

THE LUNG CENTRE

The Canadian Mesothelioma Foundation Professorship in Mesothelioma Research

AN IMPACT REPORT PREPARED FOR:
CANADIAN MESOTHELIOMA FOUNDATION

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All photos were taken either before the COVID-19 pandemic or following appropriate physical distancing guidelines.

Thank you

To the Board of the Canadian Mesothelioma Foundation,

I would like to take this opportunity to thank you for your generous foundational support of the Canadian Mesothelioma Foundation Professorship in Mesothelioma Research at University Health Network (UHN). Your support makes it possible for me and my colleagues to continue leading studies and clinical trials that help patients from across Canada access more effective therapies today while changing how we treat mesothelioma in the future.

In this report, you will find updates about our most recent work in mesothelioma research. The results of our groundbreaking Surgery for Malignant Pleural Mesothelioma After Radiotherapy (SMART) trial were published in January 2021 in *The Lancet Oncology*, a very high-impact scientific journal. The publication generated significant interest from researchers across the globe. Building on these results, the Surgery for Mesothelioma After Radiation Therapy using Extended pleural Resection (SMARTER) trial is underway. We are in the process of recruiting the final three patients, and have gathered a great deal of valuable data. Additional lab-based studies have guided the development of our clinical trials, including an exciting study published in *Science Translational Medicine* in April 2021. In this study, we found that, when combined with radiation and surgery, immune-boosting drugs increased the anti-cancer immune response and led to long-lasting control and resistance against cancer. We achieved cure in 40 per cent of cases prior to surgery, and essentially created vaccination against future tumour recurrence. These results will inform our future studies into immunotherapy to enhance mesothelioma treatment.

I am also pleased to introduce Dr. Dorinda Mullen, who is a current research fellow on our team. In this report, you will find an interview with Dr. Mullen in which she discusses her research into the impacts of genetic alteration on our SMART results.

I trust that you will enjoy reading about the research progress generously supported by the Canadian Mesothelioma Foundation, as outlined in this report. On behalf of the Toronto Mesothelioma Program at UHN, thank you for your encouragement, trust and generosity.

Sincerely,



Dr. Marc de Perrot, MD

Canadian Mesothelioma Foundation Professor in Mesothelioma Research,
Director, Toronto Mesothelioma Program,
University Health Network
Professor of Surgery and Immunology,
University of Toronto

Summary of Dr. Marc de Perrot's research progress

Mesothelioma remains associated with very poor outcomes, with most patients surviving less than a year after their diagnosis. Incidences of this devastating disease are on the rise, with 600 new cases reported every year in Canada, a number that has doubled over the past two decades.

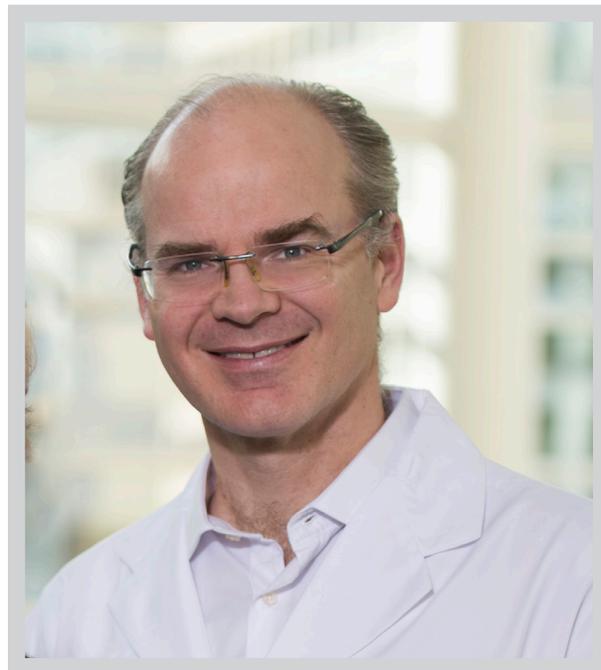
With globally-leading expertise spanning Toronto General Hospital and Princess Margaret Cancer Centre, the team at UHN sees the majority of early stage mesothelioma patients from all across Canada. Through the Toronto Mesothelioma Program at UHN, patients have access to mesothelioma-specific surgical, radiation and medical oncology expertise under one roof, facilitating multidisciplinary treatment recommendations and access to clinical trials that are often not available in patients' local cancer centres.

