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ABSTRACT

During the last FY of the award, the Cancer Institute of Long Island benefited from CPMRP funding in a manner consistent with the proposed activities of the award. In the area of core instrumentation acquisition, a Carl Zeiss Total Internal Reflection Fluorescence (TIRF) microscope has been ordered. This technology is vital to bridge the gap in CDMRP funded optics systems at Stony Brook, by providing cancer researchers with the capability to study localization at the cell membrane level. A new, state-of-the-art imaging system was requested via programmatic modification that was submitted and approved by CDMRP under separate cover; a Carl Zeiss Fluorescence Correlation Spectroscopy (FCS) Confocal Microscope, is operational and is being utilized to measure events at the single molecule level. The university has organized funds to construct a dedicated ISO Class 7 clean room to support the FCS Confocal Microscope. Consistent with the funding for this initiative were the granting of multi-year RSU packages, or Research Support Units. RSU's are a mechanism to ensure necessary support for junior faculty and work as enhancements to enable the successful establishment of their laboratories. Each RSU provided support for laboratory personnel, small or specialized research equipment, and supplies. During the last funding year three individuals were recruited into this initiative. The faculty designees for this activity are Howard Adler, MD, Assistant Professor of Urology (on-going RSU), Howard Crawford, PhD, Assistant Professor of Pharmacological Sciences (on-going RSU), Marjana Maletic-Savatic, MD-PhD, Assistant Professor of Neurology (new RSU). Dr. Adler is investigating the angiogenesis of prostate cancer from a translational approach. Dr. Crawford continues to make significant strides in understanding cell and protein signaling events in pancreatic and breast cancer. Dr. Maletic-Savtic is investigating the proliferation of brain carcinoma and demyelinating of neurons due to therapeutic measurers. The RSU's supported faculty are required to have mentors from the senior faculty.

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Introduction:

The State University of New York at Stony Brook, School of Medicine continues to develop its infrastructure to support a Comprehensive Cancer Center in central Long Island, New York. Achievements vital to this year of CDMRP funding are summarized below. CDMRP funding focused in cancer research infrastructure has greatly assisted the efforts of the School of Medicine by enabling our ability to provide a foundation for aspiring young scientists. Drs. Adler, Crawford, Maletic-Savatic received base support from this mechanism as they further develop their research programs. CDMRP funds allocated towards core technologies have enabled the School of Medicine to secure and bring on-line a new state-of-the-art FCS Confocal Microscope. A TIRF Microscope system was ordered via CDMRP support as well. Instrumentation of this type is available as cancer research center core instruments and is operated by skilled technicians. The instruments are centrally sited, and are supported by ancillary equipment made available by the School of Medicine via other funding sources (not CDMRP).

Body:

Cancer Invasion & Angiogenesis - Dr. Howard Adler, MD, Assistant Professor of Urology:

Evaluating the Role of Matrix Metalloproteinases in Prostate Cancer Progression- Working in collaboration with Drs. Stan Zucker (Research Mentor) and Jian Ciao. The goal of this project is to examine the role of membrane type 1-matrix metalloproteinase in prostate cancer progression and metastasis by establishing a stable LNCaP (an androgen dependent cell line which does not produce endogenous type-1 matrix metalloproteinase, MT1-MMP) cell lines expressing MT1-MMP/GFP chimera and a GFP control.

My research interests concern the role of matrix metalloproteinases (MMPs) in disease, mechanisms of cancer invasion and metastasis, and the function of membrane type-MMPs (MT-MMPs). My major current interest is to determine the parts played by MT-MMPs in cell function and in diseases like cancer metastasis and thormbosis. The central hypothesis is that MT-MMP is an important type-I membrane protein that functions at the cell surface to control many aspects of cell surface proteolysis and is connected with cell signalling after binding of the tissue inhibitor of metalloproteinase 2 (TIMP-2). MT-MMP also serves as a receptor for TIMP-2; this complex binds MMP-2 and activates this protease leading to degradation of extracellular matrix proteins. MT-MMPs are also present in complexes with integrins, EMMPRIN, and other membrane proteins; these complexes are enriched in invadopodia and have important functions in cell migration and signalling.

