

# HCV Drug Resistance Figure and Table Update

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# Drug Resistance Mutations & Phenotypic Data: Objectives

- Data Table, to be updated regularly, with key HCV resistance mutations and published phenotypic susceptibility data
- Figure showing most common HCV DAA RAMs for quick reference
  - linked to tabular data and references
- Not trying to be all things to all people
  - Fitness/replication capacity
  - Unpublished data
- Repository for all “known” resistance mutations
- Resistance interpretation algorithm

# Drug Resistance Mutations & Phenotypic Data Table: Content

- NS3, NS5A and NS5B inhibitor resistance-associated mutations for compounds that are approved or in Phase 3 trials
- Phenotypic data to be included:
  - replicon vector (name, subtype)
  - cell type
  - mean  $EC_{50}$  +SD
  - mean fold-resistance + SD
  - replicates (N)
  - citation(s)
  - key assay parameters (duration, read out, transient or stable, etc.)

# Drug Resistance Mutations & Phenotypic Data Table: Content

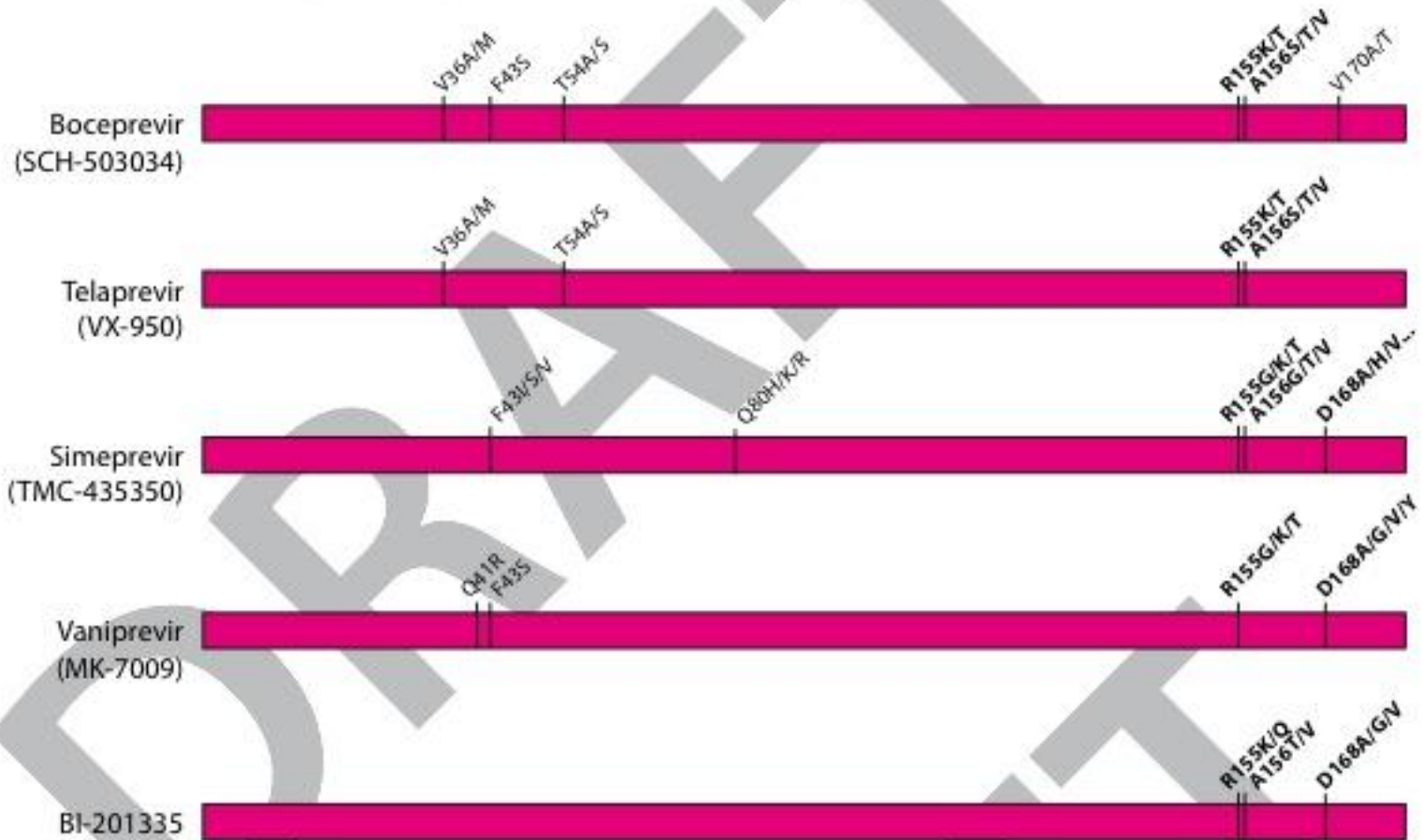
Drug manufacturer	Compound generic name	Compound aka 1	target enzyme	Compound class	resistance mutation	replicon vector	Genotype of replicon vector	cell type	replicates (N)	mean EC50 (µM)	EC50 SD	mean fold-resistance	FR SD
Merck	boceprevir	SCH-503034	NS3	PI	none	modified Bartenschlager Con1 clone	1b	Huh 7		0.18		1.0	
Merck	boceprevir	SCH-503034	NS3	PI	R155K	modified Bartenschlager Con1 clone	1b	Huh 7		0.65		3.6	
Merck	boceprevir	SCH-503034	NS3	PI	A156S	modified Bartenschlager Con1 clone	1b	Huh 7		4.3		24	
Merck	boceprevir	SCH-503034	NS3	PI	A156T	modified Bartenschlager Con1 clone	1b	Huh 7		23		128	
Merck	boceprevir	SCH-503034	NS3	PI	V170A	modified Bartenschlager Con1 clone	1b	Huh 7		3.4		19	
Vertex	telaprevir	VX-950	NS3	PI	none	pBR322-HCV-Neo-mADE	1b	Huh 7	15	0.48	0.12	1.0	0.30
Vertex	telaprevir	VX-950	NS3	PI	R155K	pBR322-HCV-Neo-mADE	1b	Huh 7	3	3.6	0.28	7.4	0.60
Vertex	telaprevir	VX-950	NS3	PI	R155T	pBR322-HCV-Neo-mADE	1b	Huh 7	3	9.6	0.87	20	1.8
Vertex	telaprevir	VX-950	NS3	PI	R155M	pBR322-HCV-Neo-mADE	1b	Huh 7	3	2.7	0.21	5.6	0.40
Vertex	telaprevir	VX-950	NS3	PI	A156S	pBR322-HCV-Neo-mADE	1b	Huh 7	1	4.7	-	9.6	-
Vertex	telaprevir	VX-950	NS3	PI	A156T	pBR322-HCV-Neo-mADE	1b	Huh 7	1	>30	-	>62	-
Vertex	telaprevir	VX-950	NS3	PI	A156V	pBR322-HCV-Neo-mADE	1b	Huh 7	1	>30	-	>62	-
Vertex	telaprevir	VX-950	NS3	PI	V170A	pBR322-HCV-Neo-mADE	1b	Huh 7	3	1.3	0.28	2.6	0.60
Vertex	telaprevir	VX-950	NS3	PI	V36M+R155K	pBR322-HCV-Neo-mADE	1b	Huh 7	3	~31	-	~64	-