At the head of this groundbreaking research and care is Dr. Marc de Perrot, Canadian Mesothelioma Foundation Professor in Mesothelioma Research. In addition to working as an expert surgeon, Dr. de Perrot leads the team's translational research lab within the Latner Thoracic Surgery Research Laboratories and performs world-leading clinical research. With dual expertise in the clinic and the lab, Dr. de Perrot and his team are well-positioned to capitalize on the benefits of both, using insights from the clinic to inform studies in the lab and vice versa.

Dr. de Perrot and his colleagues within the Toronto Mesothelioma Program – which includes other leading experts in mesothelioma such as Dr. John Cho, radiation oncologist – are working to change the devastating toll of mesothelioma, developing new treatments so that patients can live longer, healthier lives.

The SMART Trial: The foundation of a paradigm shift in treatment

Extrapleural pneumonectomy – the surgical removal of a patient's entire lung – is one common intervention for the treatment of pleural mesothelioma. However, it is associated with significant negative effects with limited



Dr. Marc de Perrot

clinical benefit for many patients.

In an article published in the prestigious journal *The Lancet Oncology* in January 2021, Dr. de Perrot, Dr. Cho and their colleagues shared the results of the Surgery for Malignant Pleural Mesothelioma After Radiotherapy (SMART) trial. In this trial, the research team demonstrated the effectiveness of combining pneumonectomy with radiotherapy to improve patient outcomes.

The team hypothesized that distant recurrence – when cancer recurs in parts of the body far from where it originally appeared – may occur due to inadvertent spreading of tumour cells during the pneumonectomy. Therefore, radiation therapy prior to surgery might inactivate these cells, delaying and potentially preventing their spread, and improving disease-free survival.

Radiation therapy was performed once a day for five consecutive days. The following week, patients underwent a pneumonectomy. After their surgery, the team followed up with patients regularly over the course of five years.

96 patients were included in the analysis. As of April 2020 when the study completed, median overall survival was 24.4 months and 25 per cent of patients had no disease recurrence. The team observed overall survival rates of 75 per cent at three years, with patients with epithelial mesothelioma experiencing better outcomes. These are the best results reported so far in large prospective clinical trials for pleural mesothelioma, both in terms of disease-free and overall survival.

Additional patients who were not included in the trial's analysis but who received treatment guided by the SMART protocol had similar survival rates to study participants, further demonstrating the consistency of treatment results.

Of considerable interest, investigators noticed that the short course of radiation triggered an immune response that impacted treatment, which is being leveraged as a platform for immunotherapy in future studies, including the SMARTER trial.

An additional challenge associated with the SMART trial is the high level of multidisciplinary expertise necessary to effectively implement treatment. The protocol is demanding, requiring significant surgical and radiotherapy expertise, which centres without multidisciplinary resources may be unable to implement.

Understanding why some patients do not respond to radiation therapy

While the short course of radiation used in SMART improved median overall survival – even leading to no disease recurrence for a subset of patients – not all patients responded to the treatment. Non-epithelioid pleural mesothelioma patients are particularly resistant to radiotherapy. Dr. de Perrot and his colleagues developed a study using an animal model to understand how radiation can be optimized to provide these patients with the same beneficial treatment.

To find these answers, the team investigated the immune

response that was triggered by the short course of radiation in the SMART trial. Proteins called GITR/GITRL are involved with activating the immune response. Some immunotherapy drugs trigger GITR signalling in order to boost immune responses against tumours.

