Nomination of Prof. Ritu Gupta

Sun Pharma Science Foundation Research Award:Medical Sciences - Clinical Research

Prof. Ritu Gupta has contributed to the understanding of the pathogenesis, clonal evolution, immune microenvironment, biomarker discovery and risk prediction models in Multiple Myeloma (MM).

Dr. Gupta reported a progressive increase in the mutations' burden especially in the 3' and 5'UTRs and cancer related signalling pathways as MM progresses from its precursor, Monoclonal Gammmopathy of Undetermined Significance. This work demonstrates the role of dysregulated cancer pathways and regulatory binding sites in pathogenesis of MM (***Am J Cancer Res 2022 & 2021; IF=6.166***). Her group demonstrated that MM progresses predominantly through branching pattern of clonal evolution with temporal changes in mutations in the driver and actionable genes (***Am J Cancer Res 2020***). Further, intraclonal heterogeneity in myeloma genome and a significant correlation between co-occurring oncogenic mutations that synchronize molecular events of drug response and myeloma pathogenesis were demonstrated (***Transl Oncol 2020***). The above concepts highlight the clinical relevance of evaluation of subclonal mutational landscapes for tailoring time and risk-adapted therapy in MM.

Dr. Gupta's lab reported for the first time the clinical significance of chromothripsis in MM and established it as an independent prognostic biomarker (***Leuk Res 2018***). Her research group identified the functionally connected hub genes and transcription factor regulatory networks with miR-16–2-3p and 30d-2-3p as prognostically relevant miRs that correlated with survival outcomes in MM. (***Sci Rep. 2021; IF=4.997***).

Dr. Gupta's lab reported functional potential of regulatory T-cells despite reduced expression levels of FoxP3 suggesting that the regulatory T-cells do not play a tumor-facilitatory role in MM. The increase in functionally competent regulatory T-cells in MM patients after anti-myeloma therapy points to a complex interaction between the immune regulatory and recovery processes in MM (***Leuk Res 2011; CI=65***).

The existing risk predictions models in MM are based on western cohorts. In a systematic evaluation of 2000 patients of MM, Dr. Gupta's team evaluated the risk predictions in the context of ethnicity-specific information and validated robust AI-based models for Indian patients that outperform the existing Revised international staging system. These models include 1) Modified risk staging (MRS) when genomic data on high risk cytogenetic aberrations is not available, a common scenario in a resource constraint setting (***Transl Oncol 2021***); 2) Consensus based risk-stratification system (CRSS) which integrates genomic data with a SHapley Additive explanation to deduce the biological relevance of the risk predictions (***Front Oncol 2021; IF=6.244***) and, 3) Graph Convolution Risk Staging (GCRS), a deep neural network based model which further improves risk stratification (***Comp Biol Med 2022; IF=6.698***). These risk prediction calculators are available online. This work is a value addition as it establishes novel and robust risk-staging models that can

be employed in India irrespective of the existing diversity and disparity of our health care infrastructure.

Dr. Gupta's team established the Next Generation Flow cytometry (NGF) assay for Measurable Residual Disease (MRD) and defined cut-offs for dynamic risk monitoring and, introduced a novel statistic of neoplastic plasma cell index (NPCI) to overcome the caveat of hemodilution that mars the utility of NGF in clinical practice (***Am J Clin Pathol 2023; IF=5.4***). Her group also described the pattern-based recognition of neoplastic plasma cells and immunomodulation after chemotherapy that impacts residual disease assessment in MM (***Clinical Cytometry 2022; Am J Clin Pathol 2009; CI=89***). This work has enhanced the disease monitoring in the clinical stem cell transplantation program at AIIMS.

I hereby recommend Prof. Ritu Gupta for the prestigious Sun Pharma Science Foundation Research Award in Medical Sciences-Clinical Research Category.

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