Resistance Profile of HIV-1 Maturation Inhibitor GSK3532795

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GSK3532795 – Profile of a Second-generation Maturation Inhibitor (MI)

- **Background** GSK3532795 (formerly BMS-955176) is a second-generation human immunodeficiency virus (HIV-1) maturation inhibitor that targets HIV-1 Gag, inhibiting the final protease cleavage between capsid protein p24 and spacer protein-1, producing immature, non-infectious virions
- Despite comparable efficacy results as EFV in Phase 2b (76%, 83%, 82% for GSK3532795 60mg, 120mg and 180mg vs. 77% for EFV), unacceptable rates of gastrointestinal AEs and treatment-emergent resistance led to the discontinuation of GSK3532795 development
- The **objectives** of these studies were to:
  - investigate the *in vitro* resistance profile for GSK3532795 and compare to genotypic profiles seen during the Phase 2a (AI468002) study; relate results to the underlying mechanism for MI resistance in the context of a structural model; review virological profiles of next generation MIs vs GSK3532795
- **Methods – Selections w/WT or Gag polymorphic backgrounds**
  - **Passage Method:** 1 or 2x EC_{50}, increasing GSK3532795 concentration 2-fold with each passage until viral breakthrough, determine genotypes
  - **Breakthrough Method**: fixed 30x EC_{50} GSK3532795, measure days to viral breakthrough, determine genotypes

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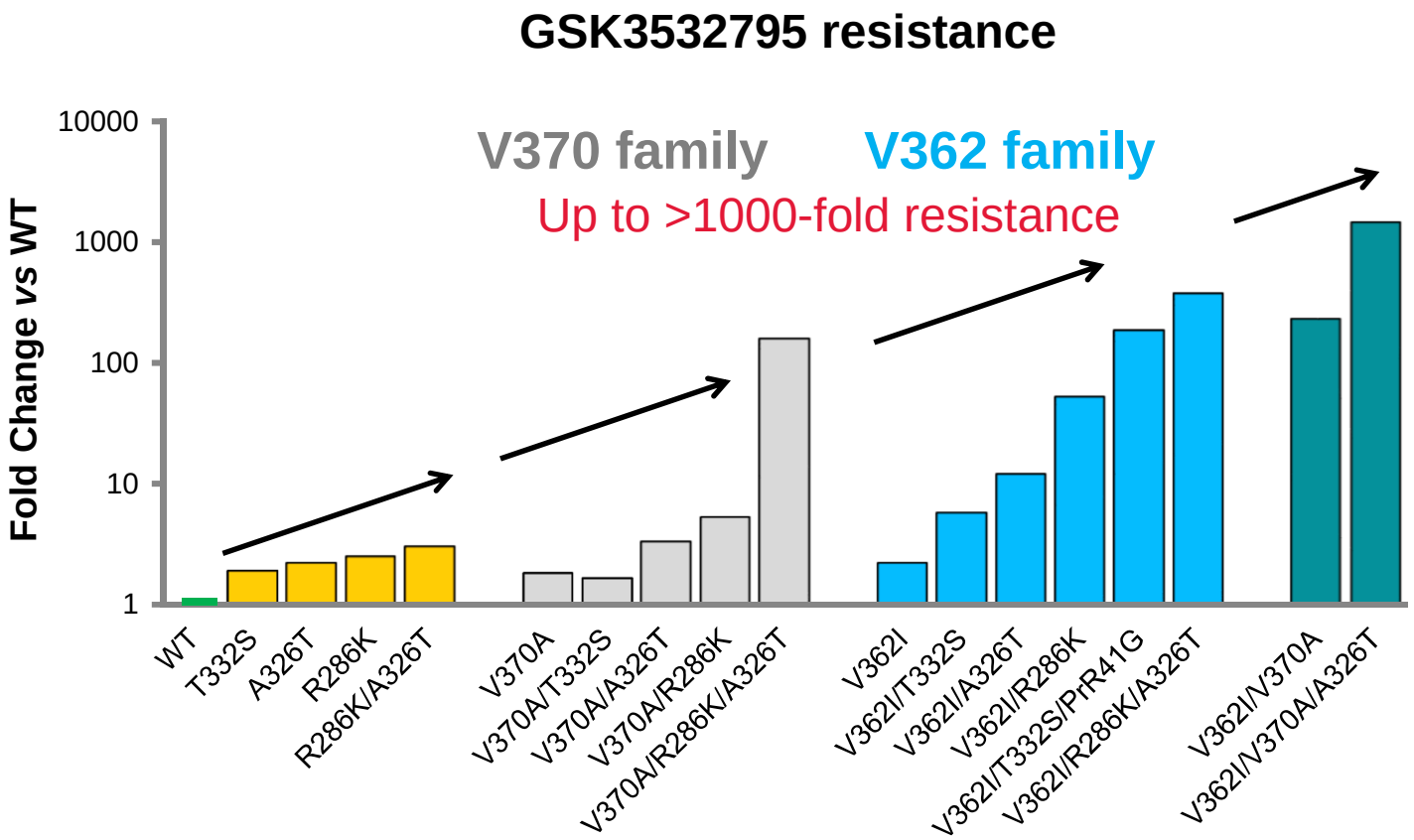
GSK3532795 *In Vitro* Resistance Mutations



