Name: Rebecca Auer | **Award Year: 1 of 3**
Institution: Ottawa Hospital Research Institute | **Period covers: 02/01/2015-01/31/2016**
E-mail address: rauer@ohri.ca | **Phone: (613) 737-8899**

Panel - Immunology, Signalling and Stem Cells **Award Category - Innovation to Impact Grants 1 - 2015**

Project Title:	Funding Source(s):	Award #:
Combining oncolytic vaccines (OVax) with surgery and immune modulation to prevent postoperative cancer recurrence and metastases	Canadian Cancer Society Partnership funding	703424

Please use the following form to describe impacts of your research that are directly related to or have been enabled by your CCS grant in the past year. If a question is not applicable to your research in the last year, but is indicated as a required field with an *, please indicate N/A in the relevant field. Your responses will help to convey to donors and volunteers the importance and value of your research. Providing specific details is important to promote your research and the impact of research in general.

***The CCSRI compiles an annual Research Impact Report that contains selected grant summaries taken from progress reports. This Impact Report is made available to the staff and volunteers of the CCS as well as the general public via our website. Do you consent to the publication of a public summary of the impacts of your grant funding?** (●) Yes ( ) No

Co-PIs/Co-Applicants/Additional Authors:

Co-Applicant: Brian Lichty, Senior Research Scientist, Dept. of Pathology and Molecular Medicine, McMaster University
Co-Applicant: John Bell, Senior Research Scientist, Centre for Cancer Therapeutics, Ottawa Hospital Research Institute
Additional Author: Lee-Hwa Tai, Postdoctoral Fellow, Center for Cancer Therapeutics, Ottawa Hospital Research Institute
Additional Author: Carolina Ilkow, Postdoctoral Fellow, Center for Cancer Therapeutics, Ottawa Hospital Research Institute
Co-Applicant: Jonathan Bramson, Professor, Dept. of Pathology and Molecular Medicine, McMaster University

Changes to Co-PIs/Co-Applicants/Additional Authors listed above (Name, Designation as co-PI, co-applicant or additional author [CP, C or A], Department, Institution, Email address):

Research impact

*Describe the single greatest impact of your research resulting from this project on fundamental knowledge in cancer research (e.g. development of new knowledge and/or scientific methods, etc.) in the past year:

We have developed a syngeneic, immune competent, orthotopic model of surgically resectable pancreatic cancer that develops postoperative spontaneous metastases. This model will allow for the study and characterization of promising perioperative cancer immunotherapies before translation to the clinic.

*Describe how your research resulting from this project has been used and/or is influencing the work of other researchers (e.g. cited in relevant scientific literature, etc.) in the past year:

Currently the perioperative period is ignored in the current cancer treatment paradigm. Research from this grant and from the prior Innovation grant is being cited in a number of reviews describing the importance of targeting cancer metastases during the perioperative period. The potential for perioperative cancer therapeutics is increasingly being recognized with reference to our preclinical research.

*Describe the single greatest impact of your research resulting from this project on policy (e.g. research cited in public policy documents, advocacy publications, etc.) in the past year:

N/A

*Describe the single greatest impact of your research resulting from this project on health care practice and program delivery (e.g. research cited in health professional education material, cited in clinical and service guidelines, used in program development, etc.) in the past year:

N/A

Research commercialization

*Describe (e.g. name, number, inventors, dates) any commercialization activity resulting from this project (e.g. patents filed/granted, invention disclosures, copyrights, licenses, etc.) in the past year:

N/A

Peer-reviewed publications

*Did you acknowledge CCS as the funder on peer-reviewed publications resulting from this project in the past year? ○ Yes ◉ No

If no, why was CCS not acknowledged as the funder?

We have not had a peer review publication resulting from this project in the past year.

Note that the CCS Open Access Policy requires that publications be made available within 12 months of the publication date. See our website for more information (www.cancer.ca/research - under Policies and Administration).

