Ovarian Cancer Statistics In Australia And Contributions Made By Australian Researchers

Ovarian cancer is the growth of abnormal cells in one or both ovaries in a women's reproductive system. These cells multiply out of control forming a tumour and if left untreated, the tumour can metastasise to other parts of the body. Being the most lethal gynaecological malignancy, ovarian cancer is the fifth leading cause of cancer death in the developed world affecting females, with approximately every year 1,600 Australian women diagnosed with cancer. Consequently, the Australian government is supporting the National Health and Medical Research Council (NHMRC) by providing an immense amount of funding for cancer research. Subsequently, Australian researchers have received funding such as David Bowtell, Ian Campbell and Judith Clements who made contributions for identifying the key molecular inhibitory pathways of the disease with potential therapeutic targets for treatment, with the integration of international scientists. In the meantime, KLK-8, CA125 and Harmine are researched to be the most effective targets for treatment inhibiting the Ras pathway and treating the disease, therefore, consisting of potential utility for early detection, risk, prognosis, diagnosis therapy and monitoring. Although current research has been implemented, more thorough research from Australian scientists is needed for developing targeted medicine to seek potential health gain by contributing towards the burden of disease in Australia

Funding of Ovarian Cancer in Australia

With the recognition of NHPA, ovarian cancer has the lowest survival rate of any women's cancer and little advancement of treatment options (Cancer Australia, 2019). The Government has provided over $800 million in funding through the NHMRC (Australia's peak body for medical research) for cancer research, in particular, ovarian cancer funding of over $8 million to reduce the burden of this devastating disease (Research Funding Data, 2017). The benefit of funding is returned by the Australian investigators who received funding are taking innovative approaches to tackle ovarian cancer through different therapeutic targets such as screening drugs targeting cell population by locating the sensitivity of cancer cells to ensure patients have another chance to respond to treatment (Lam et al, 2015 REV, National Health and Medical Research Council, 2017).

Contributions made by Australian Researchers towards ovarian cancer

Ovaries can become cancerous like other organs in the body. Detection of ovarian cancer is challenging and is generally found at an advanced stage or has already metastasised (Torpy, 2011 REV). Ovarian cancer (OC) refers to a heterogeneous disease, strong association with mutations in BRCA1 or BRCA2 (figure 1), low parity and genetic factors (Svahn et al, 2013 REV). Being the most gynaecological malignancy, OC is the fifth leading cause of cancer death affecting women aged 35 to 74 years also with an overall 40% of 5-year survival rate. Worldwide, women diagnosed annually with cancer is 225,000 and 140,000 die from the disease (Matulonis et al, 2014 REV). Ovarian cancer is classified into three types, this depends on where cancer begins on the type of cell (Desai, 2014 REV). Epithelial type begins on the

outside of the ovary (90% of most cases), Germ cell type begin from cells producing eggs (4% of most cases) and stromal type begin from supporting tissues within the ovary (rare cases) (Desai, 2014 REV).

Due to the poor survival of women diagnosed with ovarian cancer, there is persistent clinical demand in the search for effective prognostic biomarkers to evaluate outcomes of this cancer conducted by Australian researchers. Research by David Bowtell and colleagues (2017, AUS) identified the mutation of TP53 tumour-suppressor antibody serves as a biomarker promising for early detection for patients diagnosed with epithelial ovarian cancer (Yang et al, 2017 AUS). In conjunction with this biomarker, researchers from China are also focussing on the clinical significance of TP53 mutations for the development of a therapeutic target in screening and prognosis of epithelial ovarian cancer (Zhang et al, 2016 RES). Research conducted by Ian Campbell and associates (2018, AUS) focuses on investigating the germline variation genes that encode small GTPase proteins based on the Ras superfamily (Rho) associated with the risk of epithelial ovarian cancer susceptibility (Earp et al, 2018 AUS). The GTP binding proteins regulate cell proliferation and signal transduction by activating downstream effectors MAP-kinase Raf-1 (activates MEK/ERK pathway) for anti-apoptosis pathway (figure 1) (Earp et al, 2018 AUS). Consequently, international researchers from China have established therapeutic drugs to suppress mutationally activated Ras, specifically targeting the Ras/MAPK pathway (Ji et al, 2019 RES). Australian researcher Judith Clements and her colleagues (2018, AUS) contributed by their findings of tissue kallikrein peptidases (gene family encoding proteins in disease states) KLK4-7 as important therapeutic targets in ovarian cancer (figure 1) by exerting key modulatory effects on cancer-related proteins and genes (Wang et al, 2018 AUS). Clements coincides with German researchers focusing on over-expression of these kallikrein-related peptidases as novel therapeutic targets (Loessner et al, 2018 RES).

