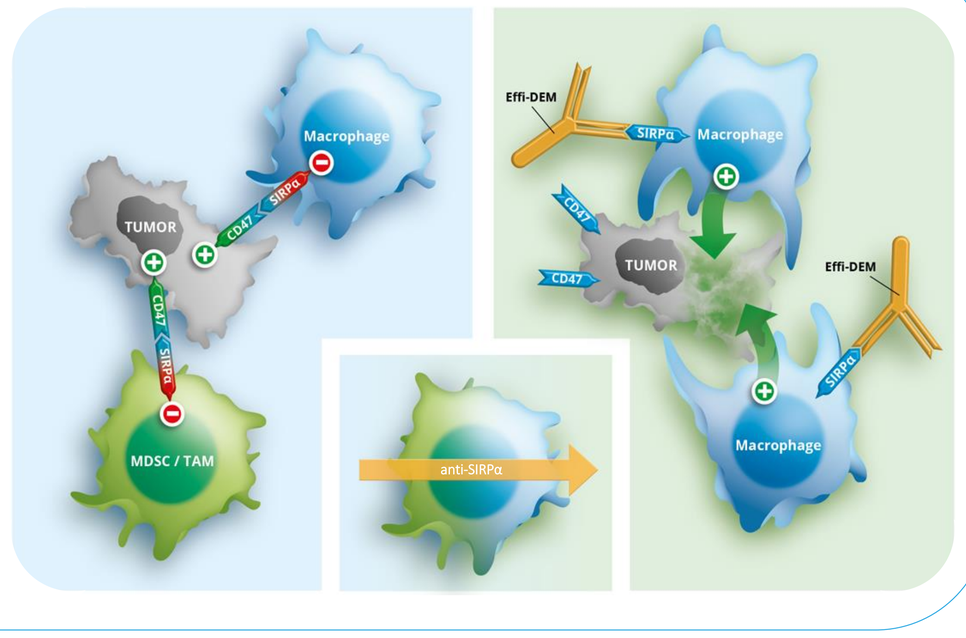
Selective targeting of the SIRPα immune checkpoint, but not CD47, controls the polarization of macrophages

Gauttier V[1,2], Pengam S[1,2], Mary C[1,2], Thepenier V[1,2], Conchon S[2], Vanhove B[1,2] , Poirier N[1,2]

[1]*Ose Immunotherapeutics, Nantes, France*
[2]*INSERM UMR 1064, Institut de Transplantation Urologie Néphrologie (ITUN), Université de Nantes, France*

