Cell autonomous and microenvironment effects of *HVEM/TNFRSF14* mutations in follicular lymphoma

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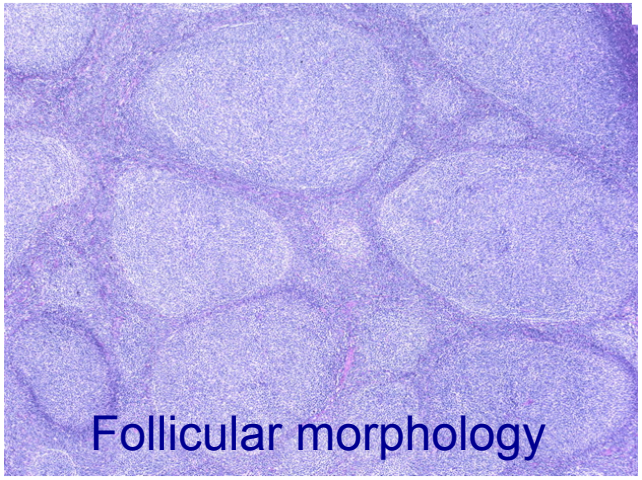
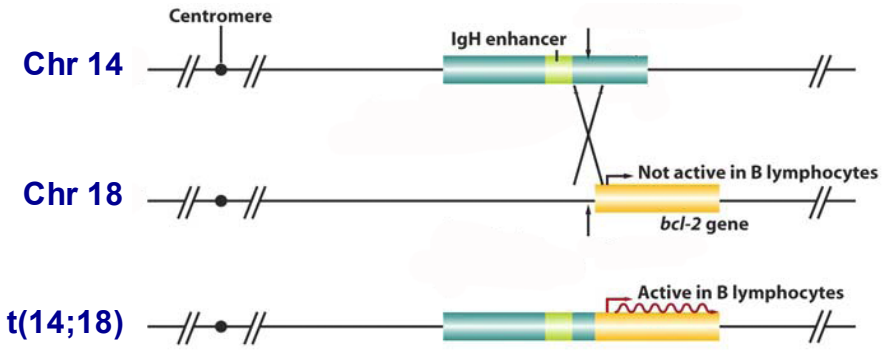
Follicular Lymphoma (FL)

- Typical follicular appearance
- *Slow* growth & relentless relapses
- Treatment chemotherapy and BMT



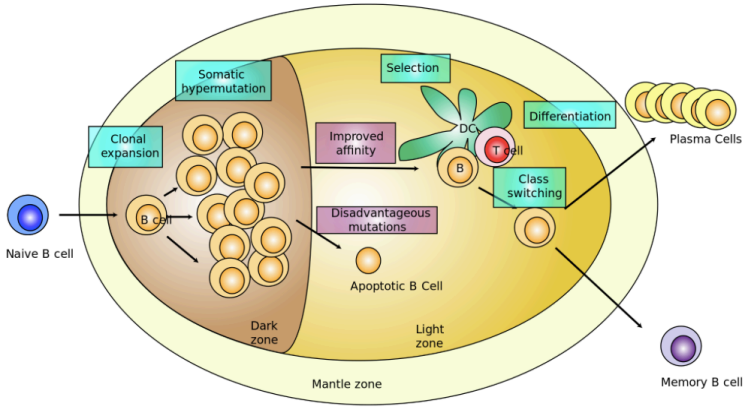
Genetic hallmark:
Translocation between chromosomes 14 and 18: t(14;18)



This fusion is found in ~50% of healthy adults…..

…. whatelse drives the disease?

FLs arise from germinal center B cells



Simplified view of GC

GCs are site of B cell maturation into plasma and memory cells.

GC B cells undergo:

- somatic hypermutation
- genomic rearrangements
- PLUS: explosive growth

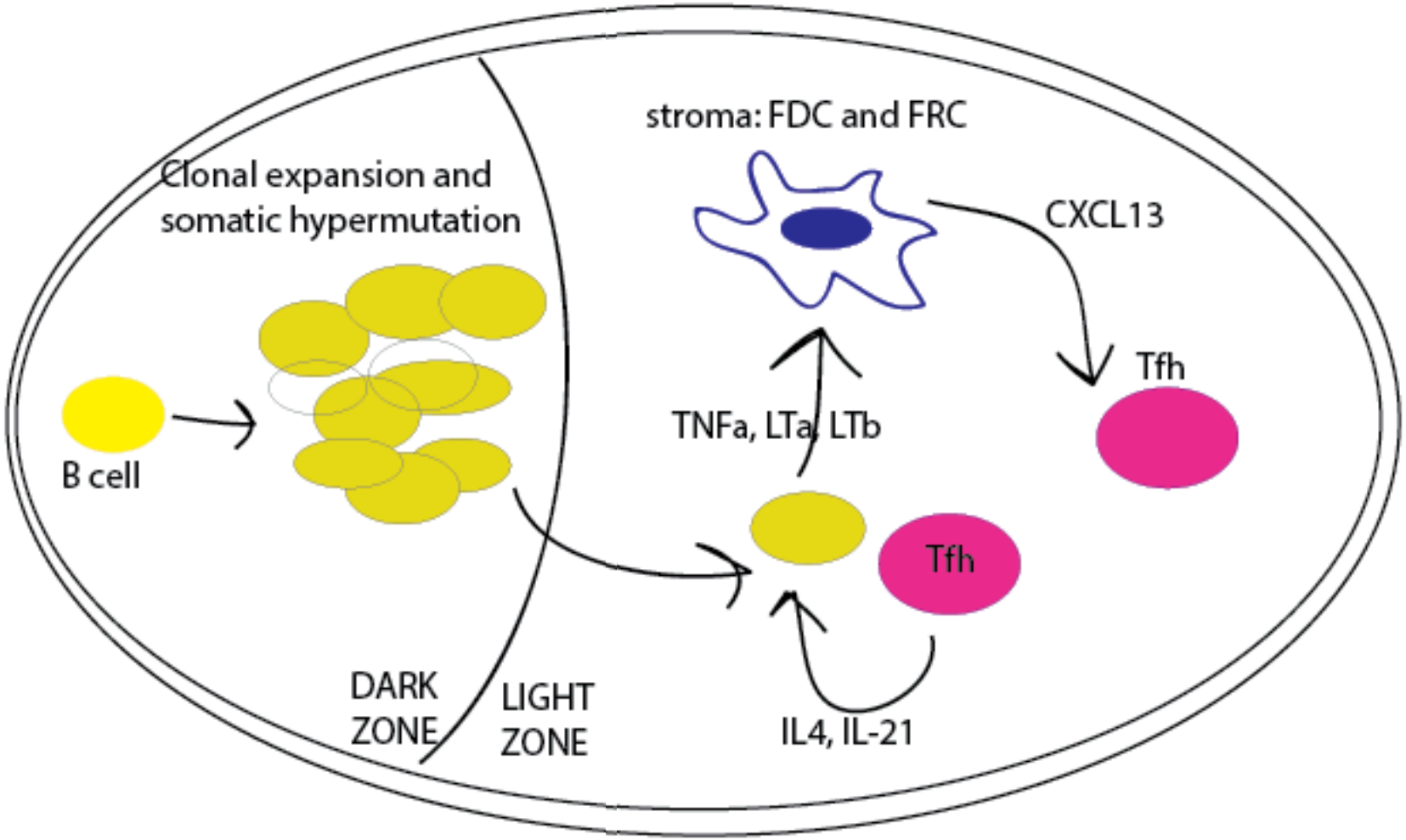
➔ Risky place!