The CDMRP support for Dr. Adler has enabled him to obtain the necessary mentorship, research funds, and protected time to achieve his academic goals. He attends and routinely participates in weekly laboratory meetings held in Dr. Zucker's laboratory at the Northport Veterans Administration Hospital, and the Cancer Institute of Long Island research meetings. Dr. Adler has been able to improve his abilities to critically evaluate research at the basic science level. There is true potential for translation of this project as it matures towards completion. Through new collaborations with other cancer investigators, Dr. Adler has been able to provide his colleagues with orthotopic prostate cancer models. His training in GU cancers has made his contribution even more distinct

in research that seeks to evaluate the chemokine regulation of prostate cancer metastasis and investigate potential new therapeutic modalities for prostate cancer.

Selected Publications:

Clin Cancer Res. 2005 May 1;11(9):3243-9.
Noninvasive detection of prostate cancer by quantitative analysis of telomerase activity.
Botchkina GI, Kim RH, Botchkina IL, Kirshenbaum A, Frischer Z, Adler HL.
Department of Surgery/Surgical Oncology, State University of New York at Stony Brook, Stony Brook, New York 11794-8191, USA.

Thromb Haemost. 2005 Apr;93(4):770-8.
Membrane type 1-matrix metalloproteinase promotes human prostate cancer invasion and metastasis.
Cao J, Chiarelli C, Kozarekar P, Adler HL.
Department of Medicine, State University of New York, Stony Brook, NY 11794-5200, USA.

Cancer Res. 2004 Mar 15;64(6):2083-9.
Prostate cancer cell adhesion to bone marrow endothelium: the role of prostate-specific antigen.
Romanov VI, Whyard T, Adler HL, Waltzer WC, Zucker S.
Department of Medicine, State University of New York at Stony Brook, HSC T09 Room 040, Stony Brook, NY 11794, USA.

II) Dr. Howard Crawford, PhD, Assistant Professor Pharmacological Sciences:
Signal Transduction – Matrix Metalloproteinase-7

Pancreatic cancer is the 5th most common cause of cancer related death in the United States. With about 30,000 Americans being diagnosed with pancreatic cancer each year, the disease incidence is relatively low compared to other cancers. However, with only a 4% 5-year survival rate, the prognosis for someone with pancreatic cancer is dismal. There are two major reasons for the difficulty in dealing with pancreatic cancer. First, it generally remains asymptomatic until the cancer has progressed to a very late stage. Second, pancreatic cancer is resistant to most current cancer therapies.

In my laboratory, we study matrix metalloproteinase-7 (MMP-7), a secreted proteolytic enzyme that is expressed in a very high proportion of pancreatic tumors. Using MMP-7 as window into pancreatic cancer, we are identifying the signal transduction pathways that are active in the diseased pancreas and using what we find to develop animal models that accurately reflect the human disease. We are also testing the function of MMP-7 in existing animal models of pancreatic cancer to determine if the use of MMP-7 inhibitors holds promise in both prevention and treatment of early stage pancreatic cancer. Finally, because MMP-7 is a secreted protein, we are testing whether screening for MMP-7 will be a useful non-invasive diagnostic tool for detecting early stage pancreatic cancer.

Recent Selected Manuscripts:

H.C. Crawford and L.M. Matrisian. Stromelysin-1 is protective against skin tumor growth and progression. *Submitted.*

H.C. Crawford, U.S. Krishna, D.A. Israel and R. Peek. *Helicobacter pylori cag*$^{+}$ strains selectively induce MMP-7 in vitro and within inflamed gastric mucosa. *Submitted.*

McCawley LJ, Crawford HC, King LE Jr, Mudgett J, Matrisian LM. (2004). A protective role for matrix metalloproteinase-3 in squamous cell carcinoma. *Cancer Res.* **64**:6965-72.

Crawford HC, Krishna US, Israel DA, Matrisian LM, Washington MK, and Peek RM. *Helicobacter pylori* strain-selective induction of matrix metalloproteinase-7 *in vitro* and within gastric mucosa. 2003. *Gastroenterology.* **125:** 1125-1136.

