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Immunotherapy targets for SCLC

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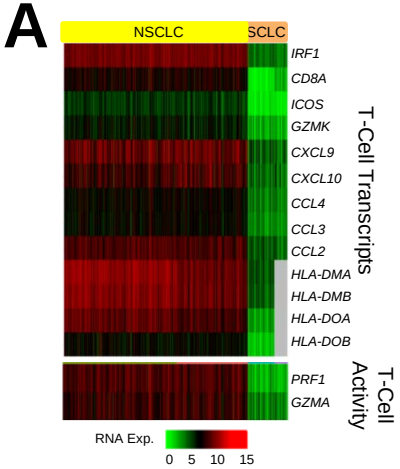
SCLC Research Consortium Meeting
NCI-Shady Grove Campus

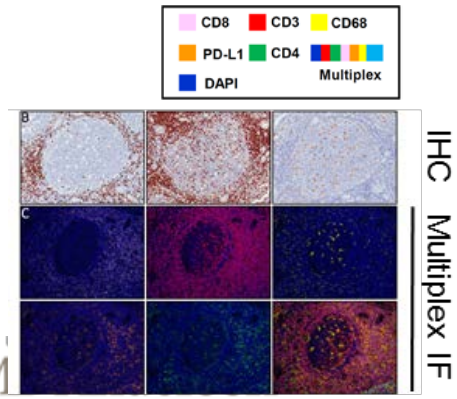
March 16, 2018

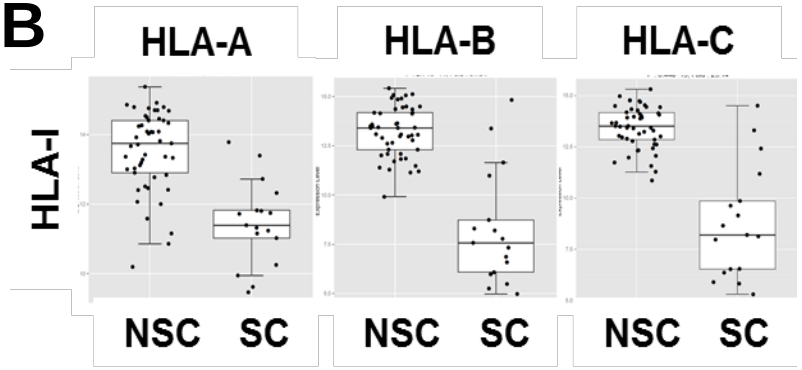
Disclosures: Advisory boards for BMS, Merck, Genentech, AZ, G1 Therapeutics, EMD-Serono, GSK, Boehringer-Ingelheim, Spectrum

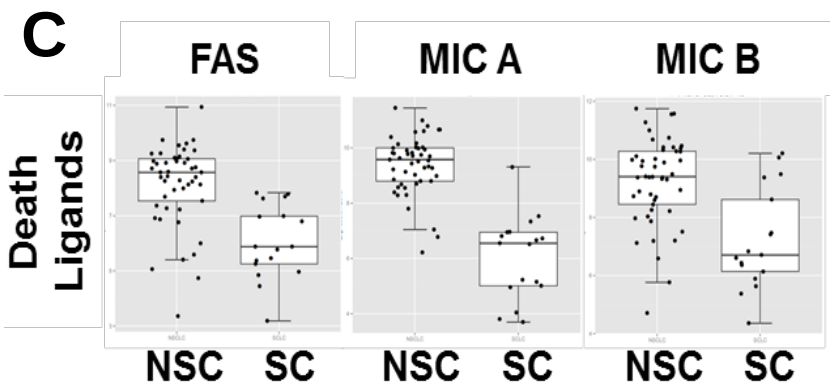
An apparent paradox: despite its high TMB, SCLC has a relatively immunosuppressed phenotype

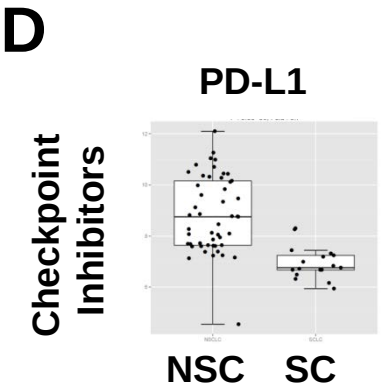
Compared to NSCLC, reduced levels of HLA, death receptors, and low checkpoint targets











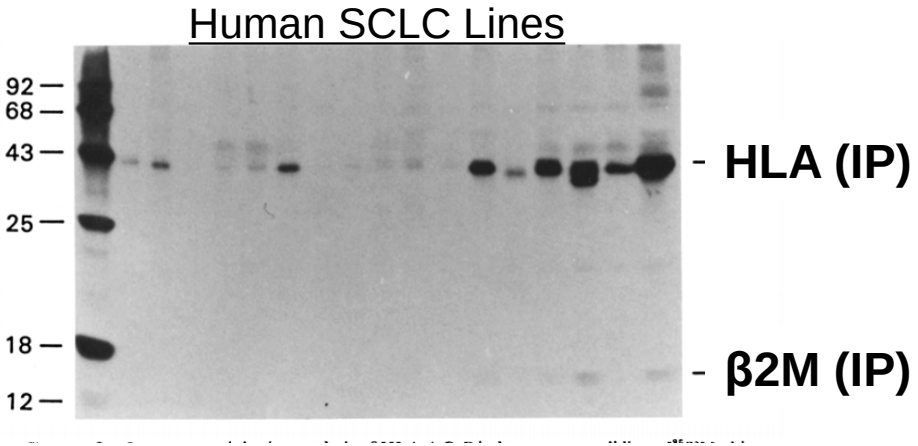
mRNA expression from cell lines

Denning, Wistuba, Heymach et al, unpublished..

Proposed mechanisms for immunosuppressed phenotype

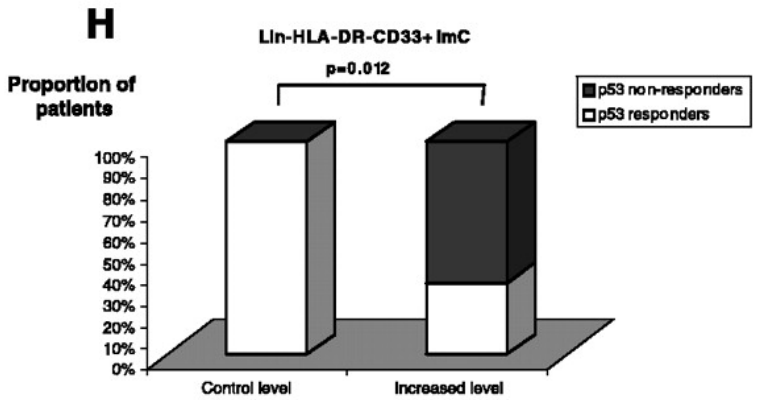
Decreased Antigen Presentation (HLA, B2M, TAP-1)

(Doyle et. al.J Ex Med.1985.)



Increase in suppressive cell populations (T regs, suppressive myeloid pop.)

(Antonia et. al. CCR. 2006)



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Proposed mechanisms for immunosuppressed phenotype

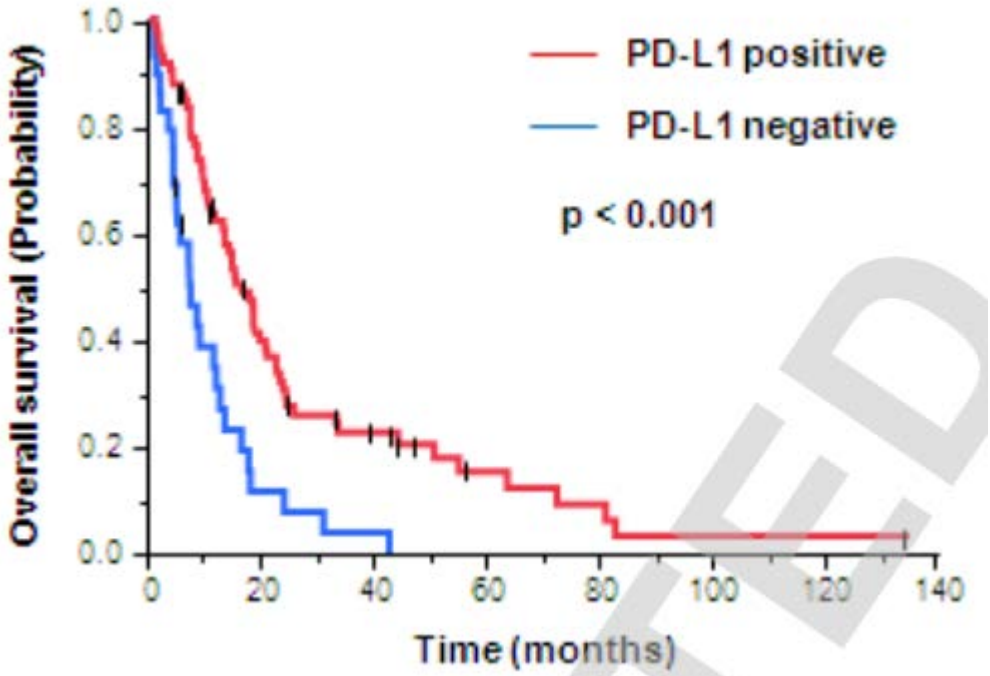
Decrease in cytokines that support T cell expansion

(Fischer et. al. Ann Oncol. 1995)

Cytokine	Controls (n = 44)	SCLC LD (n = 36)	SCLC ED (n = 22)	NSCLC M0 (n = 66)	NSCLC M1 (n = 29)
IL-1α					
Mean (pg/ml)	145	164	124	215	158
95% CI	119–171	114–214	64–183	168–262	119–197
P-value		0.9	0.5		
IL-1β					
Mean (ng/ml)	1461	2016	1372	1702	1609
95% CI	1112–1810	1304–2729	605–239	1369–2035	989–2229
P-value		0.56	0.056		
IL-2					
Mean (ng/ml)	3086	1480	1153	1426	1470
95% CI	2281–3890	988–1972	770–1537	1023–1827	909–2033
P-value		0.0001	0.0001	0.0001	0.0002
IFNα					
Mean (U/ml)	152	61	54	78	45
95% CI	86–218	41–80	24–84	57–99	32–60
P-value		0.003	0.0003	0.005	0.0002
IFNγ					
Mean (ng/ml)	71240	37297	21619	50702	43945
95% CI	53652–88829	24723–49871	12244–30993	40568–60838	27743–60148
P-value		0.001	0.0001	0.045	0.012
TNFα					
Mean (ng/ml)	995	1140	745	1228	935
95% CI	776–1214	647–1632	296–1195	863–1593	694–1176
P-value		0.47	0.012	0.9	0.8

