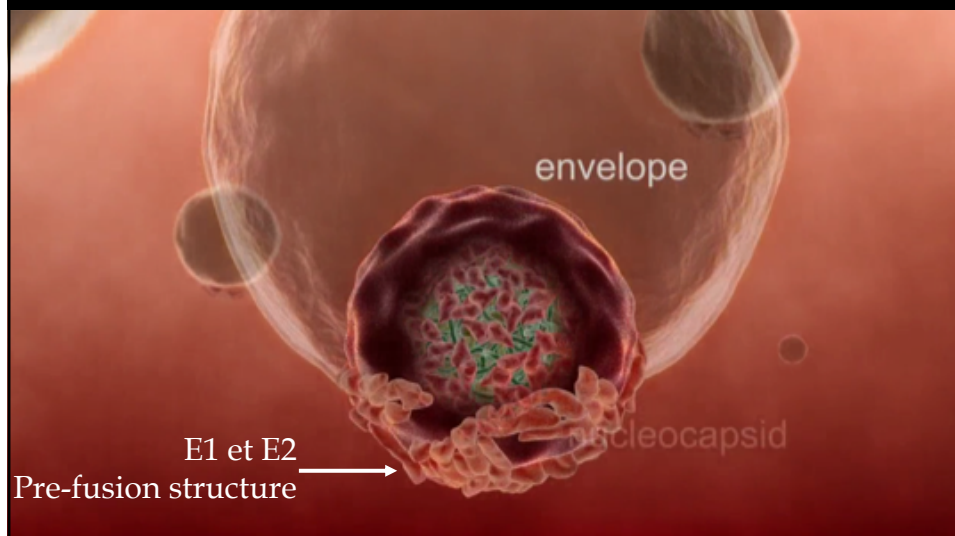


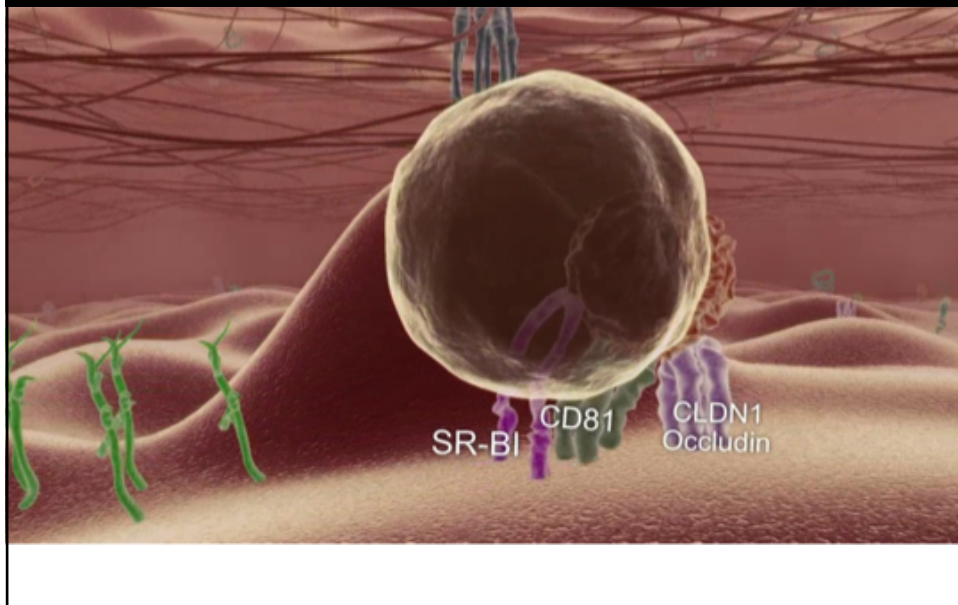
A cluster-based protein coevolution method uncovers critical features of the original HCV fusion mechanism

Comment l'étude de la co-évolution des protéines virales a permis de révéler le mécanisme de fusion membrane du VHC

