toward neoantigens (Blass and Ott, 2021; Hu et al., 2018). Finally, in line with the selection of multiple distinct neoantigens for personalized vaccines to limit the risk of tumor escape, cell products composed of multiple TCRs predicted to target distinct antigens are more likely to yield clinical benefit. This can be achieved using a TCR clustering algorithm (Glanville et al., 2017). Therefore, cell products enriched in clinically relevant TCRs combining tumor reactivity with structural avidity and multi-epitopes targeting represent a promising strategy. Of interest, a predictor integrating these different axes was recently developed (Pétremand et al., 2024). This advancement allows for the discovery of clinically relevant TCRs, which, when combined with cell engineering tools (Baulu et al., 2023), make personalized TCR-based therapies a realistic perspective.

This evolution of personalized cellular therapy is mimicking that of personalized neoantigen-based vaccines and is expected to yield similar success. As we embark on this exciting chapter, the rise of tumor-specific therapies, from vaccines to adoptive T-cell treatments, generates eager anticipation, promising to reshape the landscape of cancer treatment as we know it.

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