Oral $\alpha_4\beta_7$ integrin inhibitor MORF-057 demonstrates exposure driven biomarker response in non-human primates

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Disclosures of potential conflicts of interest:

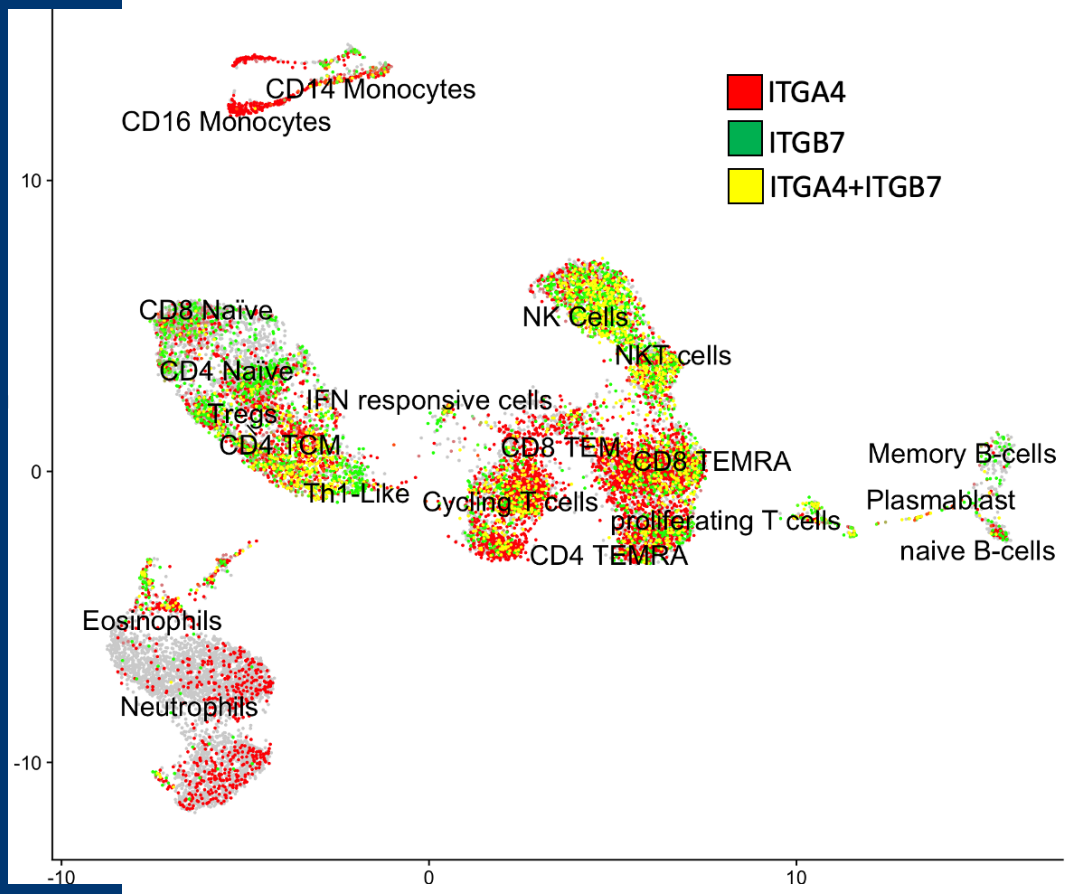
- Jamie Wong is an employee and shareholder of Morphic Therapeutic.

