Modeling a Breast-Cancer Inhibiting Pharmacophore Based Upon the Activity of alpha-Fetoprotein

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Alpha-fetoprotein, AFP, is found in the blood or amniotic fluid of pregnant women. Though the function of AFP in relation to a fetus is not well understood,[1] segments of the protein between four and nine amino acids in size inhibit the growth of estrogen-dependent breast cancer cells[2]. We have worked to determine which behavior and structure aspects result in the most effective breast-cancer inhibition. The current goal of our research is to use what we know about effective inhibition to design a non-peptide mimetic to be used as a potential drug to treat breast cancer.

The inhibition of cancerous cell growth is a result of the antagonistic binding of a beta-turn conformation of a peptide to an unknown receptor site in cancer cells. A beta-turn consists of four consecutive amino acids[3] that form a loop in which the distance between the alpha-carbons belonging to the first and fourth amino acid residues is less than 7.00 Angstroms[4]. We were able to determine how often a particular peptide adopts a beta-turn conformation using Amber's ptraj program to find the distances between these two alpha-carbons over a simulation. The peptides that assume a beta-turn conformation for higher percentages of the time are generally more active in the inhibition of breast cancer cell growth.

Our conformational studies and analysis have led us to conclude that inhibitory activity of the peptide analogues is largely due to the characteristics of each residue as well as the percentage of time the peptide forms a beta-turn. We have been working on designing possible candidates for breast-cancer treatment based on our findings. We have been using computational methods to analyze potential drug candidates, such as cyclic depsipeptide analogues similar to the active AFP derivatives. By doing so, we can effectively predict whether or not the candidates are likely to be active against breast-cancer cell growth.

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