EVALUATING THE SURVIVAL OUTCOMES OF AN ANTI-ISOASPELAVL4 RESPONSE IN A SMALL CELL LUNG CANCER MOUSE MODEL

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Background Small cell lung cancer (SCLC) has a 95% mortality rate and a 5-year survival of 8%, resulting in the death of over 20,000 Americans each year. There has been marginal improvement in therapy over the past 30 years, with the recent addition of immune checkpoint inhibition therapy to standard chemotherapy (platin-based + etoposide) modestly increasing overall SCLC patient survival from 10.3 to 12.3 months. This highlights the need for additional SCLC therapies. Previous studies have identified a subset of SCLC patients (10–20%) exhibiting a naturally occurring immune response originally called ‘anti-Hu’.

Methods Here we used the Trp53fl/fl; Rb1fl/fl inducible SCLC mouse model to examine 1) whether immunization with isoAspELAVL4 following complete response to therapy and improved survival. Previous work identified the anti-HuD antigen to be ELAVL4. The Offringa lab and collaborators determined that the antigenic epitope consists of isoaspartylated ELAVL4 (isoAspELAVL4). The protein carries isoaspartylated residues in the N-terminal region (amino acids 1–36). Anti-Hu-positive SCLC patient serum samples reacted with isoAspELAVL4, and SCLC tissue samples stained positive for isoAspELAVL4.

Methods Here we used the Trp53fl/fl; Rb1fl/fl inducible SCLC mouse model to examine 1) whether immunization with isoAspELAVL4 prior to SCLC induction is protective, and 2) whether immunization with isoAspELAVL4 following completion of 3 rounds of cisplatin+etoposide therapy increases survival. In both cases, mice were immunized with recombinant N-terminal fragment of ELAVL4 (amino acids 1–117) generated in Clear Coli and incubated under isoaspartyl-inducing conditions, emulsified in incomplete Freund’s adjuvant (IFA) or control (phosphate-buffered saline in IFA). The trajectories of mice were monitored with a detailed body metric score (Paster score) and blood draw every 2 weeks to monitor the anti-ELAVL4 antibody response.

Results Just as in human SCLC patients, we find spontaneous anti-ELAVL4 reactivity in ~15% of control animals. We are in the process of analyzing longitudinal blood samples, Paster scores and survival of the treated and control animals and will present Kaplan-Meier analyses for the two experimental arms.

Conclusions The study will provide insight into interplay between SCLC and the immune response to isoAspELAVL4.

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