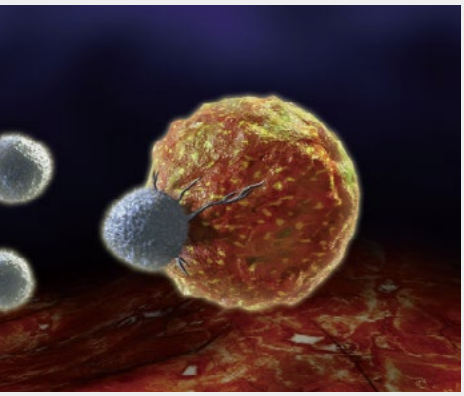
药明康德 WuXi AppTec

Oncology & Immunology

Immuno-oncology Platform

Outstanding platform to enable cancer immunotherapy with one stop service
- » Immunological function assessment
- » TIL analysis - Flowcytometry, Multiplex IF and Cytex
- » Animal models - Syngeneic and humanized models
- » Immune profiling by NGS - Single Cell RNAseq, Mutation burden and TCR/BCR repertoire
- » Clinical biomarker services - CAP certification and GCP compliance



- Biomarker
  - » Soluble biomarker – ELISA, ELISPOT
  - » Cell-based biomarker – FACS
  - » Tissue-based biomarker – Multiplex IHC
  - » Gene expression profiling-RNAseq, Nanostring
- Tumor infiltrating lymphocytes (TILs) analysis on human and murine tumor tissues
  - » CD4, CD8, MDSC, M1/M2, DC cell, NK cell, B cell
  - » PD1, TIM3, LAG3, OX40, 4-1BB
  - » Treg, Th1,2,3,17 .....
- T cell activation / Functions
  - » T cell proliferation / activation
    - 3H incorporation, SEB stimulation assay
- In vivo efficacy evaluation on animal models
  - » Syngeneic murine models
  - » Immune-checkpoint humanized models
  - » Immune-Avatar humanized models
    - » PBMC humanized models
    - » HSC humanized models

