

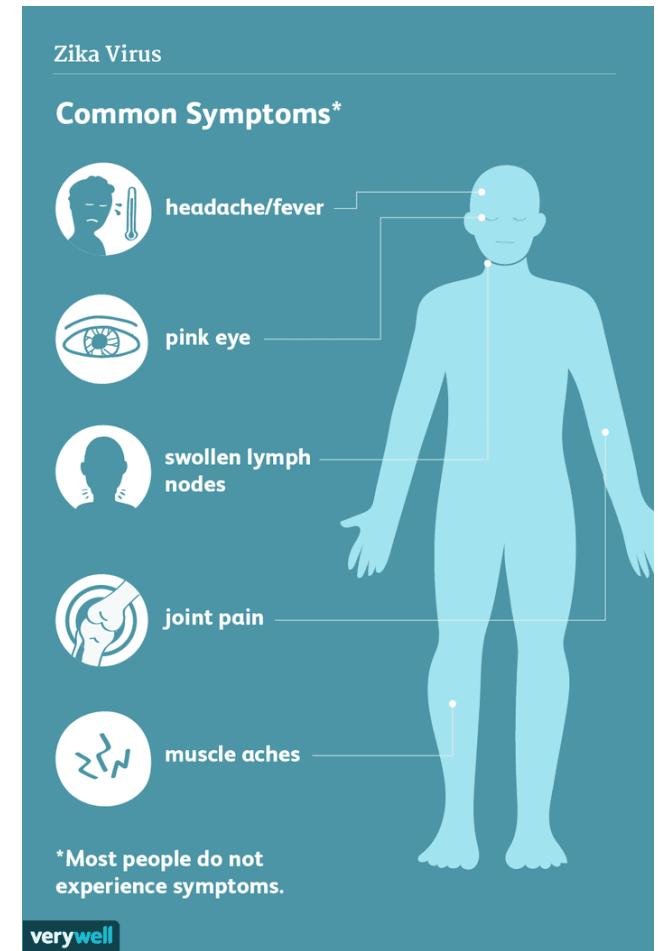
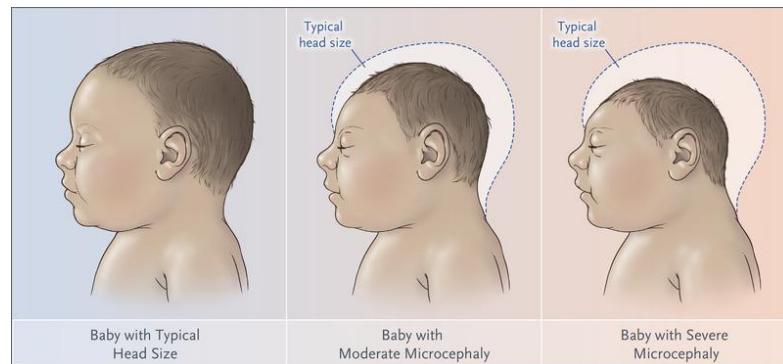
Optimization of antiviral therapies for the treatment of Zika virus by mathematical modeling

Tae Hwan Kim

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Worldwide prevalence of Zika virus (ZIKV) infection

- Serious and long-term health consequences associated with infection, especially during pregnancy, where devastating birth defects such as microcephaly, brain damage, and fetal loss have been reported.
- Neurological complications have also been linked to ZIKV infection in adults



Development of therapy against ZIKV infection

- What is the **minimal effective dose** of a drug and **how often do we need to give** that drug to maximize viral suppression and prevent resistance.
- **Antiviral therapies for ZIKV do not exist.**
- **Drug repurposing strategy:** New use for existing drug(s).
 - Safety and Pharmacokinetics (including drug metabolism) profiles are defined
 - Formulation and bulk manufacturing process are complete

Focused on Antiviral Agents with Broad-Spectrum Activity



Ribavirin

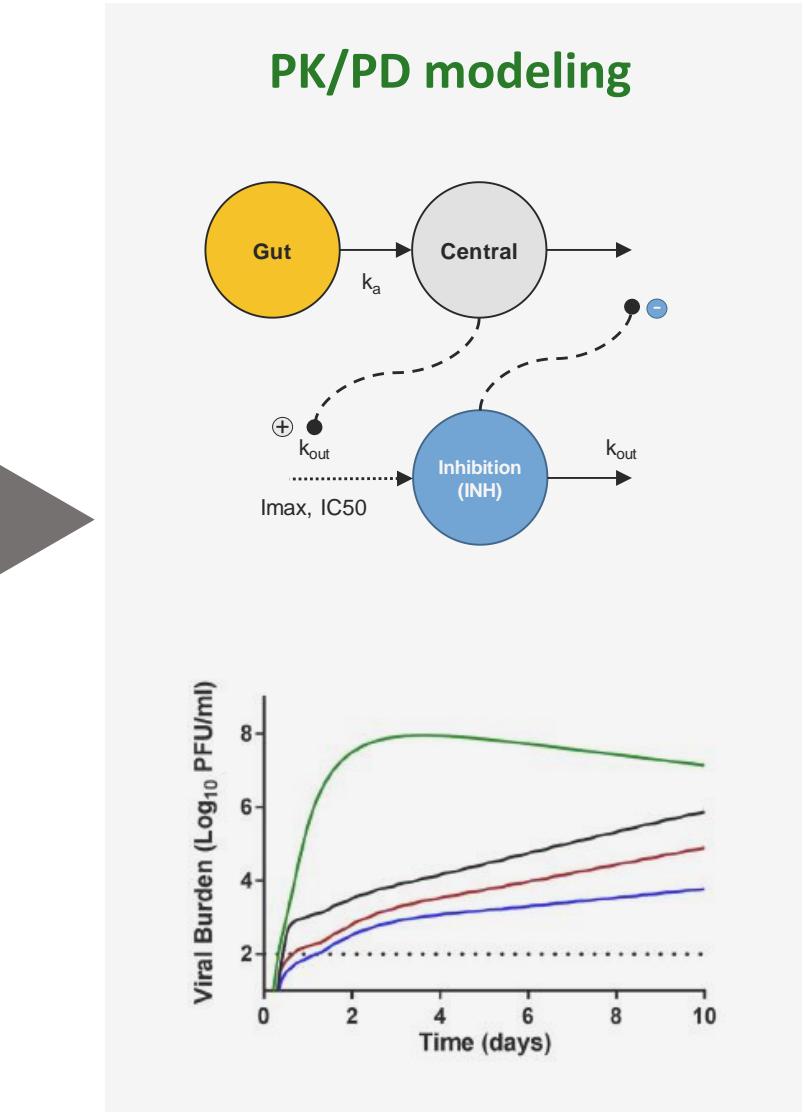
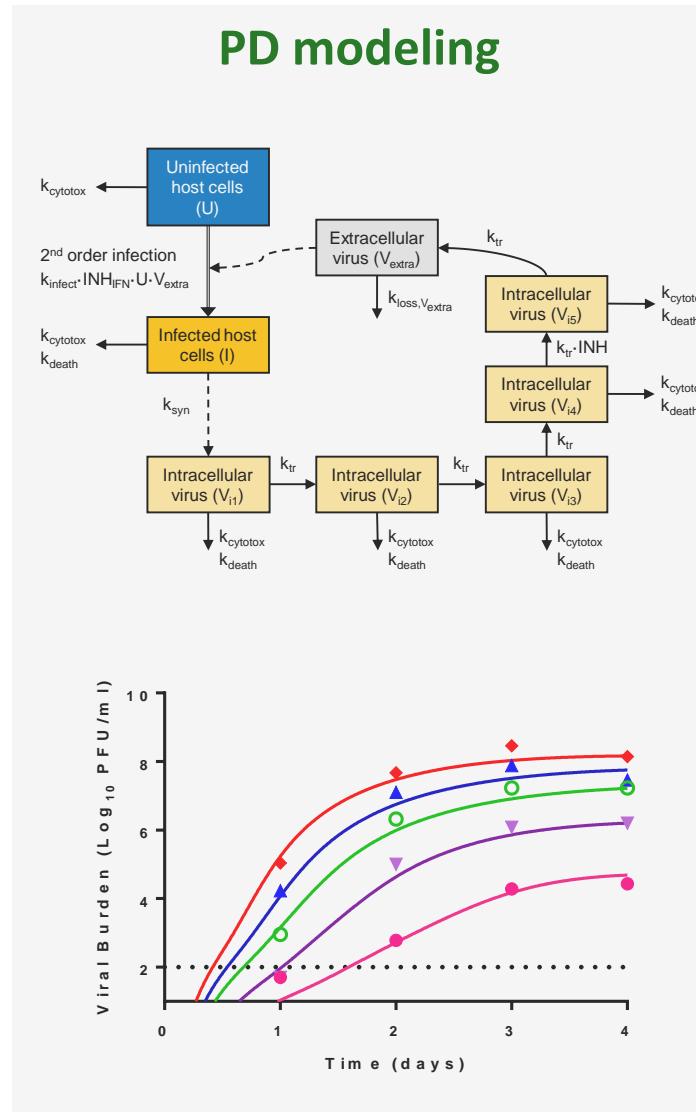
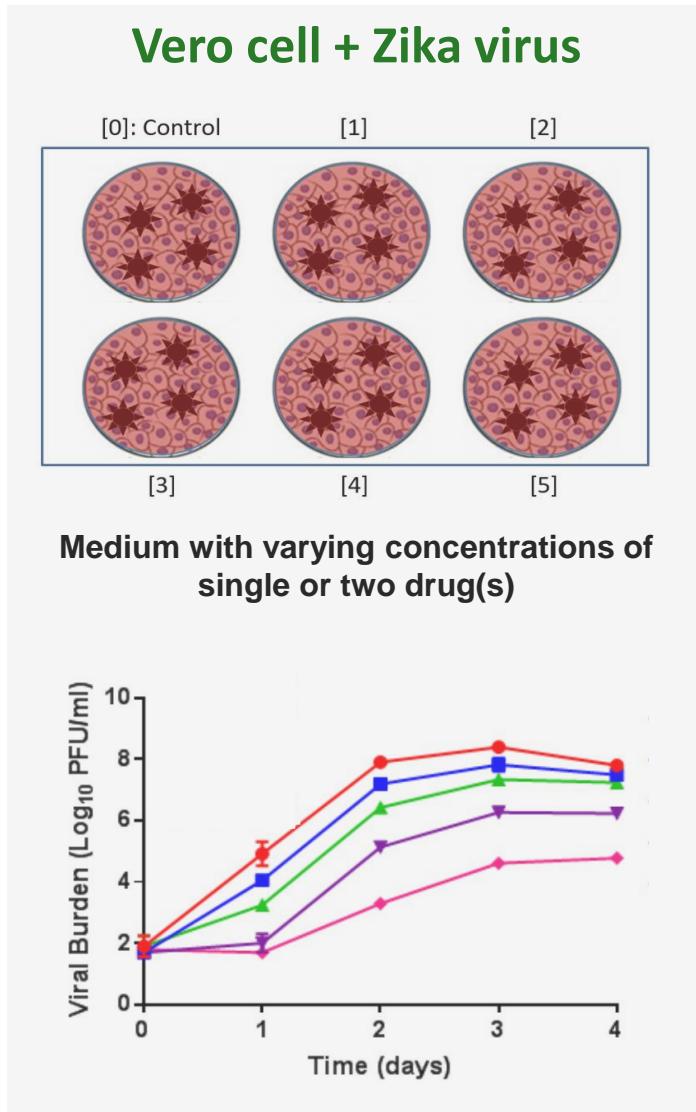


Interferon-a

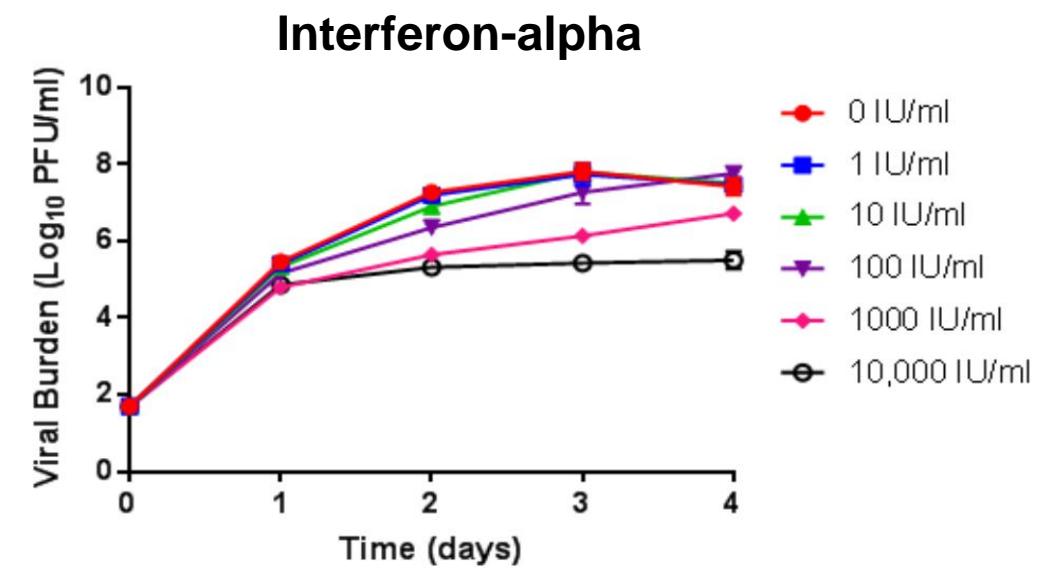
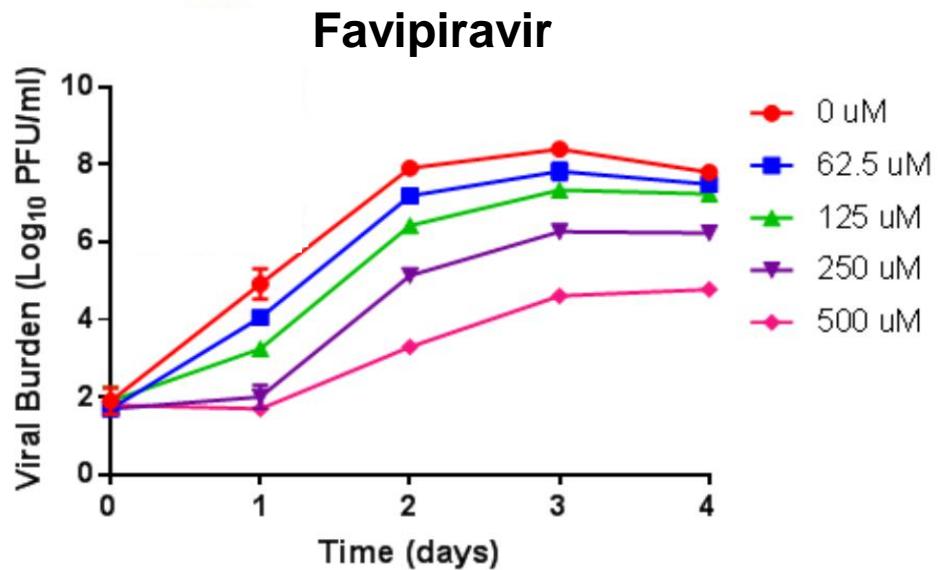


