Unlocking an untapped cytokine pathway with decoy-resistant IL-18

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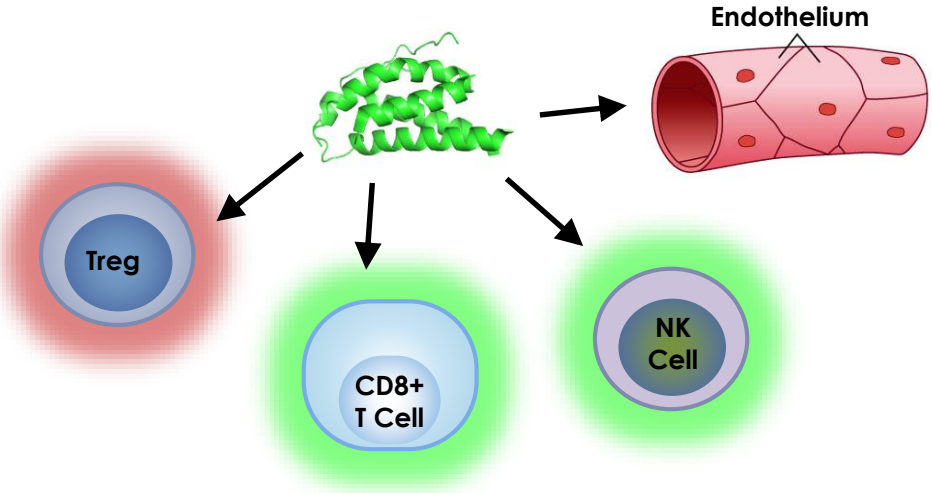
Disclosure Statement

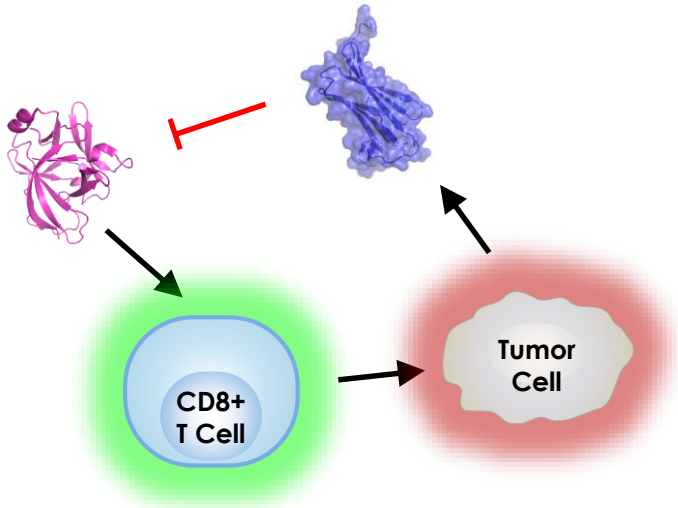
Consultant:	Medicenna Therapeutics Versant Ventures
Founder:	Ab Initio Biotherapeutics Forty Seven Inc ALX Oncology Simcha Therapeutics
Director:	Ab Initio Biotherapeutics Simcha Therapeutics

Cytokines: powerful, but problematic

Pleiotropic activation of diverse cells decreases specificity

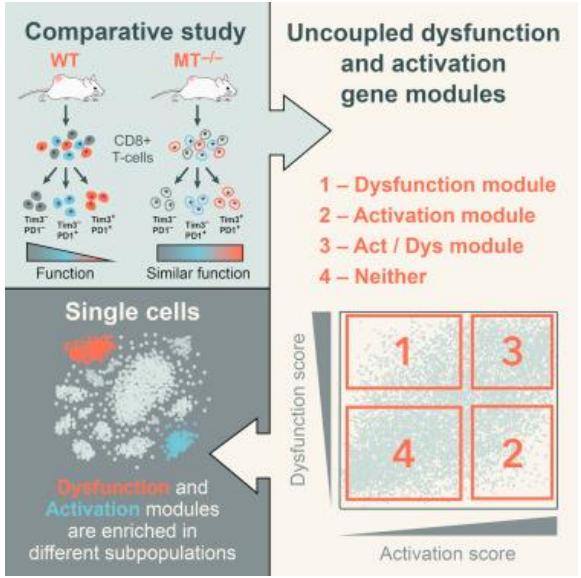


Efficacy often limited by negative regulation



“Nature’s solution” often makes for a poor therapeutic

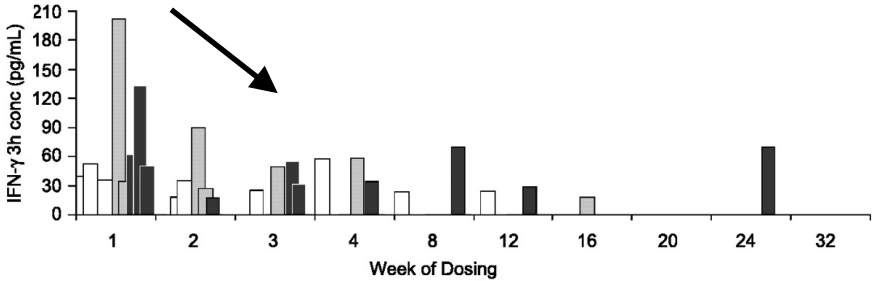
Cytokine landscape in CD8 TILs



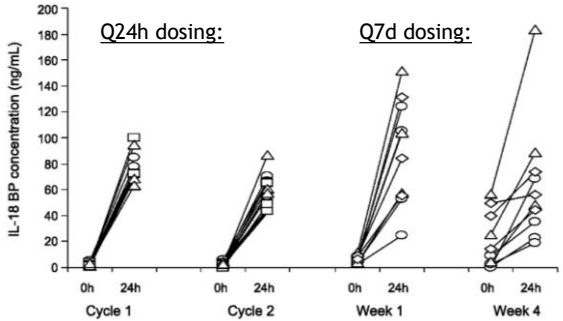
Adapted from Singer et al., Cell, 2017

Clinical experience with rIL-18 therapy: Safe, well-tolerated, but ineffective through Ph2

