The renaissance of immunotherapy is a revolution for cancer patients and for oncology

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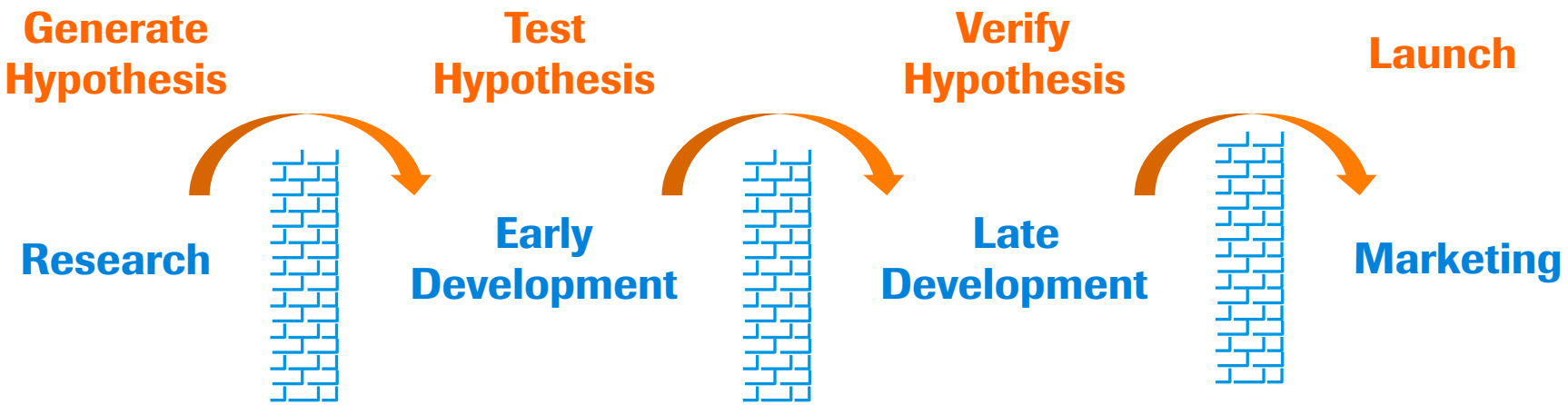
The renaissance of immunotherapy is a revolution for cancer patients

Traditional drug development

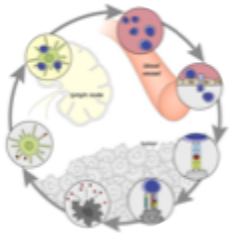
Is linear development path the best approach?



Cancer immunotherapy requires a cyclical "learning organization"

Post-Launch

Research

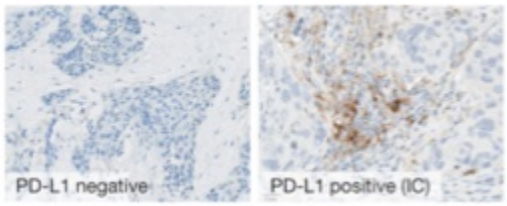


Cancer Immunotherapy Strategy Group (CITS)

Late Development

FIR	PII 1/2L Dx+ ORR
BIRCH	PII Dx+ ORR
POPLAR	PII 2L+ Dx+/- vs. Doce OS
OAK	PIII 2L+ Dx+/- vs. Doce OS

Early Development



Cancer immunotherapy at Genentech/Roche

Pipeline overview

Pre-clinical	Phase I	Phase II	Phase III
ImmTAC	Anti-PDL1 Solid tumors	Anti-PDL1 NSCLC (Dx+)	Anti-PDL1 NSCLC 2/3 L
Neg. Regulator NME 1	Anti-PDL1+Avastin Solid tumors	Anti-PDL1 NSCLC	Anti-PDL1 Bladder
IMA 942	Anti-PDL1+cobimetinib Solid tumors	Anti-PDL1+Avastin Renal	Anti-PDL1 NSCLC 1L Dx+
Anti-cytokine NME 2	Anti-PDL1+Zelboraf Met. Melanoma	Anti-PDL1 Bladder	
T-cell bispecific	Anti-PDL1+Tarceva NSCLC	CSF1R huMAb PVNS	
	Anti-PDL1 + immune m. Solid tumors		
	Anti-PDL1 + Gazyva Heme tumors		
	CSF1R huMAb solid tumors		
	CEA IL-2v		
	Anti-OX40		
	IDO (GDC-0919)		
	Anti-CD40		

Anti-PDL1 trials
Stimulator
Inhibitor
Trial planned

Note: Anti-PDL1 is listed as MPDL3280A in clinicaltrials.gov

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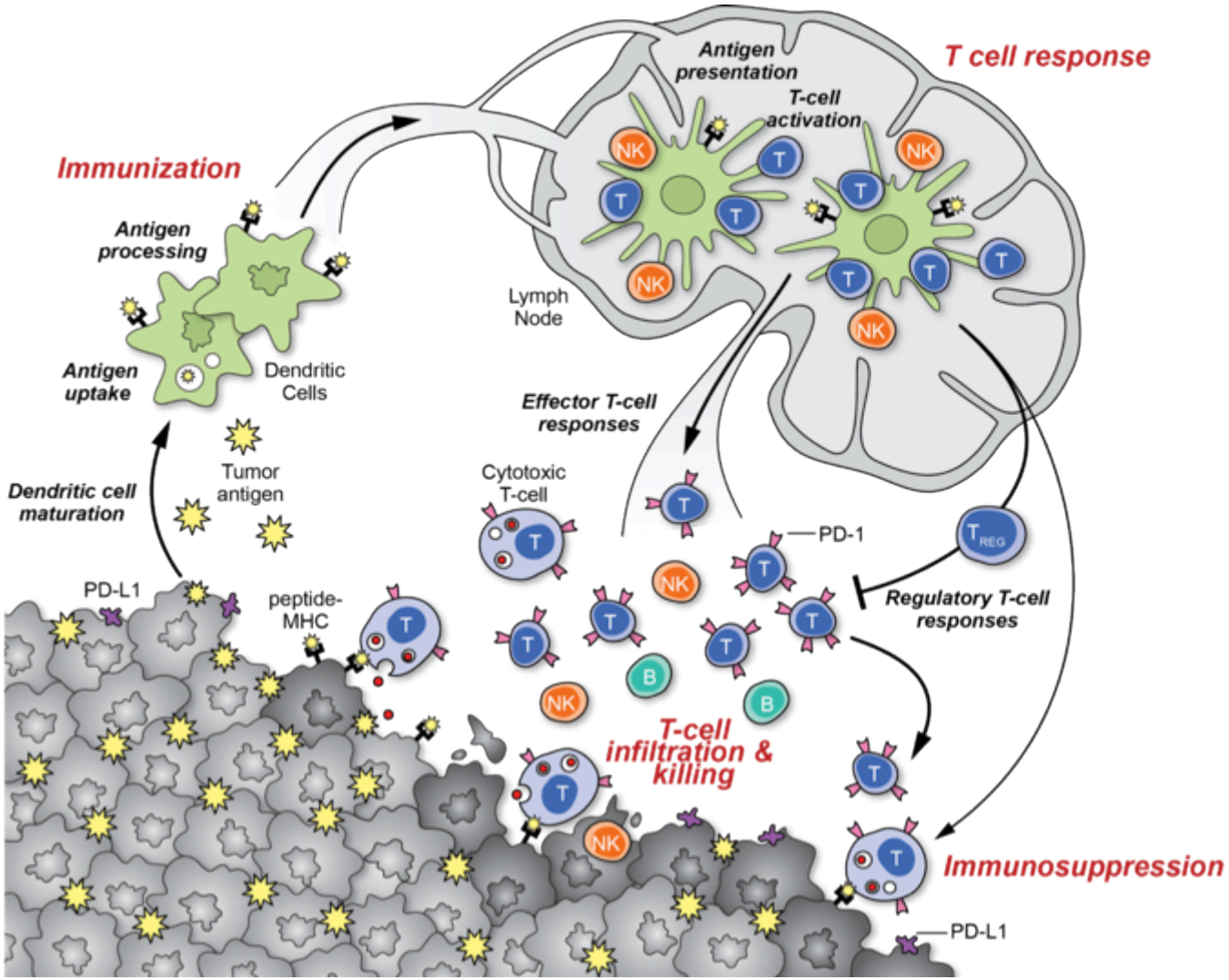
Mechanistic basis of cancer immunotherapy



Mellman et al (2011) *Nature* 2011 Dec 21;480(7378):480-9

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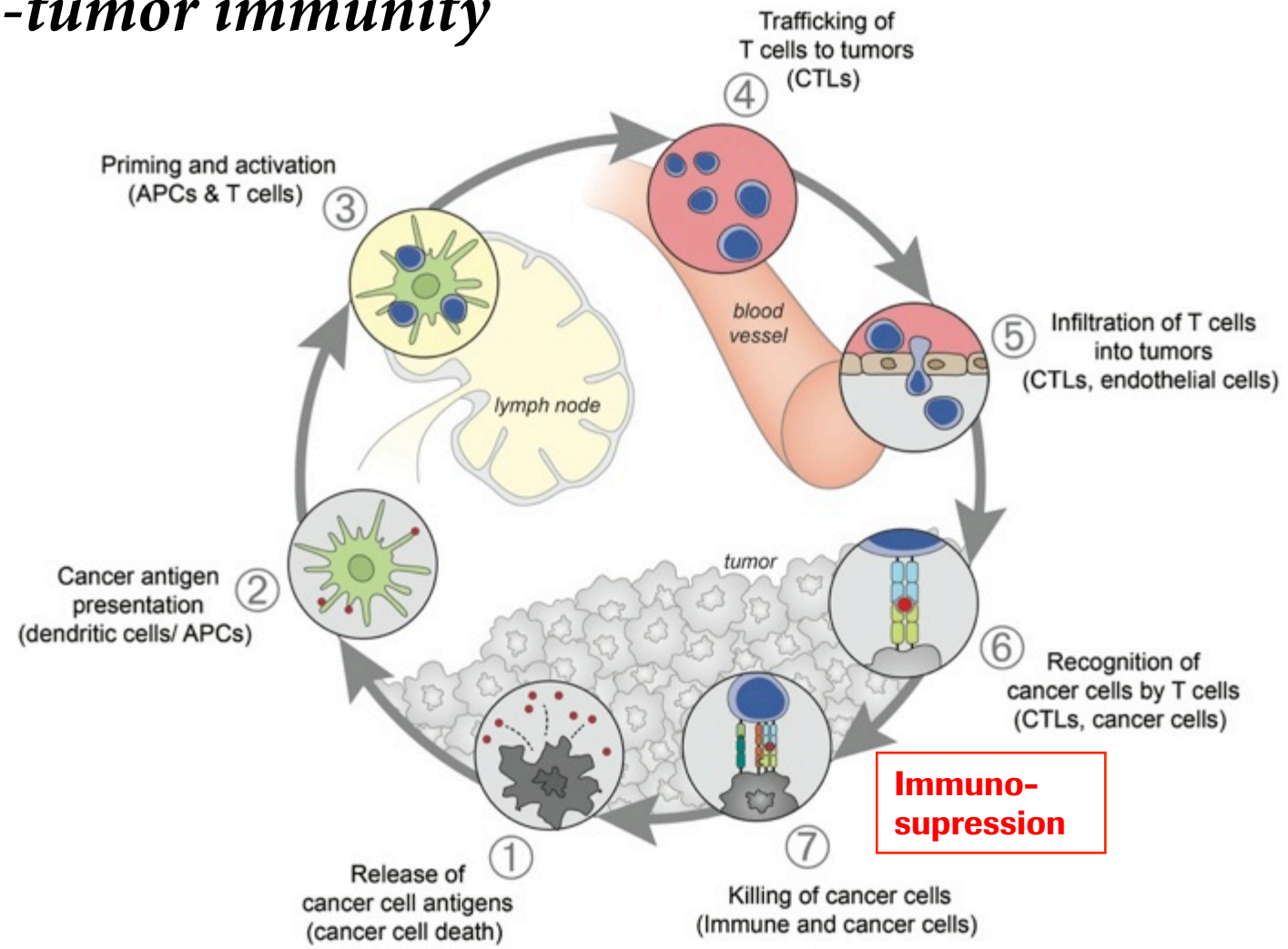
The Cancer Immunity Cycle

