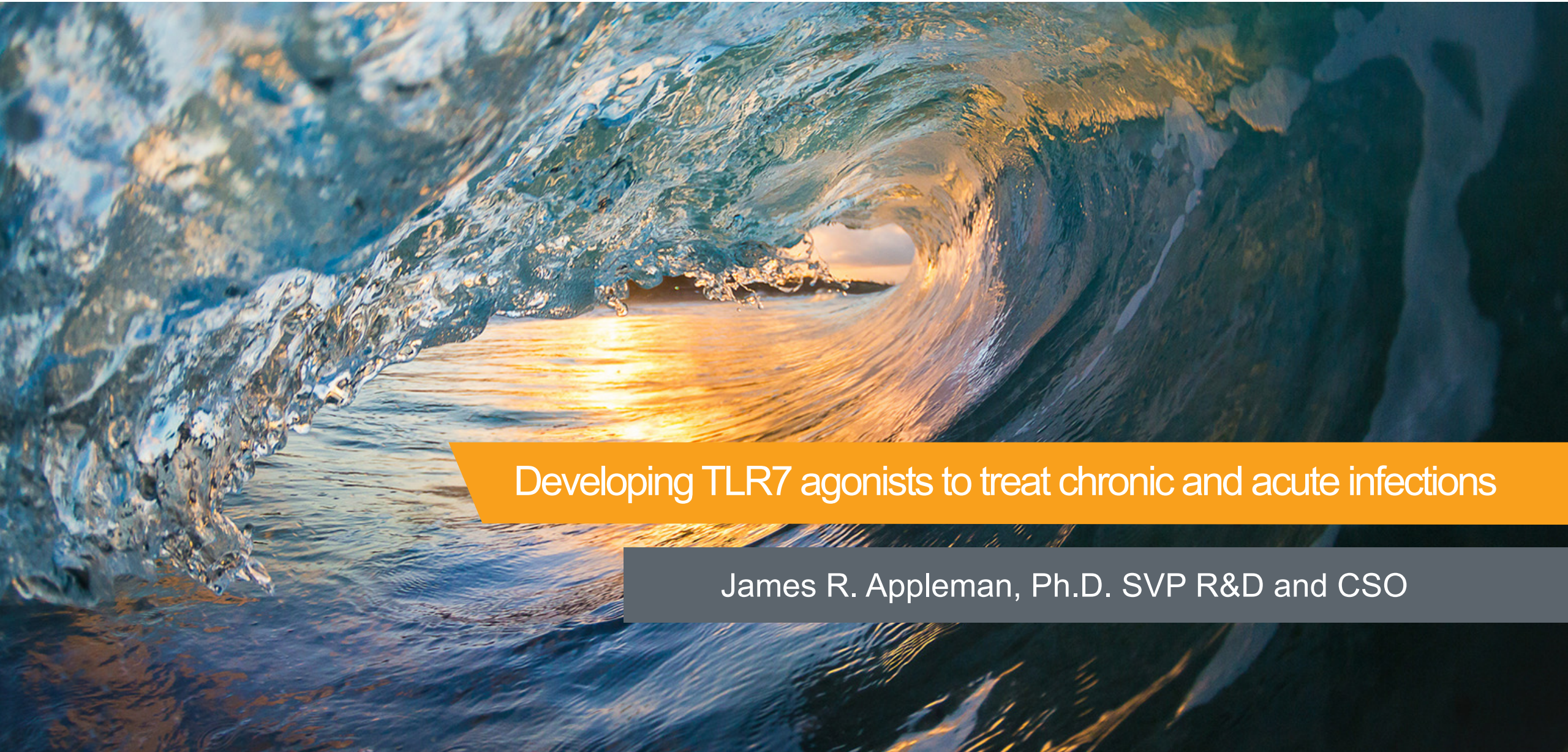
primmune Therapeutics

World Vaccine & Immunotherapy Congress West Coast
World Antiviral Congress
30 Nov – 2 Dec 2021

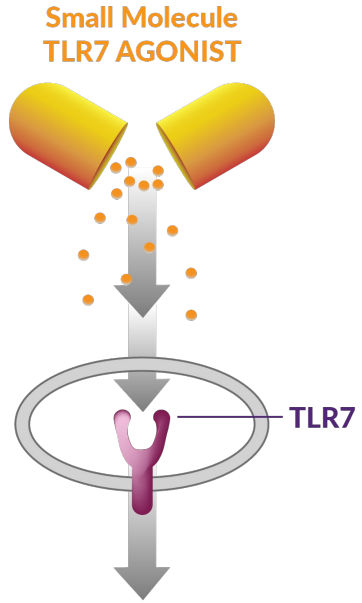


Developing TLR7 agonists to treat chronic and acute infections

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

Primmune Therapeutics Summary

Primmune Therapeutics is advancing the clinical development of PRTX007 (an orally administered TLR7 agonist), and designing novel oral SARS-CoV-2 3C Protease inhibitors



Primmune Therapeutics was founded by the world leaders in TLR7 biology and medicinal chemistry

PRTX007, activates plasmacytoid dendritic cells (pDC's) to produce a robust poly-Type I and III interferon response showing antiviral activity against a wide array of RNA viruses, including SARS-CoV-2, RSV, Influenza, Dengue and Zika

PRTX007: First-in-human SAD/MAD healthy volunteer Phase I study initiated in June 2021

Three PRTX007 clinical studies planned for 2022

- **RSV**: Phase II human challenge study – treatment and prophylaxis
- **SARS-CoV-2**: Phase Ib community study
- **HPV Dysplasia**: Phase II (CIN 2/3) driven by chronic HPV infection

2022 launch of PRTX007 Oncology Phase Ib/II study as single agent neo-adjuvant lead into a combination with Immune Checkpoint Inhibitors (CPIs)

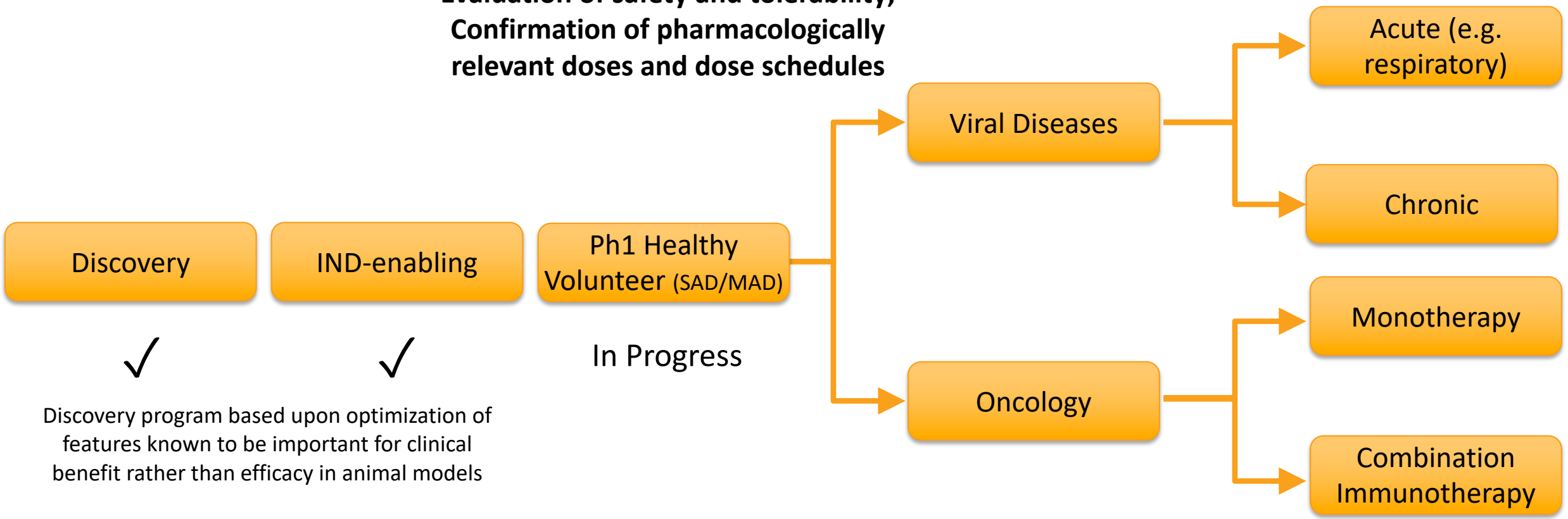
Primmune's unique insights into TLR7 agonist structure activity relationships (SAR) have enabled the design of unique orally active small molecules that can drive a tolerable systemic poly-interferon response without significant increases in NFκβ driven inflammation.

PRTX007 Development Strategy

Invention and Characterization of Clinical Candidate

Evaluation of safety and tolerability; Confirmation of pharmacologically relevant doses and dose schedules

Clinical Evaluation of Therapeutic Benefit



✓ ✓

In Progress

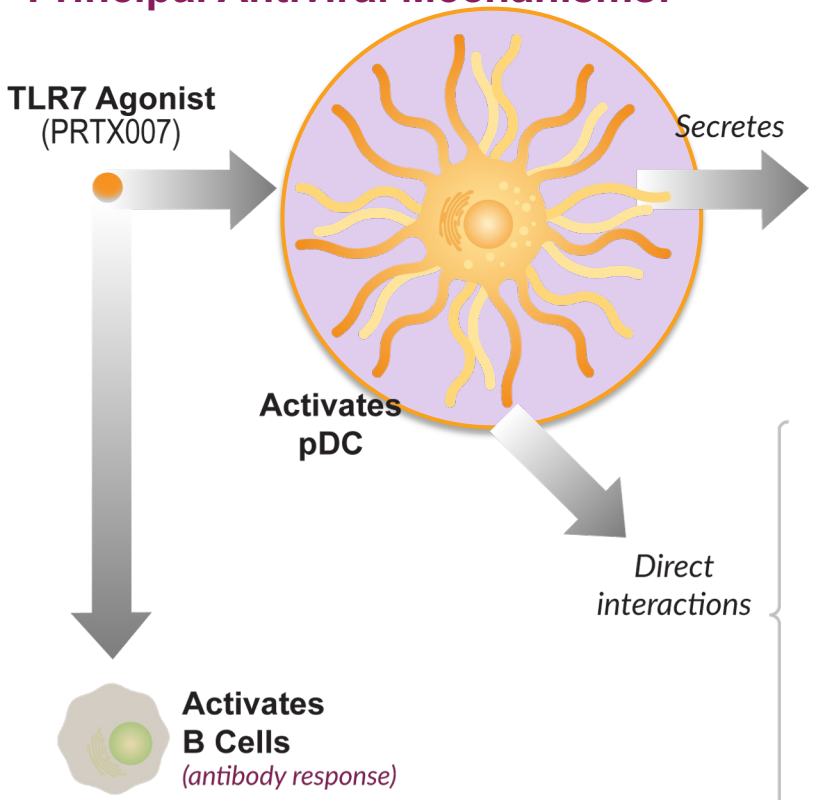
Discovery program based upon optimization of features known to be important for clinical benefit rather than efficacy in animal models

PRTX007's MOA Is Ideally Suited for Addressing SARS-CoV-2

THE PROBLEM: SARS-CoV-2 evades detection and activation of pDCs, limiting the innate immune response

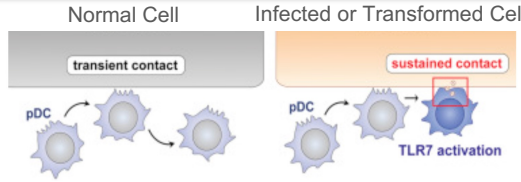
THE SOLUTION: When triggered by a TLR7 agonist, pDCs become activated and limit viral replication and infection

Principal Antiviral Mechanisms:



pDCs: on patrol and engaging danger

Assil et al 2019 Cell Host & Microbe



Type I & III Interferons (IFNs) → **Antiviral effects**

+ add'l cytokines, chemokines

- Activation of general antiviral cellular responses primed by pDCs responding to TLR7 agonists; enables endothelial and epithelial cells to block viral entry

NK Cells *(cytolytic factors)* → **NK cell killing of infected cells & enhanced ADCC**

- NK (natural killer) cell activation and enhanced antibody-mediated killing of pathogen infected cells via antibody-dependent cellular cytotoxicity (ADCC) with therapeutic mAbs as well as endogenous antibodies

Cytotoxic T Cells *(reversal of anergy)* → **Lysis of infected cells**

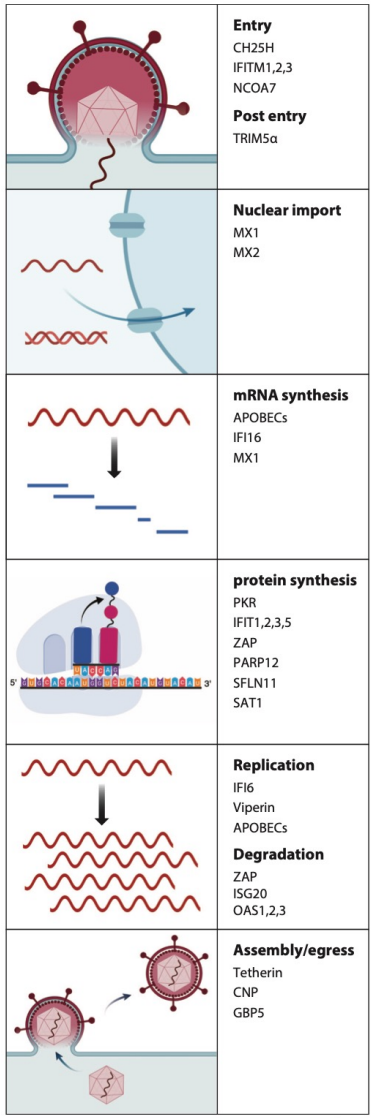
- Activation of cytotoxic T cells leads to lysis of virally infected cells

B Cells *(antibody response)* → **Proliferation; enhanced Ab production**

- Increase in proliferation and activation of B-cells leads to increased antibody mediated antiviral effects

Nineteen Types/Subtypes of IFNs Secreted by pDCs Activate Over 600 Different Genes Creating an Antiviral State Effecting Immune, Endothelial and Other Target Cells

- Target cells include lung epithelium
- IFNs stimulate increased levels of **600 - 2000** mRNA transcripts in human cells
- ~ 60 well-recognized ISGs with potent, broad-based antiviral activity
- Novel set of ISGs with activity restricted to coronaviruses identified
  Martin-Sancho 2021



