Report for Australian Head and Neck Cancer Society Research Foundation
Therapeutic potential for the treatment of adenoid cystic carcinoma

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Introduction

The natural history of adenoid cystic carcinoma (ACC) is relentless, defined by treatment failure, locoregional recurrence and metastatic disease. Treatment options are limited to palliative systemic therapy. Despite the introduction of therapies against new treatment targets, clinical trials present poor response rates and survival benefit.

Methodology

Our research aims to improve the therapeutic potential for treatment targets in head and neck ACC. Specifically, this has focused on the application of novel prochlorperazine (PCZ) combination therapy and spatiotemporal manipulation of treatment targets, with this repurposing of PCZ centred on inhibition of dynamin mediated endocytosis pathways[1].

Treatments are focused on monoclonal antibody therapy (mAb), the immune system driving increased antibody dependent cellular cytotoxicity (ADCC) and potential novel application of this technology to emerging ACC theranostics. Through its aims, this project has set out to establish a bank of patient tumour samples within our institution, utilise in vitro and in vivo ACC and treatment target expressing preclinical models, with the future aim of translation to proof of principle and future clinical trials.

Project Aims and Outcomes

Aim 1: To define the expression and localisation of therapeutic targets EGFR, PD-L2 and PSMA in ACC patient tumour samples and the relationship to clinicopathological characteristics with antibody selection optimisation.

Across independent studies, the epidermal growth factor receptor (EGFR) is overexpressed in up to 85% of ACC cases. In contrast, programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) expression is generally reported as absent. There has also been a recent interest in prostate specific membrane antigen (PSMA) with initial studies reporting expression in up to 94% of ACC cases.

Our project has aimed to combine presentation and clinicopathological correlation of these previously independent treatment targets and present updated ACC PSMA scoring with optimisation of PSMA antibody selection. Work is ongoing with 54 retrospective and prospective patient samples collected for this rare disease from 2000 through to the current period of study. Following final analysis, presentation of results is pending with completed publication.

Aims 2 and 3: To establish *in vitro* and *in vivo* preclinical models for ACC EGFR, PD-L/2 and PSMA expressing cancer cell lines to test mAb ADCC mediated therapies and PSMA theranostics.

The lack of preclinical models has been a challenge for researchers in developing new therapies for ACC due to the nature of the rarity of the disease. While a number of ACC cell lines have been developed, none are readily available for purchase from major cell banks. Furthermore, several cell lines have been found to be misidentified or cross-contaminated. Our initial researched focused on the use of MDA-ACC-01 cell line. In context of these difficulties, work was also undertaken on known PSMA expressing cell lines, chiefly prostate cancer derived cell lines LNCaP and C4-2B. Key results are presented (Figure 1 and Figure 2).

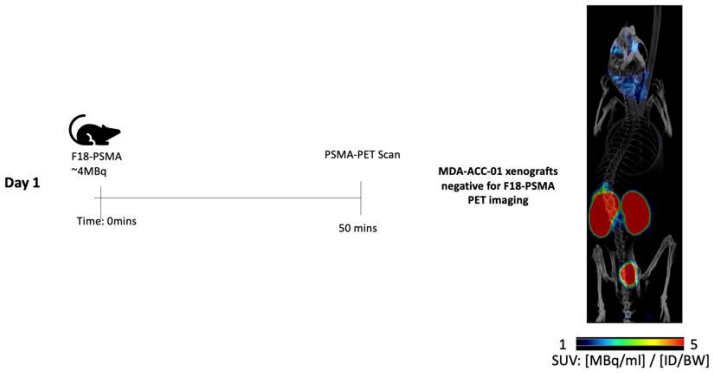

Figure 1: ACC cell line MDA-ACC-01 established in NSG-A2 preclinical model showing absent F-18 uptake on PSMA-PET with this result confirmed on tumour sample immunofluorescence and western blot (data not shown). This result limits application of this cell line in our ongoing preclinical models.

