

## Lipid Membranes Have a Role in the Mechanism of Action of HIV Fusion Inhibitors T-20 (enfuvirtide) and T-1249

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T-20 (enfuvirtide) is a HIV fusion inhibitor peptide in clinical use. T-1249 is a HIV fusion inhibitor peptide under clinical trials. Their interaction with biological membrane models (large unilamellar vesicles) was studied using fluorescence spectroscopy to ascertain a possible role of lipid bilayers in their mode of action at the molecular level. Both peptides partition extensively to the liquid-crystalline zwitterionic POPC and locate at the interface of the membrane. When other lipid compositions are used (POPC+cholesterol, gel phase bilayers and negatively charged liquid-crystalline bilayers) partition decreases, the most severe effect being the presence of cholesterol. Partition experiments and fluorescence resonance energy transfer analysis show that T-1249 adsorbs to cholesterol-rich membranes. The improved clinical efficiency of T-1249 relative to enfuvirtide (T-20) may be related to its bigger partition coefficient and ability to adsorb to rigid lipidic areas on the cell surface, where most receptors are inserted. Moreover, adsorption to the sterol-rich viral membrane helps to increase the local concentration of the inhibitor peptide at the fusion site.

AS Veiga et al (2004) *Biochem. J.*, 377, 1-4.

AS Veiga et al (2004) *JACS*, 126, 14758-14763.

S Veiga et al (2006) *BBA*, 1760, 55– 61.

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