

S/GSK1349572 Demonstrates Significantly Slower Dissociation Rates than Raltegravir when Comparing Wild Type and Raltegravir Resistant Integrase Protein

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SHIONOGI



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HIV-1 Integrase

- **HIV-1 integrase catalyzes the insertion of viral DNA into the host genome through two steps**
 - 3'- end processing
 - strand transfer
- **Integrase is an attractive target for drug design**
 - Patients on long term ART treatment have developed drug resistance
 - Drugs targeting alternative steps in the viral replication cycle are needed
 - Integrase is essential for viral replication

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Integrase Inhibitors

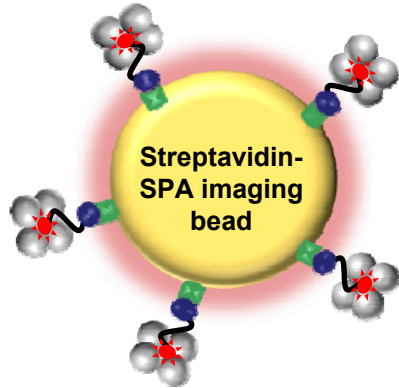
- **Raltegravir (RAL) is the only marketed integrase inhibitor (INI) and RAL-resistant mutations have developed**
 - Fast dissociation of RAL from mutant integrase may contribute to RAL resistance
- **S/GSK1349572 (572) is in development as a once daily INI with a distinctive resistance profile**
 - Extensive *in vitro* resistance profiling by Shionogi has shown that S/GSK1349572 has significant activity against HIV-1 with RAL-associated resistance mutations
- **Does slow dissociation of S/GSK1349572 contribute to its distinctive resistance profile?**

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INI Dissociation Experiment

IN-DNA-bead complex with bound ^3H -INI

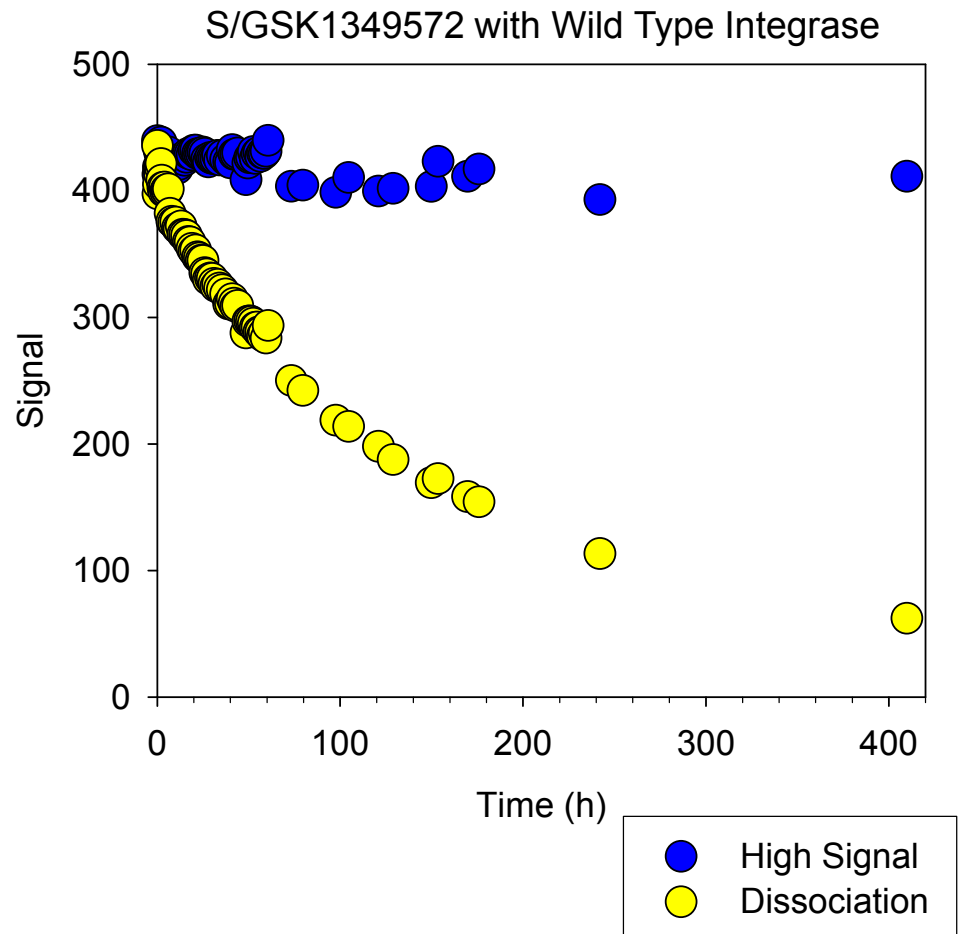
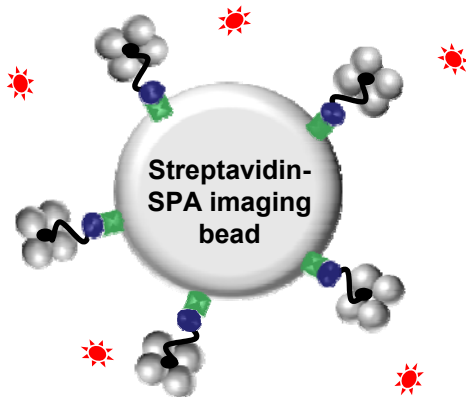
High signal



