Title of Project: Are surviving cancer stem cells a cause of prostate cancer recurrence?

Principal Investigators and Departments: Dr. John G Baust and Dr. Robert G VanBuskirk, Department of Biological Sciences/Institute for Biomedical Technology (IBT)

Funding Requested: $33,480

Project Abstract (200 words or less):

Prostate cancer recurrence depends on a myriad of factors, including stage of disease at diagnosis, first line treatment with androgens, and genetic makeup of the tumor, among others. We hypothesize that resistance to treatment and subsequent recurrence is conferred through a small subset of cancer stem cells within the primary tumor population. To test this hypothesis, we plan to expose a primary prostate cancer cell line to varying thermal insults to model cryotherapy and determine if the cells remaining post-treatment express more stem-like characteristics than the general population pre-treatment. We will utilize flow cytometry and fluorescence microscopy to determine percentages of positively staining CD44^+ cells, an established marker of PCSCs, along with aldehyde dehydrogenase activity, migration assays and spheroid formation assays. We hypothesize that the cells that remain post-treatment will be enriched in stem cell like characteristics as compared to the general population pre-treatment, thus identifying a likely cause of cancer recurrence following cryosurgery.
Title: Are Surviving Cancer Stem Cells a Cause of Prostate Cancer Recurrence?

Project Narrative

Describe the proposed hypothesis-developing research, and how it represents an innovation to an important problem in prostate cancer. Explain how the planned research will be no greater than minimal risk, exempt under 32 CFR 219.101 (B) or eligible for expedited review.

Androgen independent prostate cancer (AIPC) is an aggressive variant of prostate cancer that typically develops following first line treatment with androgen deprivation. This phenotype of prostate cancer is notoriously difficult to treat, often requiring multiple treatment modalities which may not greatly extend a patient’s survival. To understand the mechanisms by which androgen insensitive prostate cancer develops its defenses to treatment, we must first understand the makeup of the primary tumor’s heterogeneity. The tumor microenvironment is complex, with influences dependent on the cancer’s progression and stage.[1] Studies have revealed that within a single confined tumor there is a mix of cells with varying genetic makeup that are constantly evolving in response to nearby signaling[2]. In addition to complex signaling between tumor cells, nearby cells of the epithelium and stroma are influenced to contribute to the tumor microenvironment and in turn, may have increased malignant potential[1]. A more recent addition to the complexities of the tumor microenvironment has been the identification of cancer stem cells. By definition, a cancer stem cell is a cell that can self-renew and repopulate a tumor after treatment[3]. Since their initial discovery, cancer stem cells have been found in numerous types of cancers, including prostate. These small sub-populations within a tumor mass possess greater stem-like characteristics, rendering them resistant to chemo and radio therapies, and thus pose greater potential for cancer recurrence.

Our group has published extensively in the field of prostate cryotherapy and has a wealth of knowledge and experience in performing cryosurgical modeling in the laboratory. We have utilized the PC-3 cell line as a model of AIPC in numerous studies. In our studies we have found that following a thermal insult to -20°C in a 2D prostate cancer model, PC-3 cells retain between 20%-30% viability 24h post-freeze and recover fully after a 10 day period[4]. In this study, we propose to utilize antibodies to CD44, a marker that numerous studies have found to be present in prostate cancer stem cells (PCSC), to track changes in CSC populations through both flow cytometry and fluorescence microscopy. We will also use the Aldefluor assay to observe changes in the number of ALDH-bright cells following freezing, as elevated levels of ALDH are considered a hallmark of cancer stem cells. Additionally, we plan to perform migration assays to test the invasiveness of these cells pre and post-treatment as well as test the ability of these cells to form spheroids when cultured in 3D conditions. We hypothesize that this remaining population is enriched in stem-like properties which may confer an increased tumorigenic potential as well as increased protection from cryodestruction.

Experimental Outline

PC-3 cells will be exposed to freezing conditions of -15°C, -20°C or -25°C, representative of the periphery of a cryogenic lesion where cell death is often incomplete. We will utilize assays at various time points (Pre-treatment, 0h, 24h, 48h) following the freeze event to determine changes in relevant areas that would indicate stemness. The following assays will be utilized in this project:

AlamarBlue Metabolic Activity Indicator Assay- This assay measures the metabolic activity of cells and would be used to confirm the percentage of freeze induced death is consistent with past data.
Flow cytometric analysis of CD44 expression- A Guava EasyCyte Plus microcapillary system will be utilized to count cell populations that are positive for CD44 expression using a mouse monoclonal antibody to CD44 with a phycoerythrin (PE) conjugate for visualization with the 488nm laser (496/575 excitation and emission max).

