primmune Therapeutics

Primmune Therapeutics, Inc.

Driving Innate Immunity via TLR7 Agonism

May 10, 2023

Treating Cancer: Sustained Immune Pressure via Novel TLR7 Agonism

- Primmune's TLR7 agonists engage a variety of antitumor responses
- Key are those initiated by direct activation of plasmacytoid dendritic cells (pDCs).

INNATE

pDC activation mediates killing of tumor cells by:

- therapeutic engagement of NK cells and other elements of the antitumor innate immune response
- production of soluble factors including Type I/III IFNs

ADAPTIVE

Activated pDCs drive the adaptive immune response primarily through:

- reversal of intratumoral CD8+ T-cell anergy
- differentiation and activation of naïve T-cells to CD8+ T cells

PRTX007 PRODUCT PROFILE

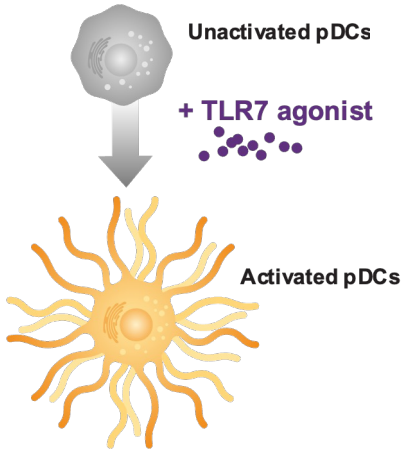
- **Orally** administered as prodrug PRTX007
- **Systemically** distributed TLR7 agonist PRX034
- **Safe** and **well-tolerated**
- **Administration every other day** to enable long-term immune pressure without counter-regulation
- **IFN centric immune activation** with little to no activation of pro-inflammatory cytokines

Pharmacology Elicited by Oral PRTX007 is Restricted to Enable Continual Immune Pressure, Combination with Other Immunotherapies

TREATMENT OF CANCER:

Addition of Agonist

1. Eliminates immunosuppression
2. Orchestrates pDC-mediated antitumor immune response

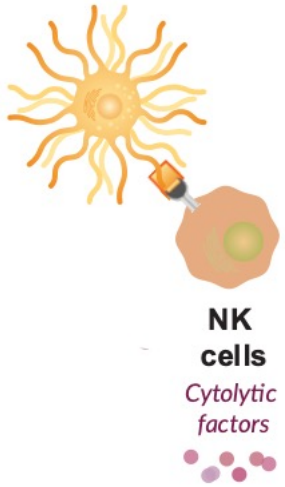


TREATMENT OF VIRAL INFECTION:

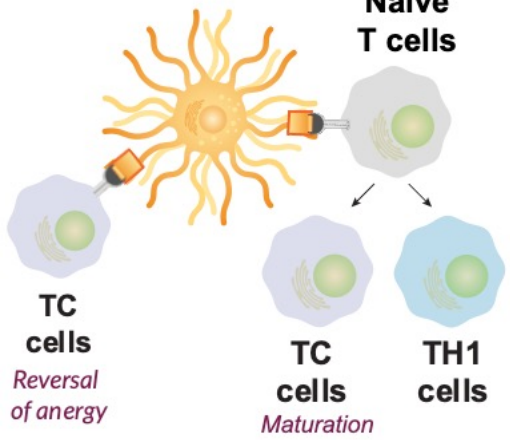
Addition of Agonist

1. Active against viruses that evade the immune system (e.g., HPV)
2. Orchestrates pDC-mediated antiviral response

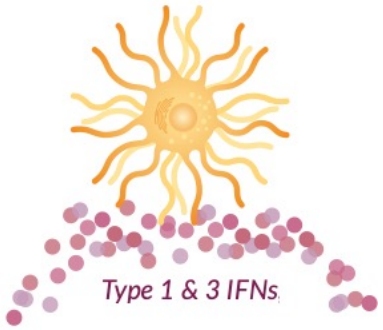
3 Activates NK cells



4 Activates CD8+ T cells



5 Induces other broad-ranging responses (e.g., ↑ antigen presentation, TME remodeling)



5 Type I & III IFNs activate many antiviral mechanisms, inhibiting entire viral life cycle

PRTX007 is an oral prodrug that delivers the TLR7 agonist **PRX034** throughout the body

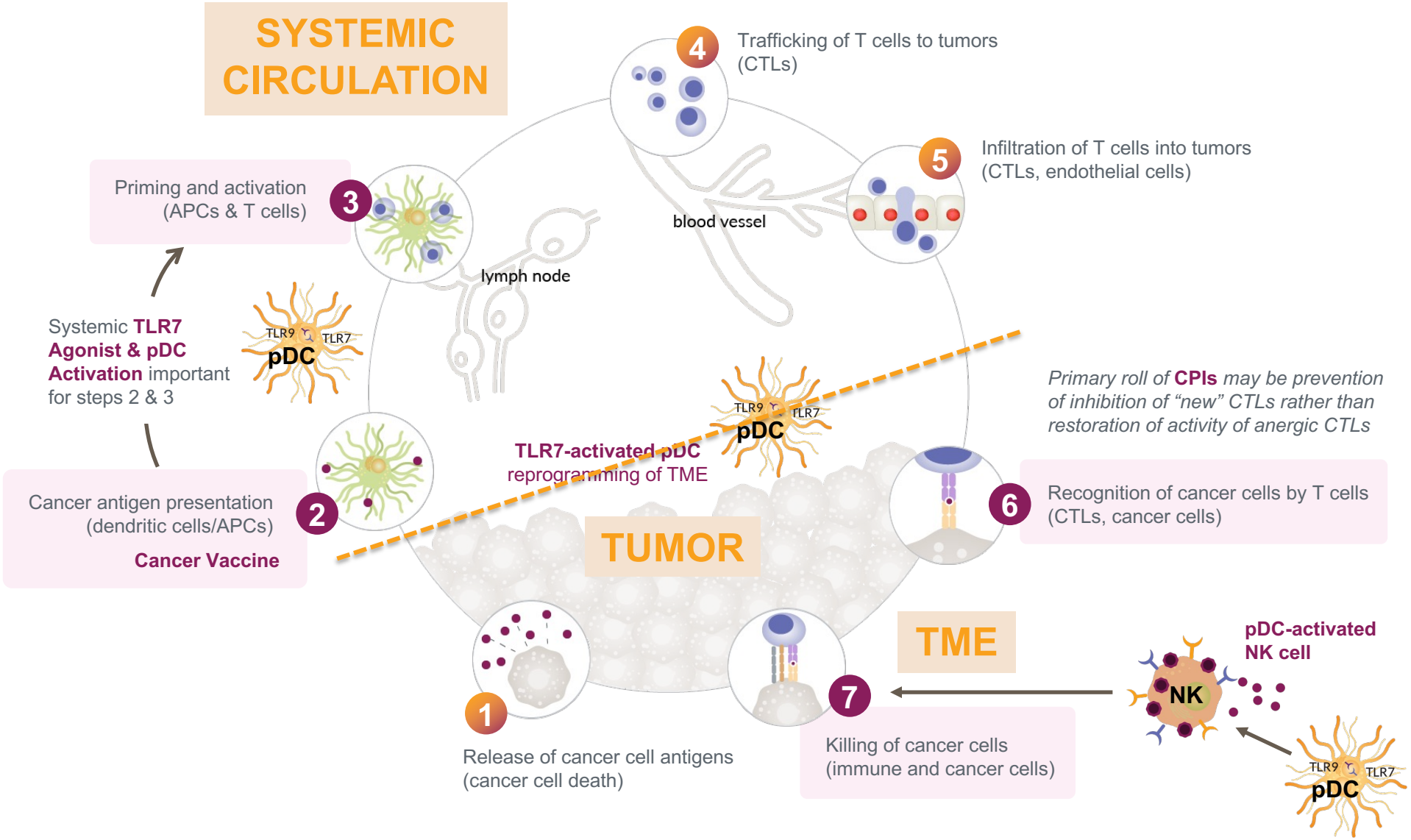
PRX034 pharmacologic activities are more restricted than most TLR7 agonists;

- Avoids induction of NFκβ-mediated biosynthesis of proinflammatory factors
- Minimizes activation of B cells

PRX034 pharmacologic activity engages CD8+ T cells and NK cells, the two most important immune cells for killing cancer cells

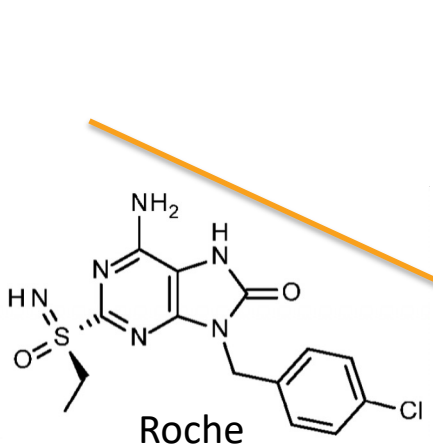
➢ **Avoids systemic inflammation while delivering therapeutic benefit**

Systemic TLR7 agonists play a role throughout the Cancer Immunity cycle, enabling synergistic effects with CPIs and vaccines

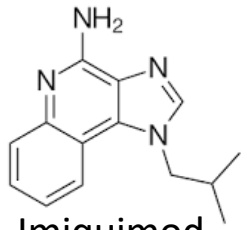


Adapted from Chen and Mellman (2013) Oncology Meets Immunology: The Cancer-Immunity Cycle

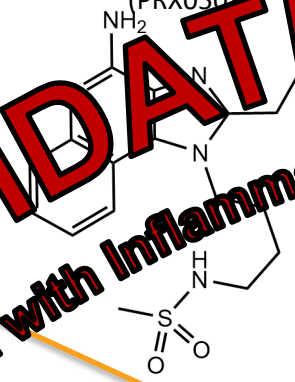
Not all TLR7 Agonists are the Same – Pharmacology is Very Compound-Dependent



Roche
RO7117418



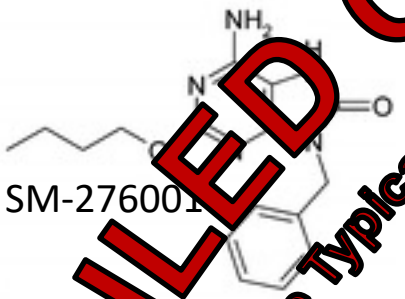
Imiquimod



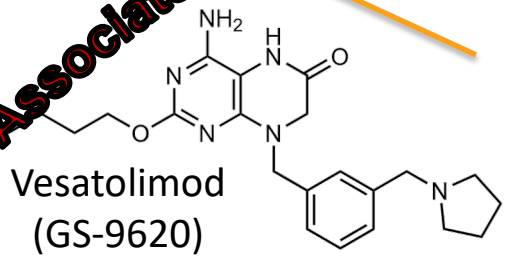
3M-852A
(PF-4878691)
(PRX050)

FAILED CANDIDATES ...

