Novel single chain antibodies to inhibit CCR7 mediated-entry of pediatric T-cell acute lymphoblastic leukemia into the CNS

H. Cunningham[1], E. Kim[2], K. August[3], C. Vines[4]

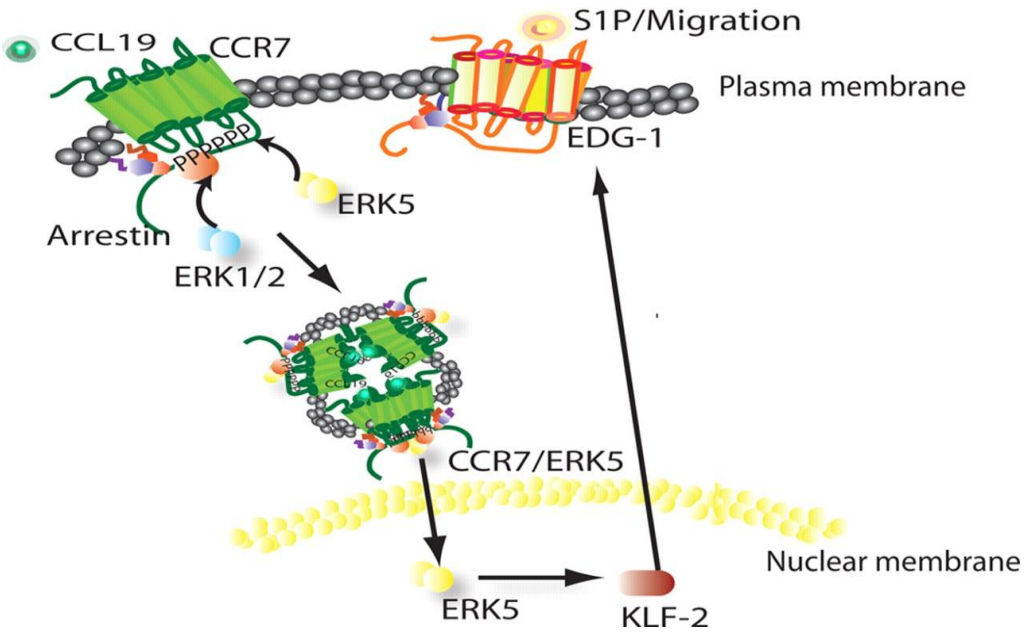
[1]University of Kansas Cancer Center, Westwood, KS, [2] MSM Proteins, [3]Children's Mercy Hospital, Kansas City, MO, [4] University of Texas, El Paso

Disclosures

I have no disclosures.

Background

- Chemokine-receptor 7 (CCR7): Naïve T-cells, B-cells, NK T cells, dendritic cells
- Regulates T-cell egress from tissues into lymph nodes, induced by EBV
- CCR7 - Up-regulated on malignant cells:
  - Hematologic: pediatric T-cell ALL, CLL, diffuse large B-cell lymphoma
  - GI: esophageal, pancreatic, CRC, gastric cancer
  - Breast cancer
  - Melanoma
  - Head & Neck Cancer
  - NSCLC
  - Lymph node metastasis



