SITC Winter School

Dendritic - NK cell mechanisms

Lewis L. Lanier
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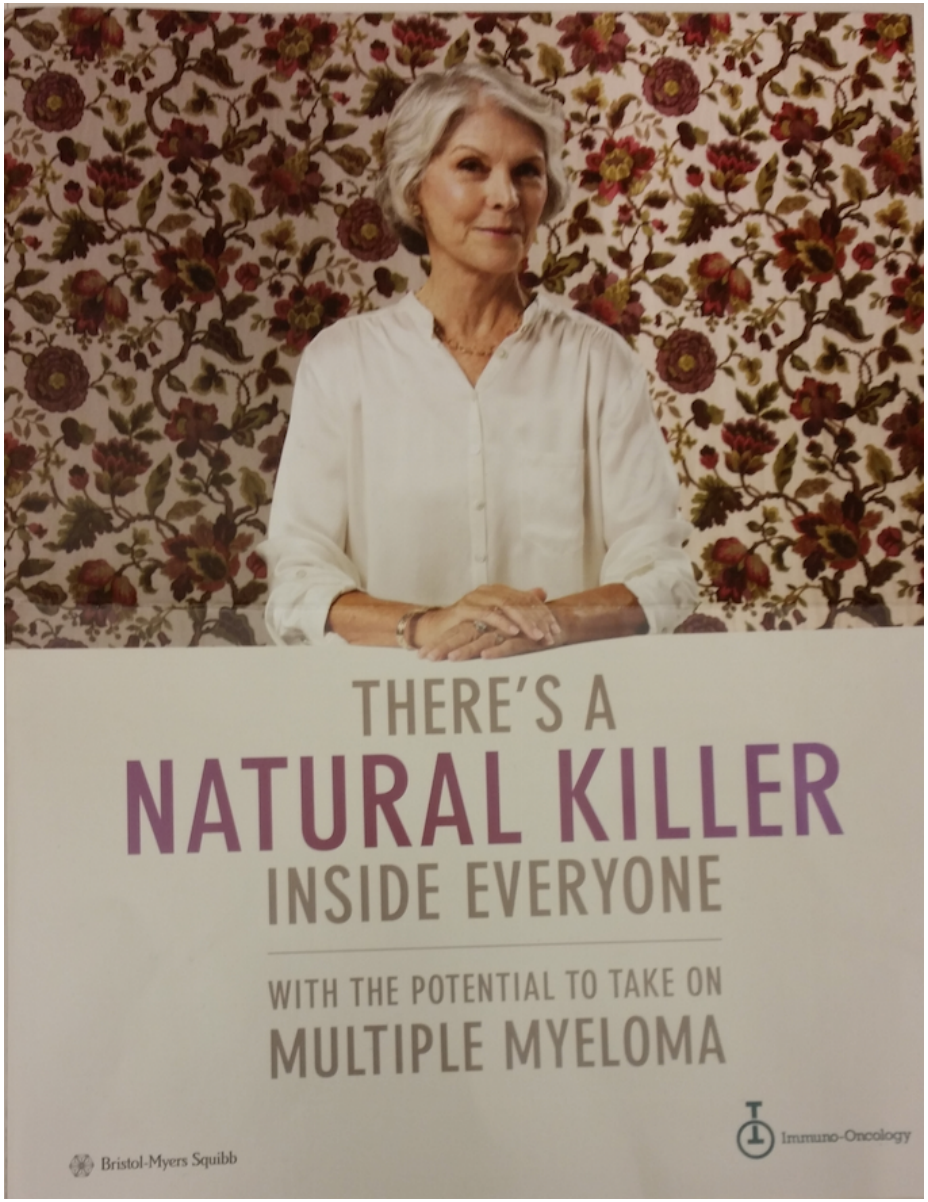
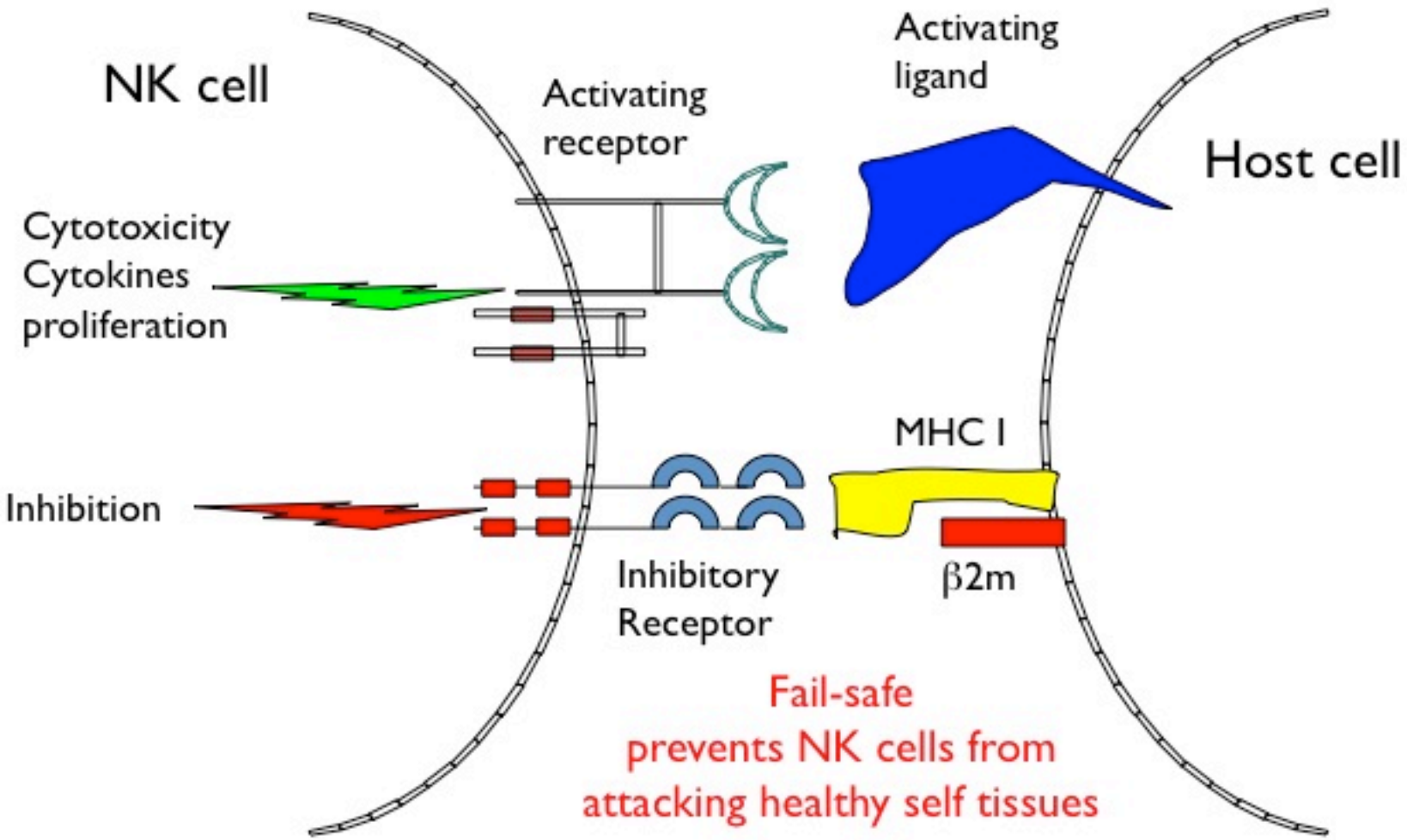
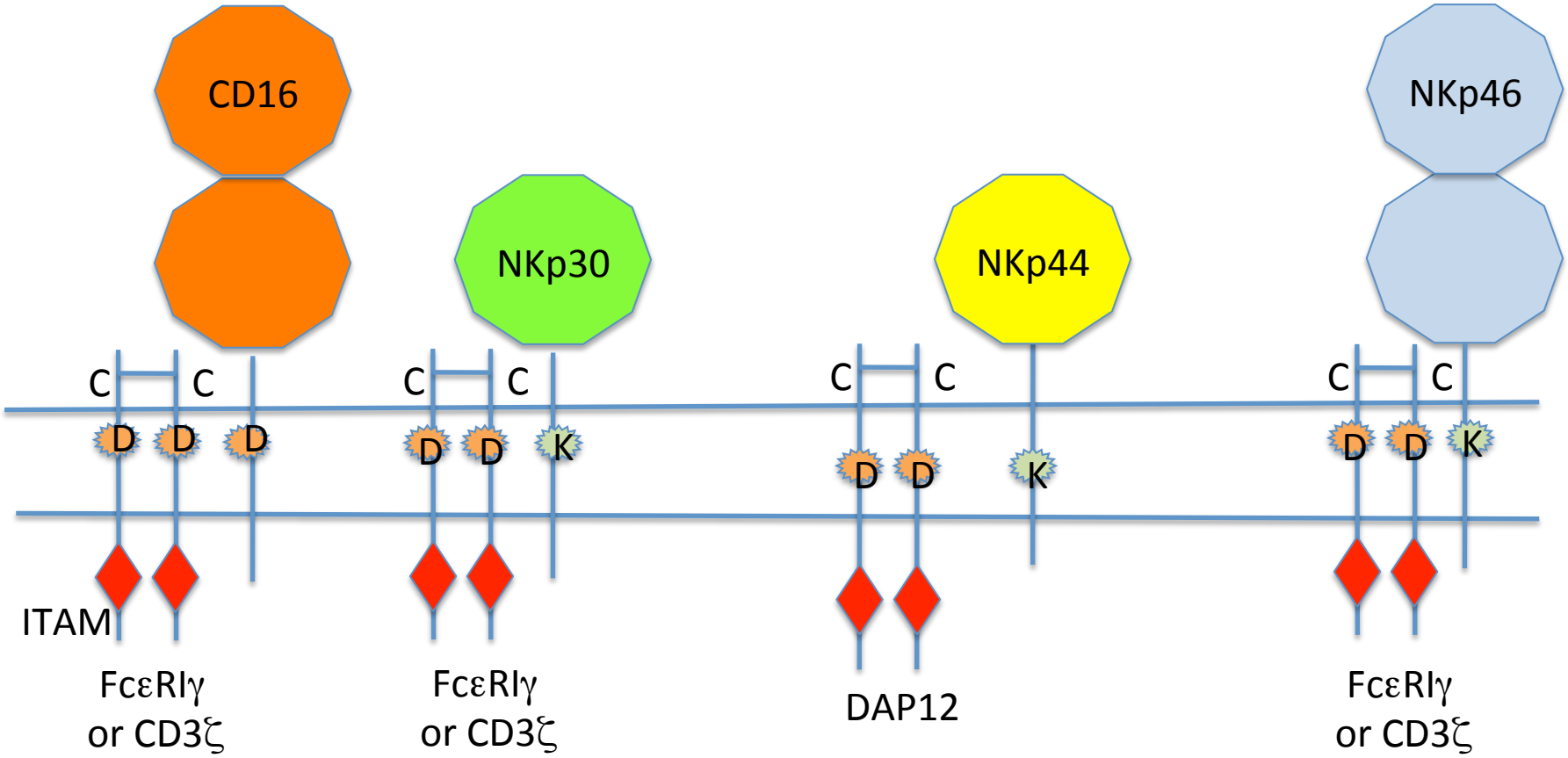

THERE'S A
NATURAL KILLER
INSIDE EVERYONE
WITH THE POTENTIAL TO TAKE ON
MULTIPLE MYELOMA
Bristol-Myers Squibb
Immuno-Oncology

NK cell functions are controlled by a balance of inhibitory and activating receptors

