Carbone Cancer Center
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SCHOOL OF MEDICINE AND PUBLIC HEALTH

Reprogramming NK cells within the TME of osteosarcoma lung metastases

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Disclosures

- Advisory board/Honorarium
  - Elephas Bio
  - Nektar Therapeutics
  - Novartis

- I will not be discussing non-FDA approved indications during my presentation.

Osteosarcoma is the most common bone tumor in pediatrics

- 400 cases in the U.S. per year
- Typically develops after age 10 years
- Localized disease has a 70% survival rate
- Metastatic disease has a 25% survival rate

<u>Standard treatment</u>
Chemotherapy (MAP)
Surgery

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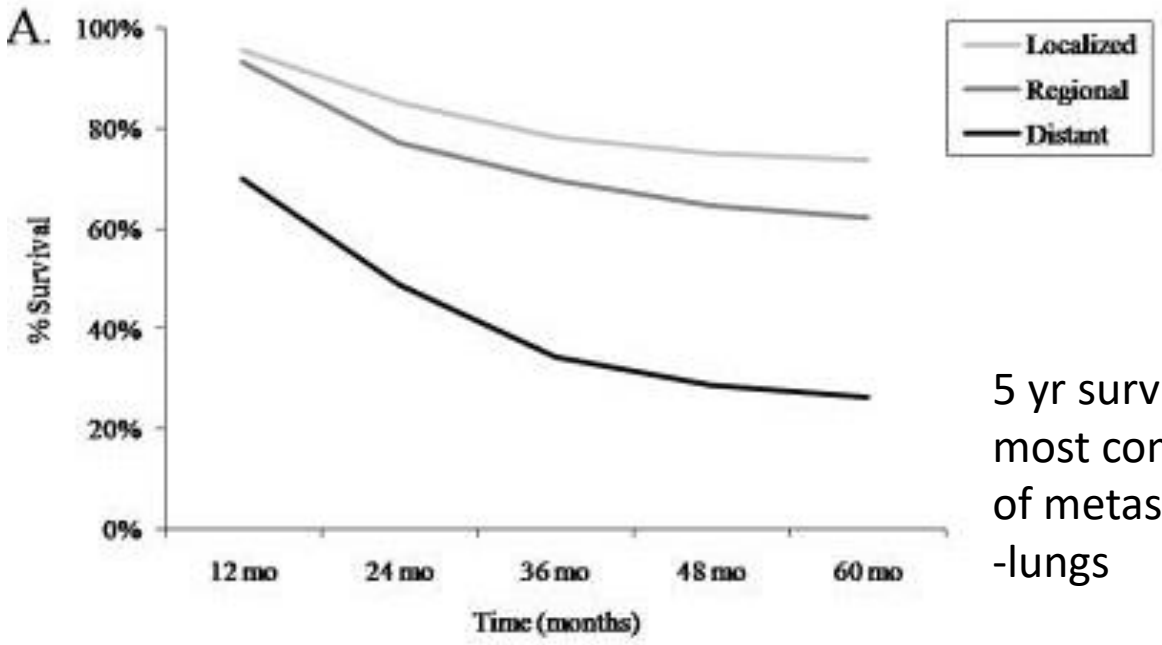
Metastatic osteosarcoma has a poor prognosis despite chemotherapy and surgery



5 yr survival 25% - most common site of metastases -lungs

Mirabello et al. 2009 Cancer

Osteosarcoma has a predilection for lung tissue in part due to recruitment of M2 macrophages

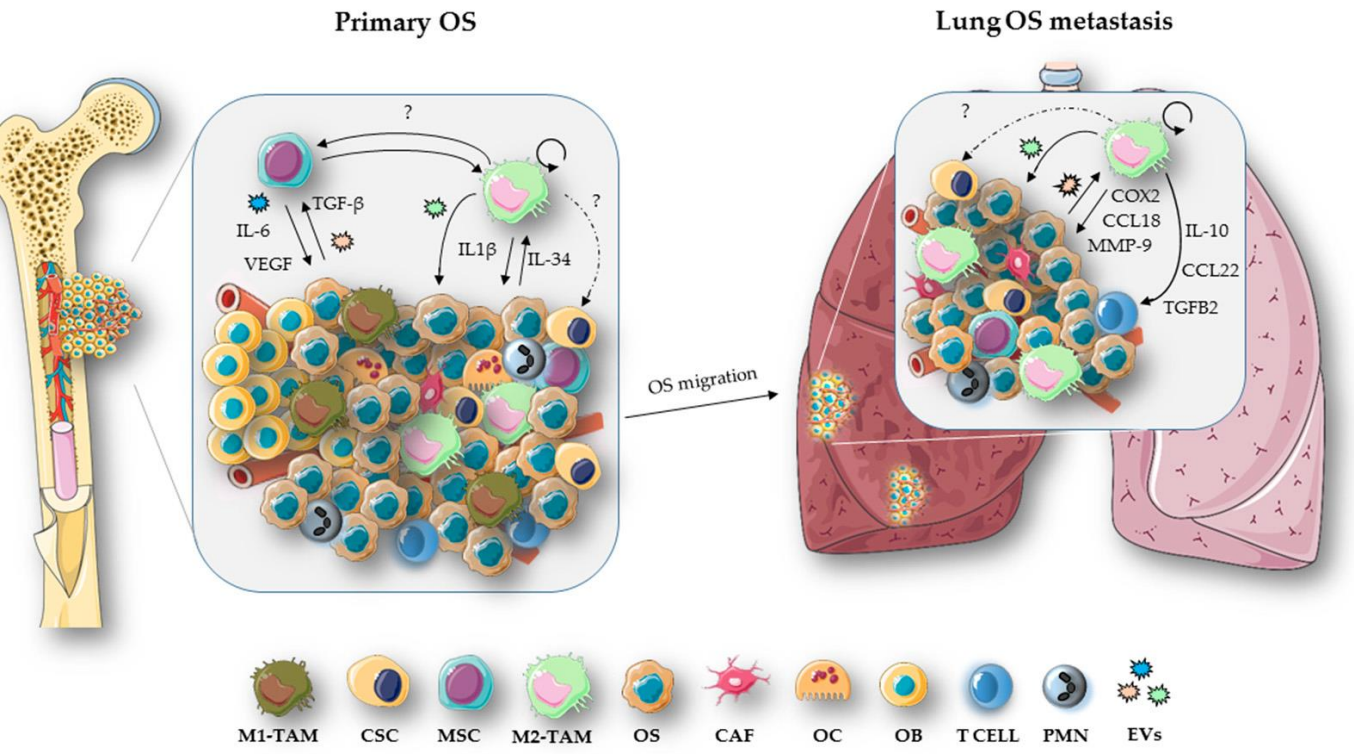


Table 2. Therapeutic agents targeting TAMs for OS treatment.

Agent	Mechanism	Phase	Ref.
All trans retinoic acid	Reduces polarization of M2-like	Pre-clinical	[8]
Mifamurtide	Induces M1-like activation	3	[145]
Esculetin	Inhibits TAMs differentiation	Pre-clinical	[150]
Zoledronate	Polarizes TAMs to M1-like	3	[151]
Natalizumab	Interferes cross-talk between cancer cells and TAMs	NCT03811886	[157]
Nivolumab	mAbs anti-PD-1	NCT02304458	[158]
Pembrolizumab	mAbs anti-PD-1	NCT02301039	[158]

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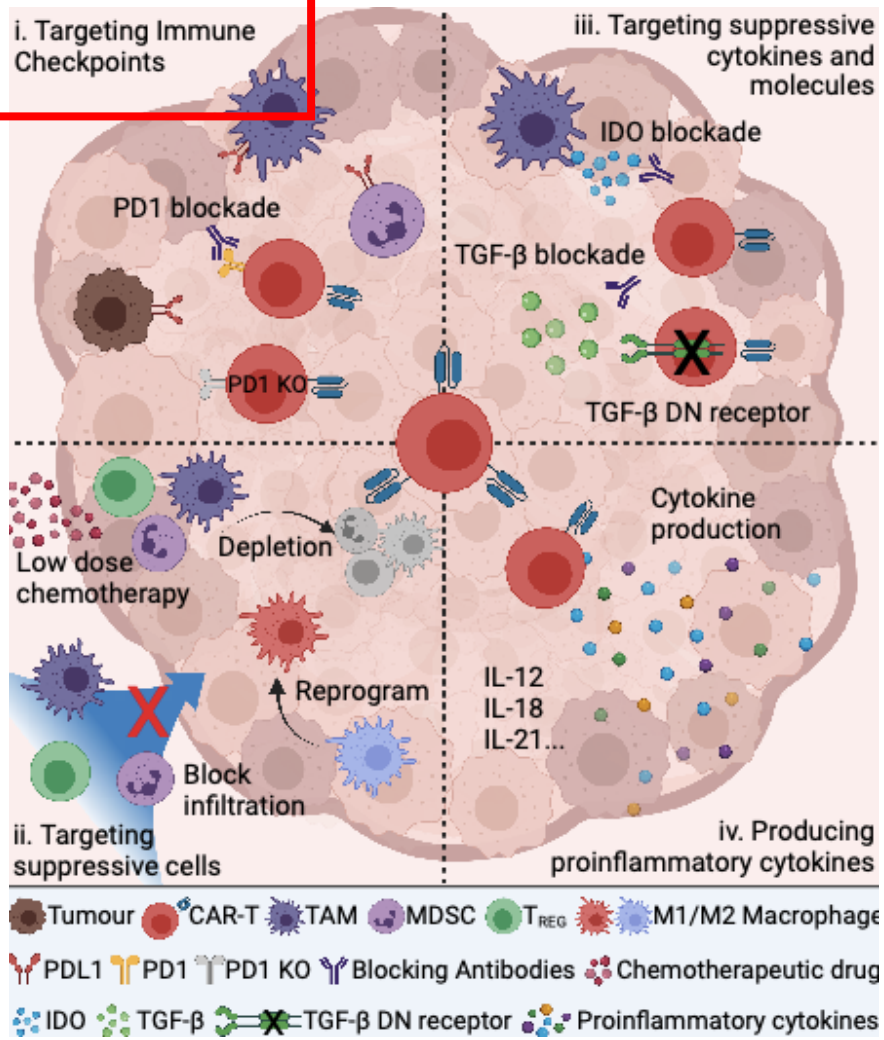
Cersosimo et al. 2020 Int J Mol Sciences

