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Development of Unique Advanced Medical Research and Development Initiatives in the Western United States and Pacific Rim

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14. ABSTRACT
Broadly, TATRC's aim is to explore science and engineering technologies ahead of programmed research, leveraging other programs and collaborative relationships to provide maximal benefit to military medicine. Simultaneously, TATRC aims to be the government model of opportunity-driven research agility. To that end, TATRC invests in cutting-edge technologies, through congressionally directed and other funding programs, and works in other ways with research partners nationwide to develop key products and research outcomes to support military medicine. TATRC is headquartered at Fort Detrick, Maryland, but also has a Field Office in Marina del Rey, California. Part of the strategy behind establishing TATRC West and the other field offices was not only to enable TATRC to establish closer ties with its existing research partners in the western half of the country, but also to build new collaborative relationships that can help advance medical technology in support of the soldier.

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INTRODUCTION

Over the past several years the expansion of the portfolio of the Telemedicine and Advanced Technology Research Center (TATRC) managed research projects has led to significant achievements in support of the goals of the U.S. Army Medical Research and Materiel Command (USAMRMC). TATRC wants to continue to have the ability to effectively leverage and bring together assets, expertise, and capabilities in the western United States to will develop new, cutting-edge advanced technology research and development efforts. This award offers a unique opportunity for the TATRC to further revolutionize military medical research in support of training and readiness, medical Command and Control, and employment of medical forces across the Department of Defense (DOD) through collaboration with the Henry M. Jackson Foundation for the Advancement of Military medicine, Inc. (HJF) in establishing the infrastructure and initial research efforts of a Western Pacific regional research center.

Background

Broadly, TATRC's aim is to explore science and engineering technologies ahead of programmed research, leveraging other programs and collaborative relationships to provide maximal benefit to military medicine. Simultaneously, TATRC aims to be the government model of opportunity-driven research agility. To that end, TATRC invests in cutting-edge technologies, through congressionally directed and other funding programs, and works in other ways with research partners nationwide to develop key products and research outcomes to support military medicine. TATRC is headquartered at Fort Detrick, Maryland, but also has a Field Office in Marina del Rey, California. Part of the strategy behind establishing TATRC West and the other field offices was not only to enable TATRC to establish closer ties with its existing research partners in the western half of the country, but also to build new collaborative relationships that can help advance medical technology in support of the soldier.

Objective/Hypothesis

HJF proposes to collaborate with TATRC's West Coast office to build partnerships and explore opportunities to further develop medical technologies for military and civilian use on the West Coast and Pacific Rim. There is a general inability of funding agencies to transfer medical technology to clinical utilization. Through the years with the support of HJF, TATRC has worked to bring collaborative efforts with academia, government and industry to allow the military to actively pursue and leverage partnerships that fuse military and civilian technologies to advance the state of medical research.

Specific Aims

The Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF) provides administrative, management, and technical expertise to assist TATRC in the pursuit and evaluation of research partnerships as its develops its long-term research and investment strategies in the Western United States and the Pacific Rim. HJF's experience in facilitating medical research in support of the Warfighter, as well as personnel strengths in Southern California, make its capabilities uniquely valuable in support of TATRC's expanding research initiatives.

Study Design
HJF and TATRC explored areas of research and collaborations in order to advance military medicine. This was facilitated by HJF's support for the TATRC West Office to explore areas of research in the Western United States and Pacific Rim that will lead to innovative research challenges and pilot projects.

Relevance: This research effort to build partnerships and collaborations has significant benefit to military and general public. The goals of the proposal developed partnerships that advanced science and medicine to emerge new products.

BODY
To accomplish the above goals over the past year, TATRC West and HJF have been working under Task 1 and 2. Task 1 of the proposal was to research and develop novel evaluative methods for proton beam radiotherapy using the ongoing and emerging work in two HJF/TATRC proton beam centers. Task 2 of the proposal was Specific research under task 2 of this award has been the following: 1) "Grand Challenge" in Military Medicine Research, 2) Packaging and Replicating Proof of Concept Program to accelerate the translation of University discoveries with application of military medicine, 3) Design and Development of a Wireless Portable Functional Near-Infrared Spectroscopy System, 4) International Health Capability and 5) Pathogen Inactivation/Reduction Technology.

Task 1 Research Objectives:
The long-term objective is to develop a methodology for integrating as well as knowledge discovery of a DICOM-Radiation Therapy electronic patient record (ePR) system to manage patients with most types of Proton Beam Therapy (PT) treatment cases across multiple sites with DOD patients. As a first step, the development will be based on utilizing patients treated with PT at Loma Linda University Medical Center (LLUMC) for proof of concept for the research design, implementation, and evaluation. A prototype DICOM-based ePR Information System integrating all necessary PT related data and images will be researched. The objectives will be focused on patient cases treated by PT at LLUMC because of the proximity and collaborative efforts between our research laboratory and LLUMC. The success of this proposal will have tremendous impact to the US Military healthcare service, specifically in two parts: 1) Integrate clinical data obtained from PT clinical sites with DOD patients and distribute globally to local peacetime stationary hospitals and clinics of cancer patients for tele-consultation and managed care. 2) Provide an infrastructure to perform large-scale horizontal and longitudinal outcome studies to improve clinical efficacy and efficiency to the patient.

Introduction:
Proton Beam Therapy (PT) is a particular treatment that utilizes energized charged particles, protons, to deliver dose to the target region. Protons are energized to specific velocities which determine where they will deposit maximum energy within the body to destroy cancerous cells, allowing for maximum dose to the target region while

minimizing dose to surrounding tissues. This is because the Proton Depth Dose (Bragg Peak) is inversely proportional to the square of the particle velocity. In comparison, Photon Depth Dose is proportional to an exponential function. Figure 1 shows a comparison between 6MV Photons from a Linear Accelerator utilized in traditional radiation therapy and different energy Protons. Each of the different energy protons have minimal dose in water but deposit their maximum dose at a target depth. This translates to less dose to normal healthy tissue in the body while depositing most of the energy within the target tumor located at a certain depth within the body. In addition, proton beams have no exit dose which also minimizes damage to health tissue beyond the target tumor. Proton Therapy is especially effective for types of cancer that require controlled high concentration dose and tumors that are close to sensitive tissue. Some examples of the types of cancer treated include: Prostate, Brain, Spinal Cord, Head and Neck, Base of Skull, Eye, Lung, and tumors in children.

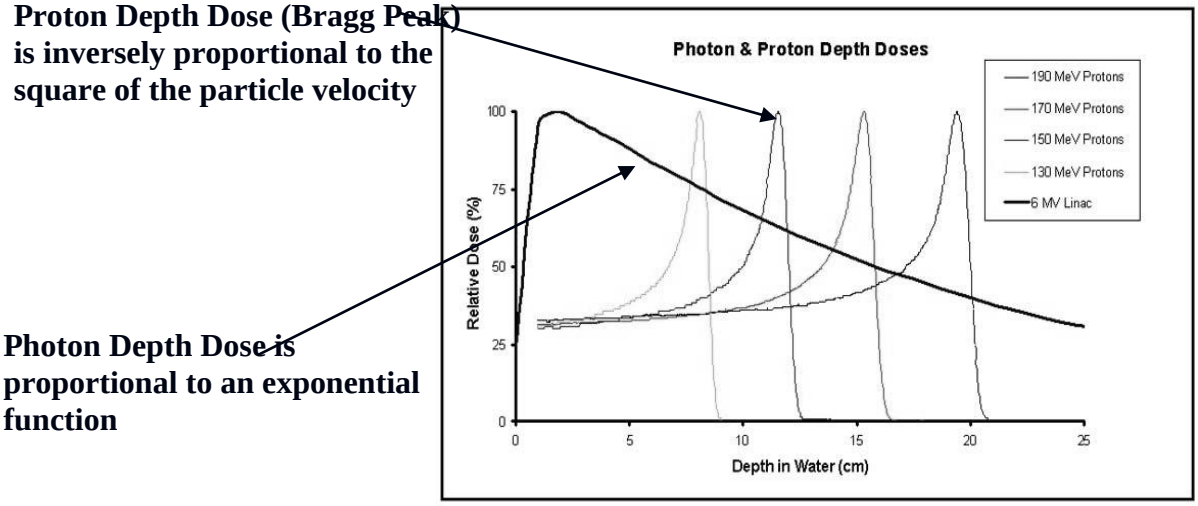


Figure 1: Graph showing a comparison between Photon Depth Dose (6MV) and Proton Depth Dose (130, 150, 170, 190 MeV) percentages as measured in water. The maximum dose from the proton can be deposited at a certain depth. This can be utilized to treat cancer tumors at a certain depth while minimizing dose to surrounding normal health tissue.

