Pharmacological Considerations in the Response of Tumors to Drug Therapy: Drug Exposure and Intrinsic Sensitivity

Traditional cancer therapy has been based on histotype-dependent drug selection and maximum tolerated dose (MTD)-based dosing. This approach is being challenged by molecular classification of individual tumors and dosing based on biological effectiveness leading to a possible future where both drug and dose will be determined by tumor and patient specific characteristics. This presentation will review the current research ongoing in my laboratory that is studying how molecular characteristics of canine tumors can influence drug treatment and outcomes as well as how patient and tumor specific characteristics can impact drug exposure and response and warrant dose modification for optimal efficacy. This research is based on the fundamentals of dose-response that relate dose-exposure via pharmacokinetics (PK) and exposure-response via pharmacodynamics (PD). PK considerations will include the tumor uptake and intracellular distribution of hydroxychloroquine (HCQ) as an inhibitor of autophagy and a discussion of autophagy inhibition as a potent strategy in veterinary oncology based on autophagy-dependence as a PD indicator of antitumor response in canine tumor cell lines. Other PD indicators of response will include tumor gene expression signatures and prediction of response to chemotherapy in adjuvant therapy of canine osteosarcoma. The discussion will focus on drug and patient specific characteristics determining PK and PD and how these can be taken into consideration to optimize patient response to therapy.

Dr. Daniel L. Gustafson earned his B.S. in Biology from Santa Clara University in 1987 and his Ph.D. in Cell and Molecular Pharmacology and Physiology from the University of Nevada, Reno in 1992. He completed his postdoctoral training in Radiation Biology and Pharmacology at Colorado State University and the University of Colorado Health Sciences Center. Following his postdoctoral training, he joined the Center for Environmental Toxicology and Technology at Colorado State University in a junior faculty position working with Drs. Raymond S.H Yang and Melvin E. Andersen on modeling projects. Dr. Gustafson then moved to the University of Colorado School of Pharmacy as an Assistant Professor in Pharmacokinetics. At the University of Colorado, he developed a Pharmacology Core laboratory to serve investigators in the University of Colorado Cancer Center on pre-clinical and clinical pharmacology studies with an emphasis on pharmacokinetics and pharmacokinetic modeling. After eight years at the University of Colorado, Dr. Gustafson was recruited back to Colorado State University where he currently resides as Professor of Clinical Pharmacology, Shipley University Chair in Comparative Oncology, and Director of Basic Research for the CSU Flint Animal Cancer Center. He also serves as the Co-Leader for the Developmental Therapeutics Program and continues to serve as the Director of the Pharmacology Shared Resource for the University of Colorado Cancer Center. He has authored or co-authored over 120 original, peer-reviewed scientific articles in journals primarily in the field of cancer chemotherapy and pharmacology.