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From Chemistry to Cures

EDP-938, a Novel Non-Fusion Replication Inhibitor of RSV, Displays a High Barrier to Resistance *In Vitro*

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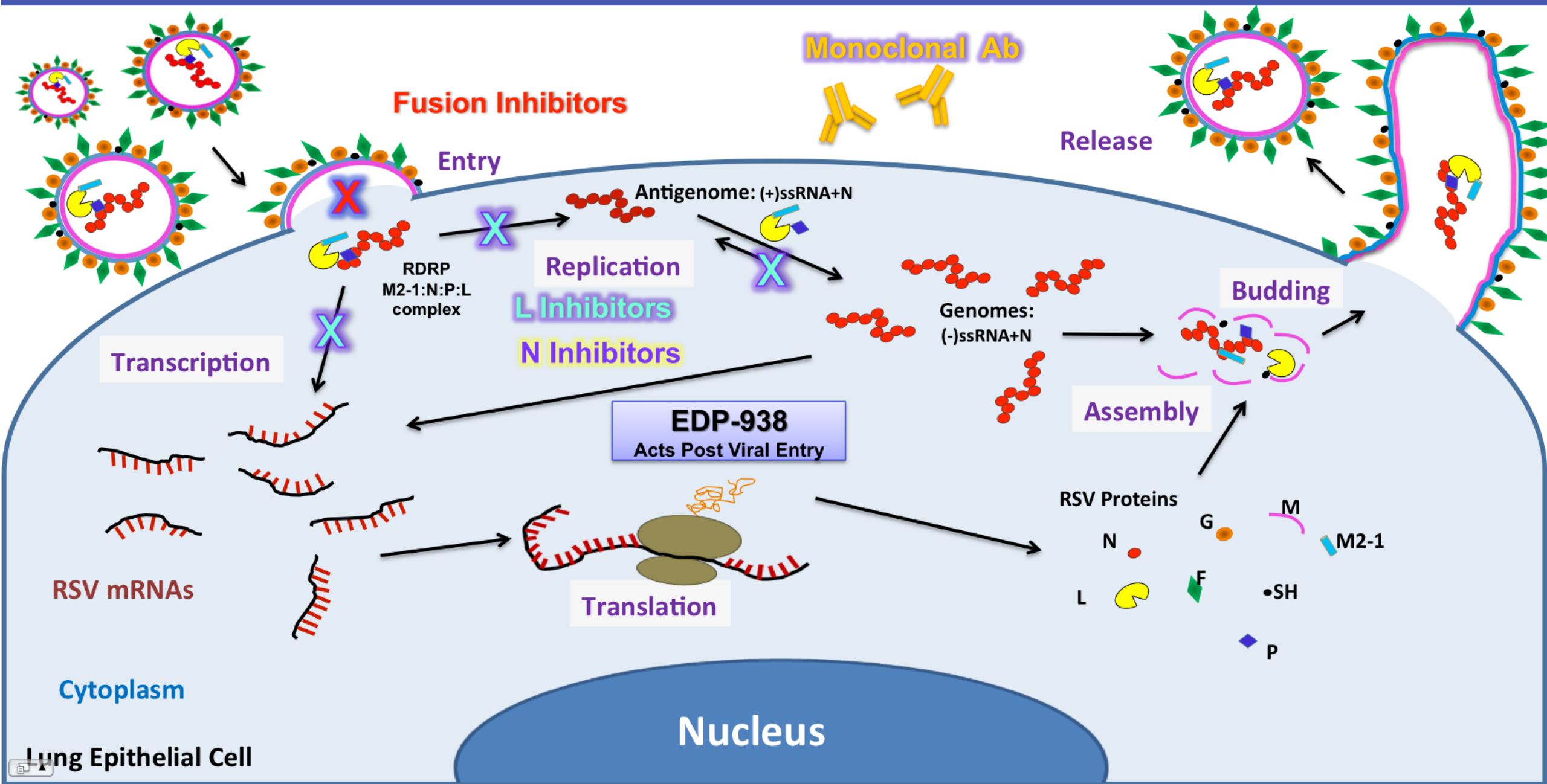
Disclosures: All contributors are employees of Enanta Pharmaceuticals.