Similar to traditional Radiation Therapy (RT), complex clinical imaging and informatics data are generated during the treatment process that guide the planning and the success of the treatment. In addition, there are few PT sites across the country due to the complex and expensive system requirements which include a synchrotron, linear accelerator, and large rotating gantry and require a very large square area footprint. Loma Linda University Medical Center (LLUMC) was the first to open a clinical PT treatment center and began treating patients starting October 1990. There are now facilities in Bloomington, IN; Boston, MA; with emerging sites in Houston, TX and the East coast, as well as established international sites. The need for a standardized and centralized clinical data repository and integrated system with proper data distribution to manage cancer patients becomes crucial. Distances between PT sites and the proprietary nature of vender-of-choice between PT sites will undoubtedly lead to a similar fate as the fractured industry market in RT. Therefore, initiating this integrated system for PT is not only

timely, but urgent in order to prevent this. In addition, as new PT facilities come online, global distribution of standardized data for information sharing of best practice can impact a greater adoption of this type of treatment for cancer patients. An integrated system of standardized data can serve as the mandate for future PT sites and drive the industry, ultimately reducing costs, improving clinical efficiency, and patient outcomes.

This report presents the initial results towards extending the medical imaging informatics methodology to develop decision-support knowledge for managing cancer patients treated with PT. A research collaboration was established with LLUMC to develop the first prototype system. To date, over 45,000 patients have been treated with PT, of which 11,562 patients were treated at LLUMC. Of the types of cancer treated, 65% were male patients with prostate cancer, which represents the largest population of patients treated with PT anywhere in the world. Currently, LLUMC is treating approximately 50 to 170 patients per day making the center one of the most efficient PT facilities nationwide. We have extended our knowledge-based imaging informatics methodology for cancer patients treated with PT, and researched and designed a prototype system and infrastructure platform for future development of the knowledge base as well as decision-support tools that can be add-on features to a standards-based ePR system for sharing of best practice data. Various generic information/management systems feature the availability of necessary clinical data within the RT department. However, the most complete clinical data model is from the proposed standards-based ePR system of this research. Furthermore, the ePR system features open system integration based on the DICOM standard instead of proprietary like other RT information/management systems. In summary, the ePR system has the following superior features:

1) Complies with DICOM-RT and DICOM-RT-ION Object definitions.
2) Global data distribution.
3) Global Treatment Updates.
4) Open System Integration.

Development and Results for Task 1: General Workflow Modeling for Cancer Patients Treated w/ PT at LLUMC

Medical Imaging Informatics Research Methodology

Figure 2 shows a summary of the research methodology for standardizing PT data objects and performing Medical Imaging and Informatics research to develop the knowledge base, the data mining, and quantification and visualization tools which ultimately become add-on features to the standard-based ePR system. With these decision-support tools, the end result is that clinicians can be assisted in their decision-making process for new cancer patient cases. This research methodology can be applied to different lesion types as well as treatment types to quickly research and develop new decision-support tools.

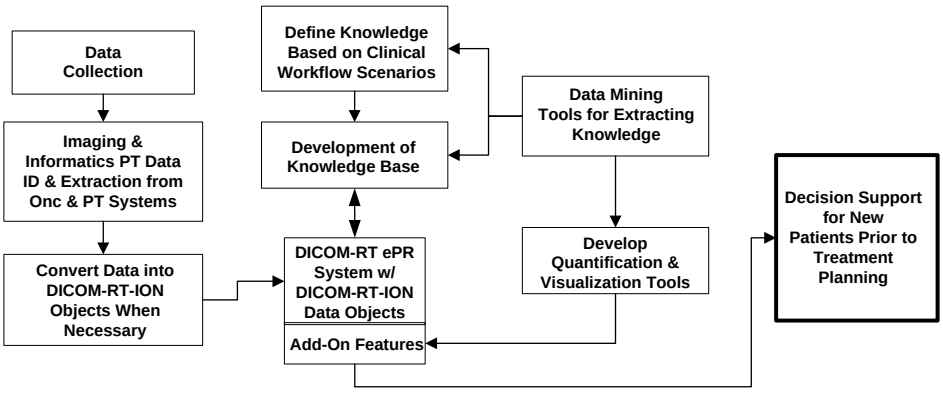


Figure 2: A Medical Imaging Informatics approach towards development of decision-support tools for the DICOM-RT based ePR system. The final results are add-on features for the ePR system to provide decision-support for new patient cases. This methodology can be applied to different lesion types as well as treatment types to quickly research and develop new decision-support tools.

Workflow Model for Proton Therapy (PT) of Cancer Patients

One of the most important first steps for system integration of clinical image and information systems is to research the workflow model of the clinical operations. Since the focus of this research will be on patients treated with PT, the workflow related to these particular treatment cases will be studied. A clinical workflow model for PT was developed for LLUMC as shown in Figure 3. The corresponding data objects at each stage of the workflow are also shown.

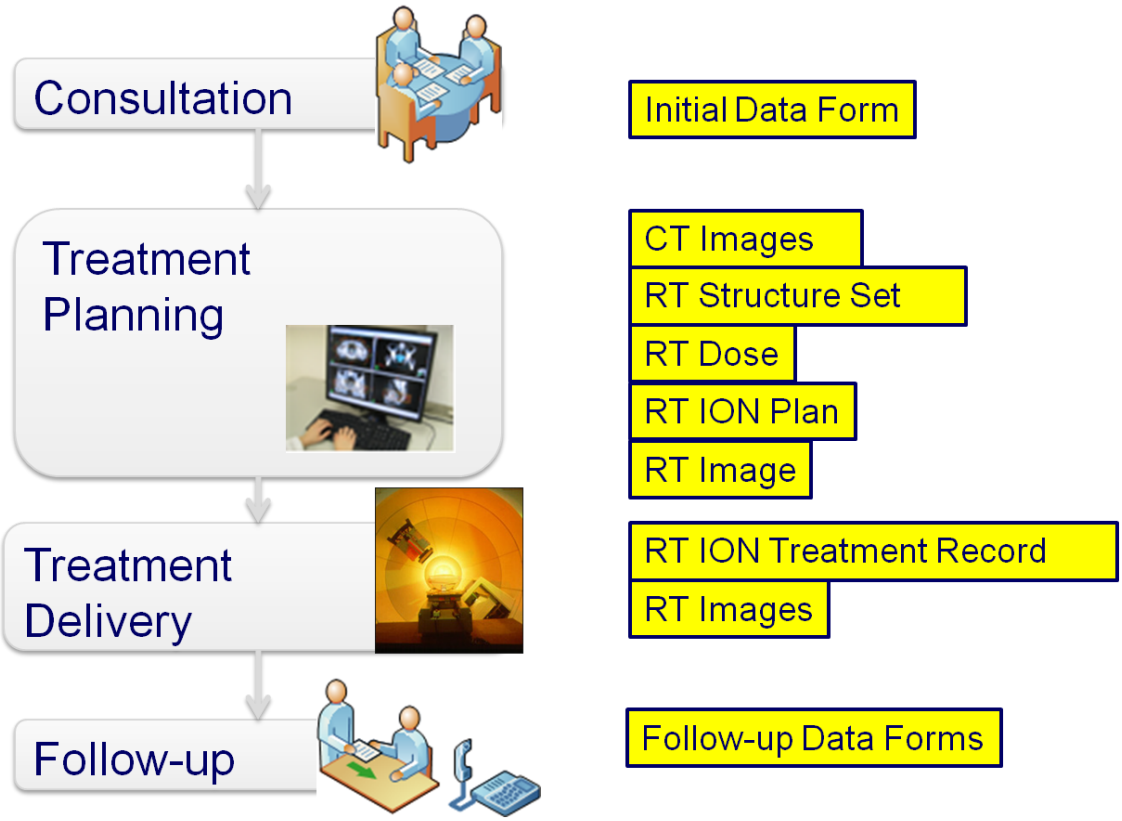


Figure 3: General Clinical Workflow for PT of Cancer Patients including associated data objects utilized in each of the workflow stages.

