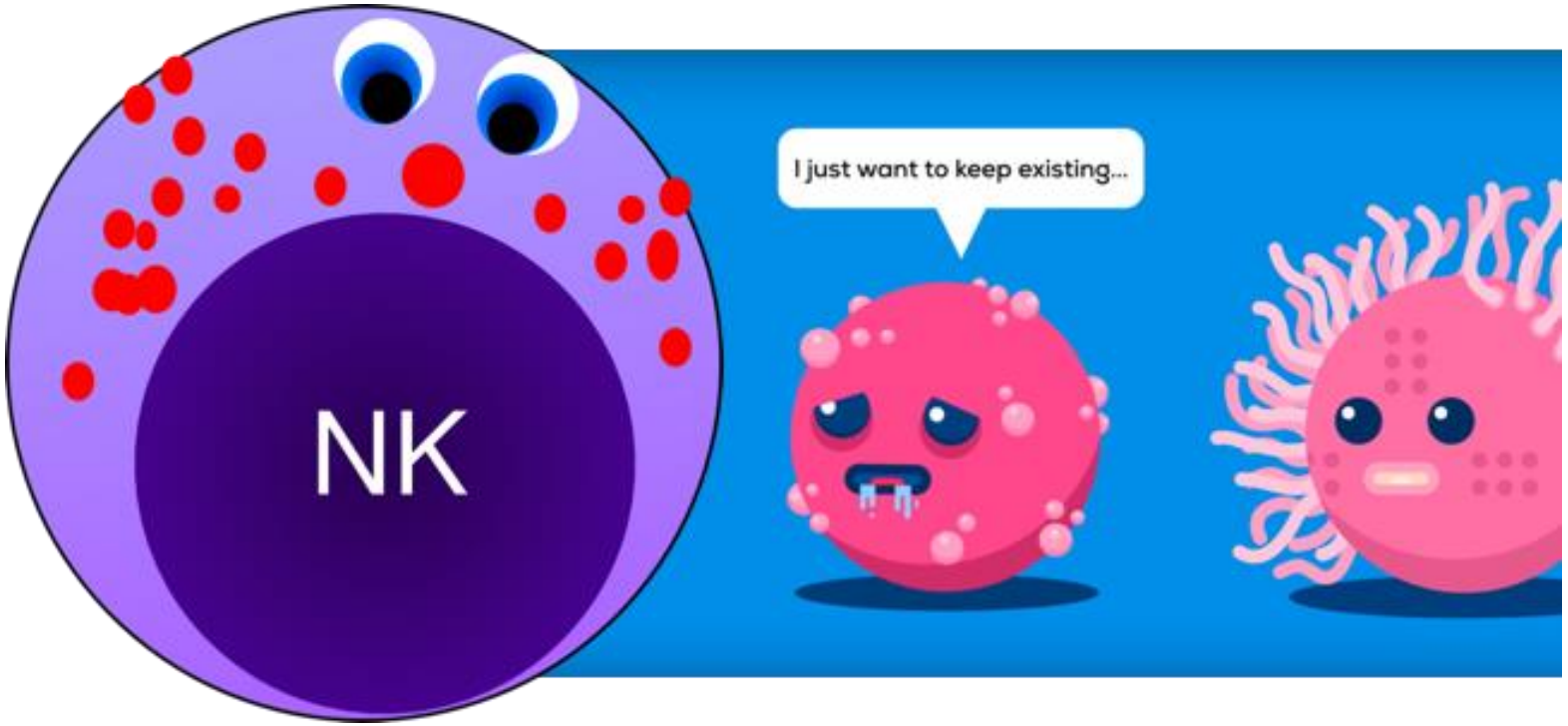
MHC class I-deficient tumor escape in the context of NK cell immunity



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SALK INSTITUTE FOR BIOLOGICAL STUDIES

Impaired MHC-I antigen presentation is a mechanism of tumor resistance to immune checkpoint inhibitors

The NEW ENGLAND JOURNAL of MEDICINE

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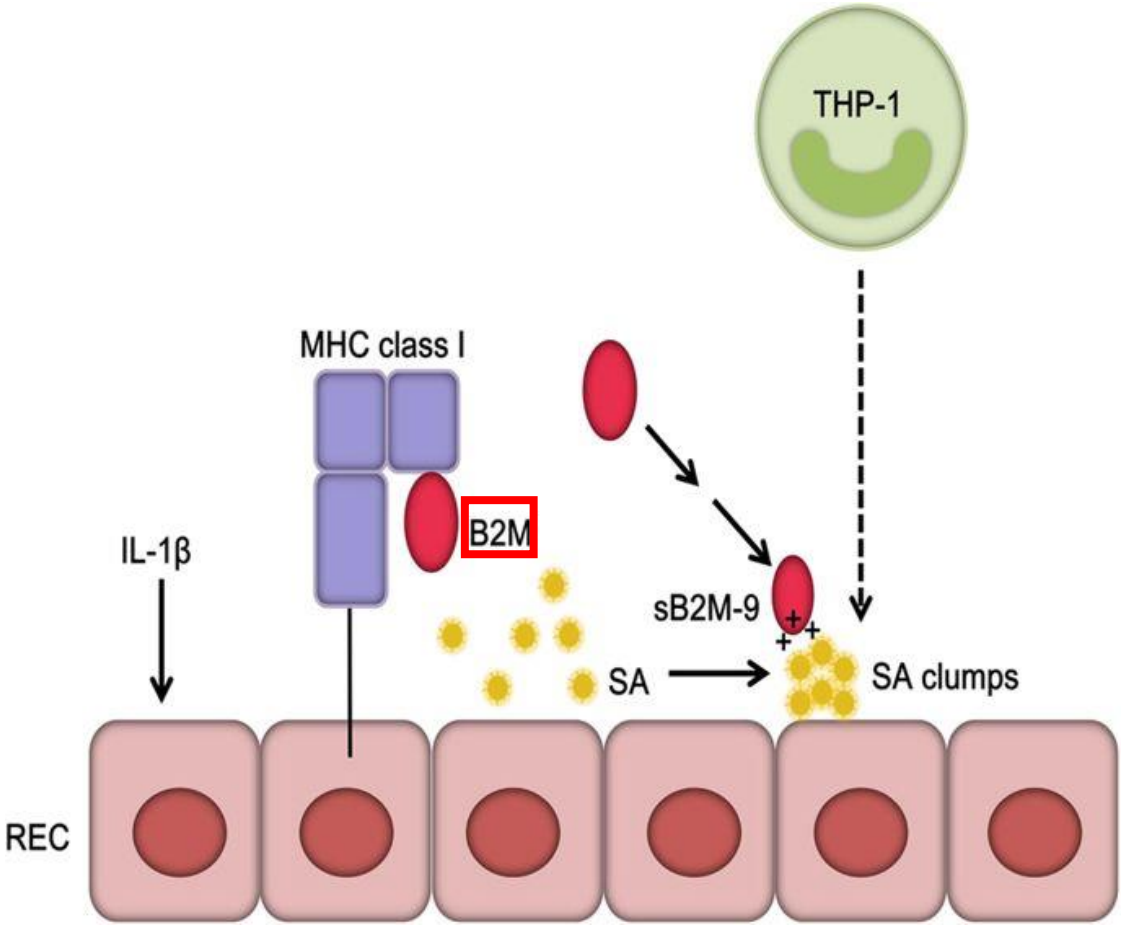
Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma

Jesse M. Zaretsky, B.S., Angel Garcia-Diaz, Ph.D., Daniel S. Shin, M.D., Helena Escuin-Ordinas, Ph.D., Willy Hugo, Ph.D., Siwen Hu-Lieskovan, M.D., Ph.D., Davis Y. Torrejon, M.D., Gabriel Abril-Rodriguez, M.Sc., Salemiz Sandoval, Ph.D., Lucas Barthly, M.Sc., Justin Saco, B.S., Blanca Homet Moreno, M.D., Riccardo Mezzadra, M.Sc., Bartosz Chmielowski, M.D., Ph.D., Kathleen Ruchalski, M.D., I. Peter Shintaku, Ph.D., Phillip J. Sanchez, Ph.D., Cristina Puig-Saus, Ph.D., Grace Cherry, R.N., N.P., Elizabeth Seja, B.A., Xiangju Kong, M.Sc., Jia Pang, B.S., Beata Berent-Maoz, Ph.D., Begoña Comin-Anduix, Ph.D., Thomas G. Graeber, Ph.D., Paul C. Tumeh, M.D., Ton N.M. Schumacher, Ph.D., Roger S. Lo, M.D., Ph.D., and Antoni Ribas, M.D., Ph.D.

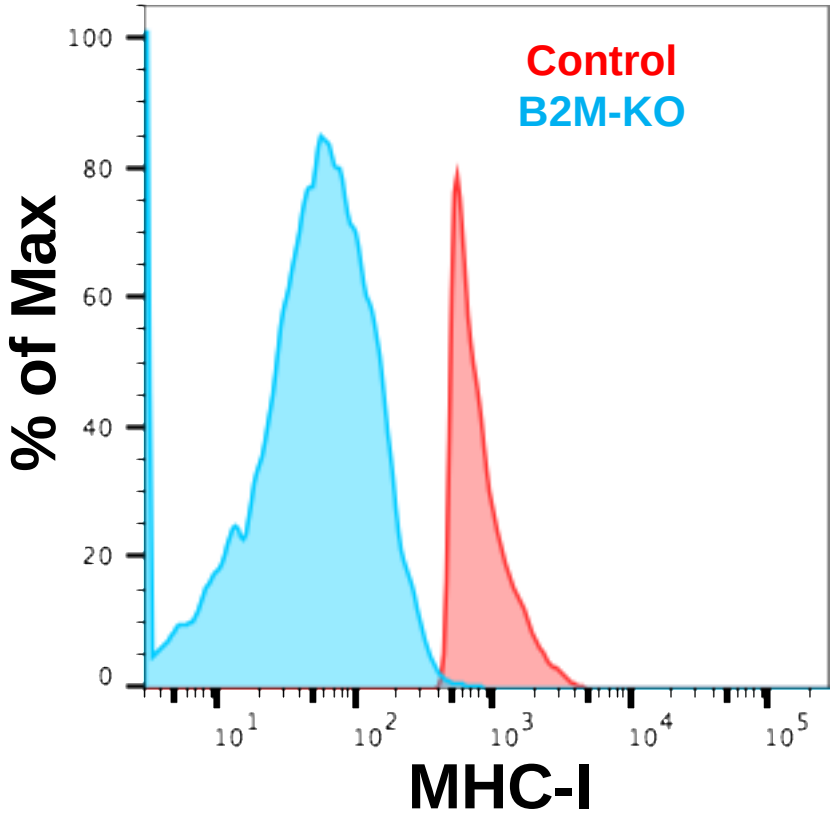
Impaired HLA Class I Antigen Processing and Presentation as a Mechanism of Acquired Resistance to Immune Checkpoint Inhibitors in Lung Cancer

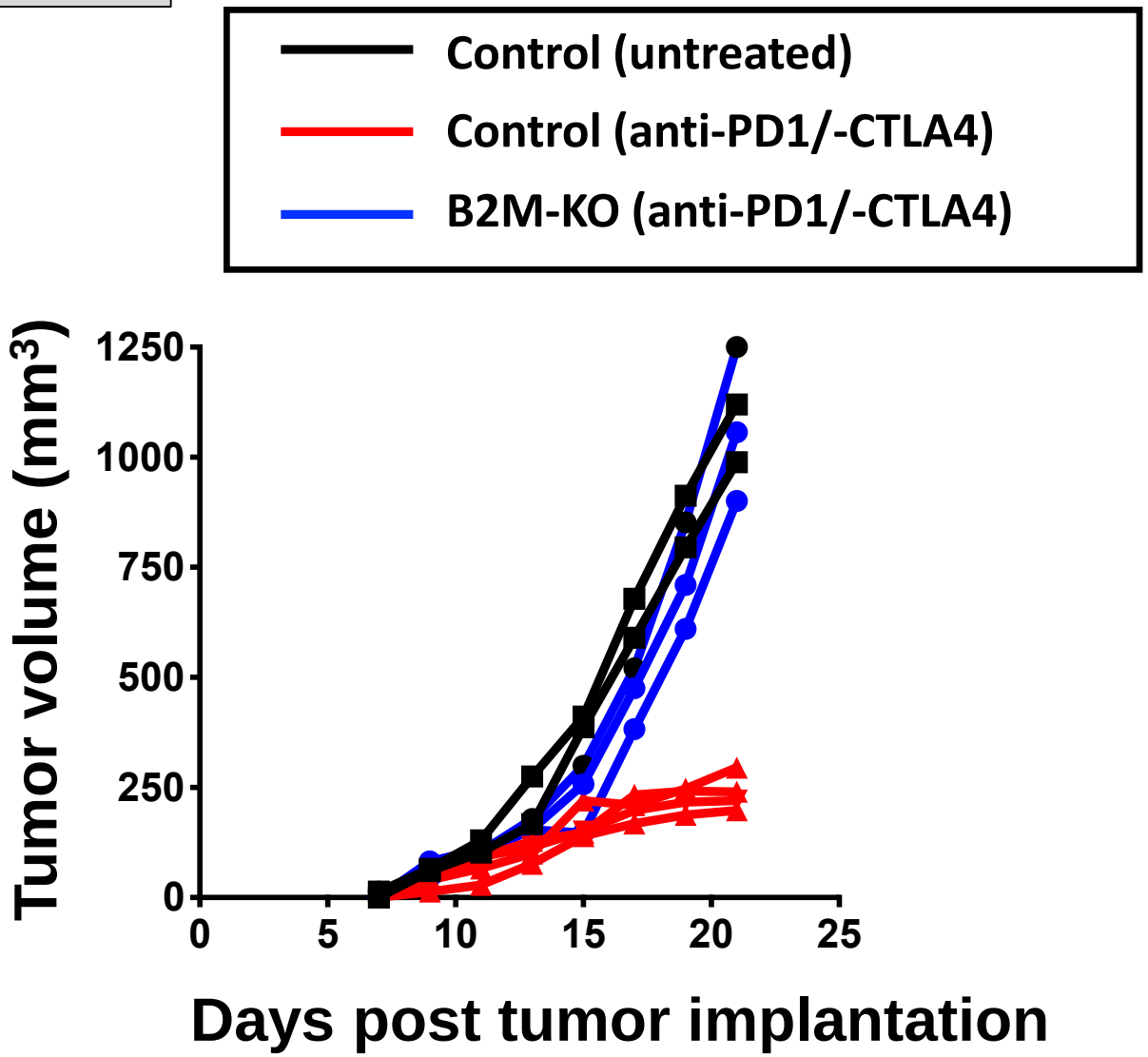
Scott Gettinger[1,2], Jungmin Choi[3], Katherine Hastings[2], Anna Truini[2], Ila Datar[4], Ryan Sowell[5], Anna Wurtz[2], Weilai Dong[3], Guoping Cai[4], Mary Ann Melnick[2], Victor Y. Du[5], Joseph Schlessinger[2,6], Sarah B. Goldberg[1,2], Anne Chiang[1,2], Miguel F. Sanmamed[5], Ignacio Melero[7,8], Jackeline Agorreta[7,8], Luis M. Montuenga[7,8], Richard Lifton[3], Soldano Ferrone[9], Paula Kavathas[2,5,10], David L. Rimm[2,4], Susan M. Kaech[2,5], Kurt Schalper[1,2,4], Roy S. Herbst[1,2,6], and Katerina Politi[1,2,4]



