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

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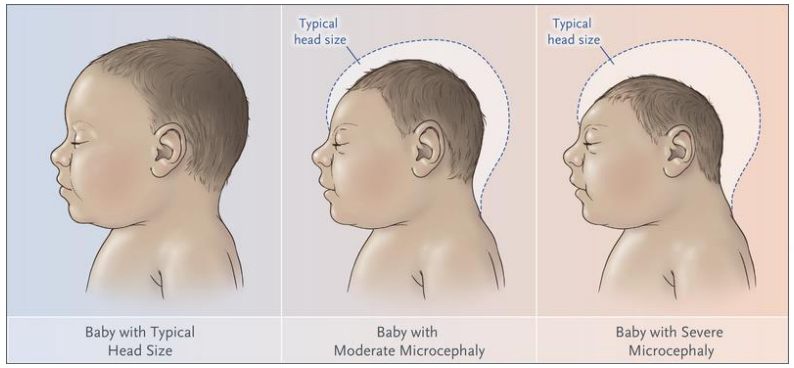
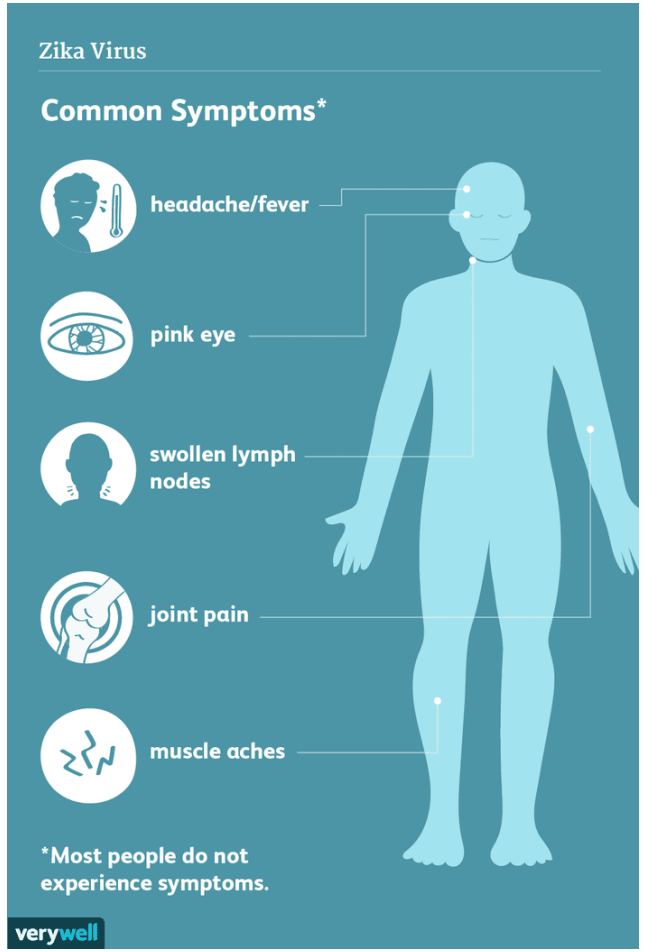
Worldwide prevalence of Zika virus (ZIKV) infection

- 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

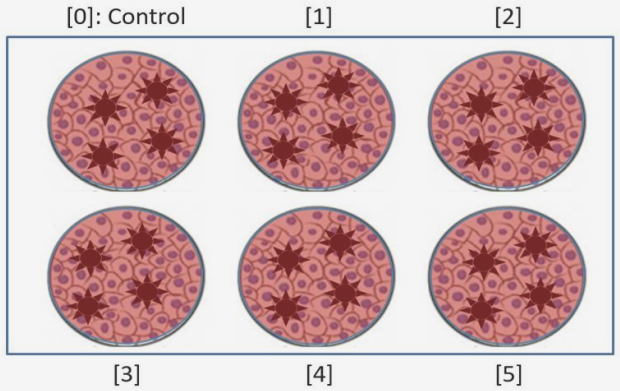
Ribavirin

Interferon-a

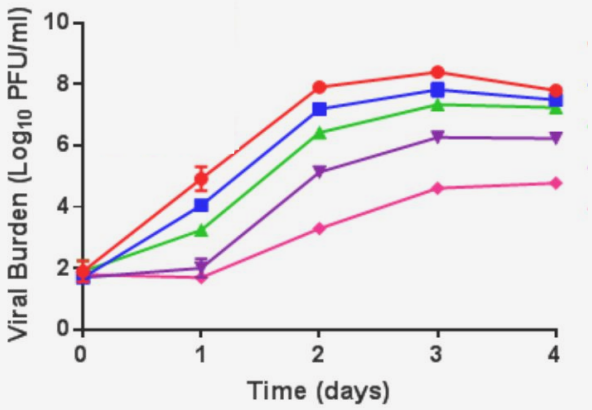
Favipiravir

Research design

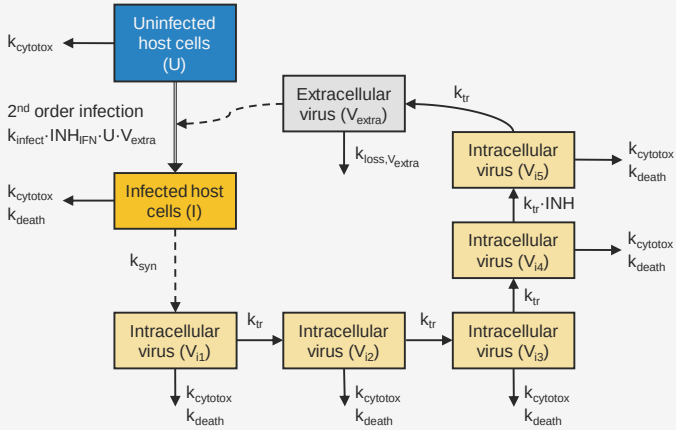
Vero cell + Zika virus

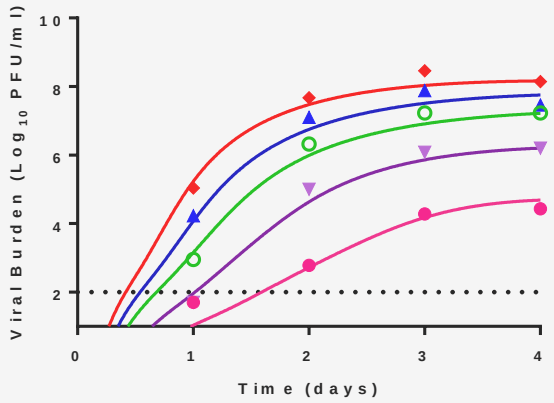


Medium with varying concentrations of single or two drug(s)