The treatment begins with the patient diagnosed with cancer lesion or multiple lesions. The patient consults with the physician(s) and determines whether to treat the tumor(s) and whether PT will be performed. The patient is entered in an oncology information system and is scheduled for treatment if the system is available, otherwise the scheduling is performed on a paper-based system. Next during the treatment planning stage, the patient is scheduled for body immobilization or head immobilization. If the treatment is to be performed for the brain or head and neck, a head cage made of lightweight plastic is cast to immobilize the head during the CT scan and the actual treatment. If the body is to be immobilized, then a plastic cradle is utilized with injected foam cushioning to immobilize the body for imaging, planning, and treatment. A diagnostic CT will be acquired to plan the treatment based on the patient being immobilized. In addition, other imaging may be acquired, such as PET or MRI to help better define the cancer to be treated. Most of the time, a CT study is adequate for treatment planning. The Radiologist and Radiation Oncologist review the patient's case and then the Radiation Oncologist defines the initial plan parameters such as dose limits and constraints, critical structures, and tumor volume to be treated. The physics team then computes the plan based on these dose constraints on the corresponding TPS. Once the initial plan is computed, the Oncologist reviews the results and makes any necessary changes. Once the treatment plan has been approved, the data is used to build a 3D computer assisted bolus made of high-grade wax and apertures made from an alloy called cerrobend that will shape the proton beam for treatment of the target tumor(s). QA and setup is performed and a simulated treatment plan will be executed in order to make any fine-tuned adjustments to the overall plan. During the treatment delivery stage, the PT session is then executed by the Radiation Therapist within the gantry and the corresponding PT plan data are stored in the treatment planning systems and some results are also inputted into the oncology information system or a Record and Verify system. Since there are a variety of tumor types, the treatment paths can differ. Therefore, it is important to research and develop a more robust workflow model that can accommodate the various treatment paths and identify points within the workflow that can be improved. Not only would this enhance the design of the DICOM-based ePR System, but also serve as the foundation for a methodology to build quantification and visualization tools for decision-support. Finally, during the follow-up workflow stage, clinical outcomes data are captured to evaluate and validate the treatment protocol and the overall treatment of the patient.

Development and Results for Task 2: Research and Development of Data Models

The DICOM (Digital Communication in Medicine) standard has been well established and widely successful for clinical imaging systems in Radiology, in particular PACS (Picture Archiving and Communication System). Image data acquired from equipment from different vendors can readily communicate with each other and integrate into a system through the DICOM standard. In 1997, the DICOM standard was extended to include radiotherapy information and further updated in the latest version released in 2003. Seven DICOM radiotherapy (DICOM-RT) objects have been included by the DICOM standards committee for transmission and storage of radiotherapy images and related information. These DICOM-RT objects are: 1) RT Image, 2) RT Plan, 3) RT

Structure Set, 4) RT Dose, 5) RT Treatment Record, 6) RT Brachy Treatment Record, and 7) RT Summary Record. In March 2006, supplement 102 was finalized to include two additional RT objects for Ion Therapy applications which include PT. These two objects include RT ION Plan and RT ION Treatment Record. These two additional objects refer to the same RT Objects: RT Image, RT Dose, and RT Structure Set. Figure 4 shows the DICOM model of the real world showing where the Radiotherapy Objects reside. Figure 5 shows in greater detail how the DICOM-RT-ION objects are added to the overall set of Radiotherapy Objects. Generally, the sources for these data come from treatment planning systems (TPS), oncology information systems, and PT systems. The DICOM-RT-ION object information models can be utilized to develop the data structure and database schema for the electronic patient record. To develop a conceptual data model, the PT workflow must be reviewed to define the data required. Additionally, clinical user input is needed as well. With these input sources, a conceptual model can be developed for a PT electronic patient record.

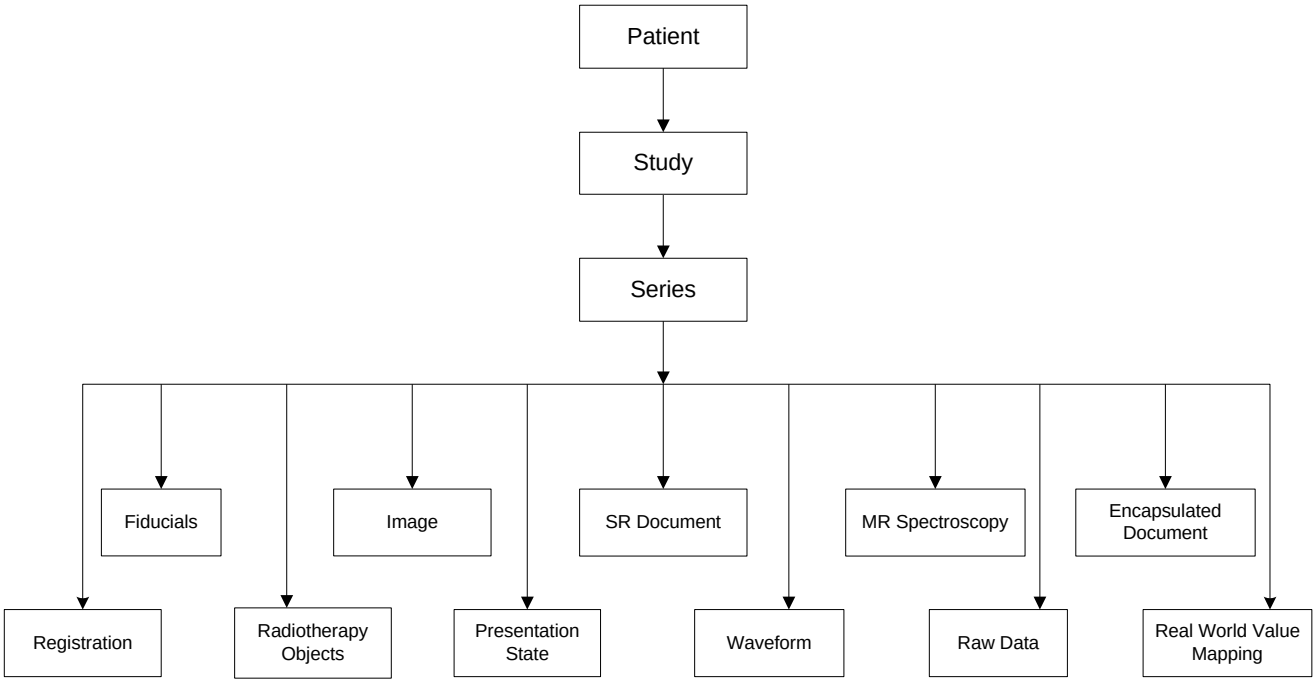


Figure 4: Portion of the DICOM Model of the Real World showing where the Radiotherapy Objects reside.

