CANCERtalk
› CONNECTING WITH MANITOBA'S HEALTH PROFESSIONALS
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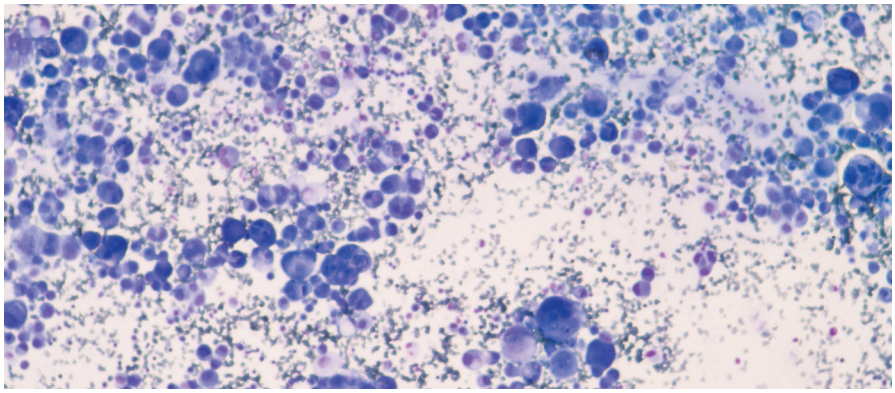
IMMUNOTHERAPY

Vamsee Torri MD FACP FRCPC

"The concept of "immunotherapy" (using the immune system to combat cancer) is not new. In the past, CancerCare Manitoba has used drugs like interferon-alpha (a relatively non-specific natural immune-booster) to treat metastatic kidney cancer, and in fact this drug is still used in some melanoma patients.

What is new is the understanding of the targets for immunotherapy. In recent years three new targets in particular have been explored. CTLA4, PD-1 and PD-L1 are all molecules that are involved in turning off the body's normal response to an invader (such as cancer), and by blocking these molecules (alone or in combination) we can re- awaken the body's ability to recognize the cancer as undesirable and trigger an immune response against it."*



Immune balance (or 'synapse') is maintained by both stimulatory and inhibitory receptors on T-cells. Tumour cells can sometimes evade immune surveillance through a process termed cancer immunoediting. Initial recognition by the immune system of antigens on tumour cells involves the presentation of tumour antigens by 'antigen-presenting cells' (APCs) to cytotoxic T cells such as CD 4 and CD 8 cells. The activated CD 4 and CD 8 cells then start to eliminate tumour cells, and this process is ramped up by a positive feedback loop: CD 28 expressed on the surface of cytotoxic T-cells interacts with CD 80 and CD86 receptors on the APC, stimulating the APC to present more antigen to the cytotoxic cells. Their ability to do so is modulated over time by the production by the cytotoxic T-cells of Cytotoxic T-lymphocyte-Associated Protein 4 (CTLA-4). CTLA-4, a so-called immune check point inhibitory receptor, is produced in response to increases in TNF, IL-6, and other mediators of inflammation. When expressed on the cell surface of the cytotoxic T-cells, CTLA-4 binds tightly to the APC's CD 80 & CD86 antigens, preventing the CD 28 antigen from binding to them,

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and thereby breaking the positive feedback loop. The immune system might then still succeed for a while in containment of tumor growth, but this state of equilibrium might be followed by "escape" of tumor cells from immune surveillance.

Blockage of immune check point inhibitory receptors can be accomplished with monoclonal antibodies directed, for example, at the CTLA-4 receptor, or at the PD-1 receptor (which interacts with PD ligand 1 or 2 receptors present on the tumour cell, thereby causing T cell inhibition). Such blockade of inhibitory immune checkpoints by monoclonal antibodies has demonstrated an anti-tumor response in preclinical models and has been confirmed in phase III clinical trials. Five years ago only 25% of patients with incurable melanoma lived one year. Now one year survival is 80% as a direct consequence of new immune therapies such as the anti-CTLA-4 antibody ipilimumab.

Ipilimumab is administered every three weeks for four doses intravenously, sometimes followed by re-introduction of the drug based on duration of response. This is considered standard of care in the treatment of metastatic melanoma and treatment - naïve unresectable melanoma. The anti-PD-1 antibody nivolumab is administered every two weeks intravenously while pembrolizumab is administered every three weeks intravenously and continued until unacceptable toxicities occur or until disease progression. These agents are considered standard of care as second line agents in treatment of metastatic melanoma and non-small cell lung cancer.