Immunosuppression is the rate limiting step to effective anti-tumor immunity



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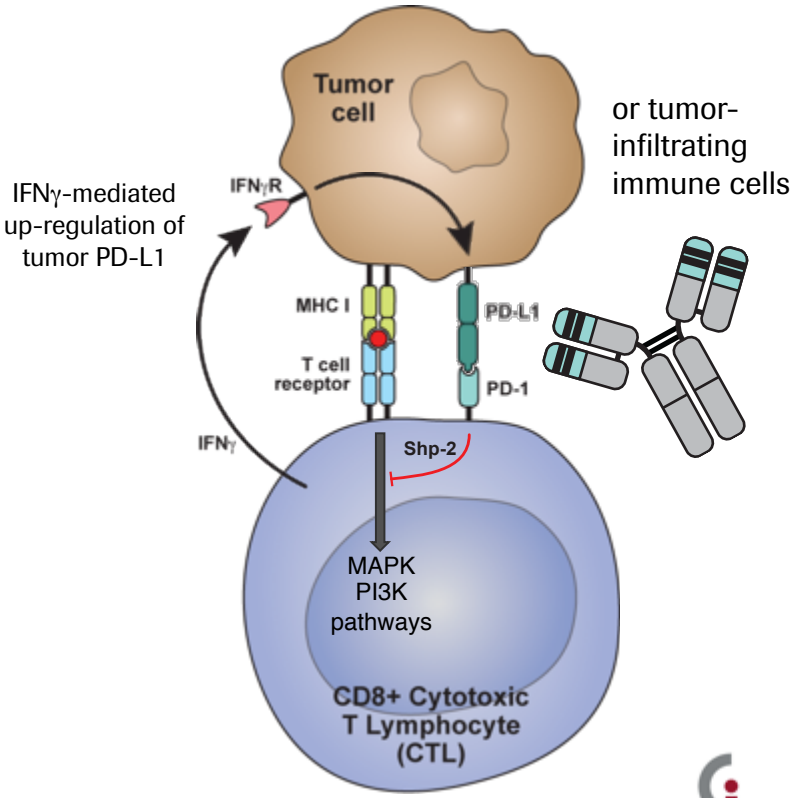
Targeting immuno-supression
PD-1/PD-L1 pathway

- PD-1/PD-L1 interaction inhibits T cell activation, attenuates target killing: **prevents overstimulation of T cells during acute virus infection**
- A large percentage of tumors also up-regulate PD-L1 and evade killing by T cells
- Blocking PD-1 binding restores effector T cell activity

"Adaptive expression" of PD-L1



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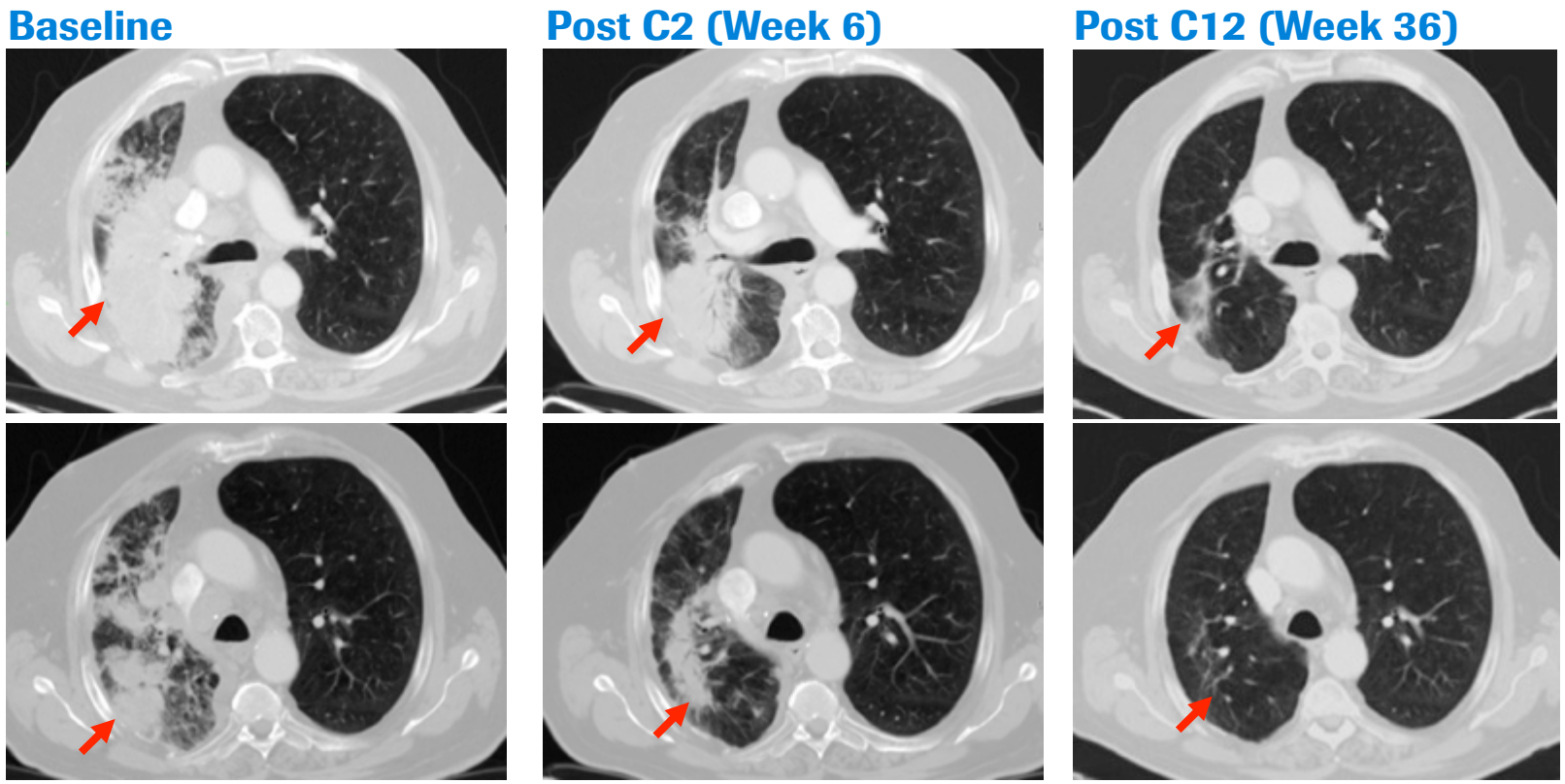
Targeting PD-L1 produces dramatic responses in many cancers (lung)

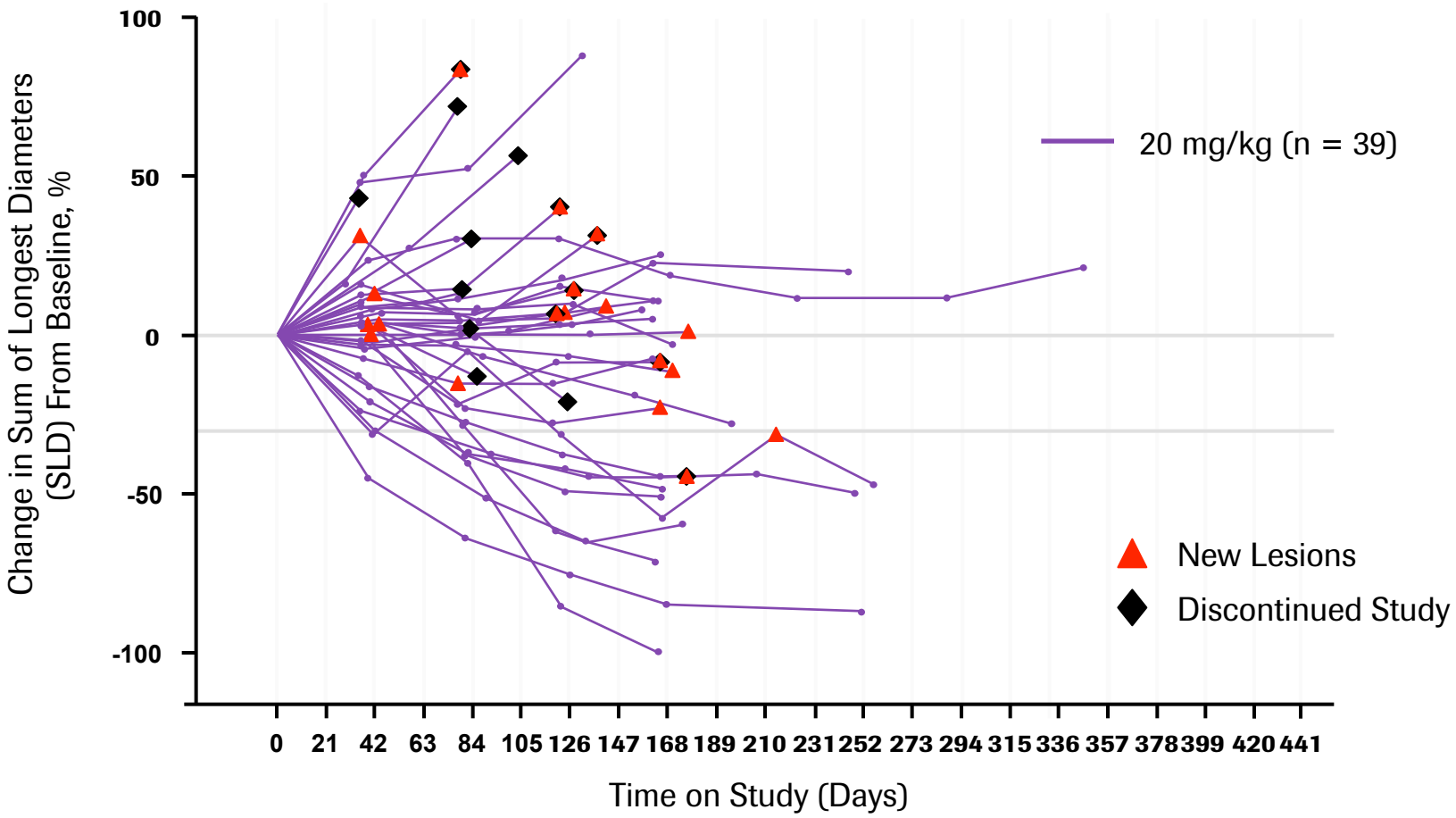


64-year-old male with squamous NSCLC s/p R lobectomy; cisplatin + gemcitabine, docetaxel, erlotinib; PD-L1 positive

Herbst et al. MPDL3280A Anti-PDL1 Phase I ASCO 2013

Hospital Universitario Vall d´Hebron (Cruz/Tabernero).

Patients with clinical benefit rarely progress



Patients dosed at 1-20 mg/kg prior to Aug 1, 2012 with at least 1 post-baseline evaluable tumor assessment; data cutoff Feb 1, 2013.