*Are you adhering to the CCS Open Access Policy for all CCS-related publications? ◉ Yes ○ No

If no, please explain the reason:

*Indicate the number of peer-reviewed publications, including those in press, resulting from this project in the past year: 0

List the peer-reviewed publications, including those in press, resulting from this project in the past year (include the full citation with PubMed ID numbers):

Non peer-reviewed publications

*Indicate the number of non peer-reviewed publications (e.g. technical reports/papers, etc.) resulting from this project in the past year: 0

List the non peer-reviewed publications (e.g. technical reports/papers, etc.) resulting from this project in the past year:

Upcoming publications

*Indicate the number of upcoming publications (including in preparation or submitted) resulting from this project: 2

List of upcoming publications (including in preparation or submitted) resulting from this project:

Ananth A, Tai L, Lansdell C, Zhang J, Stephenson K, Parato K, Bramson J, Bell J, Lichty B, Auer R. Surgical stress abrogates pre-exisitng protective T cell mediated anti-tumour immunity leading to postoperative cancer recurrence. PLoS One (in revision).

Baxter K, Tanese de Souza C, Kennedy M, Tai LT, Bell J, Atkins H, Auer R. An orthotopic, immunocompetent model of surgically resectable pancreatic cancer with spontaneous metastases. Journal of Surgical Research (manuscript in preparation).

Presentations

*Indicate the number of requests you received to make a presentation related to this project at a conference, workshop, meeting, etc. in the past year: 5

*Indicate the number of presentations resulting from this project in the past year: 4

List the presentations resulting from this project this past year:

47th Society of Toxicology of Canada Conference: Therapeutic Use of Oncolytic Viruses in the Perioperative Period for Cancer Patients (Ottawa, ON, Dec 9, 2015)

Immunotherapy: The Ontario Landscape: Infected cell vaccines: Using oncolytic viruses to create personalized

cancer vaccines (Toronto, ON, Nov 25, 2015)

Canadian Undergraduate Conference on Healthcare: From Colle's Toxins to Oncolytic Vaccines (Kingston, ON, Nov 15, 2015)

Ontario Regional Biotherapeutics Scientific Advisory Board: Preclinical Rationale for an MG1-IL12 Infected Cell Vaccine (Toronto, ON, June 22, 2015)

Consultations/Briefings

*Indicate the number of consultations/briefings to decision-makers in the public, private and non-profit sector resulting from this project in the past year:	0

Details of consultations/briefings to decision-makers in the public, private and non-profit sector resulting from this project in the past year:

Recognition and support

*Indicate the number of awards or honours you received in the past year (do not include research grants):	2

List honours or awards you received this past grant year (do not include research grants):

Jack Aaron Memorial Award (Ottawa Cancer Center)
Tier 2 University of Ottawa Clinical Research Chair

*Indicate the number of significant advisory committee memberships, leadership roles, etc. you held in the past year:	4

List advisory committee memberships, leadership roles, etc. you held in the past year:

Canadian Cancer Trials Group (CCTG, formerly NCIC)- Clinical Trials Committee Executive
Rectal Cancer Co-Chair for CCTG
Member Editorial Board for Journal Surgical Research
Executive Member of the American Society of Surgical Oncology

Media coverage

*Indicate the number of times your research findings from this project were the subject of a press release in the past year:	2
*Indicate the number of times your research findings from this project were mentioned in the media (newspaper article, radio/television interview, etc.) in the past year:	1

Details of times your research findings from this project were mentioned in the media in the past year:

CTV Ottawa Morning Live "Tender Loving Research" with Sarah Freemark (June 25, 2015)

*Indicate the number of times media requested your expert commentary in the past year:	0

Details of media requests for your expert commentary received in the past year:

Collaborations

*Indicate the number of collaborations formed with other researchers resulting from this project in the past year:	3

List and provide details (name and field of study) of collaborations with other researchers resulting from this project in the past year:

Eric Tran (Cancer Immunology, NIH Surgery Branch, Bethesda, Maryland)
Brad Nelson (Cancer Immunology, BC Cancer Agency, Victoria, BC)

