Novel cancer therapies: blocking the cells that control tumour growth

Researchers at Hudson Institute have identified a mechanism by which cancer cells are able to invade and spread, and are targeting this in the treatment of cancer.

Our team have identified a way to block tumour progression, stabilise disease, and prevent disease recurrence.

Summary

The Hudson team has discovered a molecule expressed by cancer cells that is critical for the implantation and invasion of tumours into underlying healthy tissue. Using *in vitro* and *in vivo* models, they have shown that blocking this molecule prevents invasion into the basement membrane level and thus prevents metastasis.

The team is developing this work towards a novel, effective anti-cancer strategy that can stabilise or regress disease and enhance the effectiveness of existing treatments for cancer. A direct inhibitor of metastasis will profoundly reduce cancer-related mortality, and will increase survival time for patients with primary or recurrent disease.

Targeting leader cells to prevent spread

Ovarian cancer is often diagnosed at a late stage of disease, when it has spread beyond the ovaries to other organs in the peritoneal cavity. This spread can be through cellular aggregates, or spheroids, that break off from the primary tumour site. These aggregates may then attach and invade into other locations. The ability of these aggregates to form tumour deposits and invade into healthy tissue is controlled by leader cells, or cancer stem cells. Therapies that target these leader cells are likely to be key in achieving effective, sustained remission of disease.

Our researchers have recently found that leader cells in ovarian cancer are enriched for the protein KRT14. They have also found that KRT14 is essential for the invasion of ovarian cancer cells into the basement membrane level and subsequent development of a tumour. They are currently developing a monoclonal antibody that targets a portion of KRT14 to inhibit the invasion process.

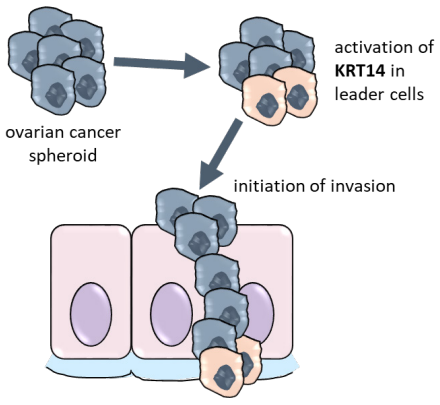

Figure 1. Schematic representation of metastatic spread of ovarian cancer cells.

Applications

Many tumour types employ this mechanism of invasion. Ovarian cancer is an example of particular need.

Ovarian cancer is the eighth most common cancer overall among women, and is the most common cause of death from a gynaecological cancer.

Current standard treatment options for women with ovarian cancer include surgery with chemotherapy. Because there is no early detection or screening test for ovarian cancer, most cases are diagnosed at an advanced stage of disease, when the 5-year survival rate is only 43%. In many cases disease is no longer confined to the ovaries and has spread to other organs in the peritoneal cavity. Approximately 75% of patients will relapse, often with chemotherapy-resistant disease which limits treatment options further.

There is an urgent and unmet need for novel therapeutic options aimed at preventing the spread of metastatic disease, to improve the management and long-term survival of cancer patients.

Key data

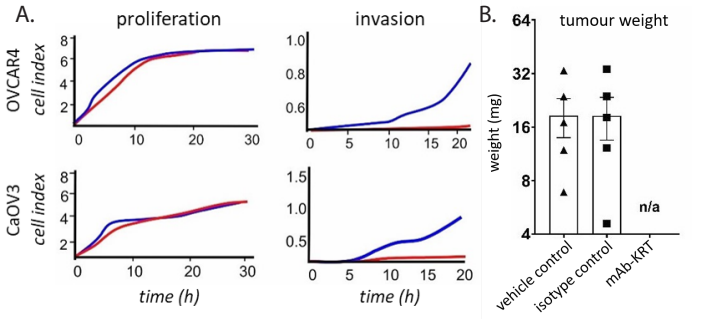

Figure 2A. KRT14 is required for migration and invasion of ovarian cancer cells *in vitro*.
KRT14 gene expression was disrupted using CRISPR technology in ovarian cancer cell lines OVCAR4 and CaOV3 ($KRT14^{WT}$, blue; $KRT14^{KO}$, red). Proliferation and invasion were measured using xCELLigence. Loss of KRT14 expression had no effect on proliferation, but completely abrogated invasion through a mesothelial monolayer *in vitro*.

Figure 2B. Administration of novel mAb-KRT causes direct regression of established tumour mass in mice.
Mice (n=10/group) with established primary ovarian tumours were administered mAb-KRT in bi-weekly 5mg/kg doses IP. Controls received either isotype-matched control antibody or PBS vehicle alone. After 3 weeks of continued treatment all animals were culled and examined, and tumour mass measured. 60% of mice that received either vehicle or isotype control antibody had primary ovarian tumours at cull. By contrast, no tumours could be identified in mice treated with mAb-KRT (mean +/-SD).

IP position

International patent application filed.

Development pathway

Our team have identified a lead candidate monoclonal antibody for inhibition of the target, and are progressing through preclinical studies. They are currently seeking opportunities for co-investment, licensing or collaboration to further develop this cancer treatment program.

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Team

This project is managed by Dr Maree Bilandzic and Dr Andrew Stephens from Hudson's Ovarian Cancer Biomarkers research group.

Dr Andrew Stephens is an Ovarian Cancer Research Foundation (OCRF) Research Fellow and head of the Ovarian Cancer Biomarkers research group. A leading authority on the application of proteomics technologies and a Senior Research Affiliate (Honorary) with Epworth Healthcare, Dr Stephens is one of Australia's foremost experts in the field of ovarian cancer research.

Dr Maree Bilandzic is a Senior Research Fellow at Hudson and has extensive experience in ovarian cancer research, with a particular focus on understanding pathways controlling critical stages of metastasis. She has developed unique laboratory models to examine these events in real-time, key to examining how early cell-cell interactions dictate disease progression.

Related publication

Keratin-14 (KRT14) Positive Leader Cells Mediate Mesothelial Clearance and Invasion by Ovarian Cancer Cells. Bilandzic M … Stephens AN, 2019 *Cancers* doi:10.3390/cancers11091228

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