An initial data survey was performed to track patient cases utilizing the clinical information systems at LLUMC. Two types of patient cases of brain and prostate tumors were tracked to determine the treatment path and outcome. The two cancer types were chosen since they represent complex treatment planning cases with surrounding critical structures that require controlled dose to the target tumor while limiting dose to normal and healthy tissue. These results were implemented into the clinical workflow model. The preliminary data collection survey was performed to determine the feasibility of data collection at LLUMC as well as to assist in the development and design of both the database schema as well as the overall ePR system design architecture. The brief survey was performed using clinical information systems to track historical patients and their

record and was performed under the HIPAA Regulations and Compliance Guidelines set forth by LLUMC.

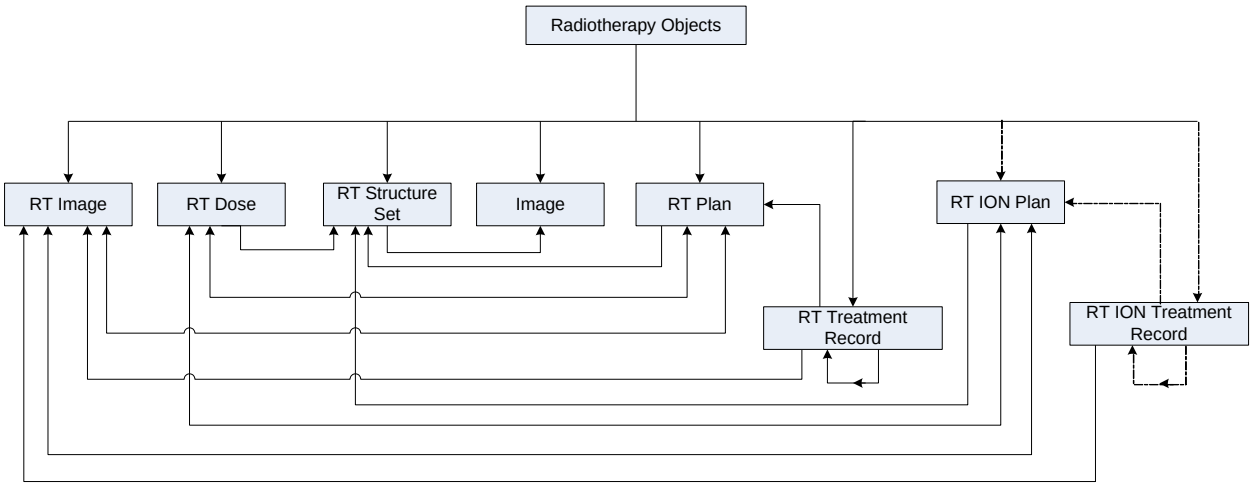


Figure 5: Portion of the DICOM model of the Real World showing the extension of the two RT-ION objects. Note: The two ION objects, RT-ION Plan and RT-ION Treatment Record, refer to the same RT objects as the two RT Objects, RT Plan and RT Treatment Record.

Figure 6 shows a portion of the results of the database schema design for the ePR system. The database schema framework was developed based on the DICOM-RT and DICOM-RT-ION standards mentioned before to insure full interoperability of the data as well as compliance to already established de-facto standards. The design of this database schema is robust, flexible, and extensible to accommodate new DICOM related objects as needed and extension of the database to include the knowledge base and related metadata (eg, outcomes results of PT gathered by LLUMC on a per patient basis) in future research development.

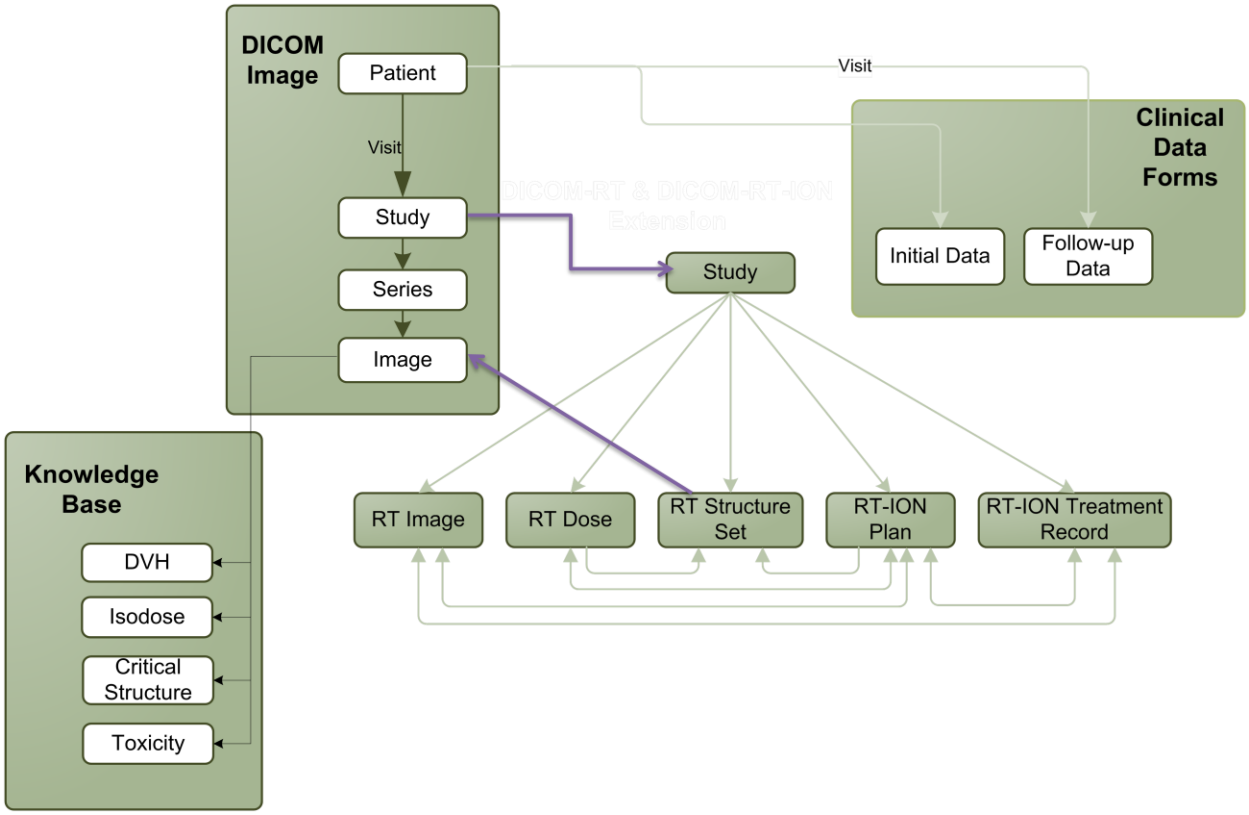


Figure 6: Portion of the Database Schema for the ePR system. Data objects are based on the de facto DICOM-RT and DICOM-RT-ION standards. The database schema can also accommodate the knowledge base as well as related metadata to enhance the overall ePR system in future research development.

Development and Results for Task 3: Design and Development of the integrated ePR System with DICOM-RT objects

Based on the clinical and data workflow models, Figure 7 shows the overall ePR system architecture design. The system architecture allows for the greatest flexibility while allowing future development. Global distribution of key imaging and informatics data and future knowledge base and data mining tools are accomplished with a web-based design. Tools to mine the database and well as quantifying knowledge can be developed in a modular approach without impacting the overall system and eliminating the need to redesign in the future.

