

Year III: Development of *M. mercenaria* Neoplastic Hemocytes as a Novel Alternative Experimental Model for BCL-2 Interactions in Blood Cancers: An Application for Targeted Drug Studies

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Anti-apoptotic B-cell leukemia/lymphoma (Bcl-2) proteins are overexpressed in around half of human cancers, linked to tumorigenesis, chemotherapy resistance, and poor prognosis. Effectively modeling this complex molecular interaction is essential for its progression as a therapeutic target, yet the costliness and time-intensive nature of current models limit study. However, disseminated neoplasia (DN), a transmissible cancer naturally occurring in the hemocyte "blood" cells of bivalve mollusks, shares notable similarities to human leukemia. To develop *M. mercenaria* as an effective model, this study examined neoplasia transmission between bivalves. Cohabitation yielded increased tumor cell fraction in healthy clams after 3 months. Exposure to hypoxic conditions promoted DN progression after 7 days, and cancer cell inoculation elevated transmission in healthy clams ($p=0.0409$). Excess lipid accumulation in tissue was characterized as a new potential DN biomarker, aiding in future disease identification. *M. mercenaria* were evaluated for functional similarities between human and bivalve Bcl-2 after exposure to inhibitors at varying concentrations. Significant changes ($p=0.0209$) in relative protein expression were observed in SDS-PAGE, suggesting Bcl-2 inhibitors downregulate Bcl-2 expression in *M. mercenaria*. Clams treated with concentrations >0.3 mg/kg maintained suppressed tumor progression in the months following exposure. Results show promise for *M. mercenaria* as naturally occurring in vivo cancer models for Bcl-2 interactions, with analogous biomarkers and physiological responses identified. Applications include high-throughput drug screening, minimizing vertebrate testing, and reducing cost per specimen >50 -fold for early novel drug candidate screening.

Awards Won:

Third Award of \$1,200