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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 Cancer Institute
Division, Buffalo, NY 14263-0001

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Fort Detrick, Maryland 21702-5012

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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.					
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I. Introduction: Myeloid-derived suppressor cells (MDSCs) comprise immature myeloid populations produced in a wide range of human cancers, including ovarian carcinoma, and play significant tumor-promoting roles by suppressing adaptive immunity and by providing a rich source of angiogenic factors¹. MDSCs are composed of two major subsets, monocytic and granulocytic, the proportion of each is influenced by the types of tumor-derived factors (TDFs) secreted *in vivo*^{1,2}. Although much attention has focused on understanding how MDSCs function, a larger gap has remained in our understanding of mechanisms that govern their development. To that end, our original proposal addressed the novel concept that the overproduction of granulocyte-colony stimulating factor (G-CSF) in ovarian carcinoma facilitates MDSC accumulation. This notion was originally born from studies in our laboratory, which revealed a prominent role of G-CSF in the generation of MDSCs in mouse models of mammary carcinoma^{3,4}. While we believe the rationale for this hypothesis remained sound, we serendipitously discovered that the levels of IL-8 (CXCL8) and IL-6 overshadowed all other cytokines/chemokines tested, including G-CSF. Thus, in contrast to mammary tumor models, we identified a different set of pro-inflammatory cytokines potentially linked to MDSC accumulation in ovarian cancer. Given these striking new findings, we *refined our original hypothesis to reflect tumor-derived IL-8 (year 1) or IL-6 (year 2), in lieu of G-CSF as major elements of MDSC-mediated ovarian tumor progression*. The following is a detailed account of our progress made for each aim and task with respect to the original SOW.

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 – 2d,** completed in year-2, and are summarized below.

Task 1a: Cell-free supernatants of human ovarian cancer cell lines will be quantified for G-CSF levels. Both metastatic SKOV-3 and NIH:OVCAR-3 cell lines (from ATCC) will be analyzed, since both have been shown to express G-CSF.

Progress: We determined that both cell lines produced G-CSF as expected. However, the concentrations were also lower than expected. Therefore, before pursuing subsequent studies, we embarked on a more comprehensive analysis of tumor-derived cytokines and chemokines, focusing on two key characteristics: association with MDSC biology and cross-reaction in human-mouse xenograft models. In so doing, we compiled a list of 12 cytokines and chemokines, including G-CSF and analyzed them by Luminex multiplex technology (Fig. 1A and 1B). While our findings confirmed G-CSF production by ELISA (< 100 pg/ml), we identified an additional five factors that were highly produced, most notably IL-8 which was common to both cell lines. IL-8 levels exceeded 2 ng/ml/10⁶ cells/24 hr.

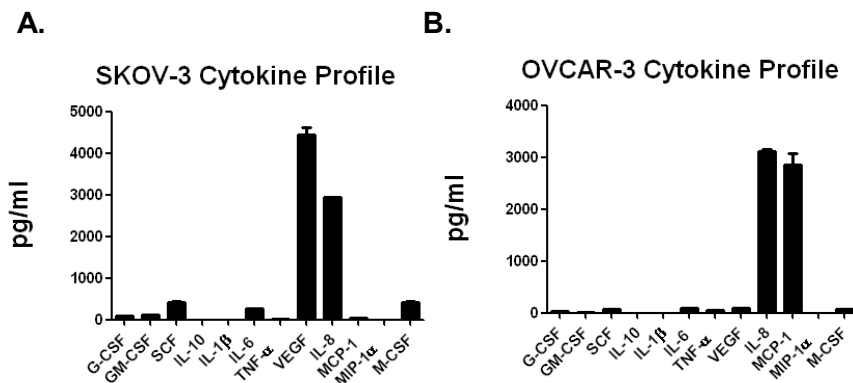


Figure 1. Cytokine production by ovarian carcinoma cell line models. Cell-free culture supernatants were analyzed by Luminex technology for the indicated TDFs. Data reported as pg/ml/10⁶ cells/24 hr.

Task 1b: RNA will be collected from the cells to verify G-CSF message levels by RT-PCR or real-time PCR.

Progress: Since our protein data was most revealing, we did not pursue molecular analysis of G-CSF in our cell line model, but confirmed IL-8 message.

Task 2a: Evaluate the ability of ovarian tumor cell lines to produce G-CSF and generate granulocytic MDSC *in vivo*.

Progress: We proceeded with orthotropic implantation of each cell line. Both cell lines were tumorigenic *in vivo*; however, SKOV3 seemed to be more tumorigenic than NIH:OVCAR-3, based on time to morbidity (Fig. 2). Therefore, since SKOV3 was more aggressive, we opted to pursue this cell line first in subsequent experiments.

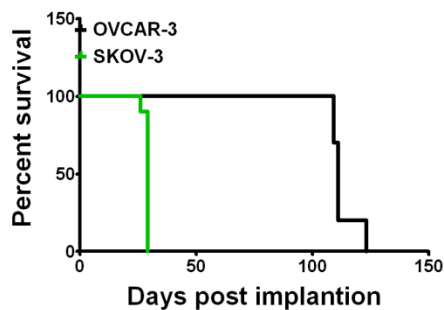


Figure 2. Human-mouse xenograft model of ovarian tumor growth. Kaplan-Meier plots of the indicated tumor-bearing mice. Tumor cells were implanted *ip* (5×10^6 /mouse) and mice euthanized immediately upon signs of morbidity ($n = 10$ /group).

Task 2b: Sera G-CSF and MDSC levels will be determined and tracked biweekly 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.

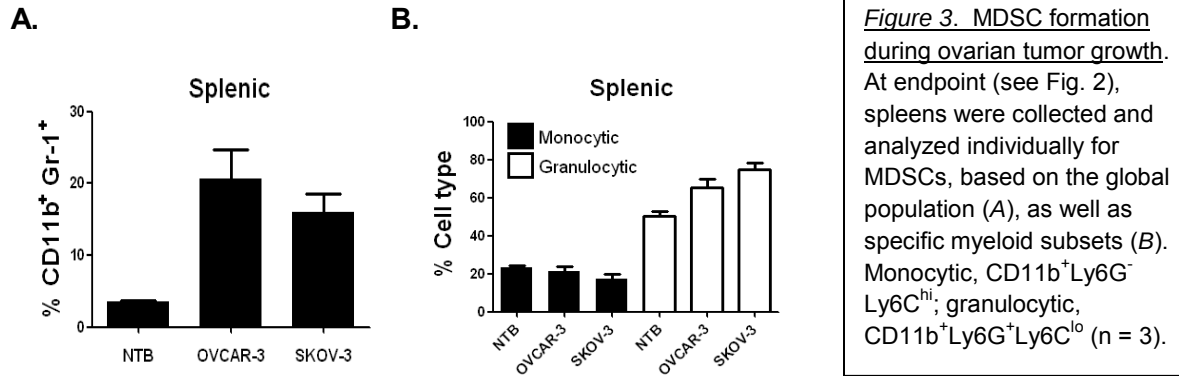
Progress: Based on results in Task 1, we analyzed sera for IL-8 levels. However, in regard to MDSC quantification, we focused on the spleen as a systemic reservoir for the accumulation of MDSCs during tumor-bearing conditions. Data are further discussed below.

