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Award Number: W81XWH-11-1-0394

TITLE: Granulopoietic Growth Factor Secretion in Ovarian Carcinoma as a Mechanism for the Emergence of Immune Suppressive Myeloid Subsets

PRINCIPAL INVESTIGATOR: Scott Abrams, Ph.D.

CONTRACTING ORGANIZATION: Health Research Inc., Roswell Park Division, New York State
Department of Health
Buffalo, NY 14263-0001

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14. ABSTRACT Among prominent mechanisms thought to impede the anticancer response is the accumulation of pro-tumor myeloid populations. However, there is a fundamental gap regarding the mechanisms that drive their accumulation. To that end, we originally hypothesized that tumor-derived granulocyte-colony stimulating factor (G-CSF) production in ovarian cancer facilitates this aberrant myelopoietic response. However, during year-1, we made the discovery implicating tumor-derived IL-8 in the mechanism of ovarian cancer-mediated immune suppression. Accordingly, this observation prompted us to further evaluate the potential clinical significance of IL-8. To do so, we analyzed the relationship between blood IL-8 levels and newly acquired de-identified patient survival data and, unfortunately, found no significant connection between these clinical factors. Consequently, we reassessed the potential clinical merit of five other myelopoietic factors we had previously identified. Interestingly, only IL-6 fulfilled three important clinical criteria. Altogether, we found that the levels of IL-6: 1) were significantly higher in patients than matched healthy donors; 2) strongly correlated with the accumulation of myeloid populations commonly observed in ovarian cancer patients; and 3) were inversely associated with patient outcome; that is, rising IL-6 levels portended worse overall survival. Although the tumor factor identified is different from the original premise, the conceptual advances made are still consistent with the original hypothesis.					
15. SUBJECT TERMS ovarian cancer, myelopoietic growth factors, myeloid suppressor cells, immune suppression, tumor progression, immunotherapy					
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I. Introduction: We have been testing the underlying hypothesis that tumor-derived signals (i.e., cytokines) perturb normal myelopoiesis resulting in the expansion of myeloid populations that paradoxically harbor tumor-promoting rather than tumor-suppressing activities. In year-2, we focused on the potential clinical merit of the six myelopoietic factors previously identified in year-1, which corresponded to sections of the SOW shown below. Interestingly, of the six cytokines identified, IL-6 but not G-CSF, IL-8, M-CSF, TNF- α or VEGF, fulfilled three important clinical criteria. Altogether, we found that the levels of IL-6: 1) were significantly higher in patients than matched healthy donors; 2) strongly correlated with the accumulation of myeloid populations commonly observed in patients with ovarian cancer; and 3) were inversely associated with patient outcome; that is, rising IL-6 levels portended worse overall survival (hazard ratio = 1.525, $P = 0.02$). The following is a synopsis of year-2, followed by a summary of the main conclusions and a brief reference to how remaining funds will be used if a NCE is granted.

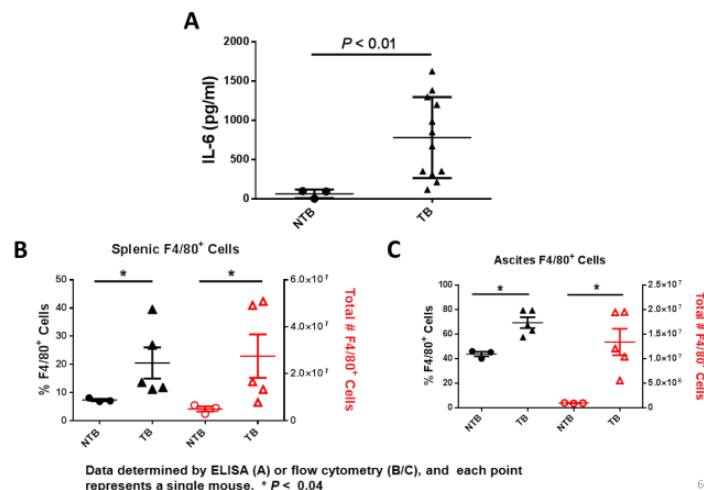
II. Body (from Original SOW):

Specific Aim 1: To quantify G-CSF levels in human ovarian cancer cell lines, and then evaluate the ability of selected G-CSF-producing cell lines to generate MDSC using human-mouse xenograft models

Task 1a, 1b and 2a: Completed in year-1.

