

**Modifications in the Cytoplasmic Domain  
of HIV-1 Env Allow Exposure of the  
Conserved Coreceptor-Binding Site  
and Enhance Neutralization Sensitivity.**

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Abstract Nr. A-029

# Introduction

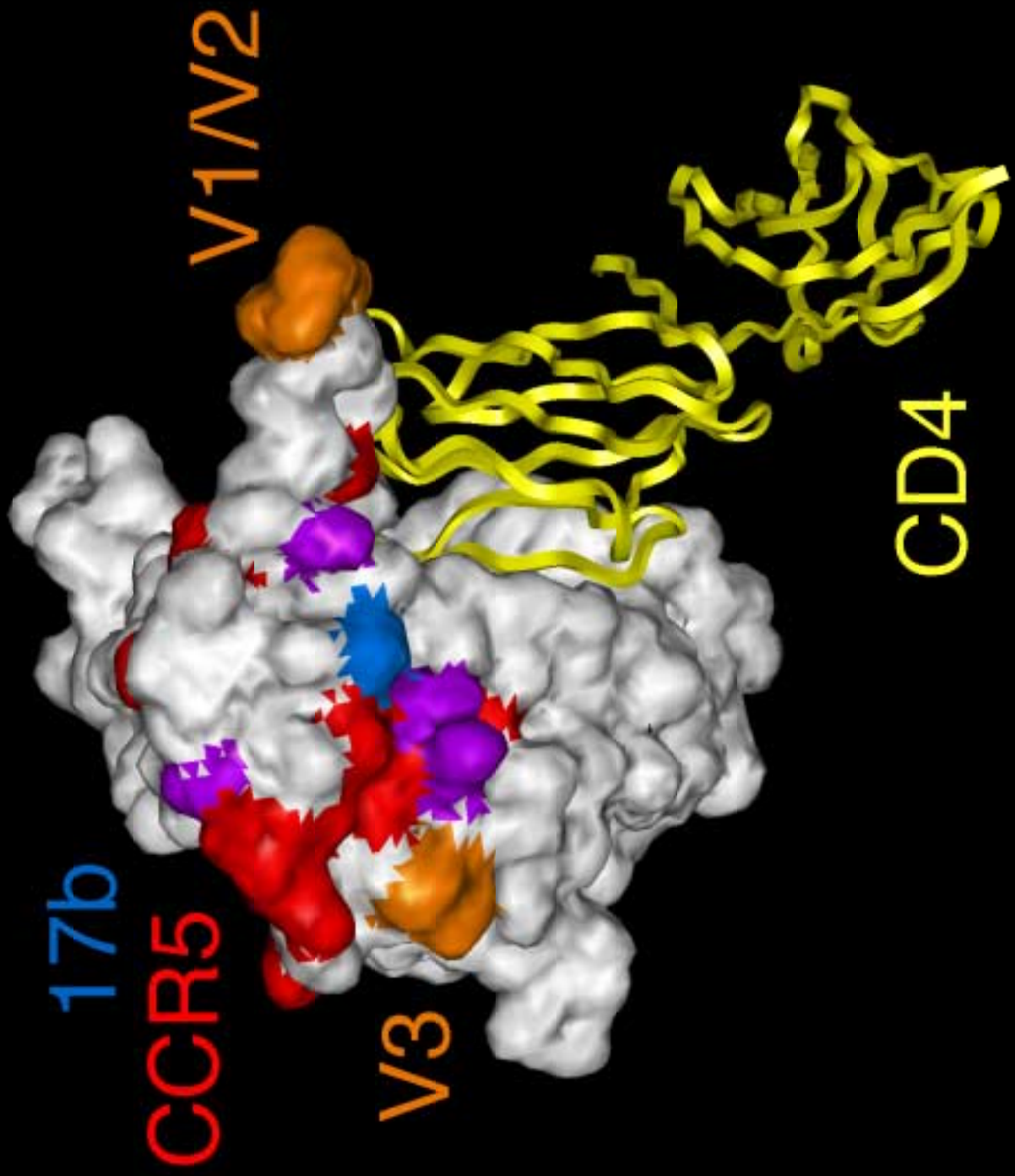
- ◆ **We have described a CD4-independent variant of HXB termed 8x, which mediates CD4-independent, CXCR4-dependent infection.**