Favipiravir

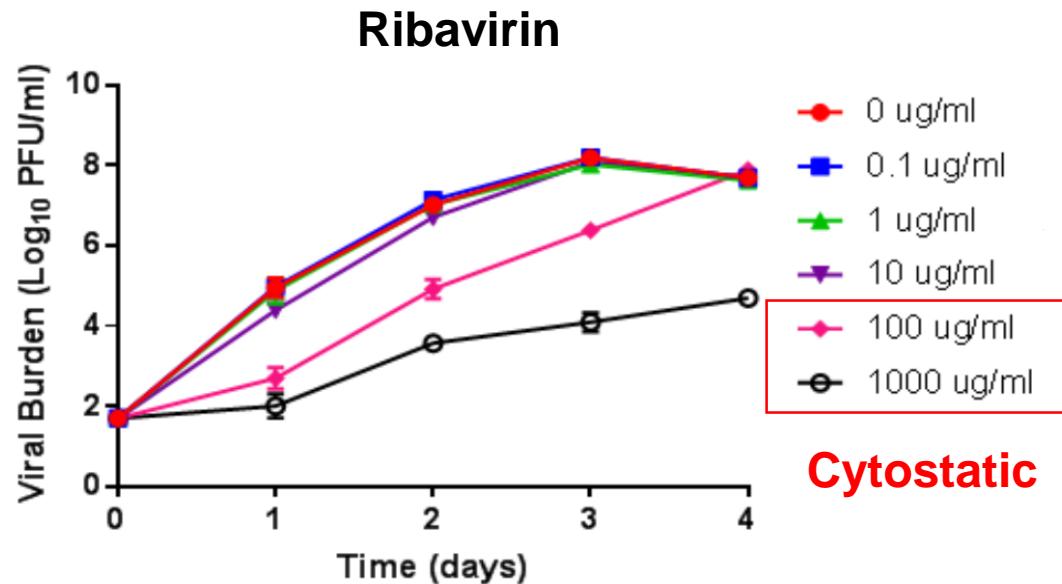
Research design



Monotherapy results



FAV and RBV
suppressed the
production of infections
ZIKV

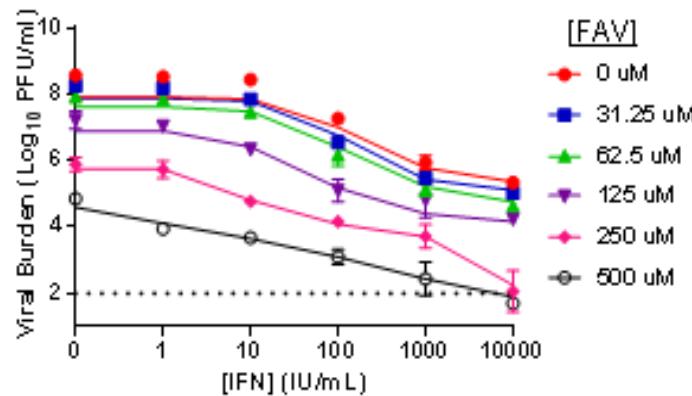


Cytostatic

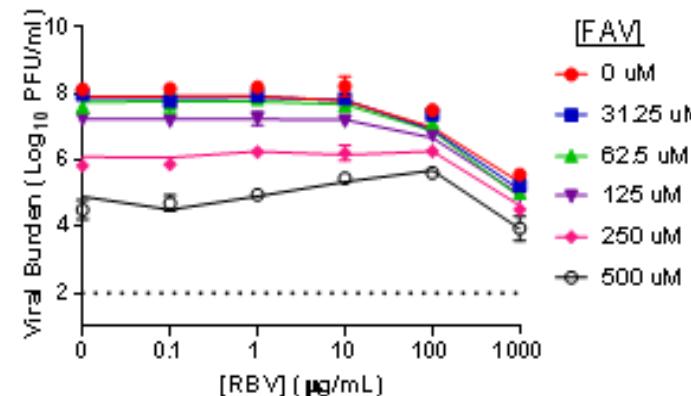
Continued suppression
was achieved
at 10,000 IU/mL of IFN

Combination therapy results

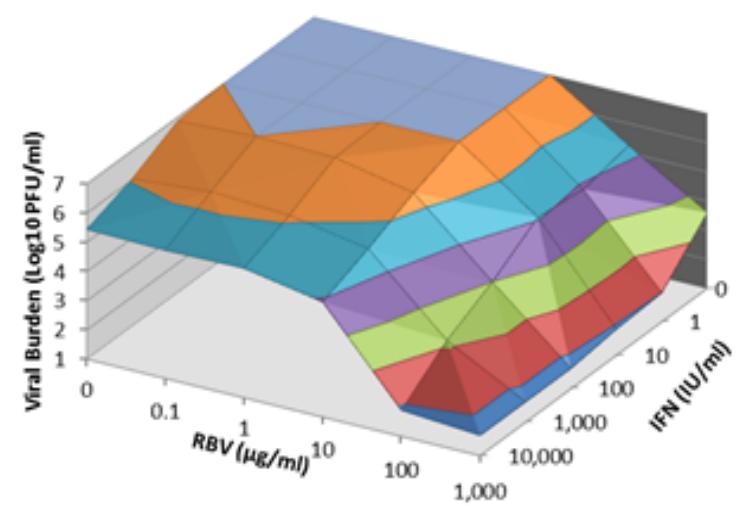
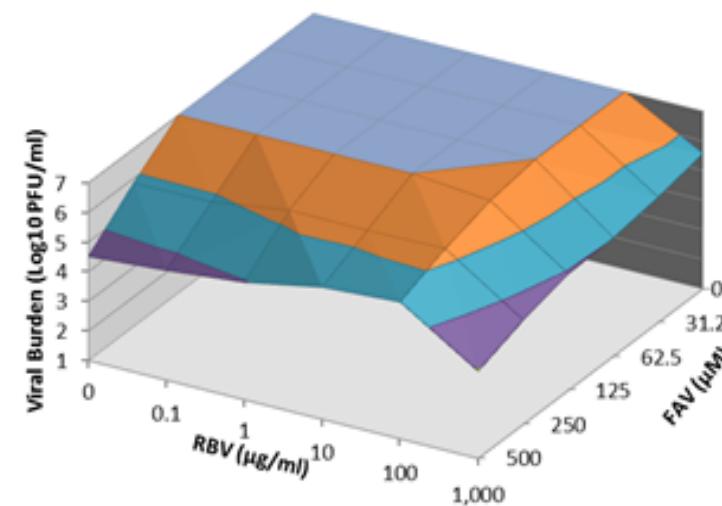
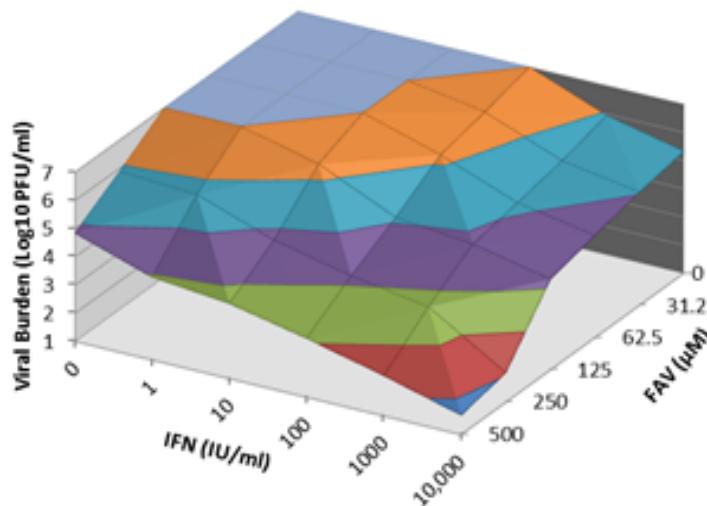
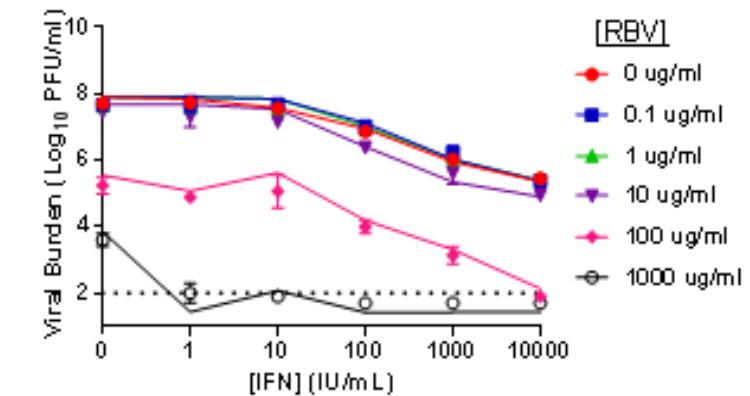
FAV+IFN combotherapy



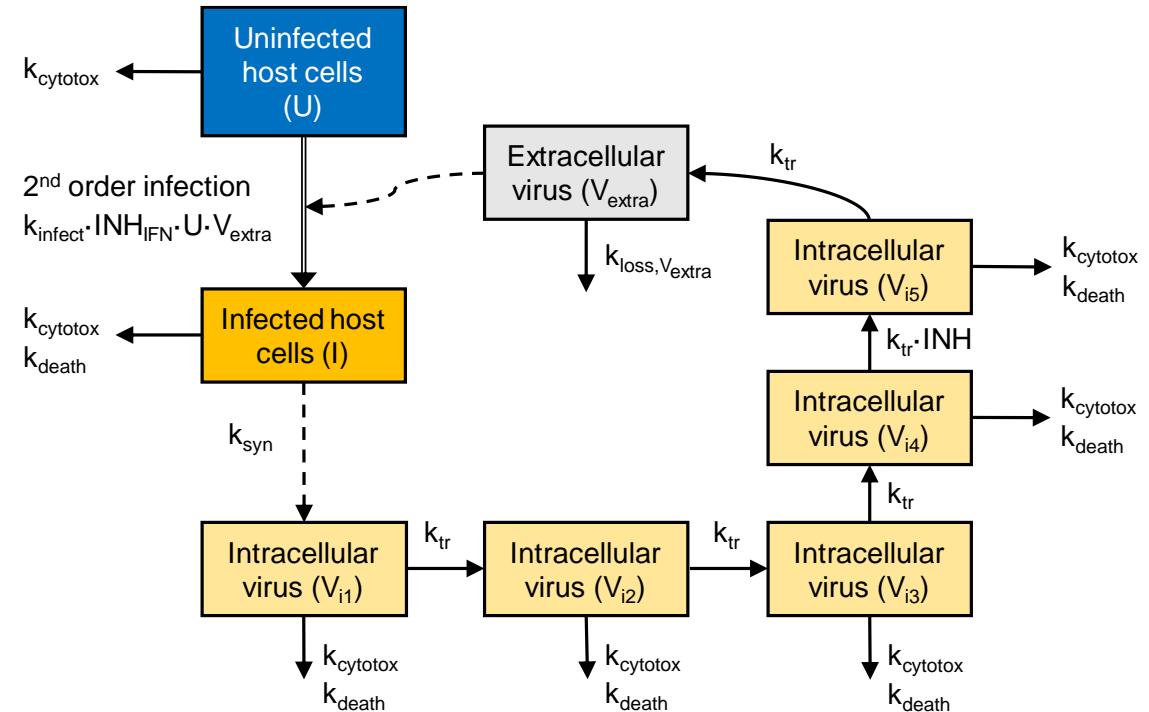
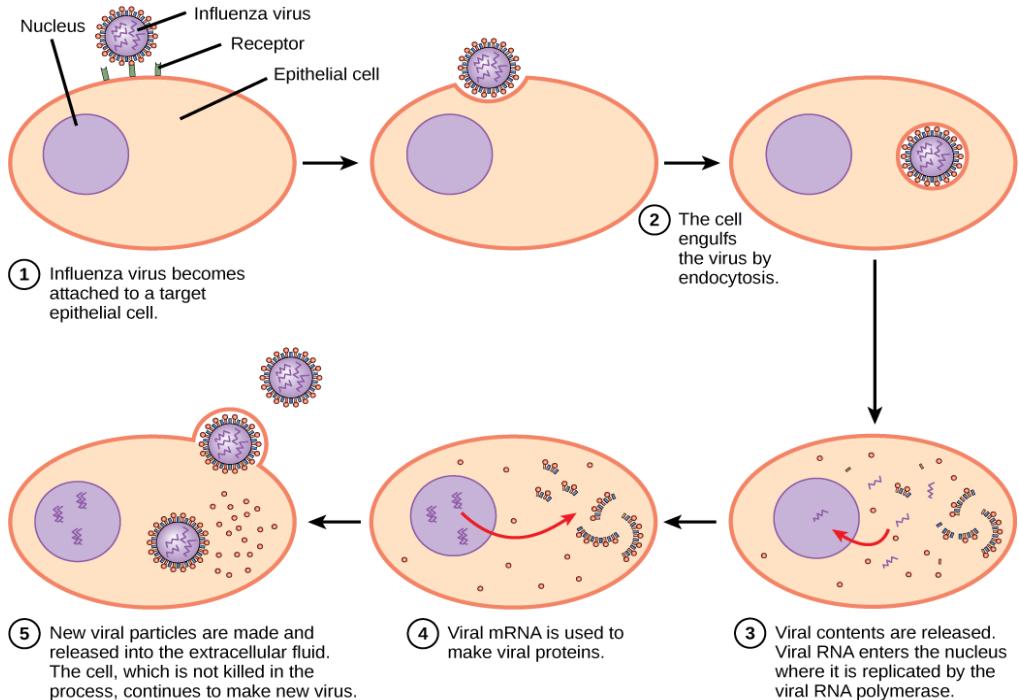
FAV+RBV combotherapy



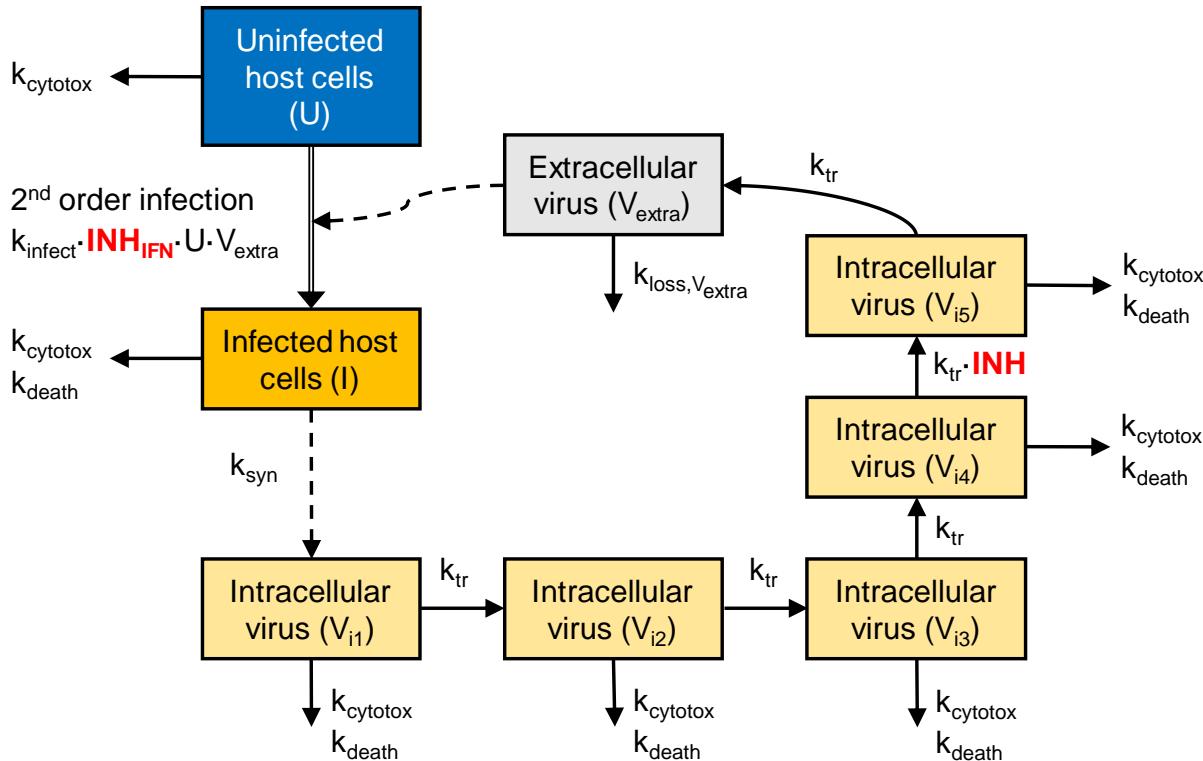
RBV+IFN combotherapy



Mechanism-based pharmacodynamic modeling



Mechanism-based pharmacodynamic modeling



k_{infect} : Infection of host cells

k_{death} : Infected cell death

$k_{cytotox}$: Cytotoxicity of RBV

k_{syn} : Intracellular virus synthesis

k_{tr} : Virus maturation and replication

k_{loss} : Loss of extracellular virus

$$INH_{IFN} = 1 - I_{max\ IFN} \times \frac{C_{IFN}^{Hill_{IFN}}}{C_{IFN}^{Hill_{IFN}} + IC_{50_IFN}^{Hill_{IFN}}}$$

$$INH_{FAV} = 1 - I_{max\ FAV} \times \frac{C_{FAV}^{Hill_{FAV}}}{C_{FAV}^{Hill_{FAV}} + IC_{50_FAV}^{Hill_{FAV}}}$$

$$INH_{RBV} = 1 - I_{max\ RBV} \times \frac{C_{RBV}^{Hill_{RBV}}}{C_{RBV}^{Hill_{RBV}} + IC_{50_RBV}^{Hill_{RBV}}}$$

$$k_{cytotox} = S_{max\ RBV} \frac{C_{RBV}^{Hill_{RBVTOX}}}{C_{RBV}^{Hill_{RBVTOX}} + SC_{50_RBV}^{Hill_{RBVTOX}}}$$