Task 2c: When mice appear moribund (as evidence of advanced disease), mice will be euthanized and spleens and ascites (tumor site) collected. Blood will also be collected as part of a terminal bleed. Single cell suspensions will be made from splenic and tumor sites, and cryopreserved for subsequent studies.

Progress: Completed; all cells and tissues collected as proposed.

Tasks 2d: Murine granulocytic MDSCs will be defined by their $CD11b^+Ly6C^{lo}Ly6G^+$ phenotype by flow cytometry, granulocytic morphology by Wright-Giemsa staining and ability to inhibit T cell proliferation.

Progress: Analysis of MDSC frequencies in the spleen revealed significant levels of MDSCs, particularly of granulocytic phenotype, relative to the non-tumor-bearing control mice (Fig. 3). This was observed in both tumor cell line models, indicating that ovarian carcinoma can generate MDSCs *in vivo*. Morphologic studies in an independent model of mammary carcinoma confirmed that the MDSCs expressing this phenotype were granulocytic. T cell proliferation studies were suspended due to exhausted funds.



Moreover, in the section on 'Potential Problems & Alternative Strategies' in Aim 1 of the project narrative, we pointed out that in addition to or in lieu 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 mouse model of ovarian cancer, termed ID8 (Fig. 4). Unfortunately, in contrast to the human cell lines, ID8 did not produce significant levels of IL-8 (known as KC in mice), as measured in the ascites of the peritoneal cavity (Fig. 4A). Instead, 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 (Fig. 4B). 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 (Fig. 4C and 4D). These differences were observed both in the periphery (i.e., spleen) and tumor microenvironment (i.e., ascites). Importantly, these observations recapitulated key findings made with patient samples (see Aim 3).

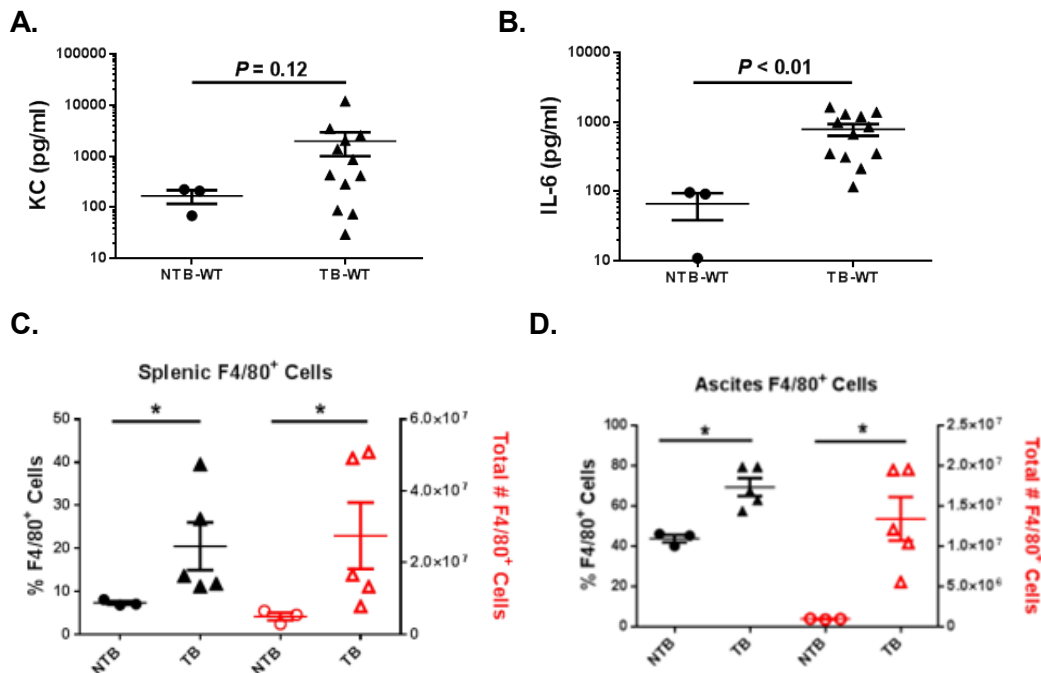


Figure 4. IL-6 and monocytic/macrophage levels correlate with tumor progression in a mouse model of ovarian cancer. Data determined by ELISA (A/B) or flow cytometry (C/D) of the indicated cell types, and each data point represents a single mouse. * $P < 0.04$

We then reasoned that if IL-6 played an important role in myeloid-mediated mechanisms of tumor progression, then neutralizing IL-6 *in vivo* using neutralizing anti-IL-6 antibody should improve overall survival. However, efforts to inhibit tumor progression via IL-6 blockade during the no cost extension period were unsuccessful.

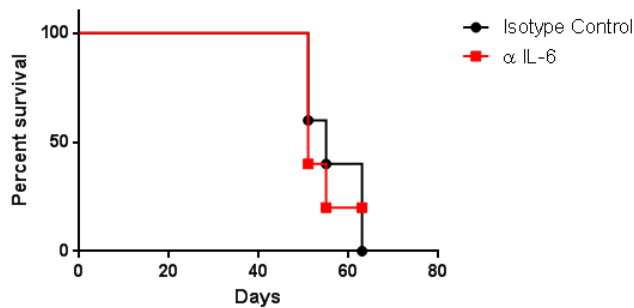


Figure 5. IL-6 blockade does not prolong survival in ID8-tumor-bearing mice. ID8 cells were injected i.p. into B6 mice and then treated with 100 μ g anti-IL6 antibody (clone MP5-20F3) or an isotype-matched control (clone HRPN) once weekly for the duration of the experiment. n =5 mice/group

Milestones for Aim 1: We completed major elements of this aim, although with mixed results. First, we identified ovarian tumor cell line models that are tumorigenic *in vivo*. Secondly, tumor growth was accompanied by a significant MDSC response, largely due to the accumulation of the granulocytic subset. And thirdly, while we did confirm the production of G-CSF, the levels of G-CSF response dwarfed in comparison to IL-8 production in both human cell line models tested. Unfortunately, using a relevant syngeneic mouse model of ovarian cancer (ID8), we identified IL-6 instead of IL-8 as ‘cytokine/myeloid cell signature’ associated with tumor progression. Undoubtedly, our inability to corroborate G-CSF, IL-8 and/or IL-6 production in the all tumor models tested compromised the extent of overall positive progress. Nonetheless, we continued to move forward in Aims 2 and Aim 3 as follows.

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: To generate ovarian tumor cell lines in Aim 1 deficient in G-CSF production by shRNA-based methodologies via our shRNA core facility.

Progress: Based on our human data in Aim 1, we replaced G-CSF with IL-8. At that time, we decided to focus on one cell line, SKOV3, due to its ability to grow more reliably and aggressively than NIH:OVCAR-3 (Fig. 6). The various sublines were successfully generated.

Task 1b: Analyze and verify the efficiency of gene knockdown in the different populations via real-time PCR analysis and ELISA.

Progress: Completed; characterization of the different sublines revealed varying degrees of IL-8 knockdown relative to the control (Fig. 6A). The magnitude of knockdown was confirmed by ELISA (Fig. 6B). Based on these criteria, we selected construct 1 for subsequent studies.

