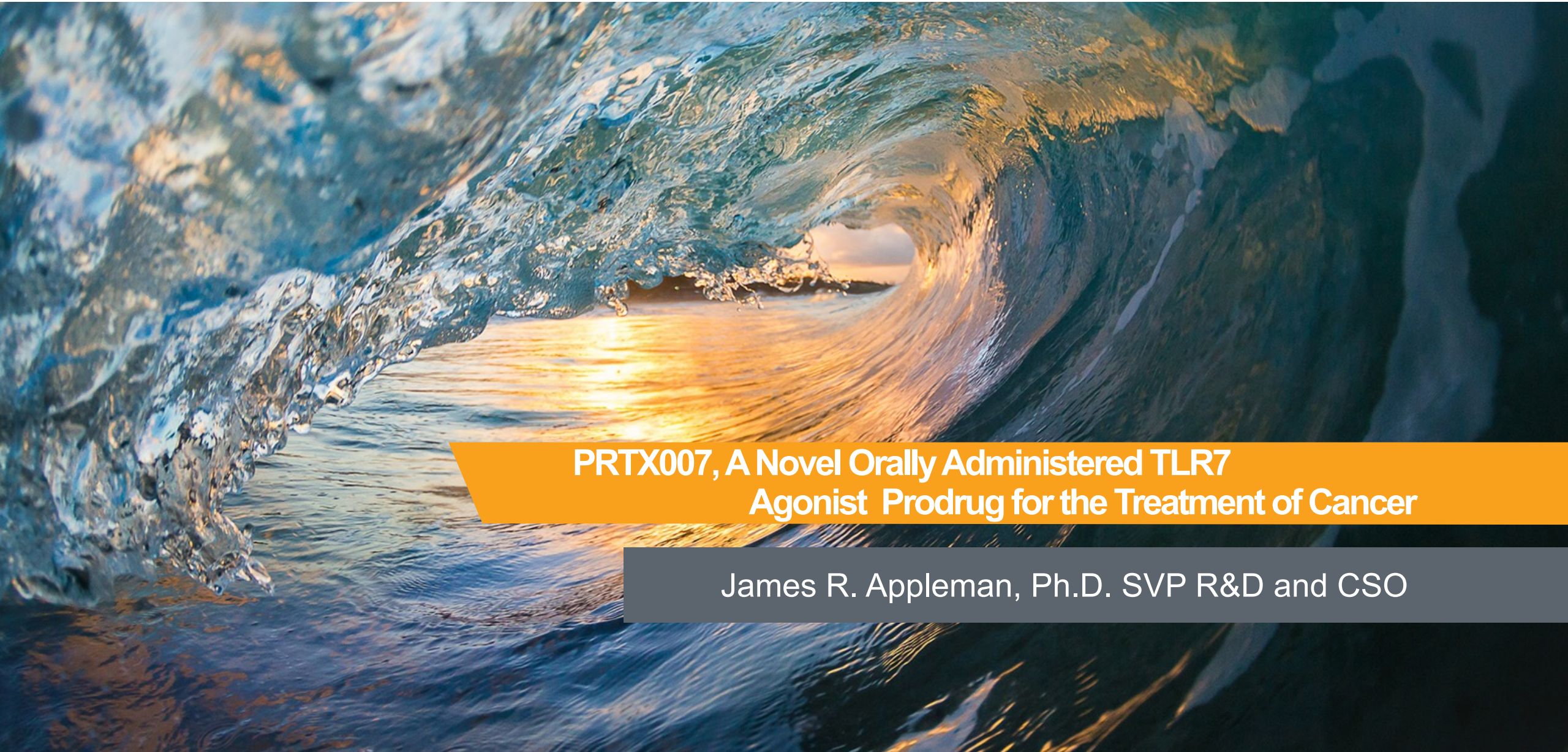
primmune Therapeutics

STING & TLR-Targeting Therapies Summit
May 25-27, 2021

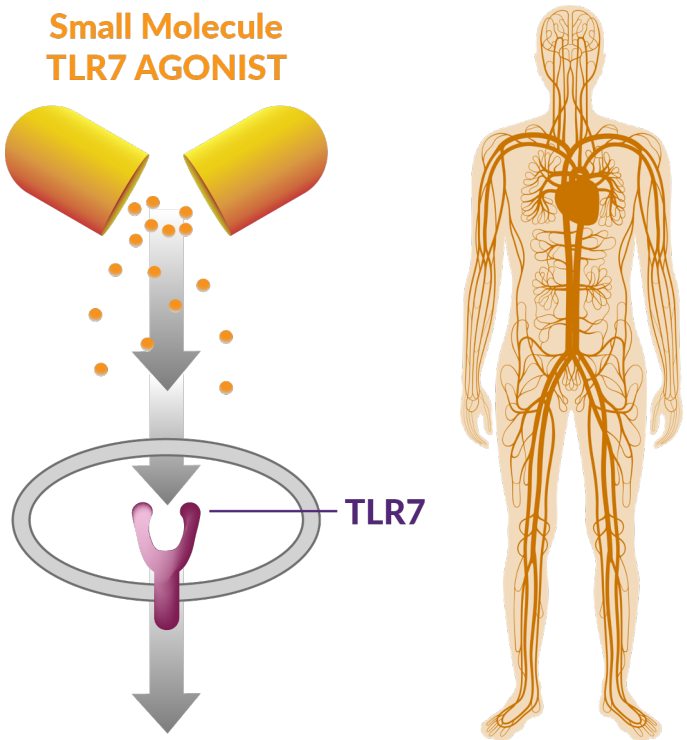


PRTX007, A Novel Orally Administered TLR7 Agonist Prodrug for the Treatment of Cancer

James R. Appleman, Ph.D. SVP R&D and CSO

Core Technology: Structurally Tuned Oral TLR7 Agonists

Maximal therapeutic benefit in cancer immunotherapy is achieved by **maintaining sustained, systemic immune pressure** involving both innate and adaptive immunity (treatment thesis)



We are therefore developing **orally administered small molecule TLR7 agonists** that precisely activate **innate immunity** to engage tumors and potentiate durable **adaptive cancer immunotherapies**

Primmune's TLR7 agonists are **differentiated** from previous small molecule agonists **by incorporation of structural elements that enable tuning** of key properties; notably:

- Relative extent of activation of IRF7 vs NFκβ pathways which mediate biosynthesis of interferons and pro-inflammatory factors, respectively
- Degree to which cellular regulation of TLR7 activation is maintained, which correlates with the ability to manage extent of immune activation by drug exposure
- Ability to maintain substained, controlled activation of innate immunity

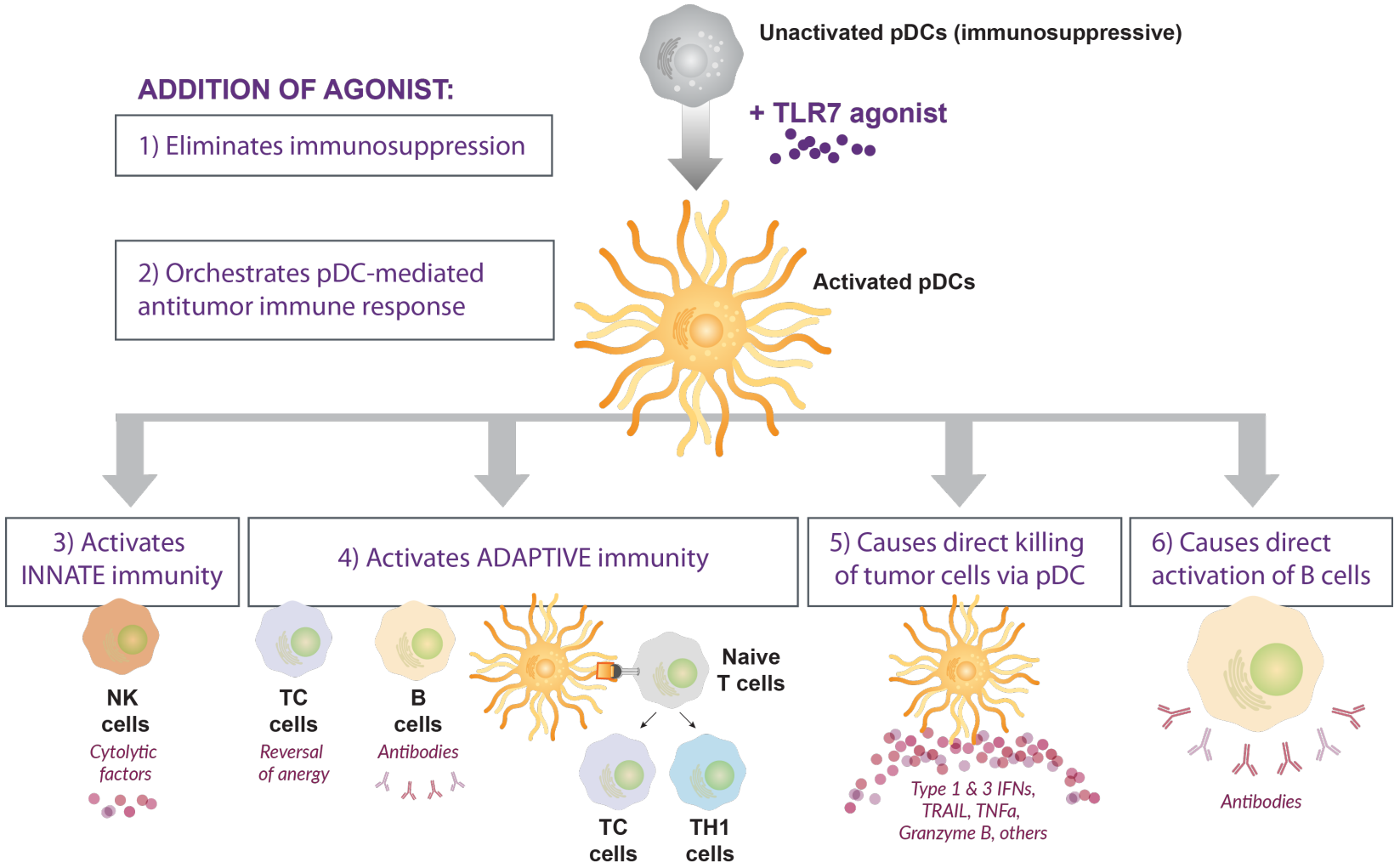
Primmune's TLR7 agonists also have **utility in the treatment of acute and chronic viral infections**

Activation of Plasmacytoid Dendritic Cells (pDCs) by TLR7 Agonists Elicits Effective Anti-tumor Responses

TLR7 agonists engage a variety of antitumor responses, most of which are initiated by activation of plasmacytoid dendritic cells (pDCs)

pDCs orchestrate the synergistic antitumor responses elicited by both innate and adaptive arms of the immune system

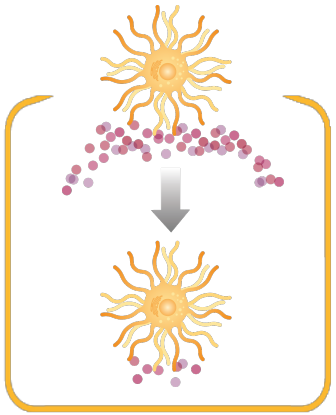
Futhermore, inactivated pDCs in the tumor microenvironment are pro-tumorogenic, whereas activated pDCs elicit a plethora of antitumoral activities