Mechanism-based pharmacodynamic modeling

Competitive interaction model

$$INH = 1 - \frac{Imax_{FAV} \cdot (C_{FAV}/PSI \cdot IC_{50_FAV})^{Hill_{FAV}} + Imax_{RBV} \cdot (C_{RBV}/PSI \cdot IC_{50_RBV})^{Hill_{RBV}}}{(C_{FAV}/PSI \cdot IC_{50_FAV})^{Hill_{FAV}} + (C_{RBV}/PSI \cdot IC_{50_RBV})^{Hill_{RBV}} + 1}$$

In FAV mono

$$INH_{FAV} = 1 - Imax_{FAV} \cdot \frac{C_{FAV}^{Hill_{FAV}}}{C_{FAV}^{Hill_{FAV}} + IC_{50_FAV}^{Hill_{FAV}}}$$

In RBV mono

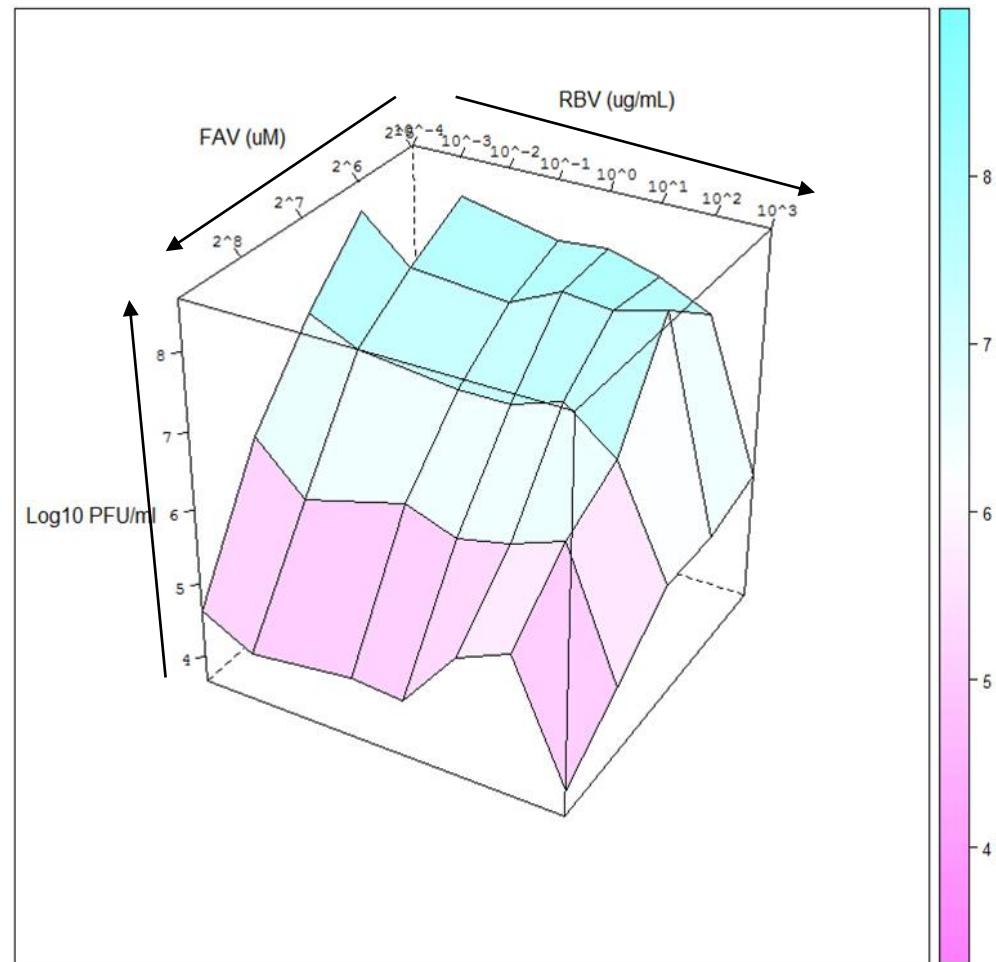
$$INH_{RBV} = 1 - Imax_{RBV} \cdot \frac{C_{RBV}^{Hill_{RBV}}}{C_{RBV}^{Hill_{RBV}} + IC_{50_RBV}^{Hill_{RBV}}}$$

Antagonism explained by

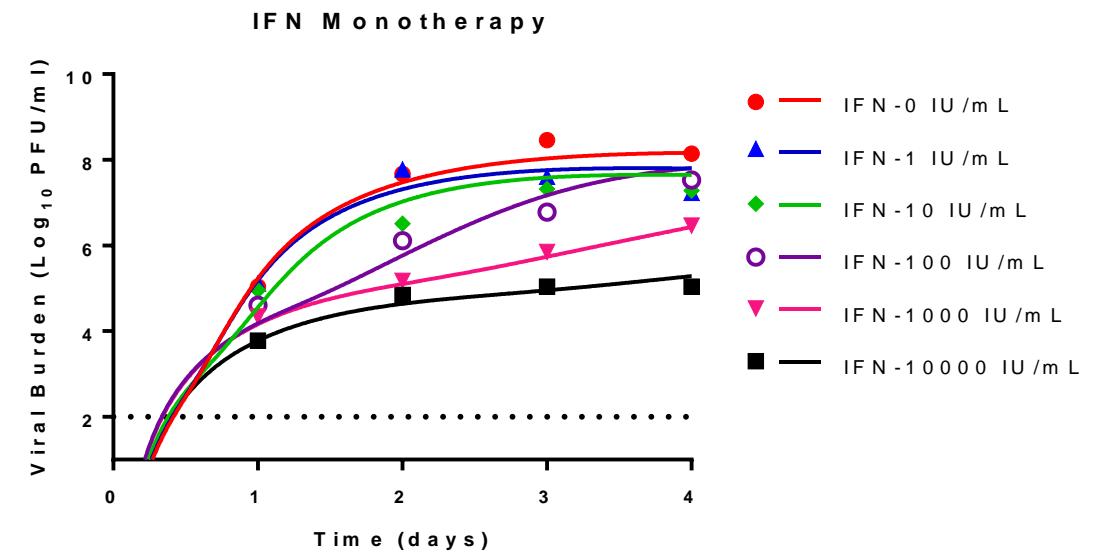
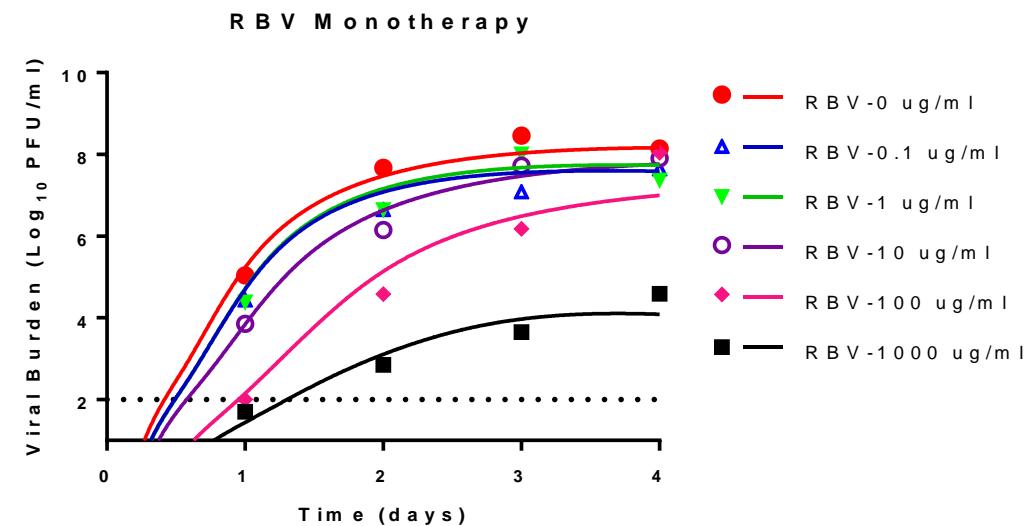
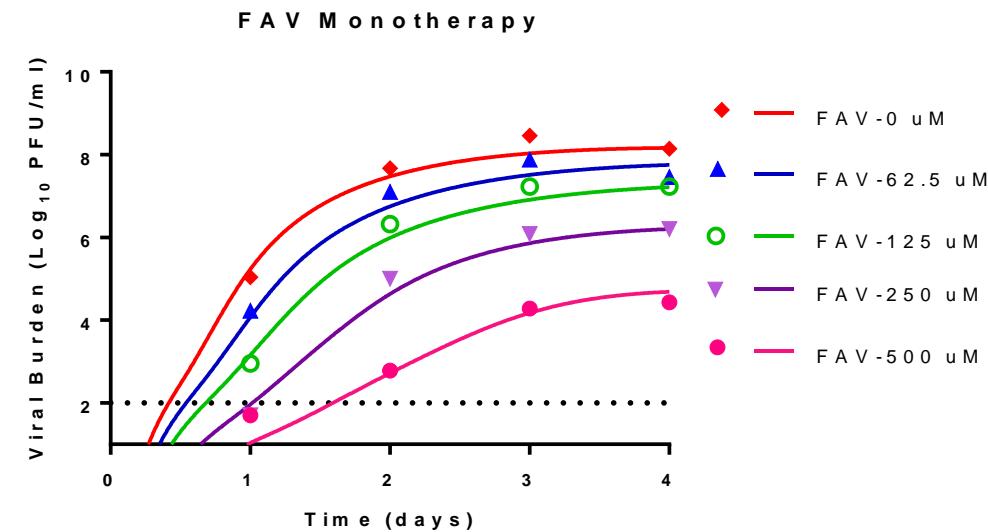
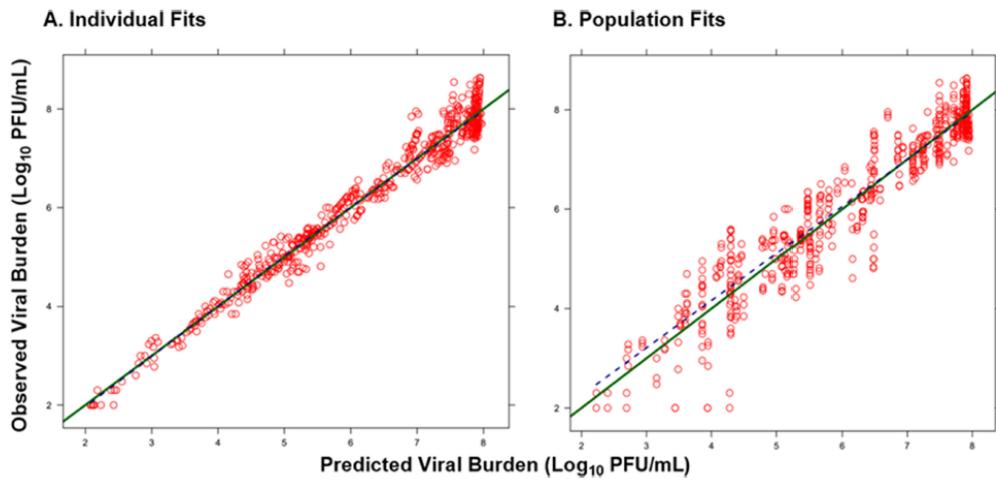
- (1) Competition target occupancy. And RBV crowd out FAV, resulting in incomplete inhibition ($Imax = 0.92$)
- (2) Interaction factor, $PSI > 1$

Chakraborty, Abhijit, and William J. Jusko. "Pharmacodynamic Interaction of Recombinant Human Interleukin-10 and Prednisolone Using in vitro Whole Blood Lymphocyte Proliferation." Journal of Pharmaceutical Sciences 91, no. 5 (2002): 1334-342. doi:10.1002/jps.3000.

INTERACTION FACTOR: PSI = 1.73 (ANTAGONISM)



Mechanism-based pharmacodynamic modeling



Pharmacokinetic modeling

T705_Report on the Deliberation Results (2014)

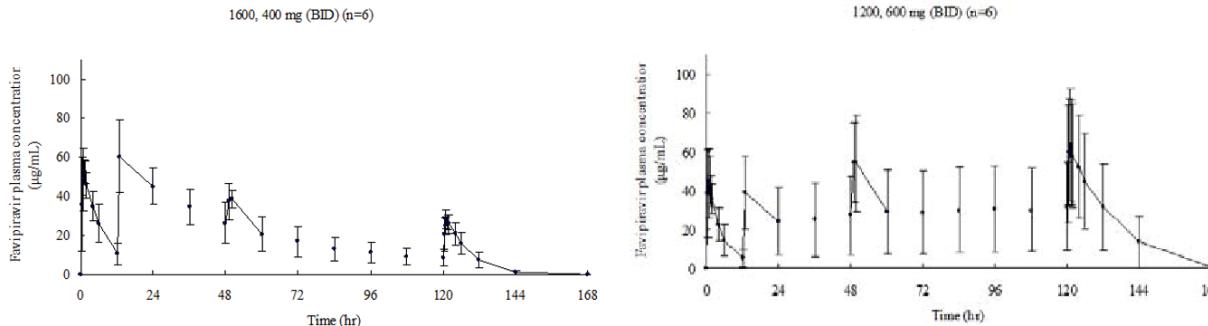
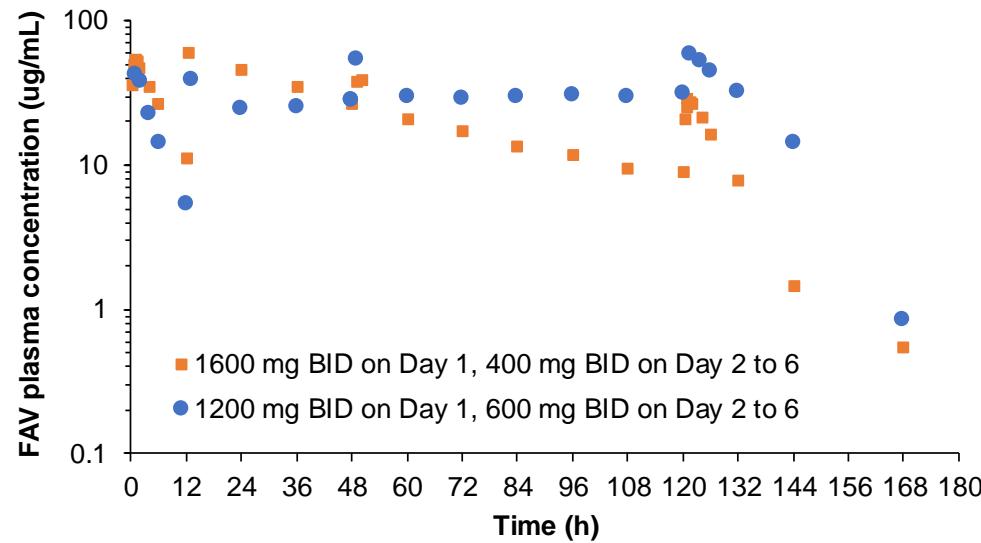


Figure. Plasma concentration profile of favipiravir (mean \pm SD)



Single dose study

Pharmacokinetic parameters of favipiravir following single oral dose of favipiravir at 30 to 1600 mg

