ENANTA Pharmaceuticals

From Chemistry to Cures

Discovery and Development of Novel and Potent Non-Fusion Inhibitors of RSV

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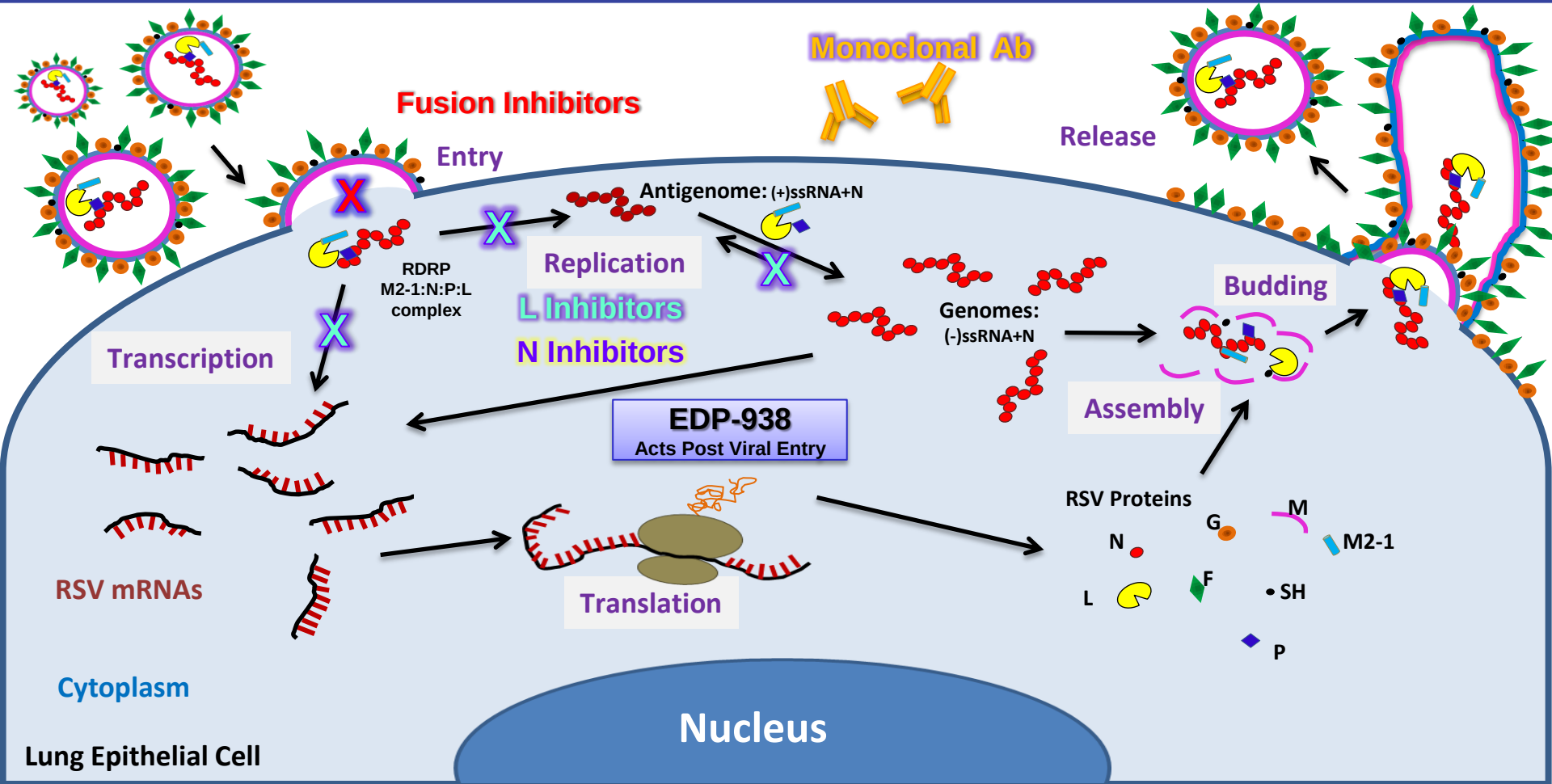
11/29/2018

Disclosures: All contributors are employees of Enanta Pharmaceuticals.