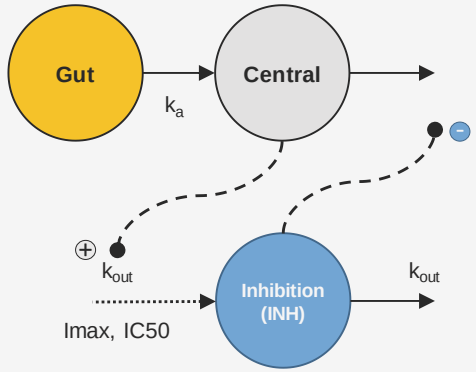


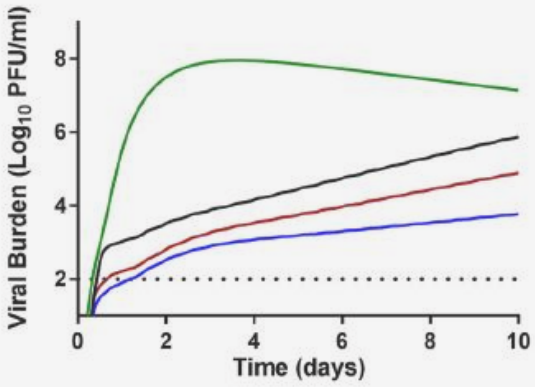
PD modeling





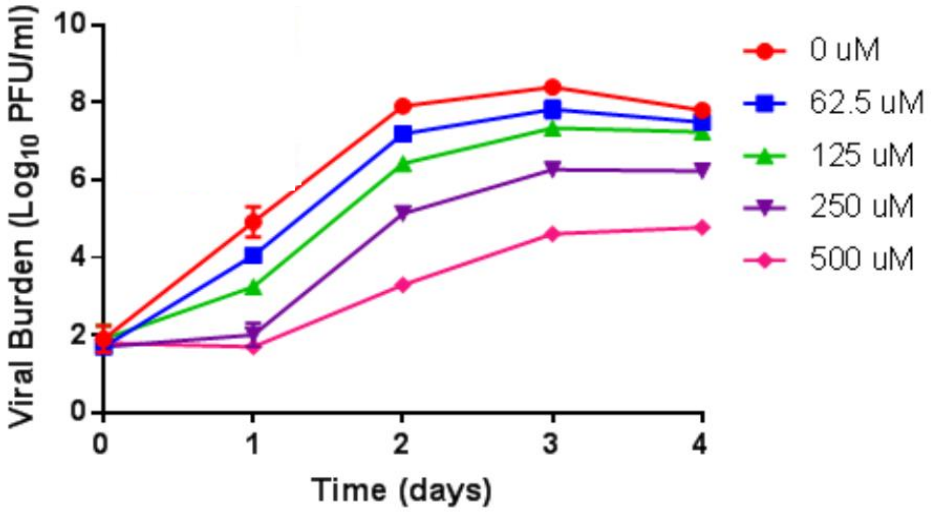
PK/PD modeling



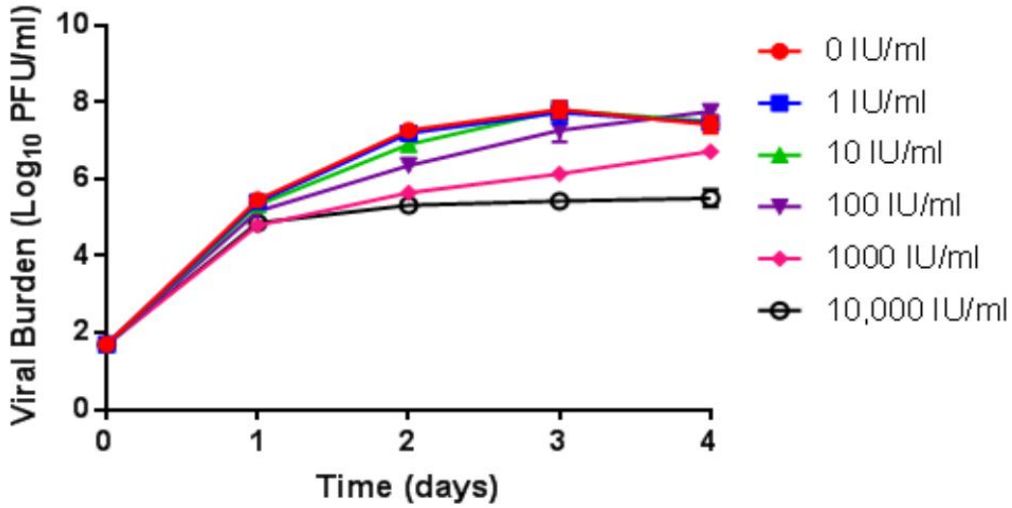


Monotherapy results

Favipiravir

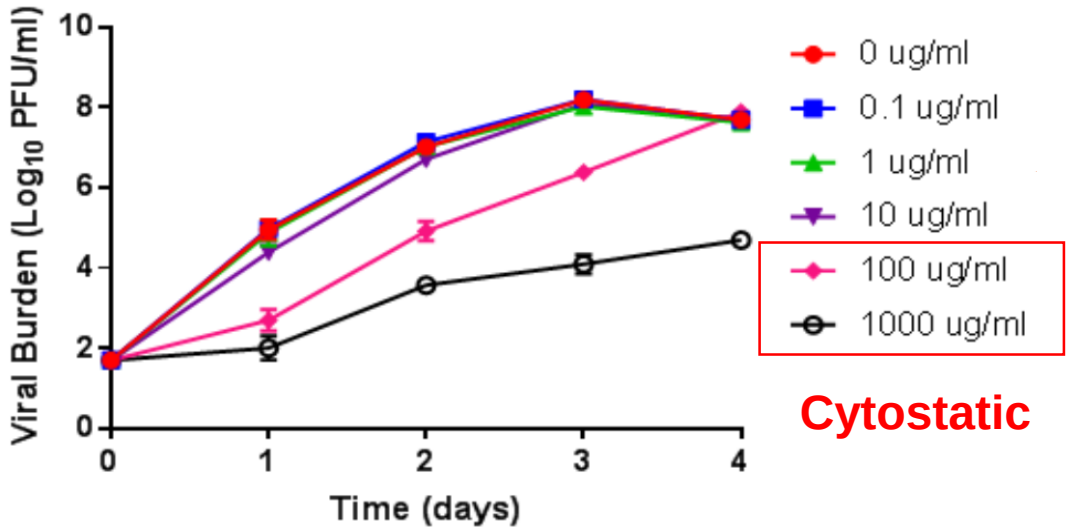


Interferon-alpha



FAV and RBV suppressed the production of infections ZIKV

Ribavirin

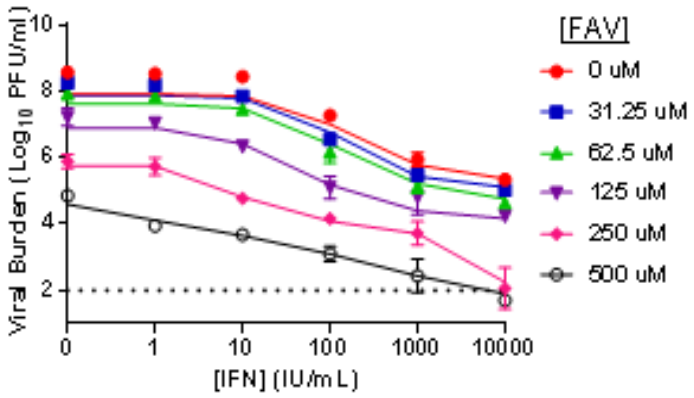


Cytostatic

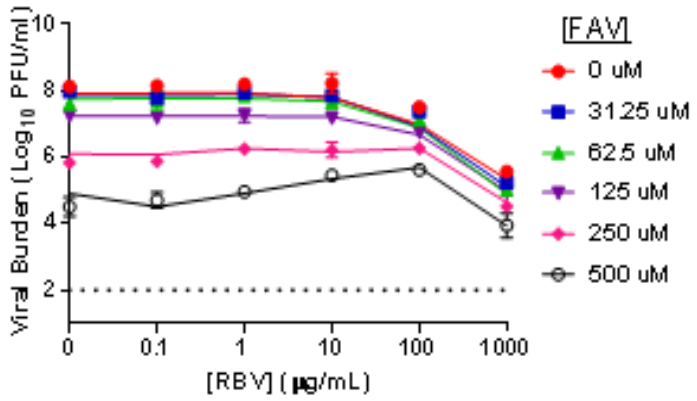
Continued suppression was achieved at 10,000 IU/mL of IFN