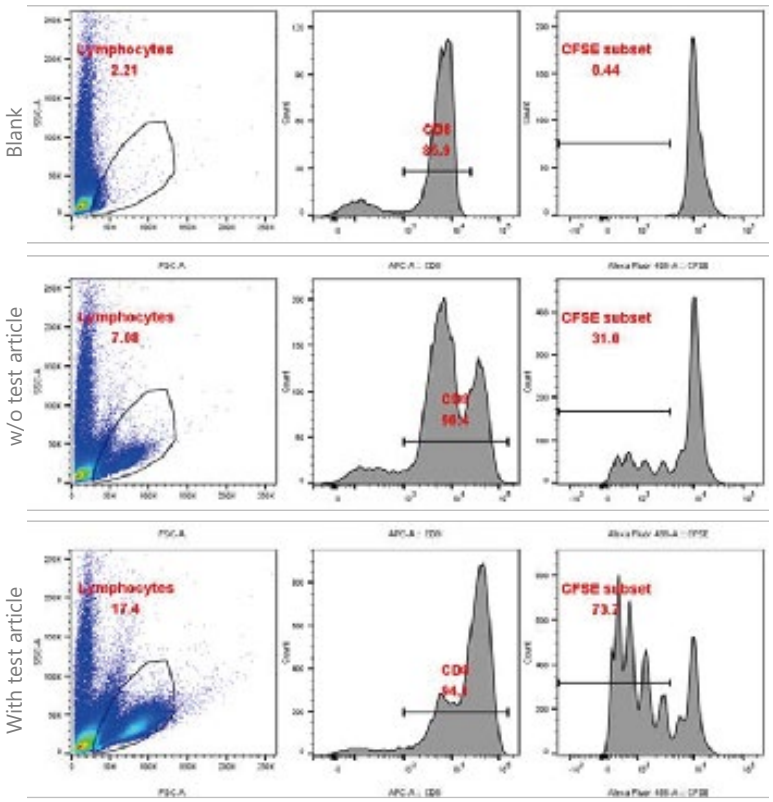
Largest collection of syngeneic model

61 syngeneic models established

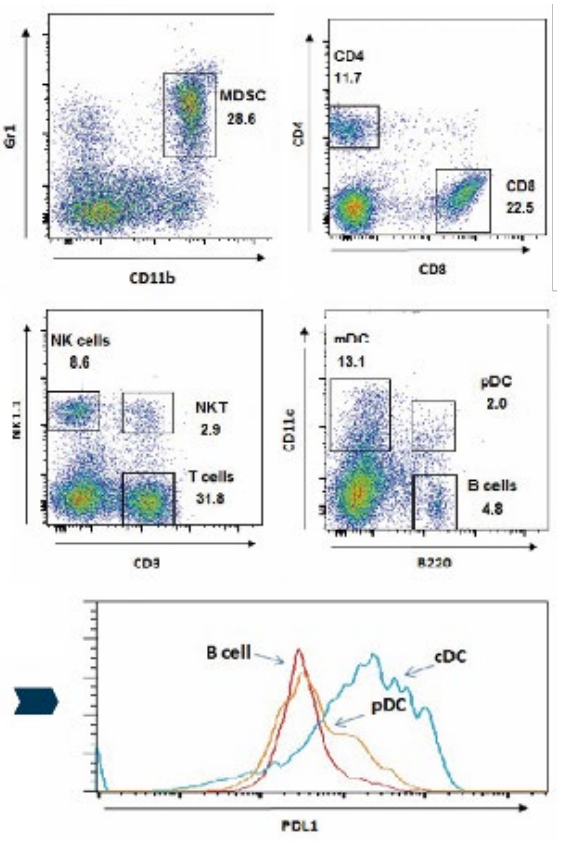
Tumor types	Cell lines
Bladder (1) :	*MBT2^{S,GT,TIL}*
Brain (2) :	*GL261^{S,GT},GL261-luc^{S}*
Breast (6) :	*4T1$^{S,GC/T,TIL}$, 4T1-luc^{S}, JC^{GC}, Eph4 1424$^{GC/T}$, EMT6$^{S,GC/T,TIL}$, FM3A*
Colorectal (3) :	*Colon-26$^{S,GC/T,TIL}$, CT-26^{S,GT,TIL}, MC38$^{S,GC/T,TIL}$*
Hemangioendothelioma (1)	*EOMA*
Liver (3)	*MH-22A^{S,GT,TIL}, H22^{S,GT}, Hepa 1-6^{S,GT,TIL}*
Lung (4)	*LLC1(LL/2)^{S,GT,TIL}, KLN205^{S,GT,TIL}, 3LL^{S,GT,TIL}, M109*
Leukemia (4)	*L1210^{S}, WEHI-3, C1498, WEHI 3BD*
Lymphoma (10)	*EL4, E.G7-OVA^{S}, A20^{S,GT}, P388D1, L5178-R, WR19L, A20-Luc^{S}, L5178-S(LY-S), L5178Y TK+/- clone (3.7.2C), P3/NSI/1-Ag4-1(NS-1)*
Myeloma (5)	*MPC-11, FO, P3X63Ag8, J558L^{S,GT,TIL}, MOPC31C*
Mastocytoma (3)	*P815^{S,GT,TIL}, P815-luc^{S}, P1.HTR*
Melanoma (6)	*B16-F10$^{S,GC/T,TIL}$, B16-F10-luc-G5, B16-F0^{S,GT}, CloudmanS91$^{S,GC/T,TIL}$, B16-F1^{S,TIL}, C57/B1*
Neuroblastoma (3)	*Neuro-2a, N1E-115, N18(Hamprecht)*
Pancreas (1)	*Pan02^{S}*
Prostate (2)	*RM-1^{S,GT},RM-1-luc*
Renal (2)	*RENCA^{S,GT,TIL},RENCA-luc*
Sarcoma (2)	*WEHI164^{S,GT}, K7M2 wt^{GT}*
Testis (1)	*MLTC-1*
ovarian cancer (1)	*OV3121^{S}*
Schwannoma (1)	*TR6Bc1*

