



Human CLEC9A antibodies deliver NY-ESO-1 antigen to CD141⁺
dendritic cells to activate naïve and memory
NY-ESO-1-specific CD8⁺ T cells

A/Prof Kristen Radford

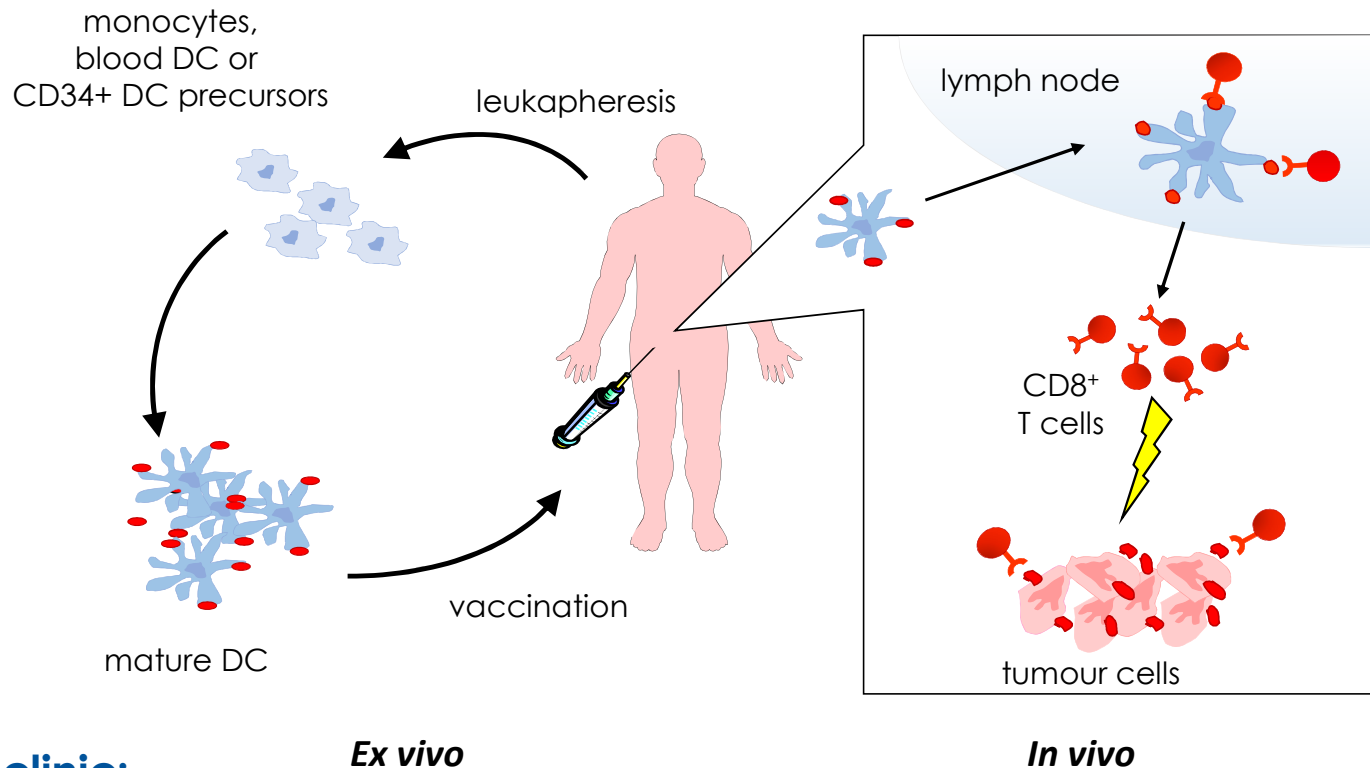
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Society for Immunotherapy of Cancer

#SITC2020

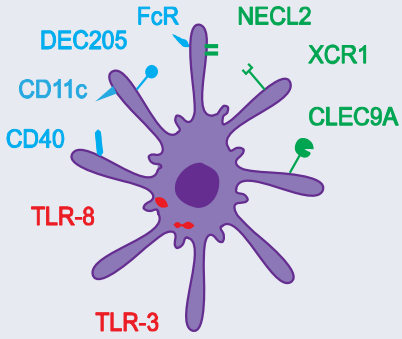
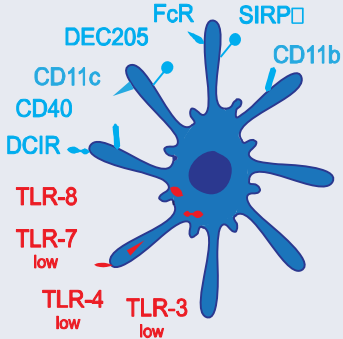
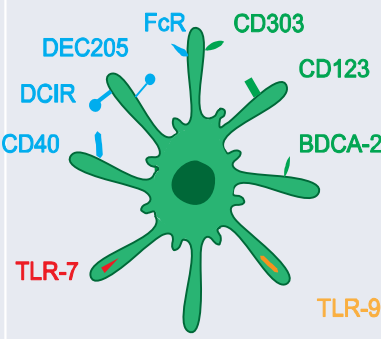
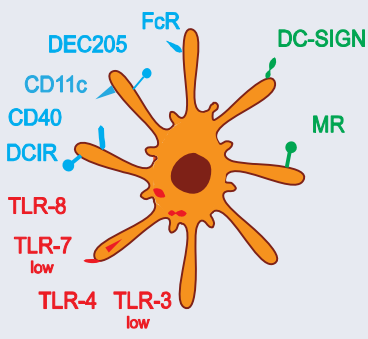
Dendritic cell immunotherapy for cancer



20+ years in the clinic:

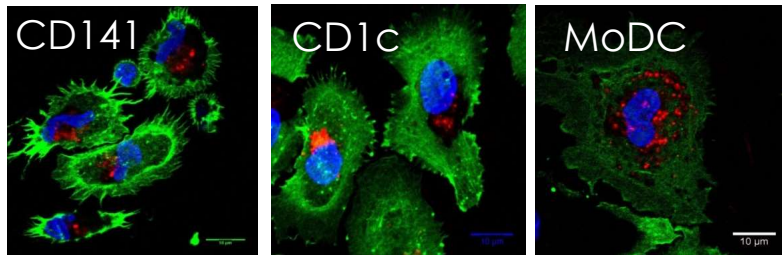
- Safe, well tolerated
- >533 registered clinical trials on ClinicalTrials.gov
- Can induce long lasting anti-tumour immune responses
- Objective clinical responses in melanoma 9%, prostate cancer 8%