Non-epithelioid mesothelioma patients tended to have higher levels of GITR/GITRL expression. However, instead of improving their defenses against the tumours, Dr. de Perrot and his colleagues discovered that this immune response was actually associated with resistance to chemo- and radiotherapy in this subset of patients. That is because, in non-epithelioid mesothelioma varieties, the tumours appear to have the ability to mimic the immune system, preventing it from activating and targeting the tumour. In these varieties, the expression of GITR/GITRL may be a method for cancer cells to escape the immune system and survive, causing cancer to recur.

These observations carry important information for the development of immunotherapy and its impact on tumour cell varieties.

Investigating the impacts of systematic therapy on vulnerable patient groups

Vulnerable subgroups, such as elderly patients or patients who do not respond to treatment, are generally underrepresented in clinical trials. That leads to a lack of data to guide clinical decision-making for patients in these vulnerable groups.

To investigate the impacts of systematic therapy on these groups, as well as to investigate the feasibility of studies involving them, Dr. de Perrot collaborated with researchers from Switzerland to analyze the Princess Margaret Cancer Centre's malignant pleural mesothelioma patient database. They looked at patients with advanced pleural mesothelioma who were cared for at UHN from 2006 until 2018. Over the 12-year period, more than 650 patients were seen at UHN, with approximately 50 per cent of

those patients receiving their full course of care at UHN. The outcomes of patients treated at UHN were compared with those who received treatment at their local cancer centres.

Their analysis showed that systemic therapy – cancer treatment which targets the entire body, such as chemotherapy – was given to the majority of patients with advanced mesothelioma. While treatments such as SMART offer promising results, only a minority of patients are currently candidates for this procedure. Therefore, an integrated, systemic treatment option is necessary.

Based on their analysis of patient records, Dr. de Perrot and his fellow researchers identified apparent benefits from systemic therapy, including in vulnerable subgroups of patients. When appropriately selected, patients who have not responded to treatment and elderly patients may have improved outcomes with systemic therapy. These insights can aid clinical decision-making and show strong justification for future studies into the importance of systemic therapy for these vulnerable groups, encouraging their inclusion in future clinical trials.

This analysis also demonstrated the benefit of the Toronto Mesothelioma Program at UHN. Investigators found that the nature of the clinic and access to consolidated data made this type of analysis possible. Importantly, the analysis demonstrated the potential value of the multidisciplinary clinic because it provides increased access to investigational systemic therapy for all patients, including those in the most vulnerable subgroups.

A SMARTER treatment protocol

To build on the exciting results of SMART, Dr. de Perrot, Dr. Cho and their colleagues launched the Surgery for Mesothelioma After Radiation Therapy using Extended pleural Resection (SMARTER) trial. The goal of SMARTER is to explore how a short course of radiation can trigger a beneficial immune response in patients with epithelioid pleural mesothelioma, causing the patient's immune

system to produce new varieties of T cells to target and help eradicate the tumour.

Lab-based studies by Dr. de Perrot and his team demonstrated that three days of radiation alternating with “rest” days is less toxic while still producing a beneficial immune reaction. Lower toxicity means that the full lung does not have to be removed in all cases, giving surgeons more choice in the most appropriate surgery for a given patient. This also expands the pool of patients who are eligible for this procedure to include those who could not tolerate such drastic surgery.

The reason SMARTER is proving effective, even with lower levels of radiation than SMART, is because of how the team is harnessing the power of the immune system, allowing the body to fight against the tumour alongside the radiation. The results from SMARTER have provided key insights into further optimizing this immune response, including the use of immunotherapeutic drugs, which has been incorporated into future trial protocols.

The SMARTER trial is currently underway, with three patients remaining to be recruited and a significant number having already undergone treatment. Patients will be followed for five years with regular consultations. After the completion of the trial, the results will be submitted for publication in high-impact journals.

Harnessing the power of immunotherapy

Based on observations from the SMART and SMARTER trials that indicated the short course of radiation triggers an immune response, Dr. de Perrot, Dr. Cho and their teams developed a preclinical model to explore how immunotherapy can enhance treatment.