Combination therapy results

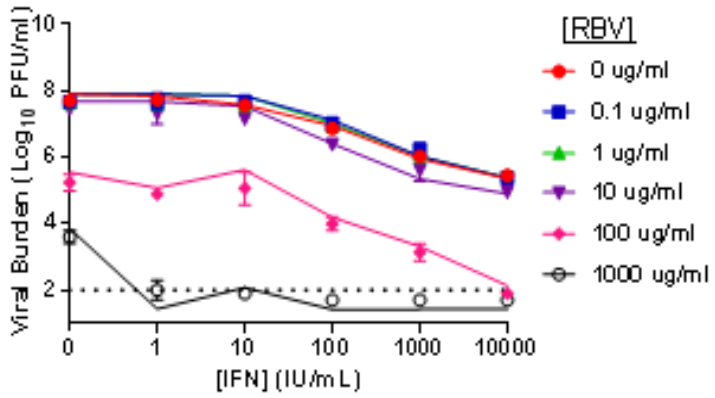
FAV+IFN combotherapy

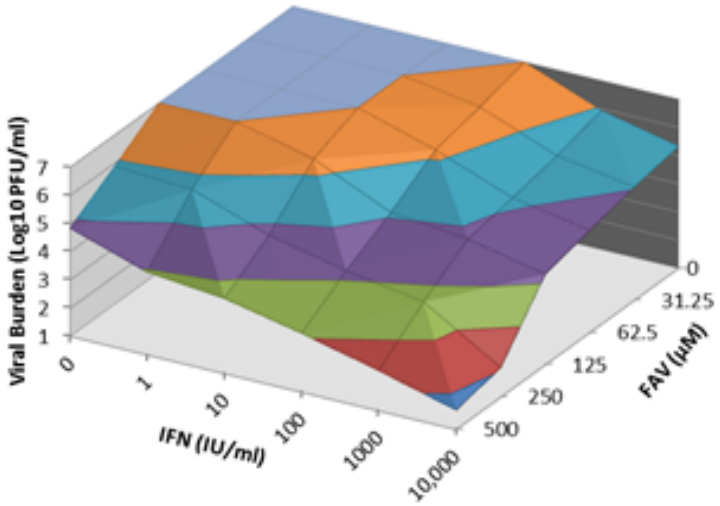


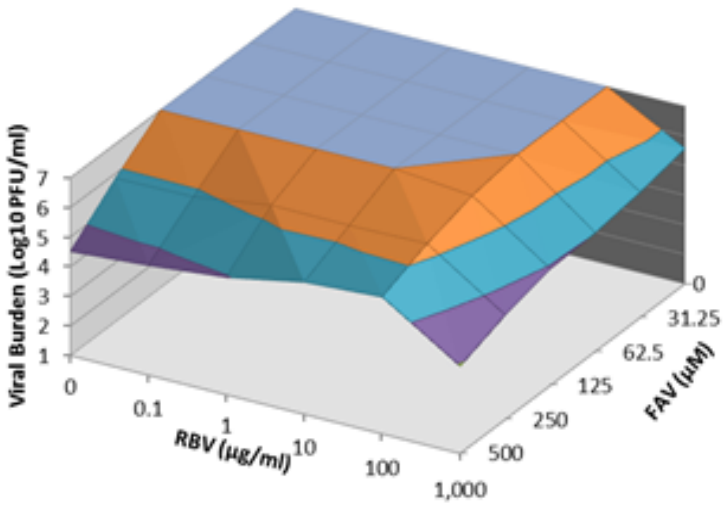
FAV+RBV combotherapy

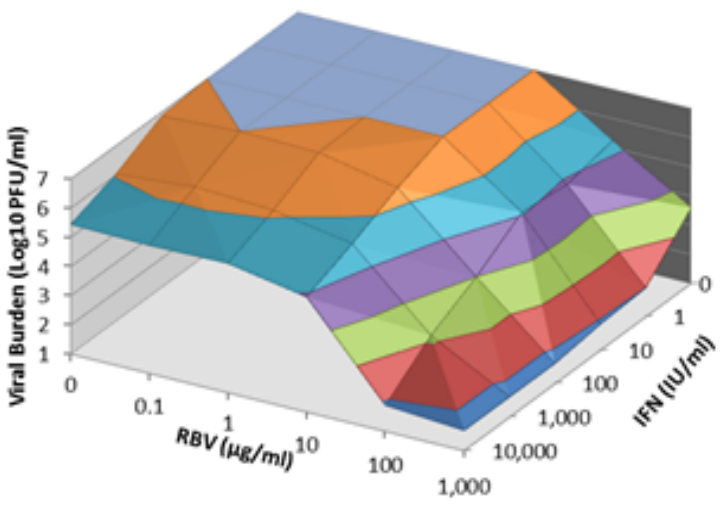


RBV+IFN combotherapy

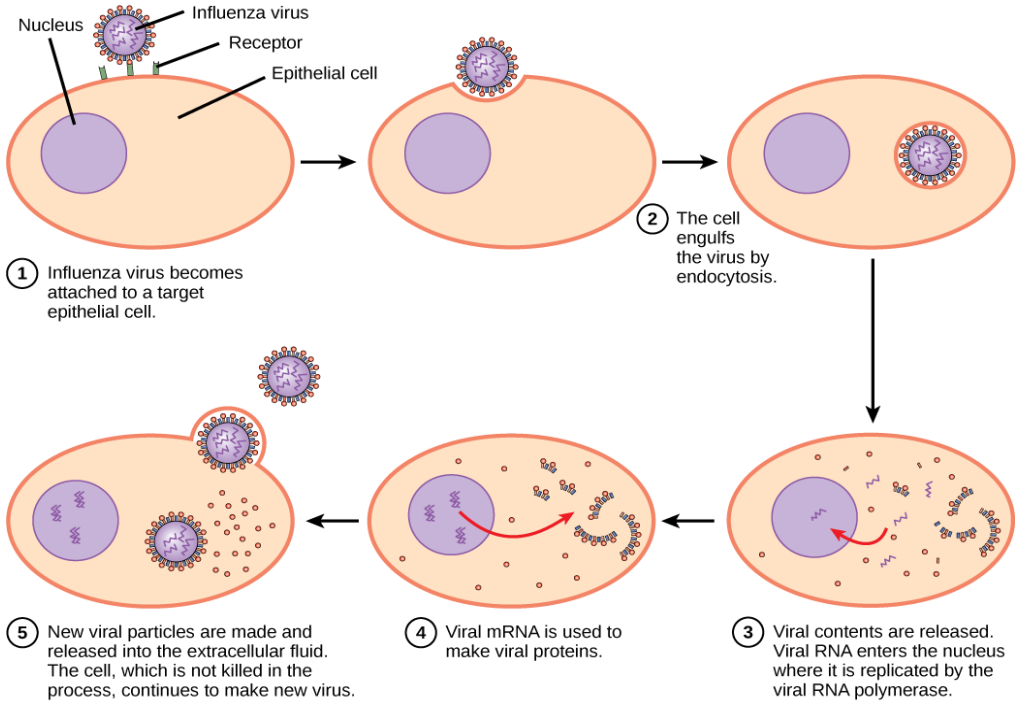


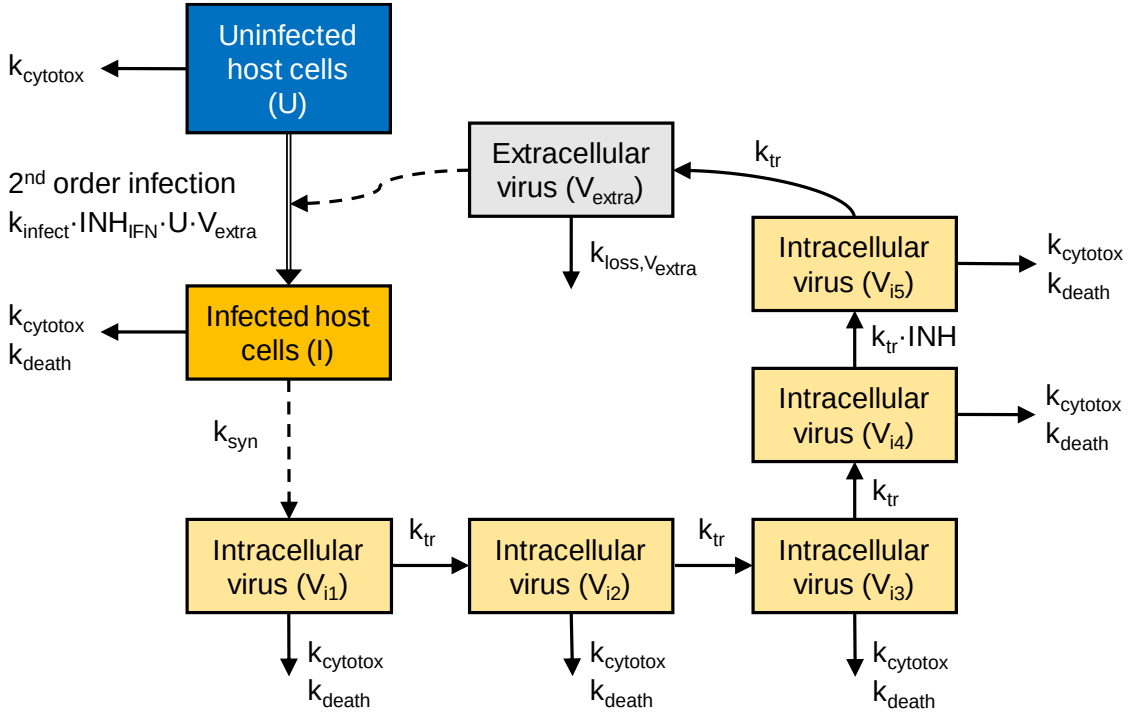




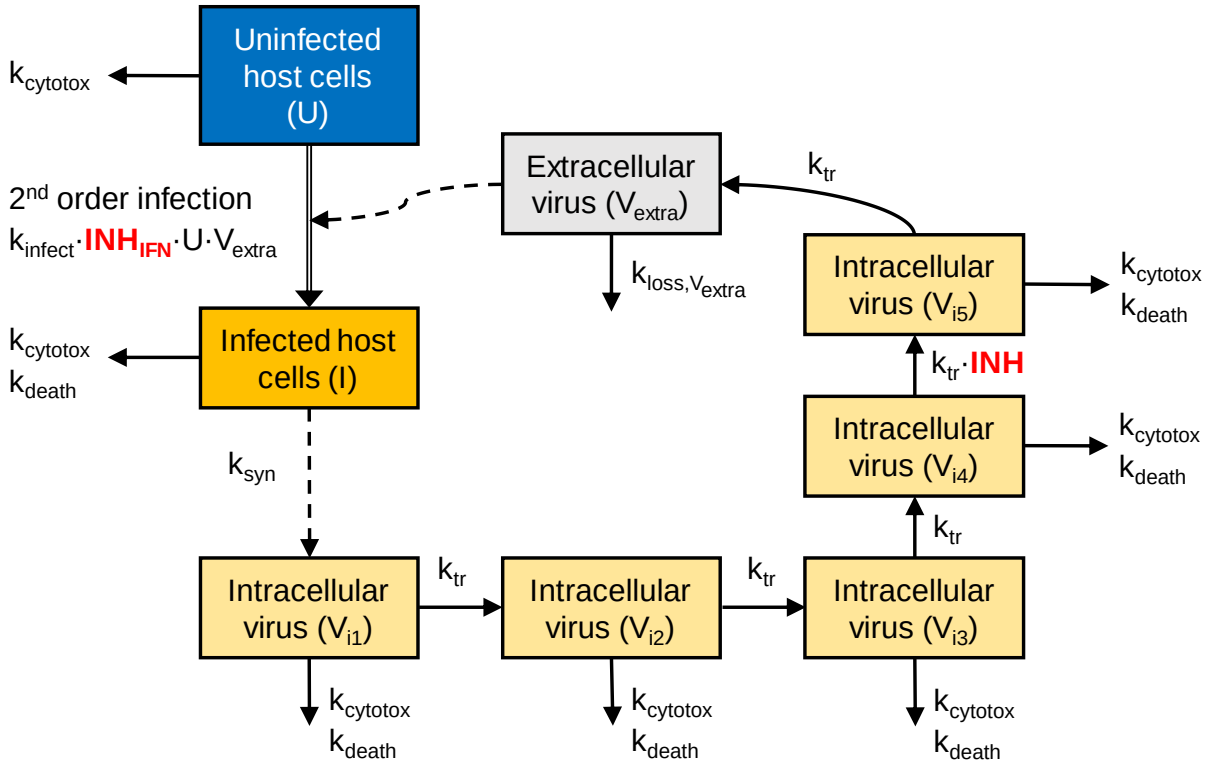


Mechanism-based pharmacodynamic modeling





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

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

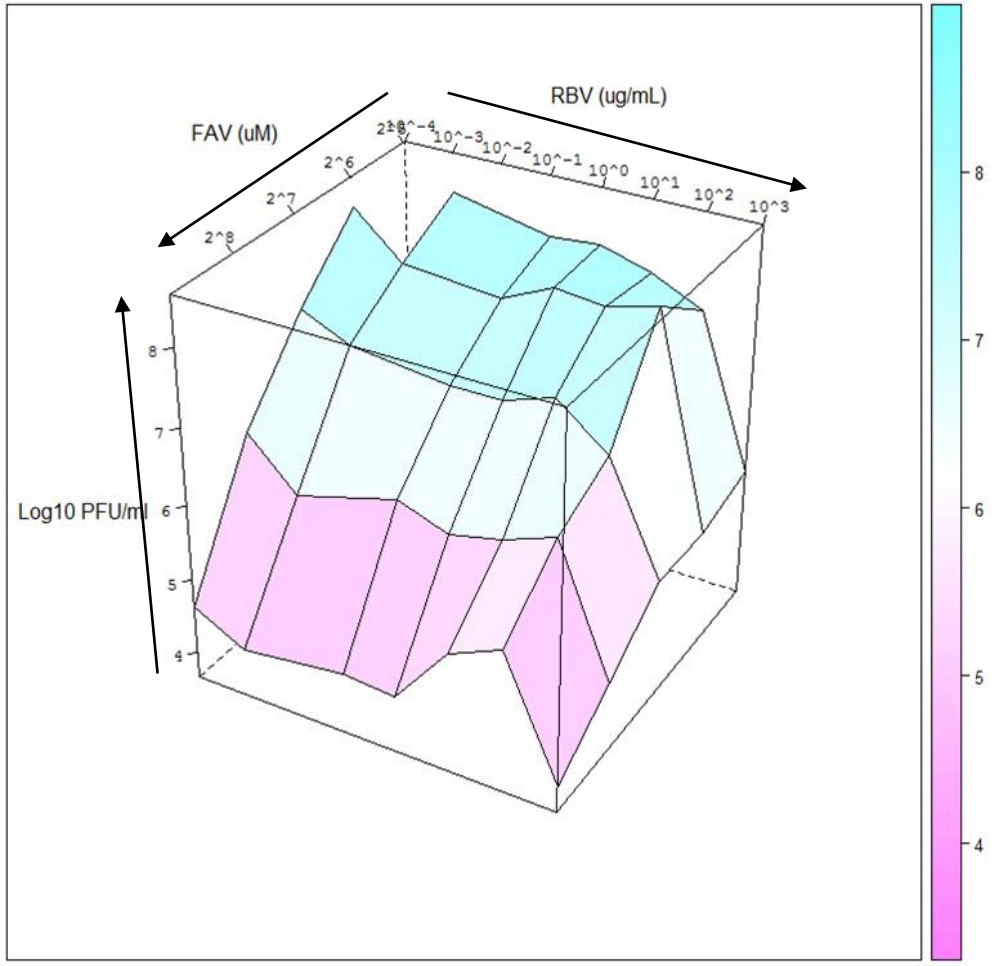
Antagonism explained by

(1) Competition target occupancy. And RBV crowd out FAV, resulting in incomplete inhibition (Imax = 0.92)

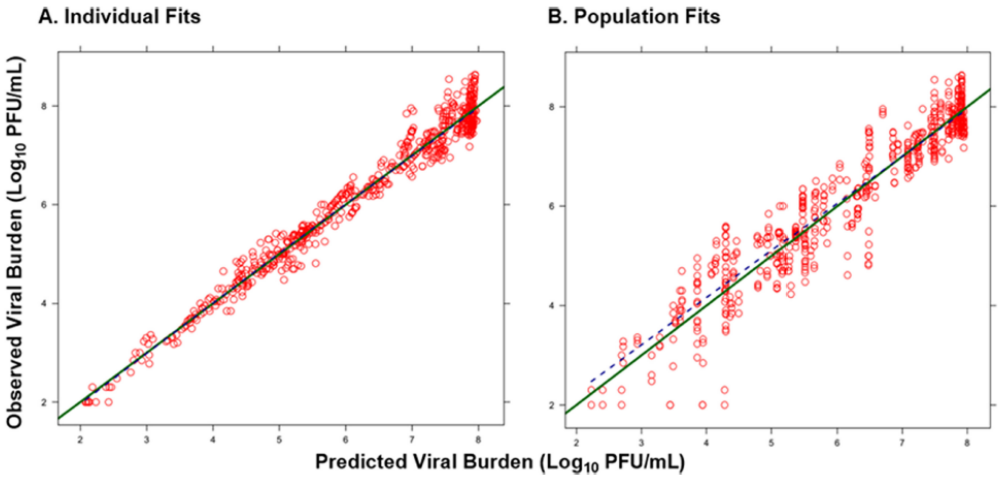
(2) Interaction factor, PSI > 1

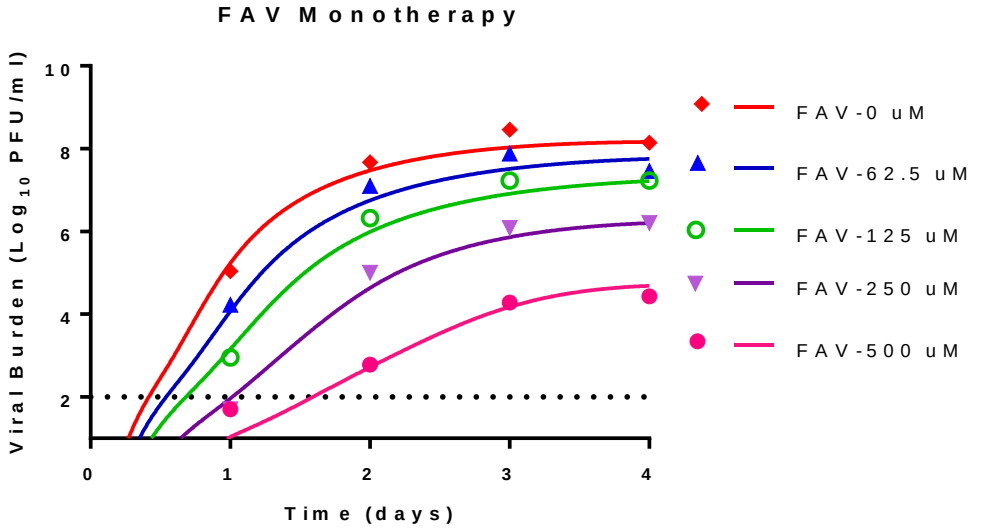
Chakraborty, Abhijit, and William J. Jusko. "Pharmacodynamic Interaction of Recombinant Human Interleukin-10 and Prednisolone Using in vitro Whole Blood Lymphocyte Proliferation." Journal of Pharmaceutical Sciences 91, no. 5 (2002): 1334-342. doi:10.1002/jps.3000.

