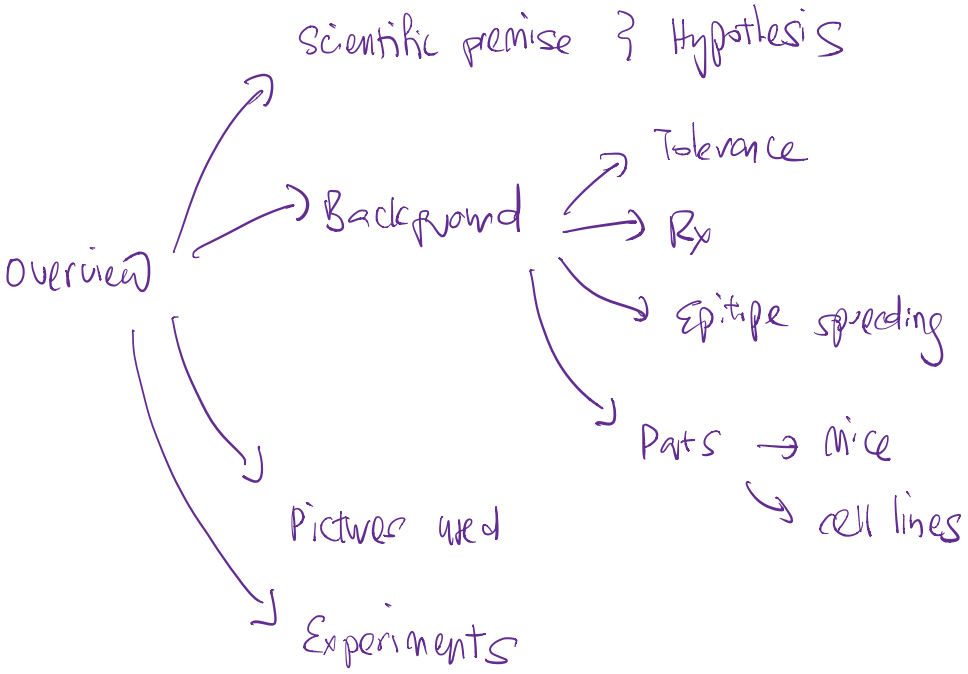
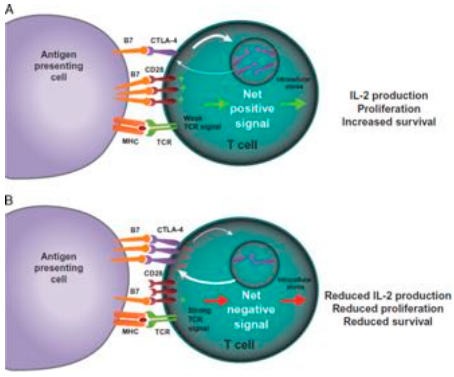
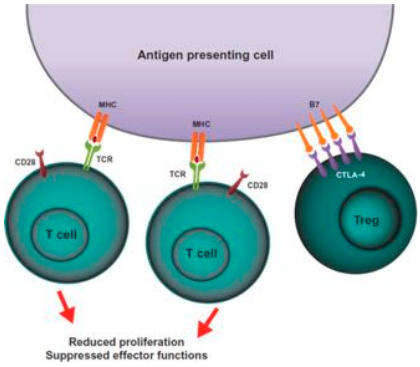
Epitope spreading toward wild type melanocyte-lineage antigens rescues suboptimal immune checkpoint blockade responses