Herbst et al., (2013) *J Clin Oncol.* 31, (suppl; abstr 3000)

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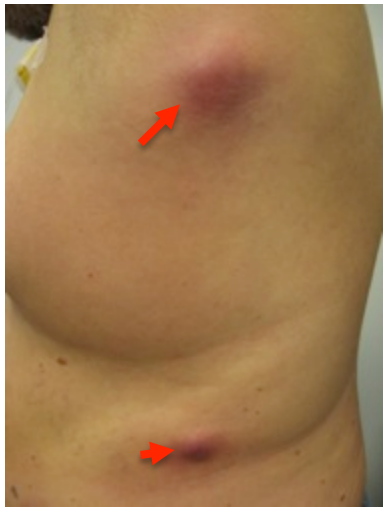
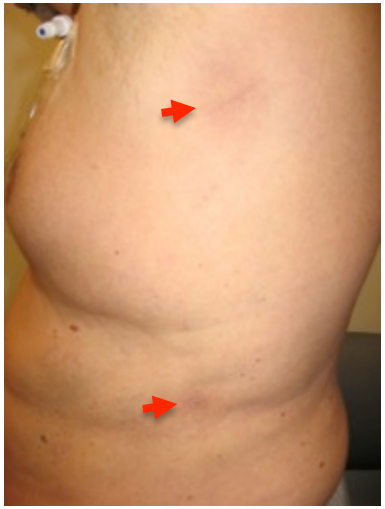
PD-L1 positive kidney cancer patient with rapid response to MDL3280A

Roche

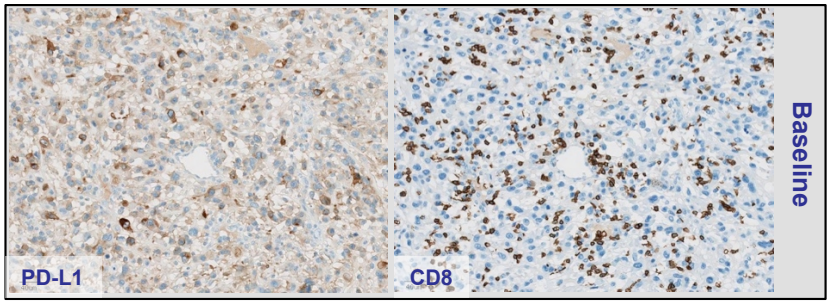
Baseline



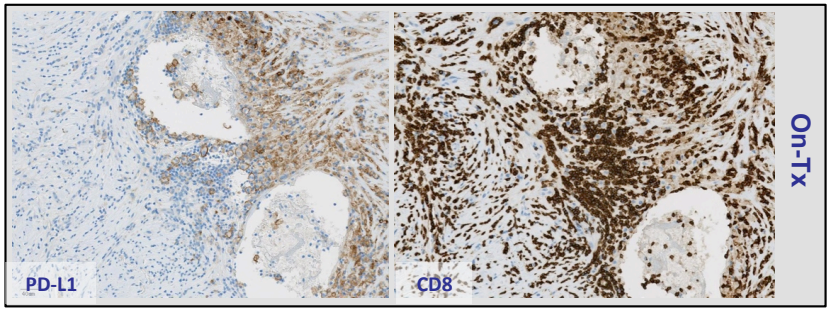
After 4 weeks



Biomarkers at baseline



Biomarkers at week 4 post C1D1



51-year-old male with RCC s/p L nephrectomy, sunitinib, XRT T9, temsirolimus

Cho et al., (2013) *J Clin Oncol*. 31, (suppl; abstr 4505)

Carolina BioOncology Institute (Powderly)

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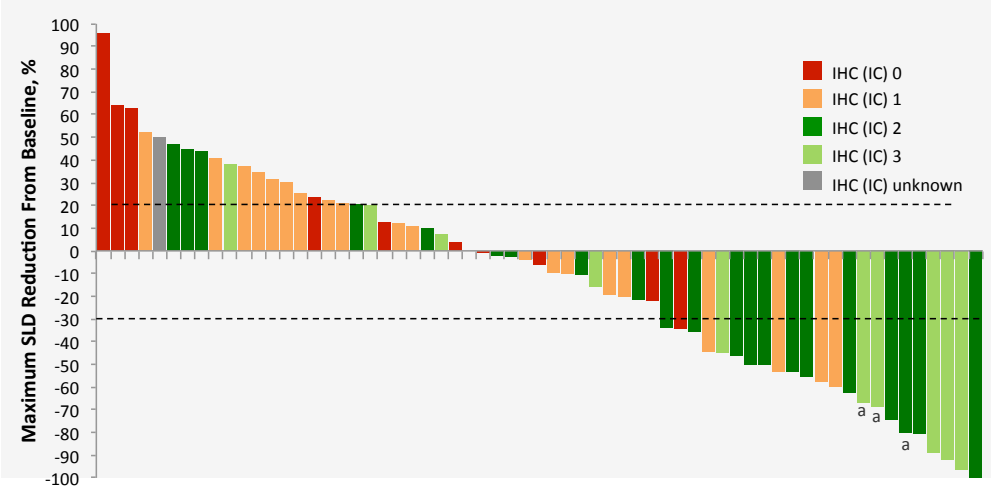
MPDL3280A Phase Ia response correlates with expression of PD-L1 on tumor infiltrating cells (bladder cancer)

PD-L1 IHC (IC)	ORR, Best Response % (95% CI)	ORR, Best Response % (95% CI)
IHC 3 (n = 10)	60% (27, 85)	**52%** (34, 69)
IHC 2 (n = 23)	48% (27, 68)	
IHC 1 (n = 24)	17% (6, 37)	**14%** (6, 28)
IHC 0 (n = 12)	8% (0, 35)	

Summary of ORR in UBC



Powles et al (2014) *Nature* Nov 26;515(7528):558-62

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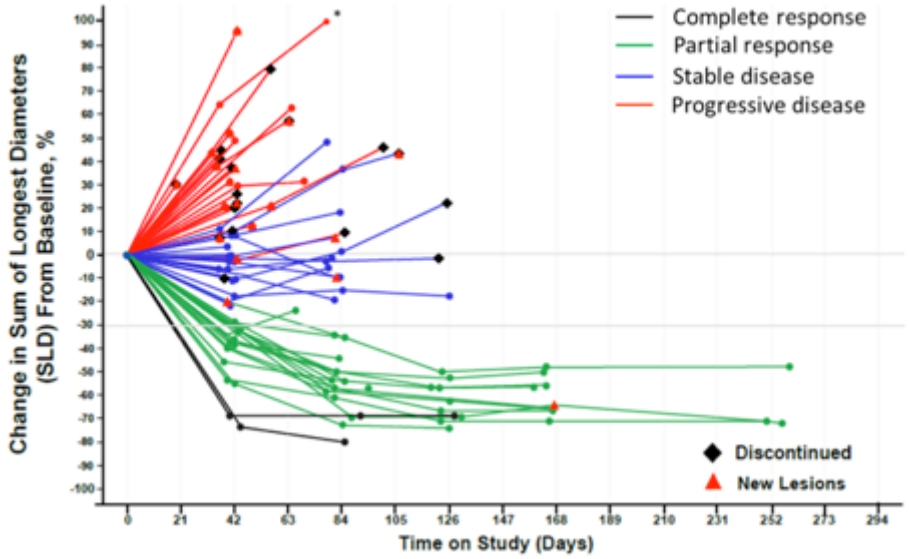
Using patient data to understand cancer immunity and find new treatments

MPDL3280A Phase 1 Data: Urothelial Bladder Cancer Patients



Progressive Disease (PD)

Why do many patients not respond?

- *No pre-existing immunity?*

Stable disease (SD)

What combinations will promote PRs & CRs?

- *Insufficient T cell immunity?*
- *Multiple negative regulators?*

Monotherapy durable responses (PR/CR)

What are the drivers of single agent response?

How can PRs be enhanced to CRs?

- *Insufficient T cell immunity?*
- *Multiple negative regulators?*

Powles et al (2014) *Nature* Nov 26;515(7528):558-62

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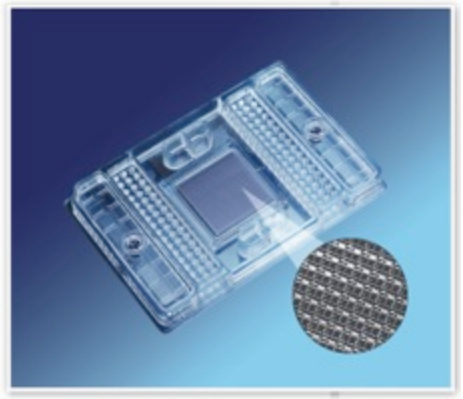
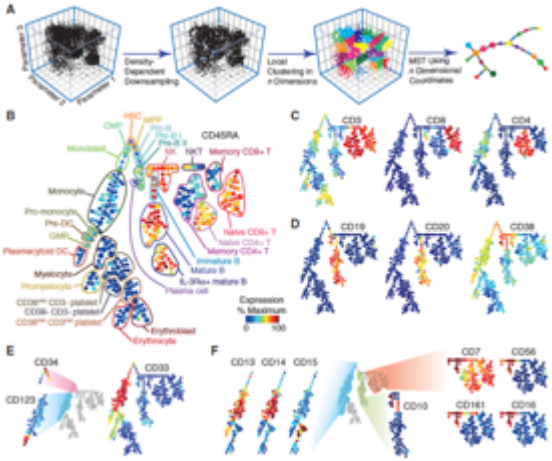
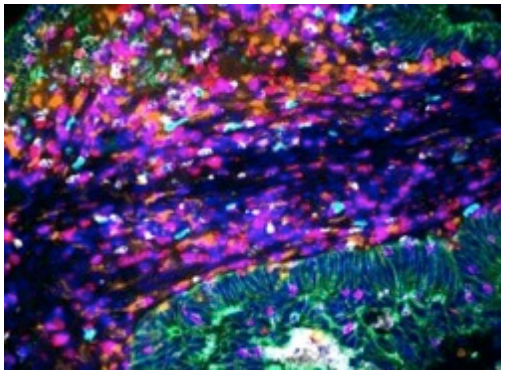
Comprehensive approach to biomarker discovery



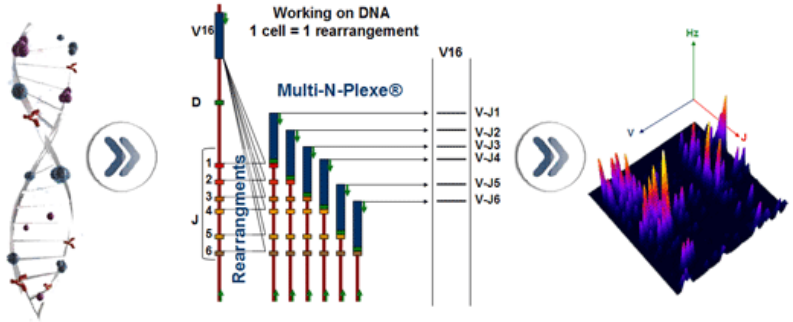
Genentech ImmunoChip



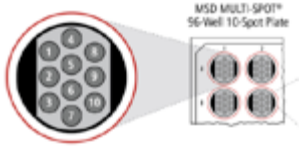
Multi-channel fluorescence activated cell sorting



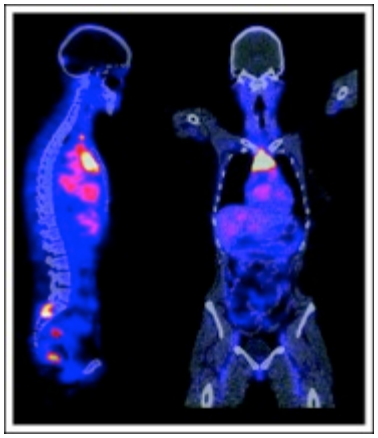
Multi-parametric immunofluorescence



T-Cell Receptor Repertoire



Mutliplex cytokine assay



Molecular Imaging

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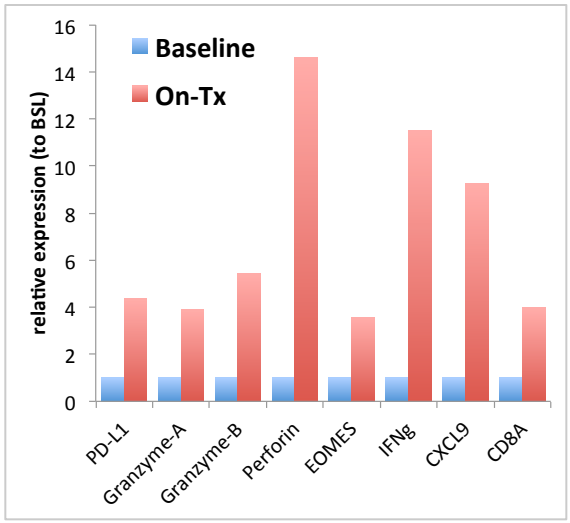
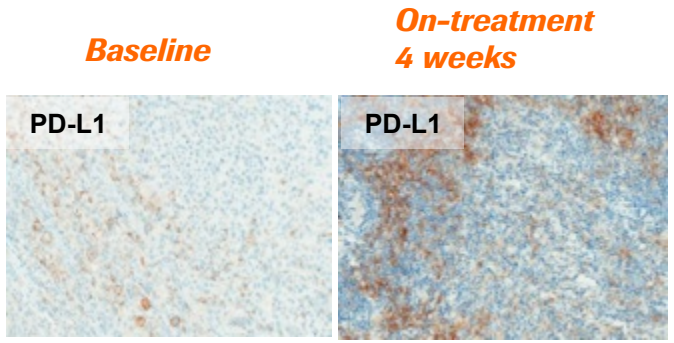
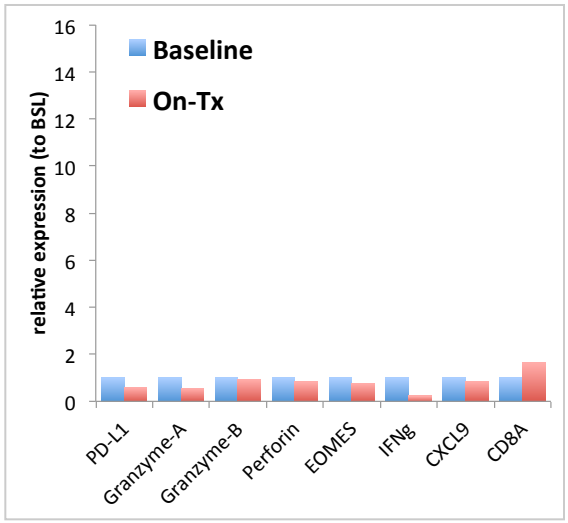
On-treatment biomarker profile defines response and lack of response