Add excess unlabeled INI

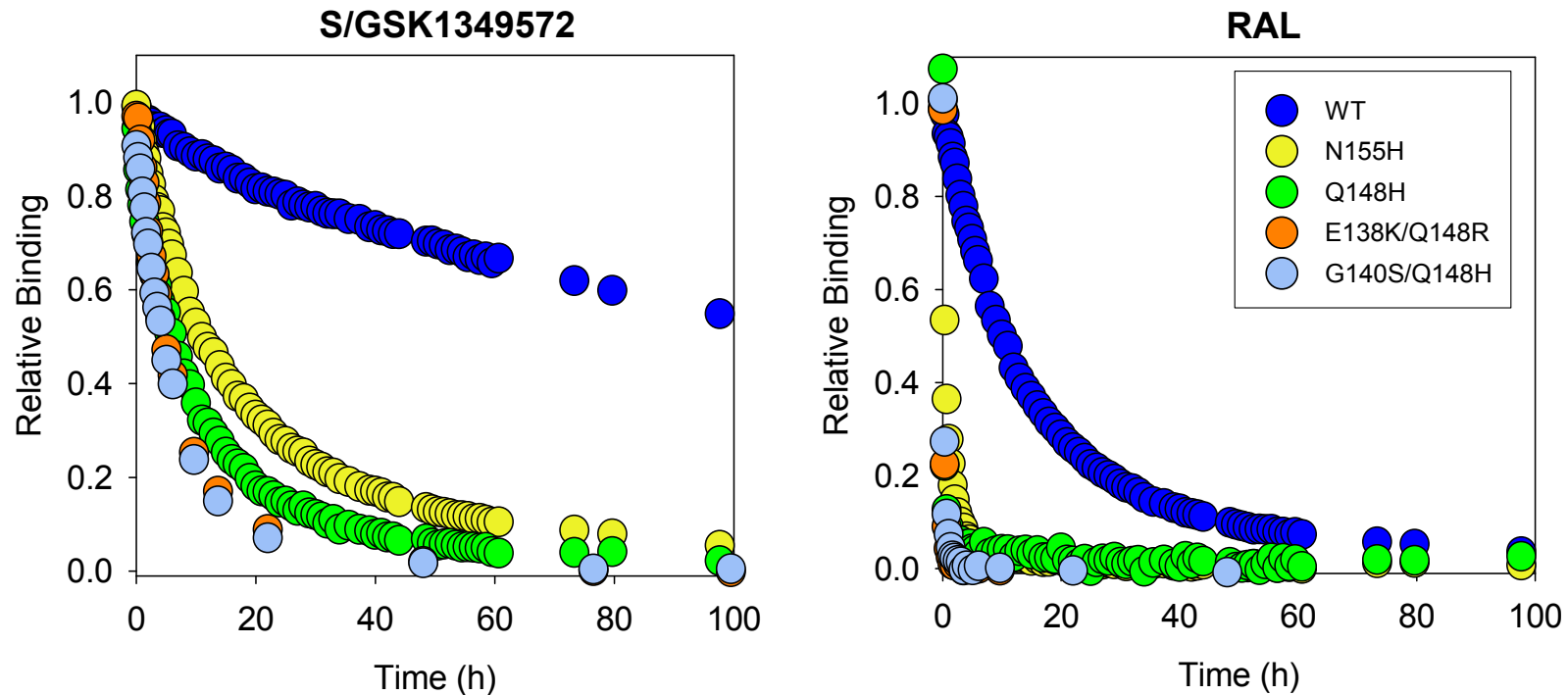
^3H -INI dissociates and is free in solution