RSV Life Cycle and Antiviral Targets

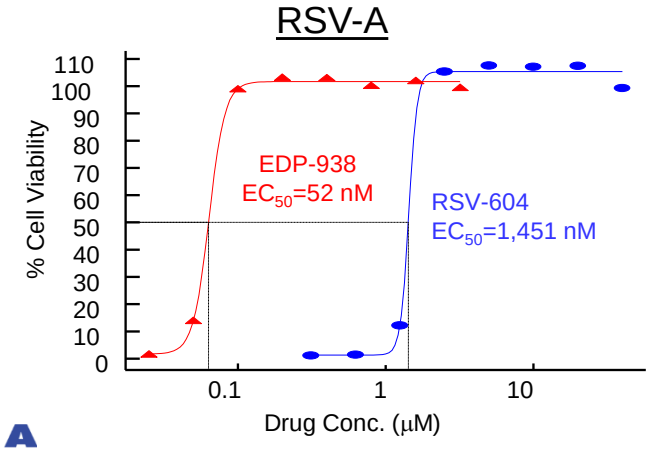


EDP-938: A Novel Potent RSV N Inhibitor

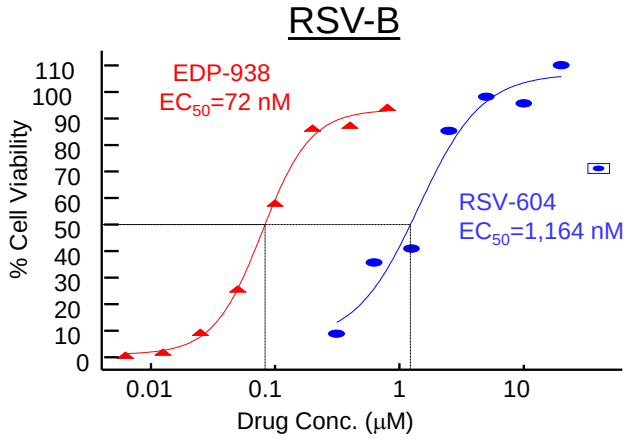
- RSV-604: the previously known RSV nucleoprotein (N) inhibitor*
  - *In vitro* resistance selection mapped to RSV N protein but exact MoA unclear
  - Clinical Proof of Concept efficacy demonstrated : 2.31-log viral load reduction after 5-day treatment in a sub-population of RSV infected stem cell transplantation 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 and Clinical Strains Tested *in vitro*

RSV laboratory strains

Subtype	Strain	Cell	Assay	EC_{50} (nM)
RSV-A	M37	HBEC	PCR	23 ± 13
		HEp-2	PCR	54 ± 5
		HEp-2	CPE	28 ± 4
	Long	HBEC	PCR	20 ± 17
		HEp-2	PCR	89 ± 15
		HEp-2	CPE	52 ± 12
	A2	HEp-2	PCR	59 ± 18
		HEp-2	CPE	28 ± 4
RSV-B	Wash	HBEC	PCR	62 ± 32
		A549	PCR	83 ± 38

Clinical isolates from the Netherlands
(mostly pediatrics)

Subtype (# of isolates)	Cell	Assay	EC_{50} (nM)
RSV-A (n=10)	HEp-2	ViroSpot	43 ± 8
RSV-B (n=10)	HEp-2	CPE	51± 9

Clinical isolates from the US

Subtype (# of isolates)	Cell	Assay	EC_{50} (nM)
RSV-A (n=12)	HEp-2	CPE	68 ± 26
RSV-B (n=10)	HEp-2	CPE	116 ± 4

CPE: **C**yto**p**athic **E**ffect
HBEC: primary **H**uman **B**ronchial **E**pithelial **C**ells

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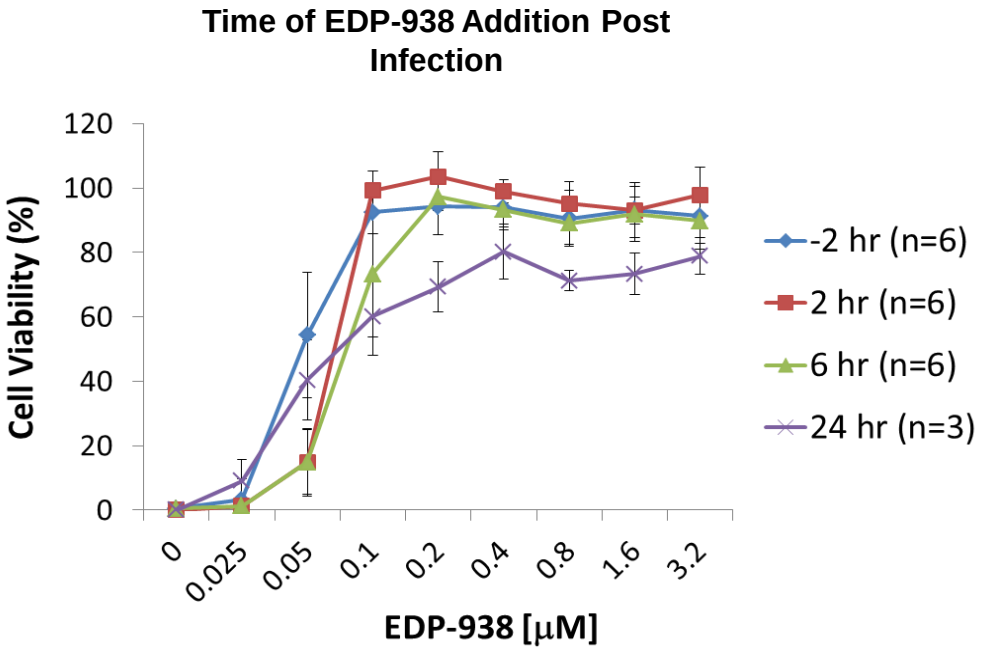
EDP-938 Shows *in vitro* Efficacy Post Viral Infection



