# **ABSTRACT, Kari Nieto, Seminar 1- Dec 9th, 2015**

**Local Controlled Release of Fenretinide for Chemoprevention of Oral Cancer**

Head and neck squamous cell carcinoma (HNSCC) is a worldwide health concern, and it is estimated that over 550,000 new HNSCC cases will be diagnosed in 2015. Despite treatment advances that include intraoperative radiation, the 5-year survival rates of persons with HNSCC is discouraging low (50%). The synthetic analogue of all-*trans* retinoic acid, fenretinide (4HPR), is a highly active and promising chemopreventive agent for oral cancers. Numerous oral cancer chemoprevention clinical trials have been conducted that employed systemically delivered 4HPR, however the disappointing results were due to an inability to achieve therapeutic levels at the treatment site. In order to derive the therapeutic benefits of 4HPR *in vitro* and alleviate systemic toxicity, we are developing a local controlled release (CR) approach for 4HPR. In order to optimize efficacy from local CR dosage forms, the objective of this research is to understand how to optimize the penetration distance into tissue of the 4HPR parent drug and respective metabolites.

* To accomplish this objective, our goal was to develop and test *in vitro* and *in vivo*: a) an implantable osmotic pump for constant release and (b) implants based on poly(lactic-co-glycolic acid) (PLGA) for intraoral injection directly below the lesion site. For the initial tissue-distribution studies, Alzet osmotic pumps were implanted subcutaneously (SC) in mice and set to deliver 4HPR locally over 7 days. Drug-tissue levels moving several millimeters away from the implant were observed in vicinity of therapeutic range at a daily dose of 60 g of 4HPR. Additionally a high-throughput method to determine drug-tissue distribution was established by tissue cryosectioning, mono-phase extraction, and assaying by UPLC. Next, 4HPR was formulated into PLGA 50/50 implants and continuous release was observed *in vitro* for > 30 days, although high levels of polysorbate 80 (2% w/w) were required in the PBS buffer to allow solubilization of the water-insoluble 4HPR upon release. After SC administration of millicylinders in rats the initial burst release of drug was similar but slower than that found *in vitro* by 7 days. Further *in vivo* release analysis is ongoing. Due to 4HPR’s extreme hydrophobicity, in certain instances several solubilizers and penetration enhancers were also incorporated into these dosage forms for future studies to optimize drug-tissue penetration in healthy mice and efficacy in mice with patient-derived tumor xenografts. Hence, these studies may be useful for developing local CR of 4HPR for primary and secondary oral cancer chemoprevention. Support: NIH R01 CA 171329.