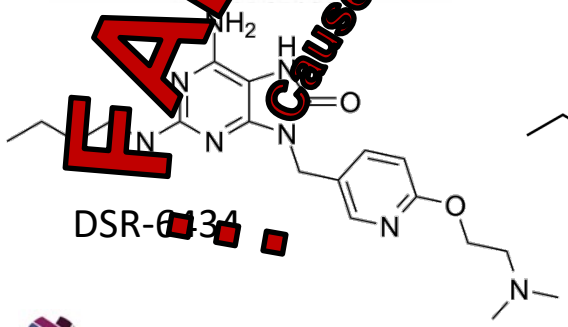
Cause Typically Associated with Inflammation



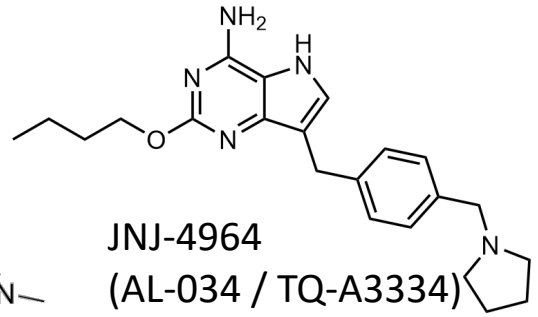
SM-276001



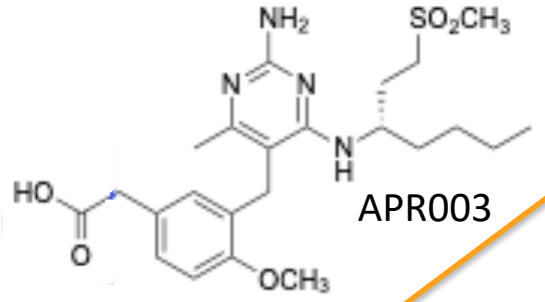
Vesatolimod
(GS-9620)
(PRX049)



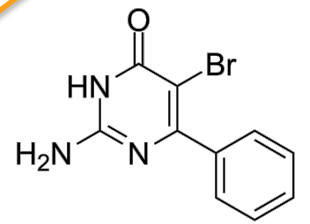
DSR-6434



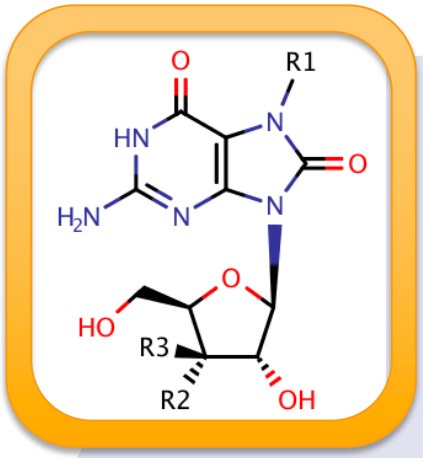
JNJ-4964
(AL-034 / TQ-A3334)



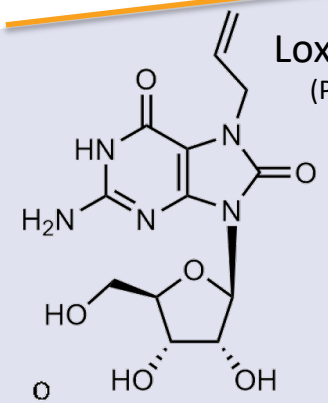
APR003



Bropirimine
(PRX044)



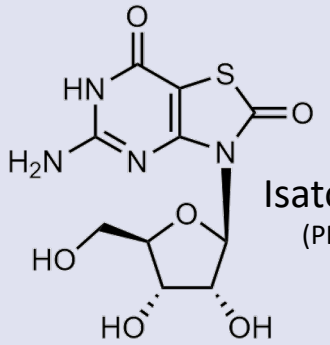
PRX034



Loxoribine
(PRX028)

RO7011785
(PRX090)

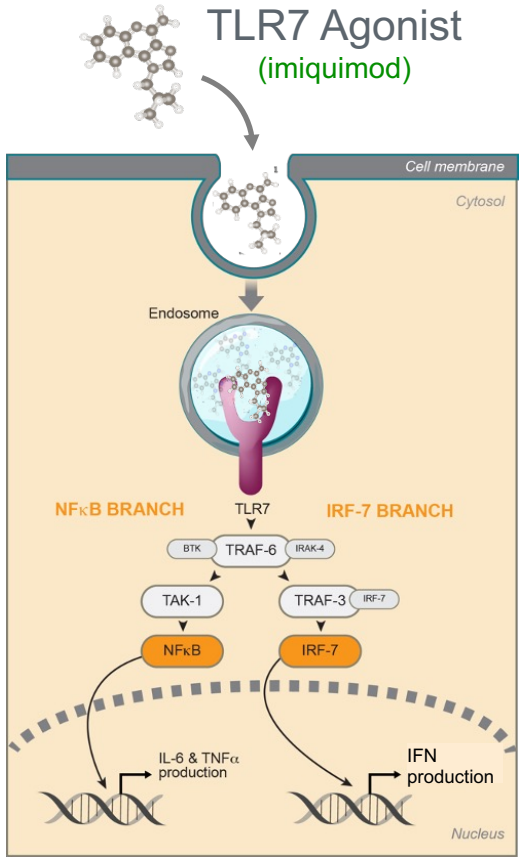
3'-deoxyisatoribine
(PRX036)



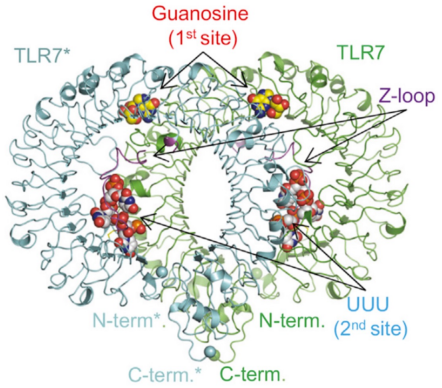
Isatoribine
(PRX029)

We have shown in vitro, in vivo and in humans the ability to separate the poly-interferon and pro-inflammatory pathways

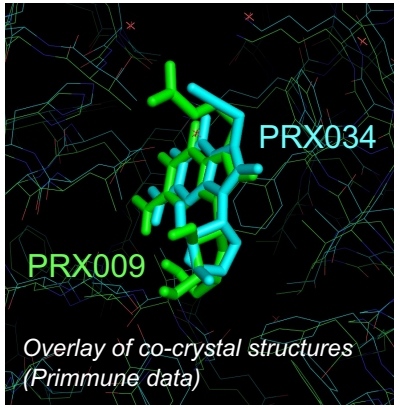
PRTX007 – Specifically Designed to be Preferential for IRF-7 and Not NFκβ