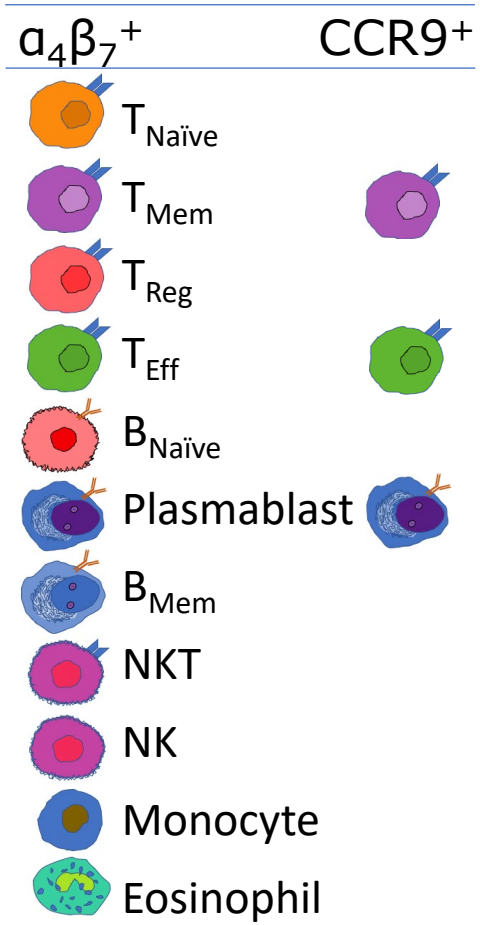
NHP as a model for demonstrating $\alpha_4\beta_7$ inhibition

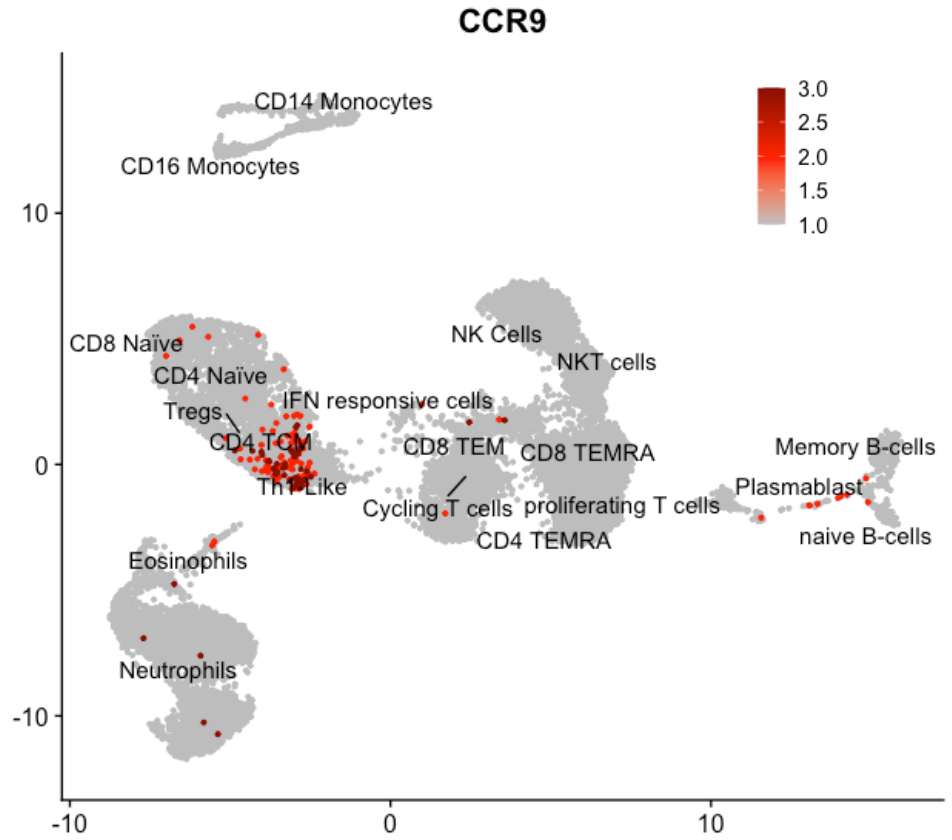
- Inhibition of $\alpha_4\beta_7$ is a clinically validated mechanism for IBD--VARSITY Trial (Sands, NEJM 2019)
- NHP valuable model system for proof-of-mechanism studies (Fedyk, 2012)

- MORF-057 an oral, small molecule $\alpha_4\beta_7$ inhibitor completed Ph1 demonstrating safety, PK, RO, and proof of biology (Ray, ECCO 2021)