Note: All 61 models have growth curve data,
31 models with reference drug treatment data (either chemotherapy/target therapy or immunotherapy) were marked as S.
28 models with genomic profiling data were marked with GC (cell-line profiled), GT (Tumor tissue profiled) or GC/T (both).
17 models with immune phenotyping by Flow-Cytometry were marked with TI

CD8 T cells activation by immune-checkpoint blockade

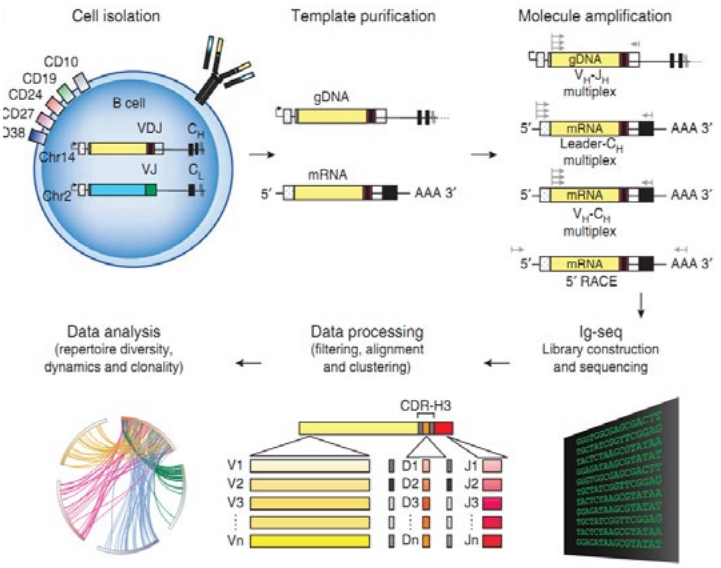