Resistance Mutations Map to Gag (C-terminus of Capsid and CA/SP1 Domain)

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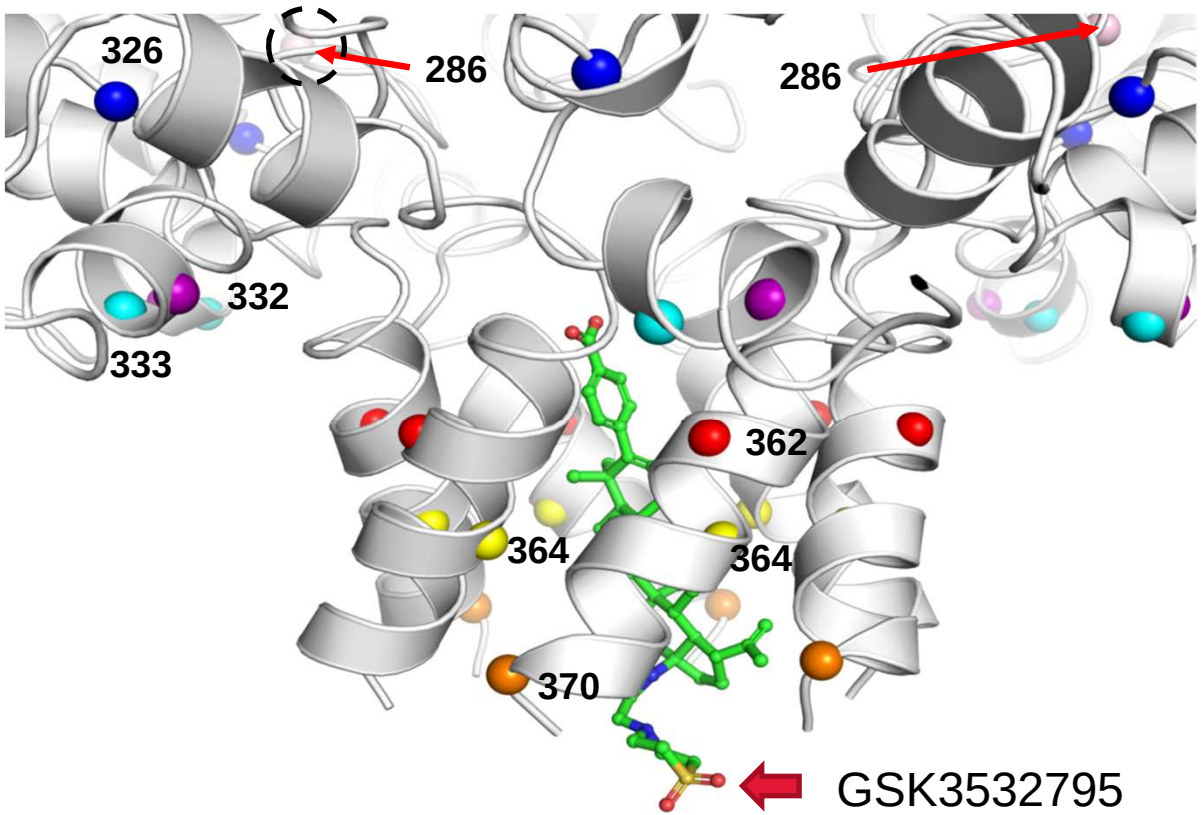
GSK3532795 *In Vitro* Resistance Mutations