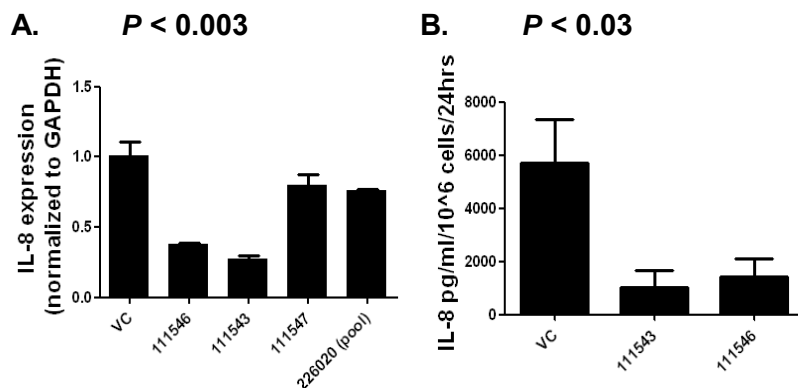
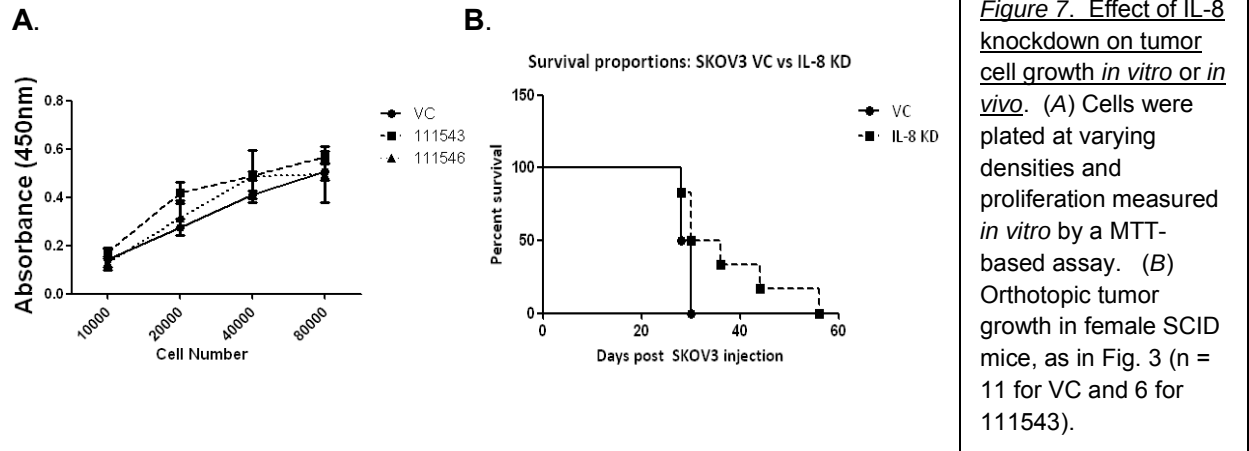


Figure 6. Generation of IL-8-deficient ovarian tumor sublines. SKOV3 cells were silenced for IL-8, based on shRNA methods. VC refers to the vector control, while each numbered code represents a given subline expressing a single construct or a pool of all 3. Data analyzed by qPCR (A) or ELISA (B) for secreted protein for the VC and the two sublines showing the highest knockdown in A.

Task 1c: For each tumor cell line, identify and select the population most deficient in G-CSF expression. Characterize each further for potential off-target biologic effects, such as changes in cell proliferation *in vitro*.

Progress: IL-8 knockdown did not alter *in vitro* proliferation (Fig. 7A).



Milestones for Task 1: Development and characterization of human ovarian tumor cell lines that are stably silenced for G-CSF production. For each tumor cell line, two populations will be generated, one deficient in G-CSF and the other serving as the vector control.

Progress: We achieved major elements of this aim and had produced both control and IL-8-deficient sublines (see Figs. 6 and 7).

Task 2a: 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: Completed for the SKOV3 model.

Task 2b: For proof-of-concept, emphasis will be on the endpoint analysis. When mice appear moribund as evidence of advanced disease, mice will be euthanized and splenocytes, ascites and serum collected and stored as in Aim 1/Task 2.

Progress: Completed for the SKOV3 model. Interestingly, we observed a significant increase in overall survival in mice bearing the IL-8-deficient subline compared to the control (Fig. 7B).

Milestones for Task 2: Determination of the impact of G-CSF-deficiency on orthotopic tumor growth using two different ovarian tumor models.

Progress: Completed for the SKOV3 model. Altogether, these data were promising and suggest an important role of tumor-derived IL-8 production in ovarian cancer progression.

Task 3a: To analyze serum G-CSF levels and MDSC accumulation in both lymphoid and tumor tissues (Experiments will be staggered so the different tumor models will be analyzed at different times).

Progress: Completed for the SKOV3 model. First, we observed a significant difference in IL-8 levels, pre- vs. post-tumor challenge in mice bearing either the vector control or IL-8-deficient subline. Whereas, pre-bleeds showed no detectable IL-8, post-bleeds revealed significant amounts of circulating IL-8 (Fig. 8A and 8B). Importantly, the level of IL-8 in sera of mice

bearing the IL-8-deficient subline was significantly lower compared to the scramble control (Fig. 8C). The post-bleeds were taken at endpoint when all mice appeared moribund. These data not only validate the IL-8 phenotype *in vivo*, but also demonstrated a correlation with survival.

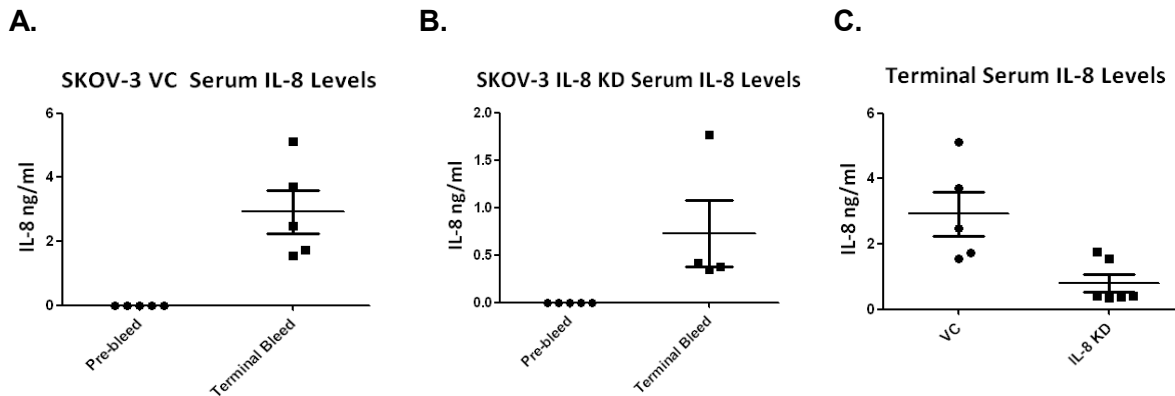


Figure 8. Serum IL-8 levels during orthotopic tumor growth. (A, B) IL-8 levels pre-implantation and post-tumor implantation at endpoint for the indicated sublines. Serum isolated from mice shown in Fig. 6 (IL-8 KD; construct 111543). (C) IL-8 levels at endpoint, comparing VC to IL-8-deficient cells ($P < 0.05$). Each data point in A-C denotes a single mouse measurement.