Immune status in SCLC is important

PD-L1 expression correlated to longer survival in SCLC patients



Could be indicative of active T cells and the presence of IFN-γ

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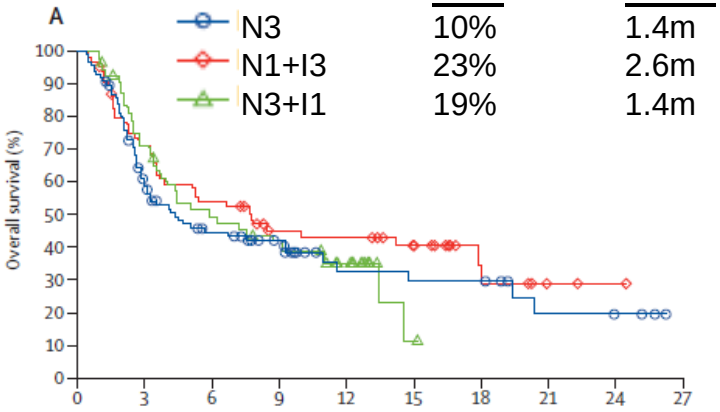
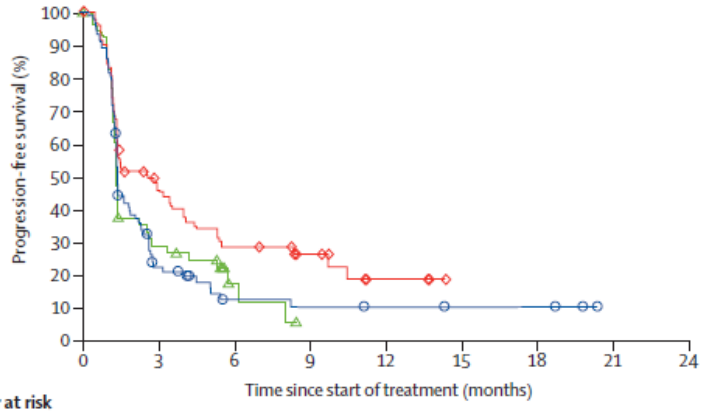
Ishii et. al. J Thorac Onc. 2014

Nivo or Nivo/Ipi for recurrent SCLC (Checkmate 32)

	ORR	mPFS
N3	10%	1.4m
N1+I3	23%	2.6m
N3+I1	19%	1.4m



Number at risk										
Nivolumab 3 mg/kg	98	53	36	25	11	10	10	4	3	0
Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	61	42	32	22	21	15	6	2	1	0
Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	55	37	25	20	12	1	0	0	0	0
Number of censored patients										
Nivolumab 3 mg/kg	0	6	11	20	30	30	30	34	35	38
Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	0	2	2	7	7	12	20	23	24	25
Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	0	3	4	5	10	19	20	20	20	20



Number at risk									
Nivolumab 3 mg/kg	98	17	6	5	4	3	3	0	0
Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	61	24	15	9	3	0	0	0	0
Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	54	14	3	0	0	0	0	0	0
Number of censored patients									
Nivolumab 3 mg/kg	0	12	17	17	18	19	19	22	22
Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg	0	5	5	10	14	17	17	17	17
Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	0	4	11	12	12	12	12	12	12

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Antonia et al, Lancet Oncol, 2016

U01: Novel therapeutic approaches for enhancing antitumor immunity in SCLC (Heymach/Byers/Sage)

Aim 1. DDR inhibition to increase neoantigen expression and anti-PD-1/PD-L1 response

1A: DDR targeting to increase the expression of tumor associated neoantigen

1B: DDR targeting ± PD-1/PD-L1 inhibition in SCLC

1C. Effect of DDR inhibition on immune infiltration and markers in SCLC patients

Aim 2. CDK4/6 inhibition to protect immune cells from chemotherapy-induced cytotoxicity and enhance anti-PD-1/PD-L1 response

2A. CDK4/6 inhibition to protect immune cells from chemo-induced cytotoxicity

2B. CDK4/6 inhibition ± immunotherapy in syngeneic and allograft SCLC models (

2C. CDK4/6 inhibition to protect immune cells from chemotherapy in SCLC patients

Aim 3. Co-activation of anti-tumorigenic macrophages to enhance T-cell based immunotherapies

3A. CD47 blockade and chemo combinations to suppress the growth of SCLC

3B. CD47 and T-cell checkpoint blockade to enhance the efficacy of single therapies in models of SCLC

Cores:

Preclinical Models Team (GEMMs, Human cell lines, allograft**s)**
Immune/Genomic Profiling Team
Biostats/Bioinformatics team

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CAR-T cells for SCLC

Warren Denning

Laurence Cooper

Denise Crossland

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CAR Rationale

If endogenous T cell elicitation is difficult to due immunosuppressive microenvironment, then ex vivo T cell culture expansion should be considered

Chimeric antigen receptor T cells provide advantages:

- HLA-independent
- Does not require stimulation by host immune system
- Targets SCLC antigens

CARs under consideration for SCLC

- **50% of patients detectable auto-antibodies to at least 1 target** (Robertson et. al. CCR. 2011.)

p53	SOX2
CAGE	Hu-D
NY-ESO-1	**CD56**
GBU4-5	**GD2**
Annexin I	GD3

- **Other potential targets include DLL3**

CD56 is an attractive target

CD56 (NCAM) selected as initial candidate for CARs

-highly expressed in SCLC and other malignancies

-also expressed in neuronal tissue, lower expression in skeletal muscle, NK cells, and Tcells (potential fratricide)

-ADCs have been tested with CD56

Distribution of NCAM in malignant tissues

Malignoma	% NCAM positive
Neuroblastoma	≈100%
Rhabdomyosarkoma	≈100%
Glioma	≈100%
Astrocytoma	≈100%
Small cell lung cancer	≈100%
Multiple myeloma	78%
Acute myeloid leukemia	53%

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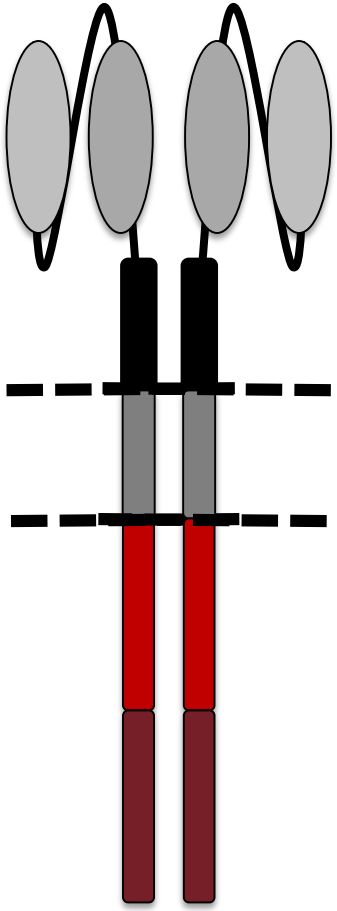
(Jensen et al. CL. 2007)

CAR Design

	2nd Gen CAR	Importance
scVf	CD56R	*Antigen binding*
scaffold	IgG Fc	*Flexibility & "Reach"*
transmembrane domain	CD3z	*Molecular Association*
signaling domain	CD28	*Co-stimulation*
	CD3z	*Activation*



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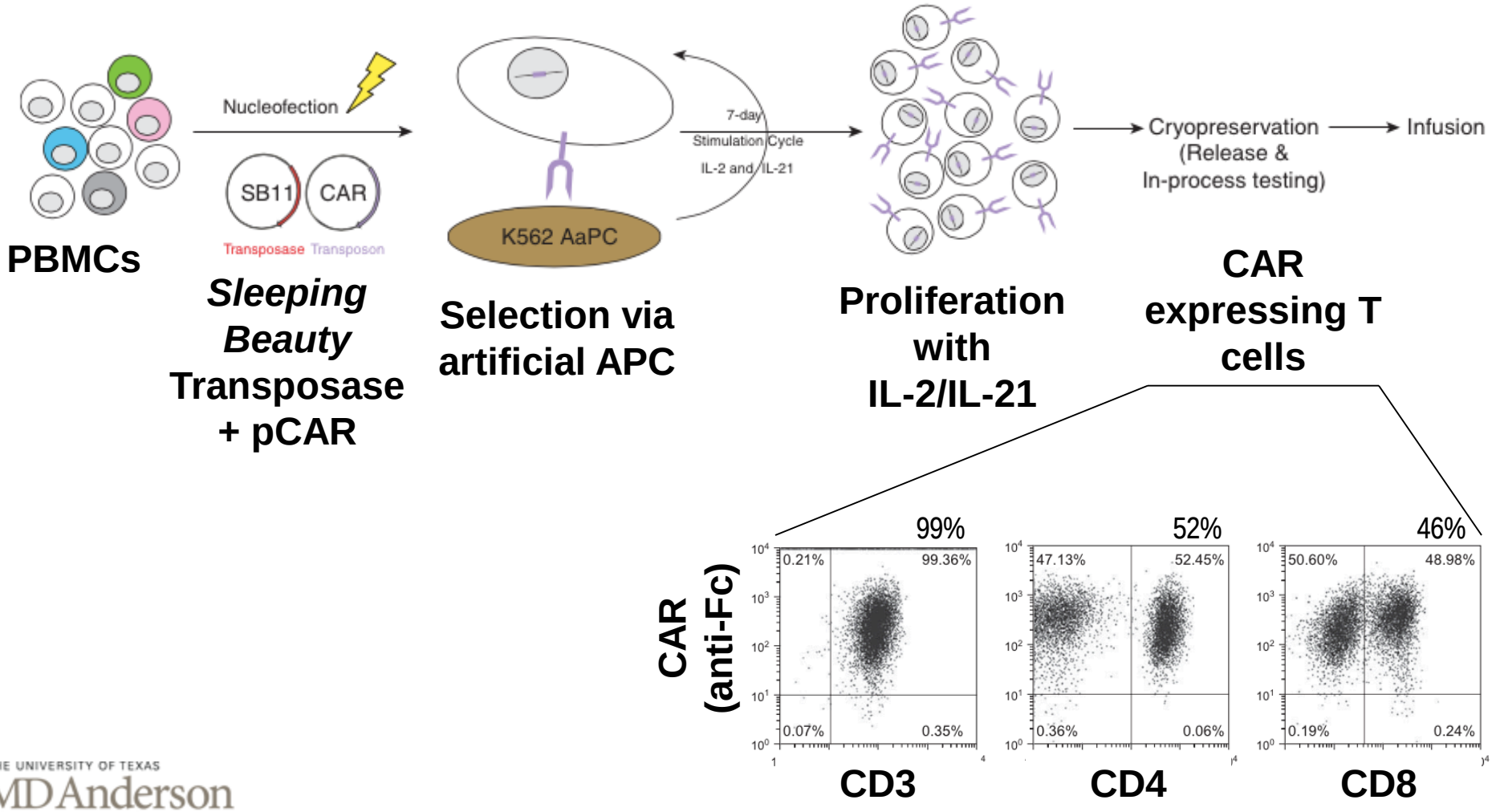
(Adapted Gilham et. al. Trends: Mol Med. 2012.)