Introduction

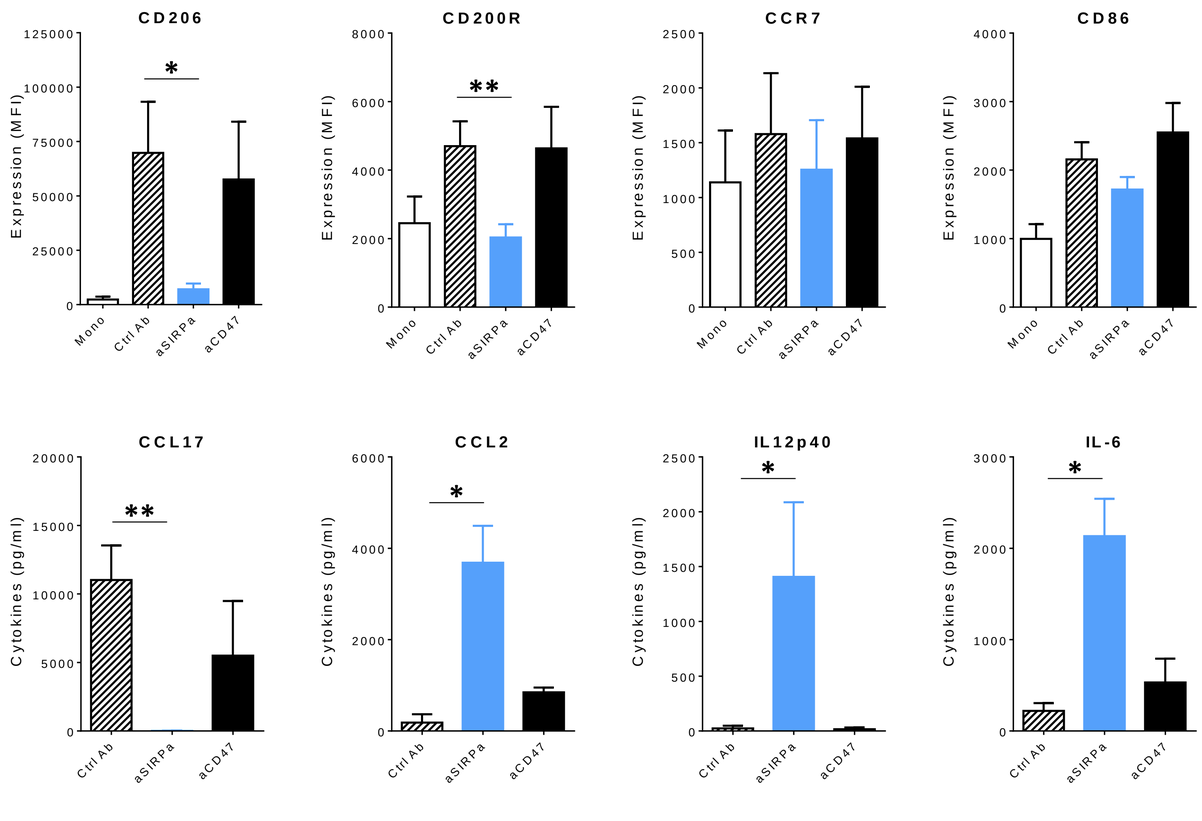
Myeloid cells, including tumor associated macrophages (TAM), represent an abundant immune cell type in solid tumors. The tumor microenvironment educates TAM to promote angiogenesis, to break down extracellular matrix allowing the spreading of metastases and to inhibit anti-tumor immune responses. Because of their plasticity, macrophages are a very attractive target of new therapeutic drugs to switch their function from pro-tumoral (M2/TAM) to inflammatory (M1) profile. SIRPα is a promising immune checkpoint target: it is known to inhibit macrophage phagocytosis and dendritic cell maturation after interaction with its ligand CD47. In this study we investigated the role of the SIRPα/CD47 pathway in human macrophages differentiation/polarization and the impact in vivo on anti-tumor responses. We found that SIRPα antagonist (Effi-DEM) promotes human M1 macrophages polarization and synergizes with T-cell immune checkpoint in vivo.

