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Simulation study of the mechanism of uptake of cell pentrating peptides in cancer cells

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It is somehow easy to understand why the mechanisms of cellular uptake of cell-penetrating peptides (CPP) is still so controversial. Although there is evidence that these peptides are capable of directly crossing the plasma membrane without any intermediate step, still several researchers claim that endocytosis is an intermediate step required for entry into the cells. It is well known that ionic interactions play a critical role for the binding to the plasma membrane and translocation of CPPs. A simulation of the interaction between arginine-glycine (RG)5 and histidine-glutamic acid (HE)5, as well as with DOPC of the lipid bilayer was conducted in order to calculate the free binding energy. The results supported the data obtained in the *in vitro* release, cell uptake and cytotoxicity studies. The absolute value of binding energy of (RG)5 with (HE)5 was the highest, however a decrease in the pH was found to diminish this strong bond. Interestingly, the conjugation of (RG)5 to PEG-PLA copolymer increased the binding energy to DOPC. In summary, the peptides tend to interact with the cell membrane which facilitates the uptake in an energy and receptor independent manner as postulated by many researchers.

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Economic implications of adopting high cost breakthrough technologies- PCSK9 inhibitors as a case study

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The proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) have shown a significant benefit in reducing the levels of low-density lipoprotein cholesterol and early evidence of improving patient outcomes by reducing the rate of major adverse cardiovascular events (MACE) compared to standard statin therapy. Based on these trials, the FDA approved two PCSK9i drugs for the treatment of hyperlipidemia. PCSK9i present an extraordinary challenge for healthcare payers. This is the first major case in which a specialty biologic drug is approved for a relatively common condition. The entire intended population for use according to the approved FDA indications is estimated at more than 9.3 million patients in the US. The annual budget needed to treat this population would be more than $130 billion. Performing a traditional cost-effectiveness analysis (CEA) using the current limited data is challenging and requires modeling and many assumptions. We therefore built a unique model with straightforward economic implications, based on the limited available data at present. The cost of preventing any one MACE would be $2,004,918 and the cost of preventing one death would be $8,777,518. These figures are one hundred fold higher than the cost of curing one Hepatitis C (HPC) patient with novel HPC drugs (~$84,000). If upcoming outcome trials will demonstrate similar rates of MACE prevention, it seems that at current prices, using these drugs to improve cardiovascular outcomes would not be affordable for many healthcare systems. The model developed could be relevant to any high cost breakthrough Technologies.

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