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From Chemistry to Cures

EDP-938, a Novel Non-Fusion Replication Inhibitor of Respiratory Syncytial Virus, Demonstrates Potent Antiviral Activities both *In Vitro* and *In Vivo*

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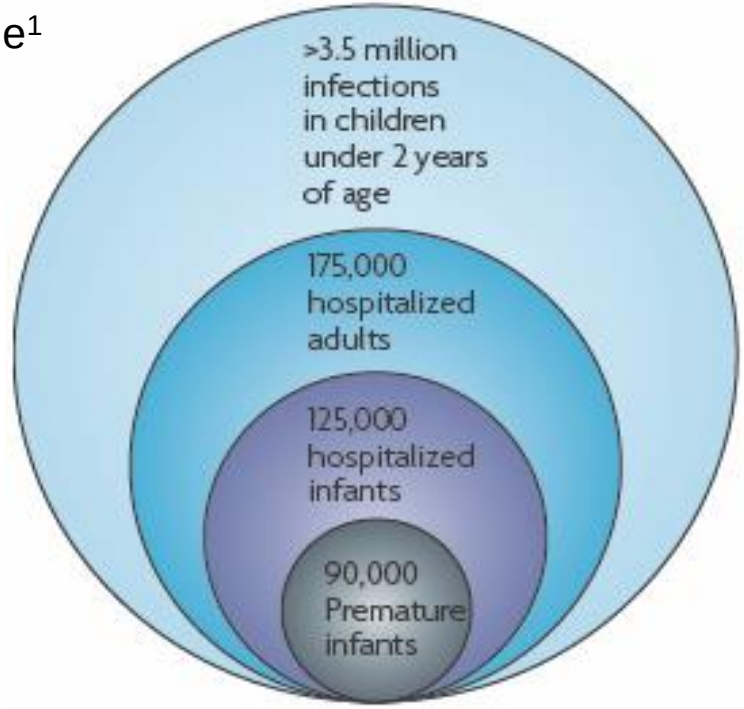
There remains a significant unmet medical need with RSV infection

- Leading cause of LRTI in infants & elderly
  - Almost all infants infected by the age of three
    - 3.4m hospitalizations, 200k deaths/year worldwide[1]
  - Elderly with underlying cardiopulmonary conditions such as COPD
    - 177k hospitalizations,14k deaths/year in the US[2]
  - Immunocompromised, particularly lung and bone marrow transplant recipients
- No vaccine or effective treatment available
  - mAb Synagis offers 50% protection as prophylaxis mainly in premature infants
  - Ribavirin, with questionable efficacy and significant side effects, is rarely used

Potential pool of patients (per year) who may seek RSV treatments[3]



[1] *Nair H et al. 2010 Lancet 375: 1545-55*
[2] *Falsey AR, et al. 2005 NEJM 352:1748-59*
[3] *Nature Reviews Drug Discovery 2010(9):15*