Failsafe mechanism:

- cellular tumor suppressors
- interactions with other GC cells

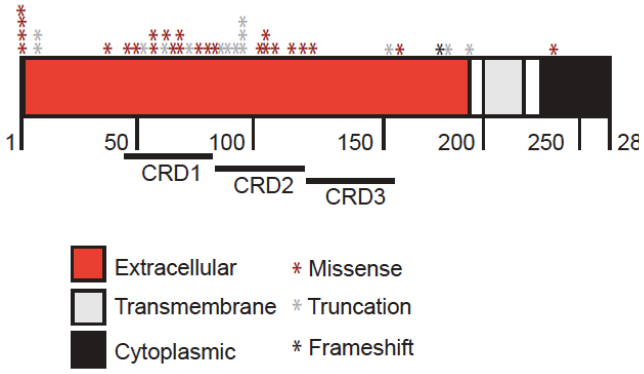
Introducing the members of the cast: FDCs, FRCs, TFHs

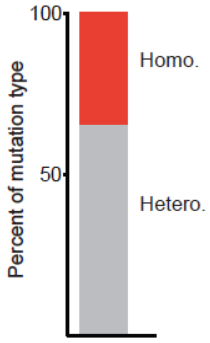
How do lymphoma B cells interact with the GC environment?



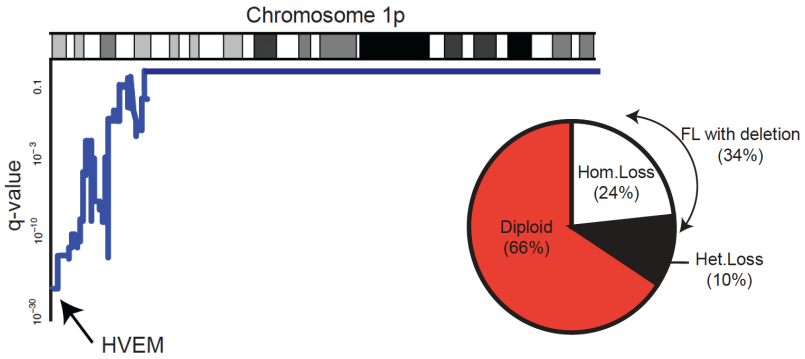
HVEM receptor mutations in FL may provide some answers…

HVEM mutations in ~38%



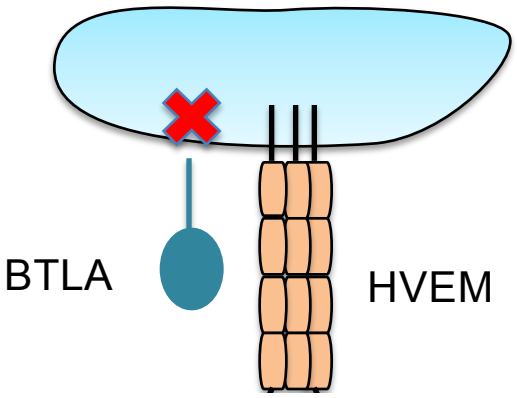


HVEM deletions in ~34%



HVEM is a major mutational target in FL

The HVEM receptor engages in cell-cell interactions



Studies in T cells have shown that HVEM interacts with:

Activating receptors (LIGHT, CD160)

Inhibitory receptor (BTLA)

For B cells we know:

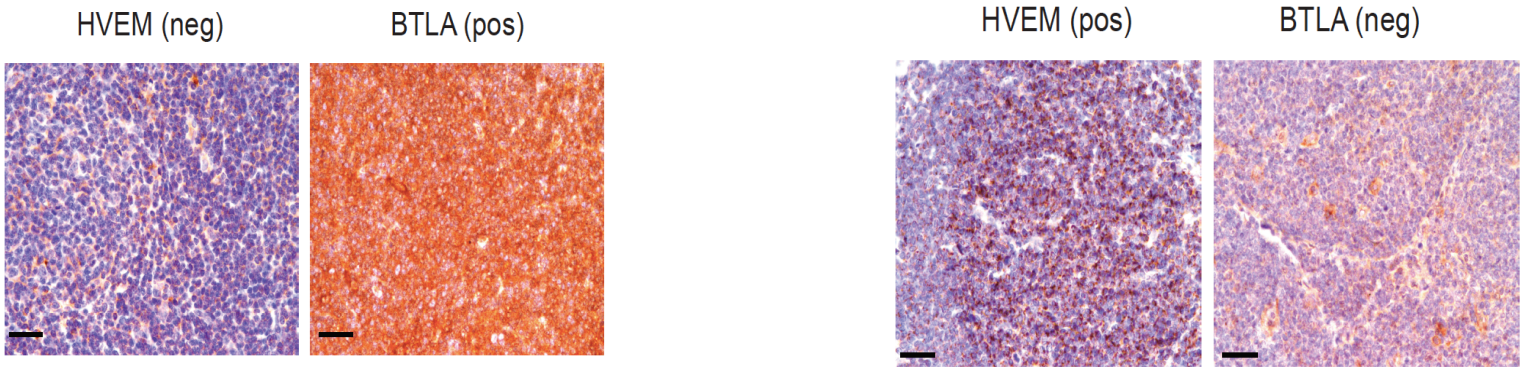
Only HVEM and BTLA are expressed

HVEM-BTLA can interact in *cis* (same cell)

