Novel, heterocyclic small molecule inhibitors of PD-1/PD-L1 pathway


SUMMARY

The PD-1/PD-L1 molecular pathway is one of the primary mechanisms of immune evasion deployed by cancer cells. Induction of PD-L1 expression on cancer cells is associated with inhibition of immune responses against cancer, thus permitting cancer progression and metastasis. Activation of PD-1/PD-L1 pathway induces apoptosis of activated T-cells, inhibits their proliferation, facilitates T-cell anergy and exhaustion and enhances the function of regulator T-cells. Therefore, blocking this pathway restores the proliferation and cytotoxicity of CTLs, inhibits the function of Tregs and results in decreased T-cell apoptosis. Although a number of therapeutic antibodies targeting PD-1/PD-L1 have been developed and approved for a number of malignancies, there is still a need for potent, selective small molecule inhibitors of the PD-1/PD-L1 pathway. Rational and structure guided de novo design approaches were used to design novel small molecule PD-1/PD-L1 pathway inhibitors, potency of these inhibitors was assessed in an in-vitro TR-FRET assay. Checkpoints signaling reporter assays as well as PD-L1 expression on cancer cells is associated with inhibition of immune responses against cancer.

In vivo efficacy of JBI-426 in RENCA syngeneic model; increase in TILs were assessed in the two treatment groups. JBI-426 administration resulted in a more significant increase in CD8+ TILs as compared to anti-PD-L1 mAb.

JBI-426 is efficacious in CT-26 syngeneic model

Biochemical characterization

Pharmacokinetic profile of JBI-426

Conclusions

Small molecule PD-1/PD-L1 inhibitors, in contrast to antibody therapies, can provide increased oral bioavailability, increased bioefficiency and shortened half life activity for a more controllable treatment, particularly in the case of auto-immune or other adverse effects. Further studies to assess additional compounds from the three chemical series are underway. The oral administration route of these PD-1/PD-L1 inhibitors would provide an attractive alternate to the currently available antibodies in treating cancer either as a stand-alone therapy or in combination with other immuno-modulatory agents, as well as other standard care agents.

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