Hoffman et al., PNAS 1999, LaBranche et al., J.Virol 1999

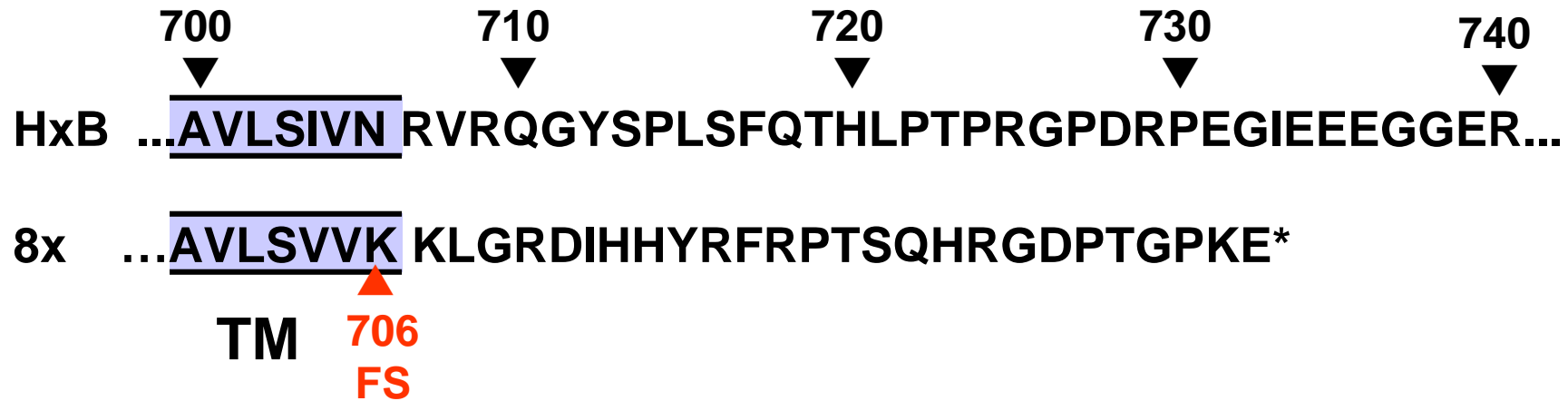
- ◆ **CD4-induced epitopes detected by Mabs 17b and 48d were shown to be exposed in absence of CD4.**

(Hoffman et al., PNAS 1999)

- ◆ **8x exists in a partially triggered state in which the chemokine receptor binding site is exposed.**