The main goal of the ePR architecture is to be standards-oriented, portable, scalable and at the same time flexible. In order to achieve this we utilized libraries, modules, servers and programming languages that are either open source or publicly available. In some cases, due to the specific requirements of the ePR we have made some changes to those libraries to fulfill those requirements. The utilization of modules or plug-ins provides a rich mechanism to extend the ePR according to any future needs, without losing the robustness for the core tasks handled by the ePR framework. The following are a list of some of the current libraries and OS utilized:

- Windows OS
- DICOM receiver: dcmtk open source library

- ePR Framework: php5, with pear and gd package installed
- DICOM module: php5 (using php-DICOM module 0.3)
- DB module: php5 (with connection to mysql 5 database)
- Additional modules: php5 with necessary wrappers for other programming languages
- Web server: apache2 open source

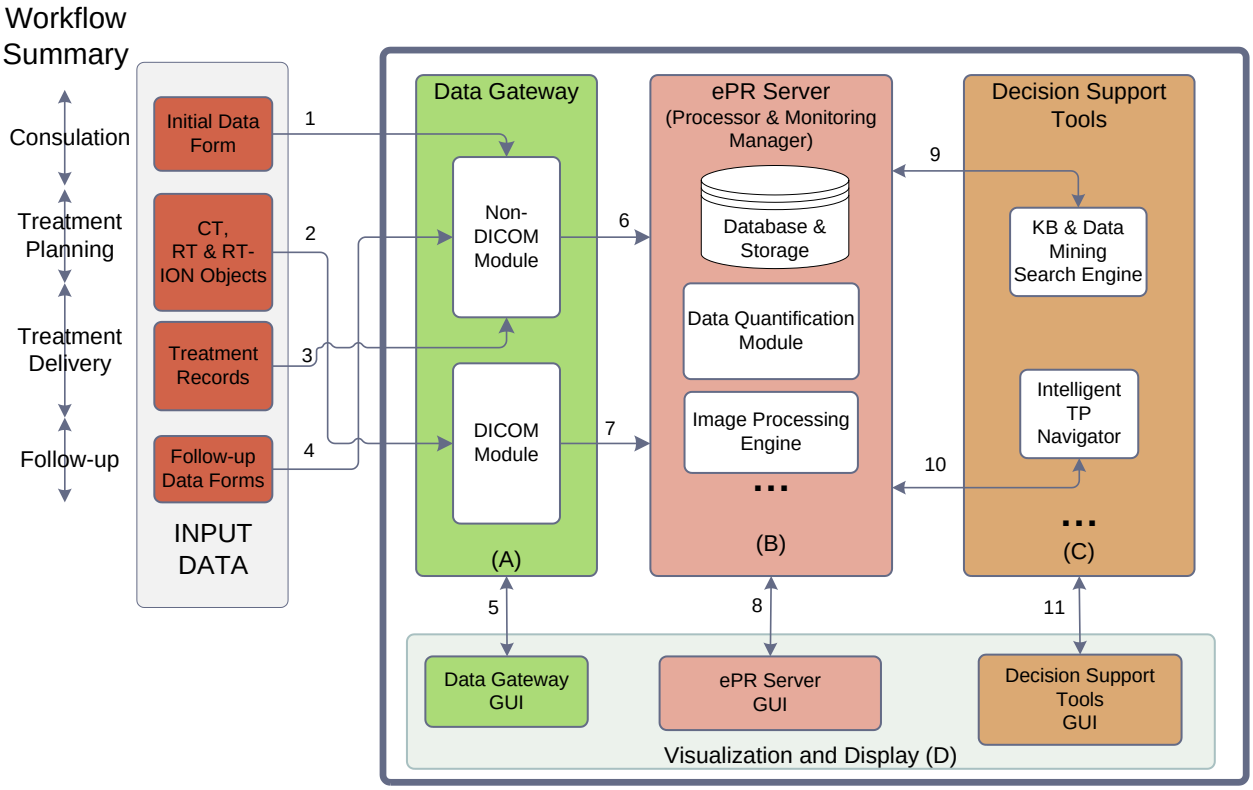


Figure 7: The DICOM-based ePR System Architecture based on the clinical workflow as shown to the left of the ePR diagram.

Figure 8 shows the Proton Therapy Data collected from one patient treated for prostrate cancer and utilized in the design of the database and the data schema. A total of 5 complete patient datasets were collected for design and evaluation of the database and ePR system.

Name	Media	Type	Digital Format	Location
Patient Initial Data Form	1 paper form	Pre-treatment Clinical Data	No	Research Spreadsheet
CT	Hundreds DICOM files	Image	Yes	PT Data Server
RT Dose	Hundreds DICOM files	Dose Image	Yes	TPS WS
RT Structure Set	1 DICOM file	Contours	Yes	TPS WS
RT-ION Plan	1 DICOM file	Plan	Yes	TPS WS
RT Image	1 DICOM file	RT Image	Yes	TPS WS
RT-ION Treatment Record	1 DICOM file	Treatment Record	No	Patient Chart
Follow-up Data Form	1 paper form	Outcome Data	No	Research Spreadsheet

Figure 8: Data objects of one patient identified for integration with ePR system and utilized in clinical outcomes analysis.

For clinical outcomes data, the current practice for collecting outcomes data utilizes hardcopy data forms. We have developed a GUI as an extension of the ePR to digitally collect and store clinical outcomes data. Figure 9 shows a screenshot of the follow-up data form where users can input directly into the ePR system key outcomes data.

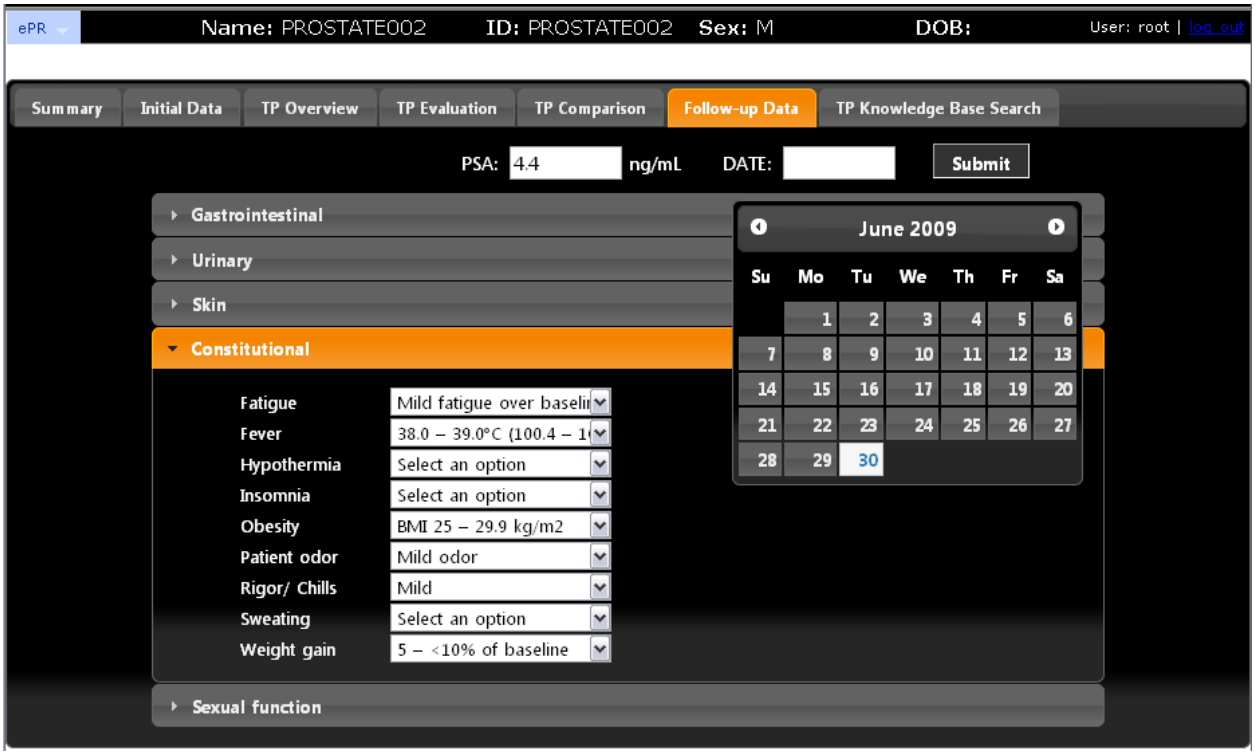


Figure 9: ePR GUI for collecting follow-up data in a prostate cancer treatment protocol utilized for outcomes analysis.