Tasks 2b-d: Both sera G-CSF and MDSC levels will be determined during the course of tumor growth. Age/gender-matched non-tumor-bearing mice will serve as controls for G-CSF and MDSC values at all measurable time-points. **Progress:** In the section on 'Potential Problems & Alternative Strategies' in Aim 1 of the project narrative, we pointed out that in addition to or in replace of the human-mouse xenograft model, we would consider testing our hypothesis in a fully syngeneic immune competent mouse model of metastatic ovarian cancer. To that end, we extended our analysis to an implantable (intraperitoneally) mouse model of ovarian cancer, termed ID8 (Figure 1). As with our patient data (showcased in Figure 5), we observed significant levels of IL-6 in the metastatic tumor-bearing (TB) microenvironment relative to peritoneal fluid collected from non-tumor-bearing (NTB) control mice (Figure 1A). Moreover, we observed significant increases in the frequency and absolute numbers of F4/80⁺ monocytes/macrophages in tumor-bearing hosts compared to those from the NTB controls (Figure 1, B and C). These differences were observed both in the periphery (i.e., spleen) and tumor microenvironment (i.e., ascites), thus recapitulating key findings made with patient samples (see Figure 5). T cell proliferation studies in this model are pending.

Figure 1: IL-6 and monocytic/macrophage levels correlate with tumor progression in a mouse model of ovarian cancer



Milestones for Aim 1: Using a relevant mouse model of ovarian cancer, we identified a 'cytokine/myeloid cell signature' associated with tumor progression, consistent with what we observed in ovarian cancer patients (see Figure 5 below).

Overall Progress for Aim 1: We have completed major elements of this aim. First, we identified ovarian tumor cell line models that are tumorigenic *in vivo*. Secondly, tumor progression was accompanied by rising IL-6 levels and an expansion of myelo-monocytic populations similarly found in patients, implicating a pro-tumor axis that may be exploited for therapeutic purposes.

Specific Aim 2: *To examine the causal link between tumor-derived G-CSF production and granulocytic MDSC development using loss-of-function approaches*

Task 1a – 1c: To generate ovarian tumor cell lines in Aim 1 deficient in G-CSF production by shRNA-based methodologies via our shRNA core facility. **Progress:** Studies are pending and will focus on the role of IL-6 in the ID8 model using neutralizing anti-IL-6 antibody. Given the limited amounts of remaining funds, as well as limitations associated with gene knockdown efficiency, we believe this alternative approach will be more informative in a mouse model of ovarian carcinoma.

Tasks 2 and 3: To evaluate the effect of G-CSF-deficiency on tumor growth; collection of serum, lymphoid and tumor tissues from mice for subsequent phenotypic and functional analyses: **Progress:** Studies will be carried out using neutralizing anti-IL-6 antibody, as noted.

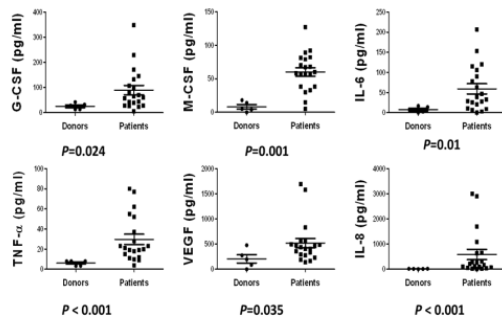
Task 4a and b: To analyze the effect of G-CSF blockade on MDSC accumulation using a neutralizing anti-G-CSF monoclonal antibody (mAb). **Progress:** Studies will be carried out using neutralizing anti-IL-6 antibody, as noted.

Milestones for Aim 2: These studies have the potential to identify for the first time that IL-6, either tumor- or host-derived, exhibits pro-tumorigenic activity through the induction of myelo-monocytic populations, and that strategies that target IL-6 may have novel predictive or therapeutic value.

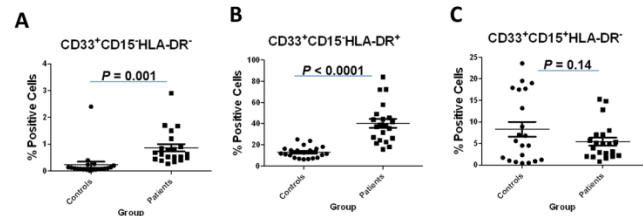
Overall Progress for Aim 2: Thus far, our data support the hypothesis that IL-6 plays an important role in ovarian carcinoma progression, and establish the basis for continuation of these studies.

