CK2 inhibition as a promising treatment for chemotherapy resistant pancreatic ductal adenocarcinoma

Diana Schuhmacher[1,2], Aji Istadi[1,2], Beatrice Zema[1], Danni Upton[1,2], Deanna Miller[1,2], Emer Cahill[1], Henry Barraclough-Franks[1], Inna Navarro[1], Johana Luhur[1,2], Silvia Lombardi[1], Yasir Mahmood[1], Diego Chacon Fajardo[1,2], Thomas Cox[1,2], Roger Daly[3], Marina Pajic[1,2]

[1] The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Sydney, New South Wales

[2] School of Clinical Medicine, Faculty of Medicine and Health, UNSW Sydney, Australia

[3]Department of Biochemistry and Molecular Biology, Monash Biomedicine Discovery Institute, Monash University, Clayton, Victoria

Introduction: Pancreatic cancer (PC) will become the 2nd most common cause of cancer-related death by 2030, with a 12.5% five-year survival rate. Inadequate early detection methods mean most PC patients are diagnosed with advanced/metastatic disease. Many patients develop resistance to the current chemotherapies, and while immunotherapy is promising in other cancers, the immune "cold" tumour microenvironment of PC results in a high resistance to immunotherapy[1,2]. Thus, understanding the mechanisms that drive therapy resistance and, how to circumvent them, is an important step in improving PC treatment. Serine/threonine kinase CK2 is a regulator of numerous signalling pathways and cellular functions and is upregulated in many cancers including chemotherapy-resistant PC[3,4]. CK2 inhibition upregulates immune response in PC murine models and increases cancer cell sensitivity to chemotherapy by inhibiting DNA damage repair pathways[5,6].

Methods: Using the CK2-selective inhibitor CX-4945/Silmitasertib, and well-defined models of PC validated in our laboratory, we will investigate CK2 inhibition impact on tumorigenesis, metastasis, chemoresistance, and immune infiltration.

Results: *In vitro* we observe varied sensitivity to CK2 inhibition across patient-derived cell lines, while CK2 subcellular localisation ranged across a microarray of patient-derived xenografts between cytoplasmic, nuclear, and endosomal compartments. Examination of chemoresistant tumours revealed an increase in nuclear CK2; nuclear accumulation of CK2 is a predictor of poor prognosis[7]. *In vivo* investigation of CX-4945/Silmitasertib treatment in combination with chemotherapy is ongoing.

Conclusion: We hypothesise that CK2 inhibition will reduce metastasis and improve survival in PC models by sensitising cells to clinically used chemotherapies and promoting activation of the existing immune system.

1. Bear, A. S., Vonderheide, R. H. & O'Hara, M. H. *Cancer Cell* 38, 788-802, doi:https://doi.org/10.1016/j.ccell.2020.08.004 (2020).

2. Parkin, A. et al. *Diseases* **6**, doi:10.3390/diseases6040103 (2018).

3. Kreutzer, J. N., Ruzzene, M. & Guerra, B. *BMC Cancer* 10, 440, doi:10.1186/1471-2407-10-440 (2010).

CK2 inhibition as a promising treatment for chemotherapy resistant pancreatic ductal adenocarcinoma

4. Liu, Z.-D. et al. *Cancer Letters* 585, doi:10.1016/j.canlet.2024.216640 (2024).
5. Nelson, N. et al. *PLoS One* 12, e0170197, doi:10.1371/journal.pone.0170197 (2017).
6. Siddiqui-Jain, A. et al. *Mol Cancer Ther* 11, 994-1005, doi:10.1158/1535-7163.MCT-11-0613 (2012).
7. Homma, M. K. et al. *Cancer Sci* 112, 619-628, doi:10.1111/cas.14728 (2021).