Siglec-15 KO mouse models

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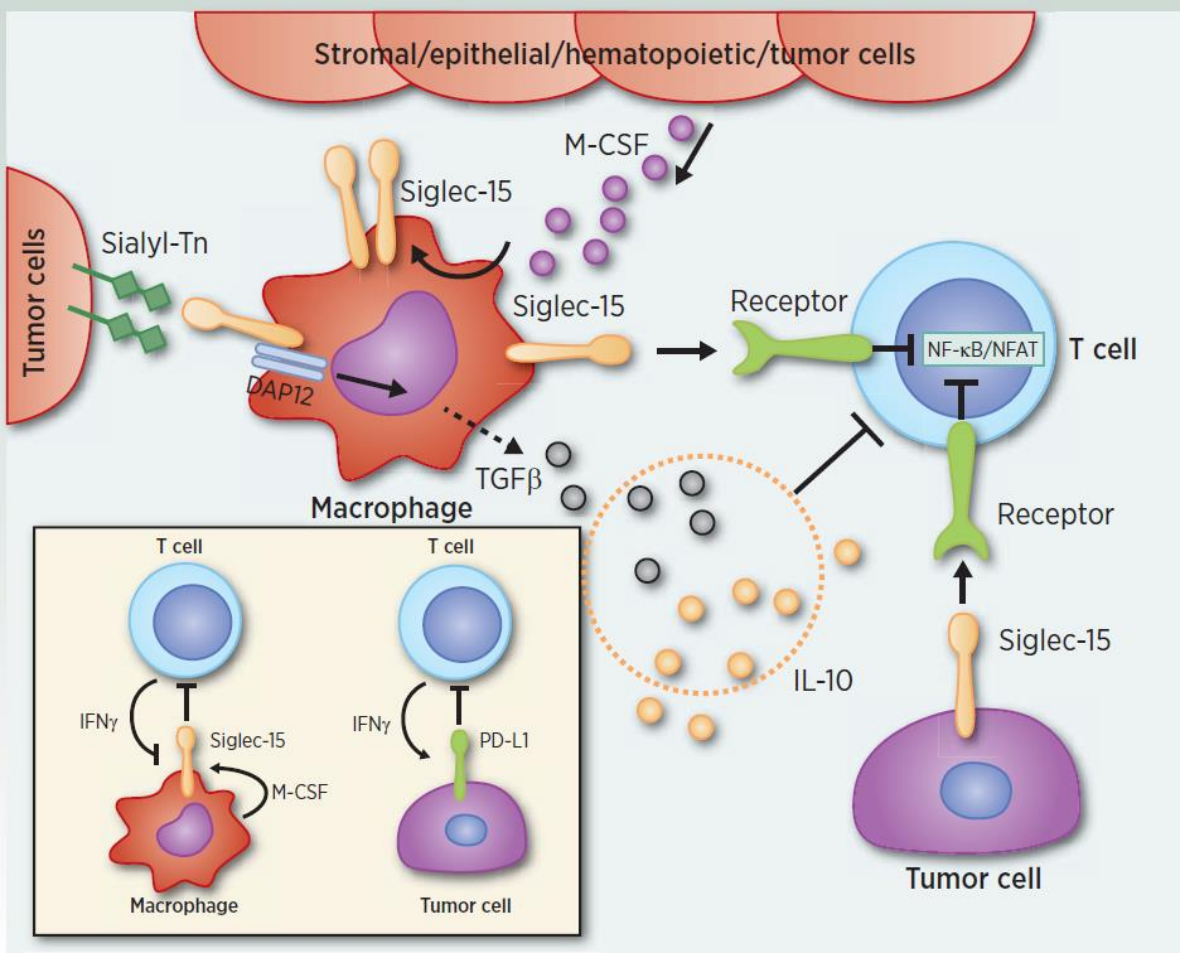
Outline