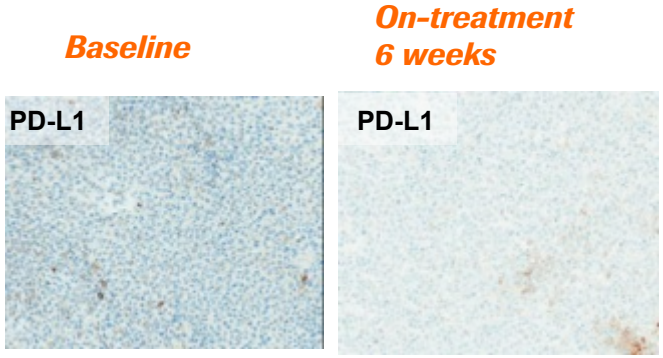
Responder





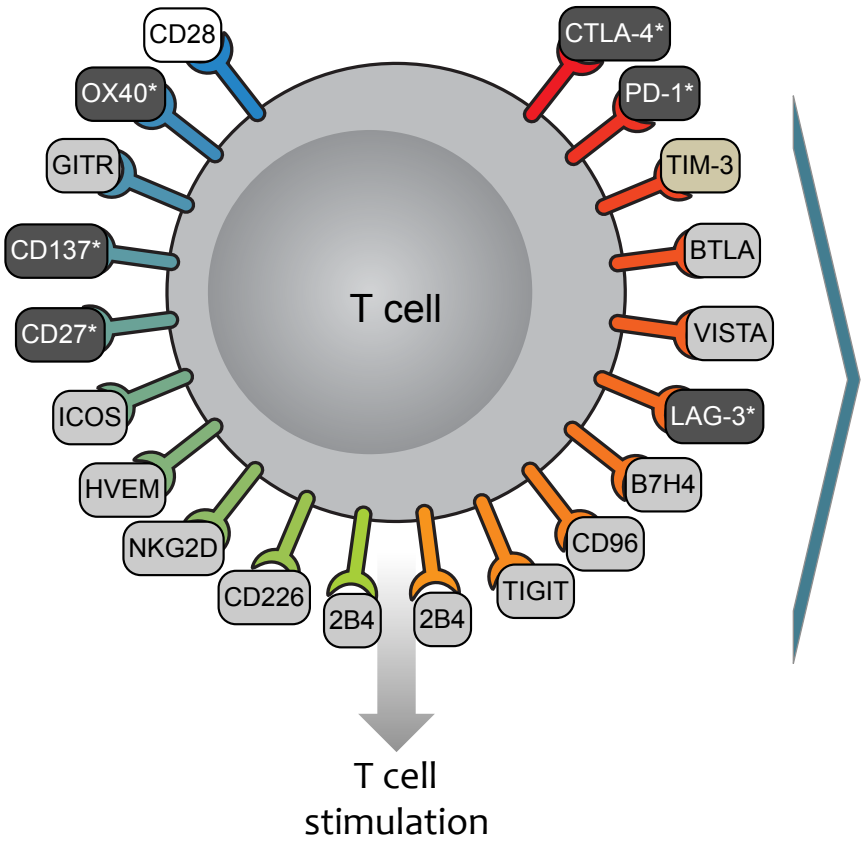
Non-responder





Herbst et al (2014) *Nature* Nov 27;515(7528):563-7

PD-L1 patient immune biomarker analysis guides research and clinical development



Targets elevated in non-responders

Compounds moving into clinic

- Negative regulator NME1
- Positive regulator: OX40

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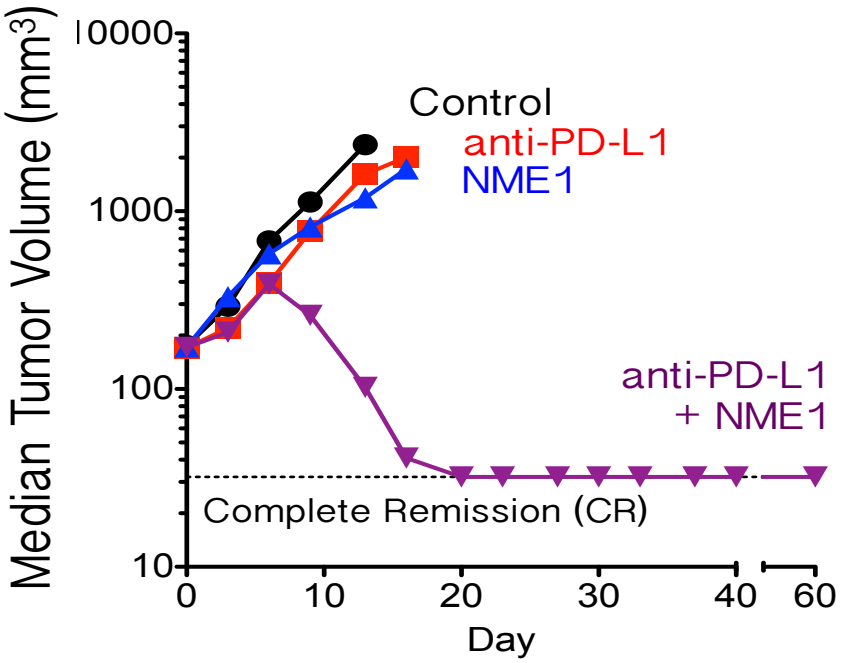
Example: NME1 is a negative regulator discovered from biomarker analysis



Negative regulator combines in PD-L1 non-responsive model

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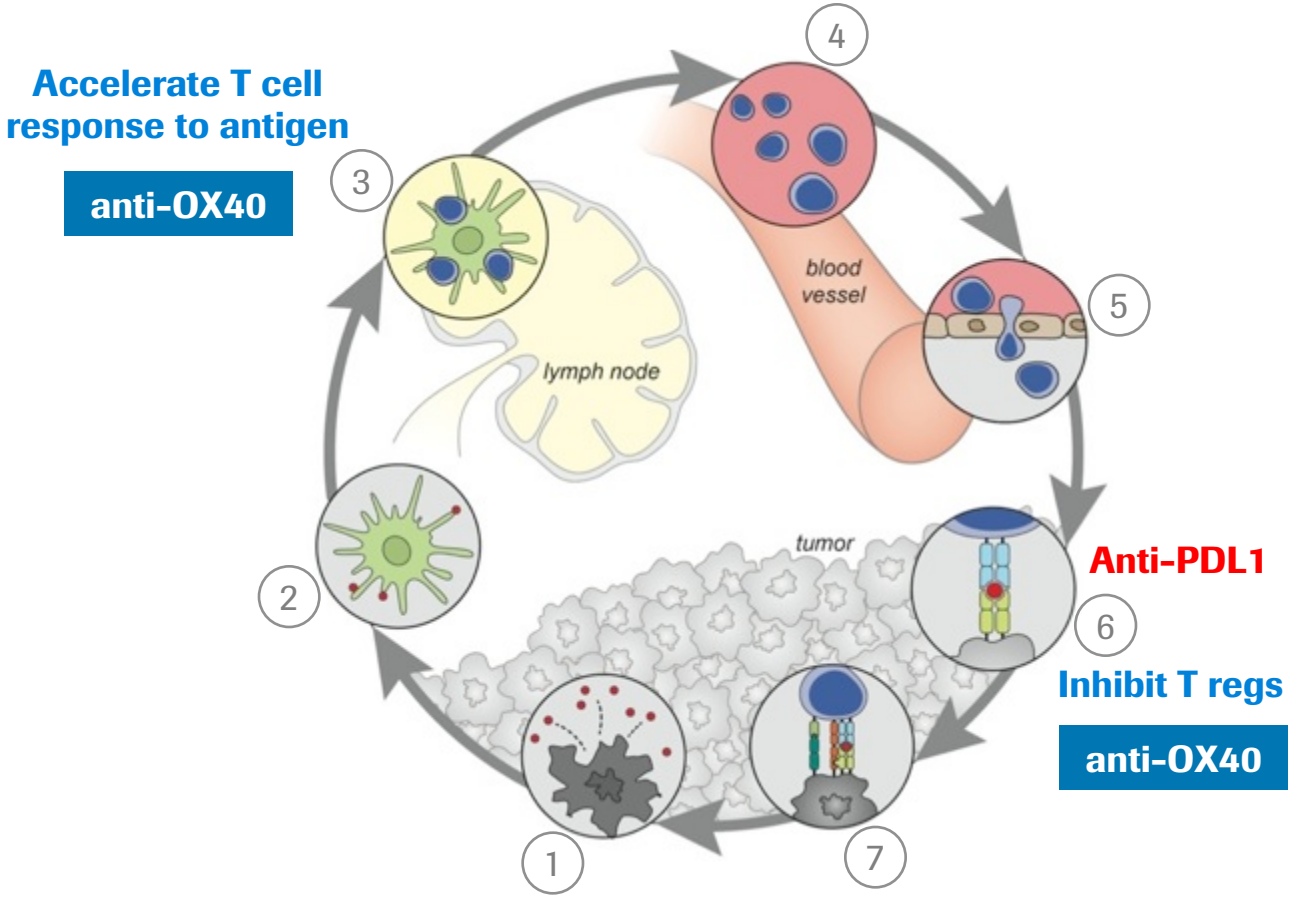
Positive regulator targeting two steps in the cycle

Anti-OX40



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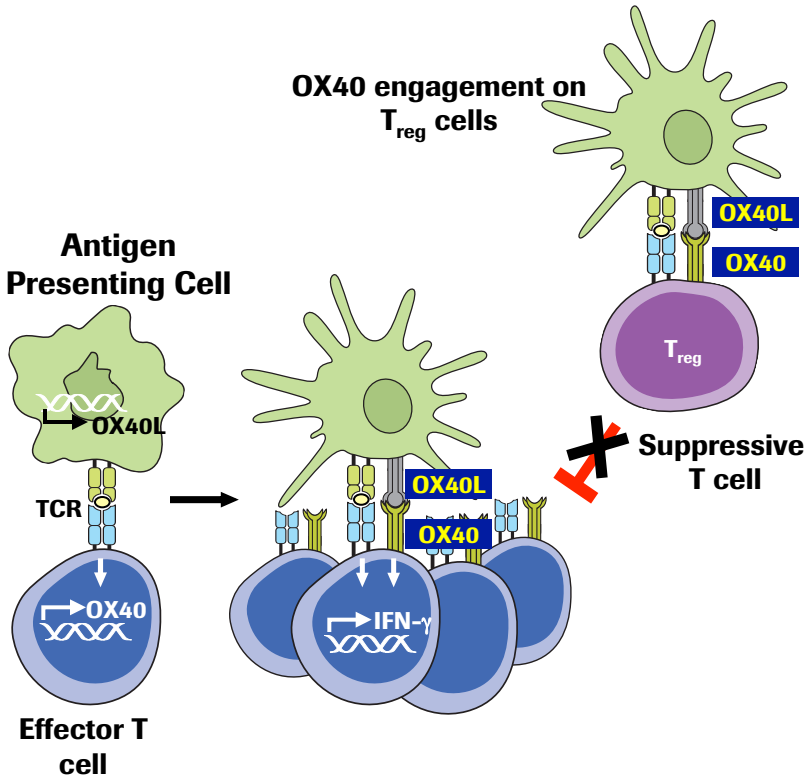
OX40 function and potential in oncology

Promote antigen dependent effector T cell activation and T regulatory cell inhibition



Rationale for targeting OX40

- Dual mode of action:
  - Co-stimulation of effector T cells
  - Inhibition of regulatory T cells
- Reduced risk of toxicity
- Complementary MoA to blocking inhibitory receptors
- Potential to overcome suppressive signals from multiple inhibitory receptors

Adapted from *Nature Rev Immunol*. 4:420 (2004).