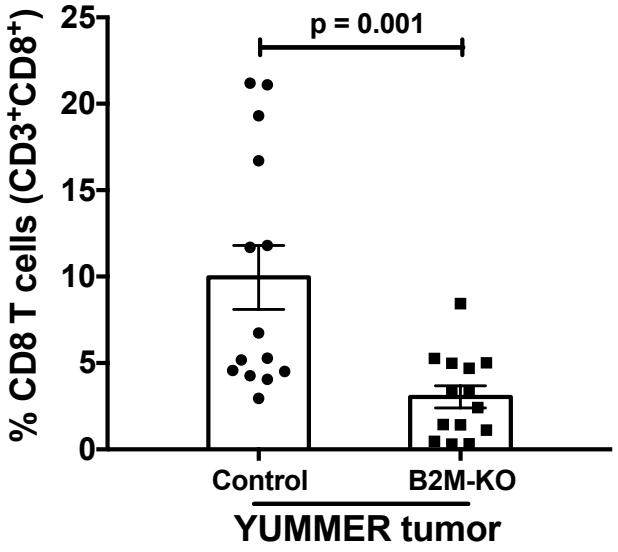
Strategy for modulating tumor response to immunotherapy by disrupting B2M expression in our murine melanoma model (YUMMER)

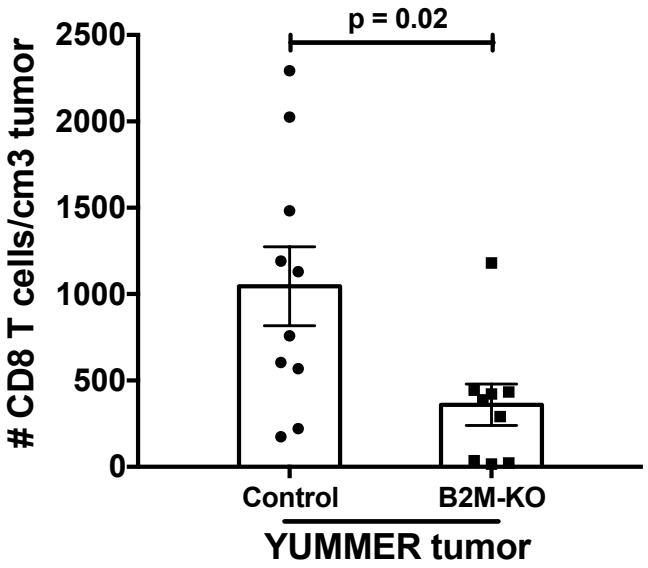
CRISPR/Cas9-mediated gene knock-out of *B2m* gene

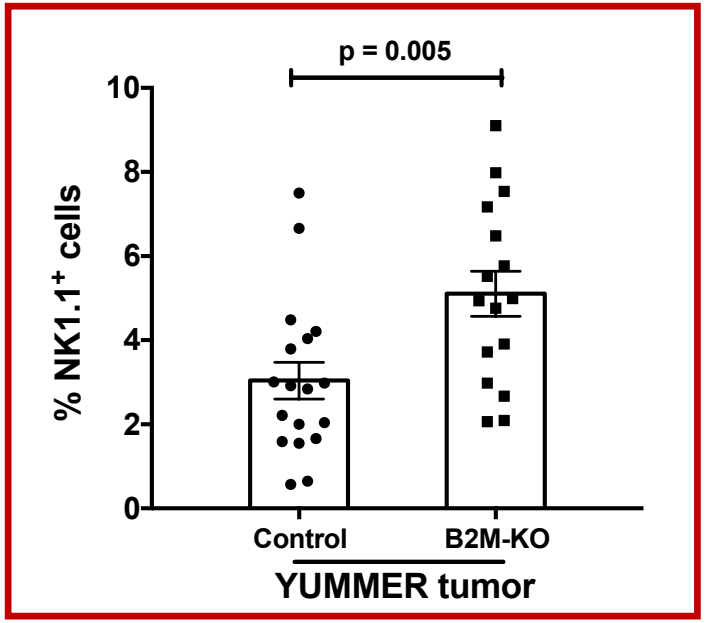


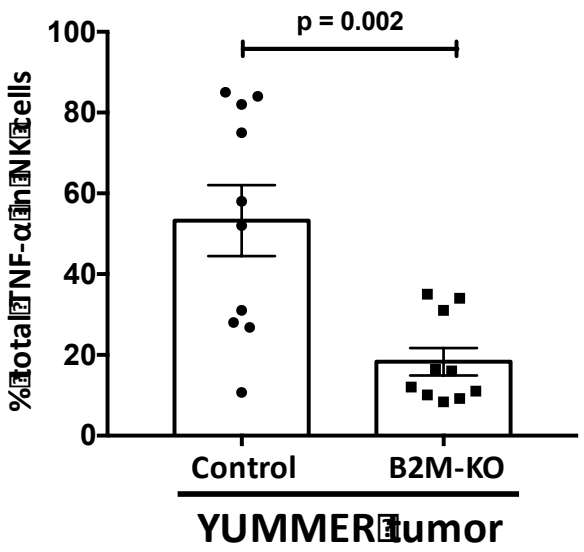


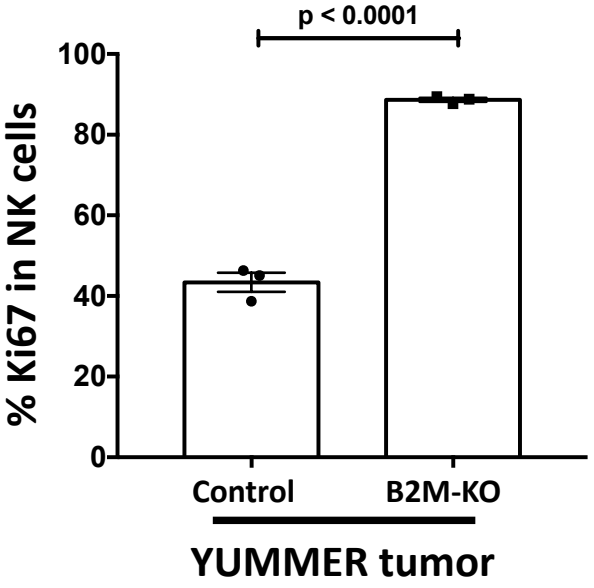
Differences in the frequency of intratumoral CD8 T cells and NK cells are seen between B2M-sufficient (control) and -deficient (B2M-KO) tumors



