**Longitudinal genomic profiling of chemotherapy-related CHIP variants in patients with ovarian cancer**

Sara Corvigno1;#; Jun Yao2;#; Asare Amma1;#; Li Zhao3;#; Joseph Celestino1; Richard A. Hajek1; Ency A. Arboleda Goette1; Ridge T Rogers1; Raymond N. Montoya1 Ping Song4; Qingxiu C. Zhang4; Xingzhi Song3 ; Mohammad M. Mohammad1; Kenna R. Shaw1; Jianhua Zhang3 ; Karen H. Lu 1; Amir A. Jazaeri1; Shannon N. Westin1; Anil K. Sood1; and Sanghoon Lee1

1Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

2Department of Molecular & Cellular Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

3Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

4Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy, IPCT Genomic Laboratory (IPCT Lab), The University of Texas MD Anderson Cancer Center, Houston, TX, USA

#These authors contributed equally.

Clonal hematopoiesis (CH) is characterized by the presence of populations of hematopoietic stem cells (HSCs) with the potential of clonally expanding and giving rise to hematological malignancies. By contrast, clonal hematopoiesis of indeterminate potential (CHIP) is the outgrowth of a single HSC clone with an acquired somatic mutation in the absence of hematological abnormalities. CHIP mutations, or variants, occur with a variant allele frequency (VAF) of at least 2% in peripheral blood. This definition does not account for less frequent mutations that give rise to hematopoietic clones. Previous studies indicate an association between CH and secondary hematologic malignancies in cancer patients who receive chemotherapy.

To discover novel candidate CHIP mutations, including those with extremely low VAFs, we performed an in-depth characterization of low-frequency CHIP variants in a highly selected group of patients with high-grade serous ovarian cancer (HGSC) before and after standard neoadjuvant chemotherapy (NACT).

We performed comprehensive ultra-high-depth whole-exome sequencing of circulating free DNA (cfDNA) and matched white blood cell (WBC) DNA from pre- (n=9) and post-NACT (n=9) samples from HGSC patients who had excellent response (ER; n=4) or poor response (PR; n=5) to platinum-based NACT. Variants present in both the WBC DNA and cfDNA from a patient were considered candidate CHIP variants.

We identified a total of 93,088 candidate CHIP variants in 13,780 genes. Compared with pre-NACT samples, post-NACT samples tended to have fewer CHIP mutations with VAFs of less than 5%, which may reflect the negative selective pressure of chemotherapy on rare hematopoietic clones. Finally, we identified CHIP variants in tumor samples matched to the liquid biopsies.

Our innovative sequencing approach enabled the discovery of a large number of novel low-frequency candidate CHIP mutations, whose frequency and composition are affected by chemotherapy, in the cfDNA of patients with HGSC. The CHIP variants that were enriched after chemotherapy, if validated, might become essential predictive markers for therapy-related myeloid neoplasia.