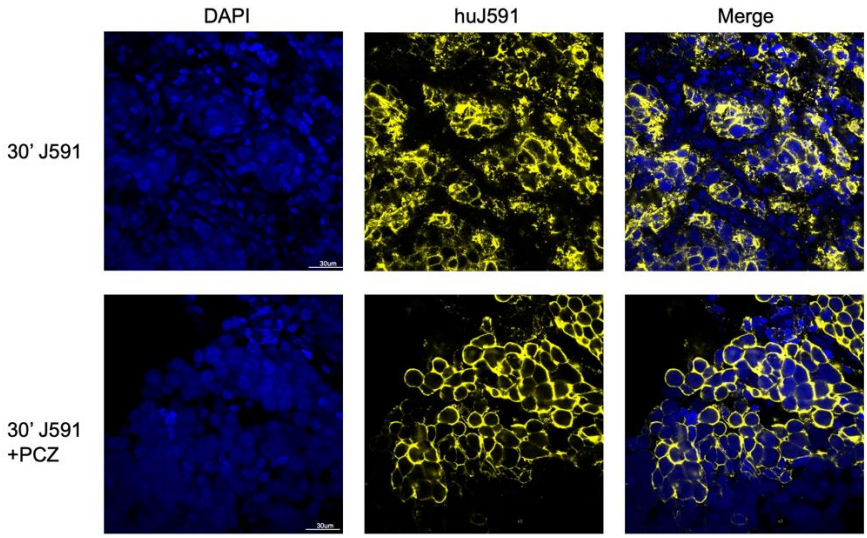

Figure 2: PSMA expression in prostate cancer cell line C4-2B established in NSG-A2 preclinical model, with *ex vivo* live uptake presenting prochlorperazine (PCZ) clustering of PSMA on the cell surface at 30 minutes when compared to punctate staining of internalised PSMA at the 30-minute control to provide the foundation for ongoing PSMA applications.

Aim 4: To apply prochlorperazine combination therapy in established preclinical models to potentially improve EGFR, PD-L1/2 and PSMA targeted imaging and therapeutic applications.

The exploration of future aims requires the successful establishment of ACC xenografts in preclinical models that maintain patient tumour characteristics and treatment target expression. Fortunately, we have collaborated with the Adenoid Cystic Carcinoma Research Foundation (ACCRF) and are continuing this aim with recently received xenografts. Preliminary results show EGFR, PD-L2, and PSMA expression across these samples with ongoing work in place to establish these preclinical models and facilitate further prochlorperazine and treatment target applications.

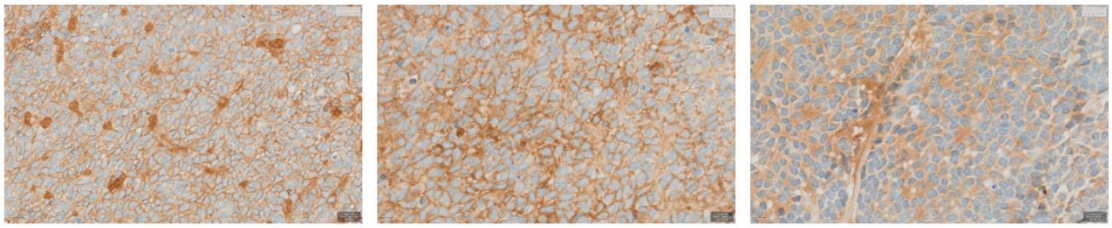

Figure 3: Representative immunohistochemical EGFR (31G7), PSMA (3E6) and PD-L2 (366C.9E5) expression detailed on screening of ACC patient xenograft tumour banks working towards establishment of preclinical models maintaining expression and presentation of these treatment targets.

Conclusion and Future Directions

This project presents the foundation for establishment of ACC preclinical models optimal for investigating the potential for improving response rates with prochlorperazine mAb therapies including EGFR, PSMA and PD-L2.

Presentations

- Therapeutic potential for the treatment of adenoid cystic carcinoma, 5th August 2021, Joint Scientific Meeting ANZHNCS and NZAPS, Queenstown, New Zealand
- PSMA: from prostate cancer to adenoid cystic carcinoma, 27th November 2020, Brisbane Cancer Conference, Brisbane, Australia
- A new treatment for adenoid cystic carcinoma – from prostate to the head and neck, 10th November, Australian Society for Medical Research (ASMR) QLD Postgraduate Conference, Brisbane, Australia

Publications

Nightingale J, Lum B, Ladwa R, Simpson F, Panizza B. Adenoid cystic carcinoma: A review of clinical features, treatment targets and advancement in improving the immune response to monoclonal antibody therapy. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2021:188523

References

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