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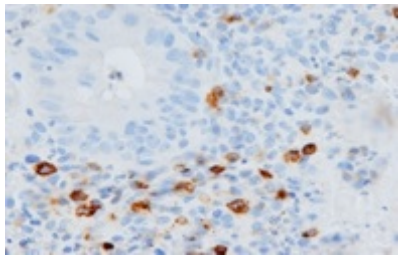
Potential for activity in multiple tumor types

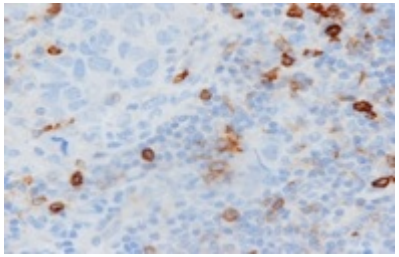
Pre-clinical efficacy and durability of response

OX40 is expressed in a variety of tumors

Colorectal cancer

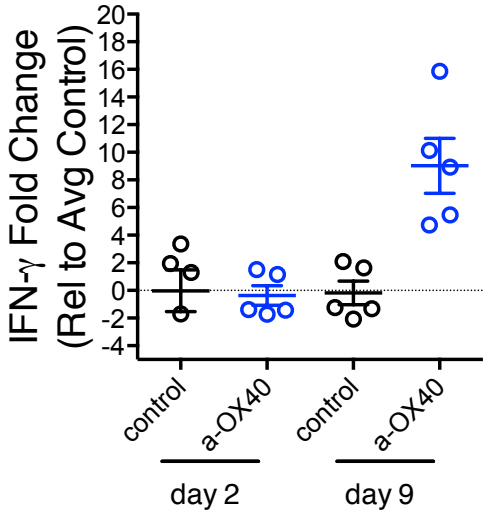


Breast cancer

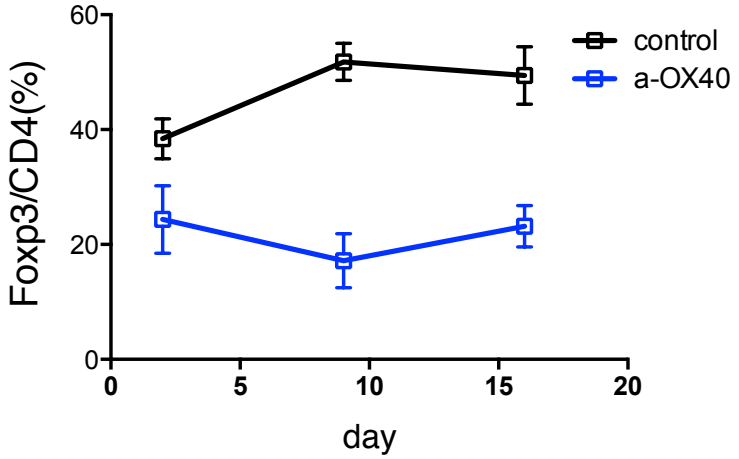


Anti-OX40 increases intratumor T_{eff} cells while depleting T_{regs}

Increase in intratumoral T_{eff} cells (CD4+CD8)



Decrease in intratumoral T_{reg} cells (FoxP3+)



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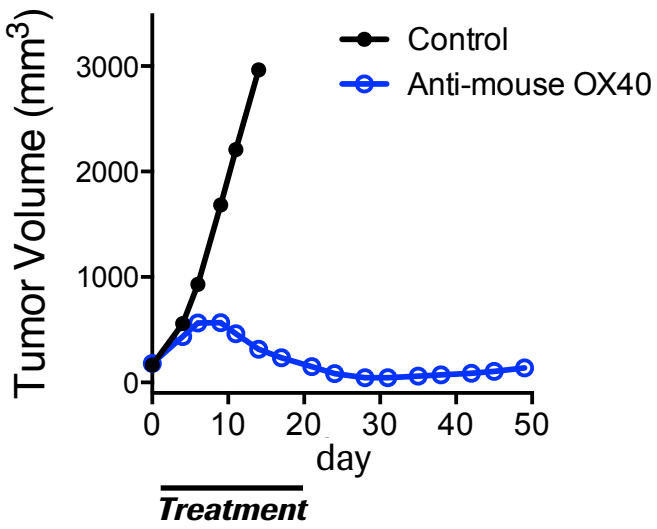
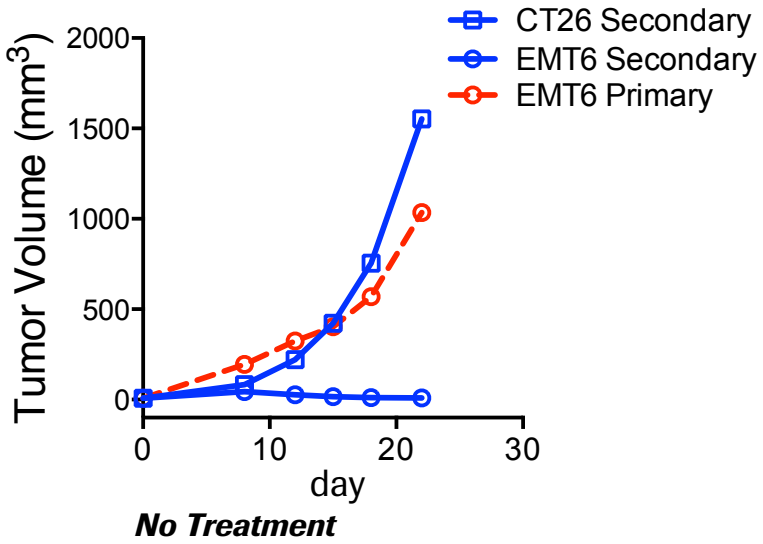
Anti-OX40 can induce durable responses and immunity as a single agent

Pre-clinical efficacy and generation of tumor-specific immunity

Primary Tumor Challenge (EMT6)



Re-challenge (EMT6 or CT26)



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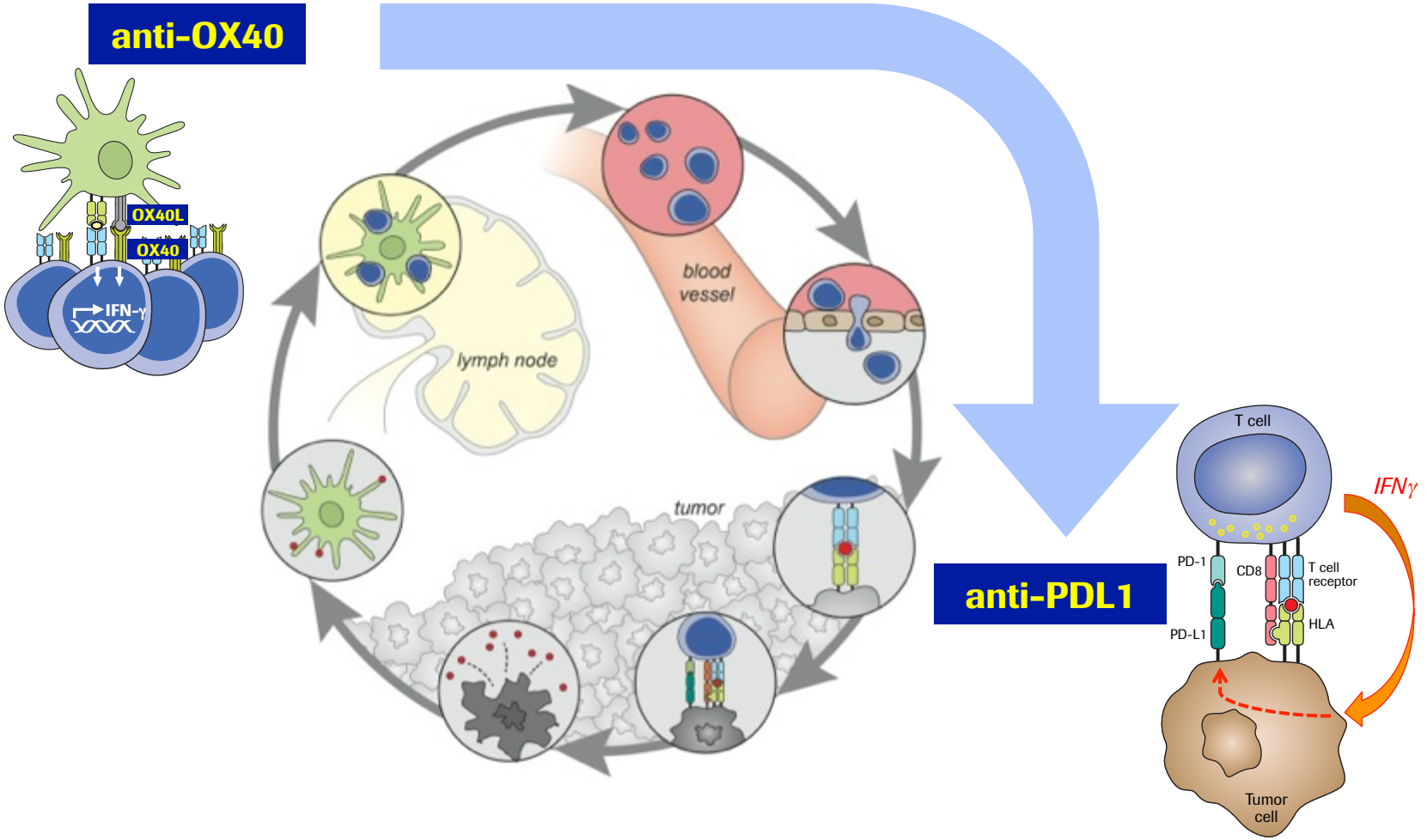
Increase in T_{eff} cells by anti-OX40 may create need to combine with anti-PDL1