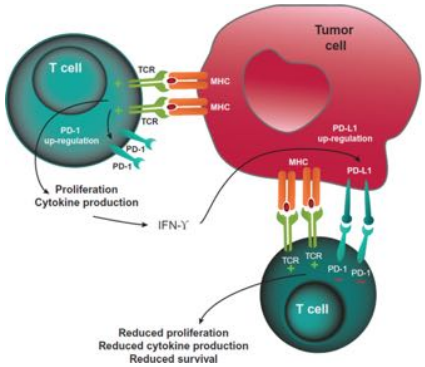


Clues ⇒ Guess

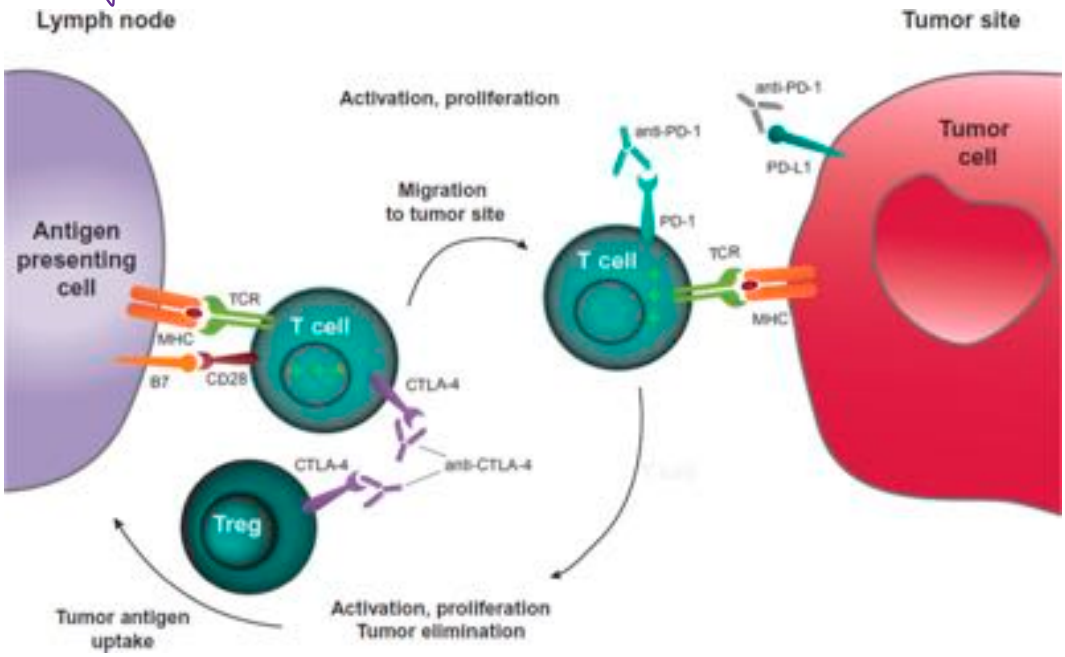
Tolerance


A
Antigen presenting cell
B7
CTLA-4
B7
CD28
MHC
TCR
Net positive signal
T cell
IL-2 production
Proliferation
Increased survival
B
Antigen presenting cell
B7
CTLA-4
B7
CD28
MHC
TCR
Net negative signal
T cell
Reduced IL-2 production
Reduced proliferation
Reduced survival

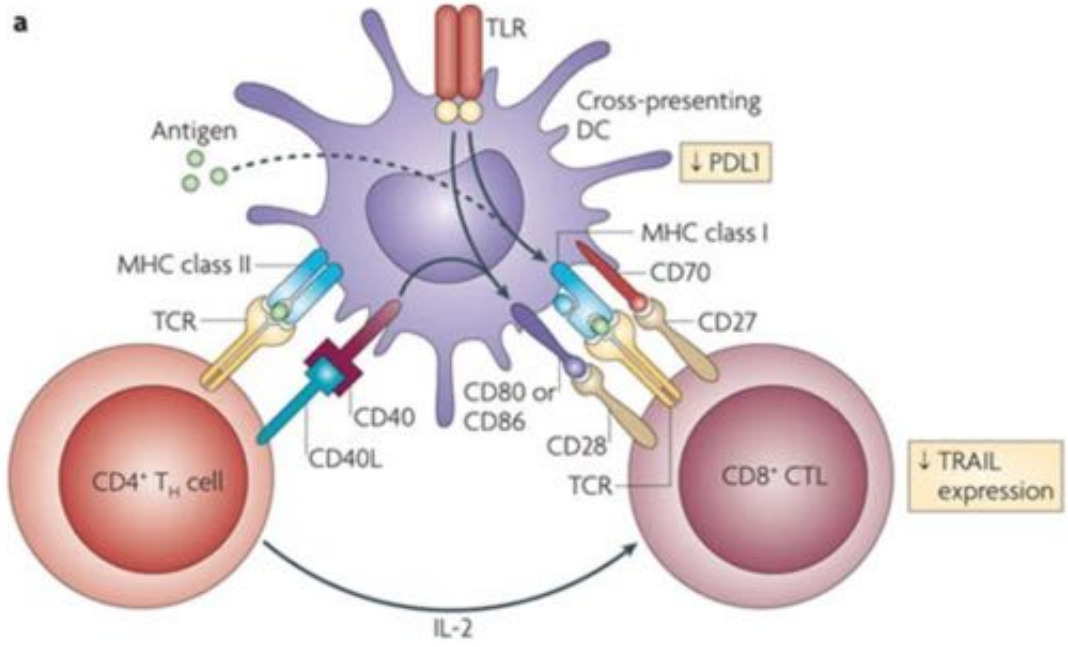

Antigen presenting cell
MHC
MHC
B7
CD28
TCR
TCR
CD28
CTLA-4
T cell
T cell
Treg
Reduced proliferation
Suppressed effector functions