# FS mutation



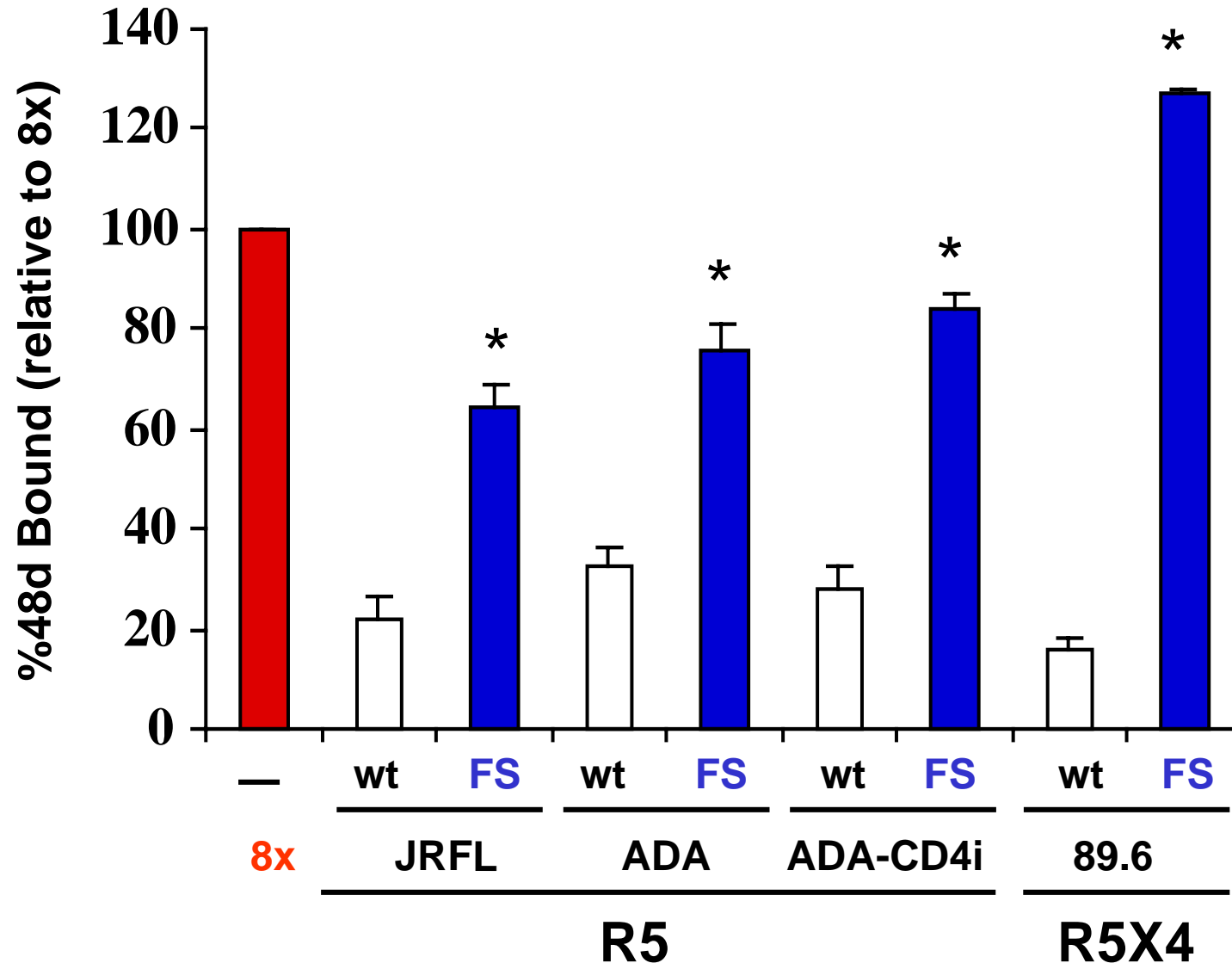
- ◆ The FS mutation correlated with increased exposure of the conserved coreceptor-binding site and increased neutralization sensitivity when introduced into HxB.