Siglec-15 in immunotherapy

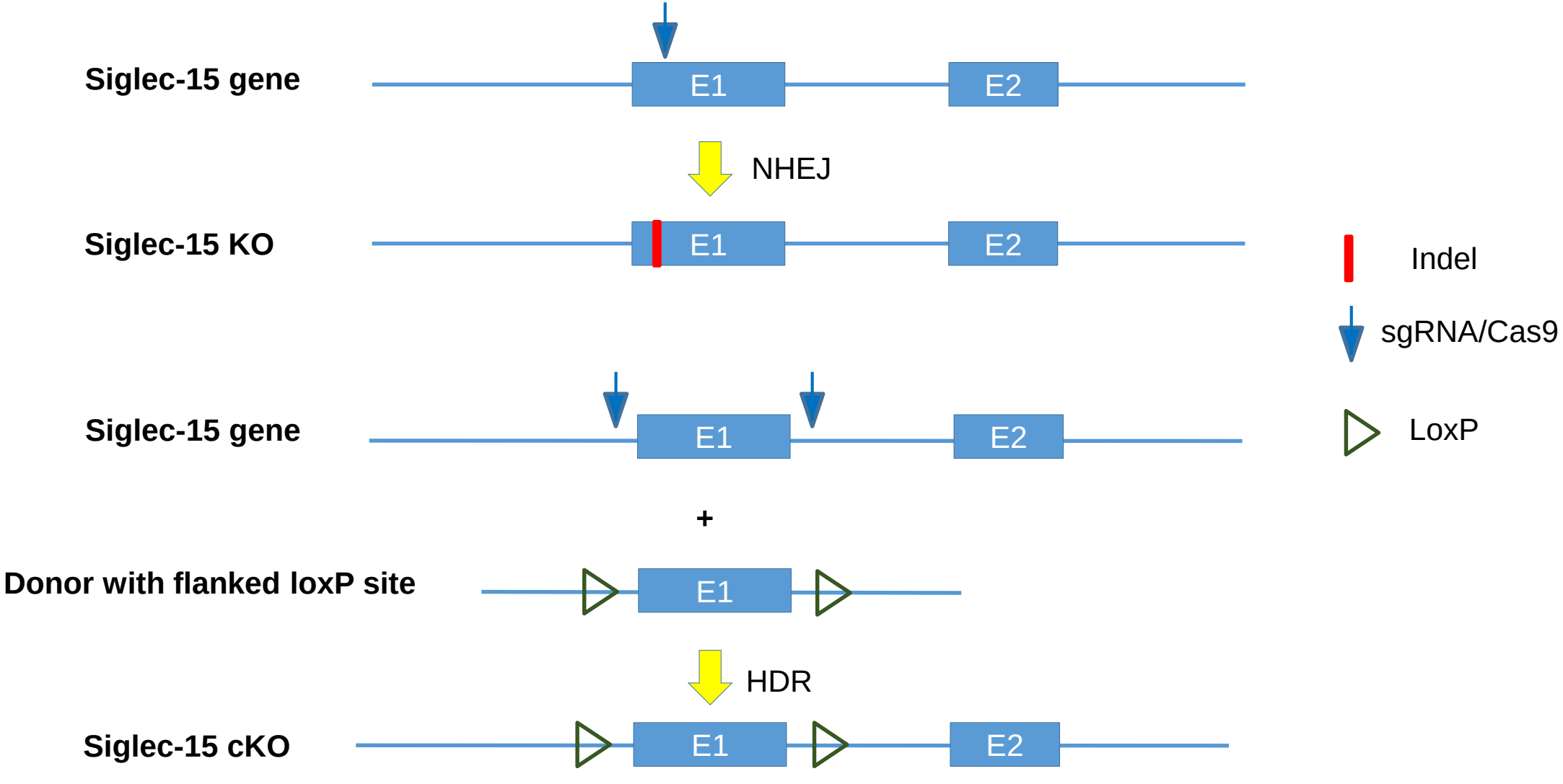
- Siglec-15 is reported by Pr. Lieping Chen's lab to suppresses antigen-specific T cell responses in vitro and in vivo. Genetic ablation or antibody blockade of Siglec-15 amplifies anti-tumor immunity in the TME and inhibits tumor growth in some mouse models. Clinical trial to test the effect of a humanized mAb (NC318) to Siglec-15 in solid tumors is ongoing.
- In order to establish a platform to study the effect of potential Siglec-15 antibodies or inhibitors, we generated Siglec-15 KO and cKO mice with CRISPR/Cas9 mediated genome editing. We tested tumor establishment on this mice with syngeneic cell lines and results showed that Siglec-15 KO inhibits syngeneic tumor growth, supporting the role of Siglec-15 as a promising target for development of new immune checkpoint blocker. We also tested the effect of Siglec-15 KO for macrophages to stimulated T cell response in vitro and in vivo but the results showed no dramatic difference. In summary we constructed a Siglec-15 KO mouse model and we may use this model to test the effect of Siglec-15 KO on tumor immunotherapy with this model.