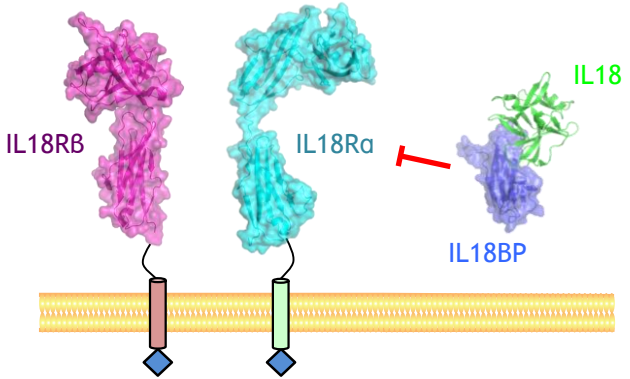
IL-18 PD activity wanes with repeated dosing



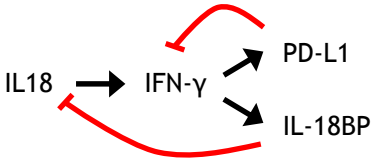
Corresponding to a massive systemic **upregulation of IL-18BP**:

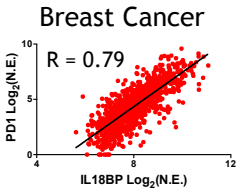


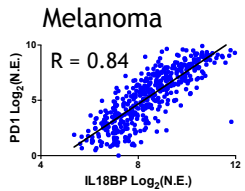
IL-18BP is a potent (2 pM) soluble decoy receptor that antagonizes IL-18



And is part of a negative feedback loop downstream of IFN-γ:

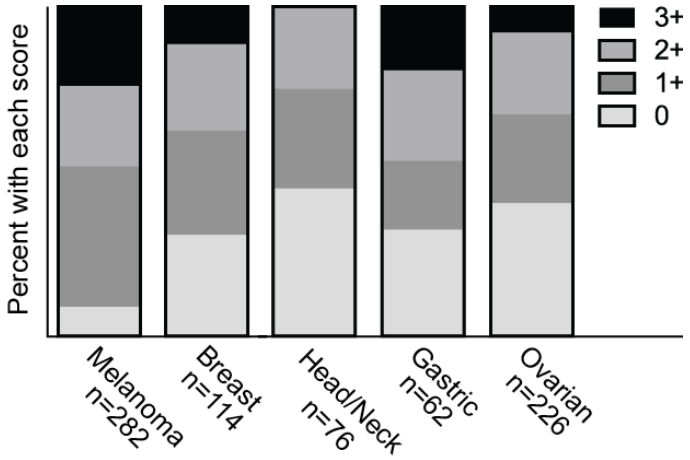


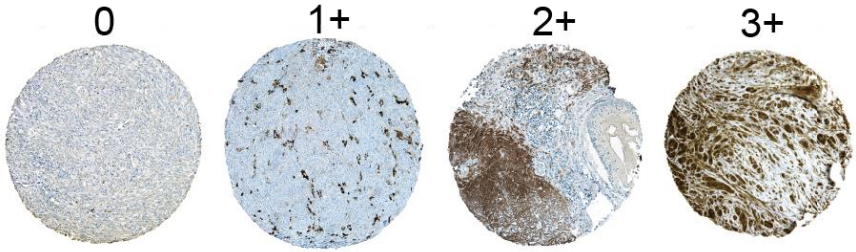


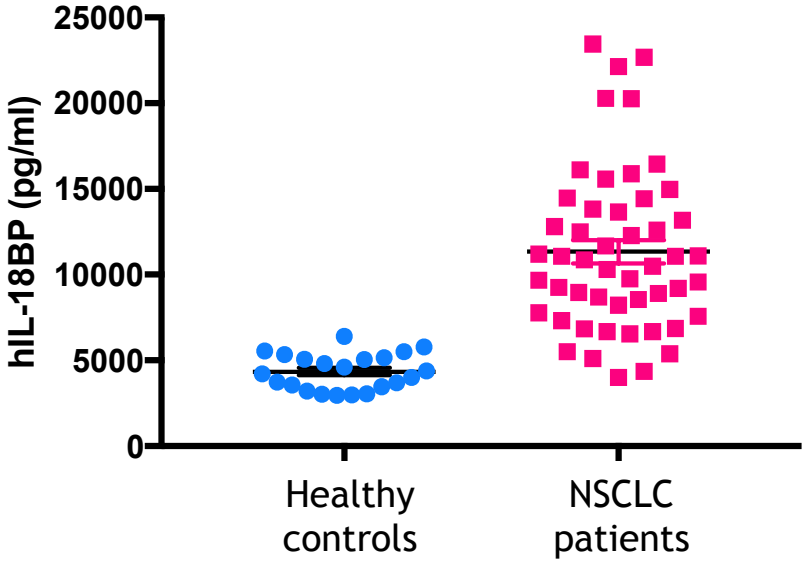


Robertson et al., Clinical Cancer Research, 2006| Robertson et al., Clinical Cancer Research, 2008