Choosing the right type of DC

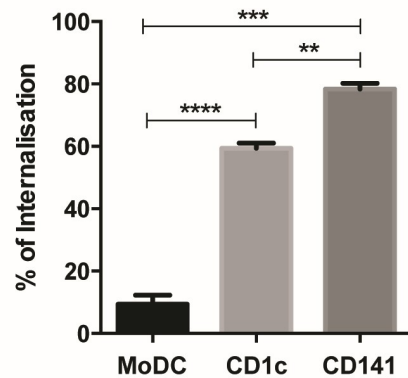
Steady state			Inflammation
cDC1	cDC2	Plasmacytoid DC	MoDC
			
Mouse: CD8 ⁺ / CD103 ⁺ DC Human: CD141 (BDCA-3) ⁺	Mouse: CD11b ⁺ DC Human: CD1c (BDCA1) ⁺	pDC	MoDC
Function: CD8 ⁺ T cells intracellular pathogens, cancer	CD4 ⁺ T cells extracellular pathogens	IFN-I	inflammation

Human cDC1 (CD141⁺ DC) are effective at uptake and cross-presentation of cellular antigen

Dead cell uptake

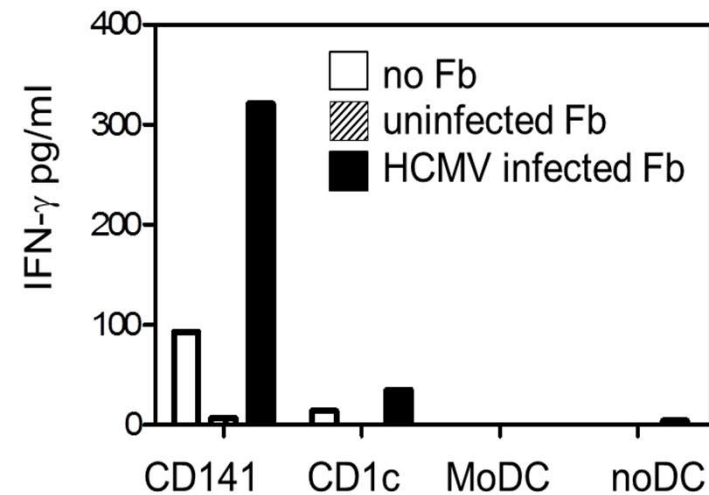


phalloidin dead cells DAPI



Chiang et al, Eur J Immunol 2016

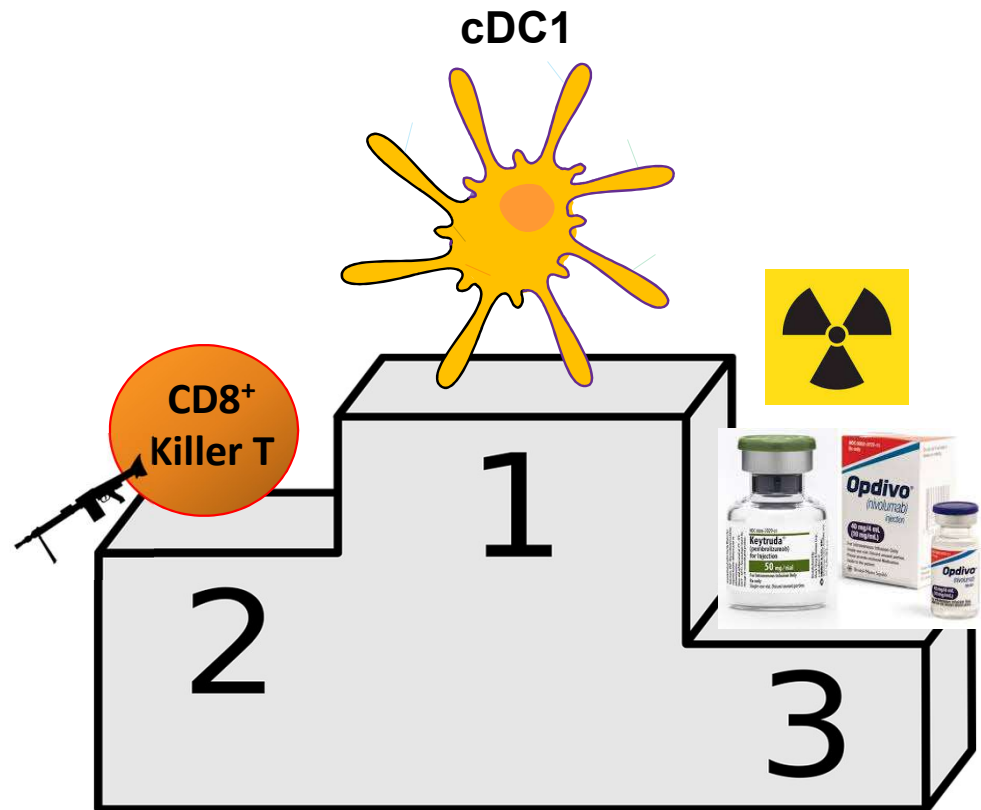
Cross-presentation to CD8⁺ T cells



Jongbloed et al, J. Exp. Med 2010

cDC1 (human CD141⁺ DC) are required for tumor immunity

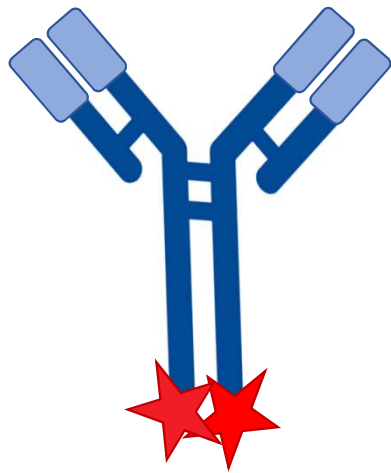
- Required for the initiation of CD8⁺ T cell mediated immunity
- Rare but accumulate in regressing tumors
- Required for efficacy of
 - checkpoint inhibitors
 - T cell therapies
 - radiotherapy
 - oncolytic viruses
- Associated with good prognosis in human tumors