$\alpha_4\beta_7$ mRNA is expressed by several immune cell subtypes







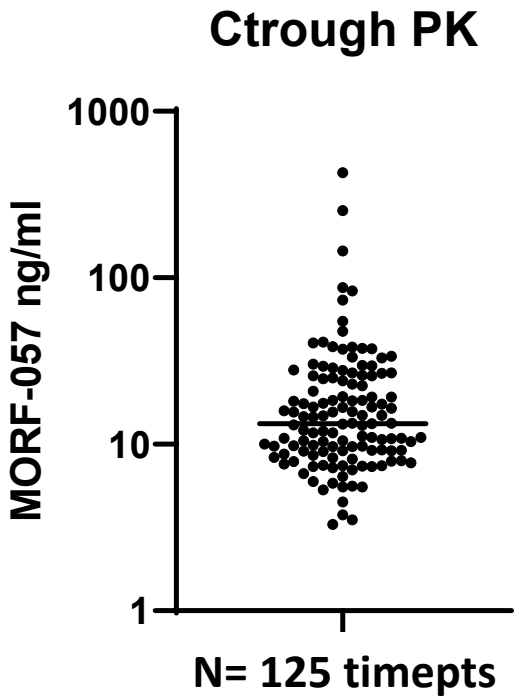
- scRNAseq data from naïve NHP CD45$^+$ PBMCs, n=2

Experimental design

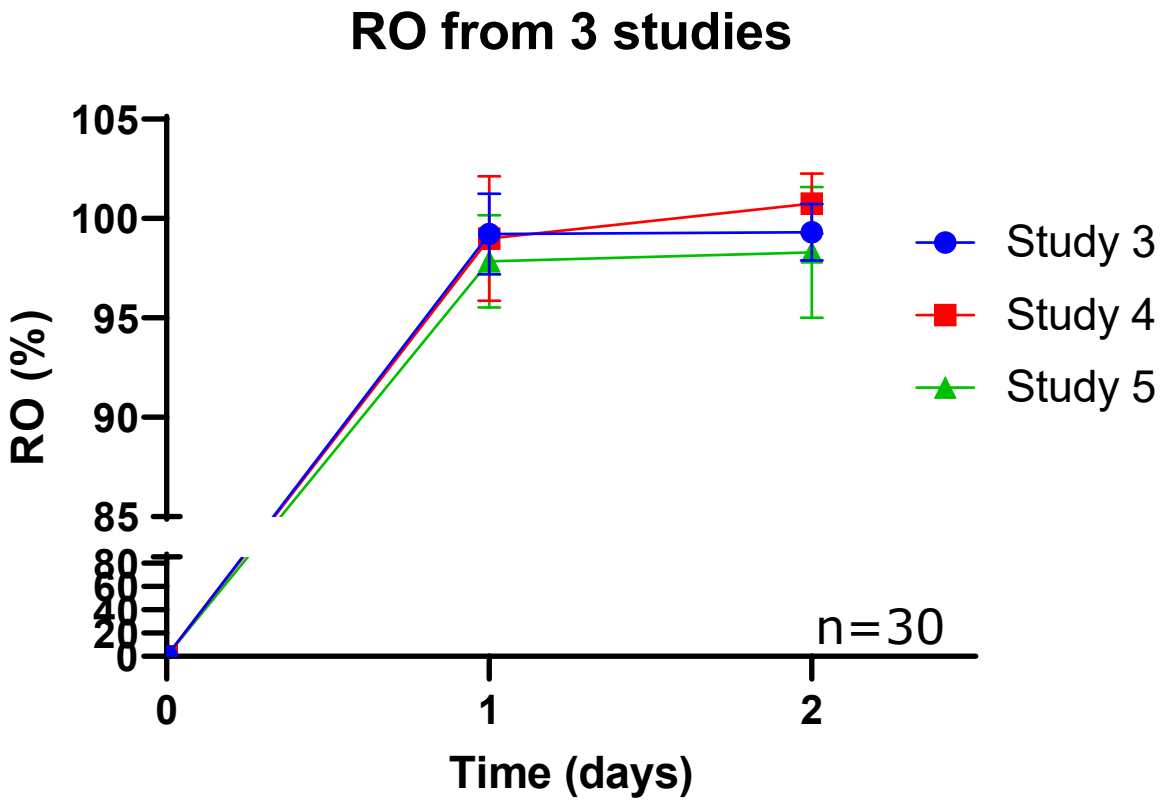
- Naïve NHPs were dosed orally, twice daily (BID), with MORF-057 10-50 mg/kg; 5 studies, total n=40
- Duration of dosing: 2-7 days

