Rational identification of colorectal cancer homing peptides using phage display and *in silico* rigid-body docking studies of surface protein-ligand interactions

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Cancer is the second leading cause of death worldwide, counting for 14 million deaths annually. Colorectal cancer (CRC) is one of the most frequent types of cancer being the fourth leading cause of cancer death1. Research and development of new technologies for early stage diagnosis is increasing exponentially. However, the lack of specific cell targeting remains the main barrier for sensitive diagnostic tools. Therefore, peptide ligands that specifically recognize cell surface receptors have been extensively used in cancer research. Phage display emerged as a powerful tool to identify/recognize specific peptides and has been proved useful for the discovery of new biomarkers (i.e. membrane protein) 2. Molecular docking is widely used to predict peptide-protein interactions (pPI), in which rigid-body calculations positions a certain peptide in protein environment while maintaining its conformational position without changing the internal geometry. This method can be applied when conformational changes do not occur, or influence, the pPI interaction. This characterizes the intermolecular interactions between CRC recognized membrane receptors and peptides selected by phage display against RKO cells (human epithelial colon carcinoma). The high-affinity selected peptides were run on the MimoDB

database[3] to detect homology with previously described cancer-specific peptides. The CRC membrane proteins structures were obtained from Protein Data Bank (PDB) and when no structure was available high resolution modeling and function determination was obtained using I-TASSER[4]. Simulation of binding affinity was performed using interactive molecular docking tools, such as ZDOCK[5]. In detail, factors influencing the accuracy of the final structure (such as the docking scores and the interaction peptide-receptors proper conformations according to root mean square deviation), were evaluated. Our results reveal the potential of docking tools to serve as a platform to selectively predict CRC-specific peptides. We foresee that this methodology can be used in other related diseases leading to new diagnostic and therapeutic perspectives.