Evaluating the In Vitro Impact of FABP5 Inhibition on Bone Marrow Stromal Cells and Myeloma Cells

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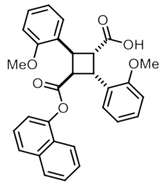
Introduction

Multiple myeloma (MM) is a hematologic malignancy caused by the uncontrolled proliferation of plasma cells, leading to bone destruction, anemia, renal dysfunction, and immunosuppression. While treatment advances have improved patient outcomes, relapse and drug resistance remain inevitable, underscoring the urgent need for novel therapeutic strategies.

Obesity is a known risk factor, which warranted us to research fatty acids and fatty acid binding proteins as potentially new treatment targets. Fatty acid binding proteins (FABPs) are a family of intracellular lipid carriers that regulate fatty acid transport and participate in pathways controlling cell proliferation and survival. Our lab has shown that FABP5 has been linked to more aggressive multiple myeloma, with higher expression correlating to poor prognosis.

Our previous work has demonstrated that pharmacologic inhibition of FABP5 can disrupt MM cell cycle progression. A first-generation FABP5 inhibitor showed efficacy in vitro against MM cells. More recently, second-generation inhibitors such as SBFI-102 and SBFI-103 have shown efficacy in therapy-resistant prostate cancer and obesity-driven hepatocellular carcinoma.



SBFI-102

Thus, we hypothesized FABP5 inhibitors like SBFI-102 and SBFI-103 would demonstrate efficacy in MM.

Methods

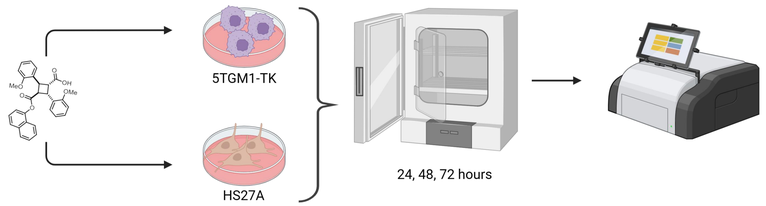
5TGM1-TK, a mouse myeloma cell line was used to determine the efficacy of the second generation FABP5 inhibitor, SBFI-102, on tumor growth, while HS27A, a human bone marrow stromal (BMS) cell line, for toxicity of SBFI-102 on normal bone marrow cells.

Cells were seeded into 96-well plates at a density of 50,000 cells per well in 2% FBS in RPMI-1640. HS27A human bone marrow stromal cells were allowed to adhere for 48 hours prior to treatment.

The FABP5 inhibitor SBFI-102 was prepared via serial dilutions in serum-free RPMI-1640 to generate concentrations ranging from 0 to 100 µM. Cells were treated with 50 µL of drug-containing media per well, with two negative control columns containing no drug.

Cell viability was assessed using the RealTime-Glo luminescence assay (Promega). Reagents were prepared at 2X concentration and 50 µL of the reagent mixture was added to each well. Luminescence was measured at 24, 48, and 72 hours with plates returned to the incubator between readings to maintain conditions.

IC_{50} values were calculated for each cell line at 24, 48, and 72 hours. Statistical analysis was performed using two-way ANOVA to compare the effects of SBFI-102 on myeloma cells versus BMS cells at selected concentrations and time points.



Results

	5TGM1-TK	HS27A
24 hours	31.53 µM	81.54 µM
48 hours	18.48 µM	38.20 µM
72 hours	14.65 µM	24.21 µM

Table 1. IC_{50} values of SBFI-102 in 5TGM1-TK and HS27A cells. The cells were treated at serial concentrations for 24, 48, and 72 hours. Myeloma cells exhibited consistently lower IC_{50} values, indicating greater sensitivity to FABP5 inhibition.

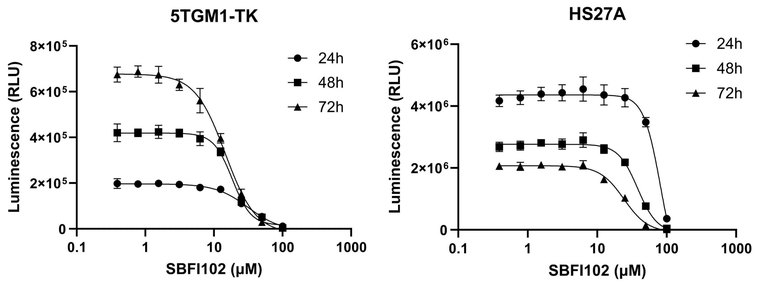


Figure 1. Cytotoxicity (Dose-response curves) of SBFI-102 in 5TGM1-TK and HS27A cells. The cells were treated with increased concentrations of SBFI-102 (*n* = 4 biologically independent samples) at indicated time points. 5TGM1-TK cells demonstrated reduced viability at lower concentrations compared to stromal cells.

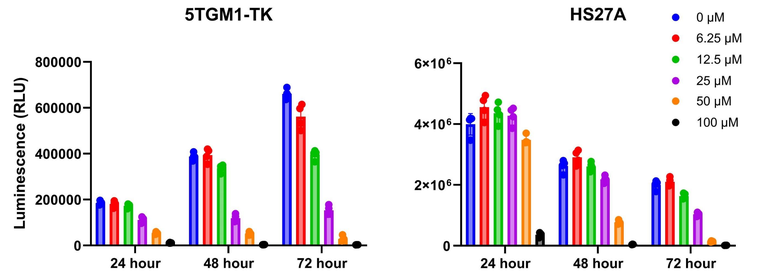


Figure 2. SBFI-102 suppresses cell viability in a dose- and time- dependent manner in MM cells. The cells were treated with indicated concentrations of SBFI-102 (*n* = 4 biologically independent samples). Luminescence readings were over 24, 48, and 72 hours following SBFI-102 treatment. Data is presented as mean ±SD. Myeloma cells showed a marked decrease in viability with increasing concentration and time, while stromal cells remained less affected. Concentrations ranged from 0 µM to 100 µM.

Results

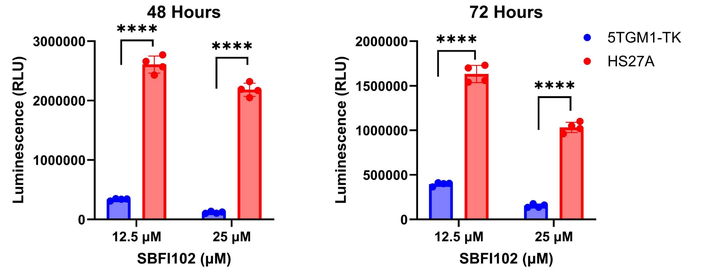


Figure 3. Cytotoxicity of SBFI-102 increases significantly in MM cells in comparison with BMS cells. The cells were treated with indicated concentrations of SBFI-102 at the indicated time points (*n* = 4 biologically independent samples). Comparison of cell viability of 5TGM1-TK myeloma cells with HS27A stromal cells was conducted using GraphPad Prism 10.1.10. Data is presented as mean ±SD (**** P< 0.0001).

Conclusion

SBFI-102 exhibited more effectiveness against 5TGM1-TK multiple myeloma cells over HS27A bone marrow stromal cells, reflected by the consistently lower IC_{50} values in the myeloma cells. These results highlight FABP5 inhibition as a promising therapeutic strategy in multiple myeloma while minimizing effects to the bone marrow microenvironment. Further research is needed to determine the efficacy and safety in vivo before being used clinically in humans with multiple myeloma.

References and Acknowledgements

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