Unfortunately there is no clear biomarker we can use in selecting patients for these therapies. In fewer than 10% of patients, pseudoprogression (an apparent increase in size of the tumor due to an inflammatory response) has been noted both clinically and radiologically. Recognition of this phenomenon has lead to development of immune mediated response criteria, which essentially recommends continued treatment for as long as the patient is stable, with close follow-up and repeat imaging after four to six weeks before concluding that the disease has progressed.

Common toxicities with the immune check point inhibitors include rash, diarrhea, elevated liver enzymes, endocrinopathies and greater incidence of pneumonitis in lung cancer patients (especially with anti-PD-1 antibodies). Prompt use of corticosteroids at 0.5 to 1mg/kg at the earliest grade 3 or prolonged grade 2 toxicities has mitigated severe toxicities with these agents.

In conclusion, treatment with anti-CTLA-4 antibody has revolutionized treatment in metastatic melanoma and anti-PD-1 antibodies are becoming a new standard of care in metastatic melanoma and non-small cell lung cancer. Based on ongoing clinical trials in other cancers (such as kidney, bladder, triple negative breast cancer and mismatch repair enzymes deficient colon cancer) and development of new agents, there will be significant change in use of immunotherapies in the next few years.

**Judy Edmond, CCMB Communications Officer, in her February 3, 2016 response to questions from Global TV on innovations in immunotherapy at CCMB.*

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Vamsee Torri MD
FACP, FRCPC

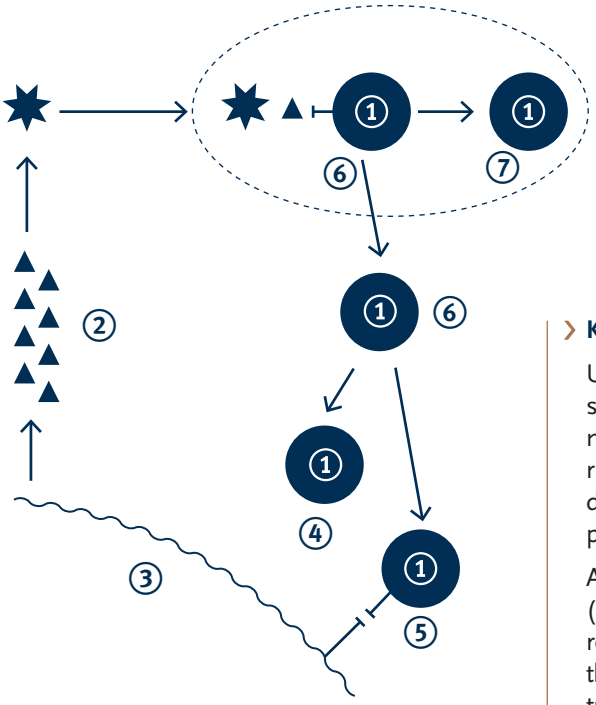
Dr. Vamsee Torri has joined the Department of Medical Oncology and Haematology at CancerCare Manitoba as a Medical Oncologist.

He completed his residency in Internal Medicine (2006) and fellowship in Hematology and Medical Oncology (2009) from New York, USA. He is a diplomate of the American Board of Internal Medicine and fellow of Royal College of Physicians and Surgeons of Canada.

Upon completion of his training he moved to Canada. Since 2010 he has been working at the University of Saskatchewan as Assistant Professor of Medicine and at Saskatchewan Cancer Agency as Medical Oncologist.

His clinical interests include thoracic, GU and melanoma. He is the chair of multidisciplinary thoracic DSG and chair of medical education at Saskatchewan cancer Agency. His other special interest includes symptom management and methods to improve clinical trial enrollment.

Antigen processed by antiden presenting cells (APC) eg: dendritic cell and presented to cytotoxic or CD 8+ T cell in the lymph nodes.



