RAPT THERAPEUTICS

Blood And Skin Biomarkers From A First-in-human Study Of RPT193 - An Oral CCR4 Antagonist For The Treatment Of Atopic Dermatitis

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7th Annual Biomarker and Companion Diagnostics Conference

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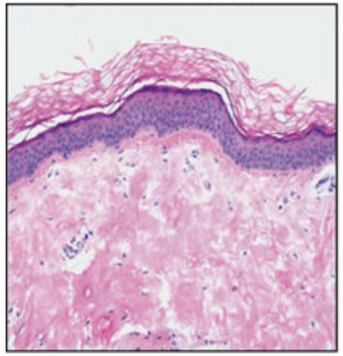
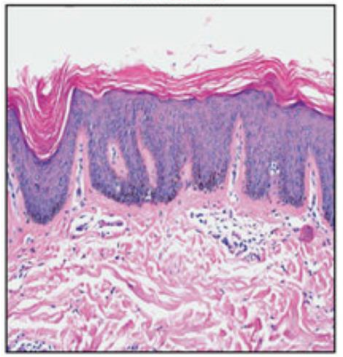
RPT193: Oral CCR4 Antagonist for Inflammatory Diseases

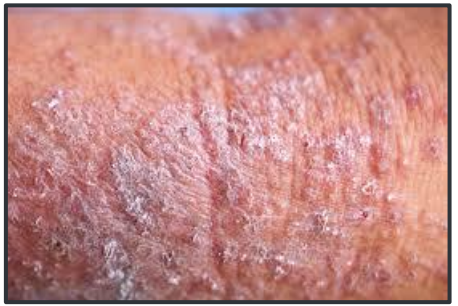
- RPT193 is a highly potent and selective once-daily oral CCR4 antagonist that targets inflammation more specifically than JAK inhibitors and acts upstream of many injectables
- Phase 1b trial demonstrated clear benefit in patients with moderate-to-severe AD, with favorable safety and tolerability
- No laboratory safety monitoring or black box warning expected
- Next steps: Phase 2b trial in AD and a Phase 2a trial in asthma