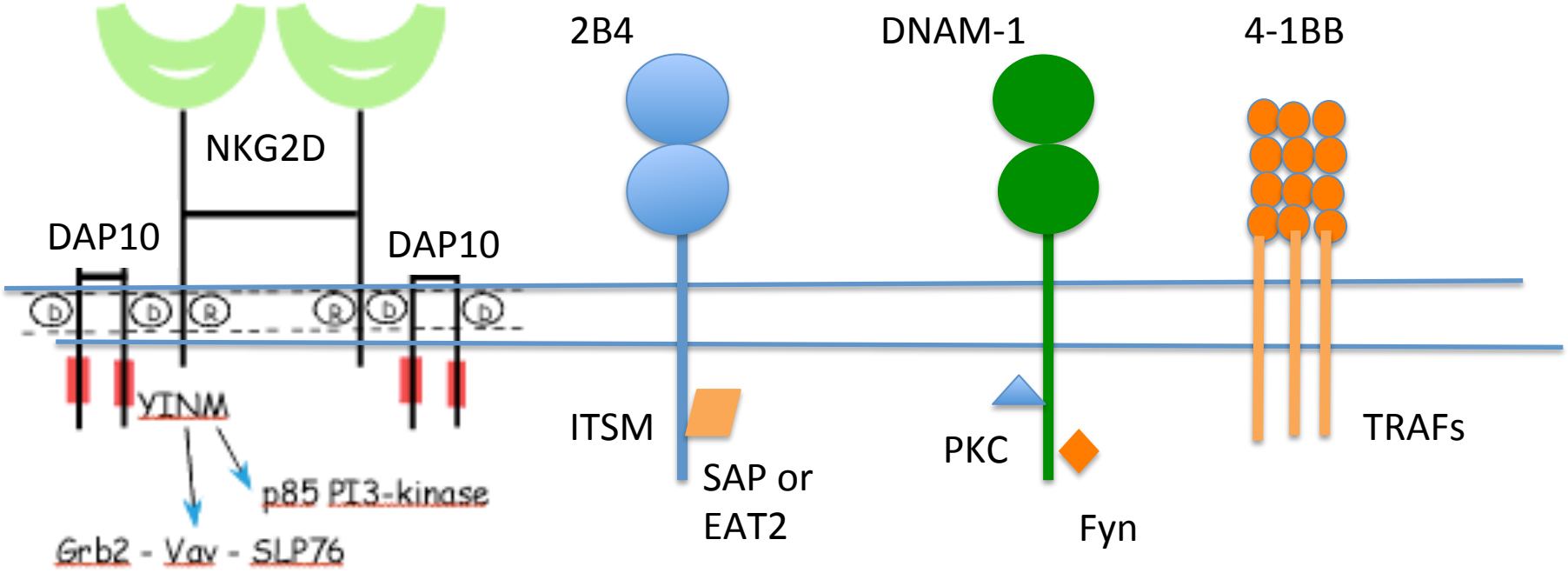


ITAM-based activating NK receptors



Miller & Lanier Ann Rev Cancer Biology 2019

Co-activating NK receptors



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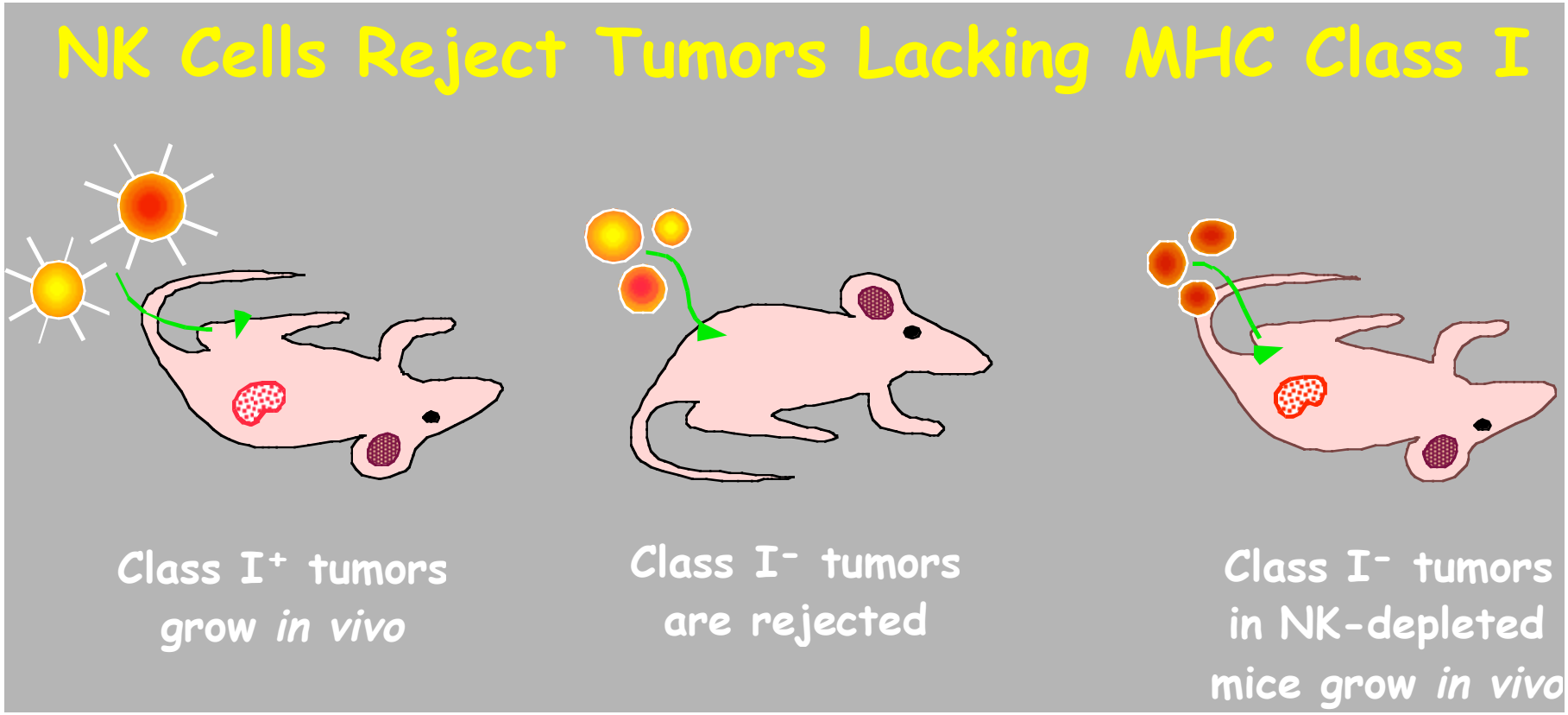
NK cells like to kill cells lacking MHC class I – "missing-self"

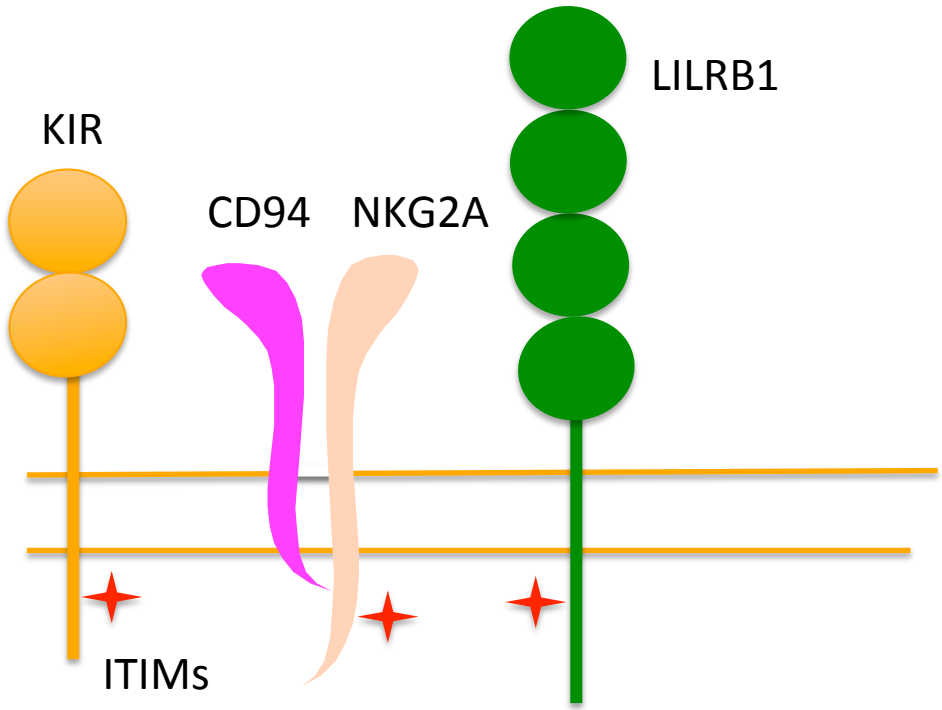


Karre *et al. 1986* Nature 319:675

Physiological role for NK cell recognition and elimination of MHC class I-negative cells

Virus	Protein	Effect on class I
Adenovirus	E3-k19	Retain in ER
HSV-1,2	ICP47	Blocks TAP
EBV	EBNA1	Block peptide generation
HCMV	US2, US11	ER to cytosol
HCMV	US3	Retain in ER
HCMV	US6	Blocks TAP
HCMV	US10	Degrades HLA-G
MCMV	m152	Retain in ER
MCMV	m04	Associates with H-2
MCMV	m06	Lysosomal degradation
HHV8	K3, K5	Endocytosis
HIV-1	Nef	Endocytosis

MHC class I Inhibitory Receptors on Human NK cells



Tumors can escape $CD8^+$ T cell surveillance by loss of MHC class I

*Membrane MHC class I expression on primary human melanoma cells ranges from 100 to 0% (median, 70%)

Lack of MHC class I expression on most of malignant cells (>50%) was observed in 34 of 92 cases (37%)

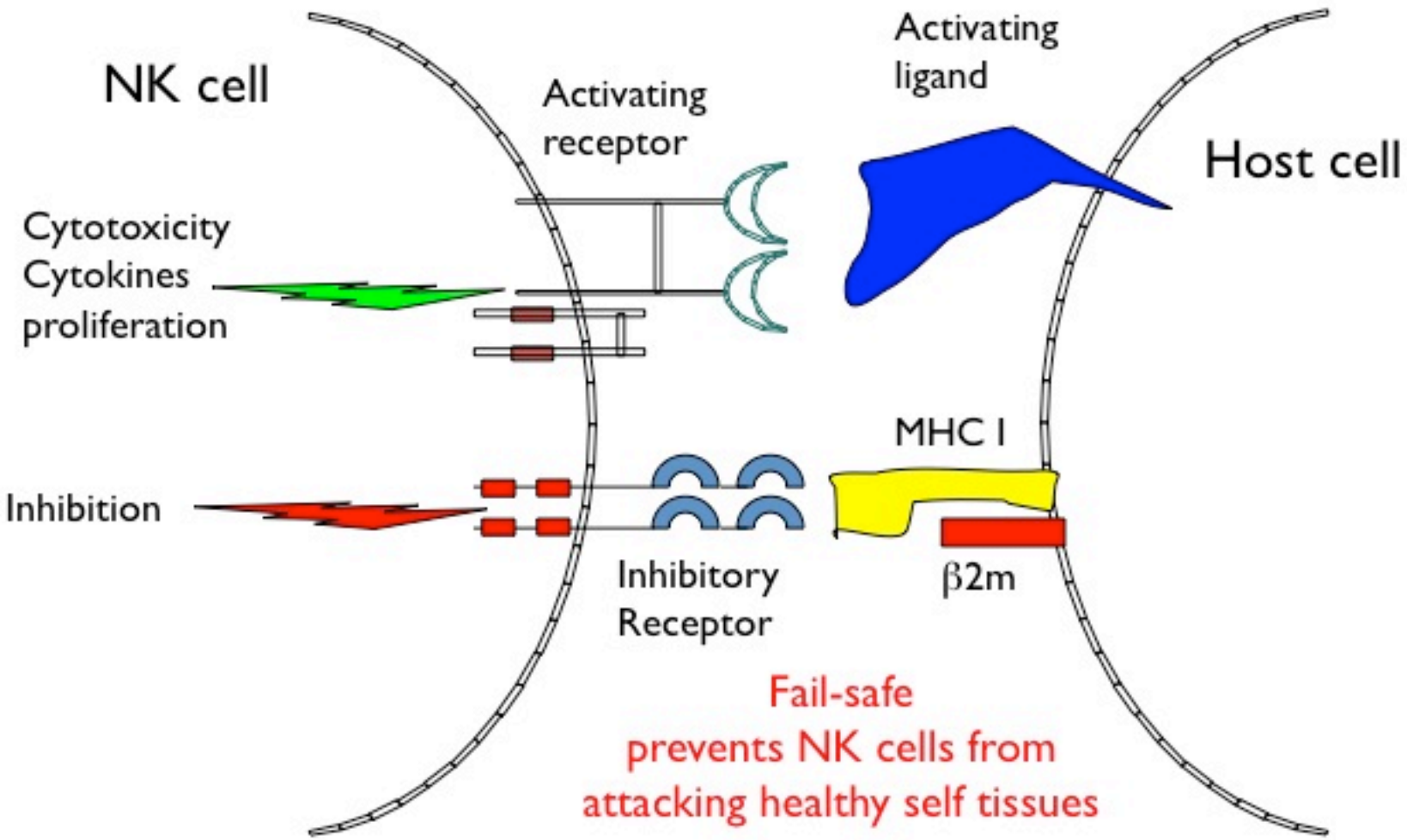
Due to transcriptional down-regulation of HLA-A,-B,-C and β2-microglobulin –not mutation

Rodig SJ, *et al. Sci Trans Med* 2018 10:eaar3342

How do MHC class I-negative tumors escape NK cell recognition and elimination?