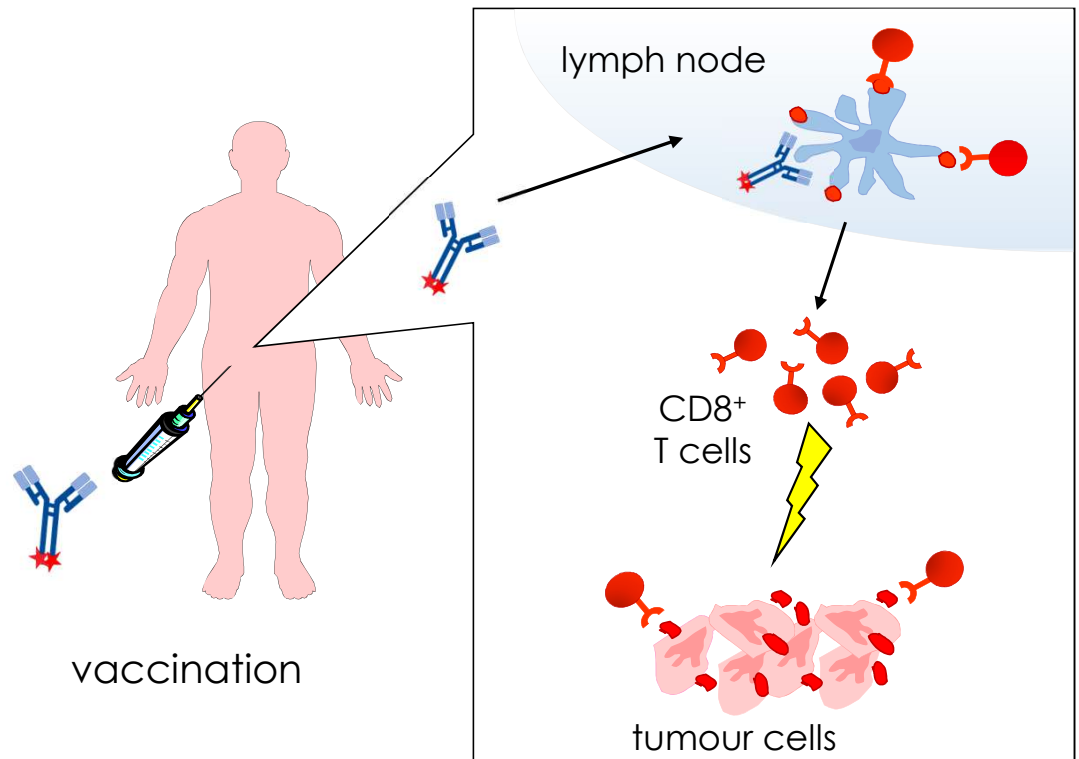
Hildner et al Science 2008
Fuentes et al J Exp Med 2011
Diamond et al J Exp Med 2011
Broz et al Cancer Cell 2014
Roberts et al Cancer Cell 2016
Sanchez-Paulete et al Cancer Discov 2015
Salmon Immunity et al 2016
Spranger et al Cancer Cell 2017
Bottcher et al Cancer Cell 2018
Barry et al Nat Med 2018

Exploiting antibodies specific for DC uptake receptors as cancer vaccines

Antibody specific for
DC surface receptor

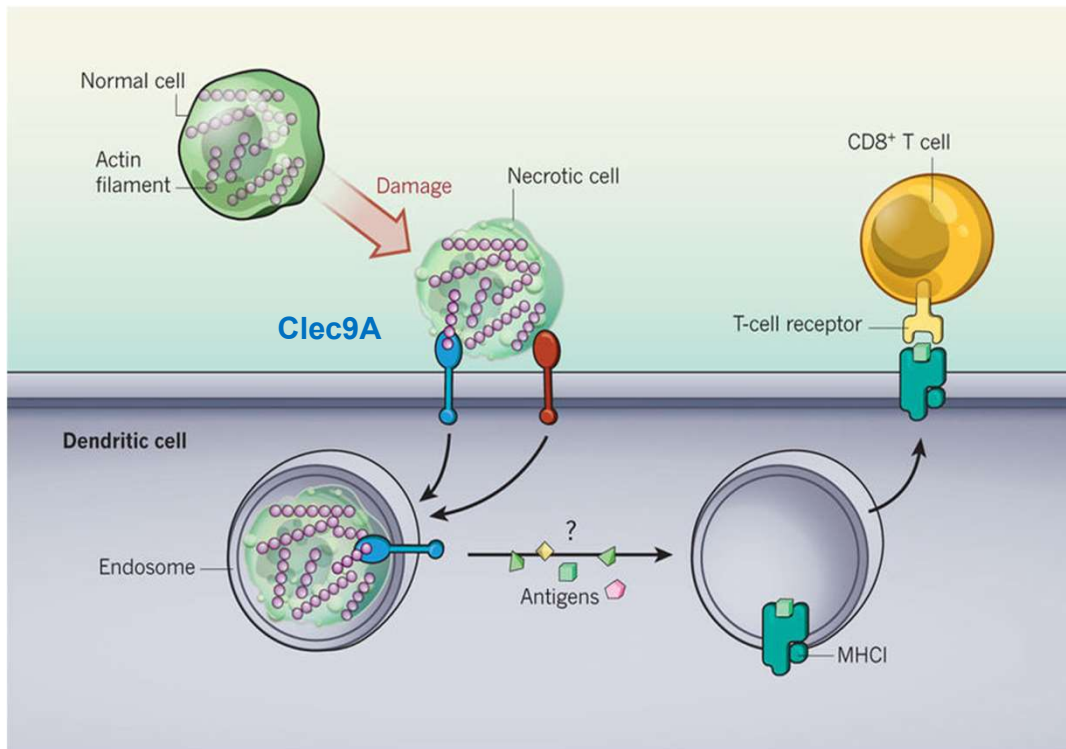


Tumour antigen

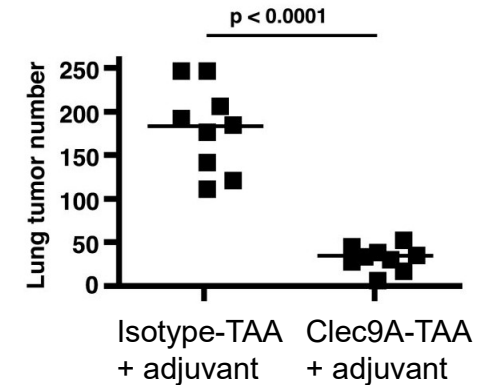


Radford et al Curr Opin Immunol 2014
Tullett et al Front Immunol 2014
Tullett et al JCI Insight 2016

