Discovery of Highly Selective Small Molecule Oral Inhibitors of Integrin α4β7 for the Treatment of Inflammatory Bowel Diseases

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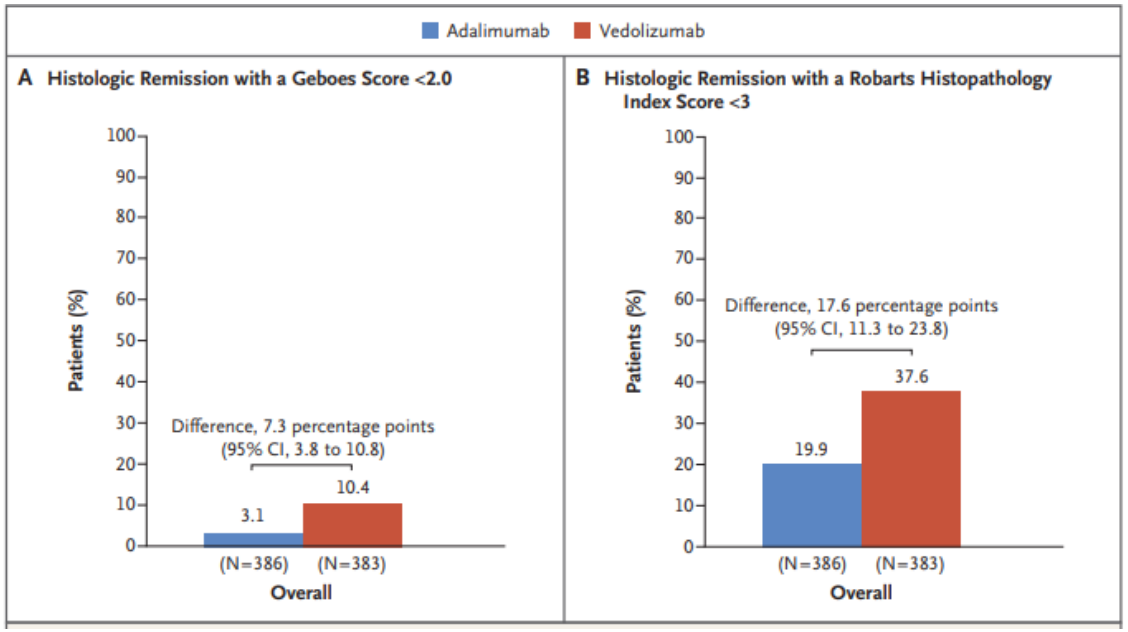
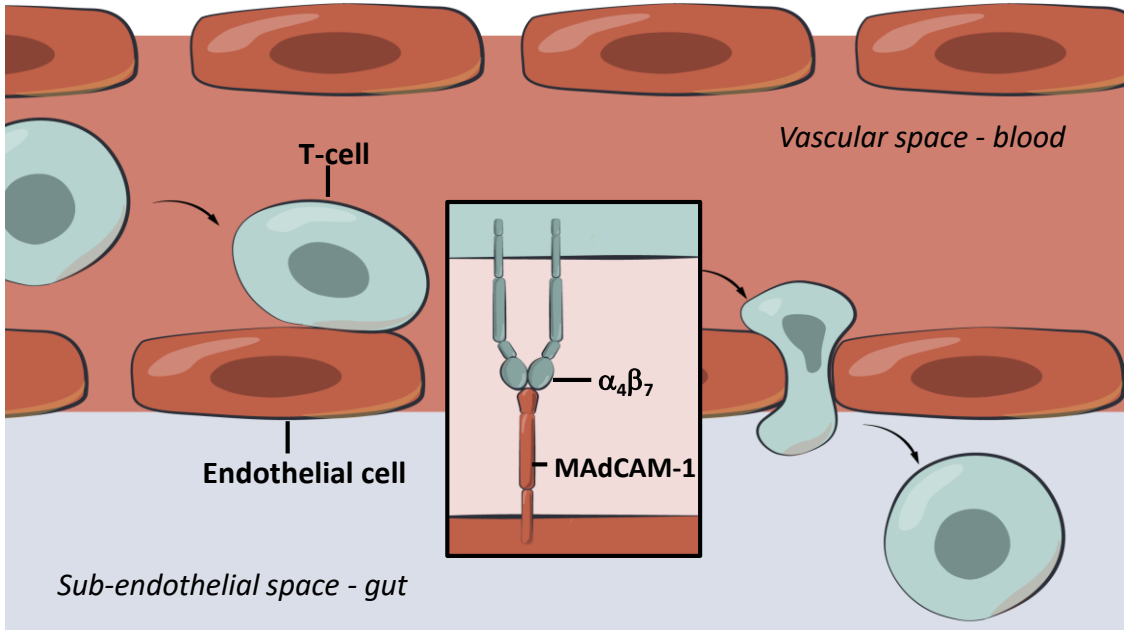
Disclosures

- Jamie Wong is a paid employee and shareholder of Morphic Therapeutic.