How can we re-engage NK cells against these tumors?

NK cell functions are controlled by a balance of inhibitory and activating receptors



Why don't NK cells kill HLA class I-negative tumors arising in cancer patients?

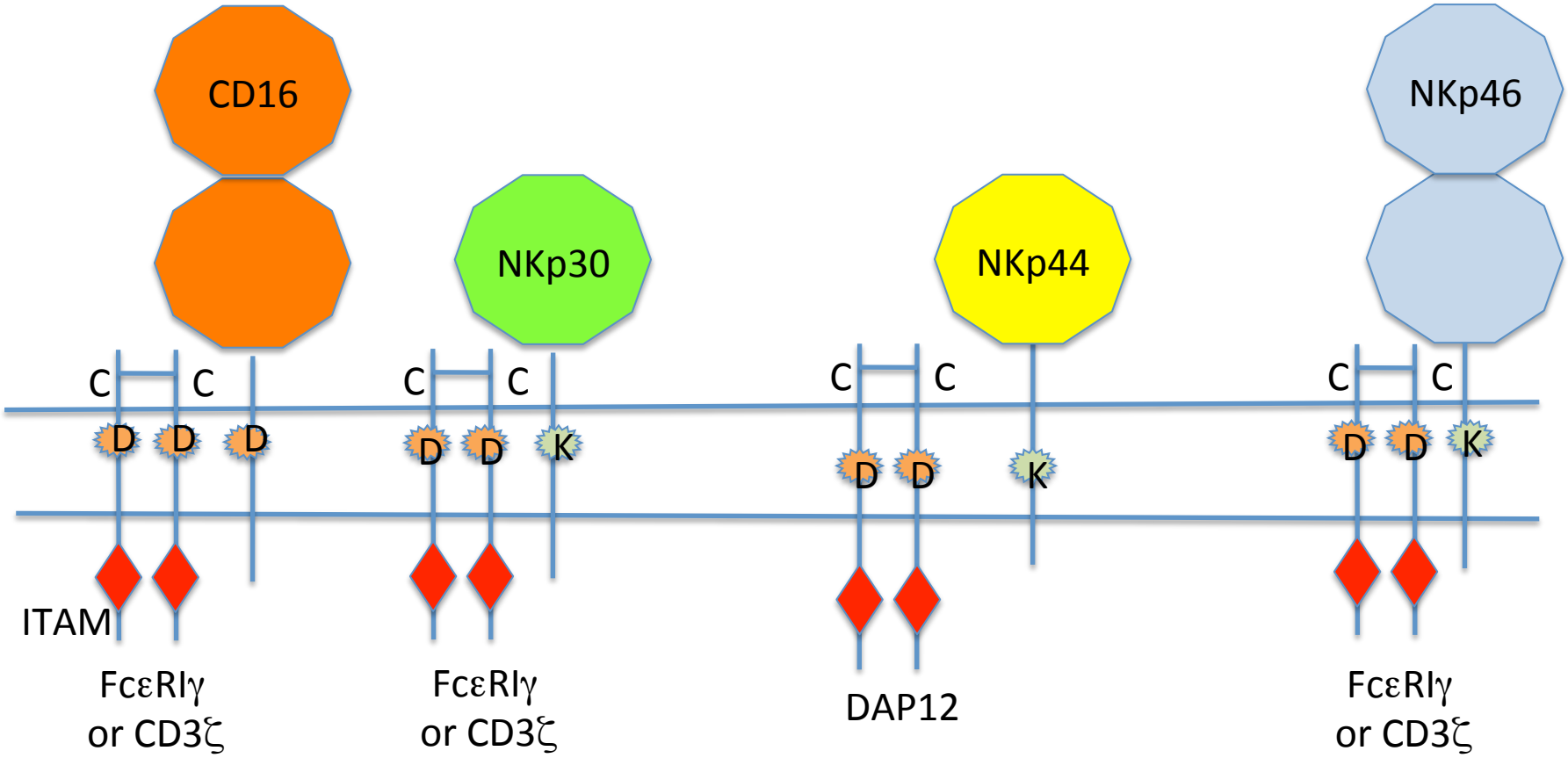
*Tumors lack ligands for activating receptors

*Redundant inhibitory receptors other than for class I dampen NK cell responses

*NK cells kill some tumors, but without cytokines don't expand – then become "de-sensitized"

*Tumor microenvironment suppresses NK cell (e.g. NK cells hate Transforming Growth Factor β)

ITAM-based activating NK receptors



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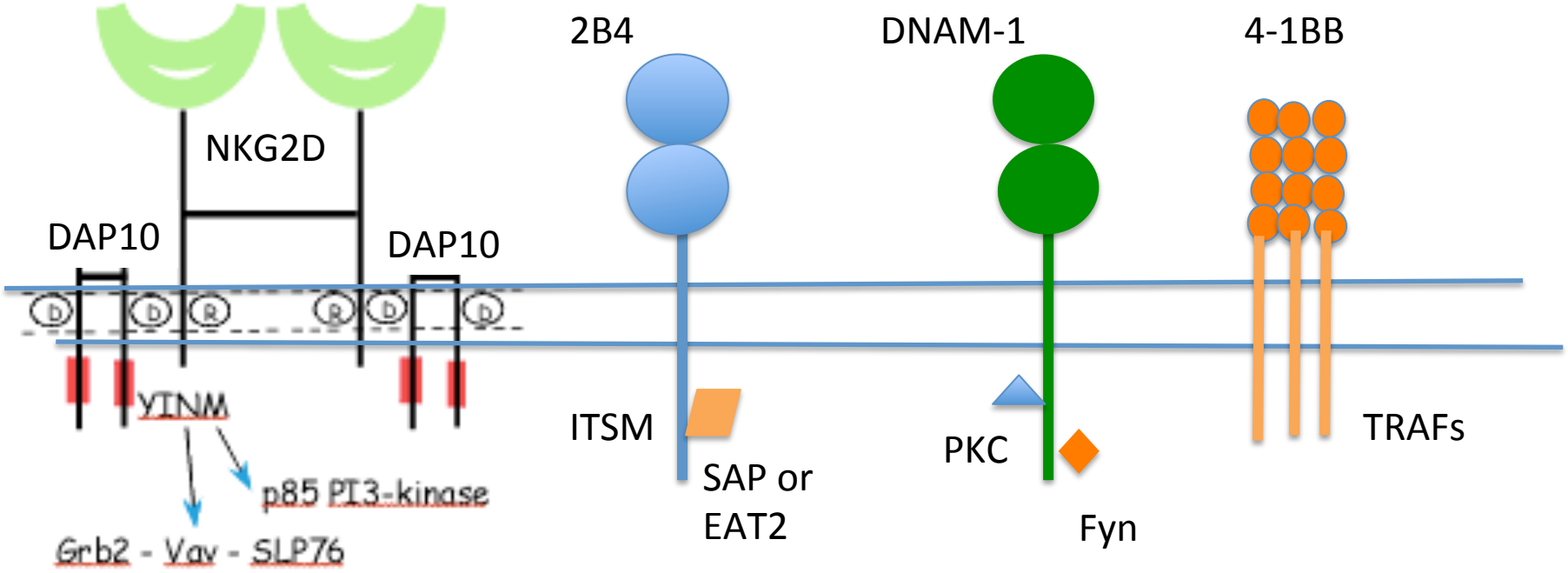
Co-activating NK receptors



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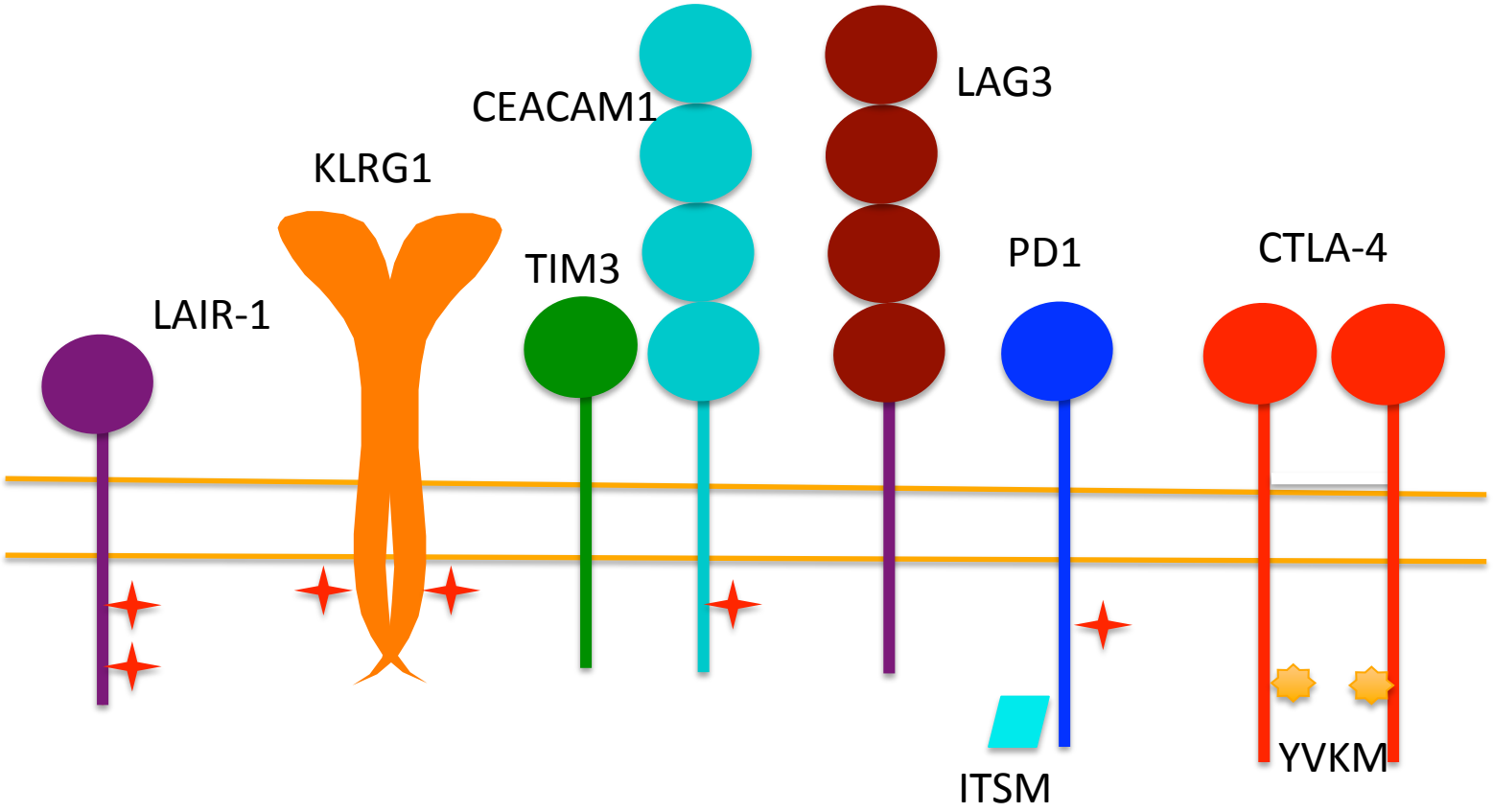
Non-MHC Inhibitory Receptors on Human NK cells