Antibodies specific for CLEC9A are promising vaccine candidates



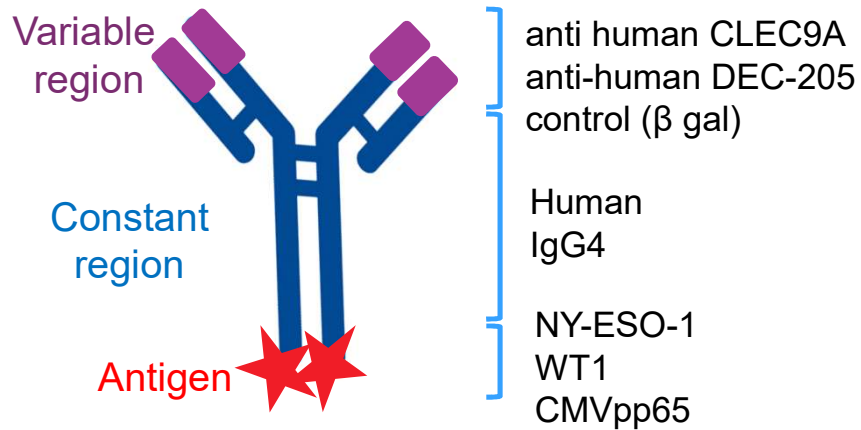
Therapeutic efficacy of Clec9A-Ab targeting on melanoma metastases



Sancho et al *Journal Clinical Invest* 2008

- recognizes f-actin on dead cells
- regulates CD8⁺ T cell responses via cross-presentation
- exclusively expressed by human cDC1 (CD141⁺ DC)

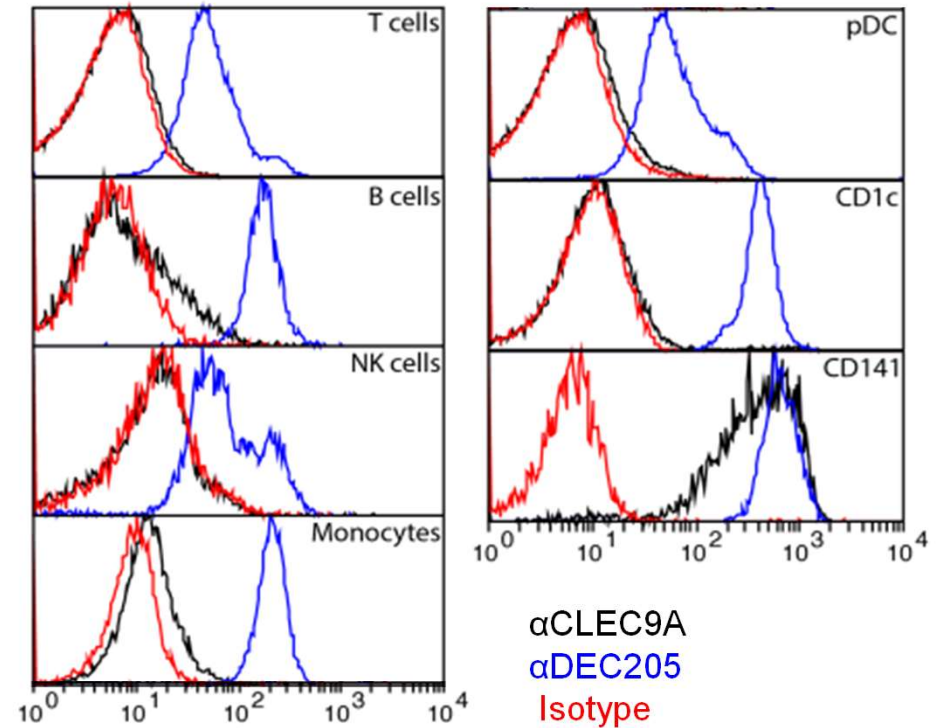
Development of human CLEC9A targeting antibodies