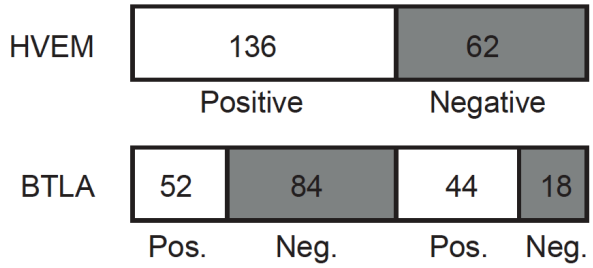
BTLA can bind and block the B cell receptor

What about HVEM and BTLA expression in lymphomas?

What is the relation between HVEM and BTLA in human FLs?

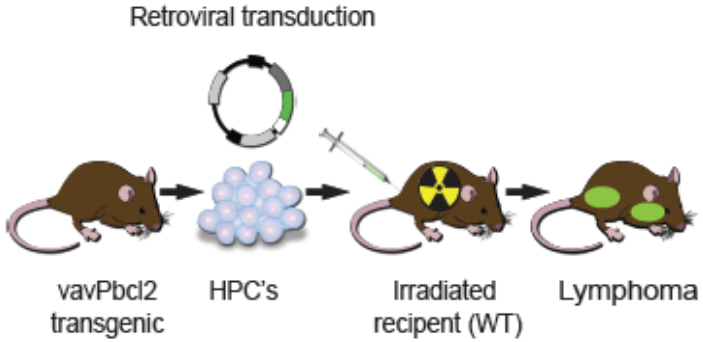


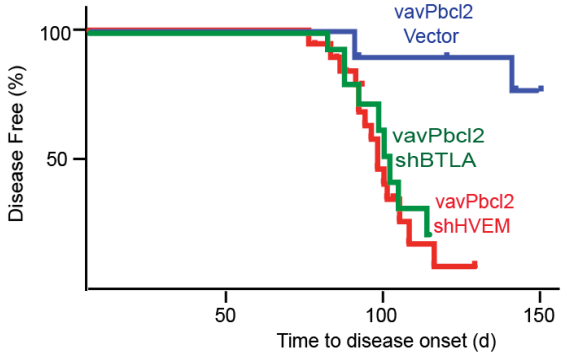
Tissue array (n = 198; p = 0.001)

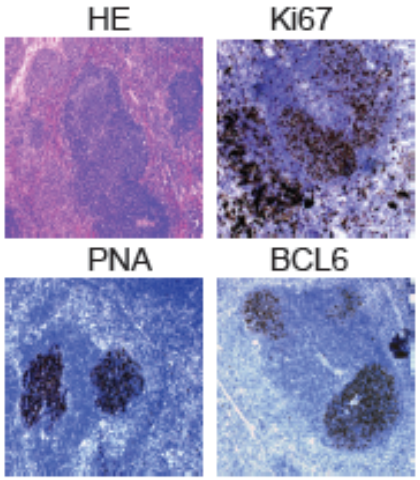


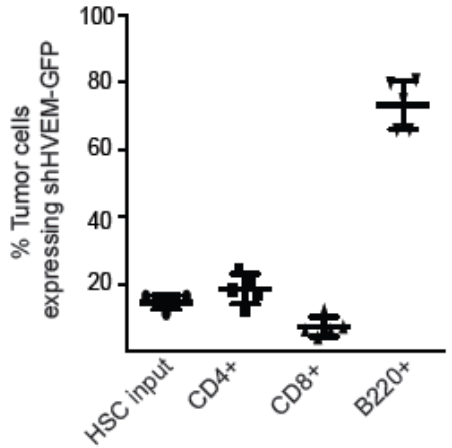
The HVEM – BTLA interaction is lost in ~75% of FLs.

Does HVEM function as a tumor suppressor gene?



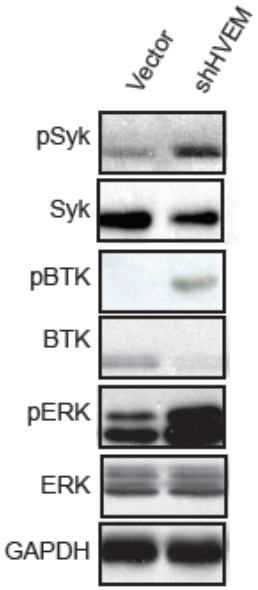




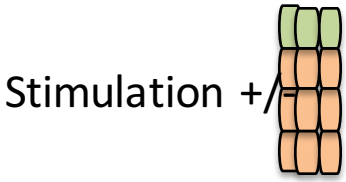


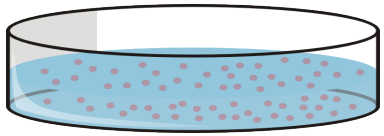
Knockdown of either HVEM or BTLA leads to GC lymphomas

How do HVEM tumors differ from control lymphomas?

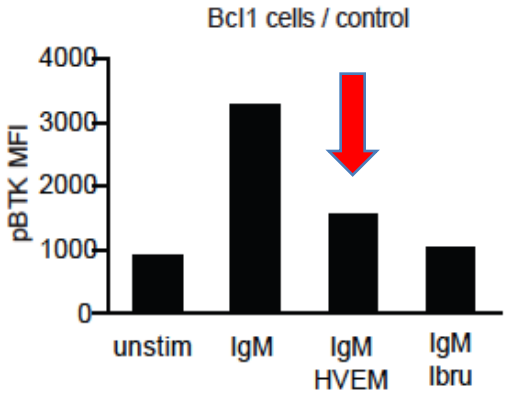


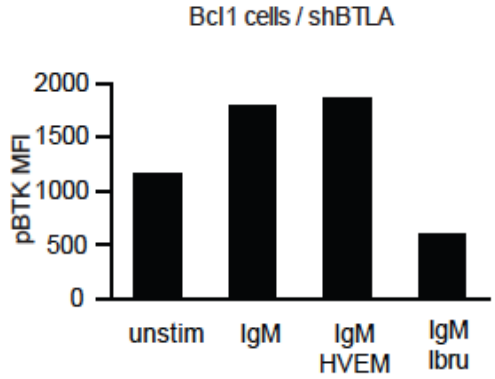
Direct effect of HVEM?