RSV-A Long, MOI = 0.1
CPE readout, 5 days post infection endpoint

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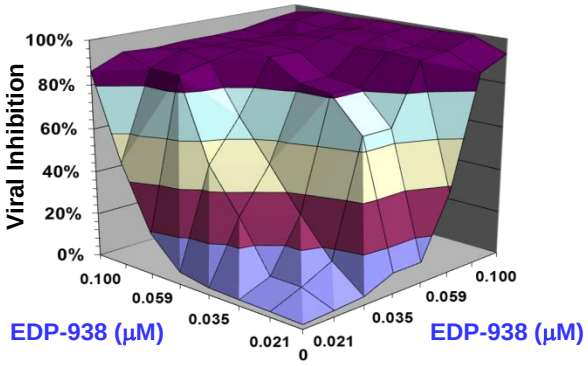
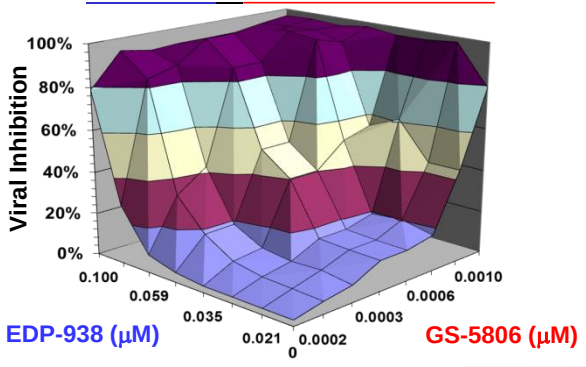
Combinations of EDP-938 with other RSV Inhibitors Result in Moderate Synergy

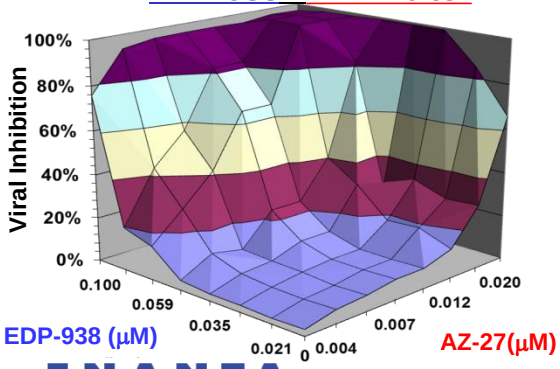
EDP-938 + EDP-938



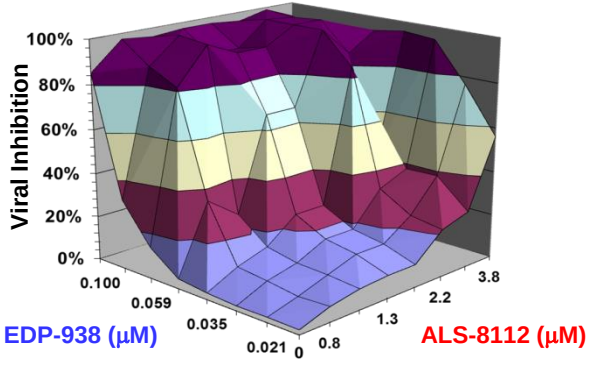
EDP-938 + Fusion Inhibitor



EDP-938 + L Inhibitor



EDP-938 + Nuc



Conditions

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

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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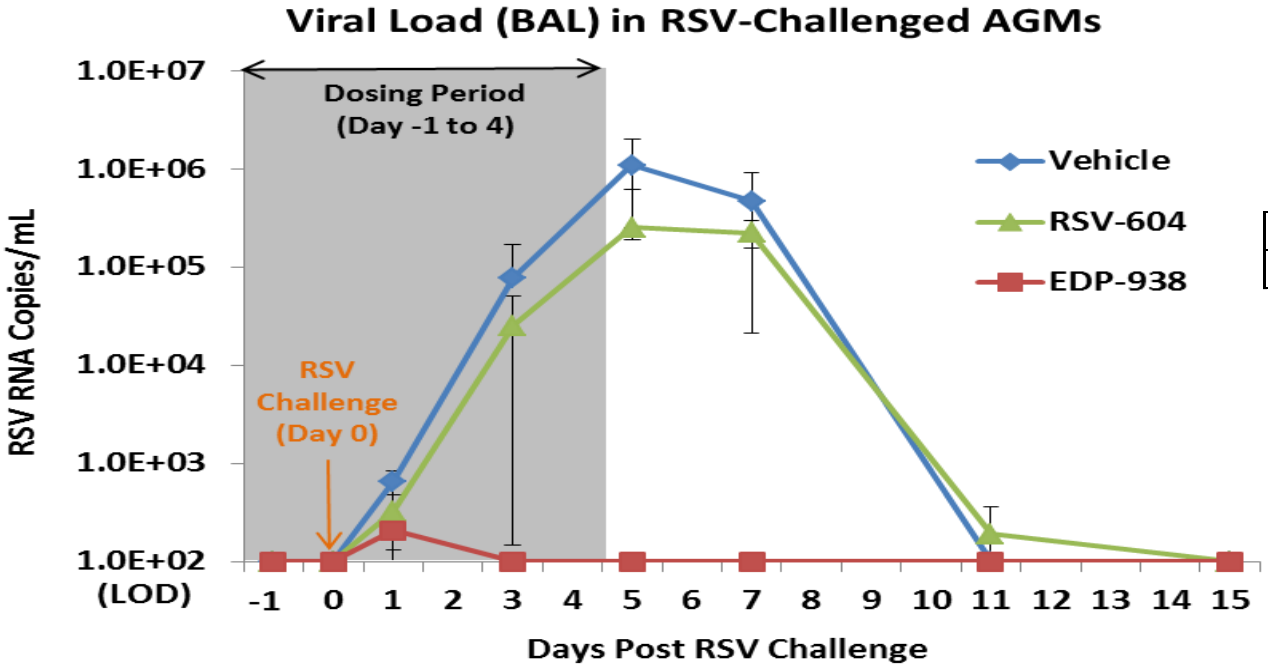
EDP-938 Demonstrates *in vivo* Efficacy in the African Green Monkey Model