Normal Human Skin

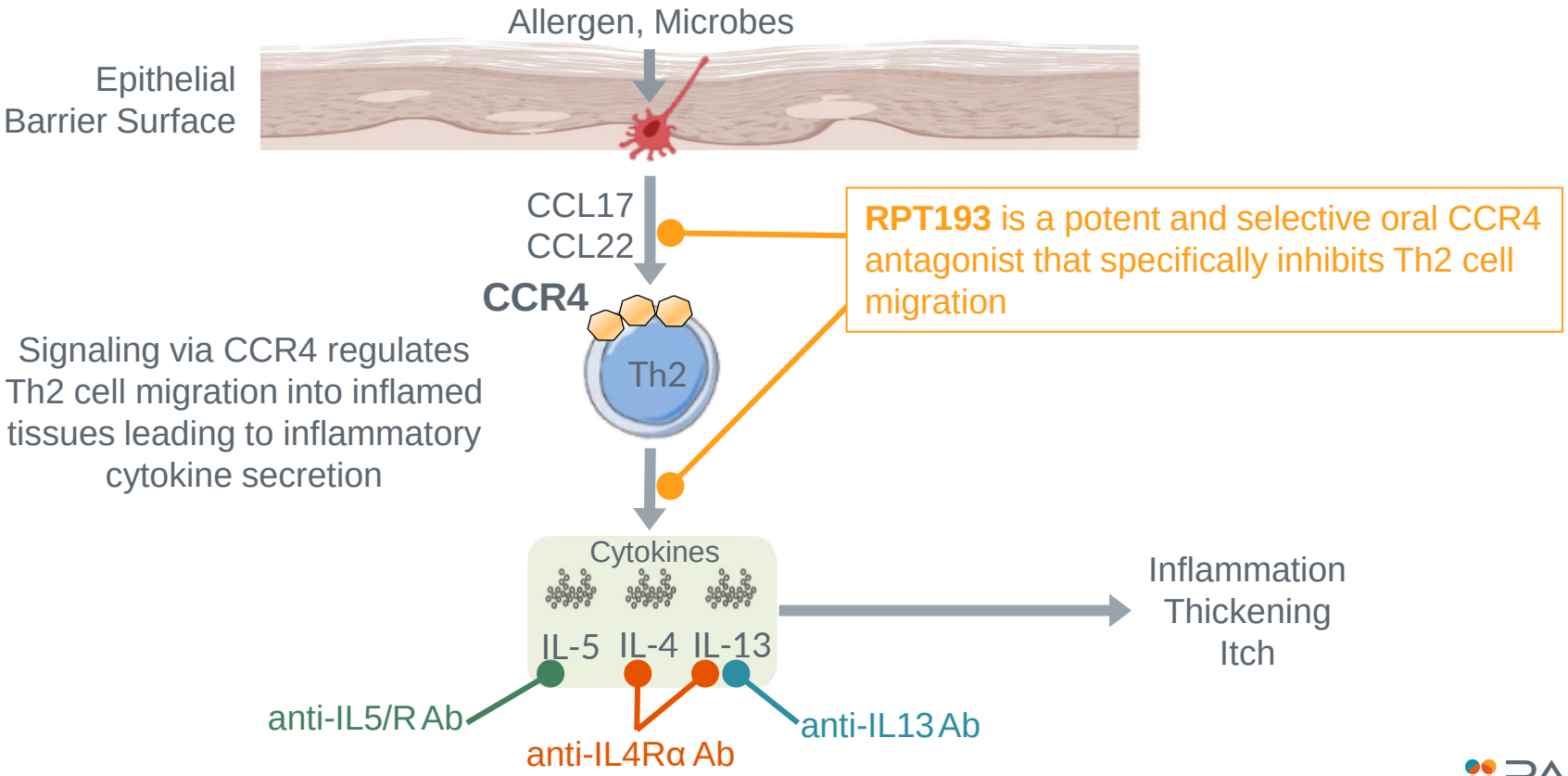


AD Lesional Skin



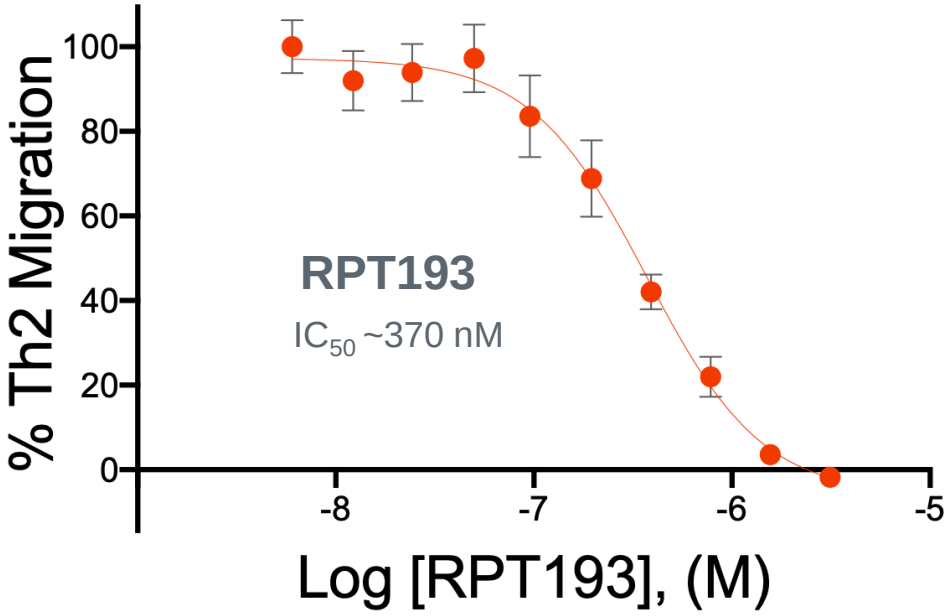


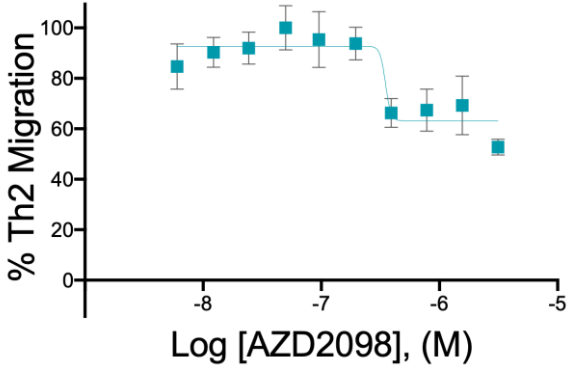
RPT193 Targets Th2 Cells: Key Drivers of Inflammation in Atopic Dermatitis, Asthma, and Other Diseases

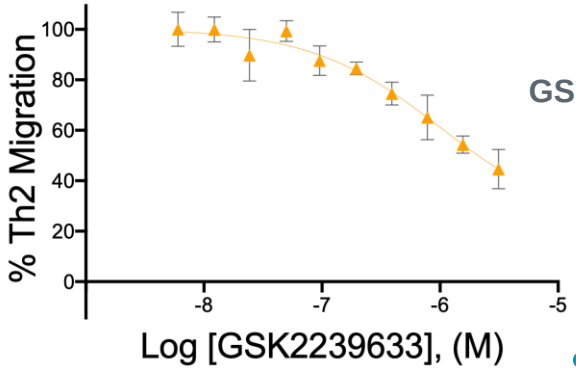


RPT193 Has Greater Potency Against Th2 Chemotaxis Than Previous CCR4 Antagonists

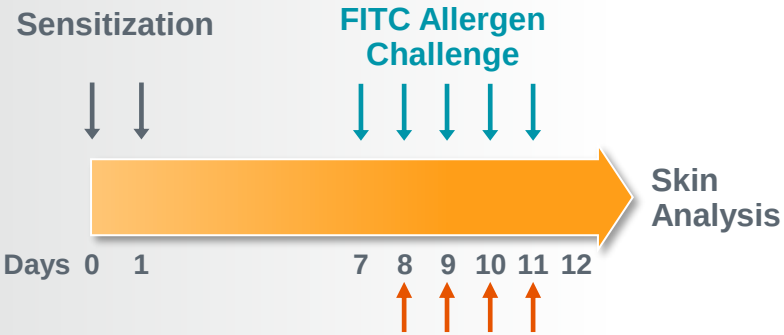
CCL22-Induced Human Th2 Chemotaxis

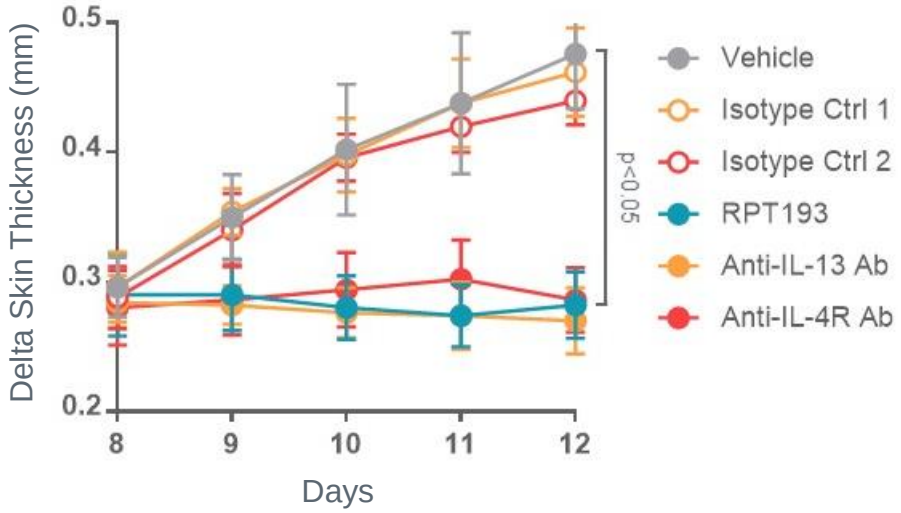




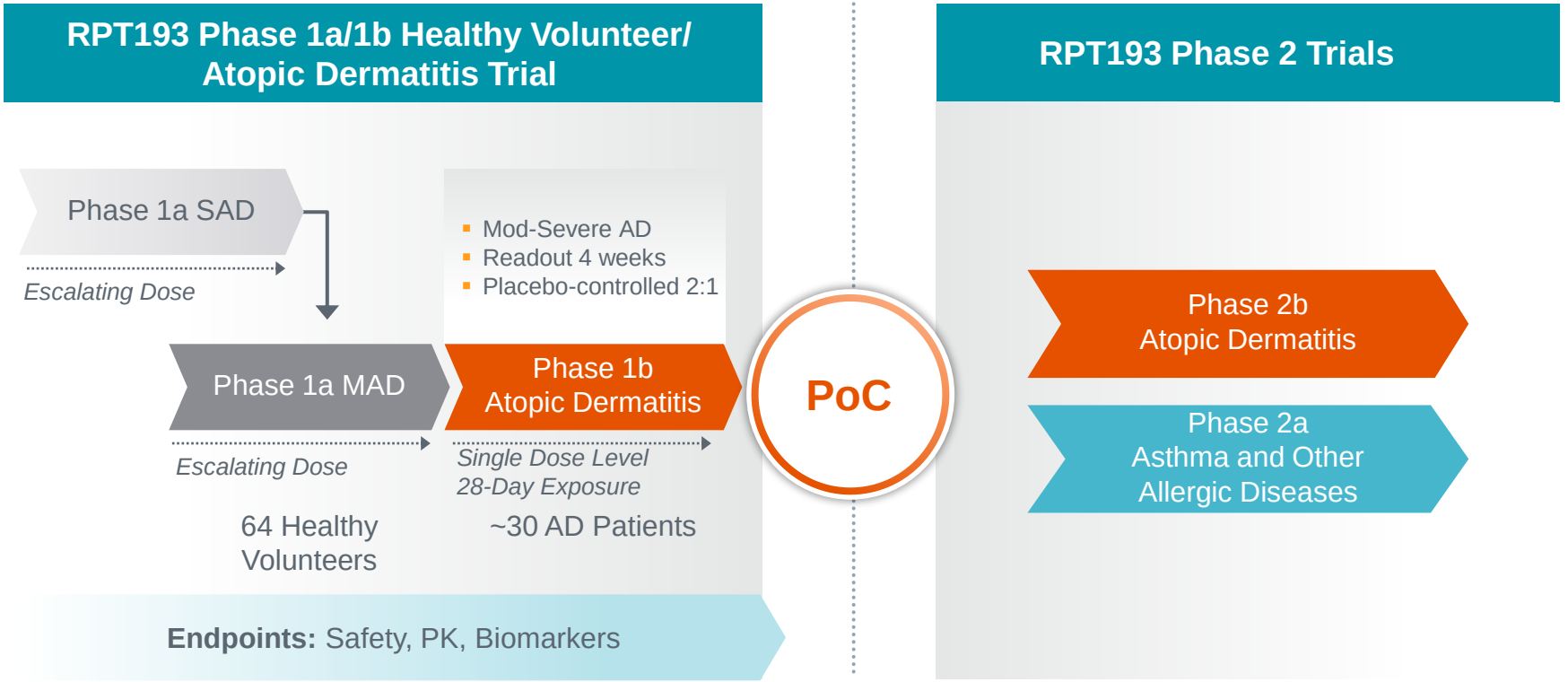


Oral Doses of RPT193 Demonstrate Similar Efficacy to Biologics in a Therapeutic Atopic Dermatitis Model





RPT193: Seamless Clinical Trial Design to PoC and Beyond



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RPT193 Receptor Occupancy

NATURE REVIEWS | IMMUNOLOGY VOLUME 11 | MAY 2011 | 355

PERSPECTIVES

OPINION

Overcoming hurdles in developing successful drugs targeting chemokine receptors

Thomas J. Schall and Amanda E. I. Proudfoot

Key conclusion:

For clinical efficacy, a compound must be at IC_{90} concentration at trough levels.