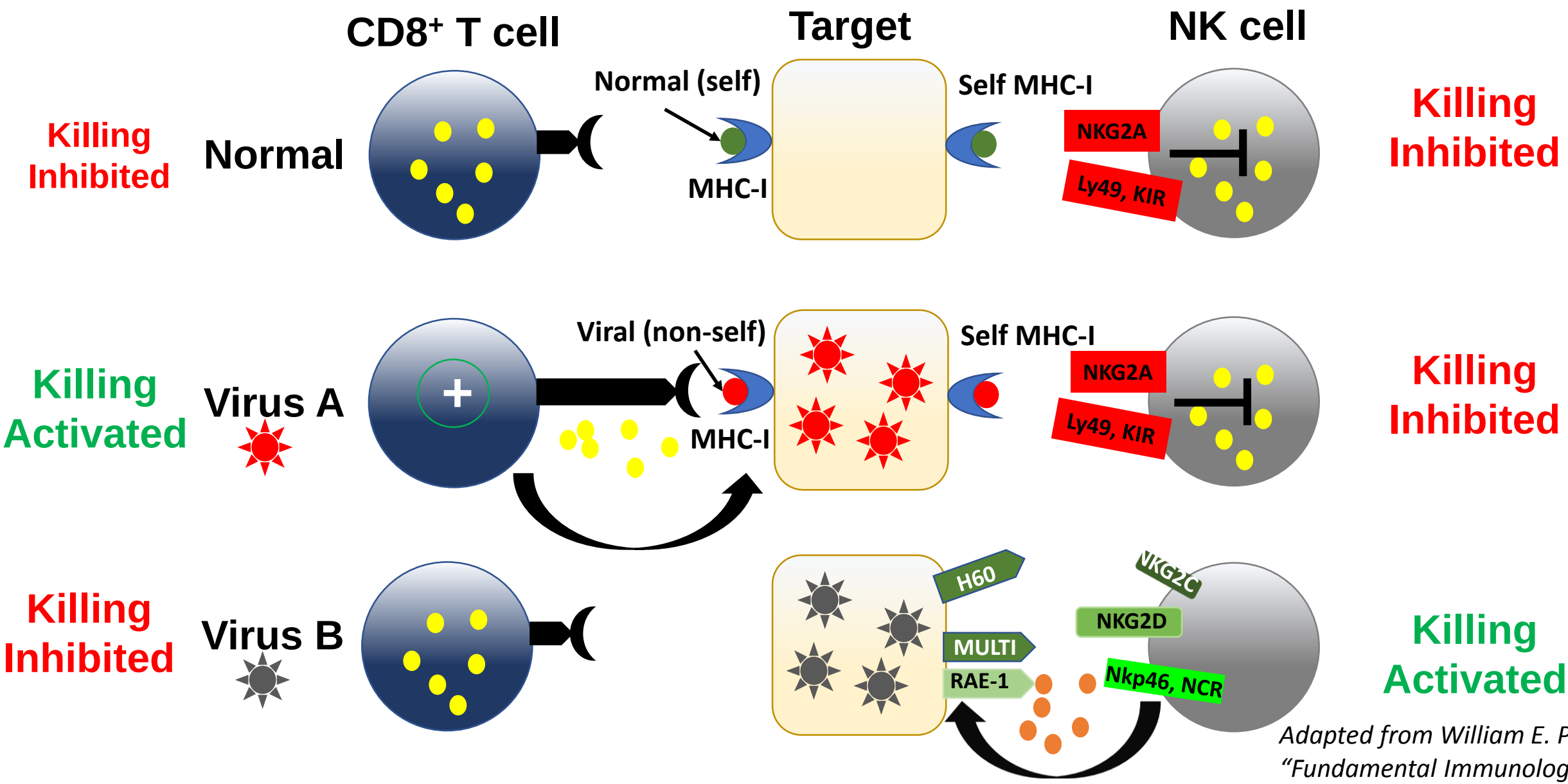








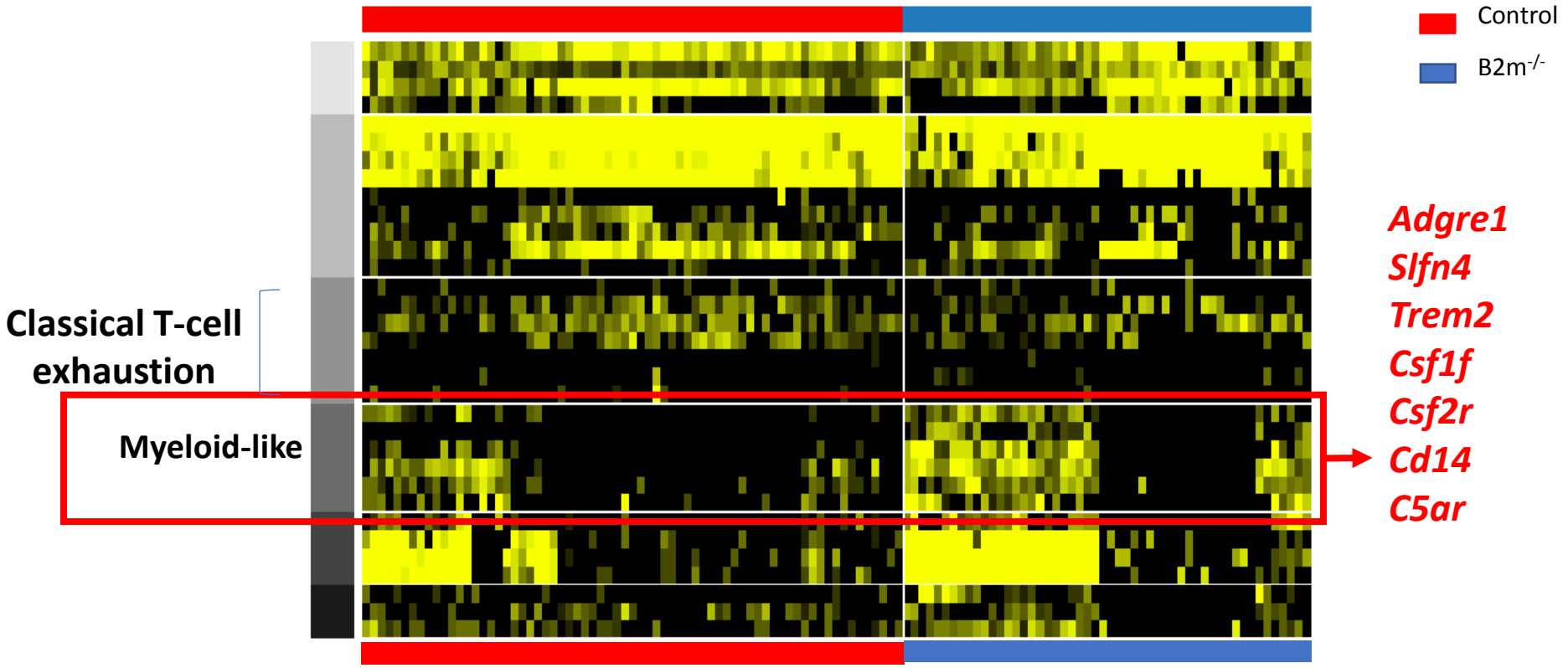
MHC class I expression and NK cell killing