# Aims

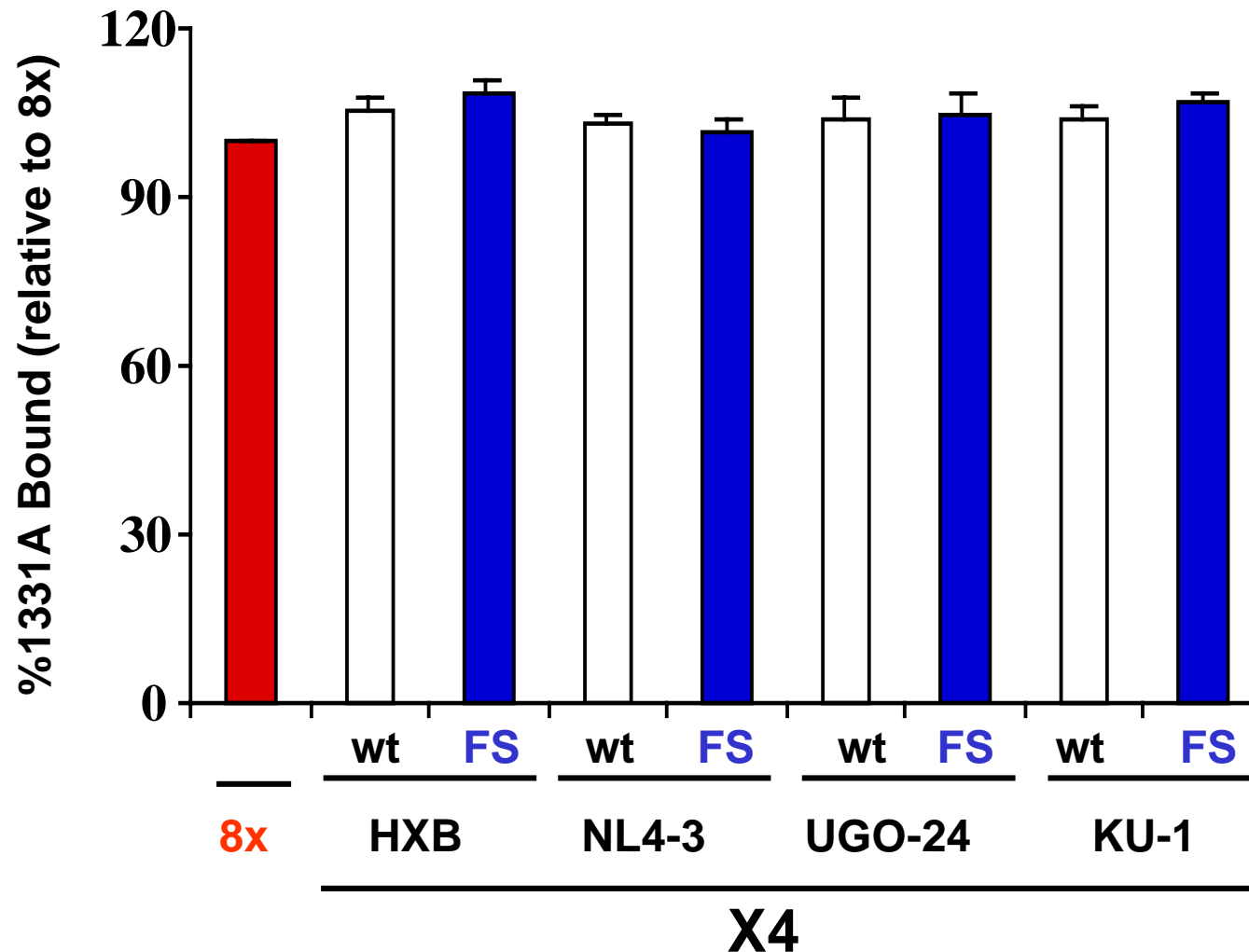
- ◆ **Investigate the effect of the FS mutation on primary and laboratory-adapted Envs.**
- ◆ **Investigate the structural consequences upon introduction of the FS mutation.**
- ◆ **Determine the functional consequences upon introduction of the FS mutation.**

# Results

Introduction of the frameshift mutation leads to increased 48d binding.