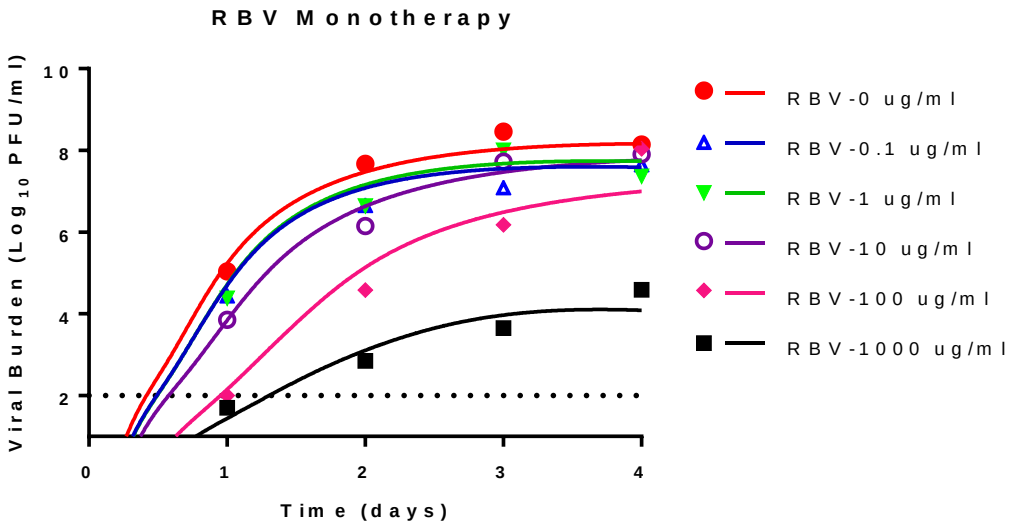
INTERACTION FACTOR: PSI = 1.73 (ANTAGONISM)

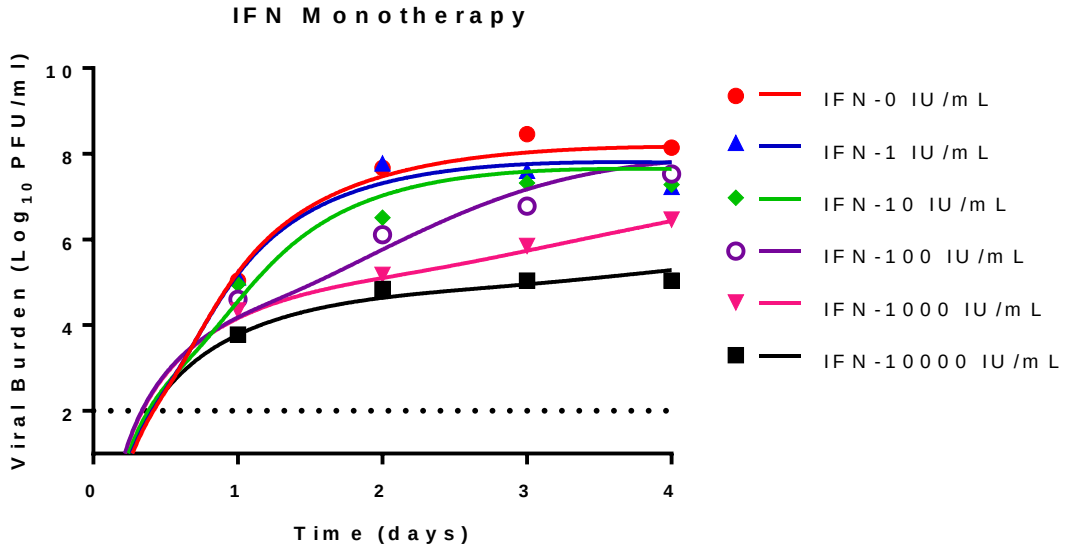


Mechanism-based pharmacodynamic modeling









Pharmacokinetic modeling

T705_Report on the Deliberation Results (2014)

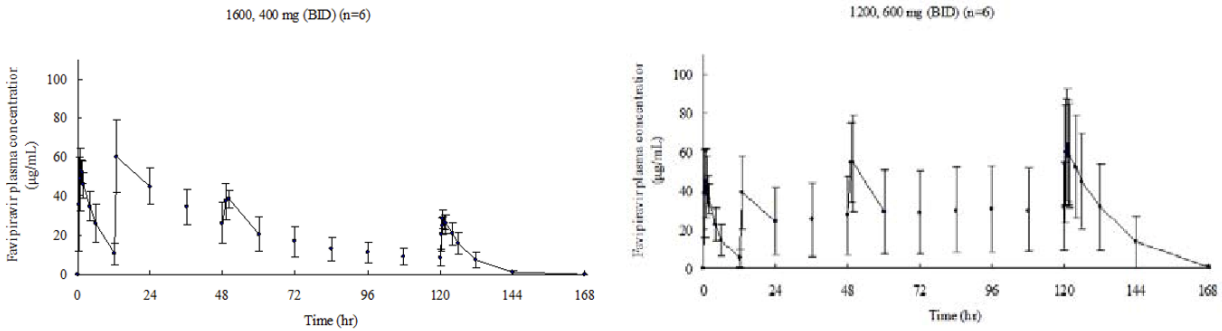
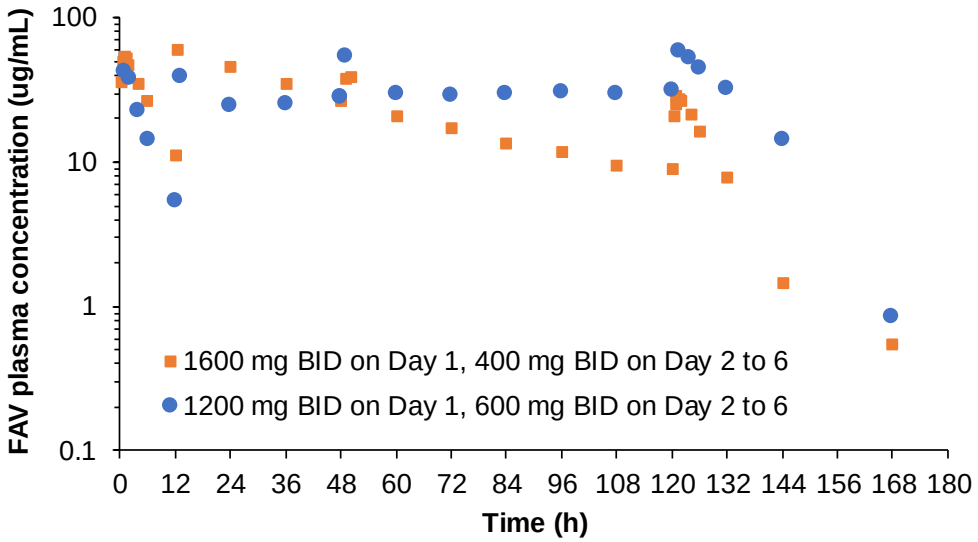


Figure. Plasma concentration profile of favipiravir (mean ± SD)



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] (μg/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] (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] (μg·hr/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] (hr)	1.3 ± 0.1	1.5 ± 0.1	1.5 ± 0.2	1.6 ± 0.2	2.2 ± 0.3	3.9 ± 0.3
CL/F [b] (L/hr)	11.80 ± 1.92	9.81 ± 1.28	10.35 ± 2.24	10.26 ± 1.63	7.31 ± 2.17	2.98 ± 0.30
Vd/F [b] (L)	21.54 ± 1.93	21.44 ± 2.86	22.61 ± 3.04	23.80 ± 3.15	22.45 ± 3.00	16.73 ± 1.55
MRT [b] (hr)	2.0 ± 0.3	2.3 ± 0.2	2.4 ± 0.3	2.5 ± 0.3	3.5 ± 0.7	7.0 ± 0.7
UR [b,d] (%)	0.0 ± 0.0	0.2 ± 0.2	0.3 ± 0.1	0.2 ± 0.1	0.3 ± 0.0	0.5 ± 0.1

a) Geometric mean (CV%), b) Mean ± 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] (μg/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] (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] (μg·hr/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] (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 [c] (L/hr)	4.16 (1.12)	1.69 (0.53)	-	-	5.88 (3.03)	1.04 (0.80)	-	-
Vd/F [c] (L)	23.91 (2.69)	10.98 (3.34)	-	-	23.18 (2.27)	7.33 (4.38)	-	-

τ = 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

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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]

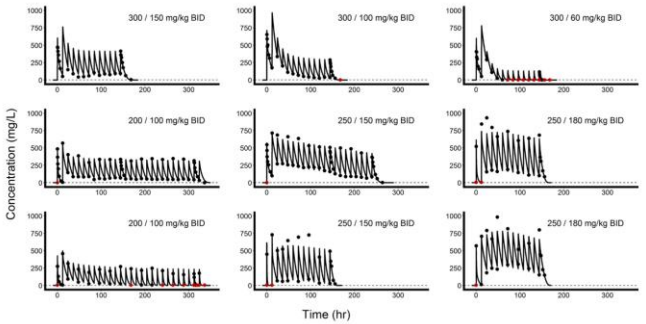
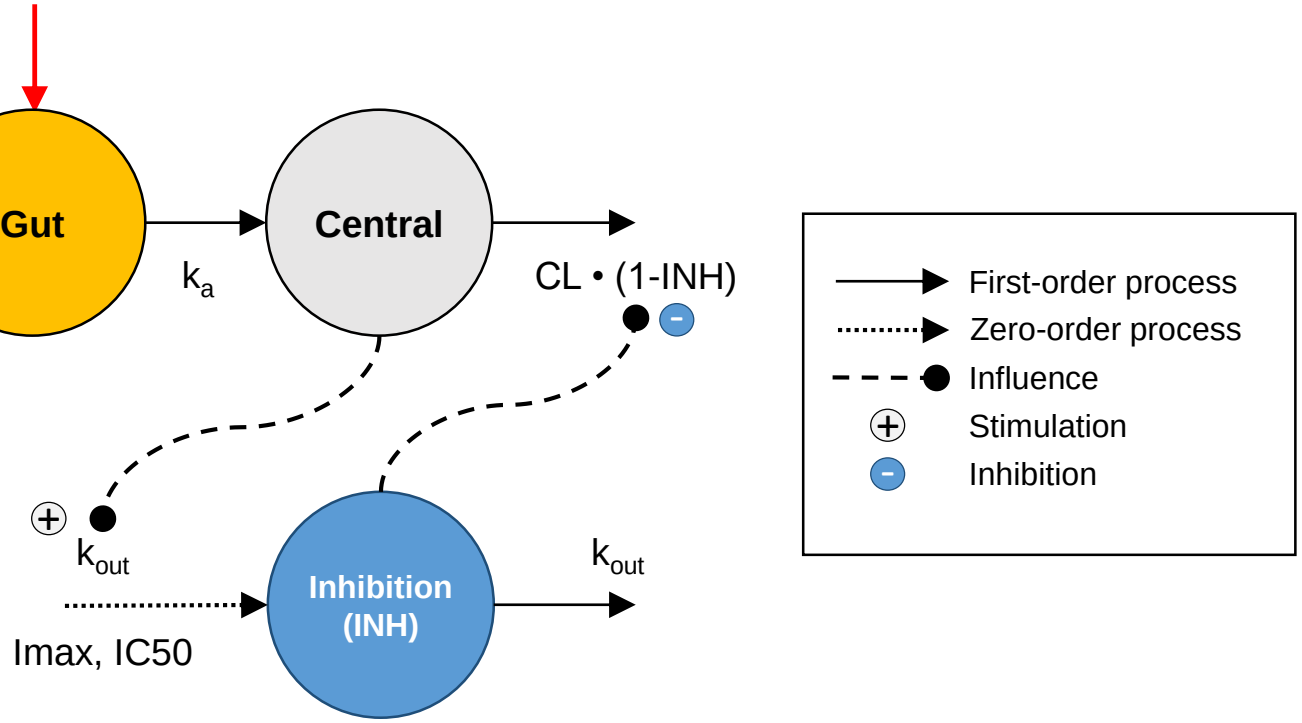


FIG 2 Individual observed concentrations (black dots) and model predictions (solid lines) for macaques treated with various dosing regimens. Red dots indicate data below the limit of quantitation, represented by dashed lines.