① CD 8+ T Cell
② Tumor Antigens
③ Tumor
④ Tumor cell death by activated T cell
⑤ Inactivated through PD-1 and PD-L1 receptor
⑥ Activared T cell
⑦ Inactivated through CTLA-4 receptor

This illustration focuses on the CD8+ or 'cytotoxic' T cell:

CTLA-4 and T cell: Presentation of peptide by APC via MHC (Major Histocompatibility Complex) class 1 to T-cell receptor (signal 1) leads to interaction of receptor present on APC (signal 2) leads to production IL-2 & cell proliferation (T-cell activation).

Twenty four hours after T-cell activation, CTLA-4 receptor competes with CD28 receptor for B.7 receptor leading to termination of IL-2 production & cell proliferation (T-cell inactivation).

PD-1 and T cell: Interaction between PD-1 (present on lymphocytes, NK cells) and PD-L1 decreases IL-2 production & cell proliferation (T-cell inactivation).

Therapeutic target: Antibodies to these receptors prevent development of inhibitory signals on T cell function leading to persistent anti-tumor activity.

Key points:

Understanding tumor immune surveillance and cancer immunoediting (elimination, equilibrium, escape) has lead to further development in immunotherapies with unprecedented results.

Anti-CTLA4 and anti-PD-1 agents (antibodies directed to inhibitory receptors on T cells) are now the standard of care in various tumors.

Side effects are similar to autoimmune flare-up and prompt initiation of corticosteroids eg: Prednisone at 0.5 to 1mg/kg decreases morbidity and mortality (the anti-PD-1 agents have far fewer toxicities than either the anti-CTLA4 antibodies or cytotoxic chemotherapy).

In near future, expect combination immunotherapies and newer agents targeting other pathways.

ONE LINK AT A TIME
BUILDING PRIMARY – SPECIALIST CARE COLLABORATION FROM THE CRADLE

Integrating primary care + cancer care in partnership

Dr. Emmanuel Ozokwelu & Dr. Jeff Sisler

Quality clinical care for cancer survivors hinges on smooth coordination and collaboration between primary care clinicians and cancer specialists. In 2015, CCMB successfully piloted an inter-specialty curriculum on survivorship care for family medicine and oncology residents at the University of Manitoba and McMaster University. Trainees studied together via online modules, interactive case-based workshops and clinical exposures in cancer clinics focusing on post-treatment issues commonly encountered by survivors of breast and prostate cancer. A variation of this curriculum is being designed for family physicians for launch in the Fall of 2016. Stay tuned to the Community Oncology Education calendar for updates!

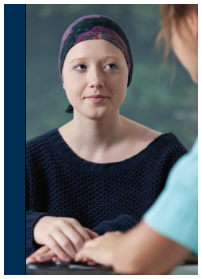
MEASURING UP WITH THE BEST: MANITOBA'S EXPERIENCE WITH THE INTERNATIONAL CANCER BENCHMARKING PARTNERSHIP

As a member of the International Cancer Benchmarking Partnership (ICBP), CancerCare Manitoba researchers have been exploring differences in cancer survival between developed countries with similar health care systems. This initiative produced findings in 2010 for six countries (Canada, Australia, Denmark, Norway, Sweden and the United Kingdom) about survival for patients diagnosed between 1995 to 2007. Survival rates were generally higher in Canada relative to other countries, and within Canada, Manitoba had the highest survival rates for lung cancer.

All of these findings generated the same question: why are there differences? Our team has continued to engage with ICBP in sub-studies designed to understand the relative roles of patient, provider and health care system characteristics on cancer survival. From these studies we can learn from each other about attaining the best patient experience and outcomes.

Since 2012, we have surveyed over 900 patients and 500 primary care providers to hear about patients' journeys following first suspicion of cancer. Response rates have been excellent (38% for patients and 62% for primary care providers) – so for those who participated, thank you! We are looking forward to sharing our findings with you over the next few months through CancerTalk.

HEARING THE PATIENT'S VOICE IN THE CANCER JOURNEY



As part of the Cancer Patient Journey Initiative (In Sixty), the Patient Participation Advisory Group (PPAG) has been working to expand the patient voice and engagement in cancer healthcare in Manitoba.

The following is an excerpt of an article prepared by CCMB Communications summarizing PPAG's recommendations in this regard.

PPAG believes that appropriate communication with patients, and between care providers, is critical to ensuring quality clinical and psychosocial care. While process improvement is necessary to transform the cancer patient journey, it is insufficient on its own. It is the belief of PPAG that improvements in process and in communication between care providers and with patients are equally critical to transforming the cancer patient journey in Manitoba.

