00502 Evaluating Personalized Treatment Modalities Stratified According to XIAP Status in Neuroblastoma

Choo Zhang'E[1], Loh Hong Pheng Amos[2], Sarit Larisch[3], Chen Zhi Xiong[4]

[1]Nanyang Technological University, [2]KK Women's & Children's Hospital, [3]University of Haifa, [4]National University of Singapore

Aims: Aberrant developmental apoptosis is implicated in pediatric nervous system tumors such as neuroblastoma (NB). Despite clinical advances and the presence of intensive multimodal therapies, the prognosis for advanced-stage and metastatic neuroblastomas remains poor in Asia. Intact apoptosis pathways protect cells against neoplastic transformation and provide mechanisms by which cytotoxic agents exert their effects. Therefore, modulating key regulator of intrinsic apoptosis such as the Inhibitors of Apoptosis (IAP) family, is particularly attractive as it bypasses upstream signalling pathways that may be impaired by resistance, and focused on target initiator and effector caspases. Hence, this study sought to evaluate the effectiveness and therapeutic value of several preclinical and clinical IAP inhibitors – BV6, LCL161, Debio 1143, CUDC-427, A4 and B3, as personalized treatment modalities in neuroblastoma.

Methodology: Cell viability post-treatment with IAP inhibitors were evaluated. The expressions of IAPs, particularly XIAP and cIAP1, were determined via Western Blot.

Result: A panel of NB cell lines were tested with IAP inhibitors. NB cell lines were found to display differential sensitivity to each inhibitor. In particular, A4 and B3, in contrary to other IAP inhibitors, were shown to have the most efficacious effect even on the most resistant NB cell line and are most tolerable in normal tissue-derived cell line. This may be attributed to the specific degradation of XIAP by A4 and B3 compared to other IAP inhibitors. Furthermore, these IAP inhibitors also act synergistically when used in combination with cytotoxic agents such as vincristine and topotecan.

Conclusion: Our findings suggest XIAP inhibition to be of significant therapeutic value either alone or in combination with cytotoxic agents. Further investigation is required to confirm the role of XIAP degradation in neuroblastoma suppression as well as to validate these results in vivo. Understanding this pathway implicated in neuroblastoma may present a new opportunity for treatment of resistant neuroblastoma.