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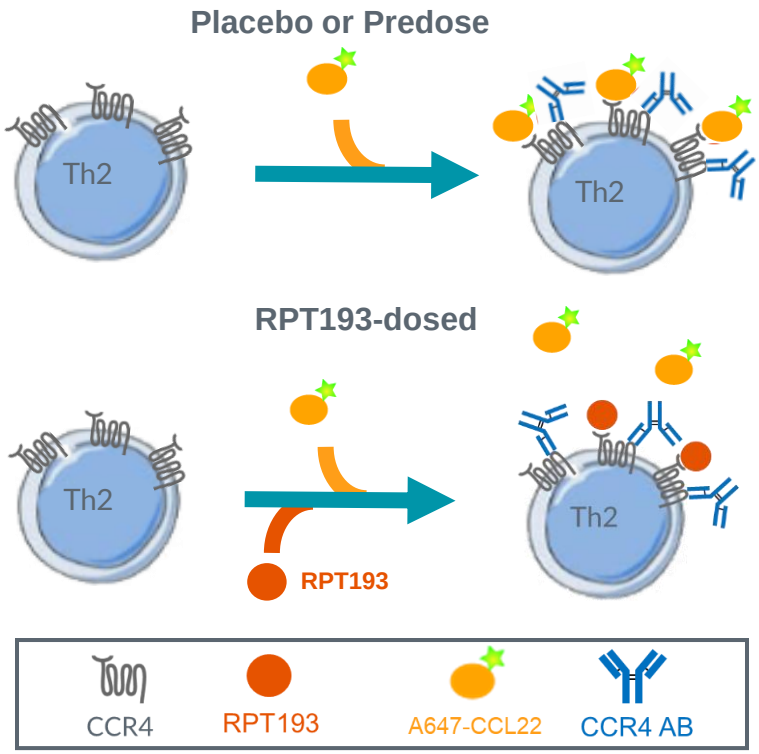
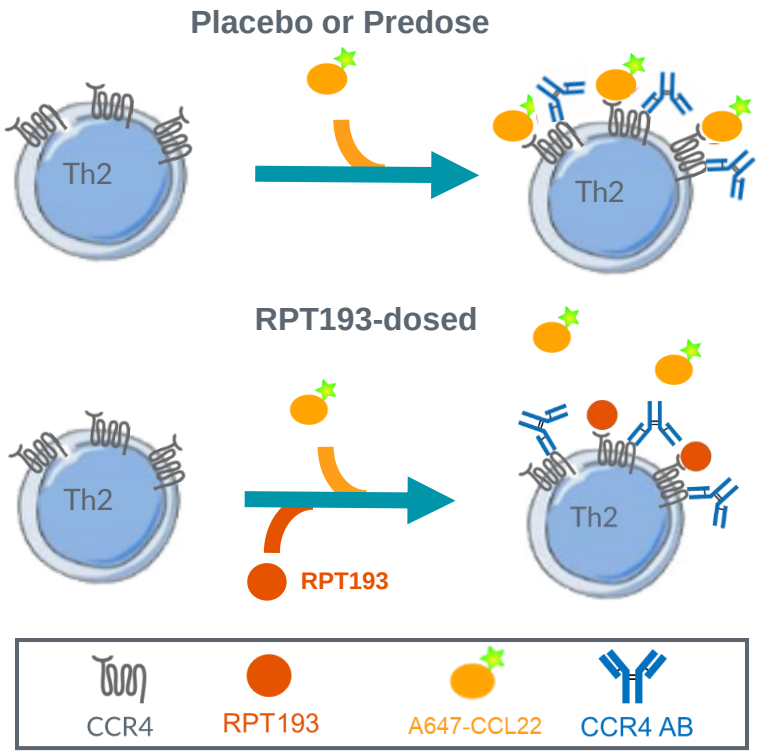
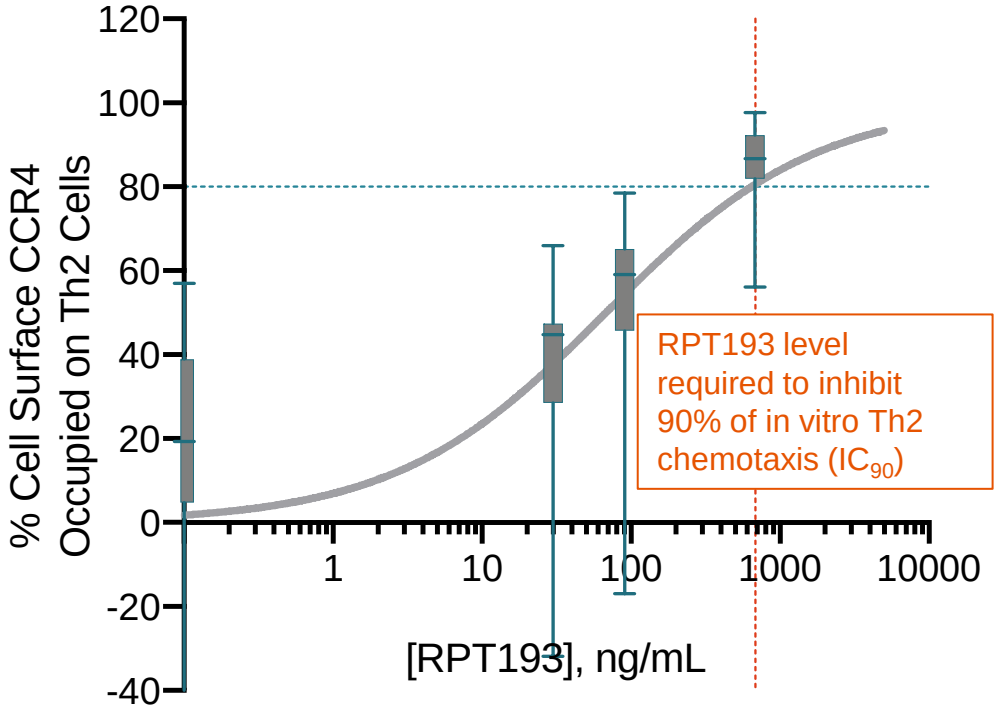
Whole Blood Assay Developed To Measure CCR4 Surface Receptor Occupancy On Human Th2 Cells