Low signal



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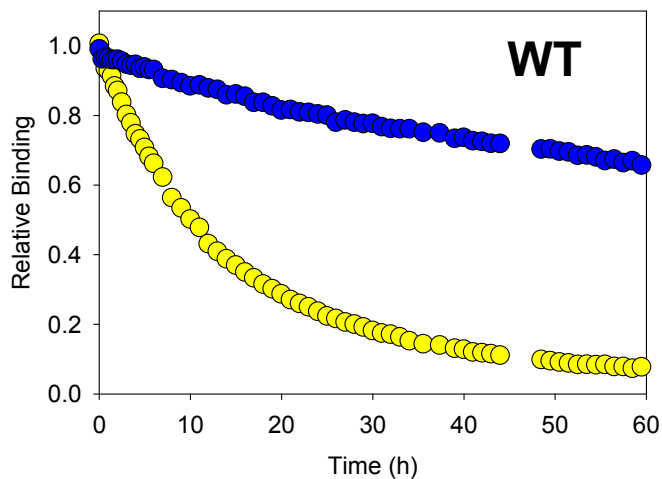
Dissociation of S/GSK1349572 and RAL at 37°C



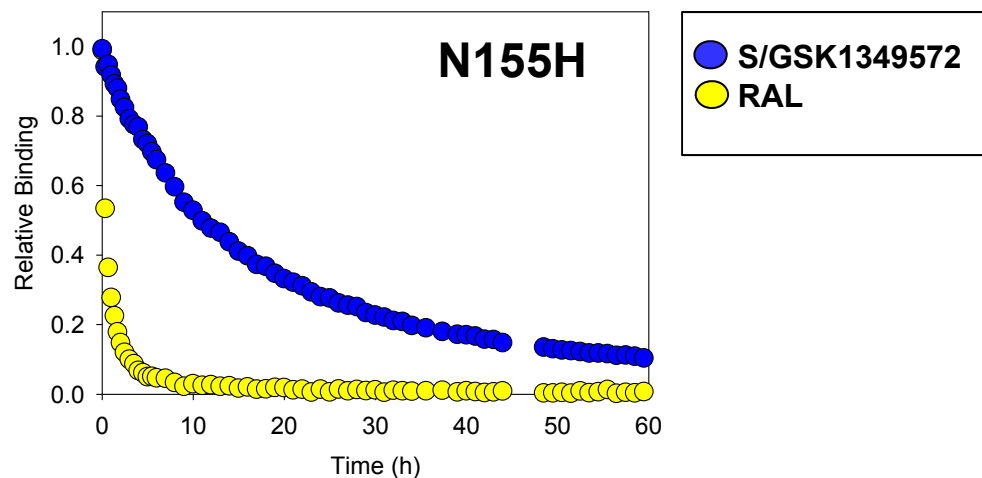
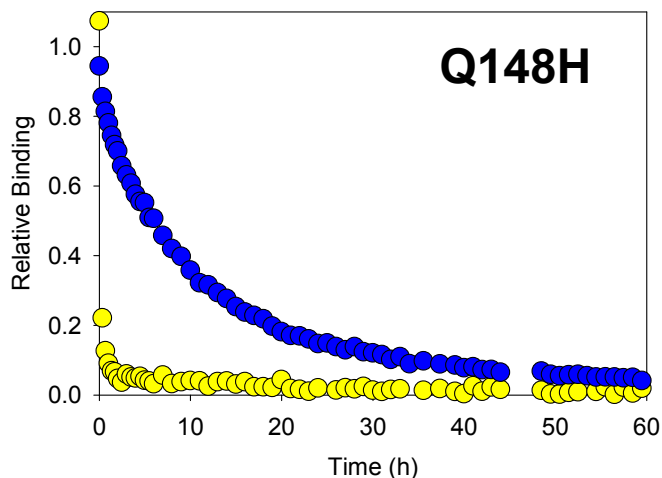
- **S/GSK1349572 dissociates slowly from an IN-DNA complex at 37°C**
- **Dissociation of both S/GSK1349572 and RAL is impacted by mutations**
- **Dissociation of S/GSK1349572 is considerably slower than RAL for wild type integrase and RAL-resistant mutants**

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S/GSK1349572 Dissociates More Slowly than RAL



- S/GSK1349572 dissociation is approximately 10-times slower than RAL with wild type integrase
- S/GSK1349572 dissociation is at least 19-times slower than RAL with Q148 and N155 mutants



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S/GSK1349572 Demonstrates Prolonged Binding with Wild Type and Mutants

Integrase	Dissociation at 37°C $t_{1/2}$ (h)		<i>In vitro</i> Resistance Mean Fold Change	
	S/GSK1349572	RAL	S/GSK1349572	RAL
Wild Type	100.4	10.1	1	1
N155H	11.6	0.6	1.2	11
Q148H	7.7	<0.3	0.97	13
Q148R	10.7	0.4	1.2	47
Q148K	15.4	<0.3	1.1	83

- Dissociation of S/GSK1349572 from Q148 and N155 mutants is comparable to dissociation of RAL from wild type integrase protein
- Fast dissociation of RAL is consistent with increased resistance *in vitro*
- *In vitro* resistance data from Seki et al., 2010, 17th CROI; Poster 555

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Multiple Mutations Impact Dissociation