III) Dr. Mirjana Maletic-Savatic, MD-PhD, Assistant Professor Neurology:
Human Neural Stem Cells – In Vivo Models for Cerebral Carcinoma

The study of human neural stem cells (NSC) in vivo has been hindered by the absence of well-defined markers that would distinguish them from other neural cell types, such as astrocytes, oligodendrocytes and neurons. We analyzed mousederived cultured hippocampal neurons, glia, and NSC in order to identify spectroscopic signatures for each individual cell type. One dimensional 1H-NMR spectra were collected using a Bruker Avance 700 NMR spectrometer, working at a hydrogen resonance frequency of 700.13 MHz. Over the past year, our preliminary data suggest the presence of specific spectroscopic profiles for each individual cell type studied, thus providing for identification and quantification of NSC. We have detected the NSC-specific spectroscopic signatures in the brain extracts as well. In collaboration with Dr. Djuric, Department of Engineering, we have developed more sophisticated data processing algorithms for extracting the NSC-specific peak from data with low resolution. More recently, we applied our results to human brain imaging and were able to extract a NSC peak from the hippocampus and not cortex, which corresponds to animal data. Our results were presented at the Keystone Symposia on stem cells. A manuscript is in preparation, also. The plan for the next year is to start characterization of the metabolite which gives the NSC-specific spectra and to continue with the human brain imaging. Our results may ultimately lay the foundation for future studies of NSC fate and function in the living human brain, with immediate consequence for the clinical management of a spectrum of neurological diseases such cerebral carcinoma, and multiple sclerosis.

Selected Publications:

Curr Neurol Neurosci Rep. 2005, May:5(3):225-31.
Manganas LN, Maletic-Savatic M
Stem cell therapy for central nervous system demyelinating disease.

Methods. 1999 Jun;18(2):231-9, 181.
Mainen ZF, Maletic-Savatic M, Shi SH, Hayashi Y, Malinow R, Svoboda K

Two-photon imaging in living brain slices.
Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724, USA.

Science. 1999 Mar 19;283(5409):1923-7.
Maletic-Savatic M, Malinow R, Svoboda K.
Rapid dendritic morphogenesis in CA1 hippocampal dendrites induced by synaptic activity.
Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, USA.

J Neurosci. 1998 Sep 1;18(17):6814-21.
Maletic-Savatic M, Koothan T, Malinow R.
Calcium-evoked dendritic exocytosis in cultured hippocampal neurons. Part II: mediation by calcium/calmodulin-dependent protein kinase II.
Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724, USA.

Cancer Imagining Core Research Support

To broadly support the research of the five-thematic integrated cancer research programs several new core imaging platforms are moving ahead under various states of maturity. These include (A) Multi-Photon Confocal Imaging System- 2003, (B) the Fluorescence Correlation Spectroscopy (FCS) Confocal Imaging System- 2004, and (C) Total Internal Reflection Fluorescence (TIRF) Imaging System- 2005.

A) The selected system is an inverted Carl Zeiss Micro-Imaging product equipped with a Coherent Laser Group *Chameleon Laser*. Since the purchase of this system the institution has successfully commissioned a 224 net ft^2 ISO Class 7 clean room. The system is 100% on-line and is currently assisting projects for over twenty-five different experiments from the cancer research community. A long and thorough national search was orchestrated by the Office of Scientific Affairs which resulted in the selection of a well-trained PhD level confocal (single-photon) microcopist. He has since been trained by Coherent and Carl Zeiss in the techniques of *Multi-Photon* image sample manipulation, image acquisition, image deconvolution, and data analysis. The instrument and the staff's expert services are available to the cancer research community. Adjacent to this laboratory is a well equipped, comfortably furnished computer laboratory with three high-speed workstations for post image analysis. The institution has provided matching funds of $100,000 to develop this aspect of the facility. Three networked PC's, a dedicated file server and three fully licensed copies of Bitplane Imaris are available to the cancer researcher. The Departments of Molecular Genetics & Microbiology, Neurobiology & Behavior, and Pharmacological Sciences, have organized a matching funds package worth $225,000 for out-year personnel support for this Cancer Institute Initiative.