SolHVEM $^{(P37\text{-}V202)}$: HVEM ectodomain

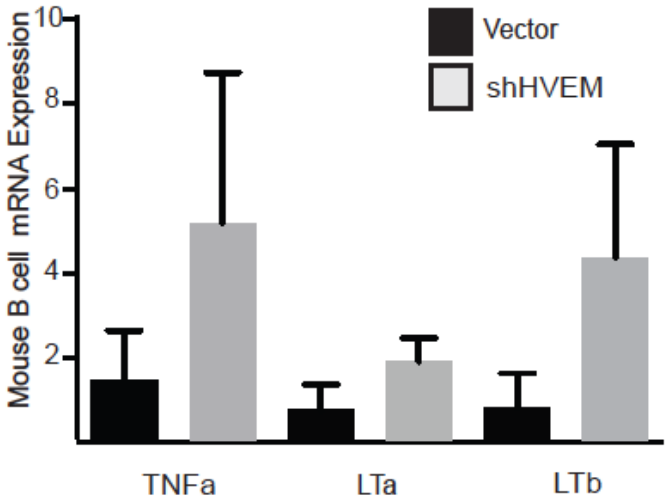




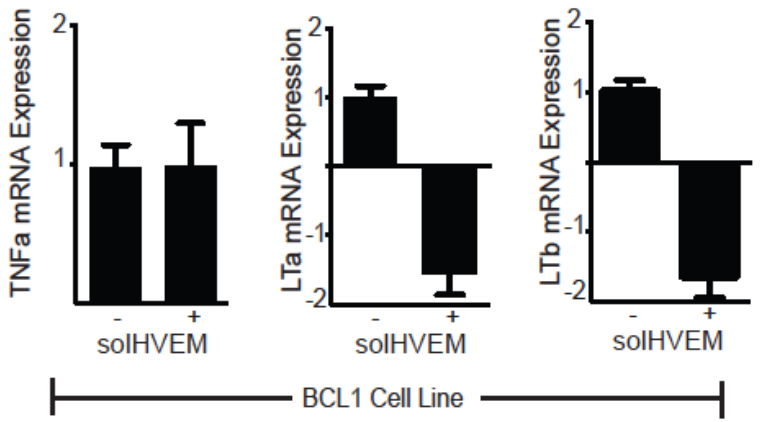
Loss of the HVEM activates BCR signaling
in a cell autonomous and BTLA dependent manner

