Detail of the Project sanctioned under the Human Resource Development scheme of Department of Health Research

1. Project Title: Evaluation of metastasis suppressor genes: Wilms tumor 1 (WT1), TGM3 and PTPN14 in patients of Oral squamous cell carcinoma undergoing chemoradiotherapy.

2. Category of fellowship: Women Scientist, Category A, Genomics

3. PI (Name & Address): Dr Seema Nayak, ICMR-HRD DHR Women Scientist, Department of Radiotherapy, King George's Medical University Lucknow, Phone No. 09451221588, Email: seemagkp@gmail.com

4. Qualifications: MSc (Biotechnology) and PhD (Biomedical Sciences)

5. Mentor or Co.PI (Name & Address)

Mentor

Prof. Madan Lal Brahma Bhatt, **HOD**, Department of Radiotherapy, King George's Medical University Lucknow. Phone No. 0941502060, Email: drmlbbhatt@yahoo.com

6. Duration of the project: 3 years

7. Broad area of Research: Genomics

7.1 Sub Area: Oncology

8. Summary of the Project

Despite various treatment options available, oral cancer patients are still faced with a high chance of recurrence and/or metastasis, which is responsible for the poor clinical prognosis, with a 5- year survival rate of only about 50 percent.

The prevention and early prediction of oral squamous cell carcinoma (OSCC) metastasis to improve overall patient survival has provided the rationale for biomarker development**. There is a continued such for prognostic/predictive biomarker in OSCC.** Recently, certain molecular biomarkers have been found to have promising diagnostic and predicting potentials and are already used in oncological practice, whereas others necessitate further evaluation.

Understanding the molecular and cellular changes involved in metastatic behavior of OSCC may identify a subset of patients which could be better amenable to systemic and more aggressive therapy in OSCC, and not local therapy only. It may further identify novel target for treatment which may reduce mortality.

The development of oral cancer is a multistep carcinogenic process that includes activation of several oncogenes and inactivation of tumor suppressor genes.

The proposed project will provide a prognostic biomarker for disease progression in OSCC by analyzing expression of metastasis suppressor genes;WT1, TGM3 and PTPN14, both at phenotypic and molecular level in tissues and blood samples as compared with normal oral mucosa and their association with chemoradiotherapy response.

The phenotypic expression will be analyzed by immunohistochemistry in biopsy proven cases of OSCC. ELISA will be done for all the proposed markers in pre and post chemoradiotherapy serum samples. Molecular expression shall be determined in frozen tissue samples by Real- Time PCR method. The conventional clinical, histopathological and epidemiological parameters shall include age, sex, tobacco and alcohol exposure, histological type and tumor grade, lymph node status, clinical stage, chemo radiation response, recorded on a predesigned proforma schedule. The data shall be analyzed by appropriate statistical tests; univariate, bivariate, multivariate analysis and logistic regression.

The study will assess the impact of WT1, TGM3 and PTPN14 expression on regional lymph node metastasis, locoregional recurrence, and prognosis. If any of biomarker expression was found significantly associated with radiotherapy response; it may serve as a biomarker for responsiveness to radiotherapy

The results may provide a rationale for exploring treatment strategies with radiotherapy to minimize radioresistance.

9. Objectives of the Proposal

1. Expression of WT1, TGM3 and PTPN14 in tissue samples of oral squamous cell carcinoma by Immunohistochemistry and its gene expression profile by using Real Time PCR.
2. Estimation of WT1, TGM3 and PTPN14 levels in pre and post chemoradiotherapy blood samples of oral squamous cell carcinoma by ELISA method.
3. Correlation of expression of above markers with metastatic behavior of oral cancer and chemoradiotherapy response.

10. Innovations in the project

Radiotherapy is currently the standard treatment for advance stage OSCC. However, radiotherapy is sometimes ineffective because some cancer cells are not so radiosensitive**.** In

an attempt to improve the outcomes of OSCC, the application of novel and effective biomarkers for **predicting prognosis and response to treatment** is so important and urgent. The findings of this study will highlight the importance of WT1, TGM3 and PTPN14 in oral cancer and their association with metastatic potential.

Out of the above 3 markers being studied if any or combination of markers is found significantly associated with radiotherapy response; it may serve as a biomarker for responsiveness to radiotherapy. If expression of any of biomarkers being significantly associated with radio resistance of OSCC patients, individuals with such over expressing biomarkers may be stratified to be treated with some other treatment modality rather than being treated with radiotherapy. **The results will provide a rationale for exploring treatment strategies to minimize radioresistance**

To the best of our knowledge, this study will be the first to demonstrate correlation of WT1, TGM3 and PTPN14 markers with patient outcome and response to therapy that will provides an opportunity of considering its potential clinical applications as a prognostic marker as well.

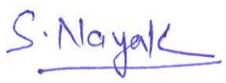
11. Significance of the outcome of the project

The limitations of conventional treatments in advanced, recurrent or distant metastases OSCC have necessitated a search for novel potential approaches. Recently, several research groups have reported certain genes and signaling molecules that were potentially involved in OSCC initiation and progression. These molecular targets could provide significant clues for early diagnosis, prognosis and new targeted therapies. Understanding the molecular and cellular changes may generate novel target for treatment and reduce mortality. **Therefore the result of the study will provide the expression of WT1, TGM3 and PTPN14; both at phenotypic and molecular level in OSCCs patients and correlates with chemoradioresponsivness underscoring their potential as candidate biomarkers for metastasis.**

Biomarker development might lead to identification of the patients whose tumors are to respond to a particular treatment. If there is any significant marker in this study was found, it may serve as a biomarker for responsiveness to radiotherapy.

12. Relevance in Public Health

Apart from their possible role as predicator of poor response to radiotherapy, if any of the genes being studied is found to be significantly associated with good response to radiotherapy they may be evaluated as a possible therapeutic target at molecular level.



Seema Nayak

Signature of the Fellow