Shannon et al. J. Biol. Chem. 2012

CCL 21

Adheres to lymphatics and HEV

Promotes migration of naïve T-cells to lymph nodes

Internalizes 20% of CCR7*

CCL19

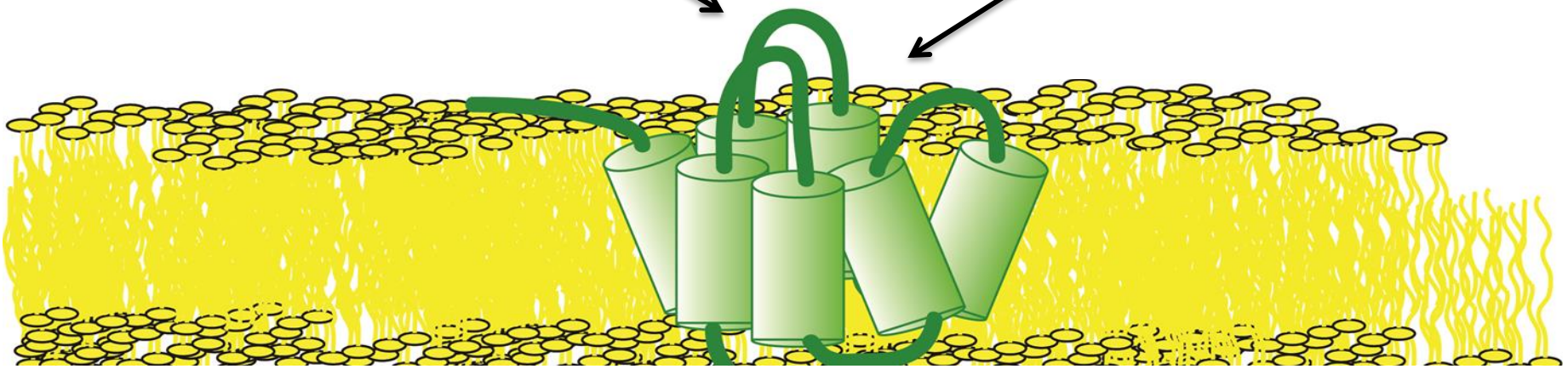
Expressed by activated dendritic cells

Promotes migration of activated dendritic cells to lymph nodes

Mediates adhesion to antigen presenting cells**

Internalizes 80% of CCR7*

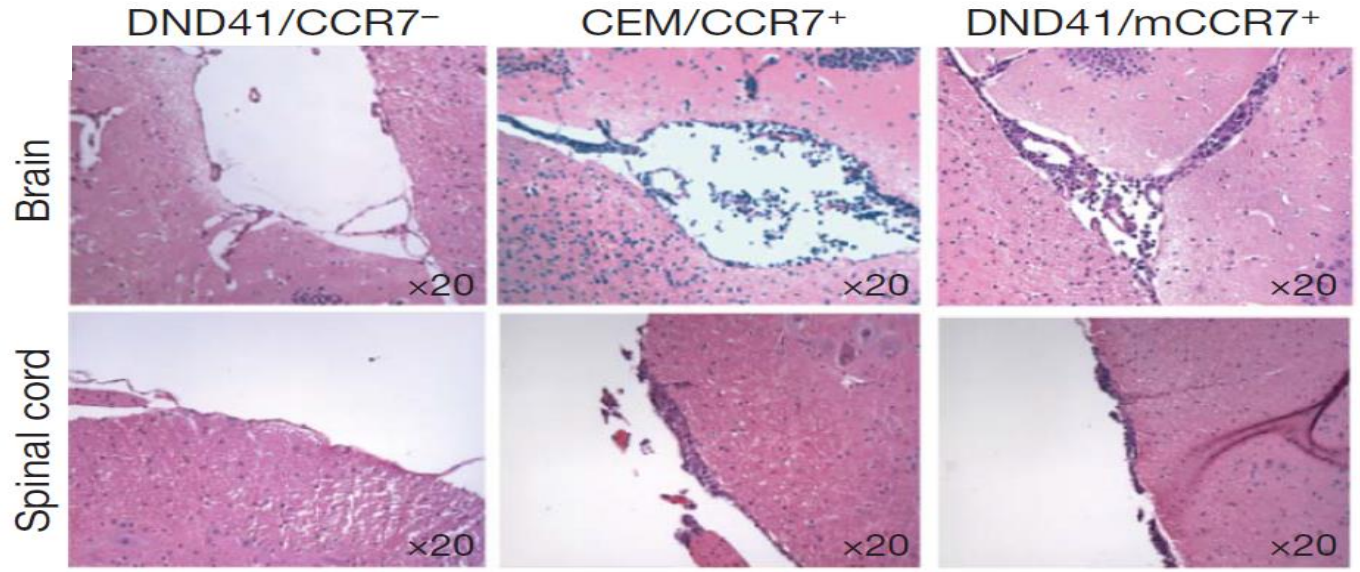
Regulates T-cell differentiation**



*Byers et al. J Immun. 2008.
**Shannon et al. J Biol Chem. 2012.