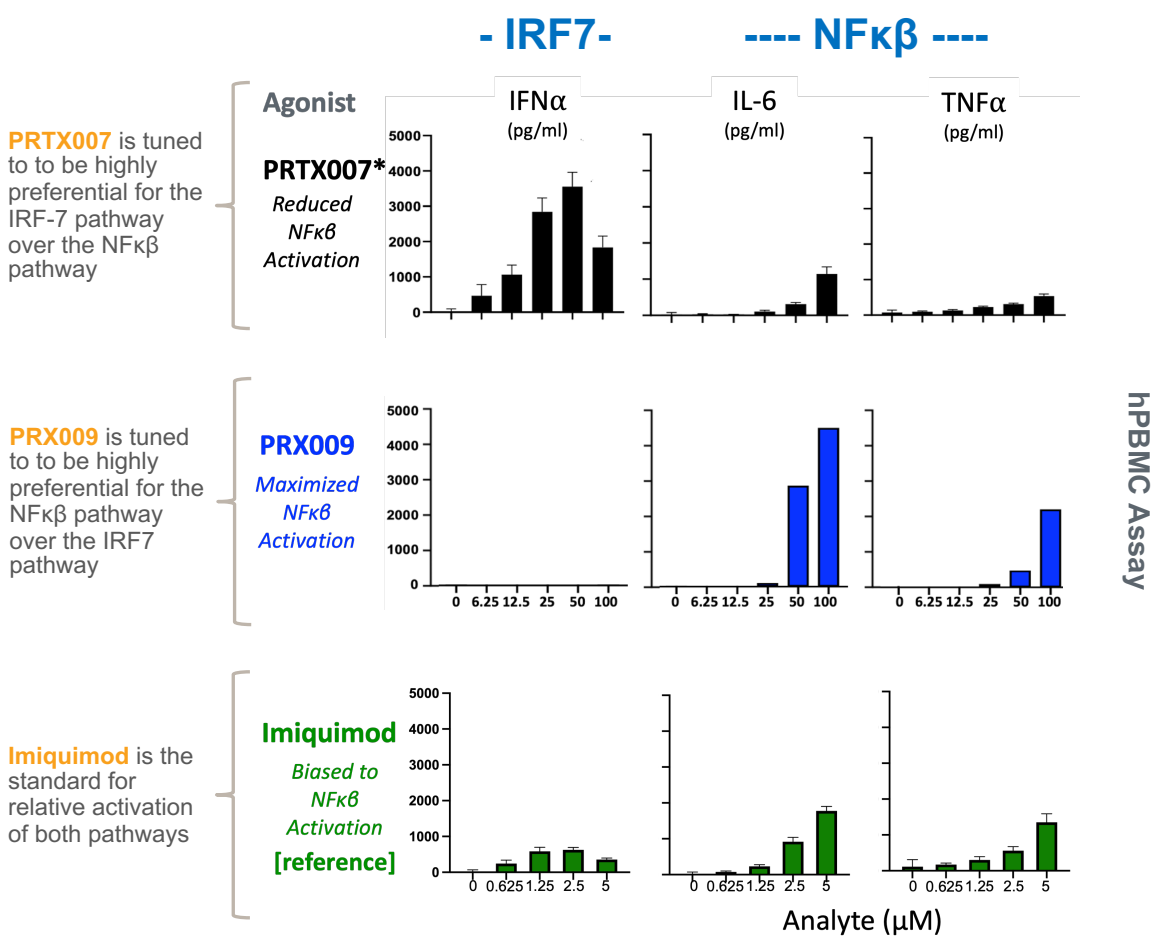
Cartoon Oversimplifies



From Zhang et al 2016



Note: pDC activation by PRX034, PRX009 & Imiquimod confirmed by FACS analysis

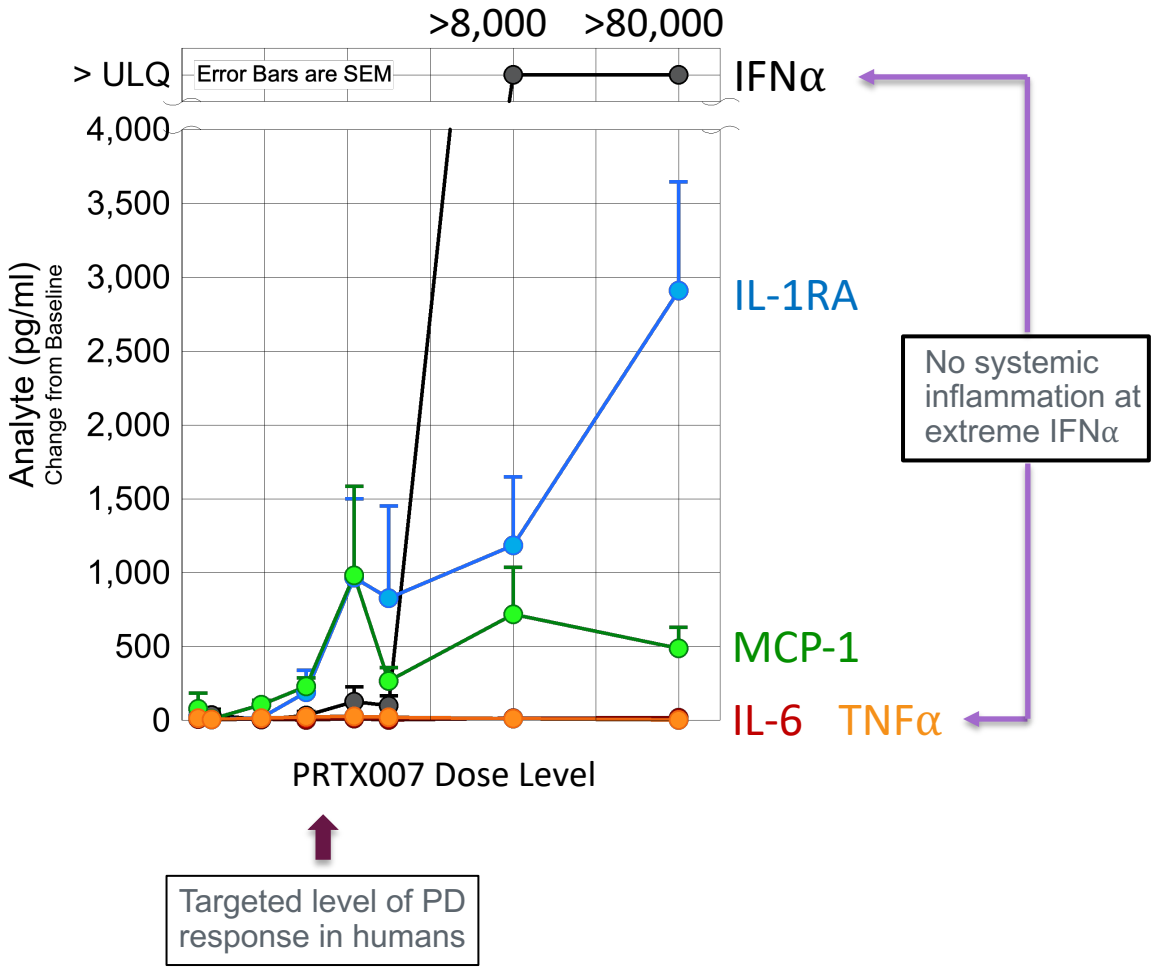


* Active metabolite of PRTX007 called PRX034 utilized for in vitro assays. hPBMC = human Peripheral Blood Mononuclear Cells.

Supporting Pharmacology

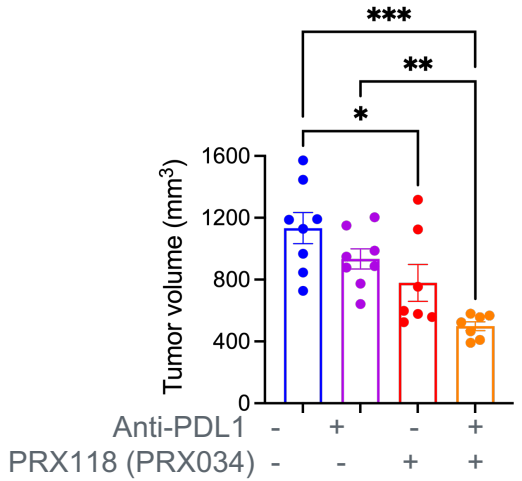
First-Dose PD Response in NHPs

Circulating Factors in Plasma



Rodent HNSCC Tumor Model

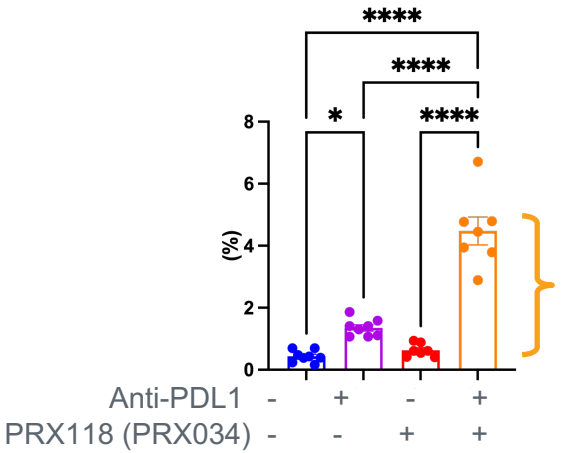
Tumor Volume



- Tumor resistant to anti-PD-L1 monotherapy (greater activity of TLR7 agonist alone)
- Best activity by combination of anti-PD-L1 mechanism by TLR7 agonist

Tumor-associated CD8+ T cells

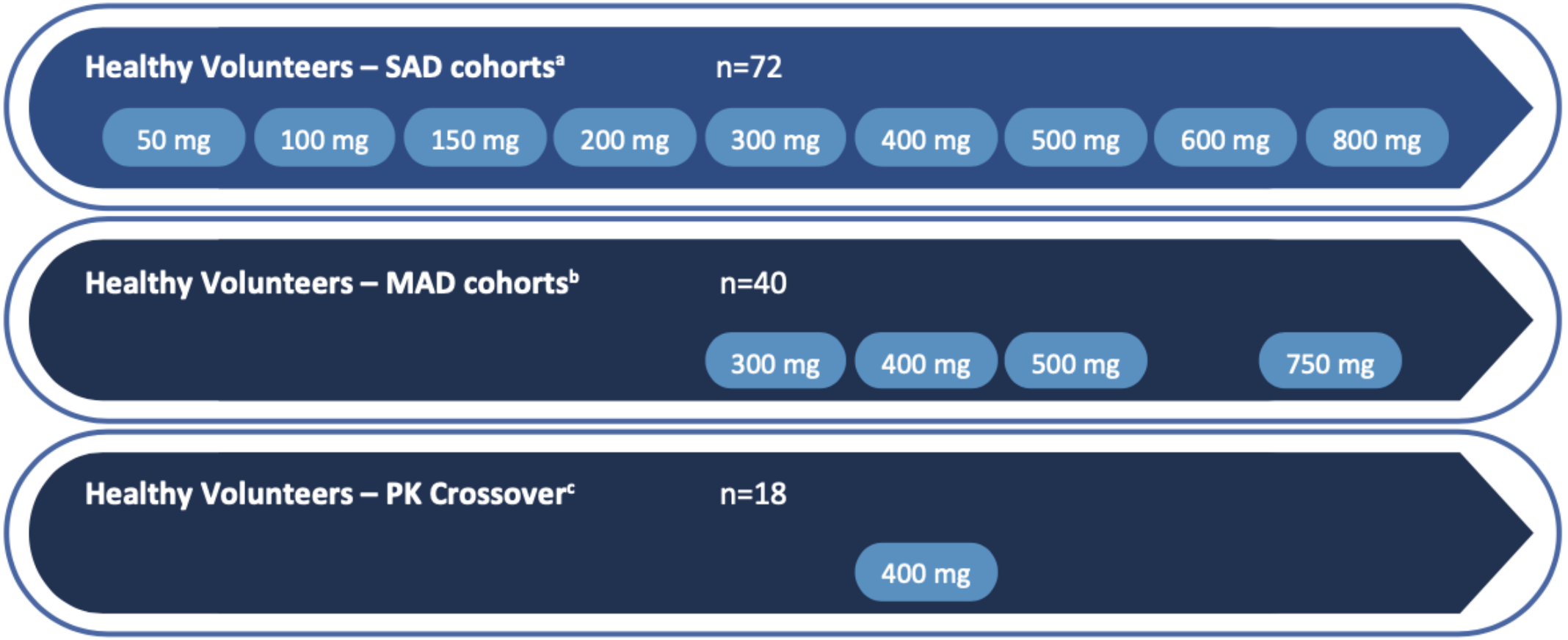
% of immune cell infiltrate



- Mechanism of tumor reduction by TLR7 agonist orthogonal to that of anti-PD-L1
- Profound enhancement of anti-PD-L1 mechanism by TLR7 agonist

Primmune's First-In-Human study efficiently examined safety, tolerability and immune activation at ascending doses in healthy volunteers

Study Design



[a]Each SAD cohort contained 6 treated and 2 placebo HVs/group; food effect study at 100 mg.
[b]Each MAD cohort contained 8 treated and 2 placebo HVs/group; administered QOD over 13 days (7 doses).
[c]Comparison of free-base and salt forms of PRTX007; single dose, crossover design.