	RSV-A2 *in vitro* CPE EC_{50} [nM]
RSV-604	670
EDP-938	28

N=4 per group, dosing:100mg/kg BID compound, LOD (limit of detection) = 100 copies/mL, virus: RSV-A2

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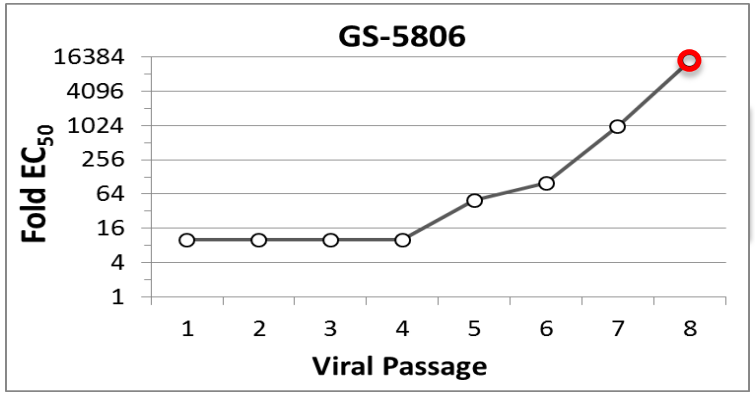
RSV Rapidly Develops Resistance to Fusion and L Polymerase Inhibitors

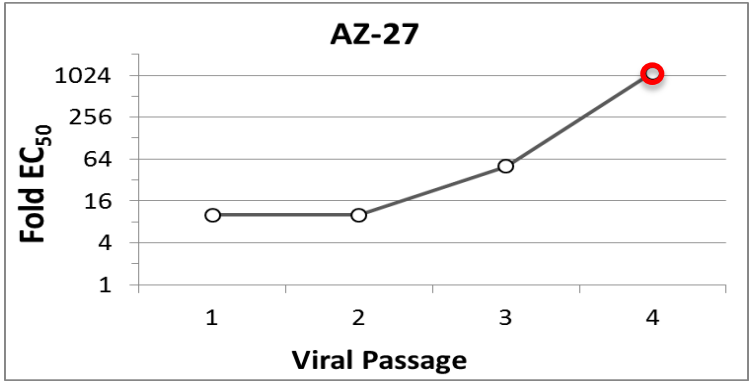
Fusion Inhibitor



Mutations in F: L141V/N197T

>40,000-fold EC_{50} shift

L Polymerase Inhibitor



Mutations in L: Y1631H/R/C

>1,000-fold EC_{50} shift

- Resistance mutations also emerged quickly in the human challenge study and in patients treated with fusion inhibitors.

- *10X EC_{50} starting concentration*
- *RSV-A Long strain*
- *0.1 MOI initial infection*

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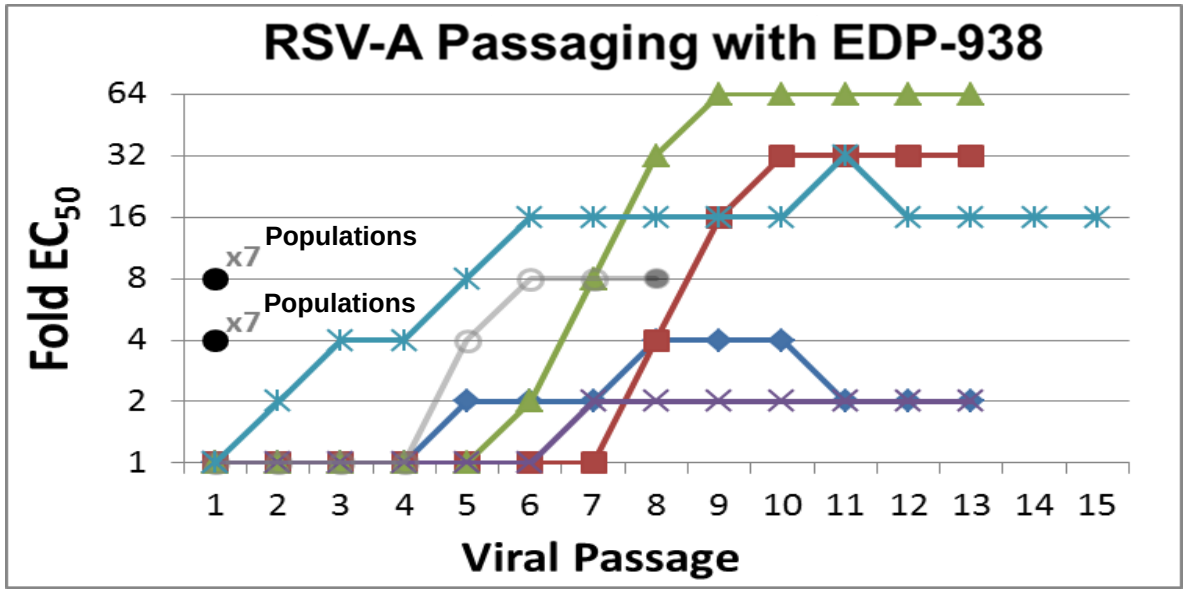
EDP-938 Displays a High Barrier to RSV-A Resistance Selection *in vitro*



- Exposing RSV-A to ≥4xEC_{50} EDP-938 resulted in complete elimination of the virus rather than selection of resistance
- A slow, stepwise increase in EDP-938 concentration, starting with 1xEC_{50}, eventually led to viral populations surviving up to 64xEC_{50} of EDP-938

Note: **Black** filled markers indicate failure of the virus to survive at any concentration level tested at or after this collection. All cultures initiated with a viral MOI of 0.1 using RSV-A Long.