Paul Karanicolas (Surgical Oncologist, Sunnybrook Cancer Center, Toronto, ON)

*Indicate the number of collaborations formed with policy makers and/or advocates resulting from this project in the past year: 0

List and provide details of collaborations with policy makers and/or advocates resulting from this project in the past year:

*Indicate the number of collaborations formed with health care practitioners and/or program delivery experts resulting from this project in the past year: 0

List and provide details of collaborations with health care practitioners and/or program delivery experts resulting from this project in the past year

*Indicate the number of collaborations formed with other stakeholders (e.g. CCS, NGOs, industry, etc.) resulting from this project in the past year: 0

List and provide details of collaborations with other stakeholders (e.g. CCS, NGOs, industry, etc.) resulting from this project in the past year:

Scientific progress report

*Provide a scientific progress report describing the research that has been performed in the past year. Please relate to the specific aims of the original grant proposal. The equivalent of a 1 to 2 page report is required, max 8500 characters.

The goal of the current i2I grant is to establish the ideal regimen for periop Oncolytic Vaccine (OVax) strategy. Our ultimate goal (the Impact) is to design and conduct a clinical trial to evaluate a therapeutic regimen that combines a prime-boost OVax (Adenovirus and Maraba MG1 expressing a tumour antigen) +/- perioperative immune modulation to reduce recurrence and improve survival in pancreatic cancer patients undergoing surgical resection. We discovered during our Innovation Grant that periop OV can prevent postop suppression of the innate immune system (NK cells) but the timing of delivery, immediately before the period of surgical stress appears critical for efficacy. With a new OVax platform emerging as our lead clinical candidate, we must now also consider the suppressive effects of surgery on the adaptive immune system (T cells). In the grant we are exploring the immunosuppressive impact of surgery on innate and acquired immunity in the context of this very promising OVax strategy.

PROGRESS ON SPECIFIC AIMS:

(1) Evaluate the timing of surgery with respect to an OVax prime-boost vaccination on the innate and adaptive immune response and on cancer recurrence/metastases.

We characterized the effect of surgery on the adaptive immune response using our established model of B16 melanoma and vaccination with a dopachrome tautomerase (DCT) expressing OVax regimen. Surgery clearly impairs T cell proliferation and cytokine secretion following antigen stimulation and T cell dysfunction contributes to tumour recurrence in this model. Fortunately we also demonstrated that these effects are reversible with appropriately timed perioperative immunotherapy. These results have been submitted to *PLOS One* (IF 3.24) and the manuscript is currently *in revision*.

(2) Explore the mechanism of surgery induced immune suppression in the context of an OVax prime-boost

vaccination and the ability of clinically viable targeted immune therapies (including MDSC depletion and cytokine stimulation) to reverse these effects.
Depletion of MDSC with anti-Gr1 antibody also appears to deplete a significant number of CD8+ T cells and therefore cannot be used to study the effects of MDSC depletion on postop T cell dysfunction. We subsequently tested the ability of several clinically available agents, that have been previously identified as mediators of MDSC activity, to augment postoperative T cell proliferation and cytokine secretion. These have included gemcitabine, 5-fluorouracil, sorafenib and sildenafil. To date only sildenafil has shown significant promise in the perioperative period. We are currently exploring the mechanism of effect on both NK cells and T cells further. We will also evaluate the effects of other cytokines, as well as low dose cyclophosphamide, on postoperative T cell function.

(3) Establish "proof of concept" in pancreatic cancer by evaluating the optimal regimen of OVax and surgery (+/- periop immune modulation) in an orthotopic, spontaneously metastasizing, murine pancreatic cancer model following distal pancreatectomy.