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

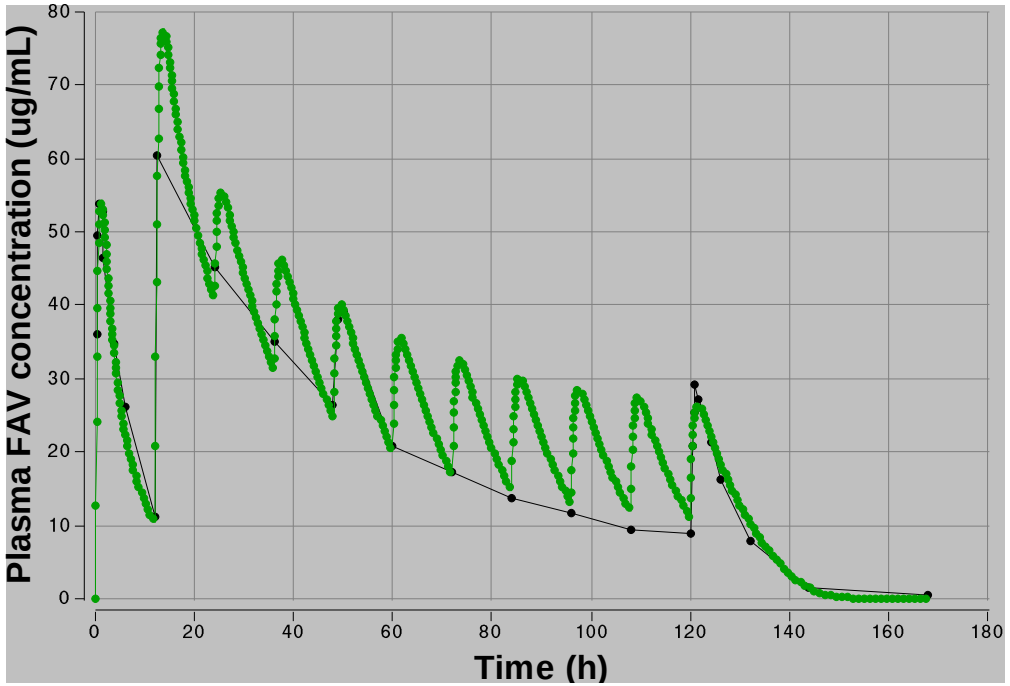
Model structure



Pharmacokinetic modeling

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

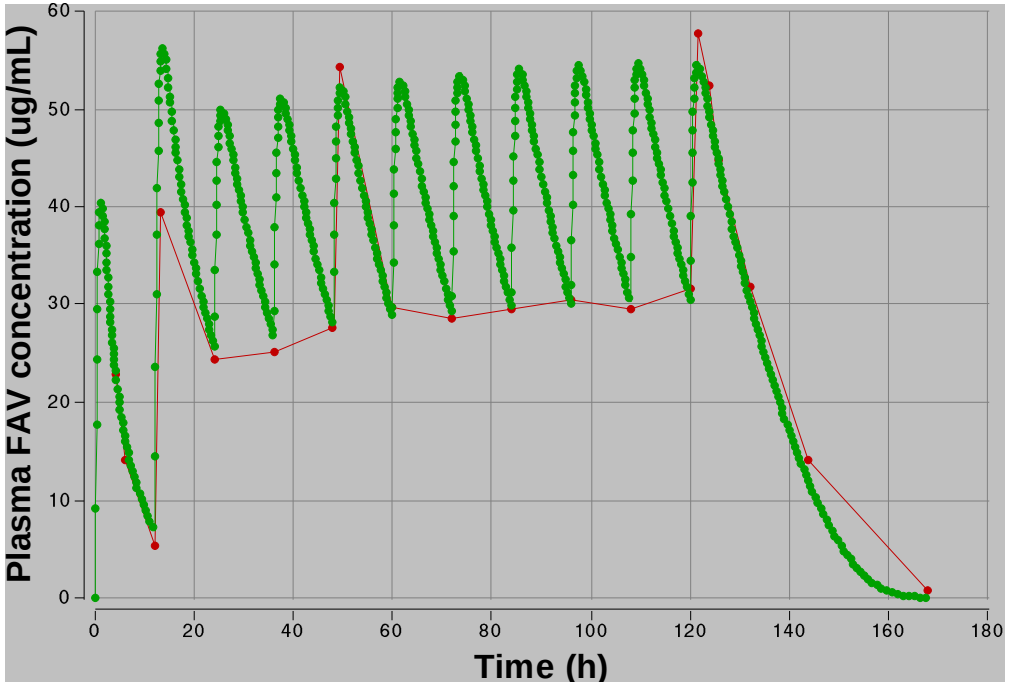
1600 mg BID for day 1 and 400 mg BID for day 2-6 (cohort 1)



Predicted

Observed

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



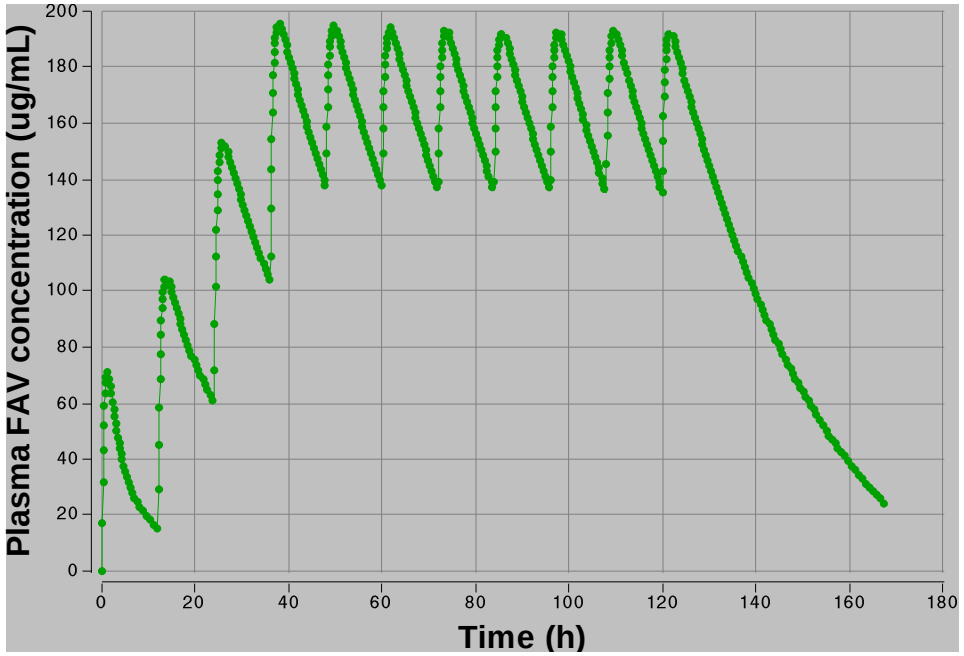
Predicted

Observed

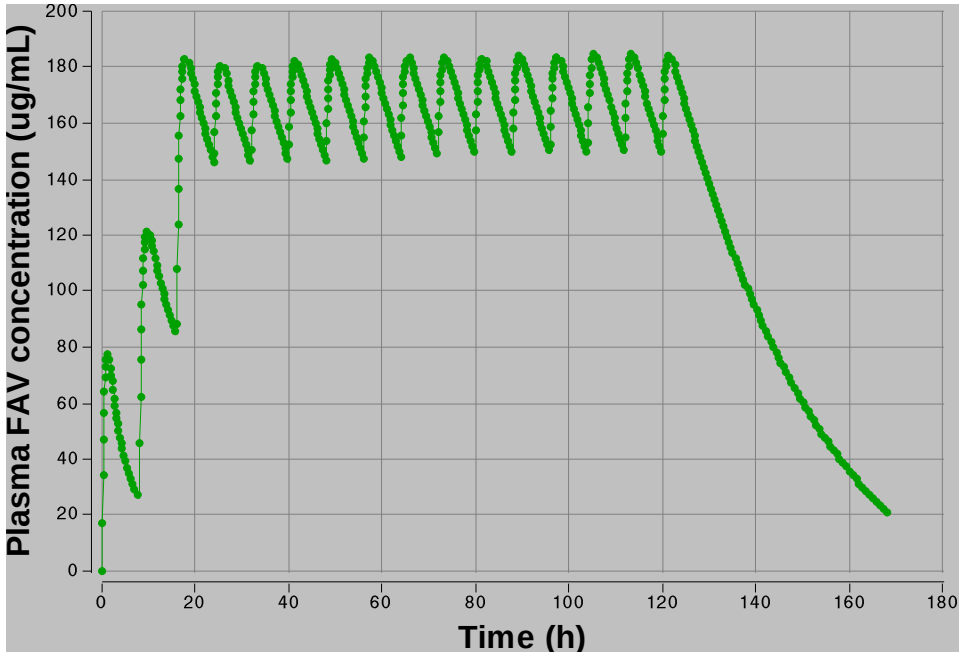
Predicted plasma concentration-time profiles (Auto inhibition model)

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

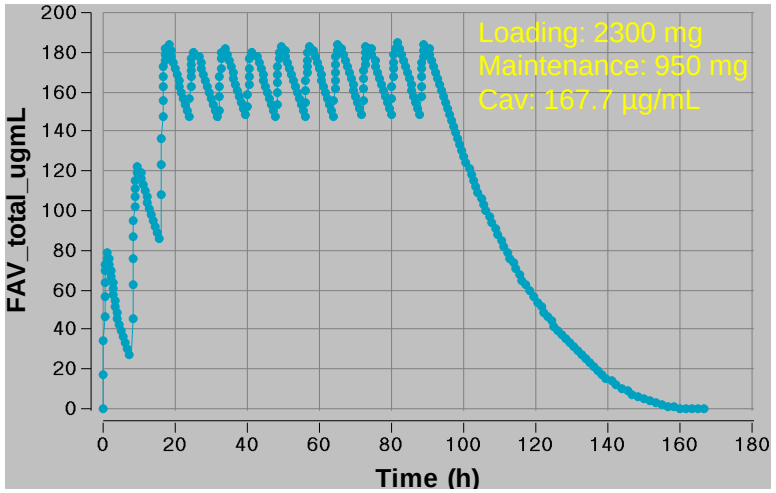


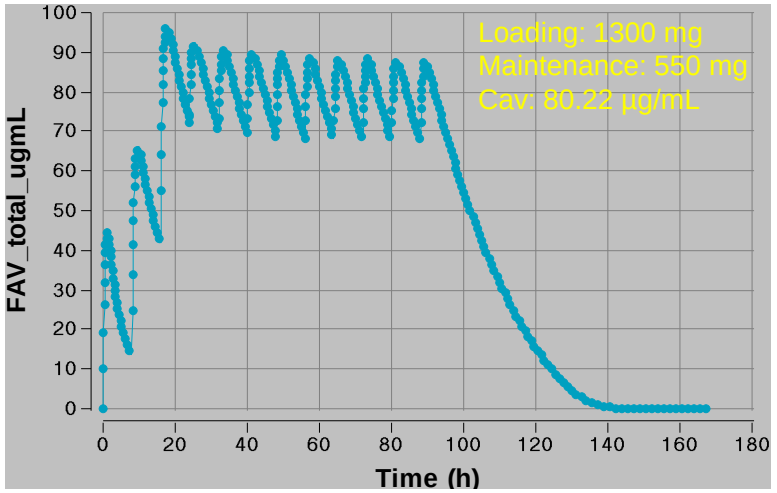
TID (interval: 8 h)
Loading dose: 2300 mg (1 day)
Maintenance dose: 950 mg

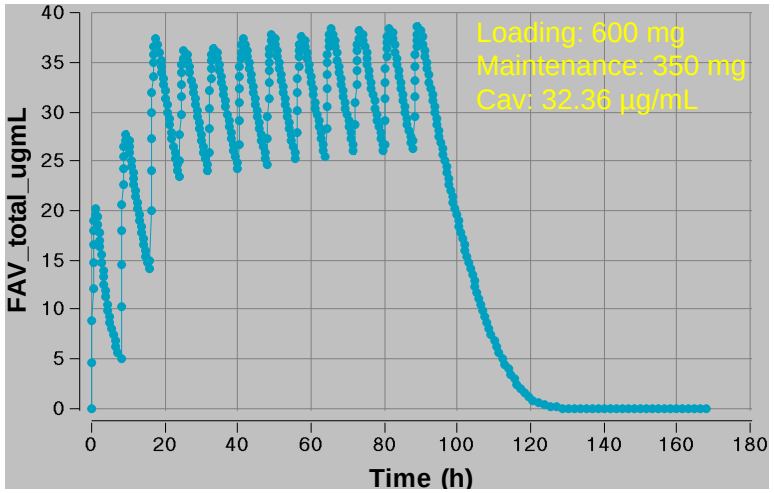
Predicted plasma concentration-time profiles (Auto inhibition model)

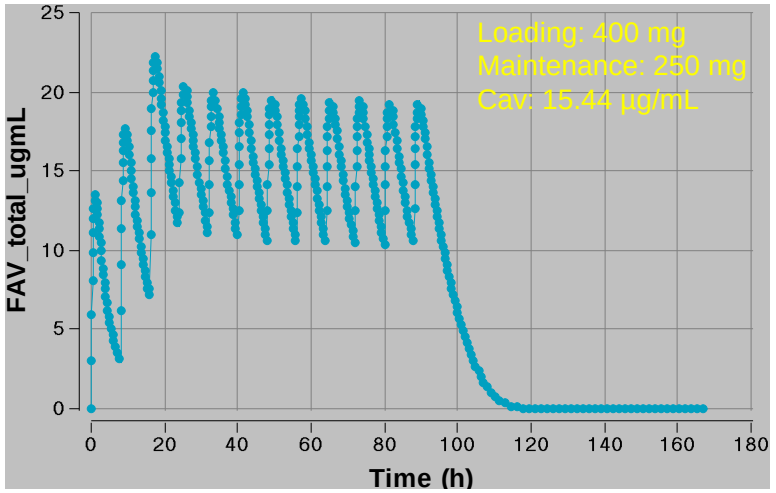
Target concentration: 165, 85, 35 µg/mL

Target (free, µM)	Target (total, µg/mL)	Regimen	Loading	Maintenance	Cavg (µg/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