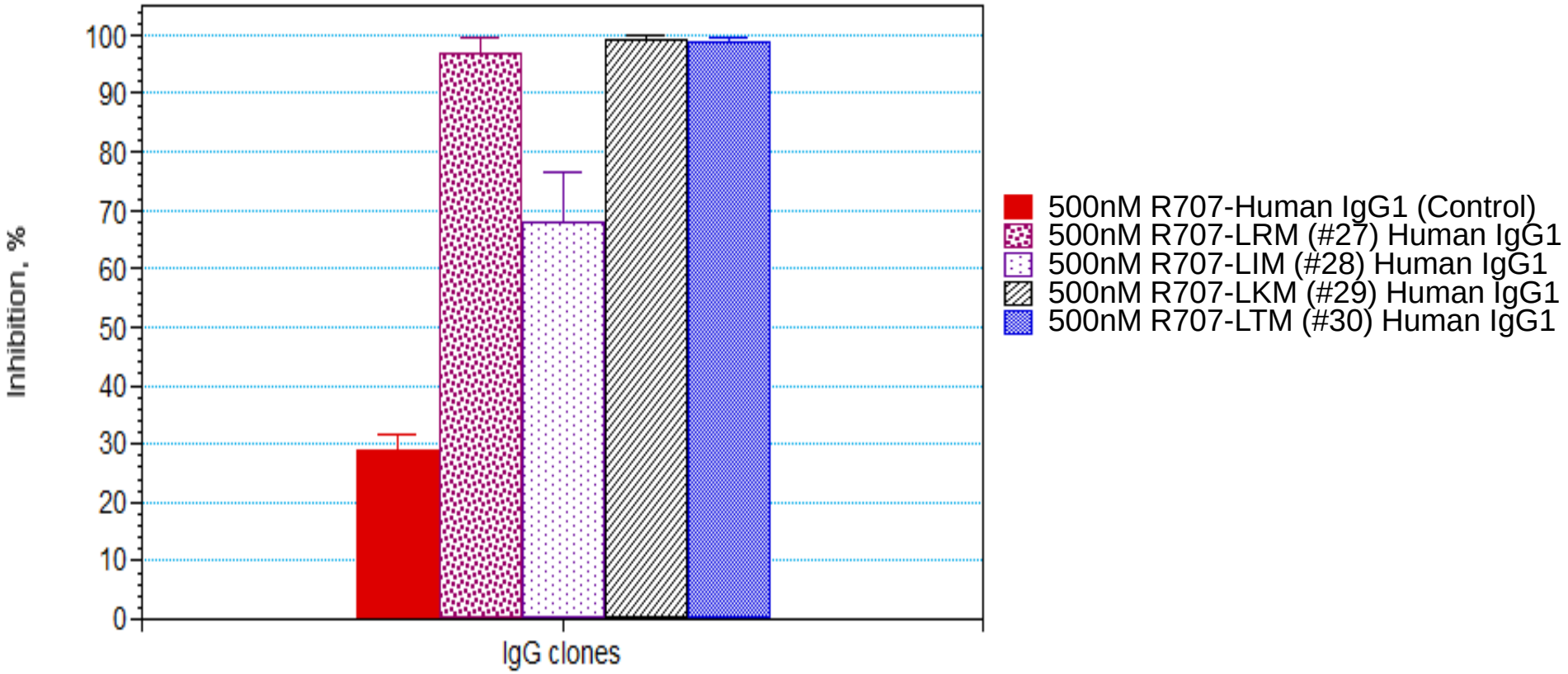
CCR7 signaling as an essential regulator of CNS infiltration in T-cell leukemia

- NOTCH 1 activation – ↑ CCR7 expression
- *Rag2*−/−*IL2rg*−/− mice - injected with human T-ALL cell line (CEM/CCR7+)
  - ↑ CNS infiltration = ↓ Overall survival
- CCL19 expression required for CNS infiltration
- CCR7 sufficient for infiltration of CD3+ leukemic cells into CNS