There are additional changes in HVEM deficient lymphomas

Sorted lymphoma B cells

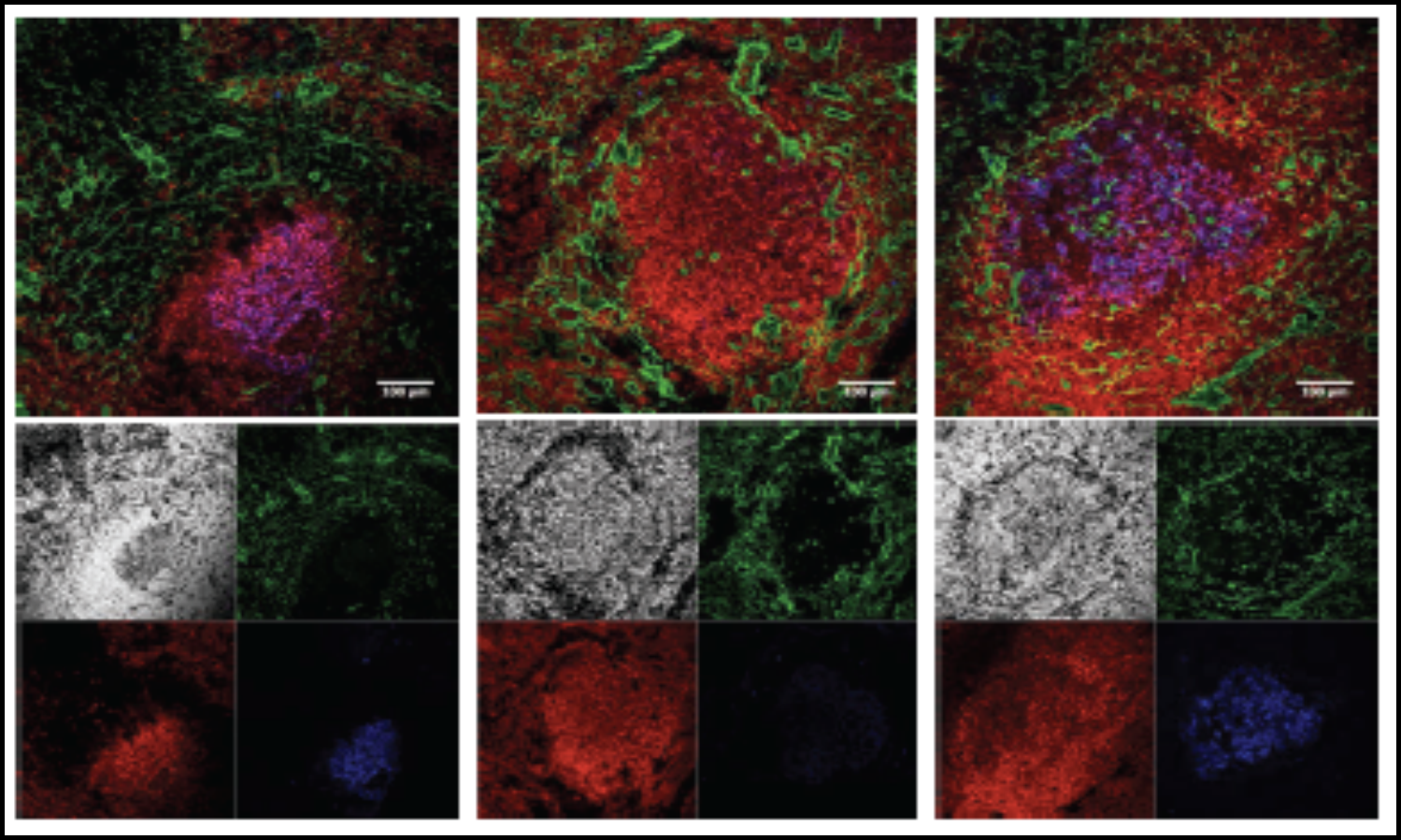


solHVEM



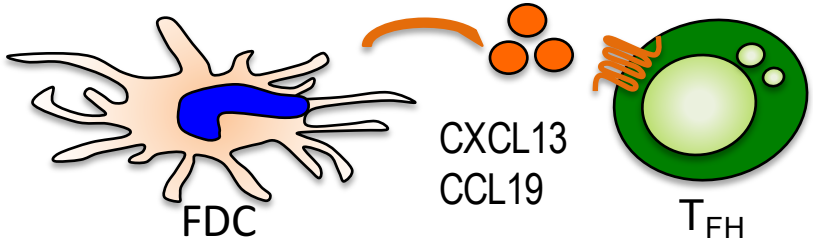
HVEM deficient lymphoma B cells produce increased amounts of stroma activating cytokines TNFa, LTa, LTb

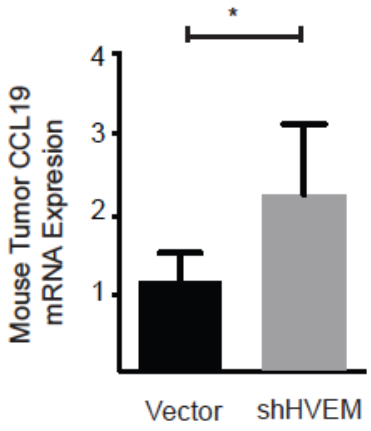
HVEM deficient lymphomas show excessive stroma activation

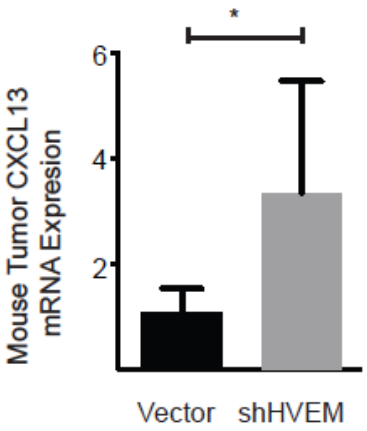


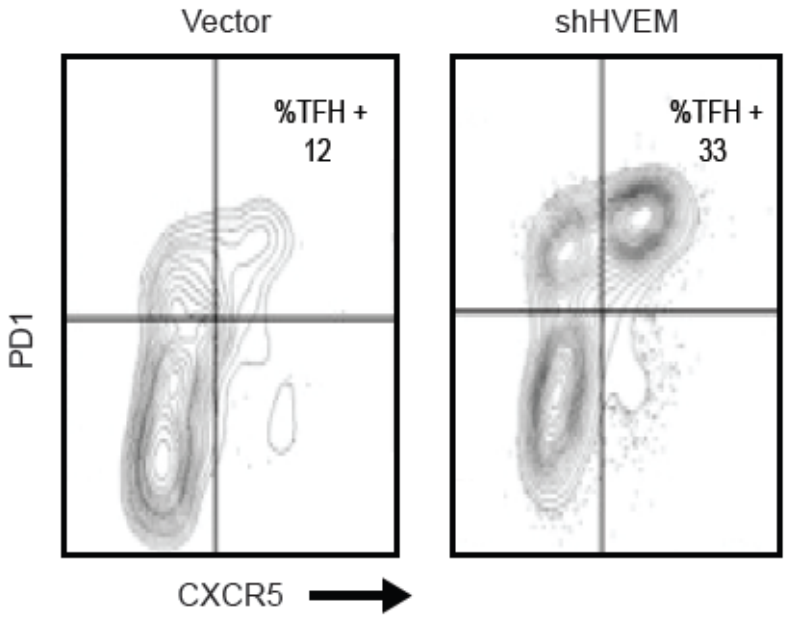
What does an activated stroma do for lymphomas?

