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PRESENTATION TITLE: Prolactin Differentiation Therapy in Breast Cancer

ABSTRACT: Breast cancer (BC) is a major disease affecting women worldwide. A woman has 1 in 8 lifetime risk of developing BC, and morbidity and mortality from BC are expected to continue to rise globally. Despite improvements in early detection and advances in treatment options BC remains a challenging disease due to its heterogeneity, recurrence and metastasis to distant vital organs including bones, lungs, liver and brain. It is estimated that 90% of deaths due to BC are a consequence of cancer recurrence and metastatic spread. Moreover, there are no current effective treatments once metastasis has occurred. Significant success in anti-cancer therapeutics has been achieved by targeting oncogenic drivers, particularly for cancer types showing oncogenic dependencies, with the use of chemical inhibitors (e.g., imatinib for treatment of chronic myeloid leukemia driven by BCR-ABL), and biologics (e.g., humanized blocking antibodies against HER2 in BCs showing HER2 amplification/overexpression). Importantly, novel targets focusing on restoring cellular differentiation and reprograming have gained notable interest as promising effective therapeutic targets particularly in cancer types that are poorly differentiated, metastatic showing no specific oncogenic vulnerability driver pathway, such as the therapeutically challenging subtypes of breast cancer. Indeed, the premise of differentiation therapy (DT) in cancer is a strategy that aims at engaging-forward differentiation and cellular reprograming restricting the proliferative, tumor repopulation, stemness, EMT and metastatic capacities of tumor cells leading to the cessation of the aggressive tumor phenotype and offering the cancer patients improved survival for decades. Extensive research including our own work has established that prolactin (PRL) hormone is a key mammary differentiation factor and is essential for mammary gland development and terminal differentiation promoting specialized tissue organization and lactation. Moreover, we have accumulated compelling evidence using patient data and bench molecular data implicating this pathway as a clinically relevant pro-differentiation pathway driving differentiation and cellular reprograming suppressing stemness, EMT, metastasis and tumorigenesis in BC. Collectively, our results position prolactin/prolactin receptor as a fundamental pathway deriving tumor differentiation that can be exploited as a more effective and less toxic therapeutic regimen in breast cancer.

BIOGRAPHY: Dr. Ali is a Professor at the Department of Medicine and Full member at the Cancer Research Program, The Research Institute of the McGill University Health Centre. Her expertise spans various domains including molecular and translational oncology, cell signaling and molecular endocrinology. Her research program focuses on the evidence that poorly differentiated tumors are the most aggressive and metastatic lethal cancers. Therefore Dr. Ali investigates the concept that restoring differentiation in cancer cells is an approach to restrict cancer progression and offer a path for the development of pro-differentiation based anti-cancer therapeutics. Indeed, in epithelial tumors, such as breast cancer, dedifferentiation and increased cellular plasticity are being recognized molecularly and clinically as major derivers of tumor heterogeneity, metastasis, cancer relapse, and therapeutic failure. On this premise, collectively, the work of Dr. Ali led to ground-breaking discoveries that prolactin/prolactin

receptor pathway is indispensable in maintaining breast cancer cellular differentiation and act as a safeguard against aggressive breast cancer progression. Thus, exploiting prolactin-dependent pathways in regulating breast tumorigenesis will be critical for the discovery of new biomarkers to improve patient prognostication and for the development of viable therapeutic regimens in breast cancer.