Proposed strategies for treating osteosarcoma TME



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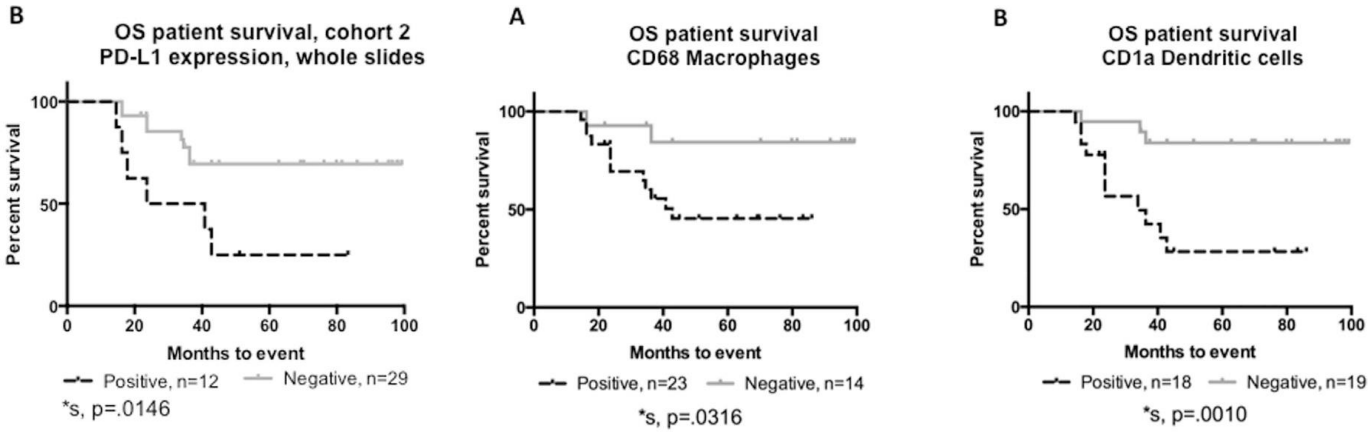
Terry et al. 2021 Cancers

Osteosarcoma has lots of APCs expressing PD-L1, which is prognostic, yet anti-PD1 therapy is ineffective



Koirala et al. 2016 Sci Reports

Davis et al. 2020 Lancet Oncol

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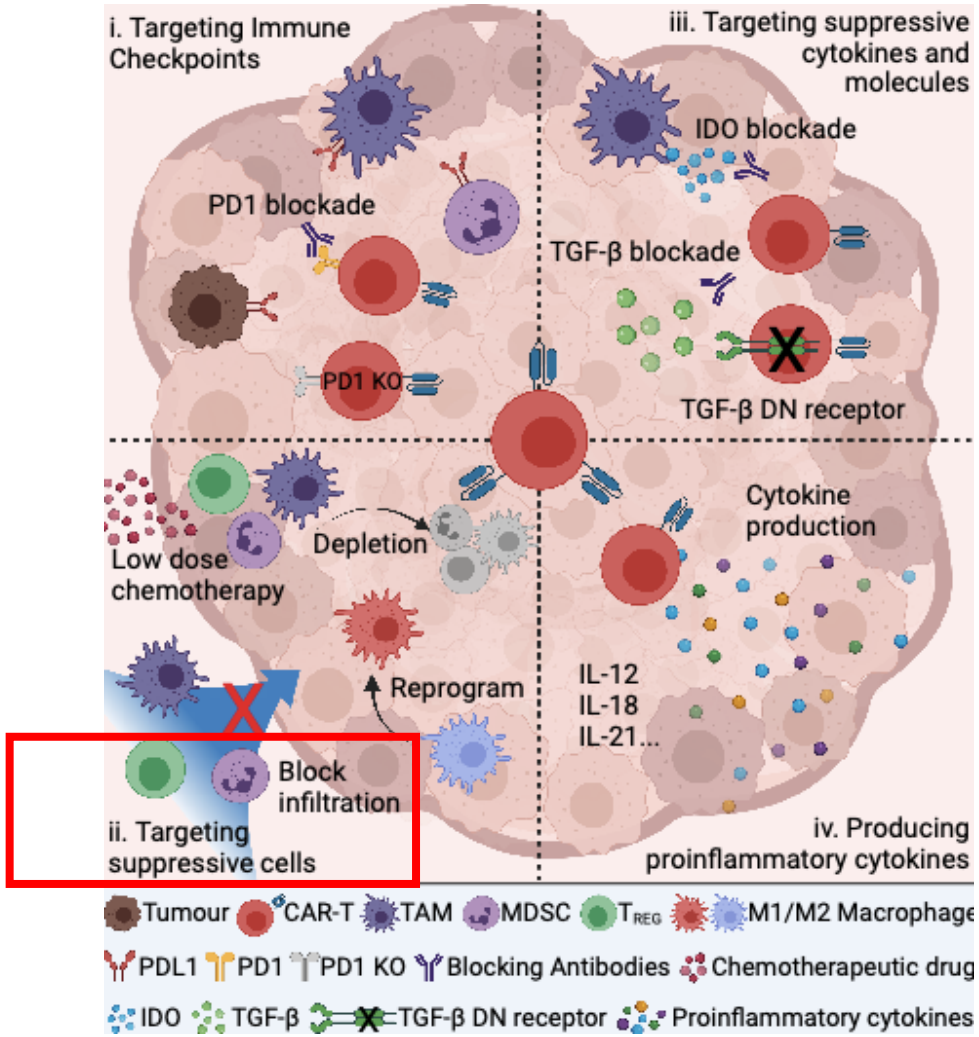
Proposed strategies for treating osteosarcoma TME



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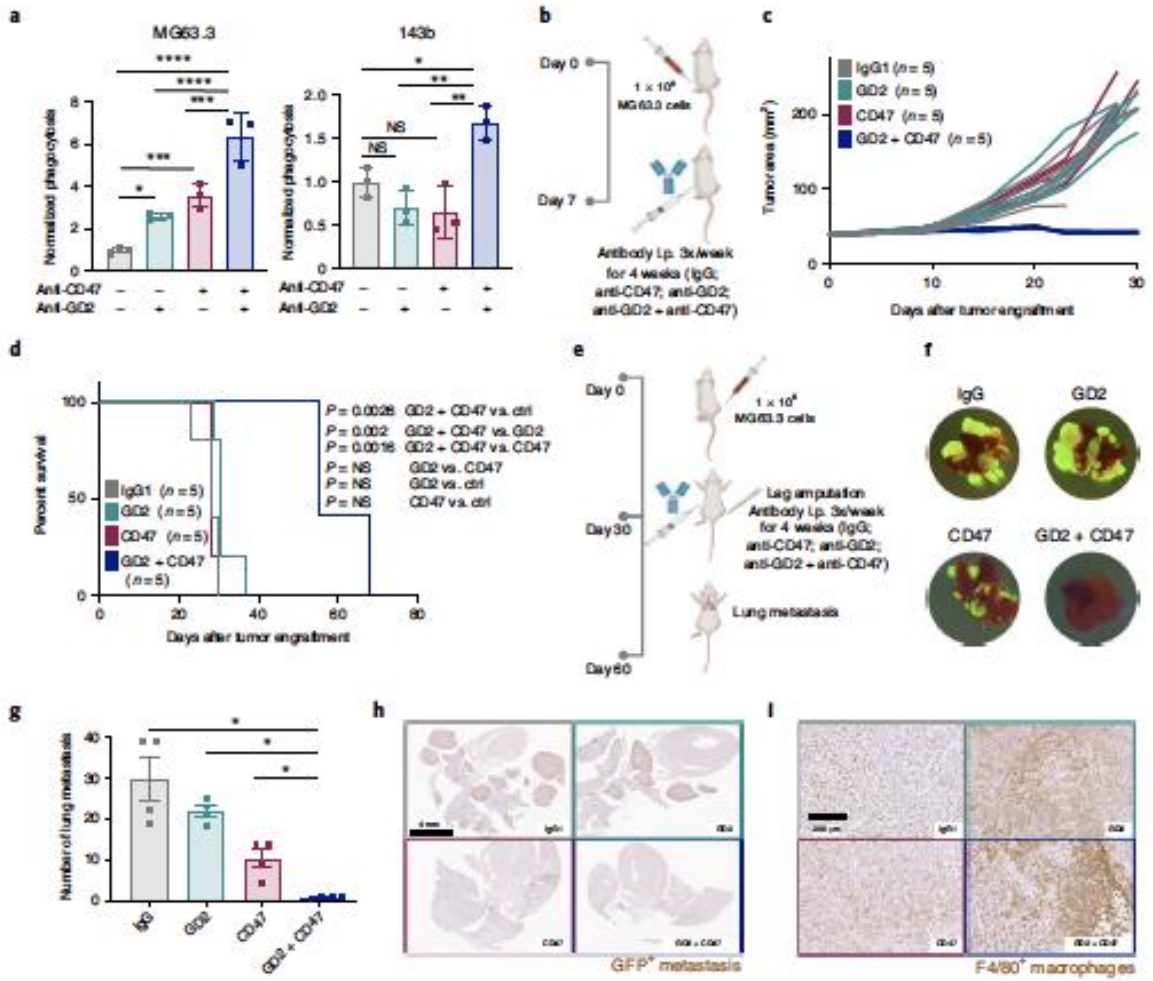
Terry et al. 2021 Cancers