Specific Aim 3: *To measure circulating G-CSF and MDSC levels in ovarian carcinoma patients and then correlate potential changes in both parameters with clinical outcome measurements.*

Tasks 1 and 2: As we reported in year-1, we identified six cytokines and chemokines associated with aberrant myelopoiesis in ovarian cancer (Figure 2 below). In year-2, we investigated the potential clinical merit of these six myelopoietic factors based on newly acquired de-identified patient data, and found significant inverse relationships between IL-6 with patient outcome. *Specifically, our data indicated that rising IL-6 levels portended worse overall survival (hazard ratio = 1.525, P = 0.02).*

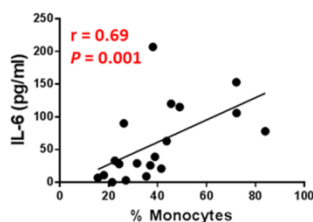
Figure 2**Elevated levels of circulating myelopoietic factors in patients with ovarian cancer**

Data determined by ELISA, and each point represents a single subject.

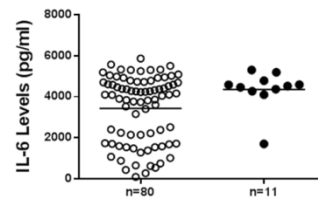
Figure 3**Elevated levels of monocytic subpopulations in patients with ovarian cancer**

Data determined by multi-color flow cytometry, and each point represents a single subject.

Since we originally hypothesized that ovarian cancer disables antitumor immunity through disruption of normal myeloid cell differentiation, we next examined patient blood for evidence of expanded myeloid populations relative to matched donors. Our data demonstrated a significant increase in 2 of the 3 myeloid populations tested, both sharing a myelo-monocytic phenotype (i.e., CD33⁺CD15⁻HLA-DR⁻ myeloid-derived suppressor cell/MDSCs or CD33⁺CD15⁻HLA-DR⁺ monocytes) compared to the matched donors (Figure 3, A and B above). Thus, we identified a potential 'cytokine/myeloid cell type' profile portending a poorer prognosis. To explore this idea in more detail, we plotted the relationship between IL-6 levels and myeloid cell type (using data from Figures 2 and 3). As a result, we identified a highly significant positive correlation between IL-6 levels and monocyte frequency (Figure 4 below). No other significant association was observed, strengthening the potential relevance of the IL-6/myelo-monocytic profile in ovarian cancer patient assessment.

Figure 4**IL-6 levels correlate with monocytic frequencies**

Data in Figures 2 and 3 were re-plotted to determine potential correlations between the indicated parameters.

Figure 5**Elevated Levels of IL-6 in Ovarian Cancer Patient Ascites**

IL-6 levels in patient ascites were quantified by ELISA from the indicated number of patients with advanced disease. Right column refers to 11 of the 80 patients in which matched sera were also tested (see Figure 2). Horizontal line in graph refers to mean.

To further validate the potential relevance of IL-6 *in vivo*, we examined IL-6 levels by ELISA in the metastatic tumor microenvironment (i.e., ascites) in a total of 80 ovarian cancer patients (Figure 5 above, left column). Our data showed that the majority of patients tested produced robust levels of IL-6. Similar results were seen in an 11-patient subgroup in which matched sera were also tested (Figure 2 and Figure 4, right column).

Task 3: If the data are statistically meaningful in Aim 3/Tasks 1 & 2, patients with earlier stage disease (n=30) will be analyzed in a similar fashion. **Progress:** Studies will be suspended (at least at this time) due to insufficient funds.

Milestones/Overall Progress for Aim 3: Of the six cytokines identified, only IL-6 fulfilled three important clinical criteria. Altogether, we found that the levels of IL-6: 1) were significantly higher in patients than matched healthy donors; 2) strongly correlated with the accumulation of myeloid populations commonly observed in patients with ovarian cancer; and 3) were inversely associated with patient outcome; that is, rising IL-6 levels portended worse overall survival (hazard ratio = 1.525, $P = 0.02$).

