their immunogenicity and promoted their rapid translocation to draining lymph nodes, resulting in robust and long-lasting humoral responses.¹ On these bases, we investigated the potentiality of HA-based technology in the design of cancer vaccines. To this aim, HA was conjugated to the extracellular domain of rat HER2/neu (rHER2/neu) and validated in the preventive and therapeutic vaccination settings.

Materials and Methods Female BALB/c or BALB-neuT mice were immunized with rHER2/neu-HA. In vivo depletion of CD4⁺, CD8⁺ T and B cells was performed, and sera and spleens were collected to characterized antigen-specific humoral and cellular responses. Vaccinated BALB/c mice were challenged and re-challenged with rHER2/neu-overexpressing TUBO cells to assess the protective or therapeutic activity of rHER2/neu-HA vaccination strategy, as well as immunological memory.

Results HA performed efficiently as robust and long-lasting humoral (IgG1, IgG2a, and IgG2b) and cellular responses were detected using very low antigen doses and number of boosters. Outstandingly, at 1-year post-vaccination, anti-rHER2/neu specific antibodies showed even improved effector functions (maturation of affinity for the receptor and increased complement-derived cytotoxicity functions). HA vaccination turned out effective in both the prophylactic (100% mice survived) and therapeutic (tumor regression in 2/12 mice) settings, and broke tolerance against rHER2/neu, delaying spontaneous tumor growth in BALB-neuT mice. Both humoral and cellular responses contributed to the success of HA-based vaccination, but CD8⁺ T cells played only a marginal role.

Conclusions Cancer vaccines have not yet achieved significant clinical efficacy due to their poor immunogenicity, and the validation of more effective adjuvants occurred sometimes at the expense of safety. HA combines the unique immunomodulatory features of a TLR agonist with the tolerability of a fully natural polymer, proving to be a promising adjuvant for the creation of effective and safe cancer vaccines with the potential for rapid clinical translation.

REFERENCES

1. Dalla Pietà A, Carpanese D, *et al.* Hyaluronan is a natural and effective immunological adjuvant for protein-based vaccines. *Cell Mol Immunol* 2021;**18**(5):1197–1210.
2. Rosato A, Montagner IM, Carpanese D, Dalla Pietà A. Hyaluronic acid as a natural adjuvant for protein and peptide-based vaccines. 30.04.2020. WO/2020/084558, PCT/IB2019/059122.

Disclosure Information D. Carpanese: None. I. Montagner: None. A. Dalla Pietà: None. V. Rossi: None. A. Penna: None. G. Zuccolotto: None. G. Pasut: None. A. Grigoletto: None. A. Rosato: None.

P09.04

IMPACT OF MAJOR ONCOLOGIC SURGERY ON IMMUNE RESPONSES IN THE IMMEDIATE POST-OPERATIVE SETTING IN OESOPHAGEAL ADENOCARCINOMA PATIENTS; A GUIDE TO HARNESSING THE DOUBLE-EDGED SWORD OF CANCER SURGERY

NE Donlon*, M Davern, A Sheppard, F O'Connell, S Ramjit, C Hayes, M Mc Clean, H Temperley, C Butler, N Ravi, C Donohoe, J O' Sullivan, MR Dunne, JV Reynolds, J Lysaght. *St James's Hospital, Dublin, Ireland*

10.1136/jitc-2021-ITOC8.54

Background Immune checkpoint inhibitors (ICIs) are being investigated for their role as an adjunct in the multimodal treatment of oesophageal adenocarcinoma (OAC). The most appropriate time to incorporate ICIs remains unknown. Our study profiles systemic anti-tumour immunity perioperatively to help inform the optimal timing of ICIs into current standards of care for OAC patients.

Methods Systemic immunity in 11 OAC patients was phenotyped prior to oesophagectomy and on post-operative days (POD) 0, 1, 3, 7 and week 6 using flow cytometry. Longitudinal serological profiling was conducted by 54-plex-ELISA. The frequency of circulating lymphocytes, T cells, T helper cells and cytotoxic T lymphocytes was profiled longitudinally. The activation status of T cells was also assessed using CD69, CD27, CD62L and CD45RA as well as the proportion of T cell subsets in circulation, which included: naïve, central memory, effector memory and terminally differentiated effector memory T cells. This study also profiled the longitudinal alteration of immune checkpoint expression on circulating T cells, which included: PD-1, CTLA-4, TIGIT, TIM-3, LAG-3, PD-L1 and PD-L2. Damage-associated molecular patterns (calreticulin, HMGB1 and MIC-A/B) were also assessed.

Results The frequency of naïve T cells increased in circulation post-oesophagectomy from POD-0 to POD-7 ($p<0.01$) but returned to baseline at week 6. Effector memory T cells had decreased by POD7 but increased substantially by week 6 ($p<0.05$). A steady increase in activated circulating CD27⁺ T cells was observed from POD-0 to POD-7 ($p<0.05$). The percentage of PD-1⁺ and CTLA-4⁺ T cells peaked on POD-1 and was substantially decreased by week 6 ($p<0.01$). Th1 cytokines were decreased in the immediate post-operative setting with a reduction in IFN- γ , IL-12p40, CD28, CD40L and TNF Alpha. In addition to this IP-10 aka cxcl-10 which is an important chemokine ligand in recruiting anti-tumour TH1 cells and polarising the immune response to a Th1 phenotype is significantly reduced perioperatively. There is a simultaneous increase in Th2 cytokines in the immediate post-operative setting with a significant increase in IL4, IL10, IL16, IL1RA and MCP1 before returning to preoperative levels at week 6.

Conclusion Our study highlights the prevailing immunophenotype and responses to surgery with a switch in balance towards a Th2 and potentially M2 phenotype and consequently, an immunosuppressive milieu. Therefore, orchestrating M2 reprogramming toward an M1 phenotype and similarly shifting the balance in favour of a Th1 phenotype would offer a potent therapeutic approach for augmenting tumorigenesis and promoting cancer regression. Consequently, this study paves the way for further studies and appropriate trial design are needed to interrogate the use of ICB as a trimodal approach with chemoradiotherapy and chemotherapy alone for locally advanced disease in the neo-adjuvant and adjuvant setting to determine the optimal timing and subset of patients for their use in the era of precision targeted therapies.

Disclosure Information N.E. Donlon: None. M. Davern: None. A. Sheppard: None. F. O'Connell: None. S. Ramjit: None. C. Hayes: None. M. Mc Clean: None. H. Temperley: None. C. Butler: None. N. Ravi: None. C. Donohoe: None. J. O' Sullivan: None. M.R. Dunne: None. J.V. Reynolds: None. J. Lysaght: None.