B) The selected system is an inverted Carl Zeiss Micro-Imaging product equipped with FCS measurement lasers capable of providing both FRET and FRAP analysis. FCS is a spectroscopic technique for the study of molecular interactions in solution. FCS monitors the random motion of fluorescently labeled molecules inside a defined volume element irradiated by a focused laser beam. These fluctuations provide information on the rate of diffusion or diffusion time of a particle and this, in turn, is directly dependent on the particle's mass. As a

consequence, any increase in the mass of a biomolecule, e.g. as a result of an interaction with a second molecule, is readily detected as an increase in the particle's diffusion time. Due to its simple underlying principle, FCS is an ideal approach for the study of thermodynamic and kinetic features of molecular interactions in solution.

FCS imaging technologies are both novel and essential to the growth and invasion of cancer in select tissue types. FCS imaging is crucial to understanding single molecular events and/or insults that are integral to a host of disease states including cancer invasion and metastasis. A specially designed ISO Class 7 clean room is under development to house this system. A dedicated 1.0 FTE PE of optical engineering has been identified to operate this instrumentation. The institution is providing the necessary funds to construction and commissioning the clean room as well as fund the FTE. The FCS system is assisting several senior faculty cancer research projects.

C) Total Internal Reflection Fluorescence (TIRF) Imaging System. The basis for TIRF is the refractive behavior of light when making the transition from an optically denser to an optically less dense medium. The analysis of images obtained with conventional wide-field fluorescence excitation is often complicated by background fluorescence emitted in out-of-focus planes. The signals from these regions radiate into the depth-of-field range and superimpose themselves upon the desired image information. The effect is due to the comparatively low Z resolution achievable with this illuminating technique. By contrast, fluorescence excited by total internal reflection (TIRF) yields excellent Z resolution, typically around 200 nm or better. This is clearly illustrated by the following example. Fluorescent beads were mixed with distilled water and put on a specimen slide, with a cover slip on top. In a fresh preparation, the beads are constantly moving between the slide and the cover slip due to Brownian motion. After a short time, however, the first beads start to deposit on the slide and on the cover slip.

In conventional fluorescence microscopy, images also show beads from above the focal plane, where as TIRF microscopy offers information exclusively from the evanescent field. In fluorescence microscopy, beads approaching the cover slip become visible long before they reach the focal plane, whereas TIRF microscopy produces a fluorescence signal only when the beads have entered the narrow band of the evanescent field. The signals suddenly vanish when the beads leave that field. The advantages of TIRF microscopy are obvious: no superimposed background fluorescence, and higher resolution, resulting in better contrast and high-fidelity detail rendition. Total reflection occurs at interface such as between glass and water. Therefore, TIRF is a useful tool for studying the reactions of individual molecules or objects at surfaces. A typical application in molecular cell biology is the fusion of vesicles with the cell membrane.

The TIRF microscope will be available to cancer researchers at Stony Brook. This technique is considered to provide an excellent bridge between the two previous confocal techniques which have been funded via the CDMRP. Left alone the TIRF technology is a powerful tool of discovery for cellular activity at the membrane level. The ability to witness the events related to cancer cell membrane breaching by novel therapeutics is obviously important to new drug

development. Due to the fact that TIRF is an epi-fluorescence based imaging technique, clinical cancer researchers acclimate easily to this instrument.

Key Research Accomplishments:

The CDMRP funding awarded to Stony Brook via this mechanism is directed towards providing infrastructure support to better serve the needs of the faculty of the Cancer Institute of Long Island, and cancer researchers throughout the campus. Accomplishments for this reporting period include:

1) Instrumentation-Carl Zeiss Multi-Photon Confocal Microscope on-line and participating in more than 25 active cancer projects *.
2) Instrumentation- Continued support for the ISO 7 clean room for the Multi-Photon Microscope *.
3) Instrumentation- Renewal of the PhD level microcopist to operate the Multi-Photon Microscope *.
4) Instrumentation- Continued support for the high-level image analysis center to support the Multi-Photon Confocal Microscope users **.
5) Instrumentation- Commissioning of FEI Philips Digital Transmission Electron Microscope for cancer imaging **.
6) Instrumentation- Installation of an ISO 7 clean room for the Digital Transmission Electron Microscope *.
7) Instrumentation- Acceptance of samples on the Ciphergen Biosystems SELDI Instrument for Cancer Proteomics acquired in 2003.**
8) Instrumentation– Commissioning of the Cancer Tissue Bank Carl Zeiss Laser Capture Microdissection Microscope acquired in 2003 **.
9) Instrumentation- Continued support for the operation of the the Cancer Institute Tissue Bank Laboratory **.
10) Instrumentation- Commissioning of a FCS Confocal Microscope *.
11) Instrumentation- Design development for the installation of a ISO 7 clean room for the FCS Confocal Microscope **.
12) Instrumentation- Commissioning and operation of an ABI 3730 High-Throughput Genetic Analyzer *.
13) Instrumentation- Continued support for the MJ Research Real-Time PCR instruments **.
14) Instrumentation- Development of protocols to further enhance the through-put capabilities in MALDI-ToF for Cancer Proteomics **.
15) Instrumentation- Newly developed overnight MALDI-ToF analysis service made available for faculty**.
16) Faculty Development- Providing start-up funds enhancement to Dr. Adler via a mentored intramural program *.
17) Faculty Development- Providing start-up funds enhancement to Dr. Crawford via a mentored intramural program *.
18) Faculty Development- Providing start-up funds enhancement to Dr. Maletic-Savatic via a mentored intramural program*.

19)More than 20 key publications produced by the cancer research faculty in the School of Medicine. A fully annotated citation list is available for review.
20) Eighteen cancer research intramural pilot and feasibility awards issued via the School of Medicine Targeted Research Opportunities Program **.
21)Creation of a Cancer Chemo-Prevention Center based upon the successful recruitment Basil Rigas, MD, Professor, Dept. of Medicine **.

*= *Benefit derivative of CDMRP funds.*
**= *Benefit derivative of funds allocated to complement CDMRP initiative at Stony Brook.*

Reportable Outcomes:
1- Research Support Units- The RSU support provided to Drs. Adler, Crawford and Maletic-Savatic have resulted in several manuscripts for peer reviewed journals. Both Drs. Adler and Crawford are aware of the requirement to cite CDMRP support in their manuscripts.
2- Cancer Genomics Core- To date this facility has provided services that have resulted in tens of thousands of sequences and validations for samples submitted by Cancer Institute researchers. The RT PCR instruments and the Genetic Analyzer are enhancing an already robust research core.
3- The Applied Biosystems Q-Star Pulsar I LC/MS/MS instrument acquired in year 01 of the CDMRP award has logged over 2,700 sample hours since its commissioning.
3- Cancer Imaging Core- The Multi-Photon capabilities have been well received by the cancer research community. The instrument performs at threshold levels. The FCS instrument is on-line and performing as anticipated. Benchmarking has been successful and user seminars will be arranged later this summer. This is six months ahead of the anticipated timeline reported to CDMRP in 2004. The TIRF microscope is expected to arrive in late summer 2005. Installation, commissioning and benchmarking will proceed with an anticipated completion of the winter holidays of 2005.

Publications of interest:
20 selected publications of interest. Reprints are available upon request.

1: Malbon CC.
Beta-catenin, cancer, and G proteins: not just for frizzleds anymore.
Sci STKE. 2005 Jul 12;2005(292):pe35.
PMID: 16014605

2: Suzuki N, Yasui M, Geacintov NE, Shafirovich V, Shibutani S.
Miscoding Events during DNA Synthesis Past the Nitration-Damaged Base 8-Nitroguanine.
Biochemistry. 2005 Jun 28;44(25):9238-45.
PMID: 15966748

3: Bembo SA, Elimian A, Waltzer W, Carlson HE.
Pheochromocytoma in a pregnant woman with a history of intracerebral aneurysms.
Am J Med Sci. 2005 Jun;329(6):317-9.
PMID: 15958874

4: Jaracz S, Chen J, Kuznetsova LV, Ojima I.
Recent advances in tumor-targeting anticancer drug conjugates.
Bioorg Med Chem. 2005 Jun 12; [Epub ahead of print]
PMID: 15955702

5: Sparmann A, Bar-Sagi D.
Ras oncogene and inflammation: partners in crime.
Cell Cycle. 2005 Jun;4(6):735-6. Epub 2005 Jun 6.
PMID: 15908805

6: Messina CR, Lane DS, Grimson R.
Colorectal cancer screening attitudes and practices preferences for decision making.
Am J Prev Med. 2005 Jun;28(5):439-46.
PMID: 15894147