The lymphoid stroma produces chemo-attractants for TFH cells



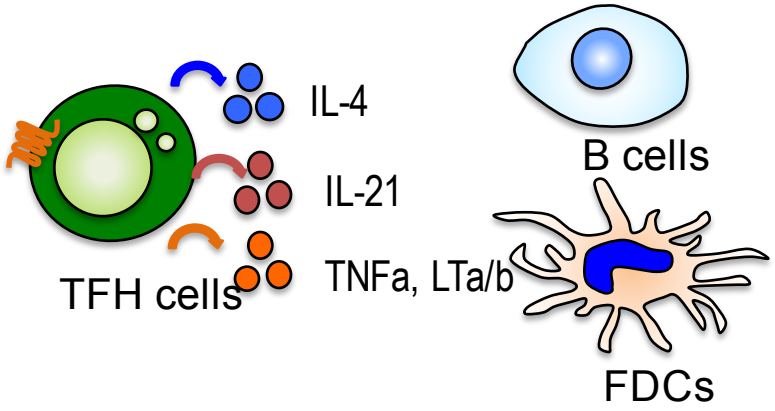


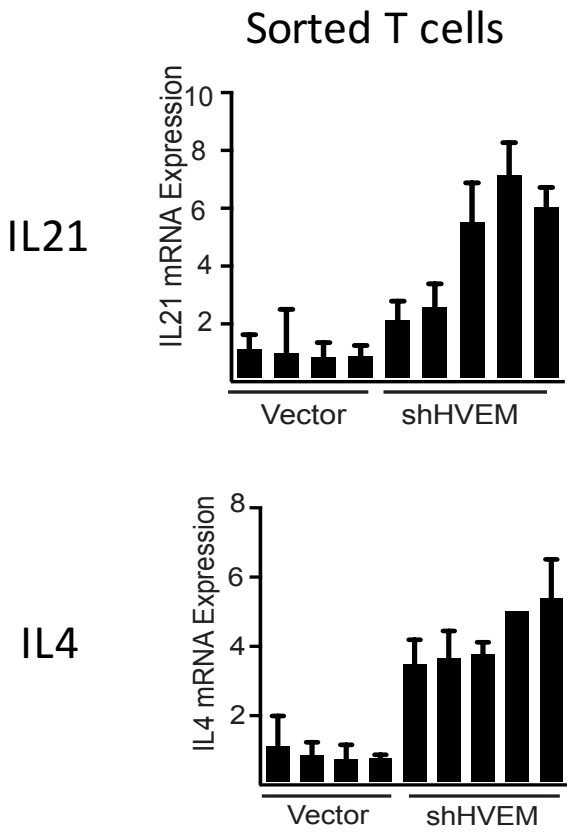




HVEM deficient lymphomas recruit ~3x more TFH cells than controls

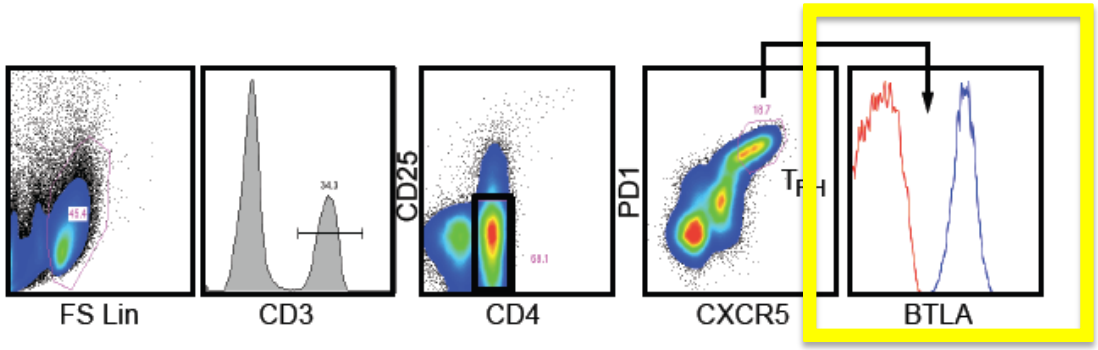
T_{FH} cells support B cells by producing IL4/IL21

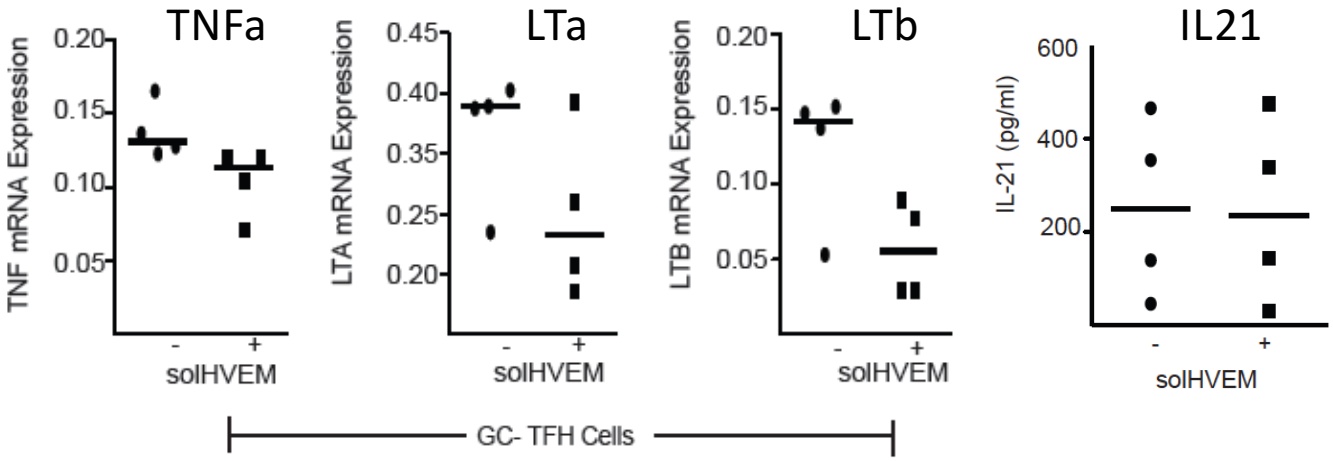




Increased T_{FH} cytokines contribute to a lymphoma supportive niche

Does HVEM also have a direct effect on T_{FH} cells?





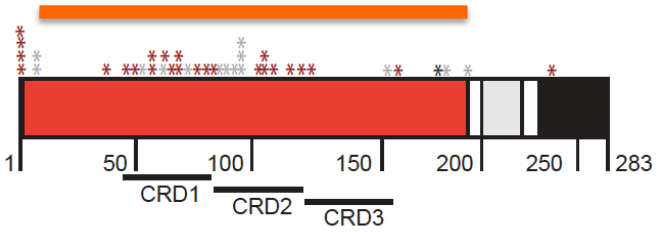
No change in TFH viability/activation

HVEM loss in B cells has a dual effect on TFH cells:

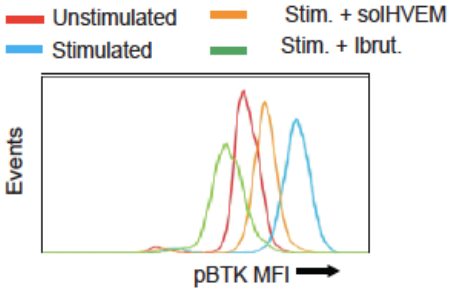
1) **Increased TFH recruitment**
2) **Augmented LTa/LTb production**

The solHVEM protein can reverse some effects of HVEM loss

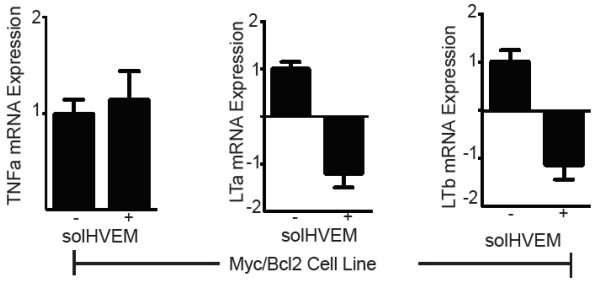
SolHVEM (P37-V202)