Aldefluor Assay- Positive staining for aldehyde dehydrogenase (ALDH) will be tested, as ALDH bright PC-3 cells have been shown to have greater tumorigenic potential.

Transwell Cell Invasion Assay- Cells will be plated onto 24 well transwell plates coated in matrigel to determine if the invasiveness of cells is affected post-freeze. Cells that have invaded the 3D matrix will attach to the underside of the transwell membrane and can be fixed, stained and counted.

Spheroid Formation Assay- The ability of cells to form spheroid structures, a well accepted stem cell assay, will be tested to determine if this characteristic correlates with other factors of stemness.

Fluorescence Microscopy- Fluorescent imaging using a Zeiss Axiovert 200 will be used to identify cells that stain positive for both CD44 and ALDH.

The proposed research will be no greater than minimal risk as there is no use of human subjects, and the human cell line will be obtained from a commercially available source (ATCC). The cell line and applicable reagents will be handled by trained personnel in a biosafety level 1 (BSL-1) facility.

Describe the project’s originality, significance, quality and future impact.

This study would be the first to investigate cancer stem cells’ involvement in androgen insensitive prostate cancer (AIPC) resistance to cryotherapy treatment. This topic is of significant clinical importance due to the current difficulties in treating AIPC and its widespread prevalence worldwide. The work proposed here would be of high quality, led by a team with extensive history of successful research in the field. The future impact of this research would not only be seen in an academic setting, but also brings the possibility of near-term clinical translation.

Describe PI and Co-investigator contributions to the project. Demonstrate the team’s experience in prostate cancer research (grant funding, publications, conference presentations, etc.) Discuss the student’s participation on the project.

Dr. John G Baust (PI) and Dr. Robert G VanBuskirk (Co-investigator) both have decades of experience in areas relevant to this project. Dr. Baust has been active in prostate cancer research for over twenty-five years and has served as a member of the American Urological Association Best Practices Panel on Cryotherapy of Localized Prostate Cancer. Dr. VanBuskirk has experience in tissue engineering and helped develop the first tissue engineered skin for MatTek company. He also was instrumental in developing the Transwell Cell Invasion Assay while a consultant for Millipore Corp. In the past two decades Drs. Baust and VanBuskirk have co-authored over 20 original research articles, review articles, and book chapters in the field of prostate cancer[4-21]. Dr. Baust has also given numerous presentations on prostate cancer at scientific conferences, including the Society for Cryobiology, American Urological Society, and the Society for Thermal Medicine annual meetings.

Kimberly Santucci, a doctoral candidate, will participate in the project by utilizing her laboratory experience to perform the experiments necessary to complete the proposed research. She has authored original research papers and given numerous presentations at scientific conferences on the topic of prostate cancer, focusing on adjuvant treatments to cryotherapy to increase treatment efficacy[6]. She will work closely with her advisors, Drs Baust and VanBuskirk, to ensure proper progress is being made.
Provide a brief statement of the benefits of this project, if funded, to the university. Specifically address the increase in fundability or visibility that would be achieved.

Through publication in peer reviewed journals, presentations at targeted conferences including the North Eastern American Urological Association (NEAUA) and associate American College of Cryosurgery (ACC) events, Binghamton University’s role in elucidating the contribution of CSC’s to prostate cancer resistance to thermal therapies will be highlighted. Additionally, potential paths to target more effective outcomes will position the university as a leader in this emerging field. Studies on hormone resistant prostate cancer, such as those presented in this proposal, represent funding priorities within the DOD and NIH NCI (listed below).

Explain the project’s ability to attract future federal, state, philanthropic or private funding.

Extensive funding in prostate cancer is available from diverse sources. The NIH’s National Cancer Institute annually funds approximately $300-400 million annually for this one cancer variant. We intend to apply for an R21 near the conclusion of this project. The American Cancer Society in 2015 funded 76 awards in prostate cancer. We intend to explore the possibility of funding from the ACS. The DOD’s Congressional Directed Medical Research Program funds eight prostate cancer programs annually. We are eligible for four categories of grants with funding levels ranging between $750 K - $2.5 M. Numerous private and philanthropic groups such as the Prostate Cancer Foundation, the American Association for Cancer Research, and nearly a dozen other groups provide grant support to basic research projects in prostate cancer. We intend to seek funding from each of these organizations. Finally, Dr. Van Buskirk is chair of the NIH study section, “Cell and Molecular Biology,” that reviews grants focused on areas covered in this project. As such, he has a network of colleagues who could collaborate in a larger, more extensive project that could involve clinical application resulting from the successful completion of this project.

