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Therapy Research"

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14. ABSTRACT Clinical data show that there is a strong correlation between the cosmetic outcome of women with early stage breast cancers treated with MSB applicator and the spacing between the MammoSite balloon surface and the skin. Many women are not able to take advantage of MSB because of inadequate balloon-to-skin distances. The implementation of a thin customizable shielding layer to the MammoSite procedure will allow dynamic control over the skin dose overlying the MammoSite balloon. Dose distribution may be monitored using a combination of methods that includes usage of a gamma camera detector system and scintillating fiber technology. Jefferson Lab's upgraded gamma camera system for BSGI may be used for imaging and dosimetric studies during IB. The objective of this project is to develop innovative techniques and advanced technologies surround the IB methodology to facilitate more women taking advantage of APBI and therefore also of BCT to reduce breast cancer recurrence and increase survival expectancy. HU faculty and students will be integrally involved in research to advance breast cancer treatment and improve patient outcomes collaborating with a national lab and a medical school gaining hands-on experience in moving technology from bench to bedside while building capabilities at HU to successfully compete for and conduct breast cancer research.					
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Introduction

Hampton University (HU) is a historically black university (HBCU) located on Virginia's tidewater peninsula, about 10 miles from the Thomas Jefferson National Accelerator Facility (Jefferson Lab). The HU physics Department offers B.Sc, M.Sc, and PhD degrees in Physics with about 30 graduate students and 30 regular faculty in the department. This project was to facilitate a collaborative research project with the research taking place largely at Jefferson Lab initially and later transferred to the HU Proton Therapy Institute (HUPTI). In the course of the collaboration, it is planned that HU researchers gain significant expertise in the high-end instrumentation-knowledge that will leveraged for future projects perhaps collaborative with Jefferson Lab and certainly competitive for mainstream funding support and sustainability research at the university.

The proposed project was an ideal choice for this model as it is crucially relevant for breast cancer care. It involves portable technology that can be initially developed at the Jefferson Lab site and then easily moved to and based at HUPTI. Strong clinical support is provided by EVMS and HUPTI. The close proximity of these three institutions with a history of working together ensures that HU researchers will have permanent access to resource otherwise inaccessible even to many large majority institutions. Jefferson Lab is a Department of Energy (DOE) nuclear physics research facility operated by Jefferson Science Associates LLC. Jefferson Lab resources for this project included the Radiation Detector and Imaging group and laboratory support groups with expertise in fast electronics, data acquisition and scientific computing. With this level of support nearby, the successful development of a breast cancer instrumentation expertise at HU had a strong probability for success.

Final Report

HU faculty training over a wide range of aspects for breast cancer research was accomplished with support from Jefferson Lab. The overarching goal of the project: *to establish breast cancer research experience and capability at HU* has been accomplished. Moreover, through this project a Cooperative Research and Development Agreement (CRADA) was entered into and continues between HU, Jefferson Lab and Dilon Technologies. Dilon Technologies a small high tech company in Newport News Virginia which sells a breast cancer detection camera and continues to advance the technology through CRADA's with Jefferson Lab. This project included both diagnosis and treatment technologies, including: advanced imaging techniques, lesion localization, breast abnormality visualization, control and graphic software, surgical application and radiation oncology. Skills and expertise were acquired in designing and building breast phantoms that allowed the use of inflated brachytherapy applicator balloons to explore possible treatment protocols. HU personnel received didactic instruction for usage of the microSelectron HDR High Dose Rate After loading System with an Ir-192 source for intracavitary brachytherapy procedures during laboratory pre-clinical imaging and dosimetry equipment testing, calibration and data processing, in collaboration with EVMS colleagues. John Okine, a Hampton University student, obtained his doctoral thesis research constructing and evaluating a fiber-based dosimetry solution for balloon-based brachytherapy in conventional radiotherapy. HU intellectual property surrounding this technology was transferred to Radiadyne, Inc, and discussions have begun to bring a first prototype product to HUPTI, which would provide continued research in thins technology using the particle treatment beam.

Mentees obtained unique and transferable skills and expertise in: 1) novel approaches in advanced radiological modalities; 2) imaging system design and data acquisition software development for applications in nuclear medicine planar imaging and tomographic imaging; 3) electronics and

detector instrumentation development; 4) breast phantom construction and implantation; 5) laboratory pre-clinical device testing calibration and data processing; 6) treatment planning algorithm development for intracavitary brachytherapy (IB); and 7) dose calculation approaches through image analysis

Key Research Accomplishments

Change in PI (from Keppel to Kenney) January 1, 2013

Aim 1 Evaluate the optimal powder arrangement, material and amount that are practical for reducing the skin dose. Data for detailed studies will be obtained utilizing relatively simple and equipment and precision Monte Carlo simulations.