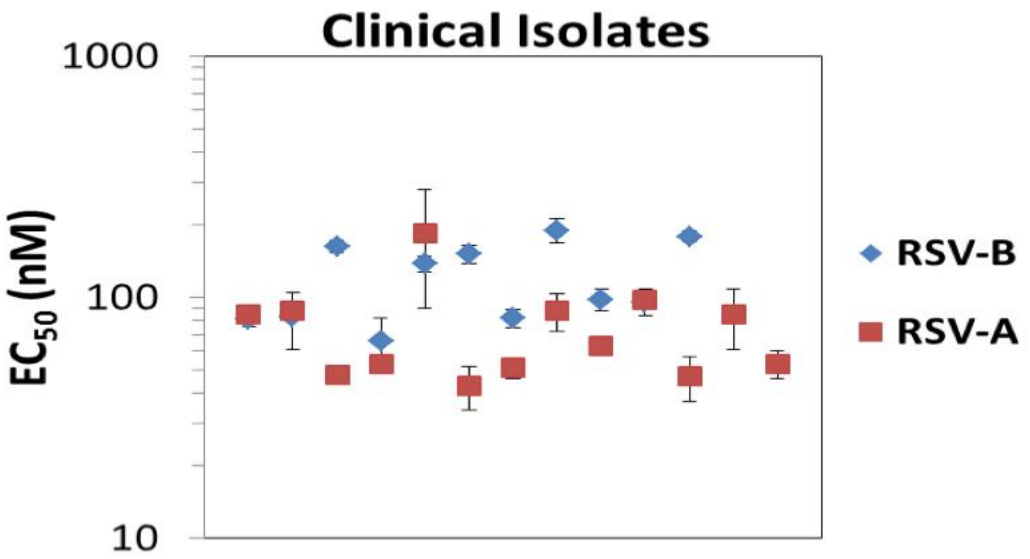
RSV Life Cycle and Antiviral Targets



EDP-938 Inhibits all RSV Lab and Clinical Strains Tested *in vitro*

Virus		Assay		EC_{50} (nM)
Sub-type	Strain	Cell	Read-out	EDP-938
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
B	Wash	HBEC	PCR	62 ± 32
		A549	PCR	83 ± 38

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



Average EC_{50} (nM)

Clinical Isolates	EDP-938
RSV-A (13 isolates)	76 ± 37
RSV-B (11 isolates)	121 ± 45

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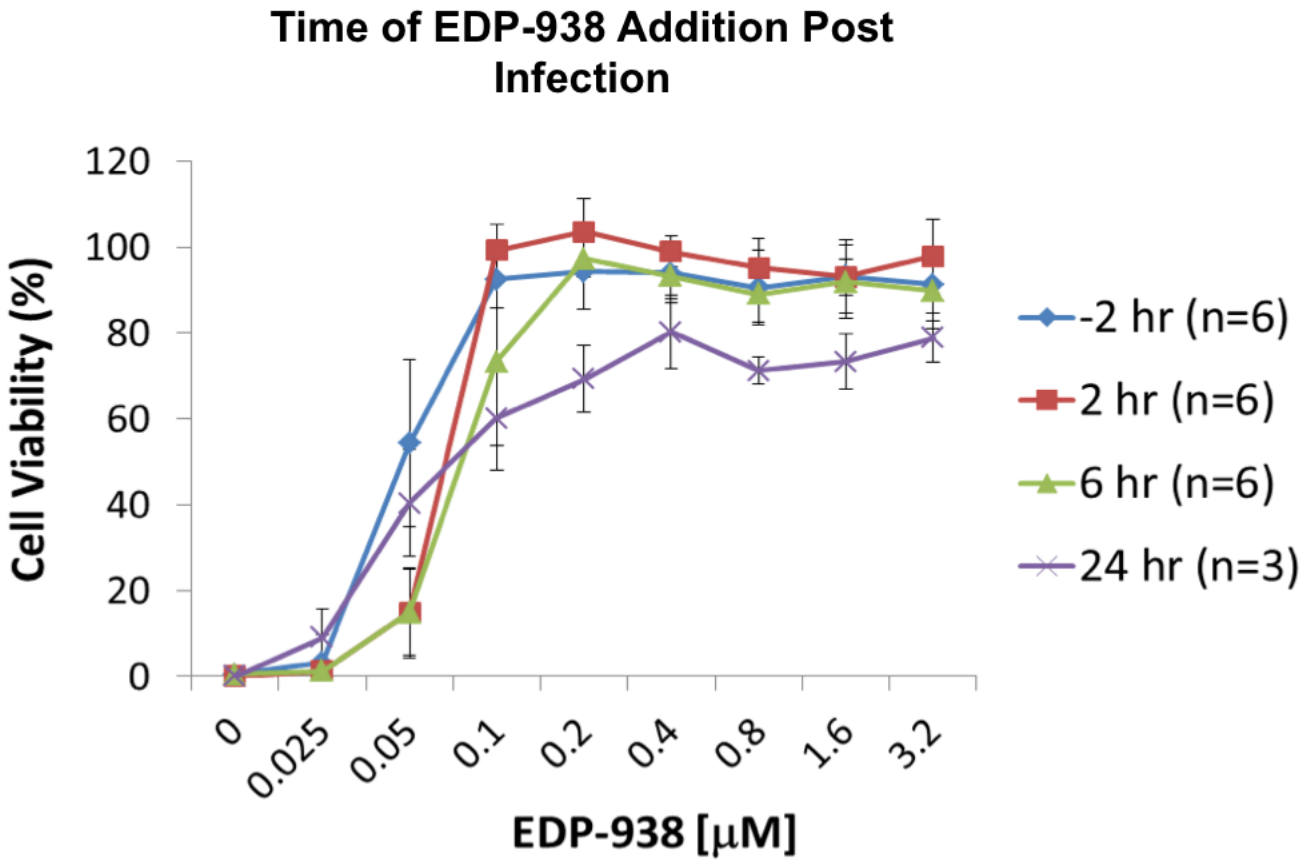
EDP-938 Shows *in vitro* Efficacy Post Viral Infection