PRTX007 Target Product Profile: Oncology

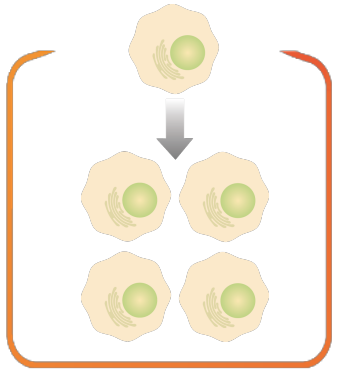
PROPERTY	ENABLEMENT
Complements immune checkpoint inhibitors and other adaptive immunity approaches	▪ TLR7 agonists activate plasmacytoid dendritic cells (“pDCs”), our primary target cell, which coordinates innate and adaptive immunity ▪ Activation of pDCs further results in proliferation and activation of natural killer cells and CD8+ cells which are important anti-cancer effector cells
Treatment of metastatic & inaccessible disease	▪ Systemic distribution of drug enables activation of pDCs systemically to treat cancer, including metastases throughout the body; does not rely on abscopal effect
Safe and well-tolerated at efficacious doses	▪ Specificity for TLR7 avoids excessive inflammation associated with other TLRs (e.g. TLR8) ▪ **Tunable elements within agonist structure allow selection of (i) relative extent of activation of IRF7 vs NFκβ pathways, (ii) steepness of post-threshold dose response and (iii) duration of exposure**
Sustained immune pressure	▪ Every other day dosing (“QOD” schedule) with an agonist with short PK $t_{1/2}$ avoids pDC immune exhaustion (“anergy”) while avoiding overstimulatation of B-cells (QD dosing regimens have led to anergy and tolerability issues). ▪ Other dosing schedules (e.g. weekly cycles of 3xQD, 4-day drug holiday) may offer greater “top end” immune induction ▪ Oral administration conveniently enables QOD or other desired dosing schedule
Long-term therapy	▪ Safety and tolerability enable dosing for up to two years for long-term immune surveillance and to match the PD-(L)1 ICPI dosing regimen

Bane of Systemic Small Molecule TLR7 Agonists (Historical)



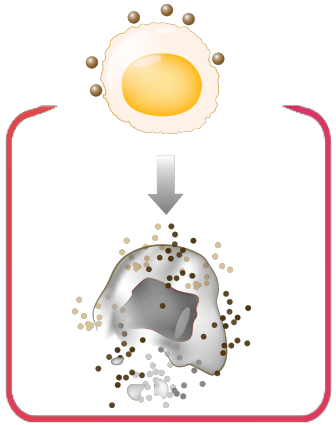
Loss of pDC Activiity

Inability to maintain immune pressure



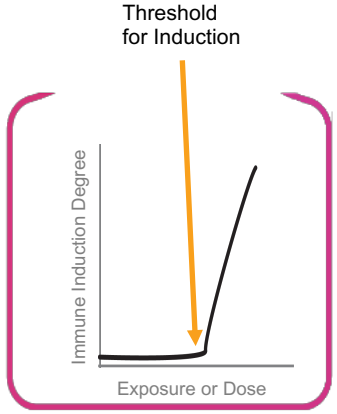
Too Much of a Good Thing

Excessive B cell proliferation



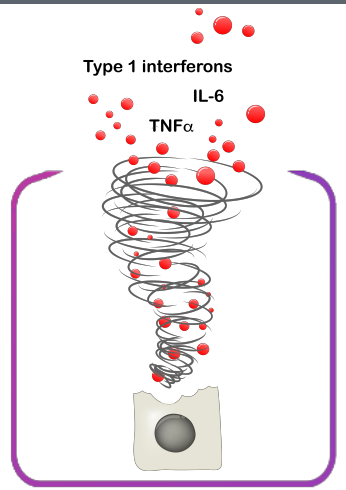
Off-target Toxicities

Off-target toxicities of agonist or metabolites



Unmanageable Dose Response

Narrow or no therapeutic index



Cytokine Storm

Excessive systemic inflammation

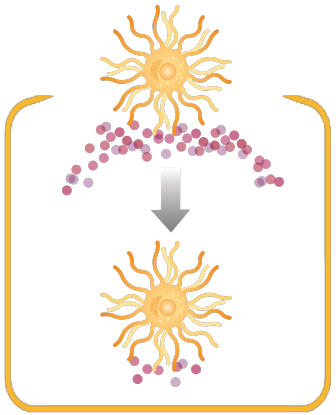
Bad Models

Mice ≠ Men

Not Understanding Differentiation

Equating TLR7 agonists & MOA with “oral interferon”

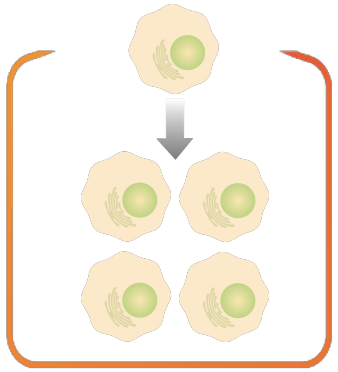
Bane of Systemic Small Molecule TLR7 Agonists (Historical)



Loss of pDC Activiity

Inability to maintain immune pressure

Most / All
(QD dosing)



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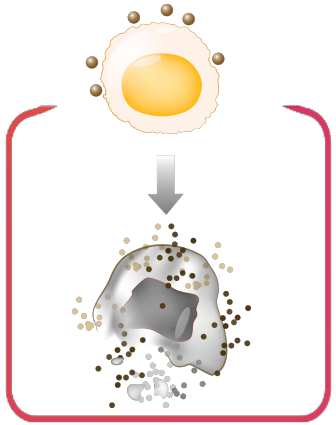
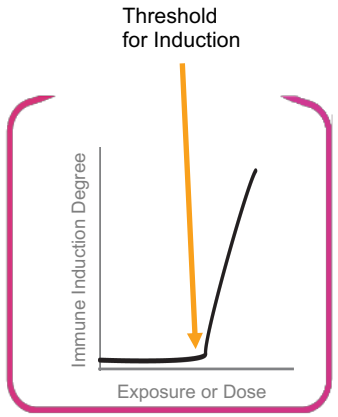


Off-target Toxicities

Off-target toxicities of agonist or metabolites

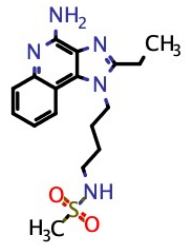
Imiquimod
Resiquimod
Bropirimine

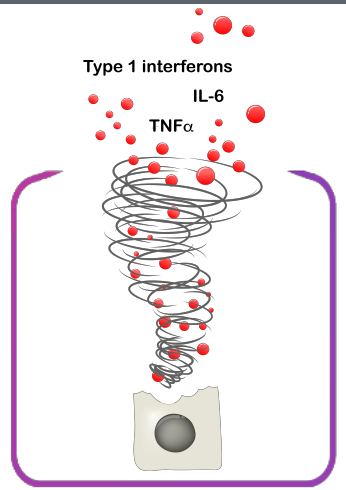


Unmanageable Dose Response

Narrow or no therapeutic index

3M - 852A
(PF-4878691)
and others





Cytokine Storm

Excessive systemic inflammation

Many
(tolerability limitation)

Bad Models

Mice
≠ Men

Divergent TLR7-mediated pharmacology

Not Understanding Differentiation

Equating TLR7 agonists & MOA with "oral interferon"

Coordinated immune response vs "going nuclear"

Competing Approaches to Increase Therapeutic Index of Agonist Present New Challenges

Direct administration into tumor (drug substance or product may include features limiting distribution of active agonist)

Difficult to avoid systemic activity

Reliance on abscopal effect for distal tumors

Oral Administration

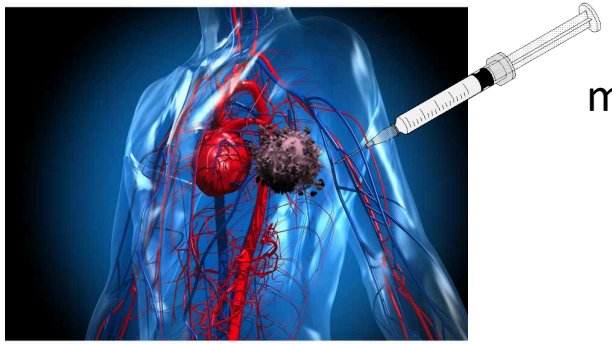
Limited applicability

Liver Retention

Agonist includes tumor-homing features (e.g. agonist coupled to Ab)

New toxicities due to drug antigenicity or organ deposition

Lack of uniformity in tumor expression of targeted protein

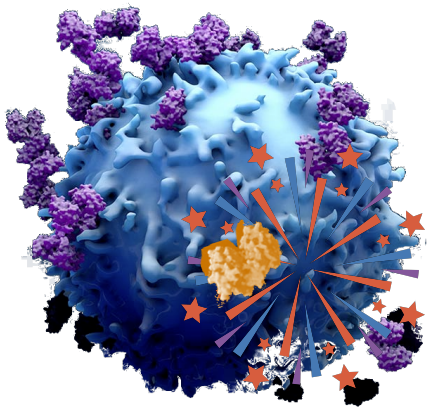


Drug is “unmasked” in tumor microenvironment / cellular target

Technical challenges

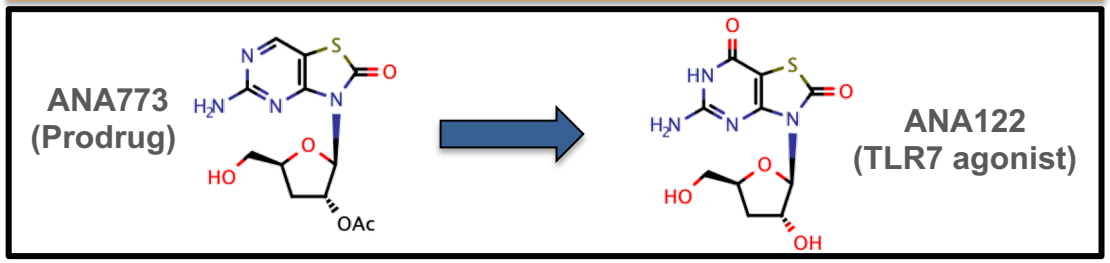
Tumor retention

Applicability to micrometastases

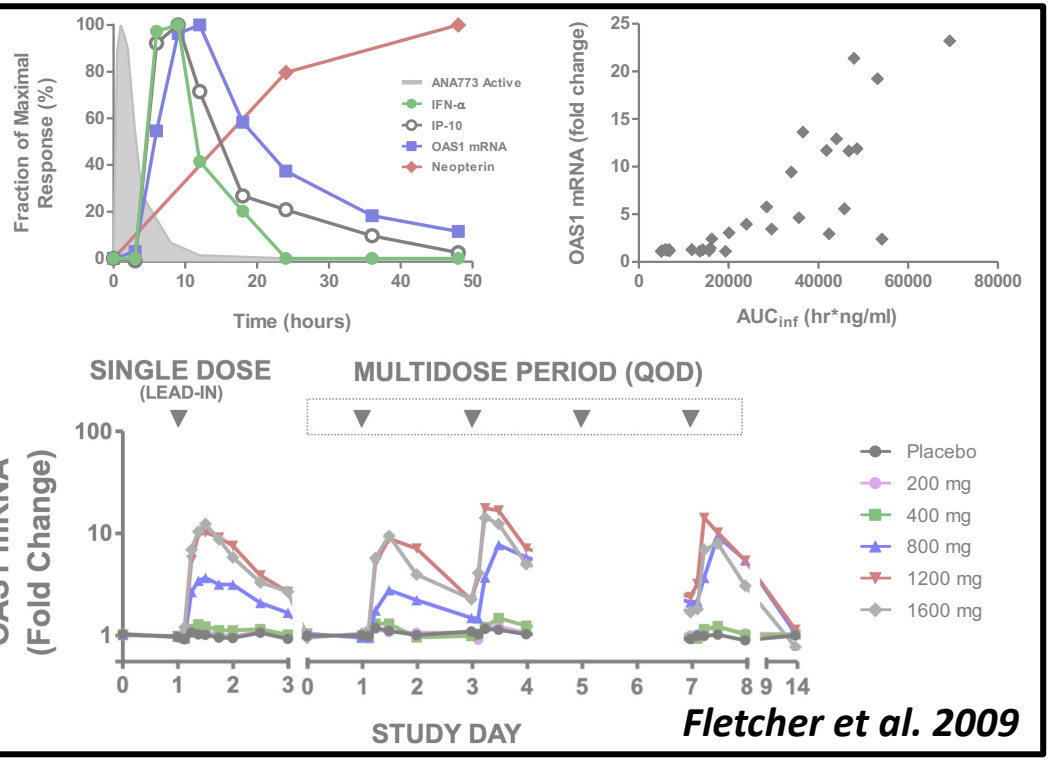


The Viability of Primmune's TPP was Demonstrated in Clinical Studies with ANA773 by Anadys Pharmaceuticals over a Decade Ago