3. Key Research Accomplishments: Altogether, we identified...

- A significant expansion of two distinct myelo-monocytic subsets in the peripheral blood of ovarian cancer patients reflecting stages II – IV (all relative to healthy donors).
- Six pro-inflammatory cytokines in matched patient sera, including IL-8, G-CSF, M-CSF, IL-6, TNF- α and VEGF-A (all relative to healthy donors). However, only IL-6 levels were significantly and positively associated with poorer clinical outcome, as determined by hazard ratio assessment.
- A significant and positive relationship between IL-6 levels and myelo-monocytic frequencies in ovarian cancer patients, revealing a previously unrecognized 'cytokine/myeloid' signature with potentially important translational/clinical value.
- Concordance between high sera IL-6 levels with high ascites IL-6 levels, suggesting that changes in blood IL-6 levels may be a reliable and convenient way to track disease progress.

4. Reportable Outcomes: Not applicable during this reporting period.

5. Conclusions: The identification of this new axis in myeloid-ovarian tumor biology has important implications for IL-6-based clinical interventions. Monitoring changes in IL-6 levels, systemically or within the tumor microenvironment, along with other clinical parameters, may serve as a novel 'biomarker' signature for disease status or response to anticancer therapy. Moreover, these studies provide the rationale to target IL-6 for therapeutic purposes in at least subsets of ovarian cancer patients.

6. References: None included, as this report is based on an unpublished synopsis of our work.

7. Appendices: Updated Curriculum Vitae

8. Supporting Data: Figures are embedded.

CURRICULUM VITAE

Name: Scott I. Abrams, Ph.D.

Citizenship: United States

Education

1981	B.S. (Biology), Delaware Valley College, Doylestown, Pennsylvania <i>summa cum laude</i>
1987	Ph.D. (Microbiology & Immunology), Indiana University School of Medicine, Indianapolis, Indiana

Chronology of Employment

1981 – 1987	Graduate Student, Department of Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, IN
1987 – 1991	Postdoctoral Fellow, Department of Molecular Biology and Pharmacology, Washington University School of Medicine, St. Louis, MO
1991 – 8/15/98	Senior Staff Fellow, Laboratory of Tumor Immunology and Biology, Division of Basic Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD
8/16/98 – 1/31/08	Investigator, Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD
2/1/08 – present	Associate Member, Department of Immunology & Associate Professor of Oncology, Roswell Park Cancer Institute, Buffalo, NY
2008 – present	Joint appointment as Associate Professor, Department of Microbiology and Immunology, State University of New York (SUNY) at Buffalo, Buffalo, NY

Societies

American Association for Cancer Research
The American Association of Immunologists
The American Association for the Advancement of Science
International Society for Biological Therapy of Cancer
Sigma Xi, The Scientific Research Society

Honors, Awards and Other Professional Activities

1987	Nominated by Faculty for the Esther L. Kinsley Dissertation Award, Indiana University's Highest Honor
1987 – 1990	Recipient of National Research Service Awards for Postdoctoral Studies
1996	NIH Federal Technology Transfer Award
1998	NIH Federal Technology Transfer Award
2000	FY 2000 Intramural Research Award, CCR, NCI, NIH
2000	"On-The-Spot Award", LTIB, CCR, NCI
2001	"On-The-Spot Award", LTIB, CCR, NCI
2002	"On-The-Spot Award", LTIB, CCR, NCI
2003	NIH Federal Technology Transfer Award
2003	Performance Award, LTIB, CCR, NCI
2004	Nominated for 2004 NCI Outstanding Mentor Award
2004	NIH Federal Technology Transfer Award
2004	Performance Award, LTIB, CCR, NCI
2005	Performance Award, LTIB, CCR, NCI
2006	NIH Federal Technology Transfer Award
2006	Performance Award, LTIB, CCR, NCI
2007	NIH Federal Technology Transfer Award
2007	Performance Award, LTIB, CCR, NCI
2011	Recipient of 2011 AAI Laboratory Travel Grant
2012	Recipient of 2012 AAI Laboratory Travel Grant

Leadership Positions at Conferences/Editorial Level

2004	Co-Chair Cancer Vaccine/Immunotherapy Block Symposium at the Experimental Biology Conference, Washington, D.C.
2005	Section Editor for "Drug Discovery Today: Disease Mechanisms". Issue on "Immune Mechanisms of Cancer"
2010	Co-Chair for the 10 th Annual Buffalo Conference on Immunology
2011	Co-Chair, Tumor Immunology mini-symposium at AAI conference San Francisco
2012	Co-Chair, Tumor Immunology mini-symposium at the AAI conference in Boston
2012	Guest Editor for Immunological Investigations for thematic Issue on "Regulatory Myeloid Cells in Neoplasia"
2013	Organizing Committee, Translational Research Cancer Center Consortium

