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

1. Project Title: Evaluation of Circulating Cell-free DNA as a prognostic marker in Breast Cancer Patients

2. Category of fellowship: Women Scientist

3. PI (Name & Address): Dr. Sobuhi Iqbal, Room No. 411, Medical Oncology Lab, 4th Floor, IRCH, AIIMS

4. Qualifications: PhD

5. Mentor or Co.PI (Name & Address): Prof. Lalit Kumar, HOD Medical Oncology, Room No. 234, 2nd Floor, IRCH, AIIMS

6. Duration of the project: 3 years

7. Broad area of Research: Breast cancer

7.1 Sub Area: Circulating cell free DNA & DNA damage mediated immune response as diagnostic and prognostic markers in breast cancer.

8. Summary of the Project: (Give in about 300 words)

Breast cancer is the second most common cancer in India, with an estimated 115,251 new diagnoses and 53,592 breast cancer deaths in 2008. Owing to the lack of awareness of this disease and in absence of a breast cancer screening program, the majority of breast cancers are diagnosed at a relatively advanced stage. Therefore, the development of tests with a clinical relevance for risk estimation and monitoring is of great interest.

Over the period of time a considerable amount of data has been generated showing the existence of high levels of DNA in serum or plasma of cancer patients than in healthy controls. In our preliminary work we also observed a significant difference in the levels and integrity of circulating cell-free DNA (CCFD) in breast cancer patients (with or without metastasis) when compared with healthy control. Furthermore, an increasing trend in the levels and DNA integrity of CCFD was observed in breast cancer patients with stage I to III. Furthermore our preliminary work shows that patients with lower levels of CCFD than median have 71.2 % five year overall survival (OS) as compared to 88.7% OS in patients with higher levels of CCFD than median.

Since there is promise for CCFD as a prognostic marker so in the present study, we plan to work further along with an objective of studying changes in CCFD levels from pre to post treatment. Furthermore we will also evaluate the expression of genes associated with DNA damage mediated immune response and correlate with the levels of CCFD, so as to study its association, if any, with immune response of the patient. There are studies which show a link between DNA damage response and anti-tumor response. The hypothesis for the present study is to see whether the increased levels of CCFD can be taken as a measure of better immune response hence to predict disease free survival. The overarching goal of utilizing CCFD as biomarkers is to set-up a non invasive diagnostic as well as prognostic tool, so to optimize medical practice, advance personalized medicine, and improve the quality of life.

9. Objectives of the Proposal:

(i) Quantification of CCFD in serum samples of breast cancer patients at baseline, after treatment (Surgery & Chemotherapy) and at follow up.

(ii) Study the expression of NKG2D on the cell surface of natural killer cells at baseline, after treatment (Surgery & Chemotherapy) and at follow up in peripheral blood.

(iii) Evaluate the serum levels of MHC class I polypeptide-related sequence A (MICA) in breast cancer patients at baseline, after treatment (Surgery & Chemotherapy) and at follow up.

(iv) To see the expression pattern of ATM and MICA in tumor as well as matched cancer free breast tissue of same patients at baseline.

(v) Correlate the molecular markers with the clinical characteristics and disease prognosis.

10. Innovations in the project: (Give in about 100 words)

DNA damage potentially represents an initiating event for carcinogenesis as it is frequently observed in precancerous lesions. It has been reported that DNA damage also activates the immune response as an additional extrinsic control mechanism that favors the natural killer cell mediated elimination of damaged and cancer cells through the induction of natural killer group 2D (NKG2D) ligand (NKG2DL) expression in tumor tissue.

In this study we will be able to correlate the levels of CCFD with the DNA damage mediated immune response markers and analyze their association with each other

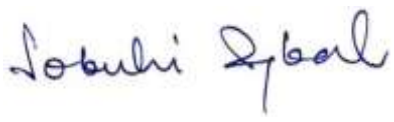
and with disease prognosis (if any). This study could assist in setting up a non-invasive blood based test for solid tumors for the screening of high-risk individuals, for prognostication and diseases management.

11. Significance of the outcome of the project: (Give in about 150 words)

The CCFD can be used as a non-invasive biomarker, as it can easily be isolated from human plasma, serum and other body fluids. In our preliminary work we observed that patients with lower levels of CCFD than median have 71.2 % five year overall survival (OS) as compared to 88.7% OS in patients with higher levels of CCFD than median. The present study may provide the information whether the increased levels of CCFD can be taken as a measure of better immune response hence to predict disease free survival. Consequently at the time of diagnosis clinician might be able to predict the further course of treatment with immune modulators or with immunotherapy for those patients who's CCFD will be less than cutoff so as to boost their immune response and hence improve the overall survival of patients.

12. Relevance in Public Health:

The idea for this study is to get access to the tumor through the blood which is relatively non-invasive compared to doing biopsy. Thus it will pave way for the use of liquid biopsy in early diagnosis as well as disease prognosis in breast cancer patients. This rapid and minimally invasive approach to index tumor-related circulating DNA has potential as a screening tool for public.



Signature of the Fellow /Faculty