Describe the plans for seeking external support for this project based upon this collaboration and include a listing of potential sponsors and timelines for proposal preparation.

The above paragraph lists many of the potential sources of prostate cancer funding. This past summer we established a relationship with the DOD - U.S. Army to fund research in association with the U.S. Military Academy of an Institute for Molecular Research at West Point. We will initially seek to expand that relationship to include prostate cancer research over the next six months. We intend to apply for a NIH NCI R-21 grant in the spring 2016. We will begin to analyze and speak with each of the private foundations beginning this winter to determine their emphasis in prostate cancer research and apply as appropriate.
Literature Cited

Budget Justification
The funds available will be used for the supplies needed to carry out the proposed research, including cells and all necessary culture reagents, antibodies and assays described. Additionally, we plan to use a portion of the funds for travel to the American Urologic Association North East Conference in Buffalo, NY. The remainder of the funds would be used for graduate student support, including tuition and stipend. A detailed budget is included below.

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</table>
BIOGRAPHICAL SKETCH

NAME
John G Baust, Ph.D.
POSITION TITLE
UNESCO Professor & Director
eRA COMMONS USER NAME

EDUCATION/TRAINING
(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

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<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
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<tr>
<td>State University of New York, Fredonia, NY</td>
<td>B.S.</td>
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<td>Inst. of Arctic Biology, Univ. of Alaska, Fairbanks, AK</td>
<td>Ph.D.</td>
<td>1967-70</td>
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A. Positions and Honors.

Positions and Employment
2011 - 2015  President, American College of Cryosurgery
2008 - UNESCO Professor
2000 -       Director, Institute of Biomedical Technology, Professor, Dept. of Biological Sciences

Other Experience and Professional Memberships
1994 – 2003        Adjunct Professor of Neurosurgery, Department of Surgery, Medical College of Pennsylvania
1986 – 87             Professor and Chair, Department of Biological Sciences, State University of New York
1984 – 87             B.J. Luyet Distinguished Professor and Director, Institute of Low Temperature Biology, University of Houston

Honors
2013                  Gold Medal Award. Intl. Society for Cryosurgery
2011                  Fellow, American College of Cryosurgery
2009                  Fellow, Society for Cryobiology
2009                  Outstanding Alumnus, SUNY Fredonia
2008                  UNESCO Professor
2002                  SUNY Chancellor’s Award for Entrepreneurship

B. Selected peer-reviewed publications most relevant to current application
C. Book Chapters (16)
2. Image Guided Thermal Therapy. Presidential Symposium. Soc.Thermal Medicine, Minneapolis,MN.
NAME
Van Buskirk, Robert G.

POSITION TITLE
Professor

eRA COMMONS USER NAME (credential, e.g., agency login)

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)

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<td>1985</td>
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A. Positions and Honors

Employment
1983 - 2001 Visiting Faculty Member, Harvard University, Cambridge, MA
1986 - 1991 Asst. Professor, Dept. Biological Sciences, State University of New York at Binghamton (SUNY-Binghamton)
1996 - 1997 Interim Chair, Department of Biological Sciences
1997 - PRESENT Professor, Dept. Biological Sciences, SUNY-Binghamton
1998 - 2001 Director of Research, BioLife Solutions, Inc., Binghamton, NY
2000 - PRESENT Assoc. Director, Institute of Biomedical Technology, SUNY-Binghamton
2000 - 2002 Chair, Dept. Biological Sciences, SUNY-Binghamton
2001 - 2004 Director, Advanced Biotechnologies Center, SUNY-Binghamton
2001 - 2002 Vice President R&D, BioLife Solutions, Inc., Binghamton, NY
2002 - 2004 Vice President of Business Development, BioLife Solutions Inc.
2004 - PRESENT Senior Vice President, Cell Preservation Services, Inc. (CPSI Biotech), Owego, NY

Selected Research Activity/Awards/Honors
- 2014 - PRESENT - SRARTUPNY Review Board
- 2012 - PRESENT - New York Academy of Sciences Blavatnik Review Board
- 2013 - Small Business Administration Tibbetts Award (Baust/Van Buskirk/Snyder of CPSI for excellence in NIH SBIR grantsmanship, entrepreneurship and economic development)
- 2006 - Small Business Administration Tibbetts Award (Baust/Van Buskirk of CPSI)
- 2002 - Chancellor’s and SUNY Research Foundation Entrepreneur Award (excellence in medical research)
- 1990 - Russell and Burch Award (for developing engineered human skin used worldwide)
- 1995 - PRESENT - Member of NSF, NIH (R01,R43/44, PO1), DoD grant review panels