Schema for generation of T-CARs via Sleeping Beauty system (Cooper et al)



(Singh, Moyes, Huls, Cooper. Cancer Gene Therapy. 2015)

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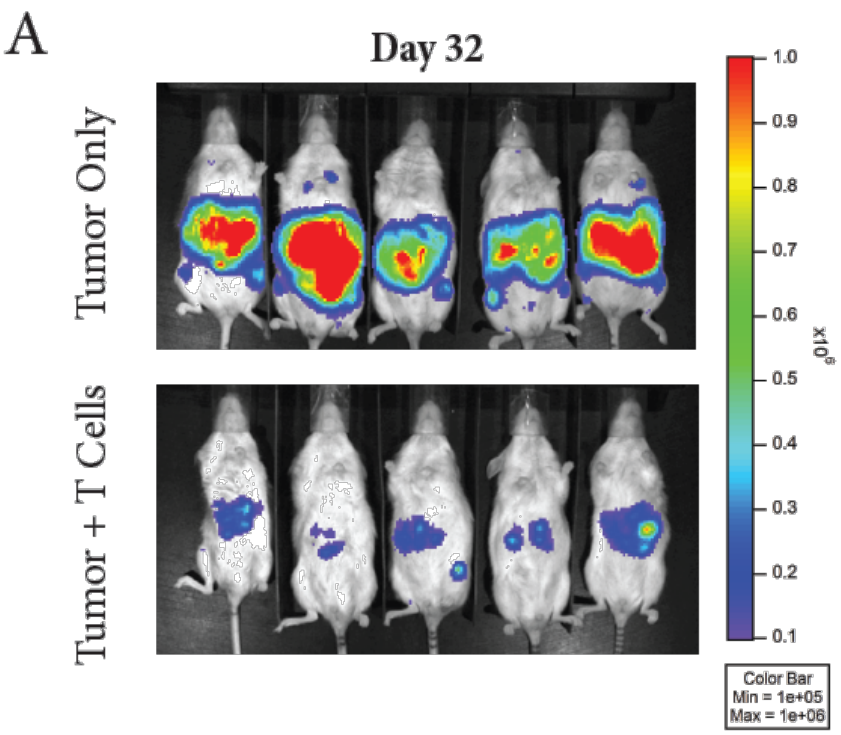
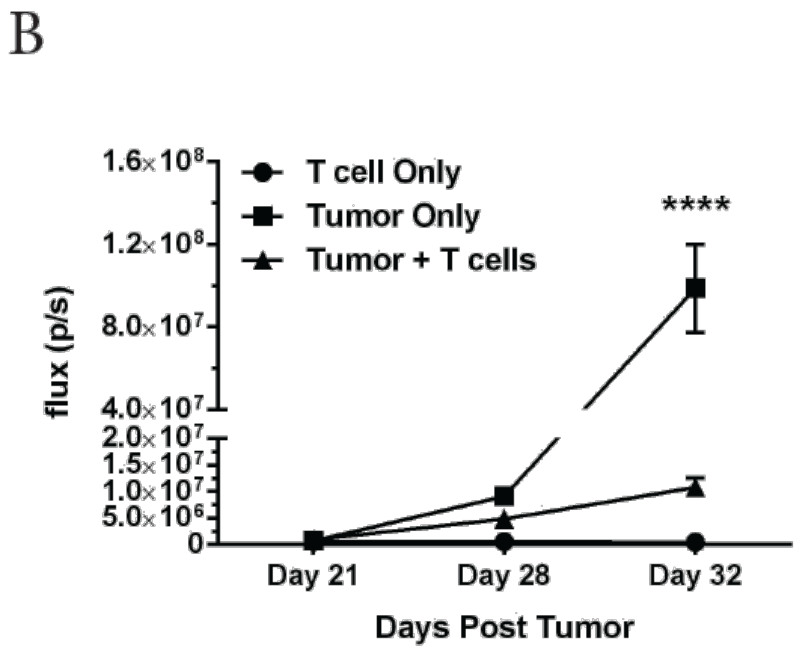
CD56R-CAR T cells inhibit tumor growth in CD56+ neuroblastoma model





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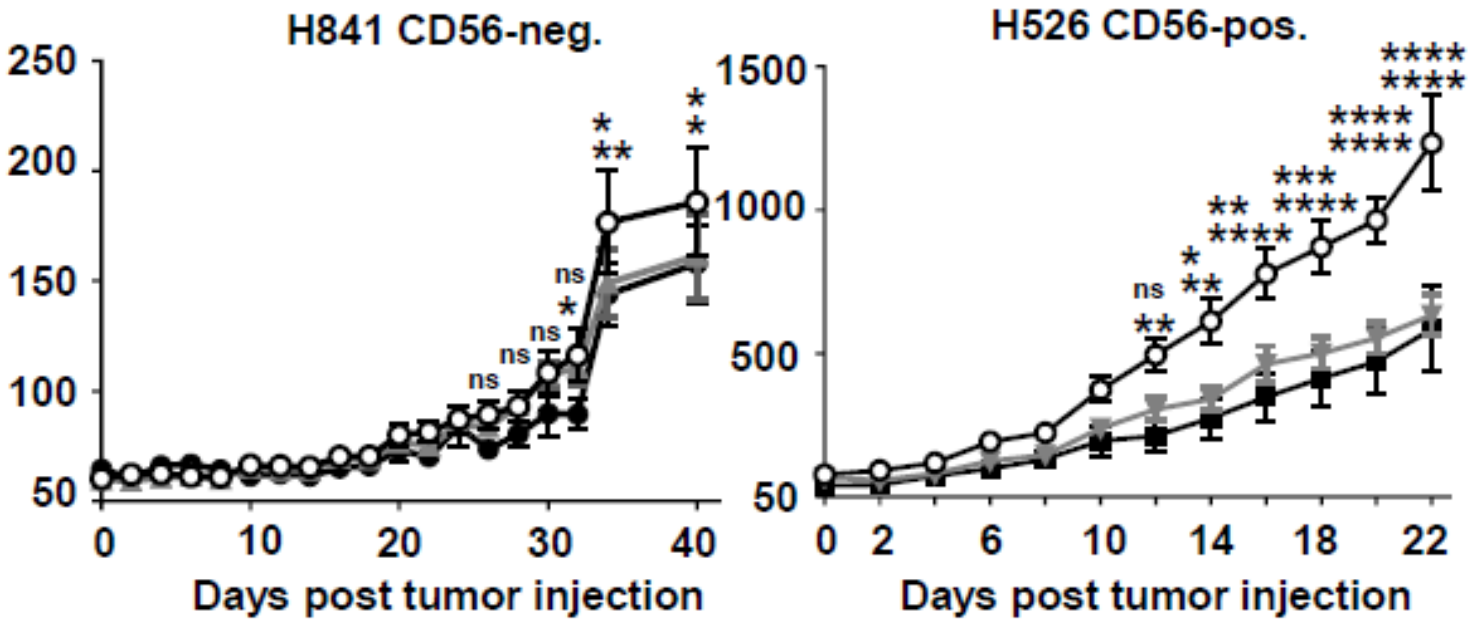
Denning et al, Oncogene, in press

CD56R-CAR Tcells inhibit tumor growth in a CD56+, but not CD56-, SCLC model



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Denning et al, Oncogene, in press

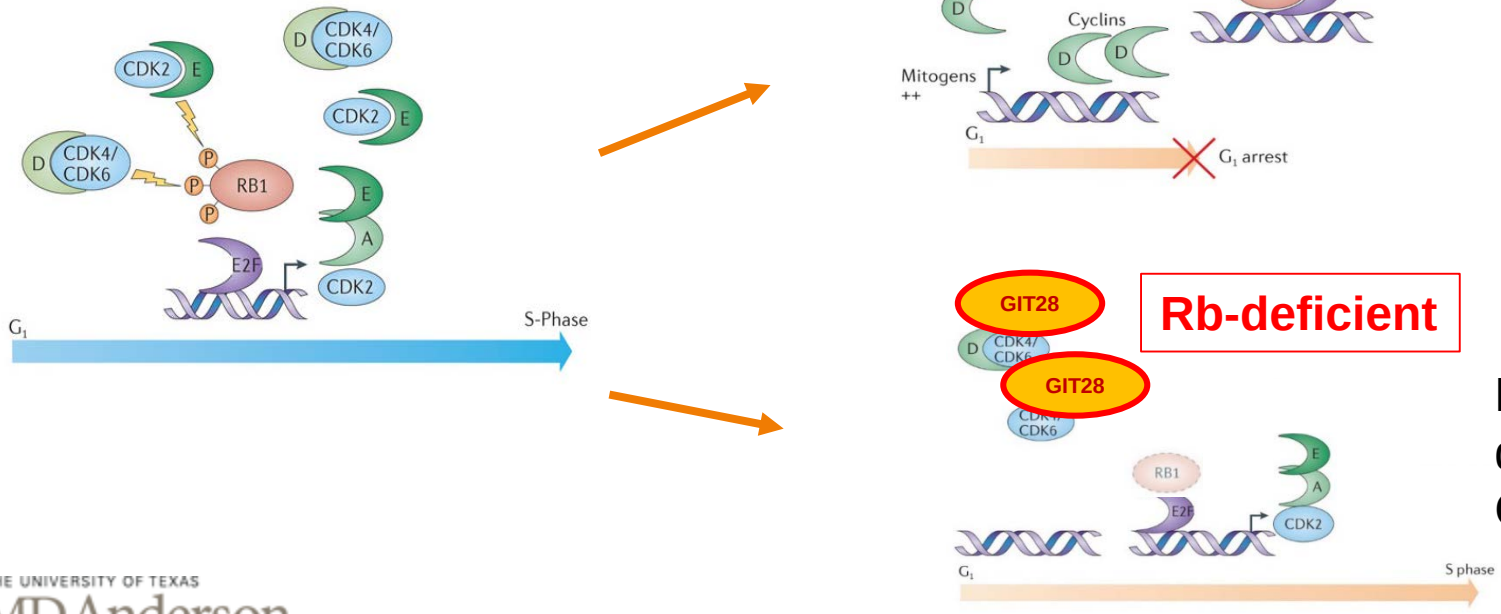
Potential concerns

CD56 is expressed on WT tissues (on target, off tissue)
Damage to the brain and other neural tissue possible similar to autoimmune already displayed in some SCLC patients.

