Targeted Therapy for T-cell Lymphomas

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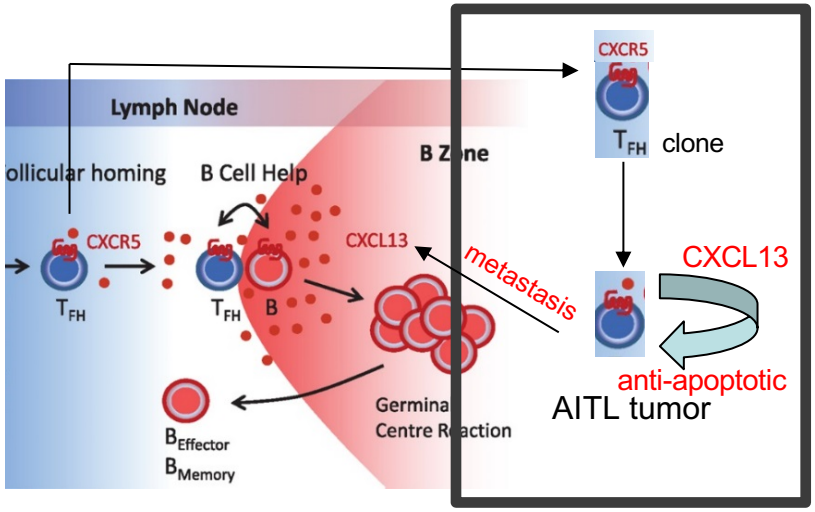
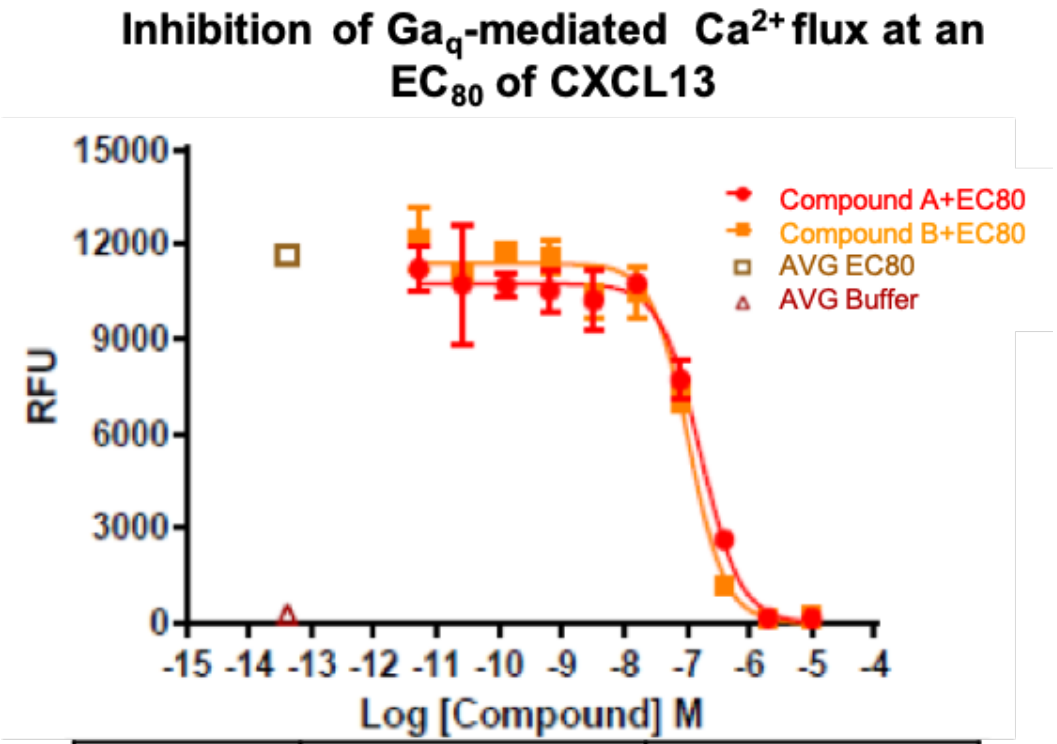
Physiological and Pathologic Roles of CXCR5: A Therapeutic Target for Angioimmunoblastic T cell Lymphoma (AITL)

- AITL is a rare T cell lymphoma, 3000 cases per year
- **Median survival** 50% at 2 years, 30% at 5 yr
- All AITL cells secrete CXCL13 and express CXCR5 receptor
- Microenvironment has increased secretion of CXCL13
- Cutaneous T cell lymphoma (CTCL) patients may also express CXCR5 on the malignant cells and expression is associated with a worse outcome



Moser, Front. Immunol., 2015

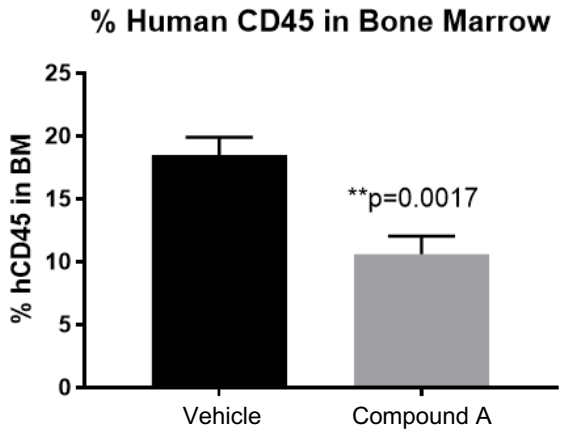
Proof-of-Principal for CXCR5 Small Molecule Antagonism at Nanomolar Concentrations