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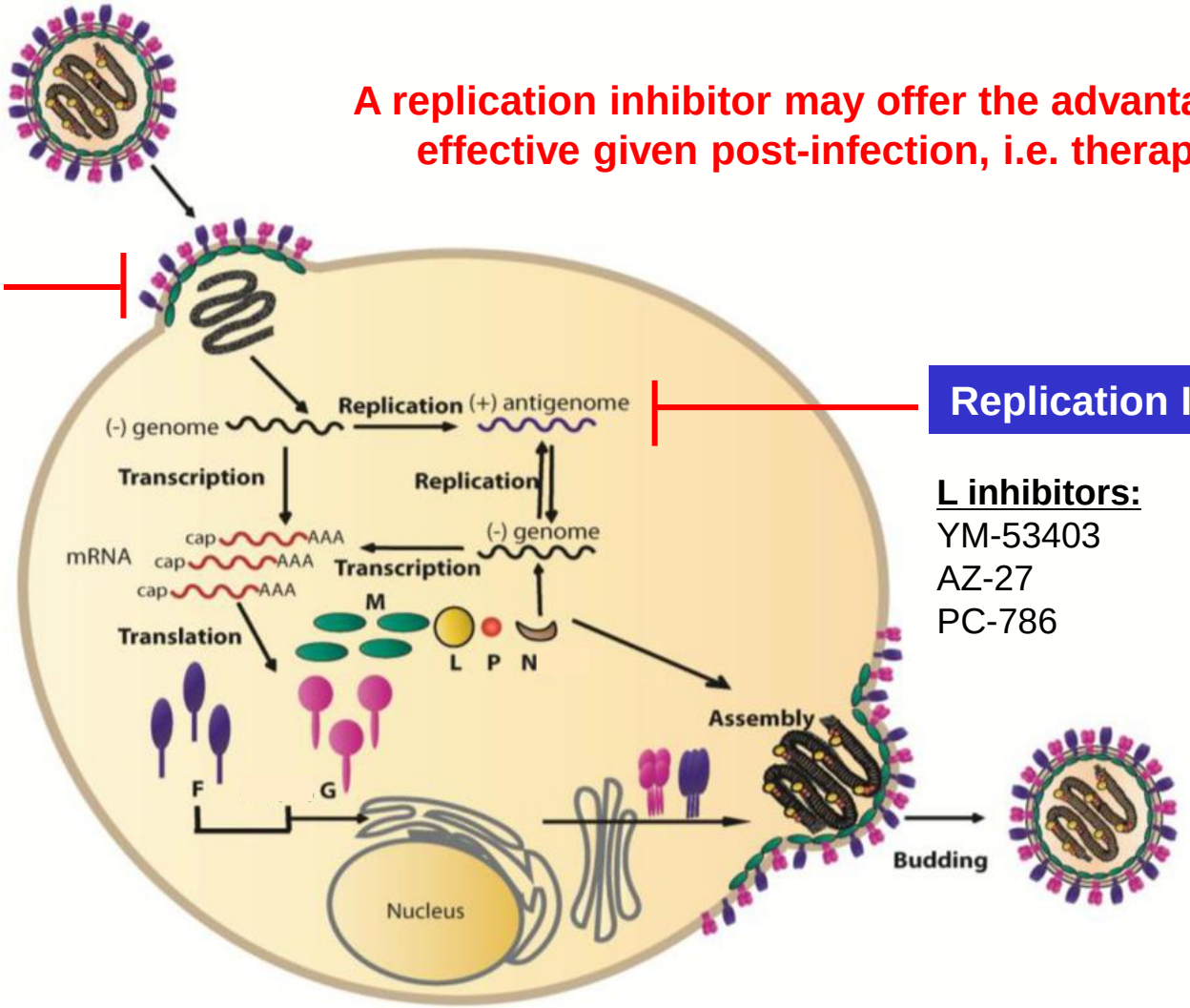
RSV life cycle & antiviral targets

A replication inhibitor may offer the advantage of being effective given post-infection, i.e. therapeutically

Entry Inhibitors

Anti-F mAb:
Synagis
MEDI-8897
REGN-2222
ALX-0171

Fusion inhibitors:
GS-5806
JNJ-678
BTA-C585
AK-0529
RV521



Replication Inhibitors

L inhibitors:
YM-53403
AZ-27
PC-786

Nucleoside:
ALS-8176

N inhibitor
RSV-604

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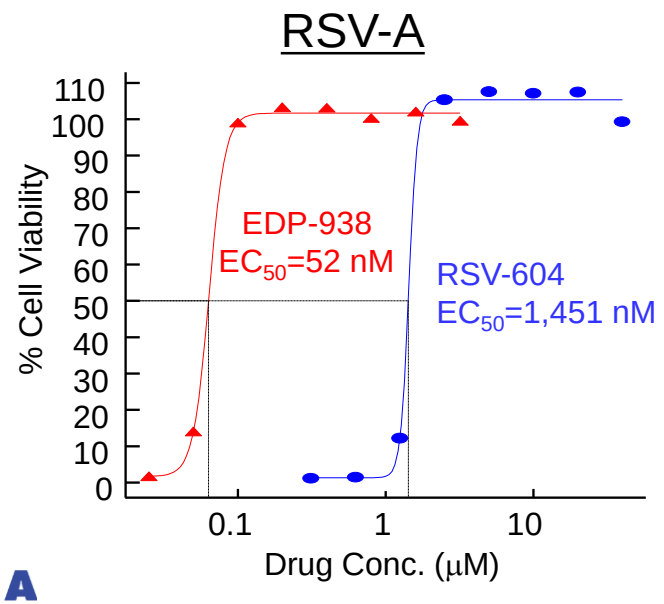
Modified from Najjar et al. Viruses 2014, 6(8), 3019-3054