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

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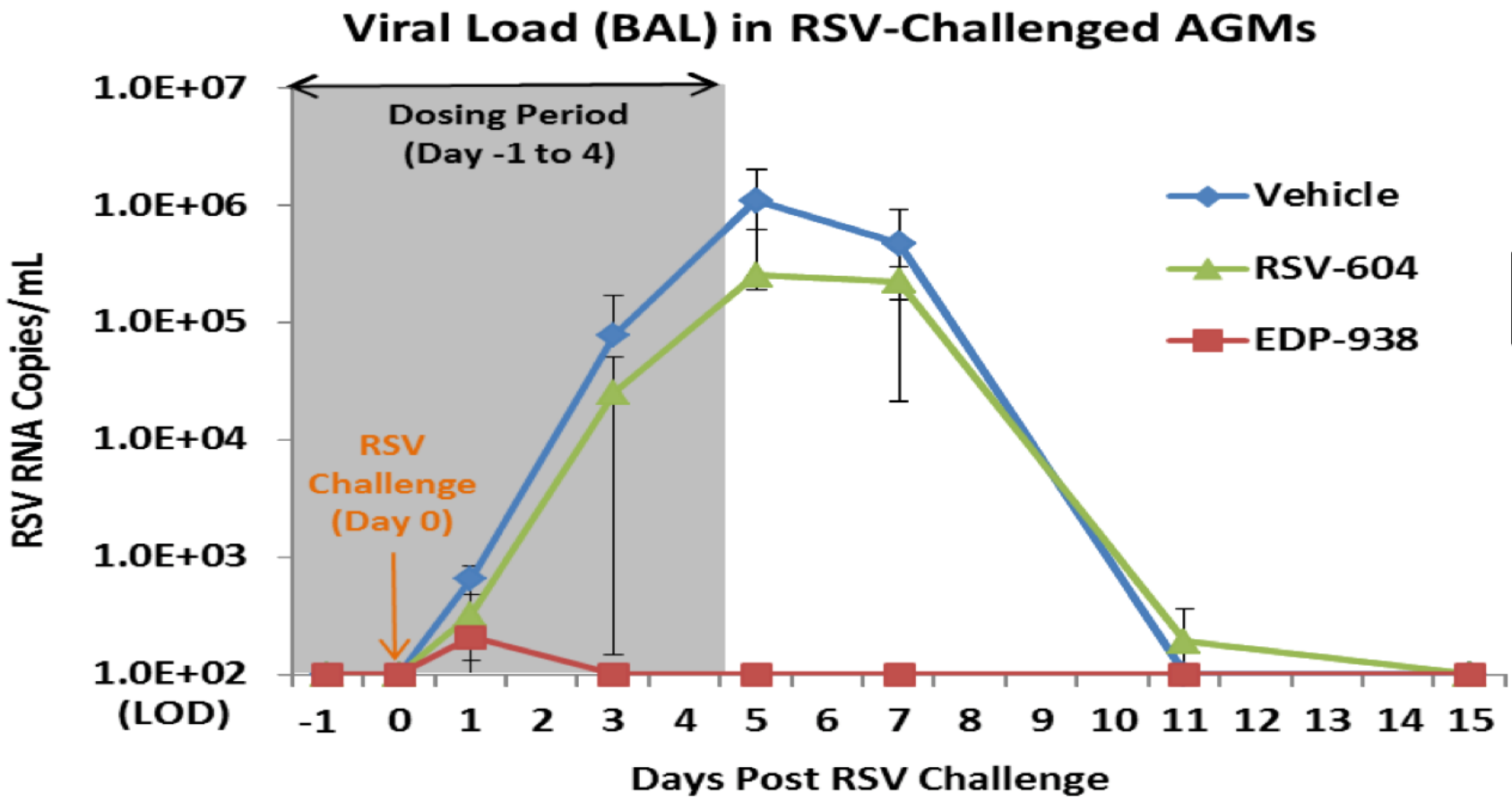
EDP-938 Demonstrates *in vivo* Efficacy in the African Green Monkey Model