Binding of MIs rigidify the structure, inhibiting protease access. Effects of resistance mutations are explained by their disruption of the structure of the CA/SP1 6-helix bundle,[1,2] increasing access and rate of CA/SP1 cleavage[2]

Capsid C-terminus and SP1 hexamer



1. Schur FK et al. Science 2016; 353:506-8, 4; 2. Lin, Z., et al. PLOS Path, 2016; https://doi.org/10.1371/journal.ppat.1005990

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On-treatment Genotypic and Phenotypic Changes in AI468002 (Day 10 Monotherapy, Phase 2a)

Dose (mg)	Baseline Gag polymorphism	Emergent genotypic mutation	CFB (ratio of FC-EC_{50} at Day 10/ Day 0)	Max viral load reduction
10	WT	A364A/V	67	-1.76
20	WT	V370I/V	1.1	-1.68
40	WT	V362I/V, A364A/V V370M	9.7 116	-1.09 -1.69
80	WT	V362I/V, A364V/A A364V/A	47 0.99	-1.50 -1.73
120	286K/R 286K	V362I V370A/V	>116 4.1	-0.83 -1.57
10	V370M	V362I/V	0.62	-1.31
20	V370A V370M	V362I/V, A364A/V A364A/V	>633 221	-1.23 -2.12
40	286K, V370M 286K/R, 370A/V	Q369Q/H None (V370A)	12 7.2	-0.93 -1.71
80	V370M	None (A366A/V)*	1.1	-1.04
120	286K, V362I/V V370A/V	None (V362I) None (V370X)	138 6.3	-0.83 -2.07

- AI468002 (Phase 2a study) genotypes are similar to those selected *in vitro* (V362I, A364V); decreases in BL FC up to >633 fold
- In the context of primary 362 and 370 changes, baseline R286K acts as a secondary resistance substitution

WT = no changes from canonical subtype B Gag V362,Q369,V370;

Red shows 9/33 (27%) subjects with **both** genotypic *Gag* changes and CFB >3.
Black shows subjects with either genotypic or phenotypic changes only.

Parenthesis indicate conversion from BL mixtures to single genotype on day 10.

*emergence of A366A/V; under study

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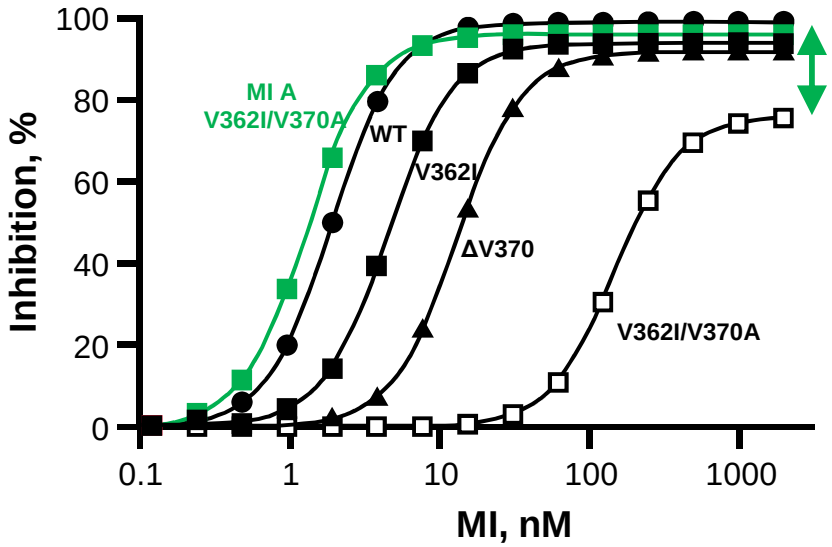
Next Generation MIs – MoA for Improved Coverage

- Next generation MIs show higher maximal activity *in vitro*, acting as complete (not partial) antagonists[2,3] with improved activity against all key baseline Gag polymorphisms and subtypes



Black curves: GSK795;
green curve: MI A toward V362I/V370A

Gag Polymorph	Maximal Percent Inhibition (MPI)[1,2]	
	GSK3532795	MI A
WT	99	99
V362I	94	99
ΔV370	92	97
V362I/V370A	76	96