Task 3b: Thaw splenocytes, and analyze for granulocytic MDSC levels (percentages/absolute numbers) based on CD11b⁺Ly6C^{lo}Ly6G⁺ phenotype by flow cytometry.

Task 3c: Purify splenic granulocytic MDSCs using magnetic bead cell separation kits and identify/verify cellular morphology based on Wright-Giemsa staining.

Task 3d: Assess purified myeloid cells for their ability to activate/inhibit T cell activity *in vitro* (via ³H-thymidine assays).

Task 3e: Analyze single cell suspensions from ascites for MDSC characteristics, as in Aim 3/Tasks 3b – 3d.

Progress: Experiments in Tasks 3b – 3e were suspended due to exhausted funds.

Task 4a: To analyze the effect of G-CSF blockade on MDSC accumulation using a neutralizing anti-G-CSF monoclonal antibody.

Task 4b: Spleens and tumor tissues will be collected 24 – 48 hr after the final mAb injection. MDSC levels/function will then be assessed as in Aim 2/Task 3.

Progress: Experiments in Tasks 4a – 4b were suspended due to exhausted funds.

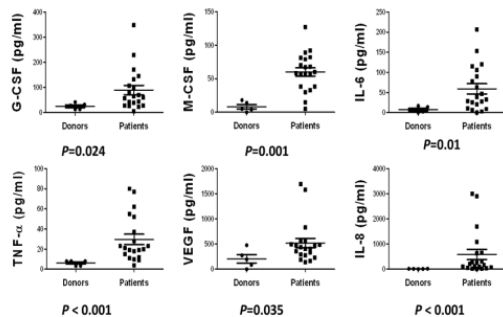
Overall Milestones for Aim 2: Thus far, our human data supported the hypothesis that tumor-derived IL-8 played an important role in tumor progression. However, our mouse ID8 studies suggested that IL-6 did so (Aim 1). Given the complexity or inconsistency of these findings, we conducted parallel studies in patient samples, which are detailed below in Aim 3.

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: Comprehensive cytokine/chemokine analysis completed for cancer patients (n=21) and matched controls (n=5). As we reported in year-1, we identified six cytokines and chemokines associated with aberrant myelopoiesis in ovarian cancer (Fig. 9). 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 9

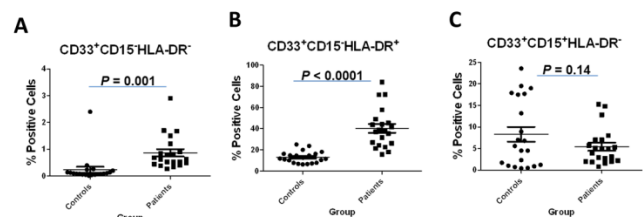
Elevated levels of circulating myelopoietic factors in patients with ovarian cancer



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

Figure 10

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. Using multi-parameter flow cytometry, we compared 21 ovarian cancer patients reflecting stages II - IV to 22 gender- race- and age-matched controls. All patient peripheral blood samples were obtained at diagnosis through the Data Bank and Biorepository (DBBR) at Roswell Park, and the mononuclear fraction was cryopreserved. We reasoned that patients with advance disease, such as stages II – IV, would best illustrate the relationship between MDSC frequencies in health vs. disease.

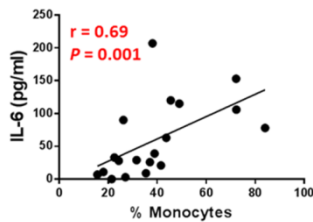
Our data demonstrated a significant increase in 2 of the 3 myeloid populations tested, both sharing a myelo-monocytic phenotype (i.e., CD33⁺CD15⁺HLA-DR⁻ myeloid-derived suppressor cell/MDSCs or CD33⁺CD15⁺HLA-DR⁺ monocytes) compared to the matched donors (Fig. 10). Thus, we identified a potential ‘cytokine/myeloid 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 Figs. 9 and 10). As a result, we identified a highly significant positive correlation between IL-6 levels and monocyte frequency (Fig. 11). No other significant association was observed, strengthening the potential relevance of the IL-6/myelo-monocytic profile in ovarian cancer patient assessment.

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 (Fig. 12, 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 (Fig. 12, right column).

Figure 11

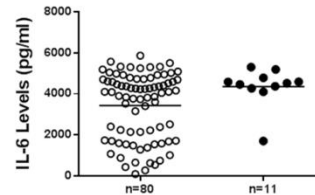
IL-6 levels correlate with monocytic frequencies



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

Figure 12

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.

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 were suspended 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 (collectively from all 3 Aims): Altogether, we identified:

- A significant accumulation 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-8 levels and MDSC accumulation in a human-mouse xenograft model (SKOV3). IL-8 knockdown in SKOV3 cells significantly improved overall survival.
- A significant and positive relationship between IL-6 levels and myelo-monocytic frequencies in an immune competent mouse model of ovarian carcinoma (ID8).

4. Reportable Outcomes: Not applicable during this total award period.

5. Conclusions: During this funding period, 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. 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 and were recapitulated in a syngeneic mouse model of ovarian cancer (ID8). Surprisingly, IL-6 blockade failed to extend survival in the ID8 model; albeit, the reasons for this remain unclear and require further study. Nonetheless, based on the patient data, 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 discovery of this new axis in myeloid-ovarian cancer biology has important implications for IL-6-based clinical interventions. Tracking 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 therapy. Moreover, these studies provide the rationale to target IL-6 for therapeutic purposes in at least subsets of ovarian cancer patients.

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4. Waight, J.D., Hu, Q., Miller, A., Liu, S. & Abrams, S.I. Tumor-derived G-CSF facilitates neoplastic growth through a granulocytic myeloid-derived suppressor cell-dependent mechanism. *PLoS ONE* **6**, e27690 (2011).

7. Appendices: Updated Curriculum Vitae attached.

8. Supporting Data: Figures are embedded within this document.

CURRICULUM VITAE

Name: Scott I. Abrams

Education

- | | |
|------|---|
| 1981 | B.S. (Biology), Delaware Valley College, Doylestown, Pennsylvania
<i>summa cum laude</i> (graduated #1 in class) |
| 1987 | Ph.D. (Microbiology & Immunology), Indiana University School of
Medicine, Indianapolis, Indiana |

Experience

- | | |
|-------------------|--|
| 1981 – 1987 | Graduate Student, Department of Microbiology and Immunology,
Indiana University School of Medicine |
| 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 |
| 2/1/08 – 10/2013 | Associate Member, Department of Immunology & Associate Professor of
Oncology, Roswell Park Cancer Institute, Buffalo, NY
Joint appointment as Associate Professor, Department of Microbiology and
Immunology, State University of New York (SUNY) at Buffalo, Buffalo, NY |
| 11/2013 – present | Member & Professor of Oncology, Dept. of Immunology, Roswell Park,
Professor, Department of Microbiology and Immunology, SUNY at Buffalo |

Societies

American Association for Cancer Research (AACR)

The American Association of Immunologists (AAI)

The American Association for the Advancement of Science (AAAS)

Society for Immunotherapy of Cancer (SITC)

