

Novel biologics for disrupting programmed cell death receptor PD-1 binding to PD-L1

Steven A Trim, Danielle McCullough, Stuart Baker and Paul Grant

Immune checkpoint inhibitors are clinically proven effective treatments for both solid tumours and haematological cancers. However, the large interaction surface of PD-1 with its ligand PD-L1 is one of the many challenges that have prevented small molecules from being effective. Thus, the clinical compounds are humanised IgG antibodies such as Atezolizumab, and these large proteins are only administrable via i.v infusion and have high cost of manufacture. Therefore, smaller therapeutic compounds are needed. Venom peptides have evolved to be stable as they are secreted into the lumen of the venom gland ready for rapid delivery in under a second. Venom peptides act with protein-protein interactions as they are ligands for a large range of receptors and channels in predators and prey. These properties make them ideal for disrupting protein-protein interactions in drug discovery also. In this study a Targeted-Venom Discovery Array™ (T-VDA™) containing 640 venom fractions was screened using the cisbio High throughput Time Resolved Fluorescence (HTRF) Human PD1/PD-L1 biochemical binding assay to detect venom peptides that inhibit PD-1 binding to its receptor. Time resolved fluorescence was measured on the CLARIOstar+ (BMG LabTech) with the HTRF filter set. Using a mini Z' on each assay plate we confirmed the expected assay robustness ($Z' = 0.78$) and identified 22 hit fractions (3.4% hit rate). The majority of hits were from elapid snakes (Mambas and Cobras) but a few viper and scorpion fractions were also identified. This poster will be the first published use of venom peptide libraries in HTRF format known and the novel identification of venom peptides as inhibitors of PD-1/PD-L1 binding will be evidenced within.