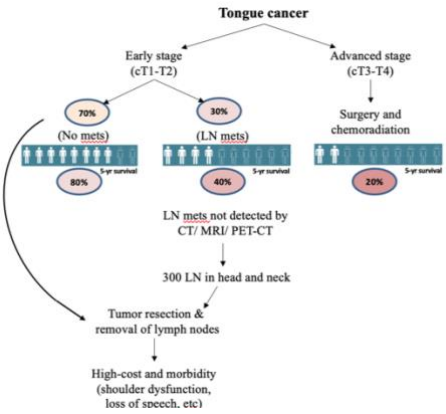
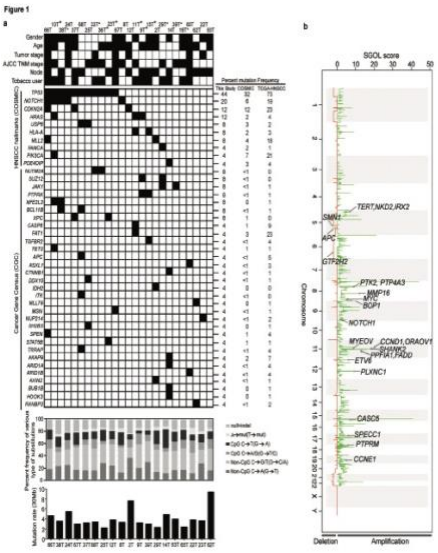
Biology of the Lymph Node Metastases in Tongue Cancer

Dr. Dutt is an established biomedical scientist who has extensively contributed to our understanding of the pathobiology and genomics of several epithelial cancers. In tongue cancer, Dr. Dutt addressed a critical issue of occult lymph nodal metastases . A unique feature of tongue squamous cell carcinoma (TSCC) compared to other subsites of oral cancer is the occurrence of occult nodal metastases observed in ~30% of early stage (pT1 or pT2) patients, undetectable by MRI/ CT. Neck dissection among 70% of patients without nodal metastases adds to morbidity, cost and overall poor survival, who could be spared of surgery with precise diagnosis. Thus, there's an unmet need for reliable and robust prognostic biomarkers to stratify the patients who are likely to have an adverse clinical outcome .

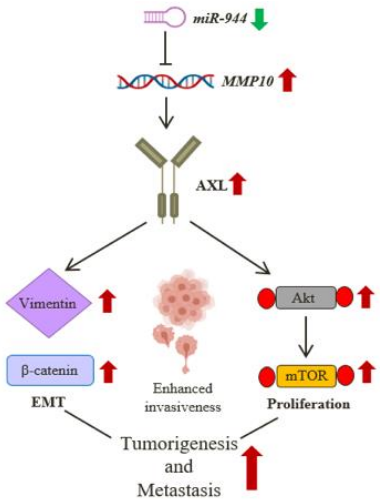


Tongue cancer – occult lymph metastasis with poor clinical outcomes.

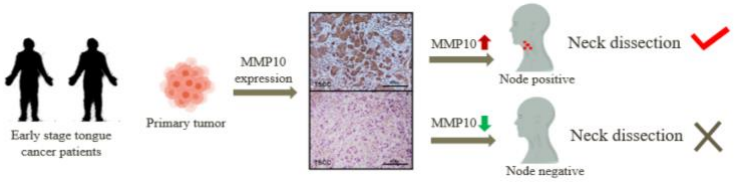
Dr. Dutt presented the first landscape of genetic alterations among tongue cancer patients of Indian origin with evidence of a lack of HPV infection and the presence of a tobacco-associated signature . He identified NOTCH1 alterations and MMP10 overexpression as a promising prognostic biomarker that could potentially aid in sparing a significant proportion of early-stage tongue cancer patients from mandatory elective neck dissection . More recently, he showed *miR-944* negatively regulates MMP10 by targeting its 3'-UTR. Furthermore, overexpression of MMP10 leads to opposite effects upregulating EMT, mediated by a tyrosine kinase gene, *AXL*, which is essential and sufficient to mediate the function6l consequence of *miR-944* downregulation or *MMP10* overexpression. In brief, he characterized an essential and sufficient role of the miR-944/MMP10/AXL-axis in lymph node metastasis using an elegant orthotopic *in vivo* tongue cancer mouse model (*in press, 2022*). A clinical trial at TMC is currently underway to validate the findings.