Patents

2002	European Patent #97 921 247.9 - Mutated <i>ras</i> Peptides for Generation of CD8 ⁺ Cytotoxic Lymphocytes
2010	U.S. Patent #7,709,002 – Mutated <i>ras</i> Peptides for Generation of CD8 ⁺ Cytotoxic Lymphocytes

Committees and Boards

Chair, Progress Committee, Dept. of Immunology, RPCI
Member, Tumor Immunology and Immunotherapy Program, RPCI
Member of Curriculum Committee, Graduate Program/Department of Immunology, RPCI
Member of Gene Targeting/Transgenic Steering Committee, RPCI
Member, Institutional Divisional Committee, RPCI
Member, Immunology Steering Committee, RPCI
Ad hoc member for Scientific Review Committee, RPCI
Member, Immunology Academic Integrity and Grievance Committee

Study Sections

Reviewer for VA Merit Review Panel (Immunology; Oncology)

Ad hoc reviewer for Wellcome Trust

Ad hoc reviewer for Association for International Cancer Research

Ad hoc reviewer for NIH study section, NCI-I (career investigator awards)

Ad hoc reviewer for NCI Special Emphasis Panel on Tumor Immunology/Therapeutics

Ad hoc reviewer for French NCI on Translational Cancer Research

Member, Medical Scientific Board for Association for Research of Childhood Cancer (AROCC)

Reviewer

Blood

Cancer Research

Clinical Cancer Research

Immunological Investigations

Journal of Immunology

Journal of Immunotherapy

Molecular Cancer Therapeutics

Oncogene

PLoS ONE

Mentorship

Pre-doctoral:

Primary Mentor for Jeremy Waight at SUNY-Buffalo/RPCI, who was

Selected for oral presentation at annual AAI conference, 2011

Awarded first place in RPCI-Graduate Student Poster Presentation Competition, 2011

Awarded second place for poster presentation at 11th Annual Buffalo Conference on Immunology, 2011

Awarded Ph.D., July, 2012

Recipient of RPCI's Excellence in Cancer Research Award, 5/13

Primary Mentor for Debarati Banik at SUNY-Buffalo/RPCI, who was

Selected for oral presentation at annual Upstate New York Immunology Conference,

Selected for oral presentation at annual AAI conference, 2012 and received travel award

Primary Mentor for Colleen Netherby, Danielle Twum and Lauren Burkard at SUNY-Buffalo/RPCI

Served/serving on > 10 Ph.D. and 3 Master Degree Thesis Committees (Three Ph.D. students recently graduated)

Post-doctoral:

Preceptor for a Postdoctoral Fellow (T. Stewart) who received a NIH Fellows Award for Research Excellence (FARE), 2007

Preceptor for a Postdoctoral Fellow (K. Greenelch) who received a NIH Fellows Award for Research Excellence (FARE), 2007

Preceptor for a Postdoctoral Fellow (T. Stewart), who received an AACR Scholar-in-Training Award at the AACR 97th Annual Meeting, 2006

Preceptor for a Postdoctoral Fellow (T. Stewart), who was selected for oral presentation at the NCI-CCR Fellow's Retreat, 2006

Scott I. Abrams

Preceptor for a Research Fellow (K. Liu), who was selected for oral presentation at the NIH Immunology Retreat, 2005

Preceptor for a Postdoctoral Fellow (T. Stewart), who was selected for oral presentation at the Combined Faculty Retreat, CCR-NCI, 2005

Preceptor for a Research Fellow (K. Liu), whose studies resulted in recognition with a competitive Travel Award at the NCI-CCR Fellow's retreat, 2005

Preceptor for a Postdoctoral Fellow (T. Stewart), whose studies resulted in recognition with a competitive Travel Award at the NCI-CCR Fellow's retreat, 2005

Preceptor for a Research Fellow (K. Liu), whose studies resulted in recognition with an AACR-sponsored Scholar-in-Training Award to a special conference entitled "Oncogenomics: Dissecting Cancer through Genomic Research", 2005

Preceptor for a Postdoctoral Fellow (T. Stewart), who was selected for oral presentation at the Experimental Biology Conference, April 2004 in the Block Symposium on Antitumor Effector Cells, Mechanisms of Tumor Rejection and Modulation of Tumor Immunity