Figure 10 shows the GUI design of a data mining tool that can query the ePR system for specific data such as "Rectal Toxicity less then 3". The query tool would then select all patient cases that fill the query criteria and return the treatment plan data for review and analysis. The integration of such data mining tools are value adds to the ePR system and can greatly facilitate large-scale clinical trials of new treatment protocols and quickly evaluate the outcomes and change treatment protocols that ultimately lead to better PT treatment of new cancer patients.

In future research development, the knowledge base along with data mining tools can be integrated within the ePR system architecture. Furthermore, key metadata such as outcomes results of PT for a particular treatment plan are integrated as well. This will form the basis of a standards-oriented, open architecture system to perform large-scale horizontal and longitudinal outcome studies to improve clinical efficacy and efficiency to the patient and sharing of best practice data to future adopters of PT.

Summary of Deliverables of the Research:

1. A Refined Clinical Workflow Model for Proton Therapy (PT) of Prostate Patients.
2. A DICOM-RT-ION Data Model for Imaging and Informatics Data from Treatment of Prostate Patients with Proton Therapy which includes a roadmap for converting proprietary data objects into the DICOM standard.
3. A Prototype System for storage, retrieval, and distribution of DICOM-RT-ION data. Software will be Open-Source and technology transferable.
4. A Database of 5 Prostate Cancer Patients treated with Proton Therapy of DICOM-RT-ION imaging and informatics data objects including associated clinical outcomes data.
5. A roadmap for integration of other sites Proton Therapy data.
6. Research and Investigate a Knowledge Base of Quantified Knowledge derived from the Prototype System for decision support.
7. Presentation of research work at 2009 ASTRO and SPIE Medical Imaging conferences.

Figure 10: GUI screenshot showing a query made through the data mining tool and the treatment plan data results returned for review. Integration of clinical outcomes data with treatment plan data in a single ePR system can greatly facilitate future outcomes analysis of new clinical trials of PT treatment protocols.

Task 2 Research Objectives

Maintain and enhance scientific, administrative, and logistical support such that TATRC can manage its advanced medical technology research and development program in a productive, value-added way. The purpose of this task is to assist TATRC funded programs in the western region of the United States to forge transformative, novel and integrative academic, industry, government partnerships that: 1) captivate, advance, and nurture well-trained multi-institutional and interdisciplinary investigators and research teams; 2) create incubators for innovative research tools and information technologies; and 3) synergize multi-institutional and inter-disciplinary clinical and translational research and researchers to catalyze the application of new knowledge and techniques to clinical practice at the front lines of patient care.

HJF has provided its administrative, management and technical expertise to assist the USAMRMC/TATRC in the development of its long-term generation portfolio and investment strategy in this regional effort to accomplish Task 2.

Specific areas of research accomplishment include the BMES Research Challenge, "Grand Challenge" in Military Medicine Research and Packaging and Replicating Proof of Concept Program to accelerate the translation of University discoveries with application of military medicine

BMES Research Challenge

HJF/TATRC worked with the Biomimetic MicroElectronic Systems (BMES) Engineering Research Center of the University of Southern California to accomplish the Medical Engineering Innovation Challenge. The goal of the program was to announce a request for innovative ideas from multi-disciplinary teams of students that broadly relate to innovative medical research for the wartime soldier or tactical team. Each proposal was to identify a near term medical technology to help today's modern wartime soldiers, surgeons, nurses and other medical staff. The challenge was for students to submit medical opportunities with applications relevant to the military that either utilize existing technologies or propose the development of new technologies that will solve an unmet need in medicine today and that will lead to products in the near future. The Medical Engineering Innovation Challenge was a success in May 2008. BMES is currently working to process awards to students to meet the deliverable of their tasks. Subaward to USC was processed. USC is currently in the process of funding proposals and is in the process of providing a detailed final report.

The BMES ERC and TATRC awarded $200,000 to four outstanding teams of science and business graduate students to develop their ideas for medical engineering products.

In a unique collaboration, the USC BMES ERC brought together USC's engineering and business schools, the U.S. Army Telemedicine & Advanced Technology Research Center (TATRC), leading technology companies, and graduate students from four universities to compete in the first ever BMES / TATRC Medical Engineering Innovation Challenge (MEIC). This ground breaking challenge awarded $200,000 to teams of science and engineering graduate students at USC, Caltech, UC San Diego and UC Santa Cruz who had partnered with MBA students to take their medical engineering idea from the laboratory benchtop to the marketplace. Eligible proposals include medical opportunities with applications relevant to the military that either utilize existing technologies or propose the development of new technologies that will solve an unmet need in medicine today and that will lead to products in the near future.

Twenty-one teams from the four collaborating universities submitted proposals, and then judges selected six finalists to formally present their ideas to a distinguished judging panel of corporate executives and senior military members on May 20, 2008. Judges included senior corporate executives and military members, already working closely with the BMES group, from Advanced Medical Optics, Bausch & Lomb, Eli Lilly, Medtronic,

National Semiconductor, Reichert, Texas Instruments and the Army, Navy and TATRC.

These distinguished judges awarded $200,000 to the following four teams for their projects:

1st Place: $78,000 was awarded to Garrett Smith, Karla Brammer, Chris Petry and Ning Wang of UCSD to develop titanium dioxide nanotubes to speed bone healing in patients with implants made of titanium or other metal alloy.

Mission: To develop a titanium implant that integrates with bone for long-lasting anchorage

Description

Soldiers frequently suffer from pain, inconvenience, and long recovery due to bone fractures, which account for 26% of all combat injuries. Titanium, the most widely used material for orthopedic and dental implants, lacks the surface properties needed for permanent bone anchorage. Our core nanotube technology accelerates bone-healing allowing for injured solders as well as civilian patients to return to an active lifestyle more quickly with less likelihood lengthy rehabilitation and repeat surgeries. Our proprietary surface coating improves bone-bonding strength by nine times clinically used implants. Our coating can be manufactured quickly and inexpensively on any size or shape metal implant including pedicle screws, bone plates, fixation devices, dental implants, spinal implants, and joint replacements.

Findings

Excellent progress has been made in the development of our core nanotube implant technology for joint replacement, spinal, and dental applications. A company has been formed (Nasseo, LLC) to fund additional pre-clinical studies through research partnerships with the University of California San Diego and Lund University in Sweden as well as active collaborations with medical devices companies in Southern California. Our first generation prototype had shown repeatable large animal data for significantly increased bone bonding and decreased inflammation due to the properties of the titanium nanotube coating. Key research findings that support the company's strategic focus have recently been published in the Journal of Biomedical Materials Research Part A and in the Proceedings of the National Academy of Sciences (PNAS), one of the most prestigious scientific journals. More funding is being sought to complete the animal studies and to further optimize the surface properties of the nanotube structure for bone healing.

Key Research Accomplishments

1. Determined the US FDA regulatory and commercialization pathways based on our intellectual property portfolio.

2. Conducted experimental studies (bisphosphonate coating, surface characterization, torque testing) that significantly adds value to the proposed business model. A portion of the testing will be conducted internationally with our collaborator (Lars Magnus Bjursten,

MD/PhD) in Europe.

2nd Place: $61,000 was awarded to Dayu Teng, Randy Chen, Mike Ye, and Li Cheng of UCSD to create an inexpensive, portable device for analyzing cells and microorganisms which can be used to address the urgent need for diagnosing AIDS in developing nations.

Mission: To initiate the business and technology development of an optical microfluidic patent from UC San Diego.