Inhibition of $\alpha_4\beta_7$ is a clinically validated mechanism for IBD



Data from VARSITY Trial (Sands et al. NEJM 2019)



- Vedolizumab inhibits immune cells that adhere to MAdCAM-1 positive endothelial surfaces in GI tract
- Vedolizumab is an effective and safe agent (150,000+ patients since approval in 2014; no PML)
- "Oral vedolizumab", if approved, could become a preferred backbone for chronic therapy in IBD

MORF-057 demonstrates high selectivity for $\alpha_4\beta_7$

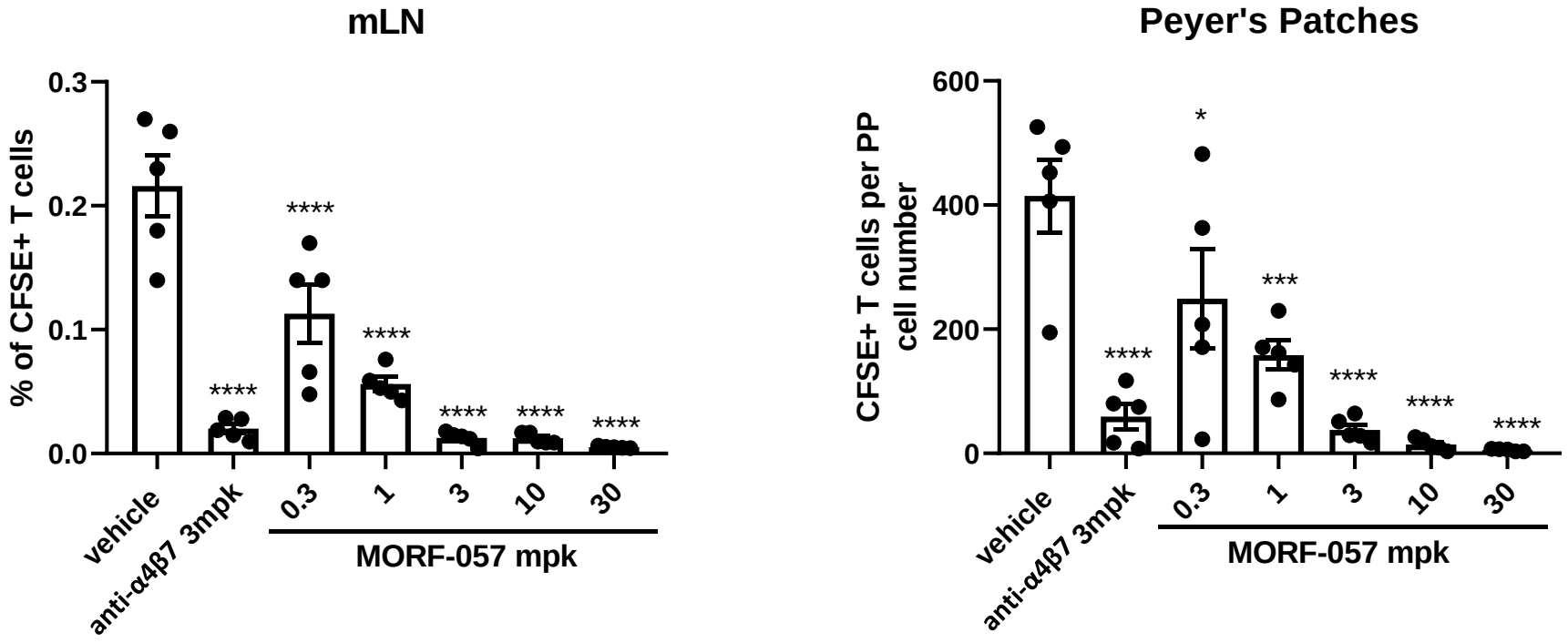
- MORF-057 has more than 41,600-fold selectivity for $\alpha_4\beta_7$ over $\alpha_4\beta_1$ in cell adhesion assays in 50% human serum

Inhibitor	$\alpha_4\beta_7$ IC_{50}*	$\alpha_4\beta_1$ IC_{50}*	Fold selectivity
MORF-057	1.2 nM	>50 µM	>41,600
Natalizumab	0.15 nM	1.8 nM	12
Vedolizumab	0.059 nM	>180 nM	>3,060
BIO 5192	>50 µM	0.65 nM	$<1.3x10^{-5}$

- MORF-057 has high selectivity against other integrins in fluorescence polarization assays with purified proteins.

