CGC-601, A NOVEL βγ-ONLY IL-2 VARIANT, ENHANCES MODERATE IMMUNE ACTIVATION WITHOUT TREG EXPANSION, AND EXHIBITS A SUPERIOR SAFETY EVIDENCE IN VIVO

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Background IL-2 was first approved by FDA for the solid tumor treatment. However, the therapeutic window of IL-2 (low dose suppresses immune system by Treg activation and high dose represents toxicity) limited its clinical use. The major dose-limiting toxicity IL-2 is vascular leak syndrome (VLS). The mechanism of VLS is mainly considered as the direct interaction of IL-2 with IL-2Rα expressed on endothelial cells in vivo1, 2 or by over-stimulation of immune cells.3, 4 To get rid of the IL-2Rα interaction, non-α IL-2 muteins were designed to deplete the Treg expansion which may contributes to its anti-tumor efficacy (figure 1). However, they still remain the risk of overstimulated immune response.

Here, we introduce our IL-2 variant, CGC-601, which abolished its binding to IL-2Rα, while obtained a structural twist on four α-helix (figure 2). This brand new molecule was designed as a non-suppressive and moderate immune agonist, through the strategy of de-coupling the IL-2 binding pattern to “βγ-only”.

Results CGC-601 does not bind to IL-2Rα or IL-2Rβ alone, while only binds to βγ complex with the similar affinity to wtIL-2 in a “fast-on, fast-off” feature (figure 3). Moreover, CGC-601 shows a low Treg response and mild CD8 T and NK activation in human PBMC (figure 4). For T cell expansion, upon 50nM treatment, CGC-601 holds a similar T cell expansion capacity with rhIL-2 (figure 5A). Meanwhile, CGC-601 expands both CD8 T cells and NK cells, but Treg expansion dramatically constrained after PBMC ex vivo expansion (figure 5B). Thus, compare with rhIL-2, CGC-601 gives “young” and less differentiated T cells after expansion (figure 6).

In the toxicity test, CGC-601 dose as high as 30 mg/kg, mice stay in good health conditions, while 10 mg/kg rhIL-2 showed a severe weight loss and a reduced activity since Day 3, suggesting CGC-601 has a much safer profile than rhIL-2 (figure 7A). Pulmonary edema is significantly reduced even CGC-601 dose reached 30mg/kg (figure 7B). CGC-601 treatment did not elevate serum IL-5 levels 6 hrs after the first dose (Fig. 7C). CGC-601 prefers C8 T cells and NK cells expansion, on the contrary, CGC-601 does not expand Tregs in vivo (figure 8).

Conclusions CGC-601 with a unique βγ-only binding property, promotes moderate CD8 T and NK expansion and diminishes immunosuppressive Tregs in vivo, has a great potential in immune-stimulation indications. CGC-601’s safety evidence sets up a platform allowing multiple application scenarios (figure 9).

REFERENCES
Abstract 1091 Figure 5  CGC-601 retains T cell proliferation activity

Abstract 1091 Figure 6  CGC-601 presents a high potential in T cell expansion

Abstract 1091 Figure 7  CGC-601 exhibits an excellent in vivo safety profile

Abstract 1091 Figure 8  CGC-601 effectively expand CD8 T and NK cells, but not Tregs in vivo

Abstract 1091 Figure 9  CGC-601 sets up a platform allowing multiple application scenarios