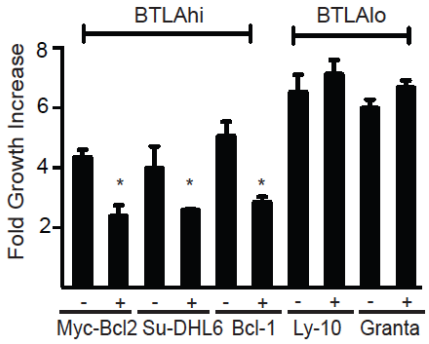
Inhibition of mitogenic signals



Partial reversal of cytokine effects

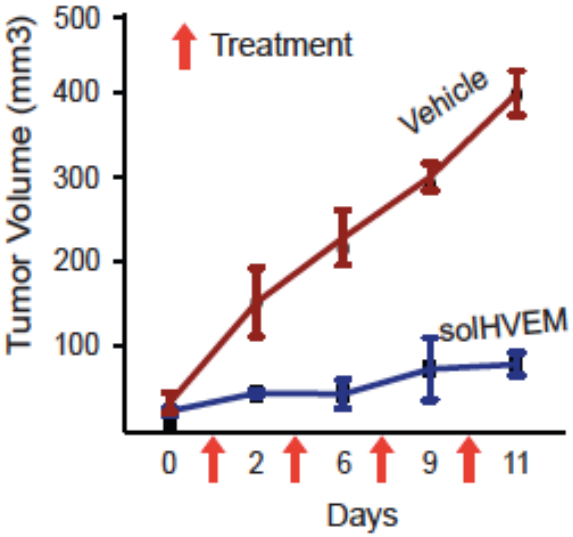


Growth inhibition

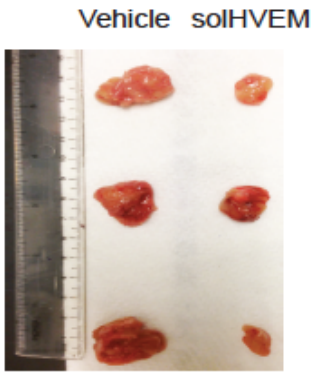


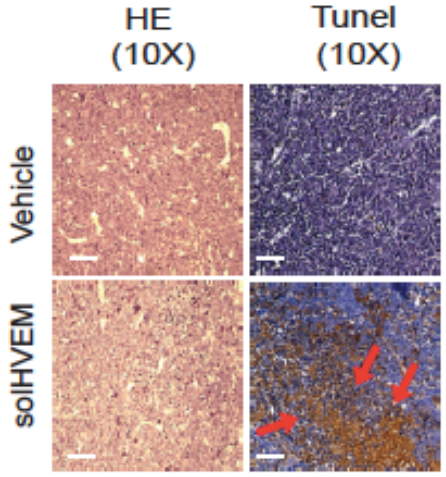
Can we use the solHVEM protein to treat lymphomas?

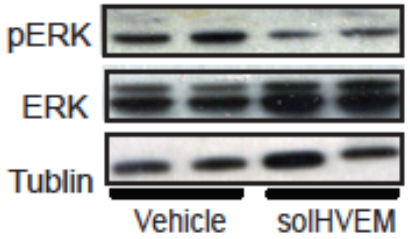
SolHVEM has anti-lymphoma effects in vivo



MYC/BCL2 mouse lymphomas; s.c. inject; 20μg

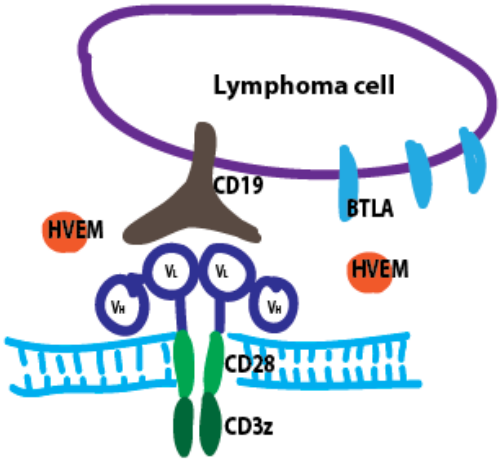




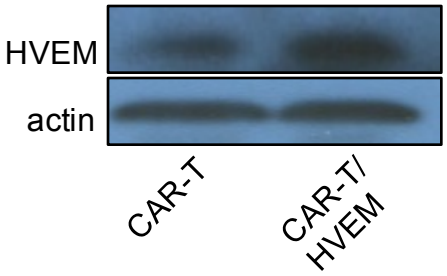


How can we best deliver solHVEM to lymphomas in vivo?

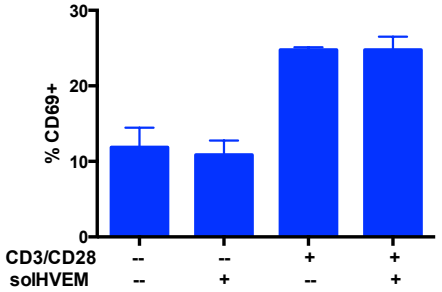
Engineering CAR-T that secrete solHVEM locally and continuously



