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14. ABSTRACT During the lifespan of this 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, many new imaging modalities were acquired, installed, commissioned and made available to cancer researchers as described within this report. Such technology is vital to imagine both in vitro and in vivo models of cancer. State-of-the-art systems in proteomics were brought on-line and rendered operational in support of cancer research. These included, but were not limited to multiple TOF platforms. There was a profound restructuring of Cancer Genomic Core services that has very neatly organized the portfolio of an otherwise complex, yet vital set of analysis tools to better understand cancer genetics. CDMRP funding also enabled many young investigators to initiate new research projects to better advance the body of understanding of how cancer invades, establishes and attacks a host. CDMRP support for these projects came in the form of specially described support units over multiple years. These research support units (RSU's) were a mechanism to ensure necessary support for junior faculty and work as enhancements to enable the successful establishment of their laboratories. RSU support provided funds for laboratory technical personnel, small and/or specialized research equipment, and supplies. Over the lifespan of this award three individuals were recruited and benefitted via this initiative. The faculty designees for this activity are Howard Adler, MD, Assistant Professor of Urology, Howard Crawford, PhD, Assistant Professor of Pharmacological Sciences, and Marjana Maletic-Savatic, MD-PhD, Assistant Professor of Neurology. Descriptions of their projects are included within this report.					
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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. Over the life-span of the award, CDMRP funding focused in cancer research infrastructure which has greatly assisted the ability to provide a foundation for aspiring young scientists. Drs. Adler, Crawford, and Maletic-Savatic received base support via this mechanism as they further develop their independent 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 instrumentation and to hire the best available technical personnel to operate/maintain them. Instrumentation of this type is available as cancer research center core instruments. All instruments are centrally sited, and are supported by ancillary equipment made available by the School of Medicine via alternative funding mechanisms (not CDMRP).

BODY: KEY RESEARCH ACCOMPLISHMENTS

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 thrombosis. 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.

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

Matrix metalloproteinase-7 (MMP-7) has been shown to contribute to both the formation and invasion of adenocarcinomas in several glandular tissues. MMP-7 expression is highly restricted in normal tissue, but is frequently found in tumor cells of benign and well-differentiated invasive tumors of the breast, intestine, prostate, esophagus, stomach and pancreas. Our research focuses on the role of MMP-7 in pancreatic cancer, the 5th most common cause of cancer-related death in the United States. We have found that MMP-7 is expressed by the tumor cells in 98% of pancreatic ductal adenocarcinoma (PDAC) patient samples examined, by far exceeding the frequency of MMP-7 expression in tumors of other tissues. MMP-7 expression ranges from the earliest stages of tumor formation through to invasive carcinoma. Strikingly, MMP-7 was also expressed by metaplastic duct epithelium in 100% of PDAC samples examined. Metaplastic duct epithelium, particularly that formed in the context of chronic pancreatitis (CP), has been hypothesized to act as a tumor precursor. With this in mind, we found that MMP-7 is expressed in the metaplastic ducts of 93% of CP samples. Most importantly, by inducing CP in mice that have had the MMP-7 locus inactivated by homologous recombination, we find that all aspects of CP are severely inhibited, including the formation of metaplastic duct epithelium. Thus, we surmise that MMP-7 is involved in pancreatic tumor formation through its ability to promote the formation of metaplastic duct epithelium. We propose to systematically dissect the multiple potential roles of MMP-7 in CP and PDAC with particular emphasis on acinar-to-ductal metaplasia.

We are currently testing the function of MMP-7 in the progression of mouse metaplasia and neoplasia by removing the gene in multiple mouse models of pancreatic cancer. Simultaneously, we are testing the effectiveness of MMP inhibitors in preventing tumor progression in these models. Finally, we are using in vitro models of pancreatic cancer to identify substrates of MMP-7 that will explain its function in PDAC progression and potentially reveal additional drug targets in the fight against PDAC.

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.

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 (fusion of DNA Microarray, DNA Sequencing and Bioinformatics Facilities)* - Early in 2006 the Office of Scientific Affairs set out to better integrate three successful, yet distinct cores under a common laboratory focused on providing animal and human genetic research support as “single-stop-shop”. Since their inception these facilities have 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. Reported analysis results of thousands of GeneChips experiments and developed dozens of customized programming scripts. The facility is led by a PhD level human geneticist, Dr. Eli Hatchwell of the Dept. of Pathology and employees five technical FTE's.

3- The Applied Biosystems Q-Star Pulsar I LC/MS/MS instrument acquired in year 01 of the CDMRP award has logged over 8,000 sample hours since its commissioning. Newly acquired instrumentation to complement this instrument includes a Thermo LTQ triple quadrupole mass Spectrometer, a Thermo LSQ TOF mass spectrometer, and Thermo Orbi-Trap mass spectrometer. A dedicated PhD level Technical Director has been recruited and a .6 FTE PhD level biochemist has been hired to meet sample preparation demands. All of these instruments have been acquired with sources other than CDMRP funds.