Pharmacokinetic parameter	30 mg	90 mg	200 mg	400 mg	800 mg	1600 mg
$C_{max}^{a)} (\mu\text{g}/\text{mL})$	1.39 (17.9)	4.06 (17.4)	8.39 (11.1)	16.59 (6.0)	33.35 (22.6)	78.61 (26.5)
$t_{max}^{c)} (\text{hr})$	0.5 (0.25, 0.5)	0.5 (0.25, 0.75)	0.5 (0.5, 0.5)	0.5 (0.25, 0.75)	0.9 (0.5, 1)	0.6 (0.5, 0.75)
$AUC^{a)} (\mu\text{g}\cdot\text{hr}/\text{mL})$	2.58 (20.2)	9.23 (12.6)	19.67 (18.2)	39.41 (16.0)	113.15 (26.6)	538.42 (9.7)
$t_{1/2}^{b)} (\text{hr})$	1.3 \pm 0.1	1.5 \pm 0.1	1.5 \pm 0.2	1.6 \pm 0.2	2.2 \pm 0.3	3.9 \pm 0.3
$CL/F^{b)} (\text{L}/\text{hr})$	11.80 \pm 1.92	9.81 \pm 1.28	10.35 \pm 2.24	10.26 \pm 1.63	7.31 \pm 2.17	2.98 \pm 0.30
$Vd/F^{b)} (\text{L})$	21.54 \pm 1.93	21.44 \pm 2.86	22.61 \pm 3.84	23.80 \pm 3.15	22.45 \pm 3.00	16.73 \pm 1.55
$MRT^{b)} (\text{hr})$	2.0 \pm 0.3	2.3 \pm 0.2	2.4 \pm 0.3	2.5 \pm 0.3	3.5 \pm 0.7	7.0 \pm 0.7
$UR^{b,d)} (\%)$	0.0 \pm 0.0	0.2 \pm 0.2	0.3 \pm 0.1	0.2 \pm 0.1	0.3 \pm 0.0	0.5 \pm 0.1

a) Geometric mean (CV%), b) Mean \pm SD, c) Median (minimum, maximum)

d) Urinary excretion rate from 0 to 48 hours (calculated from the data in 5 subjects in the 90 mg group, except for those in 1 subject who disposed of the urine)

n = 6 per group

Saturated elimination/Auto inhibition

Multiple dose study

Table. Pharmacokinetic parameters in the subjects receiving favipiravir BID

	1600/400 mg BID				1200/600 mg BID			
	Favipiravir		M1		Favipiravir		M1	
	Day 1 (1600 mg)	Day 6 (400 mg)	Day 1 (1600 mg)	Day 6 (400 mg)	Day 1 (1200 mg)	Day 6 (600 mg)	Day 1 (1200 mg)	Day 6 (600 mg)
Number of subjects evaluated	6	6	6	6	6	6	6	6
$C_{max}^{a)} (\mu\text{g}/\text{mL})$	59.43 (15.1)	30.56 (13.4)	15.34 (28.4)	2.37 (22.3)	47.86 (28.9)	61.50 (41.4)	14.40 (16.4)	2.73 (20.3)
$t_{max}^{b)} (\text{hr})$	1.0 (0.5, 1.5)	1.0 (0.5, 2)	1.3 (0.75, 1.5)	1.3 (0.75, 4)	0.9 (0.5, 1.5)	0.8 (0.5, 1.5)	1.0 (0.75, 1.5)	1.0 (1, 1.5)
$AUC^{a,d)} (\mu\text{g}\cdot\text{hr}/\text{mL})$	397.79 (30.3)	193.69 (27.1)	86.08 (11.1)	19.24 (14.6)	229.65 (50.1)	470.53 (54.8)	71.64 (10.3)	26.39 (9.9)
$t_{1/2}^{c)} (\text{hr})$	4.6 (1.2)	4.5 (0.2)	4.1 (0.8)	6.1 (0.5)	3.4 (1.5)	5.8 (2.0)	3.0 (0.6)	11.3 (6.9)
$CL/F^{b)} (\text{L}/\text{hr})$	4.16 (1.12)	1.69 (0.53)	-	-	5.88 (3.03)	1.04 (0.80)	-	-
$Vd/F^{b)} (\text{L})$	23.91 (2.69)	10.98 (3.34)	-	-	23.18 (2.27)	7.35 (4.38)	-	-

$\tau = 12$ hours

a) Geometric mean (CV%), b) Median (minimum, maximum), c) Mean (SD), d) $AUC_{0-\infty}$ for Day 1 and AUC_{τ} for Day 6

Pharmacokinetic modeling



Antimicrobial Agents
and Chemotherapy®

Favipiravir Pharmacokinetics in Nonhuman Primates and Insights for Future Efficacy Studies of Hemorrhagic Fever Viruses

Vincent Madelain,^a Jérémie Guedj,^a France Mentré,^a Thi Huyen Tram Nguyen,^a Frédéric Jacquot,^b Lisa Oestereich,^{c,d} Takumi Kadota,^e Koichi Yamada,^e Anne-Marie Taburet,^f Xavier de Lamballerie,^{g,h} Hervé Raoul^b

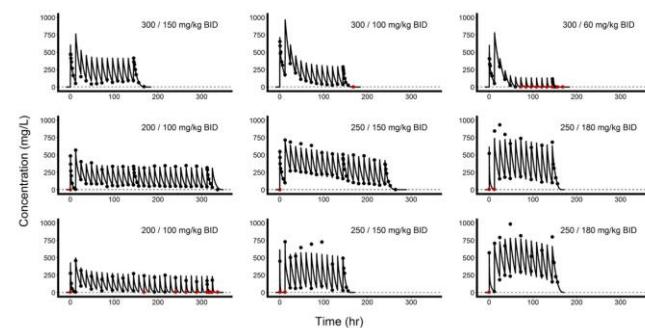
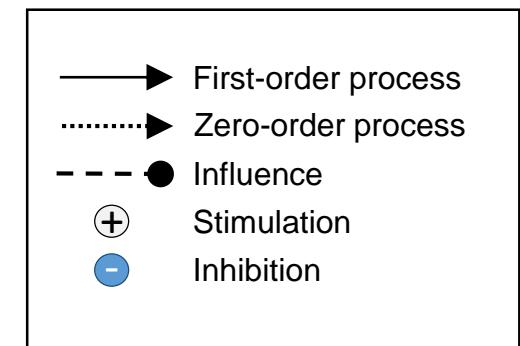
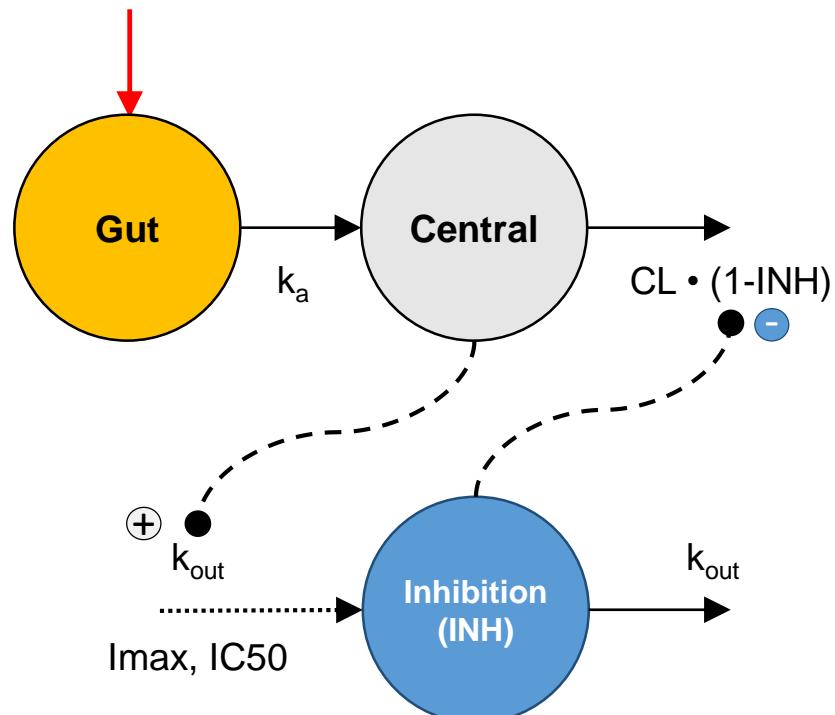


FIG 2 Individual observed concentrations (black dots) and model predictions (solid lines) for macaques treated with various dosing regimens. Red dots indicate data below the limit of quantitation, represented by dashed lines.

1600/400 mg BID (cohort 1)
1200/600 mg BID (cohort 2)

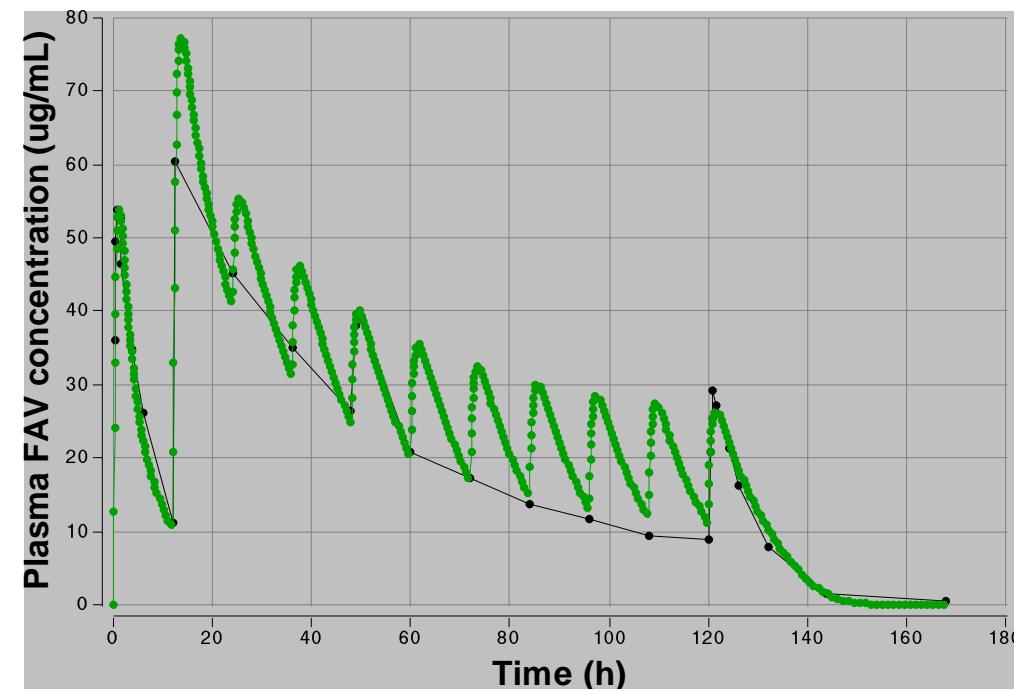
Model structure



Pharmacokinetic modeling

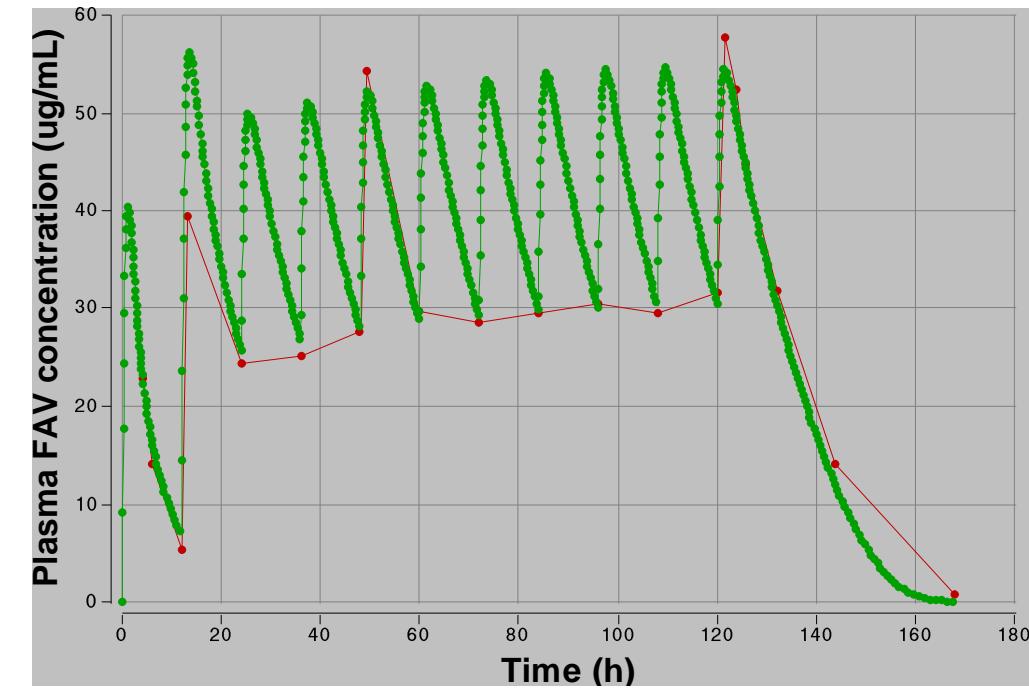
Observed vs. fitted plasma concentration-time profiles (Auto inhibition model)

1600 mg BID for day 1 and 400 mg BID for day 2-6 (cohort 1)



Predicted
Observed

1200 mg BID for day 1 and 600 mg BID for day 2-6 (cohort 2)

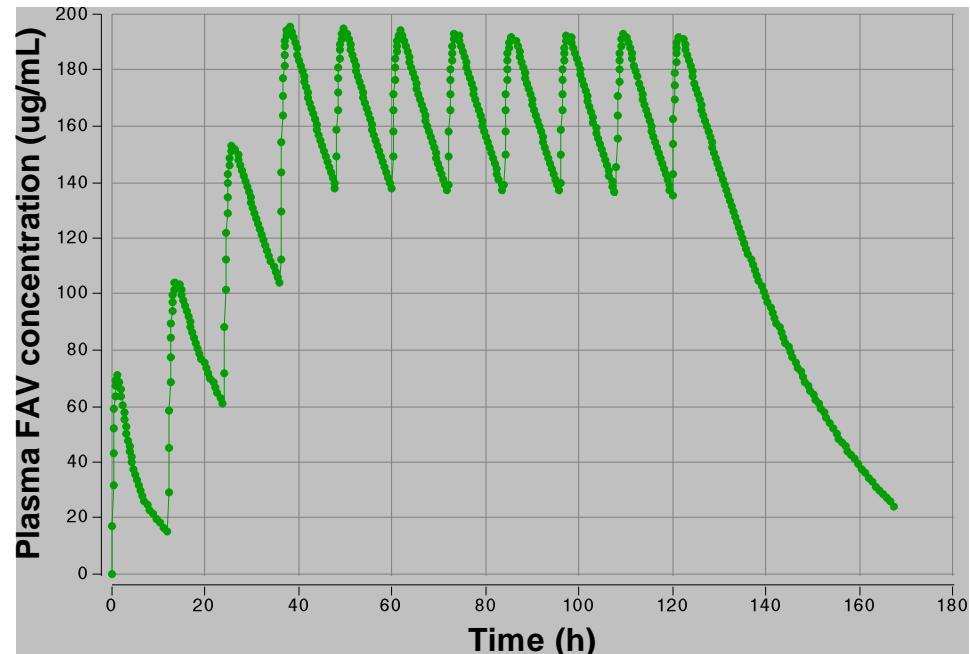


Predicted
Observed

Predicted plasma concentration-time profiles (Auto inhibition model)

Target concentration: 165, 85, 35 µg/mL

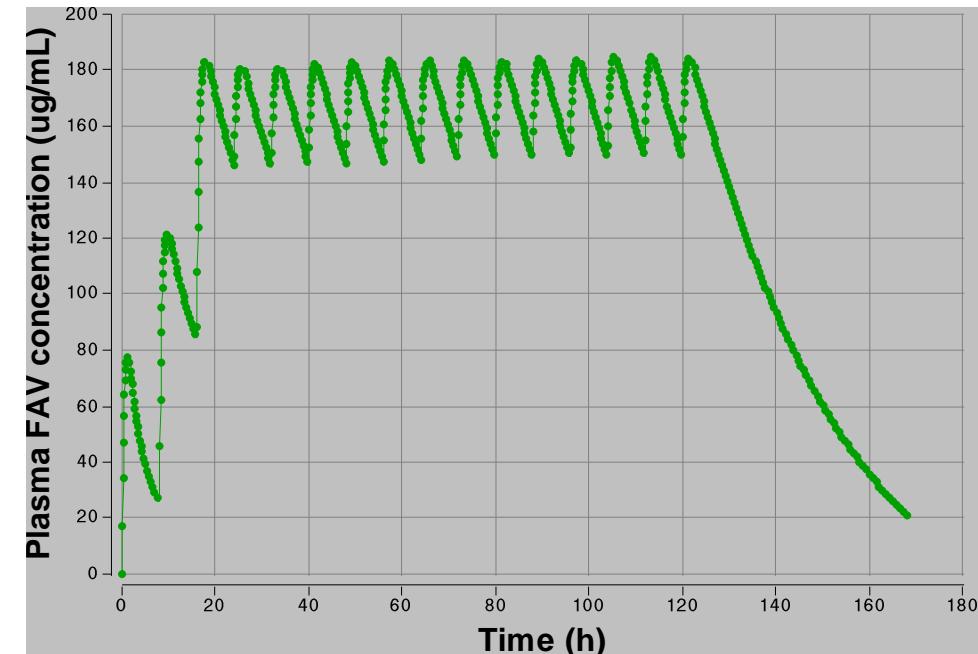
MW	157.1	157.1	157.1	
Target conc.	500	300	100	µM
Protein binding	0.53	0.53	0.53	
Plasma conc.	167.13	83.56	33.43	µg/mL