IL-18BP is detectable in the TME with IHC and is elevated systemically in NSCLC patients



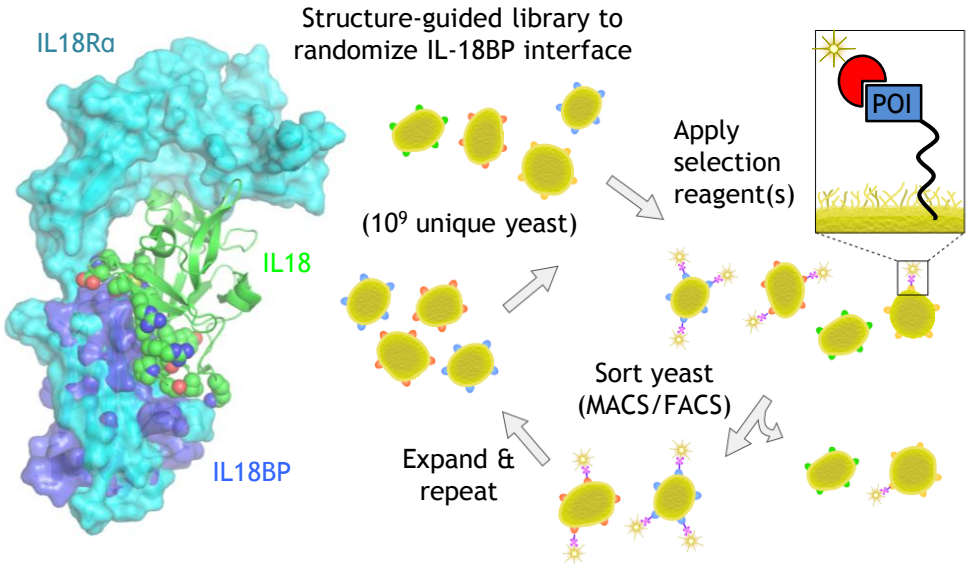




<u>Hypothesis:</u> IL-18BP is a soluble "immune checkpoint" that is the major barrier to the efficacy of IL-18 therapy

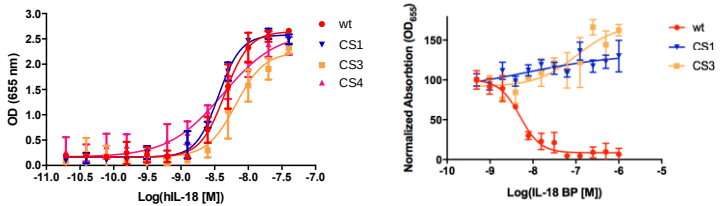
Engineering “decoy-resistant” DR-18 with directed evolution

Directed evolution process with yeast surface display:

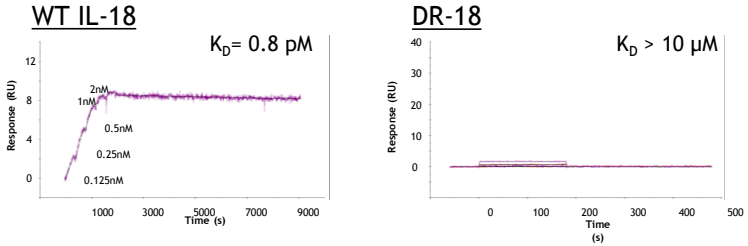


Functional characterization of DR-18 variants:

IL-18R Signaling Activity



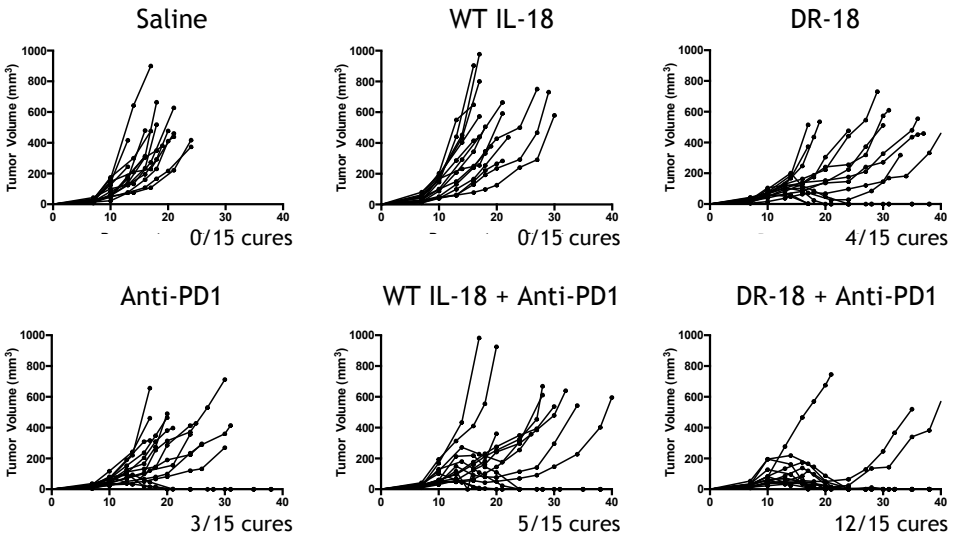
IL-18BP SPR measurements



Conclusion: DR-18 variants stimulate IL-18R with complete independence from IL-18BP

