# AB001. Keynote. Development of effective immune checkpoint cancer therapy

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**Abstract:** My group also conducted a highly translational study, which identified a link between the ubiquitination and glycosylation pathways that regulate the immunosuppressive activity of programmed cell death-ligand 1 (PD-L1). We showed that glycosylation of PD-L1 is required for its protein stability and interaction with PD-1. In addition, we demonstrated that metformin-activated AMPK kinase downregulates PD-L1 through phosphorylation of Ser-195, which alters glycosylation of PD-L1 and functionally mimics anti-PD-L1 to block PD-L1/PD-1 interaction. It exhibited a highly potent synergistic effect of combination therapy of metformin, a drug that has been treated patients with diabetes and anti-CTLA4. The therapeutic efficacy could reach to survival rate of 50–70% in different syngeneic mouse models, which were treated by this combination therapy. We also demonstrated that epithelial-mesenchymal transition (EMT) enhancesPD-L1 in cancer stem-like cells (CSCs) by the EMT/β-catenin/STT3-PD-L1 signaling axis. Etoposide, a commonly used anti-cancer chemotherapy drug is able to suppress this signaling axis, resulting in downregulation of PD-L1 to sensitize cancer cells to anti-Tim 3 therapy. These findings provide potential therapeutic strategies to enhance cancer immune therapy efficacy by targeting PD-L1 stabilization to combat multiple cancer types. We identified TNF-α as a major factor triggering cancer cell immunosuppression against T cell surveillance via stabilization of PD-L1. To this end, in collaboration with StCube Pharmaceuticals Inc., we have developed monoclonal antibodies against glycosylation-specific PD-L1. Impressive therapeutic effect was observed through antibody-drug-conjugate approach. Most recently, we unraveled an active defense system of PD-L1, previously known to only associate with passive defense activity. We discovered that cancer cells, which express PD-L1 can secrete exosomes containing PD-L1 (exosome-PD-L1). The exosome-PD-L1 is able to directly interact with PD-1 to inhibit T-cell activation as well as T-cell killing activity. Our new discoveries provide new means to enhance therapeutic efficacy of immune checkpoint therapy.

**Keywords:** Programmed cell death-ligand 1 (PD-L1); immune checkpoint; combination therapy

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