[Calvin – Dr. Gueye worked on this and had a thesis student (Nanda Karthik) involved.... Should be able to give you some text!].

Aim 2 Develop and test a practical method for application of a magnetic field for shield shaping. The method must be reproducible and provide the desired placement of shielding powders in the MammoSite balloon.

Aim 3 Develop an analytic model based on precision Monte Carlo simulations and laboratory data for determination of the required amount of powders to limit the skin dose to an optimal value deduced from several clinical trials.

Aim 4 Create an algorithm that uses the analytic model described in *Specific Aim 3* above, and provides as an output dose distribution in the treatment volume that is modified due to effect of the shielding. Modify an existing brachytherapy treatment planning program for MammoSite to incorporate this algorithm. Verify results with data.

Aim 5 Explore methods for determining the dose being delivered to the patient (breast phantom). Optimize dose monitoring via use of the gamma camera detector system, and scintillating fiber detector technology. Crosscheck these results against measurements with the MOSFET patient dose verification system to ensure accuracy and reproducibility.

- 1. Starting January 1, 2013, this award supported postdoctoral fellow, Dr. Lingyan Zhu. She has begun to contribute to some of the patient motion management/tracking research at the Hampton University Proton Therapy Institute. This research directly supports HUPTI's partial breast irradiation protocol at HUPTI, and so is in keeping with the goals of the grant. She has accrued data sufficient for publication and presentation at a regional cancer meeting such as AACR in 2015.**
- 2. PhD candidate John Okine (Department of Physics) has finalized his thesis (summarized in the Annual report 2013) and has begun manuscript preparation. He successfully defended his thesis in 2014.**

Aim 6 Bench implement the entire procedure including treatment planning, powder insertion in balloon in phantom, magnetic field application external to phantom and resulting dose measurement.

Aim 7 HU, Jefferson Lab, EVMS personnel will coordinate to expand the collaborative research endeavor to include additional breast cancer specific technology development projects.

Reportable Outcomes

As mentioned above Jefferson Lab, Dilon Technologies and HU initiated a CRADA which continues past the period of performance of this project. This provides the opportunity of future involvement of other HU personnel in advanced breast cancer research.

At HU: Provide capabilities and equipment to form the basis for continued breast cancer research with possibilities for future sponsored research support. This project provided an opportunity for HU researchers and students to facilitate the development of an improved cancer imaging methods that could greatly improve patient care. The techniques and skills developed in working on this project formed the basis of a longer-term technology development or clinical implementation.

At EVMS: The subcontract approved and signed by both parties September 2013 provided an opportunity for HU researchers and students (see previous Annual report John Okine's PhD thesis overview 2013) to facilitate the development of an improved cancer imaging modality that could greatly improve patient care.

At JLab: This project contributed to the expansion of JLab's detector and imaging expertise particularly in the area of gamma imaging for cancer detection. In particular JLab will gain experience applying its high speed digitization technology and the latest silicon photo-multiplier (SiPM) technology to non-nuclear physics applications.

At Dilon: Allow Dilon to make use of technical expertise and resources in Jefferson Lab and HU to facilitate the development of a SiPM based gamma camera which would have improved ability to detector breast cancer tumors. Development could lead to attracting additional funding to support construction of a clinical device leading to a new product for Dilon.

Description of Ongoing CRADA:

Breast cancer is one of the leading causes of death for women in the United States. Early detection is the one of the best ways of combating the increased incidence. While x-ray mammography has long been accepted as the most effective method to detect breast cancer prior to outward signs and symptoms, it has unacceptable false negative rate for patients with radio-dense breast tissue. The sensitivity of detecting cancer via screening mammography decreases from 88% in the predominately fatty breast to 62% in the dense breast. Patients with dense breasts represent the general population of premenopausal women as well as those with fibrocystic tissue disease; cancer in younger women tends to be more virulent and grow faster. Another concern is that the positive predictive value of x-ray mammography is quite low. An alternative and complementary technology that has been under development and has been implemented commercially is formerly known as scintimammography but is now referred to as breast-specific gamma imaging (BSGI) or molecular breast imaging (MBI).