EDP-938: A novel potent RSV N inhibitor

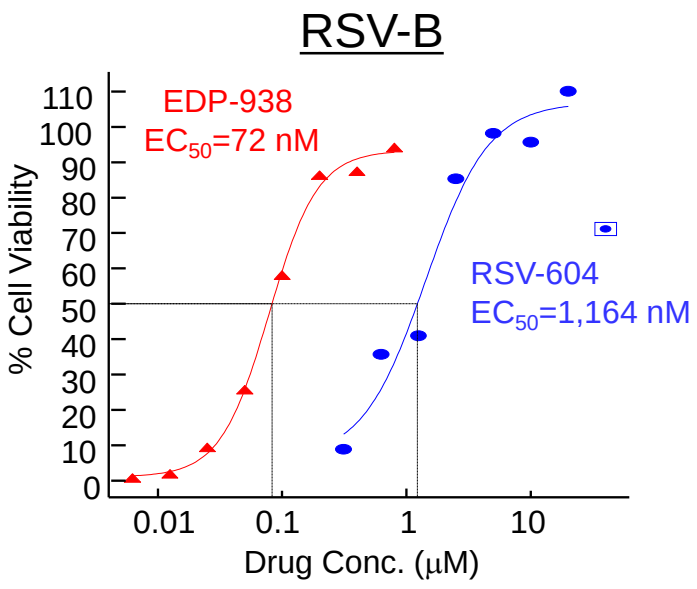
- RSV-604: the previous known RSV nucleoprotein (N) inhibitor*
  - *In vitro* resistance selection mapped to RSV N protein but exact MoA unclear
  - Clinical PoC efficacy demonstrated : 2.31-log viral load reduction after 5-day treatment in a sub-population of RSV infected stem cell transplantation patients with drug level above EC_{90}#

** Chapman et al 2007 AAC*
 # Chapman and Cockerill, 2011 Antiviral Drugs

- **EDP-938** has been discovered as a much more potent RSV N inhibitor with no significant cytotoxicity (CC_{50}>50 μM)



Long strain, HEp-2 cells, CPE assay



Washington strain, A549 cells, CPE assay

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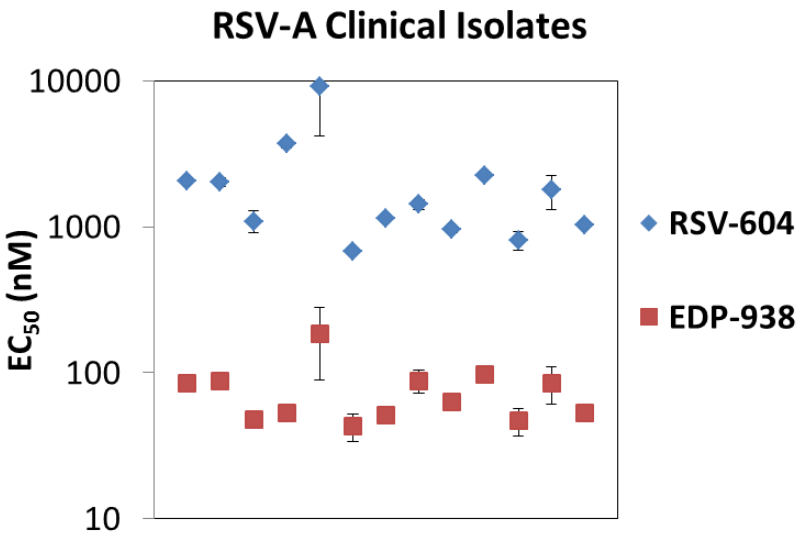
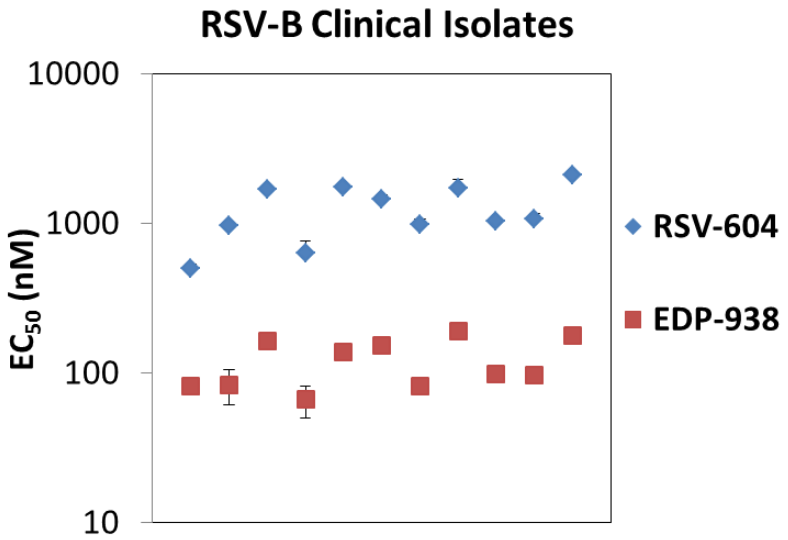
EDP-938 potently inhibits all RSV lab strains tested *in vitro*