Adapted from William E. Paul "Fundamental Immunology"

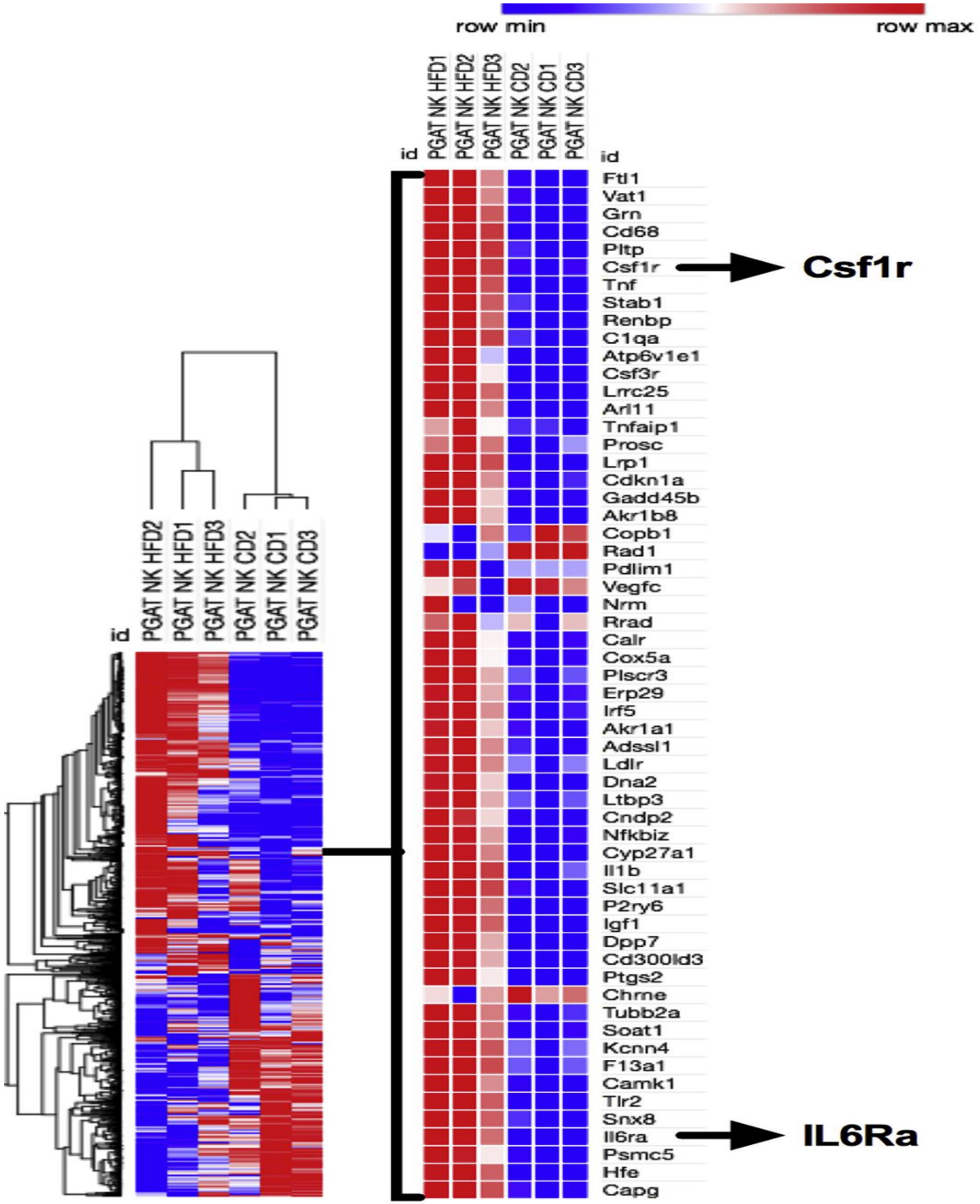
What is inhibiting these NK cells from effectively mediating tumor control in the B2M- or MHC-I-deficient tumors?

“Myeloid-like” genes are upregulated in B2M-deficient tumoral NK cells in single-cell RNAseq



Cell Metabolism

IL-6/Stat3-Dependent Induction of a Distinct, Obesity-Associated NK Cell Subpopulation Deteriorates Energy and Glucose Homeostasis



Theurich et al., 2017

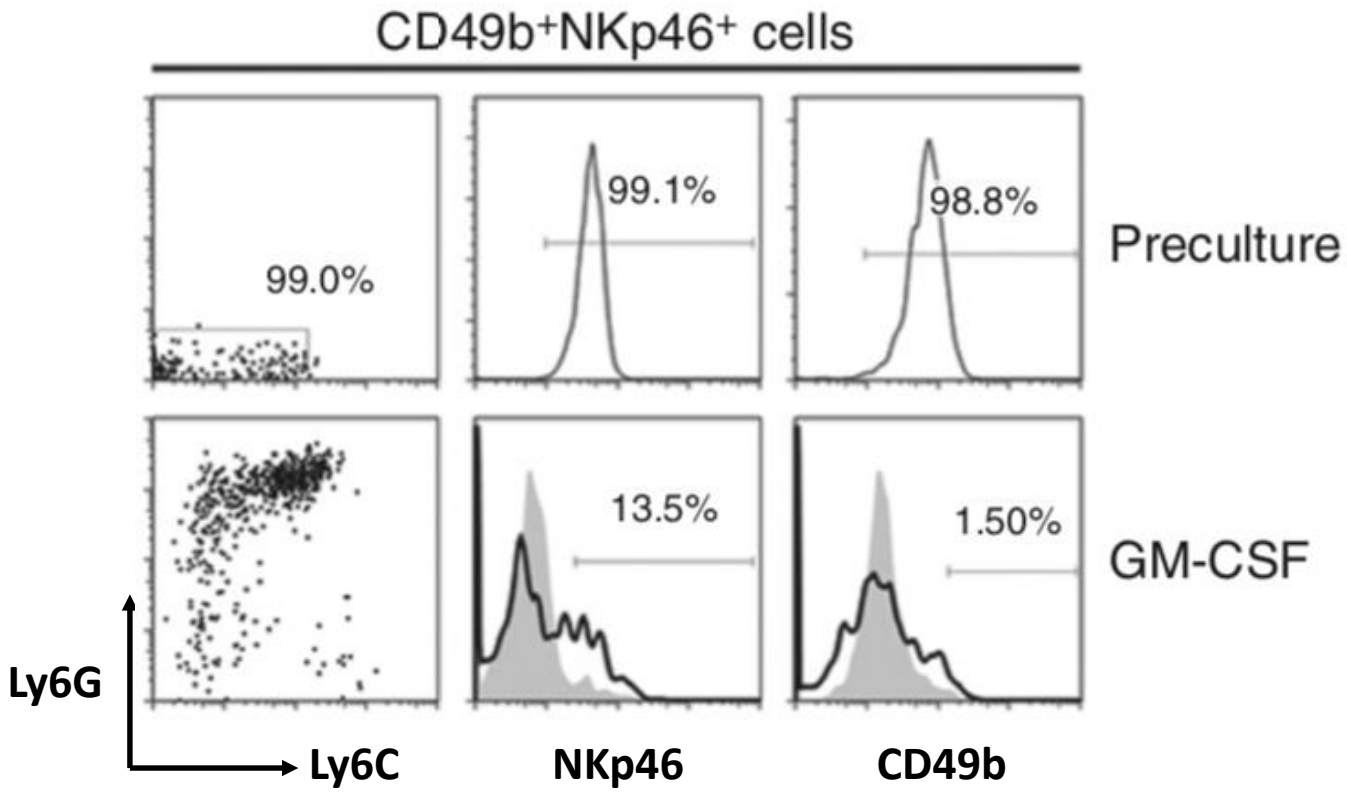
Published OnlineFirst July 18, 2013; DOI: 10.1158/0008-5472.CAN-13-0545