- Staining performed in fresh whole blood
- Th2 cells defined as: $CD4^{+}CD45RO^{+}CXCR3^{-}CCR6^{-}$
- A647-CCL22 binding normalized to cell surface CCR4 levels to determine surface receptor occupancy (sRO)
- Initial development in healthy blood; confirmed in blood of atopic dermatitis patients
- Intra/inter-assay reproducibility was good (CV <15%)

Whole Blood Assay Developed To Measure CCR4 Receptor Occupancy On Human Th2 Cells





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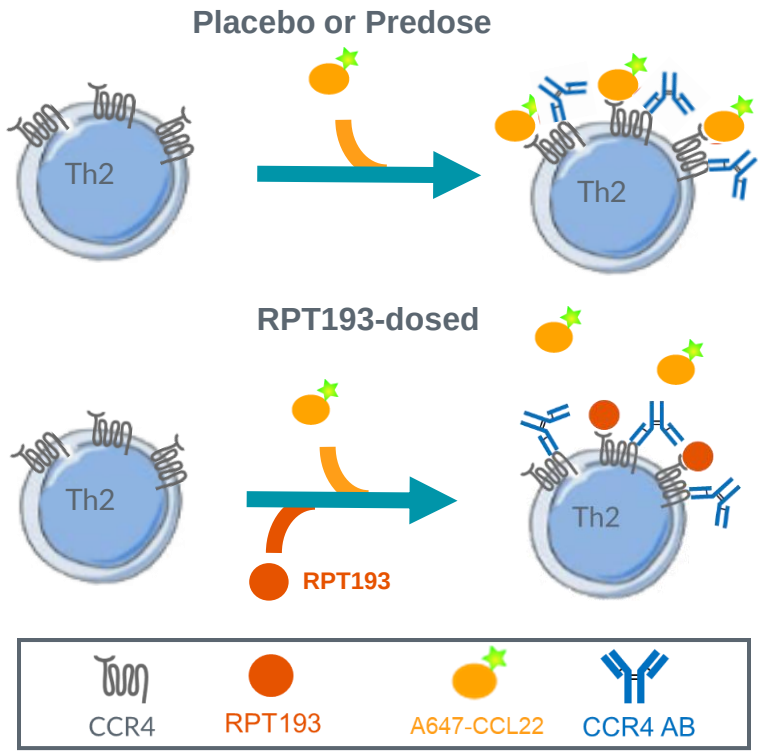
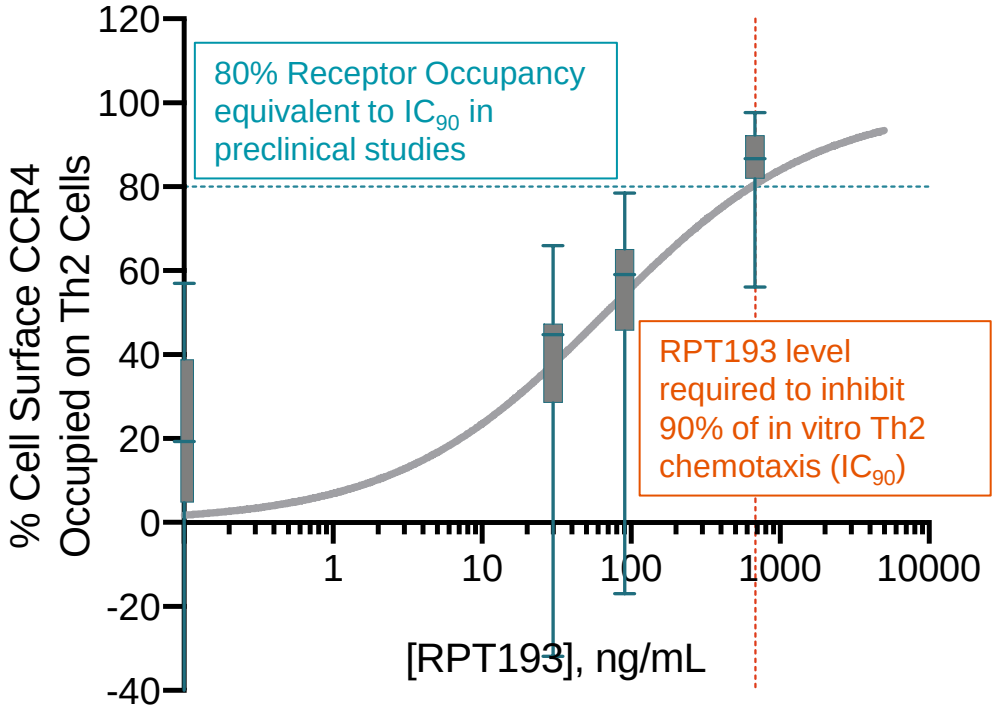
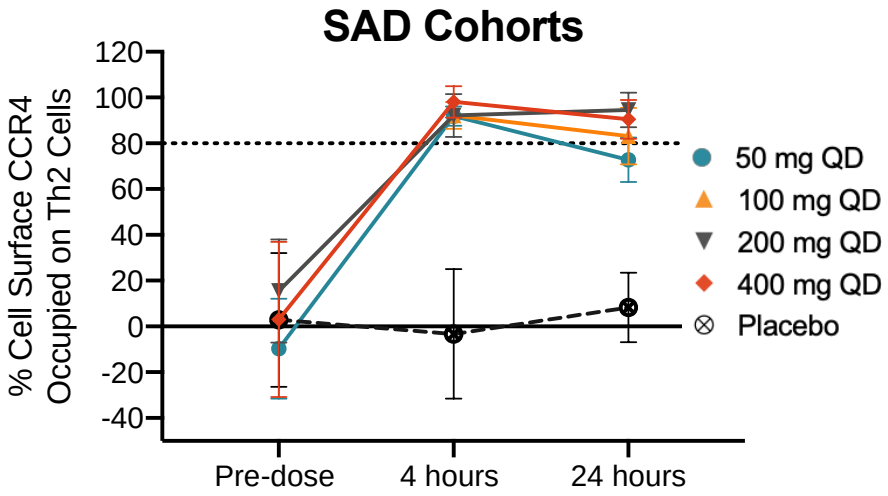




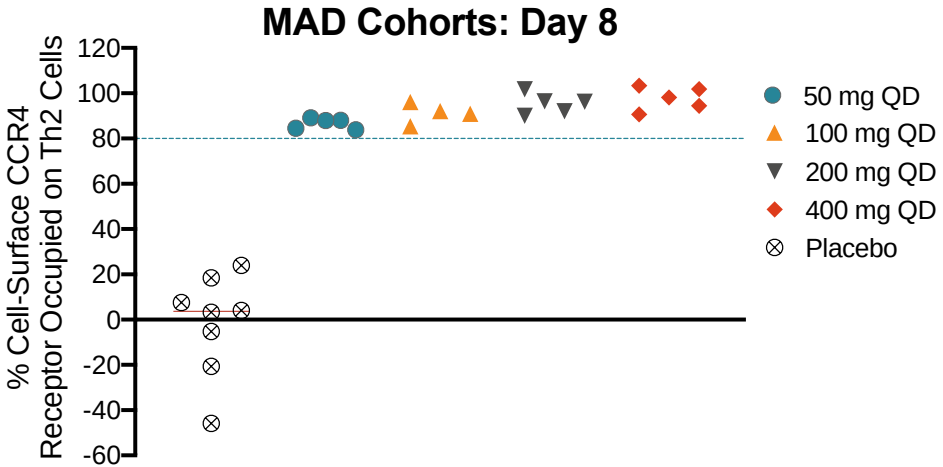
RPT193 Demonstrated Target sRO With Once Daily Dosing in Healthy Volunteers

