Modelling resistance and sensitivity to PRRT.

Kelly Waldeck (1), Jessica Van Zuylekom (1), Benjamin Blyth (1, 2), Carleen Cullinane (1, 2), Andrew Pattison (3), Aidan Flynn (3), Richard Tothill (3), Rodney J. Hicks (1, 2, 4).
(1) Molecular Imaging and Targeted Therapeutics Laboratory, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia, (2) Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia, (3) Department of Clinical Pathology and Centre for Cancer Research, University of Melbourne, Melbourne, Victoria, Australia, (4) Division of Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia.

ABSTRACT
The development of resistance is a common reason for therapy failure, and ways to overcome resistance a significant area of continual research. Peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumours (NET) is now routine, however cures remain rare, as some NET patients are inherently resistant to PRRT, while most develop resistance after initial success. We hypothesise that resistance to PRRT (here using LuTATE) is a manifestation of a general radiation resistance phenotype, mediated through enhanced recognition and repair of radionuclide-induced DNA damage, rather than loss of the PRRT target (in this case, the somatostatin receptor type 2 (SSTR2). To examine this we have established PRRT-resistant cell lines by passaging the SSTR2 expressing cell lines AR42J, H1299-7 and H69 as xenografts, and repeatedly challenging the tumours with 30 MBq LuTATE. Tumours that eventually became unresponsive to LuTATE treatment were then established as resistant cell lines in vitro and analysed using single cell RNAseq. Markers of response to LuTATE and SSTR2 expression were assessed in resistant tumours by immunohistochemistry. In addition to this, we have undertaken an unbiased genome-wide CRISPR-knockout screen within the H1299-7 cell line, which will identify genes that modify sensitivity to LuTATE treatment. Preliminary analyses of these models show that whilst the induction of DNA damage is unchanged in the resistant lines by gamma H2Ax staining, there is a role for the DNA damage repair pathways in the resolution of the PRRT-induced DNA breaks thereby mediating sensitivity to PRRT. The results of our pre-clinical analyses will further the development of new drug combinations with PRRT, in order to improve responses and hopefully overcome resistance to PRRT, in patients with advanced neuroendocrine tumours.

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The development of resistance is a common reason for therapy failure, and ways to overcome resistance a significant area of continual research. The use of Peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumours (NET) is now routine, however cures remain rare, as some NET patients are inherently resistant to PRRT, while most develop resistance after initial success. To understand this resistance we are taking a range of approaches to try to understand how resistance happens and what we can do to make the treatment more effective. In the laboratory, we have established a range of neuroendocrine cancer cells that show different responses to PRRT treatment, and we are analysing the genomic differences that these cells have from the original cells they are derived from. We are looking for genes that impact the cancer cells' sensitivity to PRRT. Combining the results of these different techniques will help us learn about the ways cancer cells become resistant to PRRT, and provide insight in to ways that we can develop different drug combinations to improve responses to the radiotherapy, and therefore improve outcomes for patients with NET.