Secreted Frizzled-Related Protein 3 (sFRP3) Inhibition as a Target for Chemotherapy-induced Cognitive Impairment Treatment

Audrey Chodkiewicz[1], Euiyeon Lee[2,3], Sang Hoon Kim[2,3], Mi-Hyeon Jang[2,3]

[1]Department of Biomedical Sciences, Quinnipiac University, Hamden, Connecticut, United States; [2]Department of Neurosurgery, Robert Wood Johnson Medical School, Rutgers University, Piscataway, New Jersey, United States; [3]Brain Health Institute, Rutgers University, Piscataway, New Jersey, United States.

Background: Despite advances in cancer treatment, quality of life after chemotherapy is a major concern for both adult and pediatric survivors. Chemotherapy-induced cognitive impairment (CICI), or "chemobrain," is characterized by cognitive dysfunction caused by the neurotoxic effects of chemotherapy. Currently, no approved treatment addresses the underlying neuronal injury. Previous studies from the Jang Lab found that secreted frizzled-related protein 3 (sFRP3), a naturally secreted Wnt/β-catenin inhibitor, showed increased expression after chemotherapy, which impaired neuronal development and cognitive function. AI-based modeling and bioinformatics identified blood-brain barrier-permeable candidate sFRP3 inhibitors. This study aimed to identify candidate compounds that reverse sFRP3-mediated suppression of Wnt/β-catenin signaling as a potential therapy for CICI.

Methods: To test this, a stable HEK293T TCF/LEF reporter cell line was developed by lentiviral transduction for measuring canonical Wnt/β-catenin activity. Six candidate compounds were screened with a TCF/LEF reporter assay. Wnt/β-catenin pathway downstream activation was assessed through RT-qPCR analysis of *AXIN2* expression and Western blot analysis of active β-catenin.

Results: Four of the six screened compounds increased canonical Wnt/β-catenin pathway activation, confirmed through RT-qPCR showing statistically significant increases in *AXIN2* expression. Western blot analysis showed increased active β-catenin levels following treatment with ABC99 and Yoda1.

Conclusion: Findings supported that ABC99 and Yoda1 may enhance Wnt/β-catenin signaling, making them promising candidates. However, ABC99 may preserve Wnt activity through NOTUM inhibition, and Yoda1 may activate β-catenin through PIEZO1-mediated signaling. Further studies using an sFRP3-overexpression model are needed to determine whether these compounds specifically counteract sFRP3-mediated suppression of Wnt/β-catenin signaling and to confirm their therapeutic potential for chemobrain. Supported by NIH R25ES020721.