A working model of Siglec-15 in immune regulation

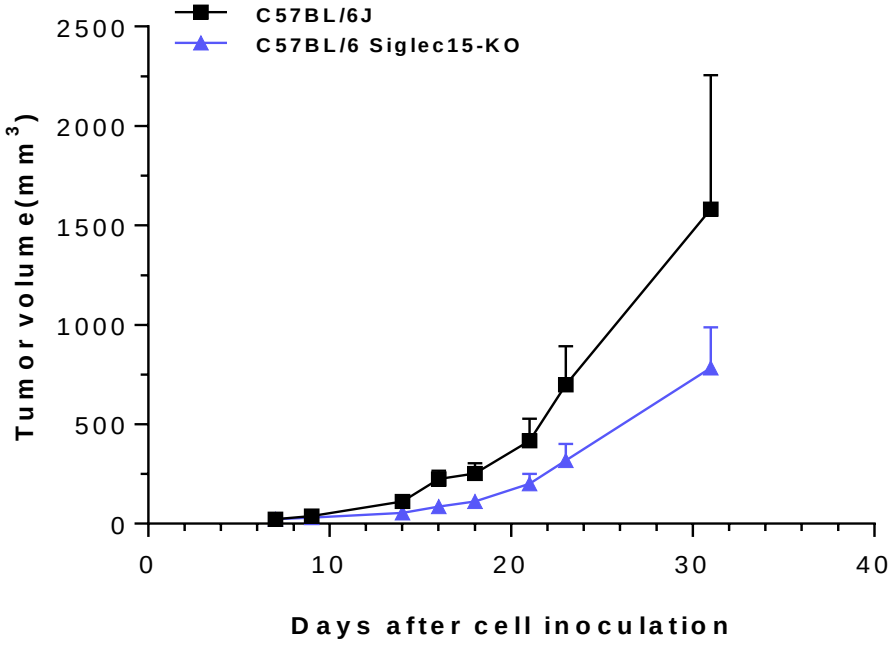


Jingwei Sun, Qiao Lu, Miguel F. Sanmanmed, et al., *Clin Cancer Res* Published OnlineFirst September 21, 2020.