Natural Killer cells loss
Would patient become more susceptible to viral infections or NK cells act as a "decoy" reducing CD56R-CAR killing at tumor site.

Antigen loss
Intense selection by CAR T cells may allow rapid generation of tumor escape variants most likely due to antigen loss

CDK4/6 inhibition arrests hematopoetic cells and other Rb-intact cells, but not Rb-deficient tumor cells, at G1 phase



Rb deficient cells do not undergo G1 arrest

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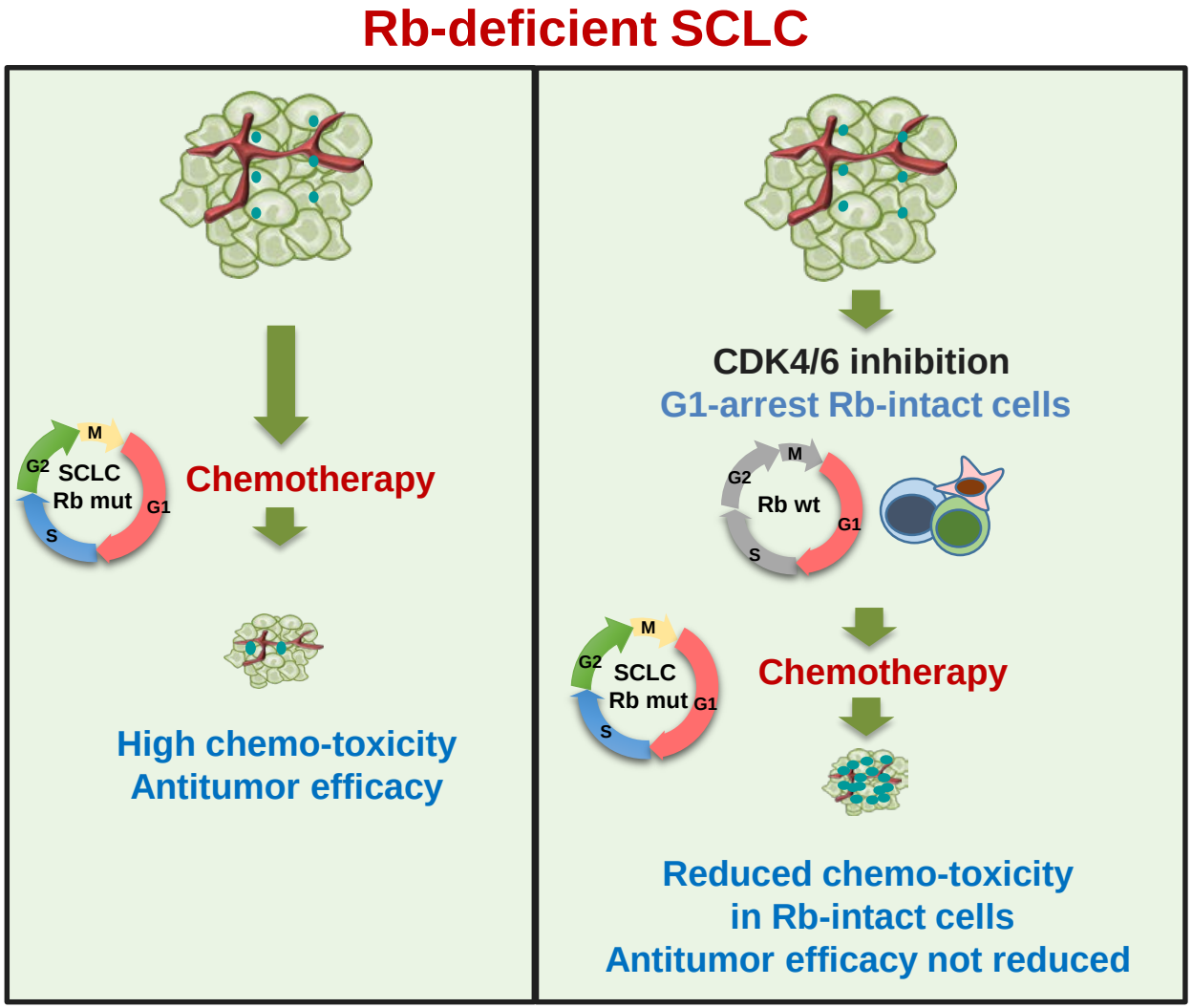
Guijarro et al; Adapted from Turner, N. C. *et al.* (2016) *Nat. Rev. Clin. Oncol*

CDK4/6 inhibition may protect Rb-intact cells from chemotherapy toxicity without diminishing the therapeutic effect in SCLC Rb mutant tumors



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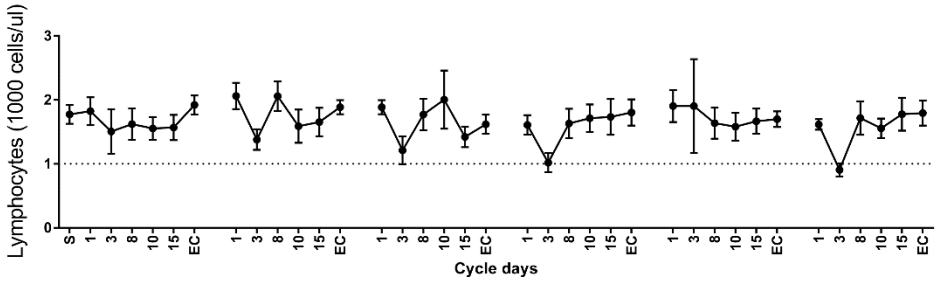
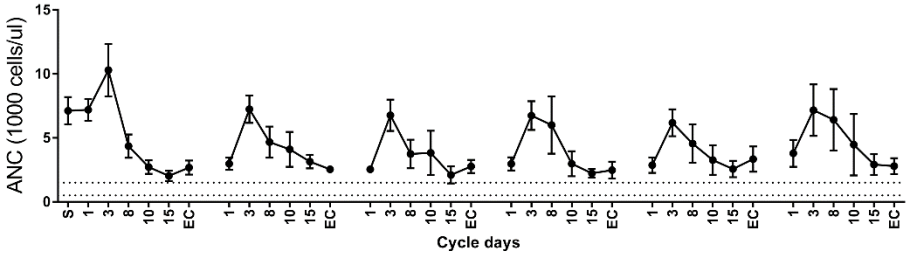
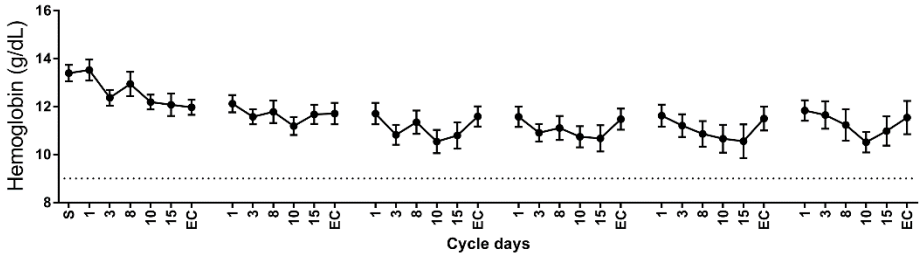
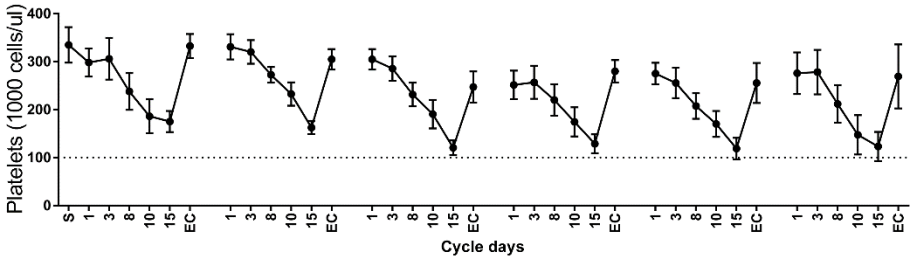
1st-line SCLC complete blood counts (CBCs): no clinically relevant myelotoxicity







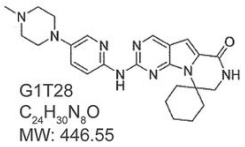


cohort 2 (n=9): Phase 2a dose of trilaciclib (240 mg/m^2)
S = baseline, EC = end cycle

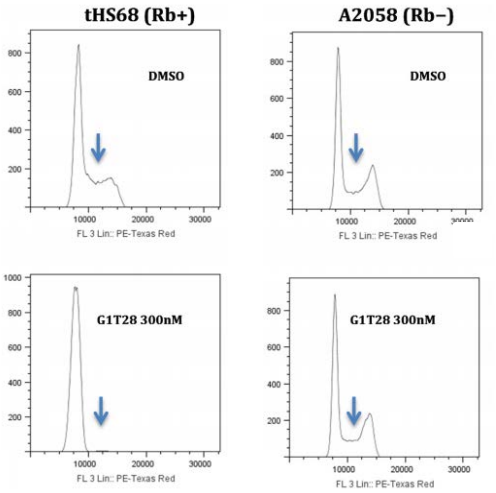
Robust myelopreservation: mean CBCs above clinically relevant cytopenia thresholds for all blood lineages, no febrile neutropenia