TILs analysis of syngeneic tumor

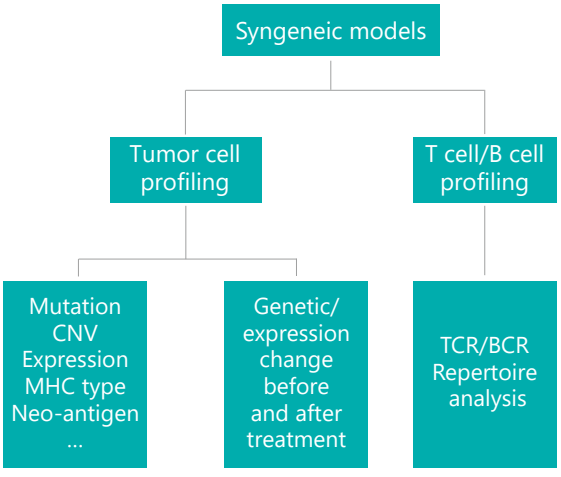


Immuno-oncology platform – immune profiling

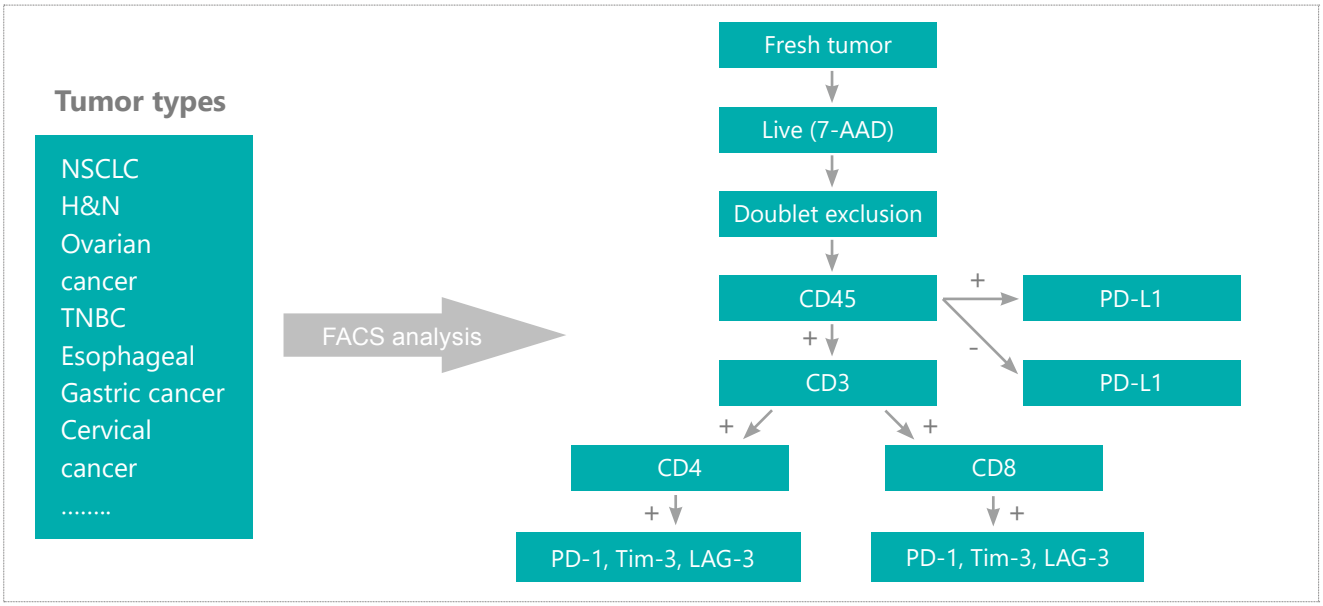
- Immune profiling capability has been established for both human and murine, including
  - » Tumor cell: exome sequence, RNAseq, neo-antigen prediction, MHC typing
  - » T cell/B cell Repertoire sequencing and analysis



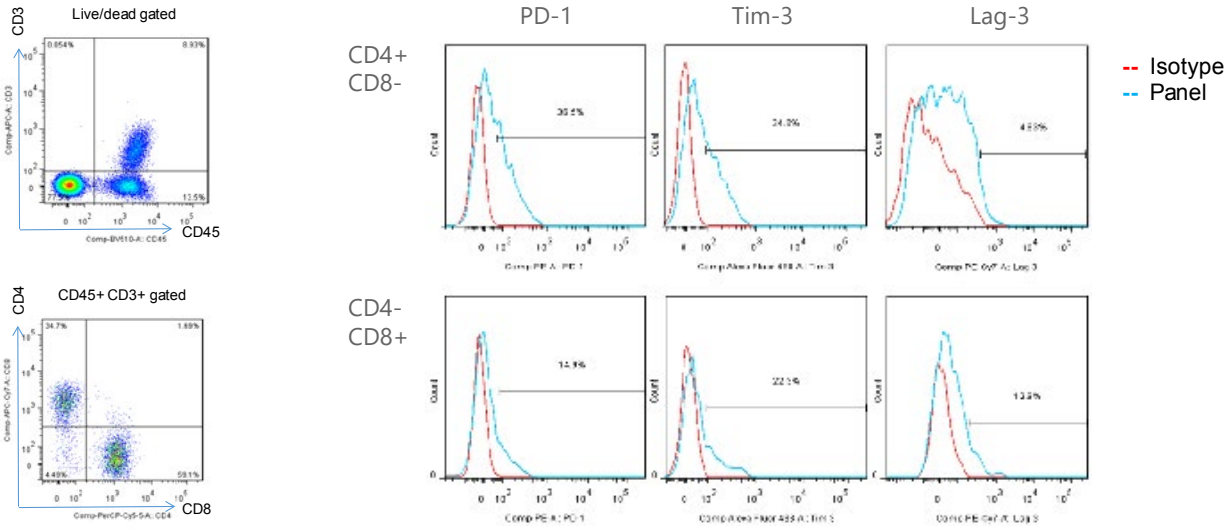
Nature Biotechnology V32, P158–168:(2014)