Sigma Xi, The Scientific Research Society

Honors and Awards

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 – 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 & 2012	Recipient of AAI Laboratory Travel Grants

National Leadership Positions

2004	Co-Chair Cancer Vaccine/Immunotherapy Block Symposium at the Experimental Biology Conference, Washington, D.C.
2005	Guest 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, Boston
2012	Guest Editor for Immunological Investigations for thematic Issue on "Regulatory Myeloid Cells in Neoplasia"
2013	Co-Chair, Translational Research Cancer Center Consortium annual conference
2014	Organizing Committee for the 14 th Annual Buffalo Conference on Immunology

Committees and Boards

2008 – present	Member, Tumor Immunology and Immunotherapy Program, RPCI
2008 – present	Member, Immunology Steering Committee, RPCI
2008 – present	Member, Gene Targeting & Transgenic Resource Steering Committee, RPCI
2010 – present	Member, Institutional Divisional Committee, RPCI
2011 – present	Ad hoc member for Scientific Review Committee, RPCI
2010 – 2012	Editorial Board Member, Immunological Investigations
2011 – 2013	Chair, Progress Committee, Dept. of Immunology, RPCI
2012 – present	Member, Immunology Academic Integrity and Grievance Committee
9/2013 – present	Director of Graduate Studies, Dept. of Immunology, RPCI
10/2013 – present	SITC Editorial Board Member of the <i>Journal for ImmunoTherapy of Cancer</i>

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

Study Sections

2010	Ad hoc reviewer for the Wellcome Trust
2010	Ad hoc reviewer for RPCI Institutional Research Grant for ACS
2011	Ad hoc reviewer for the Association for International Cancer Research
2012 – present	Standing reviewer for the VA Merit Review Panel in Immunology
2012 – present	Ad hoc reviewer for NCI Special Emphasis Panel on Tumor Immunology/Therapeutics
2012	Ad hoc reviewer for the VA Merit Review Panel in Oncology
2012	Ad hoc reviewer for NIH study section, NCI-I (career investigator awards)
2013	Ad hoc reviewer for French NCI on Translational Cancer Research
2013	RPCI Alliance Foundation
2013 – present	Standing member/reviewer, Medical Scientific Board for Association for Research of Childhood Cancer

Journal Referee

Blood; Cancer Immunology, Immunotherapy; Cancer Immunology Research; Cancer Research; Clinical Cancer Research; Journal of Immunology; Journal of Immunotherapy; Journal of Leukocyte Biology; Molecular Cancer Therapeutics; Oncogene; PLoS ONE

Invited Lectures/Seminars (gap from 2008 – 2012 reflects in part transition to RPCI)

3/2014:	Speaker at the 14 th Annual Buffalo Conference on Immunology, Mayville, NY. Talk entitled: “Molecular Mechanisms of Myeloid-Derived Suppressor Cell Development in Neoplastic Disease”
2/2014:	Speaker at the Translational Research Cancer Center Consortium (TRC3) conference; Talk entitled, “Molecular Mechanisms of Aberrant Myelopoiesis in Cancer”
10/2013:	Speaker for the Immunology Seminar Series at The Ohio State University Comprehensive Cancer Center, Seminar titled, “Transcriptional Mechanisms of Myeloid-Derived Suppressor Cell Subset Development in Cancer”
10/2012:	Keynote Speaker at the International Conference on Clinical & Cellular Immunology, Chicago IL. Talk entitled, “Granulocytic myeloid-derived suppressor cell development via G-CSF-dependent mechanisms”
10/2012:	Speaker at the International Conference on Clinical & Cellular Immunology, Chicago, IL. Talk entitled, “Transcriptional regulation of Myeloid-Derived Suppressor Cell Development in Neoplasia”
8/2012:	Speaker at the 2nd International Conference on Vaccines and Vaccination, Chicago, IL, Talk entitled, “Mechanisms of Tumor-Induced Myeloid-Derived Suppressor Cell Development”
12/2008:	Speaker for the Molecular and Developmental Genetics Seminar Series, Department of Molecular and Cellular Biology, Roswell Park Cancer Institute, Buffalo, NY. Seminar entitled, “Role of Interferon Regulatory Factor-8 (IRF-8) in Host-Tumor Immunosurveillance”

Invited Lectures/Seminars (cont'd)

- 10/2008: Speaker at the 11th Annual Upstate New York Immunology Conference, Albany Medical College, Bolton Landing, NY. Talk entitled, "IRF-8 Regulates Tumor Cell Responses to Apoptosis and Host Immunosurveillance"
- 9/2008: Speaker at the 8th Annual Buffalo Conference on Immunology, Buffalo, NY. Talk entitled, "Role of IRF-8 in Tumor-Cell Response to Immunosurveillance Mechanisms"
- 8/2007: Speaker for the Research Seminar Series, Dept. of Pediatrics, University of Texas M.D. Anderson Cancer Center. Seminar entitled, "Fas Resistance Contributes to Tumor Escape and Progression"
- 11/2006: Speaker to The GW Cancer Center and the McCormick Center, in conjunction with the Department of Microbiology and Immunology, George Washington University Medical Center. Seminar entitled, "Resistance to Fas-Mediated Lysis as a Mechanism of Immune Selection and Tumor Progression"
- 4/2006: Speaker for the Tumor Vaccine and Cell Therapy Working Group, AACR, Washington, D.C. Talk entitled, "Adoptive Immunotherapy Mediates Tumor Regression and Tumor Escape"
- 11/2005: Speaker for the Translational Immunology Seminar Series, the University of Chicago Medical Center. Seminar entitled, "Fas-Mediated Cytotoxicity as a Mechanism of Immunoselection and Tumor Escape"
- 9/2005: Major Speaker at an International Conference on "Cancer Vaccines/Adjuvants & Delivery Systems for the Next Decade", Lisbon, Portugal. Talk entitled, "CTL-Based Immunotherapy Mediates Tumor Regression and Tumor Escape"
- 11/2004: Major Speaker at the University of Colorado for a Symposium on Cancer Biology, Talk entitled, "Fas/Fas Ligand Interactions in the Regulation of Tumor Progression"
- 10/2004: Major Speaker at the University of Vermont for a Symposium on "The Course of Cancer". Talk entitled, "Interactions between the Cellular Immune System and Cancer"
- 10/2003: Speaker at the "8th World Congress on Advances in Oncology and 6th International Symposium on Molecular Medicine" in Crete, Greece. Talk entitled, "Regulation of the Fas Pathway in Tumor Immunotherapy"
- 10/2003: Speaker at the Regina Elena Cancer Institute in Rome, Italy. Seminar entitled, "Combinatorial Vaccine Strategies Employing Recombinant Vectors"
- 9/2003: Keynote Speaker at an international conference on "Biotherapy of Cancer: From Disease to Targeted Treatment" in Munich, Germany. Talk entitled, "Combinatorial Vaccine Strategies Employing Recombinant Vectors"
- 4/2003: Speaker for the Tumor Biology Program at the Georgetown University School of Medicine. Seminar entitled, "Understanding the Host/Tumor Interaction for Cancer Vaccine Development"

Invited Lectures/Seminars (cont'd)