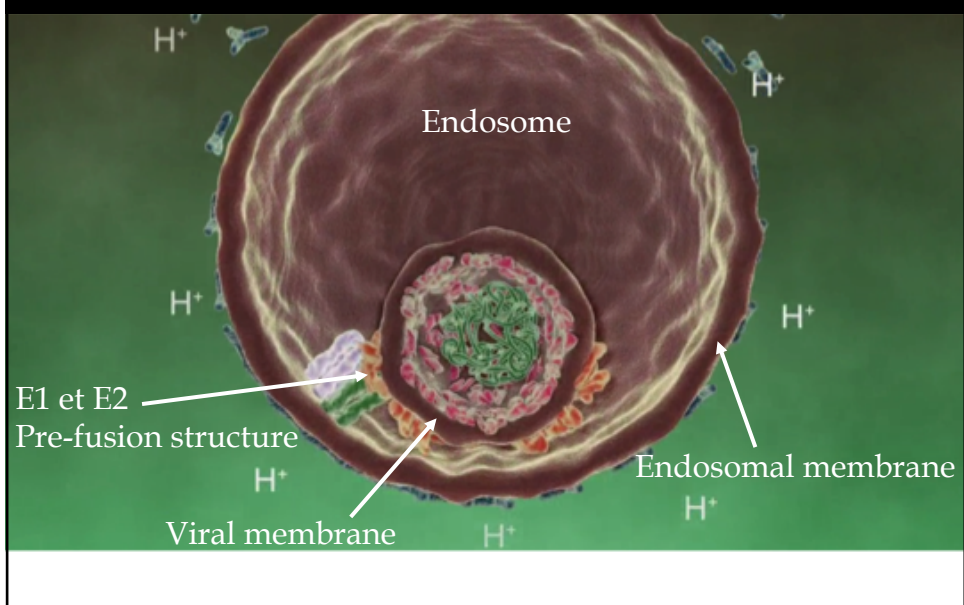
HCV E1E2 : Assembly on infectious virions