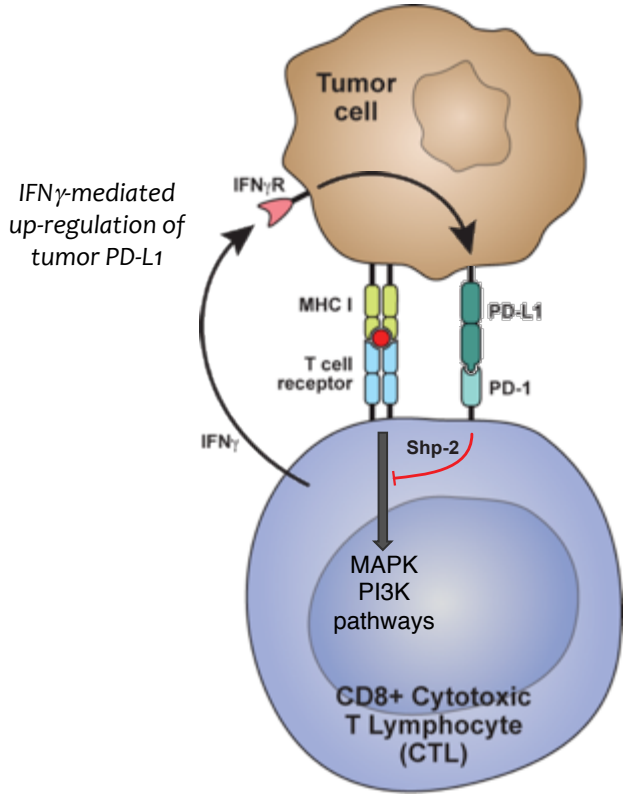


Chen & Mellman (2013) *Immunity* Jul 25;39(1):1-10

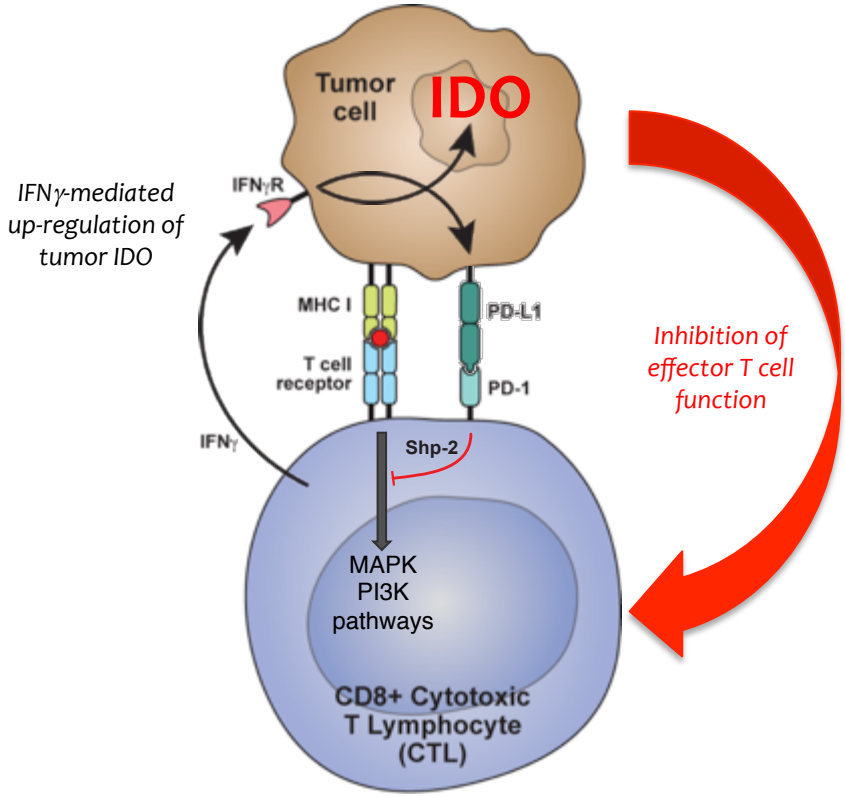
IDO (indoleamine di-oxygenase)

Another suppressor of effector T cells

Adaptive expression of PD-L1



Adaptive expression of IDO



Georgia Hatzivassiliou, Yichin Liu

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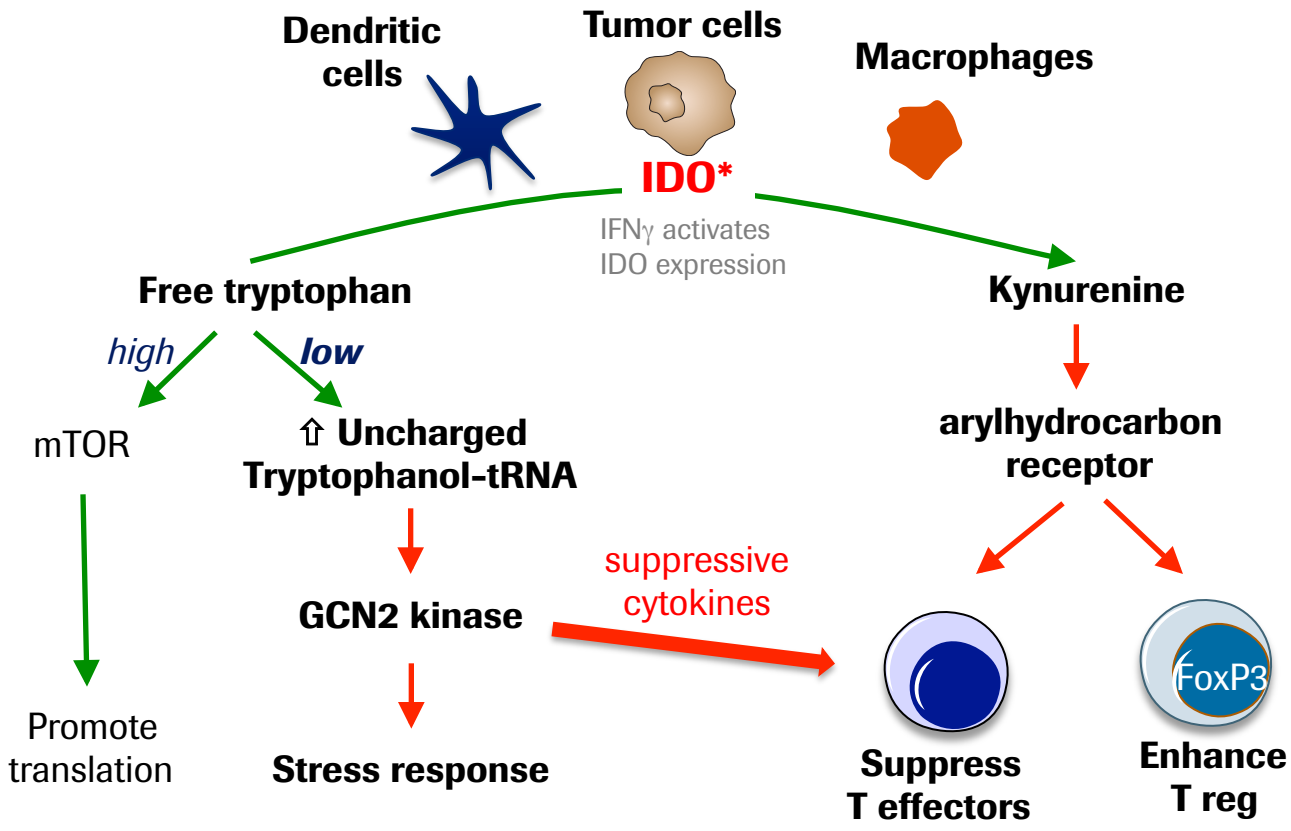
IDO mediates T cell suppression by reducing extracellular tryptophan and increasing kynurenine



*TDO (tryptophan dioxygenase) is a second related target to IDO

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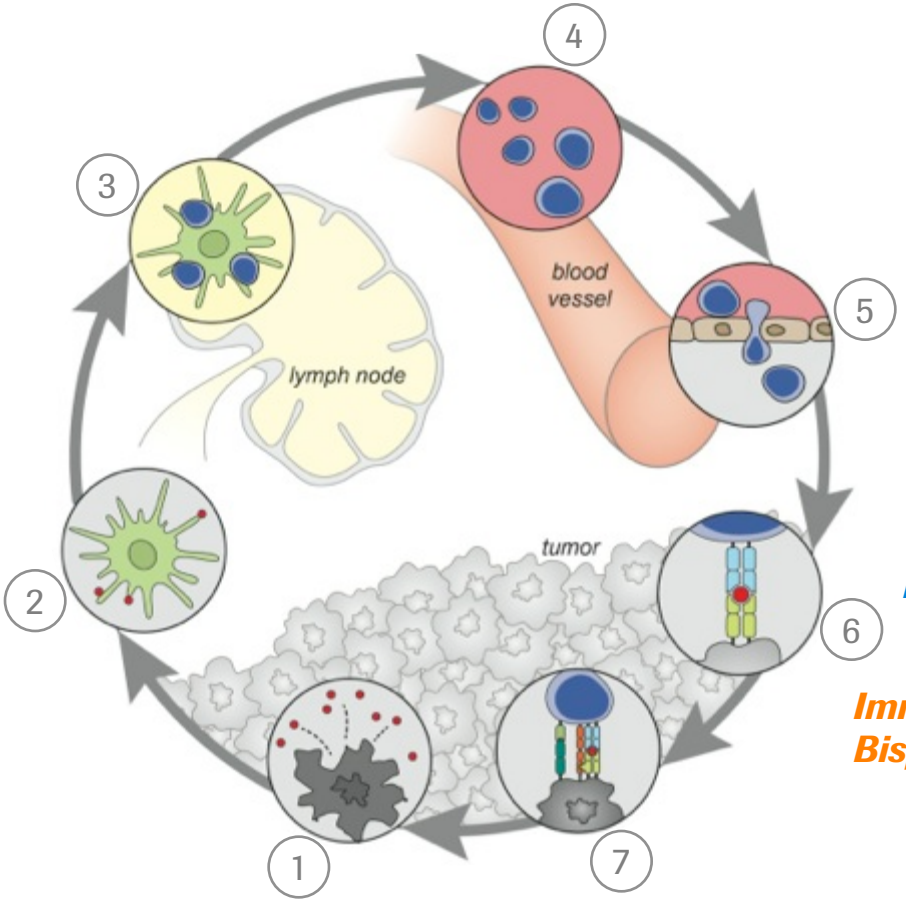
Not all patients may have pre-existing immunity:
ImmTACs and bispecific antibodies as alternatives to CAR-T cells



Recognition of cancer cells by T cells
(CTLs, cancer cells)

ImmTACs
Bispecifics

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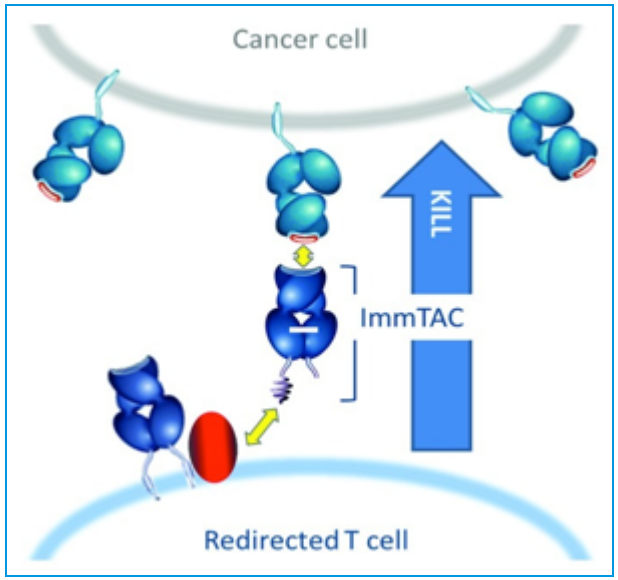
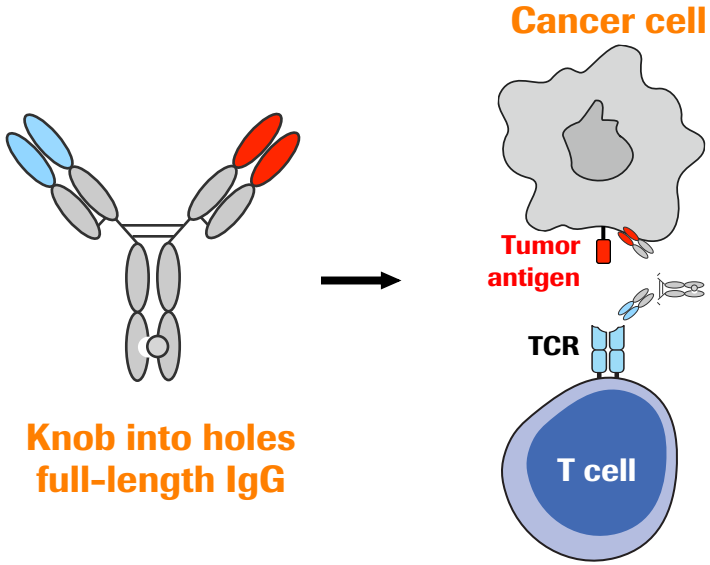
Recruiting T cells to cancer cells
ImmTACs and bispecific antibodies

