Drug Treatment:

- Secreted and transmembrane proteins are integral in promoting cancer cell proliferation, cell growth, immune evasion, and metastasis. Most of these proteins require translocation through the Sec61 translocon complex (Sec61) for entry into the endoplasmic reticulum (ER) and progression to the cell membrane (Figure 1). Inhibiting PD-1, a Sec61 client protein, has been effective in treating many cancer types.
- KZR-540, an orally bioavailable small molecule, binds to Sec61 and selectively inhibits the expression of PD-1, inducing a T cell dependent anti-tumor effect.
- Quantitative proteomic profiling was utilized to examine the subcellular fractionalization, secretome, and plasma proteome from in-vitro and in-vivo models to explore the selectivity of KZR-540 against broad broad spectrum inhibitors, KZR-834 and KZR-261.

Results

- The results of the proteomic analysis revealed that KZR-540 selectively inhibits the expression of PD-1, selectively inhibiting the expression of many cancer types.
- In vitro, KZR-540 showed comparable efficacy to KZR-834 at 250nM or KZR-540 100nM, indicating its potential for clinical development.
- The results of the proteomic analysis also demonstrated that KZR-540 selectively inhibits the expression of PD-1 in T cells of HuPD-1+/- hu Mice Bearing MC38, indicating its potential for clinical development.

Conclusions

- Quantitative proteomic profiling is a powerful technology to facilitate the investigation of differential effects of KZR-834/KZR-261 and KZR-540 on the global proteome.
- KZR-540 treatment of human stimulated T cells induces a selective and potent inhibition of PD-1, through inhibiting its translocation into the Sec61 complex.
- KZR-540 treatment has no statistically significant impact on the secretome of stimulated human T cells and H939 cancer cells, compared to the Sec61 pan-inhibitor, KZR-834.
- In vitro secretome profiling results were well translated into in vivo plasma profiling of hu-PD-1+/- mice model bearing MC39 hu-PD-L1 tumors. KZR-540 treatment has minimal impact on the mouse plasma proteome when compared to KZR-261.
- Quantitative proteomic profiling demonstrates that KZR-540 is a selective PD-1 inhibitor.

References