BID

Loading dose: 2100 mg (2 days)

Maintenance dose: 1400 mg



TID (interval: 8 h)

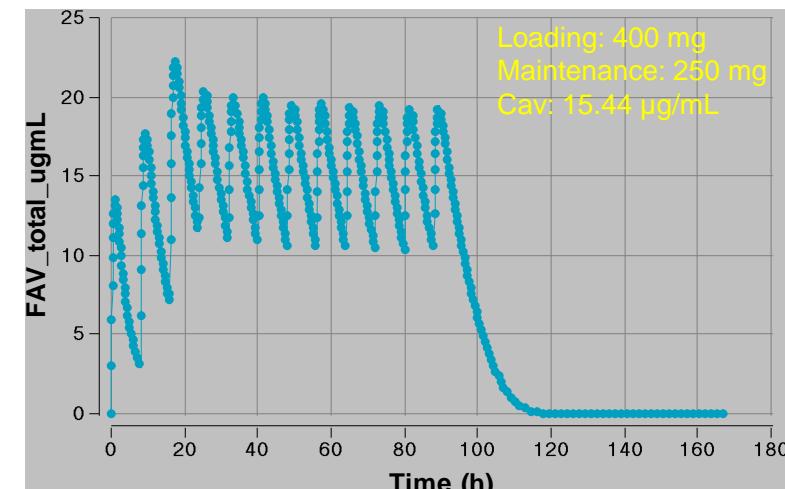
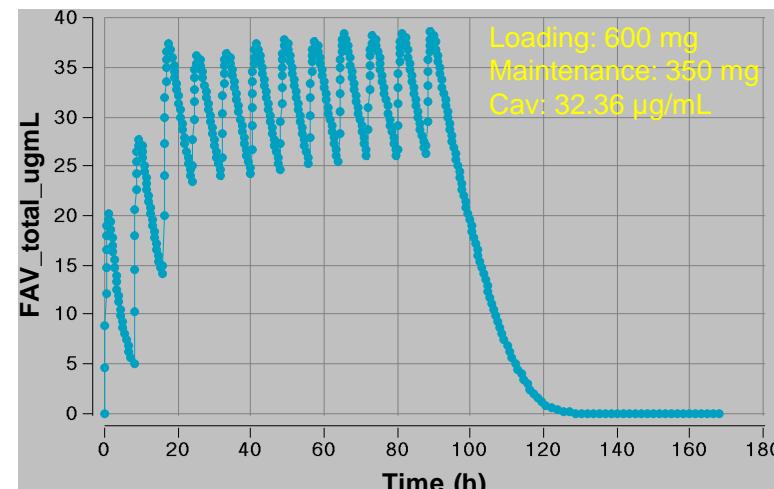
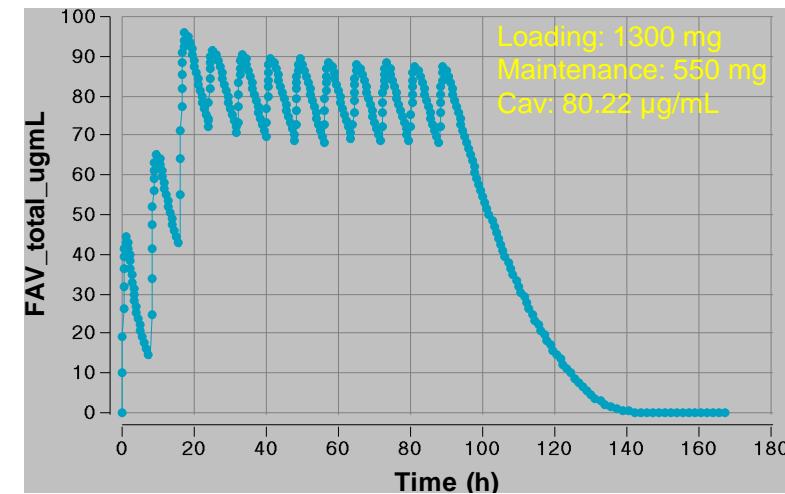
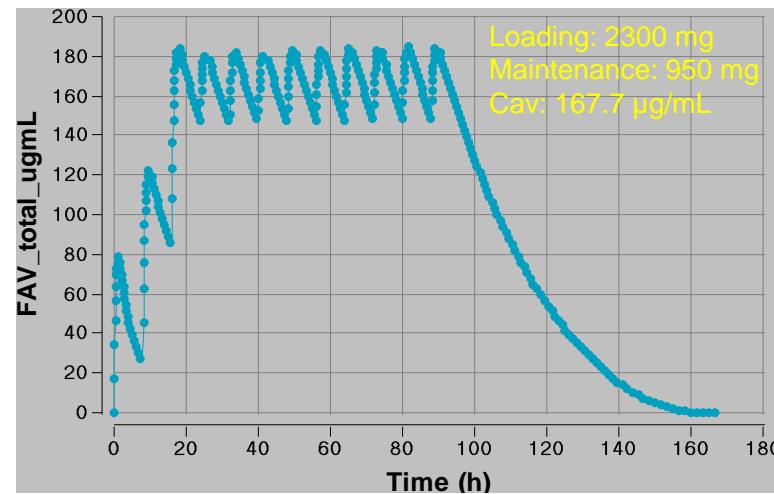
Loading dose: 2300 mg (1 day)

Maintenance dose: 950 mg

Predicted plasma concentration-time profiles (Auto inhibition model)

Target concentration: 165, 85, 35 $\mu\text{g/mL}$

Target (free, μM)	Target (total, $\mu\text{g/mL}$)	Regimen	Loading	Maintenance	Cavg ($\mu\text{g/mL}$)
500	167.128	TID	2300	950	167.77
250	83.564	TID	1300	550	80.22
100	33.426	TID	600	350	32.36
50	16.713	TID	400	250	15.44



Pharmacokinetic modeling

Recombinant Leukocyte A Interferon: Pharmacokinetics, Single-Dose Tolerance, and Biologic Effects in Cancer Patients

JORDAN U. GUTTERMAN, M.D.; SEYMOUR FINE, M.D.; JORGE QUESADA, M.D.; SANDRA J. HORNING, M.D.; JEDD F. LEVINE, M.D.; RAYMOND ALEXANIAN, M.D.; LEON BERNHARDT, M.D.; MICHAEL KRAMER, Ph.D.; HERBERT SPIEGEL, Ph.D.; WAYNE COLBURN, Ph.D.; PATRICK TROWN, Ph.D.; THOMAS MERIGAN, M.D.; and ZOFIA DZIEWANOWSKI, M.D., Ph.D.; Houston, Texas; Nutley, New Jersey; and Stanford, California

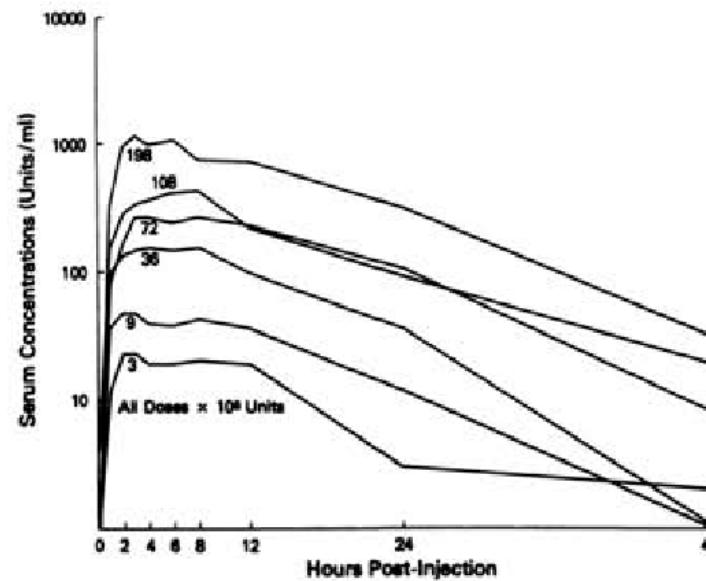
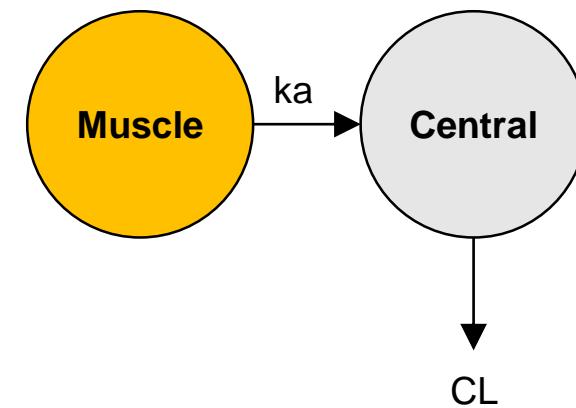


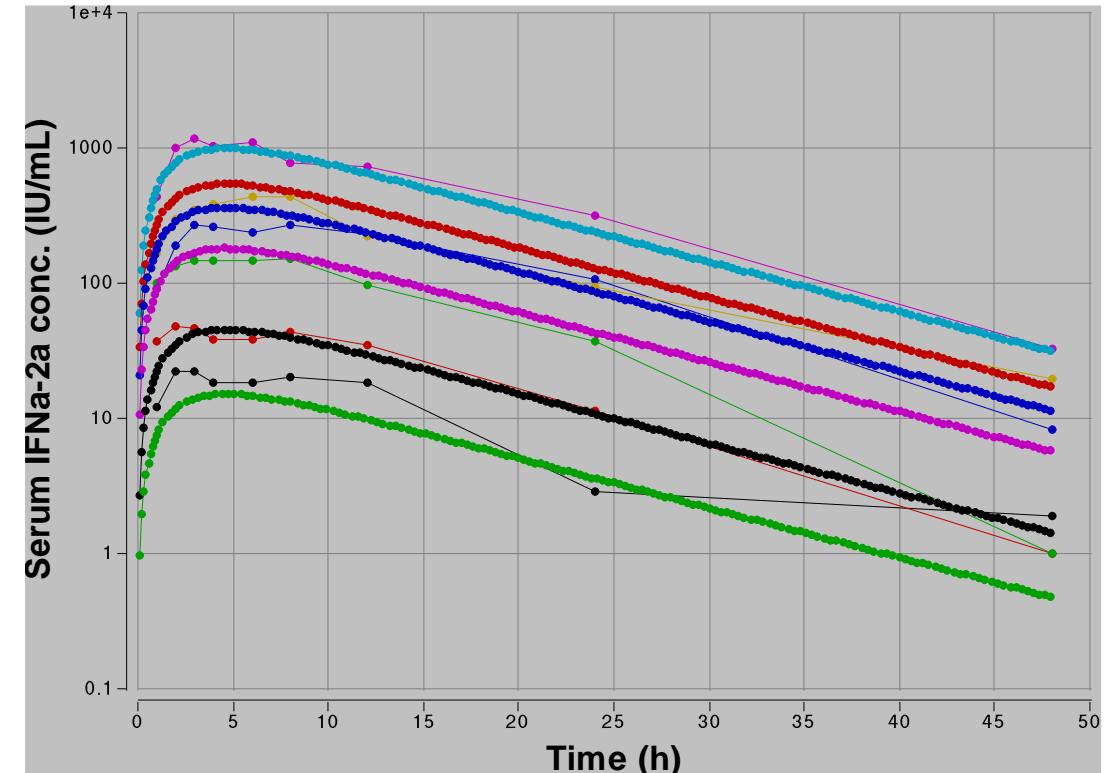
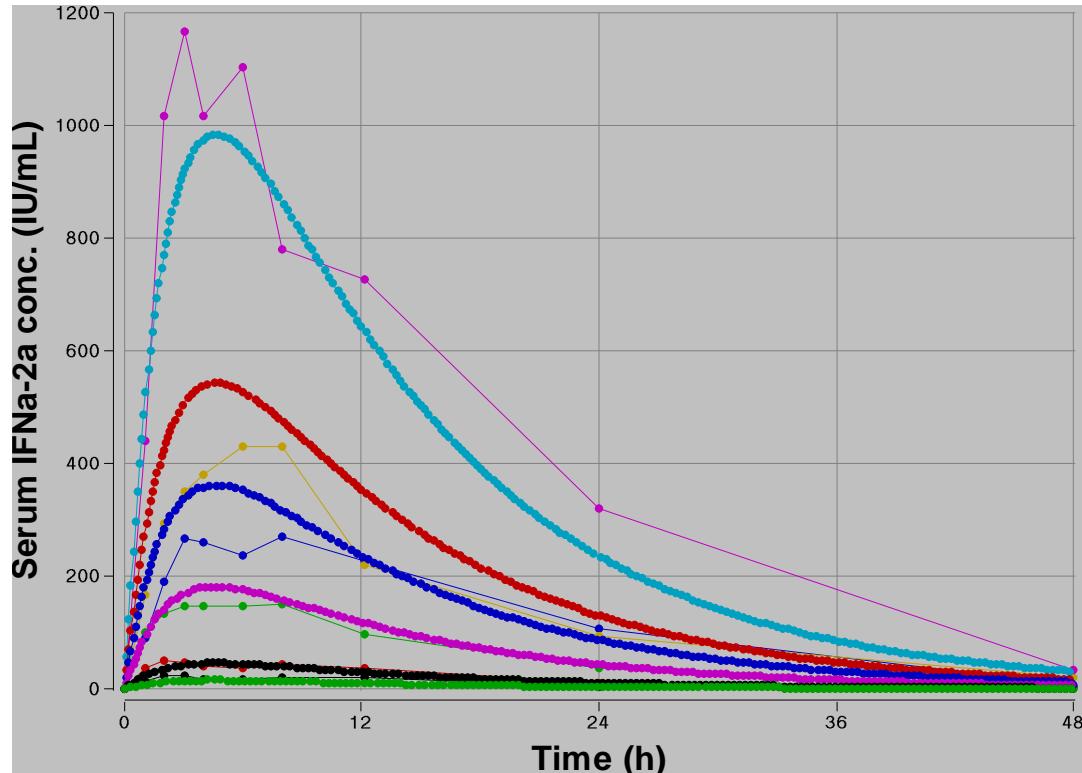
Figure 2. The arithmetic mean serum concentrations of interferon as measured by the bioassay with MDBK cells as target cells. The numbers of patients measured at 3, 9, 36, 72, 108, and 198 million units are 16, 16, 16, 16, 14, and 5, respectively.