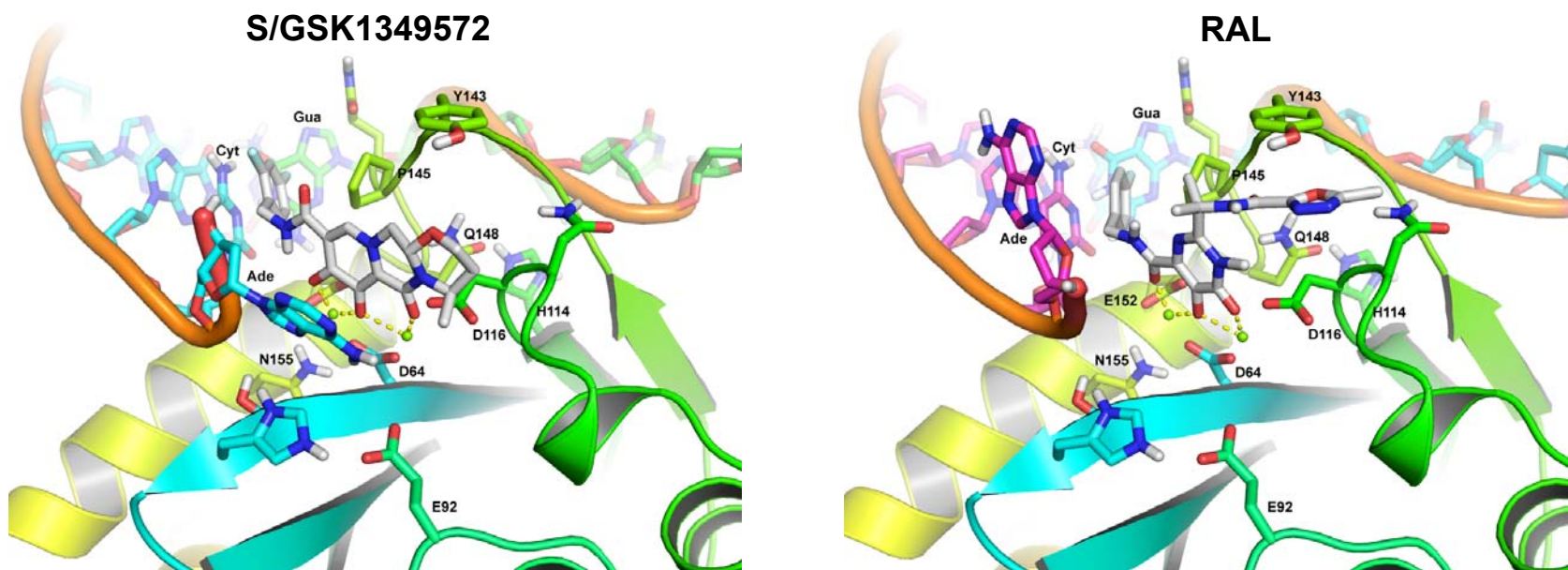
Integrase	Dissociation at 37°C $t_{1/2}$ (h)		<i>In vitro</i> Resistance Mean Fold Change	
	S/GSK1349572	RAL	S/GSK1349572	RAL
Wild Type	100.4	10.1	1	1
N155H	11.6	0.6	1.2	11
E92Q	23.6	3.9	1.6	3.5
E92Q/N155H	5.8	<0.3	2.5	>130
Q148R	10.7	0.4	1.2	47
E138K/Q148R	4	<0.3	4	110
Q148H	7.7	<0.3	0.97	13
G140S	22.7	3.7	0.86	1.1
G140S/Q148H	4.2	<0.3	2.6	>130

- Addition of a second mutation reduces $t_{1/2}$ and increases *in vitro* resistance
- *In vitro* resistance data from Seki et al., 2010, 17th CROI; Poster 555

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Dissociation Data are Consistent with Integrase Model

- Model of HIV-1 integrase with bound DNA and INI predicts that mutations at Q148 and N155 should have a greater impact on RAL than on S/GSK1349572
- Streamlined architecture of S/GSK1349572 may contribute to its activity against RAL-resistant mutants



Felix Deanda, et al. Structural models of HIV-1 integrase and DNA in complex with S/GSK1349572, Raltegravir or Elvitegravir: structure-based rationale for INI resistance profiles.

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Conclusions

- **S/GSK1349572 dissociates slowly from wild type integrase and RAL-resistant mutants**
- **Dissociation of S/GSK1349572 is significantly slower than RAL for wild type integrase and all RAL-resistant mutants studied**
- **Dissociation data are consistent with *in vitro* resistance data suggesting that the long dissociation half-life of S/GSK1349572 may contribute to its distinct resistance profile**
- **Results highlight a potential for improved activity of S/GSK1349572 against wild type HIV-1 and RAL-resistant viruses**

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All patients enrolled in the clinical trials

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