Monotherapy with a SIRPα CKI leads to dramatic change in solid tumor microenvironment and prevents metastasis development

Vanessa Gauttier[1,2,3], Justine Durand[2,3], Sabrina Pengam[1,2,3], Aurore Morello[1,2,3], Georgia Porto[2,3], Kevin Biteau[2,3], Sophie Conchon[2,3], Bernard Vanhove[1,2,3], Nicolas Poirier[1,2,3]

[1]OSE Immunotherapeutics, Nantes, France; [2]CRTI - UMR1064, INSERM, Université de Nantes, Nantes, France; [3]Institut de Transplantation Urologie Néphrologie (ITUN), CHU Nantes, Nantes, France

AACR 2018
Poster #1753

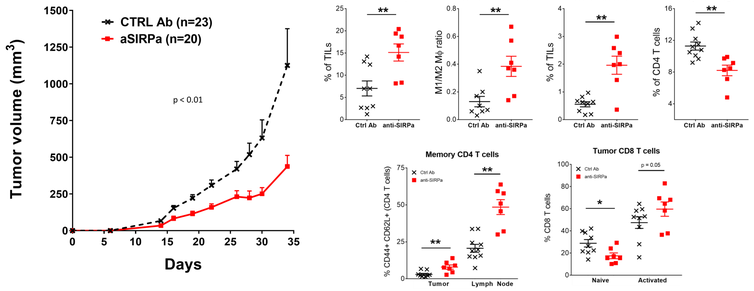
Introduction

Targeting immune checkpoints of the adaptive immunity has shown great therapeutic efficacy to fight cancers, but in a limited proportion of patients. Myeloid cells represent a major immune cell type in many solid tumors, and are often associated with a poor outcome. MDSCs and macrophages are involved in the regulation of immune responses and in tissue repair in healthy individuals, these cells can be co-opted by cancer cells to start exerting suppressor functions, preventing other immune cells from attacking the tumor. In addition to their suppressor functions, TAMs can also participate in tumor growth and metastasis through several other mechanisms. SIRPalpha (SIRPα) is an immune checkpoint expressed by nearly all myeloid cells which interacts with the ubiquitous receptor CD47 and is now well described to regulate macrophage function (e.g. phagocytosis). Here we evaluated the impact of SIRPα signaling inhibition on tumor microenvironment and metastasis development in orthotopic tumor models in immunocompetent mice.

1 Anti-SIRPα monotherapy protects from metastasis development by remodeling tumor microenvironment in an orthotopic **TNBC** model

Reduced tumor growth and tumor micro-environment modifications

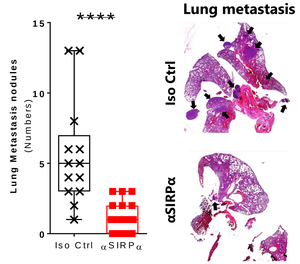
Triple negative breast carcinoma (TNBC) 4T1 cells were injected orthotopically into the mammary gland of syngeneic female Balb/c mice. Mice were treated three times a week for three weeks with a control monoclonal antibody (mAb) or an antagonist anti-SIRPα mAb (P84; 10mg/kg).



Modification of the early tumor microenvironment (d15)

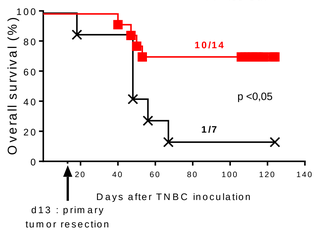
Inhibition of tumor spreading and increased survival

Tumor metastasis (d29)



Lung metastasis

Survival after primary tumor surgical resection

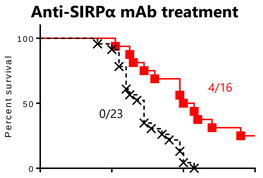


2 Blockade of SIRPα signaling in monotherapy increases survival in **Mesothelioma** and modifies orthotopic tumor microenvironment

Pharmacological (anti-SIRPα) or genetical (SIRPα-/- mice) blockade of SIRPα signaling increases overall survival

Mesothelioma AK-7 cells were injected into the pleural cavity of female C57Bl/6 mice. Mice were treated three times a week for three weeks with a control monoclonal antibody (mAb) or an antagonist anti-SIRPα mAb (MY1-mIgG1; 10mg/kg). The SIRPα mutant mice which have a truncated SIRPα without the signaling domain were challenged at 10 weeks as well as the control littermate.