BSGI uses a dedicated gamma camera system to image the distribution of the injected radiopharmaceutical ^{99m}Tc -sestamibi in the breast. The gamma camera is based on a NaI(Tl) crystal scintillator array which is optically coupled to a set of position sensitive photomultiplier tubes (PSPMTs). When the ^{99m}Tc - decays it emits a 140 keV gamma-ray which is detected by the gamma camera through the generation of scintillation light (photons). The scintillation photons are then detected by the PSPMTs which convert it to an electrical signal which is used to form an image. This ^{99m}Tc agent concentrates in breast tumors by mechanisms related to electronegative cellular and mitochondrial membrane potentials and has been extensively investigated for breast cancer detection. Unlike mammography, BSGI images are minimally affected by breast density because of the higher energy photons of ^{99m}Tc . In a recent study that included patients who had inconclusive mammographic and ultrasound studies and no palpable findings, BSGI resulted in excellent overall sensitivity (96.4%), moderate specificity (59.5%), and the sensitivity for detecting

sub-centimeter lesions, a criticism of gamma imaging of the breast, was 88.9%.

The Jefferson Lab Radiation Detector and Imaging Group has developed PSPMT based detector technology that enabled the building of BSGI detectors that has been licensed by a small high tech company called Dilon Technologies. Dilon Technologies located in Newport News VA has sold over a 100 BSGI gamma cameras (Dilon 6800 Gamma Camera) worldwide. More recently the Jefferson Lab detector group has been developing and testing nuclear physics detectors based on a new technology called silicon photomultiplier (SiPMs) based on silicon chip technology which could be used to replace photomultiplier tubes in a BSGI application. The SiPMs could allow the building 2 cm thinner and lighter BSGI detector heads. This would facilitate the construction of a dual headed system that would ultimately permit the use of lower doses of radiation for women under going BSGI imaging for cancer detection. The CRADA involves contributions of resources to the project from all three institutions.

Status of CRADA

As part of the CRADA the Jefferson Lab Radiation Detector and Imaging Group was to design and build a 15 cm x 20 cm SiPM based detector. Dilon Technologies was to loan a detector housing, a scintillator array and assist with the design and testing of the camera. The detector head is based on 728 individual SiPMs. Each SiPM has an active area of 9 mm². The scintillating crystal array supplied by Dilon Technologies is composed of NaI (Tl) crystal elements with dimensions of 2.96 mm x 2.96 mm on 3.2 mm centers. The array is hermetically sealed and has a 6.50 mm thick glass window. The glass window acts as a light spreader that spreads the scintillation light so it can be detected. The Jefferson Lab group had to determine the optimum spacing of the SiPMs to insure detection of enough scintillating photons so the individual crystal elements could be resolved. One goal was to use as few SiPMs as possible to remain on budget. A Monte Carlo simulation was developed and used to obtain the maximum separation. A pitch of 6.50 mm was determined to be adequate and in order to cover the area of the Dilon scintillator array a total of 768 SiPMs were required. The basic design of the detector head was then completed and 1000 SiPMs were acquired (please see Figure 1).

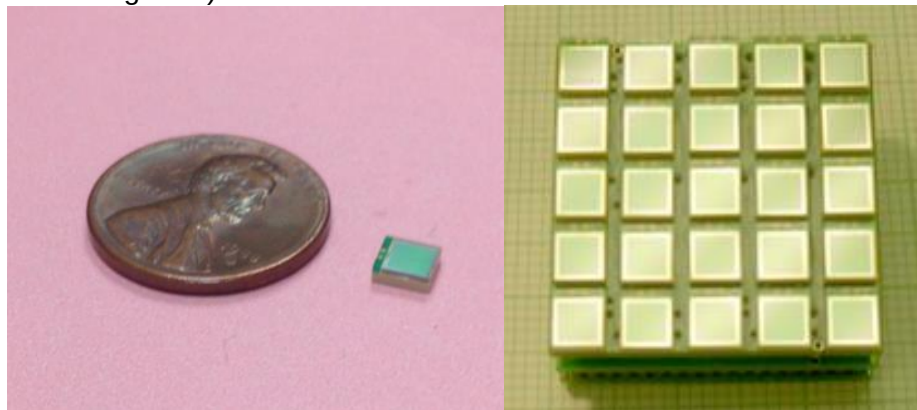


Figure 1: (Left) Photograph of a single SiPM. (Right) Photograph of an example of how the SiPMs will be mounted and arrayed once the large PCB is completed