In communicating with patients, providers and health care workers should:

- Listen to patients and act on the information provided by them.
- Understand what level of information the patient needs, and reflect that level of information to the patient. Provide the big picture when required, and the specific details when necessary.
- Ensure the patient and/or their families have the opportunity to ask questions, and ensure that it is safe for questions to be asked. No question is irrelevant or unnecessary.
- Make an effort to ensure demonstrated understanding by the patient and/or family.
- Ensure the patient is not the conduit of information between areas of care. It is the providers' and health care system's responsibility to transfer information between areas of care, not the patient's. Undertake the actions necessary to communicate between areas of care.
- Take responsibility for communication to the patient and see it through to the end of an active communication cycle by responding to questions. Do not delegate responsibility for your communication as a provider to an alternate provider. If communications with a patient are difficult for you, we recommend having a second person with you to support the communication. A health care provider's responsibility to communicate with patients is ongoing; it does not end when you have delivered your perceived "portion" of the information.
- Enable all communication to be two-way communication.
- Provide opportunities for patients to follow up with questions at later times.

For the full text of this article, please contact Judy Edmond, CCMB Communication Specialist at **jedmond@cancercare.mb.ca**.

WHAT'S NEW IN CANCER SCREENING?

Colorectal Cancer Awareness Month

March is over, but it's not too late to promote colorectal cancer screening with your patients. What can you do?

- Talk to your patients about the importance of cancer screening.
- Ask ColonCheck to send your patients an FOBT.
- Display pamphlets, posters, and other free educational resources about cancer screening.

Visit GetCheckedManitoba.ca for more information or to order resources..

FOBT Request Form

ColonCheck has developed a simple process for health care providers to request an FOBT for eligible patients. The FOBT Request Form is available on select EMR systems and in hard copy. To learn more, contact Linda at 204-788-8480 or lstarodub@cancercare.mb.ca.

Newly Released Screening Guidelines for Colorectal Cancer and Lung Cancer

In March, the Canadian Task Force on Preventive Health Care released new screening guidelines for both colorectal cancer and lung cancer.

Colorectal Cancer Screening Guidelines

The colorectal cancer screening guidelines apply to asymptomatic, average risk individuals aged 50-74 years and include the following recommendations. (Below in blue)

ColonCheck, Manitoba's colorectal cancer screening program, already works within the newly released guidelines by mailing FOBTs to eligible Manitobans aged 50-74 years. If the FOBT result is abnormal, the individual is referred for a follow-up colonoscopy. In 2013 and 2014, ColonCheck mailed over 115,000 screening invitations to Manitobans.

Lung Cancer Screening Guideline

The Task Force recommends screening asymptomatic individuals for lung cancer using low-dose computed tomography (low-dose CT). (Below in yellow)

AGE	RECOMMENDATION	STRENGTH
50-59 years	**Screen** with **FOBT** every two years or flexible sigmoidoscopy every ten years.	Weak recommendation.
60-74 years	**Screen** with **FOBT** every two years or flexible sigmoidoscopy every ten years.	Strong recommendation.
75+ years	**Do not screen.**	Weak recommendation.
50-74 years	Using colonoscopy for routine screening is **not recommended.**	Weak recommendation.
55-74 years	**Screen** with **LDCT** up to three consecutive times for • Current smokers or former smokers who quit within the last 15 years and • Have smoked one pack a day for at least 30 years (or 2 packs a day for 15 years or equivalent; ie 30 "pack-years").	Weak recommendation.
18-55 years or 75+ years	**Do not screen** with **LDCT,** regardless of smoking history or other risk factors.	Strong recommendation.
18+ years	Screening with chest x-ray, with or without sputum cytology is **not recommended**.	Strong recommendation.

The recommendations apply to asymptomatic people who meet the screening criteria; they do not apply to people who have a history of lung cancer or who are suspected of having lung cancer. Those individuals should be referred for diagnostic testing as clinically indicated.

CancerCare Manitoba will be reviewing the new lung cancer screening guidelines and meeting with stakeholders to determine the most effective ways to implement these recommendations.