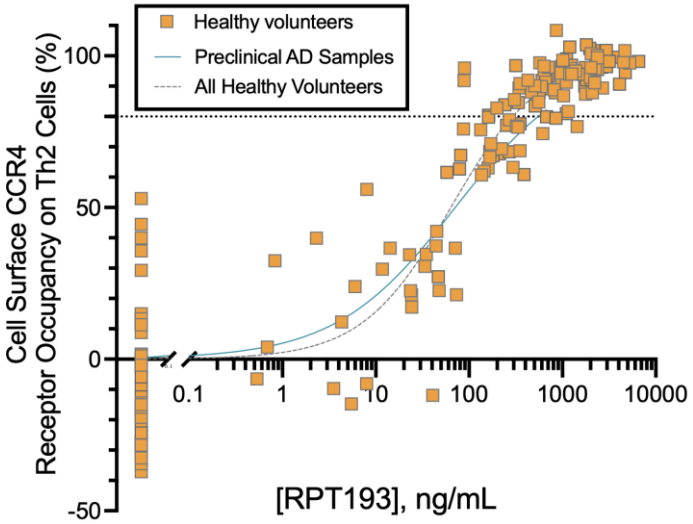


- CCR4 sRO greater than 80% was achieved by 4h post-dose in each cohort
- At 24 hour “trough”, sRO dropped below 80% target for 50 mg and 100 mg cohorts

- RPT193 has ~25-hour half-life
- Expect ~2-fold accumulation with repeated dosing

RPT193 Demonstrated Target sRO With Once Daily Dosing in Healthy Volunteers





- All RPT193 dosed subjects reached the 80% target for sRO after 7 days of dosing
- RPT193 demonstrates good PK-PD relationship

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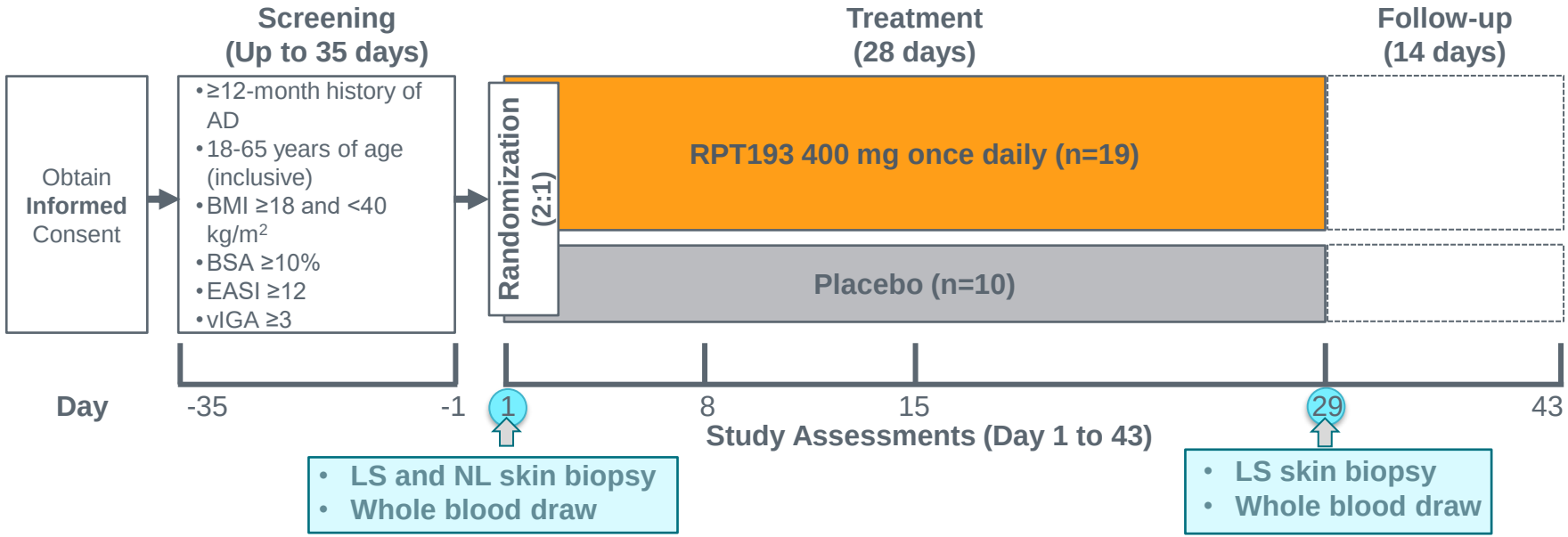
PK, PD and Safety Data Supported Progression Into Atopic Dermatitis Patients at 400 mg Once Daily

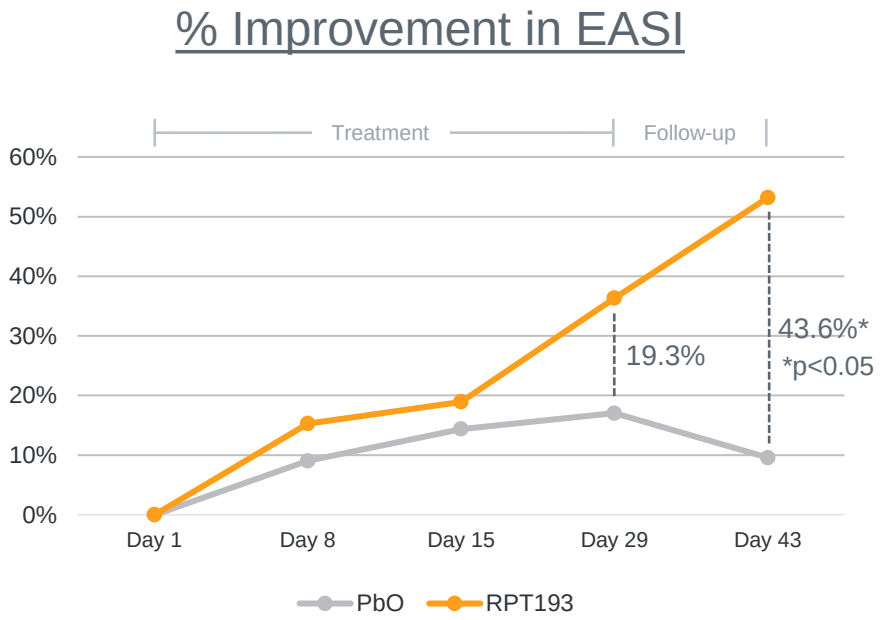
Phase 1b Trial Explored RPT193 Activity in Subjects with Moderate-to-Severe Atopic Dermatitis



- Double-blind, randomized, monotherapy study
- Primary and secondary endpoints were safety and PK
  - Trial was not powered for clinical endpoints (EASI and SCORAD were exploratory endpoints)
- In addition to skin biopsies, plasma and whole-blood biomarker assessments were performed

RPT193 Exhibits Improvement in EASI At Day 29 With Further Improvement Through Day 43

EASI = Eczema Area and Severity Index



- RPT193 demonstrated improvement compared to Placebo in multiple measures for disease severity (EASI, EASI-75, vIGA 0/1 and SCORAD)
- Once-daily, oral RPT193 was generally well tolerated after 28 days of dosing

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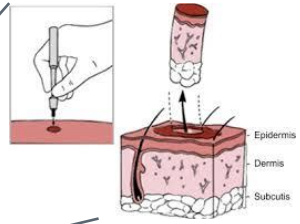
Biomarkers