Combination anti-GD2/anti-CD47 therapy to reprogram M2 macrophages to a M1 phenotype



PED-CITN-03

Testing the Combination of Two Immunotherapy Drugs (Magrolimab and Dinutuximab) in Patients With Relapsed or Refractory Neuroblastoma or Relapsed Osteosarcoma

ClinicalTrials.gov Identifier: NCT04751383

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Recruitment Status : Recruiting
First Posted : February 12, 2021
Last Update Posted : April 5, 2022

See Contacts and Locations

Sponsor:
National Cancer Institute (NCI)

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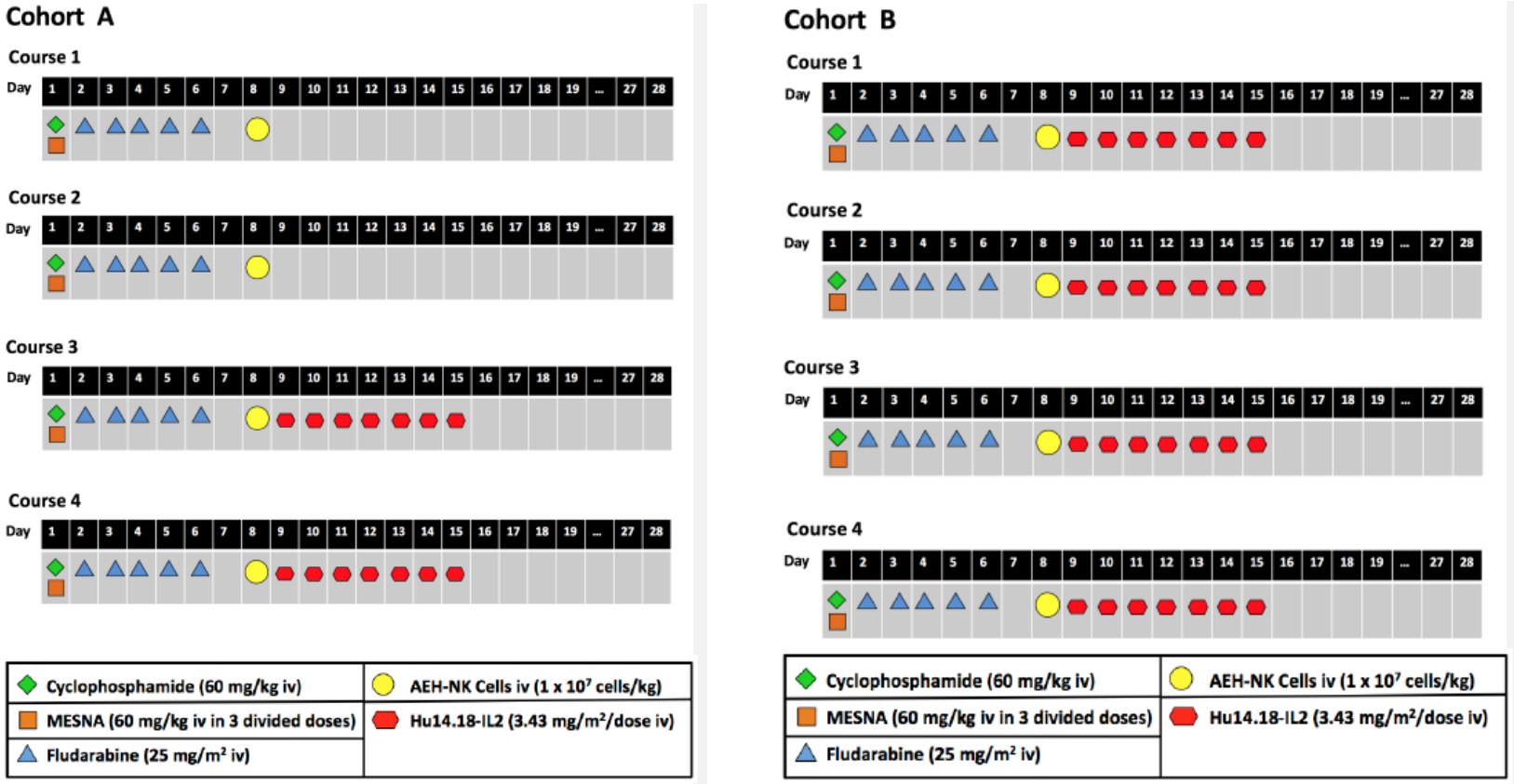
Theruvath et al. 2022 Nat Med

NCT03209869: Haploidentical CD137L/IL15 fresh and cryopreserved NK cells +/- anti-GD2/IL2 immunocytokine

PI: Ken DeSantes, MD

1 x 10^7 NK cells/kg fresh x 1

1 x 10^7 NK cells/kg cryopreserved x 3



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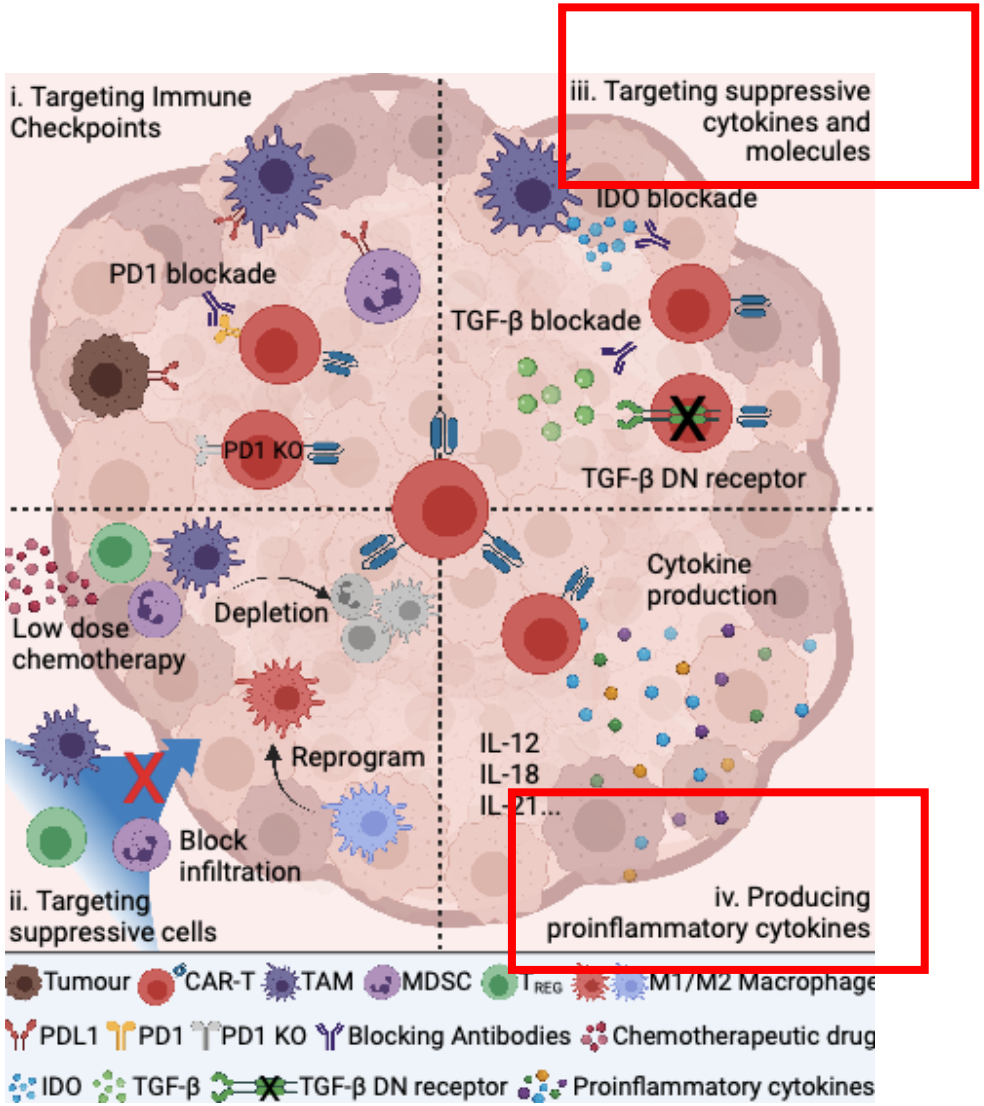
Damodharan et al. 2020 Cytotherapy
Bates et al. 2021 Front Immunol