ORALLY ADMINISTERED SYSTEMICALLY DISTRIBUTED

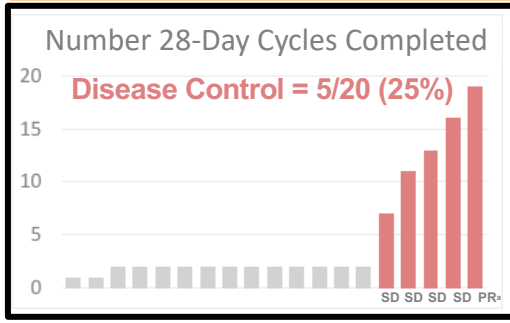


PK/PD IN HEALTHY VOLUNTEERS



Fletcher et al. 2009

MONOTHERAPY ACTIVITY IN PHASE 1 CANCER STUDY

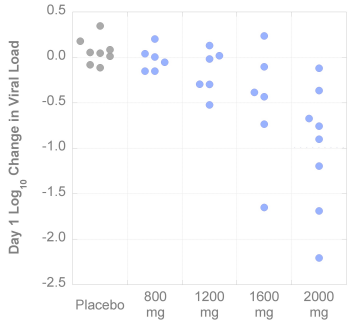


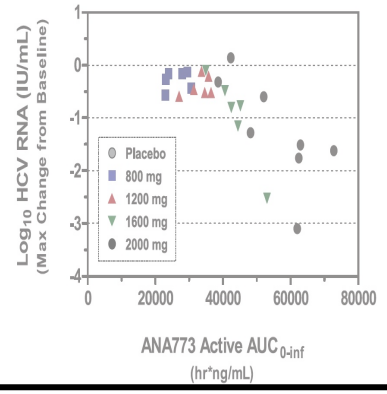
Uveal Melanoma (7 cycles)
Uveal Melanoma (11 cycles)
Stage IV Adenocystic Carcinoma (13 cycles)
Prostatic Adenocarcinoma (16 cycles)
Metastatic Melanoma (19 cycles)

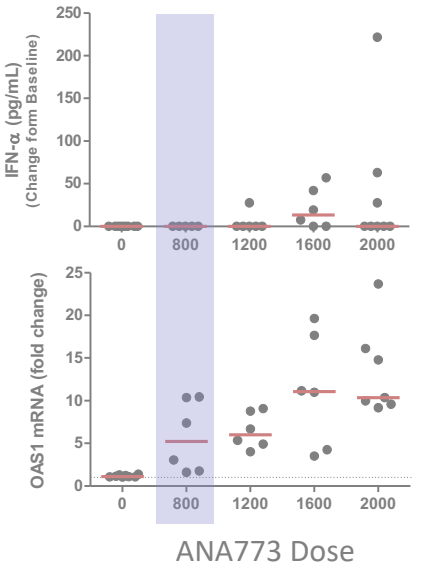
Daniels et al. 2011

MONOTHERAPY ACTIVITY IN CHRONIC HEPATITIS C

Patients with AE (%)*	Total (n=34)	800 mg (n = 6)	1200 mg (n = 6)	1600 mg (n= 6)	2000 mg (n = 8)*	Placebo (n = 8)
Headache	53	33	33	67	75	55
Fatigue	41	50	33	67	38	25
Myalgia	38	33	17	50	50	38
Abdominal pain	32	17	17	50	13	63
Dizziness	24	50	17	50	0	13
Back pain	21	0	17	50	13	25
Constipation	18	0	0	50	0	38
Nausea	18	0	0	33	50	0
Dyspepsia	15	0	0	33	25	13
Malaise	15	17	0	33	25	0
Chills	12	0	17	33	13	0
Diarrhoea	12	17	0	17	0	25
Pain in extremity	12	17	0	17	13	13
Pyrexia	12	0	0	0	38	13