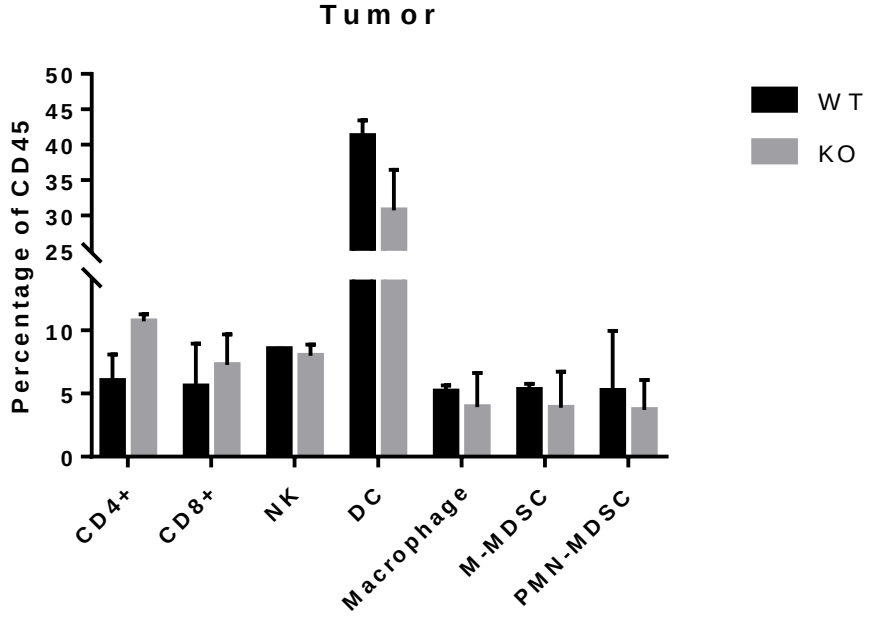
Strategy for construction of Siglec-15 KO/cKO mice



MC38 tumor growth decreased in Siglec-15 KO mice



MC38 tumor growth curve in WT or Siglec-15 KO mice



Immune profiling in MC38 tumors from WT or Siglec-15 KO mice

Clinical trials targeting Siglec-15

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	A Safety and Tolerability Study of NC318 in Subjects With Advanced or Metastatic Solid Tumors	• Advanced or Metastatic Solid Tumors • Non-Small Cell Lung Cancer • Breast Cancer • Head and Neck Squamous Cell Carcinoma	• Drug: NC318	• The Angeles Clinic and Research Institute Los Angeles, California, United States • Yale University Cancer Center New Haven, Connecticut, United States • John Theurer Cancer Center at Hackensack University Medical Center Hackensack, New Jersey, United States • (and 2 more...)
2	☐	Recruiting	The Study of NC318 Alone or in Combination With Pembrolizumab in Patients With Advanced Non-small Cell Lung Cancer	• Advanced Non-small Cell Lung Cancer	• Drug: NC318 • Drug: Pembrolizumab	• Yale University New Haven, Connecticut, United States
3	☐	Withdrawn	A Safety and Tolerability Study of NC318 in Combination With Chemotherapy for Subjects With Advanced or Metastatic NSCLC	• Advanced or Metastatic Solid Tumors • Non-Small Cell Lung Cancer	• Drug: NC318 • Drug: Pemetrexed/Carboplatin • Drug: Nab paclitaxel/Carboplatin • Drug: Docetaxel	

https://clinicaltrials.gov/ct2/results?cond=&term=nc318&cntry=&state=&city=&dist=

Summary

1. We successfully constructed Siglec-15 KO and cKO mouse model, verified by sequencing of the target region in Siglec-15 gene.
2. We tested MC38 tumor growth in the constructed Siglec-15 KO mice and found that Siglec-15 KO inhibit tumor growth, which is consistent with the reports.
3. Immune profiling of MC-38 tumor samples showed increase of CD4+ and CD8+ T cells and decrease of MDSC cells.

Reference

- Wang, J., Sun, J., Liu, L.N. *et al.* Siglec-15 as an immune suppressor and potential target for normalization cancer immunotherapy. *Nat Med* **25,** 656–666 (2019).
- van de Wall S, Santegoets KCM, *et al.* Sialoglycans and Siglecs Can Shape the Tumor Immune Microenvironment. *Trends Immunol*. 2020 Apr;41(4):274-285.
- Jingwei Sun, Qiao Lu, Miguel F. Sanmanmed, et al., Siglec-1 15 as an emerging target for next-generation cancer immunotherapy. *Clin Cancer Res* Published OnlineFirst September 21, 2020.

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