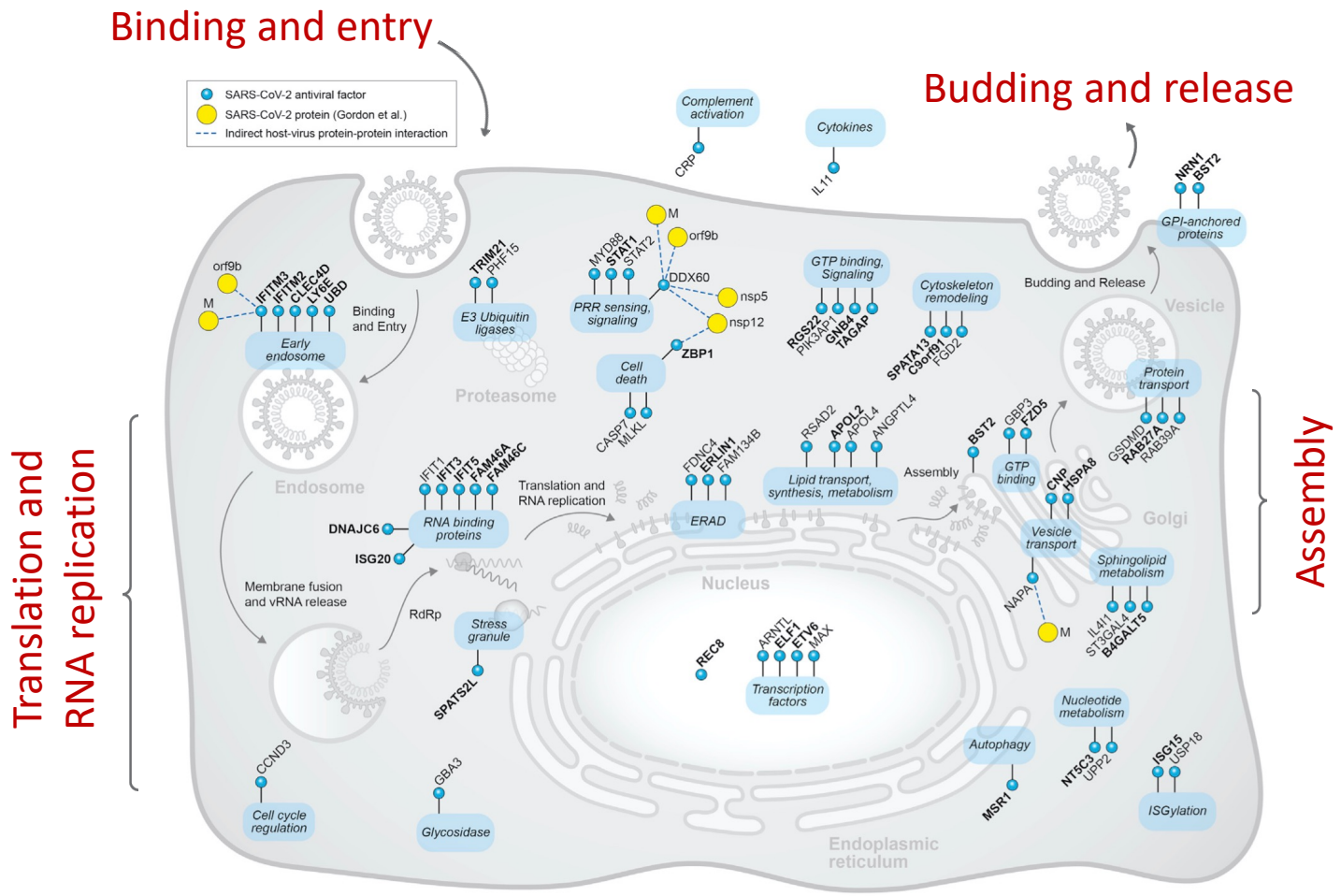
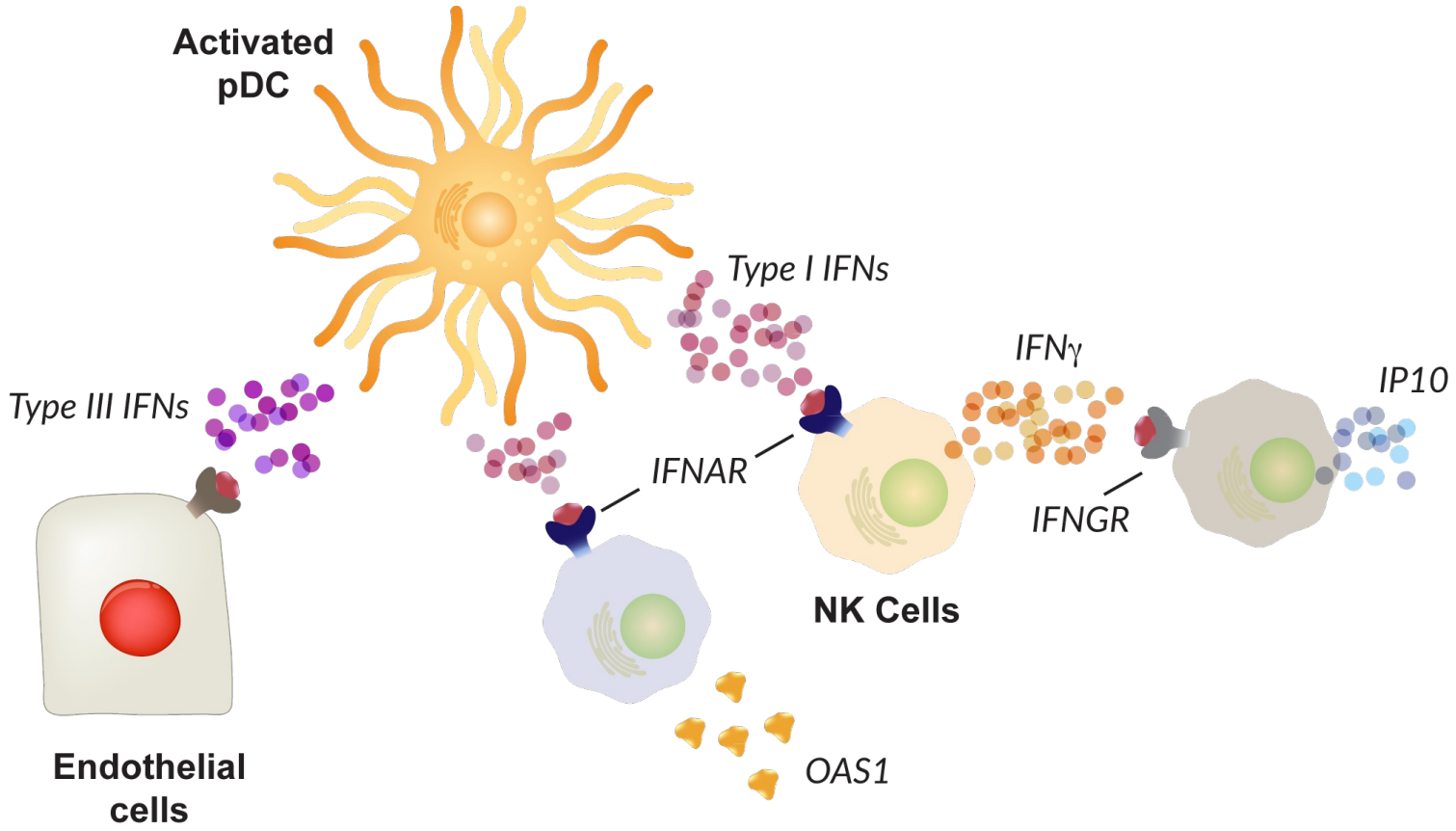


Figure 4. Integrated model of SARS-CoV-2 cellular restriction mechanisms
ISGs that inhibited SARS-CoV-2 replication were placed at specific positions along the viral infectious cycle based on experimental data generated in Figure 3 in conjunction with Gene Ontology, KEGG, and Reactome databases and the literature (see STAR Methods). Human ISGs are represented in blue circles and SARS-CoV-2 proteins in yellow circles. ISGs in bold indicate those ISGs that were validated using lentiviral transduction (Figure 1D). Dashed lines (edges) represent indirect interactions between these ISGs and the indicated viral proteins based on reported ISG interactors (Hubel et al., 2019) and SARS-CoV-2 interactors (Gordon et al., 2020).

Natural TLR7 Signaling Drives Both Tolerable Systemic Poly-IFN Production and Proper Innate and Adaptive Immune Signaling/Sequencing

TLR7 agonism drives a systemic poly-IFN release and significant *in situ* immunological activity at locations of infections via cell migration, paracrine signaling and endothelial cell hardening against viral entry/replication.



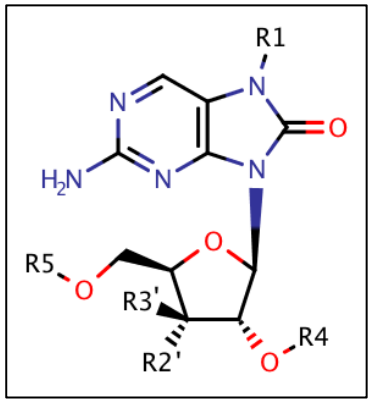
- Induction Via Paracrine Signaling and Direct Cell-Cell Interactions
- Overall circulating systemic IFN levels within normal limits
- ISG transcripts dramatically elevated
- Multi-factorial effects on immune cells and endothelial cells
- IFNs dramatically harden endothelial cells against viral infection and block viral production

PRTX007: Ideal Properties for Acute & Chronic Viral Disease and Oncology Settings

The challenge: pharmacology elicited by individual TLR7 agonists is sufficiently distinct they may **appear to be acting at completely different targets**

The solution: discovery and development requires deep characterization of biochemical and pharmacologic activity with closely related compounds

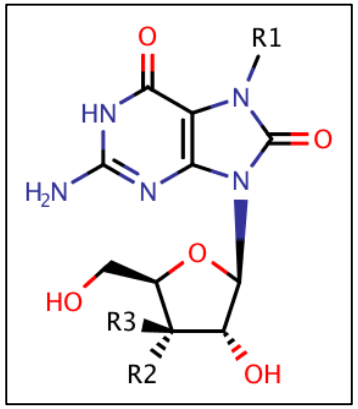
PRTX007 (Prodrug)
Clinical Candidate



(proprietary)

Converted by hepatic aldehyde oxidase on first pass through liver

PRX034
TLR7 Agonist

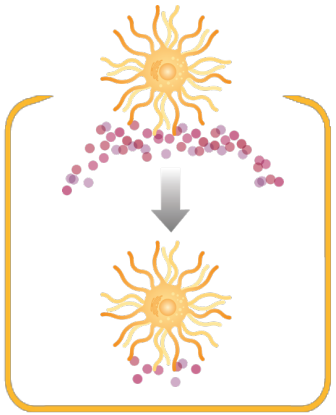


(proprietary)

PRTX007 meets essential properties for systemically acting, orally administered TLR7 agonists

Property	Consequence
Small-molecule agonist interaction with TLR7 maintains normal RNA-mediated allosteric regulation of TLR7	Enables control of immune activation by applied dose
Specificity for TLR7 and a corresponding lack of activity at TLR8	Limiting proinflammatory response enables systemic administration
Defined target profile of cytokine and chemokine induction in human peripheral blood mononuclear cells	Enables systemic administration
Efficient delivery to systemic circulation by prodrugs that intrinsically lack TLR7 agonist activity themselves	Avoids gut toxicity
PK volume of distribution ~ 1 L/kg	Broad systemic distribution
Relatively short PK $t_{1/2}$ with substantially more long-lived pharmacodynamic response	Avoids both tachyphylaxis and toxicities

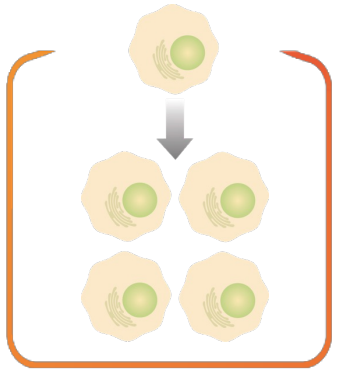
Bane of Systemic Small Molecule TLR7 Agonists (Historical)



Loss of pDC Activiity

Inability to maintain immune pressure

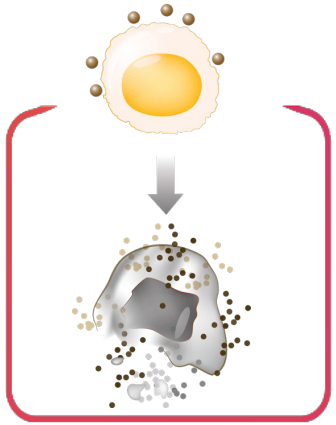
Most / All
(QD dosing)



Too Much of a Good Thing

Excessive B cell proliferation

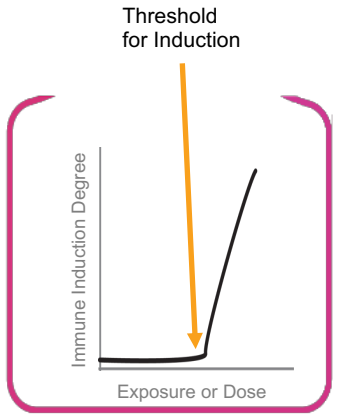
Most / All
(QD dosing)



Off-target Toxicities

Off-target toxicities of agonist or metabolites

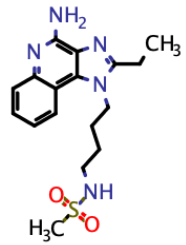
Imiquimod
Resiquimod
Bropirimine

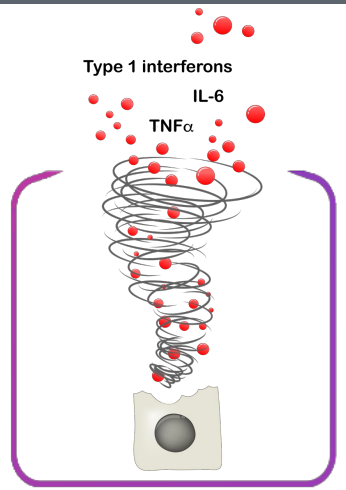


Unmanageable Dose Response

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"

Understandings Derived from Primate and Human TLR7 Agonist Pharmacology

(Anadys Pharma program lead by J. Appleman)

Essential properties for systemically acting, orally administered TLR7 agonists, particularly those used in chronic diseases

Property	Consequence
Intrinsic potency for TLR7 activation in a defined range that maintains ability to vary degree of engagement with concentration	Enables control of immune activation by applied dose
Specificity for TLR7 and a corresponding lack of activity at TLR8	Limiting proinflammatory response enables systemic administration
Defined target profile of cytokine and chemokine induction in human peripheral blood mononuclear cells	Enables systemic administration
Efficient delivery to systemic circulation by prodrugs that intrinsically lack TLR7 agonist activity themselves	Avoids gut toxicity
PK volume of distribution ~ 1 L/kg	Broad systemic distribution
Relatively short PK $t_{1/2}$ with substantially more long-lived pharmacodynamic response	Avoids both tachyphylaxis and toxicities

SCOPE OF INFORMATION USED IN ANALYSES

TLR7 and TLR7/8 Agonists Representing Multiple Structural Classes

- 3M-852A (PF4878691)*
- Imiquimod and prodrugs*
- Resiquimod and prodrugs*
- Bropirimine and prodrugs*
- SM-360320 (CL-087, 1V136) and prodrugs
- Loxoribine and prodrugs*
- Isatoribine and prodrug*,**
- Other proprietary Anadys TLR7 agonists and corresponding prodrugs*,**