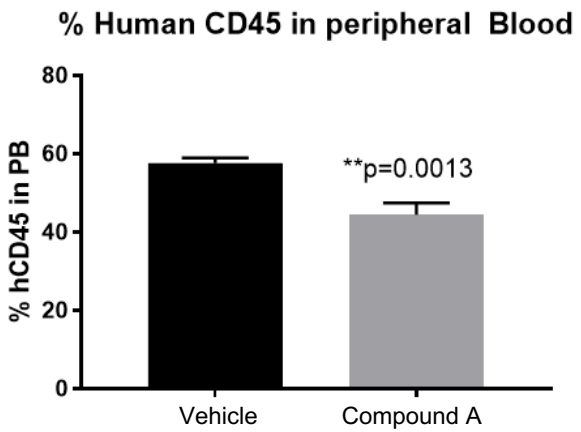
	Compound A+EC80	Compound B+EC80
Log IC50	-6.779	-6.969
HillSlope	-1.356	-1.492
IC50	1.664e-007	1.075e-007

In Vivo Proof-of-Principle in a Human AITL PDX Mouse Model

- NSG (NOD/SCID, IL-2R knockout) mice
- Patient-derived AITL tissue with CXCR5 at 50% of other patients
- Oral gavage 2x/day with vehicle or 40 mg/kg Compound A

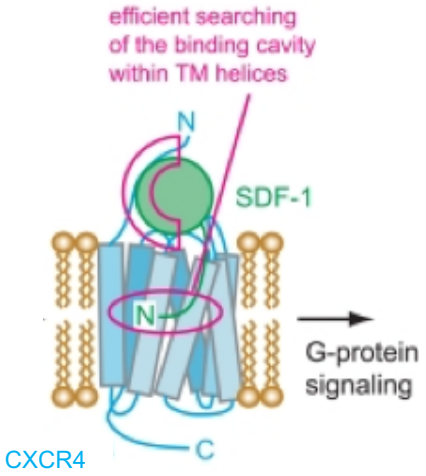


Unpaired t test	
P value	0.0017
P value summary	**
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
t, df	t=3.882 df=14



Unpaired t test	
P value	0.0013
P value summary	**
Significantly different (P < 0.05)?	Yes
One- or two-tailed P value?	Two-tailed
t, df	t=4.016 df=14

Phage Display Screen for Biotherapeutics and CAR T



- Phage display library of 168,000 CXCL13 variants used to screen for five rounds to identify potent variant CXCL13 antagonists.
- NGS and bioinformatics to determine 102 sequences likely to represent most potent sequences.

Target prevalence and enrichment factor of 24 (of 102) redacted sequences

Translation	Target prevalence	Enrichment factor	Translation	Target prevalence	Enrichment factor
| | | |	0.002748342	infinity	| | | |	0.001948505	4059.375
| | | |	0.001652557	infinity	| | | |	0.001867882	2594.27778
| | | |	0.001507676	infinity	| | |	0.001636991	2273.59722
| | | |	0.001458984	infinity	| | | |	0.001608654	2234.23611
| | | |	0.001448008	infinity	| | | |	0.001582711	3297.3125
| | | |	0.001325678	infinity	| | | |	0.001420269	2958.89583
| | | |	0.00126102	infinity	| | | |	0.001307318	2723.58333
| | |	0.002484124	2587.625	| | | |	0.001271597	2649.16667
| | | |	0.002466164	2568.91667	| | | |	0.001182793	2464.14583
| | |	0.002261215	3140.58333	| | | |	0.001176606	2451.27083
| | | }	0.002221702	4628.54167	| | |	0.001171418	4880.91667
| | | |	0.002135293	2224.26042	| | | |	0.001094188	4559.125
| | | |	0.002064848	2150.88542	| | | |	0.001071039	2231.33333
| | | |	0.002058861	8578.58333	| | | |	0.001050883	4378.66667

Business landscape

- Market
  - *Rare disease, orphan status for AITL*
- Competition
  - *Several approved agents for T cell lymphoma, all with low response rates and short progression free survival, remains unmet medical need*
- Unique aspects of this product
  - *Targeting chemokine/chemokine receptor pathways for treatment of AITL using a library of CXCR13 ligands for:*
    - A biotherapeutic
    - Chimeric Antigen Receptor targeting

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Next Steps for Mutant CXCL13 Variants

- Express, purify, characterize 102 CXCL13 variants
  - *Assay for Ca^{2+} flux to test CXCL13 variants and confirm antagonism*
  - *Characterize IC_{50} and k_{off} rate*
- Molecular biology of the most potent CXCL13 antagonist-IgG1.
  - *Expression, purify, and characterize therapeutic properties (IC_{50}, PK, ADCC)*
- Molecular biology for CAR T
  - *In vitro testing for efficacy*
- Test biotherapeutic and CAR T in AITL-PDX model?

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