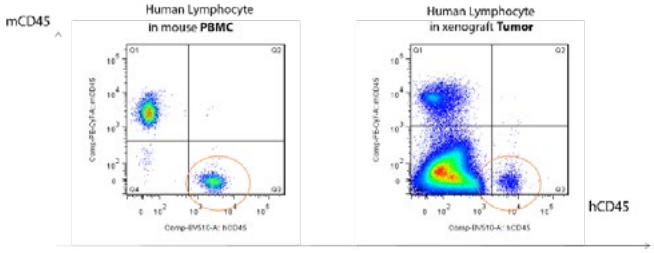
FACS analysis of TILs and immune checkpoints in Chinese cancer patients

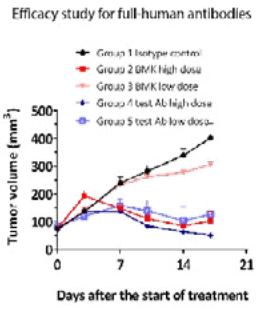


FACS analysis of TILs in clinical tumors, a case study

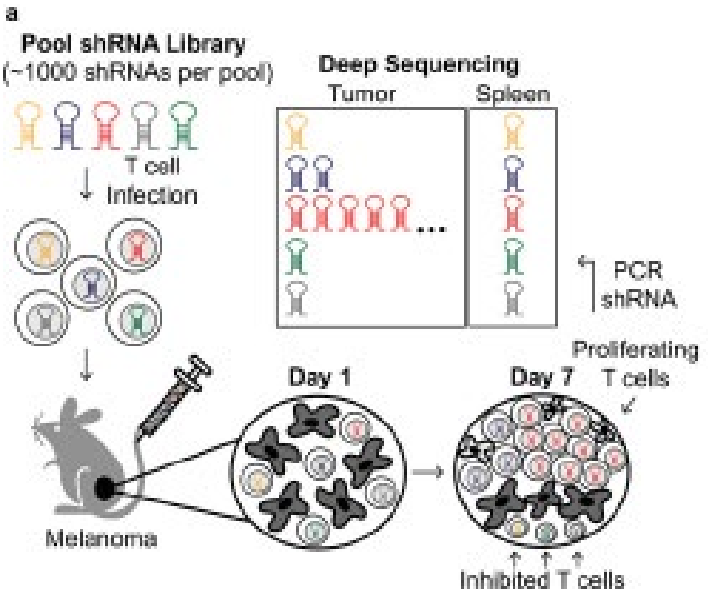


Immune-Avatar PBMC humanized models





CRISPR library screening for novel immune checkpoint targets



*Nature 2014, 506 (7486): 52-57

- Isolation T cells from transgenic mice (OT-I or DO11.10)
- Infect T cells with murine CRISPR library and selection
- Infected T cells stimulated with IL7/IL15/IL2 in vitro
- Injection of infected T cells to B16 tumor bearing C57BL/6 animals
- Isolation of T cells from tumor/ spleen/lymph nodes
- Deep sequencing to identify sgRNA enriched in tumor-infiltrating T cells

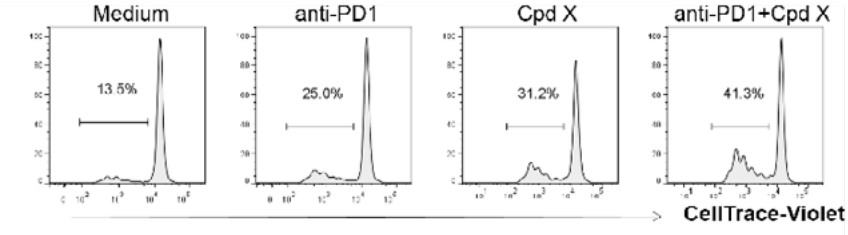
Immunology-Oncology Platform – In-vitro Assays