Note: clinical data for agonist* and prodrug(s)** either publicly available or generated in Anadys clinical programs

Pharmacokinetics (multiple cmpds)

- PK after IV administration
- Efficiency of systemic delivery and PK of agonists upon oral administration of prodrugs
- Distribution, route of clearance, …

Systemic Immune Response (multiple cmpds)

- Cytokines and chemokines
- Proinflammatory response makers
- Antiviral enzymes
- IFN-responsive genes
- B, CD8+ T, CD4+ T, NK cell status

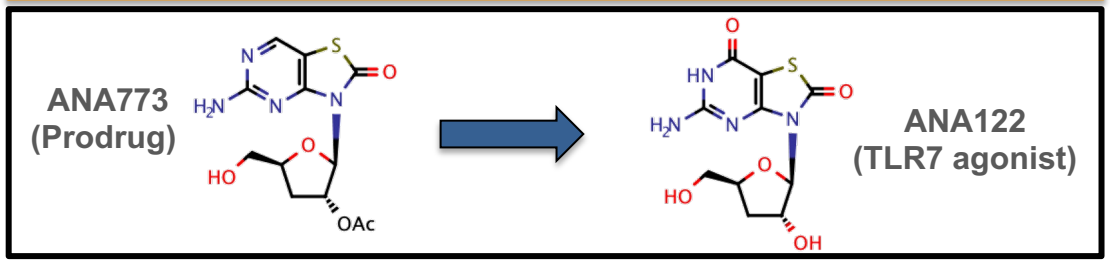
Effect of Dosing Schedules (multiple cmpds)

- QD (continuous daily dosing)
- QOD (every other day dosing)
- 3xQD, 4 day holiday (weekly cycle, “3on/4off”)
- QW (weekly dosing)

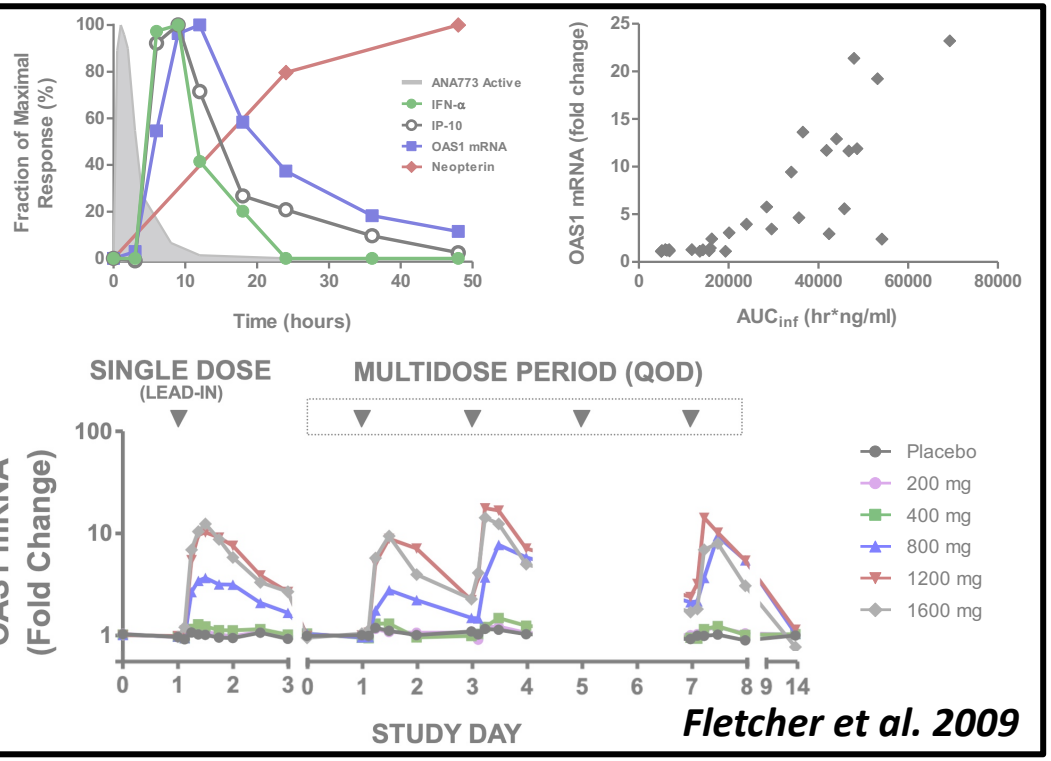
Formal safety studies with QD, QOD and “3on/4off” schedules (selected Anadys compounds)

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

ORALLY ADMINISTERED SYSTEMICALLY DISTRIBUTED

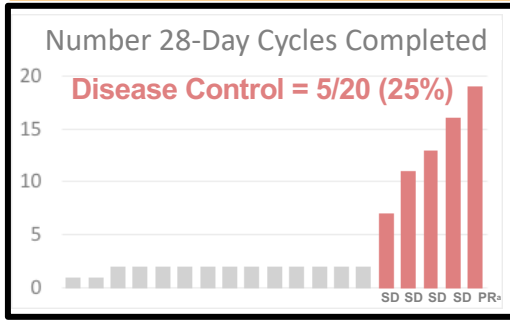


PK/PD IN HEALTHY VOLUNTEERS



Fletcher et al. 2009

MONOTHERAPY ACTIVITY IN PHASE 1 CANCER STUDY

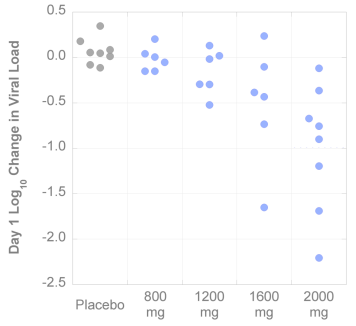


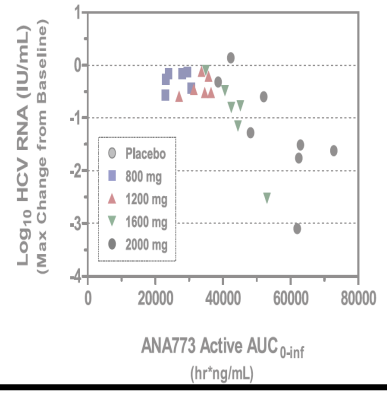
Uveal Melanoma (7 cycles)
Uveal Melanoma (11 cycles)
Stage IV Adenocystic Carcinoma (13 cycles)
Prostatic Adenocarcinoma (16 cycles)
Metastatic Melanoma (19 cycles)

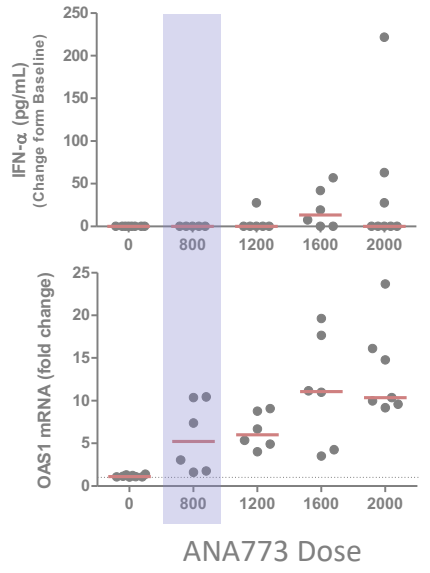
Daniels et al. 2011

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



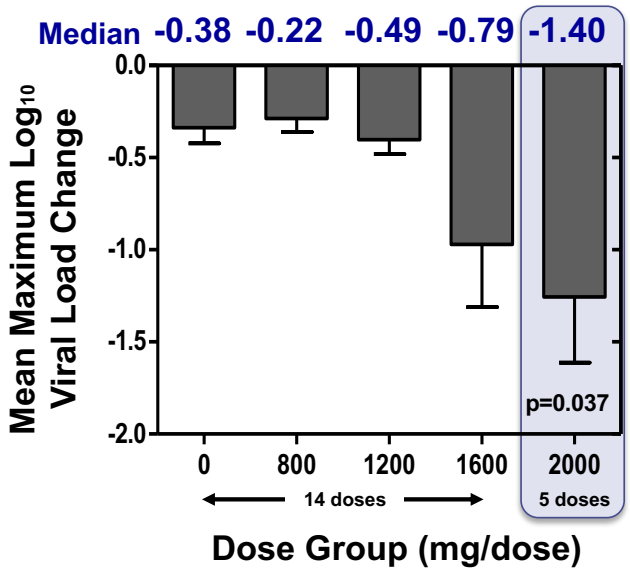


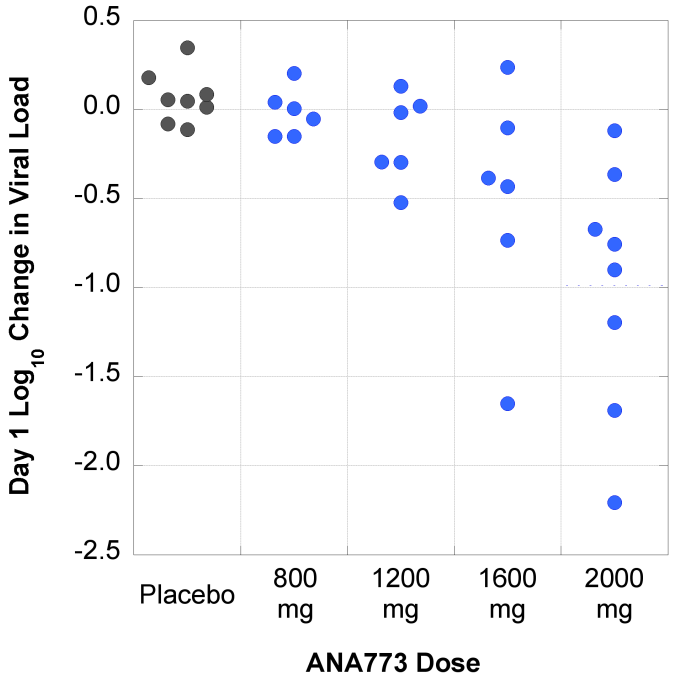


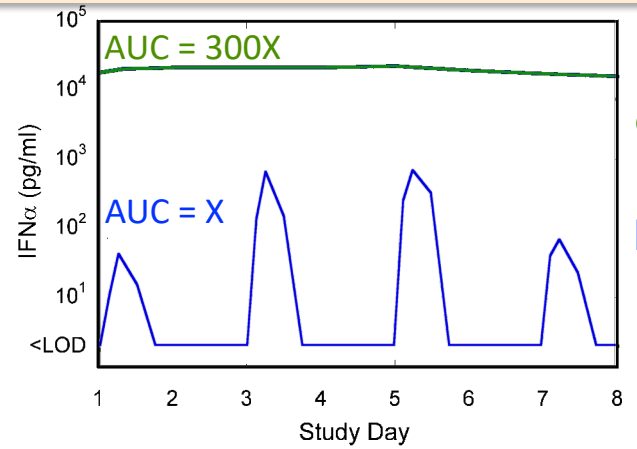
Bergmann et al. 2011

Clinical Demonstration of Single Agent TLR7 Agonist-Mediated Acute Antiviral Response in HCV Patients

Data shown* is for ANA773, an oral inducer of endogenous interferons acting via TLR7, in clinical trials to treat chronic HCV





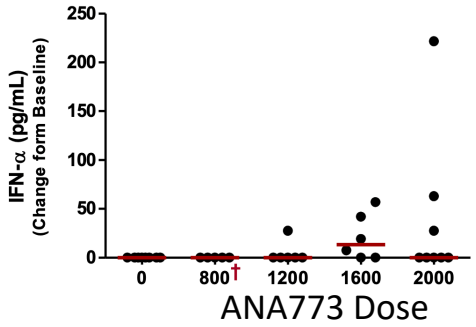


ANA773 causes IFN-responsive gene induction with very low exposure to circulating IFN as compared to exogenous IFNa2a (i.e., PEGASYS)

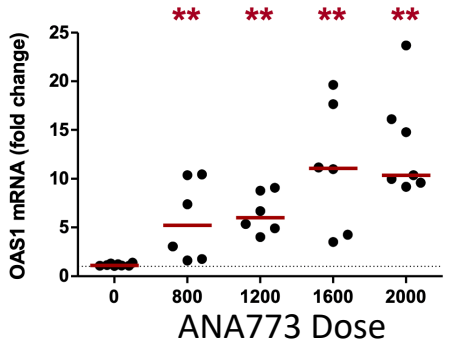
ANA773 demonstrated significant antiviral activity, exceeding the magnitude achievable with administered IFNs

A substantial dose level-dependent decrease in viral load is observed upon administration of the first dose

D1 Individual peak IFN



D1 Individual peak OAS1
(ISG gene-expression, fold-change)



Data from Bergmann et al 2011; Randomized clinical trial

Updated understandings incorporated into Primmune's program
(will discuss data relevant to three of the six key properties)

Essential properties for systemically acting, orally administered TLR7 agonists, particularly those used in chronic diseases

Property	Consequence
Small-molecule agonist interaction with TLR7 maintains normal RNA-mediated allosteric regulation of TLR7 *(revised)*	Enables control of immune activation by applied dose
Specificity for TLR7 and a corresponding lack of activity at TLR8	Limiting proinflammatory response enables systemic administration
Defined target profile of cytokine and chemokine induction in human peripheral blood mononuclear cells *(optimized)*	Enables systemic administration
Efficient delivery to systemic circulation by prodrugs that intrinsically lack TLR7 agonist activity themselves	Avoids gut toxicity
PK volume of distribution ~ 1 L/kg	Broad systemic distribution
Relatively short PK $t_{1/2}$ with substantially more long-lived pharmacodynamic response	Avoids both tachyphylaxis and toxicities

SCOPE OF INFORMATION USED IN ANALYSES

TLR7 and TLR7/8 Agonists Representing Multiple Structural Classes

- 3M-852A (PF4878691)*
- Imiquimod and prodrugs*
- Resiquimod and prodrugs*
- Bropirimine and prodrugs*
- SM-360320 (CL-087, 1V136) and prodrugs
- Loxoribine and prodrugs*
- Isatoribine and prodrug*,**
- Other proprietary Anadys TLR7 agonists and corresponding prodrugs*,**

Note: clinical data for agonist* and prodrug(s)** either publicly available or generated in Anadys clinical programs

Pharmacokinetics (multiple cmpds)

- PK after IV administration
- Efficiency of systemic delivery and PK of agonists upon oral administration of prodrugs
- Distribution, route of clearance, …

Systemic Immune Response (multiple cmpds)