Cancer Research

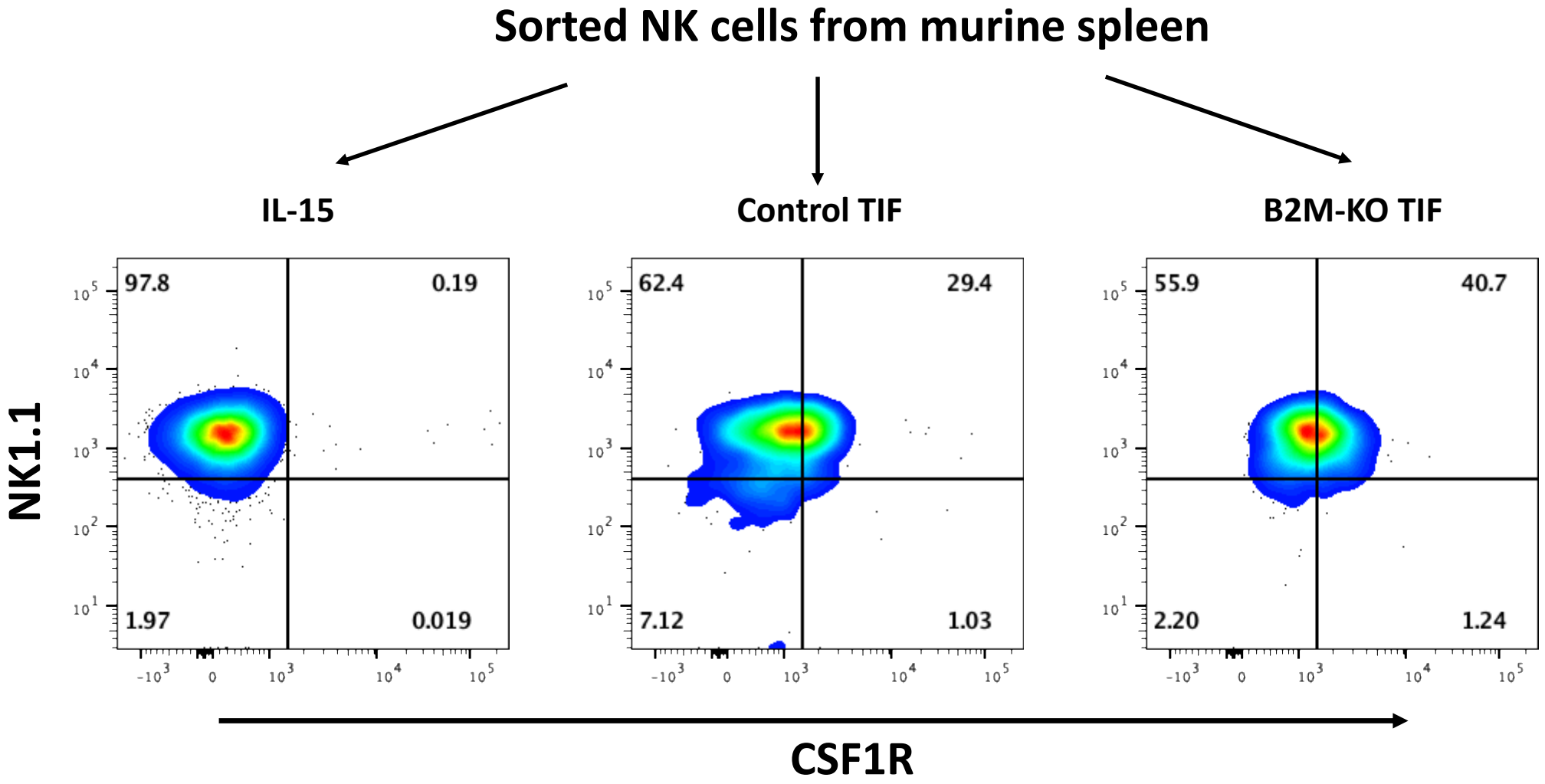
Park et al., 2013

Microenvironment and Immunology

Tumor Microenvironmental Conversion of Natural Killer Cells into Myeloid-Derived Suppressor Cells