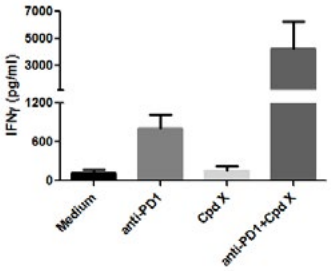
Service list of In-vitro and ex-vivo immunology assays

Assay		WuXi AppTec Capability(Human/Mouse)
Cell activation	*T cell Agonism (Antibody/SEB/CMV Recall)*	*Yes (H/M)*
	B cell activation	*Yes (H)*
	NK cell activation/expansion	*Yes (H)*
Cell differentiation/ polirization	*M1/M2 macrophage*	*Yes (H/M)*
	MDSC	*Yes (H)*
	DC	*Yes (H/M)*
	Treg, Th1, Th2, Th17 polarization	*Yes (H)*
Mixed Lymphocyte Reaction	*DC co-culture with T*	*Yes (H/M)*
Suppressive assay	*MDSC suppressive assay*	*Yes (H)*
	Treg suppressive assay	*Yes (H)*
	Tumor cell+immune cell co-culture	*Yes (H)*
Cell cytotoxicity	*Cytotoxic T lymphocyte assay (OT-1 system)*	*Yes (M)*
	NK cytotoxicity	*Yes (H)*
	ADCC, ADCP	*Yes (H)*
	CDC	*Yes (H)*
	TH17	*Yes (H/M)*
Other assays	*ADCC, CDC, ADCP*	*Yes (H)*

Co-culture

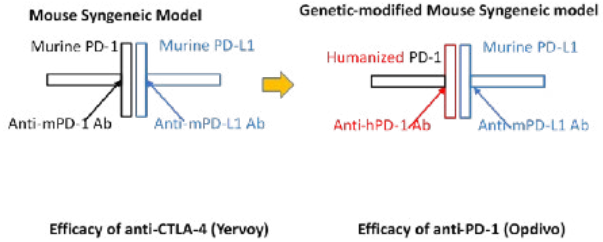
Showcase for DC and T cell (MLR assay)





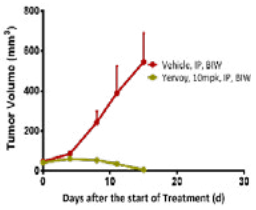
» MLR assay. Human monocyte-derived DCs were co-cultured with allogeneic T cells isolated from PBMC For 4 days. After co-culture, T cell proliferation was measured by FACS and IFN-γ production was detected with ELISA.

Immnue Checkpoint Humanized Models

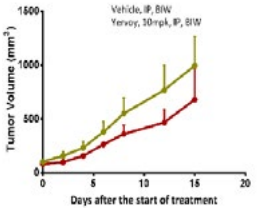


Target	Background
hPD-1	C57BL/6J, BALB/c
hCTLA4	C57BL/6J, BALB/c
hPD-1/hPD-L1	C57BL/6J
hPD-1/hCTLA4	C57BL/6J
hTIM3	C57BL/6J
hPD-1/hTIM3	C57BL/6J
hLAG3	C57BL/6J
hOX40	C57BL/6J, BALB/c
hGITR	C57BL/6J
hPD-1/hGITR	BALB/c
h4-1BB	C57BL/6J
hICOS/hPD-1	C57BL/6J
hTIGIT	C57BL/6J
hCD40	C57BL/6J
hPD-1/hCD47	C57BL/6J, BALB/c
hSIRPA	C57BL/6J
hPD-1/hSIRPA	C57BL/6J, BALB/c
hVISTA	C57BL/6J
hPD1/hCD28	C57BL/6J, BALB/c
hPD-1/hPD-L1/h4-1BB	BALB/c
hPD-1/hPD-L1/hCTLA4	BALB/c
hPD-1/hPD-L1/hTIGIT	C57BL/6J
hPD-1/hPD-L1/hOX40	C57BL/6J
hPD-1/hVISTA	C57BL/6J
hPD-1/hPD-L1/hCD73	C57BL/6J
hPD-1/hPD-L1/hLAG3	C57BL/6J