Virus		Assay		EC_{50} (nM)		EC_{90} (nM)	
Sub-type	Strain	Cell	Read-out	RSV-604	EDP-938	RSV-604	EDP-938
A	M37	HBEC	PCR	563 ± 308	23 ± 13	772 ± 389	36 ± 17
		HEp-2	PCR	1900 ± 436	54 ± 5	3474 ± 2028	85 ± 21
		HEp-2	CPE	980 ± 150	28 ± 4	1314 ± 115	34 ± 10
	Long	HBEC	PCR	689 ± 306	20 ± 17	940 ± 460	29 ± 23
		HEp-2	PCR	2200 ± 202	89 ± 15	4429 ± 2193	106 ± 34
		HEp-2	CPE	1400 ± 625	52 ± 12	1500 ± 740	60 ± 18
	A2	HEp-2	PCR	1200 ± 128	59 ± 18	1300 ± 40	70 ± 30
		HEp-2	CPE	670 ± 19	28 ± 4	900 ± 240	40 ± 3
B	Wash	HBEC	PCR	1144 ± 794	62 ± 32	1517 ± 858	74 ± 33
		A549	PCR	1900 ± 498	83 ± 38	2500 ± 1680	170 ± 53

EDP-938 is also highly active against RSV-A and B clinical isolates





Clinical Isolates	EC_{50} (nM)	
	RSV-604	EDP-938
RSV-A (n=14)	2,121 ± 2,189	76 ± 37
RSV-B (n=11)	1,264 ± 509	121 ± 45

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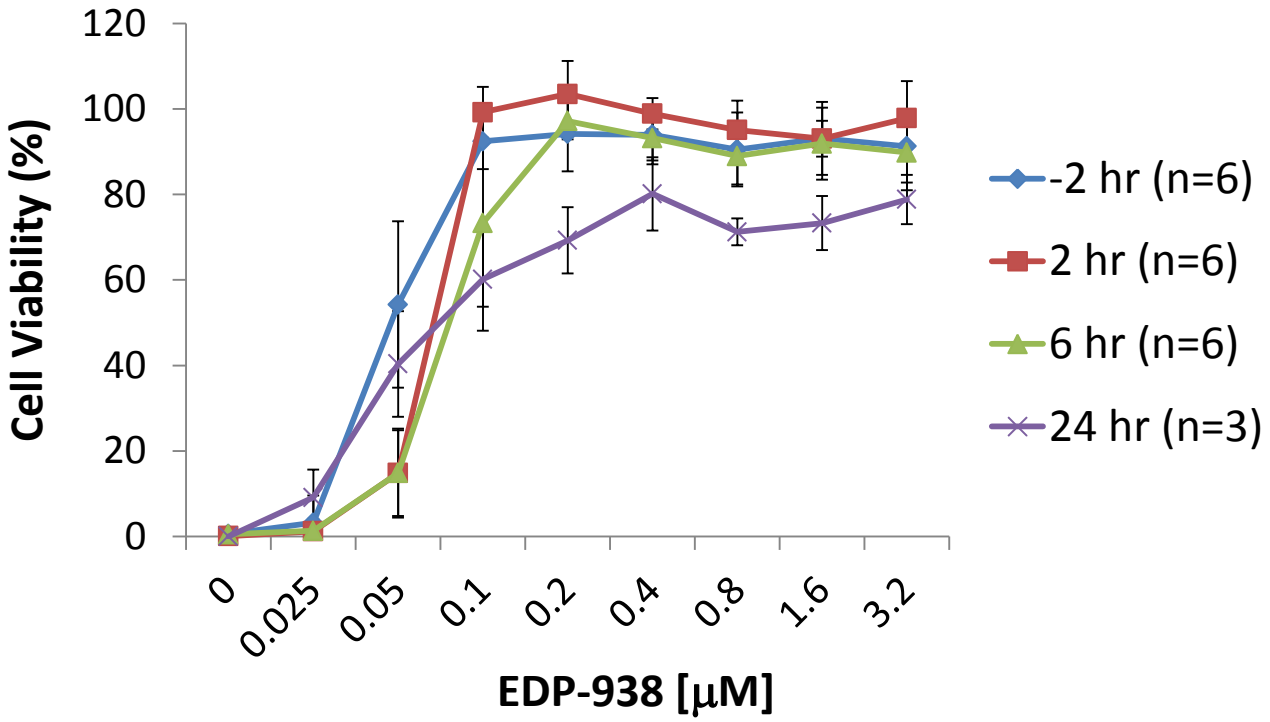
EDP-938 maintains antiviral activity against RSV even if given post-infection *in vitro*