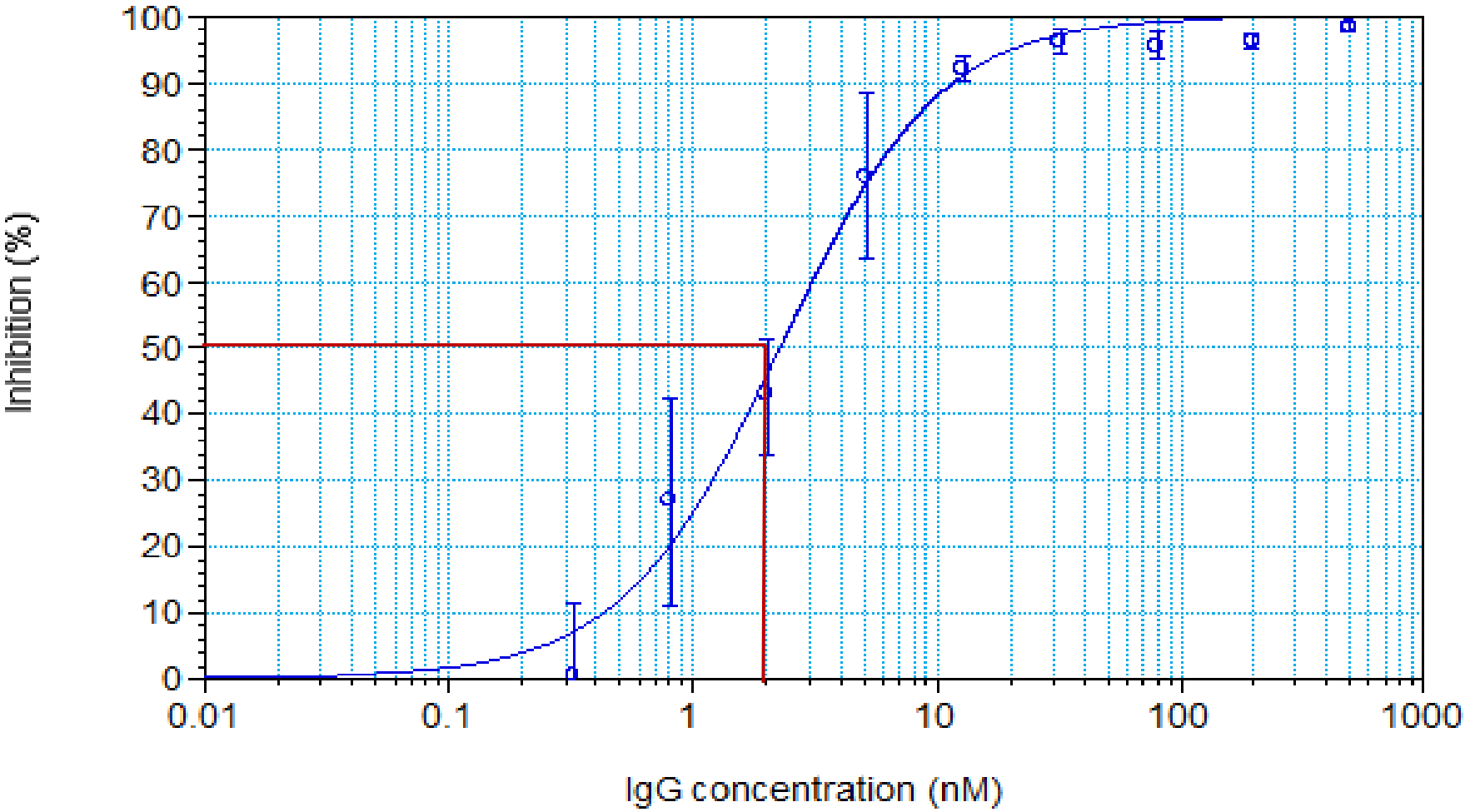
Buonamici et al. Nature. 2009.

R707 Mutants #27-30 Inhibition of CCL19-Induced Ca-Flux (MaxPoint)



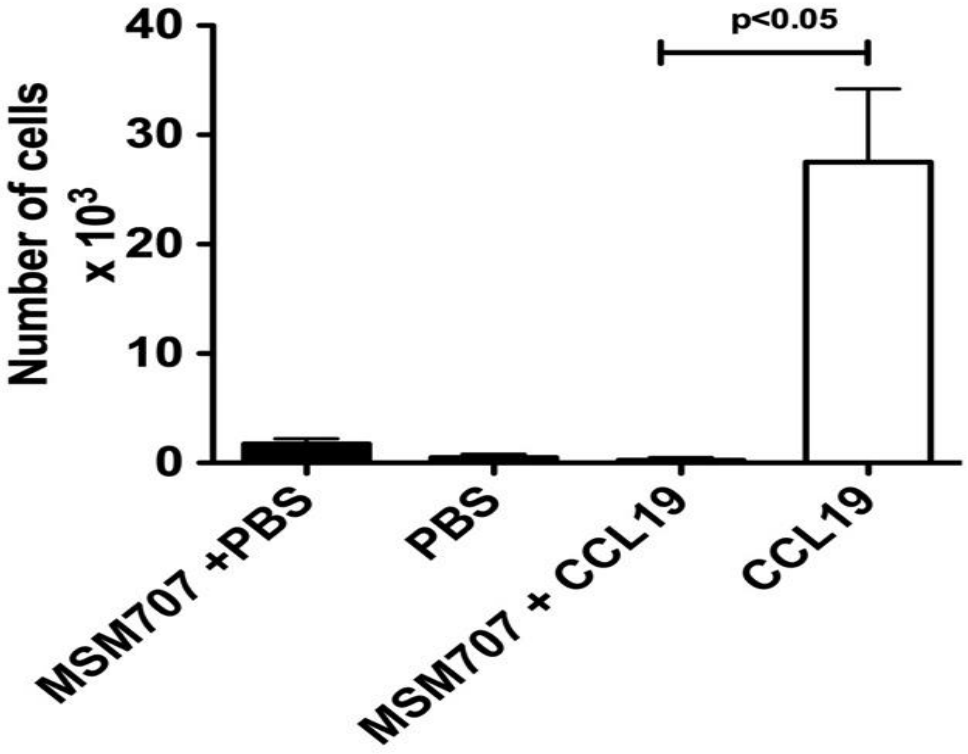
- **R707 Mutant #28 ~ 70% inhibition of CCL19-induced Ca-Flux**
- **R707 Mutants #27, 29, 30 → ~ full inhibition of CCL19-induced Ca-Flux**