We have made significant progress on Aim 3. We have developed an orthotopic model of pancreatic cancer using the Pan-02 cell line. This cell line replicates most of the hallmarks of pancreatic cancer, including incomplete glands with necrosis and vascular and perineural invasion. We have optimized this model so that the pancreatic tumour can be resected with a spleen preserving distal pancreatectomy. This is a technically challenging surgery as the blood supply to the spleen courses immediately over the tail of the pancreas but splenic preservation is critical to allow an intact immune system to support and study perioperative immunotherapies. Finally the model recapitulates the subsequent development of spontaneous metastases in over 80% of animals, which is analogous to the prognosis of pancreatic cancer patients following surgical resection. One of the challenges we have been working to overcome is the development of pancreatic fistulas (leaking of pancreatic digestive enzyme, lipase) from the surgical site, which occurs in 20% of mice. This also occurs in approximately 25% of pancreatic surgery patients and is a significant source of perioperative morbidity. A manuscript outlining the creation of this model is being prepared for submission to the *Journal of Surgical Research* (IF 2.12).

In the meantime we have also designed, cloned and rescued our Mesothelin expressing OVax viruses for use in this model. This includes an Adenovirus prime and Maraba (MG-1) boost. The insertion of the Mesothelin transgene has been verified in both viruses by sequencing and by detection of Mesothelin protein expression by Western blotting. These viruses have been purified, tittered and the cytotoxicity and replication competence of MG1 has been verified by a single and multistep growth curve. We are now in a position to use the Mesothelin OVax regimen in this murine model of pancreatic cancer.

*Keywords: provide a list of up to 10 keywords that are associated with this research project.

vaccines
perioperative period
immunotherapy
tumour associated antigens
neoplasm metastasis/therapy
oncolytic virotherapy
killer cells, natural
T-lymphocytes
pancreatic

*Have there been any significant changes to the project since the original grant submission (e.g. research methodology, cancer site, etc.): ○ Yes ◉ No

If yes, please describe changes to the project:

*Have there been any significant challenges in achieving the aims of the original grant submission? ○ Yes ◉ No

If yes, please describe the challenges:

Public summary of scientific progress

Provide an updated summary of your findings related to this research project in simple, non-technical language in the spaces below. Consider how you would describe your project to a Canadian Cancer Society volunteer who could then relay this information to the donor community.

*Project summary: (2 sentences summarizing the proposal, max 500 characters)

Surgery can promote the spread of cancer in the body by impairing the immune system. In this study, Dr Auer will investigate how the use of a novel cancer vaccine, made of a cancer killing virus (Oncolytic Vaccine) affects the immune system's capacity to fight the spread of cancer following surgery for pancreatic cancer.

*Research findings and update: (detail in 3-5 sentences what has been accomplished in this funding year, max 1000 characters)

In the past year Dr Auer and her team have developed an animal model of pancreatic cancer that can be removed with surgery but where the cancer often returns. This model is very representative of the situation in patients with pancreatic cancer, where the cancer returns in >80% of patients. She has also invented a new viral vaccine (Oncolytic Vaccine) that specifically targets the pancreatic cancer cells. Her lab is now testing if this virus works to prevent the cancer from coming back after surgery in the animal model of pancreatic cancer following surgery.

*Project description: (detail in 2-3 sentences how you are conducting the study, max 500 characters)

The current study uses animal models of cancer surgery and metastases (spread to other organs beyond the primary cancer site). We use a cancer vaccine around the time of surgery to see if it can prevent cancer from returning and then study how this is working. Specifically we look at how the vaccine and the surgery are affecting the immune system's ability to attack the cancer in order to find ways to improve upon the current treatment.

*Impact and relevance: (detail in 2-3 sentences how your studies will contribute to the reduction of cancer incidence rates for Canadians and/or cancer mortality rates for Canadians and/or enhanced quality of life for Canadians living with and beyond cancer, max 500 characters)

Pancreatic cancer is a deadly disease. The best chance to cure someone with pancreatic cancer is surgery, but even then, more than 80% will die of their disease. Oncolytic Vaccines are a promising treatment that has a good chance of working well in pancreatic cancer patients.This knowledge will get us one step closer to improving the lives of the over 2,800 Canadians who undergo surgery for pancreatic cancer every year.

