Systematic Evaluation of the Immune Microenvironment of Neuroendocrine Tumours (NET)

C. Vesely[1], A. Childs[1,2], Y. N. S. Wong[1, 3], O. Ogunbiyi[2], A. Gander[2], T. Luong[2], C. Thirlwell[1,2], M. Caplin[2], K. Peggs[1,3], T. Marafioti[1], S. A. Quezada[1,3], T. Meyer[1,2]

[1]UCL Cancer Institute, UCL, London, UK. [2]Royal Free Hospital, Pond Street, London, UK. [3] Cancer Immunology Unit, Research Department of Haematology, UCL Cancer Institute, UCL, London, UK.

Background: Immunotherapy is being explored in many tumour types with encouraging results, but its role in the management of NET is yet to be defined. Here we characterise the immune landscape of NET in order to inform a rational approach for immunotherapy in this patient group.

Methods: Peripheral blood and fresh tissue (tumour and normal) were collected from consenting patients undergoing surgical resection for midgut NET. Multicolour flow-cytometry was performed to determine the abundance of CD8+, CD4+FoxP3- effector (CD4eff) and CD4+FoxP3+ regulatory (Treg) T cell subsets, and the expression of co-inhibitory and co-stimulatory checkpoint molecules. Matched tissue was obtained for immunohistochemistry (IHC) to investigate the geographical distribution of the immune infiltrate.

Results: Samples from 31 midgut NET patients (20:G1 and 11:G2) were analysed. Overall, the tumours contained a higher proportion of Tregs compared with matched normal tissue, with an effector (CD8+ and CD4eff) to Treg ratio of 18 and 24 respectively (P=0.0004). The co-inhibitory molecules CTLA-4, PD-1, and TIM-3 showed highest expression on Tregs, and co-stimulatory molecules, including ICOS, 41BB and OX-40, were also highest on Tregs. IHC demonstrated that the majority of tumours had <5% intratumoural CD4+ and CD8+ T cells compared with 16% in peri-tumoural tissue.

Conclusion: These results provide a novel insight into the immune landscape of NET. Checkpoint molecules, such as CTLA-4 and PD-1, are potential targets in this tumour type but the extent of tumour infiltration by lymphocytes is limited. Further work will investigate the reasons for poor lymphocyte infiltration and define interventions by which this might be abrogated.