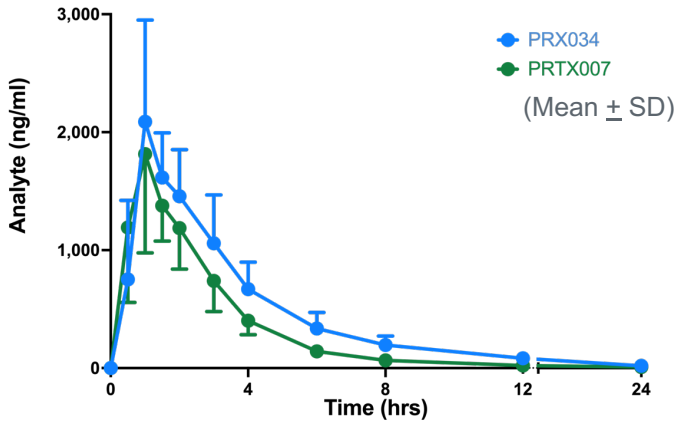
Completed First-in-Human SAD/MAD Study in Healthy Volunteers (n=130)

Overall Safety Takeaways

- **NO GRADE 3 OR ABOVE ADVERSE EVENTS**
- **NO CLINICALLY MEANINGFUL CHANGES OBSERVED IN CREATININE, BUN OR URIC ACID**
- **NO DOSE STOPPING OR DOSE MODIFICATION REQUIRED FOR ANY DRUG RELATED AES**
- **TRANSIENT HEADACHE**
  17% (12% Grade 1, 5% Grade 2) - seen in treated and placebo groups, no dose-dependence
- **ALT Elevation (>ULN)**
  5% (all Grade 1/Mild) - 4 of 5 between 1.5x and 2x ULN, 1 at ~2.5x ULN. No associated changes in AST, alkaline phosphatase or bilirubin
- **TRANSIENT FEVER**
  3% (1 - Grade 1, 2 - Grade 2) – seen at 2 highest MAD doses. Resolved within 24-36 hours and did not recur upon subsequent dosing

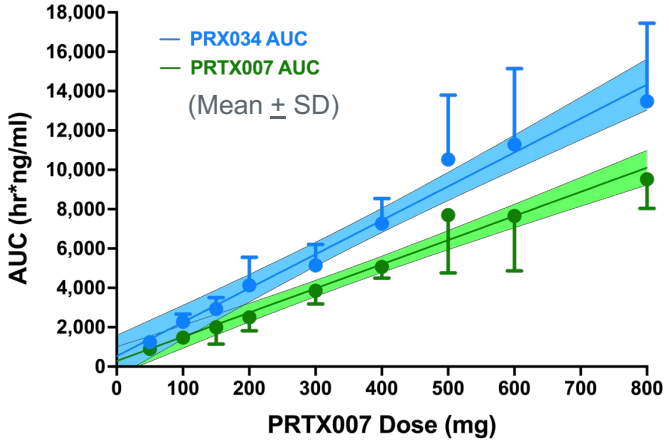
Pharmacokinetic Data Shows a Well-behaved Profile for PRTX007

PK Time Course
(400 mg cohort)



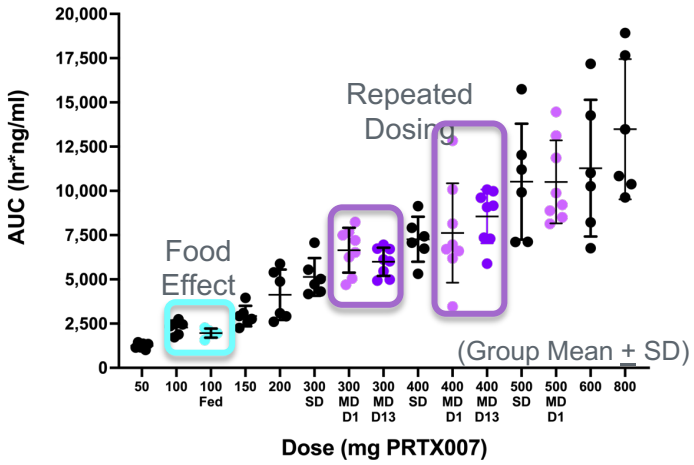
- Rapid absorption and conversion of prodrug PRTX007 to agonist PRX034 following oral administration
- Appropriate duration of pulsatile exposure to PRX034

Dose Dependence



- Dose-proportional increase in exposure to prodrug and active agonist
- Agonist/Prodrug AUC ~ 1.7 for all subjects

PRX034 Dose Dependence
(individual subjects)



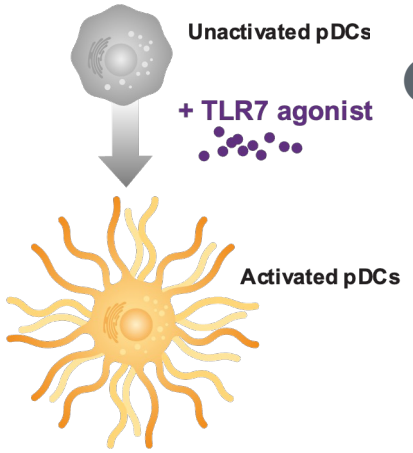
- Minimal change in exposure with high-fat meal (modest delay in absorption) (indigo box)
- Exposure unchanged between 1st (D1) and 7th (D13) doses (purple box)

Pharmacology Elicited by Oral PRTX007 is Restricted to Enable Continual Immune Pressure

TREATMENT OF CANCER:

Addition of Agonist

1. Eliminates immunosuppression
2. Orchestrates pDC-mediated antitumor immune response



1

SELECTED BIOMARKER FINGERPRINT DEMONSTRATES ENGAGEMENT OF MOA

Addition of Agonist

1. Active against viruses that evade the immune system (e.g., HPV)
2. Orchestrates pDC-mediated antiviral response

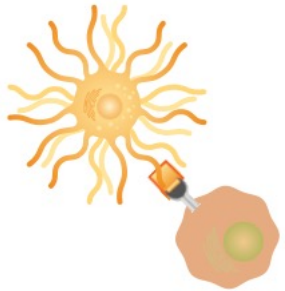
PRTX007 is an oral prodrug that delivers the TLR7 agonist **PRX034** throughout the body

PRX034 pharmacologic activities are more restricted than most TLR7 agonists;

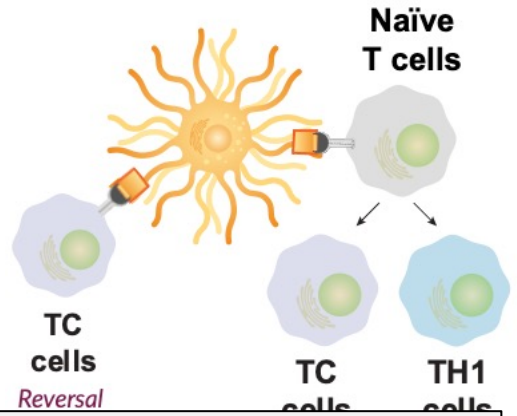
- Avoids induction of NFκβ-mediated biosynthesis of proinflammatory factors
- Minimizes activation of B cells

034 pharmacologic activity engages T cells and NK cells, the two most tant immune cells for killing cancer cells

3 Activates NK cells



4 Activates CD8+ T cells



5 Induces other broad-ranging responses (e.g., ↑ antigen presentation, TME remodeling)

5 Type I & III IFNs activate many antiviral mechanisms, inhibiting entire viral life cycle

3

CIRCULATING MARKERS SUPPORT SAFETY

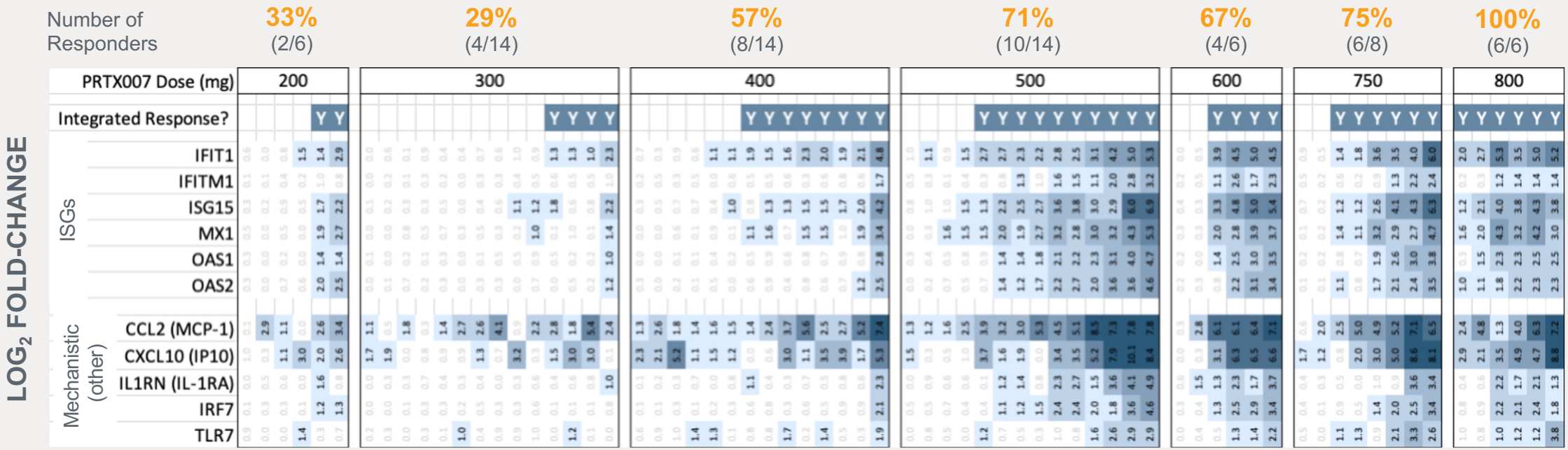
2

CELLULAR MARKERS INDICATE ENGAGEMENT OF TARGET CELLS

4

DETAILED TIME COURSE MEASUREMENTS ALLOW EVALUATION OF INDUCTION OR COUNTER-REGULATION

mRNA Transcript Induction Heat Map Demonstrates Dose-Dependent Coordinated Response Following First Dose*



Values are Log_2 $R_{max,0\text{-}24hr}$ (Log_2 maximal fold-change from pretreatment baseline during 24 hr period following administration of PRTX007).
All HVs receiving PRTX007 in the SAD 200 mg through 800 mg cohorts, and the 300 through 750 mg MAD cohorts (n=68) are shown. Color intensity is as shown in scale.
ISG=interferon-stimulated gene product.