Identification of somatic mutations and DNA copy number changes in HPV-negative early stage TSCC tumors (8).

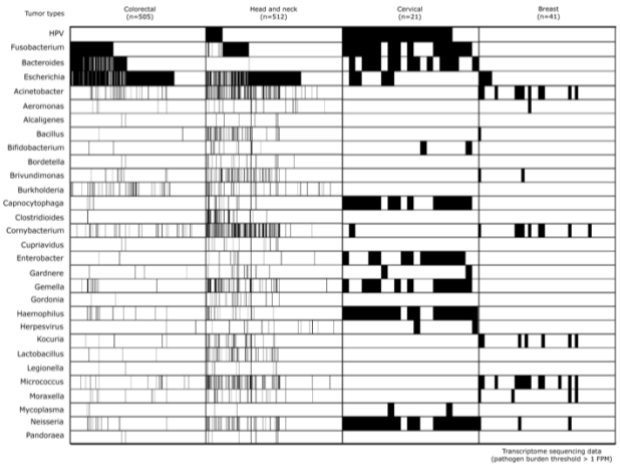


miR-944 targets 3'-UTR of *MMP10*, whose overexpression induces tumorogeesis and nodal metastasis mediated through the AXL signaling pathway by inducing EMT (in press).

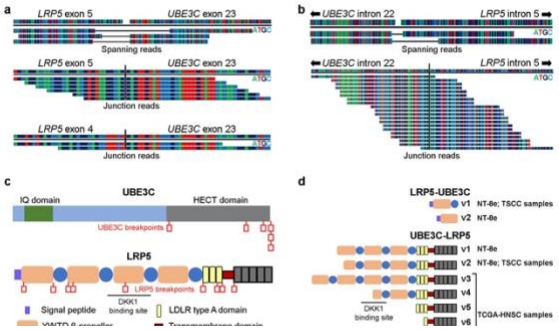


miR-944/MMP10/AXL- axis predict lymph node metastasis in early stage tongue cancer

Dr. earlier developed a novel freely distributable computational tool “HPVDetector” (currently used by over 300 labs across the globe) to detect all known HPV types along with their sites of integration in the host genome using next generation sequencing. Using HPVDetector, Dr. Dutt established the absence of HPV in tongue cancer among Indian patients, unlike Caucasian patients . Several reports have subsequently corroborated this finding. Additionally, Dr. Dutt described the first comprehensive landscape of infectious pathogens across breast, lung, gallbladder, cervical, colorectal, and oral cancer. His work establishes a significant prevalence of *Fusobacterium nucleatum* in tongue tumors among Indian patients that occurs mutually exclusive to HPV in Caucasian samples. They show that a higher burden of *Fusobacterium* is associated with poor survival and nodal metastases, defining a distinct subgroup of head and neck cancer.



Landscape of microbes associated with human cancers identifies mutual exclusivity of human papillomavirus and Fusobacterium in head and neck cancer (10).



Identification of *LRP5-UBE3C* and *UBE3C-LRP5* fusion variants (11).

More recently, The study identifies a novel fusion transcript, UBE3C-LRP5, in head and neck cancer, with potential clinical relevance. This fusion activates the Wnt/β-catenin pathway, driving cancer cell behaviors. The FDA-approved drug pyrvinium pamoate shows promise in inhibiting tumor growth linked to this fusion. Patient survival data suggests its importance. This finding proposes a new therapeutic angle for head and neck cancer, warranting larger clinical trialsOverall, his work illustrates a unique blending of basic and translational cancer genomics research and detailed functional mechanistic insights .

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(Amit Dutt)