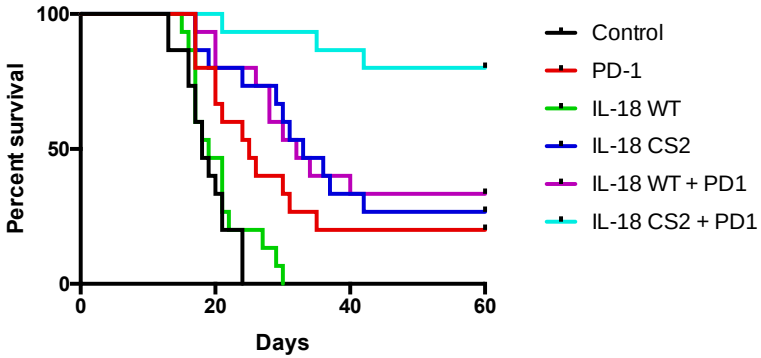
DR-18 is effective as a single agent and in combination with anti-PD1 antibodies

Yummer1.7 melanoma treatment model
Representative tumor growth spider plots:



- mIL-18/DR-18: 0.32mg/kg twice weekly
- Anti-mPD-1: 8mg/kg twice weekly

Combined survival data (15 mice/group):



Study Parameters

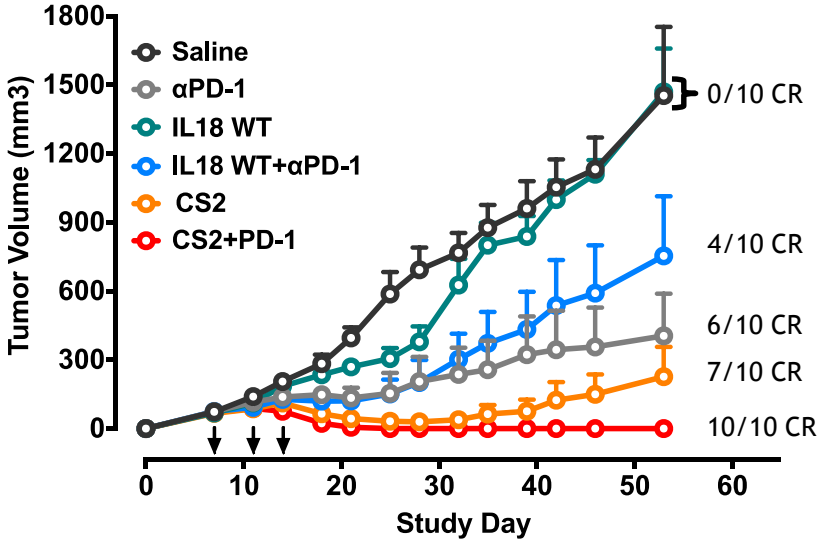
- Yummer1.7 tumors treated starting at ~50 mm^3
- Twice weekly IP dosing for max of 5 doses

Conclusions

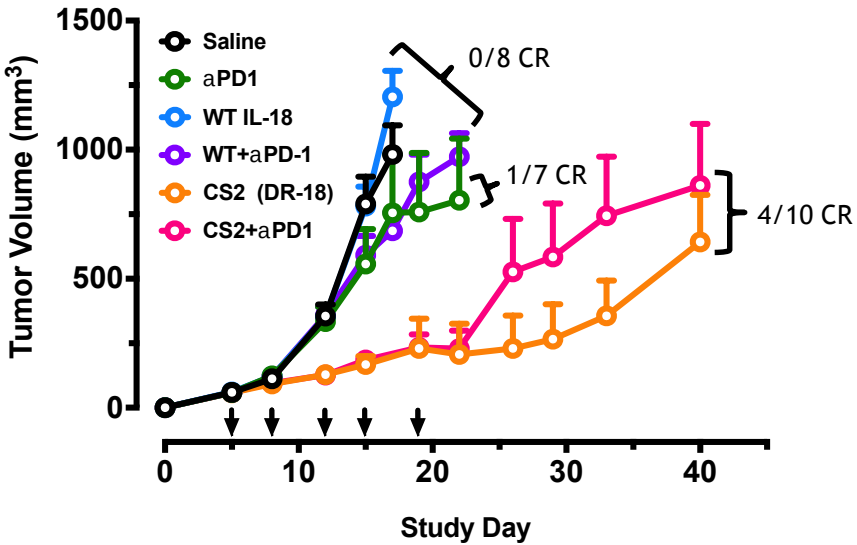
- DR-18 (variant CS2) is effective as a monotherapy and in combination with anti-PD1
- Similar efficacy observed in MC38 tumors

DR-18 has broad activity in multiple immunogenic tumor models

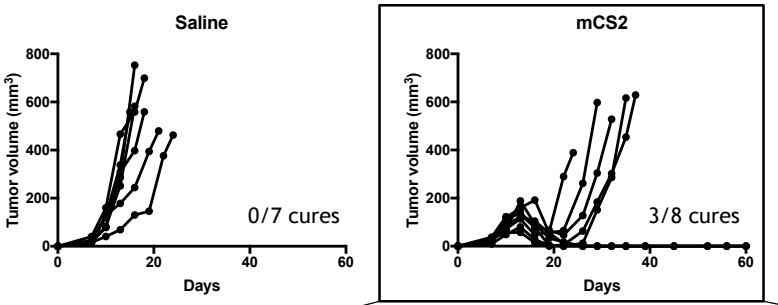
MC38 tumor model:

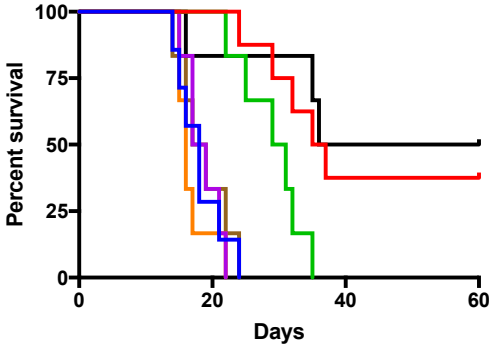


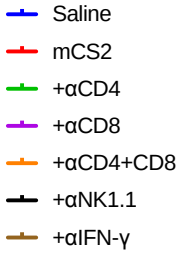
CT26 tumor model:

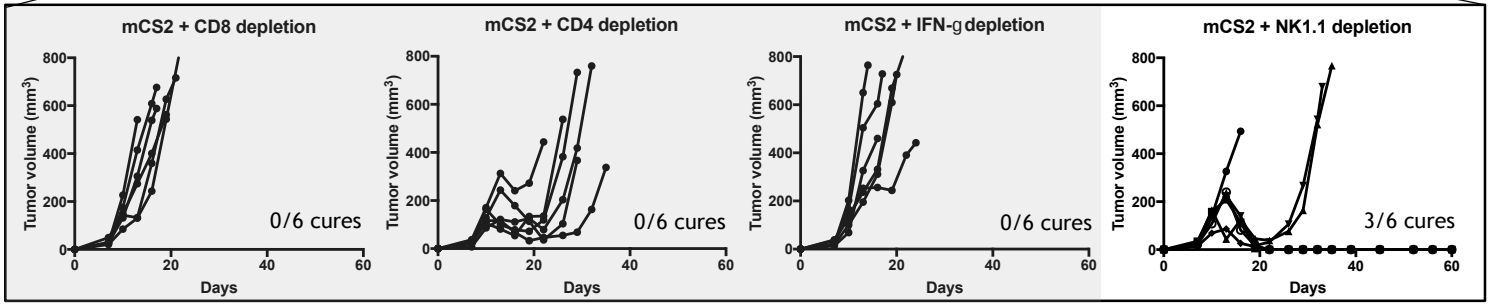


DR-18 efficacy requires CD8 & CD4 cells and IFNγ, but not NK cells in Yummer1.7 & MC38 tumors