The colorectal and lung cancer screening guidelines, as well as patient and clinician tools, can be accessed at: **canadiantaskforce.ca/ctfphc-guidelines/**

HOW TO REACH US

CCMB REFERRAL CENTRE
204-787-2176
FAX: 204-786-0621
M-F, 0830-1630, closed Stat Holidays

Emergency Referrals:
HSC PAGING: 204-787-2071
ST BONIFACE PAGING: 204-237-2053

CANCER QUESTION? HELPLINE FOR HEALTH CARE PROVIDERS
204-226-2262 (call or text / sms)
EMAIL: cancer.question@cancercare.mb.ca
WEB FORM: cancercare.mb.ca/cancerquestion
M-F, 0830-1630, closed Stat Holidays

CCMB SCREENING PROGRAMS BREASTCHECK – CERVIXCHECK – COLONCHECK
1-855-952-4325
GetCheckedManitoba.ca

CANCERCARE MANITOBA
TOLL FREE: 1-866-561-1026
(ALL DEPARTMENTS + CLINICS)
www.cancercare.mb.ca

Inquiry & Reception
MACCHARLES UNIT (HSC) 204-787-2197
ST. BONIFACE UNIT 204-237-2559

Pharmacy: 204-787-1902

COMMUNITY CANCER PROGRAMS NETWORK (CCPN) OFFICE, CCMB
204-787-5159

MANITOBA PROSTATE CENTRE, CCMB
204-787-4461
FAX: 204-786-0637

PAIN & SYMPTOM MANAGEMENT
204-235-2033 ask for pain & symptom physician on call
M-F, 0830-1630

PALLIATIVE CARE CLINICAL NURSE SPECIALIST
204-235-3363

PATIENT AND FAMILY SUPPORT SERVICES, CCMB
Psychosocial Oncology, Dietitians, Speech Language Pathology, Guardian Angel Caring Room, Patient Programs, Navigator Newsletter
204-787-2109

BREAST AND GYNE CANCER CENTRE OF HOPE
204-788-8080
TOLL FREE: 1-888-660-4866
691 Wolseley St.
Winnipeg, MB R3C 1C3

WESTERN MANITOBA CANCER CENTRE
204-578-2222
FAX: 204-578-4991
300 McTavish Ave. East
Brandon, Manitoba R7A 2B3

OTHER NUMBERS:

CANCERCARE MANITOBA FOUNDATION
DONATIONS & INQUIRIES 204-787-4143
TOLL FREE: 1-877-407-2223
FAX: 204-786-0627

CANADIAN CANCER SOCIETY
VOLUNTEER DRIVERS 204-787-4121
TOLL FREE: 1-888-532-6982

CANCER INFORMATION SERVICE
TOLL FREE: 1-888-939-3333

CANADIAN VIRTUAL HOSPICE
virtualhospice.ca

WRHA BREAST HEALTH CENTRE
204-235-3906
TOLL FREE: 1-888-501-5219

ANNOUNCEMENTS

Dr. William (Bill) Hunter

We are pleased to announce that Dr. William (Bill) Hunter has joined the Department of Radiation Oncology, CancerCare Manitoba, as a Radiation Oncologist starting January 11th, 2016.

Dr. Hunter completed a Bachelor's Degree in Electrical Engineering with Distinction at the University of Alberta and worked in research and development as a professional radio frequency engineer. He received his undergraduate medical education at the University of Calgary and went on to residency training in Radiation Oncology at CancerCare Manitoba. He has recently completed additional fellowship training at the Tom Baker Cancer Centre with a focus on stereotactic radiotherapy including hypofractionated treatments for liver, thoracic, and intracranial malignancies.

His main areas of interest include stereotactic radiotherapy program development, and research into cancer care delivery and patient experience.

Dr. Hunter will provide outpatient services in thoracic,breast and gastrointestinal DSGs at the Western Manitoba Cancer Centre in Brandon.

Dr. JL (Larry) Reynolds, MD, MSc, MHSc

Dr. J.L. Reynolds has joined the Urgent Cancer Care team at CancerCare Manitoba.

Dr. Reynolds is Professor of Family Medicine and Obstetrics and Gynecology and Medical Director for WRHA Family Medicine, and a former Head of Family Medicine at the University of Manitoba. He serves as a board member on hospital and college committees and as a member of the Manitoba Health Research Ethics Board. Dr. Reynolds has also won several teaching awards as well as awards in areas such as Internal Medicine and Internship.