PROJECT TITLE

Development of a therapeutic approach to target B cell exhaustion in high-risk early stage bladder cancer

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SCIENTIFIC SUMMARY

Bladder cancer presents as early stage non-muscle invasive bladder cancer (NMIBC) in 75% of newly diagnosed cases. The average age of bladder cancer diagnosis is 73 years. BCG immunotherapy using an attenuated strain of Mycobacterium bovis (M. bovis), also known as bacillus Calmette-Guérin (BCG; commonly used as a vaccine for prevention of tuberculosis), has remained the gold standard treatment for NMIBC over the last 45 years. Unfortunately, up to 50% patients still do not respond to BCG therapy and suffer from recurrence and progression to higher stage disease that often requires bladder removal surgery. Furthermore, novel immune checkpoint blockade therapies have shown minimal improvement in enhancing response to BCG in patients with NMIBC.

Our published analysis of large cohorts showed that increased tumor B cell density in pre-BCG treatment tumors of patients with NMIBC, associates with significantly shorter recurrence free survival and poor response to BCG immunotherapy. Among the different immune cells located within bladder tumors, B cells in NMIBC tumors were predominantly located within aggregates of immune cells called tertiary lymphoid structures (TLS). Tertiary lymphoid structures harboring exhausted immune cells with a high expression of immune checkpoint proteins, were also abundant and located adjacent to tumor epithelium in patients with a high-risk disease and deemed as BCG non-responders. Factors underlying such immunosuppression in bladder cancer patients span from older age, degree of chronic carcinogen exposure, tumor stage/grade, co-morbidities and patient sex/gender. Chronic mucosal inflammation is thus multifactorial and a major risk factor underlying bladder cancer development and progression.

While smoking accounts for 50% of incident bladder cancer cases, the role of other etiological factors that also cause chronic inflammation and potentially increase the risk of bladder cancer and poor response to BCG therapy, is not well defined. An important finding from epidemiological studies is the association between B cell dysfunction associated autoimmune conditions and increased risk for incidence of all cancers including that of the urinary bladder. In this proposed study, we will validate biomarkers discovered through our previous investigations in two large cohorts of patients. We will then integrate those with features of host immune system fitness via leveraging population level data from the Ontario cancer registry (2010-2022) and the pan-Canadian Bladder Cancer Information System to define the association between chronic inflammation and outcomes following BCG treatment in patients with NMIBC. Finally, we will develop the proof-of-principle therapeutic approach that utilizes the above information towards the next phase of early clinical translation of targeting pre-existing immune exhaustion in patients undergoing BCG treatment.

A holistic approach thus undertaken will provide real world information about the host and tumor, and have a substantial near-term impact in early identification of patients who will not benefit from any immunomodulatory therapies (BCG and other contemporary immune checkpoint blockade therapies). Importantly, the outcomes from this project will rationalize consideration of patient age and sex/gender in the design of trials for novel immunotherapies.