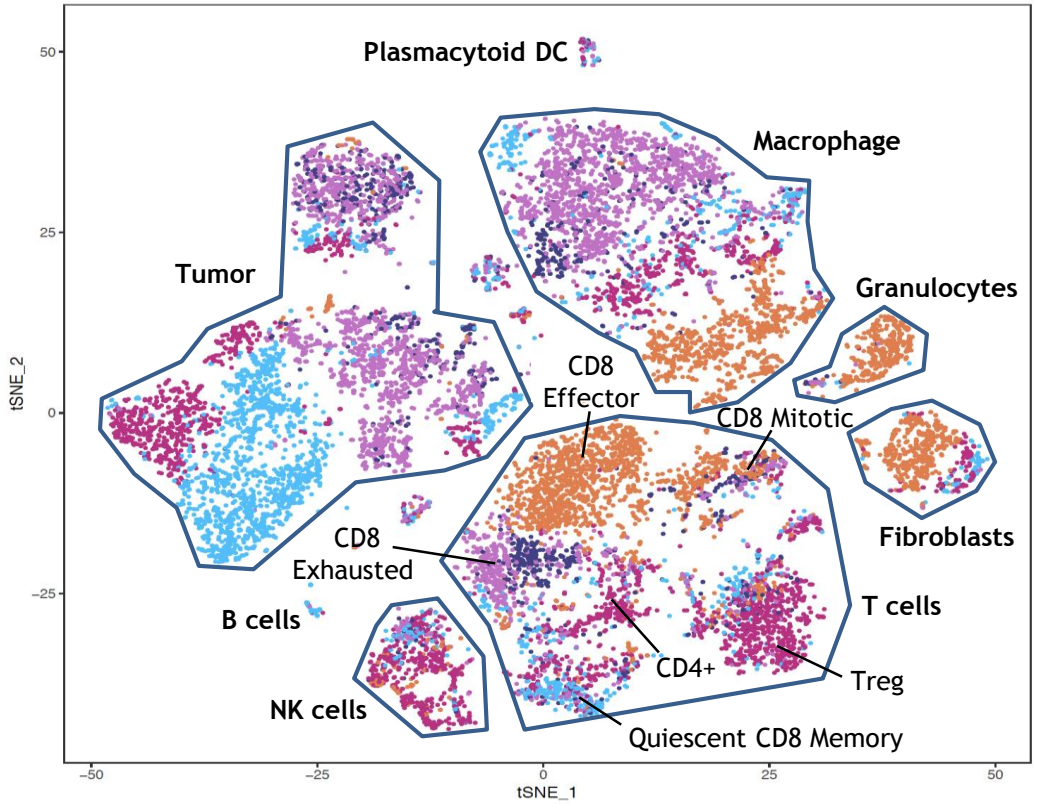








DR-18 treatment affects major changes in all immune compartments of the TME



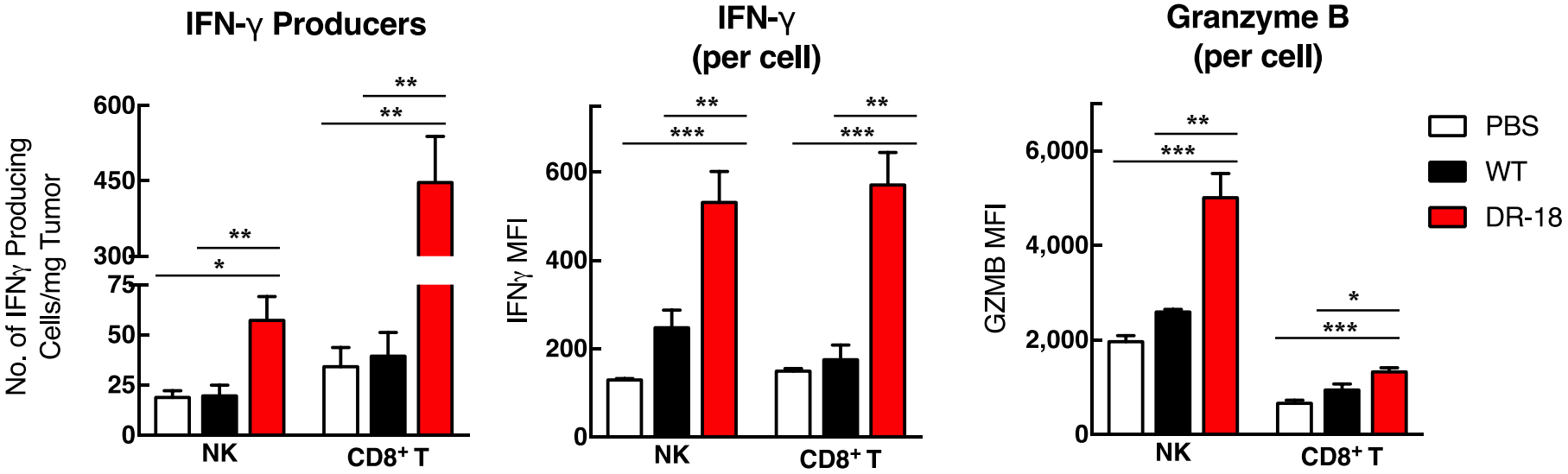
Immunogenic tumors

- Yummer1.7
- Yummer1.7 + DR-18
- Yummer1.7 + IL-18 WT

MHC class I-deficient tumors

- B2m-Yummer
- B2m-Yummer+ DR18

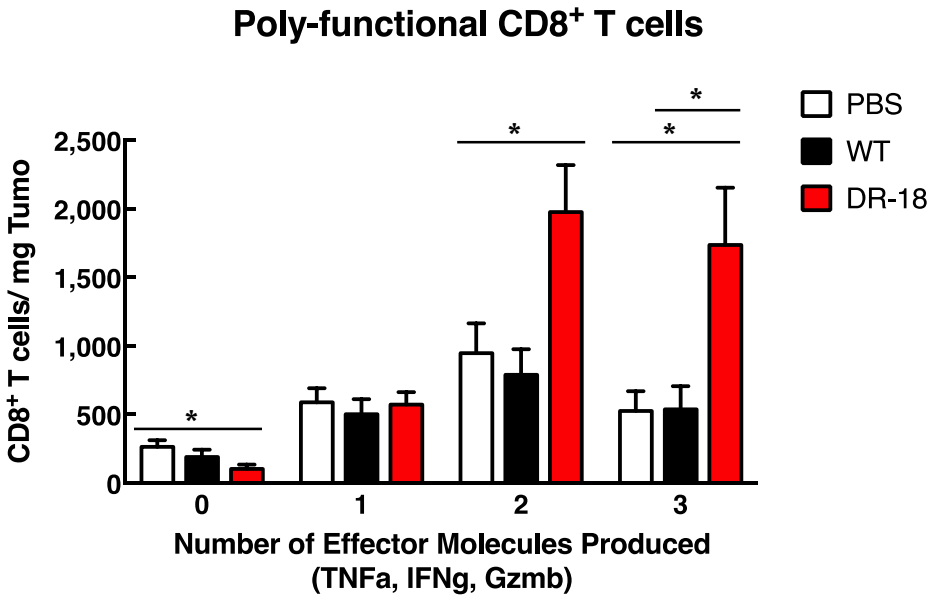
DR-18 promotes endogenous lymphocyte effector function

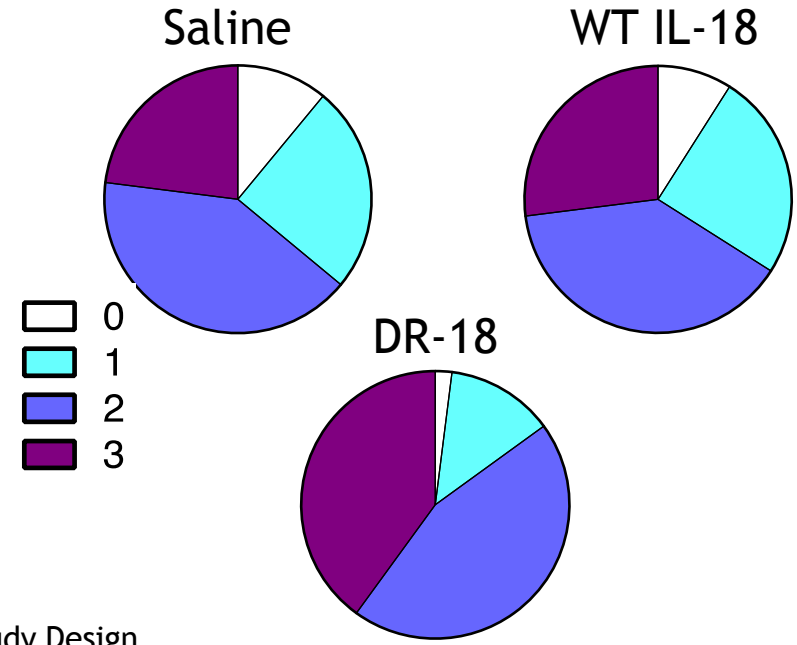


Study Design

- MC38 tumors treated at d7
- Mice sacrificed 24h after 3rd dose
- Tumors dissociated, incubated at 37ºC for 4 hours with Brefeldin A