Proposed strategies for treating osteosarcoma TME



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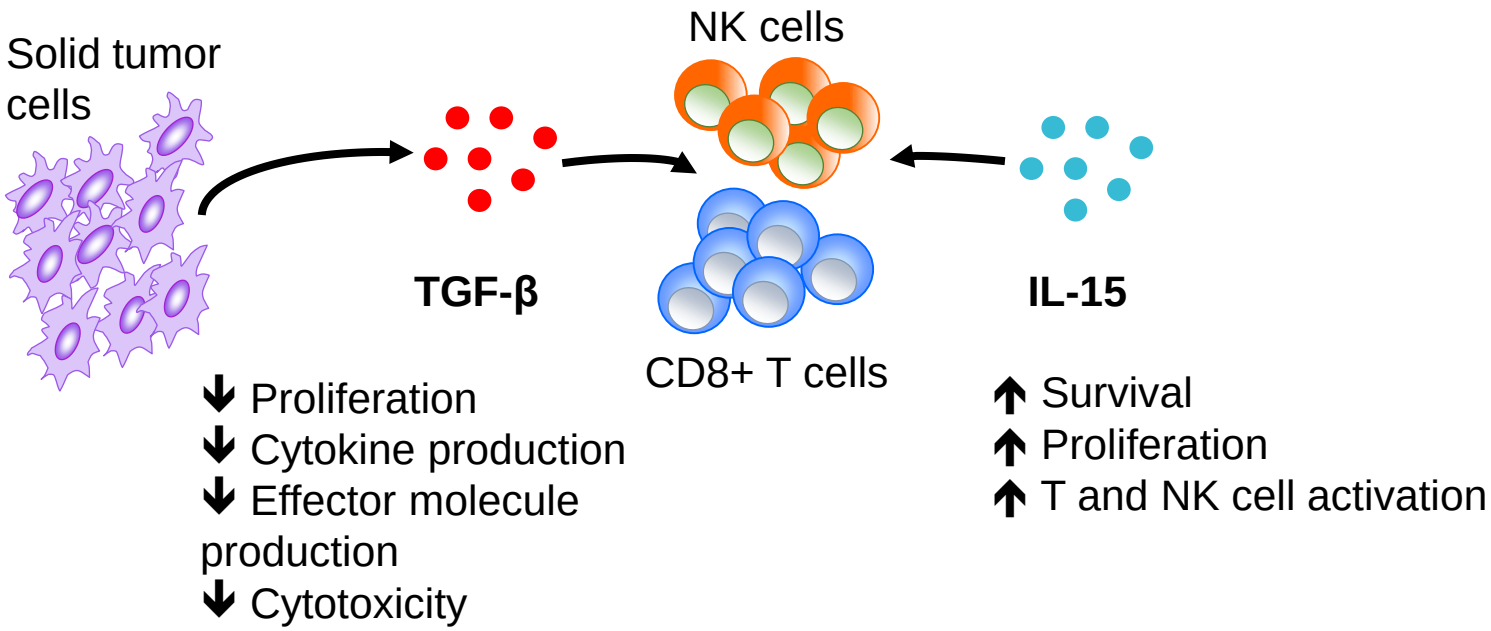
Terry et al. 2021 Cancers

Cytokines and cancer



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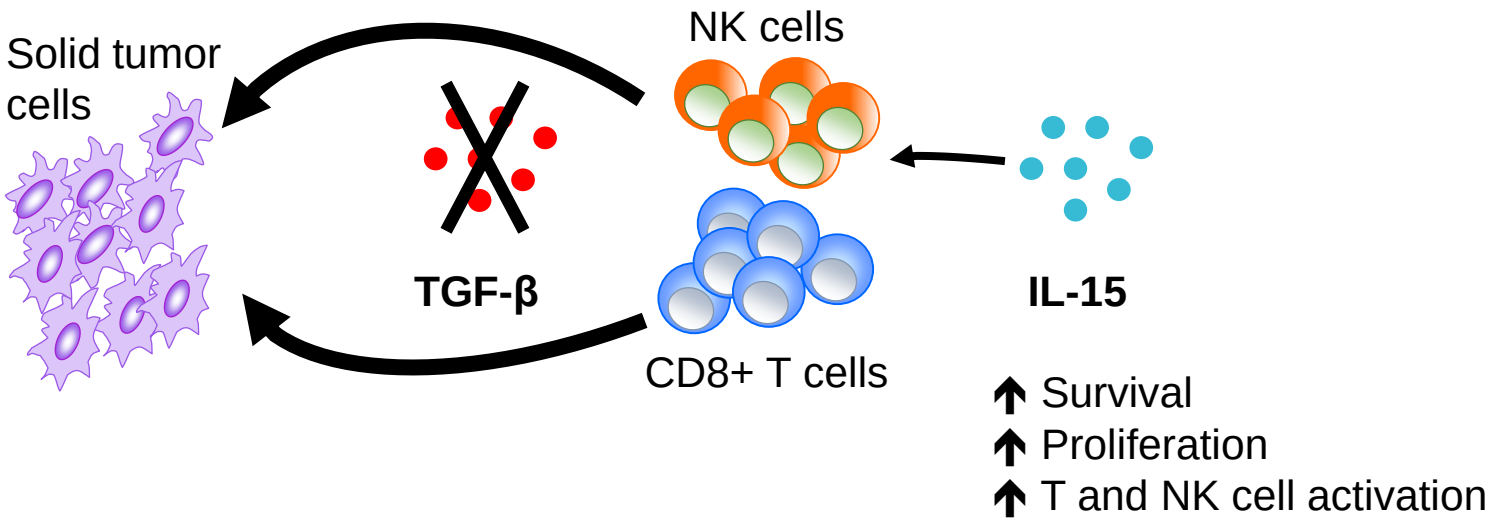
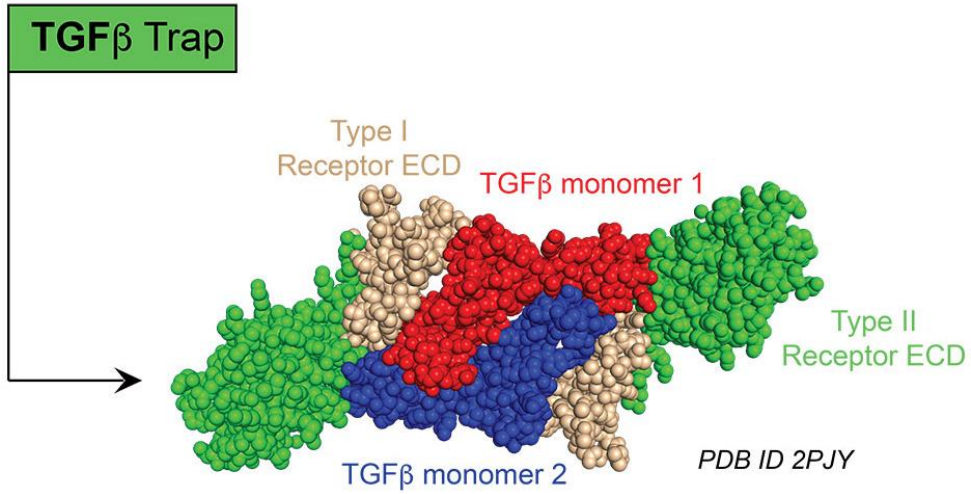
Cytokines and cancer



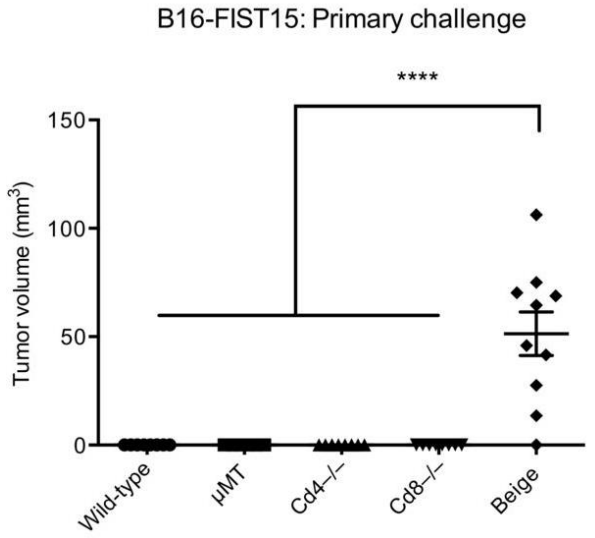
- If we neutralize tumor-derived TGF-β and provide IL-15 stimulation, could we enhance the anti-tumor effect?