ISGs

IFIT1	interferon induced protein with tetratricopeptide repeats 1
IFITM	interferon induced transmembrane protein 1
ISG15	ISG15 ubiquitin like modifier
MX1	MX dynamin like GTPase 1
OAS1	2'-5'-oligoadenylate synthetase 1
OAS2	2'-5'-oligoadenylate synthetase 2

Mechanistic (other)

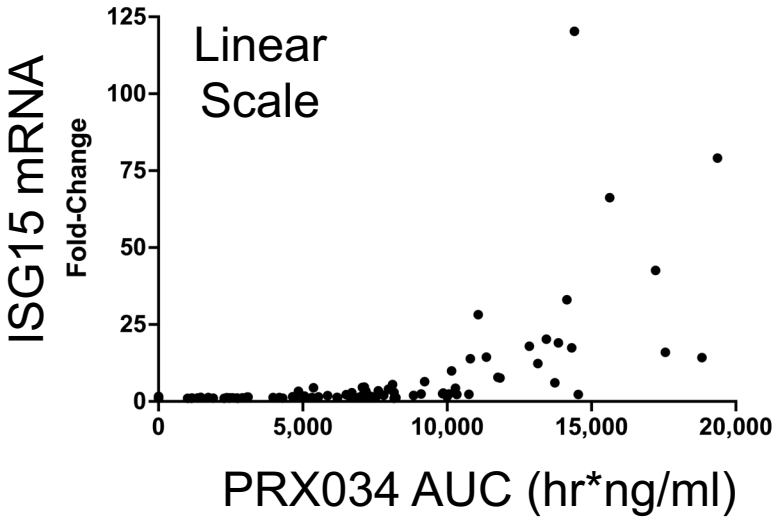
CCL2 (MCP-1)	C-C motif chemokine ligand 2; MCP-1
CXCL10 (IP10)	C-X-C motif chemokine ligand 10 ; IP-10
IL1RN (IL-1RA)	interleukin 1 receptor antagonist; IL1RA
IRF7	interferon regulatory factor 7
TLR7	toll like receptor 7

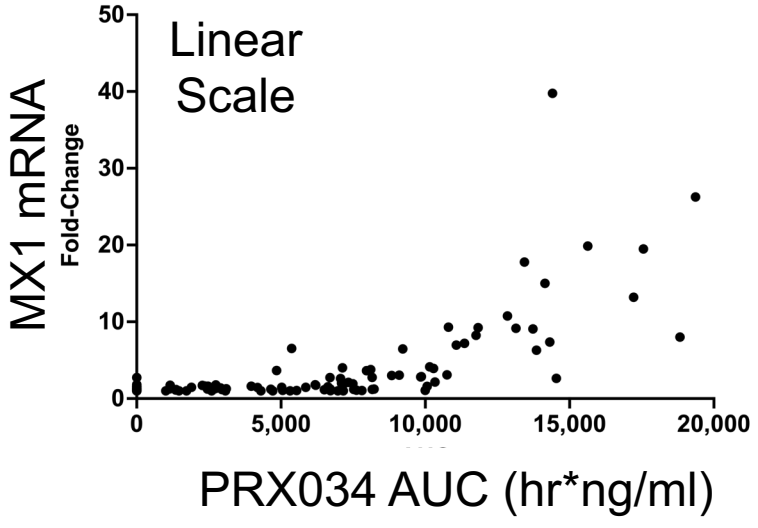
Color Scale

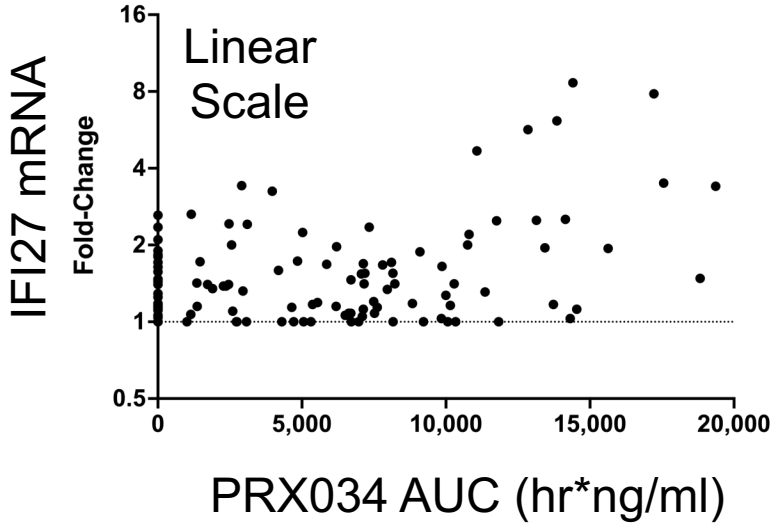
Min	Max	Color
0.0	1.0	
1.0	2.0	
2.0	3.0	
3.0	4.0	
4.0	5.0	
5.0	6.0	
6.0	7.0	
7.0	10.5	

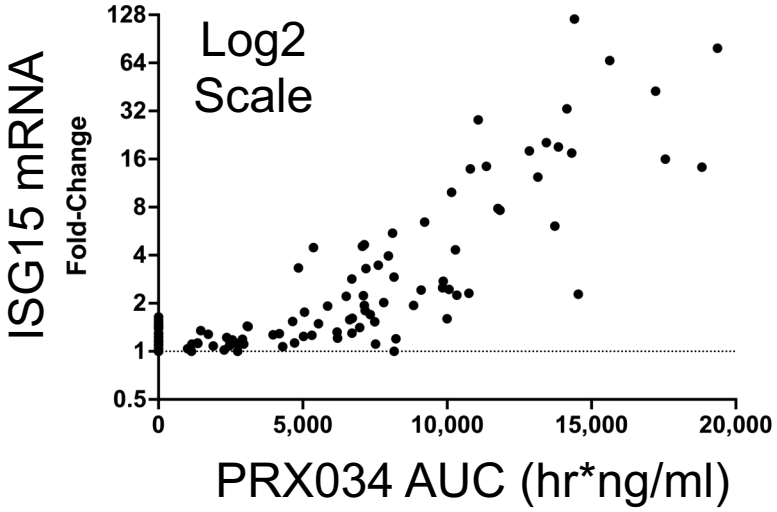
*Data through 800 mg SAD cohort and through 750 mg MAD cohort

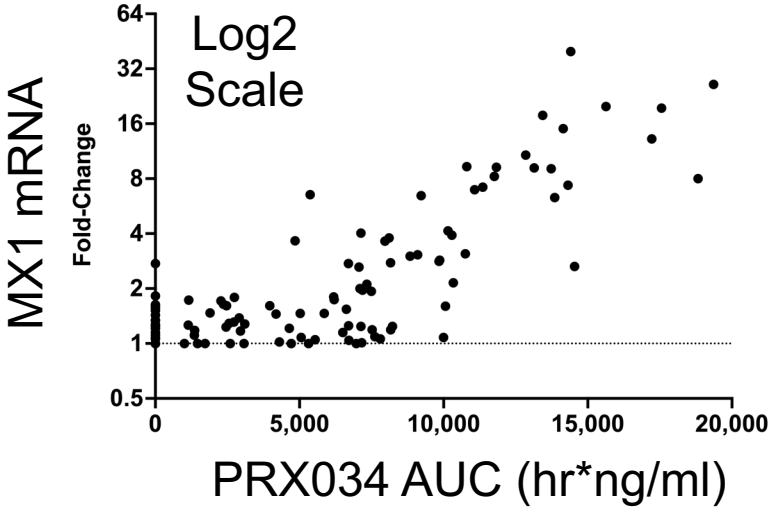
Exposure-dependent Increase in Expression of Interferon-Stimulated Genes (ISGs) Following First Dose of PRTX007