DR-18 potentiates poly-functional ‘super effector’ tumor CD8+ T Cells



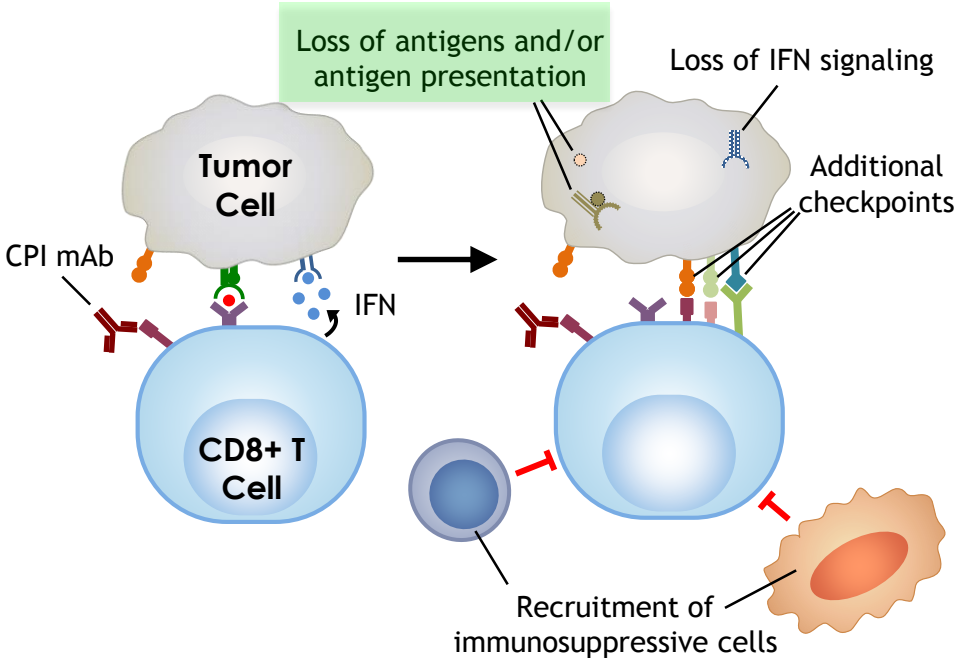


Study Design

- MC38 tumors treated at d7
- Mice sacrificed 24h after 3rd dose
- Tumors dissociated, treated with PMA/Ionomycin for 4h

DR-18 is highly effective against ICI-refractory tumors via NK cell activity

Mechanisms of resistance to immune checkpoint blockade:

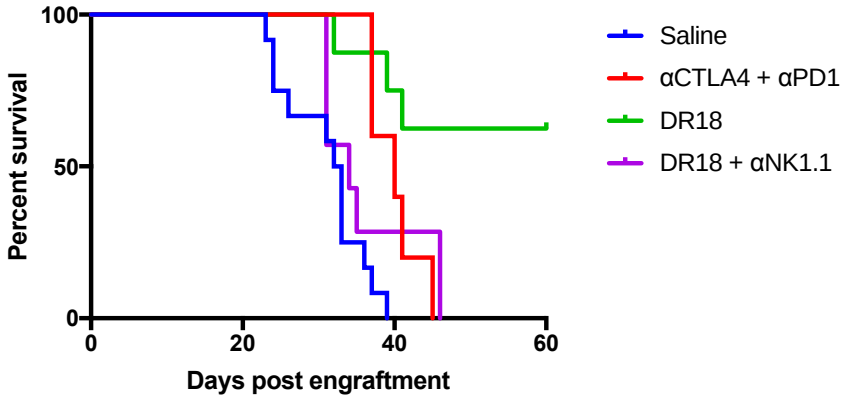


Total MHC class I loss is a common phenomenon:

Colorectal cancer	Laryngeal cancer	Cervical cancer	Bladder cancer	Prostate cancer	Breast cancer	Renal cancer	Melanoma cell lines
14%	11%	10%	25%	55%	52%	–	18%

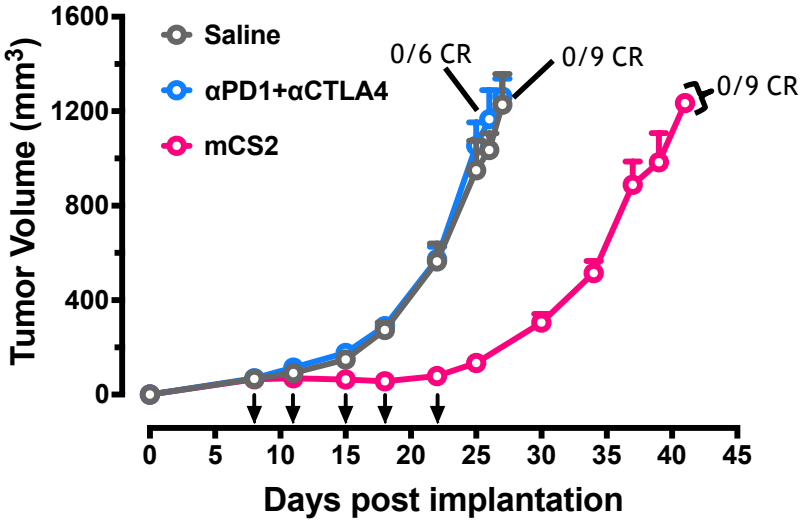
Tumor Immunology and Immunotherapy, Chapter 5. 2014