Group	t _{1/2} (h)	T _{max} (h)	C _{max} (IU/mL)	AUCall (IU.h/mL)	AUCinf (IU.h/mL)	V _{z/F} (L)	CL/F (mL/min)
3	11.6	3.0	22.6	405.7	437.5	114.9	114.3
9	7.0	2.0	48.5	895.3	905.3	100.0	165.7
36	5.3	8.0	151.6	2806.2	2813.9	97.9	213.2
72	7.3	8.0	270.9	6092.7	6179.3	123.0	194.2
108	10.4	8.0	431.0	7231.3	7528.0	215.0	239.1
198	7.9	3.0	1168.3	20681.4	21048.3	106.9	156.8

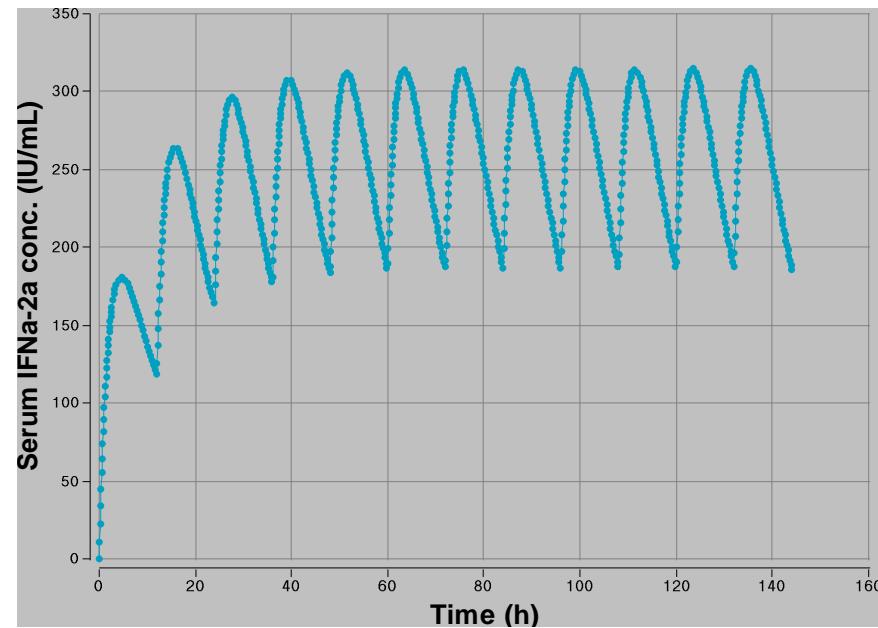
Pharmacokinetic modeling

Observed vs. fitted serum concentration-time profiles

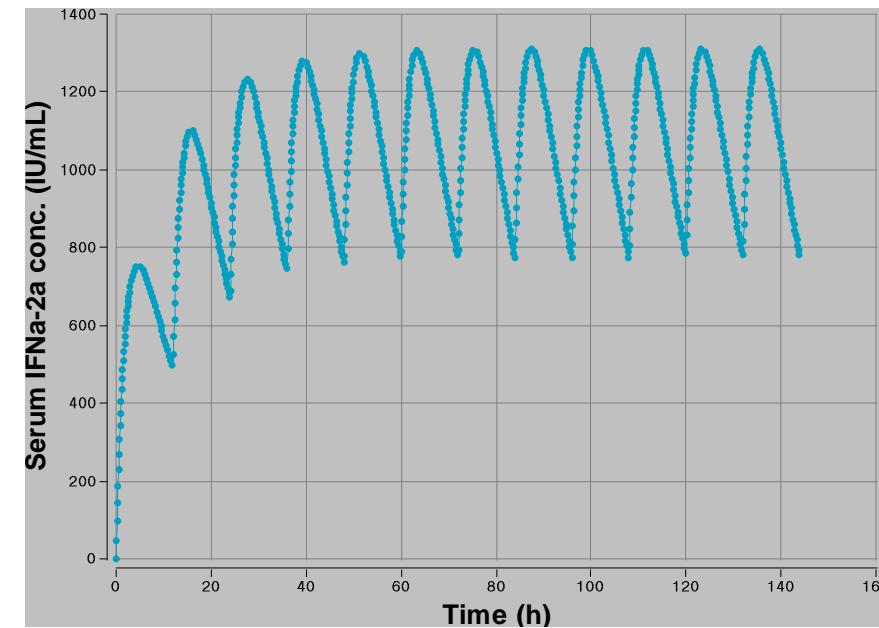


Predicted plasma concentration-time profiles
Target plasma concentration: 100-1,000 IU/mL

36 million IU, twice a day (IM injection)



150 million IU, twice a day (IM injection)

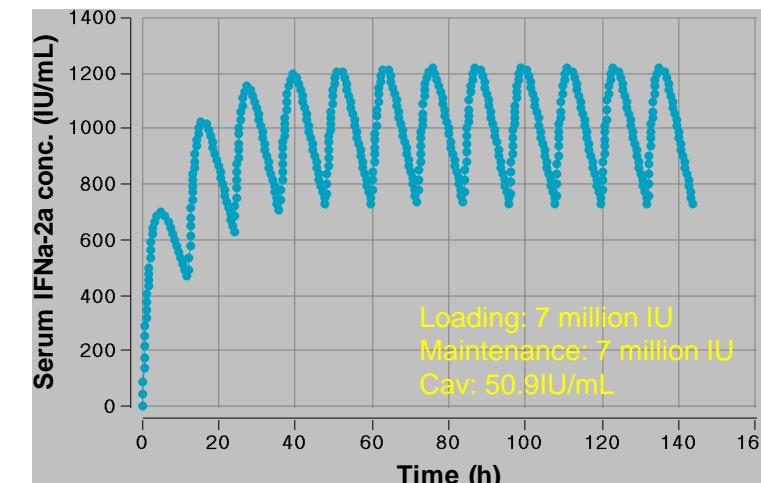
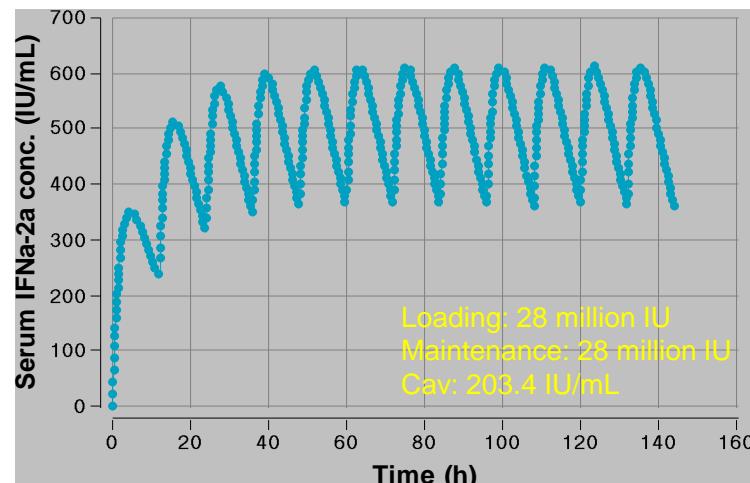
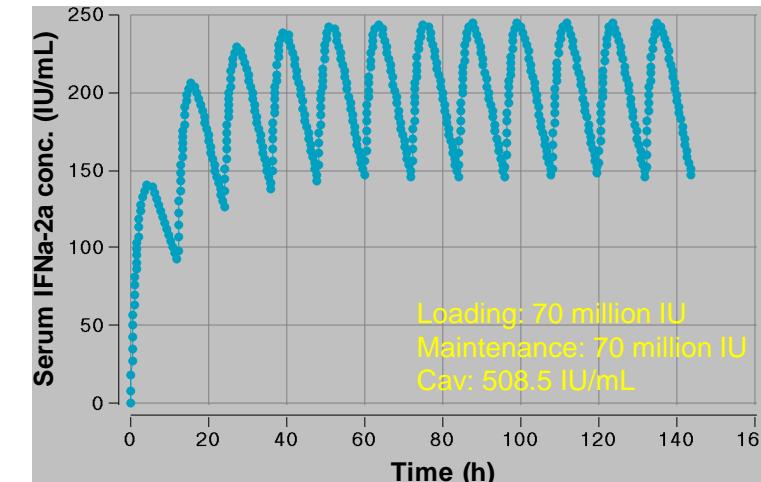
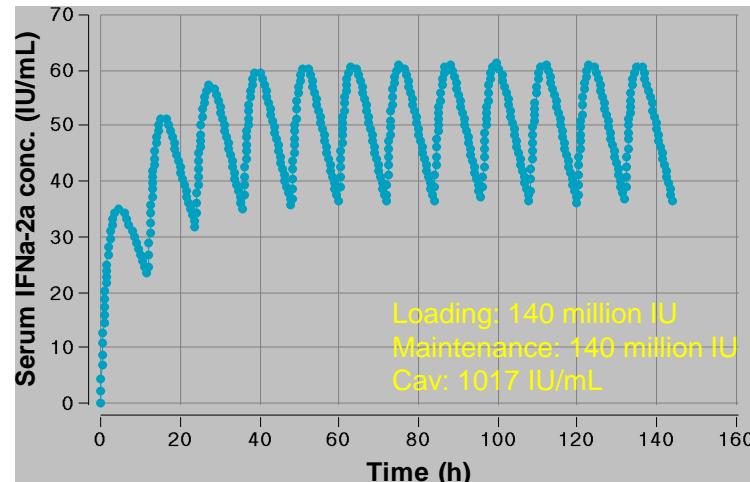


The pharmacokinetics of interferon alfa-2a after single intramuscular doses to patients with disseminated cancer and chronic hepatitis B were similar to those found in healthy volunteers. Dose-proportional increases in serum concentrations were observed after single doses up to 198 million IU. There were no changes in the distribution or elimination of interferon alfa-2a during twice daily (0.5-36 million IU), once daily (1-54 million IU), or three times weekly (1-136 million IU) dosing regimens up to 28 days of dosing.

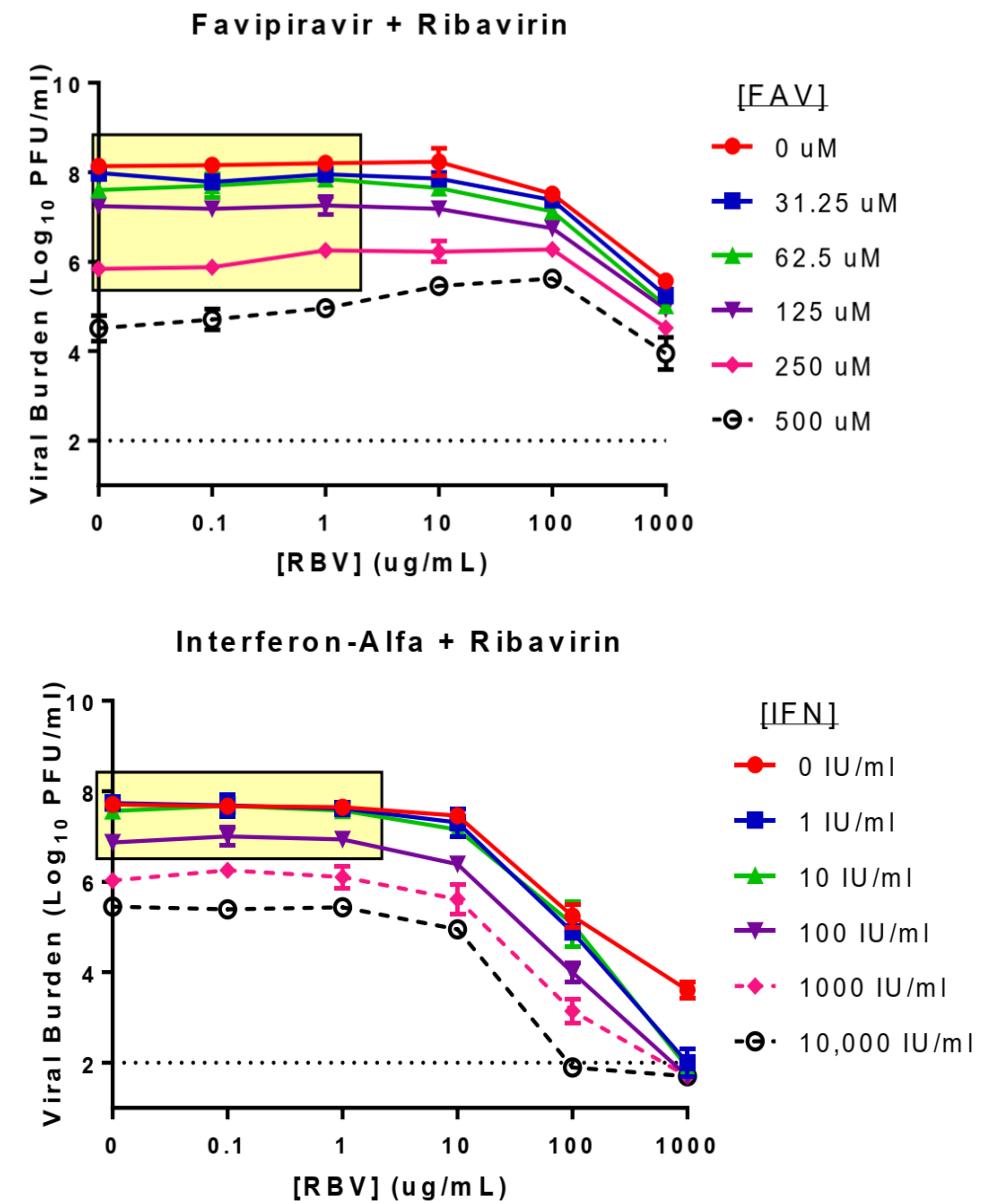
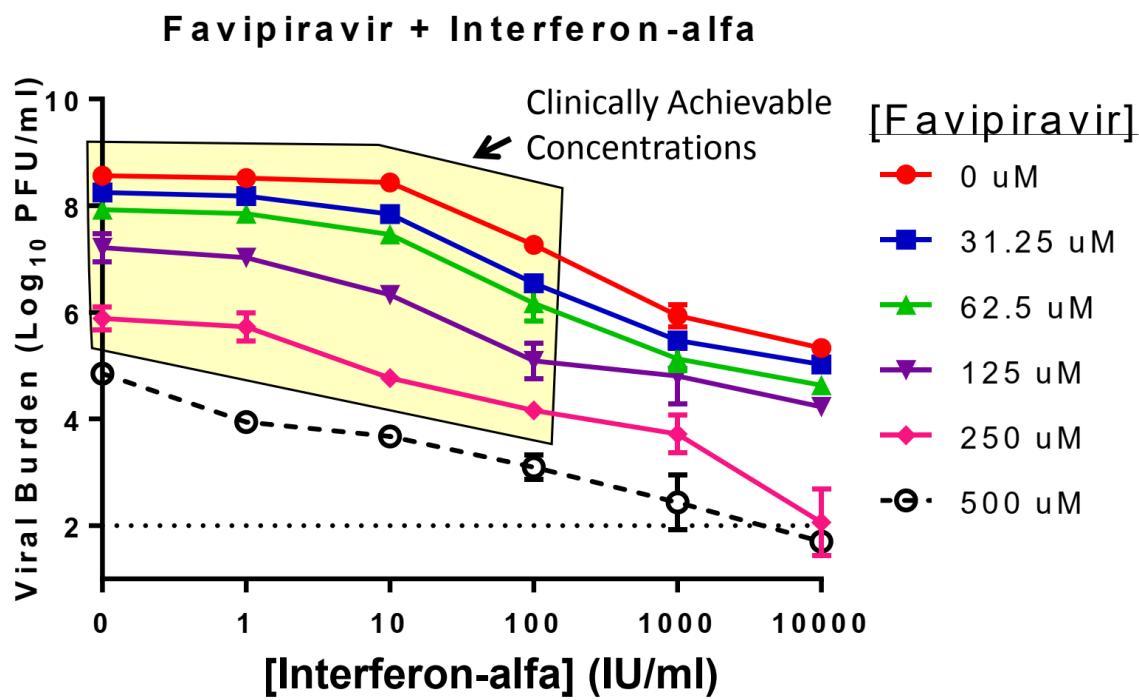
Predicted serum concentration-time profiles

Target plasma concentration: 100-1,000 IU/mL

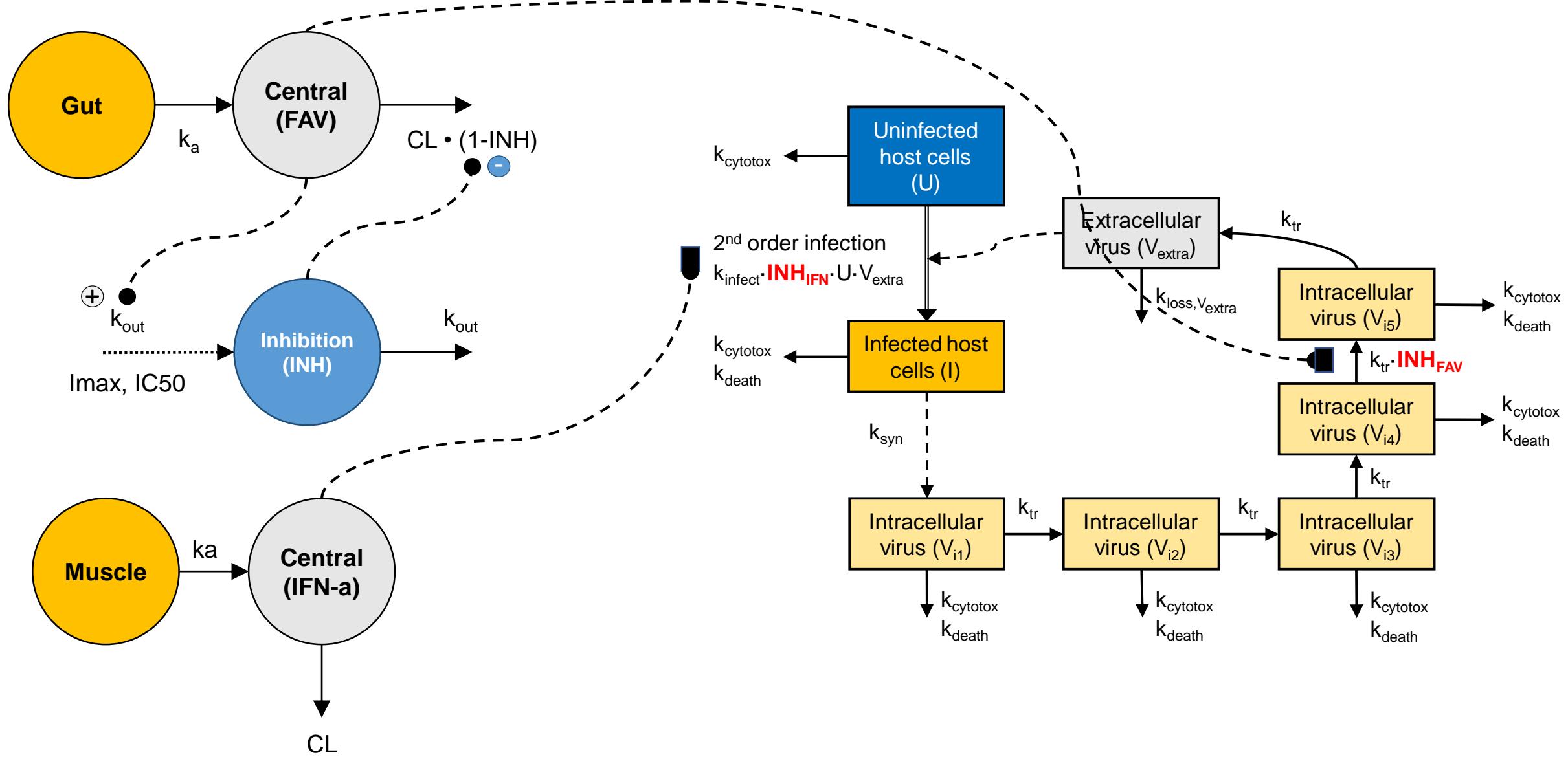
Target (IU/mL)	Regimen	Loading	Maintenance	Cavg (IU/mL)
1000	BID	140 million IU	140 million IU	1017
500	BID	70 million IU	70 million IU	508.5
200	BID	28 million IU	28 million IU	203.4
50	BID	7 million IU	7 million IU	50.9