Green color: MPI values of > 95% correspond to FC-IC_{50} values of < 2 fold

2. Lin, Z., et al. PLOS Path, 2016; https://doi.org/10.1371/journal.ppat.1005990
3. Lin, et al. 23rd CROI 2016, abstract 466

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Next Generation MIs – MoA for Improved Coverage

Subtype	% subtype B, LANL DB	GSK3532795		MI A		MI B	
		EC_{50}, µM	FC EC_{50}	EC_{50}, µM	FC EC_{50}	EC_{50}, µM	FC EC_{50}
WT	51	0.0020	**1.0**	0.0016	**1.0**	0.0024	**1.0**
V370A	15	0.0027	**1.4**	0.0019	**1.2**	0.0036	**1.5**
ΔV370	2	0.013	**6.7**	0.0036	**2.3**	0.0045	**1.9**
V362I/V370A	2	0.15	**76**	0.0013	**0.8**	0.0026	**1.1**
A326T/V362I/ V370A*	0	1.5	**750**	0.0035	**2.2**	0.004	**1.7**
R361K/V362I/ L363M†	0	1.2	**601**	0.0029	**1.8**	0.0045	**1.9**

- Next generation MIs inhibit GSK795/r viruses by binding with higher affinity[2], compensating for negative effects of destabilizing resistance changes
- Suggestive of >99% clinical coverage of Gag polymorphisms

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Conclusions

- Emergent substitutions observed *in vitro* and in clinical studies were similar, selecting mainly for changes to A364 and V362
- Certain double Gag polymorphisms in AI468002, e.g. 362 and 370, were associated with reduced *in vitro* susceptibility and sub-optimal clinical responses
- Secondary mutations in Gag (R286K, A326T, T332S, I333V) conferred reduced susceptibility only in the context of primary polymorphisms. Only R286K was observed clinically
- Next generation MIs exhibit complete antagonism resulting in pan-genotypic phenotypes with greatly improved activity against all single, double and triple Gag polymorphisms, including those causing significant reductions to GSK3532795 susceptibility

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Backup slides

On-treatment genotypic and phenotypic changes in AI468002 at Day 10

Dose (mg)	Baseline Gag polymorphism	Emergent genotypic mutation	FC-EC50 at Day 0/ Day10	CFB (ratio of FC-EC50 at Day 0/ Day10)	Day 11 VLR	Max viral load reduction
10	WT	A364A/V	0.63/42.2	67	-1.16	-1.76
20	WT	V370I/V	0.48/0.52	1.1	-1.59	-1.68
40	WT	V362I/V, A364A/V	0.39/3.8	9.7	-0.95	-1.09
		V370M	1.14/132	116	-1.69	-1.69
80	WT	V362I/V, A364V/A	3.1/146	47	-1.31	-1.50
		A364V/A	0.95/0.94	0.99	-1.73	-1.73
120	286K/R	V362I	6.05/>704	>116	-0.83	-0.83
	286K	V370A/V	3.9/15.8	4.1	-1.53	-1.57
10	V370M	V362I/V	2.5/1.6	0.62	-1.02	-1.31
20	V370A	V362I/V, A364A/V	1.7/>666	>633	-0.64	-1.23
	V370M	A364A/V	0.48/106	221	-1.94	-2.12
40	286K, V370M	Q369Q/H	1.6/20	12	-0.93	-0.93
	286K/R, 370A/V	None (V370A)	68.5/496	7.2	-0.64	-1.71
80	V370M	None (A366A/V)*	2.26/2.03	1.1	-0.93	-1.04
120	286K, V362I/V	None (V362I)	2.95/407	138	-0.81	-0.83
	V370A/V	None (V370X)	0.82/5.2	6.3	-1.54	-2.07

- AI468002 (Ph2a study) genotypes are similar to those selected in vitro (V362I, A364V); decreases in BL FC up to >633 fold
- In the context of primary 362 and 370 changes, baseline R286K acts as a secondary resistance substitution

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Schematic for Inhibition of Infectivity by MIs

PLOS | PATHOGENS

BMS-955176 (GSK3532795), HIV-1 Maturation Inhibitor Kinetic Model of Polymorphic Coverage, Partial Antagonism