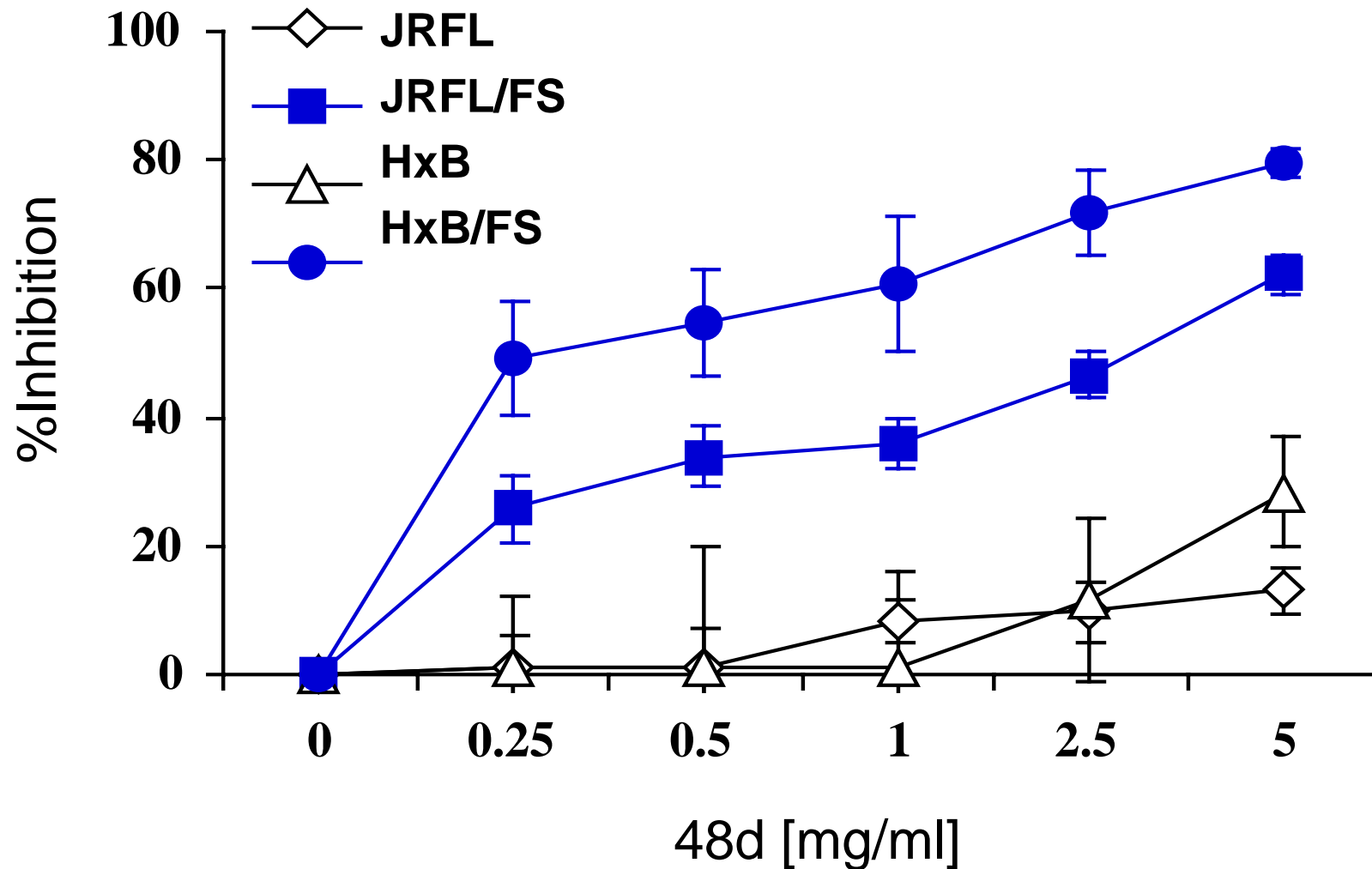
FS Envs have surface expression levels comparable to wt Envs.