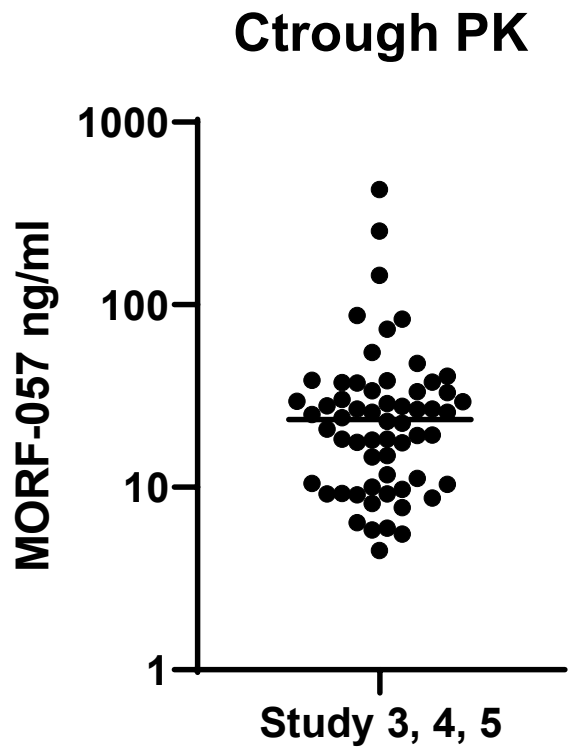
Daily measurements:

- Drug plasma concentration (LC-MS)
- Target engagement: $\alpha_4\beta_7$ receptor occupancy (FACS)
- $\beta_7$high CD4$^+$ T memory cell frequency (FACS)
- Circulating CCR9 mRNA levels (bDNA)



High receptor occupancy (RO) shown in all samples

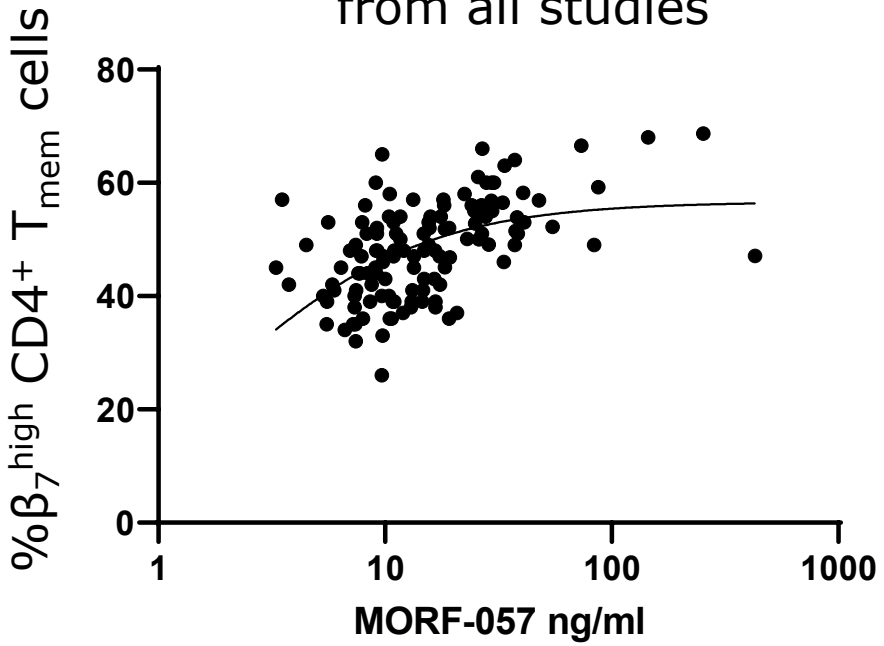




- Receptor occupancy was greater than 95% for all MORF-057 exposures measured, including the lowest, 4.5 ng/ml

