Small molecule inhibitors of CD40-TRAF6 interactions

Reference No: B72031

CHALLENGE

The co-stimulatory **CD40-CD40L dyad** is crucial in the **development and progression of immune re- sponses and chronic inflammatory diseases,** such as atherosclerosis, obesity and multiple sclerosis. However, long-term antibody-mediated inhibition of CD40L or CD40 is not clinically feasible as it results in thromboembolic events and severe immune suppression. More downstream inhibition of the CD40L-CD40 pathway is therefore preferable, especially tumor necrosis factor receptor-associated factors (TRAFs) recruited by CD40.

INNOVATION

Several TRAF knock-out mouse models indicated that CD40-TRAF6 interactions play an essential role in inflammatory diseases. Here a set of inhibitors that **selectively block CD40-TRAF6** interactions is presented. The rest of the CD40 cascade is left unaffected **preventing unwanted immune-suppressive side effects.**

COMMERCIAL OPPORTUNITIES

The new inhibitors offer promising candidates as therapeutic agents for the **treatment of chronic inflammatory diseases,** such as **atherosclerosis, obesity** and **multiple sclerosis.** The selective blockage of the CD40-TRAF6 interactions therefore strongly reduces inflammation, whereas unwanted immu- ne-suppressive side effects are limited.

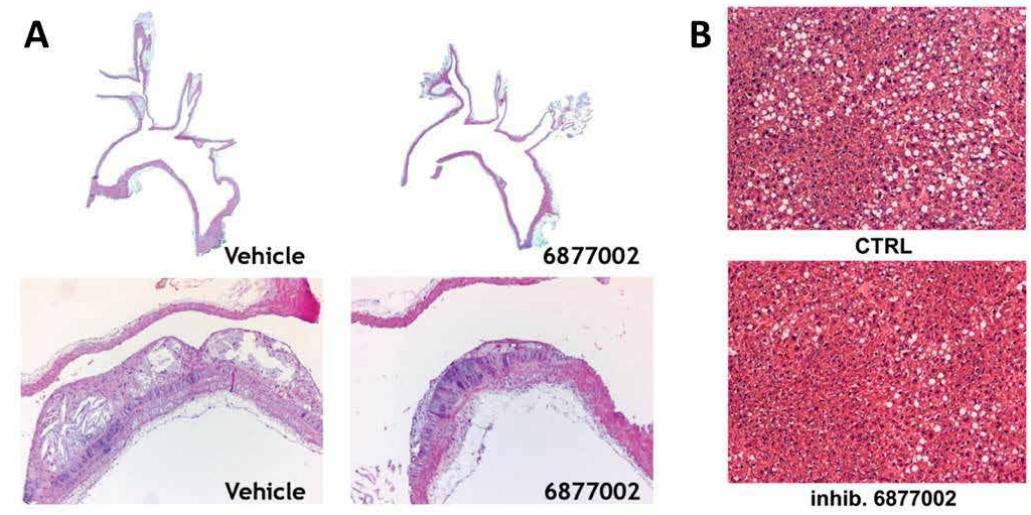

Figure A: Inhibitor treatment reduces atherosclerotic burden in Apoe-/- mice by limiting plaque inflammation; repre- sentative longitudinal images of the aortic arch and brachiocephalic trunk (H+E staining); Apoe-/- mice were treated with inhibitor at 10 µmol/kg/day for 6 weeks, starting at the age of 12 weeks. **Figure B:** Inhibitor treatment improves adipose tissue inflammation; representative H&E-stained sections from livers of control- or inhibitor-treated mice; WT mice were fed a high fat diet for 12wk receiving vehicle/inhibitor starting at week 6 of feeding.

DEVELOPMENT STATUS

- Selective small molecule inhibition of the CD40-TRAF6 pathway
- **No side effects** in mouse model observed
- Reduction of pro-inflammatory leukocytes
- **Efficacy** shown in mouse models for **metabolicdiseases (obesity, diabetes), atherosclerosis, sepsis**

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