3- *Cancer Imaging Core*- All instrumentation organized within this facility are fully commissioned and are available to Stony Brook faculty with preference of access being provided to Cancer Researchers. A detailed description is outlined below.

4- *Cancer Metaballomics Assay Core*- All instrumentation has been commissioned within this facility and are available to Stony Brook faculty with preference of access being provided to Cancer Researchers. A detailed description is outlined below.

Core Support / Development

Cancer Imaging 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) In Vivo Two-Photon Imaging System- 2003, (B) Small Animal Ultrasound, (C) Total Internal Reflection Fluorescence (TIRF) Imaging System- 2005 (D) Small Animal CT Scanner.

A) The two-photon in vivo microscope is a custom made tool used to dissect processes in the living tissue using fluorescent protein imaging. The microscope has two stages. One stage is used to perform electrophysiology and imaging of cellular and subcellular mechanisms in real time, in acute brain slices and in organotypic slice cultures. We use this methodology to observe

and manipulate the interactions between neural stem cells and the microglia, the scavengers of the nervous tissue, in order to better understand the mechanisms that determine the survival of endogenous and transplanted neural stem cells. In addition, we use slices to investigate the mechanisms that lead to formation of new neurons, and we monitor this process of neurogenesis in real time. The second stage is used for live animal imaging. We use transgenic mice in which certain cell types can be visualized due to the expression of fluorescent proteins. Therefore, the cells of interest are readily seen, up to 400 micrometer deep. We are again interested in processes that lead to incorporation of transplanted neural stem cells into the normal circuitry of the brain, as this is one of the most promising therapies for several neurological disorders, such as brain tumors and strokes. Therefore, the availability of this microscope enables us to investigate processes and mechanisms that we have never been able to investigate before, putting Stony Brook at the cutting edge of science. The software & hardware will be brought online by the Office of Scientific Affairs, SOM Bioinformatics Service. The two 1.0 FTE programmers of this unit provide IT support to all of the core technologies that are assigned to the Office of Scientific Affairs. Competitive intramural matching support from the School of Medicine and Vice-President for Research will offset partial 1.0 FTE Technician costs, and service contract costs.

B) The VisualSonics Vevo small animal ultrasound imager was acquired this year and sited in the University Laboratory Animal Facility where it receives dedicated support from a 1.0 FTE Ultrasound Technician trained in rodent anatomy. The instrument is used to phenotype a variety of cancer models, to monitor disease progression, and to quantify and inject cancer vaccines into specific organs. In particular, specially developed transgenic mouse models for 3 phenotypically distinct types of human bladder cancer are being imaged by the CS Lee Laboratory, Dept. of Urology. Transitional cell cancer (TCC) models utilizing SV40 to inactivate tumor suppressor genes produce two different models. Low copy insertions result in *carcinoma in situ* and high copy insertions in high grade invasive TCC. A third model utilizing *ras* inserted transgenes produce low grade papillary tumors in the mice. The ultrasound instrument will allow non-invasive measurement of tumor volume, shape and vascularity. We plan to study novel bladder cancer vaccines made with recombinant BCG, developed in collaboration with Michael O'Donnell at University of Iowa: rBCG-IFN- γ , rBCG-IL-2, rBCG-TNF and rBCG-GM-CSF. The vaccines can be instilled under ultrasound guidance into the bladder of the affected mice and the tumor regressions are followed in real-time. The instrument also allows guided removal of urine samples from the mice in order to study cytokines and tumor markers in those samples. Such markers are analysed in the Mouse Metabolic Phenotyping Core. Since ultrasound imaging is used to monitor human bladder cancer, the availability of this instrument will enable rapid pre-clinical studies for bladder cancer and anti-cancer vaccines that can lead directly into human clinical trials.

C) The TIRF System:

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, whereas 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 is 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.

4) The Small Animal CT Scanner:

Small laboratory rodents are routinely used in development of drugs and treatments methodologies. To recognize the internal changes to these research models as early as possible, the joint Veterans Administration Medical Center at Northport and Stony Brook University Division of Laboratory Animal Research has developed a high-resolution micro-CT scanner service for in-vivo 3D-imaging. Initial changes in the rodent can be found as features in the size range of 10 microns.