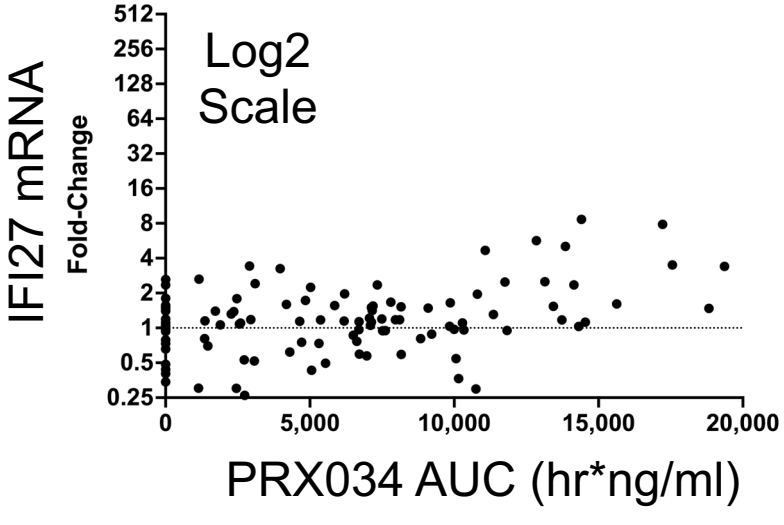






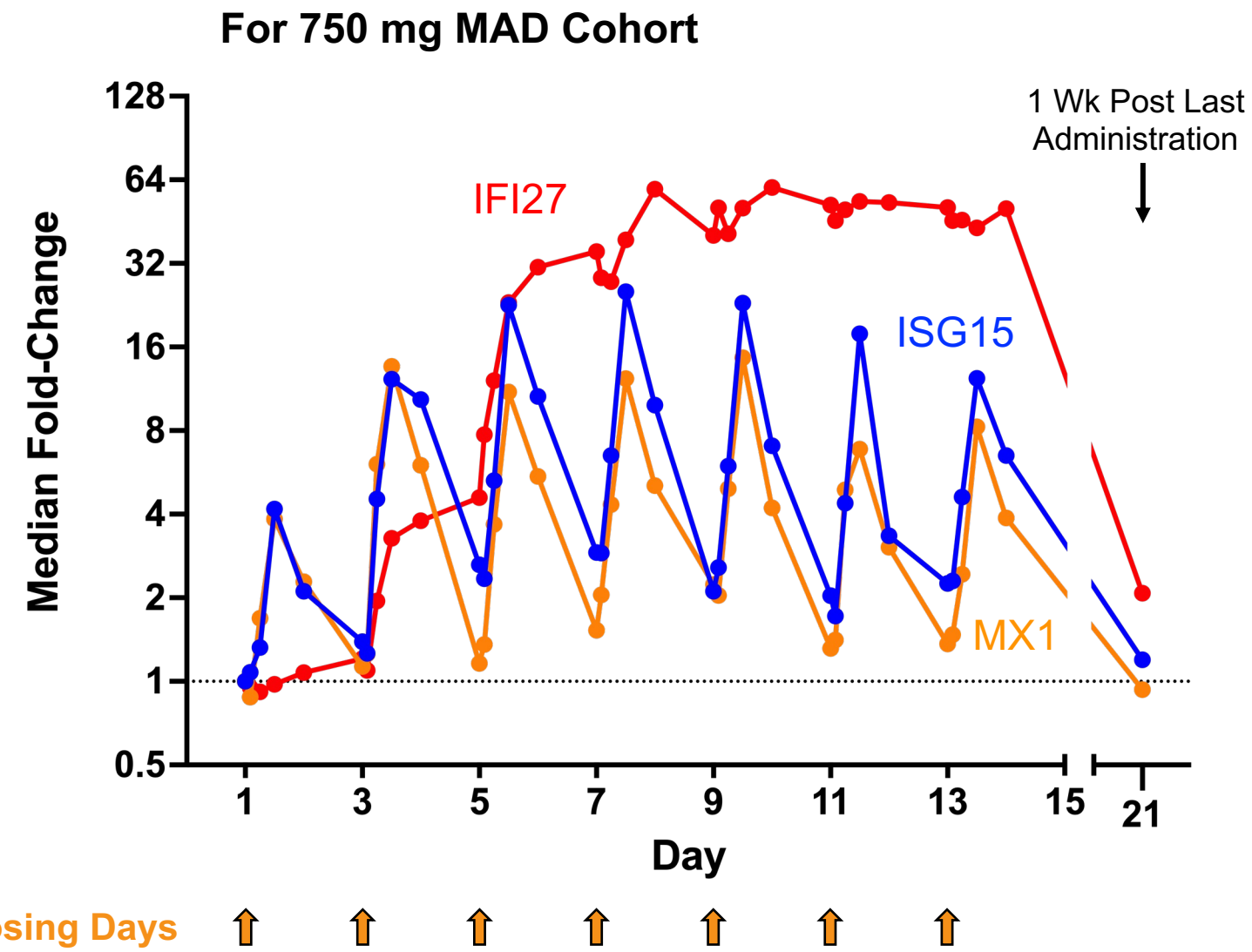






Impact of Repeated Doses on QOD Schedule is to Increase Magnitude of Response

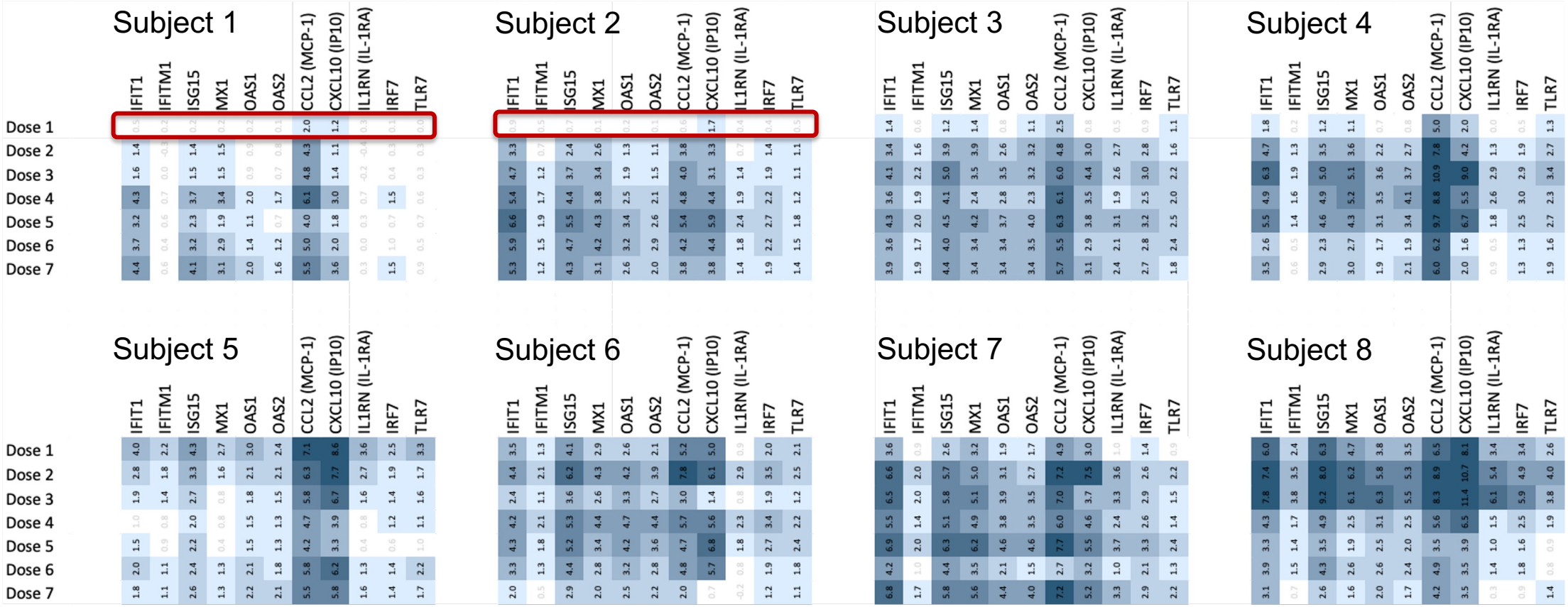
Magnitude of immune induction as measured by ISG expression in blood cells clearly increases upon repeated dosing with PRTX007 until PD "steady state" response is reached



mRNA Transcript Induction Heat Maps Individual Subjects in 750 mg in Multi-dose Cohort Maintain Coordinated Response (QOD Dosing)

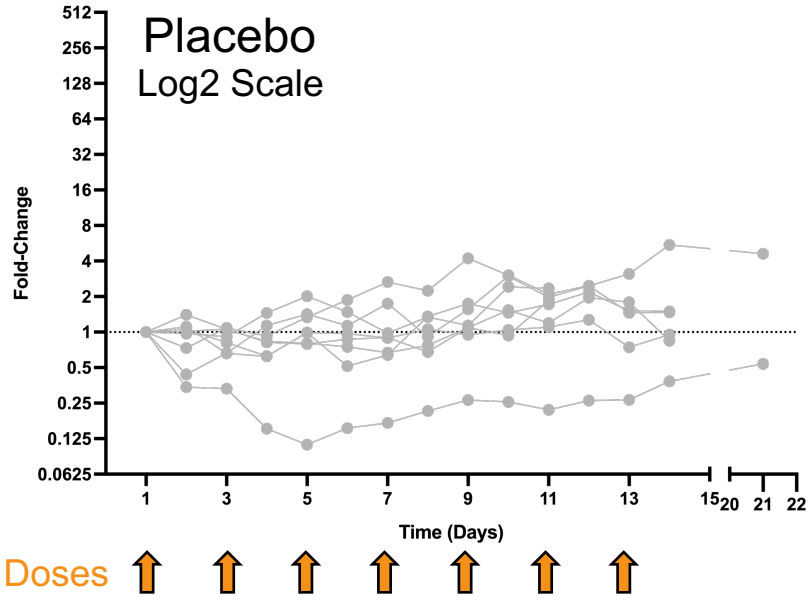
The well-controlled, coordinated immune response observed on a single dose is maintained during repeated doses

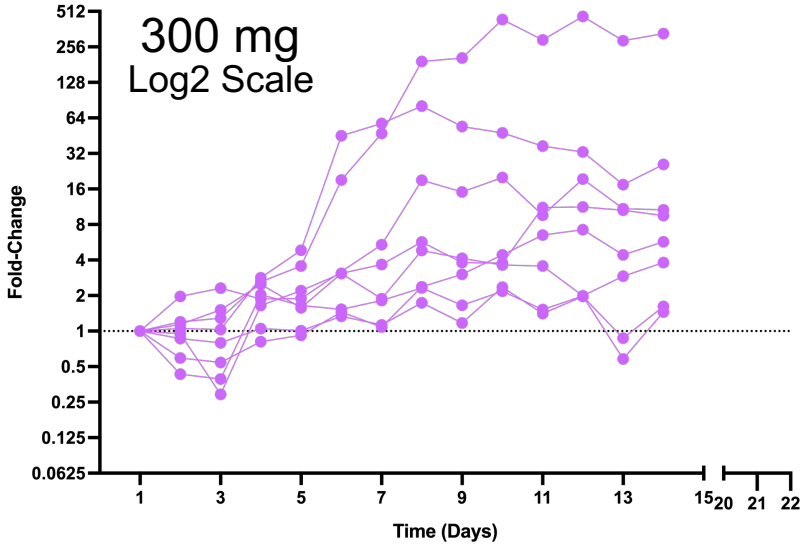
Two subjects (1 and 2) that were poorly responsive to first dose (first dose response highlighted in red) establish a robust response upon repeated dosing

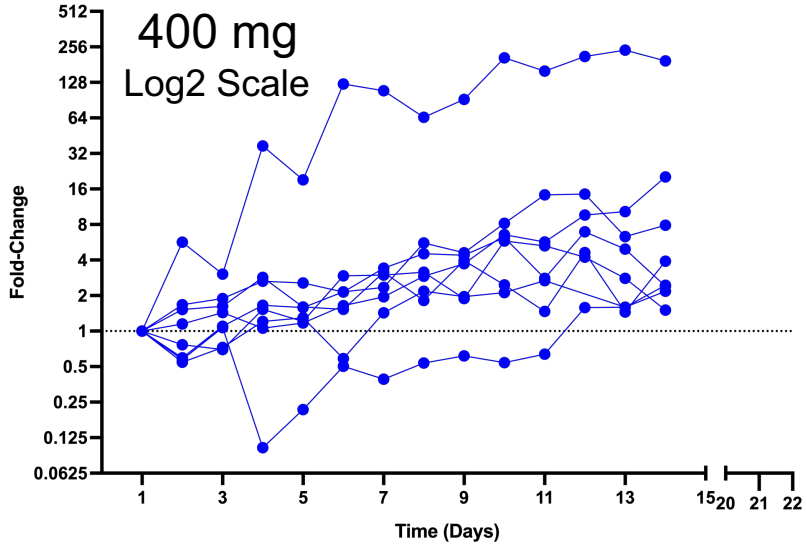


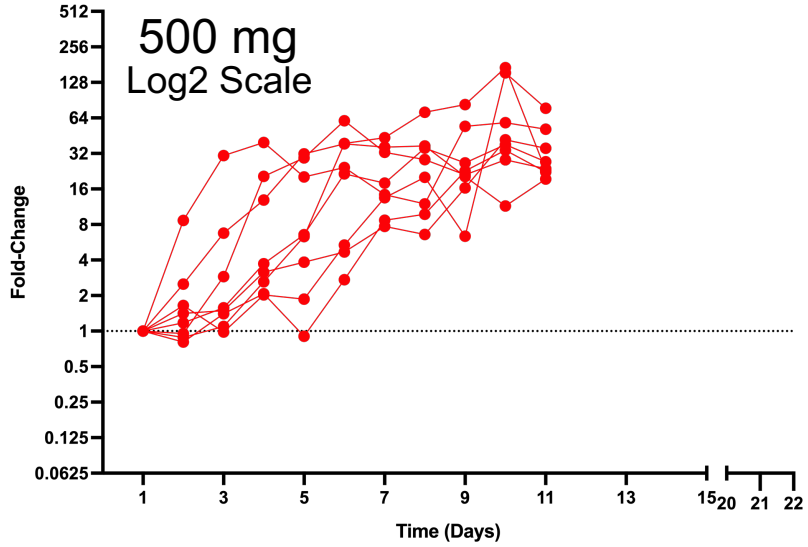
Each panel depicts the mRNA transcript induction by dose for an individual subject, color scale as in previous slide.

