INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

Name of the Student	:	**Padmavathi G**
Roll Number	:	**136106007**
Programme of Study	:	**Ph.D.**

Thesis Title: **An investigation on the role of tumor necrosis factor-α induced protein 8 (TNFAIP8) family in the development and progression of oral cancer**

Name of Thesis Supervisor(s)	:	**Dr. Ajaikumar B. Kunnumakkara**
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SHORT ABSTRACT

Cancers of oral cavity is emerging as a major health concern worldwide with highest incidence in India. Despite the huge medical advancements in cancer therapy and the easy accessibility of tumor, the 5-year survival rate of oral cancer remains as low as 50–55% and with increase in disease progression survival rate tend to decrease drastically. Unfortunately, in India, almost 2/3 of the oral cancer cases are diagnosed only in the advanced stage of the disease making it difficult to treat and decreasing the chances of survival. The remarkable decrease in the survival of advanced disease is mainly attributable to the lack of effective diagnostic, therapeutic and prognostic biomarkers. Therefore, it is essential to develop novel biomarkers for the better management of this deadly disease. In the current study, a novel tumor necrosis factor alpha induced protein 8 (TNFAIP8 or TIPE) protein family comprising of four proteins namely, TNFAIP8 (TIPE), TNFAIP8L1 (TIPE1), TNFAIP8L2 (TIPE2) and TNFAIP8L3 (TIPE3) was explored for its therapeutic and prognostic potential against oral cancer. Immunohistochemical analysis of tissue micro array (TMA) containing samples from normal, hyperplasic and neoplastic patients revealed that expression of TIPE, TIPE2 and TIPE3 were upregulated and levels of TIPE1 were downregulated in squamous cell carcinoma (SCC) tissues compared to the normal tissues and correlated with disease progression from hyperplasia to SCC. Further assuring the involvement of TIPE proteins in the development and progression of oral cancer, treatment of oral cancer cells with the major risk factor of oral cancer (i.e. tobacco and related carcinogens) resulted in a significant upregulation of TIPE, TIPE2 and TIPE3 and downregulation of TIPE1 protein. Furthermore, knockout of TIPE proteins by CRISPR/Cas9-mediated gene editing was found to significantly modulate the different cancer hallmarks associated with oral cancer. In brief, silencing of TIPE or TIPE2 or TIPE3 significantly reduced the survival, proliferation, colony formation and migration of oral tongue squamous carcinoma cells (SAS) whereas knockout of TIPE1 had an opposite effect on OSCC cells. Further, the TIPE, TIPE2 and TIPE3 knockouts mediated inhibition of proliferation was found to be facilitated through inhibition of cell cycle

progression at S or G2/M phases and downregulation of proteins involved in cell survival, proliferation, migration, invasion and angiogenesis such as Cox-2, survivin, Bcl-2, cIAP1, XIAP, CXCR4, MMP-9 and VEGF-A. Further interestingly, we found that TIPE, TIPE1 and TIPE2 proteins regulate the oral cancer development and progression through modulation of Akt/mTOR signaling cascade, whereas TIPE3 acted through an Akt-independent mTOR/STAT3 pathway. Taken together, the TIPE proteins were proved to play significant roles in the progression of oral cancer with TIPE, TIPE2 and TIPE3 being oncogenic and TIPE1 being anti-oncogenic thus claiming the therapeutic and prognostic values and the importance of specific targeting of TIPE proteins in the disease management.