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Immune Checkpoints Inhibitors: A Single Antiviral and Anticancer Magic Bullet

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Immune checkpoints constitute a distinctive set of proteins that belong to the B7 family. The engagement of these transmembrane receptors with their ligands provides critical signals to inhibit T cell activation and promote for immune tolerance. Tumor and infected cells can hide from the immune system by overexpressing these proteins, leading to T cell exhaustion [1]. Blocking these interactions emerged as a 'game changing' approach in anticancer and antiviral immunotherapy [2-4]. Current immune checkpoints blockers are limited to antibodies [5] and possess a unique mode of action; they reactivate exhausted T cells, allowing them to proliferate and recognize and kill infected and tumor cells [4,6]. Despite their outstanding success the ultimate therapeutic target or combination of targets, from these proteins is still to be determined. The list of immune checkpoints is continuously growing and new effective targets are being frequently added [7]. In addition, very little is known about the underlying mechanisms that follow the engagement of these receptors with their ligands. For example, apart from the recruitment of tyrosine phosphatases to PD-1 (CD279) [8], the mechanism by which these interactions maintain T cell exhaustion is still a mystery. Furthermore, each receptor/ligand from this family can interact with more than one protein. For example, CTLA-4 (CD158) interacts with the two ligands, B7-1 (CD80) and B7-2 (CD86), promoting for T cell exhaustion. The same ligands stimulate T cells by interacting with a different receptor, CD28 [9,10]. Another example is the PD-1 receptor, which interacts with two different ligands, namely PD-L1 and PD-L2 [11,12]. On the other hand, the ligand PD-L1 also interacts with another ligand, B7-1[11]. This small network of protein-protein interactions is aminute part of a more complex and intricate arrangement among the members of the B7 family of proteins. The complexity of this network requires a multidisciplinary effort that involves molecular and mathematical modelers [12-14], immunologists [15], structural and bio-informaticians, systems biologists, oncologists and many others to search for a magical combination of protein targets that can possibly lead to a complete clinical cure of chronic infection and malignant tumors.

A harmony among these different disciplines will not only identify the optimal combination of thesetherapeutic target(s), but can also help expand the current immune checkpoints' blocking agents beyond antibodies and use state-of-the-art technologies [13,16-23] to design small molecule inhibitors for these targets [12]. Take the PD-1, CTLA-4 and TIM-3 pathways as an example. Currently, these are the leading immune checkpoints targets, particularly, for advanced metastatic melanoma. One important aspect in prioritizing or combining these targets is their expression level in the host. A widely expressed checkpoint molecule could promote autoimmune-like side effects. For example, CTLA-4 is up-regulated on all effector T cells and is also expressed on all regulatory T cells (Tregs). Consequently, blockade of CTLA-4 could disrupt CTLA-4–driven regulation of effector T-cell responses or interfere with the function and/or number of Tregs, as has been suggested by recent studies [24-26]. Although PD-1 is similarly up-regulated on all effector T cells, autoimmune-like toxicities have been observed in a lower scale relative to CTLA-4 in patients treated with anti–PD-1 antibodies [27,28]. TIM-3, however, is not expressed on all T cells; rather, it is selectively expressed on T cells that have differentiated toward an IFN-g–producing phenotype [29], and in patients with cancer, TIM-3 seems to be expressed primarily in intratumoral T cells [30]. TIM-3–deficient mice do not exhibit autoimmunity [31], unlike both CTLA-4 deficient [9,10] and PD-1–deficient mice [32]. Thus, from an expression point of view, TIM-3 blockade is favored over CTLA-4 or PD-1. However, another important aspect in prioritizing these targets is the available structural and experimental data that can help in rationally design blocking inhibitors for these proteins. In this regard, CTLA-4 can be ranked first as it is the most understood pathway and with the most structural information available. Structurally and mechanistically, TIM-3 is ranked last relative to both PD-1 and CTLA-4, since there are only two crystal structures for the unbound mouse variant and the TIM-3 pathway is relatively new and not well understood. Although the structural information for PD-1 is not as comprehensive as that of CTLA-4, available data can be used to understand how these molecules interact in human. Taken together and although we raised here more questions rather than answers, it seems that the concept of blocking the immune checkpoints is still in its infancy and more efforts are needed to fully exploit this very new and exiting area of research toward a magic bullet for cancer and chronic infectious diseases.

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