The physics of protein folding and of non–conventional drug design: attacking AIDS with its own weapons

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Life is exact reproduction and metabolic activity. The molecules of DNA are responsible for the first function, proteins for the second.

To become biologically active, for example form the active site needed for enzymatic action, proteins, which are produced as linear chains by the ribosomes, fold into unique three–dimensional structures (native conformation). To avoid aggregation or denaturation folding has to take place in very short times. Theoretical studies indicate that to do so proteins form, early in the folding process, few Local Elementary Structures (LES) as the result of the interaction between hydrophobic, strongly interacting, highly conserved (hot) amino acids. The docking of the LES gives rise to the post critical folding nucleus (FN). This event triggers the formation of the remaining native contacts shortly after. A consequence of these results is the fact that short peptides called p–LES, displaying the same amino acid sequence as that associated with the segments of the protein corresponding to LES, are highly specific and effective inhibitors of the folding. Furthermore, these non–conventional inhibitors unlikely will induce resistance in the organism expressing the protein as they attach to the protein through hot amino acids. They are thus particular suited to fight viruses and bacteria displaying a high degree of variability (mutations).

The p–LES strategy has been used in the design of a non–conventional inhibitor of the HIV–1–Protease, an enzyme which plays an essential role in the life cycle of the Immuno Deficiency Virus (HIV). Experimental data on infected cells testify to the fact that this non–conventional inhibitor prevents the maturation of the virus,
also in the case in which the cells are infected with a variant of the virus resistant to all conventional drugs (molecules which cup the active site) available in the market.

This promising lead for developing a drug against the virus which can cause AIDS is now entering the preclinical test stage and will eventually undergo those corresponding to the clinical phases sometimes next year.

In the present paper the physics which is at the basis of the design of a non-conventional HIV–1–Protease inhibitor is reviewed. It can be used as paradigm for designing folding inhibitors of other target proteins associated with the same or other pathogenic viruses or bacteria.
Figure 1: The HIV life cycle. The HIV enter a cell (bind to it and inject their genes into the interior), copy their genes and proteins (by coopting the cell’s machinery and raw material), and pack the fresh copies into new viral particles able to spread to and infect other cells. The viral components involved in any of those steps can serve as targets for drugs. In particular the protease involved in step 8 (blue pacman–like object, the mouth being the active site, see Fig. 2).
Figure 2: The HIV–1–Protease is a dimeric protein, formed by two identical chains. (left) A tube model representation of the three–dimensional native (folded) structure of the HIV–1–Protease in complexation with a traditional (active site centered) inhibitor (yellow). This enzyme is an homodimer, that is a protein formed by two identical polypeptide chains each (monomer) containing 99 amino acids. Also shown is a schematic pacman–like structure which relates to Fig. 1 (see step 8). Mutation of the HIV expressing the protease can induce changes in the shape of the active site (mouth of pacman) making the inhibitor non–effective, without much reducing the enzymatic activity. (right) The folding of the dimer takes place in three steps in which the first two correspond to the independent folding of the monomers and the third to the dimerization. In the figure a snapshot of a numerical simulation of the dimer in presence of 3 p–LES is given. The LES are indicated as thick coloured tubes, while the p-LES (non–conventional inhibitor) are highlighted in terms of segments of thin yellow tubes. p–LES prevent the monomers to form the folding nucleus and thus to reach the native conformation and form the active site.