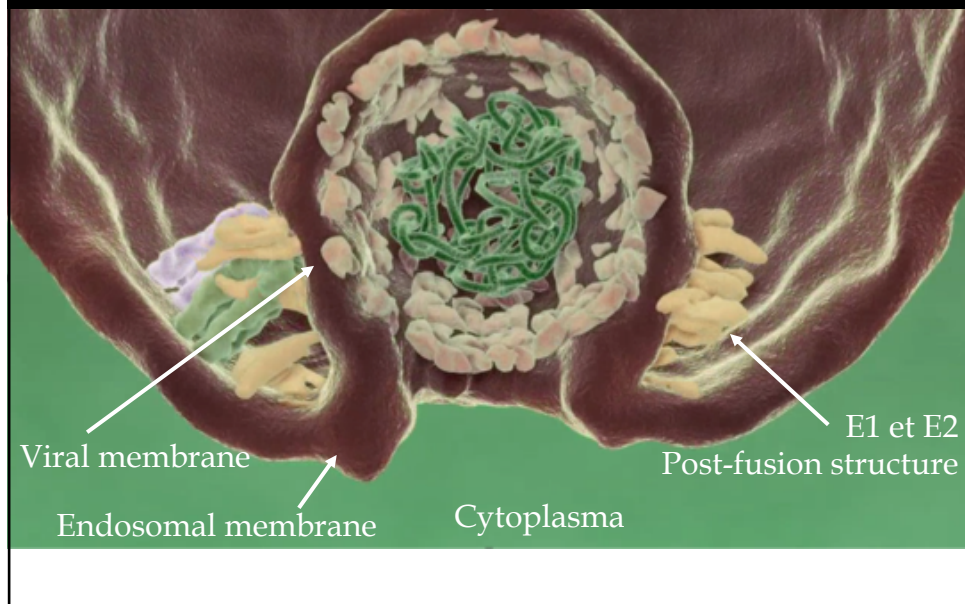
HCV E1E2 : Interaction with receptors



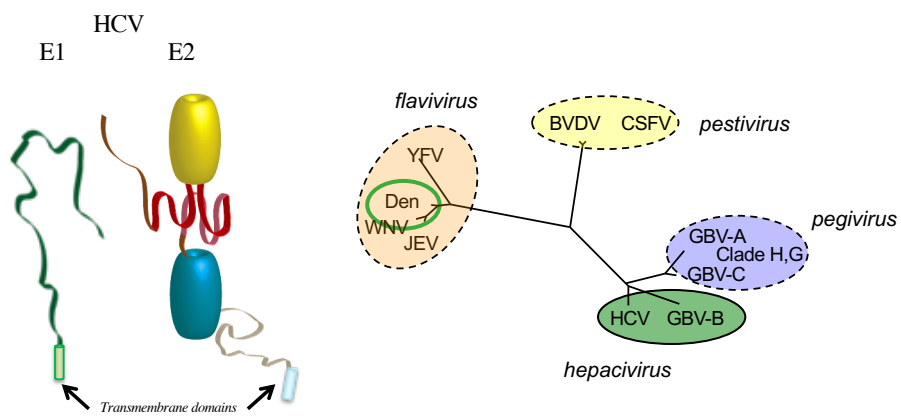
HCV E1E2 : Internalization within cells



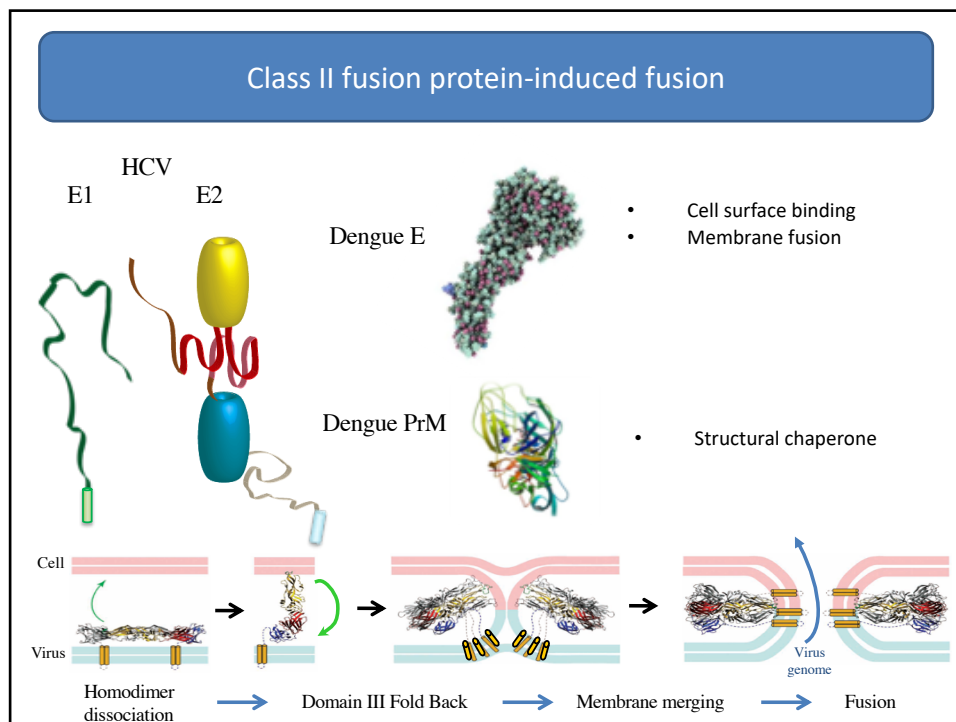
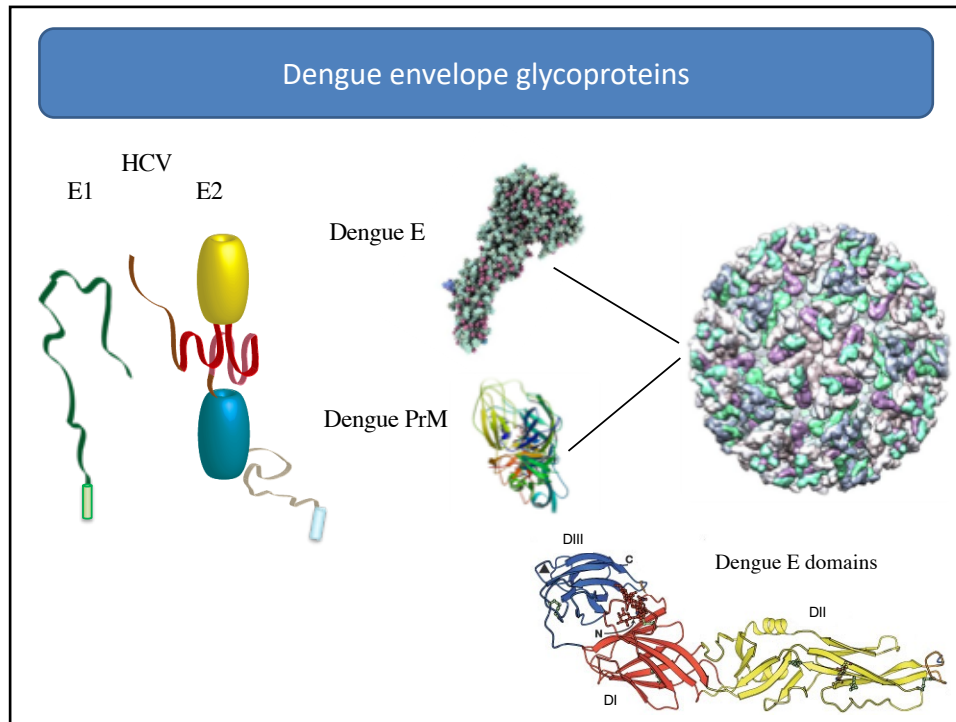
HCV E1E2 : Membrane fusion