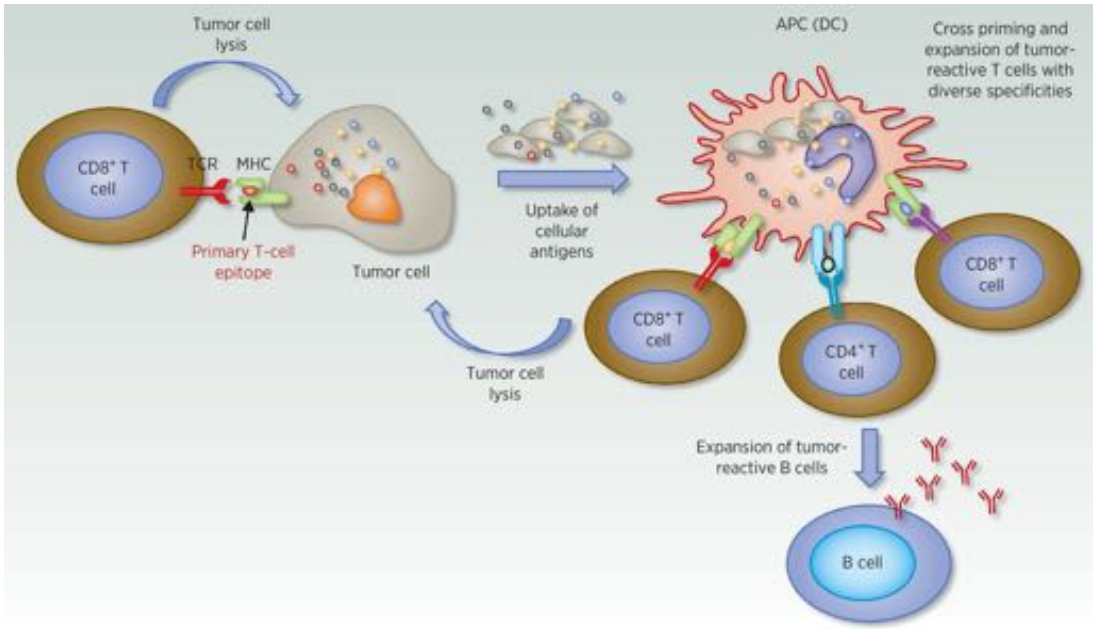

Tumor cell
T cell
TCR
MHC
MHC
TCR
PD-1 up-regulation
PD-1
PD-1
PD-L1 up-regulation
MHC
PD-L1
Proliferation
Cytokine production
IFN-γ
TCR
TCR
PD-1
PD-1
T cell
Reduced proliferation
Reduced cytokine production
Reduced survival

Therapy (ICI, Imiquimod, aFP)



Cross-priming } epitope spreading





Assays (IHC, FISH, Bulk RNA-seq)

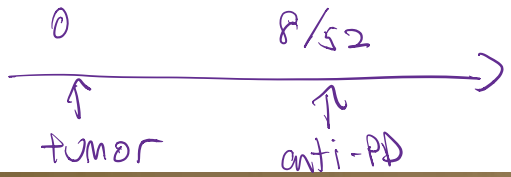
Mice (C57BL/6, NSG, BATBF-/-)

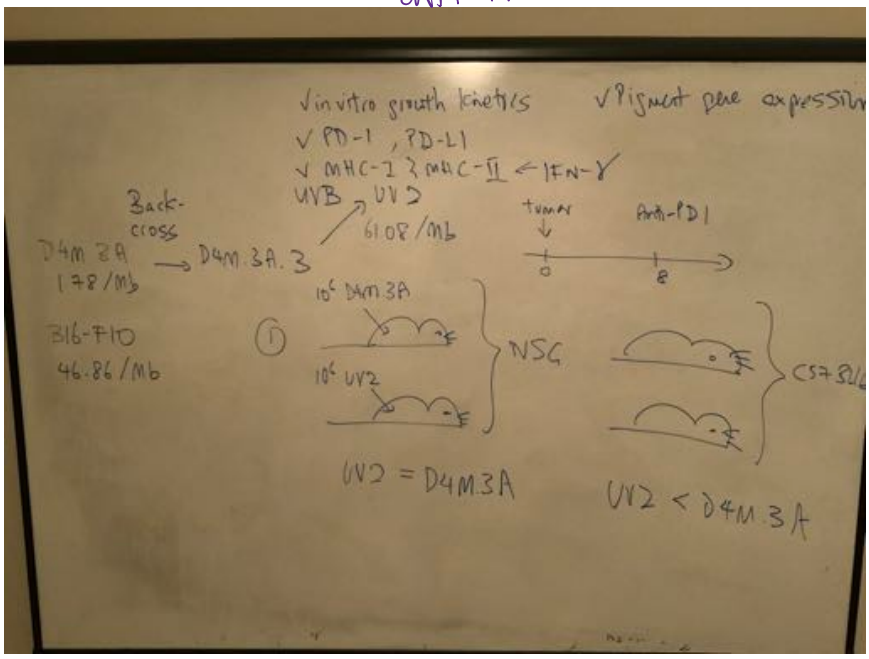
Tumor cell lines (D4M3A, D4M3A.3, UV2, KPC, KPC+5MA)