	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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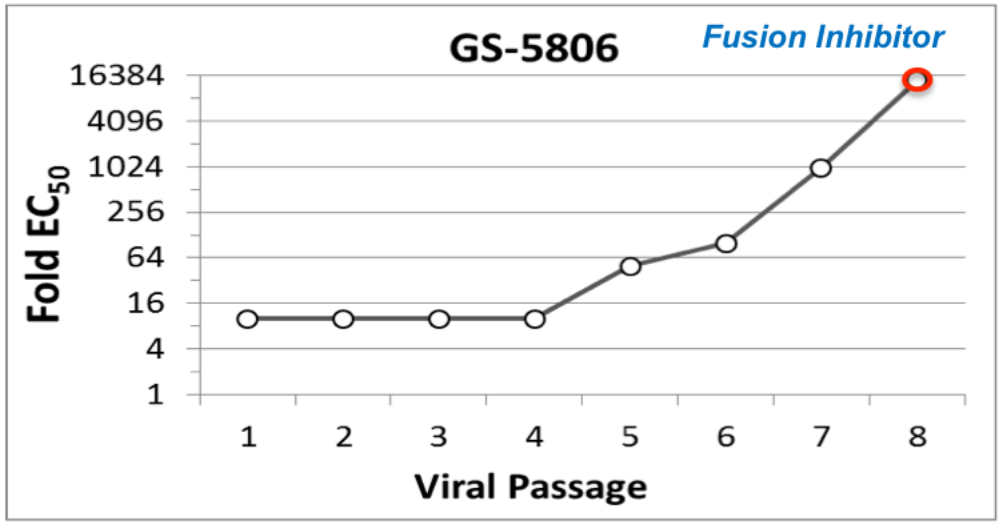
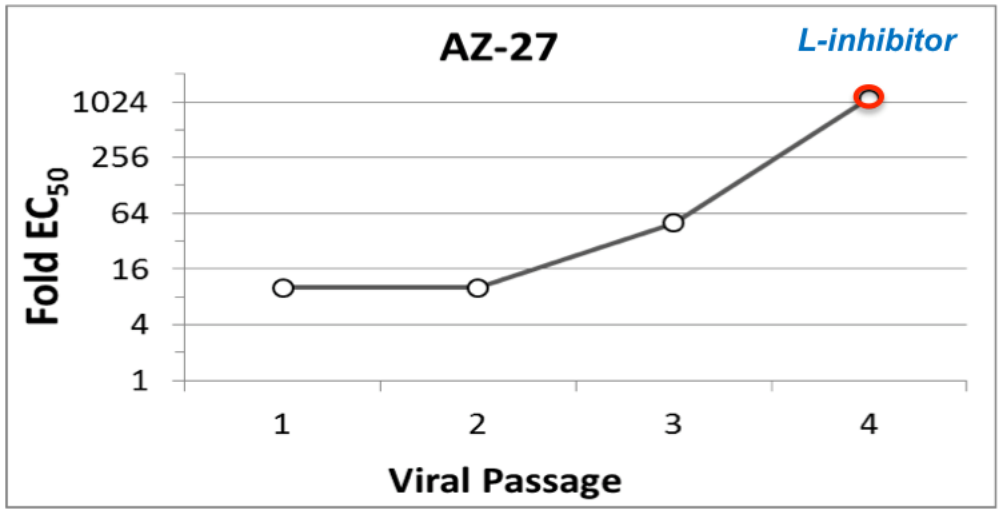
RSV-A Rapidly Develops Resistance to F and L Inhibitor Compounds