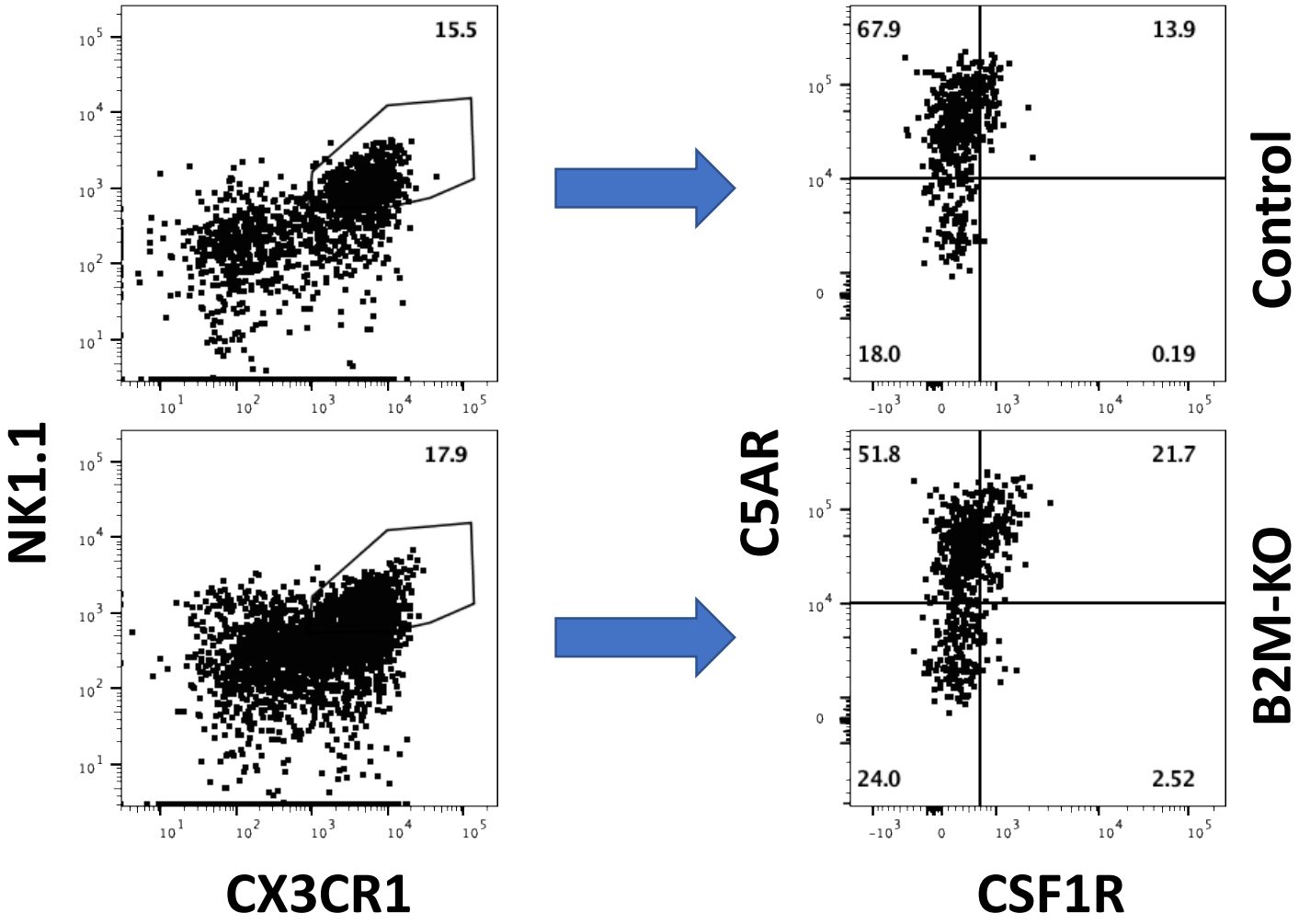


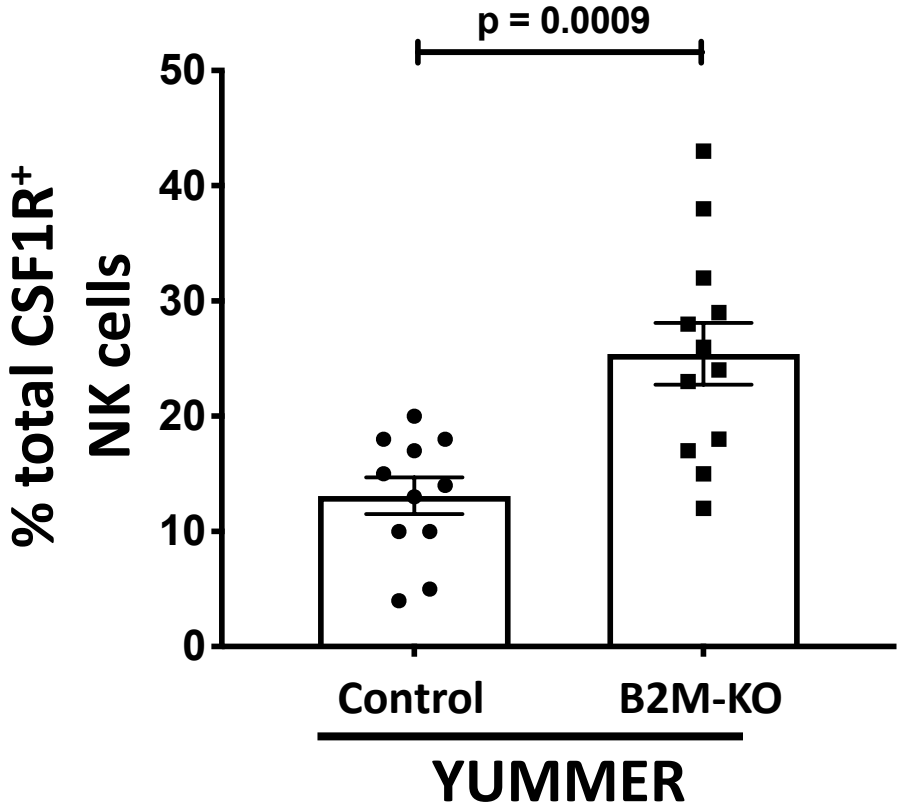
CSF1R-expressing NK cells are detected when culturing splenic NK cells with tumor-interstitial fluid (TIF)



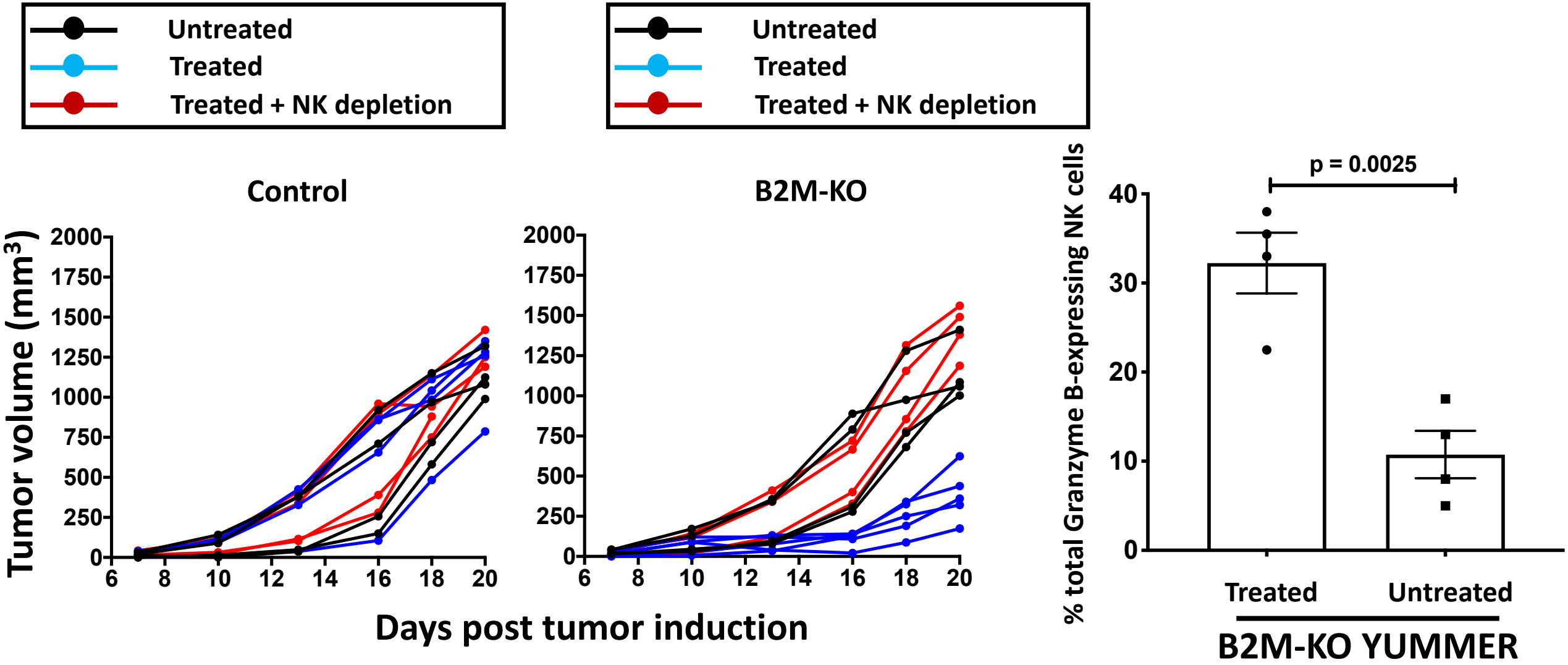
Higher co-expression of C5AR and CSF1R is seen in B2M-KO tumoral NK cells in the YUMMER model