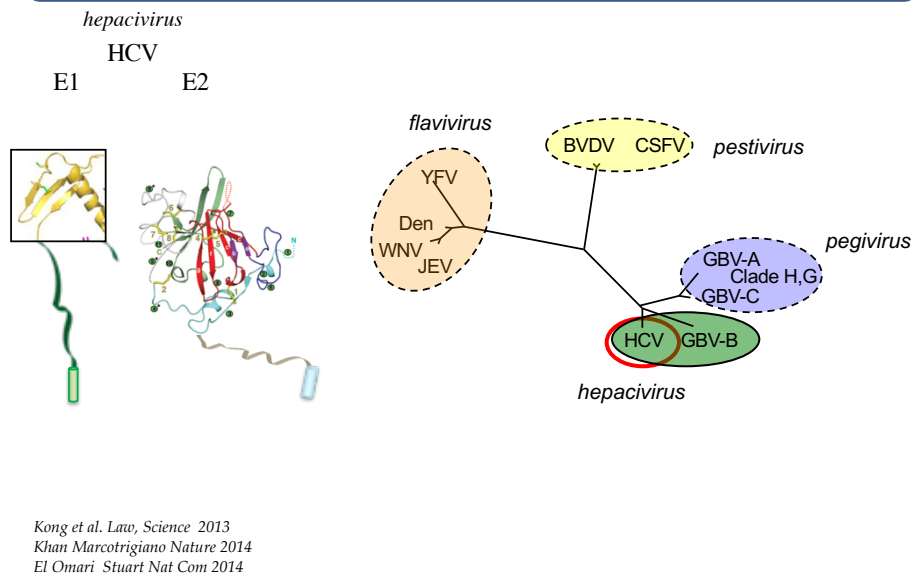
E1 and E2 functions are poorly characterized



