OFFICIAL ABSTRACT and CERTIFICATION

Investigations into the Significance of Epidermal Fatty Acid Binding Protein (FABP5) in Breast Cancer Survival and Design of Novel FABP5 Inhibitors

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In the United States, 1 in 8 women will develop invasive breast cancer in their lifetime. By the end of 2019 alone, it is expected that approximately 300,000 new cases of invasive and in situ breast cancer will be reported. Epidermal Fatty Acid Binding Protein (FABP5), predominantly targeted for the alleviation of chronic pain, has recently been implicated in the proliferation of breast cancer. Specifically, it has been demonstrated that over expression of FABP5 is directly correlated to upregulation of Vascular Endothelial Growth Factor Receptors (VEGFR), which regulate tumor metastasis in breast cancer. Experiments were conducted to investigate the effects of competitive FABP5 inhibitors SB-FI-26 and SB-FI-103 on the survival rate of breast cancer cells, through an MTT assay. Both inhibitors demonstrated decreased cell viability at 72 hours (SB-FI-26 IC50 = 11.55 μM), with SB-FI-103 exhibiting enhanced potency (SB-FI-103 IC50 = 7.886 μM). Additionally, 138 novel FABP5 inhibitors were computationally designed using the known FABP5 inhibitor, 3-(2(4-benzylpiperidin-1-yl)-2-oxoethyl)-1-methyl- 1H-indole-2-carboxylate (SB-FI-31), as a scaffold. Following in silico analysis, three putative inhibitors were identified, demonstrating both sufficient solubility (cLogP 5.0) and free binding energy (< -9.0 kcal/mol). Furthermore, all three compounds exhibited canonical interactions with Arg 129 and Tyr 131, strictly conserved residues across all members of the FABP family. Results of this study established that inhibition of FABP5 is sufficient to prohibit cell growth in an MCF-7 breast cancer cell line, suggesting these inhibitors may serve as viable breast cancer therapeutics.

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