Gated into CD3⁻ population

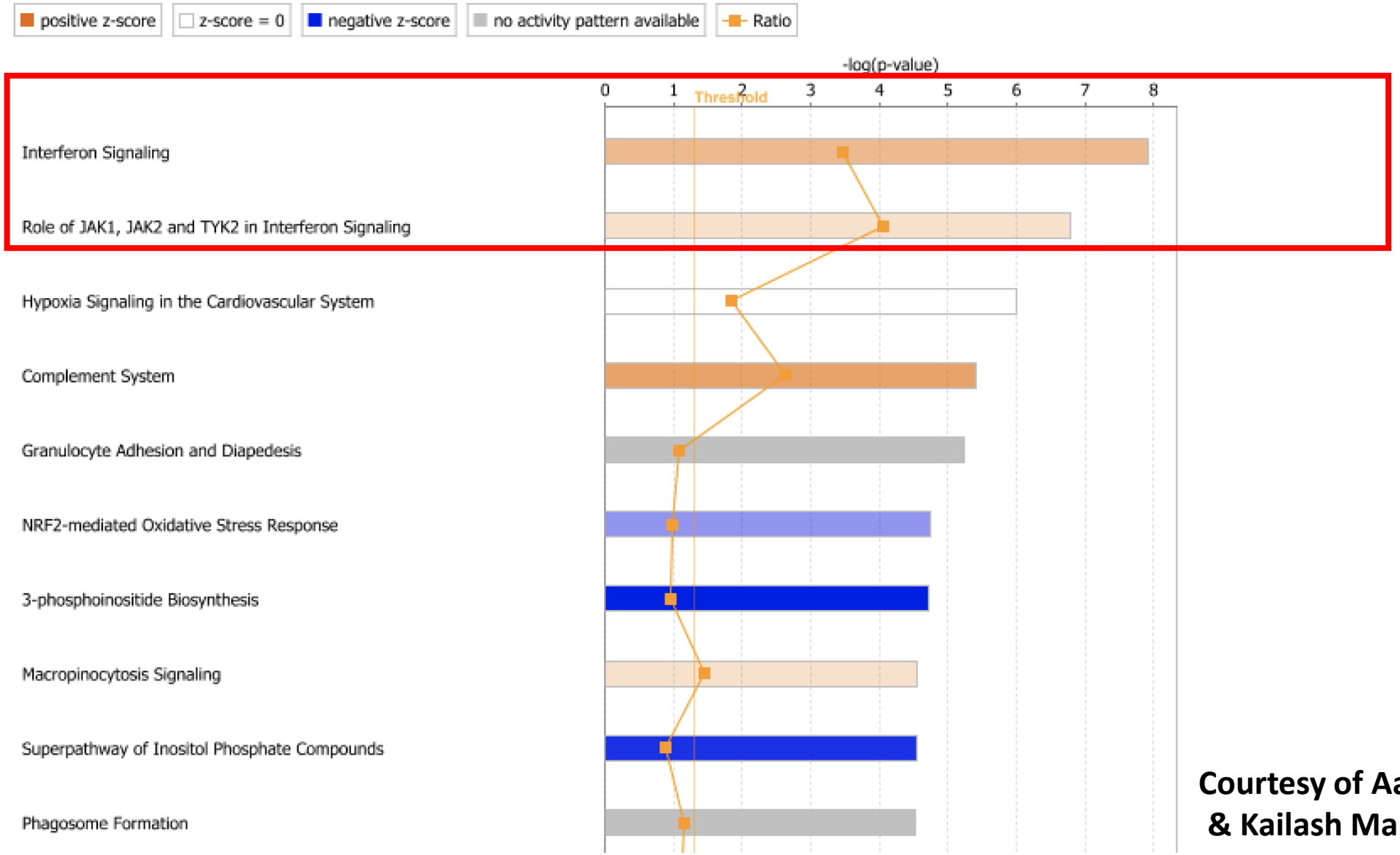




B2M-KO YUMMER tumors exhibit delayed growth in the presence of a CSF1R inhibitor treatment

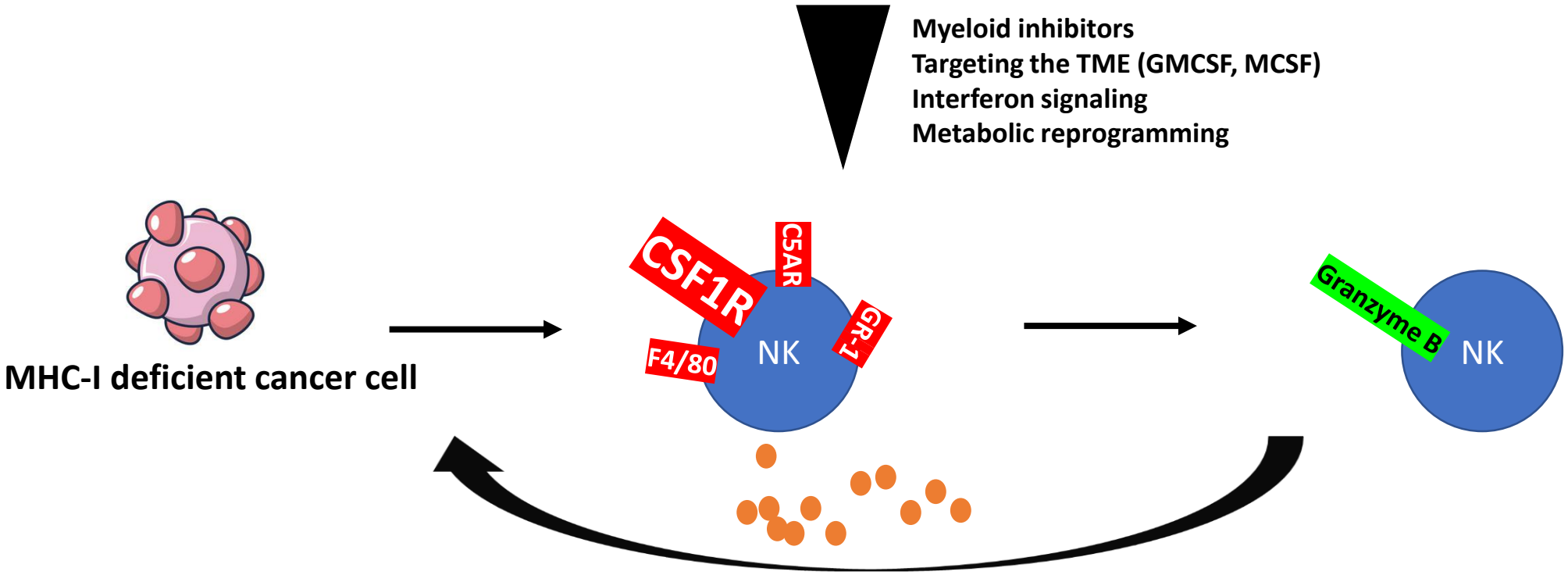


Upregulation of interferon signaling associated genes is detected in B2M-KO intratumoral NK cells



Courtesy of Aaron Wilk & Kailash Mangalhara

Take home message and future directions



Carryout studies in cancer patient samples

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Yoav Altman

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