With results published in April 2021 in *Science Translational Medicine*, Dr. de Perrot and his team combined immune-boosting drugs with radiation and surgery to increase the survival and anti-cancer immune response in an epithelioid pleural mesothelioma animal model. In a

series of experiments, the team found that combining two immunotherapy drugs can stimulate and amplify the anti-tumour response first triggered by the short course of radiation.

The drugs used in this investigation select and expand the number of T cells in the immune system, which target and destroy any remaining mesothelioma cancer cells. Of particular importance are memory T cells, which “remember” the tumour, potentially preventing recurrence. Because the T cells selectively attack cancer cells, leaving healthy cells untouched, this treatment may be more effective and less toxic than other methods.

Excitingly, the team found that immunotherapy led to long-lasting control and resistance against cancer. The team reinjected tumour cells into the experimental models 12 weeks after the initial course of treatment. The immune system destroyed the injected cancer cells, leading to a cure in 40 per cent of cases prior to surgery. In addition to destroying existing tumour cells, the treatment essentially acts as a vaccine against the tumour, training the immune system to prevent recurrence. Based on these encouraging results, Dr. de Perrot, Dr. Cho and the team are continuing to explore the applications of immunotherapy to enhance mesothelioma treatment.

Looking ahead: Launching the SMARTEST trial

Building on the significant insights gained through SMART, SMARTER and related research, Dr. de Perrot, Dr. Cho and their team developed the Surgery for Mesothelioma After Radiation Therapy using Exquisite Systematic Therapy (SMARTEST) trial. This randomized trial will investigate the use of three drugs to optimize the immune response triggered by radiation. The team will be targeting key pathways in the immune system to optimize the long term benefits of treatment, aiming to delay or prevent recurrence.

SMARTEST will be a randomized trial, with half of the

patients receiving immune therapy drugs in combination with the SMARTER radiation and surgery protocol, and half receiving radiation and surgery without the additional drugs. The trial, which will launch in March 2022, will be the first in the world to combine immunotherapy with radiation and surgery to treat mesothelioma. It will also be one of the very few randomized trials ever performed with

“This has the potential to change the way in which we treat this cancer. We're taking advantage of the body's own immune system to fight against the cancer.”

– Dr. John Cho, radiation oncologist, UHN



Dr. John Cho

mesothelioma patients undergoing surgery. This world-leading study has the potential to significantly enhance global understanding of the disease.

Trial participants receiving immune therapy will be administered a low dose of a drug called cyclophosphamide, which is widely used for chemotherapy and immune therapy. They will receive this treatment in the seven days between their radiation and surgery to investigate whether this drug enhances the immune response against the tumour in combination with radiation and may make the tumour more susceptible to radiation.

As seen in previous studies, the immune response triggered by the radiation causes the immune system to develop new types of T cells that target the tumour. These memory T cells are capable of “remembering” how to fight the tumour, which may delay or prevent future recurrence. Dr. de Perrot and Dr. Cho hypothesize that administration of cyclophosphamide may help these memory T cells proliferate.

After surgery, participants will receive tremelimumab-durvalumab, a combination of two immunotherapy drugs, which will be administered at regular intervals for a period of up to one year. Its role is to consolidate the anti-tumour activity of the memory T cells, contributing to longer lasting resistance against recurrence.

With access to cutting-edge technology, the team will gather valuable data about treatment response. For example, they will be performing single-cell RNA sequencing, a technique which allows them to capture thousands of cells and study the biology of each cell, providing invaluable insights into how tumours change in response to treatment. They will also be using new microfluidic technology that enables them to isolate the T cells in a patient’s blood – something that is incredibly challenging, given the tiny size and relatively low numbers of these cells. By isolating T cells, the team will be able to get a more accurate idea of the quantity of memory T cells

"It's a new paradigm in cancer treatment that offers the potential of cure even in late-stage cancer."

– Dr. Marc de Perrot

circulating in the blood, and how that impacts long-term protection against recurrence.