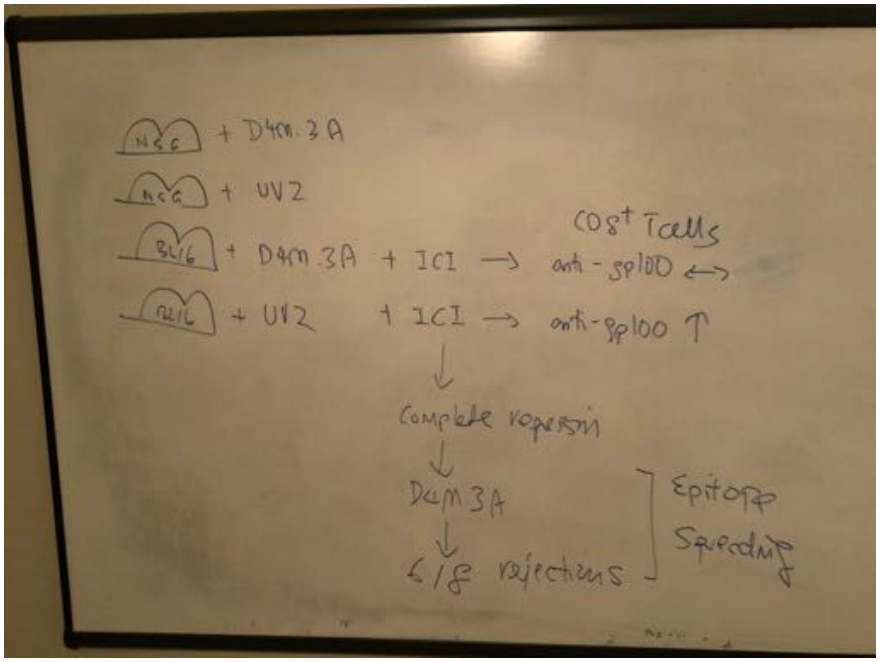
Figures (Growth curves, Survival curves, Gene set enrichment,
Bar charts, scatter plots, IHC images)

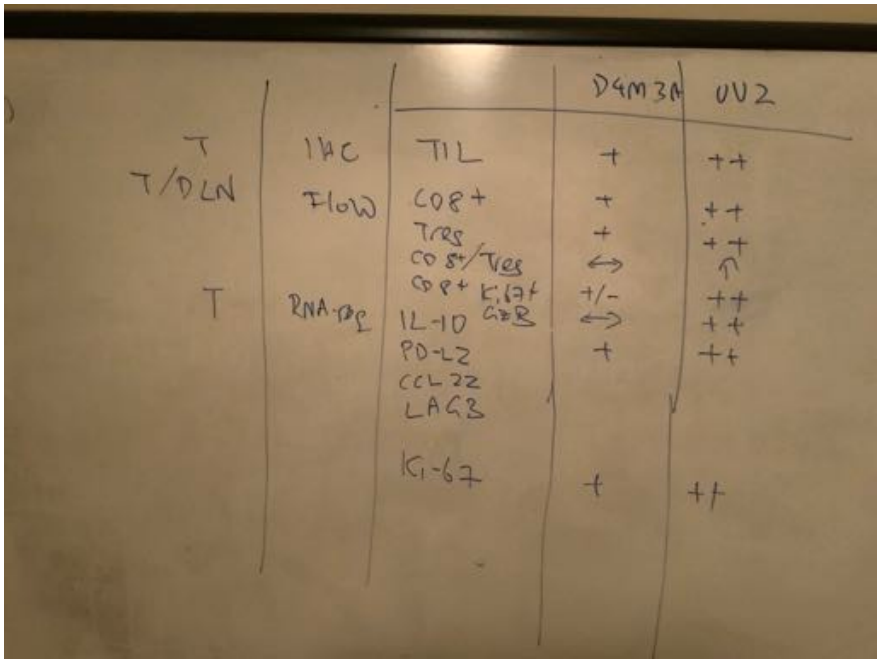
Experiment #1 (Fig 2 + Fig 3)