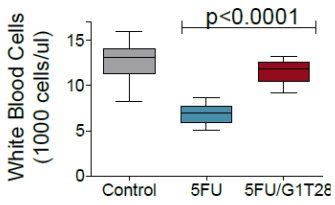
Data from Rocha Lima et al., ASCO 2017

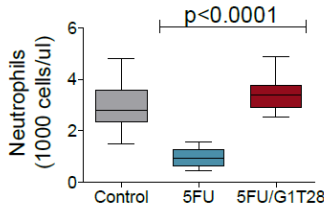
The CDK4/6 inhibitor G1T28 enhances chemo-protection of all blood lineages *in vivo*

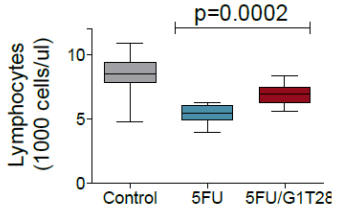


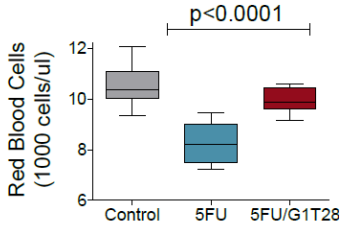
Compound	IC_{50} (uM) CDK4	IC_{50} (uM) CDK6	IC_{50} (uM) CDK2/E	IC_{50} (uM) CDK2/A
G1T28	0.0008	0.006	1.7	1.7
G1T38	0.001	0.006	3.6	1.5
Palbociclib	0.011	0.011	10	5.0

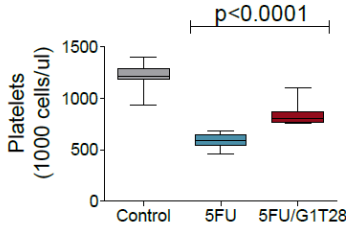


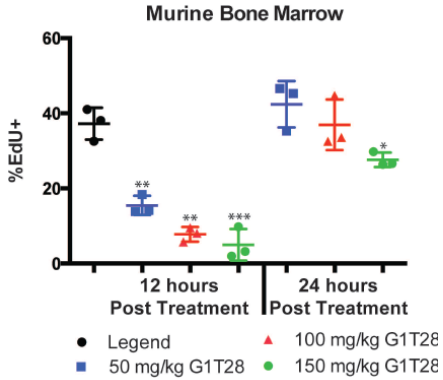












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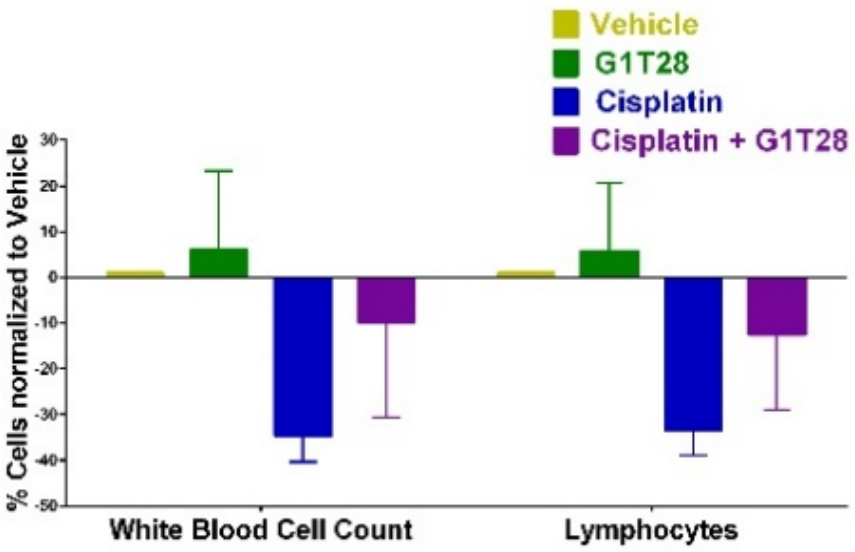
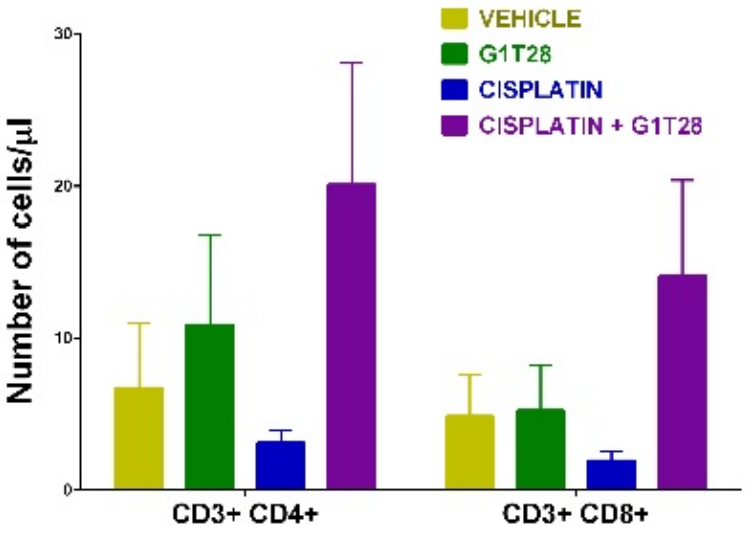
John E. Bisi et al. Mol Cancer Ther 2016

CDK4/6 inhibition by G1T28 protects peripheral CD4+ and CD8+ cells from cisplatin-induced cytotoxicity *in vivo*





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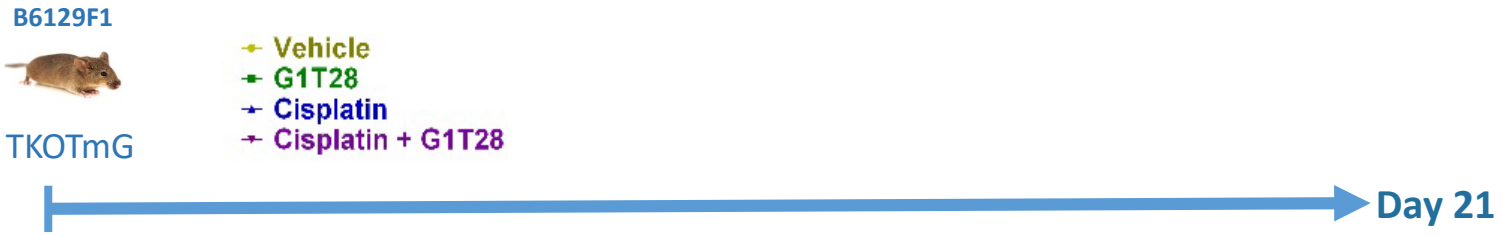
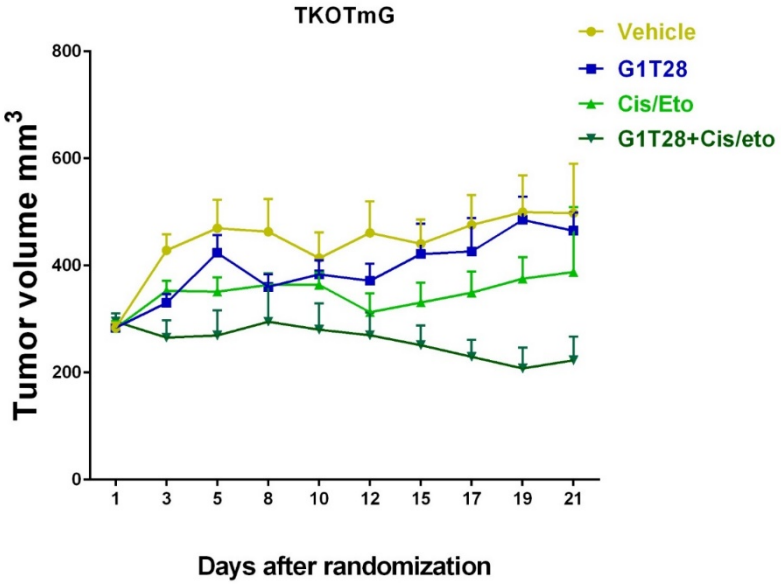
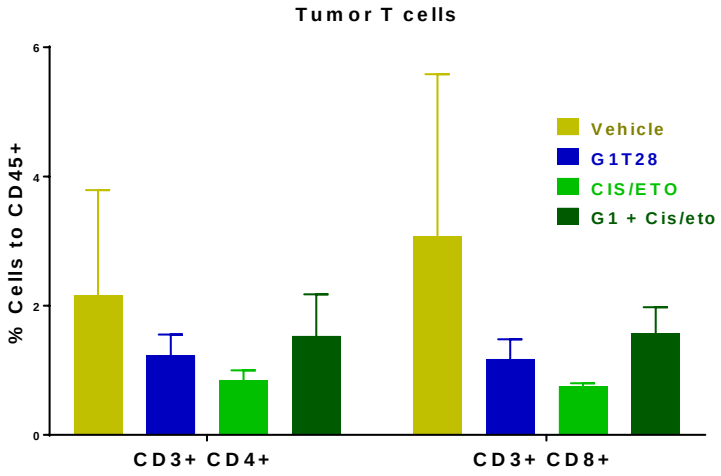
Guijarro et al, (Heymach lab) unpublished

The CDK4/6 inhibitor G1T28 enhanced chemotherapy toxicity and protect TILs *in vivo*