Comprehensive Biomarker Program for RPT193

Blood Draw

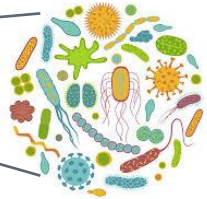
CBC
Immune cell phenotyping
Plasma Cytokines/chemokines
Plasma CCL17/IgE

Skin Biopsies



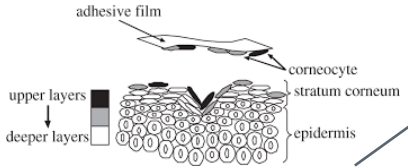
H&E
IHC
RNAseq

Skin Swab



Microbiome analysis
- Staph. aureus
- 16s RNAseq

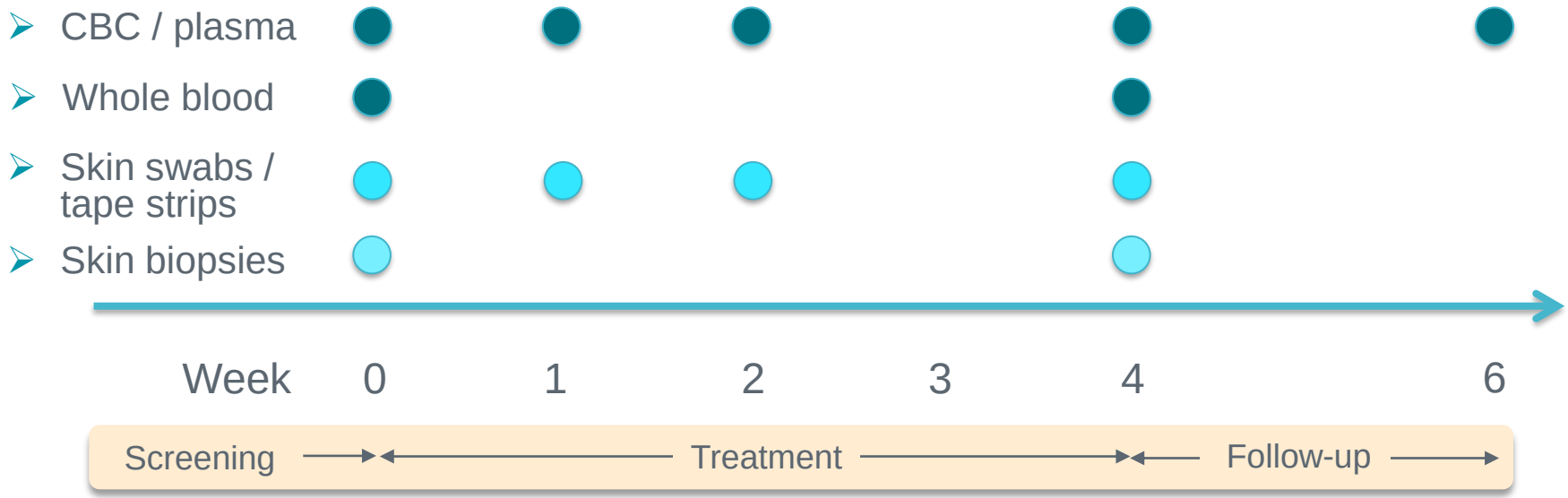
Skin Tape Strips



RNASeq

RPT193 Biomarker Program

- Comprehensive biomarker program for the AD portion of the RPT193 trial evaluating skin tissue, skin microbiome, plasma biomarkers (e.g. CCL17) and peripheral immune cell phenotypes (including neutrophils and eosinophils)



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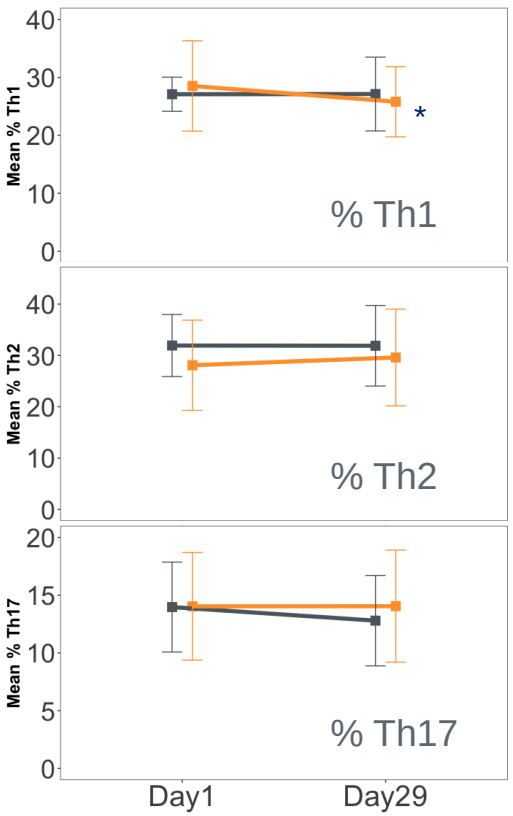
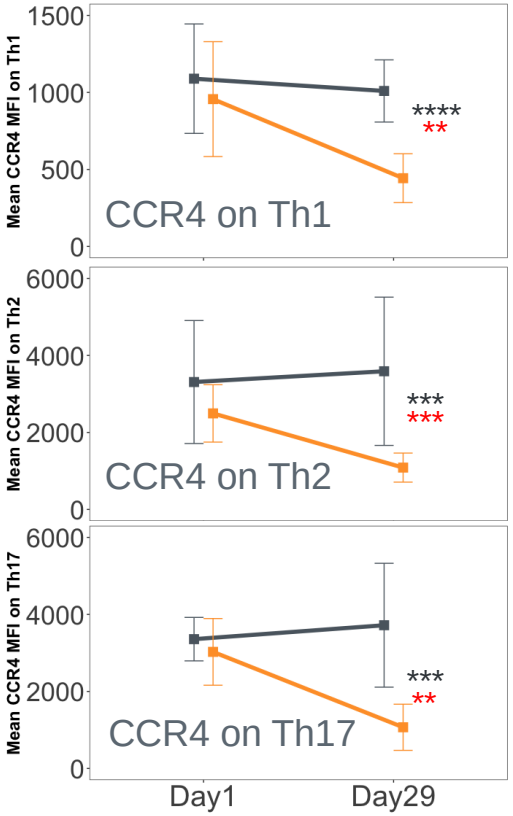
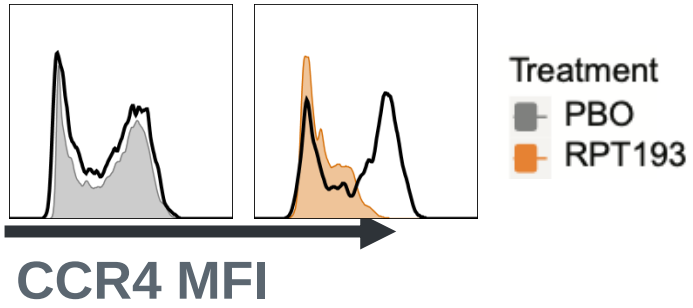
Whole Blood Immunophenotyping

CCR4 Surface Levels Significantly Decreased with RPT193 Treatment: Peripheral Th Subsets Not Changed Compared to Placebo







****(p<0.0001), ***(p<0.001), **(p<0.01), *(p<0.05)
Red (PBO vs RPT193), Black (Day 29 vs Day 1)
Linear mixed effect model with treatment and timepoint as factors