Cancer Proteomics Core Research Support –

To further support the institutional-wide effort Protein Chemistry and Analysis Laboratory was developed to support investigators committed to this initiative throughout the campus. This laboratory is located in approximately ~1,500 square feet of dedicated, newly renovated, wet-bench space on the 9th floor of the Basic Sciences Tower. It is staffed by two PhD level Mass Spectroscopists, and two MS level technicians. Services offered in this core include:

- Research Grade MALDI-ToF mass analysis via an ABI Voyager DE Star
- Research Grade LC/MS/MS mass analysis via an ABI Q-Star Pulsar I
- Research Grade LC/MS/MS mass analysis via an Thermo LTQ Triple Quad (high throughput)
- Research Grade LC/MS/MS mass analysis via an Thermo LSM (low mass detection)
- Analytical and Preparative HPLC
- Automated 2D Gel processing via Bio-Rad Proteome System
- Automated Protein Digestion via Perkin Elmer Multi-Probe HT
- BioCore Plasmon Resonance Detector

To date this facility has provided services for cancer sample analysis to over forty researchers, representing eleven

Geneomics Core -

The selected system is an Applied Biosystems 3730 Genetic Analyzer. This high-throughput instrument is situated in the existing University DNA Sequencing Core. This facility has a long, outstanding service record as an institutional core. It provides the cancer research community with access to a staff of 2.0 well-trained molecular biology FTE's. Ancillary support instrumentation includes two robotic liquid handling instruments for sample preparation and two Real Time-PCR instruments. The institution provided the support for the RT-PCR instrumentation as targeted needs required that these instruments were on-line prior to what was anticipated at the time of CDMRP funding. The cancer research community was hampered, however, by a medium through-put capillary DNA analyzer. It was therefore determined to be a priority that a new, faster, and more sensitive analyzer is made available. The integration of the GeneChip Microarray facility and the Bioinformatics service have enabled FTE's to be leveraged and new analysis systems to be pursued. The most notable additions are the Bioplex system, and Pyrosequencing techniques. The facility is very busy and highly sought after as we now have the ability to better assist human researchers

Cancer Metaballomics Assay Core

The focus of the integrative Cancer Mouse Metaballomics Assay Core is to determine collateral endocrine disruption due to cancer therapeutics. Among the tasks will be monitor and develop novel phenotypical mice that exhibit a variety of adverse responses to cancer therapeutics. Using a host of complicated assays the core staff (2.0 FTE's) will develop a reference set of downstream complications that will challenge pharmacological intervention. There is little understanding of the field of metaballomics within the domain of cancer. Stony Brook will seek to leverage its scientific expertise in diabetes to begin to tease out the complications of metabolic damage in cancer. The core will be located within our Division of Laboratory Animal Resources facility in the Health Sciences Center. Additional capabilities provided to this facility are Aglient and Thermo GCMS instrumentation.

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 43 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- On going of FEI Philips Digital Transmission Electron Microscope for cancer imaging **.
- 6) Instrumentation- Continued support of an ISO 7 clean room for the Digital Transmission Electron Microscope *.
- 7) Instrumentation- On going suport and operation of an ABI 3730 High-Throughput Genetic Analyzer *.
- 8) Instrumentation- Continued support for the BioRad and ABI Research Real-Time PCR instruments **.

- 9) Instrumentation- Development of protocols to further enhance the through-put capabilities in MALDI-ToF for Cancer Proteomics **.
- 10) Instrumentation- Newly developed Manual Tryptic Digestion Protocols service made available for faculty**.
- 11) Faculty Development- Providing start-up funds enhancement to Dr. Adler via a mentored intramural program *.
- 12) Acquisition of a Small Animal UltraSound *.
- 13) Acquisition of a Small Animal CT Scanner**.
- 14) Faculty Development- Providing start-up funds enhancement to Dr. Maletic-Savatic via a mentored intramural program*.
- 15) 70 + key publications produced by the cancer research faculty in the School of Medicine. A fully annotated citation list is available for review in the appendix of this report **.
- 16) Dozens of cancer research intramural pilot and feasibility awards issued via the School of Medicine Targeted Research Opportunities Program **.
- 17) Ongoing support for the Cancer Chemo-Prevention Center Laboratory in the Dept. of Medicine **.

*= Benefit derivative of CDMRP funds.

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

CONCLUSIONS:

The beneficial infrastructure support that the CDMRP provided to the School of Medicine over the lifetime of this award enabled our ability to actively support the newest scientific technologies available to cancer researchers anywhere. The new integration of the cancer cores and development of an assay specific resource service are examples of expansion of an already robust research infrastructure. The longtime derivative effect of this award will help Stony Brook researchers to continue in the fight against cancer.

APPENDICIES:

72 Selected publications of interest. *(Reprints are available upon request).*

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Structural evidence for feedback activation by Ras.GTP of the Ras-specific nucleotide exchange factor SOS.
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Wnt signaling, Ca²⁺, and cyclic GMP: visualizing Frizzled functions
Science. 2003 Jun 6;300(5625):1539-30

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Overexpression of mitogen-activated protein kinase phosphatases MKP1, MKP2 in human breast cancer
Cancer Lett. 2003 Mar 10;191 (2):229-37

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