APCRC-Q Australian Prostate Cancer Research Centre Queensland

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# *Regulation of nutrient uptake controls cancer cell growth and metabolism*


## A/Prof Jeff Holst (PhD)

Head, Origins of Cancer Program

**Centenary Institute**


When: 1:00pm-2:00pm

Monday, 19th October 2015

Where: Seminar Room 2003, Translational Research Institute, 37 Kent Street, Woolloongabba

Jeff completed his PhD (UNSW; 2003) before undertaking a postdoc at St Jude Children's Research Hospital in the USA. He is currently Faculty at the Centenary Institute, and Conjoint Associate Professor at the University of Sydney. As part of what's been termed 'The Holst Effect', his laboratory has uncovered how amino acid transporters regulate nutrient uptake in different cancers and cancer subtypes, and is currently supported by Movember/PCFA, NBCF and CCNSW. His recent work continues to determine how these amino acid transporters function in melanoma, breast cancer, prostate cancer and metabolic syndrome, as well as developing novel therapeutics aimed at blocking nutrient uptake in cancer.

## Abstract


Solid tumours activate angiogenic signals to ensure an adequate blood supply. In parallel, amino acid transporters on the cell surface are also increased so as to provide nutrients for the higher metabolic and growth demands of cancers. We are studying a number of amino acid transporters, including L-type amino acid transporters (LAT1 and LAT3) and alanine-serine-cysteine transporter 2 (ASCT2) that mediate uptake of amino acids including leucine and glutamine. Leucine and glutamine are critical for the activity of mTORC1, which regulates protein translation and cell growth, as well as contributing to cellular energy and as carbon and nitrogen donors.

Our laboratory utilises a variety of *in vitro* and *in vivo* techniques to dissect out how these transporters are regulated, the pathways they modulate, and use high throughput drug screening to develop novel inhibitors as putative therapeutics. Our work has shown that cancer cells respond to the demand for amino acids through integrated developmental and stress-mediated pathways, leading to increased amino acid transporter expression and cell growth. Some of these expression patterns are both cancer and stage/subtype specific, with some cancers more reliant on leucine, and others more reliant on glutamine. Furthermore, we have shown the knockdown of these transporters inhibits the growth of melanoma, prostate and breast cancer cells both *in vitro* and using in subcutaneous prostate and orthotopic breast cancer xenograft experiments. These data have shown that ASCT2 (glutamine transporter), LAT3 and LAT1 (leucine transporters) may provide novel therapeutic targets in early and late stage prostate cancer as well as other solid tumours such as melanoma and breast cancer. We have also developed new lead compounds targeting these three transporters, which are being further developed and tested in our preclinical mouse and patient explant models.


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