The role of MAPK/ERK and PI3K signalling pathways in ovarian cancer

Signal transduction is recognised as a potential target for cancer treatment and much effort has been made by Australian scientists to produce therapeutic agents to target signal transduction pathways (Wang et al, 2018 AUS, Yang et al, 2017 AUS) (figure 1). Based on the Reactome and Kegg databases along with research provided by the Australian scientists, the major enriched pathways for ovarian carcinomas were the Phosphoinositol 3 kinase (PI3K) pathway and the RAS pathway for cell proliferation and survival (Reibenwein and Krainer, 2008 REV). Mutations and dysregulations in ovarian carcinomas such as KRAS and BRAF (Earp et al, 2018 AUS) and also disruption of the tumour suppressor gene E-cadherin due to being oncogenic potential (Earp et al, 2018 AUS). This results in the loss of cell-cell adhesion which gains further motile and invasive behaviour this is the process known as the epithelial-to-mesenchymal transition (EMT) (figure 1) which is a crucial event under pathological conditions involving cancer progression (Gheldof and Berx, 2013 REV).

RAS signalling pathway is involved with the transduction of signals of several growth factors, cytokines and proto-oncogenes (Earp et al, 2018 AUS). For ovarian cancer cells, MAPK's play a critical role in stimulating the growth of the cells by the membrane receptor signals for Gonadotrophins (figure 1) (Smolle et al, 2013 REV). RAS proteins regulate signalling transduction and are also critical regulators of several aspects of malignant transformation and cell growth (De Luca et al, 2012 REV). The PI3K pathway is activated and altered in 70% of

ovarian cancer cases (De Luca et al, 2012 REV). The abnormal activation of the PI3K pathway results in increased activity of tumour onset, progression and invasion in ovarian cancer (fig 1). In accordance with the inhibition of the PI3K/Akt/mTOR signalling pathway it was found that it can re-sensitise chemoresistant cancer cells to chemotherapeutic drugs, there are established rational therapies by the Australian scientists and international research that target and inhibit both RAS pathway inhibiting tumour growth, spread and survival (Tanaka et al, 2011, Earp et al, 2018 AUS) (figure 1).

Implementing potential therapeutic targets of KLK-8 and CA125

Higher Human Kallikrein Gene 8 (KLK8) researched by Judith Clements (2018, AUS) is a new discovery from the members of the kallikrein-related peptidases undertaken as a potential biomarker in 147 malignant ovarian tissues refining our understanding of determinants of the prognosis in OC. (Wang et al, 2018 AUS, Loessner et al, 2018 RES). Due to these proteomics-based expression profiling technologies, increased amounts of prognostic biomarkers associated with tumours in relevance to ovarian carcinomas have been discovered contributing a promising therapeutic for the monitoring, prognosis and diagnosis of the disease (Wang et al, 2018 AUS). Coinciding with the recognition of the antigen CA125 (serum marker) also being a target for immunotherapy and an early detection marker (Scholler and Urban, 2007 REV). CA125 contain functional properties and specific locations which make it a choice for therapeutic targets also injecting anti-CA125 is considered a potential benefit of survival (Scholler and Urban, 2007 REV).

International researchers are implementing the natural drug Harmine which can be useful to treat ovarian cancer due to being associated with oncogenic Ras mutations (Ji et al, 2019 RES). This herbal drug belongs to the alkaloid family beta-carboline found in medicinal plants functioning to inhibit Ras in order for suppressing tumour growth (Ji et al, 2019 RES). Coinciding with the Australian scientist Ian Campbell who focuses on inhibiting the Ras pathway and ovarian cancer susceptibility (Earp et al, 2018 AUS).