Preceptor for a Postdoctoral Fellow (S. Caldwell), who was selected for oral presentation at the NIH Immunology Retreat, 2003

Preceptor for a Research Fellow (K. Liu), who was selected for oral presentation at the NCI-CCR Fellow's Retreat, 2003

Preceptor for a Postdoctoral Fellow (S. Caldwell), who was selected for oral presentation at the NCI-CCR Fellow's Retreat, 2003

Preceptor for a Postdoctoral Fellow (M. Ryan), who was selected for oral presentation at the NCI-DBS Fellow's Retreat, 2000

Preceptor for a Research Fellow (E. Bergmann-Leitner), whose studies resulted in recognition with a NIH Fellows Award for Research Excellence (FARE), 1999

Preceptor for a Postdoctoral Fellow (J. A. Bristol), whose studies resulted in recognition with a NIH Fellows Award for Research Excellence (FARE), 1997

Teaching Activities (at RPCI and UB-SUNY)

Molecular Immunology (MIR511)

Trends in Tumor Immunology (MIR509)

Interferons and Cytokines (BIR530)

Advanced Topics in Immunology (MIR508)

Co-Chair of Student Journal Club (MIR522 throughout academic year)

Basics in Grantsmanship (MIR510)

Fundamentals of Immunology (MIC 512/412)

Oncology for Scientists (RPN530)

Faculty member, Howard University/RPCI Scholar's Program

Invitations to Speak

Invited Keynote Speaker at the International Conference on Clinical & Cellular Immunology, Chicago, IL, October 22-24, 2012. Title of Seminar: "Granulocytic myeloid-derived suppressor cell development via G-CSF-dependent mechanisms"

Invited Speaker at the International Conference on Clinical & Cellular Immunology, Chicago, IL, October 22-24, 2012. Title of Seminar: "Transcriptional regulation of Myeloid-Derived Suppressor Cell Development in Neoplasia"

Invited Speaker at the 2nd International Conference on Vaccines and Vaccination, Chicago, IL, August 20, 2012. Title of Seminar: "Mechanisms of Tumor-Induced Myeloid-Derived Suppressor Cell Development"

Invited Speaker to the Molecular and Developmental Genetics Seminar Series, Department of Molecular and Cellular Biology, Roswell Park Cancer Institute, Buffalo, NY, December 4, 2008. Title of Seminar: "Role of Interferon Regulatory Factor-8 (IRF-8) in Host-Tumor Immunosurveillance"

Invited Speaker at the 11th Annual Upstate New York Immunology Conference, Albany Medical College, Bolton Landing, NY, October 19-22, 2008. Title of Seminar: "IRF-8 Regulates Tumor Cell Responses to Apoptosis and Host Immunosurveillance"

Invited Speaker at the 8th Annual Buffalo Conference on Immunology, Buffalo, NY, September 8 – 9, 2008. Title of Seminar: "Role of IRF-8 in Tumor-Cell Response to Immunosurveillance Mechanisms"

Invited Speaker to the Tumor Immunology Seminar Series, Department of Immunology, Roswell Park Cancer Institute, Buffalo, NY, May 27, 2008. Title of Seminar: "Role of Interferon Regulatory Factor-8 in Myeloid-Derived Suppressor Cell Development and Function"

Invited Speaker to the Research Seminar Series, Dept. of Pediatrics, University of Texas M.D. Anderson Cancer Center, August 2007. Title of Seminar: "Fas Resistance Contributes to Tumor Escape and Progression"

Invited Speaker to The GW Cancer Center and the McCormick Center, in conjunction with the Department of Microbiology and Immunology, George Washington University Medical Center, November 2006. Title of Presentation: "Resistance to Fas-Mediated Lysis as a Mechanism of Immune Selection and Tumor Progression"

Invited Speaker to the Tumor Vaccine and Cell Therapy Working Group, AACR, Washington, D.C., April 2006. Title of Presentation: "Adoptive Immunotherapy Mediates Tumor Regression and Tumor Escape"

Invited Speaker to the Translational Immunology Seminar Series, Section of General Surgery, the University of Chicago Medical Center, November 2005. Title of Seminar: "Fas-Mediated Cytotoxicity as a Mechanism of Immunoselection and Tumor Escape"