Graduate students

*Indicate the number of graduate students working on this project in the past year:	2
*Indicate the number of graduate students working on this project in the past year that are paid for, in whole or in part, from this grant:	1

Names of graduate students working on this project in the past year that are paid for, in whole or in part, from this grant (last name, first name, email):

Baxter, Katherine (kbaxt090@uottawa.ca)

Undergraduate / Summer students

*Indicate the number of undergraduate / summer students working on this project in the past year:	2
*Indicate the number of undergraduate / summer students working on this project in the past year that are paid for, in whole or in part, from this grant:	1

Names of undergraduate / summer students working on this project in the past year that are paid for, in whole or in part, from this grant (last name, first name, email):

Xu, Rebecca (rxu069@uottawa.ca)

Fellows

*Indicate the number of fellows working on this project in the past year:	1
*Indicate number of fellows working on this project in the past year that are paid for, in whole or in part, from this grant:	0

Names of fellows working on this project in the past year that are paid for, in whole or in part, from this grant (last name, first name, email):

Training of New Researchers

*Beyond the trainees (i.e. fellows, students, etc.) working on this project as outlined in the previous sections, describe the single greatest impact of your research resulting from this project on the training of new researchers (e.g. research cited in text books, reading lists, etc.) in the past year:

None

*Indicate the number of trainees (i.e. fellows, students, etc.) who worked on this project that have gone on to work as independent cancer researchers in the past year:	0

Other Highly Qualified Personnel (i.e. individuals with university degrees at the bachelors' level and above)

*Indicate the number of other highly qualified personnel (excluding students and fellows already listed) working on this project in the past year:	2
*Indicate the number of other highly qualified personnel (excluding students and fellows already listed) working on this project in the past year that are paid for, in whole or in part, from this grant:	1

Names and positions of other highly qualified personnel (excluding students and fellows already listed) working on this project in the past year that are paid for, in whole or in part, from this grant (last name, first name, position):

Tanese de Souza, Christiano (ctanesedesouza@ohri.ca)

Leveraged funding and in-kind support

*Indicate the total amount of leveraged funding (e.g. additional funding obtained to support linked research, funding to further develop research findings directly related to this grant, industry contracts, etc.) resulting from this project obtained in the past year:	0

List and provide details of leveraged funding (include the funder, term, and amount) resulting from this project obtained in the past year:

*Indicate the total estimated value of in-kind support resulting from this project obtained in the past year:	0

List and provide details of in-kind support resulting from this project obtained in the past year:

Promoting the Canadian Cancer Society

Our funded researchers are expected to promote the Canadian Cancer Society through public presentations, participation in fundraising efforts, displaying the CCS lab sticker, etc. List any such activities you or your research colleagues have been involved in during the past year. To acknowledge funding, researchers should state "This research is funded by the Canadian Cancer Society (grant #XXXXXX)".

CCS Lab Tour (Fall 2015), Display CCS lab sticker, My students are involved in CCS Research Information Outreach Team

*Are you fluent in both official languages? (•) Yes ( ) No

*Are you fluent in any other languages? ( ) Yes (•) No

If yes, please list:

Students and Post-Doctoral Fellows promoting the Canadian Cancer Society

Young researchers are uniquely positioned to generate enthusiasm about cancer research. List the names of any students or post-doctoral fellows working on this project who would be suitable for or interested in making presentations to the public about their work. List their hometowns, as these trainees may be invited to speak by their local Society offices, and provide contact information, if different from your own.

Name, student or fellow (S or F), hometown, email:

Speakers bureau

As a recipient of funds provided from charitable donations by the Canadian public, you may be called on to make presentations to volunteers, donors or the public about cancer research. List, in lay terms, topics on which you are able to speak (e.g. angiogenesis, breast cancer, cancer prevention, genetic markers of cancer):

Cancer Immunotherapy, Oncolytic Viruses, Cancer Surgery, Colorectal Cancer, Soft Tissue Sarcoma

Our policy prohibits grantees from accepting funding from the tobacco industry. (See our tobacco policy at www.cancer.ca/research - under Policies and Administration).

***Please indicate if you have received tobacco funding during this grant year:** ○ Yes ◉ No