- 11/2002: Speaker for the NCI-Frederick Seminar Series. Seminar entitled, "Fas-Based Interactions in Tumor Regression and Progression"
- 7/2001: Speaker at the 11th International Congress of Immunology, Stockholm. Talk entitled, "Role of Fas in Human Antigen-Specific Cytotoxic T Lymphocyte-Colon Carcinoma Cell Interactions"
- 10/2000: Speaker for the Lombardi Cancer Center's Tumor Biology Seminar Series at the Georgetown University School of Medicine. Seminar entitled, "Regulation of the Fas/FasL Pathway in Cytotoxic T Lymphocyte-Colon Carcinoma Cell Interactions"
- 7/2000: Speaker for the Cancer Center Distinguished Lecture Series at the Medical College of Wisconsin. Seminar entitled, "ras Oncogene Products as Targets for Tumor Immunotherapy"
- 5/1998: Speaker to the Department of Microbiology and Immunology, Indiana University School of Medicine. Seminar entitled, "ras Oncogenes as Targets for Cancer Immunotherapy"
- 5/1996: Speaker at the Conference for Immunology and Immunotherapy of Metastasis, Talk entitled, "Recombinant Vaccines to Point-Mutated ras and CEA: Analyses of Patient T-Cell Responses", Lake Tahoe, CA. Also, Chairperson of one of the scientific sessions at this same meeting, entitled, "Immunotherapy of Metastasis"

Trainees/Mentorship Roles

A. Pre-doctoral fellows (dates reflect time in my laboratory)

- 2008 – 2012: Major Advisor for Jeremy Waight at RPCI/SUNY-Buffalo
- Selected for talk 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 (bestowed 5/2013)
 - Pursuing postdoc at EMD Serono Research Institute in cancer immunology program
- 2009 – Major Advisor for Debarati Banik at RPCI/SUNY-Buffalo
- Selected for talk at annual Upstate New York Immunology Conference, 2011
 - Selected for talk/travel award at annual AAI conference, 2012
- 2012 – Major Advisor for Colleen Netherby at RPCI/SUNY-Buffalo
- Selected for talk/AAI travel award at annual Upstate New York Immunology Conference, 2013
 - Awarded "AAI Young Investigator Award", TRC3, 2014
 - Selected for talk/travel award at annual AAI conference, 2014
- 2013 – Major Advisor for Danielle Twum at RPCI/SUNY-Buffalo
- 2013 – Major Advisor for Lauren Burkard (MD/PhD student) at RPCI/SUNY-Buffalo

Trainees/Mentorship Roles (cont'd)

B. Doctoral Thesis Committees in RPCI Graduate Program

<u>Student</u>	<u>Degree Status</u>
Jonah Riddell*	defended 2011
Cheryl Rozanski	defended 2011
Jason Muhitch	defended 2013
Chandana Koorella	defended 2013
Matthew Farren	defended 2014

B. Doctoral Thesis Committees in RPCI Graduate Program

<u>Student</u>	<u>Degree Status</u>
Amy Chu*	QE passed/pursuing thesis research
Jason Eng*	QE passed/pursuing thesis research
Benjamin Paluch	QE passed/pursuing thesis research
Stephanie Sass*	QE passed/pursuing thesis research
Haley Spangler*	QE passed/pursuing thesis research
Adam Utley	QE passed/pursuing thesis research
Adaobi Amobi*	QE pending
Mark Bucsek	QE pending
Kelly Singel*	QE pending

*Committee Chair

Master's Thesis Committees in RPCI Graduate Program

<u>Student</u>	<u>Degree Status</u>
Michelle Golding*	defended 2013
Michael Diehl	defended 2012

Doctoral Thesis Committees in SUNY-UB Graduate Program

<u>Student</u>	<u>Degree Status</u>
Allen Chung	defended 2013
Thomas Sajda	QE passed/pursuing thesis research

C. Postdoctoral fellows (while I was a PI at NCI/NIH)

2002 – 2008: Trina Stewart, Ph.D.

- Selected for talk at the Experimental Biology Conference, block symposium on Antitumor Effector Cells/Mechanisms of Tumor Rejection, 2004
- Received a competitive Travel Award at the NCI-CCR Fellow's retreat, 2005
- Selected for talk at the Combined Faculty Retreat, CCR-NCI, 2005
- Selected for talk at the NCI-CCR Fellow's Retreat, 2006
- Received an AACR Scholar-in-Training Award at the AACR 97th Annual Meeting, 2006
- Received an NIH Fellows Award for Research Excellence (FARE), 2007
- Currently, Principal Investigator, Griffith Health Institute School of Medical Sciences, Griffith University, Australia

2004 – 2007: Kristy Greeneltch, Ph.D.
- Received an NIH Fellows Award for Research Excellence (FARE), 2007
- Currently, Patent Agent at Sterne, Kessler, Goldstein and Fox, Washington, D.C.

2001 – 2005: Kebin Liu, Ph.D.
- Selected for talk at the NIH Immunology Retreat, 2005
- Received a competitive Travel Award at the NCI-CCR Fellow's retreat, 2005
- Received an AACR-sponsored Scholar-in-Training Award to a special conference on "Oncogenomics: Dissecting Cancer through Genomic Research", 2005
- Currently, Associate Professor (with tenure), Department of Biochemistry and Molecular Biology, Georgia Regents University, Augusta, GA

C. Postdoctoral Mentorship (cont'd)

2001 – 2004: Sheila Caldwell, Ph.D.
- Selected for talk at the NIH Immunology Retreat, 2003
- Selected for at the NCI-CCR Fellow's Retreat, 2003
- Currently, Program Director, Division of Training, Workforce Development and Diversity, NIGMS, NIH Bethesda, MD

Graduate Education (range varied from 1 – 4 lectures/course, each 90 – 120 min in length)

First Semester ('Fall')

2008 – present MIR 511: Molecular Immunology (Course Coordinator starting 2014)
2009 – present MIR 509: Trends in Tumor Immunology
2011 – present RPN 530: Oncology for Scientists

Second Semester ('Spring')

2008 – present MIR 508: Advanced Topics in Immunology
2010 – present BIR 530: Interferons and Cytokines
2011 – present MIC 512/412: Fundamentals of Immunology (at UB)
2011 – present MIR 510: Basics in Grantsmanship

Full Academic Year

2009 – 2013 MIR 522: Chair of Student Journal Club
2013 – present Faculty member, Howard University/RPCI Scholar's Program

Ongoing Research Support

NIH/NCI; R01 CA140622 (Abrams, PI) 9/1/11 – 8/31/16

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

This research tests the 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

P50 CA159981 (Odunsi, PI; Abrams Co-I on Project 4)

NCI/NIH

9/1/13 – 7/31/18

RPCI-UPCI Ovarian Cancer SPORE

Project 4: "Myeloid Derived Suppressor Cells in Ovarian Carcinogenesis"

The proposed research will study the association between MDSCs and ovarian cancer prognosis. Such data will be used in designing/identifying promising novel immunotherapeutic approaches.

Overlap: None

C028252 (Repasky, PI; Abrams, Co-I)

9/1/13 – 8/31/15

NYS Dept. of Health

Peter T. Rowley Breast Cancer Scientific Research Projects

“Is the immune response against breast cancer inhibited by lack of available metabolic energy?”