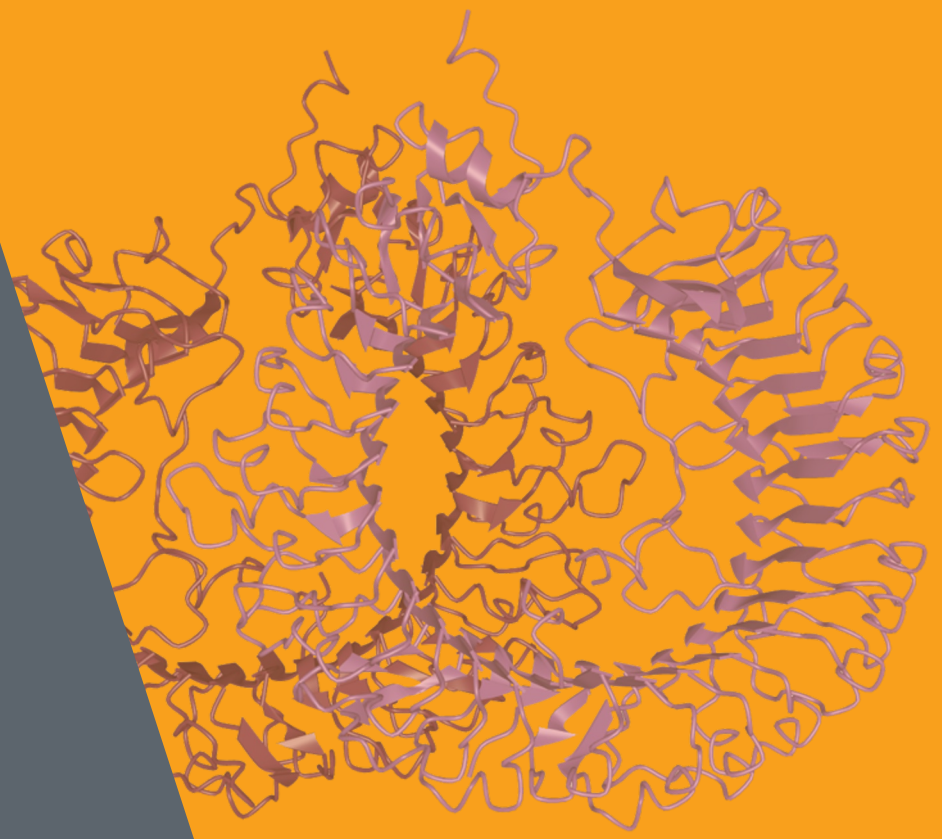
- Cytokines and chemokines
- Proinflammatory response makers
- Antiviral enzymes
- IFN-responsive genes
- B, CD8+ T, CD4+ T, NK cell status

Effect of Dosing Schedules (multiple cmpds)

- QD (continuous daily dosing)
- QOD (every other day dosing)
- 3xQD, 4 day holiday (weekly cycle, "3on/4off")
- QW (weekly dosing)

Formal safety studies with QD, QOD and "3on/4off" schedules (selected Anadys compounds)

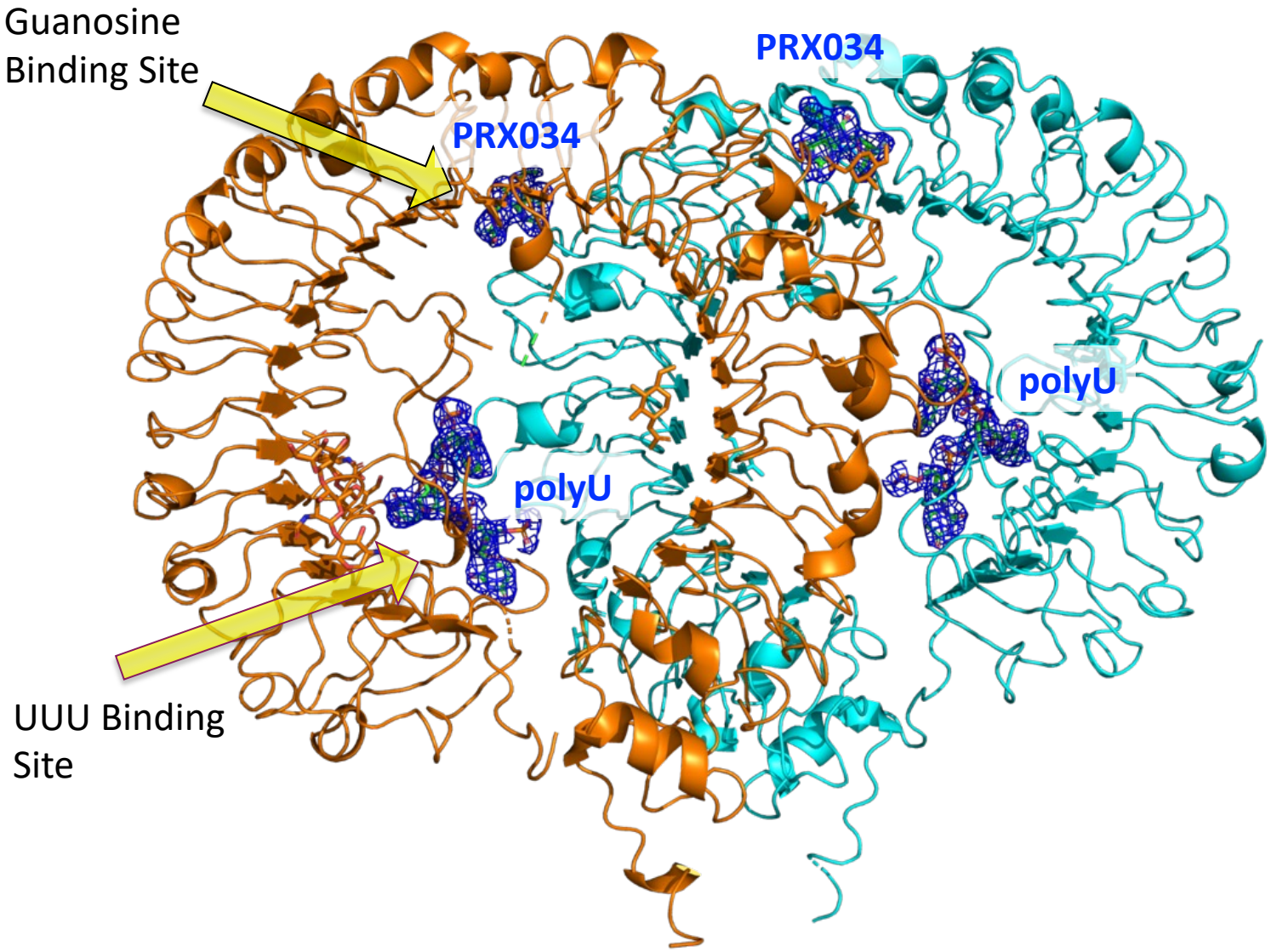
primmune Therapeutics

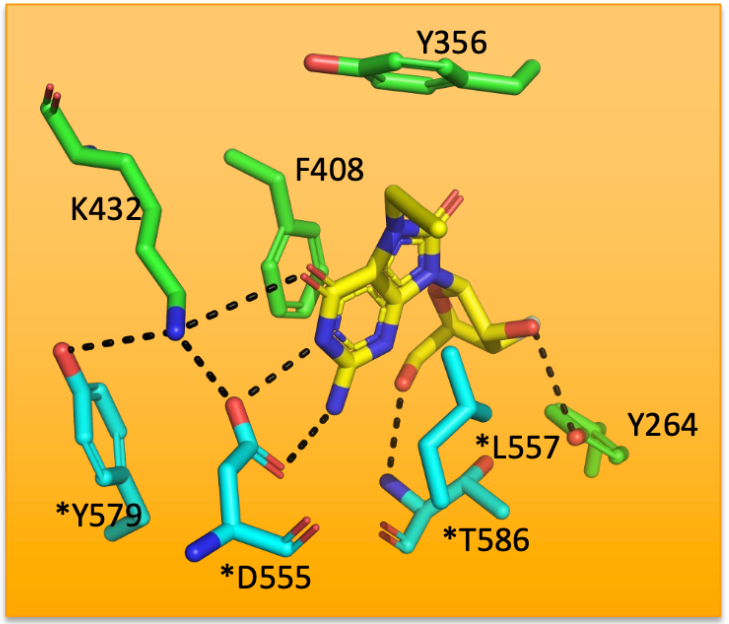


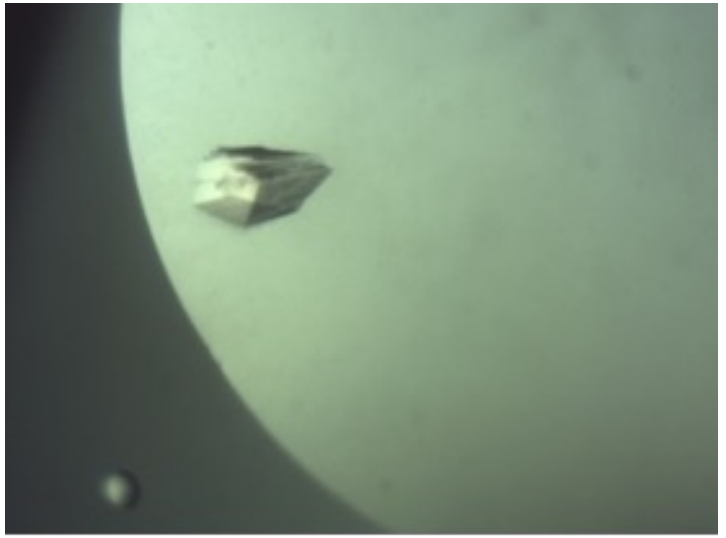
PRTX007

Experimental Data

Primmune's TLR7 Agonists Bind to Guanosine Binding Site

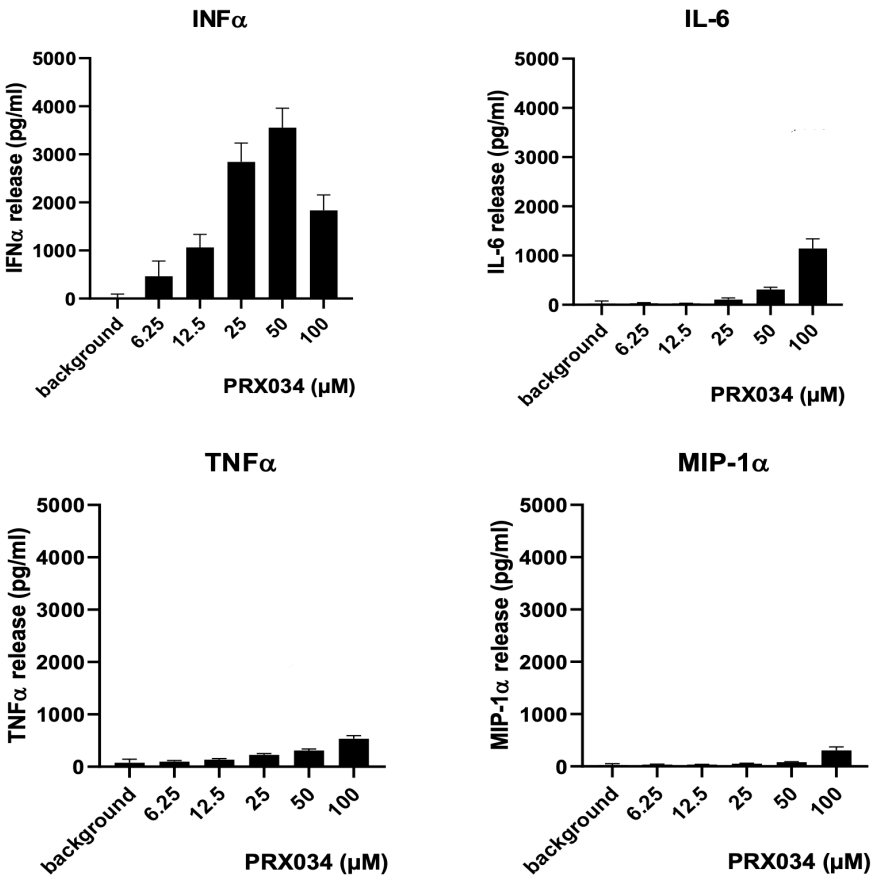




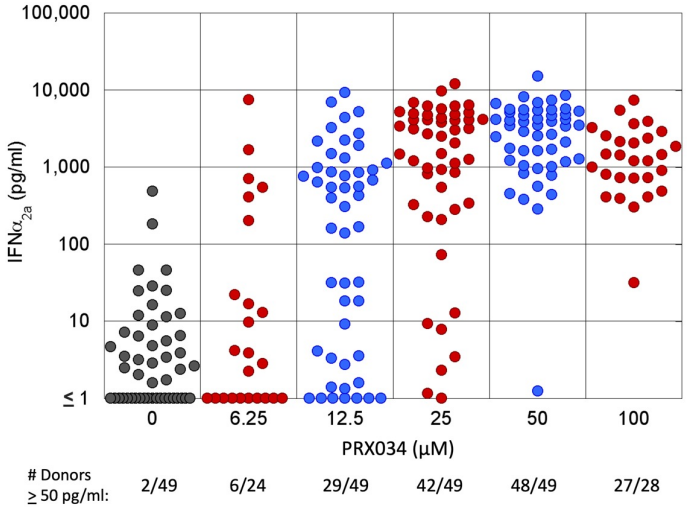


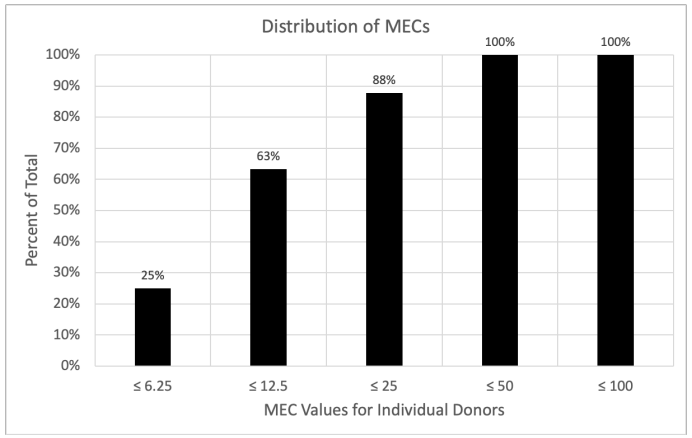
PRX034 in Human PBMCs: Preferential Induction of IFNs

IFN, Cytokine & Chemokine "Fingerprint"