Targeting intracellular tumor markers



Immune-mobilizing mTCR Against Cancer*

Targeting extracellular tumor markers

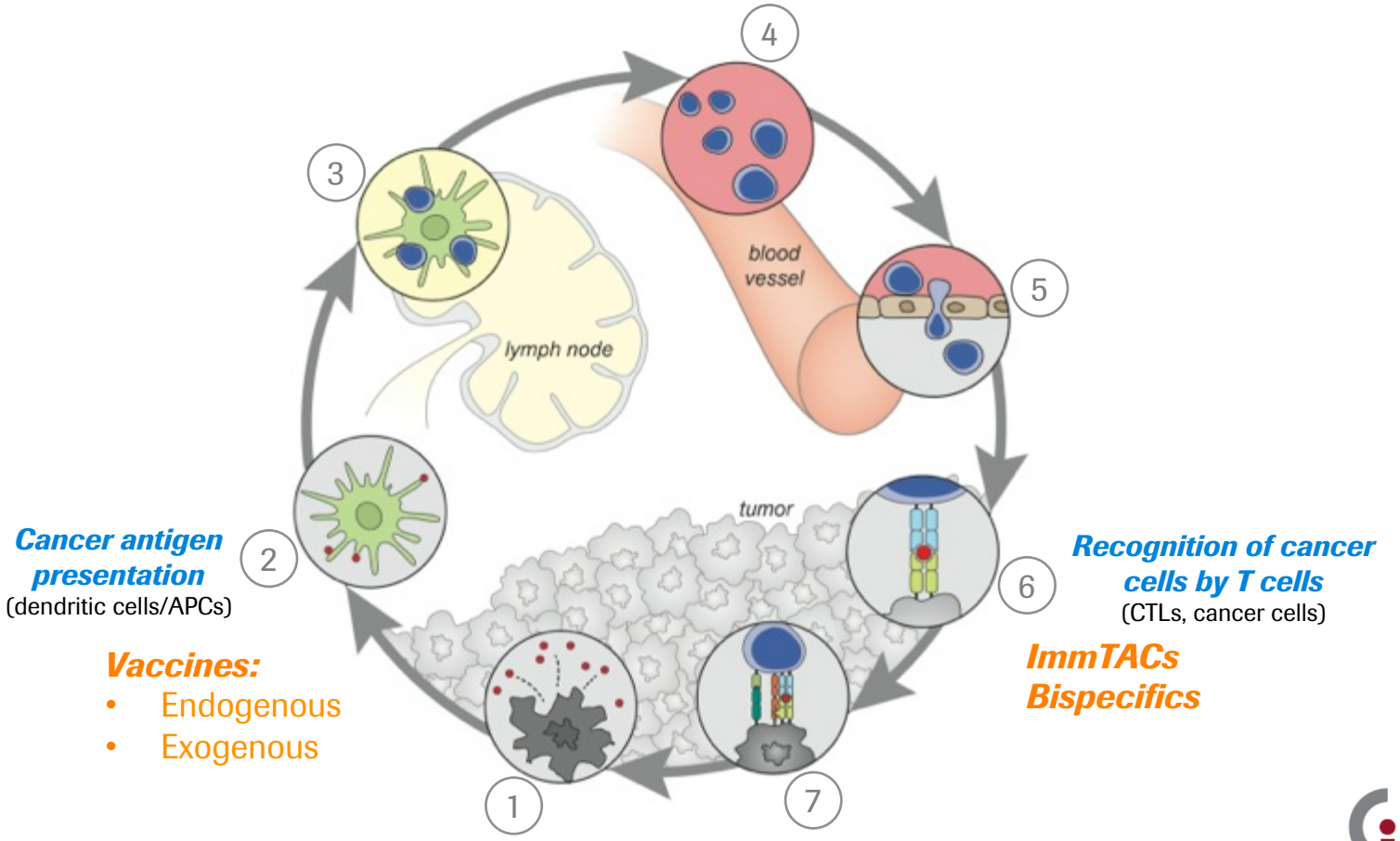


Knob into holes full-length IgG

T-cell Dependent Bispecific

*In colalboaration with Immunocore

Not all patients may have pre-existing immunity:
Patient data defines a path to rational vaccines



Cancer antigen presentation
(dendritic cells/APCs)

Vaccines:
- Endogenous
- Exogenous

Recognition of cancer cells by T cells
(CTLs, cancer cells)

ImmTACs
Bispecifics

CancerImmunology

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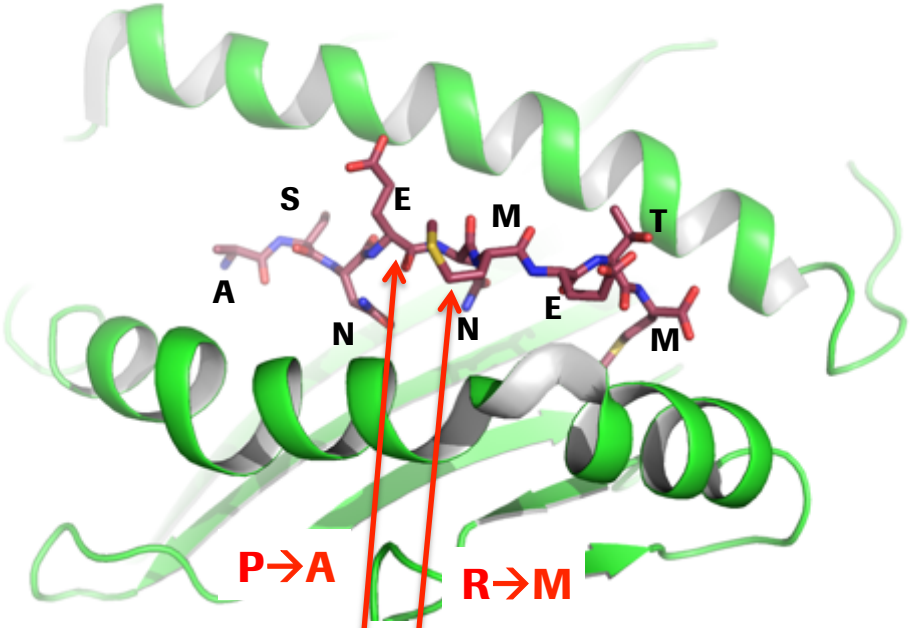
Chen & Mellman (2013) *Immunity* Jul 25;39(1):1-10

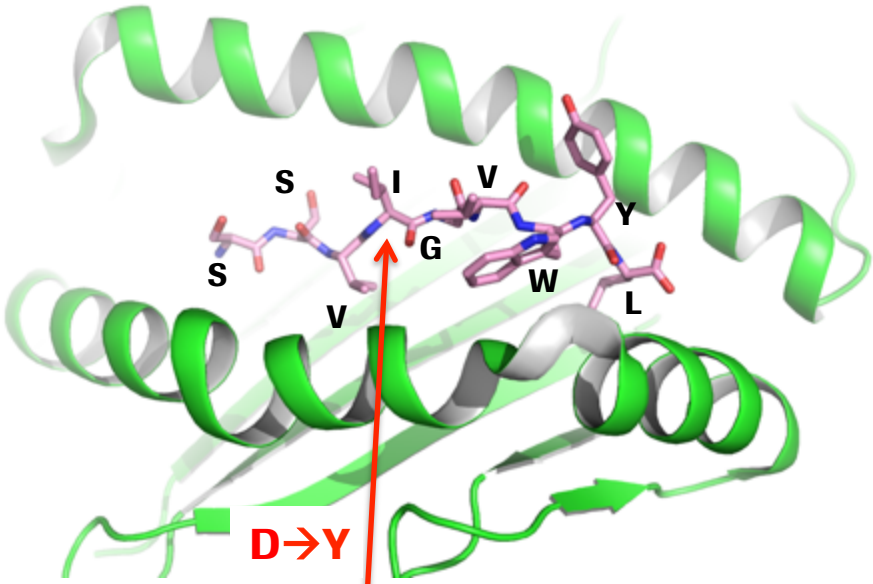
Structural analysis suggests that only some mutations will be accessible to T cell receptors

Immunogenic solvent-exposed mutation



REPS1	AQLPNDVVL
ADPGK	ASMTNRELM
FLU-NP	ASNENMETM

Non-immunogenic mutation in MHC groove



Copine-1	SSPDSLHYL
H60	SSVIGVWYL

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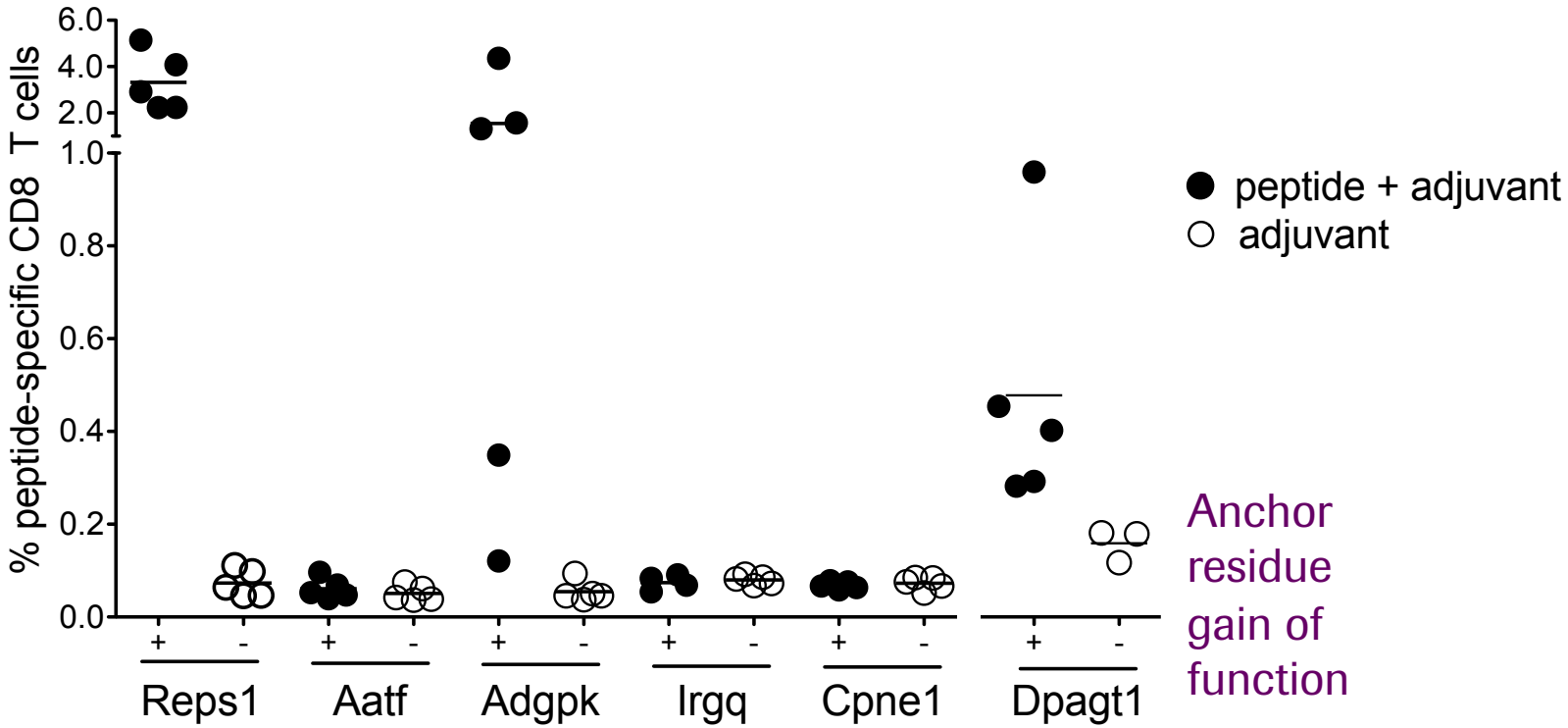
Yadav et al (2014) *Nature* Nov 27;515(7528):572-6

Mutated peptides predicted to be immunogenic induce CD8 T cell responses upon immunization

Roche

Prime/boost immunization
elongated peptides + anti-CD40 + pIC

T cell response measured 7d after boost (MHCI dextramer staining)



