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My research program is focused on the translational genomics and functional genomics of head and neck squamous cell carcinoma (HNSCC). Our goal is to understand the genomic alterations in HNSCC and translate them to improve patient care. We completed the first large-scale multiplatform integrated genomic analysis of the tongue cancer genome, and have since had a major role in many genomic studies of HNSCC, including with The Cancer Genome Atlas (TCGA) HNSCC and pan-squamous projects. These and other initial characterizations of the head and neck cancer genome have set the stage for the next phase of studies that will combine genomics with more detailed clinical annotations, controlled treatment regimens, and mechanistic in vitro studies. We are currently performing targeted DNA sequencing, exome sequencing, and/or RNAseq as collaborators on multiple clinical studies, and we have performed genomic analysis of unique clinical cohorts, including cutaneous SCC, young tongue SCC, and HNSCC in HIV+ individuals. Our knowledge from these patient studies is being combined with in vitro mechanistic studies to understand the functions of key identified genomic alterations. One project, as part of the MD Anderson HPV Moonshot, has identified a signature for poor outcome in HPV+ oropharyngeal SCC. The signature may be used to stratify patients to higher or lower treatment intensity. Another project has used functional genomic screening in vivo, to identify the CREBBP/EP300 genes as regulators of the response to radiation. These genes are druggable and targeting them in CREBBP/EP300 mutant tumors may be a new path to radiosensitization. These efforts will facilitate an understanding for the clinical and functional relevance of the genomic alterations, and hopefully translate to improved treatment outcomes for HNSCC patients.