

# Cancer Therapeutics — Harnessing Integrin Inhibition Property of Modified Naturally Secreted Peptide

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Targeted peptide cancer therapies which are less toxic compared to synthetic chemotherapies, is a research field of growing interest. Cell surface receptors Integrin- $\alpha\text{v}\beta 3$  ( $\alpha\text{v}\beta 3$ ), which recognizes RGD motifs of ligands, is upregulated in endothelial cells and tumor cells. Ligand Fibronectin (FN) interacts with  $\alpha\text{v}\beta 3$  via its RGD (Arg-Gly-Asp) motif, promoting angiogenesis and tumor cell invasiveness.  $\alpha\text{v}\beta 3$  has been explored as a therapeutic target for years, but there hasn't been any FDA approved  $\alpha\text{v}\beta 3$  antagonist. Cyclic Lasso peptides are promising anti-cancer peptides with low toxicity/drug resistance, high stability and resistance to proteases. This study evaluates interaction of peptide secreted by E. coli, Microcin J25 (MccJ25) with  $\alpha\text{v}\beta 3$ . MccJ25 variant with RGD motif (MccJ25v; sequence: GGAGHVPEYFVRGDTPISFYG) is selected. Docking between selected active sites of  $\alpha\text{v}\beta 3$  with MccJ25v and FN monomer with RGD was performed on softwares HADDOCK/PyRx. Binding energies and scores in interactions of  $\alpha\text{v}\beta 3$  and MccJ25v were superior to interactions with FN. Next, MccJ25v was evaluated for: allergenicity, toxicity, angiogenesis, IL-4 induction, anti-cancer ability, and hemolysis. MccJ25v showed undesired induction of IL-4 and less anti-angiogenesis. To eliminate undesired effects, mutations were done and a novel mutation in MccJ25v (GGGGHHPEDFVRGDFPISFCK) with no undesired effects was selected. Repeat docking with mutated MccJ25v and  $\alpha\text{v}\beta 3$ , resulted in best binding with  $\alpha\text{v}\beta 3$  and involvement of majority of selected  $\alpha\text{v}\beta 3$  active sites as well as additional sites in interaction. Drug likeness of MccJ25v with novel mutation is acceptable. MccJ25v with novel mutation can inhibit  $\alpha\text{v}\beta 3$  function while competing with FN and can be developed as cancer therapy. Experimental evaluations are next steps to assay therapeutic effect of MccJ25v.

**Awards Won:**