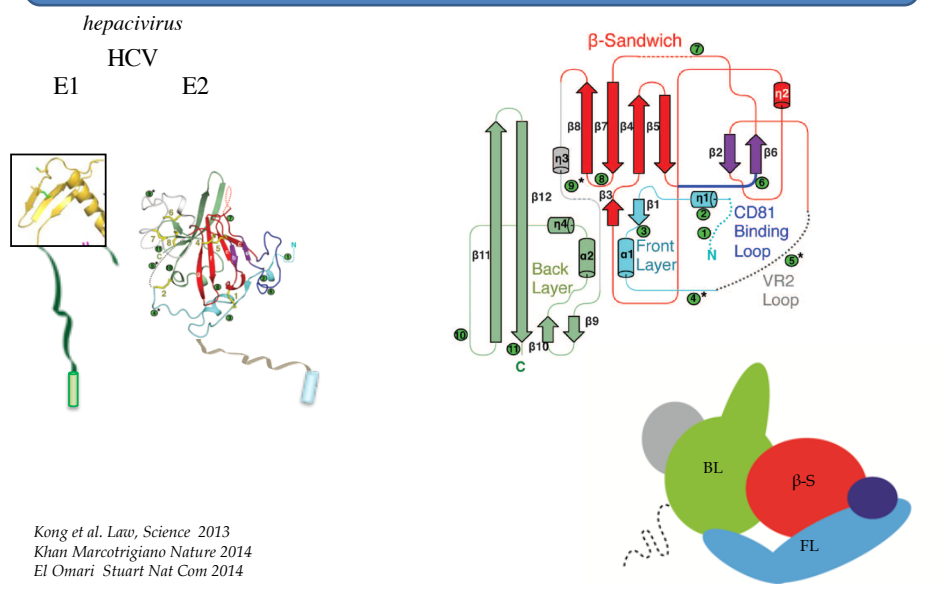
Adapted from Krey et al, 2010

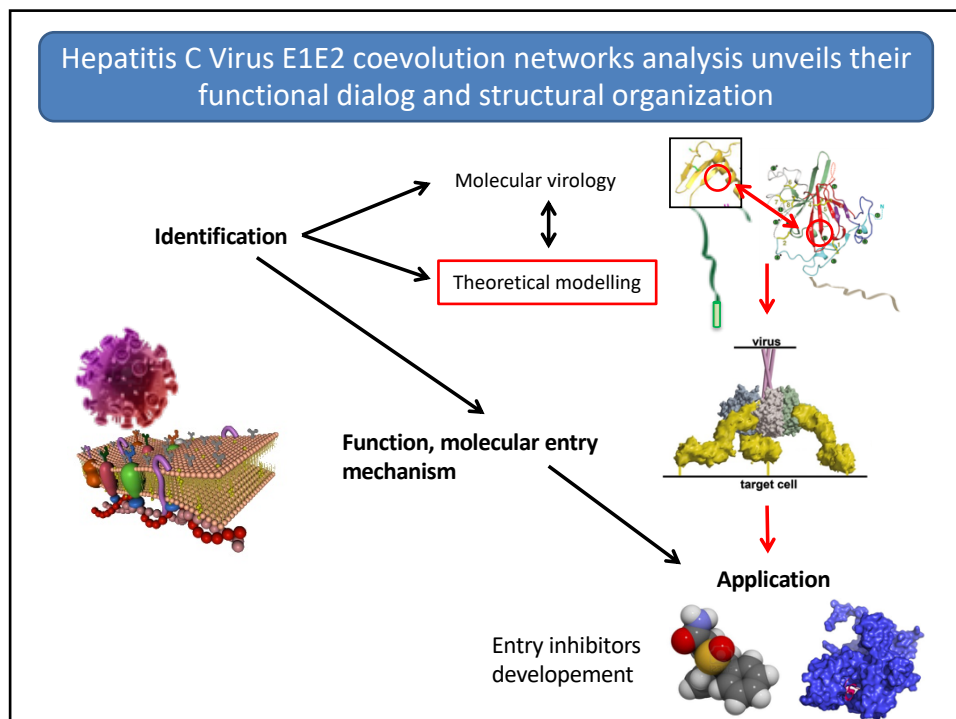
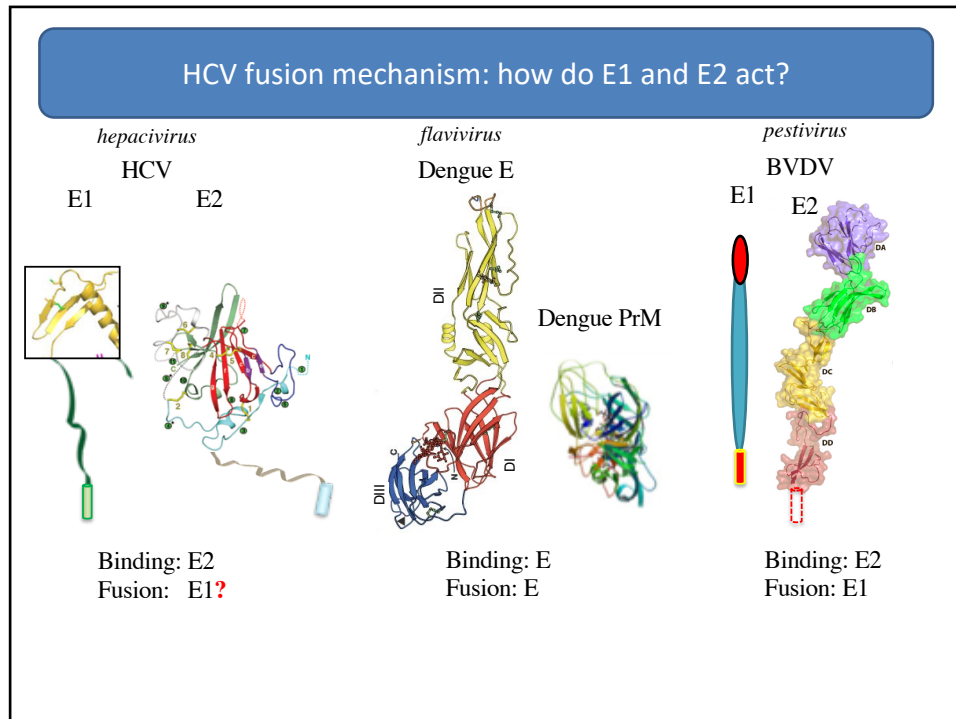


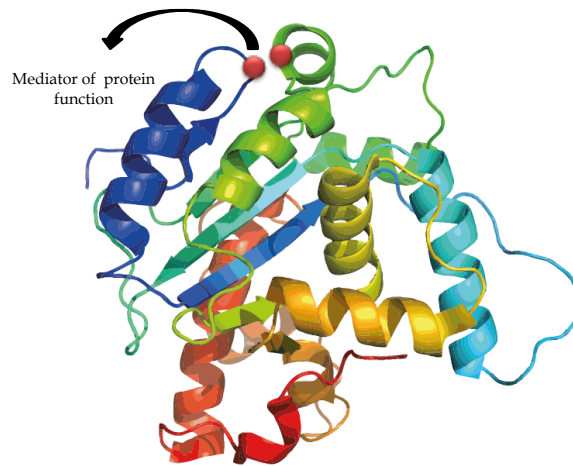
E2 is not a Class 2 fusion protein



E1 and E2 functions are still poorly characterized

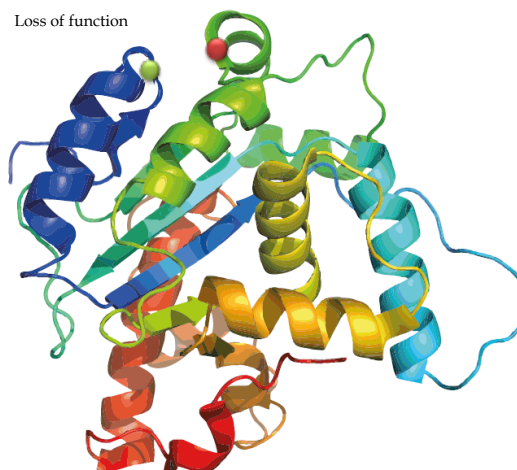






Protein coevolution signals are strong mediator of protein functions.