MFI=Mean Fluorescence Intensity

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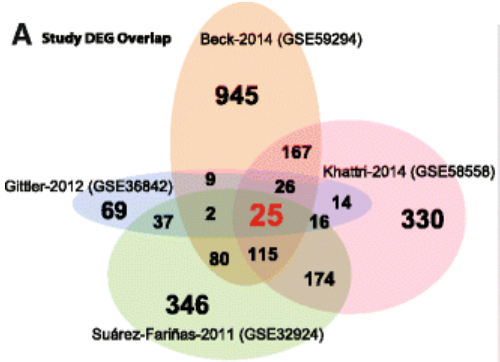
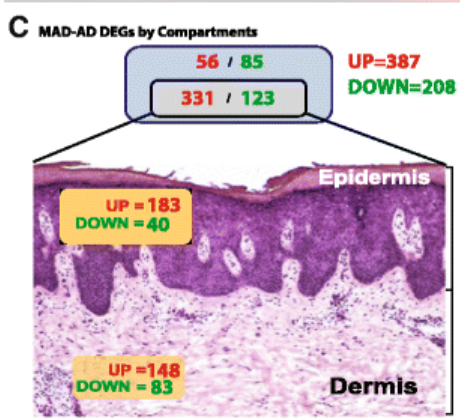
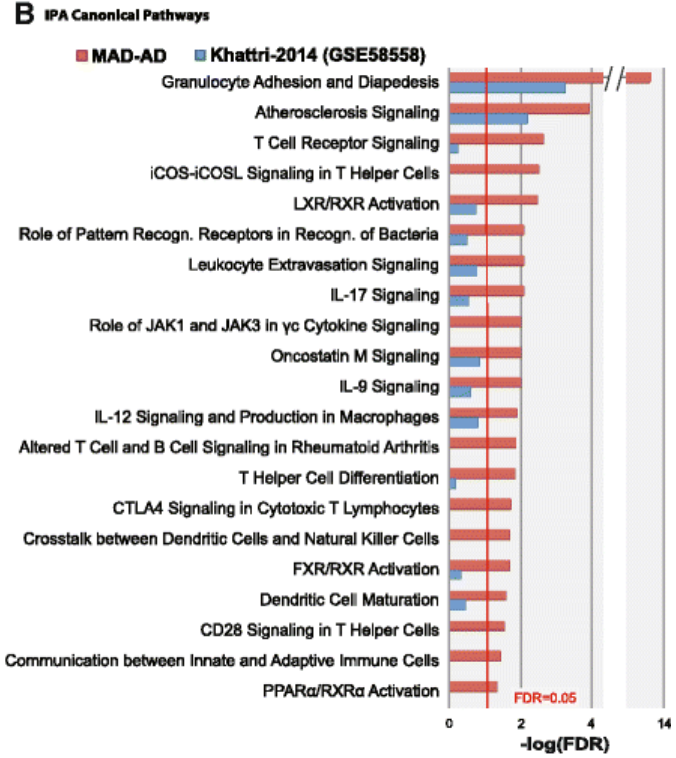
Skin Biopsy RNA-seq Transcriptomic Analysis

The following slides and analysis of RAPT data are in collaboration with Dr. Emma Guttman-Yassky

Meta-analysis-derived AD Transcriptome (MADAD)



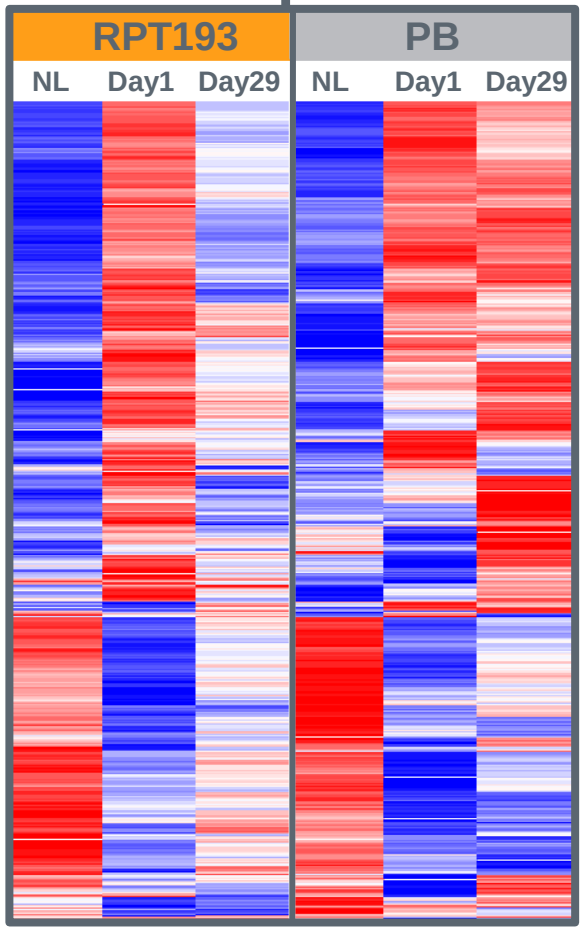


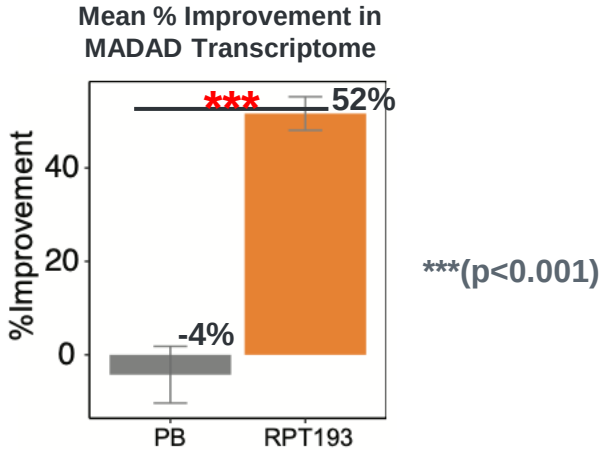


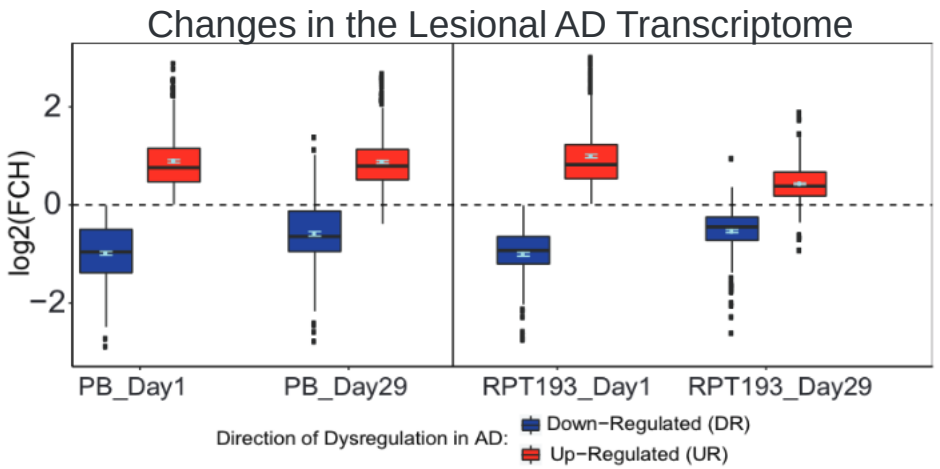
- 4 studies and 97 samples
- Uniform pre-processing pipeline
- Random effects model
- |FCH| ≥ 2, FDR ≤ 0.05
- Identified a set of 595 DEGs (387 up- and 208 downregulated)

