Background The translational pipeline for novel immunotherapeutics is often stymied due to the lack of relevant immune-competent pre-clinical animal models, which can facilitate the path to human clinical trials. Our group has developed a novel tumor-specific mRNA-vaccine and nano-liposome platform capable of delivering increased mRNA payload and inducing antigen-specific immunity. In order to assist clinical translation, we investigated the feasibility, anti-tumor activity, and immunogenicity of therapeutic personalized RNA-nanovaccines in head and neck cancer pre-clinical murine models and client-owned felines with spontaneously occurring oral cancer.

Methods 1) C57B/6 mice were injected with syngeneic mouse oral cancer cell lines MOC1 or MOC2 orthotopically (tongue) or subcutaneously (flank). Mice were treated with tumor-derived mRNA nano-vaccines intravenously weekly, x3 weeks. Tumor volumes and survival was recorded. Immune cell infiltration of tumors and spleens were analyzed using flow cytometry. 2) A client-owned feline clinical trial was initiated (UF College of Veterinary Medicine, protocol #IACUC202200000077) to treat pet cats with spontaneously occurring oral squamous cell carcinoma. Tumor biopsies were obtained from enrolled felines (N=4), and tumor-specific mRNA-nano-vaccines were generated from the surgical specimen. The felines were administered three cycles of biweekly vaccines administered intravenously. The cats were monitored for adverse events and followed for clinical outcomes. Flow cytometry was performed to evaluate immune responses.

Results 1) Mice treated with tumor-derived mRNA-nanovaccines had significantly decreased tumor volumes compared with controls in both MOC1 and the more aggressive MOC2 cell lines (p<0.001). Orthotopic models for MOC1 tumors were more responsive to RNA nano-vaccine administration than subcutaneous (flank) models. Treatment response was characterized by intra-tumoral and systemic activated CD4+ (p=0.027) and CD8+ (0.041) T-cell infiltration as well as decreased intra-tumoral immunosuppressive myeloid cell infiltration compared to controls. 2) Feline subjects (N=4) experienced no toxicities or adverse events. Profound CD8+ and CD4+ T cell activation was noted in blood following vaccine administration (4h). There was significant survival benefit with 0/6 untreated felines surviving, while 3/4 of the treated pets are living with either stable or undetectable disease.

Conclusions Personalized RNA-nanovaccines are effective and safe in preclinical murine and feline models of oral cancer demonstrating safety in a large animal study and immune activity. This agent is currently in clinical trials for human brain cancer (NCT04573140). Data from studies in both large and small preclinical models will inform our human clinical trial design for head and neck cancer patients with recurrent/metastatic disease.

REFERENCES