We believe that….

“Research resilience, perseverance, stamina, rigor, continuous learning capacity, teamwork, and humility, are fundamental tenets to accelerate discoveries for improving human health”

The primary research interest in Dr. Telleria’s laboratory is in the field of ovarian cancer biology and preclinical therapy. Ovarian cancer is the deadliest gynecologic malignancy in developed countries. The 5-year average survival rate for these patients is <40% and has not improved since the introduction, more than 30 years ago, of platinum (Pt)-based chemotherapy following debulking surgery. This is because 70% of patients are diagnosed with advanced disease as early signs and symptoms are difficult to recognize. Pilot programs to guide early diagnosis associated with low-volume resectable disease are beginning to evolve yet much work lies ahead before predictive screening tests reach the clinic. Most patients diagnosed with the disease have numerous tumoral masses within the abdominal cavity making debulking surgery a difficult task. If optimal debulking surgery is achieved—meaning that no macroscopic disease remains—and the patient completes 6 cycles of Pt-based chemotherapy, the standard responder still recurs within 16-24 months, rarely responds to a second round of Pt-based therapy, and poorly responds to alternative cytotoxic drugs, eventually succumbing to the disease. While these patients are clinically in remission, they do not receive any maintenance therapy; this time-frame is a missing opportunity to intervene with a low toxic therapeutic approach to prevent residual cellular clones escaping Pt toxicity to timely grow back into sizable tumors. Thus, the long term goal in our laboratory is to develop a maintenance therapeutic approach to be offered to patients diagnosed with ovarian cancer after they recover from debulking surgery and the subsequent cycles of chemotherapy, to maintain residual ovarian cancer cells, which had escaped initial therapy, in a non-proliferative or dormant status, keeping the disease in remission.

Clinical translational value of the use of maintenance therapy in the context of platinum (Pt)-based chemotherapy for ovarian cancer. Pt is often given formulated as cisplatin or carboplatin in combination with a taxane (e.g. paclitaxel). The ascending arcs following the sharp drops in disease progression after each Pt treatment represent repopulation events of escaping clones during the resting periods in between Pt cycles.
Research Projects

**Tumor Burden in Ovarian Cancer.** This project utilizes various epithelial ovarian cancer cell lines ranking the highest in their genomic matchup to the genotype of high grade serous ovarian cancer tumors, which account for 2/3 of cases of ovarian cancer, and assess their capacity to develop peritoneal disease in mouse models. The project aims to standardize multifaceted—anatomical, physiological, and behavioral—longitudinal descriptors of disease progression that can be utilized by the scientific community, broadly and affordably, to study, within the environment of the abdominal cavity, the biology and response of high-grade serous ovarian tumors to novel therapies.

A macroscopic human ovarian cancer tumor growing in the abdominal area of an immunosuppressed female mouse depicts two distinct histological patterns: (i) diffuse solid pattern (A, D, G); and (ii) papillary, showing irregular slit-like spaces (B, E, H at lower magnification; C, F, I at higher magnification). Tumors express mutant p53 and, in particular, express CA125 in cells bordering the slit-like spaces. Scar bar = 50 μm. L: liver; Tu: tumor; Sto: stomach. H&E: hematoxylin and eosin staining.

**Ovarian Cancer Multicellular Structures.** This research proposal is to assess the tumorigenic capacity of ovarian cancer cells that arrange as multicellular structures free-floating in the abdominal cavity. As these multicellular structures seem to be active mediators of ovarian cancer evolution, development of therapeutic interventions to interrupt their formation may be an efficient tool to interject disease progression.

Proposed model for the role of ovarian cancer multicellular structures (MCS) in peritoneal carcinomatosis. Selected cells from microscopic nodules with distinctive capacity to form MCS, adapt, survive, and grow in the peritoneal fluid developing irregular and organized spheroidal MCS that might evade chemotherapy and/or preserve ovarian cancer
initiating cells (CIC), leading to a feed-forward, chemo-resistant, and self-renewal recurrent seeding. MCS committed to develop the solid component of the disease will adhere, disaggregate, migrate, and invade the mesothelial cell layer covering the surface of the peritoneum (maroon), and form foci that neo-vascularize and grow (green). Other MCS might develop non-invasive nodules that amplify the cellularity within the “liquid” compartment causing ascites. Blue: highly differentiated ovarian cancer cells. Pink: less differentiated cancer cells with self-renewal capacity. Red: new blood vessels. Gray: extracellular matrix. Yellow: fibroblasts.