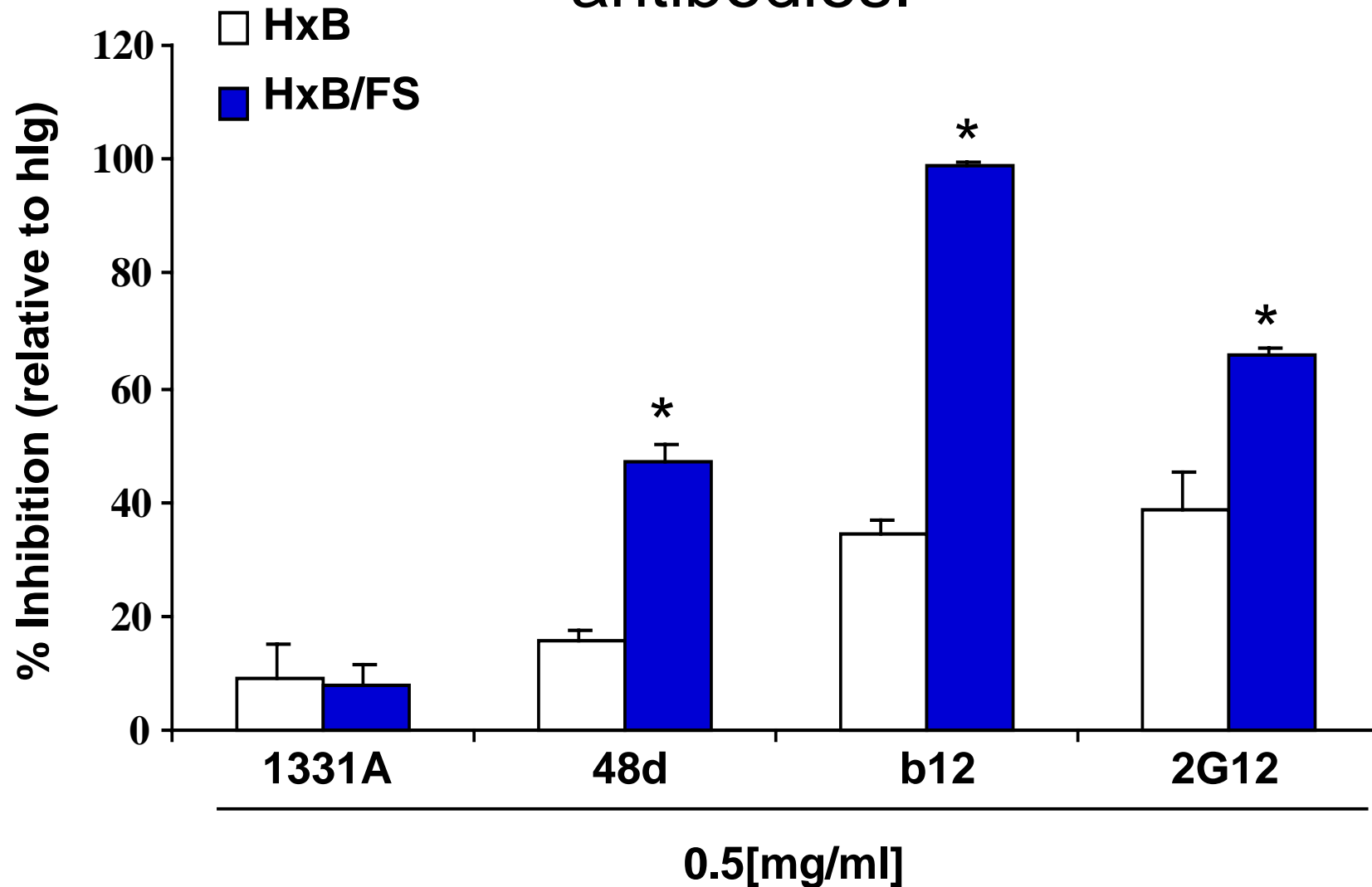
Additional conformational changes result from the introduction of the FS mutation.

<b>MAbs</b>	<b>Epitope</b>	<b>Effect on binding</b>
<b>F105</b>	<b>CD4bs</b>	<b>Increased</b>
<b>b12</b>	<b>CD4bs</b>	<b>Increased</b>
<b>2G12</b>	<b>Complex</b>	<b>Increased</b>
<b>697D</b>	<b>V2</b>	<b>Same</b>
<b>694/98D</b>	<b>V3</b>	<b>Same</b>
<b>246D</b>	<b>gp41</b>	<b>Increased</b>