Major Invited Speaker at an International Conference, entitled "Cancer Vaccines/Adjuvants & Delivery Systems for the Next Decade", Lisbon, Portugal, September 2005. Title of Presentation: "CTL-Based Immunotherapy Mediates Tumor Regression and Tumor Escape"

Scott I. Abrams

Invited Speaker, Hematology Branch, NHLBI, NIH, July 2005. Title of Seminar: "Combinatorial Approaches involving Immunotherapy and Radiation Enhance Tumor Regression"

Invited Speaker, Immunology Faculty, NCI, February 2005. Title of Seminar: "Positive and Negative Consequences of Fas/Fas Ligand Interactions in the Antitumor Response"
Major Invited Speaker at the University of Colorado for a Symposium on Cancer Biology, November 2004. Title of Presentation: "Fas/Fas Ligand Interactions in the Regulation of Tumor Progression"

Major Invited Speaker at the University of Vermont for a Symposium on The Course of Cancer, October 2004. Title of Presentation: "Interactions Between the Cellular Immune System and Cancer"

Invited Speaker at the Gerber Adult Seminar series on Science & Technology, Rockville, MD, November 2004. Title of Seminar: "The Development of Vaccines for Cancer"

Invited Speaker at the Breast Cancer Faculty, CCR, NCI, October 2004. Title of Seminar: "Immunologic Characteristics of a Transgenic Mouse Model of Primary and Metastatic Mammary Carcinoma"

Invited Speaker at the "8th World Congress on Advances in Oncology and 6th International Symposium on Molecular Medicine" in Crete, Greece, October 2003. Title of Presentation: "Regulation of the Fas Pathway in Tumor Immunotherapy"

Invited Speaker at the Regina Elena Cancer Institute in Rome, Italy, October 2003. Title of Seminar: "Combinatorial Vaccine Strategies Employing Recombinant Vectors"

Invited as a Keynote Speaker at an international conference on "Biotherapy of Cancer: From Disease to Targeted Treatment" in Munich, Germany, September 2003. Title of Presentation: "Combinatorial Vaccine Strategies Employing Recombinant Vectors"

Guest Lecturer in the Tumor Biology Program at the Georgetown University School of Medicine, April 2003. Title of Lecture: "Understanding the Host/Tumor Interaction for Cancer Vaccine Development"

Invited Speaker for the NCI-Frederick Seminar Series, November 2002. Title of Seminar: "Fas-Based Interactions in Tumor Regression and Progression"

Guest Lecturer in the Tumor Biology Program at the Georgetown University School of Medicine, April 2002. Title of Lecture: "Understanding the Host/Tumor Interaction for Cancer Vaccine Development"

Invited Speaker at the 11th International Congress of Immunology, Stockholm, July 2001. Title of Presentation: "Role of Fas in Human Antigen-Specific Cytotoxic T Lymphocyte-Colon Carcinoma Cell Interactions"

Invited Speaker in the Lombardi Cancer Center's Tumor Biology Seminar Series at the Georgetown University School of Medicine, October 2000. Title of Seminar: "Regulation of the Fas/FasL Pathway in Human CD8+ Cytotoxic T Lymphocyte-Colon Carcinoma Cell Interactions"

Scott I. Abrams

Invited Speaker in the Cancer Center Distinguished Lecture Series at the Medical College of Wisconsin, July 2000. Title of Seminar: "ras Oncogene Products as Targets for Tumor Immunotherapy"

Guest Lecturer, "Immunotherapy of Cancer", George Washington University School of Medicine, Molecular and Cellular Oncology Program, November 1999

Invited Speaker to the Department of Microbiology and Immunology, Indiana University School of Medicine, May 1998. Title of Seminar: "ras Oncogenes as Targets for Cancer Immunotherapy"

Invited Speaker at the Conference for Immunology and Immunotherapy of Metastasis, Title of Presentation: "Recombinant Vaccines to Point-Mutated ras and CEA: Analyses of Patient T-Cell Responses", Lake Tahoe, CA, May 1996. Also, Chairperson of one of the scientific session at this same meeting, entitled: "Immunotherapy of Metastasis"

Invited Speaker at the First International Conference on Gene Therapy & Vaccines for Cancer, Washington, D.C., 1994. Title of Presentation: "Peptides Reflecting Mutated ras p21 Epitopes Induce Host Cellular Immune Responses"