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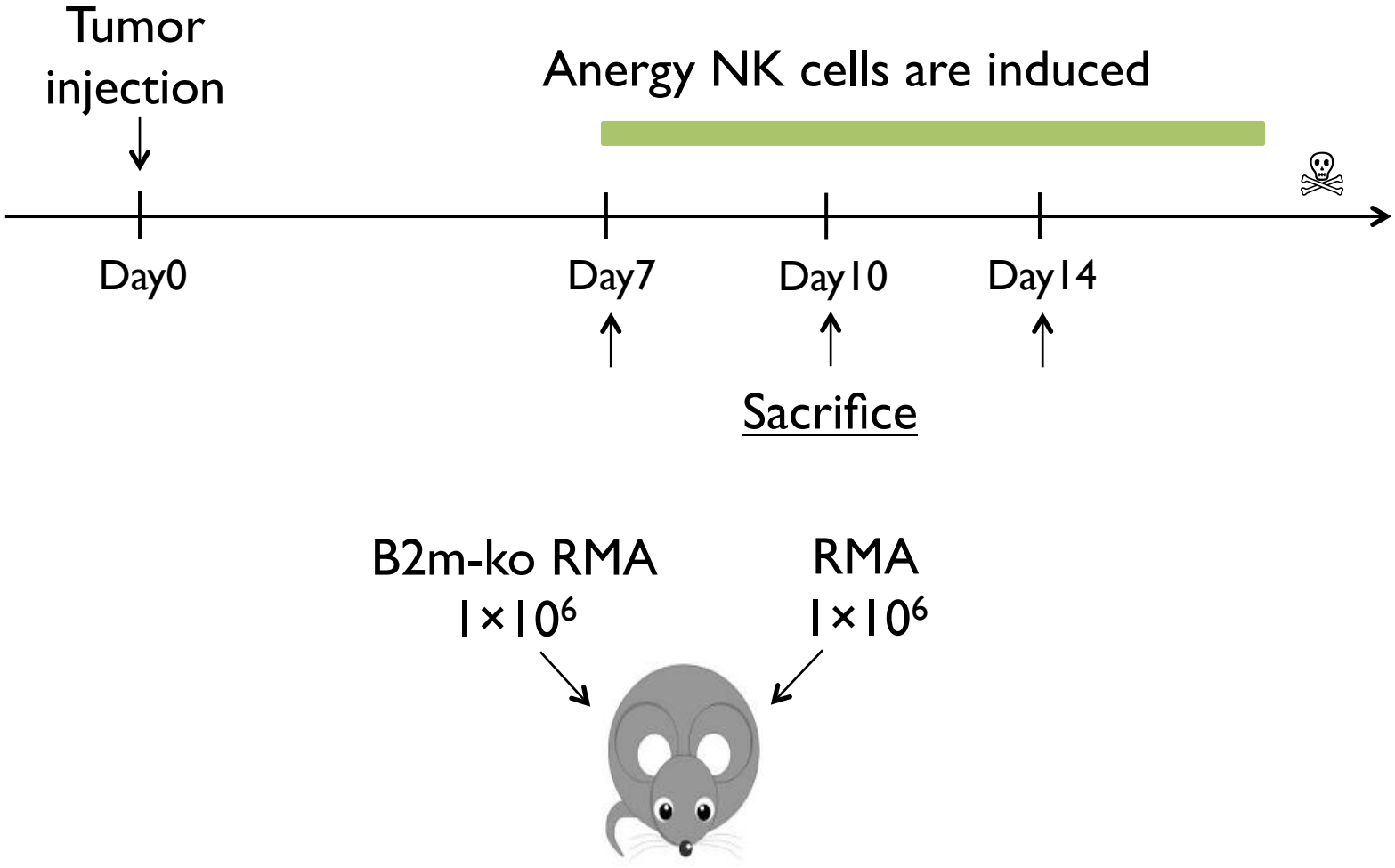
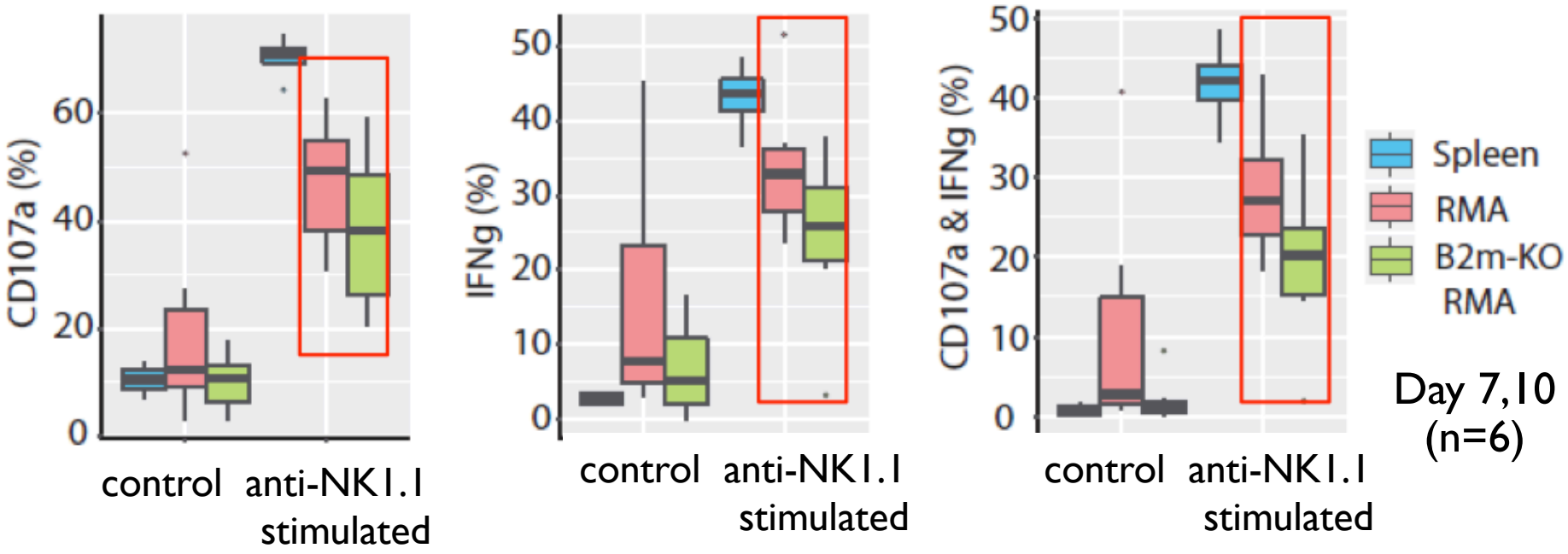
In vivo model of anergy NK cells induced in tumor MHC class I –negative tumor environment

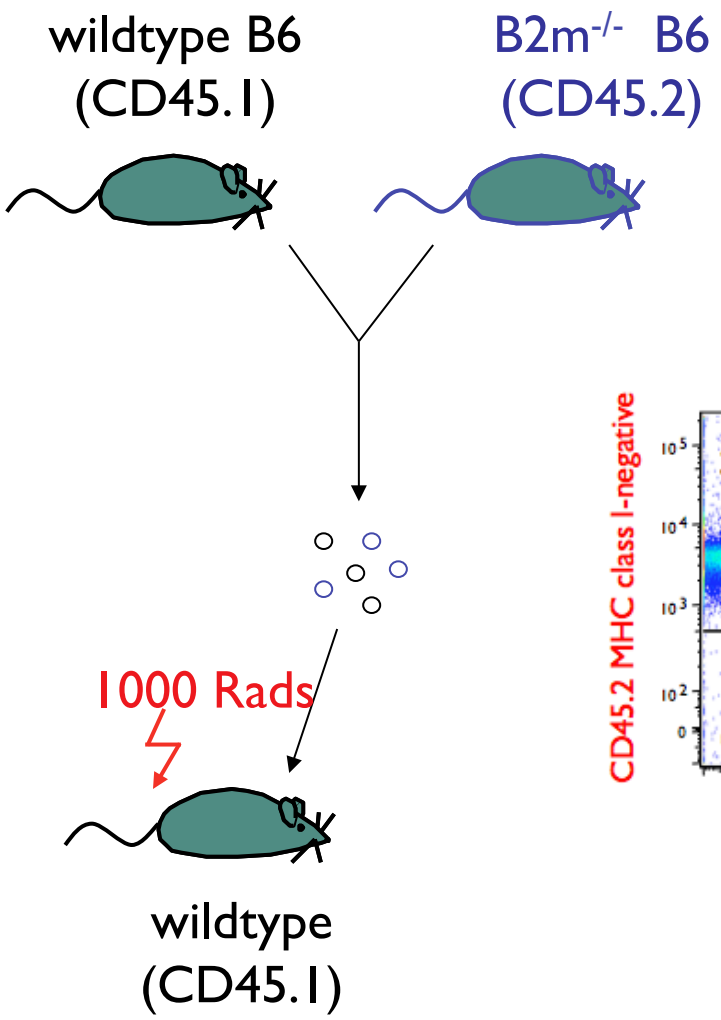


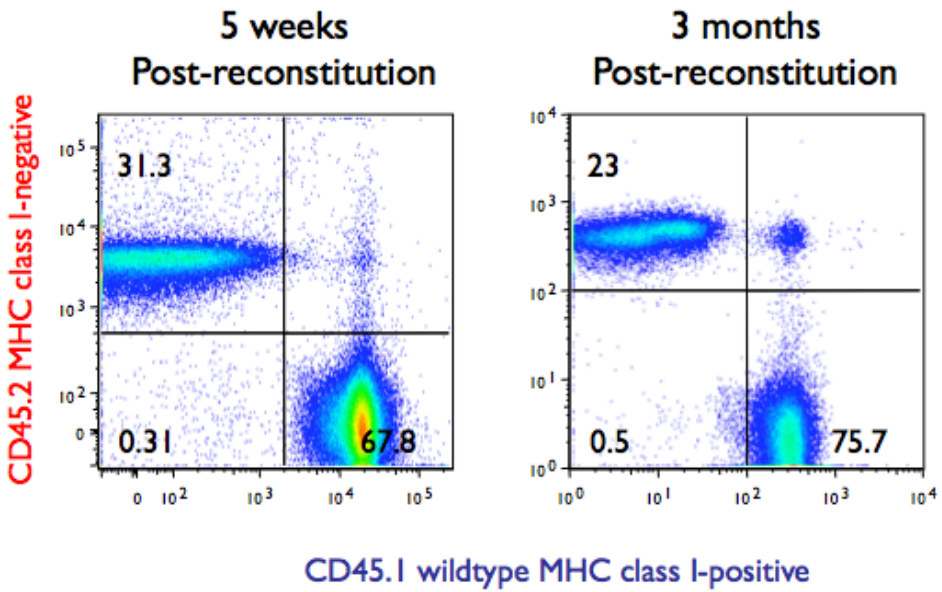
NK cells infiltrating B2m-ko RMA tumor are hypo-responsive *ex vivo*



