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Pre-clinical studies evaluating the safety and efficacy of a recombinant Listeria expressing HER2/neu in dogs with spontaneous HER2+ bone cancer

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HER2/neu is a membrane bound receptor tyrosine kinase belonging to the erbB family. ErbB2 gene amplification and HER2/neu over-expression is reported in 30-40% of patients with mammary carcinoma and serves as an important immune therapeutic target. HER2/neu is also expressed in 40% of pediatric osteosarcoma patients and we have found similar HER2 expression in pet dogs with spontaneous osteosarcoma (OSA). We have taken advantage of this naturally occurring spontaneous HER2+ tumor in dogs to evaluate the safety and efficacies of a recombinant Listeria expressing a chimeric human HER2/neu (Lm-LLO-cHuHer2) to generate potent HER2-specific T cell mediated immunity and prevent metastatic disease after standard of care amputation and chemotherapy. Administration of 3 doses of Lm-LLO-cHuHer2 at three-week intervals was found to be safe and effective at prolonging progression free survival and overall survival in dogs. Side effects that occurred were low grade and transient. IFN-γELISpot analysis revealed that Lm-LLO-cHuHer2 was able to break tolerance to HER2/neu supporting the hypothesis that HER2 specific T cell mediated immunity was preventing disease relapse. A second clinical trial was performed on dogs whose owners elected not to perform amputation or chemotherapy to determine the effects of combination radiotherapy and Lm-LLO-cHuHer2 immunotherapy on primary HER2+ appendicular OSA. Dogs received 16 Gyradiation, delivered as 2 fractions on consecutive days to the primary tumor site. Dogs then received a total of 8 doses of Lm-LLO-cHuHer2 administered intravenously at 3-week intervals and were then monitored for acute and chronic toxicities, primary tumor progression and development of metastatic disease. We found that repeat administrationsofLm-LLO-cHuHer2 were safe, broke tolerance to HER2/neu, delayed the progression of the primary tumor and delayed/prevented metastatic disease. In conclusion, we show that systemic administration ofLm-LLO-HER2/neuis well tolerated, breaks tolerance to HER2/neu, can prevent metastatic disease when administered in the setting of minimal residual disease, and can act synergistically with RT on HER2+ bone lesions to delay disease progression. These findings may have important translational relevance for human patients with HER2+ cancers such as mammary carcinoma.

Biography

Nicola Mason is a graduate of the Royal Veterinary College, London and is board certified in Veterinary Internal Medicine. She earned her PhD in Immunology from the University of Pennsylvania where she performed her Post-doctoral fellowship in the laboratory of Dr. Carl June. She is an Associate Professor, the Pamela Cole Chair in Companion Animal Medicine and Associate Director of the Mari Lowe Center for Comparative Oncology in the University of Pennsylvania's School of Veterinary Medicine. Her research focuses on developing immune therapeutic approaches to effectively target cancer and prevent metastatic disease in companion dogs, with the ultimate goal of identifying and accelerating successful therapies into the human and veterinary clinics. Her lab is currently focused on two main therapeutic strategies, recombinant listeria-based technologies and chimeric antigen receptor T cells (CAR-T) for canine osteosarcoma, lymphoma and hemangiosarcoma.

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