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



F:
L141V, N197T
>40,000 fold shift



L:
Y1631H/R/C
>1,000 fold shift

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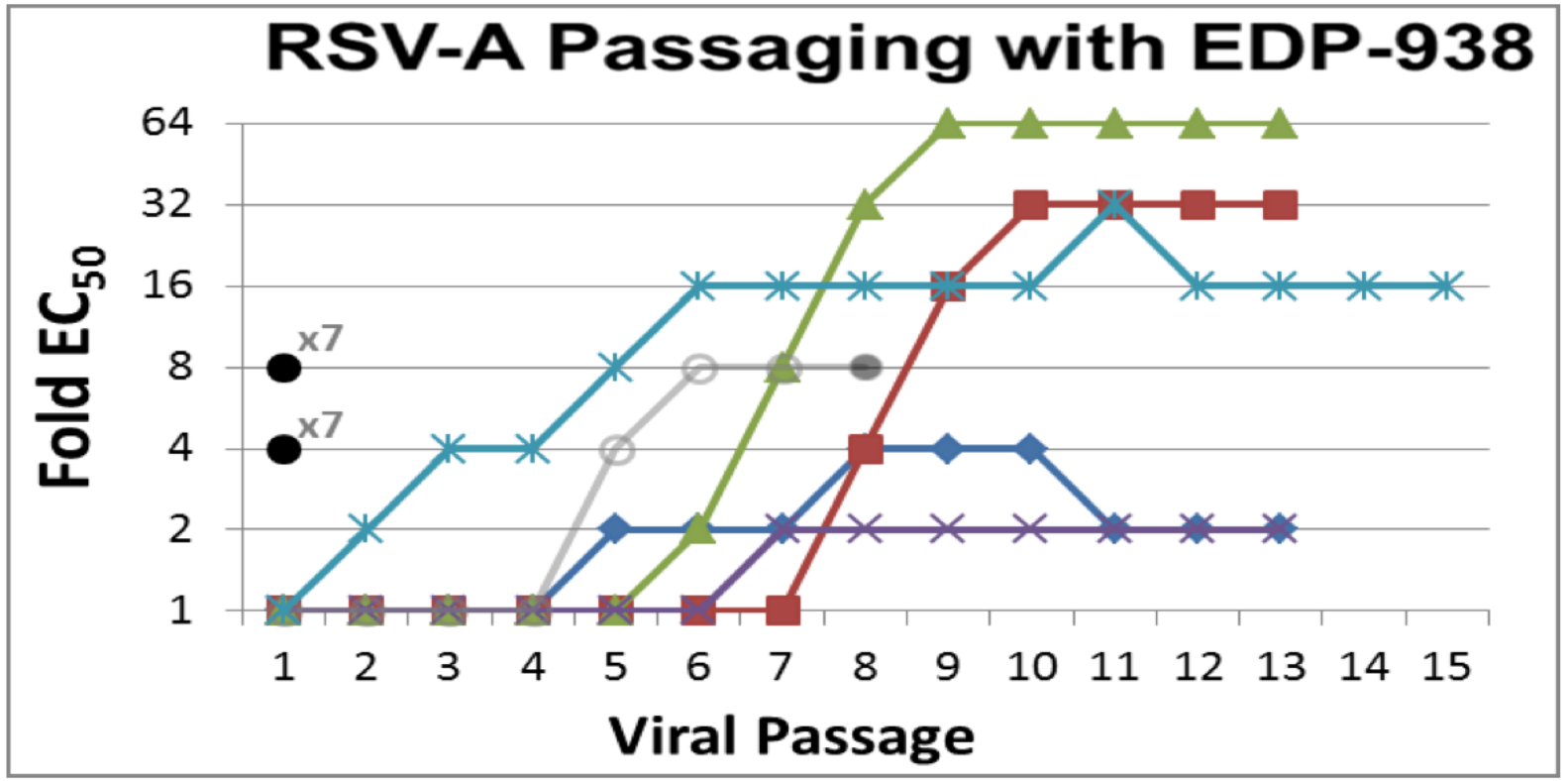
EDP-938 Displays a High Barrier to RSV-A Resistance Selection *in vitro*



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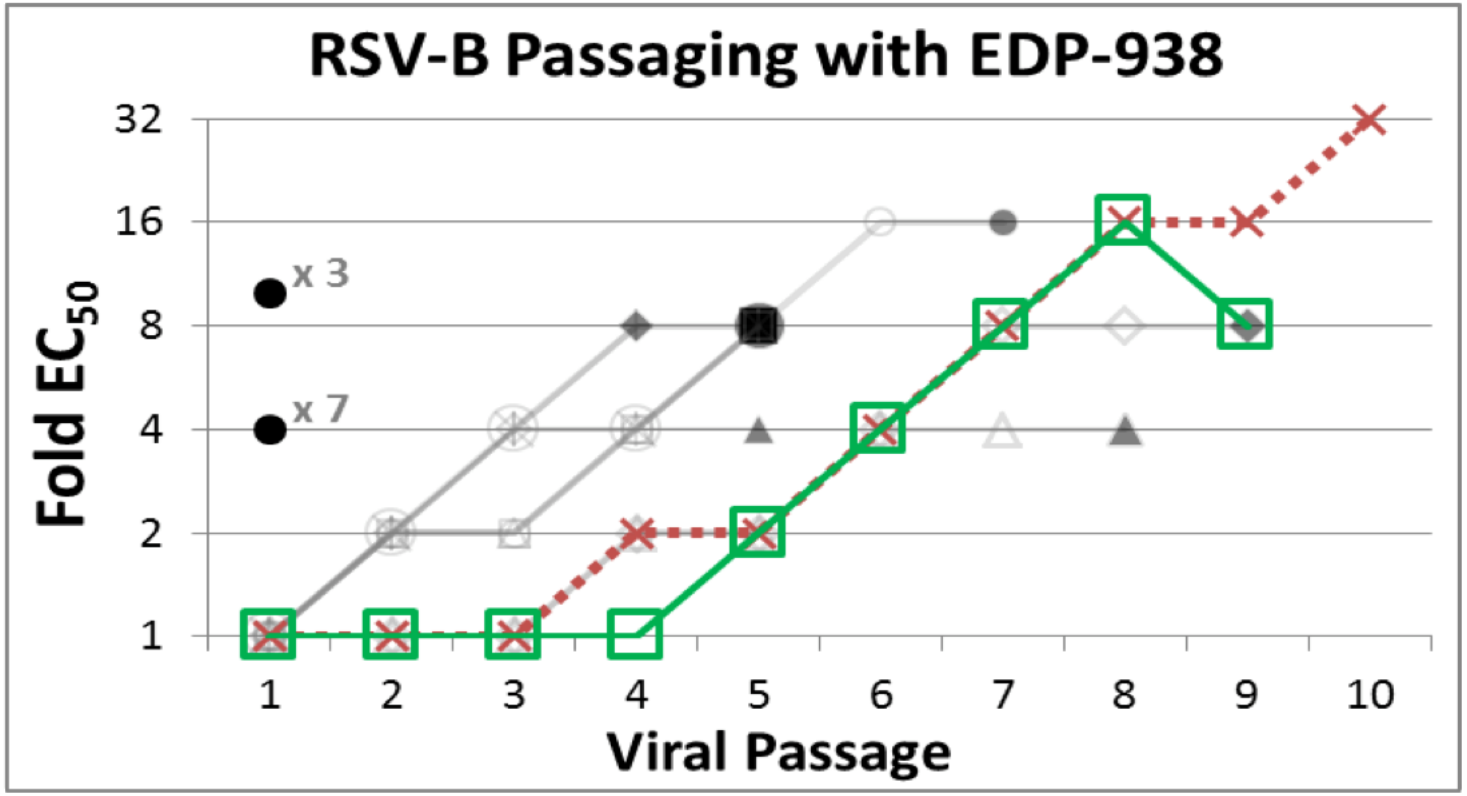
EDP-938 Displays a High Barrier to RSV-B Resistance Selection *in vitro*