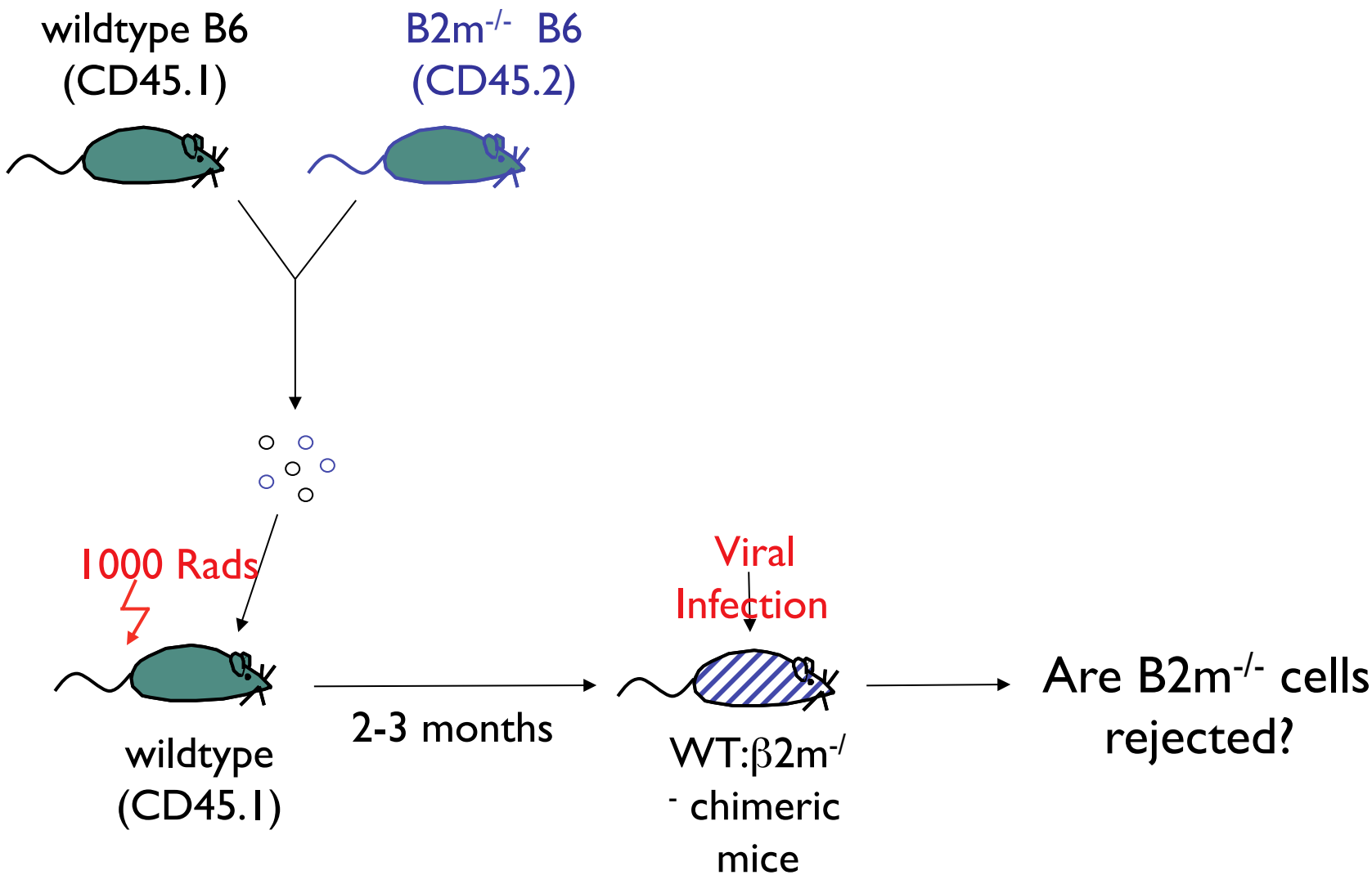
In progress – RNA-Seq on NK cells infiltrating RMA versus B2m-ko RMA

NK cells tolerate MHC class I-deficient hematopoietic cells in mixed bone marrow chimera

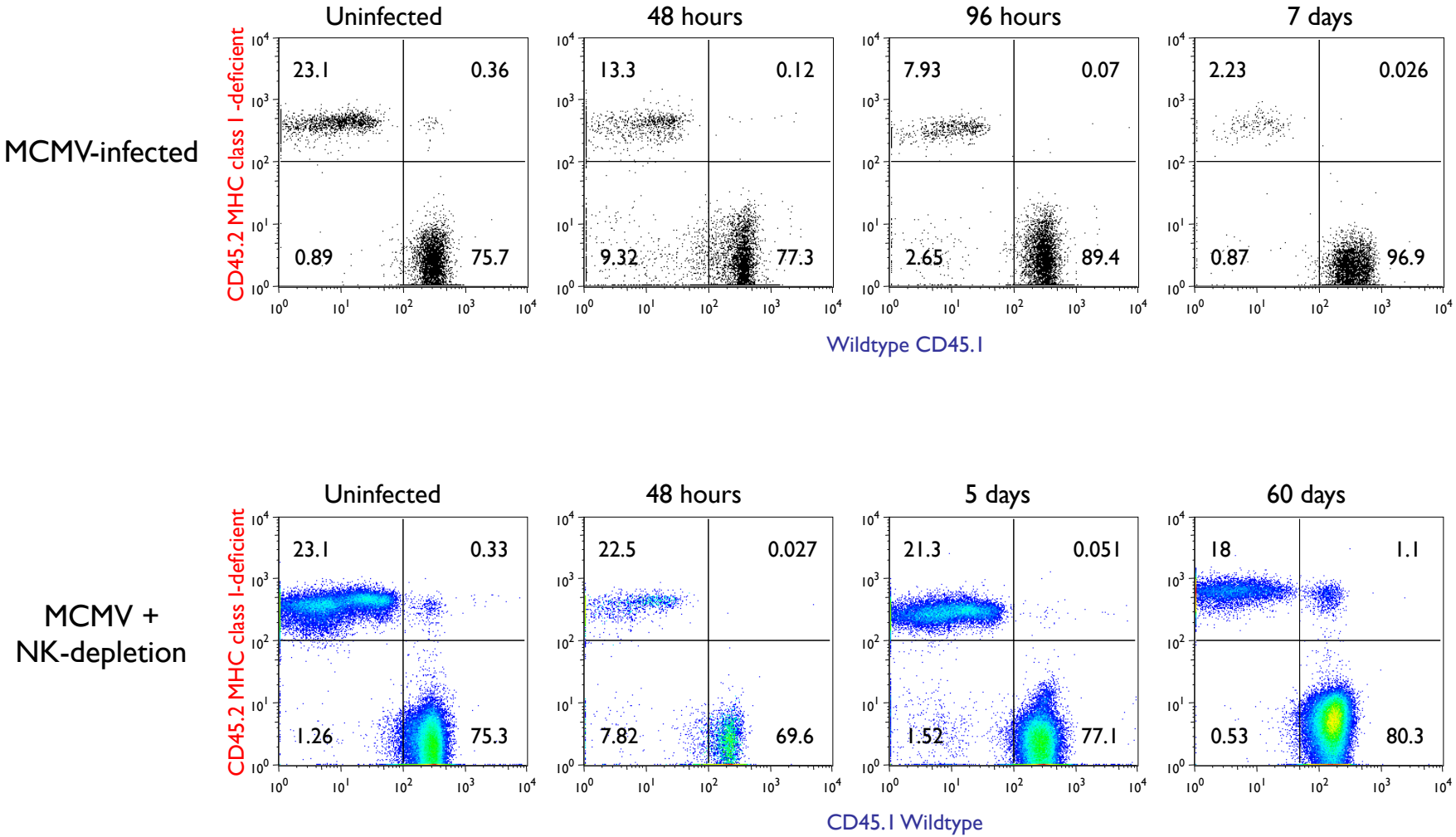




Can NK cell tolerance to MHC class I-negative cells be broken by NK cell activation?



NK cells reject MHC class-I negative hematopoietic cells in chimeric mice after viral infection -tolerance is broken



Engaging NK cells to kill MHC class I-negative tumors

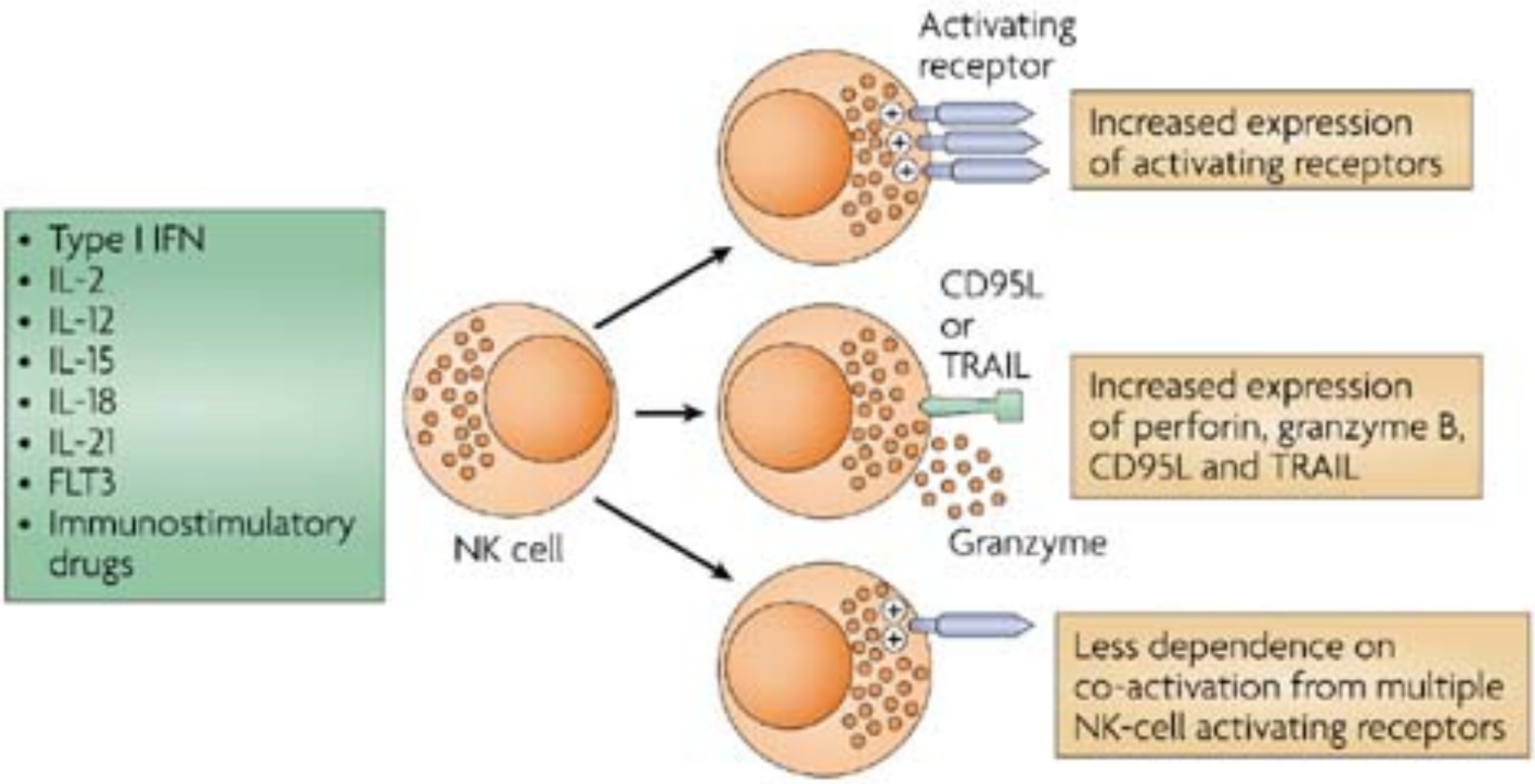
*Chronic exposure to MHC class I-negative tumors can render NK cells tolerant

*Blocking KIR or NKG2A MHC class I inhibitory receptors alone in cancer patients may simply result in NK cell tolerance

*Activation of NK cells with cytokines (IL-12 and others) can brake the tolerance and allow kill of MHC class I-negative tumors