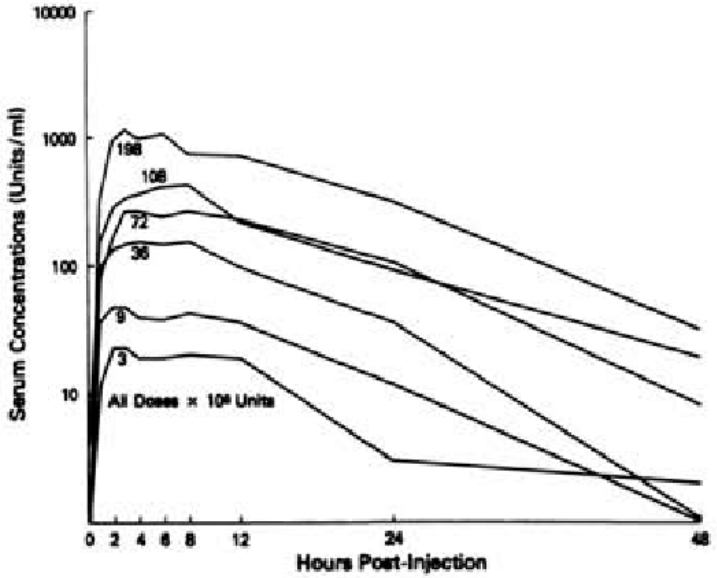
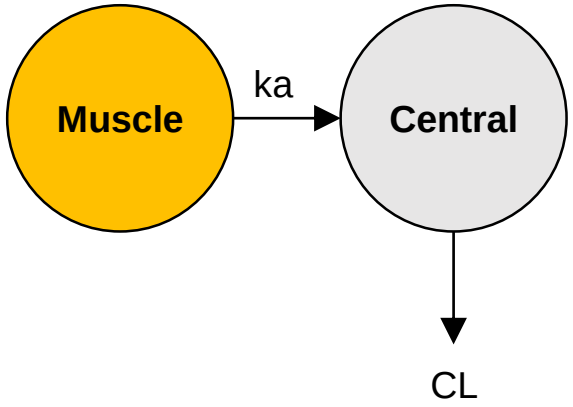


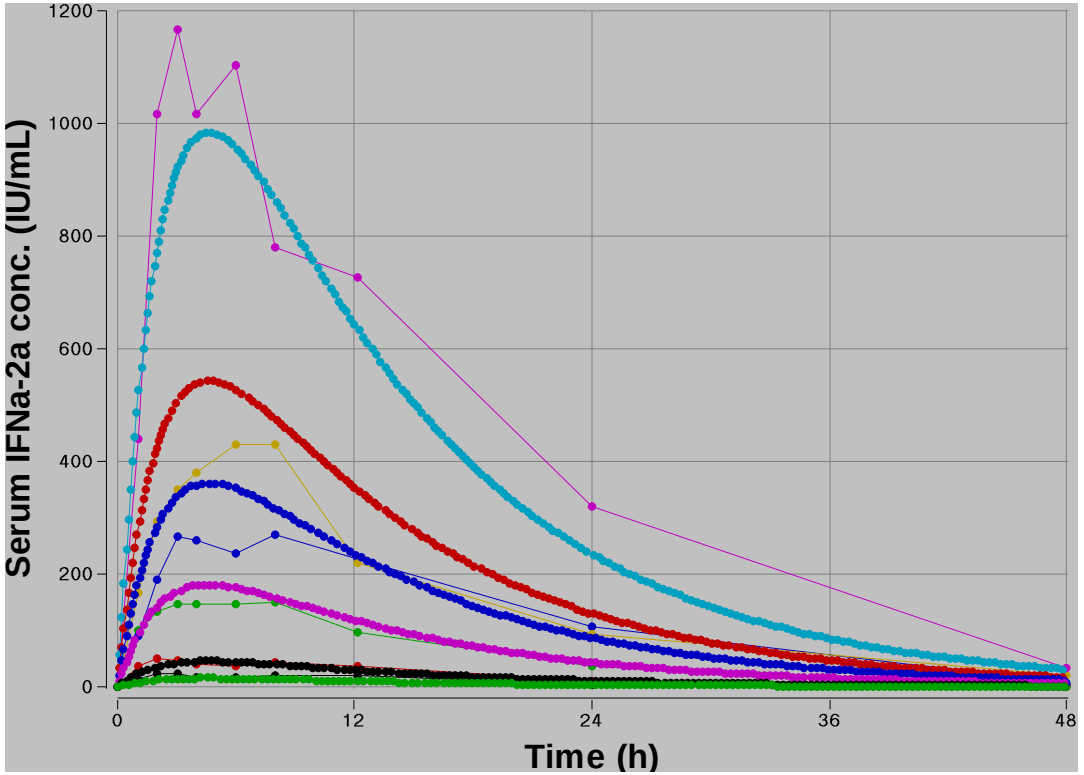
Figure 2. The arithmetic mean serum concentrations of interferon as measured by the bioassay with MDBK cells as target cells. The numbers of patients measured at 3, 9, 36, 72, 108, and 198 million units are 16, 16, 16, 16, 14, and 5, respectively.

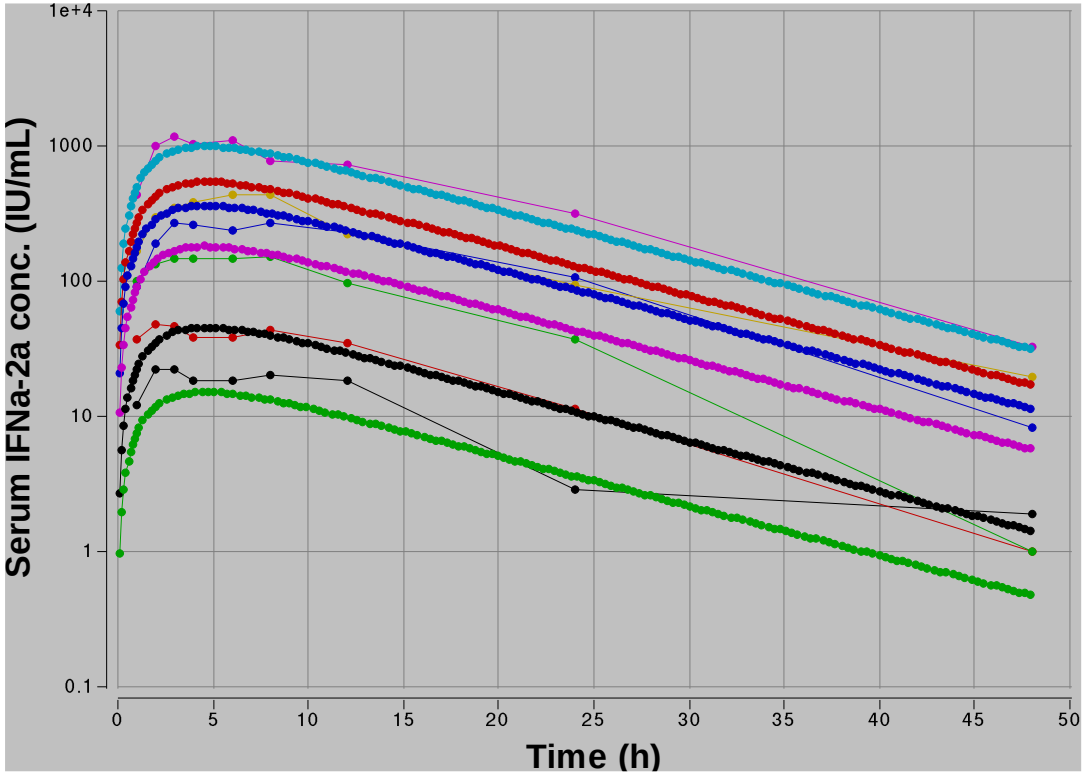


Group	t1/2 (h)	Tmax (h)	Cmax (IU/mL)	AUCall (IU.h/mL)	AUCinf (IU.h/mL)	Vz/F (L)	CL/F (mL/min)
3	11.6	3.0	22.6	405.7	437.5	114.9	114.3
9	7.0	2.0	48.5	895.3	905.3	100.0	165.7
36	5.3	8.0	151.6	2806.2	2813.9	97.9	213.2
72	7.3	8.0	270.9	6092.7	6179.3	123.0	194.2
108	10.4	8.0	431.0	7231.3	7528.0	215.0	239.1
198	7.9	3.0	1168.3	20681.4	21048.3	106.9	156.8

Pharmacokinetic modeling

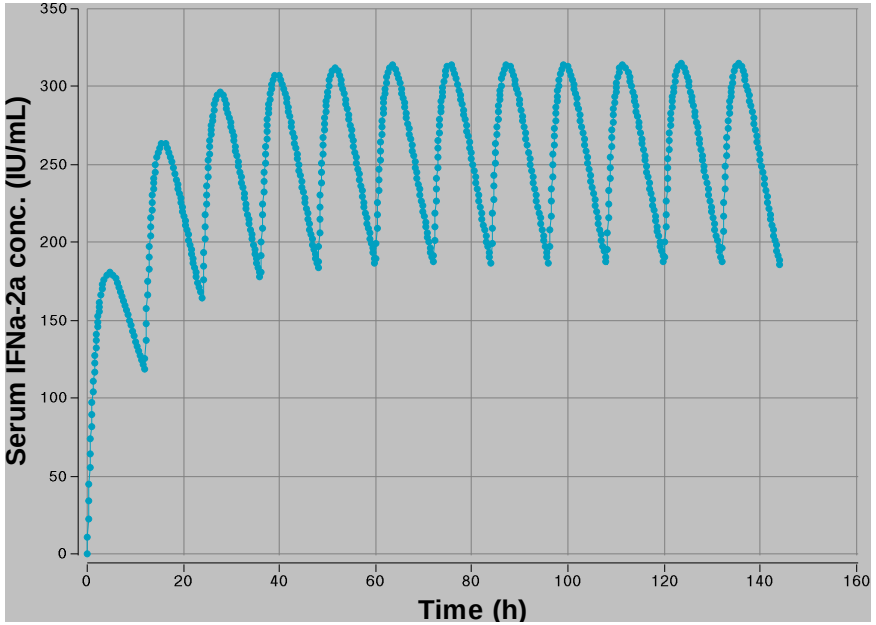
Observed vs. fitted serum concentration-time profiles



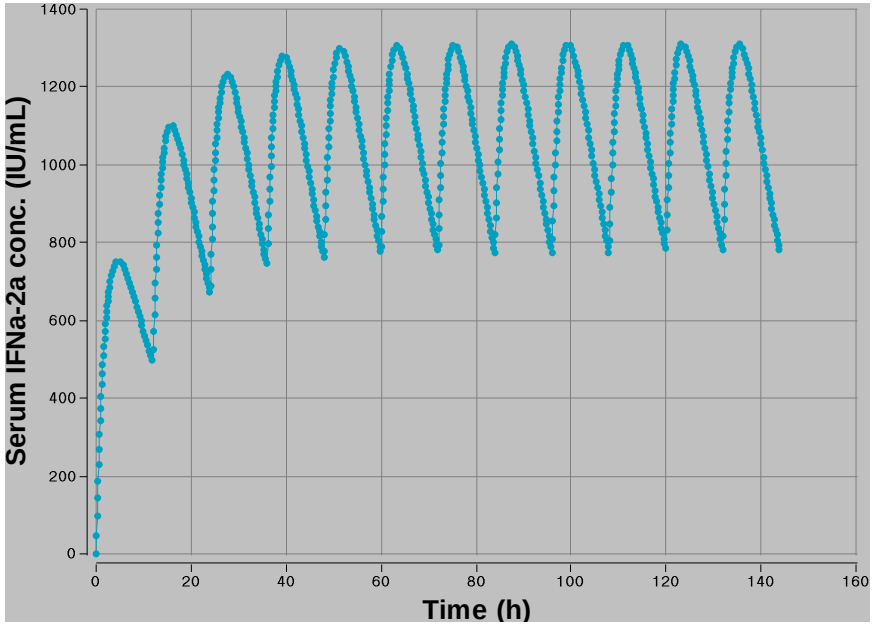


Predicted plasma concentration-time profiles
Target plasma concentration: 100-1,000 IU/mL