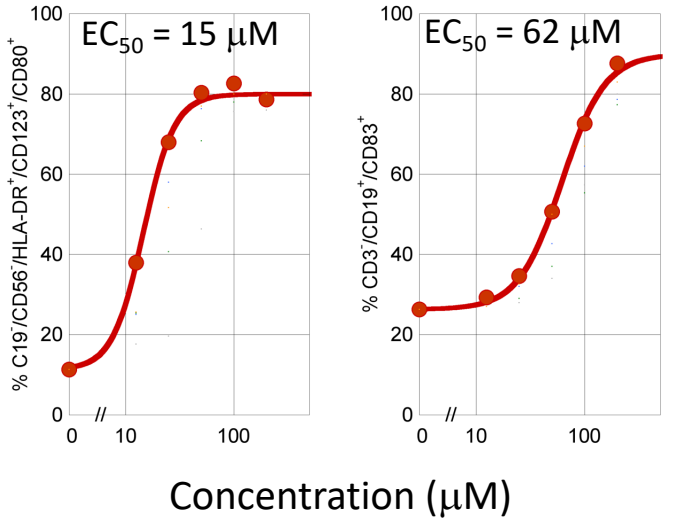
Individual Donor Response



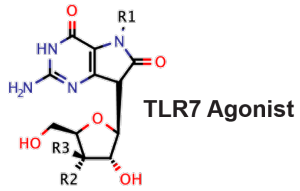


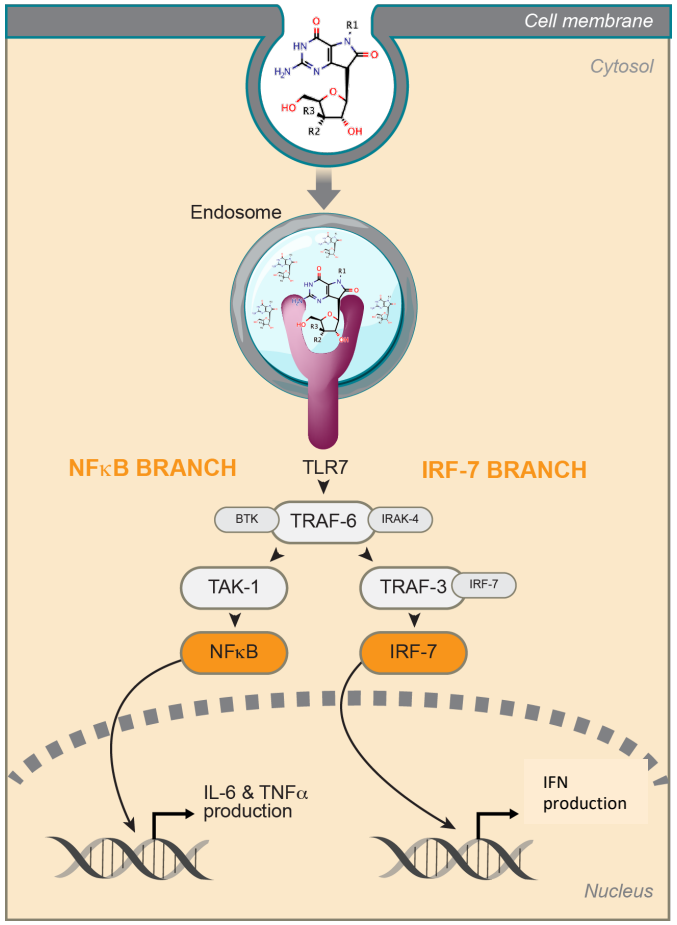
MEC = lowest concentration of agonist which increases IFN by 50 pg/ml

Cellular Activation by FACS Analysis



Differentially Tuned TLR7 Agonists (hPBMC Assay)

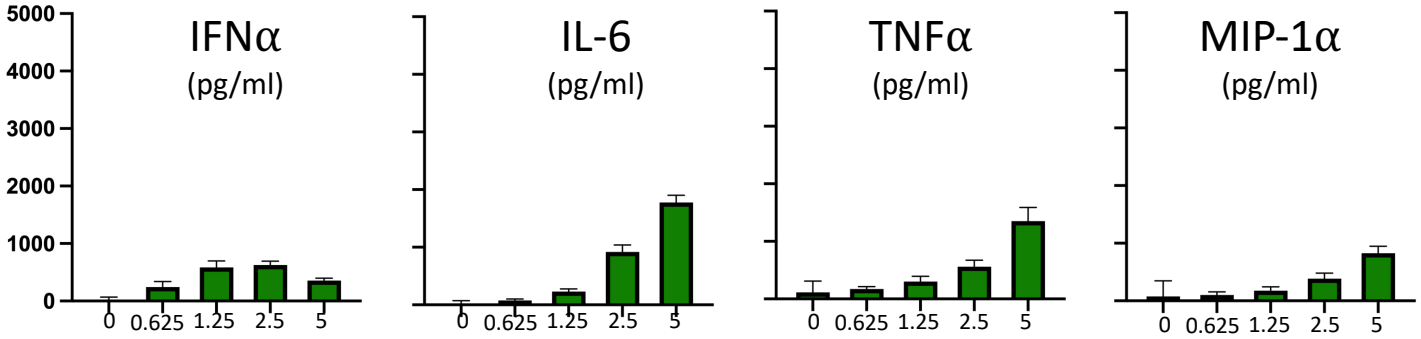




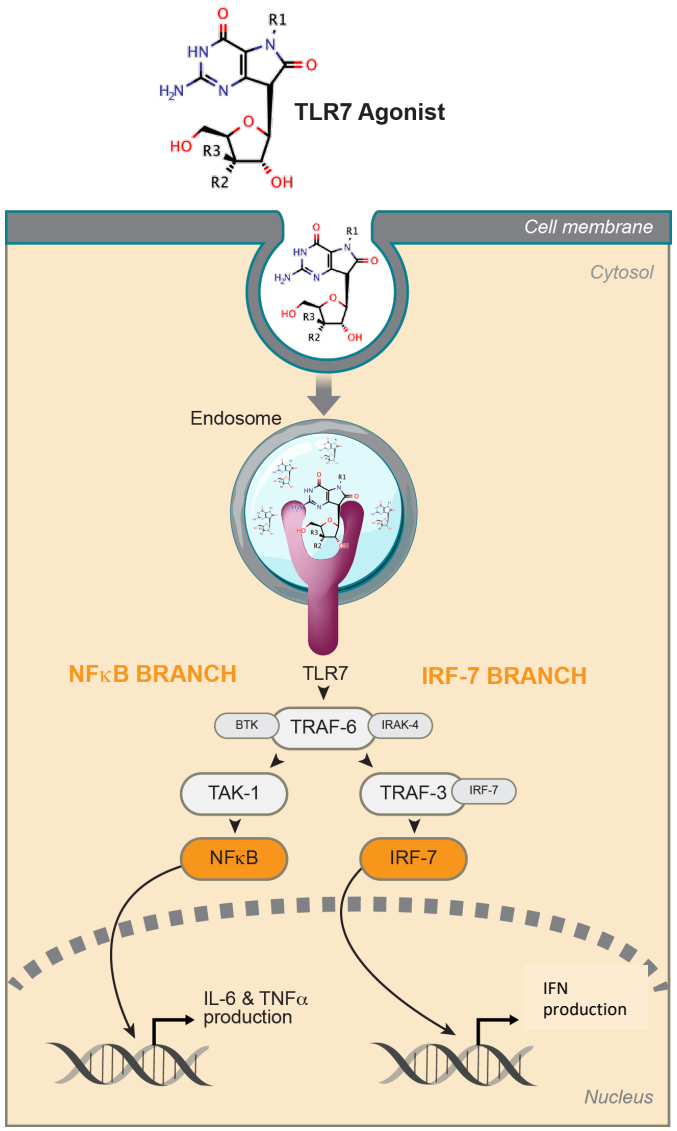
Imiquimod

Biased to NFκβ Activation

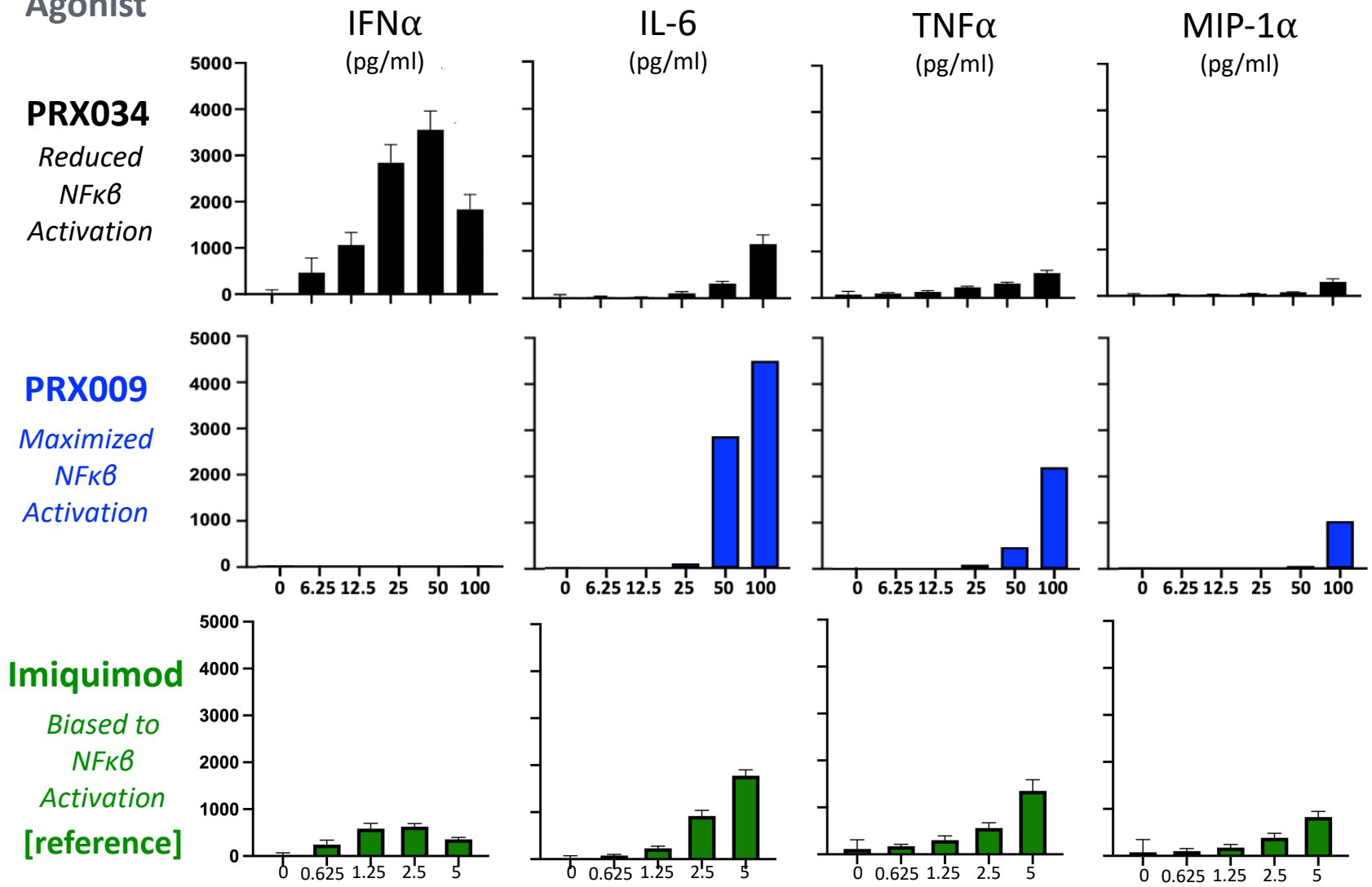
[reference]



Differentially Tuned TLR7 Agonists (hPBMC Assay)



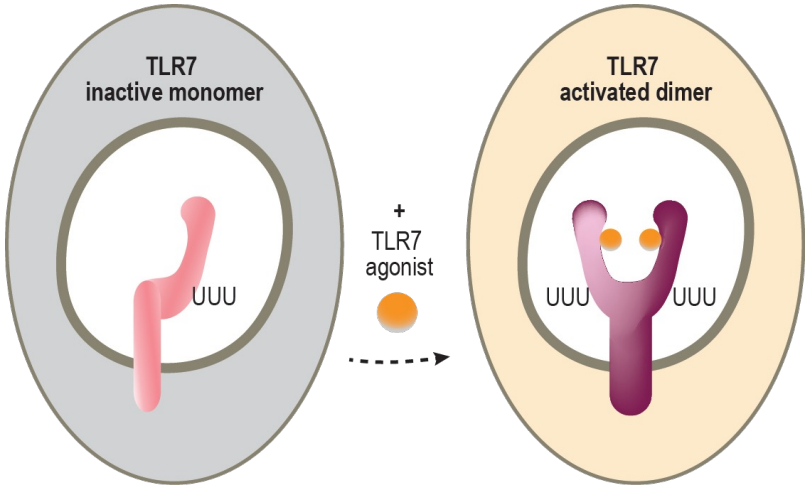
Two TLR7-Specific Agonists Elicit Distinct Cellular Pharmacology