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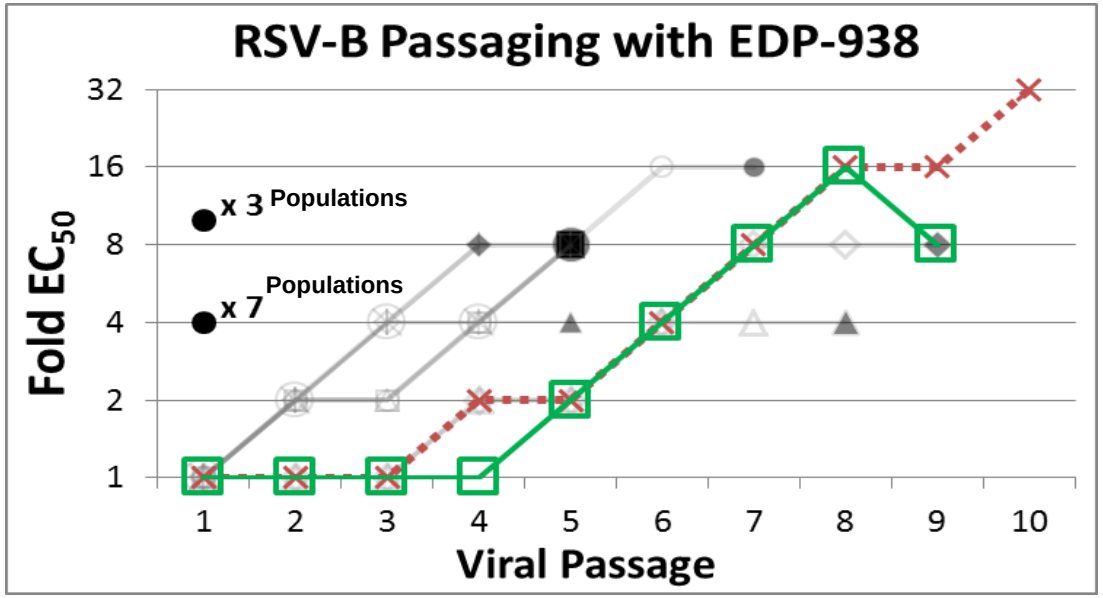
EDP-938 Displays a High Barrier to RSV-B Resistance Selection *in vitro*



- Exposing RSV-B to ≥4xEC_{50} EDP-938 resulted in complete elimination of the virus rather than selection of resistance
- A slow, stepwise increase in EDP-938 concentration, starting with 1xEC_{50}, eventually led to viral populations surviving up to 32xEC_{50} of EDP-938

Note: **Black** filled markers indicate failure of the virus to survive at any concentration level tested at or after this collection. All cultures initiated with a viral MOI of 0.5 – 1 using RSV-B VR-955.

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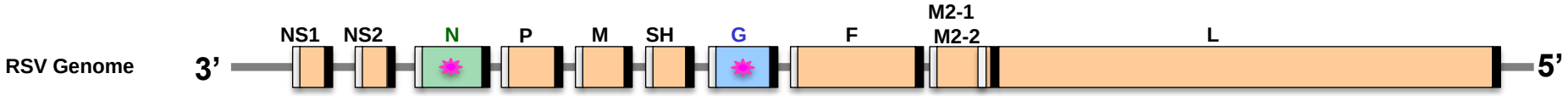
RSV Resistance Mutations Against EDP-938



Virus			Mutations in RSV Proteins		EDP-938 EC_{50} Fold Change vs. WT
			N	G	
Wild-Type (WT) A / B			-	-	1
RSV-A	Plaque Purified EDP-938 Resistant Clones	#1	M109K	-	67
		#2	Q102L M109T I129M	K205G K213G T219A	60
		#3	V90A S134T	-	3.8
		#4	T29S S134T	-	3.3
		#5	M109I	R8H	3.1
		#6	K136R	-	2.7
		#7	S134T	-	2.6
RSV-B	Population 1		L139Q*	-	42
	Population 2		M109T	E226G*	6.6

* Observed as a dual WT/mutant population

- *Of note:* N is the most conserved RSV gene while G is the least.