STRATEGIES FOR THERAPEUTICALLY MODULATING NK CELL FUNCTION

Factors boosting NK cell lytic activity



Ljunggren & Malmberg NRI 2007

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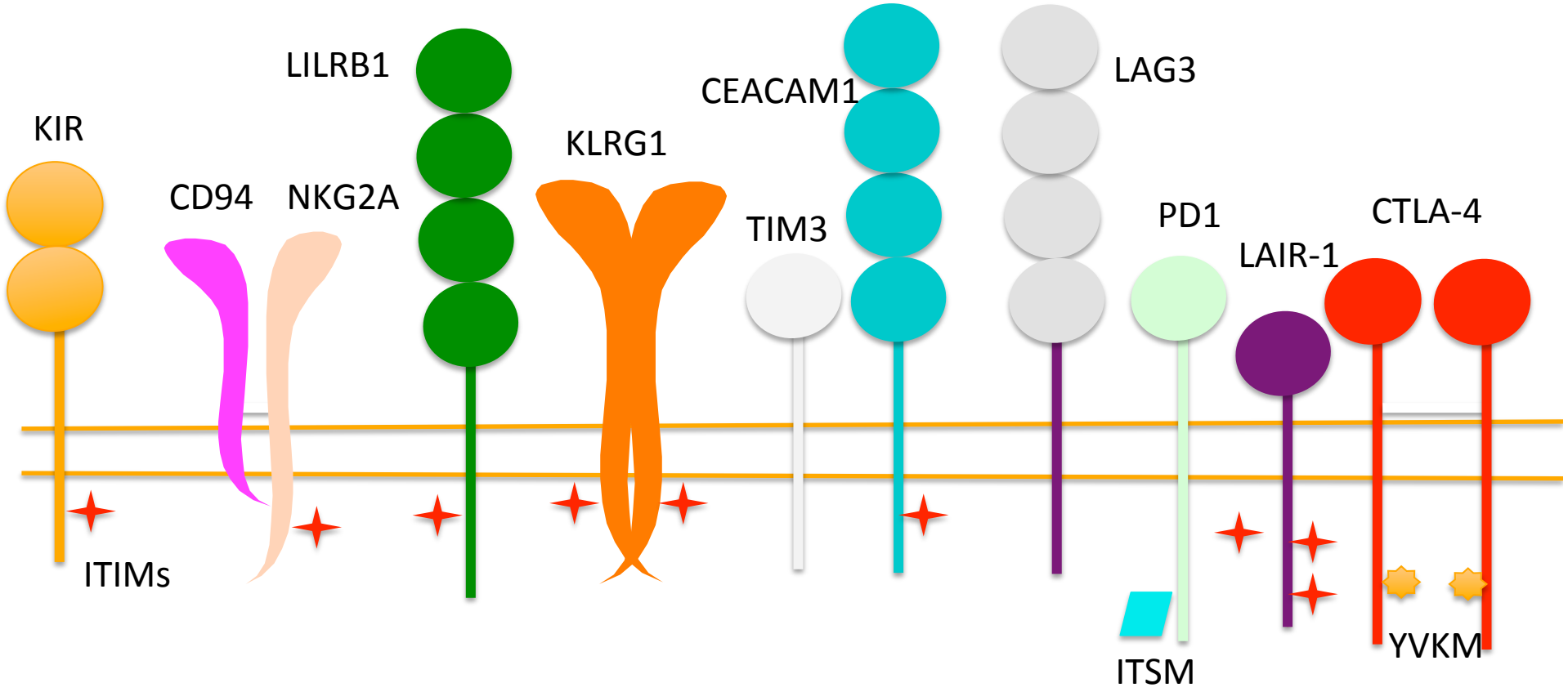
Inhibitory Receptors on Human NK cells



Checkpoint blockade therapies

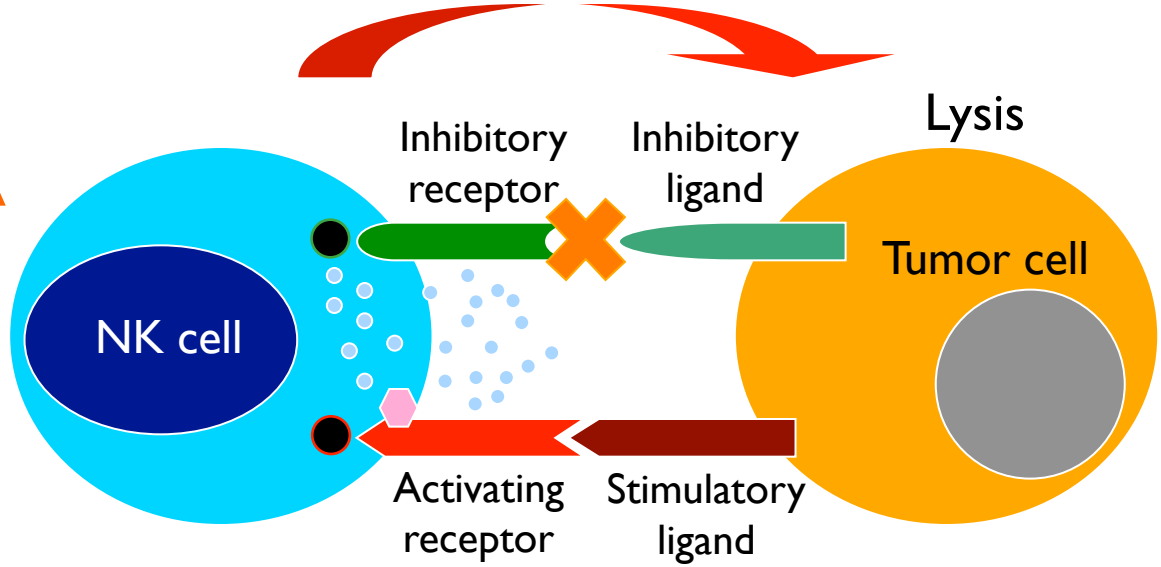
anti-KIR

anti-NKG2A

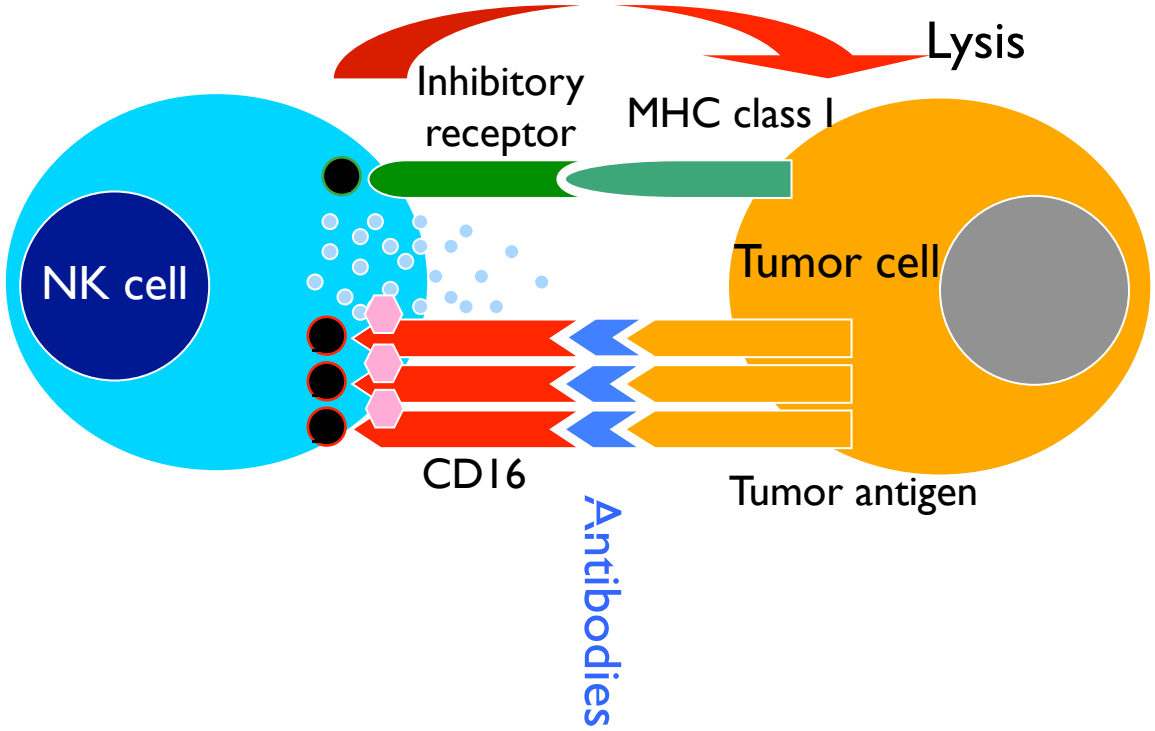
anti-PD1

anti-Tim3

anti-LAG3



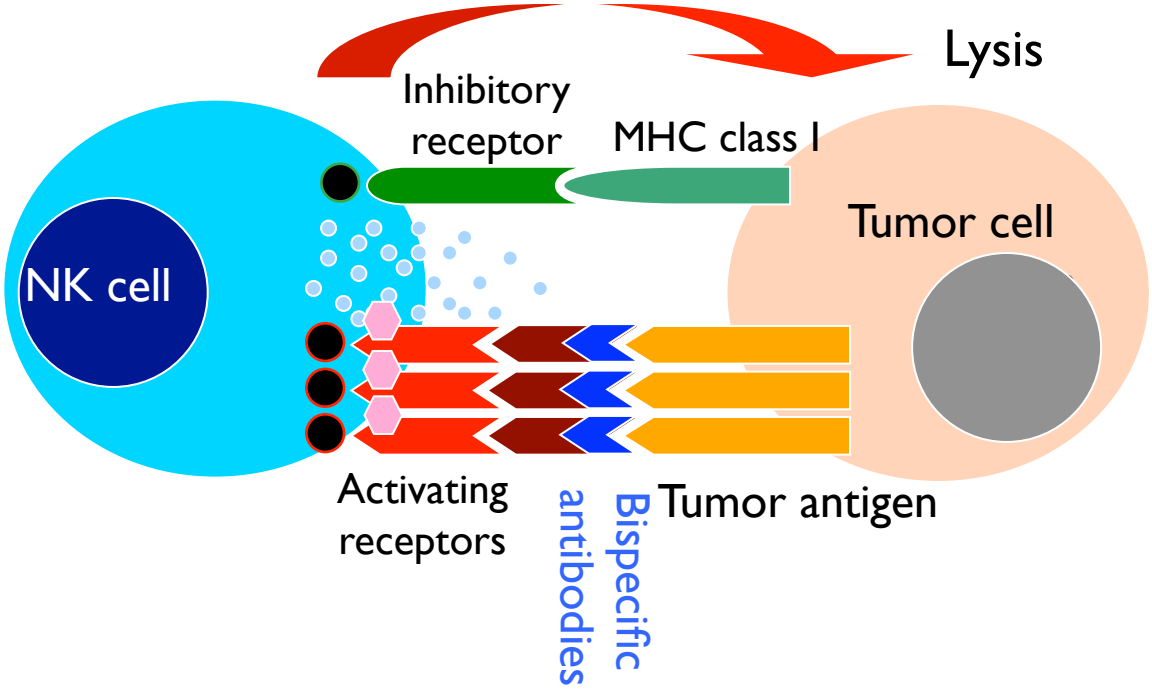
Antibody-dependent cellular cytotoxicity



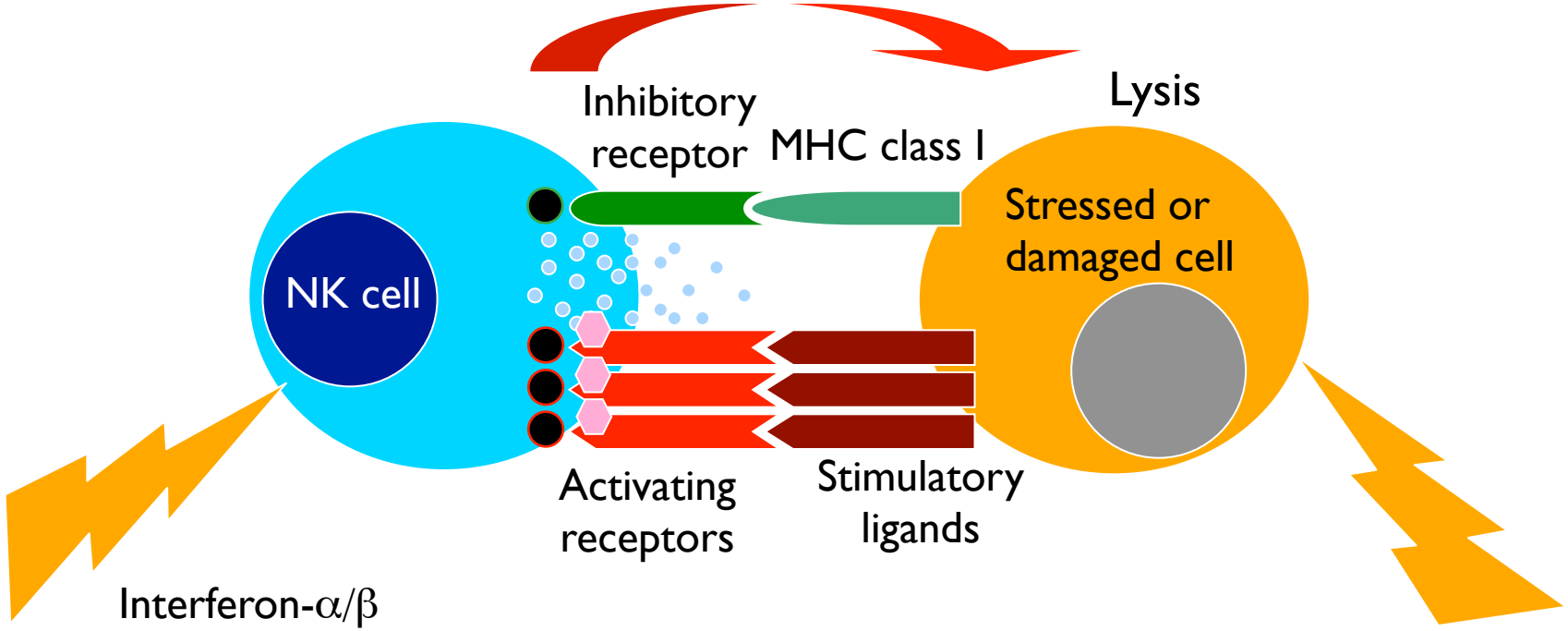
rituximab, trastuzumab, daratumumab

Bispecific antibodies

– anti-tumor x anti-NK activating receptor



Therapies that up-regulate stress-induced ligands on tumors or agents that activate NK cells



