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GNUV205, A BIFUNCTIONAL PROTEIN OF ENGINEERED IL-2 FUSED WITH A NOVEL ANTI-PD1 ANTIBODY, EXHIBITS SUPERIOR TUMOR SUPPRESSING EFFICACY *IN VIVO*

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Background While the introduction of immuno-oncology drugs, especially anti-PD-(L)1s, has revolutionized the strategy for fighting against cancer, there is still a huge demand for the development of novel anti-tumor drugs from the majority of patients who exhibit refractory or no response to the current immunotherapy options. Meanwhile, cytokine therapy, such as recombinant IL-2, is largely limited due to its high dose-associated severe adverse effects. To overcome this limitation, a novel therapeutic drug which can activate immune cells with higher specificity and stronger potency should be developed and investigated.

Methods GNUV205 is an investigational immuno-cytokine molecule which comprises anti-PD-1 antibody (GNUV201) and engineered IL-2 (interleukin-2). Due to GNUV201's inter-species cross-reactivity to PD-1, GNUV205 can be directly assessed in a murine model without the need for a surrogate antibody. Also, the unique slower dissociation and much stronger binding affinity of GNUV201 to PD-1 in TME (tumor microenvironment)-mimicking low pH condition allows superior selectivity and less side effects of GNUV205. Meanwhile, engineered IL-2 is designed and expected to have minimal adverse effects attributed to its no-alpha (IL-2R α) and beta/gamma receptor (IL-2R $\beta\gamma$)-biased engineered structure.

Results ELISA and SPR analysis showed that GNUV205 binds to IL-2R $\beta\gamma$ (CD122/CD132) with attenuated affinity but not to IL-2R α (CD25). We observed that GNUV205 exhibits enhanced affinity to PD-1 in the low pH condition, a hallmark of the TME. In addition, cell-mediated reporter assay indicated that GNUV205 delivers IL-2 signaling in a PD-1-dependent *in-cis* manner. When assessed in a MC38 syngeneic *in vivo* model, multiple- and even a single-dose of GNUV205 were able to exhibit significant anti-tumor efficacy in a dose-dependent manner, with more than 80% tumor clearance at 300 pmole (ca. 2.74 mpk) or higher and without significant effects on body weight change even at 10 x fold higher dose (3,000 pmole). Furthermore, in the tumor re-challenge test, GNUV205 proved to induce tumor-specific long-term immunological memory response as evidenced by 100% tumor rejection even 7 months after the 1st challenge of the cancer cells. We also confirmed GNUV205's excellent tumor suppressing efficacy in other syngeneic tumor models such as B16F10 and Pan02.

Conclusions In summary, these data strongly suggest that GNUV205 is a candidate-stage bifunctional immuno-cytokine for solid cancer therapy expected to overcome the limitations of current standard-of-care therapies, such as IL-2 or anti-PD-(L)1s.

Ethics Approval Every animal experiment used in this study was reviewed and approved by internal IACUC (E-IACUC2022-002).

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