Retinoblastoma (RB) is an intraocular malignancy of early childhood. Although enucleation has led to successful outcomes in RB, there is recent emphasis on chemotherapy to preserve the affected eye(s) and visual function. Regardless of the initial therapy, RB patients undergo a lifetime of follow-up evaluations and must remain vigilant about the potential for RB tumor progression, recurrence or secondary tumors. My laboratory was the first to report on subpopulations of retinoblastoma cells with stem cell properties, including the expression of ABCG2, a calcium-sensitive cell surface protein that confers resistance to over 20 different chemotherapeutic agents. In this presentation, I will discuss our studies of retinoblastoma in terms of stem cell markers, neuronal differentiation potential, as well as a novel targeted antibody-drug conjugate therapy that we have designed to overcome chemoresistance in RB.