Identification of Potential Therapeutic Perturbagens for CNS-Metastatic Retinoblastoma Using In Silico Analysis of RB1 Gene Signatures

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Background: Germline retinoblastoma is a malignant retinal tumor, classically presenting bilaterally in infants with leukocoria, strabismus, and visual impairment due to an autosomal dominant RB1 mutation. Despite advances in intraocular treatments, effective drugs treating retinoblastoma metastasized to the central nervous system (CNS) remain limited (1).

Objective: This *in silico* study aims to identify novel retinoblastoma perturbagens that may reverse the molecular effects of germline retinoblastoma with metastasis to the CNS. Methods The Kaleidoscope data exploration tool identified knockdown (KD) and overexpression (OE) iLINCS signatures for the RB1 gene. KD signatures were processed through Sig2Lead to find drug candidates with significantly positive or negative concordance. Candidates with the most negative concordance with RB1 KD signatures were further evaluated for their ability to penetrate the blood-brain barrier (BBB).

Results: Kaleidoscope identified 12 RB1 KD iLINCS signatures and one OE signature. Sig2Lead revealed three top candidates that consistently reversed all 12 KD signatures: galantamine (concordance = -0.355), AZD-1775 (-0.343), and amuvatinib (-0.337). While carboplatin, vincristine, and etoposide are standard treatments, only vincristine (-0.333) and etoposide (-0.306) showed effectiveness in reversing KD signatures, with vincristine reversing four and etoposide reversing seven signatures.

Conclusion: Carboplatin does cross the BBB, but it was not found to reverse any RB1 KD signatures (3). Meanwhile, vincristine and etoposide were effective in reversing KD signatures, but both have limited BBB permeability (4). The acetylcholine esterase inhibitor galantamine does cross the BBB and is

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currently being investigated as a treatment of visual deficits in neurotrauma, making it a strong candidate for treatment of retinoblastoma with CNS involvement (5). Additionally, AZD-1775 can penetrate the CNS and is being studied as a treatment of p53-deficient tumors when combined with carboplatin (6-7). Future studies should investigate the efficacy of galantamine and AZD-1775 paired with carboplatin as potential therapeutic agents for CNS-metastatic retinoblastoma.

Keywords: Retinoblastoma, Oncology, Metastatic Cancer, Pharmacotherapy, Potential Drugs, RB1, Genetics

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