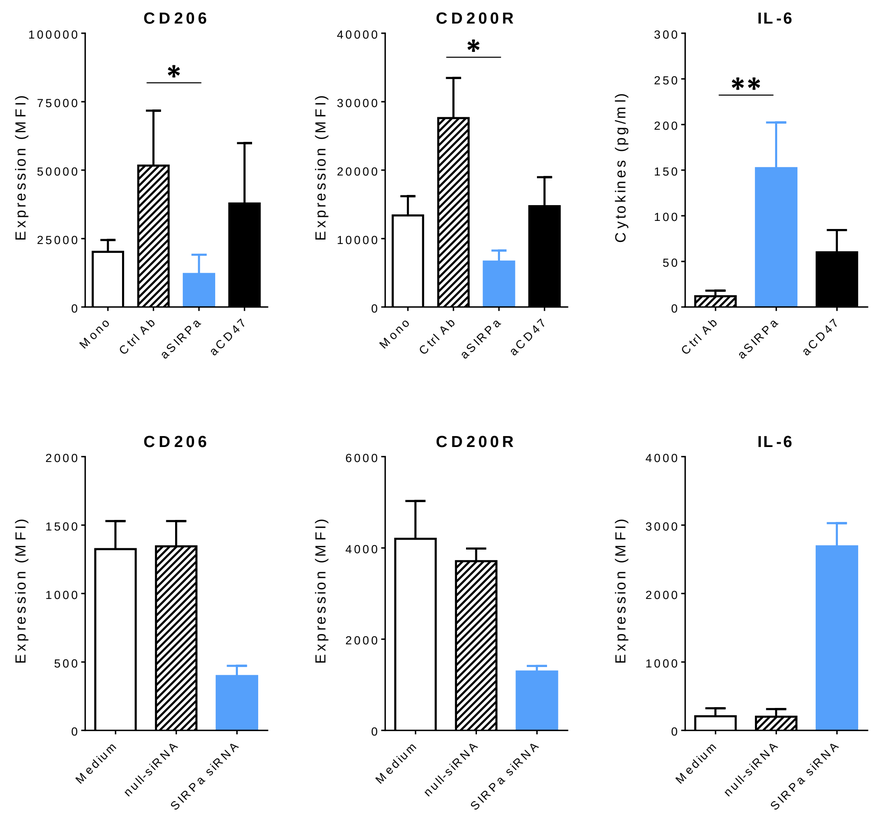


Results

Selective SIRPα antagonist prevents M2 macrophage polarization while promotes M1 inflammatory cytokines

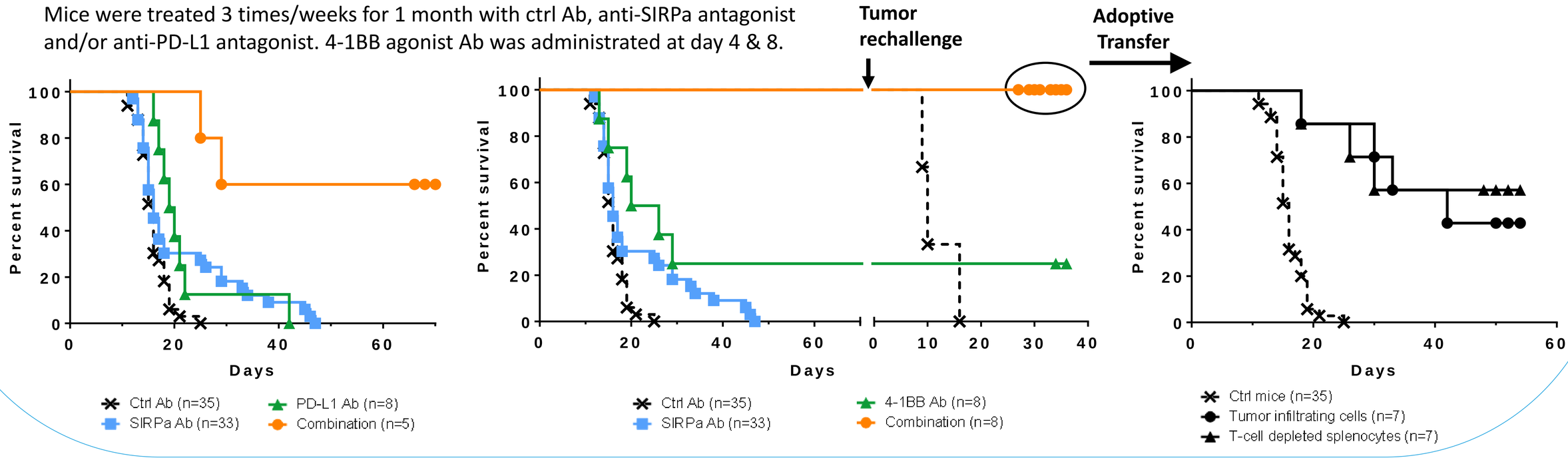
Human blood monocytes were differenciated in macrophage with M-CSF (10 ng/ml) and GM-CSF (2 ng/ml) for 6 days (Left) or polarized specifically in M2 macrophage with IL-4 (20 ng/ml) during 48 hours after differenciation for 6 days with M-CSF (100 ng/ml) (Right). mAbs were added at 10 µg/ml at day 0 (Left) or day 6 (Right).





Anti-SIRPα antagonist synergizes with T-cell checkpoint inhibitor or co-stimulatory mAbs

Syngeneic orthotopic mouse model of hepatocellular carcinoma (Hepa1.6):
Mice were treated 3 times/weeks for 1 month with ctrl Ab, anti-SIRPa antagonist and/or anti-PD-L1 antagonist. 4-1BB agonist Ab was administrated at day 4 & 8.



Conclusion

These findings suggest that SIRPα is a novel immune checkpoint that controls macrophage polarization in humans, in addition to the previously recognized control of phagocytosis. Immunotherapy targeting selectively at SIRPα has the potential to re-polarize M2/TAM into pro-inflammatory macrophages, potentiate anti-tumor immune responses in vivo and induce robust immune memory.