- Create a new protein that combined IL-15 with TGF-β neutralization.

FIST15 is a fusokine with combines IL-15/IL-15Rα-sushi with TGFβ receptor and stimulates NK cells in vivo



https://www.cancer.gov/news-events/cancer-currents-blog/2018/y-trap-immunotherapy-drug



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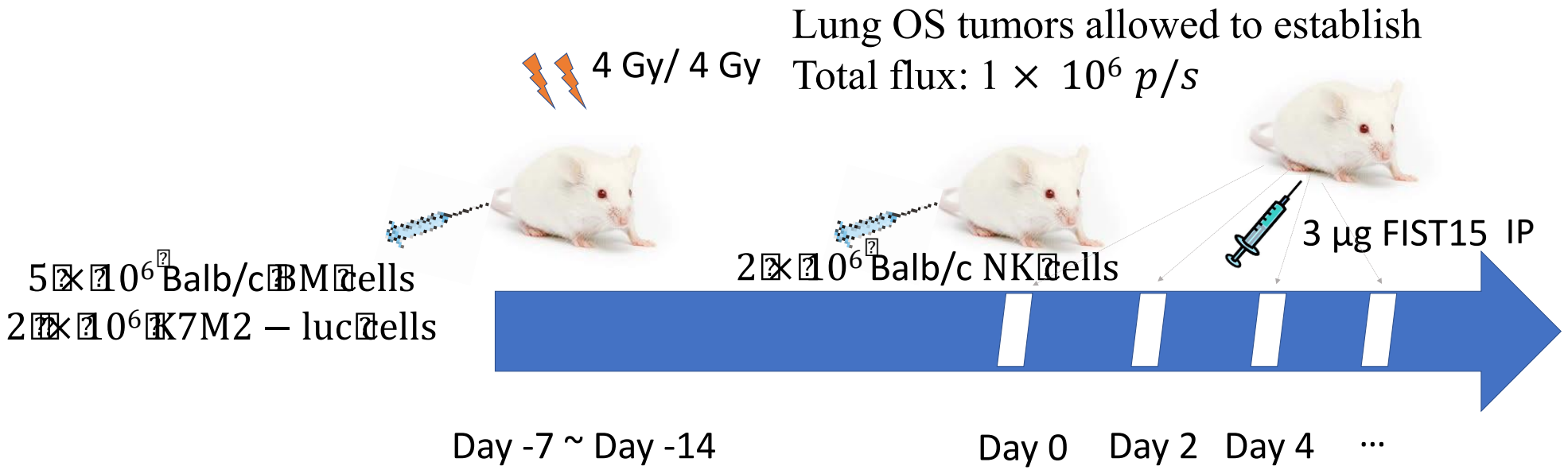
Ng et al. 2016 Cancer Res

Syngeneic bone marrow transplant model of pulmonary osteosarcoma to test combination of FIST15 and NK cells



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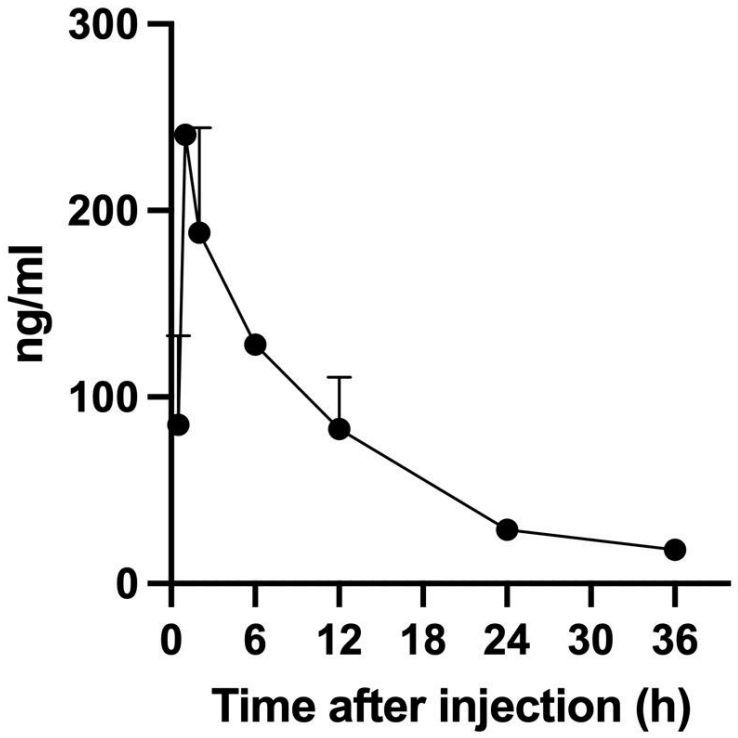
IL-15 peaks 2 hours after FIST15 administration and clears by 36 hours after injection



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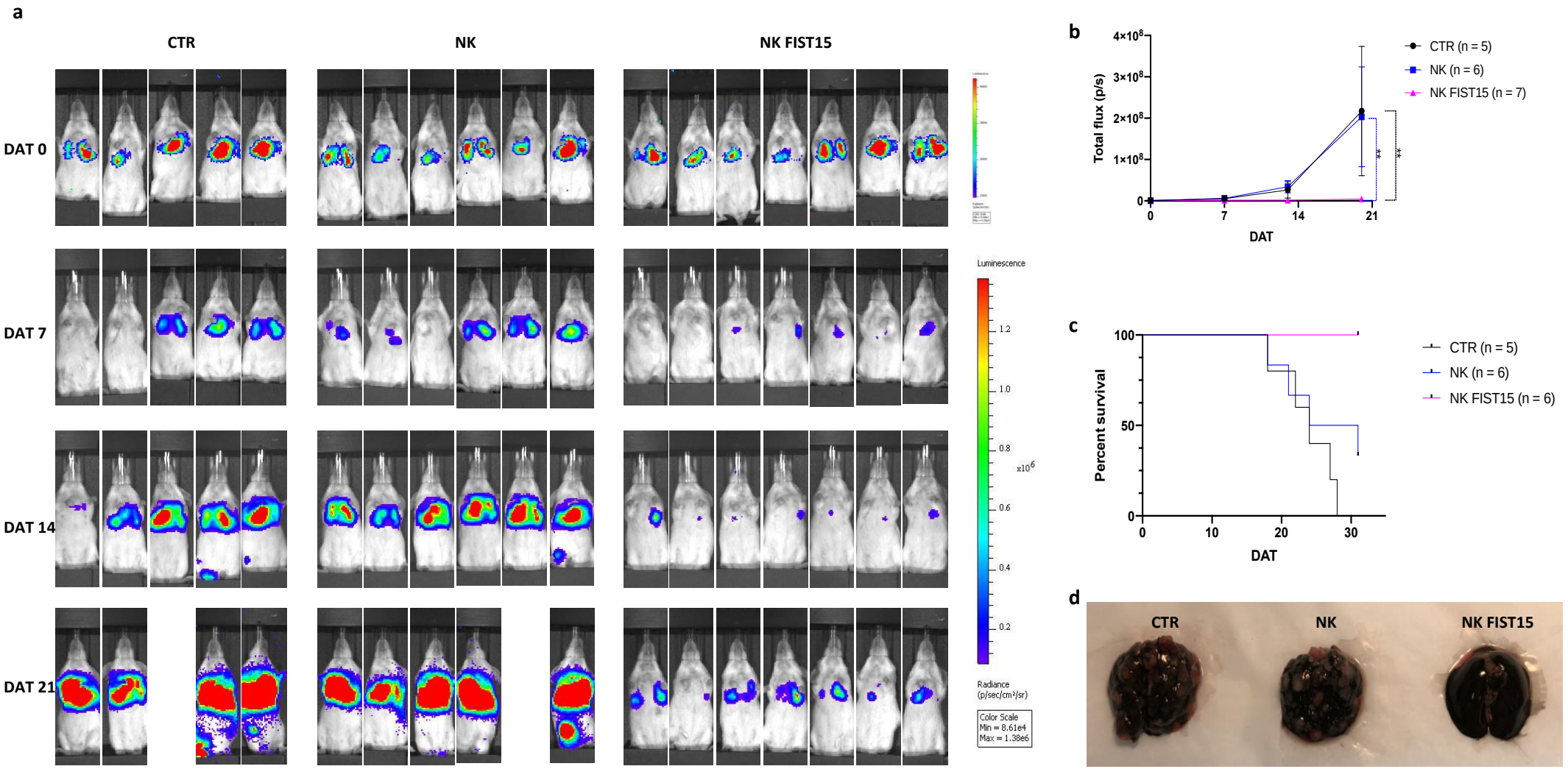
FIST15 enhances anti-tumor effects of NK cells against K7M2 osteosarcoma after syngeneic BMT by reducing pulmonary metastases and enhancing survival