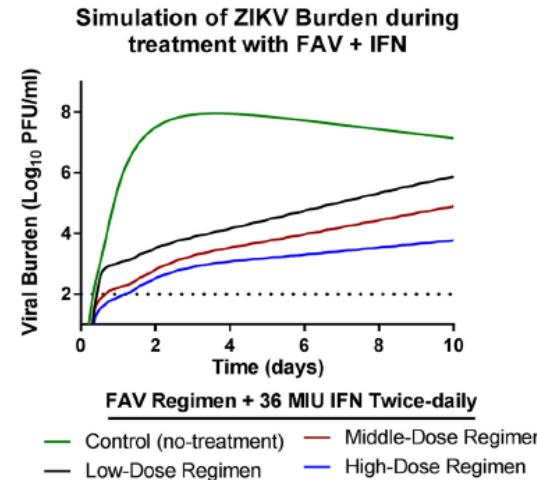
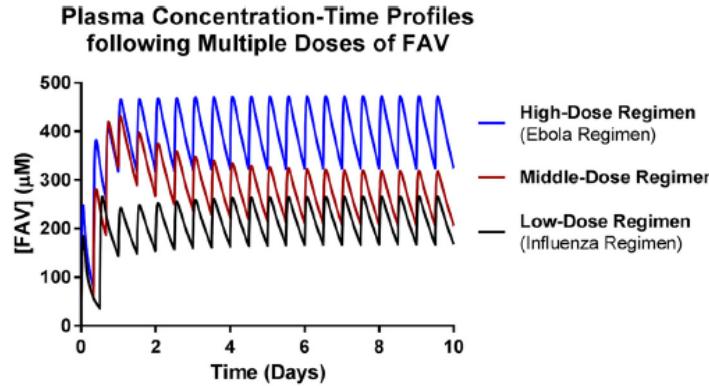
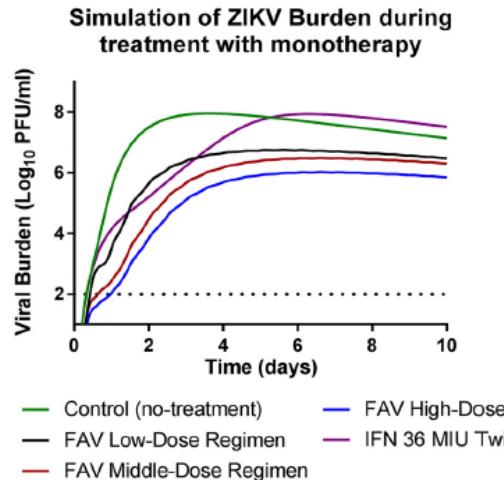
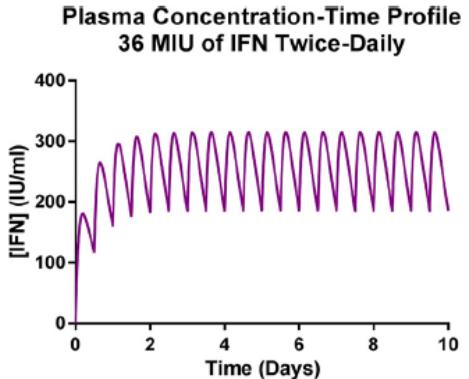
Combination therapy results



PK/PD modeling



Prediction of anti-viral effect in humans



Time (h)	FAV Dose (mg)		
	High	Middle	Low
0	2400	1800	1800
8	2400	1800	-
12	-	-	1800
16	1800	1800	-
24 (BID)	1200	900	800



Clinically relevant FAV and IFN combination regimens have great potential as a treatment strategy for ZIKV infections

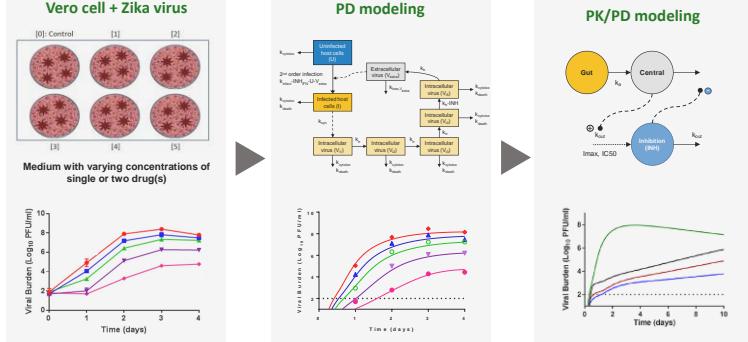
Summary

Worldwide prevalence of Zika virus (ZIKV) infection

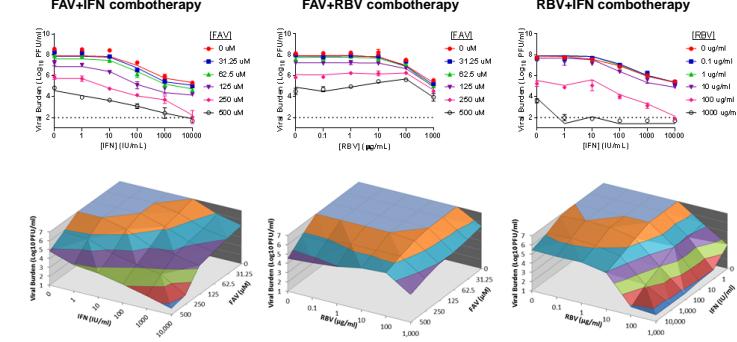
- Serious and long-term health consequences associated with infection, especially during pregnancy, where devastating birth defects such as microcephaly, brain damage, and fetal loss have been reported.
 - Neurological complications have also been linked to ZIKV infection in adults



Research design



Combination therapy results



Pharmacokinetic modeling

T705_Report on the Deliberation Results (2014)

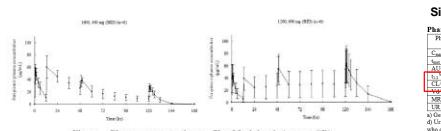
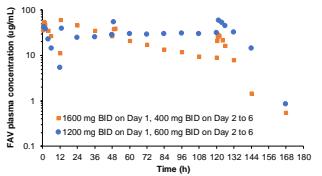


Figure. Plasma concentration profile of favipiravir (mean \pm SD)



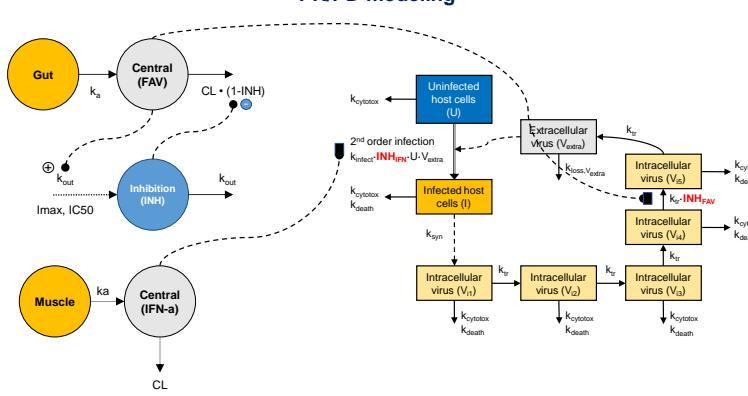
Favipiravir

1705_Report on the Deliberation Results (2014) Single dose study

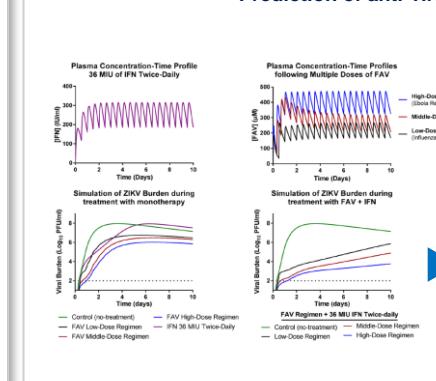
Single-dose study						
Pharmacokinetic parameters of favipiravir following single oral dose of favipiravir at 30 to 1600 mg						
	30 mg	90 mg	200 mg	400 mg	800 mg	1600 mg
Mean (SD) peak concentration (μ g/L (\pm SE))	0.03 (0.03)	0.03 (0.03)	0.03 (0.03)	0.03 (0.03)	0.03 (0.03)	0.03 (0.03)
AUC _{0-∞} (h· μ g/L)	9.38 (2.02)	9.23 (2.16)	9.67 (1.12)	39.41 (16.66)	39.26 (16.66)	35.82 (19.07)
CL/F (L/h)	11.80 ± 2.92	9.81 ± 1.28	10.35 ± 2.24	10.26 ± 1.63	7.31 ± 2.13	7.95 ± 2.36
N_{eff} (n)	20	20	20	20	20	20
N_{obs} (n)	20	20	20	20	20	20
CV (%)	3.0 ± 0.5	3.3 ± 0.2	4.4 ± 0.7	7.7 ± 0.7	4.0 ± 0.6	7.0 ± 0.7
CV (%) (mean \pm SE)	3.0 ± 0.5	3.3 ± 0.2	4.4 ± 0.7	7.7 ± 0.7	4.0 ± 0.6	7.0 ± 0.7
CV (%) (mean \pm SD)	3.0 ± 0.5	3.3 ± 0.2	4.4 ± 0.7	7.7 ± 0.7	4.0 ± 0.6	7.0 ± 0.7

Saturated elimination/Auto inhibition

PK/PD modeling



Prediction of anti-viral effect in humans

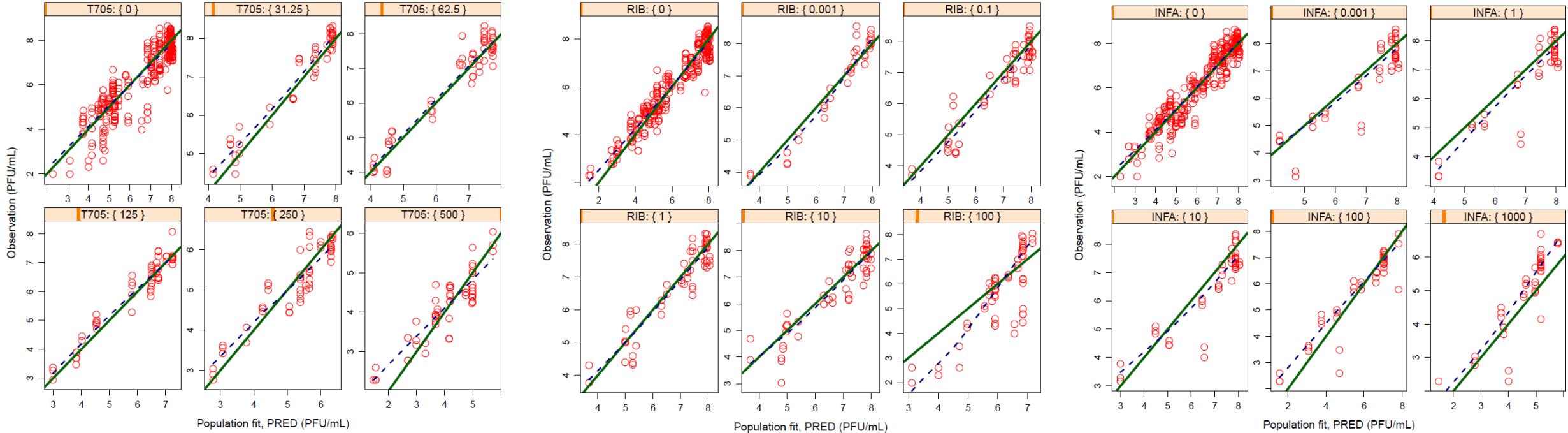


Time (h)	FAV Dose (mg)		
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0	2400	1800	1800
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Clinically relevant FAV and IFN combination regimens have great potential as a treatment strategy for ZIKV infections

감사합니다

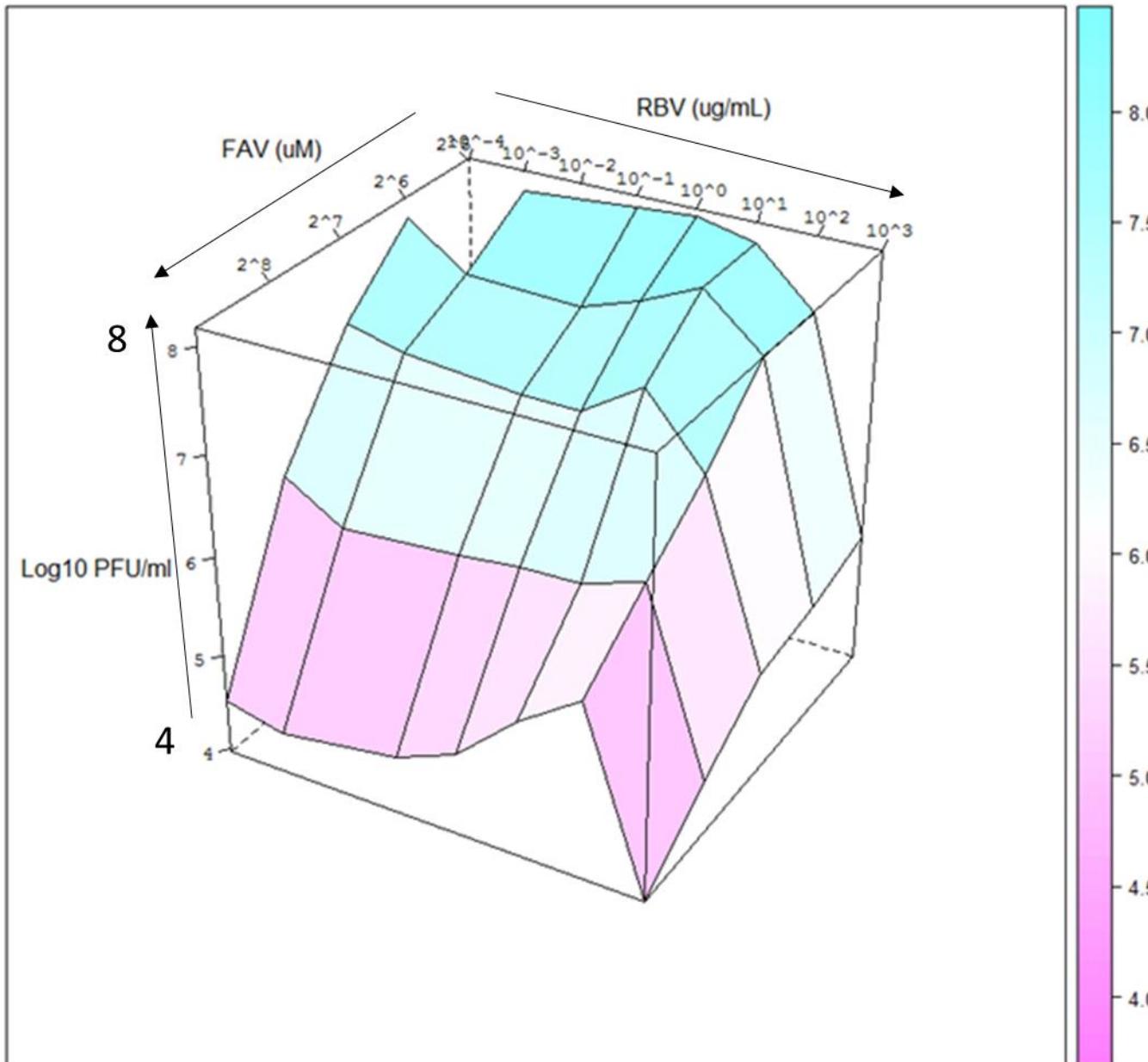
Mechanism-based pharmacodynamic modeling