Yervoy on MC38 models



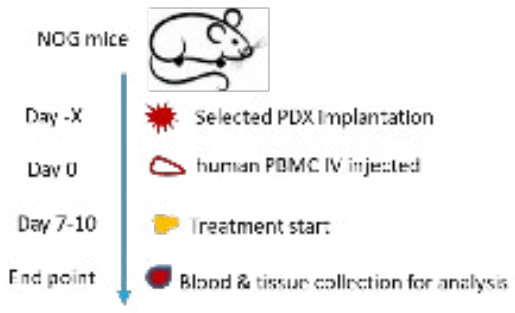
huCTLA-4 KI C57BL/6

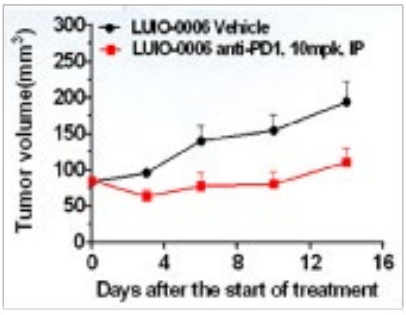


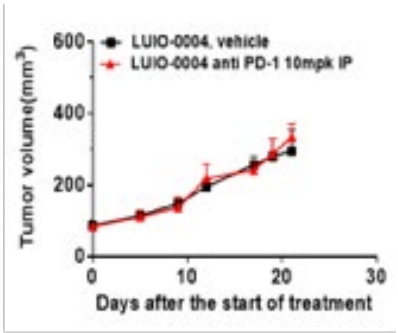
Wild type C57BL/6

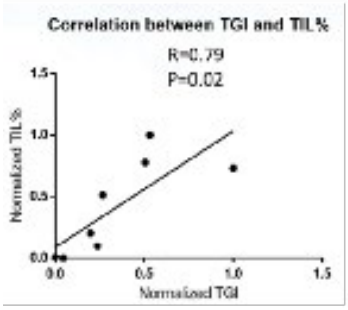
Immune Avatar Humanized Models

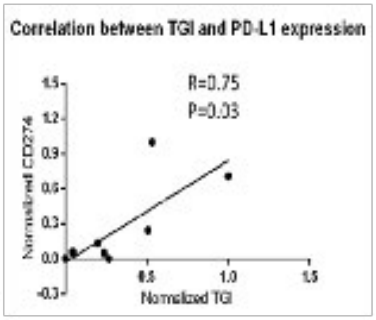
Show case of anti-PD-1 efficacy in EGFR mutant tumor models x hPBMC reconstituted mice

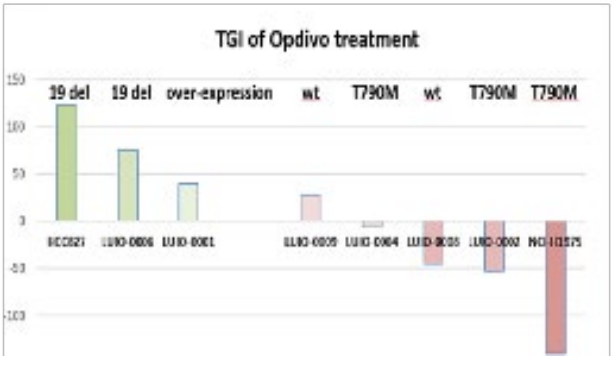












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