Granulosa Cell Tumour Research Foundation

Working to discover effective treatments for GCT of the ovary

2022 Research Grant Awards

The Granulosa Cell Tumour Research Foundation (GCTRF) is pleased to announce that research grants have been awarded to three (3) researchers. The total investment for these awards is $240,000 USD, bringing the total amount we have invested in GCT research since 2006 to over $600,000 USD. A summary of the new awardees follows below.

GCTRF can only make these awards thanks to the generosity of your donations to our research program. On behalf of all the women we strive to serve, we offer our sincerest gratitude for your support.

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Awardee: Dr. Simon Chu
Hudson Institute for Medical Research
Clayton, Victoria, Australia

Title: *Elucidating the druggable interface(s) of the FOXL2^{C134W} protein using cryo-Electron Microscopy (cryo-EM)*

Summary: Adult Granulosa cell tumours (aGCT) represent a specific subset of malignant ovarian tumours. Approximately 80% of patients with advanced or recurrent tumours die from their disease. The therapeutic options for aGCT are very limited. Despite the impact of this disease on affected women, remarkably little is known about the molecular changes that give rise to GCT.

A specific mutation in the FOXL2 gene (C134W) is unique to aGCT (present in ~97% of all aGCT), being not been observed in juvenile GCT. FOXL2 encodes a transcription factor belonging to the Forkhead superfamily, and is expressed in the granulosa cells of the ovary during development and throughout female reproductive life, playing a key role in maintaining ovarian identity. As the C134W-FOXL2 mutation is unique to the majority of aGCT, it is a potentially attractive therapeutic target. Additionally, investigating how the FOXL2 mutation interacts with other key genes and/or intracellular signalling pathways (eg SMAD proteins) may also identify other therapeutic targets for the treatment of aGCT.

Significance: In this project, we will use a powerful technique known as cryo-electron microscopy (cryoEM), to elucidate the three-dimensional (3D) structure of the C134W-FOXL2 protein to compare it with the wild-type FOXL2 protein, as well as its interactions with the SMAD protein family, in order to discover regions of the protein that may be uniquely targeted with designed drugs. The power of this technology is the ability to draw the 3D structure of the protein in its native state, as well as its association with interacting proteins and DNA at any given time, providing information that cannot be obtained using more conventional x-ray crystallography.

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Awardee: Dr. So-Youn Kim
University of Nebraska Medical Center
Omaha, Nebraska, USA

Title: *Investigation of the Role of PPARγ in Growth and Metabolism of Granulosa Cell Tumor*

Summary: PPARγ is a nuclear protein and regulates genes for energy metabolism. PPARγ is highly expressed in granulosa cell tumors, however, its function in GCT has been unknown. The proposed works will help us understand the role of PPARγ in the development of granulosa cell tumors. Such understanding will benefit the developing interventions and treatments for GCT patients.

Significance: Even though GCT shows a favorable prognosis for 5 years after initial treatments, GCT recurrence occurs late after more than 5 years and significantly drops survival rates in GCT patients. Tumor size and stage at initial diagnosis are associated with high recurrence risk. Therefore, the need for lifelong management and treatment of GCT for those at high risk for primary GCT incidence and recurrence has been long recognized.

However, besides debulking surgery, there are no recommendations and/or interventions for the GCT patients, and such limitations reflect a poor understanding of the nature of GCT development and progression. Our proposed research is expected to unveil the metabolic characteristics of GCT and its association with GCT growth by establishing PPARγ as a feasible and long-term target molecule for the health outcomes of GCT patients.

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Awardee: Dr. YangXin Fu
University of Alberta
Edmonton, Alberta, Canada

Title: *Investigating combination treatments for GCT in preclinical animal models*

Summary: Studies on GCT are hampered by availability of only a single established cell line and few animal models, none of which are ideal (some develop tumors at low frequency, others lack a particular mutation characteristic of adult GCT). One goal of this study is to establish a mouse model that carries the characteristic mutation and forms tumors at a high frequency. This model would greatly enhance our ability to investigate potential therapies for GCT. In addition, we propose to test a novel combination treatment that we predict will attack GCT from multiple angles including direct tumor cell killing and inducing an anti-tumor immune response, potentially providing lasting protection from GCT recurrence. We will make best use of limited reagents by employing preclinical testing in the lab and in the most representative animal models to optimize the way these agents are combined to give maximum antitumor effect.

Significance: Information gained from this study should ultimately lead to a predicted strategy for combining these agents for clinical development in treating GCT patients.