**Peritoneal Ovarian Cancer Dormancy.** This project aims at identifying where the disease hides within the peritoneal cavity in a dormant state after ‘successful’ front line surgery and chemotherapy, and studying the molecular drivers of cellular dormancy. Knowing the molecular network, the cells set in motion to drive the process of dormancy and the subsequent awakening period, we hope to find an Achilles' heel of the process in which a medical intervention can be attained, to either extend the dormant state, and, consequently, the progression free survival following front line standard of care, or, instead, prevent the awakening process when cells grow back into sizable tumors that make the patient sick again. Total elimination of ovarian cancer cells is the ideal goal, yet the alternative of developing a therapy that keeps ovarian cancer in a chronic dormant state is relevant as patients would have a chronic manageable asymptomatic disease or ‘cancer without disease.’

![Hypothetical model of ovarian cancer dormancy after debulking surgery and platinum-taxane (PT) therapy, relapse after chemotherapy-associated dormancy, and potential stages of the disease where therapeutic intervention is envisioned. DFS, disease free survival; OS, overall survival; MRD, minimal residual disease.](image)

**Proteotoxic Stress: Target of Ovarian Cancer?** Because cancer cells in general and ovarian cancer cells in particular have high metabolic rate, including elevated protein synthesis, folding, and degradation, the intracellular organelles and macromolecular systems in charge of regulating protein homeostasis, such as the endoplasmic reticulum (ER) and the proteasome, operate under constant stress; this provides an opportunity for developing novel therapeutic approaches leading to protein intoxication or proteotoxicity of the ovarian cancer cells that would allow killing the cells that had escaped initial chemotherapy but are not dividing or recurring. One such approach under evaluation is the use of drugs that sensitize ovarian cancer cells to the toxicity of proteasome inhibition by causing sufficient ER stress to tipping cell fate toward ER-mediated cell death.
Drug Repurposing. The focus of this investigation is to create strategies for repurposing or repositioning compounds originally developed for reproductive medicine (e.g. antiprogestins) or HIV treatment (e.g. HIV inhibitors), to treat ovarian cancer in conjunction with standard chemotherapy. Dr. Telleria’s laboratory demonstrated that these compounds are potent blockers of ovarian cancer cell growth. The ultimate objective is to contribute with a therapeutic approach to convert ovarian cancer into a treatable chronic disease.

Projects in Collaboration

Uterine Hyperplasia and Polycystic Ovarian Syndrome. Polycystic Ovary Syndrome (PCOS) is a common endocrine system disorder occurring among women of reproductive age. The syndrome is defined by oligo or anovulation, ovarian cysts and/or hyperandrogenism. It is also associated with several conditions such as insulin resistance, metabolic syndrome, obesity, type 2 diabetes, heart disease, mood disorders, inflammation, infertility, and predisposition to uterine cancer. This project, in collaboration with Dr. Motta from the University of Buenos Aires, Argentina, uses a PCOS murine model to investigate whether the animals are prone to develop initial traits of uterine hyperplasia that may explain the high correlation found in patients having PCOS that later on develop uterine cancer.

Endometriosis and Ovarian Pathophysiology. Endometriosis is a chronic, inflammatory disease defined by the identification of endometrial tissue outside the uterus. In this project, in collaboration with Dr. Casais from the University of San Luis, Argentina, we study the proliferative capacity of ovarian tissue and endometrial lesions in wildtype and TNFRp55 knockout mice. The project intends to link a potential origin of ovarian cancer in patients with preceding endometriosis.
Laboratory Members

Sarah Alghamdi, MBBS, MSc Candidate. Sarah’s research involves the recreation of peritoneal ovarian cancer disease in immunosuppressed mice. She is a native of Saudi Arabia.

Robert Dube, BSc, MSc Candidate. A McGill graduate, Robert’s research deals with investigating the potential utilization of novel anti-glucocorticoid agents not having anti-progestational activity, for the treatment of ovarian cancer. Rob is a native of Montreal.