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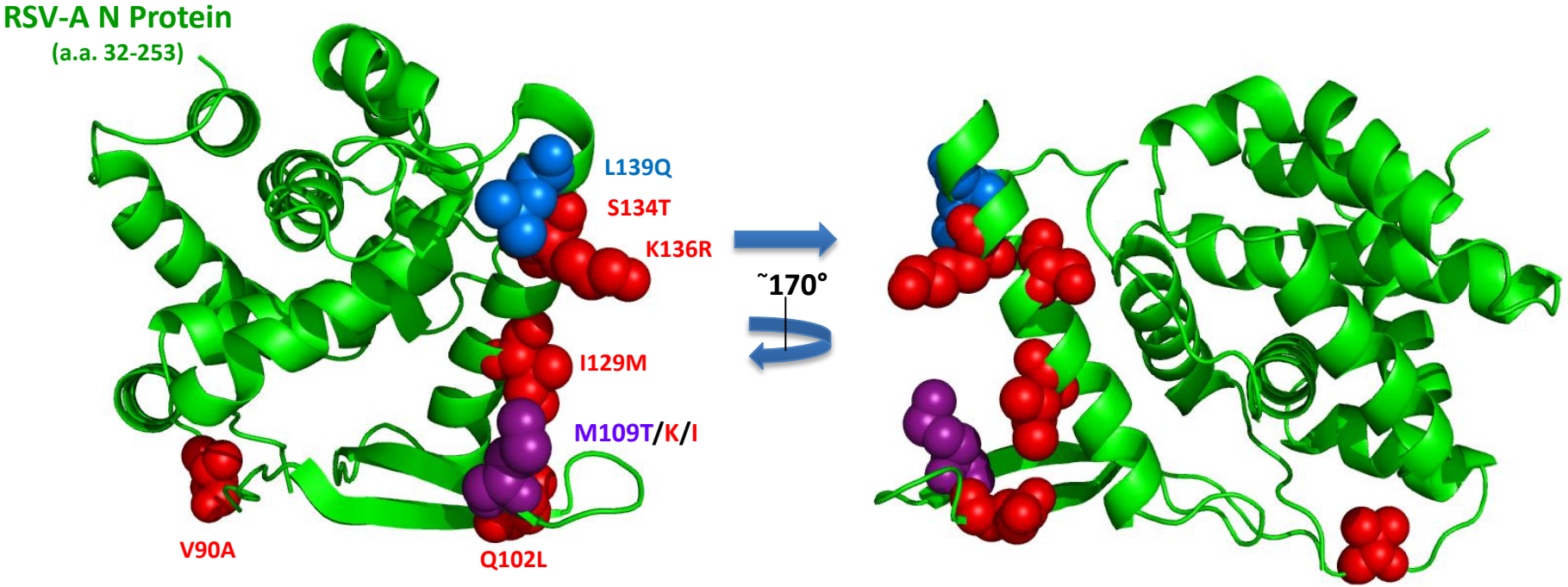
Location of Mutations Found in the RSV N Protein of RSV-A & -B



Red = RSV A drug resistant mutation
Blue = RSV-B drug resistant mutation
Purple = Both

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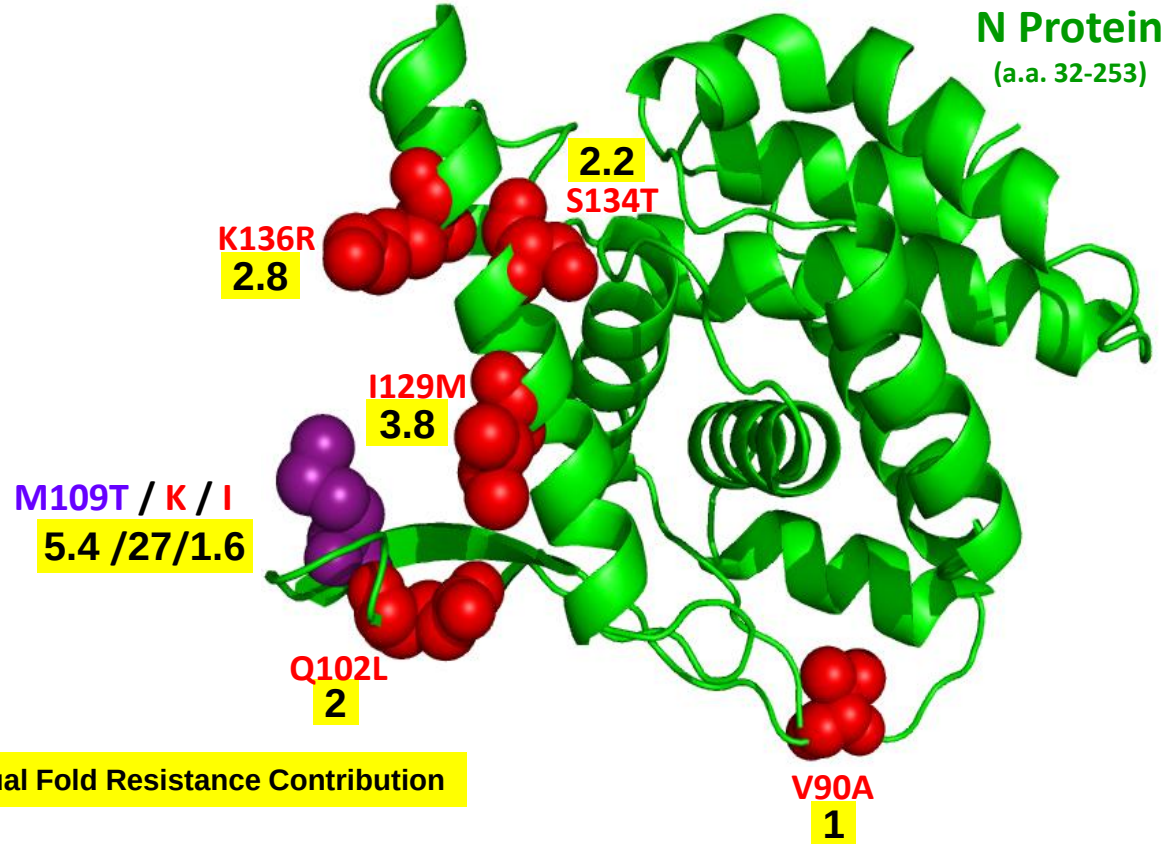
RSV-A Reverse Genetics System: Fold Resistance Contribution by Mutation