36 million IU, twice a day (IM injection)



150 million IU, twice a day (IM injection)

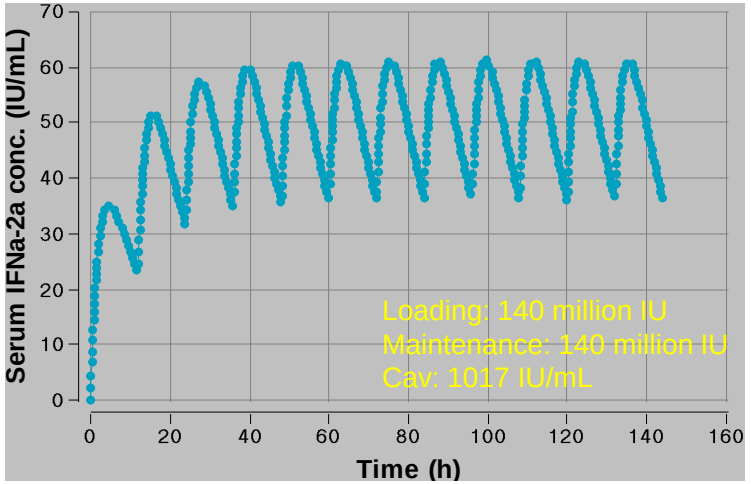


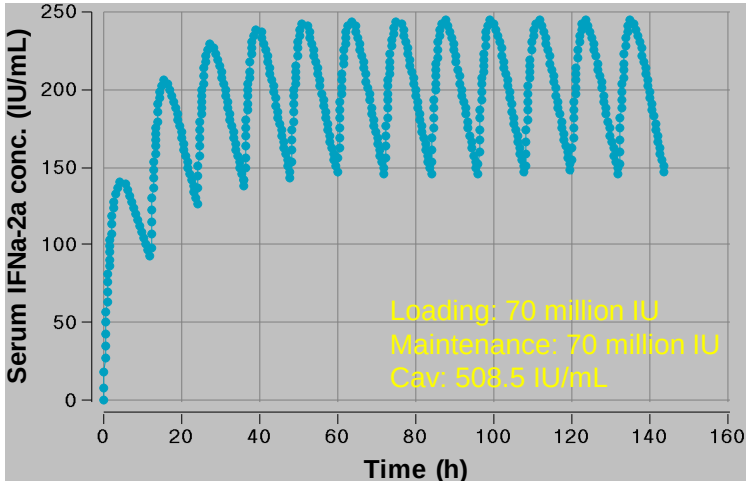
The pharmacokinetics of interferon alfa-2a after single intramuscular doses to patients with disseminated cancer and chronic hepatitis B were similar to those found in healthy volunteers. Dose-proportional increases in serum concentrations were observed after single doses up to 198 million IU. There 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.

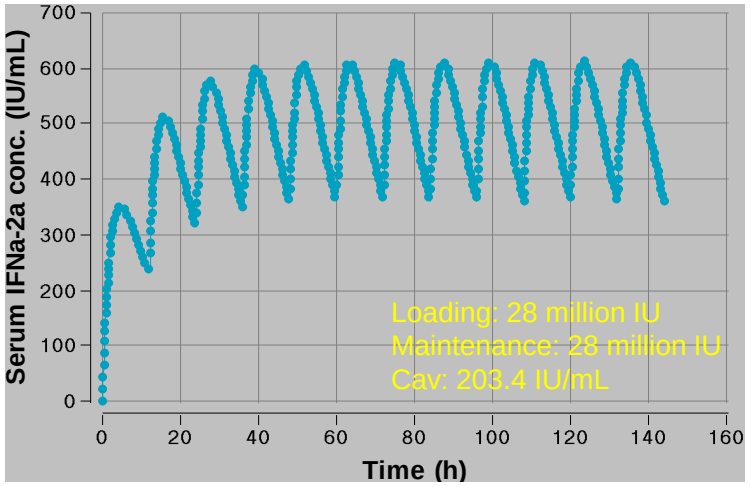
Predicted serum concentration-time profiles

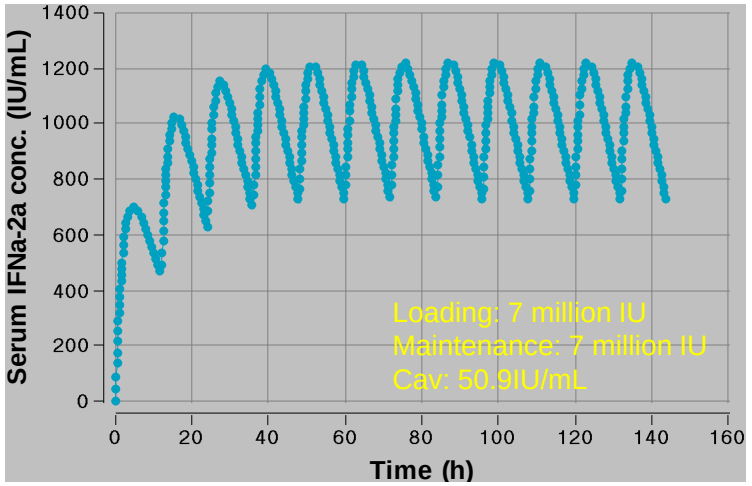
Target plasma concentration: 100-1,000 IU/mL