Given the world-first nature of this research, Dr. de Perrot and Dr. Cho have been able leverage your support and create partnerships to ensure this trial is fully funded. The team has been awarded a competitive grant from the Ontario Institute for Cancer Research to fund this trial. They are also in conversation with a major pharmaceutical company that has expressed interest in providing the necessary drugs for the trial. Dr. de Perrot also anticipates future opportunities for international partnerships, including potential for a large-scale multi-institutional study, based on the significant interest that SMART has generated internationally.

This world-first research has the potential to have a major impact on the treatment of mesothelioma, and is a crucial step for the incorporation of immuno-oncology in the fight against this devastating disease.

Training future leaders in mesothelioma research and care

My name is Dr. Dorinda Mullen and I am a histopathologist from the west of Ireland. I have always been interested in laboratory medicine and completed a BSc. in Biomedical Science and a MSc. in Clinical Chemistry before obtaining my medical degree from the University of Limerick. I completed my specialist histopathology training with the Royal College of Physicians of Ireland and have been on Fellowship here in Canada since July 2020.

Why did you apply for this Fellowship?

The Lung Program at Toronto General is globally recognized as being one of the best in the world and I was excited to have an opportunity to apply for a fellowship here, allowing me to work with one of the best multidisciplinary teams currently involved in thoracic patient care.

How did you first come to hear about the Toronto Mesothelioma Program at UHN and Dr. de Perrot?

I became aware of the Toronto Mesothelioma Program and Dr. de Perrot back in 2014, when they published a paper in the journal of *Thoracic Oncology* on the SMART approach for resectable pleural mesotheliomas. Mesothelioma survival rates are quite poor and they were reporting improved survival rates with the SMART treatment protocol. Malignant mesothelioma is a rare yet highly aggressive disease with a very poor prognosis and it was wonderful to see this exciting research with their improved outcomes.

Can you describe your research in lay terms?

Cancers arise due to genetic damage, and our research is looking at genetic alterations in two proteins – BAP1 and p16 – in malignant pleural mesotheliomas. The SMART protocol involves radiotherapy treatment before mesothelioma surgery. We are testing the mesothelioma tissue from these patients to see if they have evidence of these alterations. Not all mesothelioma patients have these specific genetic findings but some are born with them, while others may develop them over time. We



Dr. Dorinda Mullen

correlate our results with clinical findings, looking at relationship of genetic alterations with features such as mesothelioma subtype, disease recurrence and overall patient survival.

What is the scope of the health problem that you are researching?

Malignant mesothelioma is not as common as other cancers and rare diseases can be quite challenging to study. Consequently, researching these tumours and developing improved treatment approaches can take time. As stated, mesothelioma is very aggressive, has poor survival rates and also can be difficult to diagnose. UHN is in the unique position of being one of the largest groups actively researching this terrible disease. The ability to study larger patient cohorts is so important for the generation of data that can be translated into targetable treatments. This is paramount in finding new and improved ways to care for mesothelioma patients.

How has this opportunity assisted you in your research and career goals?

It is wonderful to have been given the opportunity to work with Dr. de Perrot and the mesothelioma multidisciplinary team, to be involved in this exciting SMART research. We are actively working on the preliminary data, which is already showing promising results in regards to disease prognosis and stratifying malignant mesothelioma cases with a view to identifying

patients who will respond to therapy. At this time, we hope to continue our work with investigating the molecular markers in mesothelioma.

The opportunity to be involved in a project like this, which has and will continue to have such an impact on an aggressive disease, has reinforced the importance of research for me in my work and my career. Without donor funding it would not be possible to support this research that I am currently involved in.

“The funding that donors provide to support the fellowship programs here at UHN is so important for doctors-in-training. It grants us the opportunity to improve our medical knowledge in global centers of excellence and gives us the experience of working alongside those involved in cutting-edge research.

It is through the generosity of these donors that funded research has the potential to provide answers which can improve and save the lives of patients. I will always be grateful to the generous people that donate to UHN that have allowed me to have this fellowship opportunity.”

– Dr. Dorinda Mullen



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