Interferon-α/β

IL-15

IL-12

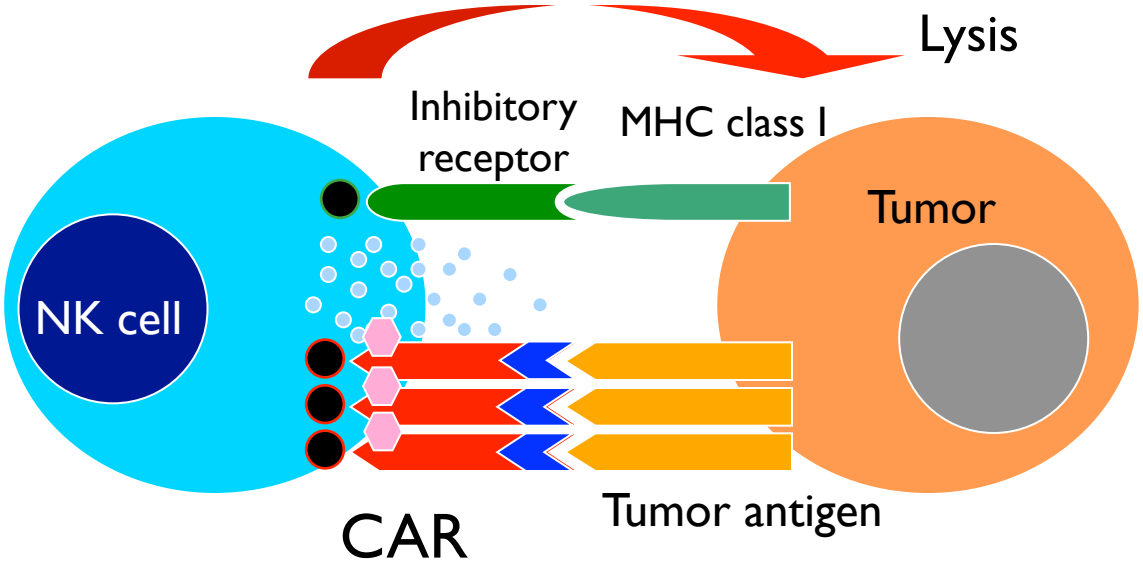
Agonist co-stimulatory antibodies (e.g. CD137, NKG2D)

Irradiation

Chemotherapy

CAR NK cells

Chimeric antigen receptors



CAR

anti-CD19-cytoplamic CD137-CD3ζ

ARTICLES
https://doi.org/10.1038/s41591-018-0085-8
nature medicine

A natural killer–dendritic cell axis defines checkpoint therapy–responsive tumor microenvironments

Kevin C. Barry[1,2], Joy Hsu[1,2], Miranda L. Broz[1,2], Francisco J. Cueto[1,3,4], Mikhail Binnewies[1], Alexis J. Combes[1,2], Amanda E. Nelson[1,2], Kimberly Loo[2,5,6], Raj Kumar[1,2], Michael D. Rosenblum[6], Michael D. Alvarado[6], Denise M. Wolf[7], Dusan Bogunovic[8], Nina Bhardwaj[9], Adil I. Daud[6], Patrick K. Ha[10], William R. Ryan[10], Joshua L. Pollack[11], Bushra Samad[1,2], Saurabh Asthana[2], Vincent Chan[1,2] and Matthew F. Krummel[1,2*]

Melanoma patients with more "stimulatory" dendritic cells have better survival

a

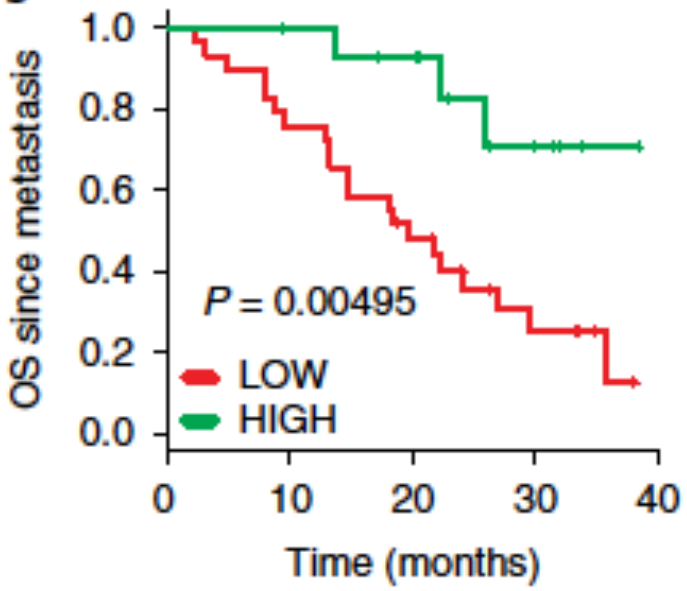
Cell type:

SDC: stimulatory DCs
($CD103^+$ $BDCA\text{-}3^+$)

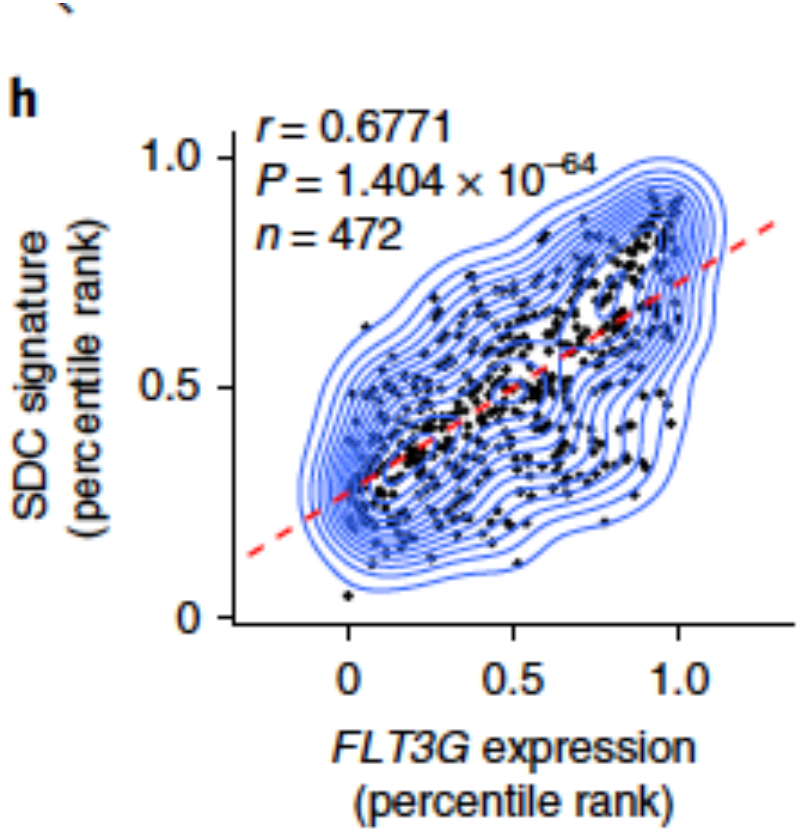
Signature genes:

