

**Abstract Submission No.: A-0127**

## **Targeted Anti-IL-1 $\beta$ Bacteroides fragilis Outer Membrane Vesicles Alleviate Inflammatory Injury in Diabetic Nephropathy**

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**Objectives :** This study aimed to construct renal-targeted *Bacteroides fragilis* outer membrane vesicles (OMVs) loaded with interleukin-1 $\beta$  (IL-1 $\beta$ ) single-chain variable fragments (scFv) for the treatment of diabetic nephropathy (DN). These OMVs derived from human commensal non-toxicogenic *Bacteroides fragilis* have been proven to play an immunosuppressive role in the intestine and distant organs. This targeted drug delivery platform built with this as a carrier is expected to relieve kidney inflammation in the development of DN.

**Methods :** We recombinantly expressed the scFv based on the Gevokizumab sequence in *Escherichia coli*, and loaded it into the OMVs derived from *Bacteroides fragilis*. The targeting peptide was connected to the membrane surface through a copper-free catalyzed click chemistry reaction. The package, which consisted of OMVs and the scFv targeting IL-1 $\beta$  in the kidney (OMV-KTP-scFv) was obtained. OMV-KTP-scFv intervened in HK-2 cells and healthy mice respectively, and evaluated its in vitro and in vivo drug safety. The concentration of IL-1 $\beta$  scFv in blood and kidney tissues at different time points were measured using streptozotocin (STZ)-induced diabetic mice. In vitro, OMV-KTP-scFv was used to prevent inflammation in mouse primary renal tubular epithelial cells induced by high glucose, and in vivo to alleviate kidney injury in STZ-induced diabetic mice.

**Results :** The prepared OMV-KTP-scFv had high stability, effectively extended the plasma half-life of scFv, and could deliver scFv accurately to the proximal renal tubules. Furthermore, OMV-KTP-scFv also had good safety in vitro and in vivo, and no obvious biotoxicity was found during long-term in vivo administration. In addition, our results show that OMV-KTP-scFv significantly alleviated renal tubular injury.

**Conclusions :** Our findings demonstrated that OMVs of *Bacteroides fragilis* targeting the kidney can deliver the IL-1 $\beta$  scFv to the renal tubulointerstitium and reduce the renal interstitial injury in DN by antagonizing local inflammation.