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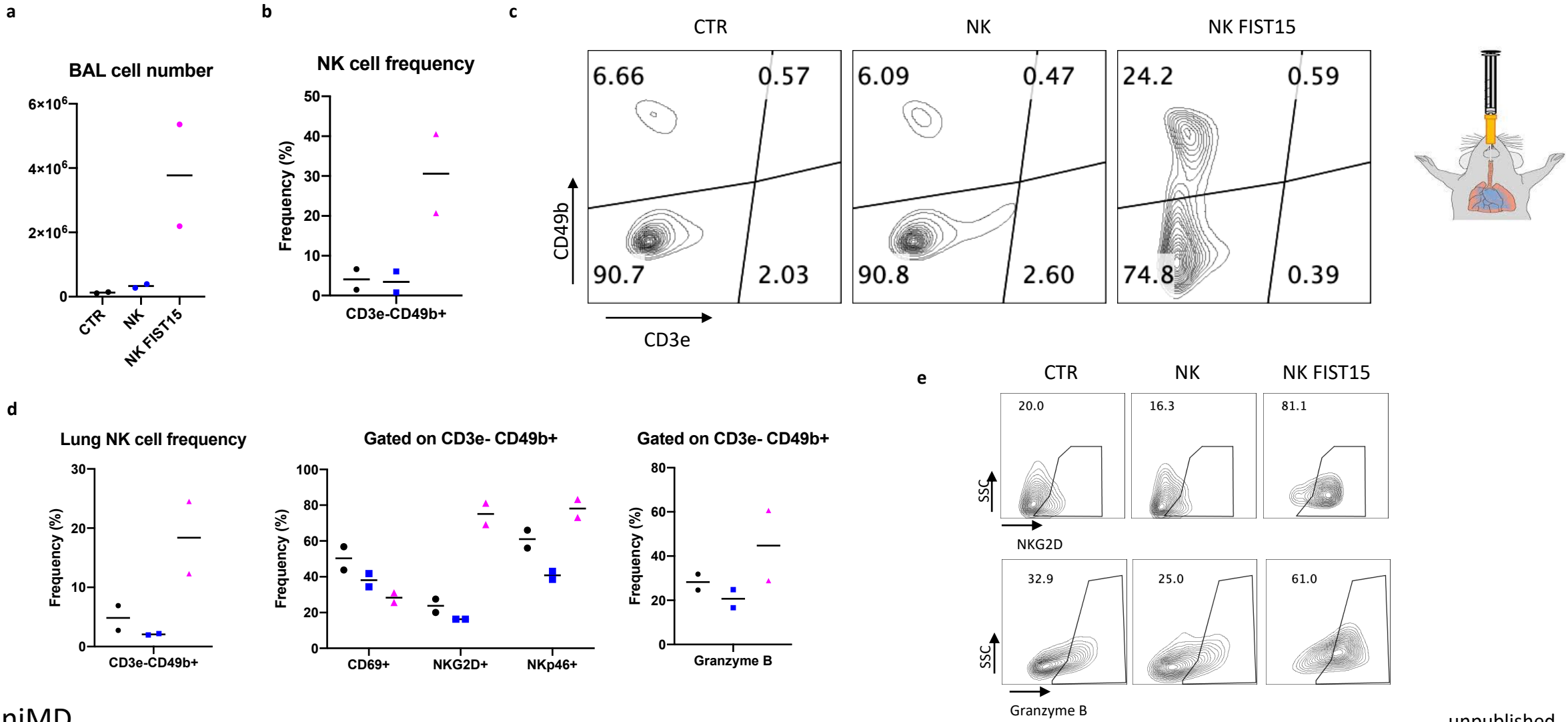
FIST15 facilitates NK cell migration to lungs

Day 5

Day 7



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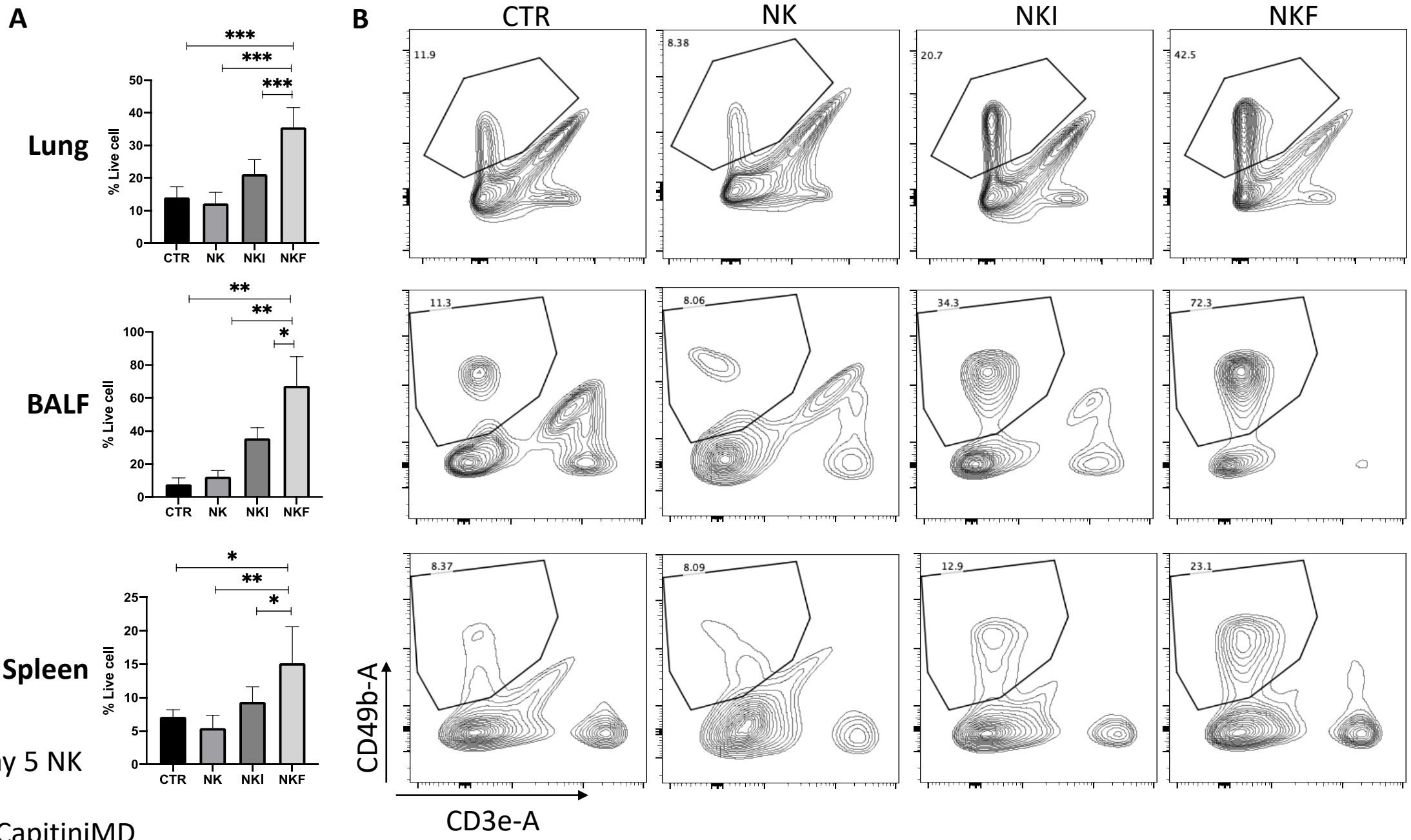

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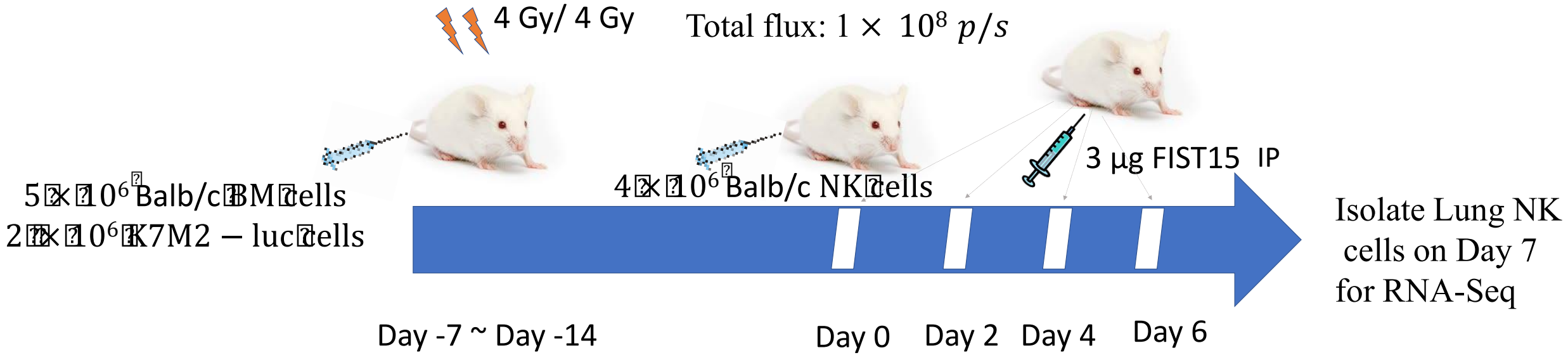
Syngeneic bone marrow transplant model of pulmonary osteosarcoma to test impact of FIST15 on gene expression of tumor infiltrating NK cells