Additional Tuneable Properties Impacting Therapeutic Utility

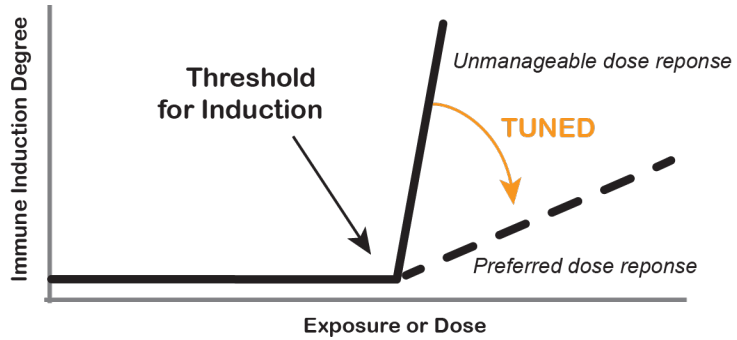
Tunable Property

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

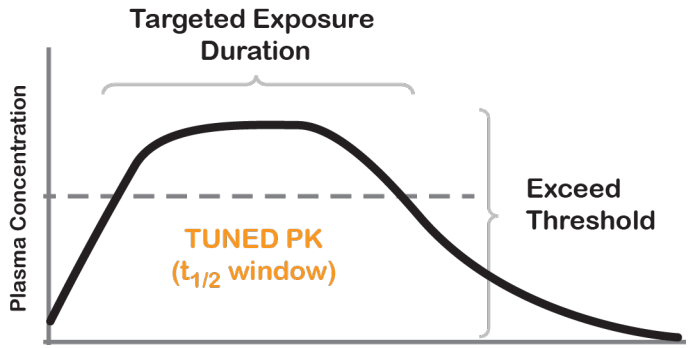


Treatment Benefit

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



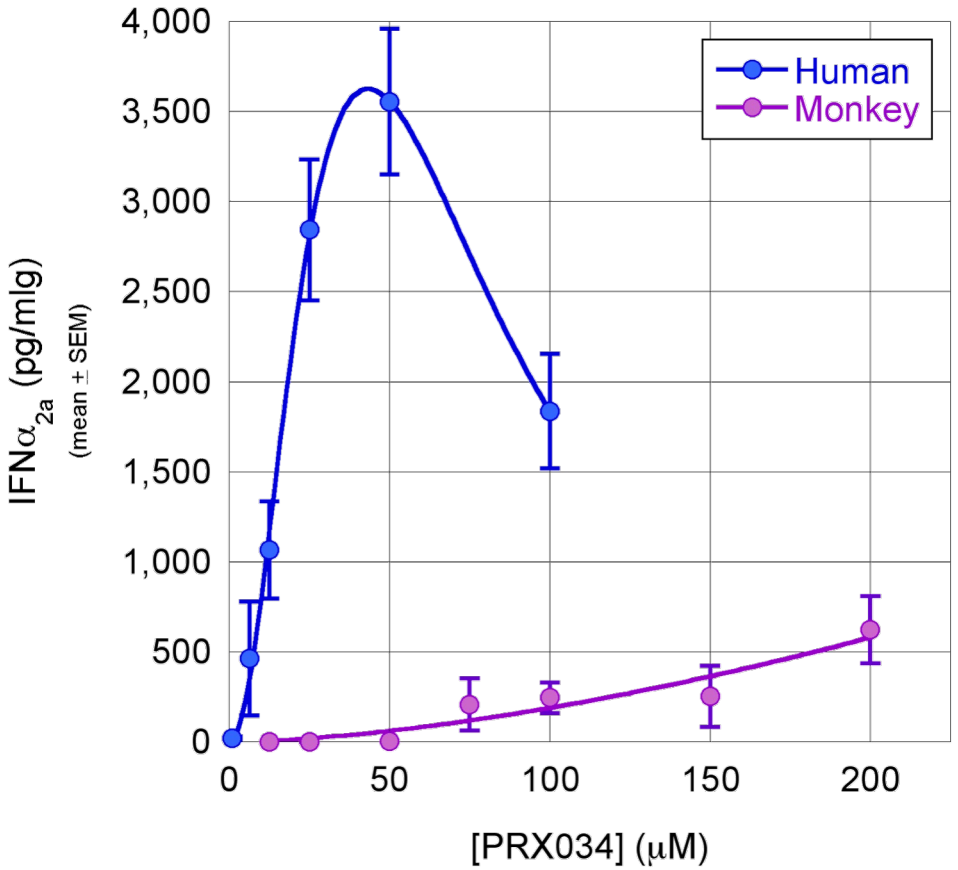
Controlled “time over threshold” window for plasma level of TLR7 agonist



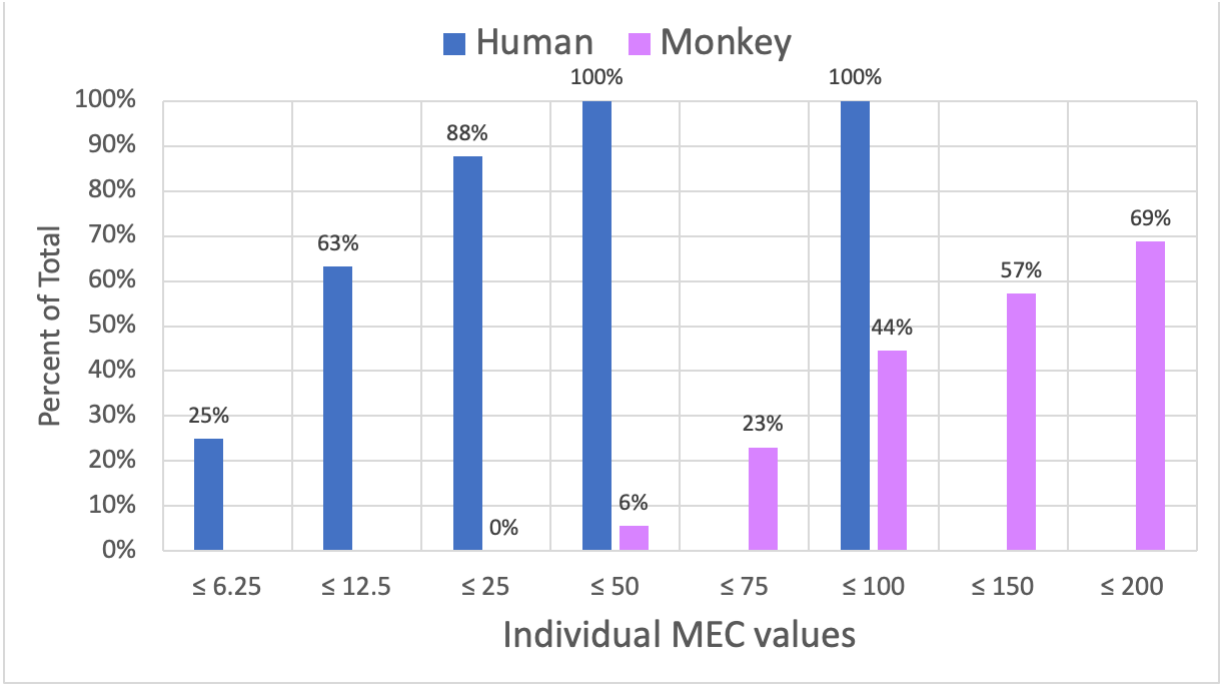
Ability to dose frequently (e.g. QOD) and indefinitely while achieving well-tolerated, therapeutically relevant degree of immune induction

ASIDE: PRX034 13-fold More Potent in Human than Monkey PBMCs
(doses required in monkeys therefore much greater than in humans)

$IFN\alpha_{2a}$ in PBMC Assays
(mean ± SEM)

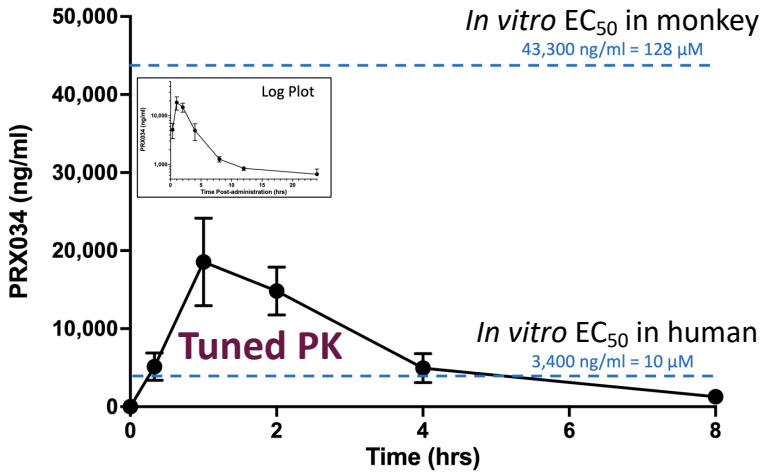


Minimal PRX034 Concentration Eliciting Response

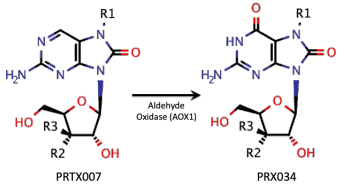


Profile Maintained in Cynomolgus Monkey Studies

First Dose PK (125 mg/kg)



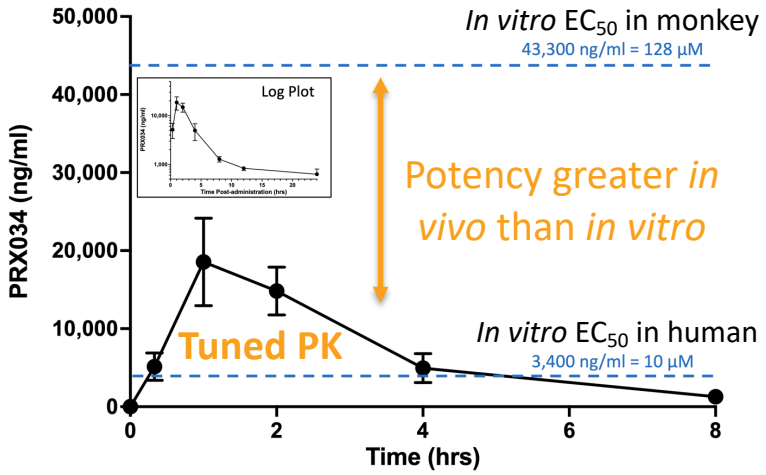
Note: The TLR7 agonist PRX034 is efficiently delivered into systemic circulation by oral administration of PRTX007



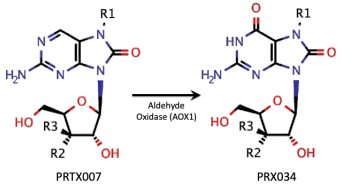
Profile Maintained in Cynomolgus Monkey Studies

First Dose PK (125 mg/kg)

***In vitro* assays underestimate *in vivo* potency**

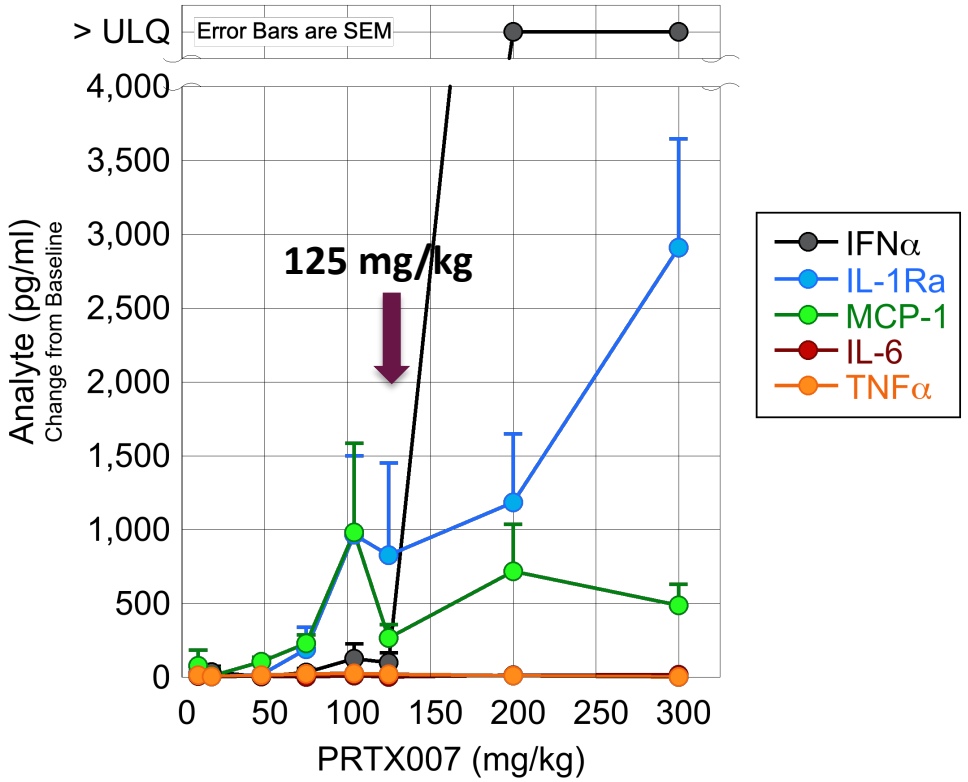


Note: The TLR7 agonist PRX034 is efficiently delivered into systemic circulation by oral administration of PRTX007



Prodrug TLR7 Agonist

First-Dose Response



Profile Maintained in Cynomolgus Monkey Studies

First Dose PK (125 mg/kg)

***In vitro* assays underestimate *in vivo* potency**

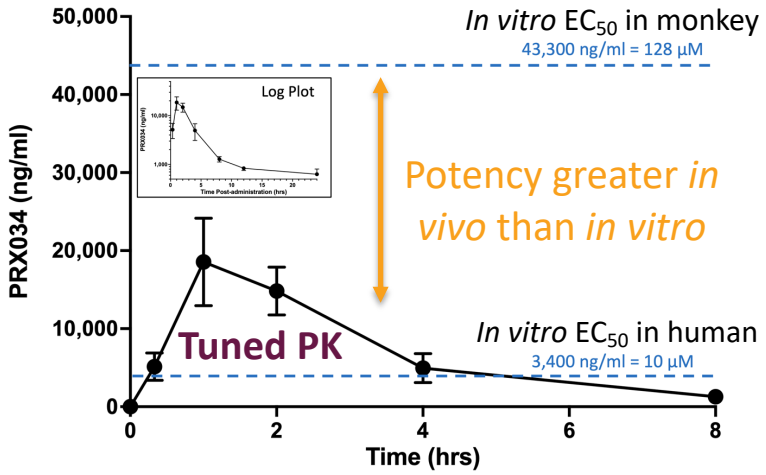
Note: The TLR7 agonist PRX034 is efficiently delivered into systemic circulation by oral administration of PRTX007

First-Dose Response

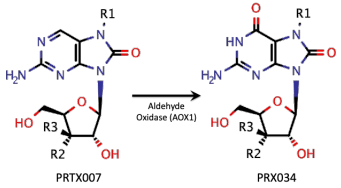
Interferon Stimulated Genes …

First Dose PK (125 mg/kg)

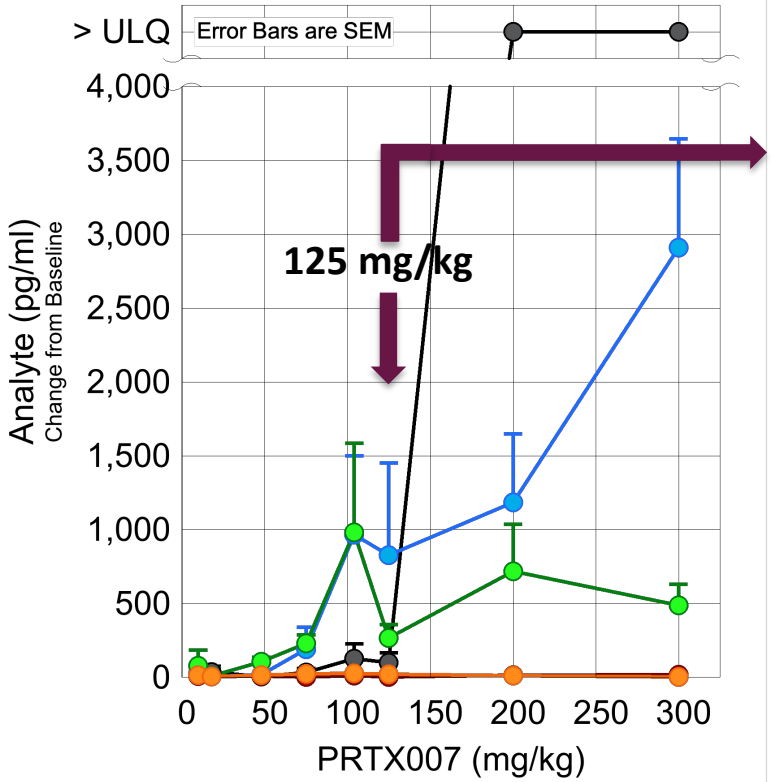
***In vitro* assays underestimate *in vivo* potency**



