Computational Design of a Small Peptide that Inhibits Breast Cancer

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Breast cancer is the most common cancer diagnosed in woman and is the second leading cause of cancer death among women, closely following lung cancer.(*1*) Many breast cancer drugs, like tamoxifen, have limited long term efficacy and often have undesirable side effects, leading researchers to search for new breast cancer drugs.

Alpha-fetoprotein (AFP), an embryo specific serum alpha-globulin glycoprotein, is synthesized by the fetal yolk sac and circulates through the serum of pregnant women.(*2*) A growth-regulating hormone, AFP has the capacity to both stimulate and inhibit growth, although scientists remain uncertain of the exact pathways involved.(*3*) In the last several decades, clinical researchers have discovered the anti-estrogenic cancer properties of AFP.(*4*) A number of studies have since shown its effectiveness as a therapeutic agent to treat estrogen-dependent breast cancer, as well as its ability to prevent pre-malignant foci from developing into breast cancer.(*5*)

Researchers at Albany Medical College performed studies on AFP, parsing it down to a smaller peptide chain of 34 amino acids that retained the same anti-estrogenic activity as the original molecule.(*6*) Continuing research attempted to identify smaller subchains of the original AFP molecule that remained active, finding an 8-mer that they named P472-2.(*5*) Antiestrotrophic activity was then measured in a uterine mouse assay. The original AFP molecule, its 34 amino acid analogue, and P472-2 all showed comparable activity in prohibiting estradiol-induced growth in the uterus. P472-2 has been shown to inhibit estrogen-induced T47D breast cancer cells in culture as effectively as the original AFP molecule.(*5*)

Information about the pharmacophore has been previously obtained by substituting amino acids in P472-2.(*7*) Cyclic analogs nine amino acids long have been synthesized that also retain full activity. All efforts to create a peptide under eight residues resulted in the loss of anti-cancer activity. We have used Replica Exchange(*8, 9*) Molecular Dynamics techniques(*10*) to model selected active analogs of the linear and cyclic peptides to explore their conformational space. Our results reveal that the peptide's critical region is a four amino acid sequence that has a turn conformation. We present here a new lead compound that shows anti-cancer activity as measured in T47D breast cancer cells in culture and in animal assays (11-13).

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