BI		BI-201335	NS3	PI	none	129S, H77	1a	Huh 7	7	0.0065	0.0009	1.0	
BI		BI-201335	NS3	PI	D168V	129-S.16	1a	Huh 7	14	8.7	2.5	620	180
BI		BI-201335	NS3	PI	R155K	129-S.16	1a	Huh 7	11	5.0	1.3	360	90
BI		BI-201335	NS3	PI	none	S22.3, Con1	1b	Huh 7	9	0.0031	0.0012	1.0	
BI		BI-201335	NS3	PI	none	pIT2, Con1	1b	Huh 7	79	0.013	0.0042	1.0	
BI		BI-201335	NS3	PI	A156V	pIT2, Con1	1b	Huh 7	3	1.5	0.096	150	10
BI		BI-201335	NS3	PI	R155Q	R3	1b	Huh 7	4	0.30	0.043	60	9
BI		BI-201335	NS3	PI	R155K	716	1b	Huh 7	3	1.8	0.071	350	14
BI		BI-201335	NS3	PI	A156T	R3	1b	Huh 7	9	1.4	0.49	270	98
BI		BI-201335	NS3	PI	D168G	S22.3-7/44	1b	Huh 7	7	0.38	0.13	80	30
BI		BI-201335	NS3	PI	D168A	R3	1b	Huh 7	5	3.5	1.7	690	332
BI		BI-201335	NS3	PI	D168V	716	1b	Huh 7	7	4.9	1.3	970	256
Tibotec	simeprevir	TMC-435350	NS3	PI	WT	Con1 clone ET	1b	Huh7 lunet		0.011		1.0	
Tibotec	simeprevir	TMC-435350	NS3	PI	R155K	Con1 clone ET	1b	Huh7 lunet		0.26		30	
Tibotec	simeprevir	TMC-435350	NS3	PI	A156G	Con1 clone ET	1b	Huh7 lunet		0.21		16	
Tibotec	simeprevir	TMC-435350	NS3	PI	A156T	Con1 clone ET	1b	Huh7 lunet		0.38		44	
Tibotec	simeprevir	TMC-435350	NS3	PI	A156V	Con1 clone ET	1b	Huh7 lunet		2.1		177	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168N	Con1 clone ET	1b	Huh7 lunet		0.079		6.6	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168E	Con1 clone ET	1b	Huh7 lunet		0.30		40	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168T	Con1 clone ET	1b	Huh7 lunet		4.1		308	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168Y	Con1 clone ET	1b	Huh7 lunet		6.2		666	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168H	Con1 clone ET	1b	Huh7 lunet		5.7		368	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168A	Con1 clone ET	1b	Huh7 lunet		6.4		594	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168V	Con1 clone ET	1b	Huh7 lunet		18		2591	
Tibotec	simeprevir	TMC-435350	NS3	PI	D168I	Con1 clone ET	1b	Huh7 lunet		23		1807	
Tibotec	simeprevir	TMC-435350	NS3	PI	F43S+Q80R	Con1 clone ET	1b	Huh7 lunet		1.8		286	
Tibotec	simeprevir	TMC-435350	NS3	PI	F43S+D168E	Con1 clone ET	1b	Huh7 lunet		3.6		694	
Tibotec	simeprevir	TMC-435350	NS3	PI	Q80K+R155K	Con1 clone ET	1b	Huh7 lunet		4.6		364	
Tibotec	simeprevir	TMC-435350	NS3	PI	Q80R+R155K	Con1 clone ET	1b	Huh7 lunet		2.9		270	
Tibotec	simeprevir	TMC-435350	NS3	PI	Q80R+D168E	Con1 clone ET	1b	Huh7 lunet		5.9		412	
Tibotec	simeprevir	TMC-435350	NS3	PI	Q80H+D168E	Con1 clone ET	1b	Huh7 lunet		1.4		163	
Tibotec	simeprevir	TMC-435350	NS3	PI	Q80R+D168A	Con1 clone ET	1b	Huh7 lunet		17		2655	