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

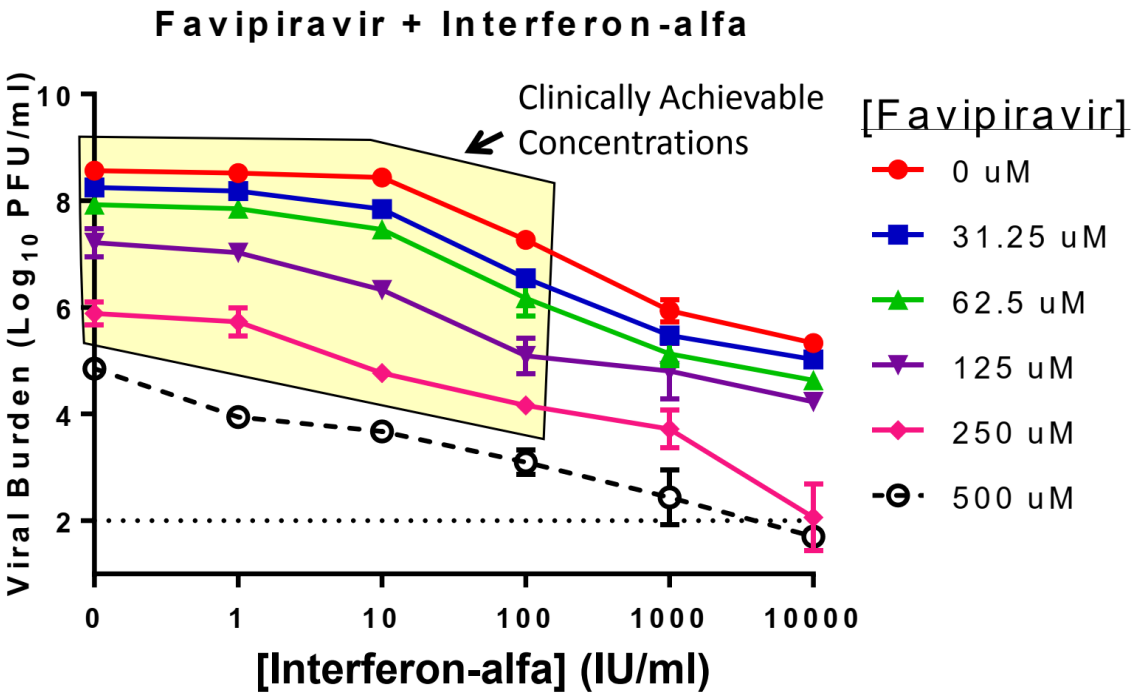


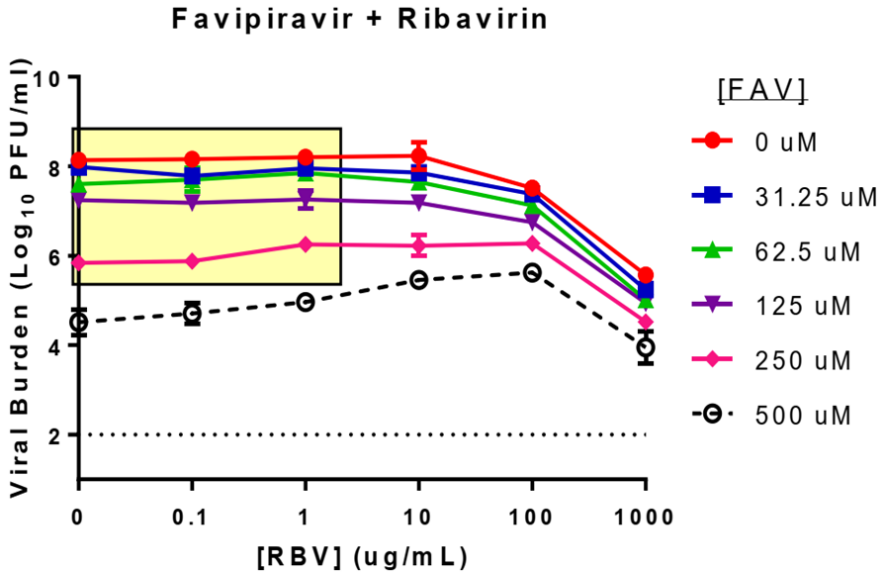


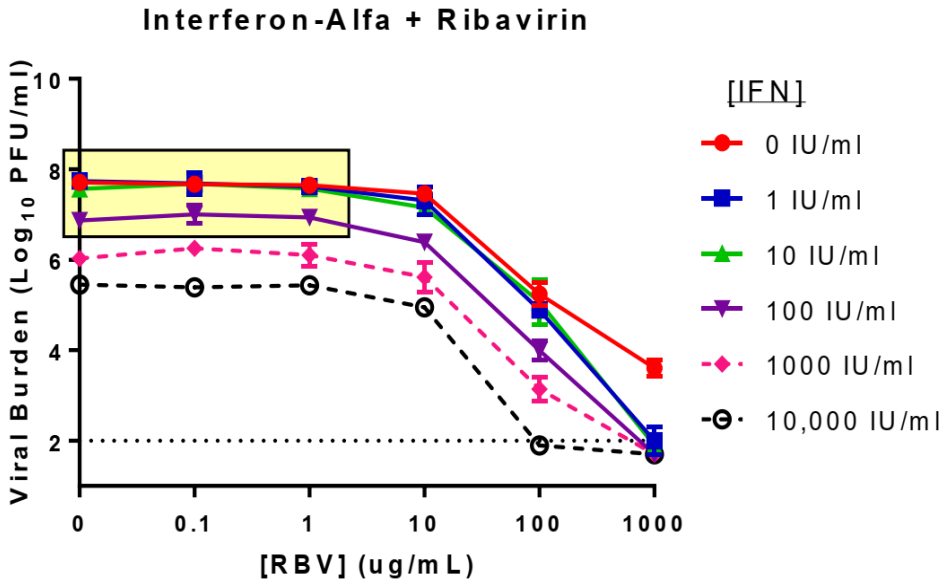




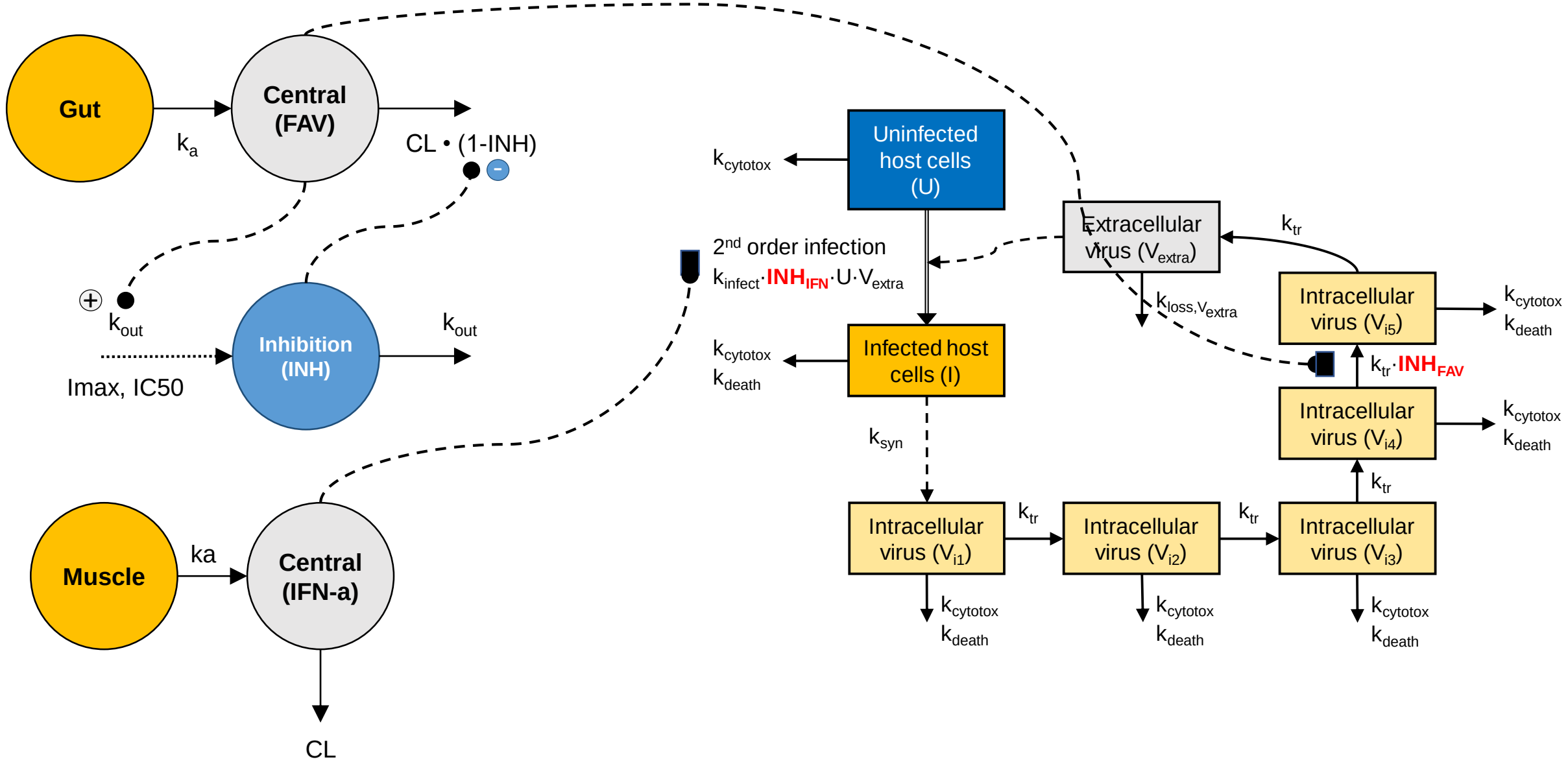
Combination therapy results



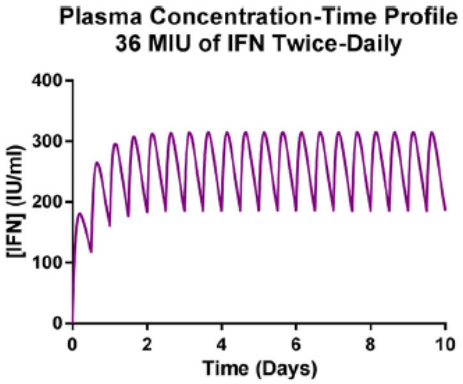


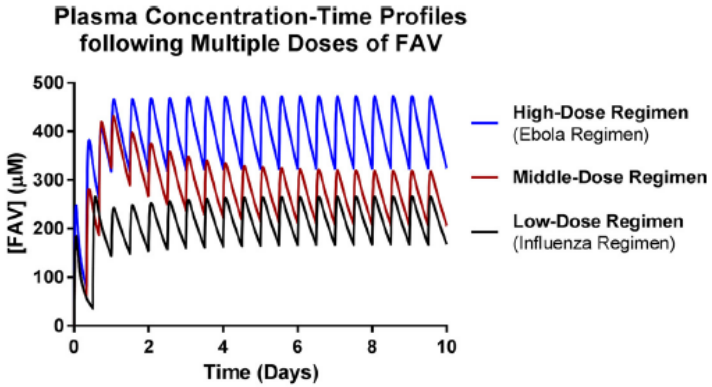


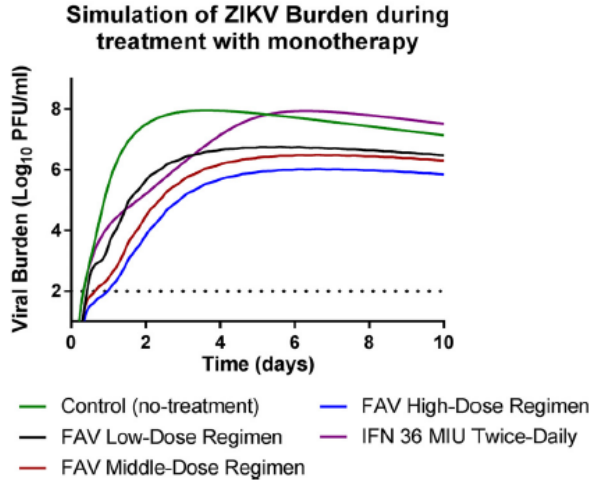
PK/PD modeling

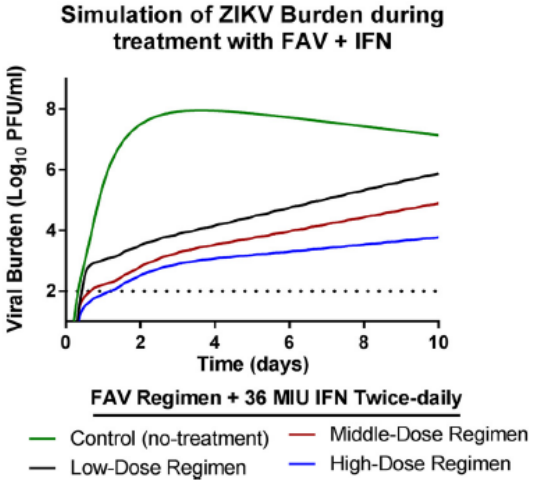


Prediction of anti-viral effect in humans









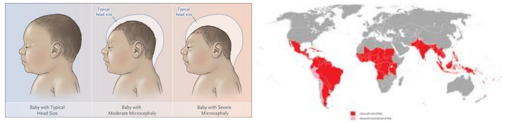
Time (h)	FAV Dose (mg)		
	High	Middle	Low
0	2400	1800	1800
8	2400	1800	-
12	-	-	1800
16	1800	1800	-
24 (BID)	1200	900	800

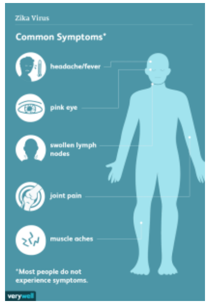
Clinically relevant FAV and IFN combination regimens have great potential as a treatment strategy for ZIKV infections

Summary

Worldwide prevalence of Zika virus (ZIKV) infection

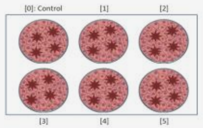
- Serious and long-term health consequences associated with infection, especially during pregnancy, where devastating birth defects such as microcephaly, brain damage, and fetal loss have been reported.
- Neurological complications have also been linked to ZIKV infection in adults



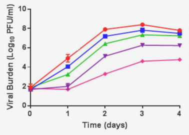


Research design

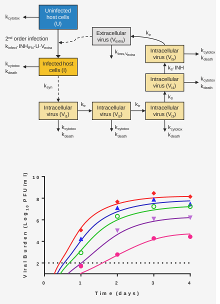
Vero cell + Zika virus



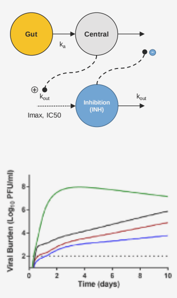
Medium with varying concentrations of single or two drug(s)



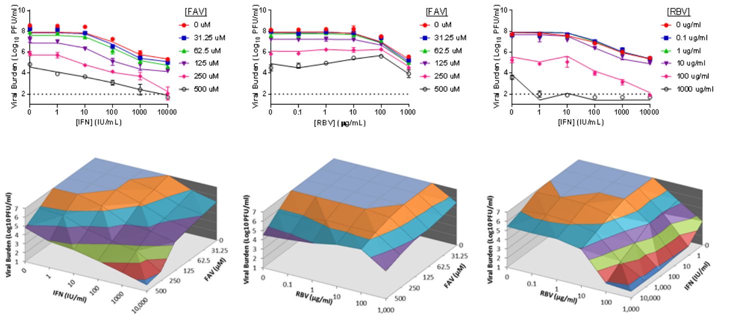
PD modeling



PK/PD modeling



Combination therapy results



Pharmacokinetic modeling

Favipiravir

T705_Report on the Deliberation Results (2014)

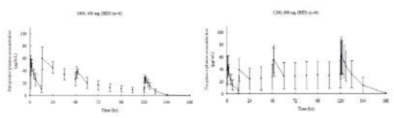
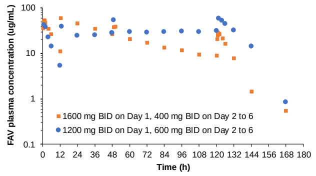
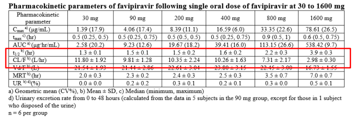


Figure. Plasma concentration profile of favipiravir (mean ± SD)

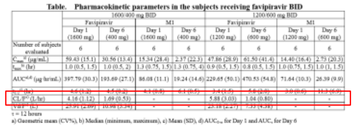


Single dose study



Saturated elimination/Auto inhibition

Multiple dose study



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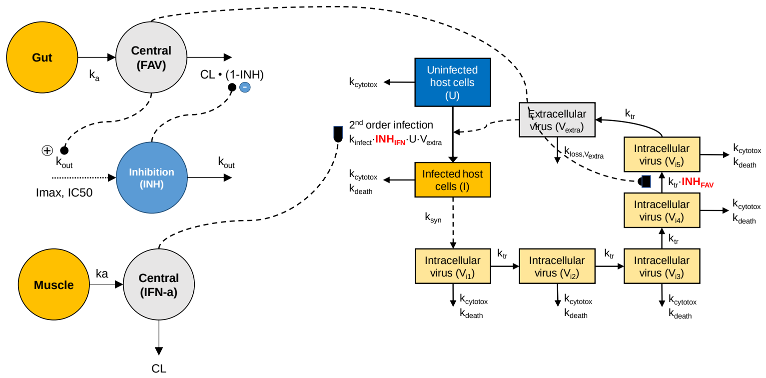
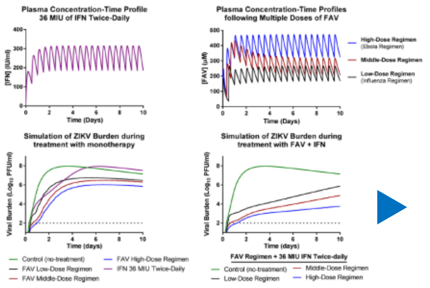


Prediction of anti-viral effect in humans



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감사합니다