R707-29 (R707-LKM) IgG1 Inhibition of CCL19-Induced Ca-Flux on CCR7+ Cells

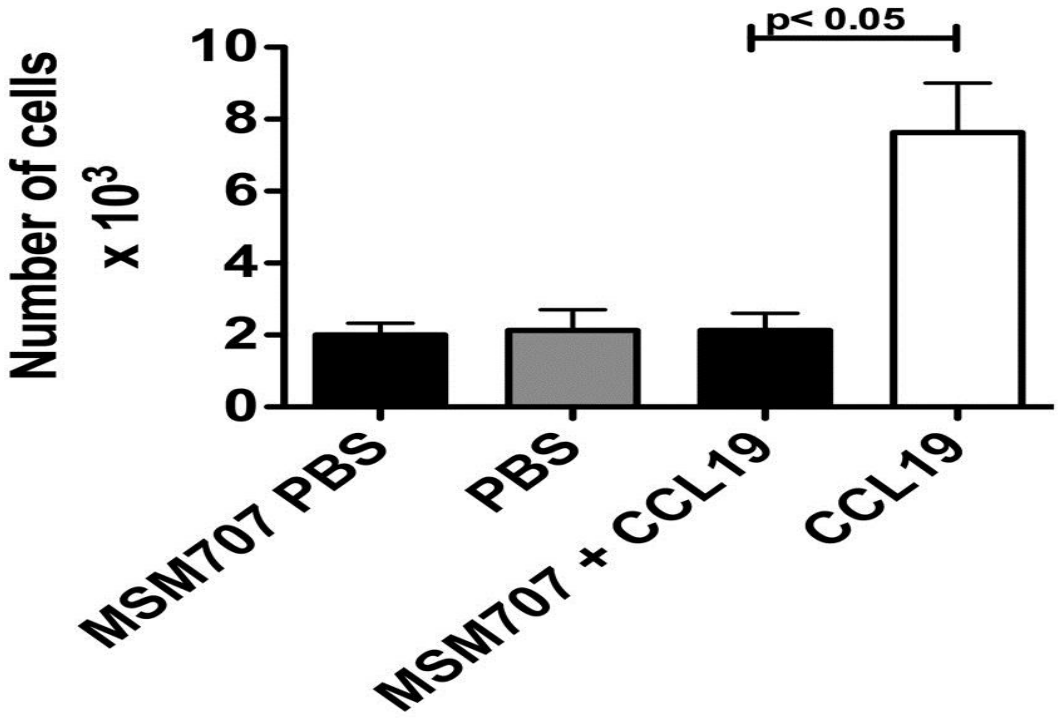


IC50 ~ 2.3nM

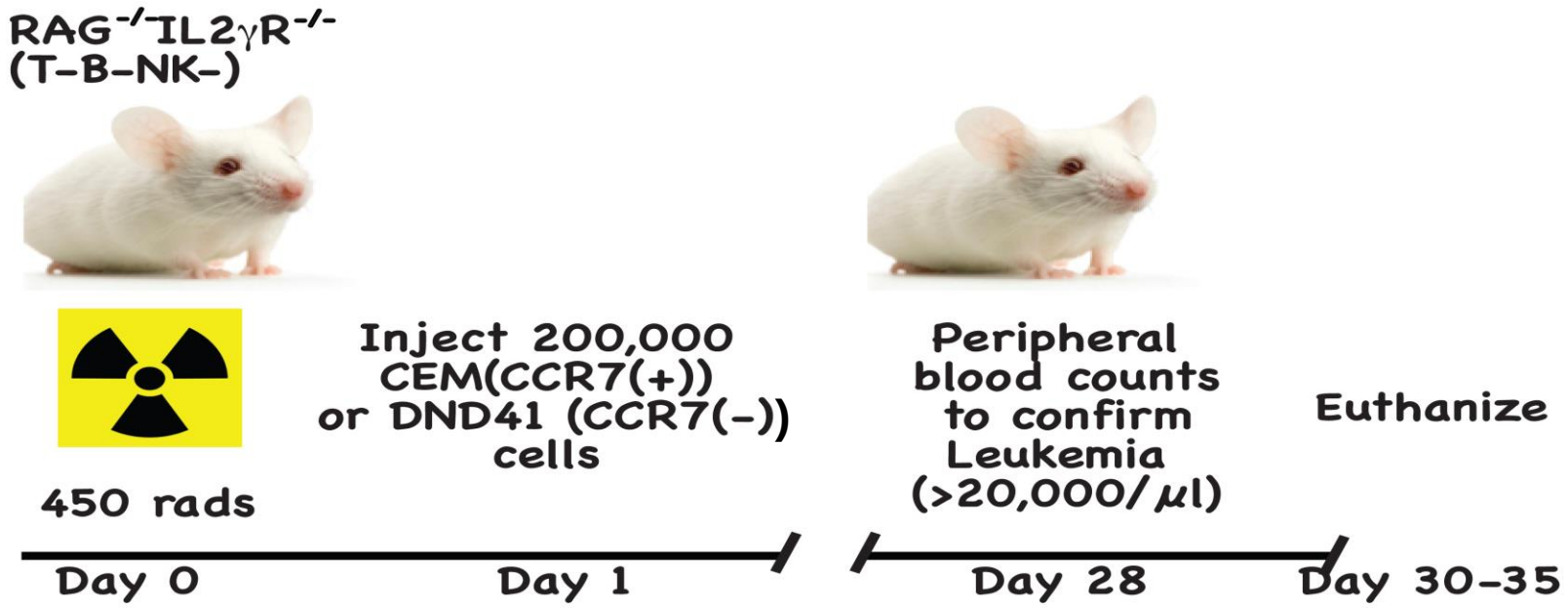
MSM707 Blocks Migration of the CEM cell line to 200nM CCL19 on Fibronectin

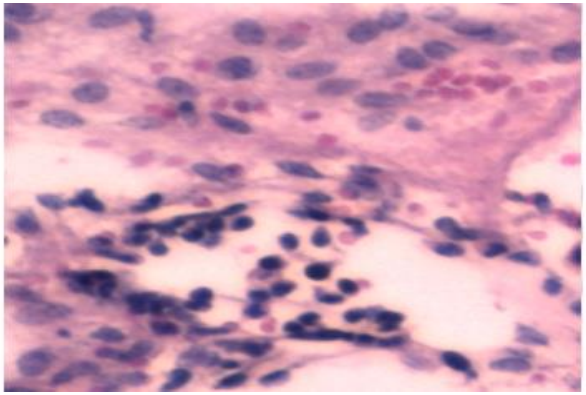


MSM antibody 707 blocks migration of pediatric primary T-ALL via $\alpha_V\beta_3$

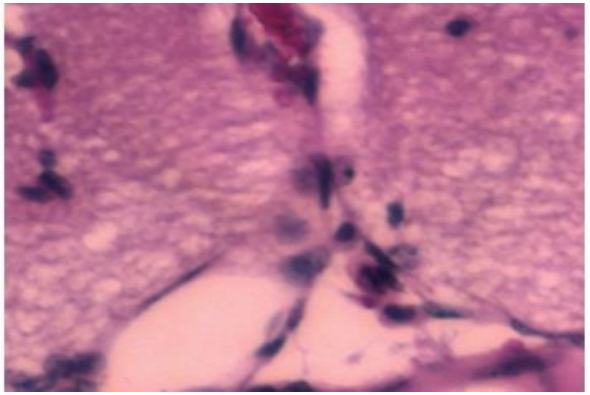


CCR7 sufficient for infiltration of T-ALL cells into the CNS





CEM/(CCR7+)



DND41/(CCR7-)

Conclusions

- Single chain-antibody (MSM 707) blocks migration of pediatric T-cell ALL cells (both CEM/CCR7+ and primary cells) in vitro
- CCR7 sufficient for infiltration of T-cell ALL into the CNS in murine model
- Goal of single-chain CCR7 antibody therapy - minimize systemic toxicity from chemotherapy/radiation
- CCR7 antibody - broad therapeutic potential across several malignancies

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