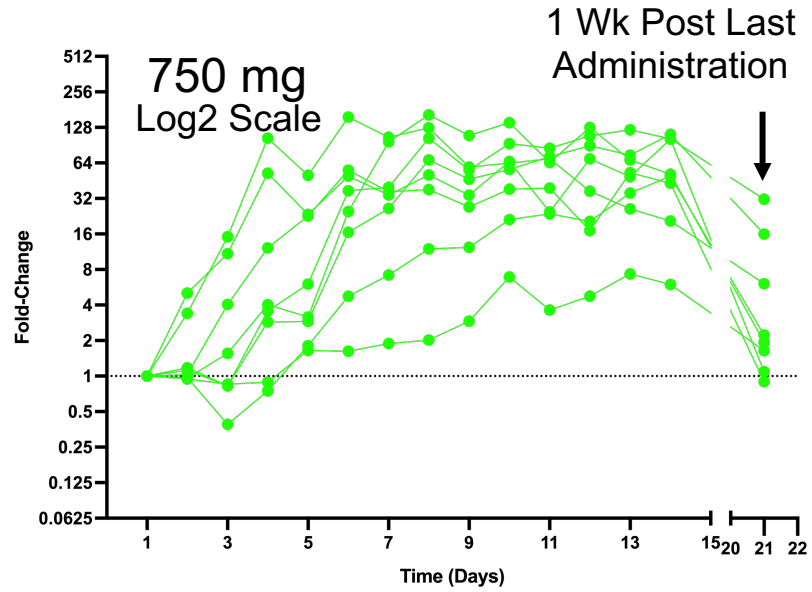
Individual IFI27 Time Courses Demonstrate Dose Level Differentiation







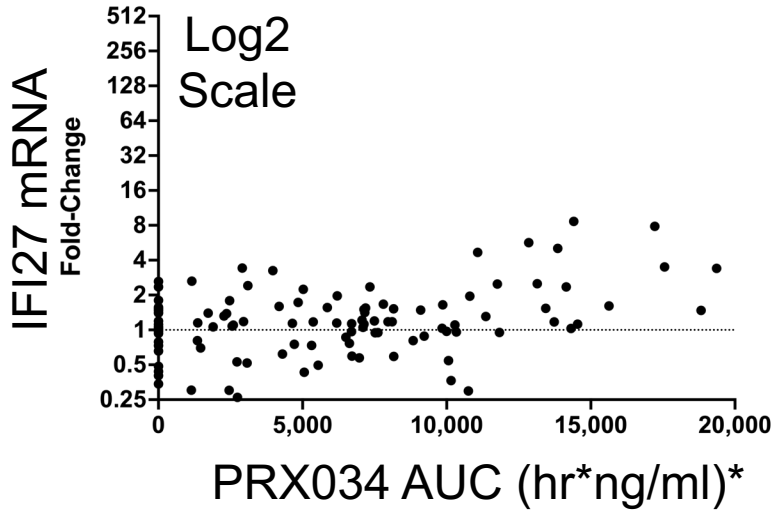




Data Shown for Predose & 24 hr Post-Dose Time Points Only (uniformly measured across all cohorts)

Substantially Increased Expression on Repeated Dosing Even for ISGs Like IFI27 That Is Poorly Induced by First Dose

Only modest induction of IFI27 is observed following the first dose of PRTX007 (below)

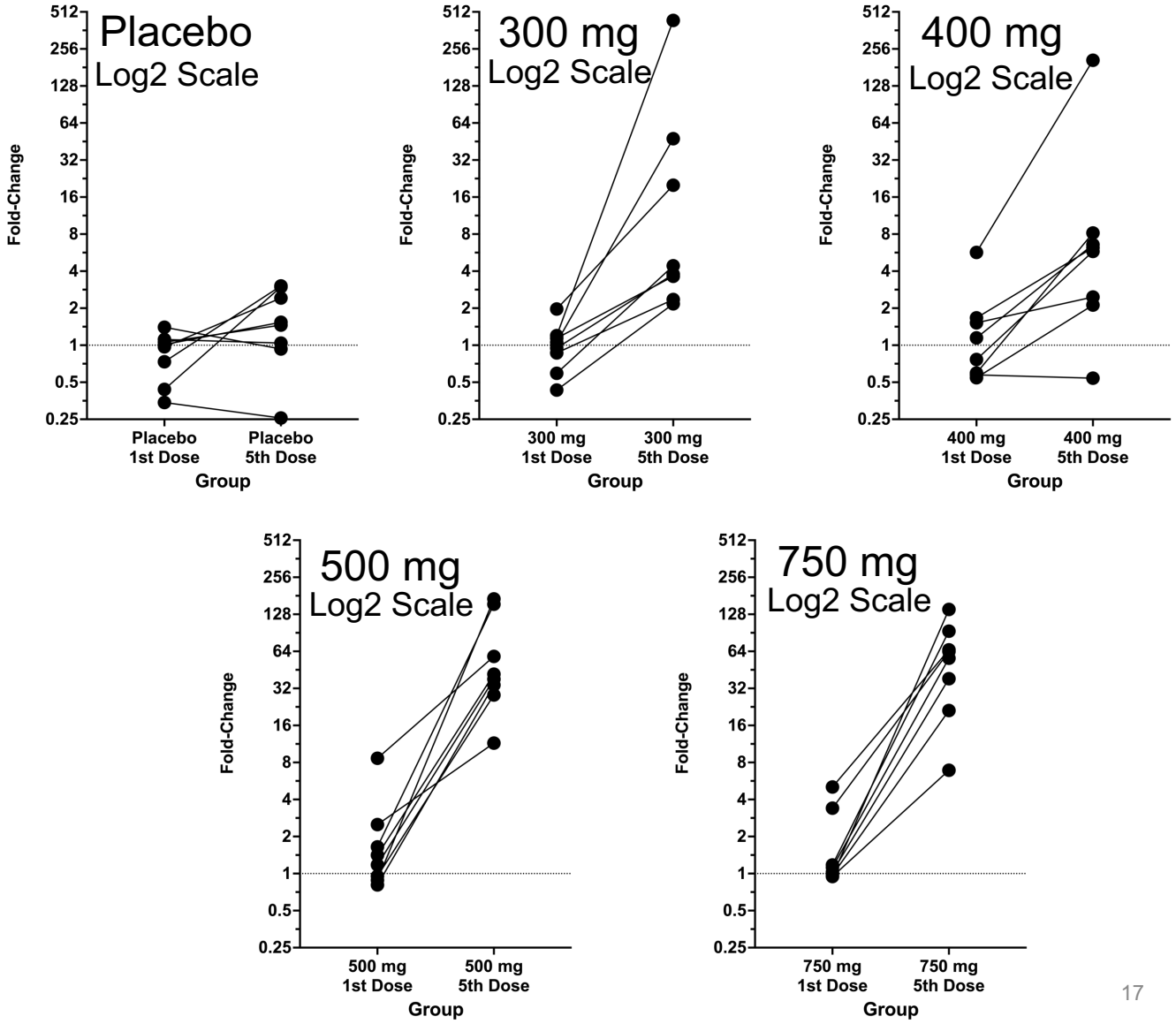


*Exposure dependence of IFI27 response 24 hrs after first dose for all subjects whether in SAD or MAD cohorts

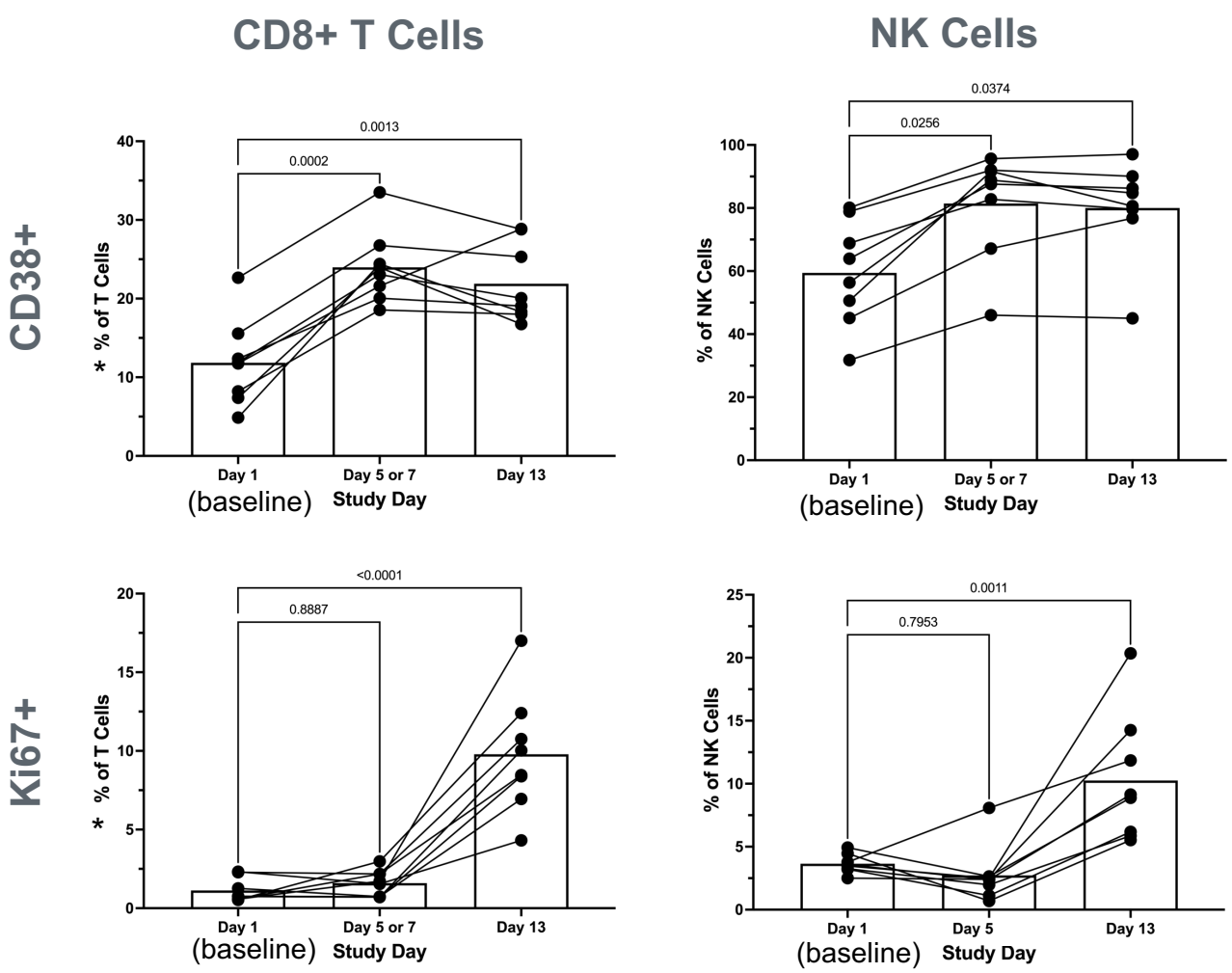
However, profound dose-dependent IFI27 induction is observed upon repeated administration (right)

