Project DE-1

Characterization of C5aR2 expression and function in Toxoplasma gondii infection

(Supervisors: Prof. Jörg Köhl, Prof. Doris Wilflingseder)

Toxoplasma gondii (T. gondii) is a widespread obligate intracellular protozoan parasite. It is of major medical importance during pregnancy and in immunocompromised individuals. The parasite is sensed by complement resulting in the fixation of C3 cleavage fragments. The role of the C5a/C5a receptor (C5aR) axes has not been addressed. The Köhl laboratory observed increased parasite load in the brain associated with increased mortality in *C5ar1*$^{-/-}$ mice. Mechanistically, C5aR1 activation controlled early *T. gondii* infection by IL-12 production from splenic DCs, which is crucial for IFN-γ production from NK cells and subsequent iNOS expression in the brain. Surprisingly, we found that NK cells express C5aR2 but not C5aR1. *In vitro* experiments suggest that C5aR2 activation regulates IL-12/IL-18-mediated IFN-γ production from NK cells. We hypothesize that C5aR2 activation on NK cells controls early *T. gondii* infection given the importance of NK cell activation during this infection phase. To test this hypothesis, the student will monitor C5aR2 expression during early parasite infection using floxed tdTomato-C5aR2 knock-in mice generated in the Köhl lab (Karsten et al. J. Immunol 2017). Also, s/he will infect *C5ar2*$^{-/-}$ and wildtype mice, determine disease progression, assess systemic and splenic IL-12 cytokine family and IFN-γ expression in DCs and NK cells. Further, s/he will infect NK cell-specific C5aR2-deficient mice to specifically define the role of C5aR2 on NK cells in this infection model. Since the interaction of NK cells with DCs is of major importance for NK cell activation, the student will assess the role of C5aR2 on DCs for DC-mediated activation of NK cells while staying 6 months in our partner lab in Innsbruck (AT). Currently, no monoclonal antibodies (mAbs) are available that reliably stain and/or neutralize C5aR2. Thus, the student will generate mAbs against C5aR2 in Lübeck (DE) and test their functional properties *in vitro* and *in vivo* models. During the 6 months visit of Hycult Biotech (NL), the student will exploit the commercial value of such mAbs and learn to produce C5aR2-specific mAbs in large quantities and couple them with fluorochromes or enzymes for their use in different application fields.

General description of your individual PhD-schedule:

- Your main university will be University of Lübeck (Germany) with Prof. Köhl as supervisor.
- You will have a 6-months research secondment at Medical University of Innsbruck (Austria) with Prof. Wilflingseder as supervisor, where you continue to scientifically work on your thesis project.
- You will have a further 6-months research secondment at Hycult Biotech (Uden, Netherlands) where you will generate and characterize C5aR2-specific mAbs.
- You will have a 1-month clinical training at University Hospital Helsinki (Finland).
- You will have a 1-month entrepreneur training at Hycult Biotech.
- You will finally receive a PhD issued by University of Lübeck and Medical University of Innsbruck if you fulfil the respective requirements.

Application

The position is advertised from 10.09.2019 – 10.11.2019 on **www.corvos.eu**. Please apply via this homepage during that time.