Description
Findings: Due to the limitation of PDMS mass production, we are transferring the design on to PMMA materials. Initial designed were produced. The new design needs to be tested. Other design possibilities will also be explored. UCSD is supportive of the entrepreneurial initiative. A serious negotiation of the license is underway. A potential investor has also entered the picture with initial investments in facility and technical supports.

Key Research Accomplishments and Reportable Outcomes
The commercialization of the technology is more of an industrial process rather than academic one. This is because the focus of the commercialization is more on the manufacture and market, which have little academic value. Therefore, the product-oriented development of the technology is better carried out in an industrial setting. As a result, much of the efforts this year were spent on establishing a sound industrial environment, a company that houses the development of the product based on the proposed multi-channel optical microfluidic technology. A company, Ten Medical Systems, Inc was established in 2008. A serious licensing negotiation with UCSD is underway. The final licensing contract is expected to be completed in 60 days. A private investment firm, Dubilier & Co. has expressed interests in the technology. One of Dubilier's portfolio companies, ODC-Nimbus is a CD/DVD mastering industry leader. Under a partnership deal, we can leverage ODC-Nimbus's existing facility and expertise in optics on polymer. This partnership allows rapid prototyping with less capital investments. The first round of PMMA based chip has been produced. It follows the similar design as in the patented technology, but with a few dimension changes accommodating the new material and processing methods.

3rd Place: $36,000 was awarded to Alan Horsager of USC to develop a novel neurotherapeutic platform, which compensates for damaged or lost neurons with unprecedented specificity and controllability. He expects this development to lead to a therapy to treat patients blinded by photoreceptor diseases and ultimately epilepsy, Parkinson's disease, and chronic pain.

Mission: Photoreceptor diseases such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD) cause blindness in 15 million people worldwide1, a number that continues to increase with the aging population2. Recent gene therapy efforts have shown great clinical success in treating a relatively rare form of RP (i.e., an RPE65 mutation) in humans patients3-7. However, the use of gene therapy for vision loss is

complicated by the extraordinary genetic heterogeneity of retinal degeneration (over 180 different genes are associated with RP)8 and the loss of photoreceptors9. An ideal therapy would be able to restore vision in blind patients independent of the specific gene mutation and subsequent loss of photoreceptors by targeting a downstream point in the visual pathway. Indeed, the use of microelectronic retinal prostheses has shown fundamental success in generating visual percepts in blind subjects by electrically stimulating spared neurons of the inner retina10-12. Still, electrically activating these neurons requires large disc electrodes (at least 25 times the diameter of a retinal ganglion cell), leading to broad and indiscriminant activation of multiple cell types13, greatly complicating the normal spatial and temporal process of the retina14, 15. Thus, there is great need for a therapy capable of 1) treating photoreceptor degeneration independent of the mutation or cause, and 2) accurately driving specific retinal cell subpopulations so as to mediate naturalistic neural responses and high resolution visual perception. *Accordingly, we are developing the first safe, effective, high spatial and temporal resolution method to restore retinal responsiveness to optical information, using a novel class of light activated molecule to directly sensitize spared bipolar neurons to light.*

Description

Using an adeno-associated virus (AAV), we have expressed channelrhodopsin-2 (ChR2), a photosensitive cation channel16, in the bipolar cells of the inner retinae of blind mice with approximately 50% efficiency using the GRM6 promoter sequence, and this expression of ChR2 has restored visual light sensitivity in these mice as measured through a behavioral task. Targeting retinal bipolar cells with ChR2 allows the retina to respond to external light and, more importantly, convey visual information to the brain in the absence of photoreceptors. Recently, several groups have separately demonstrated the building blocks for a successful therapy in which spared retinal neurons are sensitized to light; but they have not assembled these ideas into a coherent translational technology, which is capable of treating blindness. One group used AAV to safely and permanently label retinal ganglion cells in the *rd1* mouse with 20% expression efficiency of ChR217, rendering ganglion cells light sensitive. Masland et al. was able to express melanopsin, another light-sensitive protein, in nonmelanopsin expressing ganglion cells and restore light sensitivity in *rd1* mice. However, targeting ganglion cells bypasses substantial inner retinal circuitry, much of which is involved with spatial and temporal processing of visual input14, 18. Another group targeted ChR2 to the ON bipolar cells of *rd1*mouse pups using electroporation and the *GRM6* promoter, leading to improved physiological and behavioral responses to light stimuli19. However, ChR2 expression levels were low (~7%) and delivery was conducted via electroporation, a technique that is not clinically viable. Thus, we have combined these findings into a viable translational therapy (an AAV-*GRM6*- ChR2-GFP construct) to restore light sensitivity to the photoreceptor-less retina, and will subsequently test both physiological and behavioral responses in 3 different mouse models of blindness (*rd1, rd16,* and rhodopsin -/-).

Key Research Accomplishments and Reportable Outcomes

We have successfully completed the goals of our research and have utilized the TATRC funds to achieve these goals. Below is the list of reportable outcomes from this work:
1. We have established the AAV serotype that leads to the best and most specific

expression in retinal bipolar cells.
2. We have measured efficacy of our AAV-GRM6-ChR2-GFP therapy using both physiological and behavioral techniques.
3. We have evaluated the basic safety of our AAV-CBA-ChR2 therapy.
More broadly, we have established the proof-of-concept work for our blindness therapy. This data set the foundation for further key optimization research our continued push towards preclinical development. 'In addition to the above achievements, we have also reached a number of key milestones within the company, Eos Neuroscience, Inc. They are:
1. Received our first NEI/NIH SBIR, which has allowed us to hire our first two scientists, establish a laboratory space in downtown Los Angeles, and continue our optimization process.
2. We are in the process of writing up and submitting two publications that will establish our group as a leader within the field.
3. Engaging the FDA in the next month in the form of a pre-pre-IND meeting to formalize our preclinical plan.
4. We received a very competitive score on our NIH RAID application that will supply resources, which will allow us to complete preclinical development through an IND filing.

4th Place: $25,000 was awarded to Lada Rasochova and Jamie Phelps to develop diagnostic tests for faster and more accurate detection of food pathogens that will enable even better and faster monitoring of food supply safety to prevent both unintentional and intentional food borne disease outbreaks.

Mission
Provide safe food for civilians and military.

Description
The focus is on providing significantly faster and more accurate tests for detection of pathogen contaminants in foods, improving detection sensitivity, increasing throughput, reducing testing time and therefore lower holding and inventory costs for food suppliers and distributors. Current methods for food pathogen detection are inadequate due to outdated culture based technology that cannot handle the need for speed, detection sensitivity, sample volume, throughput, and expanded testing for wide variety of pathogens. These unmet needs can be addressed by developing the next generation, ready-to-use testing kits based on antibody based diagnostic technology. The target customers include food distributors, farmers, and food retailers whose ability to do business depends on preventing food pathogen outbreaks and costly recalls. In addition to the civilian use, the technology has considerable applications in military settings where it enables better and faster monitoring of food supply safety to prevent food borne disease outbreaks among military personnel. If successful, the technology is suitable for testing of other pathogens and is expandable to other areas, such as meat and diary, frozen and processed food products, and water safety testing.