Kirsteen Tullett

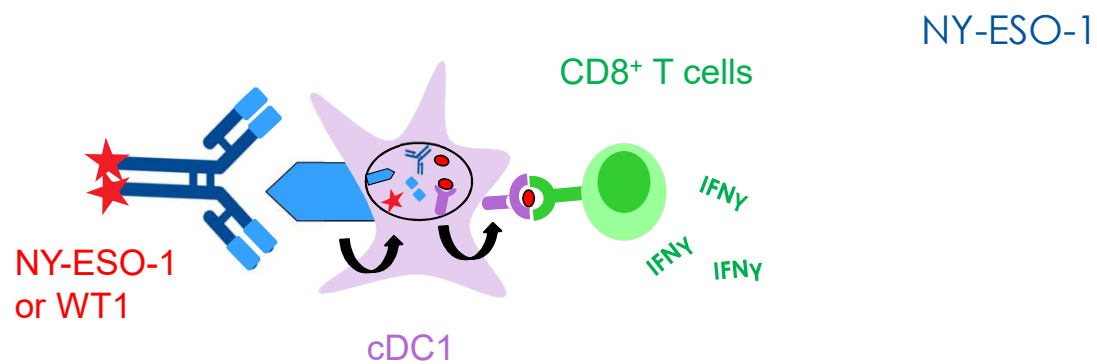


Mireille Lahoud



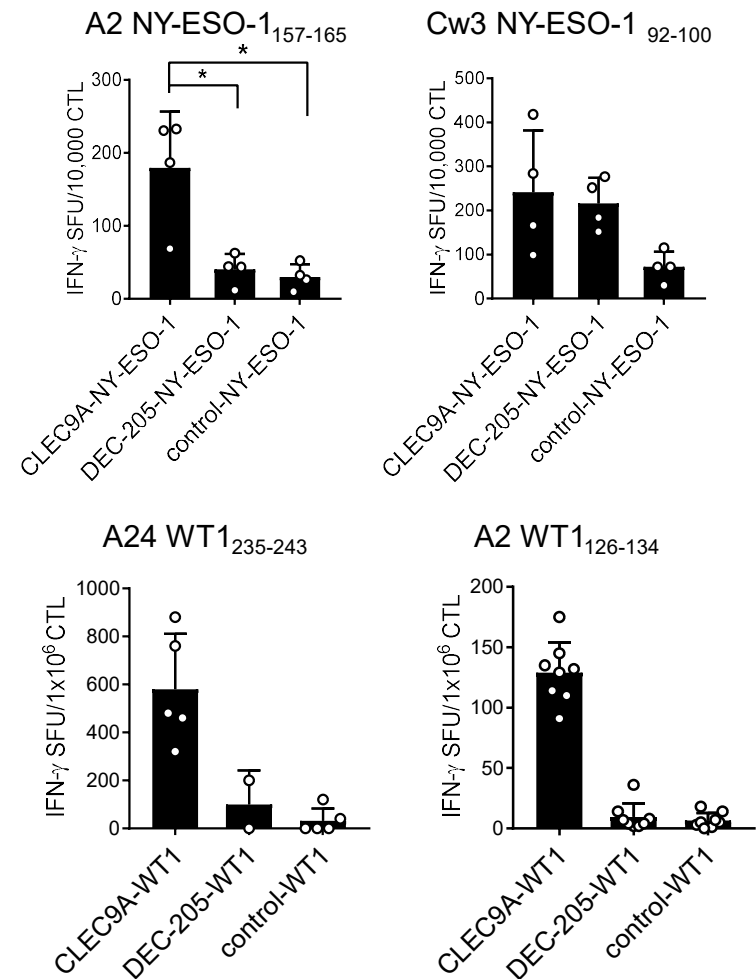
Tullett et al JCI Insight 2016
Pearson et al Clin Trans Immunol 2020
Masterman et al J Immunother Cancer 2020

CLEC9A cross-presents multiple tumor specific CD8⁺ T cell epitopes



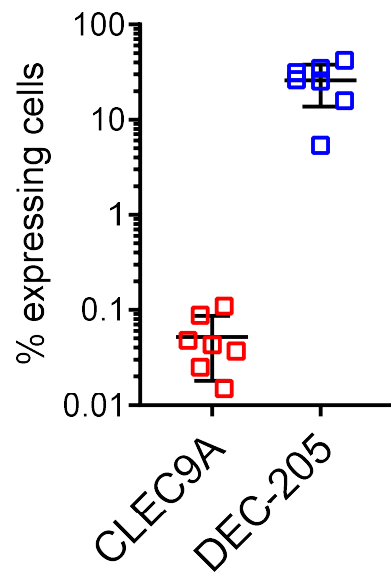
Pearson et al Clin Trans Immunol 2020
Masterman et al J Immunother Cancer 2020