Such signals represent interesting tools to unveil viral protein dynamic rearrangements and uncover potential therapeutic targets.



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Restoration of function



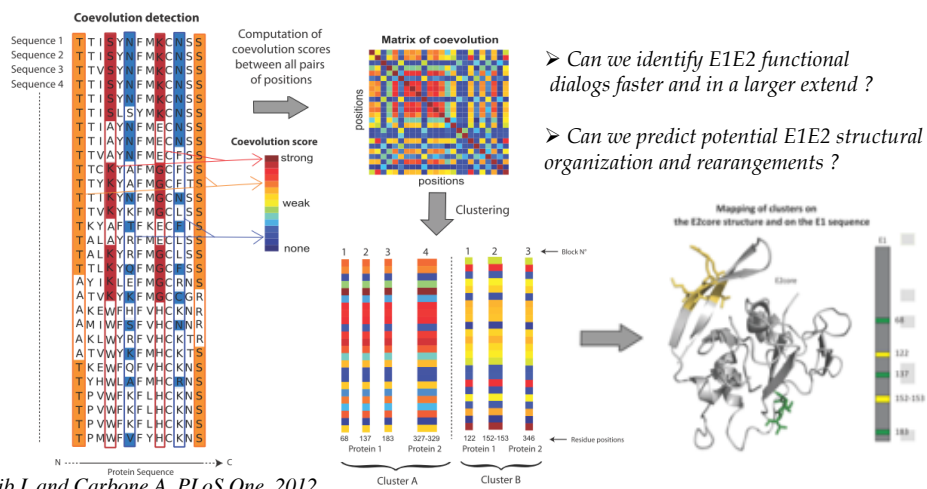
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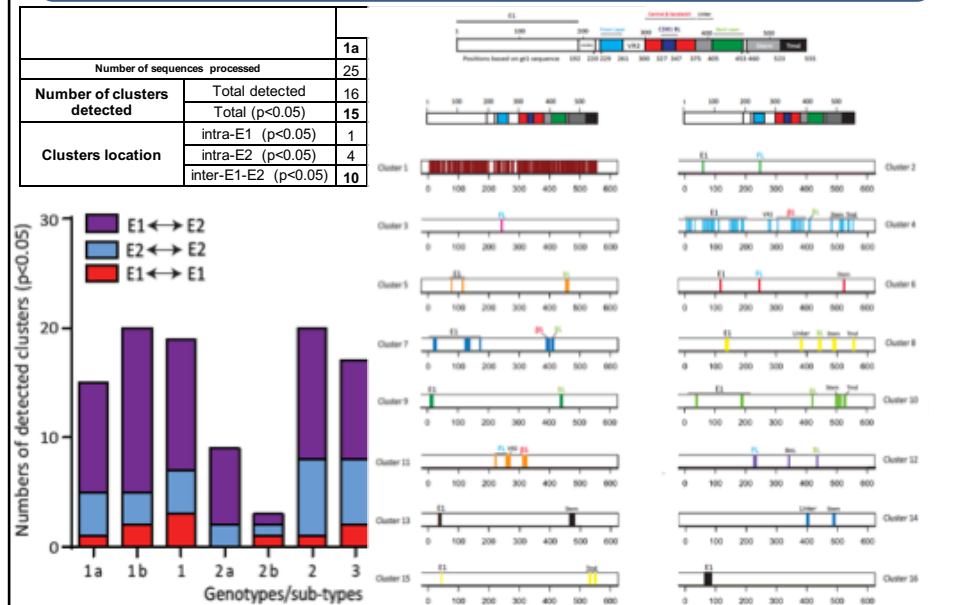
The BIS Model

A computational detection of amino acid co-evolution

- * Allows identification of networks and dialogs within proteins
- * Principle: Small protein fragments can be used as basic building blocks to reconstruct networks of co-evolving amino acids



Application of BIS model to two envelope glycoproteins: HCV E1E2



Clusters map important residues described in the literature

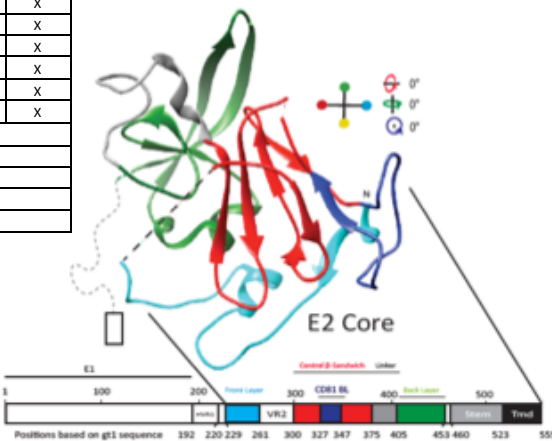
E2 - Genotype 1a clusters



Douam et al. In press.