Ewald et al. *(2015) BMC Med Genomics* **8,** 60

RPT193-Treated Subjects Exhibit Improvement in MADAD Transcriptome

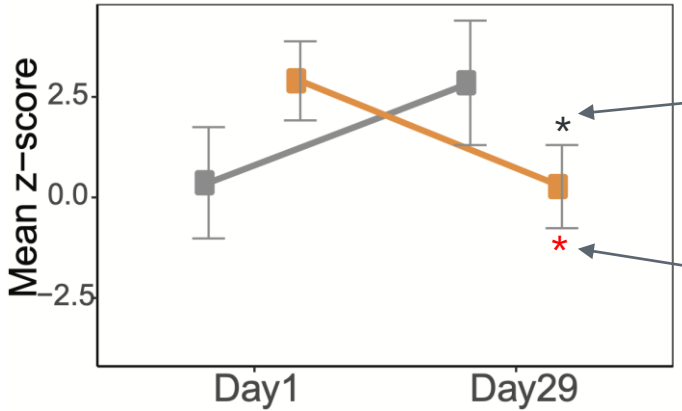






MADAD, Th2, Th22 and Th1 Immune Pathways Show Decreases

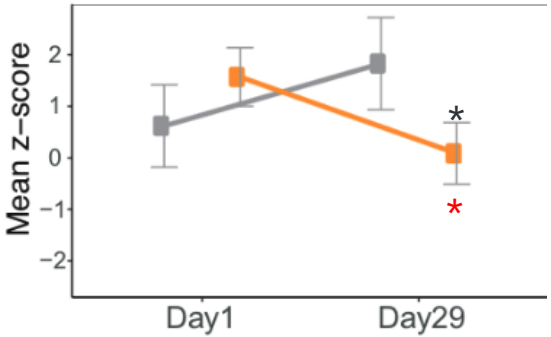
MADAD Immune Gene Set



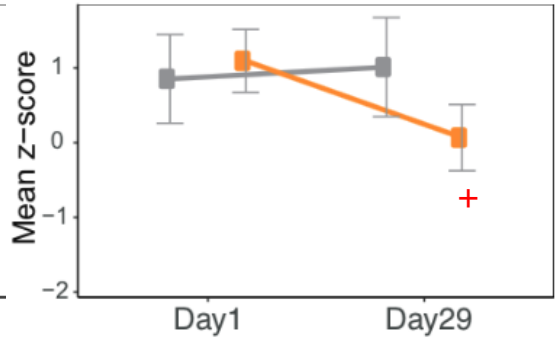
Black * indicates significance relative to baseline (same group)

red * or + indicates significance vs placebo

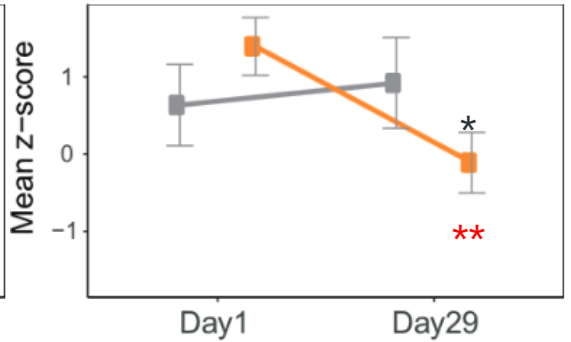
Th1



Th2

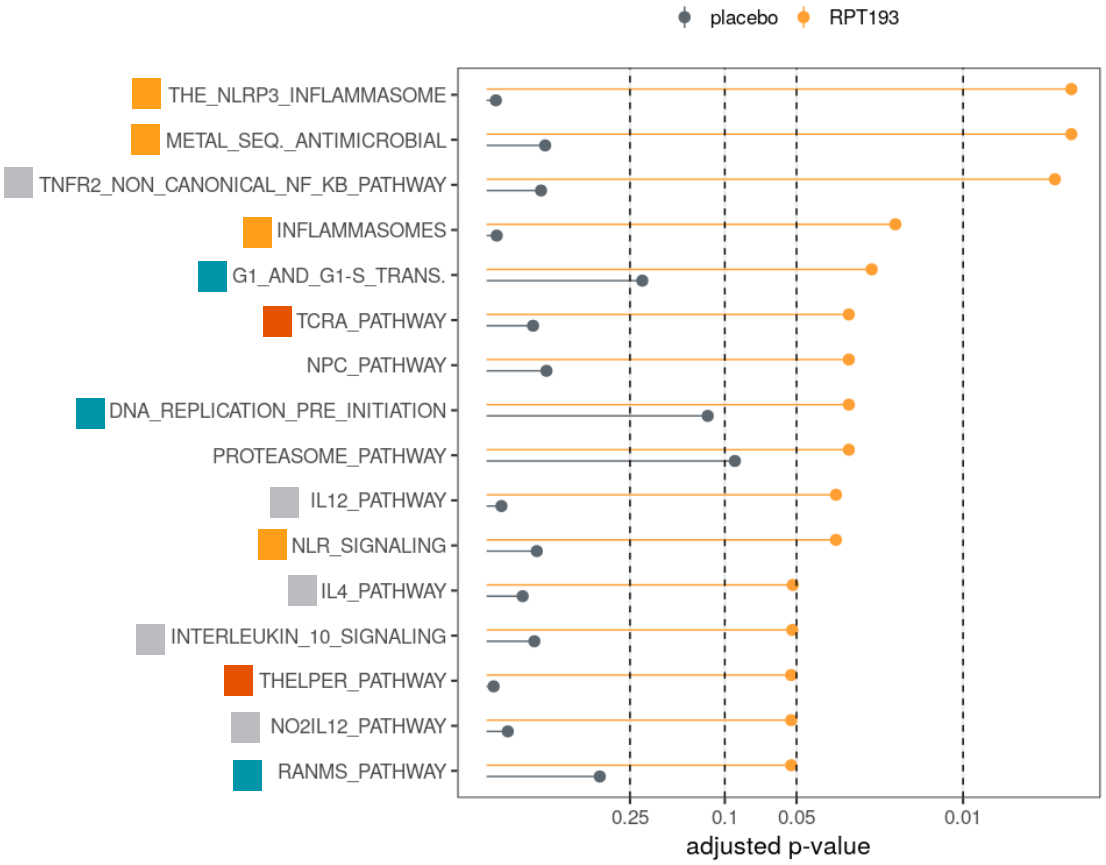


Th22



*** (p<0.001), **(p<0.01), *(p<0.05), +(p<0.1)

Gene Set Enrichment Analysis Indicates Multiple Pathways Are Changed on RPT193 Treatment



- Anti-microbial/ NLR/ Inflammasome signatures
- Cytokine pathway signatures
- Proliferation signatures
- T cell signatures

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Summary

- RAPT is developing an oral, selective and potent CCR4 small molecule antagonist for the treatment of AD and other Th2-driven diseases
- RPT193 has demonstrated clinical efficacy in a small, randomized Phase 1b study in moderate to severe atopic dermatitis
- Once daily dosing of RPT193 results in excellent surface CCR4 receptor occupancy at trough concentrations
- Cell surface CCR4 is decreased following RPT193 treatment
- RPT193 treatment results in improved MADAD transcriptome, a gene signature for key pathways of AD that is being used to evaluate therapeutic responses
- RPT193 is currently being tested in a Phase 2b study for AD and will be tested in a Phase 2 study in asthma

Acknowledgements

RAPT Drug Discovery

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Angel Pagan
Yeriel Estrada

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Robert Bissonette

Participants in RAPT clinical trials

Thank You