Major Achievements:
- Awarded 80 grants and contracts (NSF, NIH, DoD, NYS, Private, Pharma)
- Chair, NIH IMSTJ 15 Study Section "Cell and Molecular Biology" 6/14 to current.
- Developed tissue engineered human epidermis (skin) now sold internationally by MatTek Corp. (Ashland, MA) and used by many US and international cosmetic and pharmaceutical companies as well as basic research scientists.
• Originated concept of and co-developed the CytoFluor 2300 fluorescent plate reader while a consultant for Millipore Corporation. First plate reading spectrofluorometer developed.
• Co-developed BioLife Solutions Inc’s (BLFS; Nasdaq) HTS-FRS storage solution now in approx. 150 cell therapy clinical trials. These and related solutions are used for the short term and long term storage of cells in a variety of applications.
• Past Vice President of Research/Business Development, BioLife Solutions, the first incubator biotechnology company on the SUNY Binghamton campus.
• Vice President of CPSI Biotech, the second incubator biotechnology company on the SUNY Binghamton campus.
• Past consultant for MatTek Corporation, US Army Medical Research Institute of Chemical Defense, Corning Corporation, Millipore Corporation and Cryomedical Sciences Inc.
• Authored CD-ROM as electronic companion for Cell and Molecular Biology. Author of two problem-solving text books in cell and molecular biology (Scientific American/W.H. Freeman; Cogito)

B. Selected Peer-Reviewed Publications and Patents (limited to 5)

Patents (limited to 5):

D. Active Research Support
NYS DOH New York State Baust and Van Buskirk (PIs) 11/1/15 - 1/31/17
Prostate Cancer Hypothesis Development Grant Goals: To develop innovative approaches to treating prostate cancer through two graduate fellowships. RVB role: co-PI
DHP15-014 DoD Van Buskirk (PI) 9/28/15 - 9/27/20
Optimal Rewarming Solutions for Cryopreserved Tissue Specimens Goals: To test a variety of cell stress modulators as both pre-conditioning and post-conditioning agents as a means to improve vitrification of cells and tissues. RVB role: PI
1R43CA195948-01A1 NIH/NCI Baust (PI) 9/1/15 - 8/31/16
Development of a Minimally Invasive Surgical Device for the Treatment of Esophageal Cancer
BIOGRAPHICAL SKETCH

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<td>Kimberly L. Santucci</td>
<td>Doctoral Candidate</td>
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**eRA COMMONS USER NAME (credential, e.g., agency login)**

**EDUCATION/TRAINING** (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>MM/YY</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
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<tr>
<td>State University of New York at Binghamton</td>
<td>B.A.</td>
<td>05/08</td>
<td>Biological Sciences</td>
</tr>
<tr>
<td>State University of New York at Binghamton</td>
<td>Ph.D.</td>
<td>In Progress</td>
<td>Cell and Molecular Biology</td>
</tr>
</tbody>
</table>

**A. Positions and Honors**

**Positions and Employment**
- August 2008 – Present: Graduate Research Fellow, Cell Preservation Services, Inc.
- August 2008 – May 2012: Graduate Teaching Assistant, State University of New York at Binghamton
- June 2008 – August 2008: Research Intern, Cell Preservation Services, Inc.

**Other Experience and Professional Memberships**
- 2011-Present: Member, American Society for Cell Biology
- 2011-2012: Guest Lecturer, Biology 311, State University of New York at Binghamton
- 2008-Present: Member, Society for Cryobiology

**Honors**
- 2010: Society for Cryobiology Student Travel Award

**B. Selected Peer-Reviewed Publications**


**C. Selected Presentations (* poster)**


D. Research Support

Graduate Teaching Assistantship
State University of New York at Binghamton, Department of Biological Sciences, 8/2008-5/2012

NYSTEM N09C-009   New York State   Van Buskirk (PI)
7/1/10 – 6/30/12
The Business and Biology of Stem Cells in Cell Therapy
Goals: To develop a unique set of stem cell courses that include developing student-written business plans, reviewing stem cell bioethics and overseeing a laboratory exposure module in stem cell differentiation. RVB role: PI of project and chief architect responsible for course design and implementation. KLS Role: Laboratory Module Leader for CPSI Biotech.

GRANT APPLICATIONS

National Institutes of Health, Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellows (Parent F31) PA-11-111, Submitted for Cycle I, April 6, 2012. Project Title: Cell cycle based cryosensitization approaches for prostate cancer ablation