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



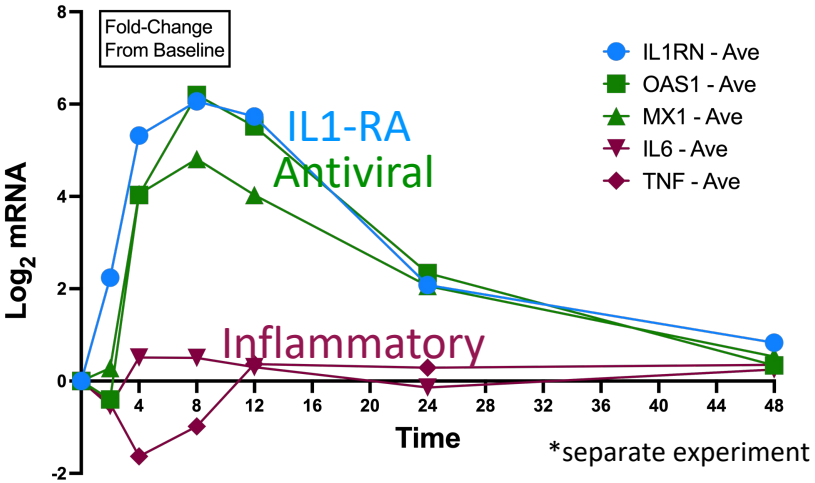
First-Dose Response



Substantial Induction IFNα-Regulated Genes

Extended Duration PD Response

125 mg/kg Dose Group (n=5)*

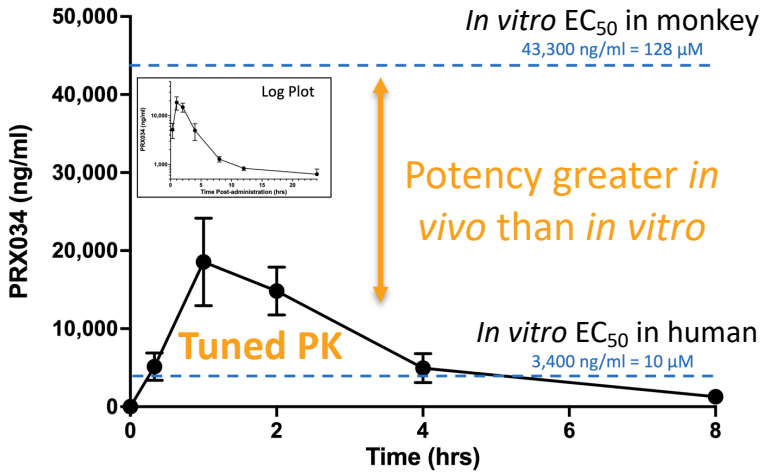


*separate experiment

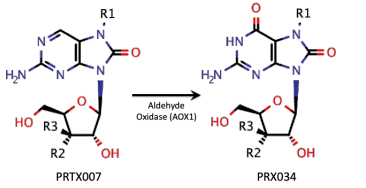
Interferon Stimulated Genes Engaged With Minimal / No Circulating INFα

First Dose PK (125 mg/kg)

In vitro assays underestimate *in vivo* potency

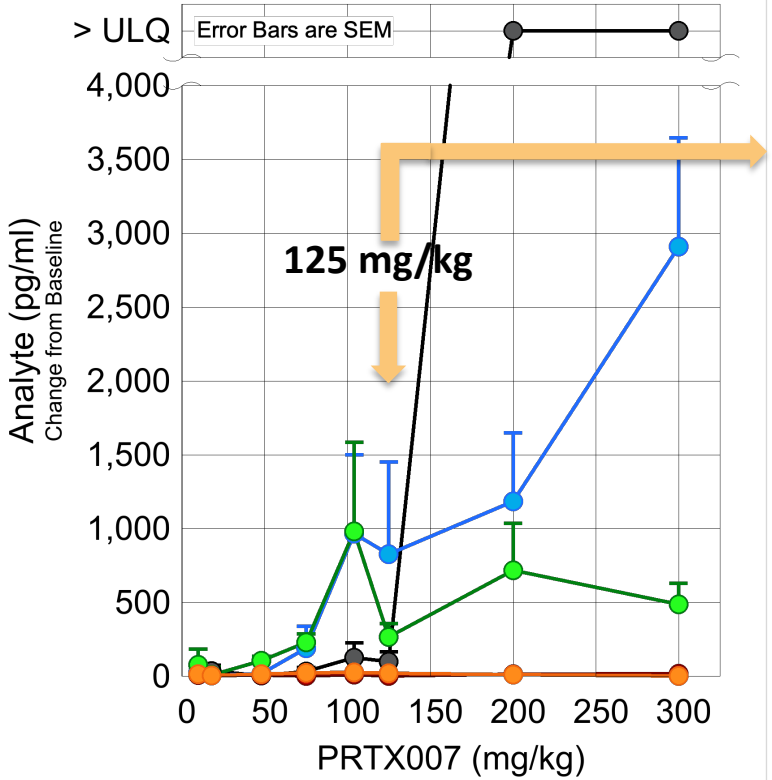


Note: The TLR7 agonist PRX034 is efficiently delivered into systemic circulation by oral administration of PRTX007



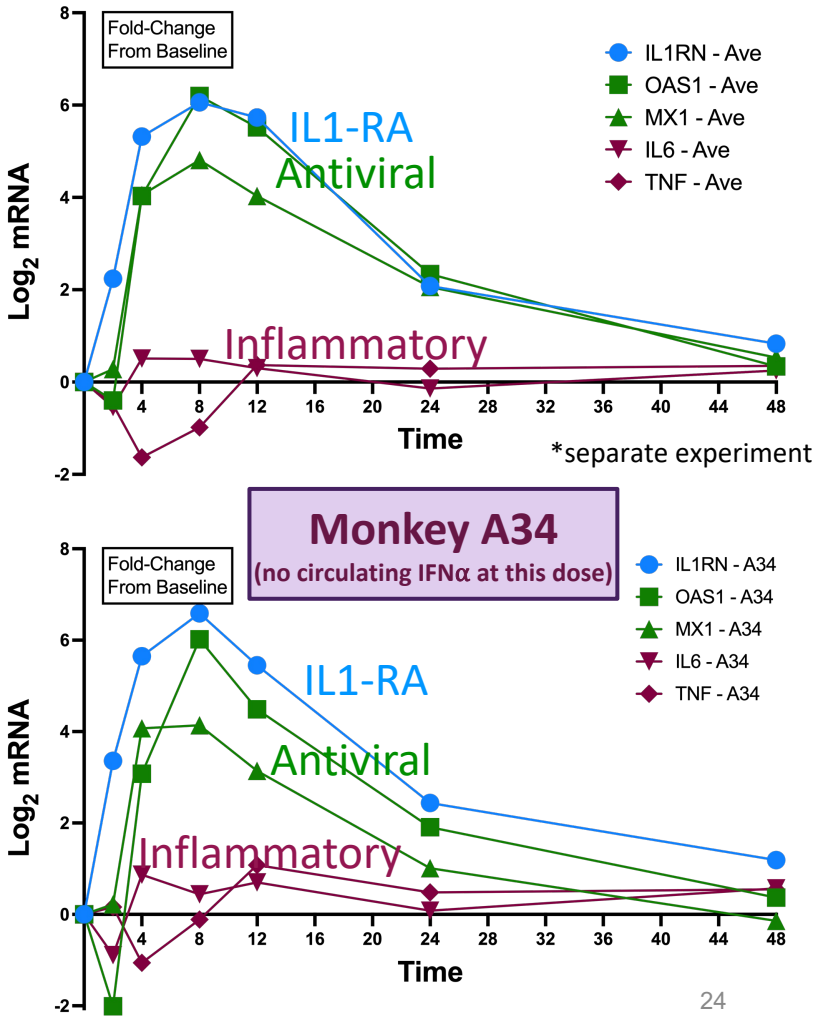
Prodrug TLR7 Agonist

First-Dose Response



Substantial Induction IFNα-Regulated Genes

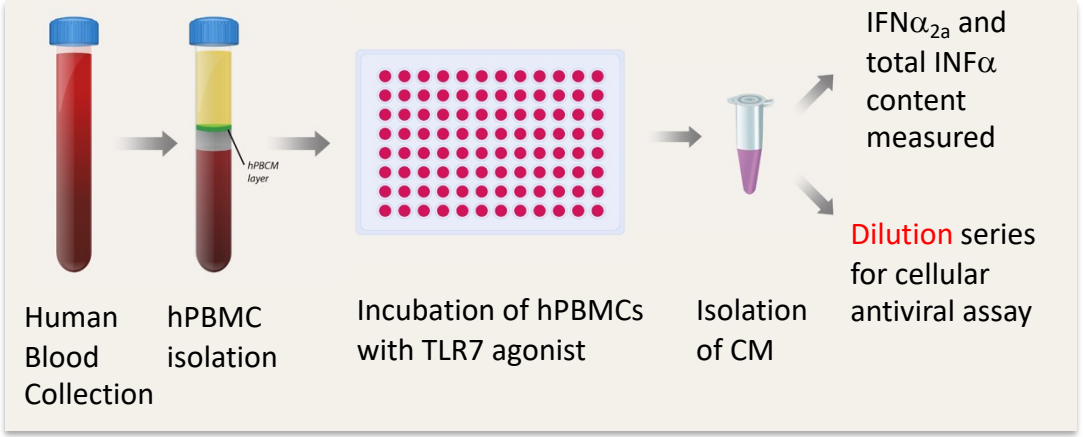
125 mg/kg Dose Group (n=5)*

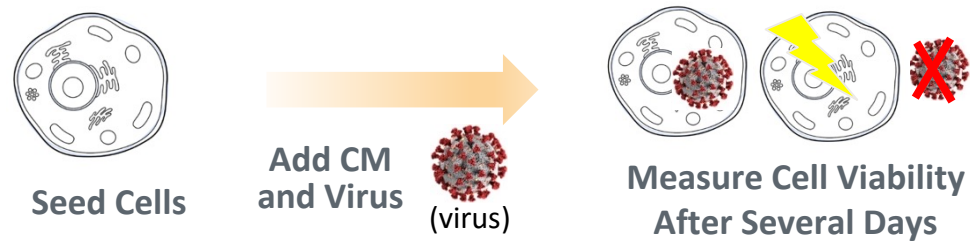


PRTX007 *In Vitro* Viral Challenge Studies: Broad-Spectrum Antiviral Activity Demonstrated Against SARS-CoV-2 and Other RNA Viruses

Inhibition of viral replication by PRTX007 Conditioned Media (CM) is substantially greater than an equivalent amount of IFNα2a added directly to the assay (EC_{50} ratio>1)

Immune Evasion in Serious Disease	EC_{50} as IFNα2a in Assay (pg/ml)		
	CM IFNα2a	Exogenous IFNα2a	Exog. IFNα2a/ CM
✓ SARS-CoV-2 USA WA1/2020	44	5,000	113
Coronavirus 229E*	< 3	< 3,000	-
Influenza H1N1	19	54	2.9
✓ RSV A2**	21	1950	16
Rhinovirus-15	12.9	1,000	77
✓ HCV 1b (Replicon)	< 0.03	< 0.3	-
✓ Dengue Serotype 2	< 3	< 300	-
✓ Zika PRVABC59	0.5	5	10





- Evaluates solely the impact of secreted factors, notably IFNs from pDCs
- Does not include the antiviral benefits of cell-cell interactions in controlling virus-associated cellular pathology and transmission

*6 days post-infection. **prophylaxis

Primmune's Systemically Administered TLR7 Agonist Is Active In A Difficult To Treat Mouse Model of RSV Lung Infection

Primmune's systemic TLR7 agonist:

- Was administered by IV bolus as PRX118, a very soluble form of the clinical candidate
- Achieved viral load reduction comparable to that observed with intranasal IFNα and imiquimod *(virus measured in the lung by RT-PCR* [Viral RNA] *and infectivity of cultured cells* [Viral Titer]*)*
- **No evidence of toxicity or adverse effects of treatment with this systemic TLR7 agonist**

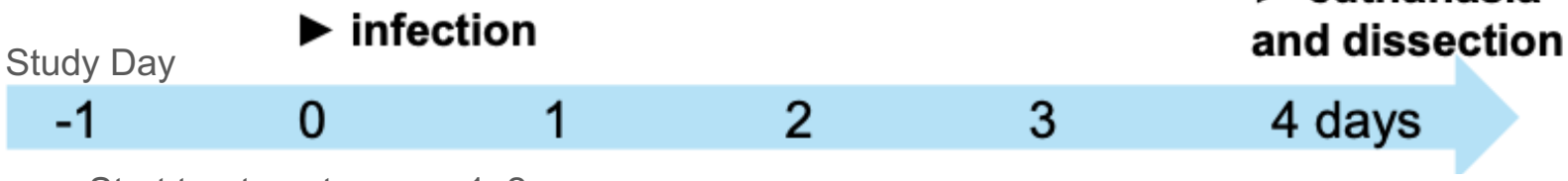
➢ **Results of this study support clinical investigation of PRTX007 in RSV-infected patients**

Treatment Groups

1) Control
2) IV PRX118 28 hrs prior to infection (Q12h)
3) IV PRX118 4 hrs prior to infection (Q12h)
4) Intranasal interferon (Q24h)
5) Intranasal imiquimod (Q24h)

Animals
Balb/c mice (n=6/group)

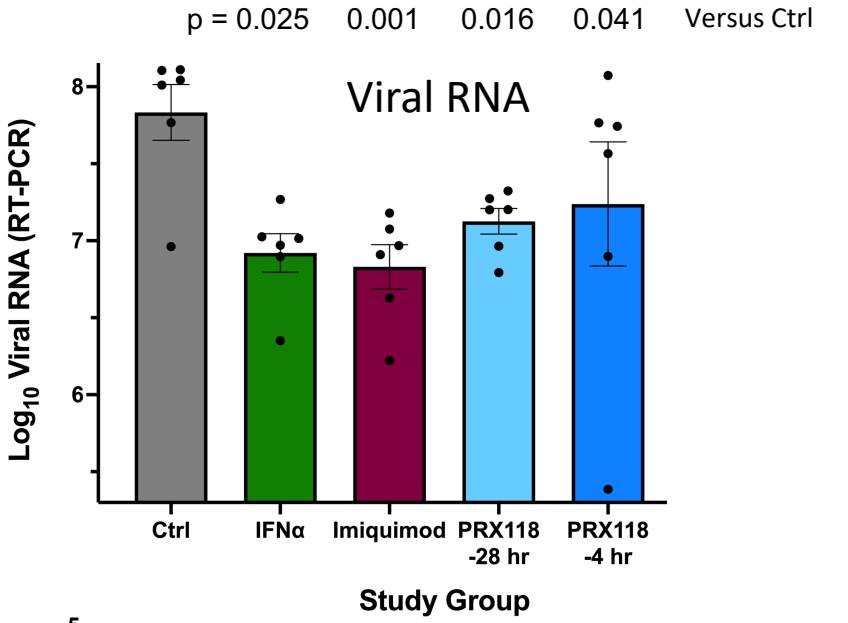
Infection
Intranasal infection with RSV-A2 across both nares, ~6x10^6 pfu/ml