KIT, *CCR7*, *BATF3*, *FLT3*,
ZBTB46, *IRF8*, *BTLA*, *MYCL1*

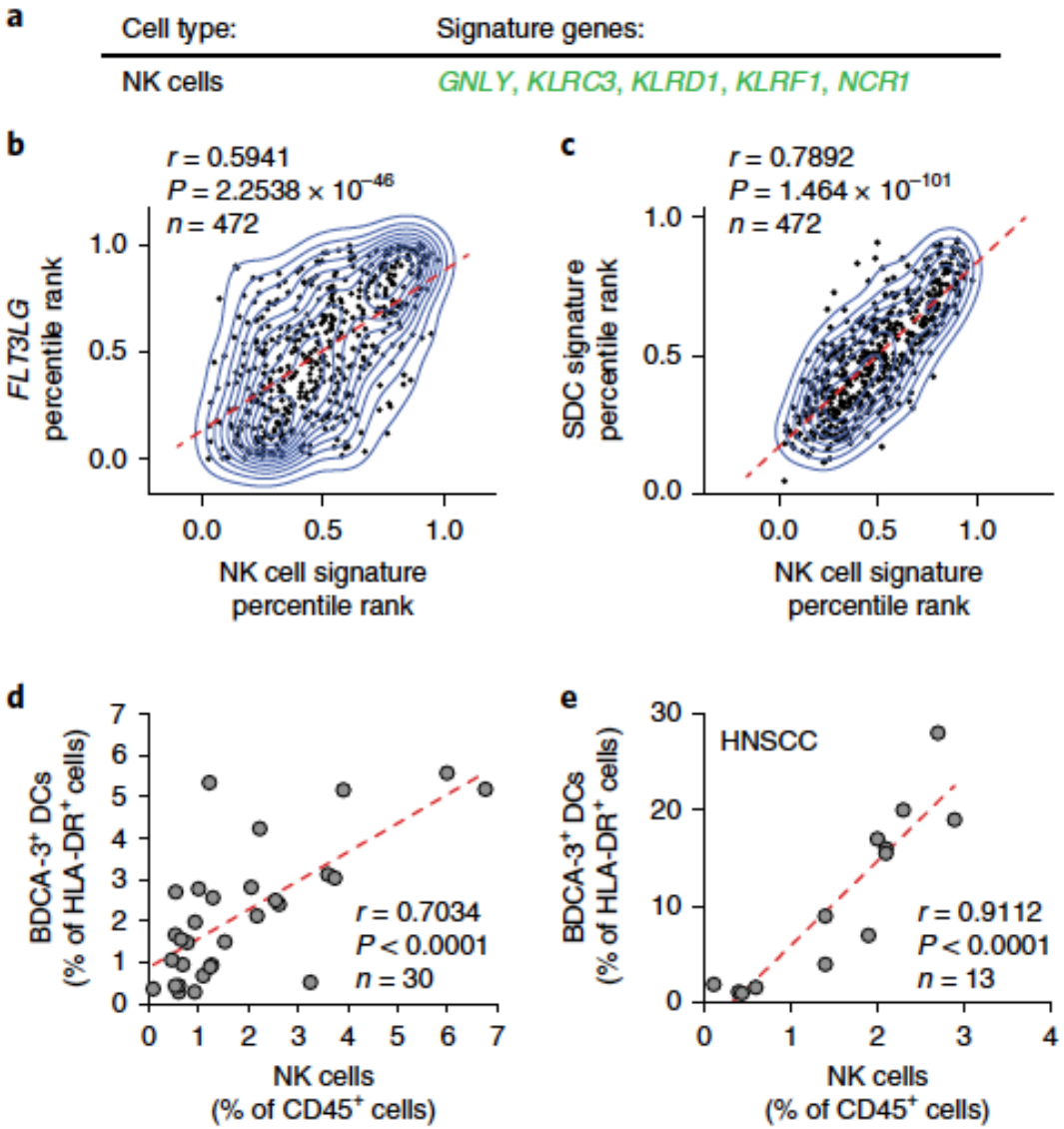
b



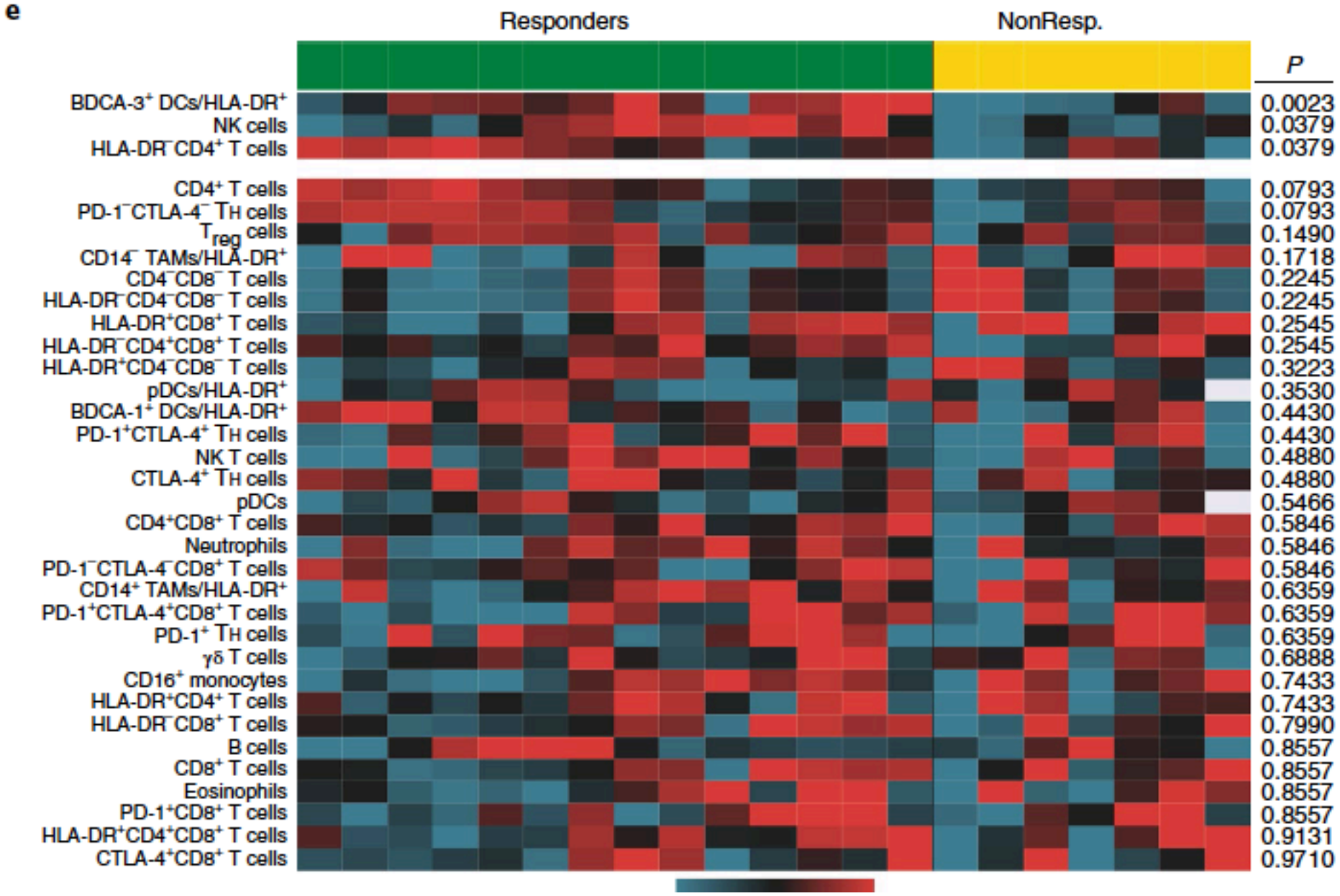
"stimulatory" dendritic cell gene expresssion tracked with FLT3LG cytokine expression



FLT3LG expression correlates with NK cells in melanoma and head & neck cancer patients



Response to PD1 blockade in melanoma correlates with NK cells and DC in TIL



CANCER

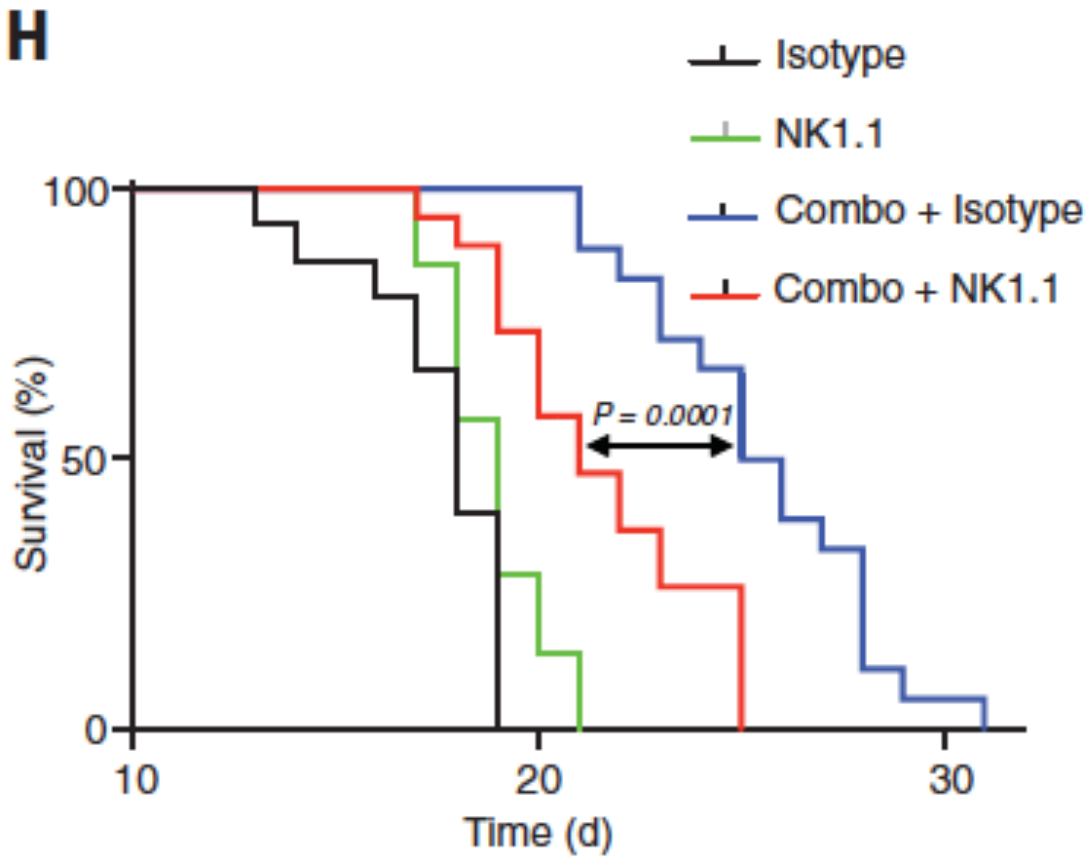
NK cell–mediated cytotoxicity contributes to tumor control by a cytostatic drug combination

Marcus Ruscetti[1*], Josef Leibold[1*], Matthew J. Bott[1*], Myles Fennell[1], Amanda Kulick[2], Nelson R. Salgado[1], Chi-Chao Chen[1], Yu-jui Ho[1], Francisco J. Sanchez-Rivera[1], Judith Feucht[3], Timour Baslan[1], Sha Tian[1], Hsuan-An Chen[1], Paul B. Romesser[1], John T. Poirier[2,4], Charles M. Rudin[2,4], Elisa de Stanchina[2], Eusebio Manchado[1], Charles J. Sherr[5,6], Scott W. Lowe[1,6]†

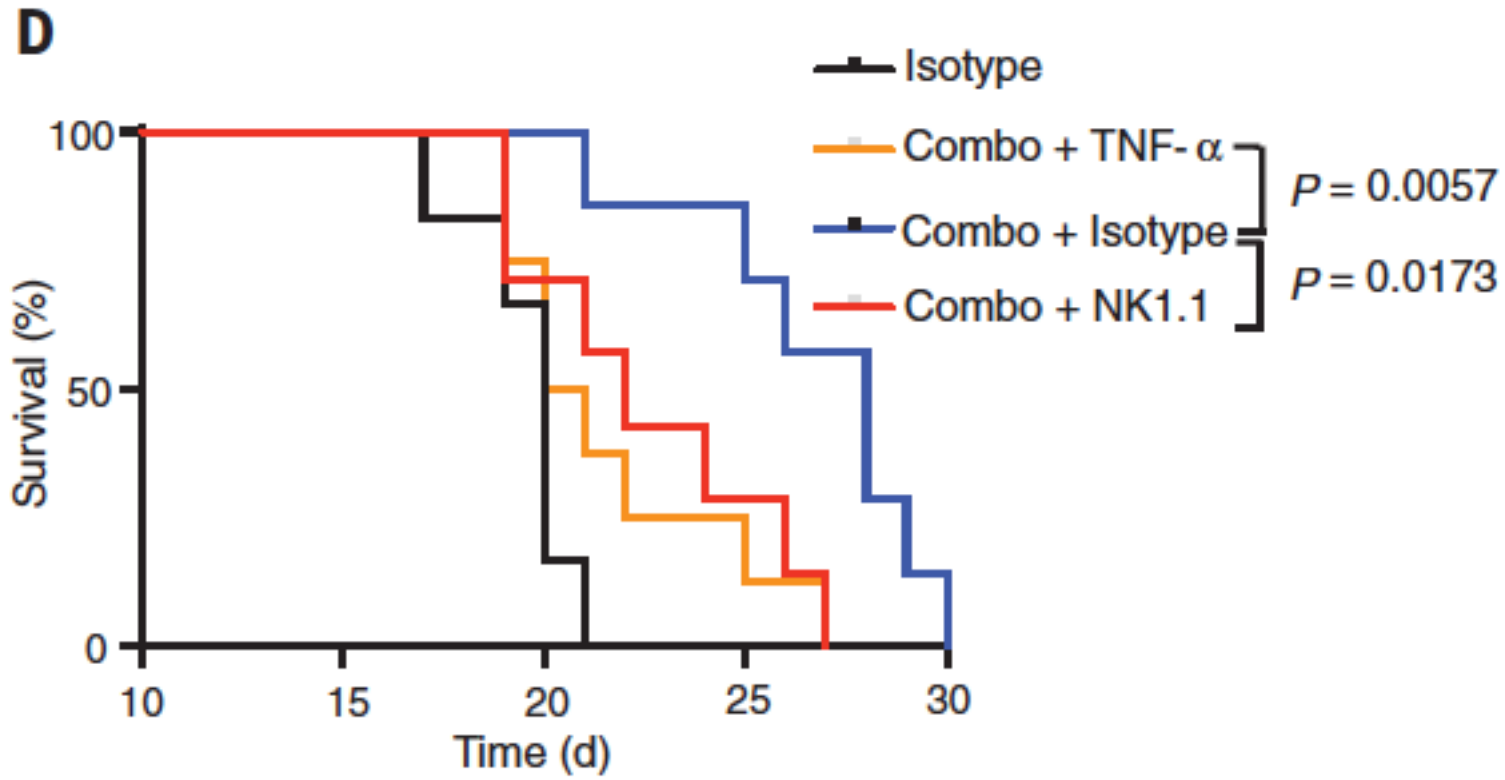
Molecularly targeted therapies aim to obstruct cell autonomous programs required for tumor growth. We show that mitogen-activated protein kinase (MAPK) and cyclin-dependent kinase 4/6 inhibitors act in combination to suppress the proliferation of KRAS-mutant lung cancer cells while simultaneously provoking a natural killer (NK) cell surveillance program leading to tumor cell death. The drug combination, but neither agent alone, promotes retinoblastoma (RB) protein-mediated cellular senescence and activation of the immunomodulatory senescence-associated secretory phenotype (SASP). SASP components tumor necrosis factor–α and intercellular adhesion molecule–1 are required for NK cell surveillance of drug-treated tumor cells, which contributes to tumor regressions and prolonged survival in a KRAS-mutant lung cancer mouse model. Therefore, molecularly targeted agents capable of inducing senescence can produce tumor control through non–cell autonomous mechanisms involving NK cell surveillance.

Science 2018

NK cells are required for optimal chemotherapy
(MEK and CDK4/6 inhibitors)
in transplantable mouse KP lung tumor model



NK cell-dependent TNF is required for optimal chemotherapy (MEK and CDK4/6 inhibitors) in mouse transplantable KP lung tumor



NK cell-dependent TNF is required for optimal chemotherapy (MEK and CDK4/6 inhibitors) in mouse GEMM lung tumor model