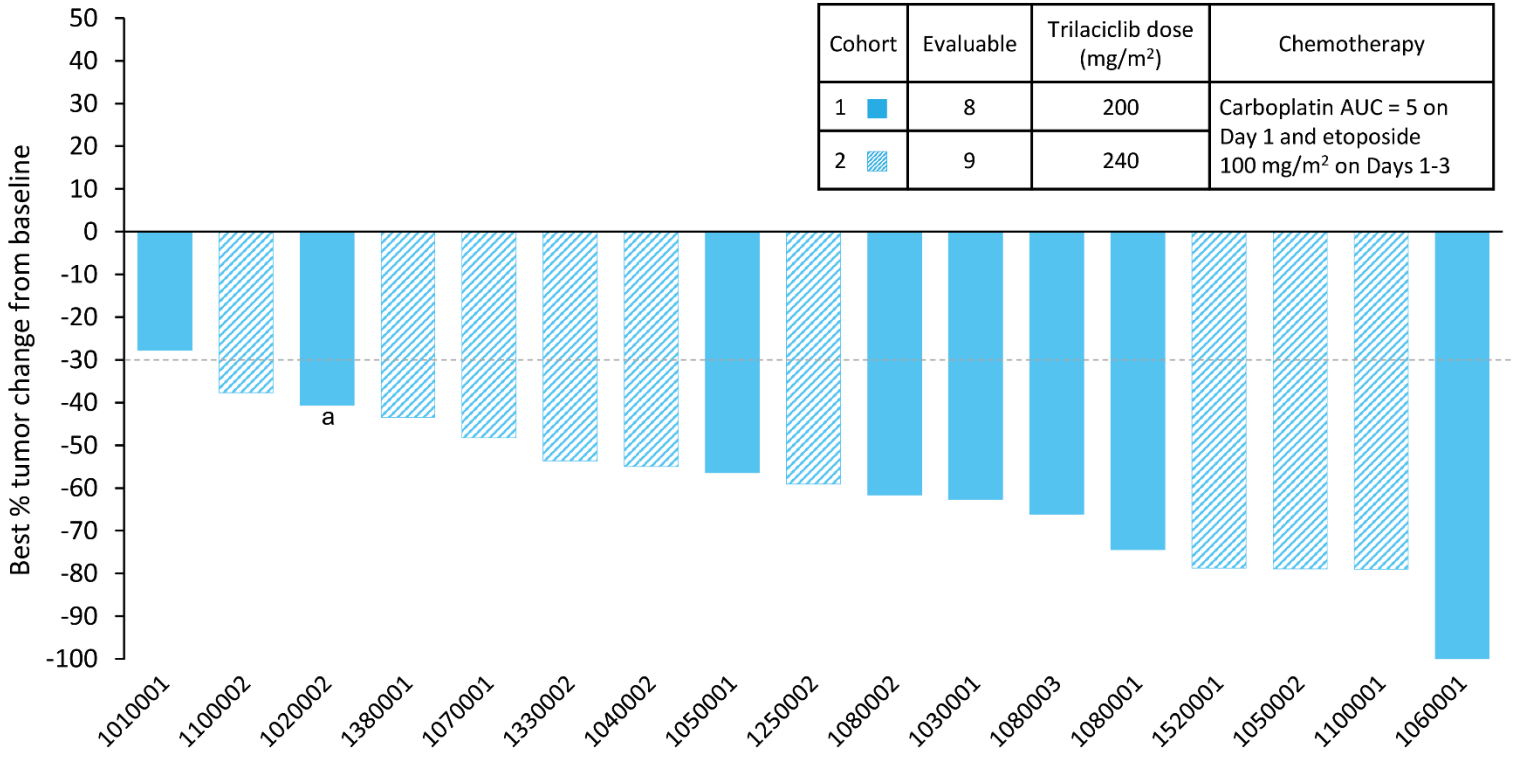
Guijarro et al, (Heymach lab) unpublished

Three ongoing POC trials in extensive–stage SCLC

Setting	Combination	Phase		Total # Patients	Primary Endpoints	Secondary Endpoints	Current Status
1st-line	carboplatin (AUC=5) and etoposide (100 mg/m^2)	1b: open label	2a: randomized (1:1), placebo-controlled	96 1b: 19 2a: 77	myelo-preservation: e.g. FN, transfusions	ORR, PFS, OS	2a enrollment completed; top-line data expected in 1Q18
2nd/3rd-line	topotecan (0.75 mg/m^2 and 1.5 mg/m^2)	1b: open label	2a: randomized (2:1), placebo-controlled	~ 120 1b: 32 2a: ~ 90	myelo-preservation: e.g. FN, transfusions	ORR, PFS, OS	2a enrollment completion anticipated 2Q18; top-line data expected 4Q18
1st-line	carboplatin/ etoposide/ atezolizumab	2: randomized (1:1), placebo-controlled		~ 100	OS	ORR, PFS, myelo-preservation	enrollment completion anticipated 3Q18

Open-label data: no febrile neutropenia (FN) in 51 patients, >250 cycles chemo (historical FN rates ~ 30% with topotecan)

1st-line SCLC: trilaciclib does not compromise efficacy of chemo



Cohort	Evaluable	Trilaciclib dose (mg/m^2)	Chemotherapy
1	8	200	Carboplatin AUC = 5 on Day 1 and etoposide 100 mg/m^2 on Days 1-3
2	9	240	

Evaluable	CR	PR	SD	PD	ORR	CBR
17	1	14	1	1	88%	94%

Literature* etop/carb efficacy (n=387)

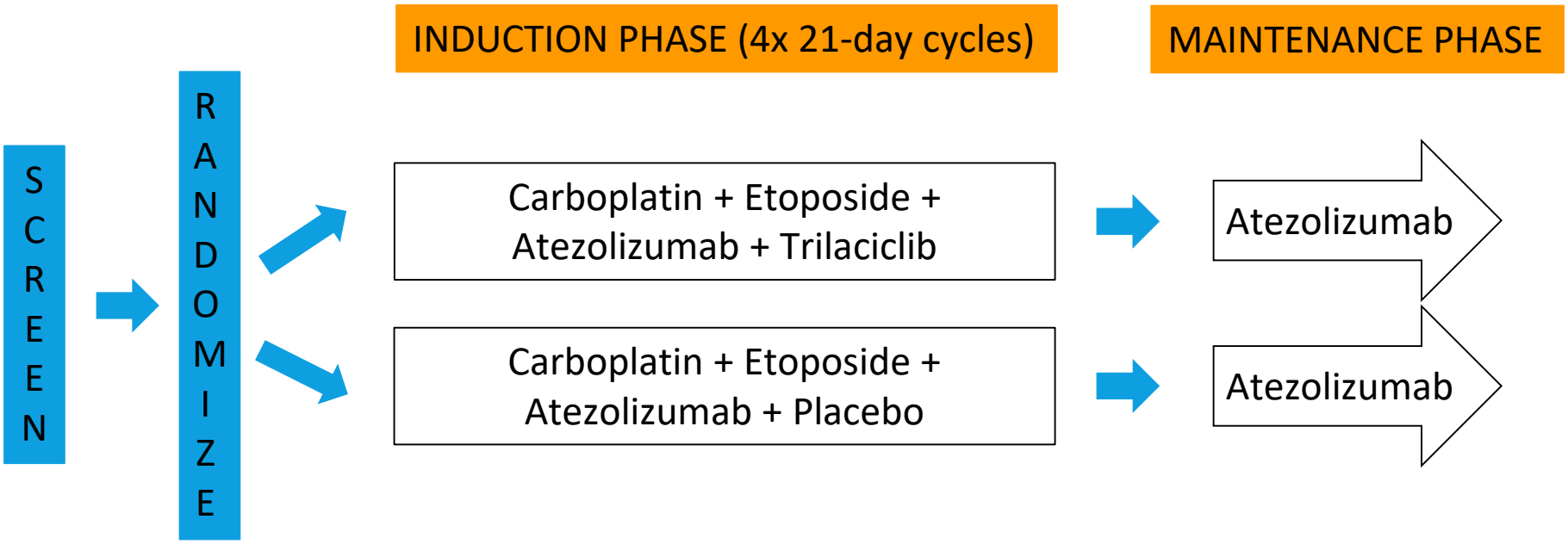
- 52% ORR (*only 1 CR*)
- 75% CBR

*Socinski et al, 2009

[a]Target lesion change consistent with PR at cycle 2; best response was PD due to occurrence of new lesions at cycle 2

Data from Rocha Lima et al., ASCO 2017

Trilaciclib/EP/atezolizumab in 1st-line SCLC



- Phase 2, randomized (1:1), global, double-blind, placebo-controlled
- Key objectives: PFS, OS, RR, safety in newly diagnosed ES SCLC patients
- Sample size: 100 patients
- NCT03041311

G1 Therapeutics Announces Positive Trilaciclib Phase 2a Topline Data Showing Robust Myelopreservation Benefits in Patients with Small Cell Lung Cancer

- 77 1L ES SCLC patients, EP+/- trilaciblib. Primary endpoint: myelopreservation
- Improved myelopreservation endpoints including G3/4 Heme Aes
- ORR trilaciclib 66.7%, placebo 62.2% (p=0.6759)
- PFS **trilaciclib 6.2 months, placebo 5.0 months** (hazard ratio 0.6, p=0.06)

Parameter	EP(1) + placebo Patients N = 37	EP + trilaciclib Patients N = 38	% Reduction	P-value (2)
Patients with Gr 3/4 Hematologic TEAEs	27 (73.0%)	9 (23.7%)	67.5%	<0.0001
Patients with Gr 3/4 Neutropenia	30 (81.1%)	15 (39.5%)	51.3%	0.0002
Patients with Gr 4 Neutropenia	16 (43.2%)	2 (5.3%)	87.7%	0.0001
Patients with Gr 4 Neutropenia in Cycle 1	13 (35.1%)	1 (2.6%)	92.6%	0.0003
Cycles with Febrile Neutropenia	5	1	80.8%	0.1542
Patients with Febrile Neutropenia	3 (8.1%)	1 (2.6%)	67.9%	0.2773
Patients with G-CSF Administration	24 (64.9%)	4 (10.5%)	83.8%	<0.0001
Patients with Chemotherapy Cycle Delays	25 (67.6%)	15 (39.5%)	41.6%	0.0170
Patients with Chemotherapy Dose Reductions	13 (35.1%)	3 (7.9%)	77.5%	0.0033

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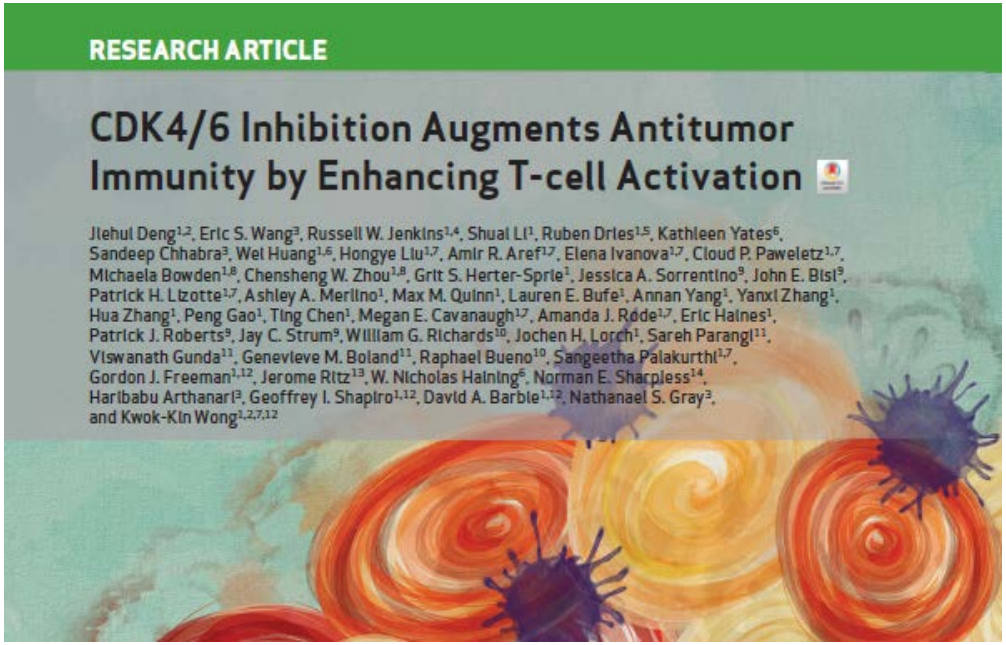
G1 Therapeutics press release, 3/5/2018

CDK4/6 inhibition affects anti-tumor immunity



Short-term exposure to small-molecule inhibitors of CDK4/6 significantly enhances T-cell activation, contributing to antitumor effects in vivo.