WT1

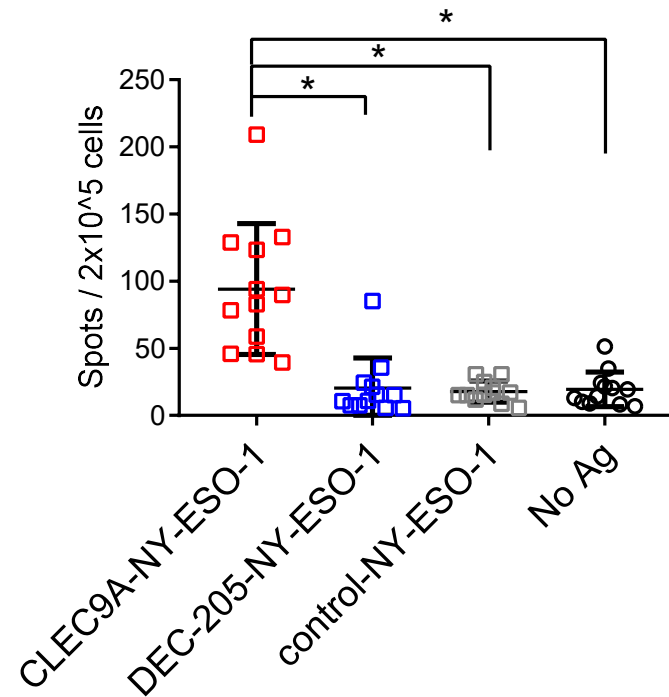


CLEC9A-NY-ESO-1 reactivates NY-ESO-1 specific responses in melanoma patients

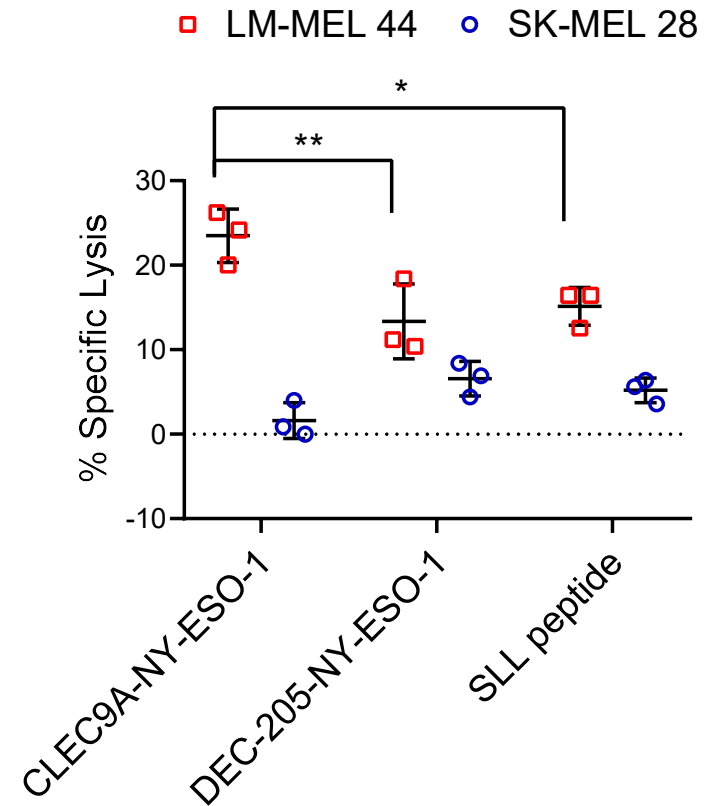
binding to PBMC



IFN γ production

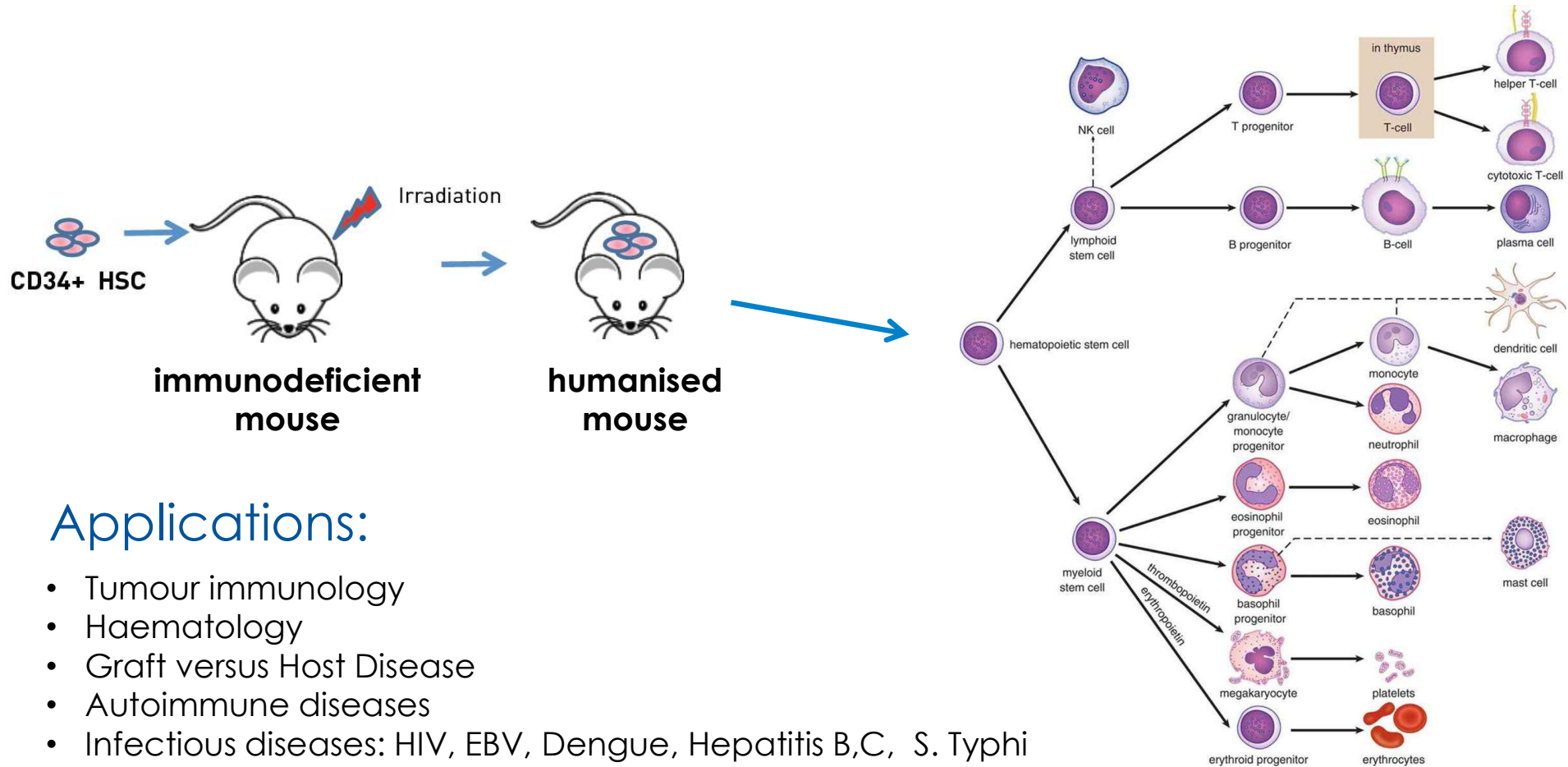


Tumour killing



Humanised mice

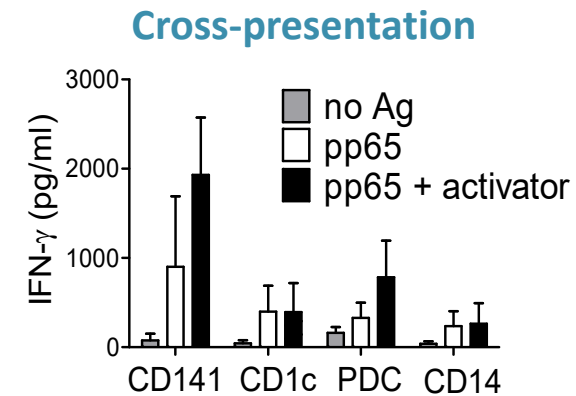
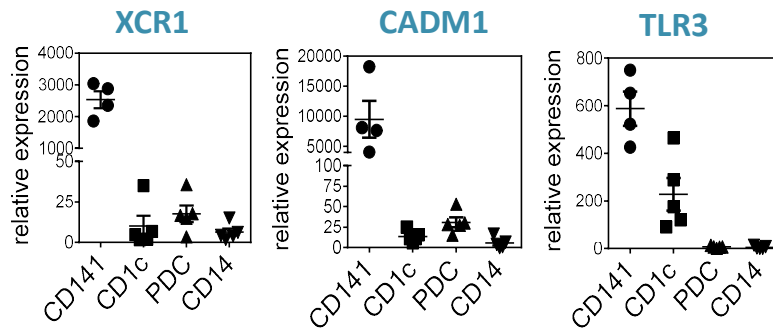
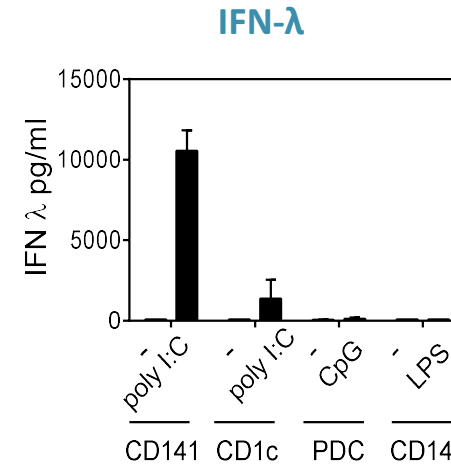
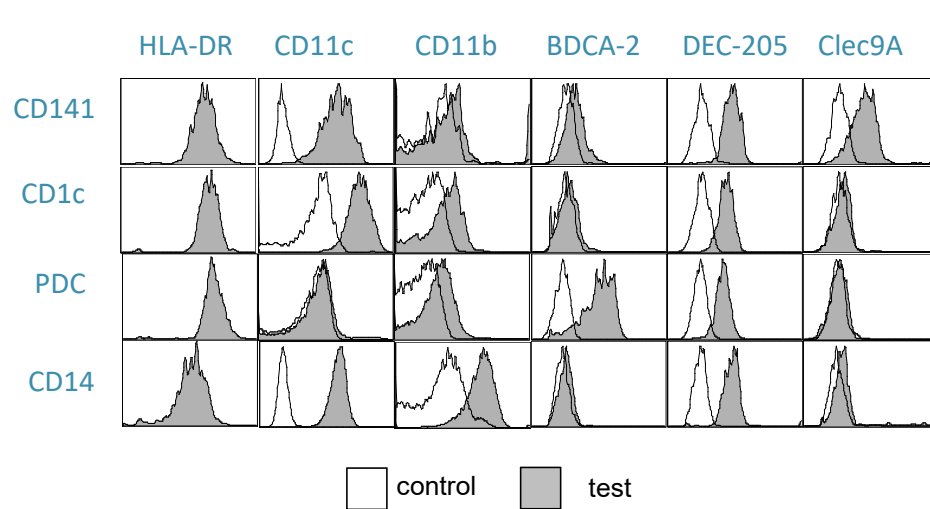