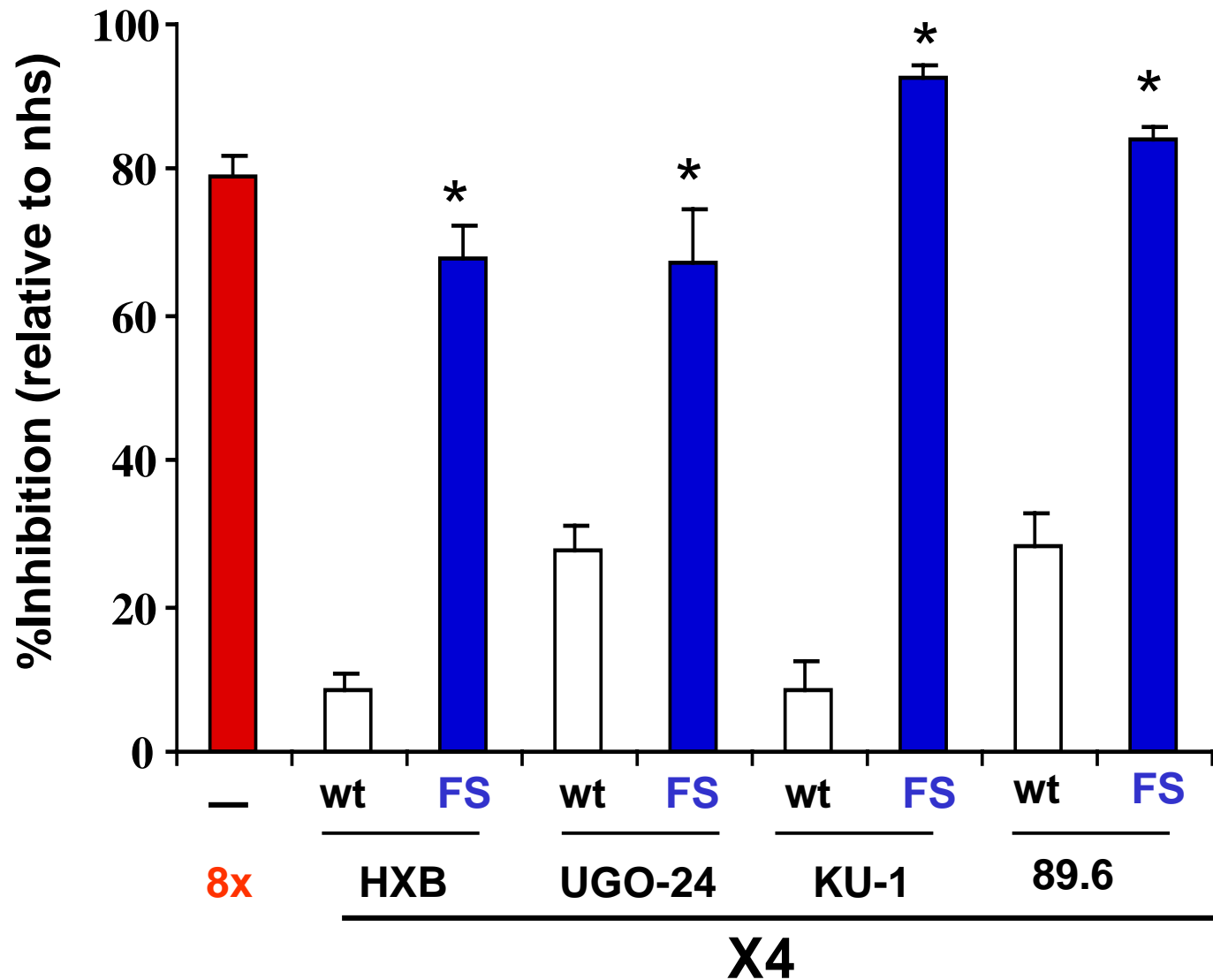
Frameshift envelopes are susceptible to 48d neutralization.



Pseudotyped virions bearing FS Envs are more sensitive to neutralization by monoclonal antibodies.



# Pooled HIV<sup>+</sup> human sera potently neutralizes FS Envs.



# Conclusions and Discussion

- ◆ The FS mutation alters the conformation of the ectodomain.
- ◆ The phenotype was transmitted to R5, X4, R5X4 strains whether laboratory adapted or primary strains  
⇒ context independent.
- ◆ The FS mutation results in enhanced exposure of conserved, neutralization epitopes in gp120.
- ◆ FS Envs are neutralization sensitive including by HIV-positive human sera samples.
- ◆ Will immunization with FS Envs result in a more potent humoral immune response to primary HIV-1 isolates ?

- ◆ The immune response to FS Env transfected cells is currently evaluated in rabbits and mice.
  
- ◆ Two goals are pursued:
  - Try to evaluate the humoral response with these new immunogens.
  
  - If we obtain potent antibodies include them in our ongoing testings for potent microbocides.

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