- HEp-2 cells were treated with EDP-938 at 2h before or 2, 6 and 24h after infection with RSV-A Long at MOI=0.1



- Suggests that EDP-938 inhibits RSV at a post-entry, replication step

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EDP-938 presents a high barrier to resistance and no cross-resistance to other RSV inhibitors

- Resistant virus can only be selected with EDP-938 starting at low concentration of the drug (1xEC_{50}) followed by a slow increase to 16xEC_{50} after multiple passages
- Selection with higher concentration of the drug results in elimination of the virus rather than development of resistance
- The level of resistance (fold increase in EC_{50}) with EDP-938 is much lower compared to those with fusion and L inhibitors
- There is no cross-resistance between EDP-938 and other RSV inhibitors

Compounds	wt RSV EC_{50} (nM)	Drug Resistant (^{R}) Virus					
		EDP-938^R EC_{50} (nM)	Fold Change	AZ-27^R EC_{50} (nM)	Fold Change	GS-5806^R EC_{50} (nM)	Fold Change
EDP-938	53 ± 5	250 ± 53	5	68 ± 8	1	<100	< 2
AZ-27 (L inhibitor)	19 ± 2	29 ± 5	2	>20,000	>1,060	5 ± 1	0.3
GS-5806 (F inhibitor)	5 ± 0.4	2 ± 0.6	0.4	6 ± 0.3	1	>20,000	>40,000

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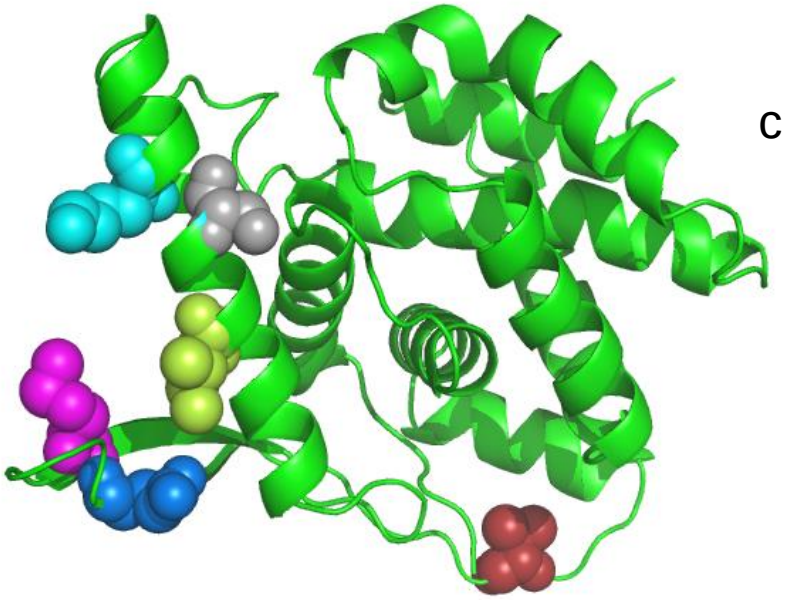
The anti-RSV effect of EDP-938 appears to be mediated through viral N protein

Mutations selected with EDP-938 located in P-binding domain



RSV N^{31-252} crystal structure

- Mutations selected *in vitro* with EDP-938 mainly localized in RSV N protein (similarly to previous report with RSV-604), suggesting the antiviral effect of the inhibitor is mediated through N
- The exact MoA is under further investigation