Anti-SIRPα mAb treatment



Median survival

Iso Ctrl	29 days	
αSIRPα	42 days	**

SIRPα mutant mice

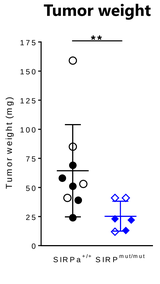
Median survival

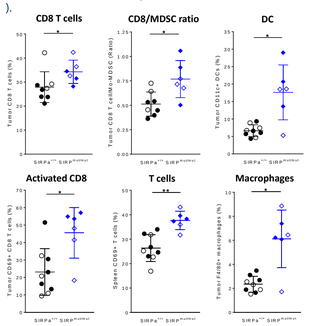
Control	29 days	
SIRPα mutant mice	unreached	***

Blockade of SIRPα controls tumor growth and modifies mesothelioma tumor microenvironment

Immune cells infiltrating the tumor was analyzed by flow cytometry one month after tumor injection. Mice received anti-PD-L1 mAb ( ) injected 3 times a week for 3 weeks at 8mg/kg or PBS ( ).

Tumor weight

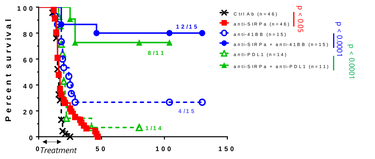




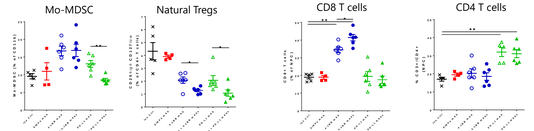
3 Anti-SIRPα combinations modifies the Lymphocyte infiltration in an orthotopic **HCC** model

High response rate and tumor elimination in orthotopic syngeneic HCC mouse model

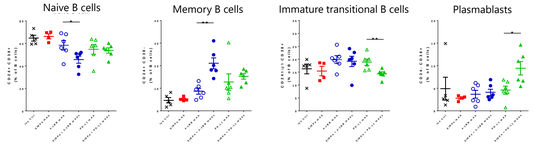
Mice were treated three times a week for three weeks with a control antibody or an αSIRPα mAb (MY1-mIgG1; 10mg/kg). The αPD-L1 mAb (10F-9G2; 8mg/kg) was injected two times a week for three weeks and the α4-1BB mAb (3H3; 4mg/kg) was injected twice (Days 4 & 8). All treatments have been started four days after Hepa1.6 hepatoma cell line injection through the portal vein. Tumor microenvironment was evaluated by flow cytometry and gene analysis 13 days after tumor inoculation.



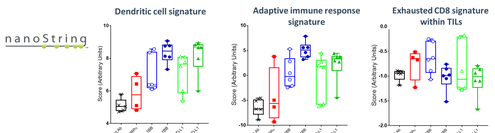
Dramatic tumor microenvironment modification associated with potent anti-tumor responses



Modified intratumoral B-cell subsets



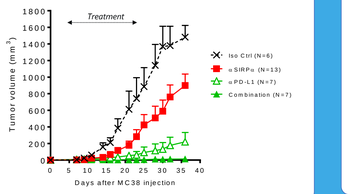
Increased & improved inflammatory adaptive immune responses



Memory anti-tumor responses and mechanisms are described on the ***Poster #1684***

4 Monotherapy with an anti-SIRPα reduces also **CRC** development

Colon carcinoma MC38 were injected subcutaneously in male C57Bl/6 mice. Mice were treated three times a week for two weeks with a control monoclonal antibody or an anti-SIRPα mAb (MY1-mIgG1; 10mg/kg) starting to d4.



Conclusion

Blockade of SIRPα as a monotherapy :

- Reduces tumor growth and significantly increases survival in several orthotopic tumor models
- Prevents tumor lung and liver metastasis
- Dramatically improves the tumor microenvironment in both the innate and adaptive immune arms with increased effectors and dropped regulatory immune cells