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NK cells that trafficked to lungs after FIST15 vs IL-15/IL-15Ra show downregulation of angiogenic genes and upregulation of cell cycle-related and adhesion genes

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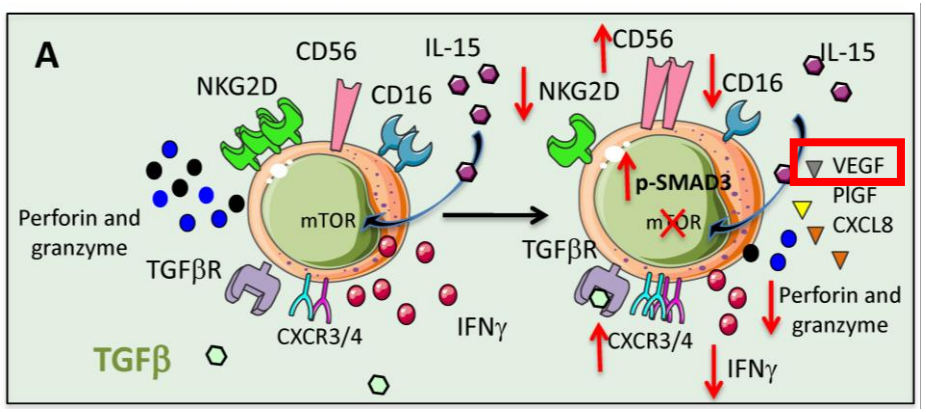
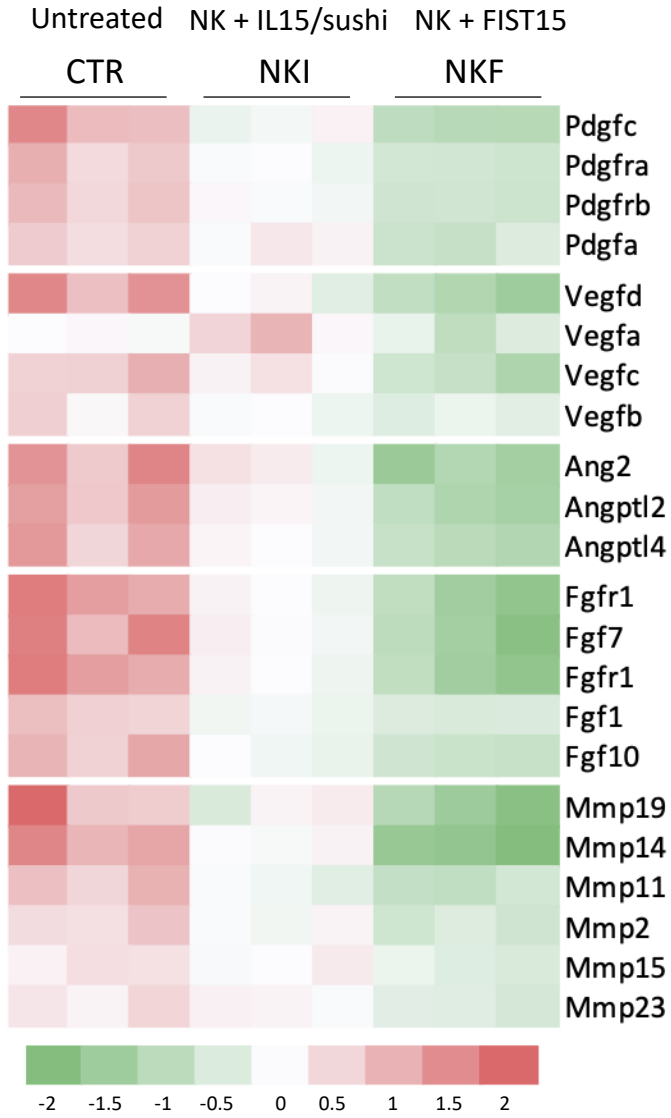
Expression of proangiogenic genes in NK cells is downregulated in FIST15 treated animals



Bassani et al 2019 Cancers



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KEGG pathway analysis of NK cell exome from lungs show downregulation of angiogenic genes and upregulation of cell cycle-related and cytotoxicity genes after FIST15 vs IL-15/IL-15Ra

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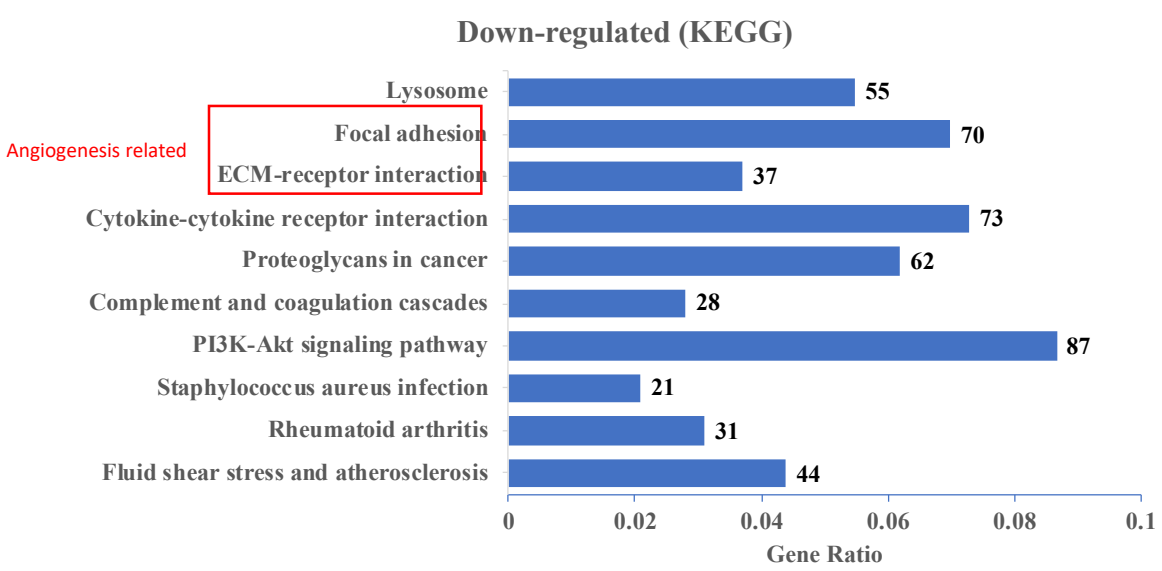

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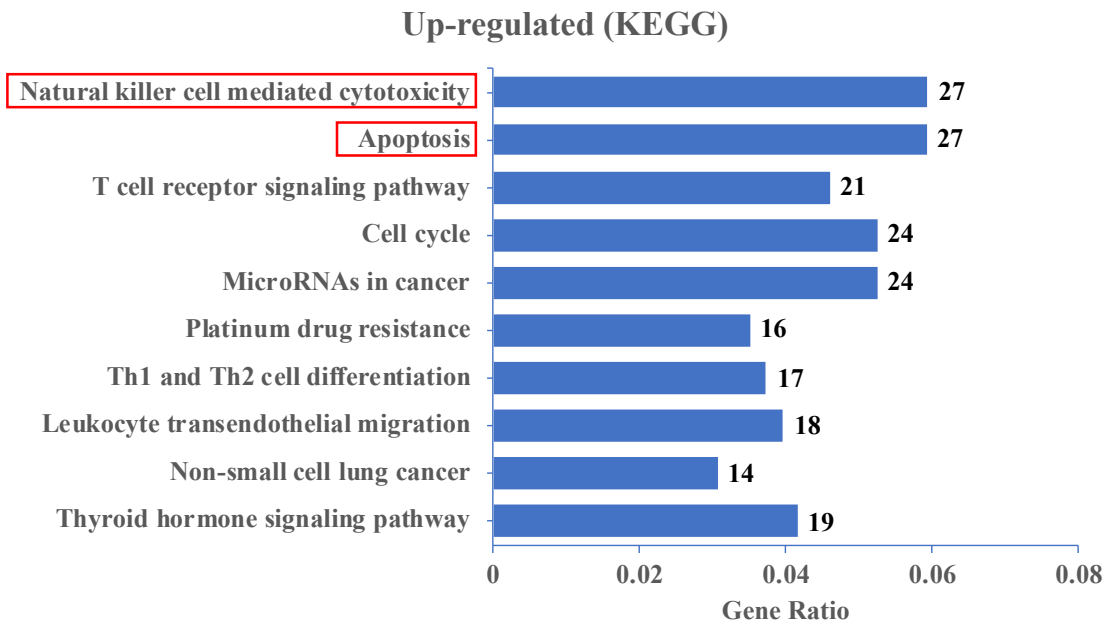