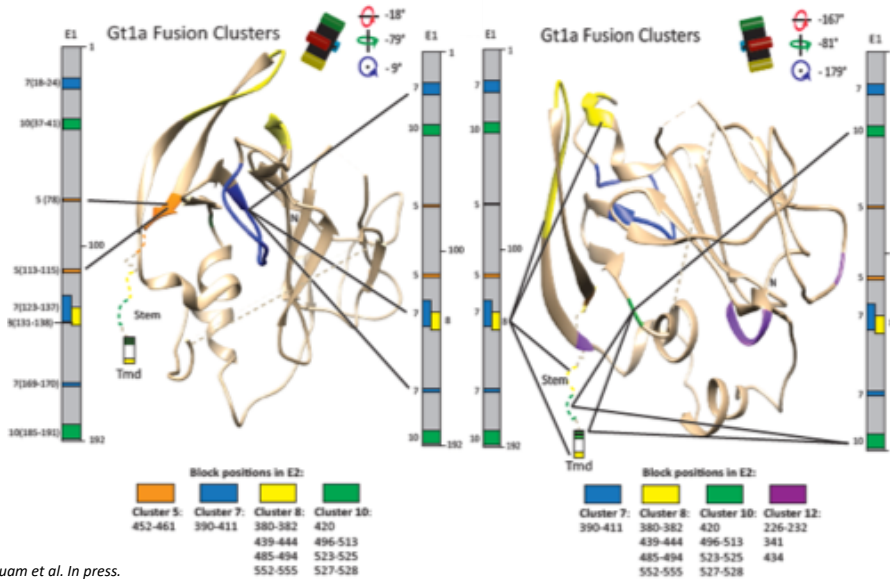
E1E2 clusters map important residues described in the literature

Genotype 1a clusters				
Structural Clusters (folding, heterodimerization, binding)	2		X	
	6	X	X	
	11		X	
Membrane fusion Clusters	5			X
	7	X		X
	8			X
	10	X		X
	12		X	X
Multifunctional Clusters	4	X	X	X
	16	X	X	X
Undefined role	3		?	
	9		?	
	13		?	
	14		?	
	15		?	



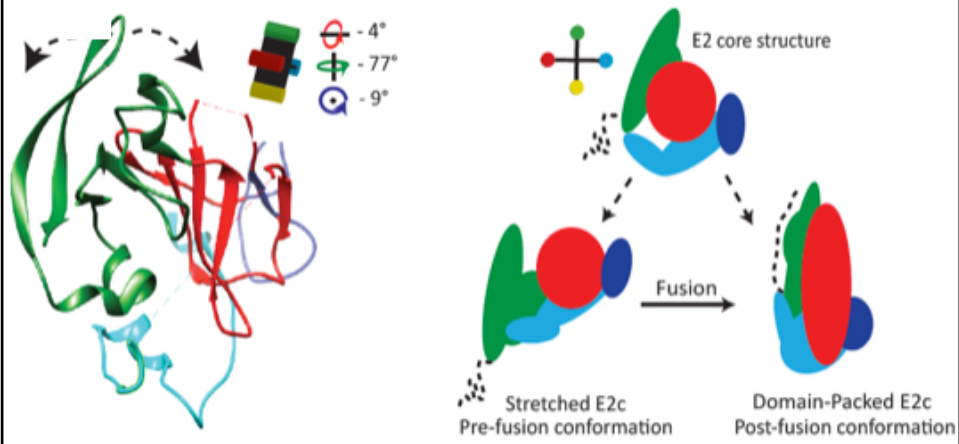
Douam et al. In press.