The overall goal is to explore the mechanisms by which energy allocation, modulated by ambient temperature and dietary fat, impacts the antitumor immune response and implement these findings to improve the outcome of breast cancer therapy.

Overlap: None

NIH/NCI; R21 CA164475 (Kozbor, PI; Abrams, Co-I)

7/1/12 - 6/30/14

“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.

Overlap: None

Alliance Developmental Award (Abrams, PI)

7/1/12 – 6/30/14

RPCI Alliance Foundation

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

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

Overlap: None

Alliance Developmental Award (Abrams, PI)

6/1/13 – 5/31/14

RPCI Alliance Foundation

“Novel TRL5-based Immunotherapies against Metastatic Colon Cancer”

This research investigates 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 potently 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: Non

Pending

R01 CA175350 (Abrams, Lee, Co-PIs)

NCI/NIH

“Mechanisms of STAT3-induced aberrant Myelopoiesis in Cancer”

This research tests the hypothesis that tumor-derived factors block dendritic cell differentiation, a major myeloid population integral for antitumor immunity, via activation of STAT3 and consequent downregulation of two key downstream targets of myelopoiesis, IRF-8 and PKCβII.

Overlap: None

R01 CA172105 (Abrams, PI)

NCI/NIH

“Mechanisms Underlying Functional Programs of Tumor-Associated Macrophages”

This research tests the hypothesis that differential expression of IRF-8 constitutes a previously unrecognized transcriptional mechanism of TAM functional status.

Overlap: None

Completed Research Support

Department of Defense; W81XWH-11-1-0394 (Abrams, PI) 5/1/11 – 4/30/14 (1-yr NCE granted)
“Granulopoietic Growth Factor Secretion in Ovarian Carcinoma as a Mechanism for the Emergence of Immune Suppressive Myeloid Subsets”

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

Overlap: None

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

1. Bray, R., **Abrams, S.**, and Brahmi, Z. Studies on the mechanism of human natural killer cell-mediated cytotoxicity. I. Modulation by dexamethasone and arachidonic acid. Cell. Immunol. 78: 100-113, 1983.
2. **Abrams, S. I.**, Bray, R. A., and Brahmi, Z. Mechanism of action of phorbol myristate acetate on human natural killer cell activity. Cell. Immunol. 80: 230-40, 1983.
3. **Abrams, S. I.**, and Brahmi, Z. Compared mechanisms of tumor cytotoxicity by human natural killer cells and activated polymorphonuclear leukocytes. J. Immunol. 132: 3192-3196, 1984.
4. Brahmi, Z., Bray, R. A., and **Abrams, S. I.** Evidence for an early calcium-independent event in the activation of the human natural killer cell cytotoxic mechanism. J. Immunol. 135: 4108-4113, 1985.
5. **Abrams, S. I.**, and Brahmi, Z. The functional loss of human natural killer cell activity induced by K562 is reversible via an interleukin-2-dependent mechanism. Cell. Immunol. 101: 558-570, 1986.
6. **Abrams, S. I.**, and Brahmi, Z. Target cell directed NK inactivation. Concomitant loss of NK and antibody-dependent cellular cytotoxicity activities. J. Immunol. 140: 2090-2095, 1988.
7. **Abrams, S. I.**, and Brahmi, Z. Mechanism of K562-induced human natural killer cell inactivation using highly enriched effector cells isolated via a new single-step sheep erythrocyte-rosette assay. Ann. Inst. Pasteur/Immunol. 139: 361-381, 1988.
8. **Abrams, S. I.**, McCulley, D. E., Meleedy-Rey, P., and Russell, J. H. Cytotoxic T lymphocyte-induced loss of target cell adhesion and lysis involve common and separate signaling pathways. J. Immunol. 142: 1789-1796, 1989.
9. **Abrams, S. I.**, and Russell, J. H. CD4⁺ T lymphocyte-induced target cell detachment. A model for T cell-mediated lytic and nonlytic inflammatory processes. J. Immunol. 146: 405-413, 1991.
10. Russell, J. H., Rush, B. J., **Abrams, S. I.**, and Wang, R. Sensitivity of T-cells to anti-CD3-stimulated suicide is independent of functional phenotype. Eur. J. Immunol. 22: 1655-1658, 1992.
11. Kantor, J., Irvine, K., **Abrams, S.**, Kaufman, H., DiPietro, J., and Schlom, J. Antitumor activity and immune responses induced by a recombinant carcino-embryonic antigen-vaccinia virus vaccine. J. Natl. Cancer Inst. 84: 1084-1091, 1992.
12. Kantor, J., Irvine, K., **Abrams, S.**, Snoy, P., Olson, R., Greiner, J., Kaufman, H., Eggensperger, D., and Schlom, J. Immunogenicity and safety of a recombinant vaccinia virus vaccine expressing the carcinoembryonic antigen gene in a nonhuman primate. Cancer Res. 52: 6917-6925, 1992.

13. **Abrams, S. I.**, Wang, R., Munger, W. E., and Russell, J. H. Detachment and lysis of adherent target cells by CD4⁺ T cell clones involve multiple effector mechanisms. Cell. Immunol. 147: 188-202, 1993.
14. Wang, R., **Abrams, S. I.**, Loh, D., Hsieh, C-S., Murphy, K. M., and Russell, J. H. Separation of CD4⁺ functional responses by peptide dose in T_h1 and T_h2 subsets expressing the same transgenic antigen receptor. Cell. Immunol. 148: 357-370, 1993.
15. Kantor, J., **Abrams, S.**, Irvine, K., Snoy, P., Kaufman, H., and Schlom, J. Specific immunotherapy using a recombinant vaccinia virus expressing human carcino-embryonic antigen. Ann. N.Y. Acad. Sci. 690: 370-373, 1993.
16. Conry, R. M., LoBuglio, A. F., Kantor, J., Schlom, J., Loechel, F., Moore, S. E., Sumerel, L. A., Barlow, D. L., **Abrams, S.**, and Curiel, D. T. Immune response to a carcino-embryonic antigen polynucleotide vaccine. Cancer Res. 54: 1164-1168, 1994.
17. Bei, R., Kantor, J., Kashmiri, S. V. S., **Abrams, S.**, and Schlom, J. Enhanced immune responses and anti-tumor activity by baculovirus recombinant CEA in mice primed with the recombinant vaccinia CEA. J. Immunother. 16: 275-282, 1994.
18. Hodge, J. W., **Abrams, S.**, Schlom, J., and Kantor, J. A. Induction of antitumor immunity by recombinant vaccinia viruses expressing B7-1 or B7-2 costimulatory molecules. Cancer Res. 54: 5552-5555, 1994.
19. Hodge, J. W., McLaughlin, J. P., **Abrams S. I.**, Shupert, W. L., Schlom, J., and Kantor, J. A. Admixture of a recombinant vaccinia virus, containing the gene for the costimulatory molecule B7 and a recombinant vaccinia virus containing a tumor-associated antigen gene, results in enhanced specific T-cell responses and antitumor immunity. Human Gene Ther. 8: 851-860, 1997.
25. Prasad, G. L., Lee, H-S., Iwahashi, M., Milenic, D., **Abrams, S.**, Schlom, J., and Kashmiri, S. *In vivo* gene inoculation of a recombinant single-chain antitumor antibody induces anti-immunoglobulin response. Cancer Gene Ther. 4: 253-259, 1997.
26. McLaughlin, J. P., **Abrams, S.**, Kantor, J., Dobrzanski, M. J., Greenbaum, J., Schlom, J., and Greiner, J. W. Immunization with a syngeneic tumor infected with recombinant vaccinia virus expressing granulocyte-macrophage colony-stimulating factor (GM-CSF) induces tumor regression and long-lasting systemic immunity. J. Immunother. 20: 449-459, 1997.
27. **Abrams, S. I.**, Khleif, S. N., Bergmann-Leitner, E. S., Kantor, J. A., Chung, Y., Hamilton, J. M., and Schlom, J. Generation of stable CD4⁺ and CD8⁺ T cell lines from patients immunized with *ras* oncogene-derived peptides reflecting codon 12 mutations. Cell. Immunol. 182: 137-151, 1997.
28. Bristol, J. A., Schlom, J., and **Abrams, S. I.** Development of a murine mutant *ras* CD8⁺ CTL peptide epitope variant that possesses enhanced MHC class I binding and immunogenic properties. J. Immunol. 160: 2433-2441, 1998.

