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FINAL REPORT

Project / Program Title		Investigating Desmoglein-2 as a Superior Biomarker and Therapeutic Target for Multiple Myeloma
Name		Dr Craig Wallington-Beddoe
Award Received		2020 The Servier Staff 'Barry Young' Research Establishment Fellowship
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PROJECT SUMMARY

Multiple myeloma is an incurable aggressive cancer of the bone marrow. In Australia, almost 1,900 new cases are diagnosed every year with a 5 year survival rate of 50% and treatment costs exceeding $700,000 per patient. We have identified Desmoglein-2 (DSG2), a cell surface protein, to be expressed by 20% of myeloma patients who are 3 times more likely to die within 6 years of diagnosis. This study examines a new prognostic tool to rapidly identify these patients as well as new reagents to treat them.

PROJECT AIMS / OBJECTIVES

The HYPOTHESIS is that for a subset of multiple myeloma (MM) patients, DSG2 is overexpressed on their malignant plasma cells and correlates with the poorest outcome via regulation of tumour cell adhesion, proliferation and survival. This will be tested this via the following aims:

AIM 1: Assess the expression and prognostic significance of DSG2 in MM patients. DSG2 expression will be analysed prospectively in newly diagnosed/untreated MM patients by flow cytometry/ELISA, and results correlated with cytogenetics, therapy response and clinical outcomes. We have now analysed by flow cytometry the expression of DSG2 on the surface of bone marrow plasma cells from 60 newly-diagnosed patients with multiple myeloma who have presented to Flinders Medical Centre, Adelaide SA. Approximately 20% of these patients have been classified as DSG2-positive. These patients appear to be manifest a 3 times higher risk of their MM progressing/relapsing than patients with low DSG2 expression. Serum has been collected form these patients and ELISAs are being undertaken to detect the soluble fragment of DSG2 that circulates in blood. Bone marrow and serum DSG2 results are currently being correlated with tumour cytogenetics, response to induction chemotherapy, progression-free and overall survival. Results are pending as this is a prospective study.
AIM 2: Determine the potential of therapeutically targeting DSG2 in MM. The anti-MM activity of DSG2 blocking monoclonal antibodies (mAb) and DSG2 targeting mAb/siRNA loaded into porous silicon nanoparticles (pSiNPs) will be examined in vitro using adhesion and viability assays together with the most appropriate clinically available MM therapies. The best performing approach will be examined in vivo using orthotopic mouse models of human MM including patient-derived xenografts.

This aim is in progress. We have manufactured a DSG-specific monoclonal antibody in preparation for these animal experiments.

SIGNIFICANCE AND OUTCOMES

Multiple myeloma (MM) is an incurable malignancy of the bone marrow (BM) caused by the uncontrolled proliferation of neoplastic antibody-secreting plasma cells (PC). It is the second most common haematological malignancy with approximately 140,000 newly-diagnosed patients each year worldwide and 1,876 new cases diagnosed in Australia in 2018. Despite recent therapeutic advances, the 5-year survival rate is 50% and treatment costs exceed $700,000/patient. The disease can not only cause BM failure leading to severe infections and bleeding, but also kidney failure and weakened bone resulting in pathological fracture. We are investigating the utility of the adhesion protein Desmoglein-2 (DSG2) for both prognostic and therapeutic purposes. Our preliminary results suggest that DSG2 is overexpressed in 20%-30% of MM patients, helps to anchor MM-PCs to BM microenvironment cells and importantly, portends a poor prognosis. However, currently, prognostic evaluation of MM patients to guide decisions on therapy selection requires BM biopsy and genetic screening that delay the start of treatment. Our work aims to (i) establish DSG2 as a novel biomarker that can rapidly identify the top 20%-30% of MM patients with the poorest prognosis and (ii) provide new DSG2-targeting reagents, specifically DSG2 function-blocking monoclonal antibodies and DSG2-targeting porous silicon nanoparticles, to better treat these poor prognosis MM patients.

PUBLICATIONS / PRESENTATIONS

There are no items of interest to report at this time but a publication is being prepared for submission to Molecular Oncology before the end of 2021.

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