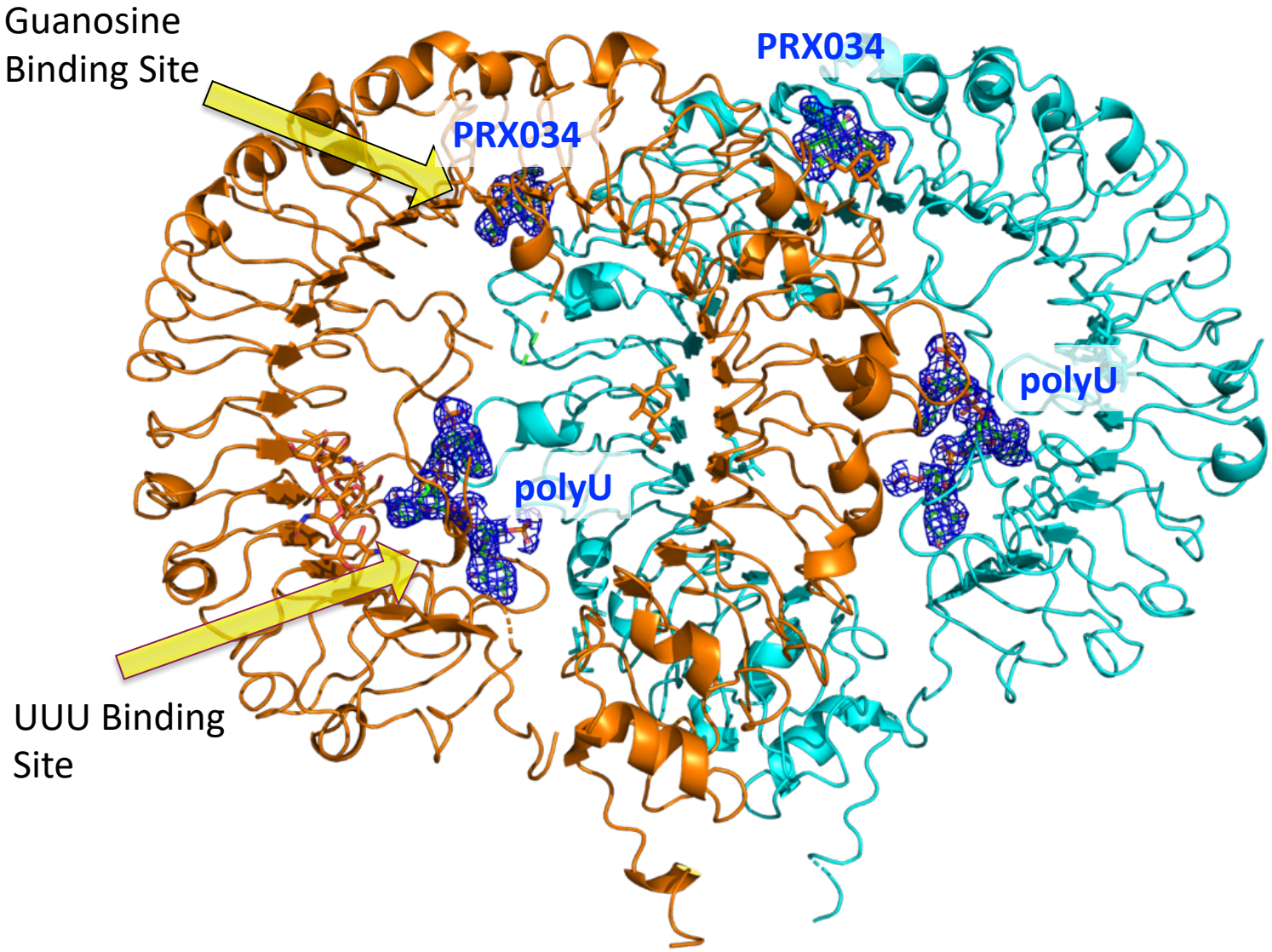


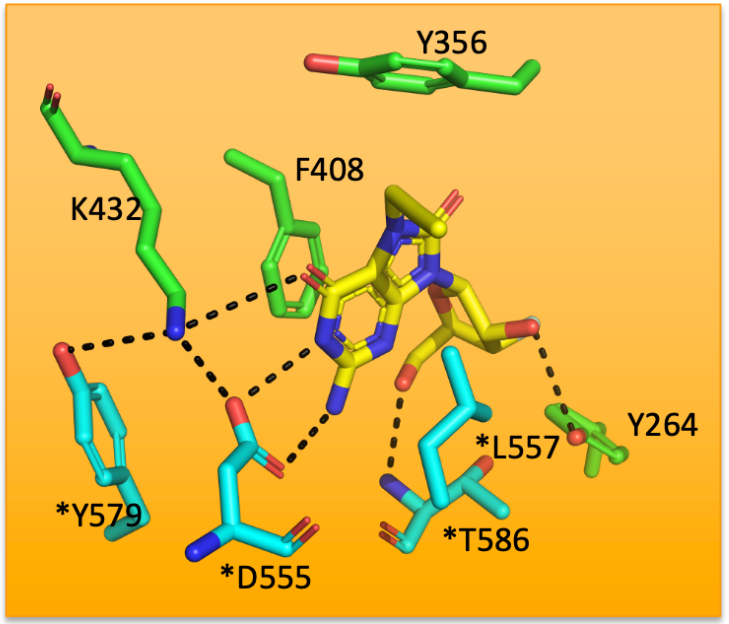


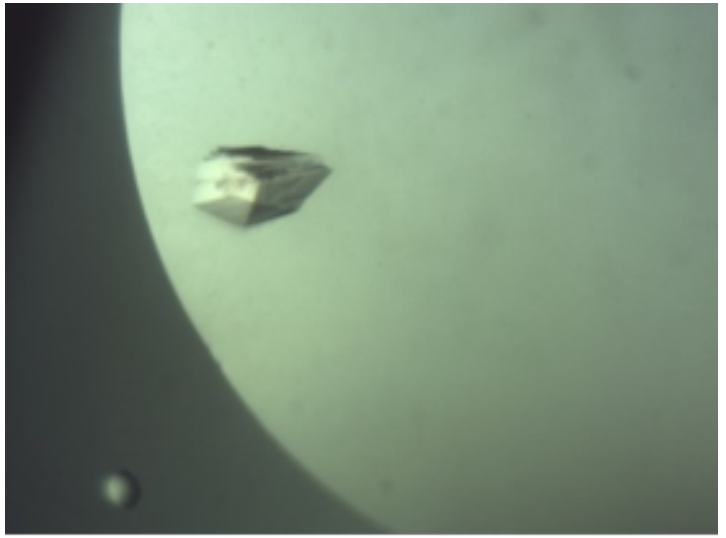


Bergmann et al. 2011

Primmune's TLR7 Agonists Bind to Guanosine Binding Site

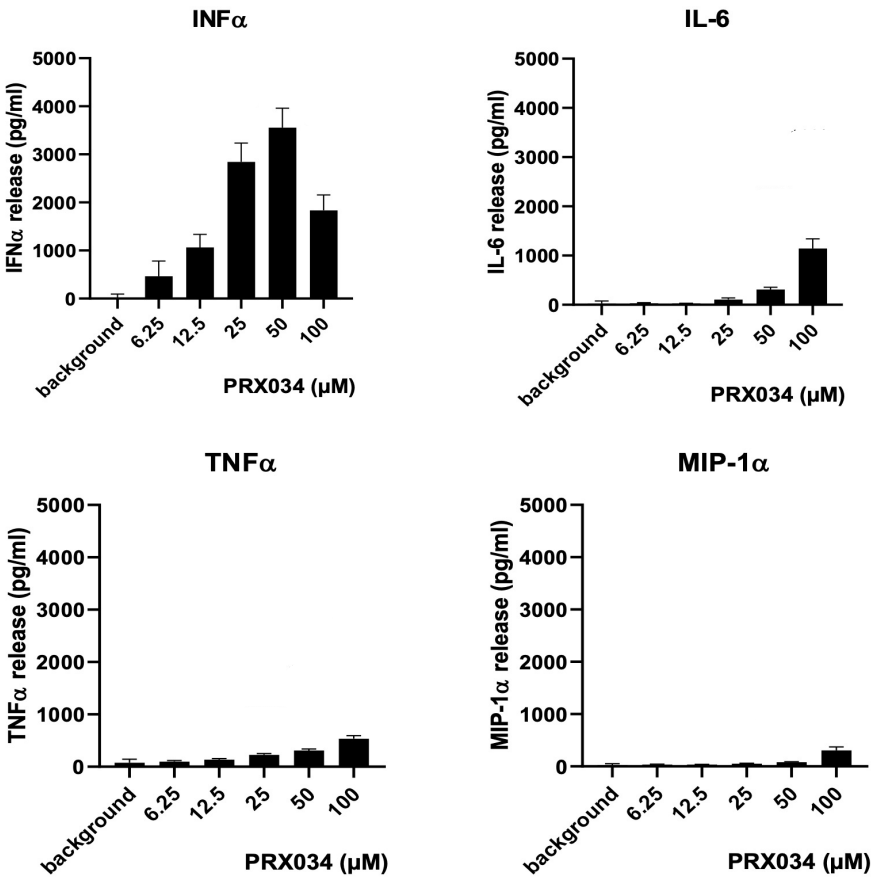




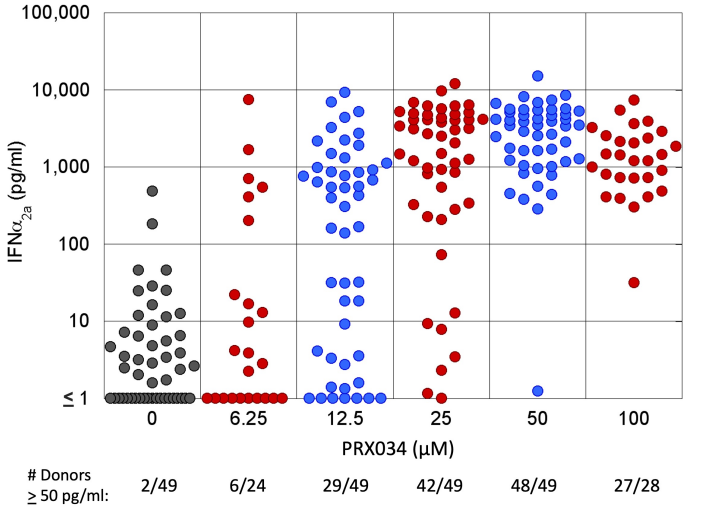


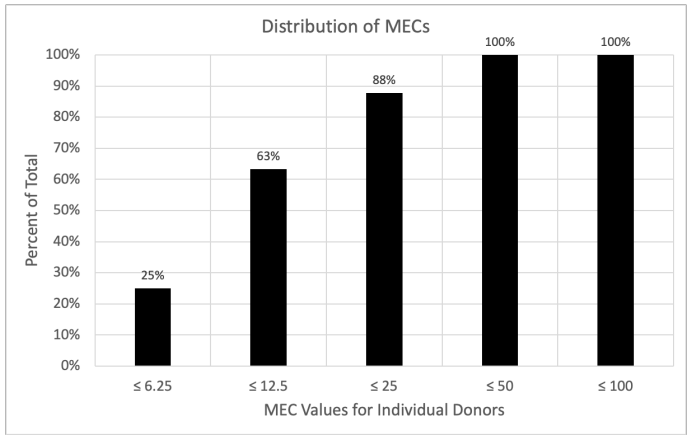
PRX034 in Human PBMCs: Preferential Induction of IFNs

IFN, Cytokine & Chemokine "Fingerprint"



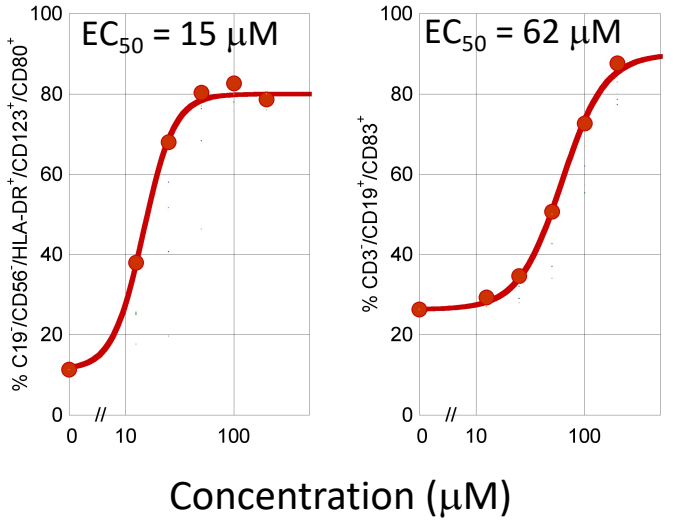
Individual Donor Response



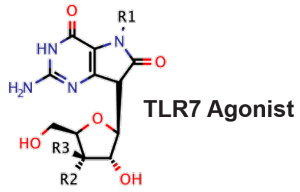


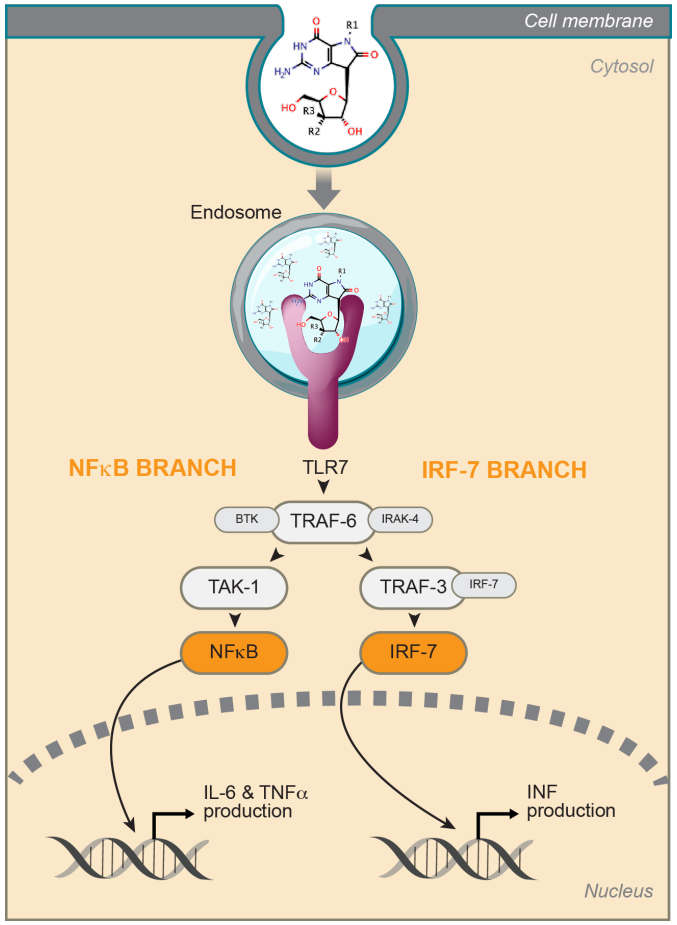
MEC = lowest concentration of agonist which increases IFN by 50 pg/ml

Cellular Activation by FACS Analysis



Differentially Tuned TLR7 Agonists (hPBMC Assay)