“immunodeficient mice engrafted with human haematopoietic cells or tissues”



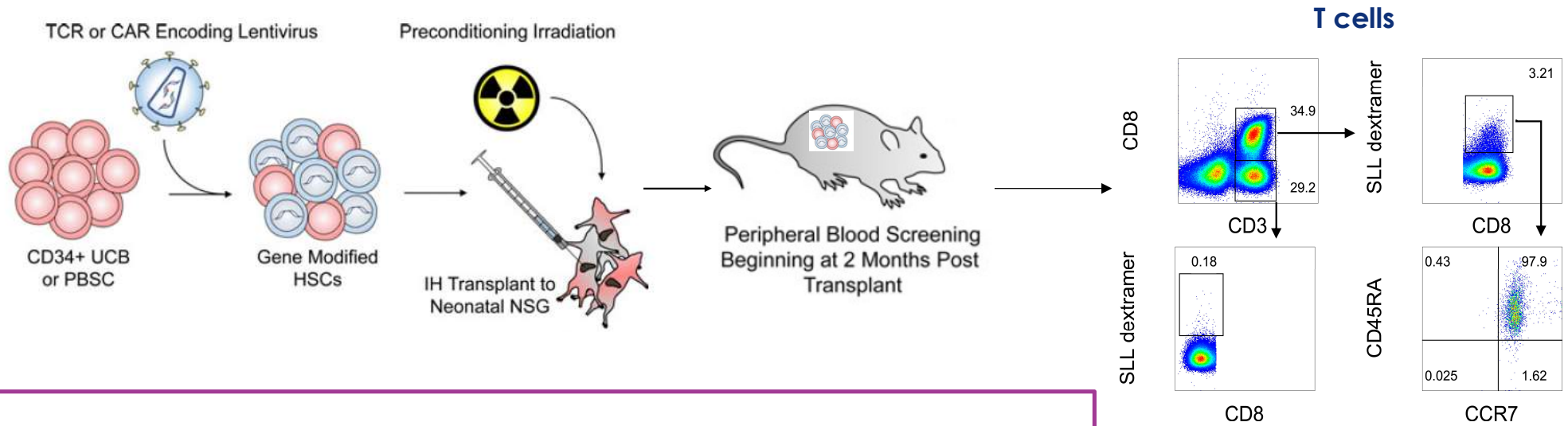
Applications:

- Tumour immunology
- Haematology
- Graft versus Host Disease
- Autoimmune diseases
- Infectious diseases: HIV, EBV, Dengue, Hepatitis B,C, S. Typhi

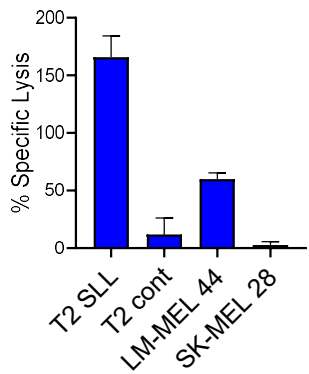
DC in hu mice resemble those in human blood



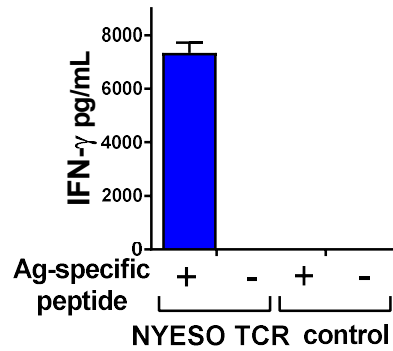
Naïve tumour antigen-specific CD8⁺ T cells develop in humanised mice