Mechanism-based pharmacodynamic modeling

Parameter	Symbol (unit of measure)	Population mean estimate (SE [%])	CV ^c of estimate for between-curve variability (SE [%])
PD parameters			
Log ₁₀ of 2nd-order infection rate constant	k_{infect}	-4.10 (2.39)	0.0841 (128 ^b)
Synthesis rate constant of virus	k_{syn} (1/h)	9.35 (7.09)	0.068 (219)
Mean delay time until release of virus in the absence of drug	$T_{\text{Delay}} = 5/k_{\text{tr}}$ (h)	40.0 (2.56)	0.0238 (97)
Mean survival time of infected cells	$MST_{\text{Infected}} = 1/k_{\text{death}}$ (h)	70.5 (8.92)	0.152 (141)
Mean survival time for extracellular virus	$MST_{\text{Virus}} = 1/k_{\text{loss,virus}}$ (h)	14.3 (10.4)	0.172 (112)
Log ₁₀ initial no. of uninfected cells	Log_U	6.30 (fixed)	0 (fixed)
Log ₁₀ initial no. of infected cells	Log_I	3.38 (2.66)	0.365 (29)
Maximum extent of inhibition by FAV	I_{maxFAV} (normal scale)	0.9999 (~0.9992–1.00 ^a)	0.793 ^a (88.8)
FAV concn causing 50% I_{max}	IC _{50_FA} (μM)	41.7 (2.55)	0.039 (180)
Hill coefficient of FAV	Hill _{FAV}	2.79 (4.53)	0.1 (fixed)
Maximum extent of inhibition by RBV	I_{maxRBV} (normal scale)	0.954 (~0.924–0.973 ^a)	0.44 ^a (120)
RBV concn causing 50% I_{max}	IC _{50_RB} ($\mu\text{g/ml}$)	7.86 (9.99)	0.491 (84.3)
Hill coefficient of RBV	Hill _{RBV}	2.90 (16.5)	0.1 (fixed)
Maximum extent of inhibition by IFN	I_{maxIFN} (normal scale)	0.999997 (~0.99990–1.00 ^a)	0.859 ^a (62.4)
IFN concn causing 50% I_{max}	IC _{50_IF} (IU/ml)	4.12 (15.9)	0.131 (383)
Hill coefficient of IFN	Hill _{IFN}	2.00 (fixed)	0.1 (fixed)
Interaction factor between FAV and RBV	PSI = 1 if monotherapy, PSI = SYNANT ^d if combination therapy	1.37 (8.21)	0.05 (427)
Maximum extent of cytotoxicity by RBV	$MST_{\text{TOX}} = 1/S_{\text{maxRBV}}$ (h)	11.9 (7.21)	0.354 (39.3)
RBV concn causing 50% S_{max}	SC _{50_RB} ($\mu\text{g/ml}$)	150 (11.3)	0.226 (110)
Hill coefficient of RBV for toxicity	Hill _{RBVTOX} (normal scale)	4.16 (12.5)	0.1 (fixed)
Residual-error parameter			
Additive error for viral load on log ₁₀ scale	SDin	0.333 (4.67)	

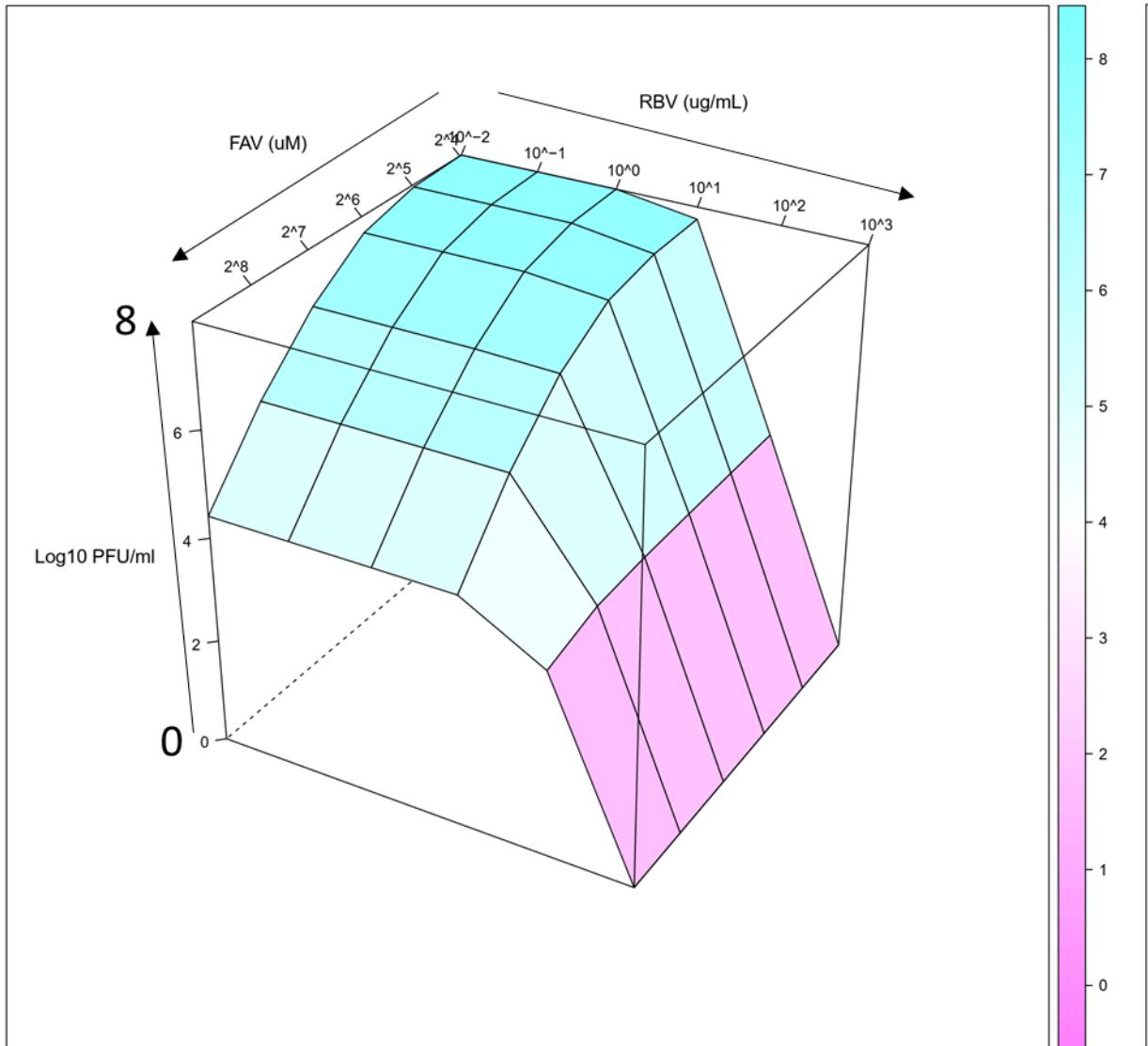
3D Surface Plot for Antagonism Diagnosis between FAV and RBV



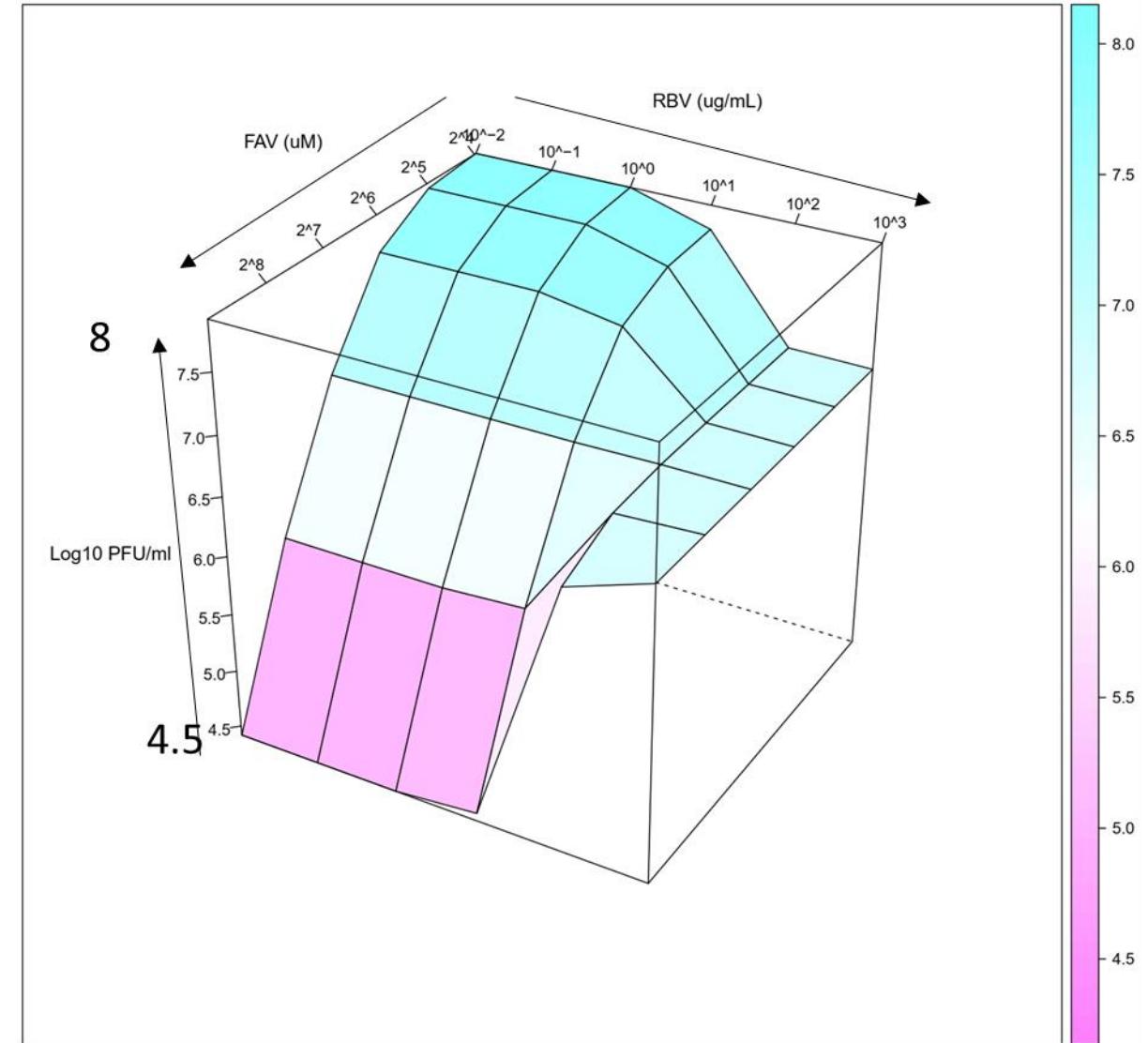
1. RBV cannot achieve complete inhibition.
2. Antagonism between FAV and RBV
3. RBV cytotoxicity identified.

de Mello CP, Tao X (Co-first authors),
et al. *Antimicrobial Agents Chemother*
2018; 62:e01983-17

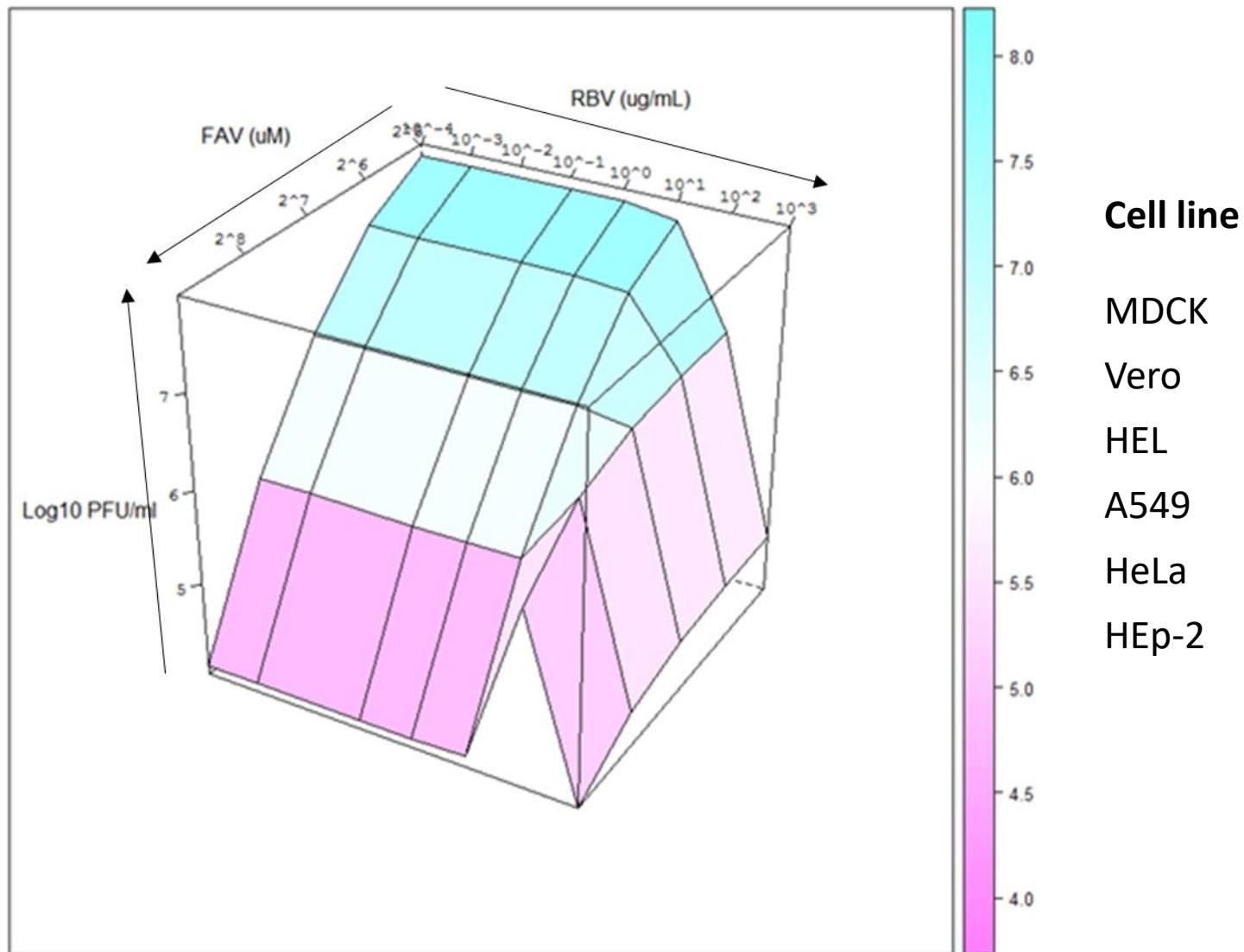
$I_{max_FAV} = 1$ and $I_{max_RBV} = 1$



$I_{max_FAV} = 1$ and $I_{max_RBV} = 0.92$



RBV induced cytotoxicity



Drug concentration causing
50% of cytotoxicity

Cell line	FAV	Ribavirin
MDCK	>1,000	23
Vero	>1,000	59
HEL	>1,000	19
A549	>1,000	75
HeLa	>1,000	11
HEp-2	>1,000	7.8

de Mello CP, Tao X (Co-first authors),
et al. Antimicrobial Agents Chemother
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