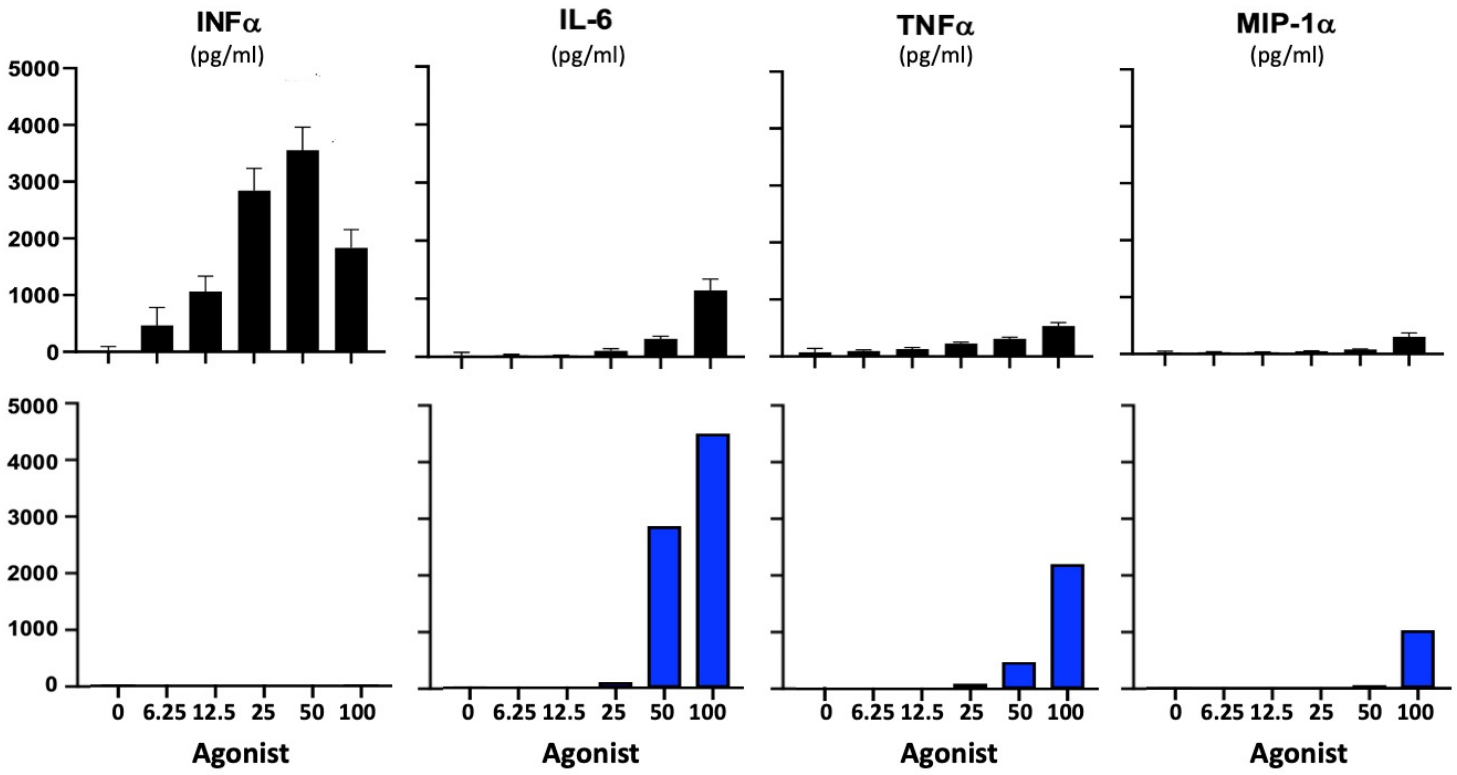


Two TLR7-Specific Agonists Elicit Distinct Cellular Pharmacology

Agonist

PRX034
Reduced NFκβ Activation

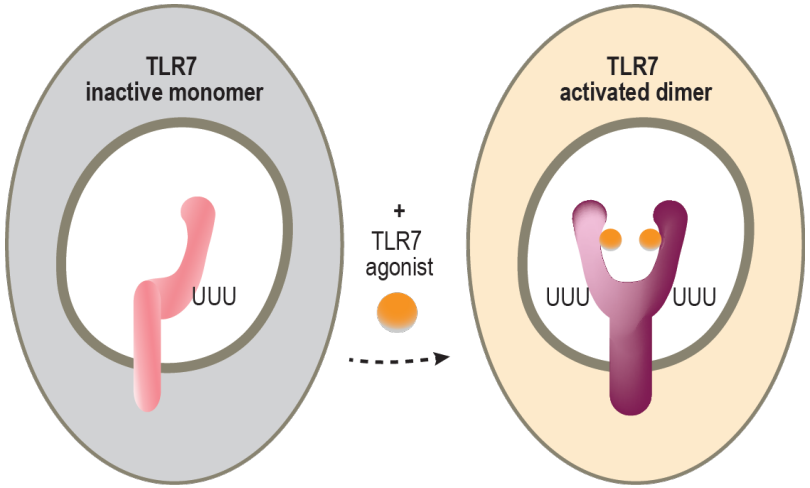
PRX009
Maximized NFκβ Activation



Additional Tuneable Properties Impacting Therapeutic Utility

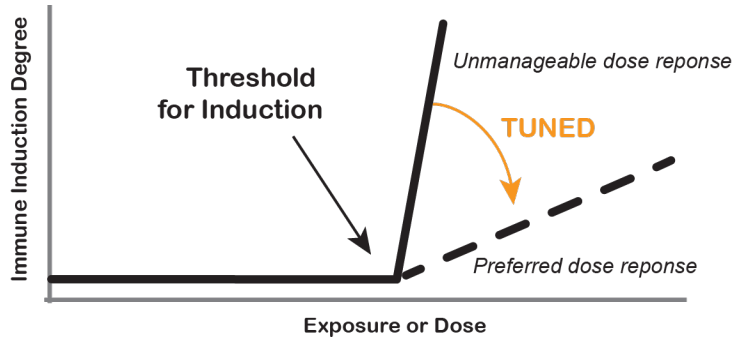
Tunable Property

Induction of TLR7 dimerization by TLR7 agonist as measured by biophysical techniques **requires presence of polyU**

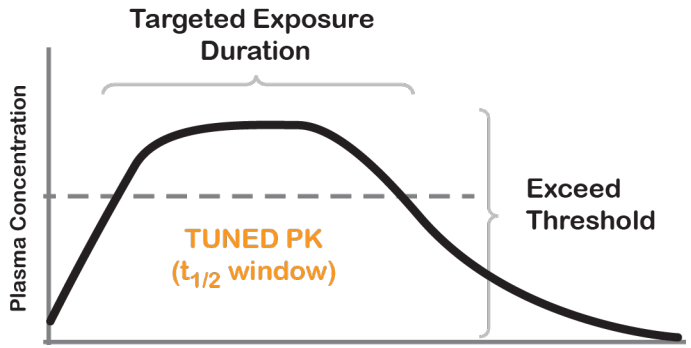


Treatment Benefit

Preferred dose response profile; degree of immune induction is responsive to dose



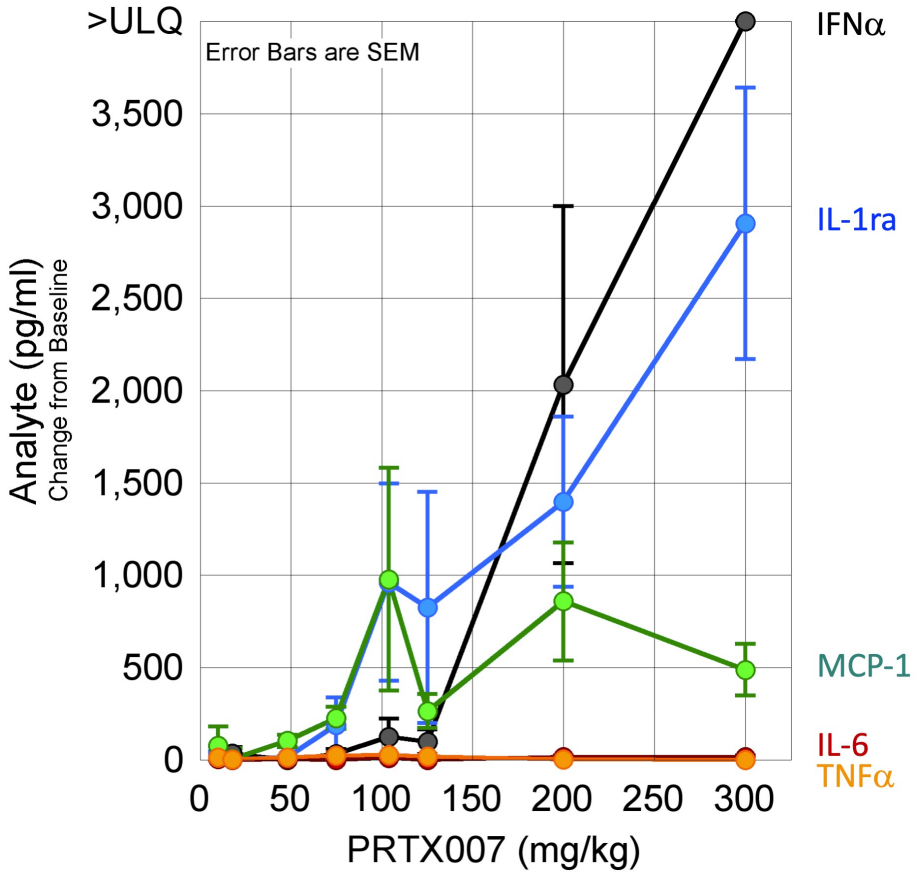
Controlled “time over threshold” window for plasma level of TLR7 agonist



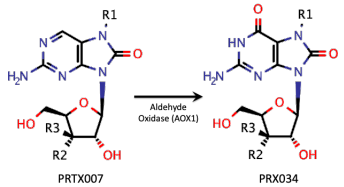
Ability to dose frequently (e.g. QOD) and indefinitely while achieving well-tolerated, therapeutically relevant degree of immune induction

Profile Maintained in Repeat-Dose Cynomolgus Monkey Study

First-Dose Response



Note: The TLR7 agonist PRX034 is efficiently delivered into systemic circulation by oral administration of PRTX007



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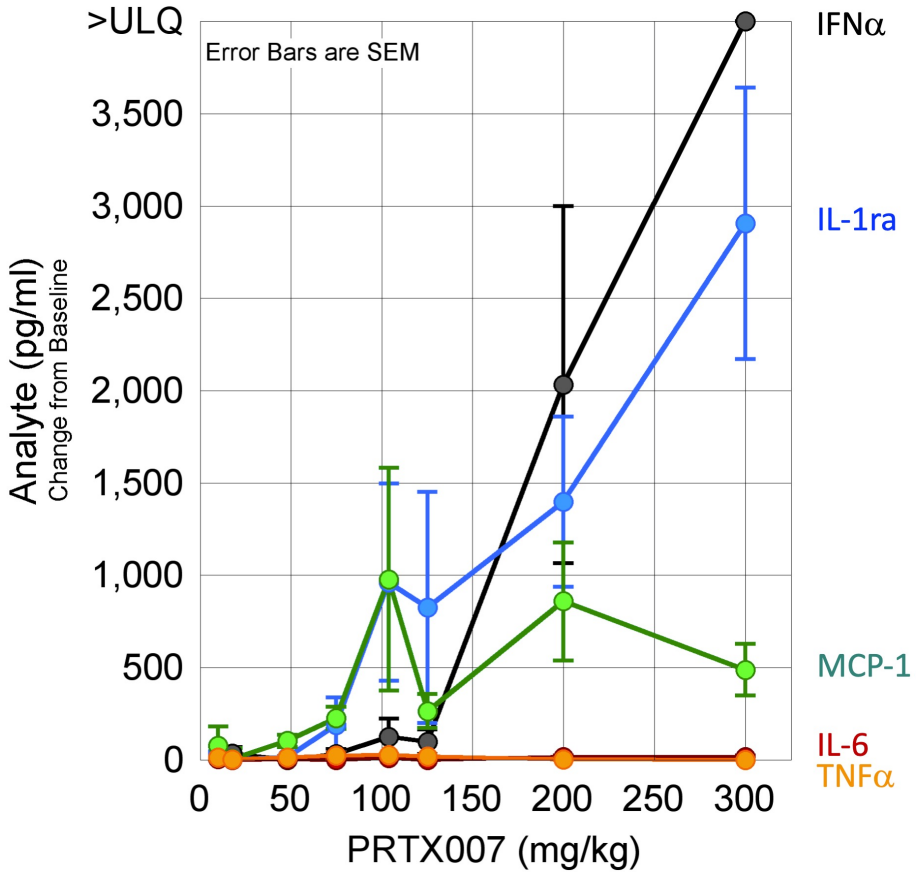