↑ neoantigens → ↑ immune response





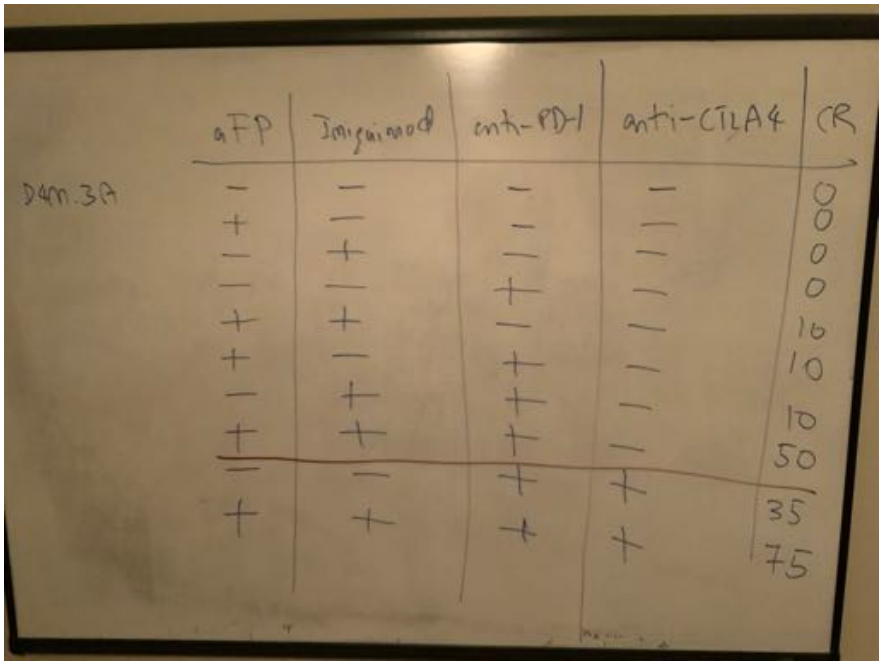




Expt #2 (Fig 4, Fig 5A-5E) *What 2mi does

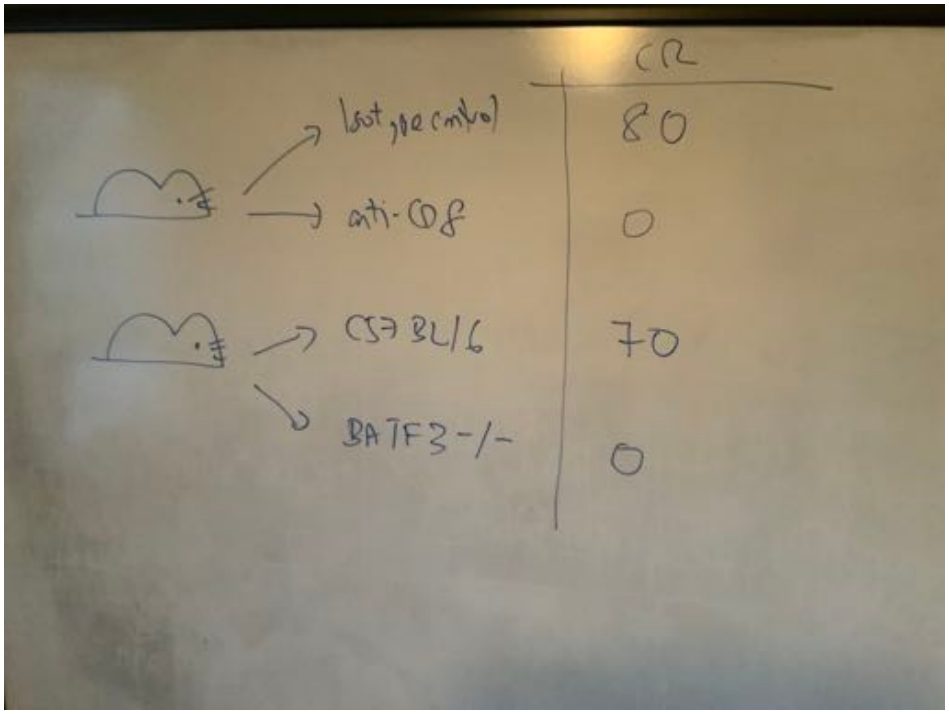
3Rx → Epitope spread

Fig 5D, 5E



Expt #3 (Fig 5F/5G)

Block of ov cross-priming → No tumor rejection



Expt #4 (Fig 6)

↑ epitope spreading → long-term broad protection