OVERCOMING SYSTEMIC TOXICITY OF IL-12-BASED IMMUNOTHERAPY BY TUMOR-TARGETING AND IL-12 ATTENUATION

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Background Cytokines are well-known immunomodulators. Thanks to recent success of immune checkpoint inhibitors there is a renewed interest in cytokines as a promising cancer immunotherapy option. Several inflammatory cytokines including IL-12 showed potent anti-tumor activities but severe immune adverse events when administered systemically greatly hindered using them as anti-tumor agents.

Methods Previously (SITC 2020) we showed that IL-12 activity was reduced by our introduced mutation (termed as mut1) if measured by pSTAT4 AlphaLISA assay. But when it was treated in human immune cells IFNg production was not reduced as expected. Thus, we further attenuated IL-12 activities by protein engineering and created our candidate molecule KNP-101.

Results We showed that KNP-101 maintained potent anti-tumor activities in vivo but gained greatly improved toxicity profiles. When we measured pSTAT4 signals, KNP-101 showed about 30-fold attenuation in IL-12 activities compared with rIL-12. IFNg production from human PBMC was also reduced. Although the IL-12 activity was weakened in order to reduce its systemic toxicity, our KNP-101 mouse surrogate still maintained good anti-tumor potency in various mouse syngeneic models with a single intravenous injection as low as 2 ug/head. In combination with anti-PD-L1, KNP-101 surrogate showed a synergistic anti-tumor effect and further FACS analysis of tumor infiltrated lymphocytes demonstrated that the effects were mediated by immune cell infiltration. Importantly, in CD1 naïve mouse toxicity test, KNP-101 surrogate was tolerable up to 50 ug/head and no survival issue was observed. However, that was not the case with the control group, non-tumor-targeting null/IL-12 showing survival issues with all tested dose levels. Compared with the control, KNP-101 surrogate also showed much safer profiles in terms of organ weight and serum chemistry such as ALT level. We also performed similar toxicity study in tumor-bearing mice. KNP-101 surrogate again showed a very safe profiles being tolerable up to 500 ug/head and no survival issue. Noticeably, when serum IFNg was measured in tumor-bearing mice, our KNP-101 surrogate induced far less IFNg in serum compared to null/IL-12 suggesting that systemic toxicity was greatly reduced.

Conclusions Together, we demonstrated that systemic toxicity of IL-12 cytokine therapy can be overcome by tumor-targeting and IL-12 attenuation. Our KNP-101 has a widen therapeutic window by maintaining potent anti-tumor activities and showing much improved safety profiles. We hope that KNP-101 can benefit patients in the future who suffer from primary and acquired resistance of the current anti-PD-1/PD-L1 treatments.