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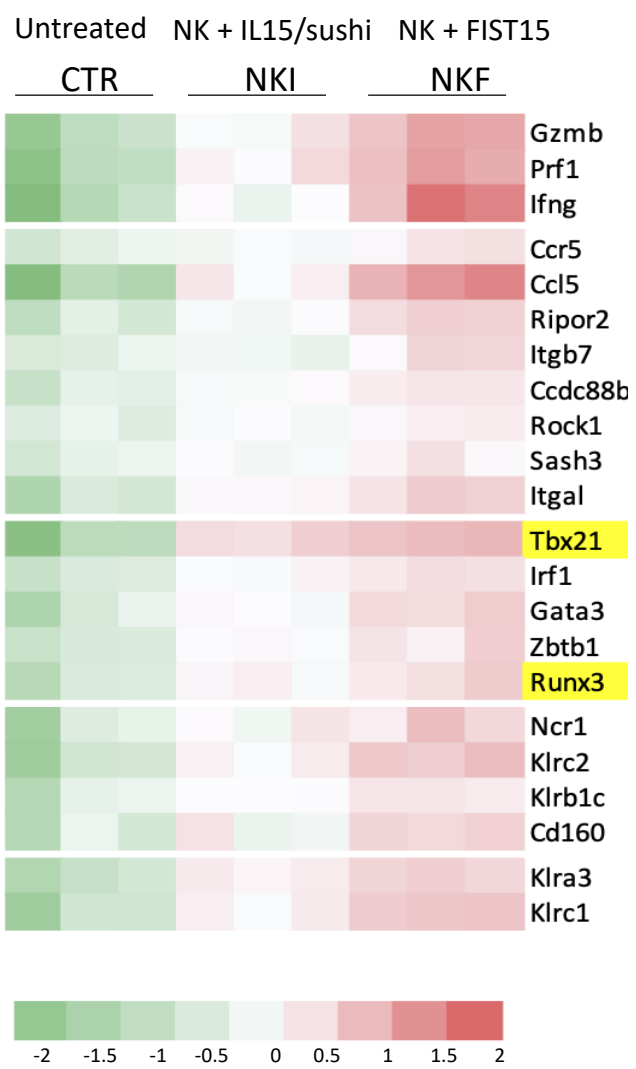
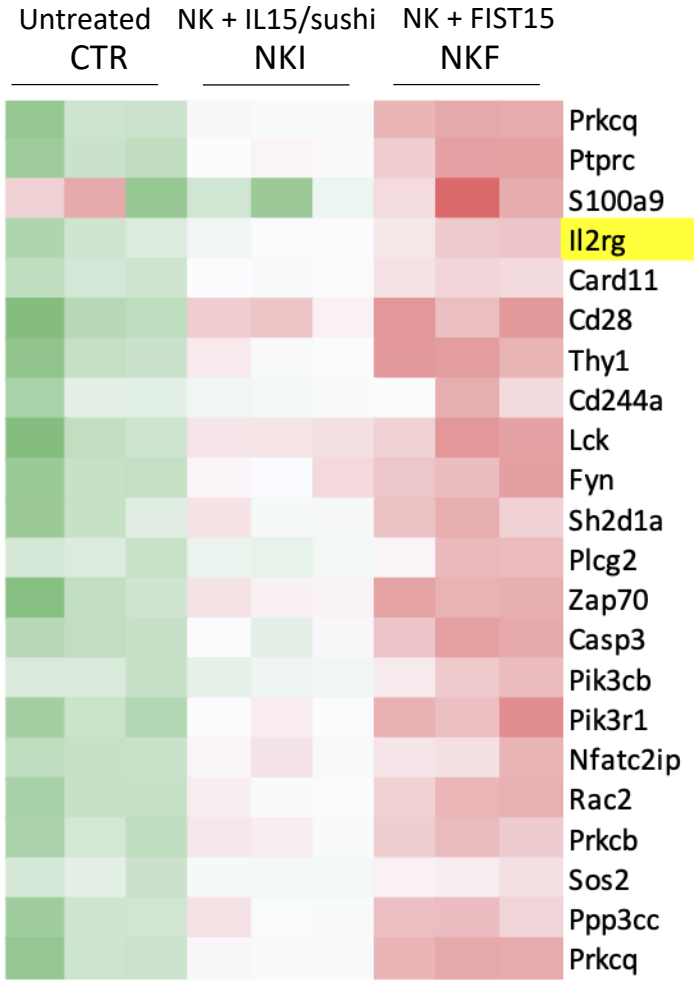
Expression of NK cell mediated cytotoxicity related genes is upregulated in FIST15 treated mice





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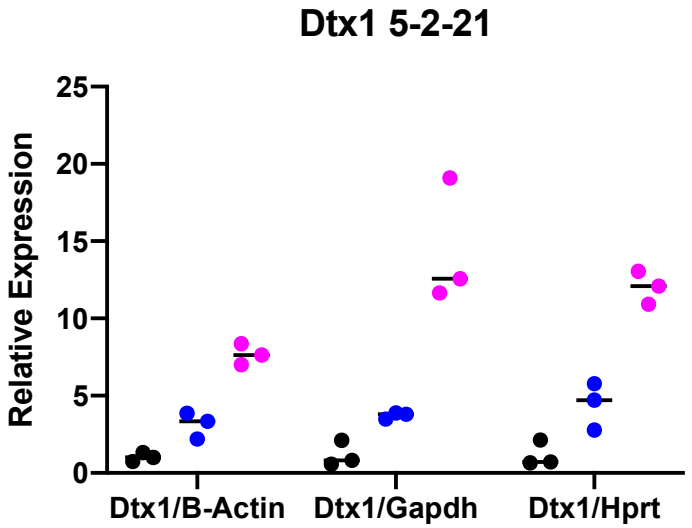
FIST15-treated animals with osteosarcoma have NK cells with increased gene expression of DTX1, a ubiquitin ligase and positive regulator of the Notch pathway

Day 7 Lung



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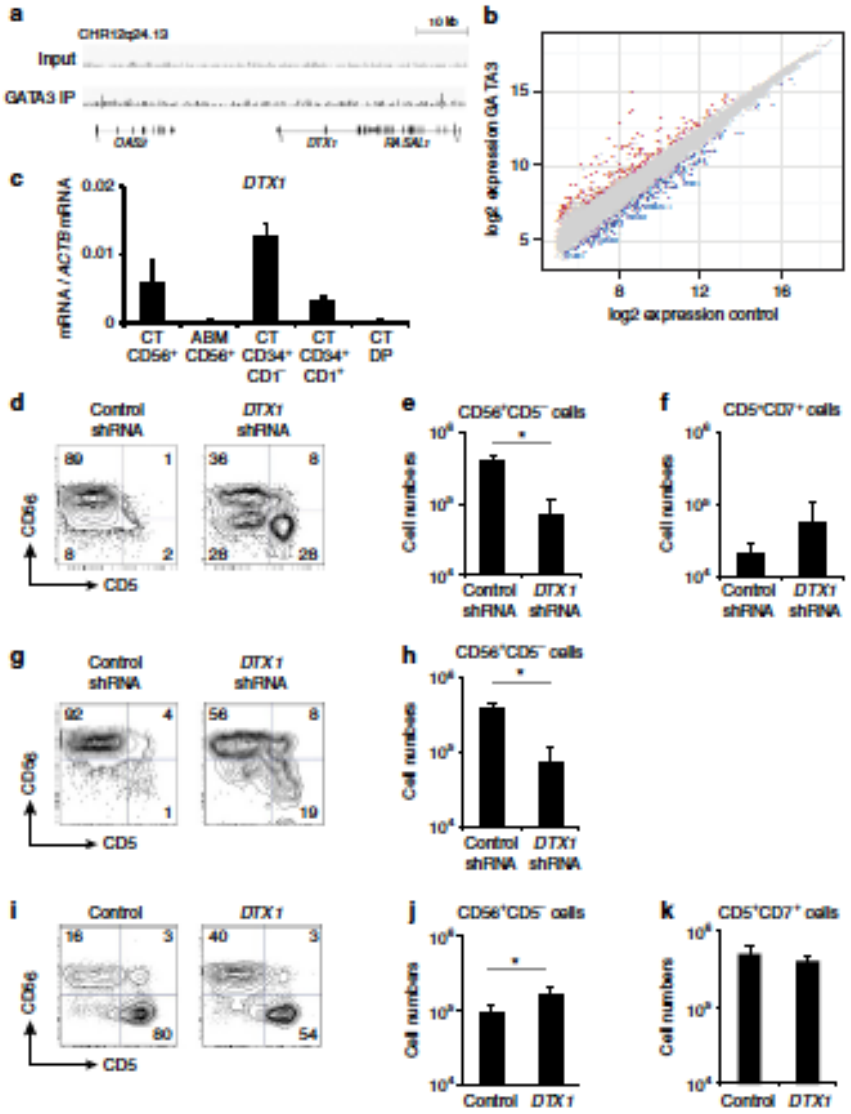
DTX1 regulates thymic development of NK cells through GATA3



Van de Walle 2021 Nat Communications

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Conclusions

- Combination FIST15 with adoptive NK cell therapy induces regression and/or stabilization of pulmonary metastatic osteosarcoma
  - Reduced disease burden and rate of progression
  - Superior to no treatment, NK alone, or NK + IL-15
  - Increased NK cell trafficking seen by bronchioalveolar lavage with FIST15 treatment
- Reduced gene expression of angiogenesis
- Increased gene expression of cytotoxicity, adhesion and apoptosis-related genes
- FIST15 may be enhancing generation or recruitment of NK cells to the lung through DTX1

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