Invited Speaker to the Department of Pathology, "Immunology Seminar Program" at The Ohio State University College of Medicine, January 1994. Title of Seminar: "Induction and Characterization of Host Cellular Immune Responses to Mutated ras p21 Epitopes"

Ongoing Research Support

W81XWH-11-1-0394 (Abrams, PI)	05/01/11 - 04/30/13 (NCE requested)	1.8 calendar
DOD	\$99,457 TDC/yr	months

"Granulopoietic Growth Factor Secretion in Ovarian Carcinoma as a Mechanism for the Emergence of Immune Suppressive Myeloid Subsets"

This research tests the novel hypothesis that human and/or mouse ovarian cancer cells produce myelopoietic growth factors that participate in the generation of pro-tumor myelo-monocytic cells.

Overlap: None

R01 CA140622-01 (Abrams, PI)	09/01/11 - 08/31/16	3.6 calendar
NCI/NIH	\$207,500 TDC/yr	months

"IRF-8 as a Negative Regulator of CD11b⁺Gr-1⁺ Myeloid Cell Production and Function"

This research tests the novel hypothesis that MDSCs accumulate or become pro-tumorigenic because neoplastic cells cause a profound alteration in IRF-8 that is normally essential for controlling fundamental properties of the myeloid cell family.

Overlap: None

Alliance Developmental Award (Abrams, PI)	07/01/12 - 06/30/13	1.2 calendar
RPCI Alliance Foundation	\$90,597 TDC/yr	months

"IRF4, a Novel Tumor Suppressor in Pediatric BCR-ABL⁺ B-ALL"

This research tests the novel hypothesis that IRF4 downregulation contributes to BCR-ABL⁺ acute pediatric B lymphoblastic leukemia, and that the mechanism of IRF4 loss involves STAT5-mediated repression of IRF4 transcription.

Overlap: None

Alliance Developmental Award (Abrams, PI)	06/01/13 - 05/31/14	0.6 calendar
RPCI Alliance Foundation	\$20,000 TDC/yr	months

“Novel TRL5-based Immunotherapies against Metastatic Colon Cancer”

This research will investigate a new approach to the treatment of metastatic colon cancer in animal models. Earlier work led to development of a novel therapeutic, termed Entolimod™ that potentially triggers both innate and adaptive immune responses. Our aims will focus on the mechanism of action, as well as examine the efficacy of Entolimod™ in combination immunotherapies.

Overlap: None

R21 CA164475-01A1 (Kozbor, PI)

07/01/12 - 06/30/14

0.36 calendar

NIH/National Cancer Institute

\$125,000 TDC/yr

months

“Oncolytic Viruses with Therapeutic Genes in the Treatment of Breast Cancer”

The goals of this proposal are to target the CXCR4/CXCL12 interaction in mammary cancer models using a novel oncolytic virotherapy and then define the immune mechanisms underlying antitumor activity.

Role: Co-Investigator

Overlap: None

Completed Research Support

Alliance Developmental Award from the Roswell Park Alliance Foundation

Title: Development of Myeloid-Derived Suppressor Cells in Mammary Carcinoma through Interferon Regulatory Factor-8-Dependent Mechanisms

Role: PI

Duration of funding: 11/1/10 – 10/31/11

Goal of Study: RPCI Alliance Foundation awarded seed funding to explore the relationship between MDSC accumulation/IRF-8 expression and disease status or outcome in patients with breast cancer.

NO8G-370 - NYSTEM (New York State Stem Cell Science)

Title: Role of Cancer Stem Cells in Resistance to Targeted Therapy and Tumor Recurrence

Role: Co-Investigator

Duration of funding: 1/1/09 – 6/30/11

Goal of Study: NYSTEM awarded seed funding for an exploratory study investigating the sensitivity of pancreatic cancer stem cells to a novel death-inducing agent, Apo2L/TRAIL in a large cohort of patient tumors.

Alliance Developmental Award from the Roswell Park Alliance Foundation

Title: Regulation of Interferon Regulatory Factor-8 in Neoplastic Cells to Augment Responses to Apoptosis and Immunotherapy

Role: PI

Duration of funding: 1/1/09 – 12/31/09

Goal of Study: This study tested the hypothesis that histone deacetylase inhibitors, a novel class of epigenetic modifiers, enhance Fas-mediated apoptosis through IRF-8-dependent mechanisms.

Publications

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Book Chapters

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Invited Reviews

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