Silvana Ferreira, BSc, PhD Candidate. Silvana is pursuing her doctorate from the University of Buenos Aires with the Co-DIRECTION of Dr. Telleria here at McGill University. She shares research time in Argentina and Montreal. Her project revolves around the study of uterine hyperplasia associated with Polycystic Ovarian Syndrome (PCOS) using an animal model of disease.

Alicia Goyeneche, PhD. Researcher. Alicia’s research focus on understanding the pathobiology of multicellular structures that free-float in the peritoneal cavity of patients with advanced ovarian cancer. She has a strong training in cancer biology and laboratory medicine. She obtained her PhD in her native country, Argentina.

Michael Licio, BSc, MSc Candidate. A McGill graduate, Michael’s research focuses on the study of the clonal evolution of ovarian cancer. He is a native of Montreal.

Sabrina Ritch, BSc, PhD Candidate. A McGill Graduate, Sabrina’s research is geared towards the investigation of the migratory and invasive capabilities of high-grade serous ovarian cancer cells along disease progression and the potential treatment with antiprogestins. She is a native of Montreal.
**Mahbuba Subeha, MBBS, MSc, PhD Candidate.** A native of Bangladesh, Mahbuba is pursuing her doctorate in experimental pathology investigating the potential anti-ovarian cancer efficacy of drugs usually utilized to treat HIV patients.

**Federica Ghersa, PhD Candidate.** Federica is pursuing her doctorate from the University of San Luis, Argentina. She is an exchange student that joined our laboratory with an ELAP (Emerging Leaders in the American Program) scholarship from Global Affairs Canada, to investigate the histopathological impact of endometriosis on the ovary using a mouse model of endometriosis in TNFalpha-P55 KO mice.

### Publications

Click [here](https://www.ncbi.nlm.nih.gov/pubmed/?term=Telleria+C) to see Dr. Telleria list of publications registered in PubMed.

### Laboratory Miscellaneous

“we do western blot a lot”
Images Generated in the Laboratory

Immunofluorescence showing E-Cadherin expression in irregular and spheroidal multicellular structures (MCS) of PEO6 ovarian cancer cells after being cytocentrifuged. The green fluorescence represents E-cadherin, whereas the nuclei are stained in blue with DAPI. (A) Composite image showing the distribution of E-cadherin in the cell membrane. (B) E-cadherin expression without DAPI overlay.

Green-fluorescence protein expressing A2780 ovarian cancer cells within spontaneously formed MCS free-floating in a culture dish. The upper panel shows a spheroidal MCS whereas the lower panel shows irregular MCS.
Non-adherent clusters of PEO6 high-grade serous ovarian cancer cells with cuboidal and flat appearance (A). Floating MCS embedded in Histogel™ followed by fixation in paraformaldehyde, embedding in paraffin, sliced, and stained with hematoxylin; image shows structures either with spheroidal or with grape-like appearances (B).

MCS within peritoneal effusions proliferate, depict compact (asterisks) and hollow (arrowheads) structures as shown by inverted confocal microscopy. EDU labeling denotes cells synthesizing DNA; Green denotes expression of E-cadherin; Hoechst stains the DNA.

Invasion of clear cell SKOV-3 ovarian cancer cells through a polycarbonate membrane of 8 µm and stained with phalloidin (red) to denote F-actin distribution in the cytoplasm, and SYTOX Green to denote the nuclei. The image was taken after letting the cells migrate for 24 h before fixation and staining.

Useful Links

Ovarian Cancer Canada / Cancer de l’ovaire Canada
http://www.ovariancanada.org/got-ladyballs

Rivkin Center for Ovarian Cancer Research
https://www.rivkin.org/

Canadian Cancer Society
http://www.cancer.ca/en/?region=qc

NIH National Cancer Institute
https://www.cancer.gov/types/ovarian

Canadian Conference on Ovarian Cancer Research (CCOCR)
http://www.ccocr.org/
Canadian Cancer Research Conference
http://conference.ccra-acrc.ca/

American Association for Cancer Research
http://www.aacr.org/Pages/Home.aspx

American Cancer Society
https://www.cancer.org/

Canadian Institutes for Health Research
http://cihr-irsc.gc.ca/e/193.html

American Society of Clinical Oncology
https://www.asco.org/

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