HCV fusion cluster support E1E2-interdependent rearrangements



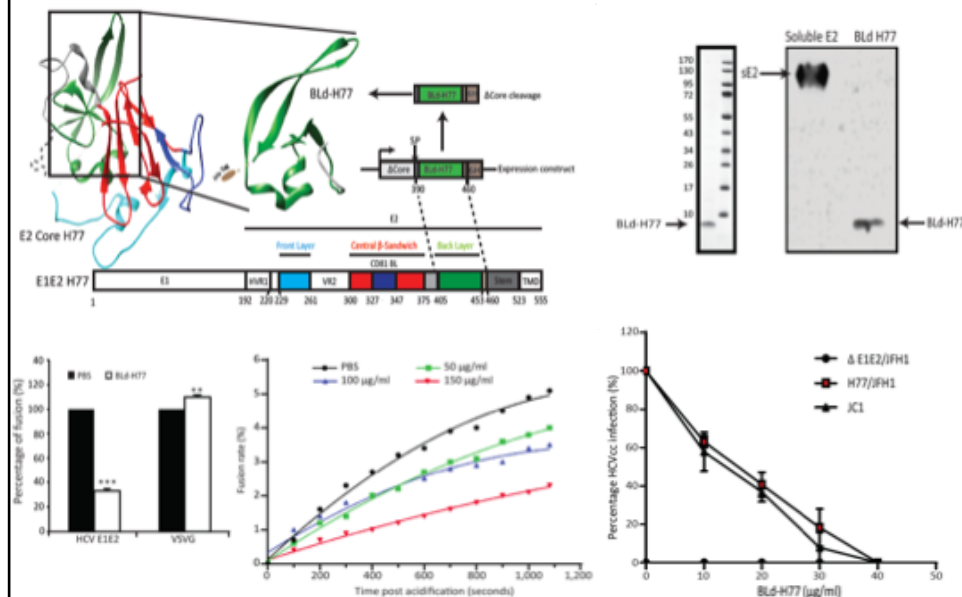
Douam et al. In press.

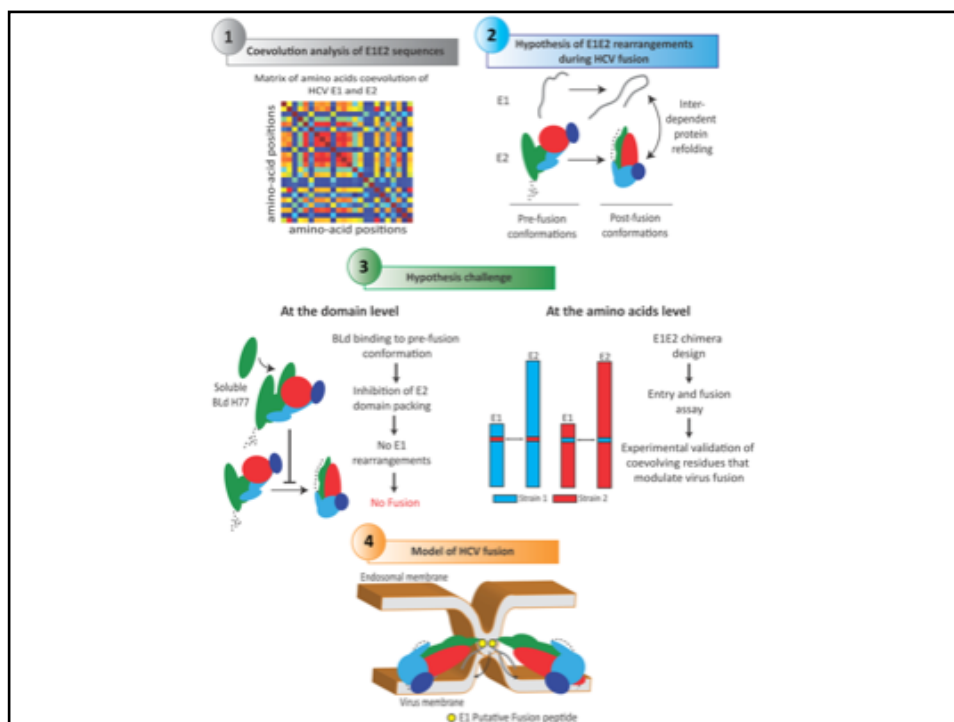
HCV fusion cluster support E1E2 interdependent rearrangements



Douam et al. In press.

Soluble BL inhibits HCV entry







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A protein coevolution method uncovers critical features of the Hepatitis C Virus fusion mechanism. Florian Douam, Floriane Fusil[#], Margot Enguehard[#], Linda Dib[#], Francesca Nadalin[#], Lo  c Schwaller[#], Gabriela Hrebikova, Jimmy Mancip, Laurent Mailly, Roland Montserret, Qiang Ding, Carine Maisse, Emilie Carlot, Ke Xu, Els Verhoeven, Thomas F. Baumert, Alexander Ploss, Alessandra Carbone[ ], Fran  ois-Lo  c Cosset[ ] and Dimitri Lavillette[ ]. 2018. *PLoS Pathogens*. In press.