Paired Response by Subject to 1st and 5th Dose*

*Response measured 24 hours post-dose



FACS Analysis: Activation and Proliferation Markers Demonstrate CD8+ T-cell and NK cell Engagement in 750 mg PRTX007 Cohort

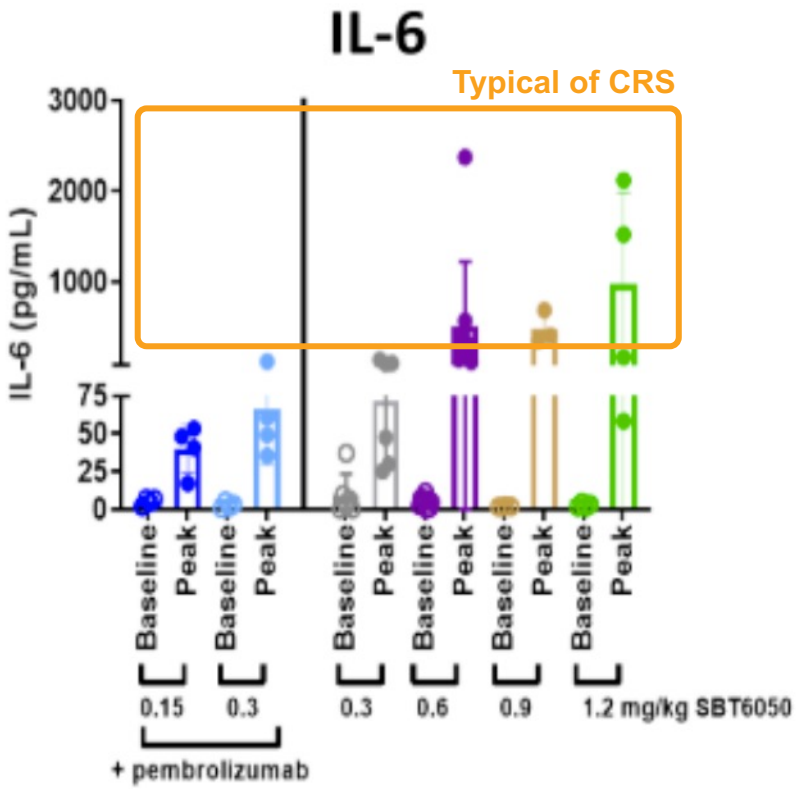


- The proportion of CD8+ T cells and NK cells expressing CD38 and Ki67 increase upon repeated administration of PRTX007
- In contrast, minimal change in activation and proliferation markers are observed for CD4+ T cells and B cells

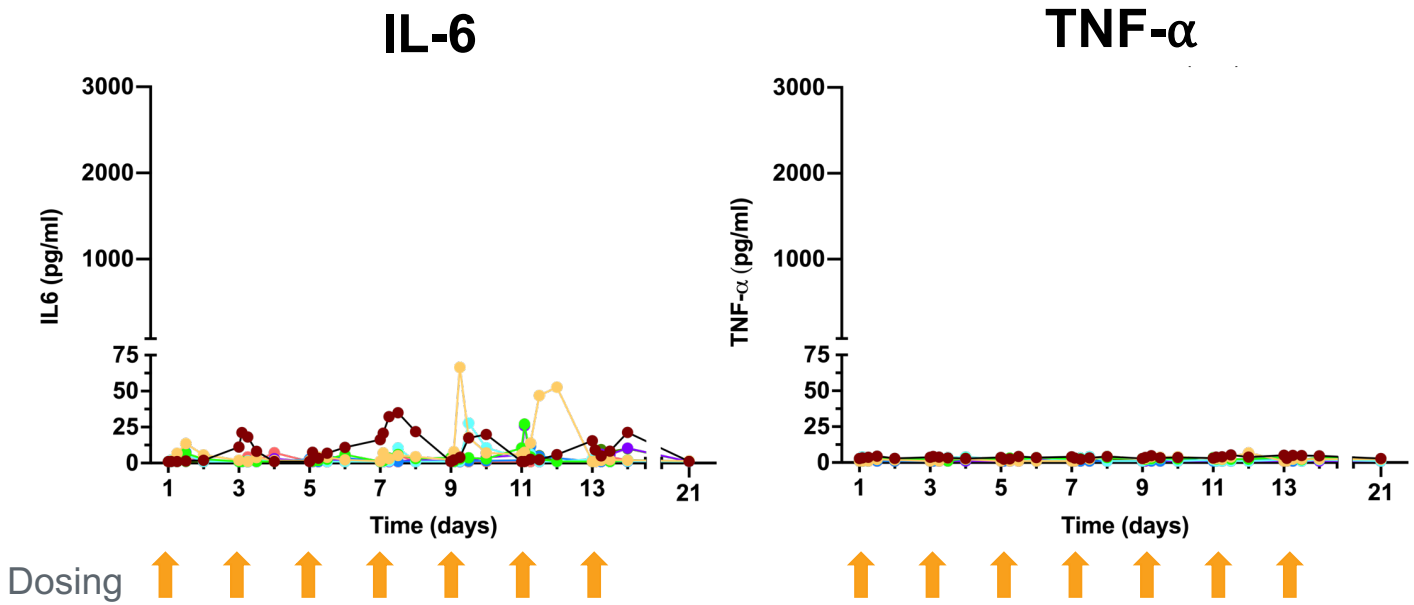
* Percent of CD8+ T-cells

PRTX007 Immune Cytokine Profile Compatible with Checkpoint Inhibitor in Combination

Silverback SBT6050 (First Dose)
(failed due to inability to combine with CPI)



PRTX007, 2 Wks Administration to Eight Healthy Volunteers
7 doses at 750 mg/dose QOD; Complete Individual Time Courses Shown Here



No evidence of signals associated with systemic toxicities like those observed with SBT6050

PRTX007 Clinical Study Summary

Kinetics of various measures of PD response

- ISGs and cytokine / chemokines clearly different
- All have reached a stable, favorable response by fourth dose

Dose response and dose selection

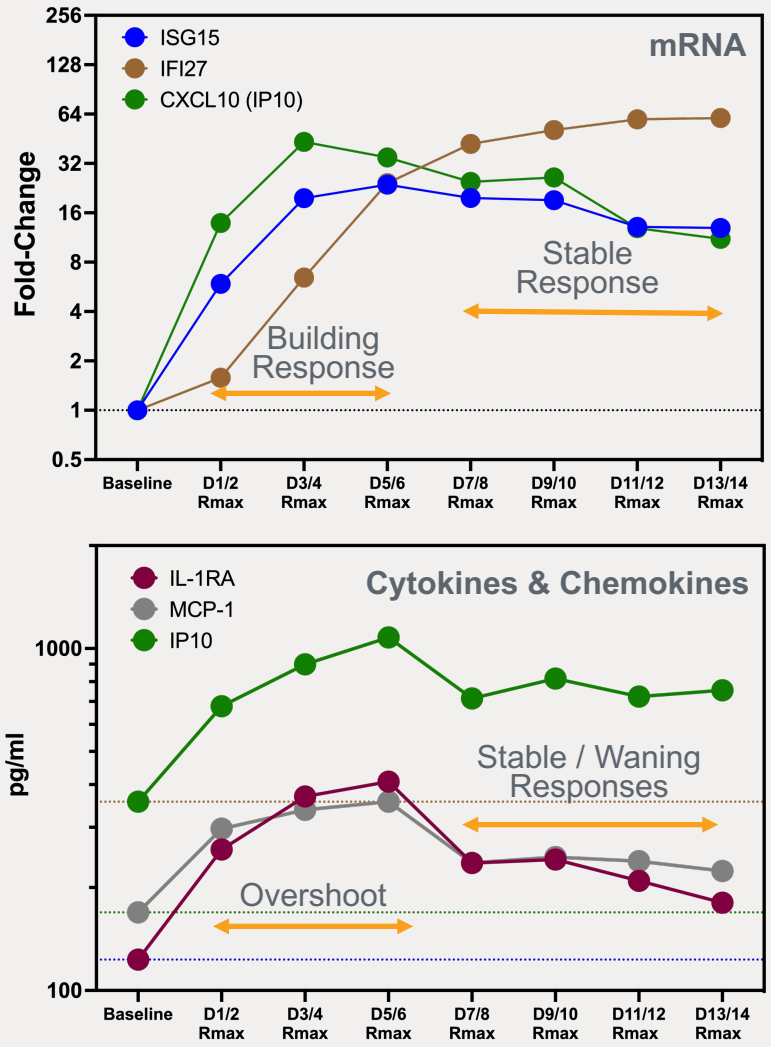
- **Gene expression**: minimal / modest increase in response at 750 mg vs 500 mg at steady-state
- **Cytokines/chemokines:** peak response at 750 mg somewhat higher than at 500 mg
- Anti-tumor effectors CD8+ T cells and NK cells activated at 750 mg

Other observations

- Nothing of concern with respect to systemic inflammation
- Responses return to or trend towards baseline within 8 days of last dose

Results consistent with moving 500 and 750 mg doses administered QOD into patient studies

Peak Response Following Each Dose



Data from 750 mg MAD Cohort