In order to test the appropriate electronics circuitry to read out the signals of each SiPM, two series of test circuitry were designed and used to construct prototype SiPM modules. The modules were used to inform the further design of the final electronics for the readout of the large number of SiPMs. The development process is described in detail below in the following section. The design is complete and vendors are being identified to build the complicated multilayer circuit board. Once the board is complete. We will populate individual with SiPMs. A novel installation method to insure high tolerance placement of the SiPMs to insure a good optical surface for the scintillator. Once

complete the board will be installed in a Dilon Technologies detector housing. The Jefferson Lab group in light of its other responsibilities anticipates the detector will be done in the summer of 2016. The timeline for the completion of various tasks leading to the completion of the detector is shown in Table 1. There are several parallel tasks:

- A. Circuit design and debug, (in progress)
- B. Mechanical design (PCB shape, fastening, supports, etc.)
- C. Mounting of SiPMs on the SiPM board

Table 1

Circuit Design and Debug	
debug initial front end circuit design PCB V1	2 weeks
revise schematics and PCB design (to include mounting) and re-fabricate (V2)	6 weeks
fab and populate PCB V2	4 weeks
retest front end circuits PCB V2	2 weeks
test initial SiPM PCB for pin/socket feasibility, revise as necessary	1 weeks
discuss with assembly vendors options for precision SiPM mount	1 weeks
finalize/select SiPM mounting vendor/approach	0.1 weeks
send out one SiPM PCB for test run SiPM mounting	2 weeks
fab/assemble SiPM boards	2 weeks
test SiPM Boards	1+ weeks
Mechanical Design	
design mounting arrangement – brackets, supports, I/O connections	4 weeks
fabricate mechanical mounts brackets and supports (3D print?)	2 weeks
Mounting of SiPMs on the SiPM Board	
assemble SiPM boards to main board (PCBV2)	0.5 weeks
assemble detector with scintillator in bucket with I/O	0.5 weeks
test assembly	1+ weeks

With Dilon's assistance electronics to interface the outputs to the Dilon data acquisition system will be built and tested. We will also develop the appropriate interface to allow use to test the system with more precision using the Jefferson Lab flash ADC data acquisition architecture. The collaboration will then work with Dilon to evaluate the final system using breast phantoms.

Conclusion

HU faculty, Postdoc and PhD candidates have been integrally involved in research to advance breast cancer treatment and imaging. Jefferson Lab, Dilon Technologies and HU initiated a CRADA to develop advanced breast cancer detector technology. This CRADA continues past the period of performance of this project thus increasing the possibility of future involvement of other HU personnel (faculty, undergraduate and graduate students) in advance breast cancer research. A research and development partnership between HUPTI and Radiadyne, Inc. may prove to be an additional positive outcome of the research supported under this award.

REPORT OF INVENTIONS AND SUBCONTRACTS (Pursuant to "Patent Rights" Contract Clause) (See Instructions on back)								Form Approved OMB No. 9000-0095 Expires Jan 31, 2008			
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SECTION I - SUBJECT INVENTIONS											
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						d.					
						(1) UNITED STATES		(2) FOREIGN			
						(a) YES	(b) NO	(a) YES	(b) NO	(a) YES	(b) NO
None		None									
f. EMPLOYER OF INVENTOR(S) NOT EMPLOYED BY CONTRACTOR/SUBCONTRACTOR						g. ELECTED FOREIGN COUNTRIES IN WHICH A PATENT APPLICATION WILL BE FILED					
(1) (a) NAME OF INVENTOR (Last, First, Middle Initial)		(2) (a) NAME OF INVENTOR (Last, First, Middle Initial)		(1) TITLE OF INVENTION				(2) FOREIGN COUNTRIES OF PATENT APPLICATION			
(b) NAME OF EMPLOYER		(b) NAME OF EMPLOYER									
(c) ADDRESS OF EMPLOYER (Include ZIP Code)		(c) ADDRESS OF EMPLOYER (Include ZIP Code)									
SECTION II - SUBCONTRACTS (Containing a "Patent Rights" clause)											
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NAME OF SUBCONTRACTOR(S) a.		ADDRESS (Include ZIP Code) b.		SUBCONTRACT NUMBER(S) c.		FAR "PATENT RIGHTS"		DESCRIPTION OF WORK TO BE PERFORMED UNDER SUBCONTRACT(S) e.		SUBCONTRACT DATES (YYYYMMDD)	
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