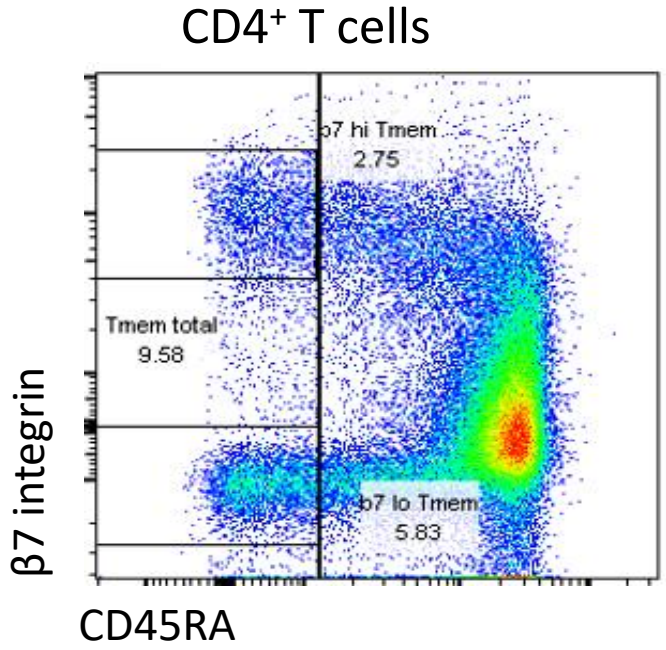
*RPMI8866 and Jurkat cell lines used for $\alpha_4\beta_7$ and $\alpha_4\beta_1$, respectively

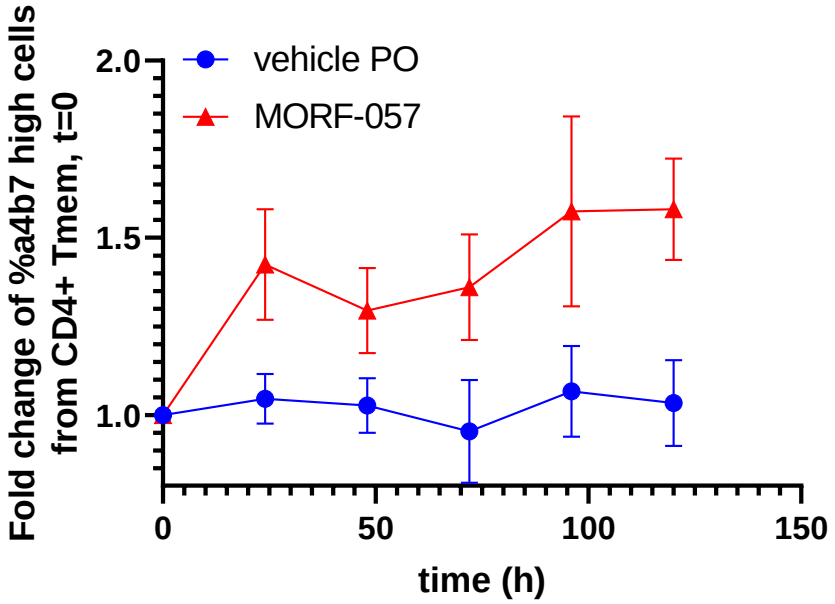
MORF-057 inhibits gut homing leukocytes in mice



- Treatment with MORF-057 blocks gut homing of $\alpha_4\beta_7^+$ cells in mice
- MORF-057 achieves inhibition of gut trafficking equivalent to antibody treatment

Orally dosed MORF-057 blocks memory T cell trafficking in Cynomolgus Monkeys





15mpk, 5 days; N=5

- Oral treatment with MORF-057 causes sustained increases in $\alpha_4\beta_7^{hi}$ memory cells in blood reflecting blockage of gut homing in monkeys

Conclusions

- Vedolizumab is a safe and effective therapy for Ulcerative Colitis but an oral therapy would be advantageous
- MORF-057 is a potent, selective, and orally bioavailable small molecule inhibitor of $\alpha_4\beta_7$
- MORF-057 inhibits gut homing in mouse and increases systemic $\alpha_4\beta_7^{hi}$ cells in monkeys
- Potential IND mid-2020

Contributors:
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