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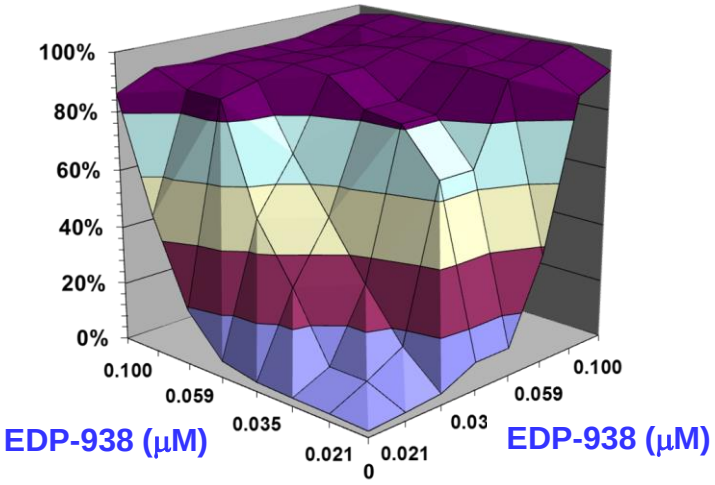
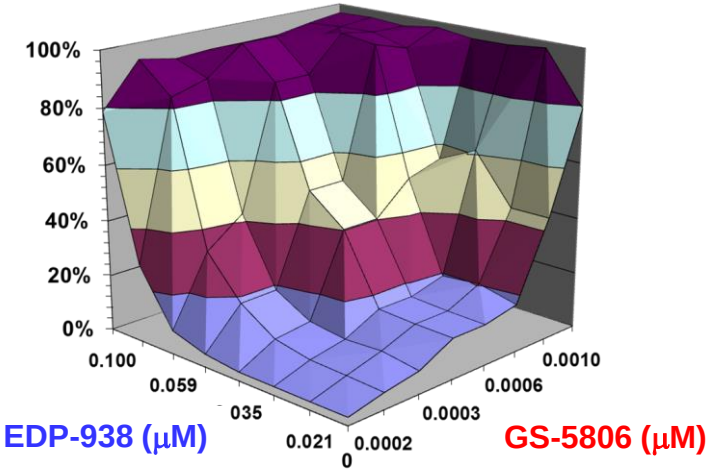
Combinations of EDP-938 with other RSV inhibitors result in stronger antiviral effect than single agents

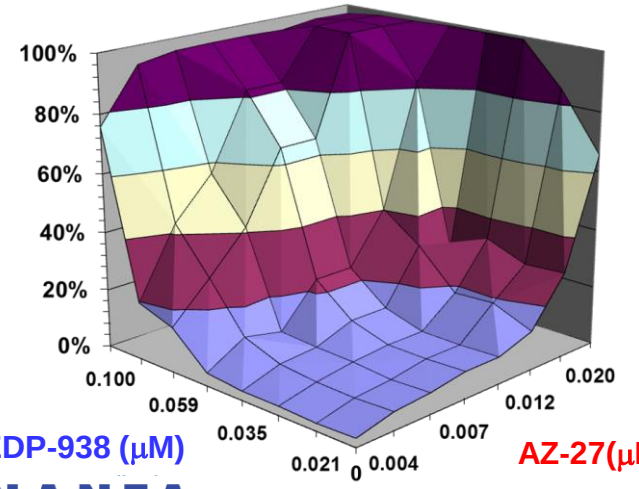
EDP-938 + EDP-938



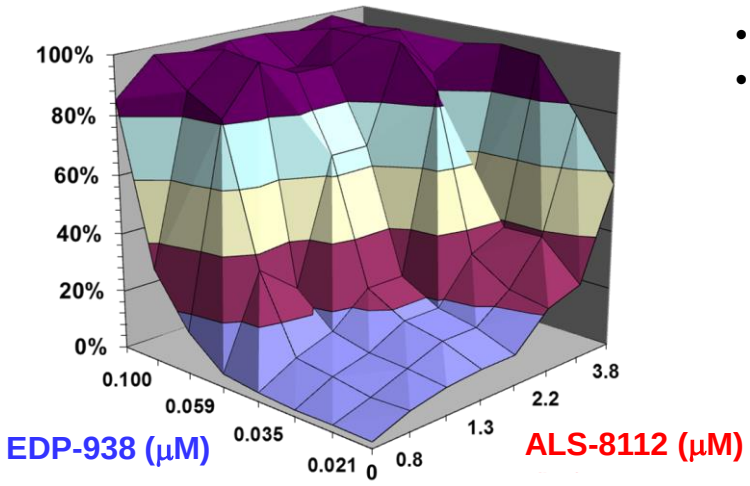
EDP-938 + Fusion Inhibitor



EDP-938 + L Inhibitor



EDP-938 + Nuc



- RSV-A Long
- HEp-2 cells
- MOI=0.1
- CPE assay

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The effects of combinations are moderately synergistic

Analysis using Loewe additivity model

Compounds	Ave. Combination Index (CI) at				
	EC_{50}	EC_{75}	EC_{90}	EC_{95}	Ave.
EDP-938 + EDP-938	0.8	0.8	0.9	0.9	0.9
EDP-938 + ALS-8112	0.7	0.6	0.5	0.4	0.6
EDP-938 + AZ-27	0.8	0.6	0.5	0.4	0.6
EP-938 + GS-5806	0.9	0.7	0.6	0.5	0.7