29. Bergmann-Leitner, E. S., Kantor, J. A., Shupert, W. L., Schlom, J., and **Abrams, S. I.** Identification of a human CD8⁺ T lymphocyte neo-epitope created by a *ras* codon 12 mutation restricted by the HLA-A2 allele. Cell. Immunol. 187: 103-116, 1998.
30. Bristol, J. A., Schlom, J., and **Abrams, S. I.** Persistence, immune specificity, and functional ability of murine mutant *ras* epitope-specific CD4⁺ and CD8⁺ T lymphocytes following *in vivo* adoptive transfer. Cell. Immunol. 194: 78-89, 1999.
31. Khleif, S. N., **Abrams, S. I.**, Hamilton, J. M., Bergmann-Leitner, E., Chen, A., Bastian, A., Bernstein, S., Chung, Y., Allegra, C. J., and Schlom, J. A phase I vaccine trial with peptides reflecting *ras* oncogene mutations of solid tumors. J. Immunother. 22: 155-165, 1999.
32. Bergmann-Leitner, E. S., and **Abrams, S. I.** Differential role of Fas/Fas ligand interactions in cytolysis of primary and metastatic colon carcinoma cell lines by human antigen-specific CD8⁺ CTL. J. Immunol. 164: 4941-4954, 2000.
33. Bergmann-Leitner, E. S., and **Abrams, S. I.** Influence of interferon- γ on modulation of Fas expression by human colon carcinoma cells and their subsequent sensitivity to antigen-specific CD8⁺ cytotoxic T lymphocyte attack. Cancer Immunol. Immunother. 49: 193-207, 2000.
34. Bristol, J. A., Orsini, C., Lindinger, P., Thalhamer, J., and **Abrams, S. I.** Identification of a *ras* oncogene peptide that contains both CD4⁺ and CD8⁺ T cell epitopes in a nested configuration and elicits both T cell subset responses by peptide or DNA immunization. Cell. Immunol. 205: 73-83, 2000.
35. Ryan, M. H., and **Abrams, S. I.** Characterization of CD8⁺ cytotoxic T lymphocyte-tumor cell interactions reflecting recognition of an endogenously expressed murine wild-type p53 determinant. Cancer Immunol. Immunother. 49: 603-612, 2001.
36. Alper, O., Bergmann-Leitner, E. S., **Abrams, S.**, and Cho-Chung, Y. S. Apoptosis, growth arrest and suppression of invasiveness by CRE-decoy oligonucleotide in ovarian cancer cells: Protein kinase A downregulation and cytoplasmic export of CRE-binding proteins. Mol. Cell. Biochem. 218: 55-63, 2001.
37. Bergmann-Leitner, E. S., and **Abrams, S. I.** Positive and negative consequences of soluble Fas ligand produced by an antigen-specific CD4⁺ T cell response in human carcinoma immune interactions. Cell. Immunol. 209: 49-62, 2001.
38. Bergmann-Leitner, E. S., and **Abrams, S. I.** Treatment of human colon carcinoma cell lines with anti-neoplastic agents enhances their lytic sensitivity to antigen-specific CD8⁺ cytotoxic T lymphocytes. Cancer Immunol. Immunother. 50: 445-455, 2001.
39. Ryan, M. H., Bristol, J. A., McDuffie, E., and **Abrams, S. I.** Regression of extensive pulmonary metastases in mice by adoptive transfer of antigen-specific CD8⁺ cytotoxic T lymphocytes reactive against tumor cells expressing a naturally occurring rejection epitope. J. Immunol. 167: 4286-4292, 2001.

40. Liu, K., and **Abrams, S. I.** Coordinate regulation of IFN consensus sequence binding protein and caspase-1 in the sensitization of human colon carcinoma cells to Fas-mediated apoptosis by IFN- γ . J. Immunol. 170: 6329-6337, 2003.
41. Chakraborty, M., **Abrams, S. I.**, Camphausen, K., Liu, K., Scott, T., Coleman, C. N., and Hodge, J. W. Irradiation of tumor cells upregulates Fas, enhances CTL lytic activity and CTL adoptive immunotherapy. J. Immunol. 170: 6338-6347, 2003.
42. Liu, K., and **Abrams, S. I.** Alterations in Fas expression are characteristic of, but not solely responsible for, enhanced metastatic competence. J. Immunol. 170: 5973-5980, 2003.
43. Caldwell, S. A., Ryan, M. H., McDuffie, E., and **Abrams, S. I.** The Fas/Fas ligand pathway is important for optimal tumor regression in a mouse model of CTL adoptive immunotherapy of experimental CMS4 lung metastases. J. Immunol. 171: 2402-2412, 2003.
44. Lindinger, P., Mostböck, S., Hammerl, P., Hartl, A., Thalhamer, J., and **Abrams, S. I.** Induction of murine *ras* oncogene peptide-specific T cell responses by immunization with plasmid DNA-based minigene vectors. Vaccine 21: 4285-4296, 2003.
45. Liu, K., McDuffie, E., and **Abrams, S. I.** Exposure of human primary colon carcinoma cells to anti-Fas interactions influences the emergence of pre-existing Fas-resistant metastatic subpopulations. J. Immunol. 171: 4164-4174, 2003.
46. Chakraborty, M., **Abrams, S. I.**, Camphausen, K., Coleman, C. N., Schlom, J., and Hodge, J. W. External beam radiation of tumors alters phenotype of tumor cells to render them susceptible to vaccine-mediated T-cell killing. Cancer Res. 64: 4328-4337, 2004.
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48. Liu, K., Caldwell, S. A., and **Abrams, S. I.** Immune selection and emergence of aggressive tumor variants as negative consequences of Fas-mediated cytotoxicity and altered IFN- γ -regulated gene expression. Cancer Res. 65: 4376-4388, 2005.
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50. Liu, K., Caldwell, S. A., Greenelitch, K. M., Yang, D., and **Abrams, S. I.** CTL adoptive immunotherapy concurrently mediates tumor regression and tumor escape. J. Immunol. 176: 3374- 3382, 2006.
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