Development of Precise Preclinical Tools for High Grade Serous Ovarian Cancer (HGSOC)

Shamundeeswari Anandan
Centre for Cancer Biomarkers, Dep. of Clinical Science, University of Bergen, Bergen, Norway
and Dep. of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway

Supervisors: Line Bjørge and Emmet Mc Cormack

Abstract

Background: In 70% of all cases, HGSOC is diagnosed at an advanced stage. Despite primary treatment with surgery and chemotherapy most patients relapse with 70% of them being chemoresistant. Based on the improved recognition of cellular and molecular diversity within the disease, a seven steps roadmap of research priorities has been suggested, which focuses mainly on development of precise preclinical tools to better characterize the tumor microenvironment (TME) in order to discover more precise biomarkers and immunotherapeutic targets.

Objectives: The project *aims* to establish preclinical tools for individual tumor characterization, and to portray the tumor microenvironment (TME). Improvement of existing animal models and standardization of a HGSOC specific immunogram will be the focus. The final endpoints are to develop more precise HGSOC Xenograft Models - representing both chemosensitive and carboplatin resistant clinical conditions, and to develop a HGSOC specific immunogram to better define patient specific treatment options.

Methods:
Cancer Immunogram – Set up includes seven different parameters, (i) Neoantigen load (ii) General immune status (iii) Immune cell infiltration (iv) Checkpoint inhibitors (v) Soluble inhibitors (vi) Tumor metabolism (vii) Sensitivity to effector mechanism. The mass cytometry panel is being developed to assess the checkpoint inhibitors, immune cell infiltration and sensitivity to effector mechanism.
Xenograft models - HGSOC cell lines – OV90, Caov3, COV318 were selected based on the literature, transduced and injected into immunodeficient mice – intraperitoneally (I.P), subcutaneously (S.C) and intrabursally (I.B) to develop the xenograft models. Carboplatin resistant forms of these cell lines are under development through constant exposure to carboplatin in the growth media with a regular pulse rate increase in the carboplatin dosage. Once the carboplatin resistant cells are established they will be injected into mice to develop the carboplatin resistant models.

Conclusions: Tumor dissemination pattern observed in all the three models is comparable to patients, with usual sites of metastasis and tumor burden. The resistance levels of the different cell lines to carboplatin is different ranging from partial to complete resistance as observed in patients. Microscopic pictures of both cell types show interesting morphological differences. The different parameters of the cancer immunogram is being set-up based on literature. After extensive literature review different markers for the mass cytometry panel has been selected and titrations are under process.

Future Perspectives: The Immunogram will be a set up to find treatment specific biomarkers and patient specific treatment options. The next step, will be to have a closer look at the differences in the TME between naïve, relapse and resistant patients. The xenograft models will serve as powerful tools to test *in vivo* efficacy of novel biomarkers and immunotherapeutic targets. They will form the basis to generate more advanced HGSOC preclinical surgical and immunocompetent models.