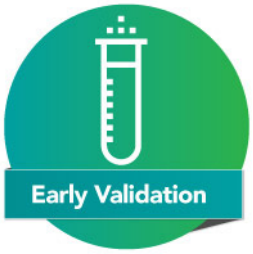
PROJECT TITLE

Antibody-based therapy targeting cell surface GRP78 for the treatment of prostate cancer



PRINCIPAL INVESTIGATOR

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PROJECT SUMMARY

Prostate cancer (PCa) is the most common cancer to affect Canadian men. One in seven men will be diagnosed with PCa in their lifetime. Advanced stages of prostate cancer (PCa) are often incurable and current therapies fail to eliminate the disease. Over the past 10 years, we have characterized a novel pathway that drives cancer cell growth/survival. Specifically, PCa cells display a unique cell surface protein, termed GRP78, that not only enhances tumour growth but causes the immune system to produce anti-GRP78 autoantibodies in the blood of PCa patients. Unfortunately, these anti-GRP78 autoantibodies further enhance the growth/survival of PCa cells, thereby accelerating tumour growth. It is worth noting that cell surface GRP78 possesses two important regions: an N-terminal domain linked to cell growth/survival which is recognized by these anti-GRP78 autoantibodies, and a C-terminal domain known to activate PCa cell death pathways. We have now produced using molecular biology techniques a recombinant antibody (rAB) that targets the C-terminal domain of cell surface GRP78. We have now shown that, in the presence of the anti-GRP78 autoantibodies, this rAB dramatic induces cell death in cultured PCa cells, leading to a dramatic regression of tumours in mice. Given that PCa patients already have elevated blood levels of these anti-GRP78 autoantibodies, we hypothesize that treatment with this rAB would selectively kill cancer cells by activating cellular death pathways, thereby resulting in tumour regression. This new discovery is the first to answer an unmet medical need of defining a novel target for advanced PCa. We plan to determine the optimal dose of the rAB that shows the greatest anti-tumourigenic effects in mice. Furthermore, we are actively mapping the specific site in GRP78 recognized by the rAB. This important information will allow us to develop new medicines that act in a similar fashion to that of the rAB. If successful, we will have created a new class of medicines that target cell surface GRP78 for the treatment and management of advanced PCa. Targeting cell surface GRP78 would be a particularly effective treatment strategy in PCa patients with metastatic disease having elevated blood levels of anti-GRP78 autoantibodies.