CI <0.9 = synergy
CI >1.1 = antagonism
CI 0.9 - 1.1 = additivity

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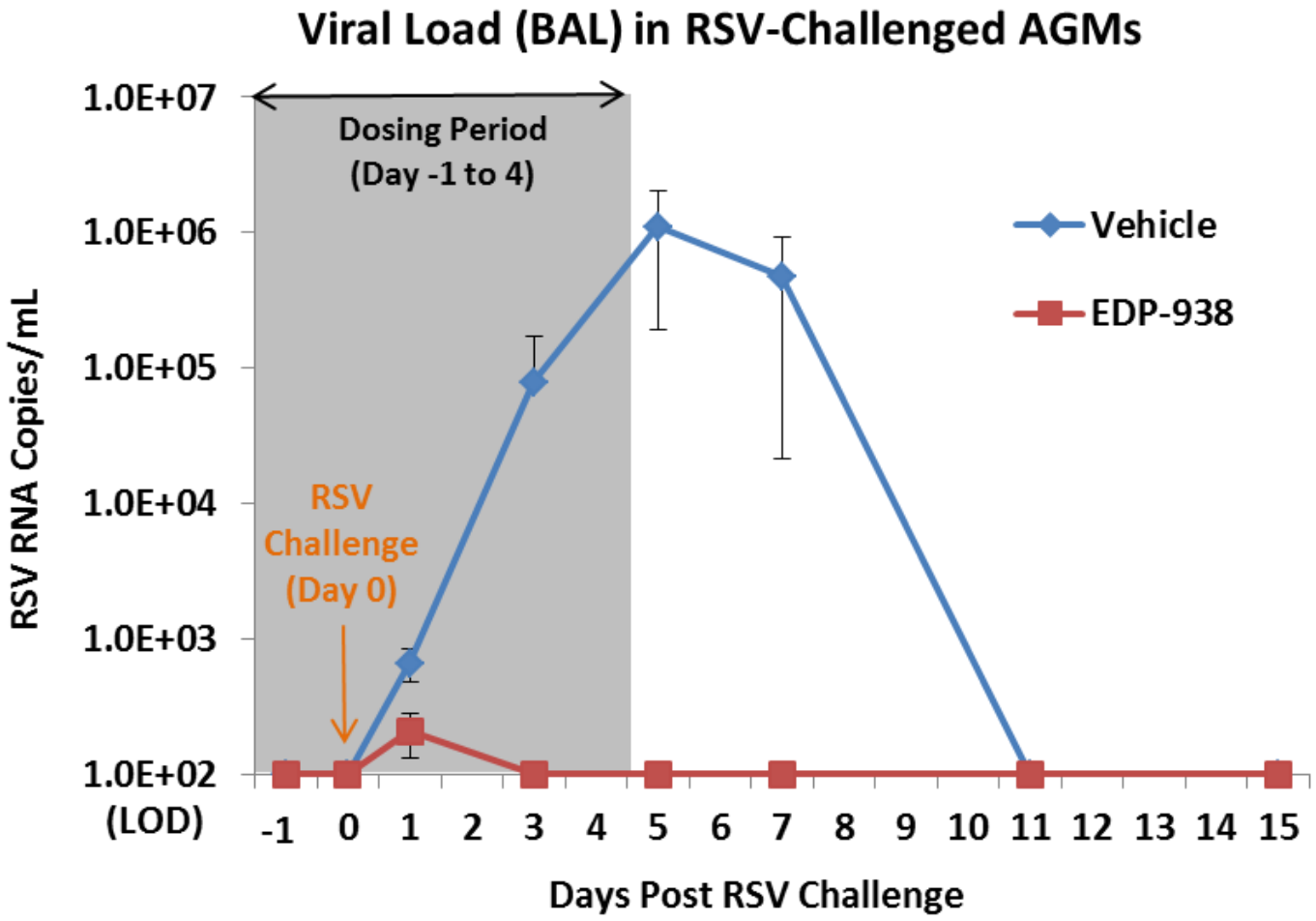
Evaluating *in vivo* efficacy of EDP-938 in African Green Monkey model

- African Green Monkey (AGM) model selected for evaluating *in vivo* efficacy of EDP-938, because
  - Permissive for human RSV infection
  - Support RSV replication at a higher level than cotton rats and BALB/c mice
  - Model validated for evaluating potential vaccine and antiviral drugs*
- Study design:
  - AGMs were each inoculated with 2x10^5 PFU of RSV A2 on Day 0
  - EDP-938 (100 mg/kg BID, n=4) or vehicle control (n=4) was given orally starting at 24h prior to RSV challenge for a total of 6 days (Day -1 to 4), and followed up for 11 more days
  - Samples were taken on Days 1, 3, 5, 7, 11 and 15 through Bronchoalveolar Lavage (BAL) and Nasopharyngeal (NP) Swab to measure RSV level