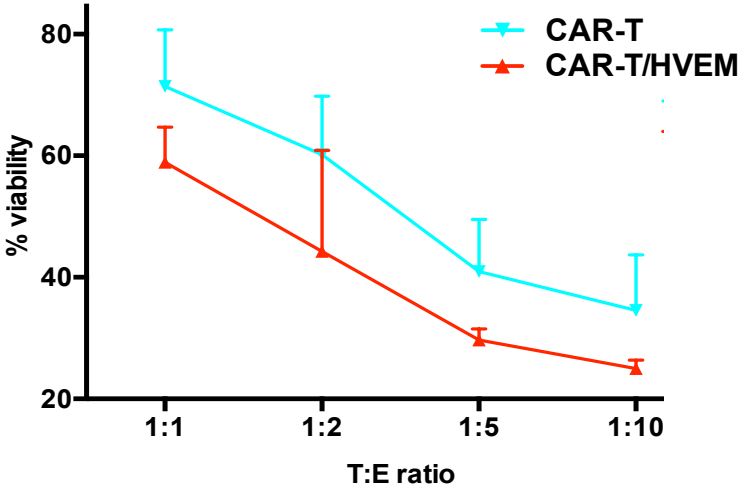
HVEM production



Effect on T cell

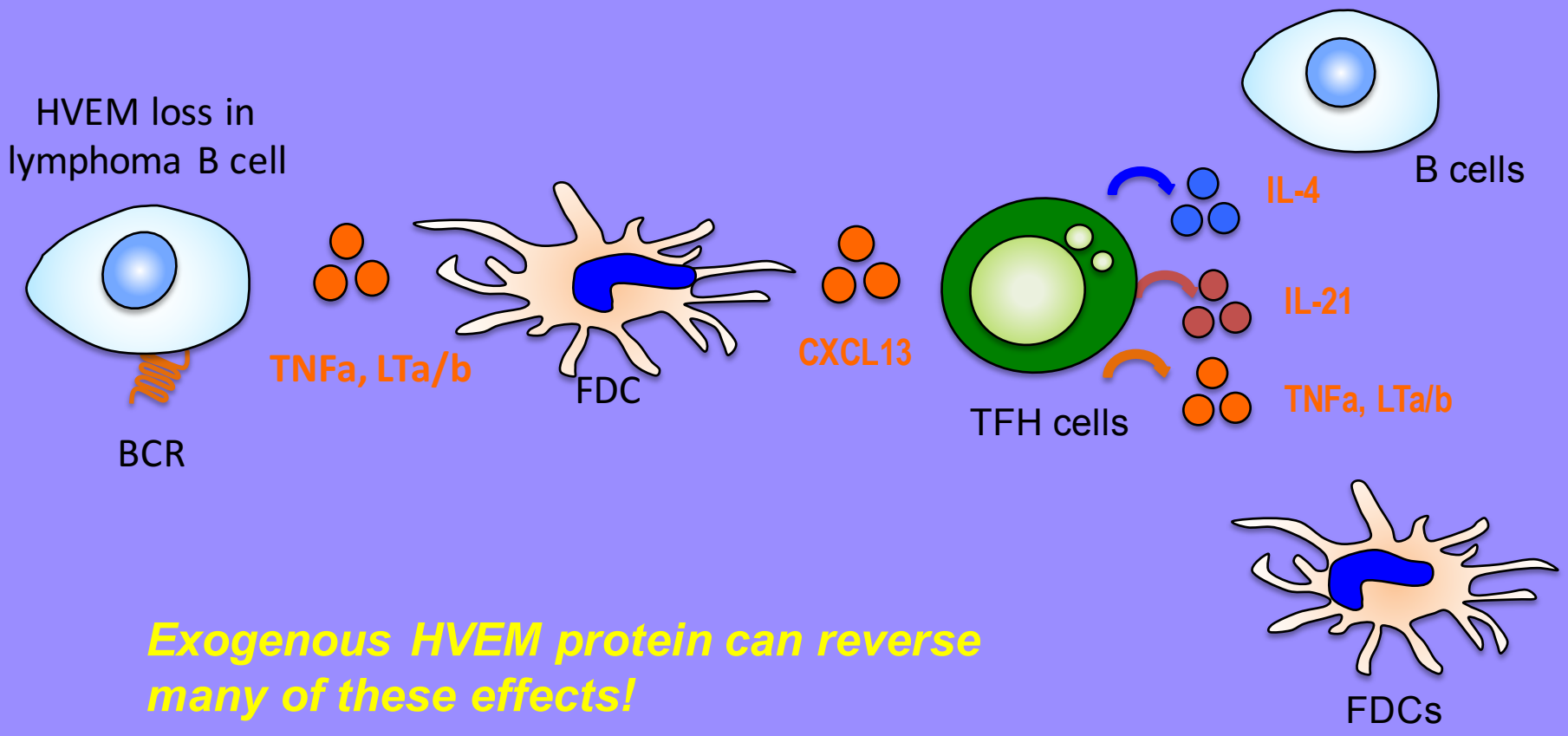


DoHH2 cell kill



We are currently testing these "micro-pharmacies" *in vivo.*
The goal is to increase CAR-T efficiency against lymphomas

SUMMARY: HVEM loss activates B cells and creates a supportive niche



Exogenous HVEM protein can reverse many of these effects!

Acknowledgments

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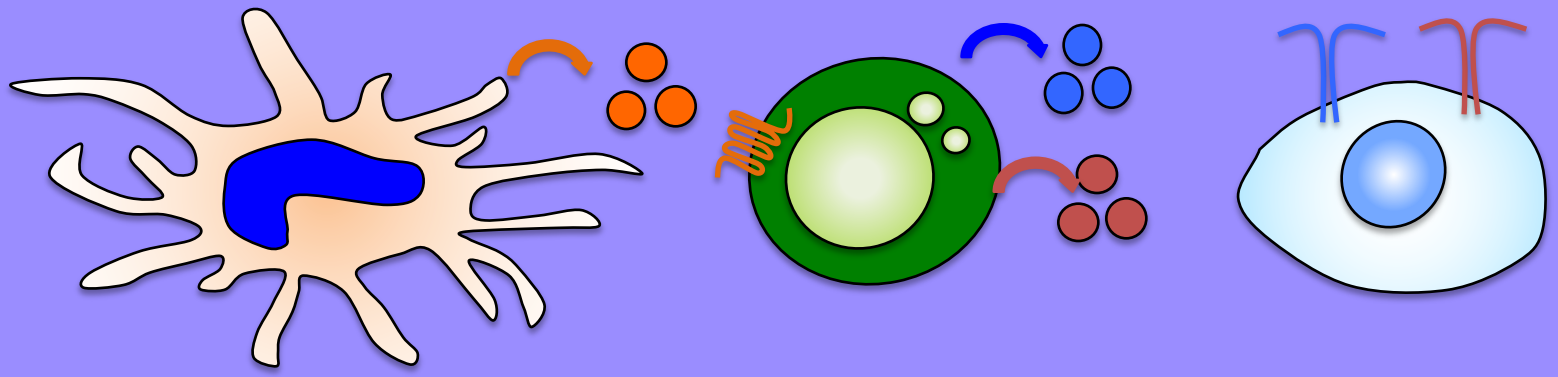
Sami Malek (U. Mich.)



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