CDK4/6 inhibition augments the response to PD-1 blockade in multiple in vivo murine syngeneic models.

CDK4/6 inhibitor trilaciclib: the bottom line

In preclinical models:

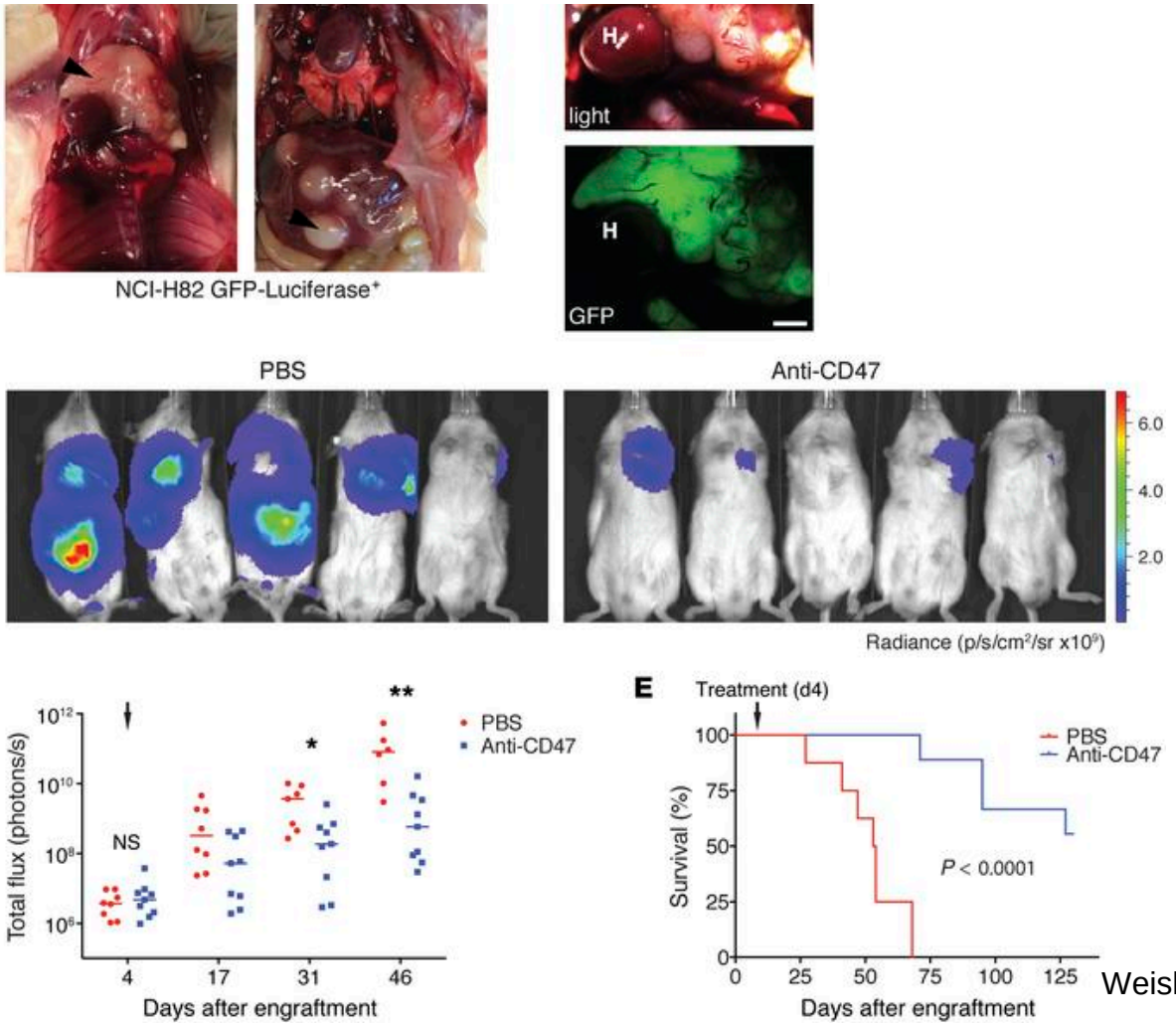
- Causes G1 arrest in Rb-intact but not Rb-deficient cells
- Given ***before*** chemo, protects HSPCs, peripheral and tumor infiltrating CD4+ and CD8+ lymphocytes from chemotherapy-induced cytotoxicity in vivo
- Mitigates bone marrow exhaustion;
- Enhances the efficacy of chemotherapy in SCLC models
- Ongoing studies for enhancing IO with chemo, RT

Clinical testing:

- Promising clinical results for myelopreservation
- Three randomized trials:
  - 1L: EP+/- trila
  - 2L: topotecan+/- trila
  - 1L: EP+atezo, +/- trila

CD47-blocking immunotherapies stimulate macrophage-mediated destruction of small-cell lung cancer

Kipp Weiskopf,[1,2,3] Nadine S. Jahchan,[3,4,5] Peter J. Schnorr,[1,2,3] Sandra Cristea,[3,4,5] Aaron M. Ring,[1,2,3,6,7] Roy L. Maute,[1,2,3] Anne K. Volkmer,[1,2,3,8] Jens-Peter Volkmer,[1,2,3] Jie Liu,[1,2,3] Jing Shan Lim,[3,4,5] Dian Yang,[3,4,5] Garrett Seitz,[3,4,5] Thuyen Nguyen,[3,4,5] Di Wu,[2,3,6,7] Kevin Jude,[2,3,6,7] Heather Guerston,[9] Amira Barkal,[1,2,3] Francesca Trapani,[10] Julie George,[11] John T. Poirier,[12] Eric E. Gardner,[12] Linde A. Miles,[12] Elisa de Stanchina,[12] Shane M. Lofgren,[3,4,5] Hannes Vogel,[3,13] Monte M. Winslow,[5,13] Caroline Dive,[10] Roman K. Thomas,[11,14] Charles M. Rudin,[12] Matt van de Rijn,[13] Ravindra Majeti,[1,2,3] K. Christopher Garcia,[2,3,6,7] Irving L. Weissman,[1,2,3,13] and Julien Sage[3,4,5]



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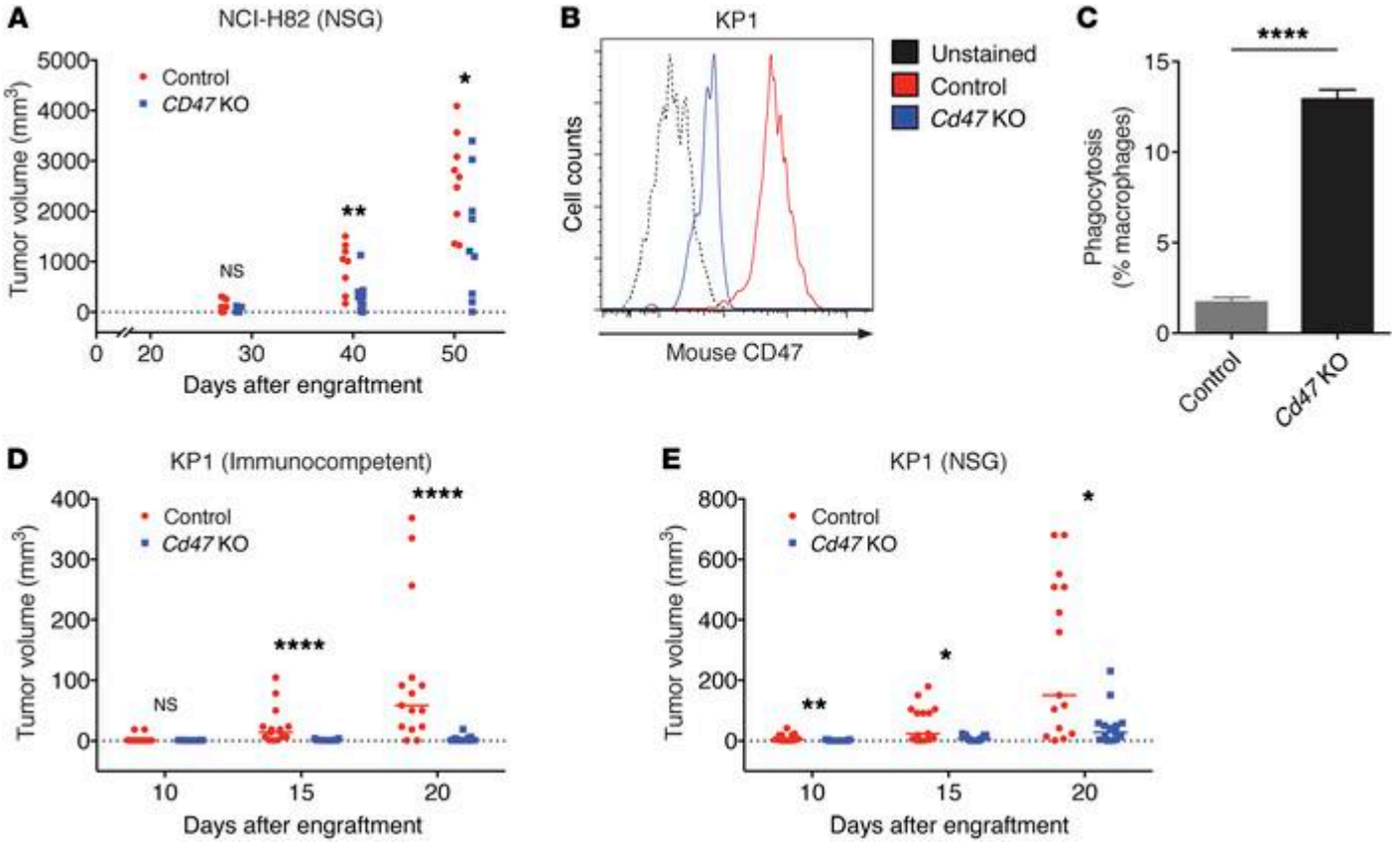
Weiskopf et al, JCI, 2016