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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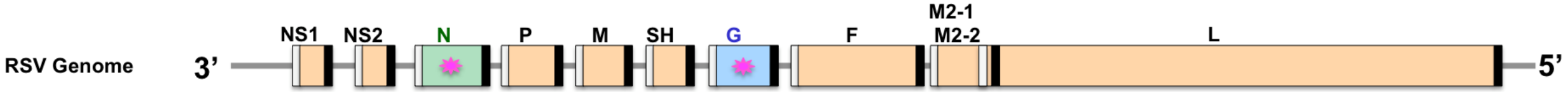
RSV Resistance Mutations Against EDP-938



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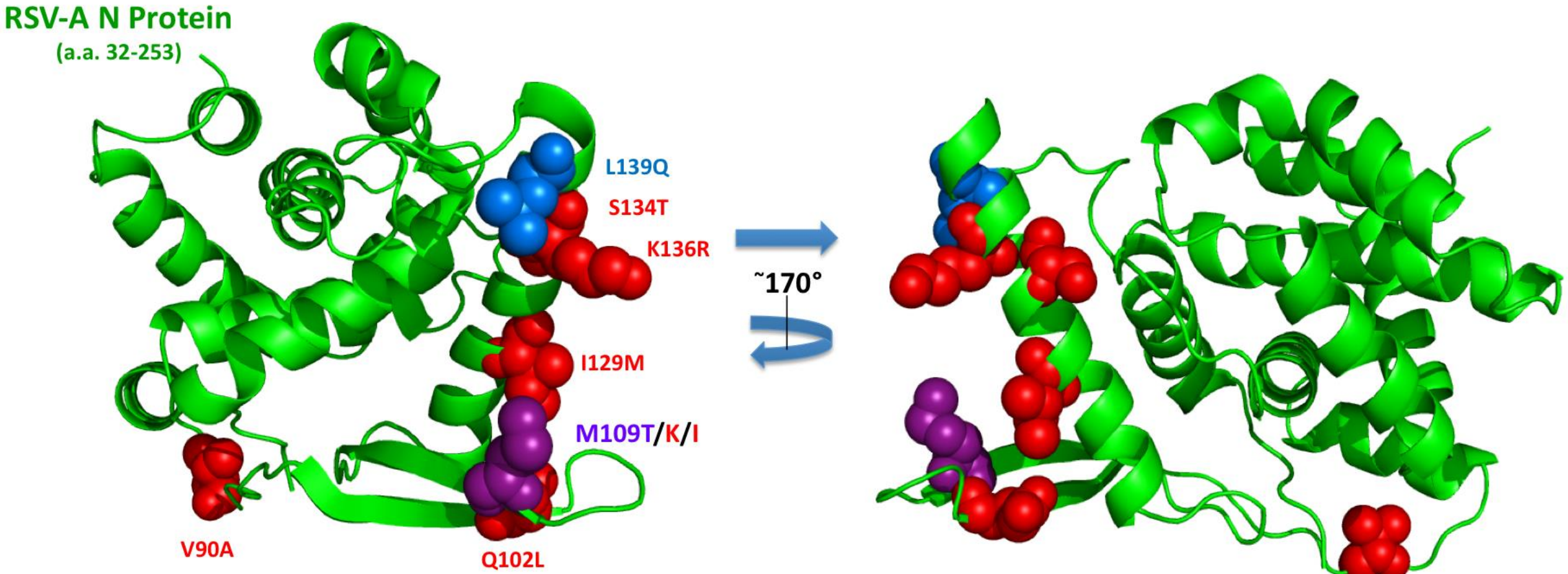
Location of Mutations Found in the RSV N Protein of RSV-A & -B



