**Do We Need Small Molecule Inhibitors for the Immune Checkpoints?**

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T lymphocytes preserve the immunological balance between defending against cancer and preventing continual activated immune responses. The balance between the two extremes requires an intricate network of protein-protein interactions (PPIs) that can either inhibit T cell-mediated immune responses targeted against self-antigens or stimulate them to defend against cancer [1]. While T cells’ specificity against cancer is determined by the interaction between the T-cell receptor complex (TCR) and antigenic peptides bound in surface major histocompatibility complex (MHC) molecules, the full activation of T cells requires a second signal obtained by the binding of the co-receptor CD28 on T cells to CD80/86 molecules on activated antigen presenting cells (APCs). Once mobilized, T cells also express other receptors that inhibit their proliferation and cytokine production. Among these receptors are three immune inhibitory checkpoints: Cytotoxic T Lymphocyte Antigen-4 (CTLA-4), programmed death-1 (PD-1) and T cell immunoglobulin mucin-3 (TIM-3). Tumors can evade the immune system via inhibitory checkpoints to attenuate T cells’ signaling, leading to a state of immune tolerance [2]. Blocking the immune inhibitory checkpoints pathways recently emerged as a ‘game changer’ approach in cancer immunotherapy [3-5], with antibodies directed toward PD-1, for example, being selected as ‘drug of the year’ for 2013 by the Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada.

References

3. Merelli B, Massi D, Cattaneo L, Mandalia M (2014) Targeting the PD1/PD-L1 interaction of small molecules toward these targets. This is mainly due to the limited structural information on these proteins. For example, current PD-1 crystal structures describe PPIs of mouse PD-1 and human PD-L1 [19] or with mouse PD-L2 [20]. Similarly, there is only one structure for the mouse TIM-3 [21]. Lacking the detailed human protein-protein interactions is a barrier to rationally design small molecule inhibitors for these targets. With the current shortage in understanding these interactions experimentally, Molecular modelling [22-29] can come into play an important role to develop these models and use them to develop small molecules for the immune checkpoints. The last decade has witnessed many successful examples of designing small-molecule modulators for many protein-protein interactions, including orthosteric inhibitors, allosteric regulators, and interfacial binders. Recent examples include discovering small molecule inhibitors for menin and mixed lineage leukemia (MLL) interactions [30]. Some of these molecules can inhibit the menin–MLL interaction at a nanomolar concentration [31]. A more challenging example involves small molecule blockers for the shallow interaction between Interleukin-2 (IL-2) and the IL-2 receptor (IL-2Rα) [32,33]. The lead compound, SP4206, traps IL-2 in an unusual conformation and binds with 60nm concentration [34]. Other successful stories include, the discovery of small molecule inhibitors for the EWS-FLI1/RNA helicase [35], the Ras/SOS1 interaction, the xLAP/caspase interaction [36,37], BRaf/CRaf heterodimerization and activation [38,39], urokinase-type plasminogen activator (uPA), urokinase receptor (uPAR) [40], interaction of Interferon-α with Interferon-α receptors (IFNAR2) [41], interaction of ERCC1 with XPF [42], interaction of ERCCI with XPA [43,44] interaction of p53 with MDM2 and interaction of p53 with MDM4 [45]. All these successful stories call for a similar application of the same methods toward designing small molecules abrogators for the immune checkpoints’ protein-protein interactions to provide a safer and more effective alternative for current antibodies (work in progress) [46].

Received December 09, 2014; Accepted December 09, 2014; Published December 12, 2014

Citation: Barakat K (2014) Do We Need Small Molecule Inhibitors for the Immune Checkpoints? J Pharma Care Health Sys 1: e119. doi:10.4172/2376-0419.1000e119

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