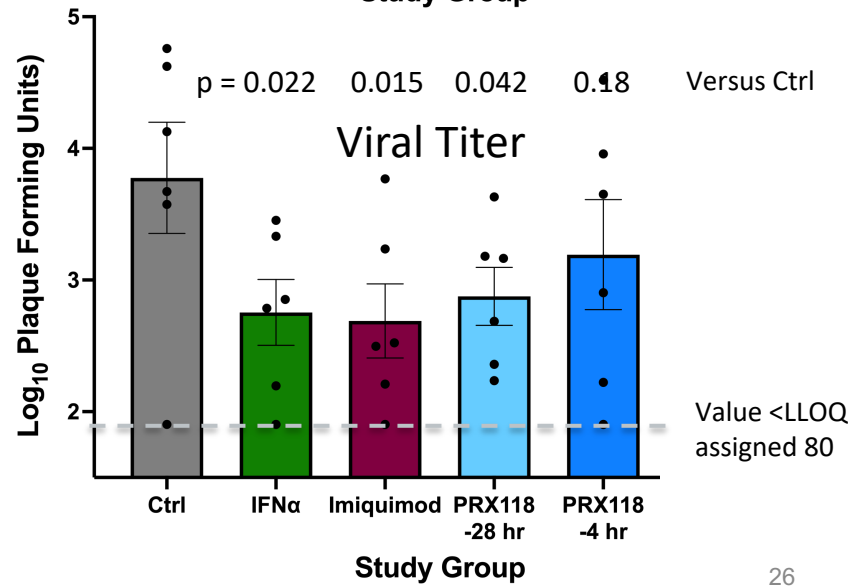


> Start treatment groups 1, 2

> Start treatment groups 3, 4, 5*

* intranasal drug adminstration initiated 1 hr post infection (Groups 4, 5)



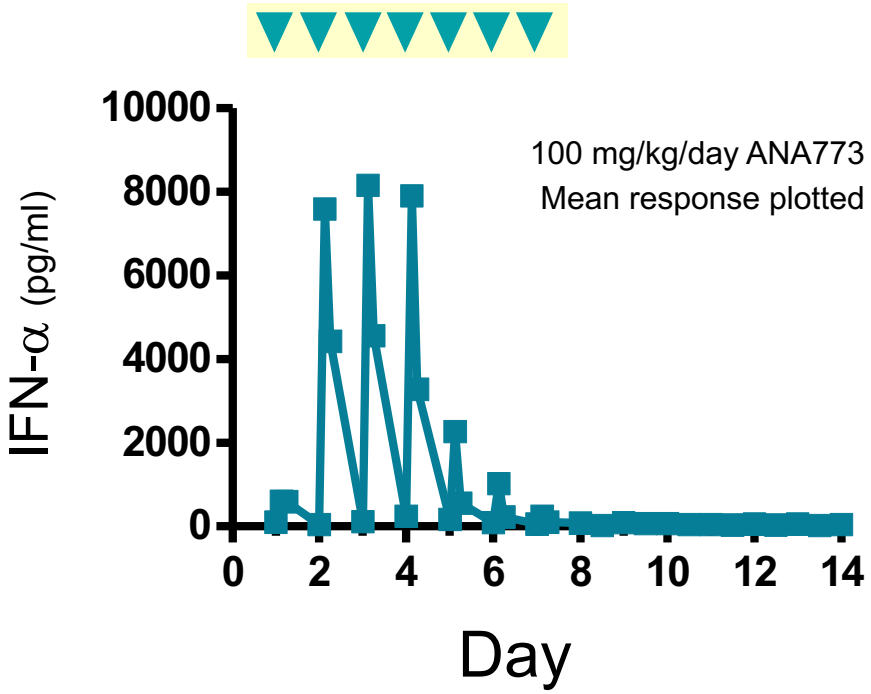


In Conclusion

- 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, have features that make it ideal for treatment of early-stage SARS-CoV-2 infection and other viral infections
  - Minimal proinflammatory potential
  - Systemic distribution and activation of target cells
  - Frequent (e.g. QOD) dosing to maintain immune pressure while avoiding counter-regulation
  - Some of these features make PRTX007 highly appropriate for chronic use in treating viral infections and cancer, including in combination with immune checkpoint inhibitors
- Clinical evaluation of PRTX007 on a QOD dosing schedule in healthy volunteers is in progress
  - Findings to date as expected based upon preclinical experimental results

Backup

QD Dosing of ANA in Primates: Induction and Tolerance in Cytokine Response



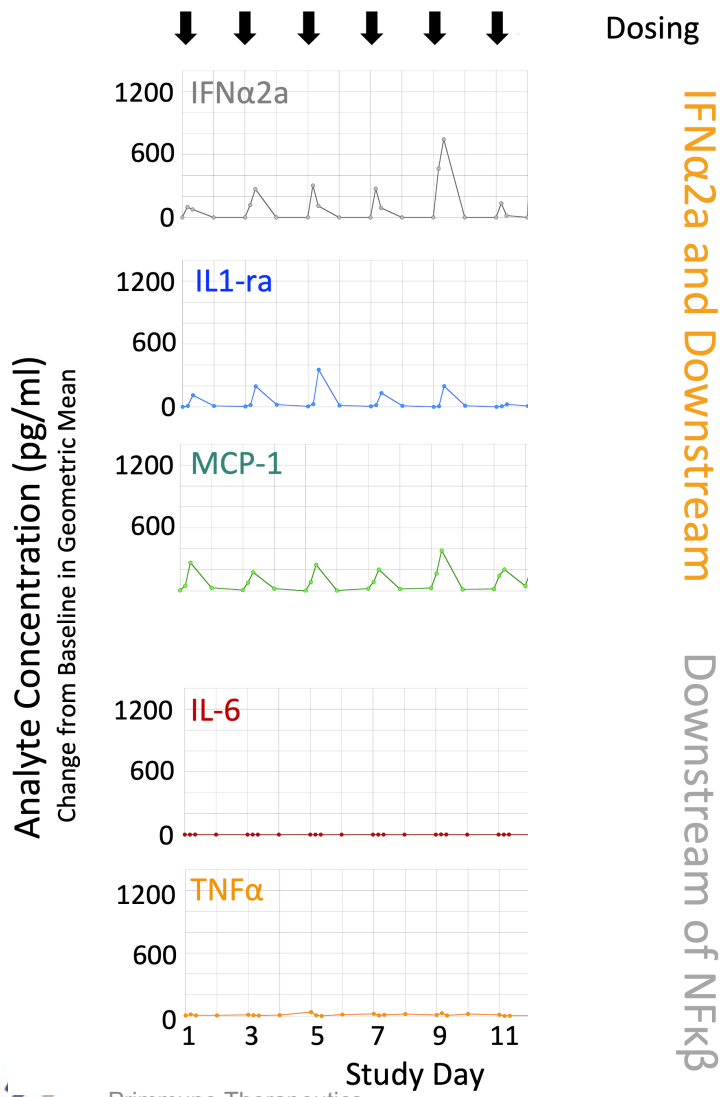
Tan et al. AACR 2008 Abstract 2079

- This pattern of response is observed:
  - when measuring levels of a variety of cytokines and chemokines
  - with TLR7 agonists of entirely different structural classes
  - independently of route of administration
  - even at low doses of agonist where extent of maximal stimulation is relatively small (i.e. independent of magnitude of cytokine response)
- This pattern is not attributable to changes in exposure to agonist over time
- **Immune cell proliferation does not display this tolerance**

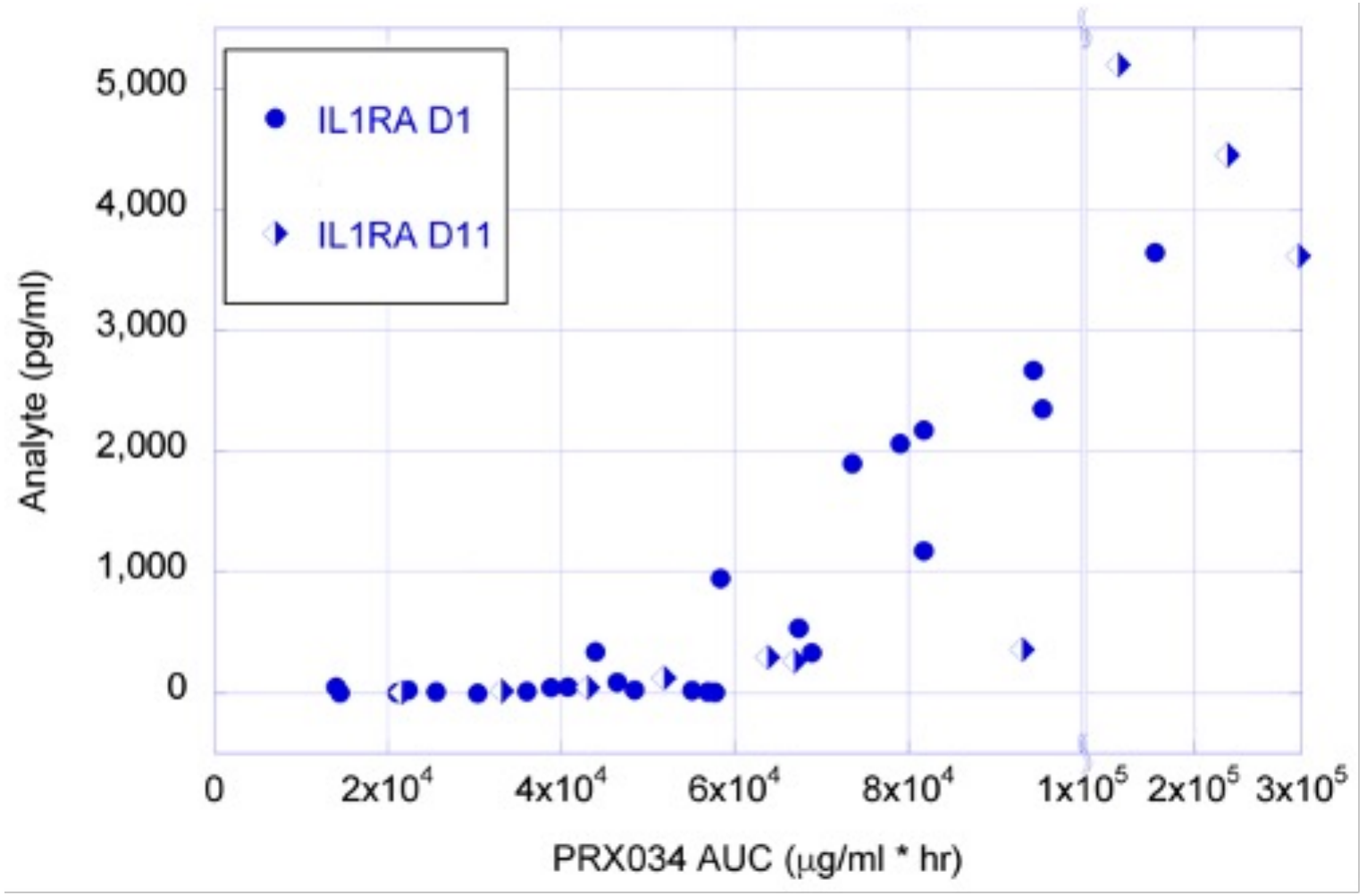
Profile Maintained in Repeat-Dose Cynomolgus Monkey Study

Repeate Dose Response

(125 mg/kg)



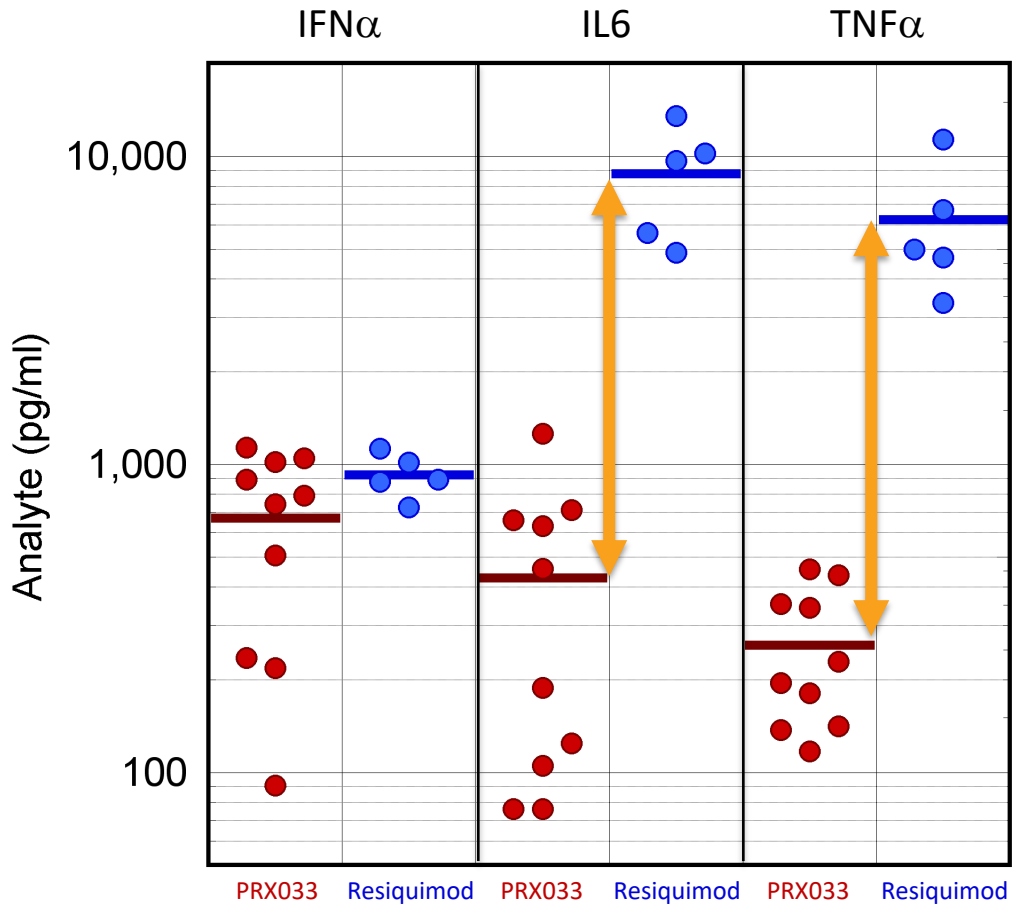
D1/D11 PK/PD Maintained



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

TLR7 Expression in Mice Includes Macrophages & Other Producers of Pro-inflammatory Factors



PRX033: 40 mg/kg Resiquimod: 0.6 mg/kg

primmune
Therapeutics