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

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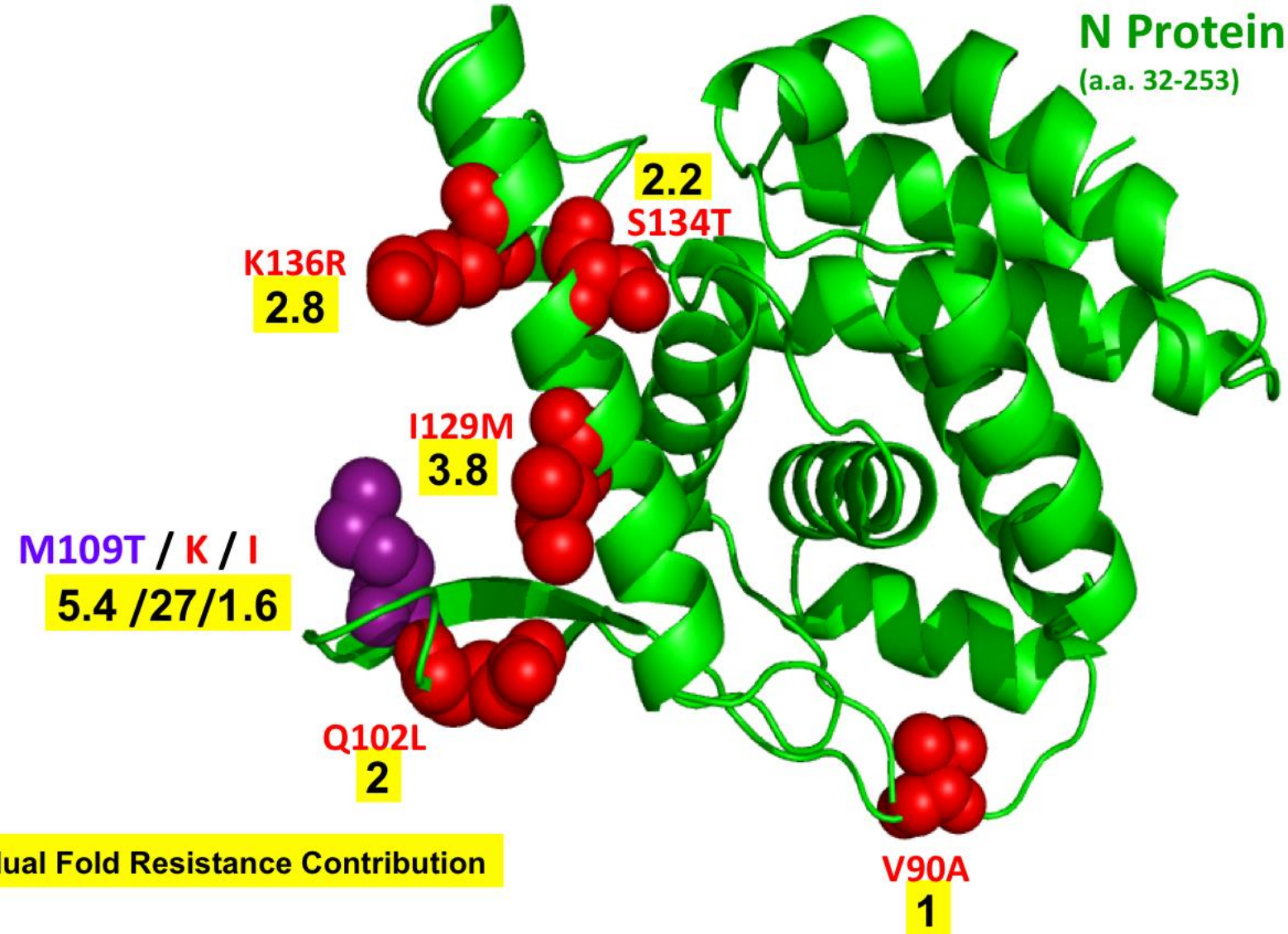
RSV-A Reverse Genetics System: Fold Resistance Contribution by Mutation