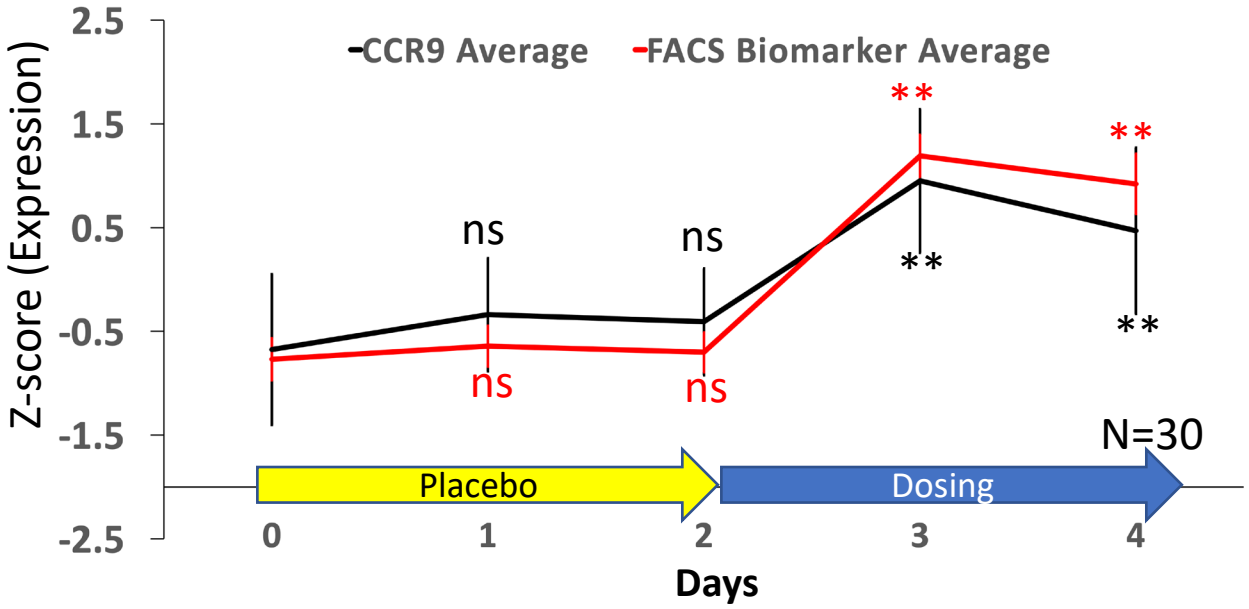
T_{mem} cell and CCR9 blood biomarkers increase with MORF-057 exposure

T_{mem} biomarker data from all studies



CD4+ T memory cells defined by: CD45+CD3+CD20- CD4+CD8-CD45RA-

Comparison of CCR9 and T_{mem} biomarker changes



Circulating CCR9 mRNA levels were measured in comparison with housekeeping genes (ACTB, IPO8, B2M, TBP)

- β_7^{high} CD4+ T_{mem} biomarker increases with plasma exposure and dosing correlated with elevated CCR9 transcript

CCR9 expression and Tmem biomarker values were transformed to Z-score for plotting purpose. Student t-test was used to calculate significance for each time with respect to 0 day. ns= Non-significant and ** = p-value < 0.001

Conclusions

- Circulating $\beta_7$high T memory cells are a sensitive biomarker, and demonstrated a dose-dependent response to MORF-057 exposure
- CCR9 mRNA levels also showed similar exposure related changes
- scRNAseq data shows expression of $\alpha_4\beta_7$ on other cell types beyond T memory cells including: T_N, T_{Reg}, T_{Eff}, NK, NKT, B_N, B_{Mem}, plasmablasts, monocytes, and eosinophils
- Pharmacodynamic changes in NHP are consistent with MORF-057 human Phase 1 data in healthy volunteers (Ray, ECCO 2021); Phase 2 initiation for UC anticipated 1Q2022

Contributors:
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