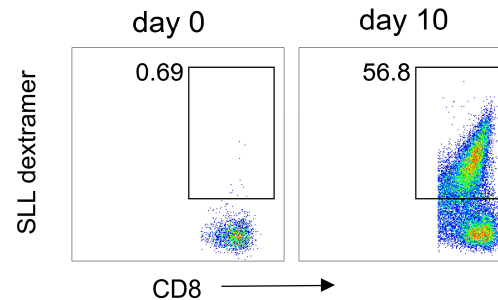
Tumour killing



IFN γ

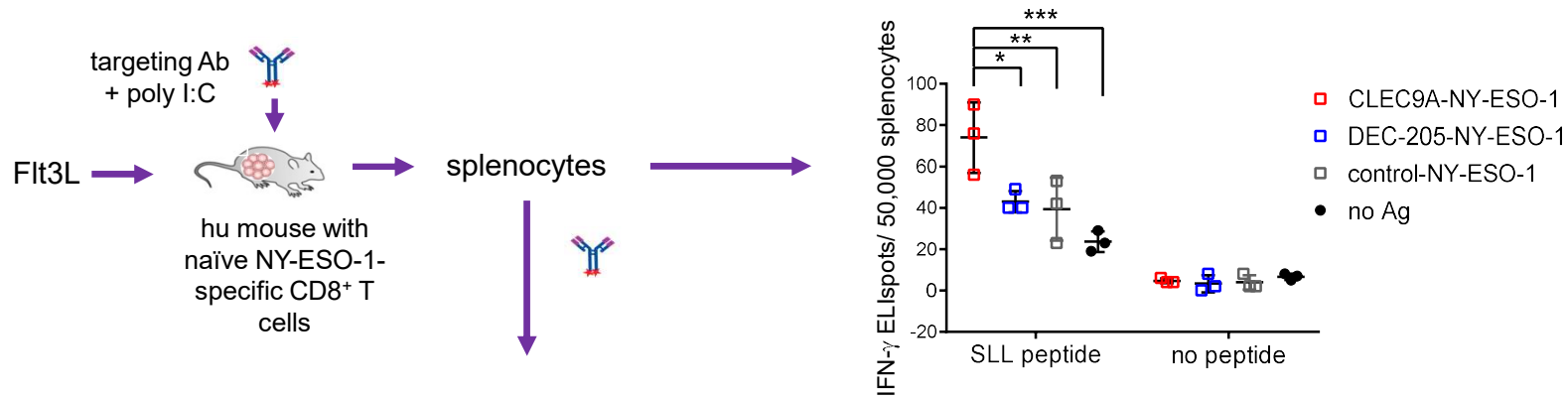


NY-ESO-1 specific T cells

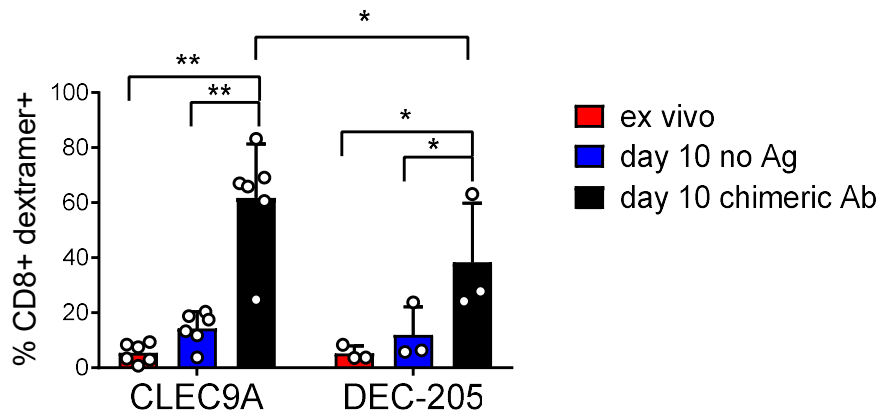


In vitro priming

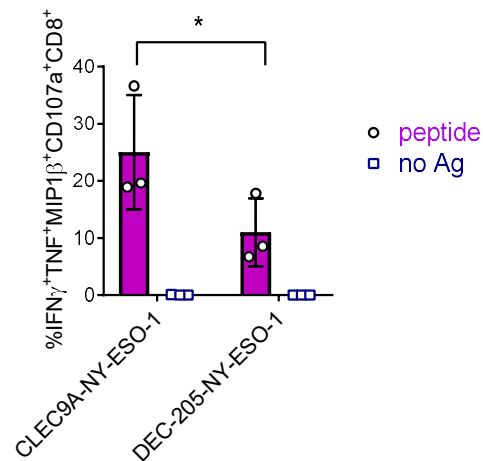
CLEC9A-NY-ESO-1 primes naïve NY-ESO-1 specific CD8⁺ T cells for expansion and effector function



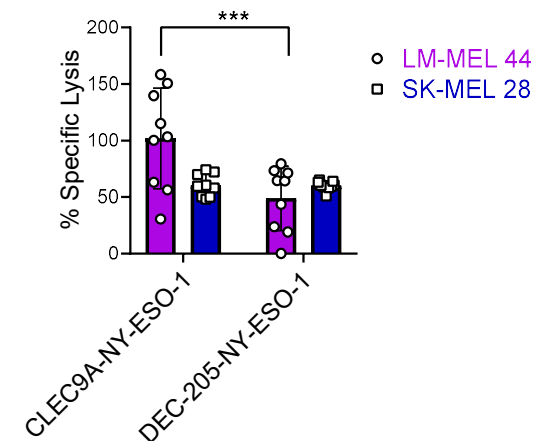
In vitro expansion



% polyfunctionality



Tumour killing



Summary

- **Human cDC1 (CD141⁺ DC) are attractive targets for cancer immunotherapy**
- **Human CLEC9A targeting antibodies**
 - ✓ Specifically target human cDC1
 - ✓ Deliver human tumour antigens to cDC1 for cross-presentation of multiple CD8⁺ T cell epitopes
 - ✓ Deliver antigens for activation of CD4⁺ T cells
 - ✓ Reactivate tumour specific memory T cell responses
 - ✓ Prime naïve human tumour specific CD8⁺ T cells
 - ✓ Superior to targeting all DC with DEC-205

Acknowledgements

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