RSV-A Virus	Mutations in RSV N	EDP-938 EC_{50} Fold Change vs. WT
WT	-	1
Mutant Clones	M109K	67
	Q102L M109T I129M	60
	V90A S134T	3.8
	T29S S134T	3.3
	M109I	3.1
	K136R	2.7
	S134T	2.6

Assay MOI = 0.1
WT = 45 ± 21 nM



Individual Fold Resistance Contribution

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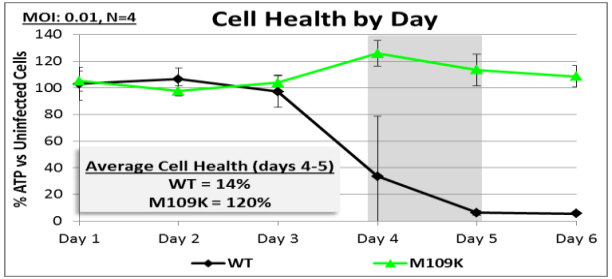
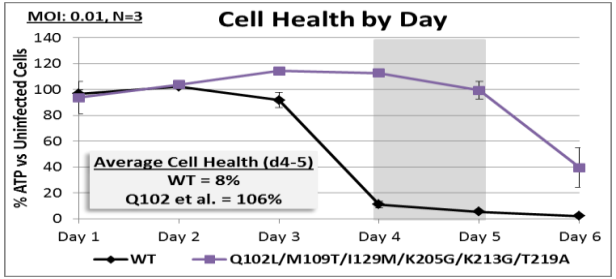
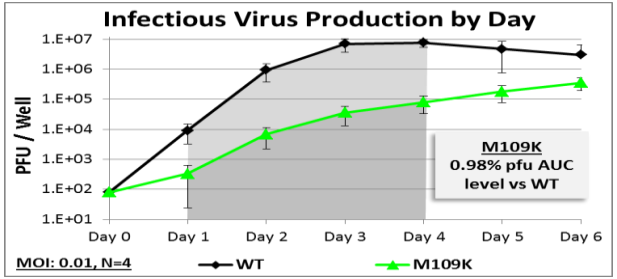
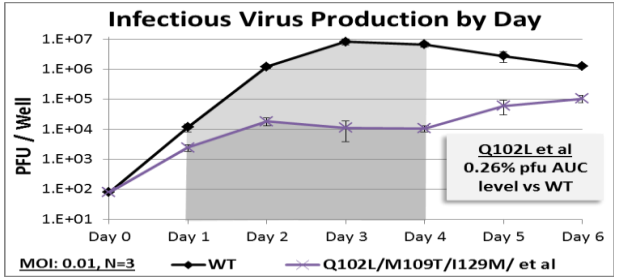
Fitness of Mutants Inversely Correlates with Resistance









RSV-A^R Clones: Mutations in Proteins		EDP-938 EC_{50} Fold Change vs. WT	Average % Cell Viability Days 4-5 Post Infection	% Mutant PFU vs WT AUC days 1-4
N	G			
-	-	1	11	100
M109K	-	67	120	0.98
Q102L M109T I129M	K205G K213G T219A	60	106	0.26
V90A S134T	-	3.8	66	26
T29S S134T	-	3.3	69	38
M109I	R8H	3.1	23	54
K136R	-	2.7	48	65
S134T	-	2.6	24	59

- Cytopathic effect and infectivity of mutant virus decreases with increased resistance to EDP-938
- The 2 most resistant mutants are also the least fit (100 times less than wild-type)

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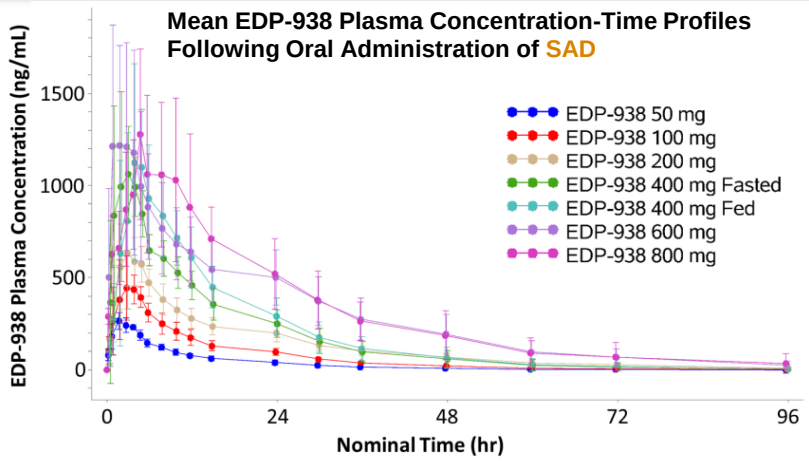
EDP 938-001: Phase 1 Study, First-In-Human (FIH)
Overall Safety Data During SAD and MAD

