Docket #: S19-403

A METHOD OF IDENTIFYING SMALL MOLECULE INHIBITORS FOR PD-1

Researchers at Stanford, funded in part by the Chan Zuckerberg Biohub, have generated a crystal structure for human PD-1 in complex with one of its ligands, PD-L2, for use in small molecule inhibitor design.

Immune checkpoint inhibition of programmed death 1 (PD-1) and its ligand 1 (PD-L1) by monoclonal antibodies (mAbs) has dramatically increased patient survival in many cancer types. While mAbs are clinically beneficial, there is still a need for other small molecule immune checkpoint inhibitors of PD-1. Unfortunately, previous attempts to develop PD-1 small molecule inhibitors have been unsuccessful, due to both the natural structure of PD-1 and the small cavity formed after ligand binding. The development of PD-1 small molecule inhibitors will provide cheaper and more accessible cancer treatment alternatives.

Stage of Research
The inventors performed deep mutational scanning of several loops within human PD-1 and identified a triple mutant with markedly increased affinity for the ligand PD-L2. Crystal structures of the triple mutant alone and in complex with PD-L2 revealed the formation of a small cavity upon ligand association. This pocket provides an attractive impetus for the future rational design, identification and synthesis of small molecules for PD-1 immune checkpoint inhibition.

Stage of Development
Research – *in vitro*

Applications

- The pocket identified here in human PD-1 can serve as a template for virtual drug discovery (26)and opens up additional avenues for the discovery of small-

molecule PD-1 inhibitors.

Advantages

- Previously there was no structure of human PD-1 bound to PD-L2

Publications

- Tang S and Kim PS. A High-affinity human PD-1/PD-L2 complex informs avenues for small-molecule immune checkpoint drug discovery. Proc. Natl. Acad. Sci. USA 116(49):24500-24506 (2019).

Patents

- Published Application: 20210088528
- Issued: 10,684,287 (USA)

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