Letter of Intent: **Marshfield Clinic/Marshfield Clinic Research Institute-UW Madison Collaborative Research Pilot Award**

Title of proposed research project: *Piloting DELPHI and Genome-wide Methylation analysis of OMPD and OCC*

1. **Name, address, telephone number, and email address of the Lead Applicant(s).**

Marshfield Clinic Research Institute (MCRI) UW Madison/UW School of Medicine and Public Health (UWSMPH)

Name: Ingrid Glurich, PhD Name: Randall Kimple, MD, PhD

Project Scientist, (ORSS) Director of Cancer Biology and Translational Medicine

Cancer Care and Research Center (CCRC) Associate Professor, Dept of Human Oncology

Center for Oral and Systemic Health (COSH) Associate Professor Dept of Medical Physics

Address: Address:

Marshfield Clinic Research Institute Univ. of Wisconsin School of Medicine and Public Health

Cancer Care and Research Center Department of Human Oncology

1000 North Oak Avenue 1111 Highland Avenue

Routing: 1R4 3107 WIMR

Marshfield, WI 54449 Madison, WI 53705

Telephone # 715-389-3072 Telephone # 608-265-3716

E Mail: [glurichi@marshfieldclinic.org](mailto:glurichi@marshfieldclinic.org) E Mail: [rkimple@humonc.wisc.edu](mailto:rkimple@humonc.wisc.edu)

**Names and roles of key personnel crucial to the design and conduct of the proposed research**;

@ MCRI- Co-Investigators:

* Steven Schrodi, PhD (Center for Precision Medicine Research (CPMR)): Dr. Schrodi is a geneticist and will provide expertise and participate in data analysis surrounding DELPHI and Methylation data
* Shicheng Guo, PhD (CPMR): Dr. Guo is a post-doctoral fellow in Dr. Schrodi’s laboratory with expertise in epigenetics and will provide analytical expertise on methylation data and DELPHI analysis
* Neel Shimpi, BDS, PhD (COSH and CCRC) Dr. Shimpi is a dental surgeon and bioinformatician with expertise in machine learning (ML) and will assist with ML and clinical interpretation of epigenetic/genetic data relative to oral cavity cancer (OCC).

Clinician Co-Investigators:

* Adedayo Onitilo, MD, PhD. MSCR (MCHS Oncology Service Line Director, Oncologist/Hematologist and Director of CCRC: will assist with identification and referral of patients to the study and participate in clinical interpretation of epigenetic/genetic data relative to oral cavity cancer (OCC).
* Urquhart, Andrew MD, FACS (Depart. of Otolaryngology): As head of surgery at MCHS Dept of Otolaryncology, Dr. Urquhart will assist with identifying and referring eligible patients to the study, champion the study to Department colleagues and assist with clinical interpretations of OCC and Oral Potentially Malignant Disorders (OPMD)
* Todd Kroll, MD, PhD: will consult with the team as an anatomic and molecular pathologist and profile OPMD/OCC pathology.

@ UW Madison- We propose to utilize the UW Biotechnology Center’s Gene Expression Center as the service laboratory to conduct genetic and epigenetic analyses.

1. **Participating institutions and organizations:** UWSMPH, UW Gene Expression Center, MCRI, ICTR at Madison

**Description of the proposed activities:** (See workflow diagram: **Figure 1**). Because reliable biomarkers to detect malignant transformation of OPMD, OCC is frequently first diagnosed at late stages and is associated with high morbidity and mortality. A novel approach defined by Christiano *et al* (2019),‘DNA evaluation of fragments for early interception’ (DELPHI), demonstrated capacity to specifically differentiate and profile various cancers and their tissue of origin by genome-wide fragmentation analysis of cell-free DNA (cfDNA) shed into the blood. OCC was not examined in their study. In this study, we propose to pilot adaptation of DELPHI to DNA methylation-sequencing data (meDELPHI) and apply meDELPHI and DNA methylation (such as methylation haplotype, methylation entropy) to test feasibility for detection of dysplasia and malignant transformation associated with OPMD and OCC in saliva/blood and simultaneously profile epigenetic changes across the trajectory of OCC from OPMD through stage IV cancer. This study will pilot identification of genomic loci associated with OCC evolution and profile differential methylation. Meanwhile, we will compare the fragmentation patterns between cell-free DNA in blood and saliva to determine which one is the better non-invasive diagnosis spot. The study will define novel insight into epigenetic contribution to OCC etiology and progression, molecular mechanisms of OCC pathogenesis and potential novel molecular targets.

***Figure 1:*** *Workflow diagram*

The letter of intent should be sent to **Peggy Hatfield**, **(pmhatfie@wisc.edu)** on or before **November 1, 2019.**