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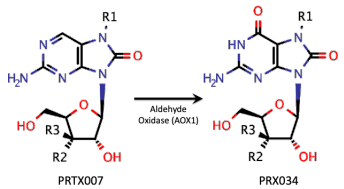
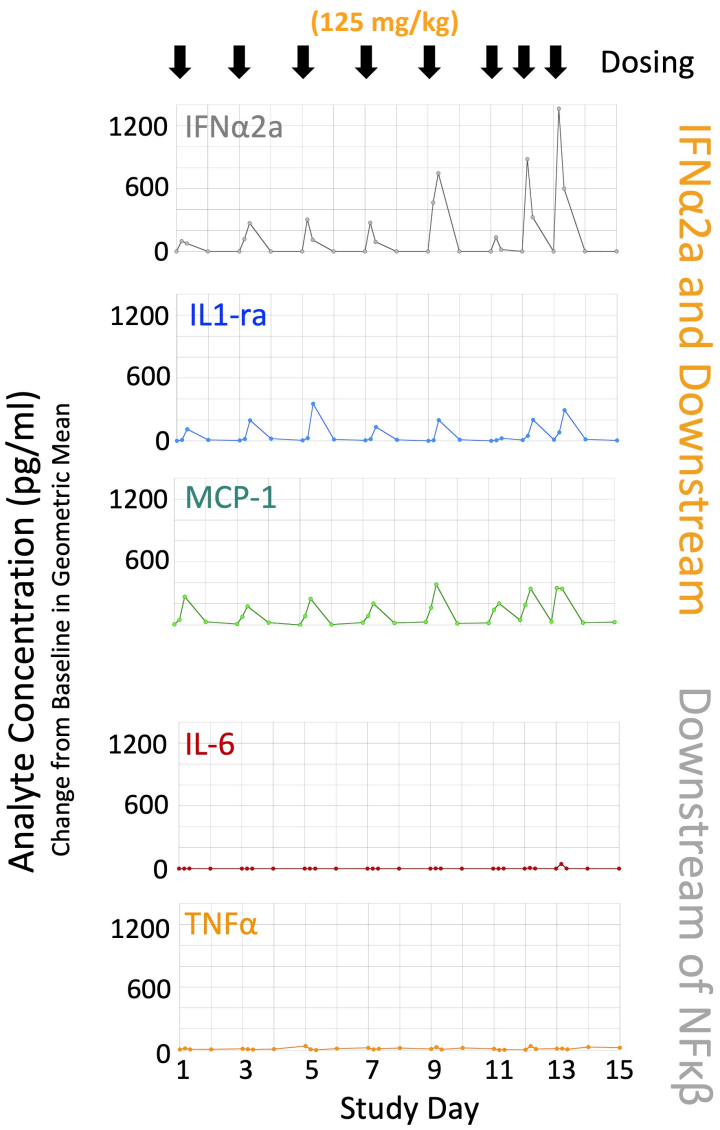
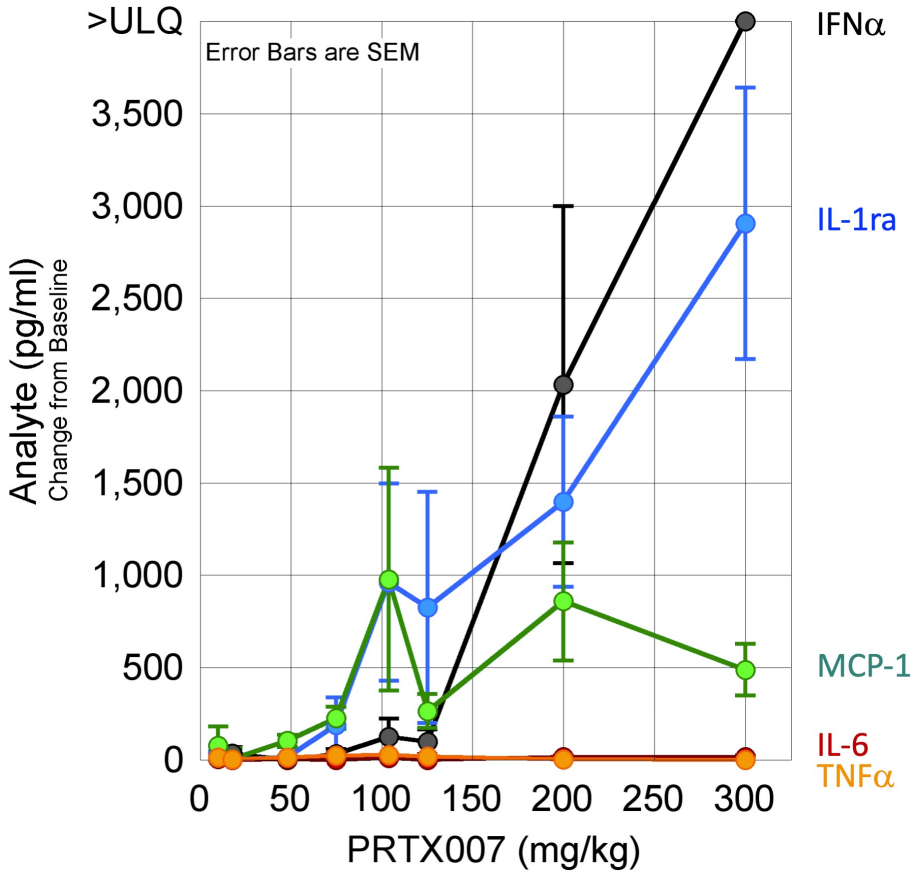


Repeate Dose Response



Profile Maintained in Repeat-Dose Cynomolgus Monkey Study

First-Dose Response



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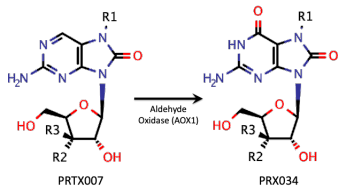
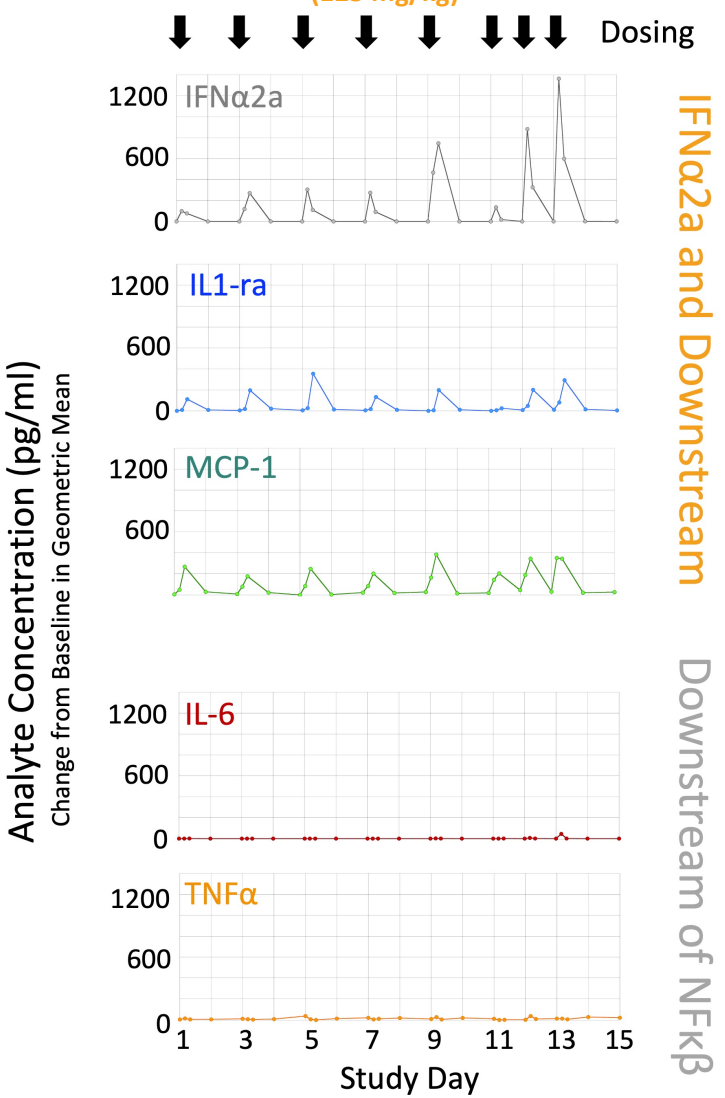


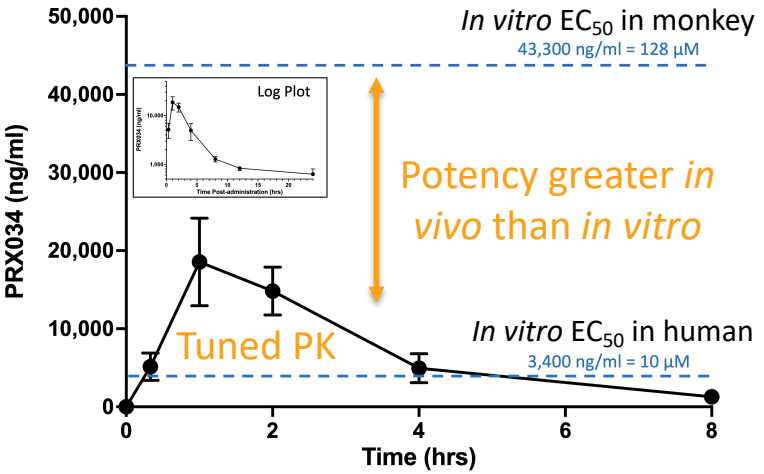
Repeate Dose Response

(125 mg/kg)



First Dose PK (125 mg/kg)

In vitro assays underestimate *in vivo* potency



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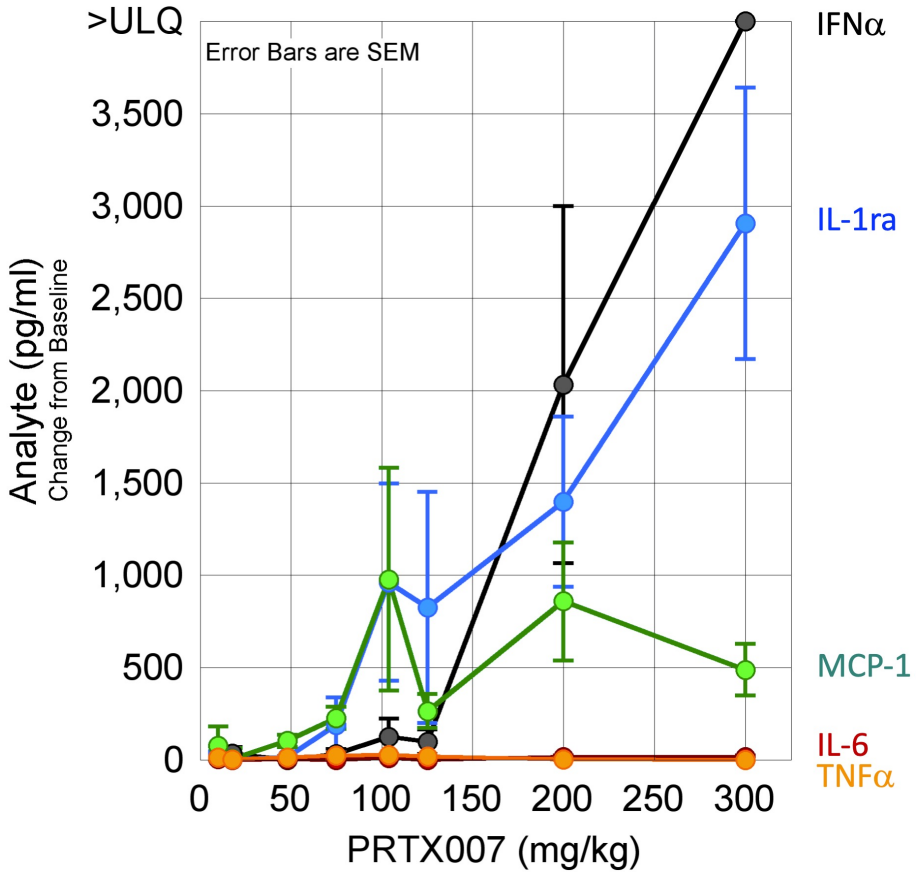
First-Dose Response



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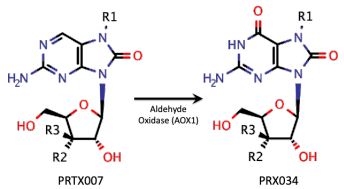
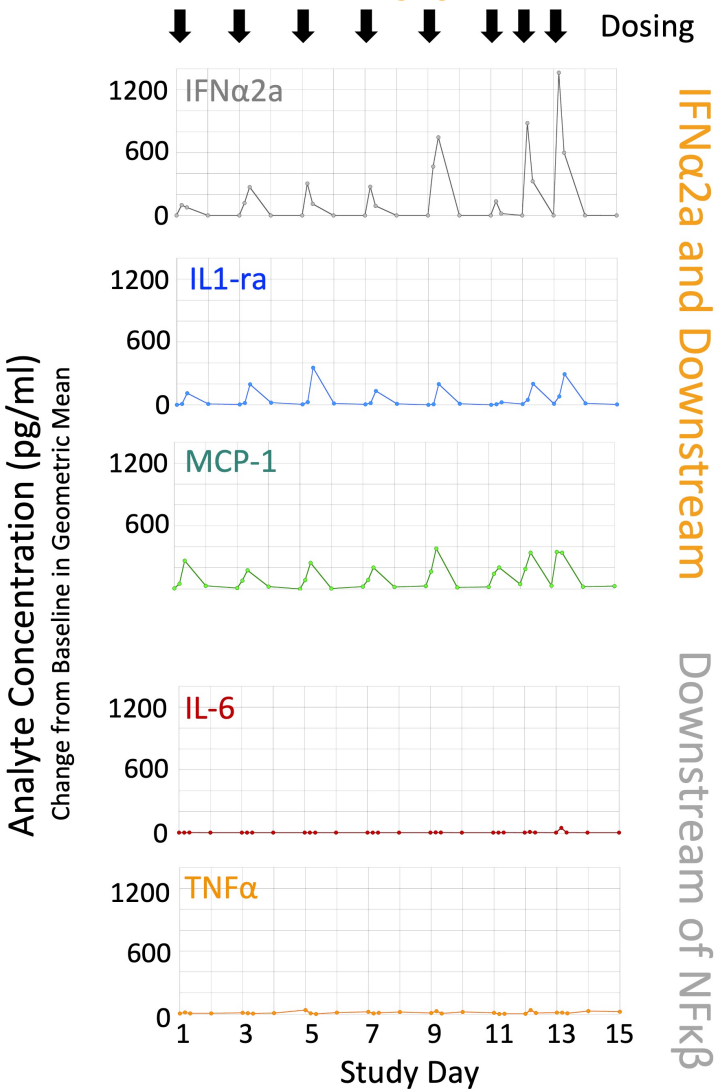