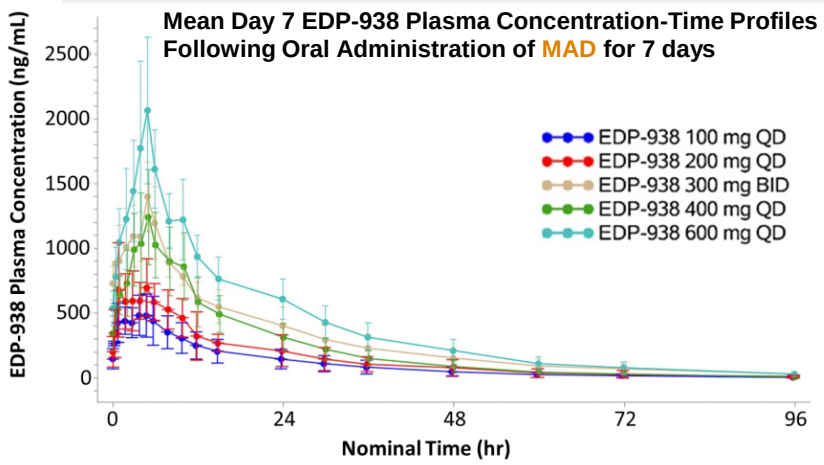
- In the EDP 938-001, a randomized, double-blind, placebo-controlled study:
  - A total of 90 subjects enrolled (N = 50 in SAD/FE; N = 40 in MAD)
- All randomized subjects completed the study in both SAD and MAD phases

- EDP-938 was generally safe and well-tolerated across all cohorts
  - Adverse events (AEs) were of mild intensity
    - Headache was the most frequent AE in the SAD and MAD with the majority reported as possibly related to EDP-938 or placebo, and with no relationship to dose
  - No SAEs or AEs that led to study drug discontinuation were reported

Ahmad A, Sanderson K, Dickerson D, and Adda N (2018). EDP-938, a novel, non-fusion replication inhibitor of respiratory syncytial virus: final results of a phase 1 study in healthy subjects. 11th International Respiratory Syncytial Virus Symposium. Abstract ARSVA0160. Asheville, NC USA, Oct 31-Nov 3.

EDP 938-001: Phase 1 Study, First-In-Human (FIH)
Overall Pharmacokinetics Data





- EDP-938 absorbed rapidly with dose dependent exposure
  - Median T_{max} ranged from 2.0 – 5.0 hr across all cohorts
  - Little accumulation from Day 1 to Day 7 with a mean accumulation index of 1.1 to 1.4 QD, 1.5 BID.
- PK suitable for once or twice daily oral dosing regardless of food intake
  - Mean half-life ranged from 12.9 – 17.6 hr across all cohorts
- **Mean EDP-938 exposures were approximately 7-31x higher than the EC_{90} against RSV-infected human cells**
  - Mean C_{24} ranged from 146-610 ng/mL following 100 mg to 600 mg QD dosing (Day 7)
  - Mean C_{12} was approximately 618 ng/mL following 300 mg BID dosing (Day 7)

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Ahmad A, Sanderson K, Dickerson D, and Adda N (2018). EDP-938, a novel, non-fusion replication inhibitor of respiratory syncytial virus: final results of a phase 1 study in healthy subjects. 11th International Respiratory Syncytial Virus Symposium. Abstract ARSVA0160. Asheville, NC USA, Oct 31-Nov 3.

EDP-938 Summary

- Highly active against all RSV-A and B laboratory strains and clinical isolates tested
- Excellent *in vivo* efficacy in the African green monkey model
- High barrier to resistance
  - Unlike fusion and L polymerase inhibitors, difficult to select resistance *in vitro*
  - EC_{50} shift <100-fold vs. >1,000-40,000 fold with fusion and L polymerase inhibitors
  - The most significant resistance mutants >100 times less fit than the wild-type
- Phase 1 study in healthy subjects
  - Safe and well tolerated after a broad range of single and multiple ascending doses
  - Exhibited PK suitable for once or twice daily oral dosing, without regard to food
- Currently being evaluated in a Phase 2 Proof of Concept Challenge Study

Acknowledgements

Enanta Pharmaceuticals, Inc.:

- **Nicole McAllister**, **Jonathan Castillo**, Nalini Bisht, Susan Clugston, Nathan Manalo, Bryan Goodwin, **Kai Lin** (Virology/Biology)
- In Jong Kim, Jianming Yu, Adam Szymaniak, Tom Blaisdell, Kevin McGrath, Solymar Negretti-Emmanuel, Kaicheng Zhu, Brian Shook (Chemistry)
- Falguni Gadkari, Andrew Hague, John Zhao, Matthew Ronsheim (CMC)
- Xiang Luo, Susanne Fyfe, Khanh Hoang (In Vivo Pharmacology)
- **Nathalie Adda, Alaa Ahmad, Kajal Larson, Kristin Sanderson** (Clinical)
- Pallabi De (Medical Writing)
- Lijuan Jiang, Sean Liu, Lisha Xu, Jonathan Kibel (DMPK)
- Brenda Yamamoto, Sokleang Koy, Kellye Daniels (Toxicology)
- Yat Sun Or (SVP R&D, CSO)

Collaborators:

- AGM Study: Bioqual, Inc.
- N Protein Structure: Evotec AG
- RSV Reverse Genetics: Martin Moore (Emory U.)
- Statistical Support: Jeff Sorbel (Triangle Biostatistics, LLC)
- Clinical Investigator: Daniel Dickerson (PRA)
- PK Support: Mohit Gandhi (PRA)
- Clinical Isolates: Pedro Piedra (Baylor U.)
  Kelly J. Henrickson (Med. College Wisconsin)
  Viroclinics Bioscience BV

We extend our thanks to the subjects who participated in this study and the PRA team and site personnel for their involvement in the study

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Thank you!

Questions?

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