Yadav et al (2014) *Nature* Nov 27;515(7528):572-6

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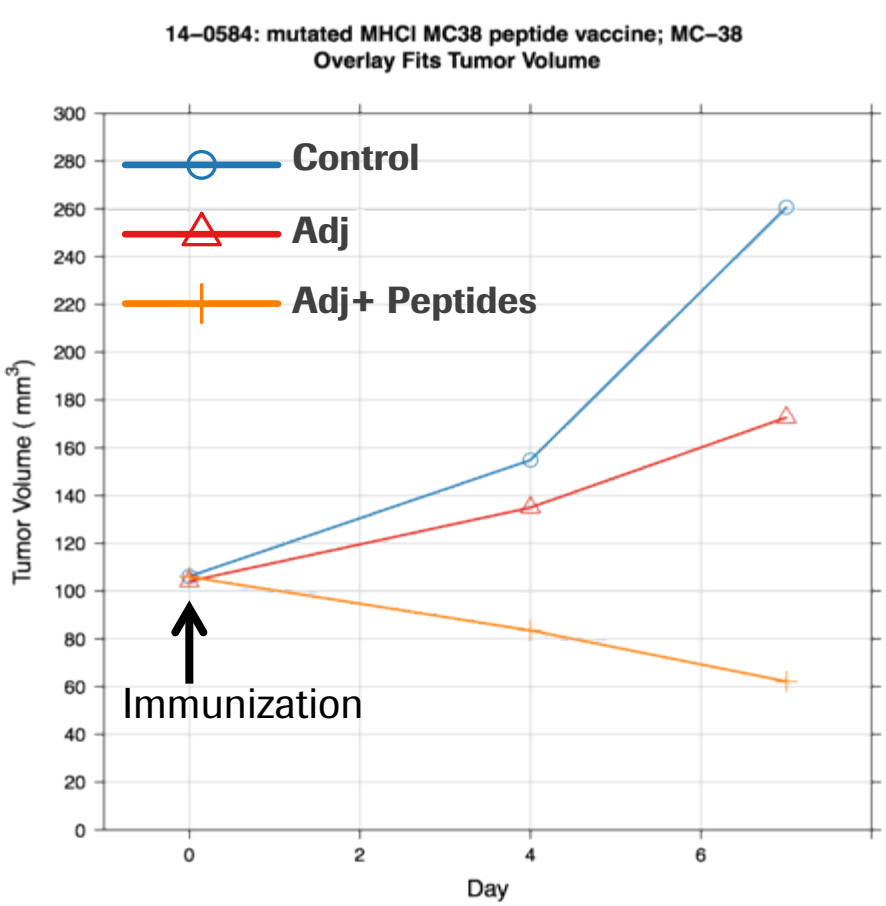
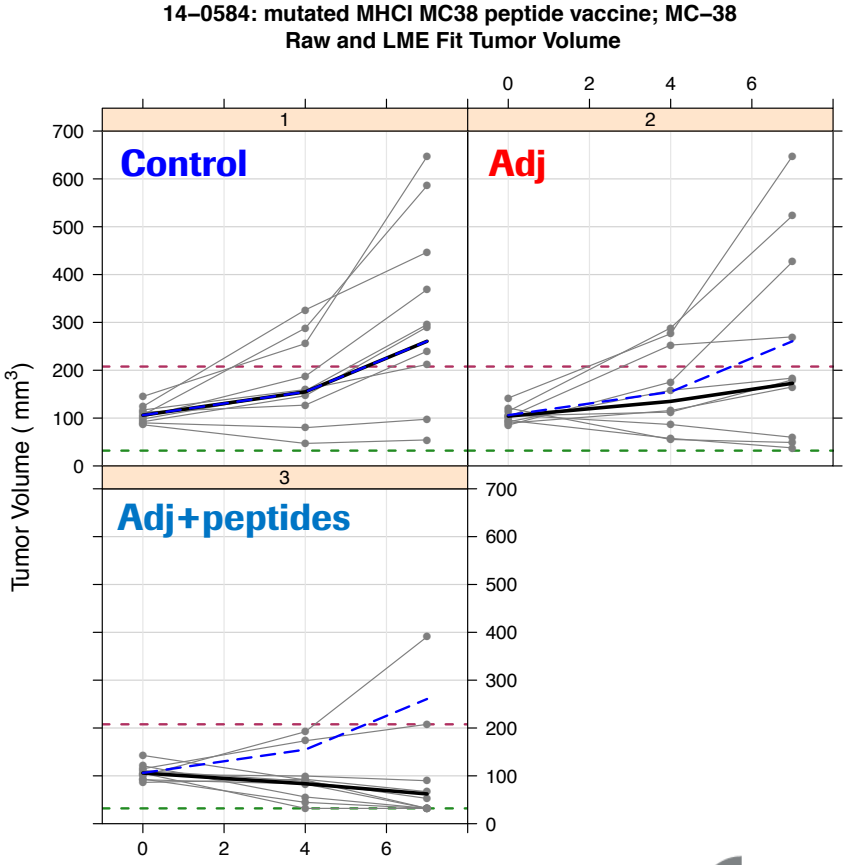
Promise for a PHC vaccine?

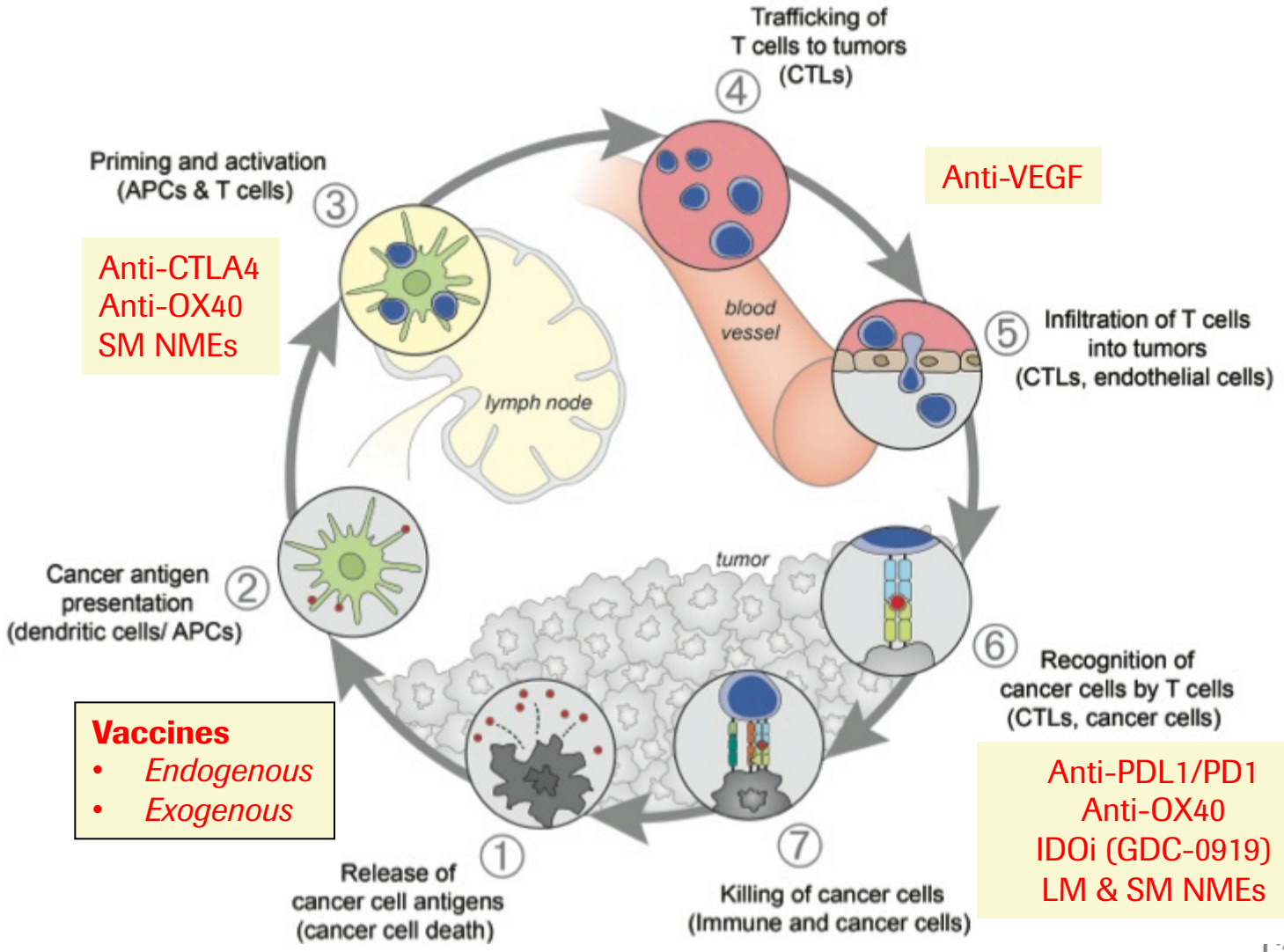
Immunization with antigenic peptides regresses growth of established MC38 tumors





Yadav et al (2014) *Nature* Nov 27;515(7528):572-6

Building a portfolio based on the emerging appreciation of the cancer immunity cycle



Chen & Mellman (2013) *Immunity* Jul 25;39(1):1-10

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Substantial investment in developing PD-L1 combinations with in house and partnered molecules

		Roche/GNE (PD-L1 inhibitor)	BMS (PD-1 inhibitor)	Merck (PD-1 inhibitor)	AZ (PD-L1 inhibitor)
Immunotherapies	aCD40	✔			
	Vaccines	P	P	P	P
	aCTLA-4	P	✔	P	✔
	aOX40	✔			✔
	aCD27	P	P		
	a4-1BB/CD137		✔	P	
	GITRi			✔	
	aCEA-IL2v	✔			
	T Cell Bispecifics	✔			
	ImmTACs	P			
	aPDL1/PD1				✔
	aLAG-3		✔		
	IDOi	✔, P	P	P	P
	aKIR		✔		
	aCSF1R	✔	P		
	Cytokines, anti-cytokines	✔	✔	✔	P
Other	aVEGF	✔	P	P	
	aAng-2-VEGF	✔			
	VEGF TKI		P	P	
	EGFRi	✔	P	P	✔
	ALKi	✔	P	P	
	BRAFi	✔	P	P	P
	MEKi	✔	P	P	P
	BTKi	✔	P		P
	aCD20	✔			
	aHER2	✔		P	
	Chemo	✔	✔	✔	
	XRT	✔			✔

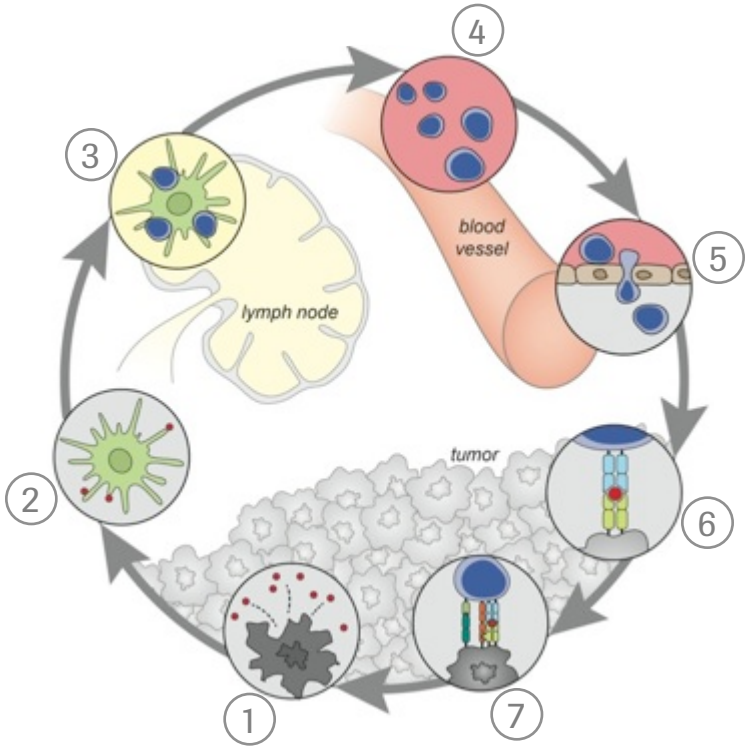
P Partnered external combo
✔ Internal combo

Sources: TrialTrove, company presentations, clinicaltrials.gov

Last updated: 3 Dec 2014

Genentech's competitive advantage: Lead the field by focusing on the science

- Identification and validation of new targets & combinations based on our **understanding of cancer immunity cycle**
- An ever-expanding patient **biomarker database**
- Diverse, innovative **portfolio**
- Leverage **small molecule** expertise
- Leverage **oncology expertise**
- A uniquely **integrated team**, from Research to Late Stage…and back



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