Name of the candidate: **Naseem Akhter, Department of Biosciences, JMI, New Delhi**

Title of the thesis: **Molecular Analysis of p21 Gene in Indian Female Breast Cancer Patients**

Name of the supervisor: **Professor (Dr) Syed Akhtar Husain, Department of Biotechnology, Jamia Millia Islamia, New Delhi**

Name of the co- supervisor**: Professor (Dr) N. K. Shukla, Department of Surgical Oncology, DR. BRA-IRCH, AIIMS, New Delhi**

Findings of the study:

- The G> T transition (GAG> TAG) at codon 107 manifested as the substitution of glutamic acid by stop codon.
- The A> C transition (AGC> CGC) at codon 146, manifested as a substitution of arginine by serine.
- 29 mis- sense and 4 silent sporadic mutationsof p21 account for increased susceptibility for development of cancer in individuals harboring these mutations.
- Non- sense as well as mis- sense mutations, observed in tumors largely exhibited poorly differentiated histological grade, advanced clinical stage (III & IV), lymph node positivity, and ER- & PR- negativity.
- Promoter hypermethylation was observed in 36 breast cancer patient samples with majority of tumors exhibiting lymphnode positivity and ER- & PR- negativity.
- Majority of the samples showing promoter hypermethylation were from the tumor clinical stage III and IV i. e 58% (21/36), poorly differentiated i. e 58% (21/36) and nodal status positive 86% (31/36).
- Twelve percent of breast cancers (14/115) were entirely negative for p21 immunostaining. The majority of breast carcinomas (88%) demonstrated staining for p21. However, this immunostaining was heterogeneous in nature, and the expression of p21 protein was found to be relatively low in 83% of the samples. Nearly ninety percent (104/115) breast cancers were immunopositive for p53.
- A subgroup of patients exhibited the p21-/ p53+ which may be of clinical relevance concerning the response to chemotherapy/ hormonotherapy.
- No evidence of p21 codon 231 polymorphism with an increased breast cancer risk was found in our study.
- A significant association of GG allele in p53 Arg72Pro with breast cancer risk was observed in this study.
- A significant protective association of p53 heterozygous arginine variant with breast cancer was found in total, premenopausal and postmenopausal women.
- A/A genotype in CCND1 found associated significantly with the breast cancer risk in total and premenopausal women.

- The findings showed that p21 CC or CA genotype was not associated with pre- or postmenopausal breast cancer risk when analyzed alone.
- A significant protective association with the breast cancer in total, premenopausal and postmenopausal women was observed when CC genotype was analyzed in combination with p53 Arg/Pro G/C and p53 Pro/Pro C/C.
- A significant breast cancer risk association in total, premenopausal and postmenopausal women was observed when CC genotype was analyzed in combination with p53 Arg/Arg G/G.
- Statistical analysis of all possible combinations for C to A (codon 31 in p21) and G to A (CCND1) polymorphism revealed significant association of CC: AA with breast cancer risk in total and premenopausal women and a significant protective association of CC: GA with breast cancer risk in total and premenopausal women.
- Statistical analysis of all possible combinations for p53 (G72A) and CCND1 (G to A) polymorphism revealed significant association of GG: AA with breast cancer risk in total and premenopausal women. None of control postmenopausal women showed GG: AA genotype, however, a significant breast cancer risk association of GG: GA+ AA was observed in total, premenopausal and postmenopausal women.
- A significant protective association of GC (p53): GA (CCND1) with breast cancer was observed in total, premenopausal and postmenopausal women. Furthermore, a significant protective association of GC: GA+ AA with breast cancer in total, premenopausal and postmenopausal women.
- Interestingly, CC (p53): AA (CCND1) genotypic combination showed a significant breast cancer protective association in total women, while CC: GA+ AA genotypic combination showed a significant breast cancer protective association in total and post menopausal women.