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 responses 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 immune-suppressive side effects are limited.

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 metabolic diseases (obesity, diabetes), atherosclerosis, sepsis, EAE

REFERENCES:
1. Aarts et al., J Neuroinflammation. 2017;14(1):105
3. Chatzi@georgiou et al, PNAS. 2014;111(7):2686-91