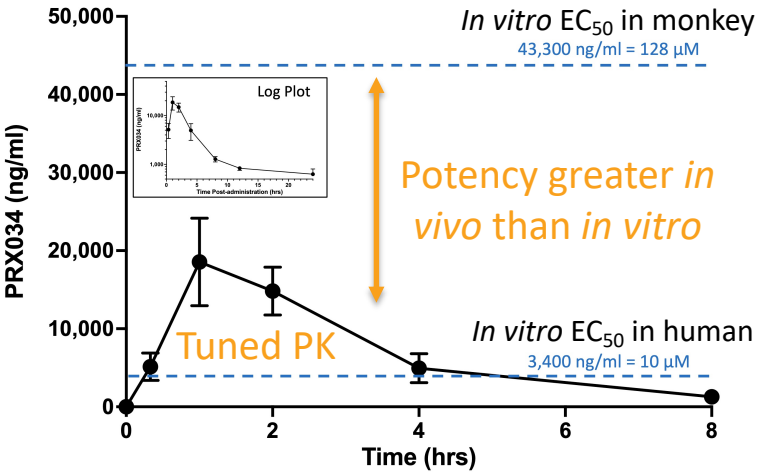
Repeate Dose Response

(125 mg/kg)

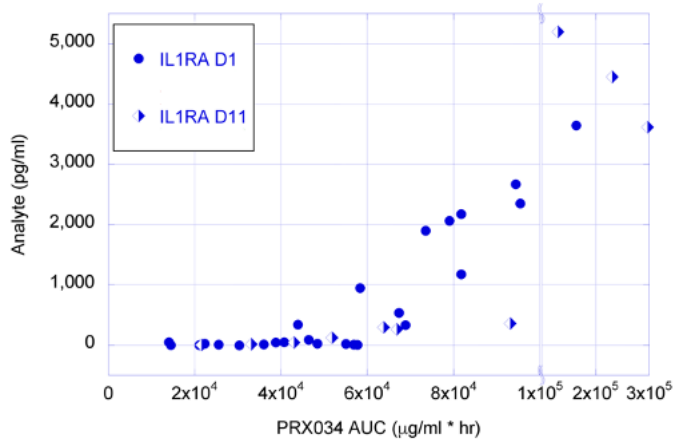


First Dose PK (125 mg/kg)

In vitro assays underestimate *in vivo* potency



D1/D11 PK/PD Maintained



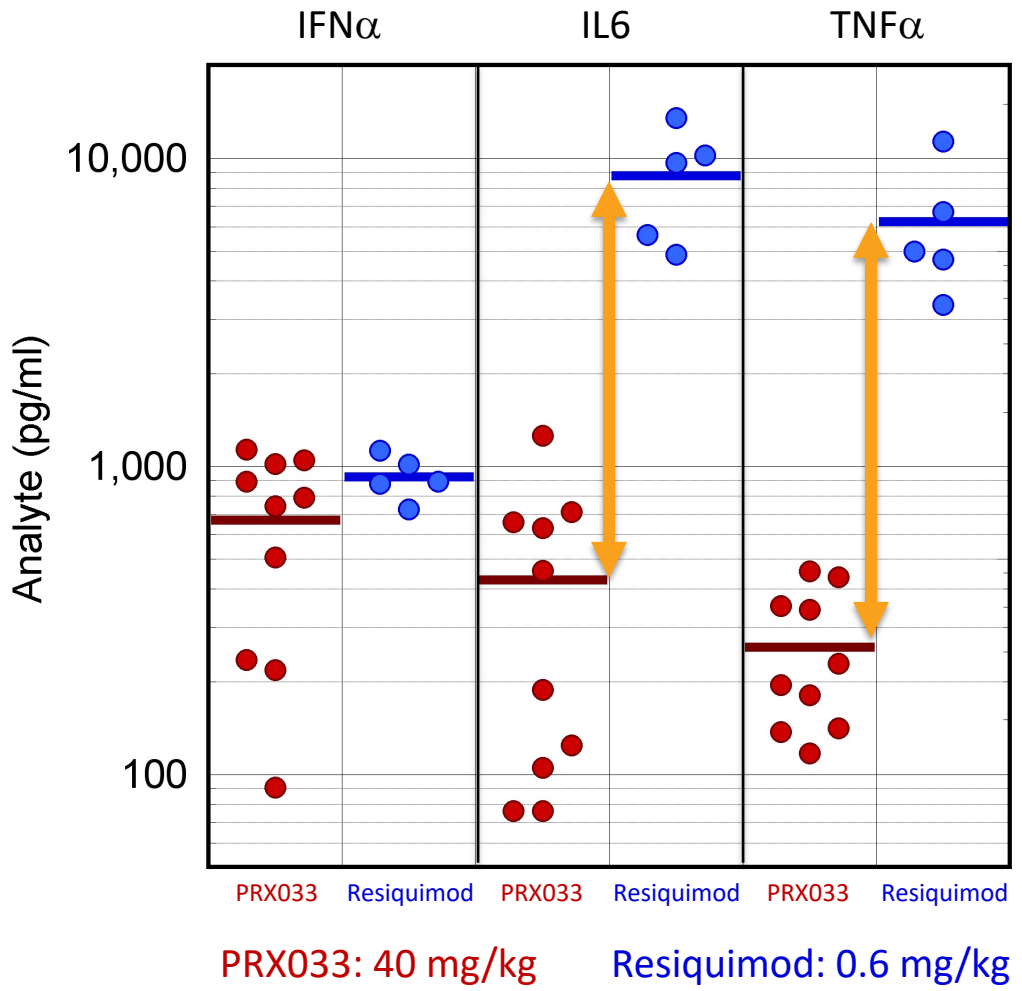
In Conclusion

- Primmune has discovered a series of proprietary TLR7 agonists and prodrugs that incorporate molecular features enabling tuning of pharmacology to optimize clinical utility
- PRTX007 is the first of these molecules selected for clinical investigation
- This prodrug and its corresponding agonist, PRX034, were specifically designed for chronic use in combination with immune checkpoint inhibitors
    - Minimal proinflammatory potential
    - Systemic distribution and activation of target cells
    - Frequent (QOD) dosing to maintain immune pressure
  - Some of these features make PRTX007 ideal for treatment of early-stage SARS-CoV-2 infection
- All regulatory requirements for clinical testing of PRTX007 on a QOD dosing schedule have been met

Backup

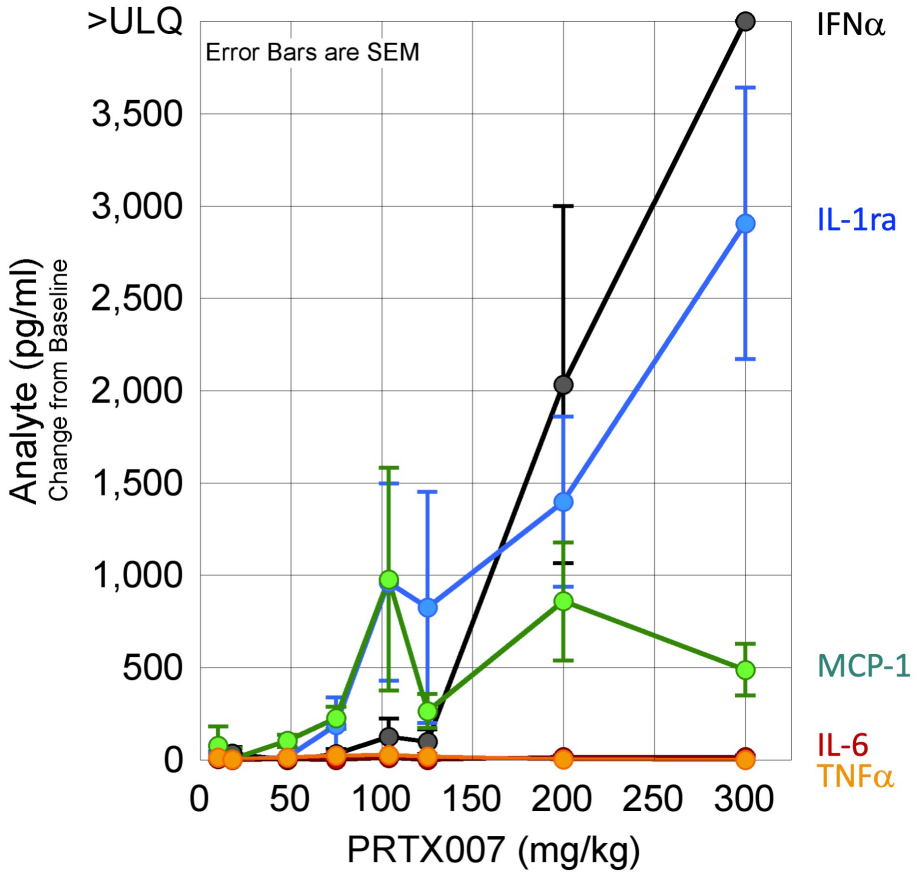
Treatment with resiquimod (R848) is fundamentally more inflammatory in mice than IFN-tuned Primmune TLR7 agonists (PRX033 as exemplar)

- Study outline
  - A single dose of either PRX033 (40 mg/kg) or resiquimod (0.6 mg/kg) was administered to C57BL/6 mice by tail vein injection
  - PK and PD samples were taken at various time points
  - Concentrations of selected analytes at 1 hr post-administration (analyte peak) are shown at right
- Both drugs induce significant IFNα production
- Resiquimod, which is presumed to act exclusively through TLR7 in mice, also induces substantial IL6 and TNFα
- These results demonstrate that Primmune's TLR7 agonists elicit distinct pharmacologic profiles