7: Kim SY, Suzuki N, Laxmi YR, McGarrigle BP, Olson JR, Sharma M, Sharma M, Shibutani S.
Formation of tamoxifen-DNA adducts in human endometrial explants exposed to alpha-hydroxytamoxifen.
Chem Res Toxicol. 2005 May;18(5):889-95.
PMID: 15892583

8: Qiu H, Zappacosta F, Su W, Annan RS, Miller WT.
Interaction between Brk kinase and insulin receptor substrate-4.
Oncogene. 2005 May 2; [Epub ahead of print]
PMID: 15870689

9: Botchkina GI, Kim RH, Botchkina IL, Kirshenbaum A, Frischer Z, Adler HL.
Noninvasive detection of prostate cancer by quantitative analysis of telomerase activity.
Clin Cancer Res. 2005 May 1;11(9):3243-9.
PMID: 15867219

10: Singh BK, Aleyas S, Hu Y, Zamkoff KW, Gladstone DE.
Granulocytic sarcoma presenting as bilateral adrenal masses.
Am J Hematol. 2005 May;79(1):73-5.
PMID: 15849765

11: Sachs S, Bilfinger TV, Komaroff E, Franceschi D.
Increased standardized uptake value in the primary lesion predicts nodal or distant metastases at presentation in lung cancer.
Clin Lung Cancer. 2005 Mar;6(5):310-3.
PMID: 15845183

12: Cao J, Chiarelli C, Kozarekar P, Adler HL.
Membrane type 1-matrix metalloproteinase promotes human prostate cancer invasion and metastasis.
Thromb Haemost. 2005 Apr;93(4):770-8.
PMID: 15841326

13: Chughtai B, Sawas A, O'Malley RL, Naik RR, Ali Khan S, Pentyala S.
A neglected gland: a review of Cowper's gland.
Int J Androl. 2005 Apr;28(2):74-7. Review.
PMID: 15811067

14: Rigas B, Kashfi K.
Cancer Prevention: A New Era beyond Cyclooxygenase-2.
J Pharmacol Exp Ther. 2005 Jul;314(1):1-8. Epub 2005 Apr 1.
PMID: 15805430

15: Bembo SA, Pasmantier R, Davis RP, Xiong Z, Weiss TE.
Osteogenic sarcoma of the sella after radiation treatment of a pituitary adenoma.
Endocr Pract. 2004 Jul-Aug;10(4):335-8.
PMID: 15760777

16: Smouha EE, Yoo M, Mohr K, Davis RP.
Conservative management of acoustic neuroma: a meta-analysis and proposed treatment algorithm.
Laryngoscope. 2005 Mar;115(3):450-4.
PMID: 15744156

17: Jura N, Archer H, Bar-Sagi D.
Chronic pancreatitis, pancreatic adenocarcinoma and the black box in-between.
Cell Res. 2005 Jan;15(1):72-7. Review.
PMID: 15686632

18: Petrenko O, Moll UM.
Macrophage migration inhibitory factor MIF interferes with the Rb-E2F pathway.
Mol Cell. 2005 Jan 21;17(2):225-36.
PMID: 15664192

19: Sparmann A, Bar-Sagi D.
Ras-induced interleukin-8 expression plays a critical role in tumor growth and angiogenesis.
Cancer Cell. 2004 Nov;6(5):447-58.
PMID: 15542429

20: Yasui M, Suzuki N, Miller H, Matsuda T, Matsui S, Shibutani S.
Translesion synthesis past 2'-deoxyxanthosine, a nitric oxide-derived DNA adduct, by mammalian DNA polymerases.
J Mol Biol. 2004 Nov 26;344(3):665-74.
PMID: 15533436

Conclusions:

T the beneficial infrastructure support that the CDMRP provides to the School of Medicine enables our ability to fund of the three active RSU packages (Drs. Adler, Crawford, and Maletic Savatic). The RSU's made available to these junior faculty in 2004-2005 have helped them advance their research significantly. CDMRP funds have helped the institution acquire several new platforms for cancer research. This new, state-of-the-art, instrumentation has helped advance cancer research at Stony Brook.

References:

Not applicable. CDMRP funding is targeted towards infrastructure support.