# Drug Resistance Mutations Figure

- Mutations observed *in vivo* vs. *in vitro*
  - Include mutations observed *in vitro* if *in vivo* data not available
  - Limit to most frequently observed mutations in patients treated with the licensed dose – the list may not be comprehensive
  - Emphasize mutations observed in >25% (or 10%?) of patients with virological failure (bold)
- Replication capacity data
  - Not included in figure
  - May be captured in linked data table, with caveats

# Drug Resistance Mutations Figure (PIs)

## NS3 Protease (180 aa)



# Drug Resistance Mutations Figure (NS5A and NIs)

NS5A Domain I (213 aa)



NS5B Polymerase (591 aa)



# How to Represent Genotype/Subtype Differences

- Different genotypes or even subtypes of HCV may have different mutation patterns following treatment with the same DAA
  - e.g. R155K/T (1a) vs. R155Q or A156S/T/V (1b) after TPV exposure
- However, interpretation of the impact of any mutation is not dependent on genotype/subtype
- Therefore, these subtleties are not represented in the figure, but will be captured in footnotes to the table



# Drug Resistance Mutations & Phenotypic Data: Publication Plan

- *Annals of the Forum for Collaborative HIV Research* (online publication)
- Forum website: high level overview with the ability to look at the data in greater detail
  - Mutations and drugs linked to details in data table
  - Table can be sorted and filtered by user
  - Links to external sites/databases e.g. LANL, euHCVdb, Japanese HCV db...

# Discussion Points

- Criteria and frequency threshold for mutations to include in Figure and Table
  - Bold/not bold
  - Different for different drugs? Based on amount of information available
  - Importance of comparator treatment arms
- Linkage
- Frequency of updates
  - Quarterly may be needed to “keep up”
  - Annual may be more practical

# Drug Resistance Mutations & Phenotypic Data: Next Steps

- Complete gathering of data from *in vivo* studies
  - BMS-790052
  - PSI-7977
  - Debio025? (NS5A)
- Table structure and formatting
- Final list of mutations for Figure
- Final approval by drug companies
- Publication