RSV-A Virus	Mutations in RSV Protein	EDP-938 EC_{50} Fold Change vs. WT
	N	
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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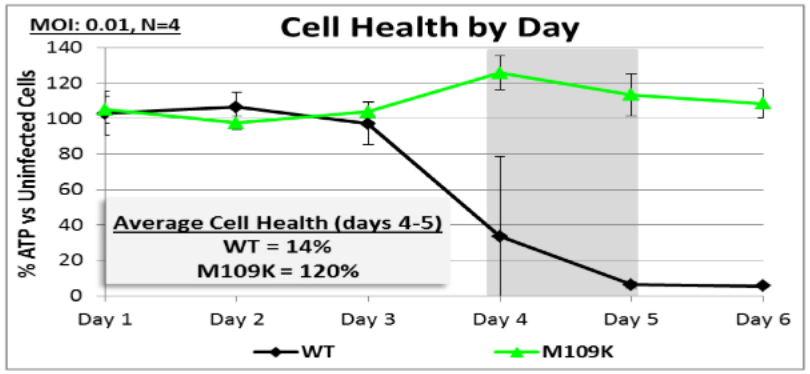
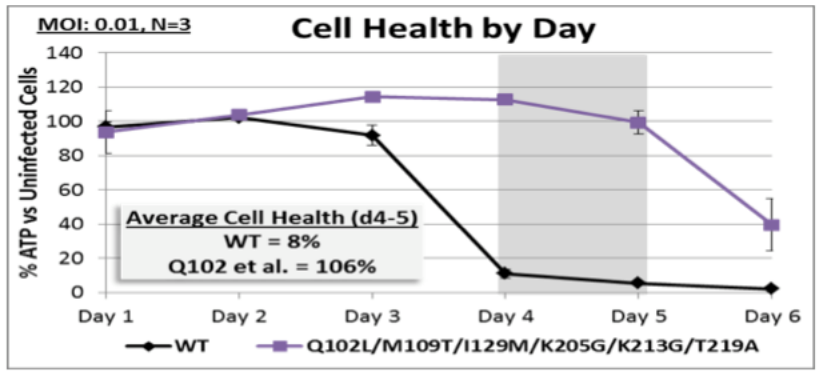
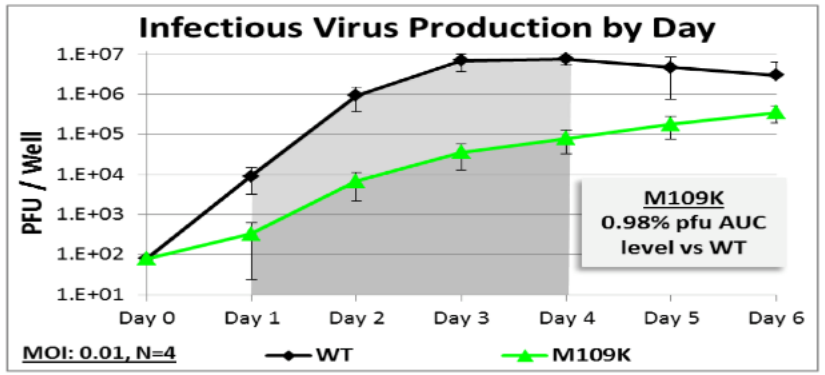
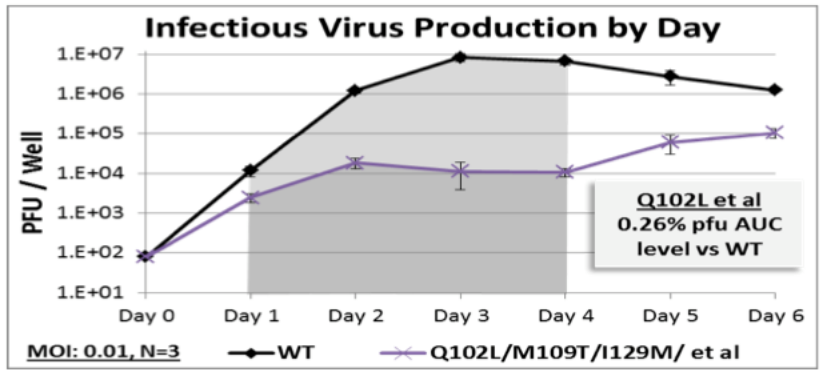
Fitness of Mutants Inversely Correlates with Viral Resistance: CPE and Plaque Forming Units (PFU)









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 K213GT219A	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

- The 2 most resistant mutants are also the least fit
- CPE and PFU formation decreases with increased resistance to EDP-938

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EDP-938 is Progressing Through Clinical Trials

EDP-938 has undergone Phase 1 testing and will be reported on in a poster presentation by Enanta's Clinical Team

Please visit them for more info

Poster

EDP-938, a Novel, Non-Fusion Replication Inhibitor of Respiratory Syncytial Virus: Preliminary Results of a Phase 1 Study in Healthy Subjects (HS)

Session 2: Friday, Nov. 2nd 8:30pm

In Summary

EDP-938

- demonstrates both *in vitro* and *in vivo* antiviral activity
- has a high barrier to developing resistance mutations *in vitro*
  - Unlike fusion and L polymerase inhibitors, RSV can not survive a starting 4x EC_{50} concentration of EDP-938
- has efficacy shifts of <100-fold versus resistant strains
  - Most individual mutations bestow <10-fold resistance, vs. >1,000 fold with fusion and L polymerase inhibitors
- mutation mapping suggests direct involvement of N-protein
- resistance appears inversely correlated to viral fitness
  - The most significant resistance mutants >100-fold less fit than the wild-type

Acknowledgements

Enanta's RSV Team:

- **Chemistry**: Yat Sun Or, Brian Shook, In Jong Kim, Jianming Yu, Adam Szymaniak, Tom Blaisdell, Kevin McGrath, Solymar Negretti-Emmanuel, Kaicheng Zhu
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- **In vivo**: Xiang Luo, Susanne Fyfe, Khanh Hoang
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- **Monkey Studies**: performed by Bioqual, Inc.
- **N Protein X-Ray Crystal Structure**: performed by EvoTec

Thank you!

Questions?