** Jin 2003 Vaccine 21:3647–52; Deval 2015 PLOS Pathogens*

EDP-938 demonstrated excellent *in vivo* efficacy in the AGM model



LOD (limit of detection) = 100 copies/mL

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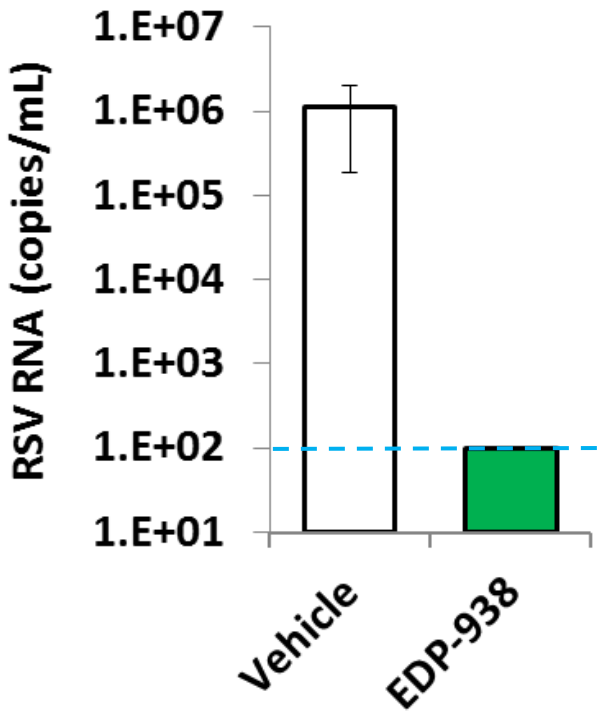
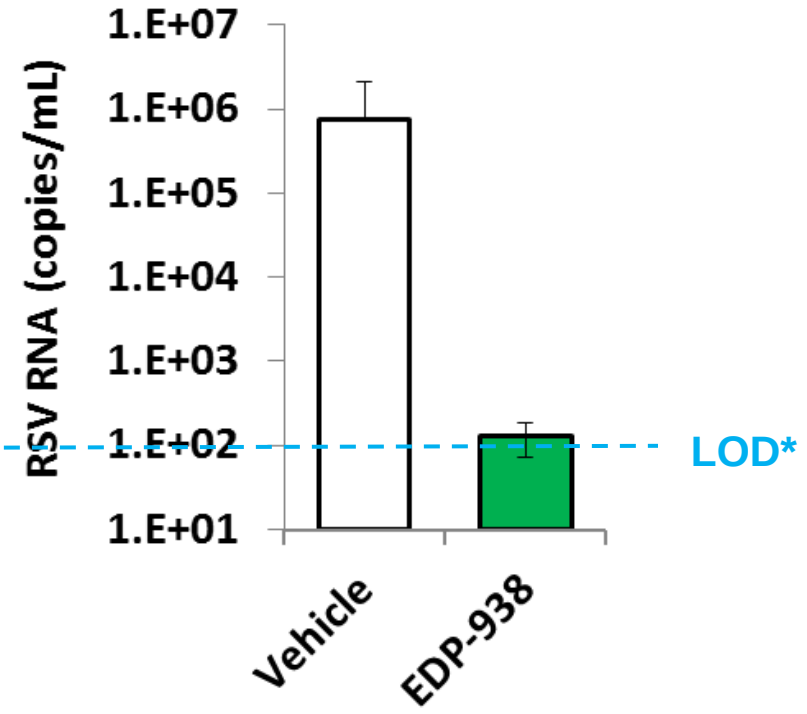
There was a 4-log viral load reduction in both BAL and NP swab in EDP-938 treated AGMs

BAL Viral Load on Day 5



NP Swab Viral Load on Day 7



* Limit of Detection (LOD) = 100 copies/mL

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EDP-938 Summary

- A novel non-fusion replication inhibitor that appears to modulate the RSV N protein
- Highly active against all RSV-A and B strains and clinical isolates
- Inhibits RSV at a post-entry replication step and is effective given post infection, i.e. therapeutically
- Presents a high barrier to resistance *in vitro* with no cross-resistance to fusion or L polymerase inhibitors
- Leads to synergistic antiviral effect when used in combination with other RSV inhibitors *in vitro*
- Showed excellent *in vivo* efficacy in the African Green Monkey model
- Phase 1 clinical study initiation planned for Q4 2017

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