Genetic ablation of Cd47 inhibits SCLC growth in vivo



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Weiskopf et al, JCI, 2016

Immunotherapy targets for SCLC: the bottom line

- Despite high TMB, SCLC typically has a more immunosuppressed phenotype than NSCLC
  - DDR agents may “warm up” cold tumors
- PD1+CTLA4 has activity in ES SCLC, especially in TMB high group
- CAR-T cells targeting CD56 demonstrate preclinical activity. Other CAR-Ts being developed.
- CDK4/6 inhibition a promising strategy for myelopreservation and potentially enhancing IO when given with chemo or RT.
- CD47 another potential target.

Acknowledgements

Heymach Lab
Irene Guijarro (CDK4/6i)
Warren Denning
Monique Nilsson
Emily Roarty
Alissa Poteete
Huiying Sun
Youhong Fan
Sungnam Cho
Tina Cascone
Haifa Hamdi
Fahao Zhang

Cooper Lab
Denise Crossland
Sonny Ang
Simon Olivares
Natalya Belousova
Alan Guerrero
Ana Korngold

Byers lab
Sage lab

Minna lab
UTSW

Support

- U01 (Heymach/Byers/Sage)
- UTSW/UTMDACC Lung SPORE Grant 5 P50 CA070907
- Lung Cancer Moon Shot
- Lung Cancer Research Foundation
- NIH Cancer Center Support Grant CA016672

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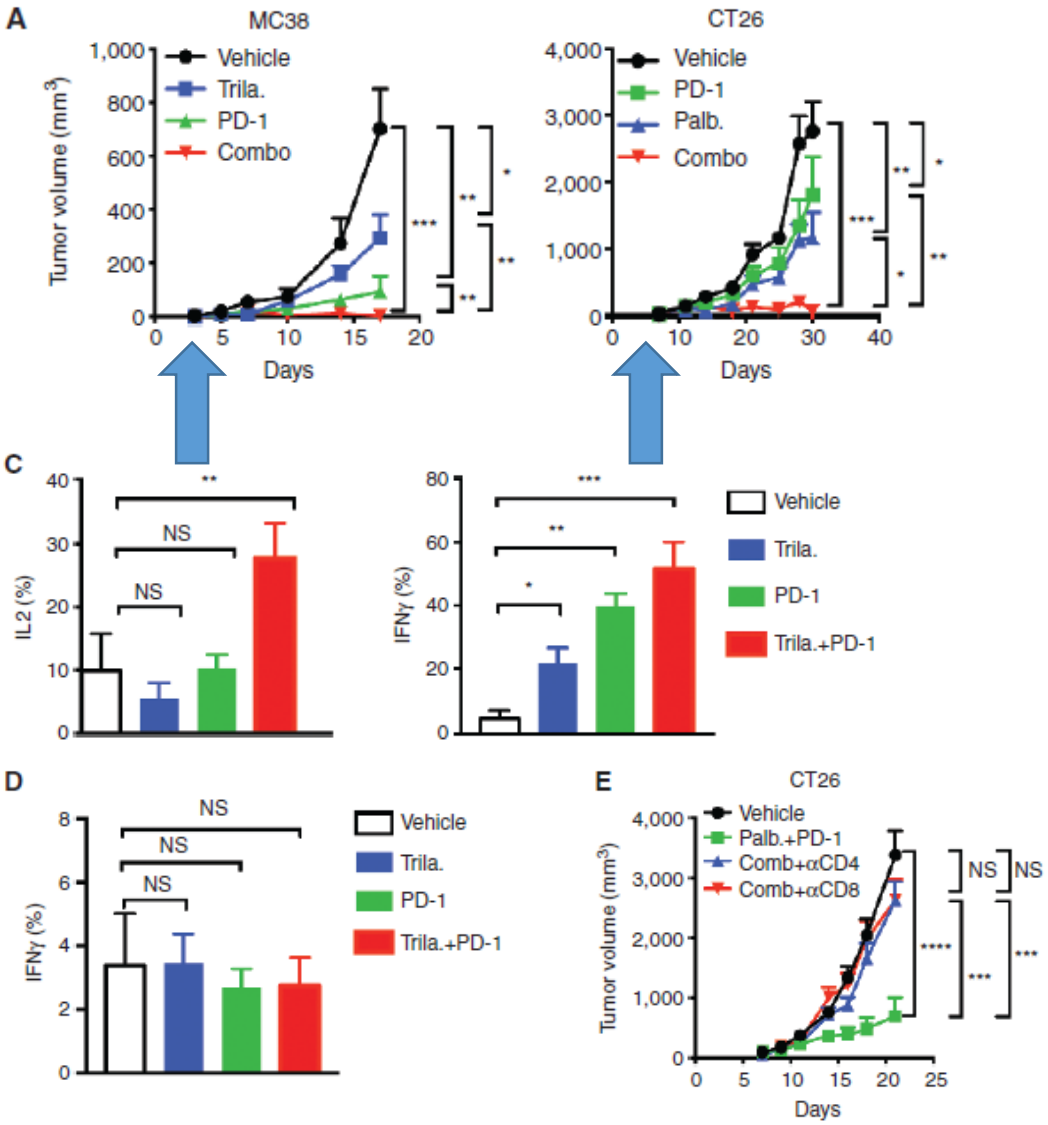
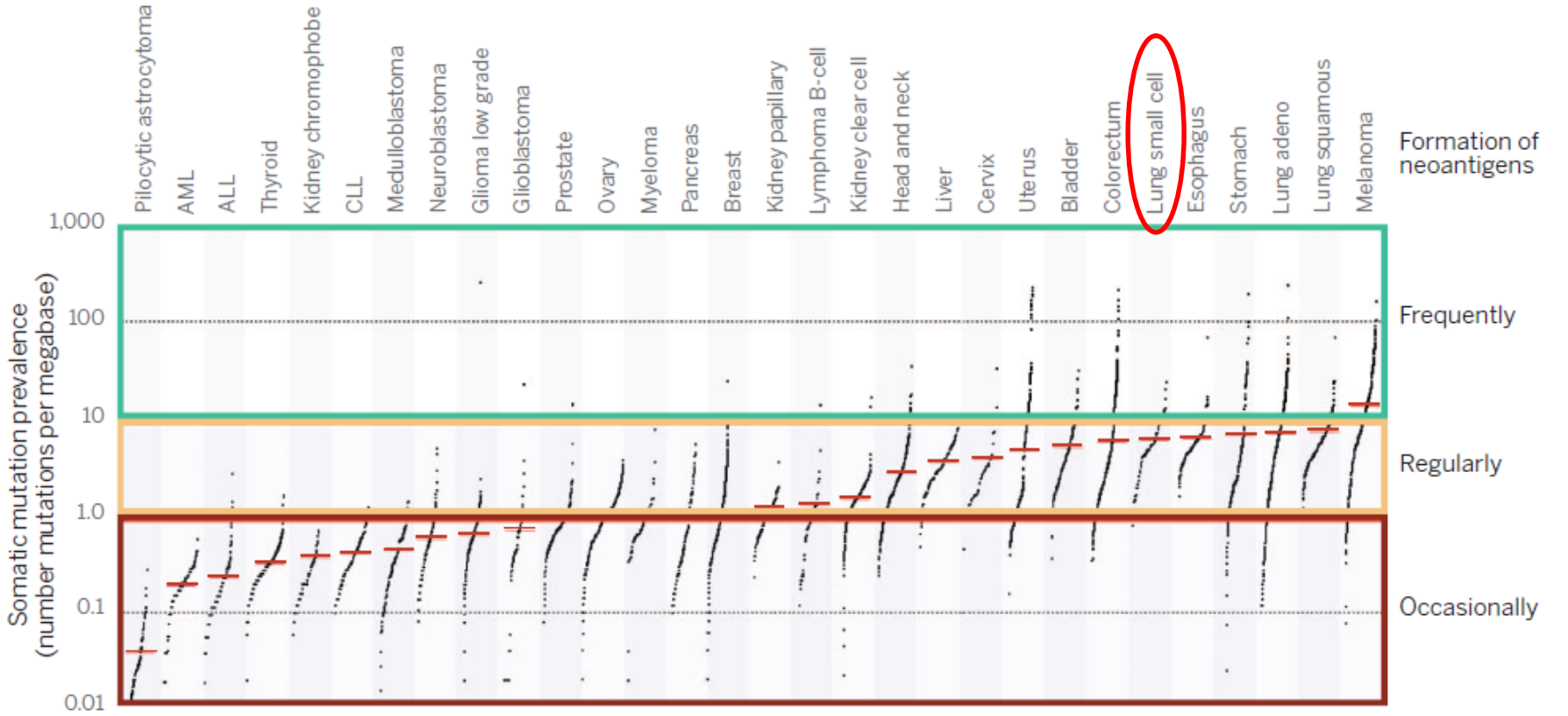
Combination treatment of CDK4/6 inhibitors synergize anti–PD-1 antibody–induced antitumor immunity through T cells



Treatment schedule: The mice were treated with either CDK4/6 inhibitor [trilaciclib (Trila.) or palbociclib (Palb.), 100 mg/kg] **intermittently (3 days on, 4 days off)** with or without PD-1 antibody (200 μg/mouse, 3 times a week) as indicated starting from day 3 (MC38) or day 7 (CT26).

Deng J Cancer Discovery 2017

High mutation burden in SCLC – but discordant immunotherapy response



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Alexandrov et al., 2013; Schumacher and Schreiber 2015