Profile Maintained in Repeat-Dose Cynomolgus Monkey Study

First-Dose Response



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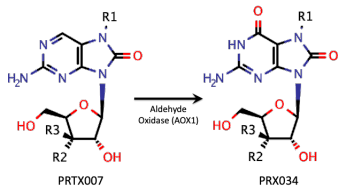
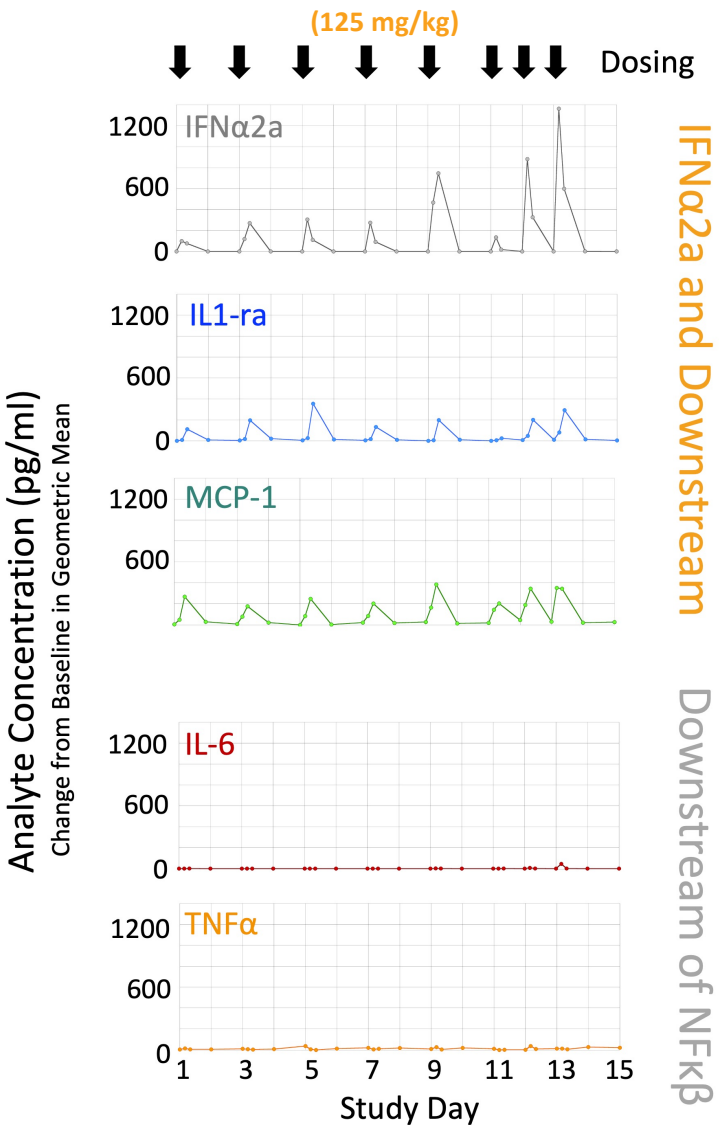
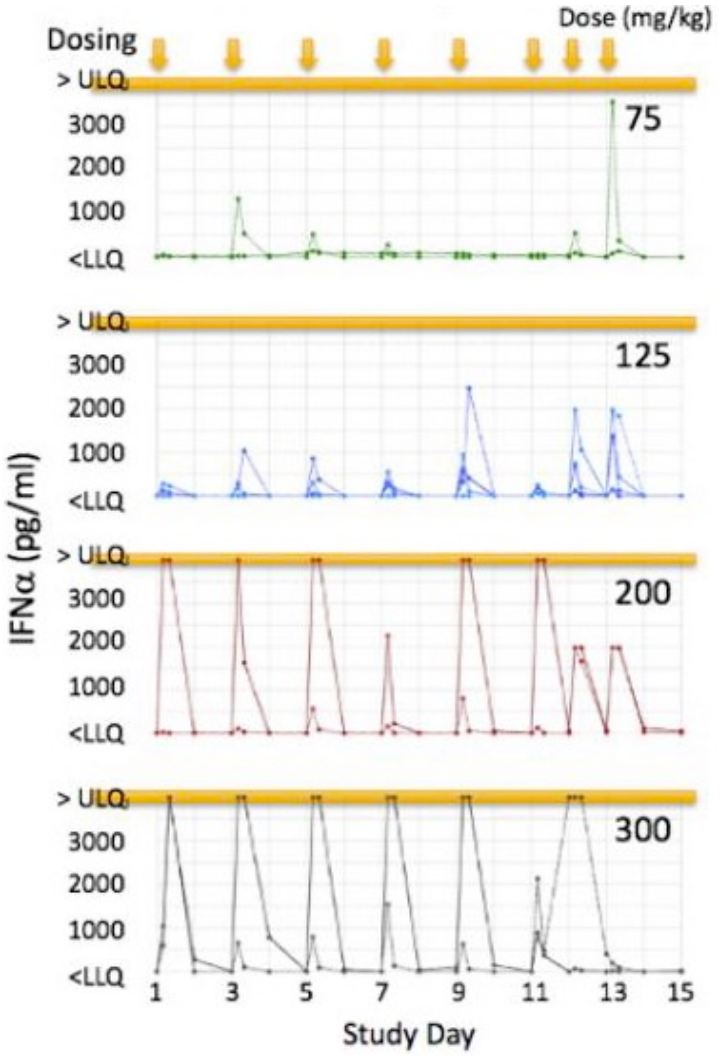


Repeate Dose Response



IFN in Individual Animals



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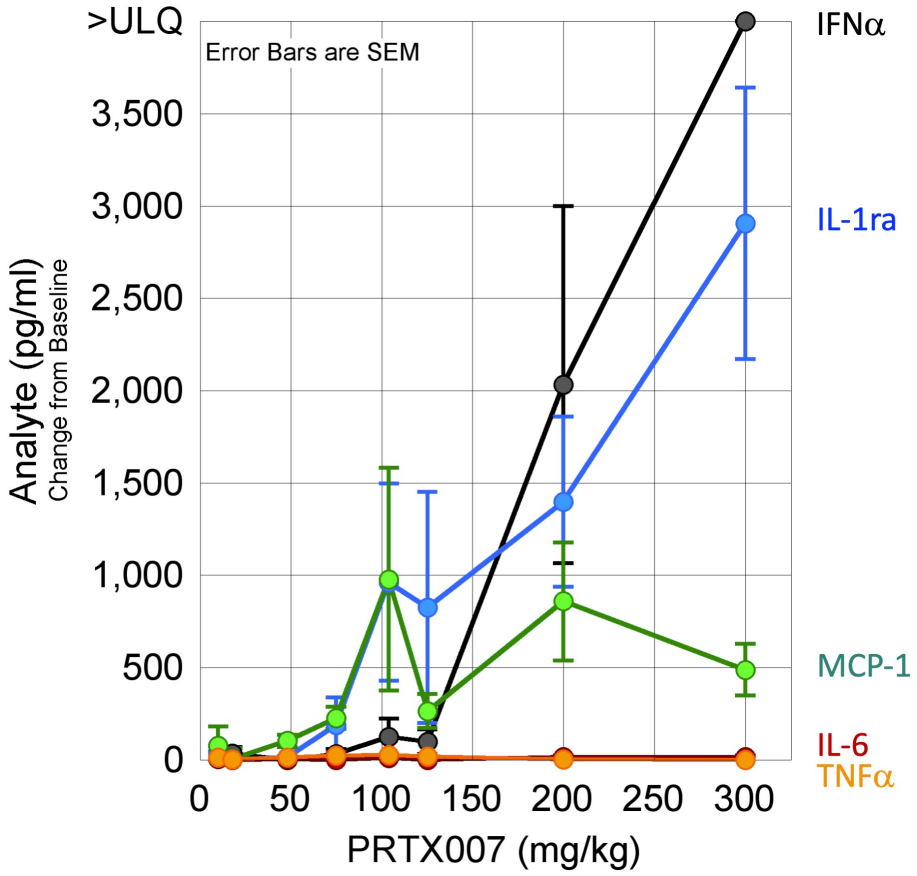
First-Dose Response



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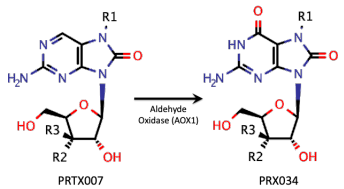
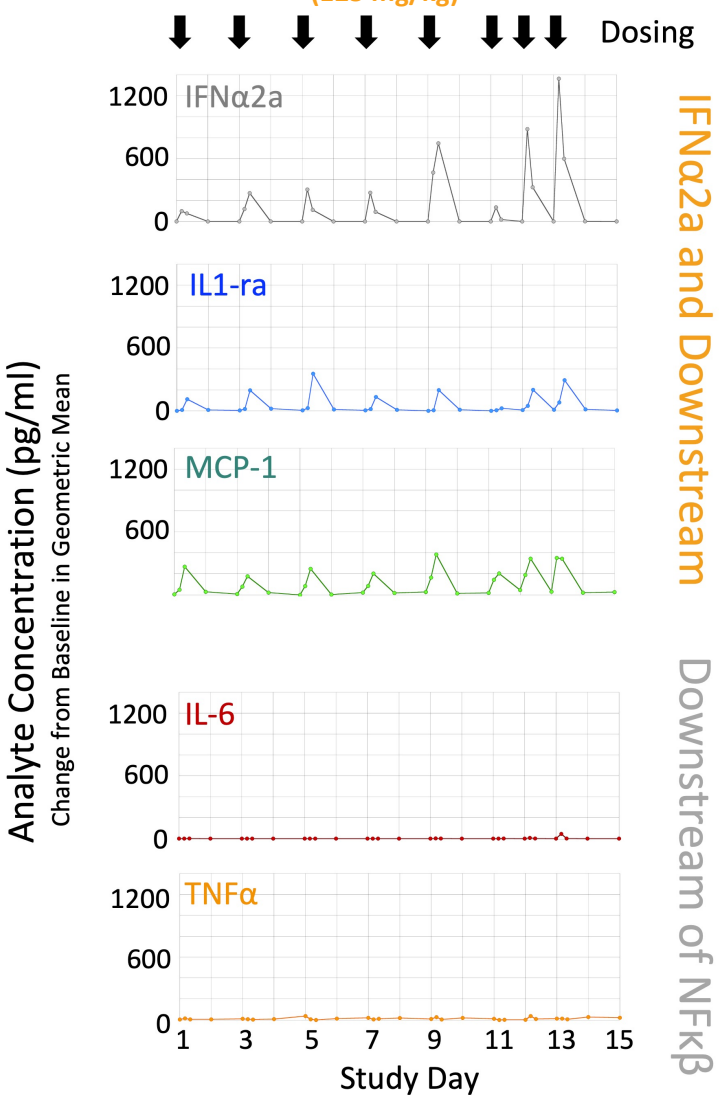
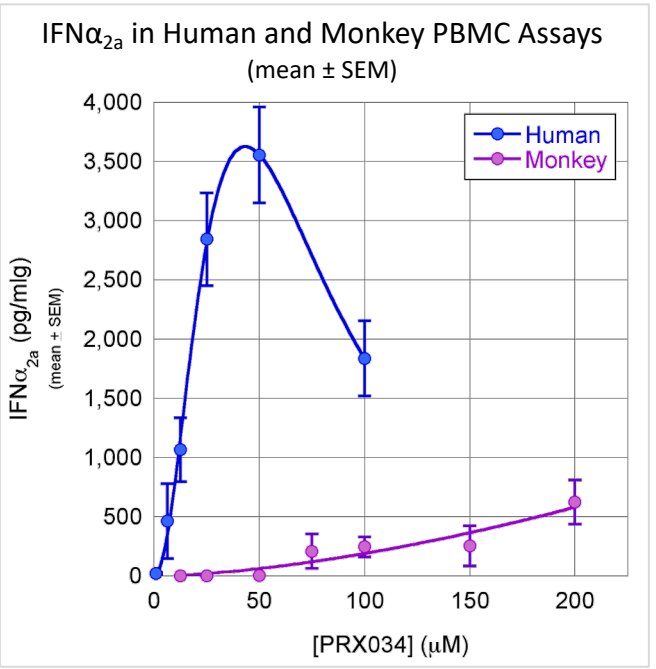


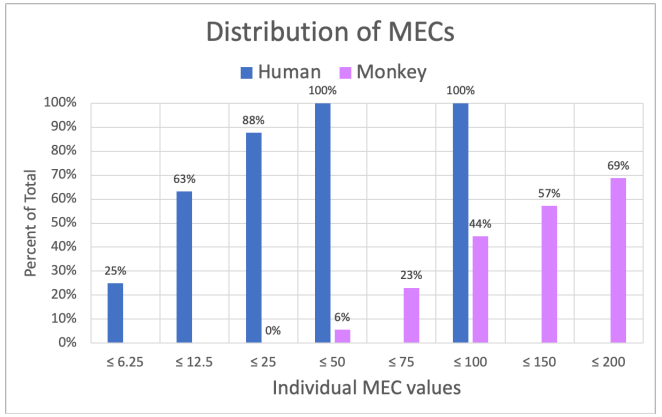
Repeate Dose Response

(125 mg/kg)



Human > 10x More Sensitive than Monkey






primmune
Therapeutics