$B2m^{-/-}$ Yummer1.7 treatment model:

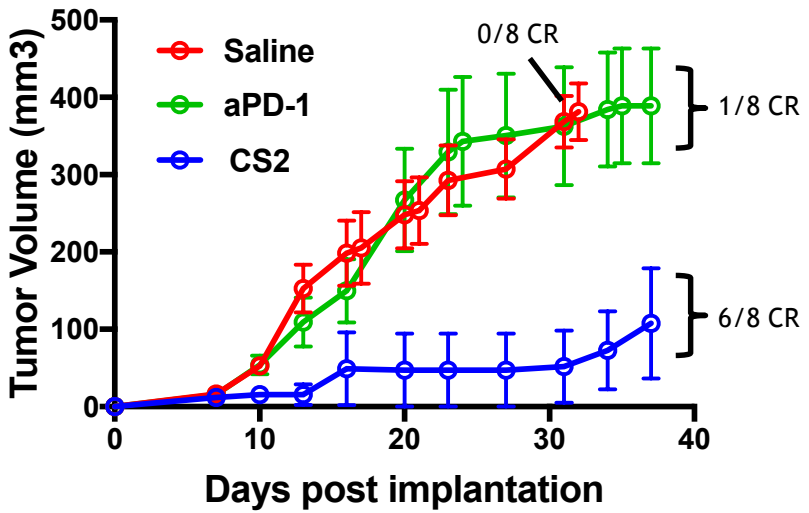


DR-18 is efficacious in multiple MHC class I deficient tumor models

B2m$^{-/-}$ MC38 tumor model:

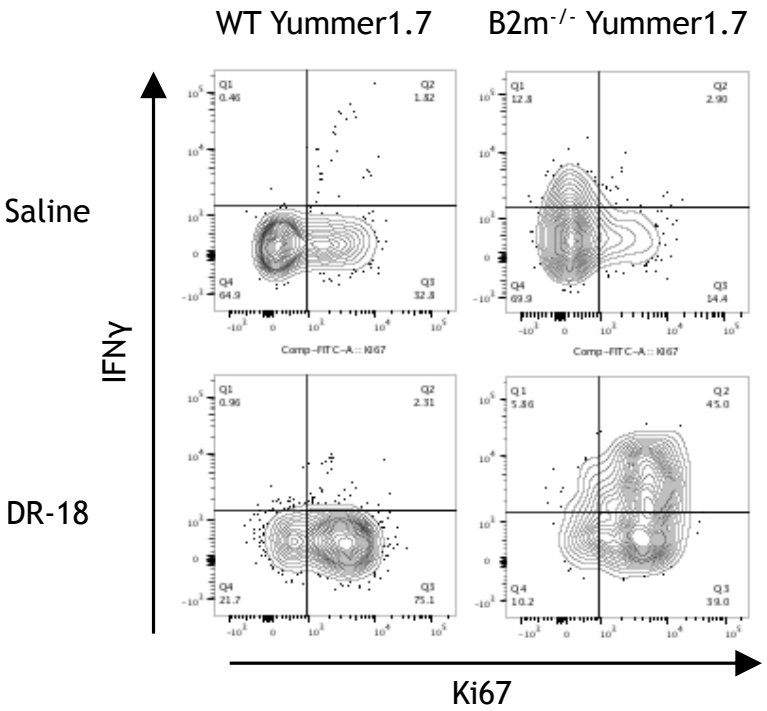


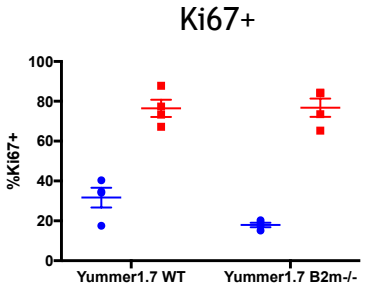
RMA/S tumor model:

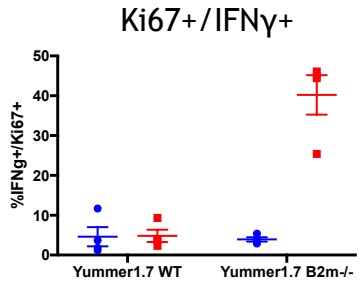


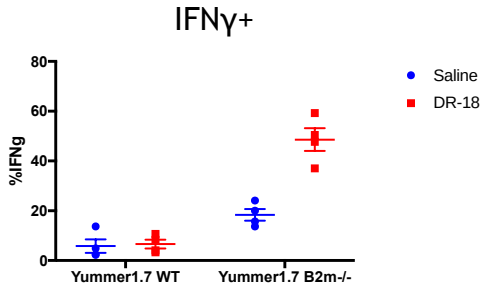
DR-18 stimulates proliferation and function of NK cells within MHCI deficient tumors

Intratumoral NK cell phenotyping:









Study Design

- Yummer1.7 tumors treated at d7
- Mice sacrificed 24h after 3rd dose
- Tumors dissociated, treated with PMA/Ionomycin for 4h

Summary

- Key anti-tumor cells (CD8 TILs and NK cells) express the IL-18R
- IL-18 activity is greatly limited by IL-18BP, a “soluble immune checkpoint” that is produced in the TME and systemically elevated in some patients
- DR-18 variants are completely independent of IL-18BP and have dramatically improved efficacy in tumor models
- DR-18 mechanism of action appears distinct from other cytokine treatments
- DR-18 is capable of treatment ICI-refractory tumors that have lost MHC class I through stimulation of anergic/exhausted NK cells

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