Key Research Accomplishments and Reportable Outcomes

Market Research

Classification of Food Contaminants:

The food supply chain is facing a crisis - an increased frequency of food pathogen outbreaks. Every year there are 5,000 deaths, 325,000 hospitalizations and 76 million illnesses caused by food pathogens in the U.S. alone. This has created a growing demand for improved pathogen detection products that is currently unmet in the marketplace. Rapid-test market is a nascent market. The two viable competitors are DuPont and Matrix. DuPont has licensed PCR from Applied Biosystems, to market a PCR based kit for food pathogens. This is a real-time PCR test. The issues with this test are three fold: technical, operability and price. The technical hurdle is that PCR will detect DNA from both live and dead pathogens. The operability challenge is that PCR works best in a clean room environment - not a side room at a processing plant. The price is the last and greatest challenge - $35,000 initial cost and $80/sample. Matrix is a small company out of the UK, using a colorimetric assay incorporated with their magnetic bead capture step. The capture step is robust; however, the detection step is not as sensitive. The food testing market is a fast growing industry, under increased scrutiny by the FDA (USDA
and Homeland Security, Food Technology). The fresh produce market is a particularly attractive section of this market, where the recent food-borne illness outbreaks have already resulted in dramatic changes. New products such as ready-to-eat salads are gaining in popularity. Ready Pac had 20 new packaged fresh produce products released and over $437M in annual sales in 2007 with an 18% annual growth. The financial risk of a potential outbreak, translates into a willingness to pay for a faster and more sensitive test to detect microbial contamination. Earthbound Farms, for example, spends about $1.5 million a year on food testing to avoid recalls. The overall produce market in 2007 is over $100B with an annual growth rate of 3%. The $6.7B organic produce market is growing at 20% per year (The Organic Trade Association's Manufacturer Survey). FDA oversees $240 billion of domestic food and $15 billion of imported food. In addition, roughly 600,000 restaurants and institutional food service providers, an estimated 235,000 grocery stores, and other food outlets are regulated by State and local authorities that receive guidance and other technical assistance from FDA. The FDA stated during an April 2007 meeting that the buyers are now requiring a supply chain verification of Good Agricultural Practices (GAP). Supermarkets and other establishments that sell fresh produce have started to require

testing certification from their suppliers. This trend will continue in the future. Experts predict that food pathogen testing will be mandated in the near future by the government. Mandated testing will increase the testing volume and eventually lead to industry growth and then consolidation. Even in the absence of government mandated testing, the market pressures from food retailers are forcing food distributors to incorporate some level of testing in their processes. There is a need for a superior (faster, more sensitive and quantitative) test. Industry insiders state that the current food testing market is estimated to be $200 million with projected growth rate of 20% over the next five years. The end consumers would be the large food producers (fresh produce, meats, poultry, dairy, and packaged foods), the food processors and the wholesale food distributors. *Salmonella, E. coli* 0157:H7, and *Listeria* in packaged fresh produce is the most promising initial market segment. The detection tests have to meet the following customer needs: speed, quality, flexibility, and ease of use to the customer.

"Grand Challenge" in Military Medicine Research

HJF proposes to support a research effort in collaboration with the Regents of the University of California for the Meeting of TATRC "Grand Challenge" in Military Medicine Research. The objective of this program is to enhance the participation of the students, faculty and research scientists in military relevant research, especially to participate in research projects fostered by TATRC. The hypothesis is that the holding of the Grand Challenge meeting at the UC System-wide Bioengineering Symposium will provide the best venue and opportunities and that the selection of the most outstanding, military medicine relevant student projects presented at the Symposium will be the best approach to realize this objective. The specific aims are to increase awareness of military specific interests and requirements among members of the research community, to enhance their exposure to the military needs and to DoD funding opportunities, to encourage researchers to address key problems in military medicine, and to foster an applied, product-oriented approach to research that will be valuable to the military.

Introduction

The collaboration between TATRC and BIC began on July 18, 2007, when COL Friedl and his team visited the Headquarters of the Bioengineering Institute of California (BIC) at UCSD. The discussions led to a series of successful collaborations. TATRC West co-sponsored the 9th System-

wide Symposium at UC Riverside and the 10th Symposium at UC Merced, where TATRC Chief Scientist Dr. Charles Peterson's inspiring plenary lecture set the stage for TATRC's special "grand challenge" to the students and faculty in the ten campuses of the UC system and three National Laboratories. This then led to a series of discussions between TATRC West (Director of Operations Jessica Kenyon and Project Officer Elias Wilson) and the BIC through face-to-face meetings, teleconferences and e-mail exchanges for the planning of Meeting of TATRC Grand Challenge in Military Medicine Research at the 11th Annual UC System-wide Symposium organized by UC Davis in collaboration with the Bioengineering Institute of California (BIC), on June 17-19, 2010. At the Symposium, five outstanding awardees were selected from over 20 applicants. This was followed by the 12th UC System-wide Symposium organized by UC Santa Barbara in collaboration with BIC. The awardees made outstanding presentations in a session on June 13, 2011, chaired by Manja Lenkin, IPA, TATRC West. The presentations showed the innovative ideas and outstanding results of the awardees. There were active discussions with excellent questions and answers. The session fully achieved the goals of increasing military-specific interest among members of the UC research community, addressing key problems in military medicine, and encouraging an applied, product-oriented research approach. This event sponsored by TATRC for the most outstanding military medicine-relevant student projects generated a great deal of interest among the student population. Although there was no funding from TATRC for a new round of Grand Challenge Competition at the 12th System-wide Symposium at Santa Barbara, the meeting organizers were successful in holding a session on Grand Challenge Competition with a greatly reduced budget. Out of 25 applicants, eight finalists were chosen to give presentations on June 13, 2011, immediately before the TATRC Grand Challenge session mentioned above in another session chaired by Manja Lenkin, IPA, TATRC West. The superb presentations stirred many meaningful discussions. Following rigorous review, three winners were chosen, with Timothy Downing of UC Berkeley receiving the top prize. At the 13th Annual UC System-wide Symposium organized by UC Berkeley on June 21-23, 2012, in collaboration with BIC, although there was no additional funding for the TATRC Challenge Award, the Symposium had many papers relevant to military significance, and the attendees were made aware of the TATRC support in the preceding years. These activities at the UC System-wide Symposia fully achieved the specific aims of the Meeting of TATRC Grand Challenge in Military Medicine Research:

(1) To increase the awareness of military-specific interests and requirements among members of the University of California (UC) research community,
(2) To enhance the exposure of the research community to the needs of the military and to DoD funding opportunities,
(3) To encourage researchers to address key problems in military medicine, and
(4) To encourage an applied, product-oriented approach to research.
The BIC has worked with TATRC to follow up with the awardees on their research progress and a joint review meeting will be held on December 11, 2012, at UC San Diego.

Body

TATRC “Grand Challenge” in Military Medicine Research

The BIC continues to follow up on the research progress of the five winners of the TATRC “Grand Challenge” in Military Medicine Research who gave their reports on June 13, 2010 during the 12th UC System-wide Bioengineering Symposium held at University of California, Santa Barbara. The progress reports of these five winners are given below.

Progress Reports of Five TATRC Grand Challenge Award Winners in 2010:

1. Yu M. Chi (Advisor: Gert Cauwenberghs), UC San Diego

Wireless Uniform Embedded ECG/EEG Physiological Monitoring

We are continuing to characterize the performance of the non-contact sensor in various ECG and EEG applications. We have focused on further developing the non-contact biopotential sensor. We have demonstrated a new custom integrated analog front-end that greatly reduces the sensor’s input noise while simultaneously enhancing its sensitivity and accuracy. Compared to the discrete components used in previous research, the new custom integrated amplifier achieves a 50x higher input impedance and a 2.3-9x lower noise floor. In addition, the design of the sensor does not require any manual tuning or adjustment. As a result, this research may enable, for the first time, the inexpensive production of high quality non-contact electrodes. The sensor technology was subsequently patented by UCSD and licensed to Cognionics, Inc. We have also spent a significant amount of effort of characterizing the performance of the non-contact sensor in various ECG and EEG applications. Under a simultaneous comparison of standard wet electrodes, older non-contact sensors and the current design, we verified that the new integrated front-end enables a much more accurate ECG to be acquired, even through thick clothing. The extremely high input impedance of the sensor practically eliminates the frequency

response and gain errors, which plagued previous sensor designs. Moreover, we have collaborated with the Swartz Center for Computational Neuroscience to test and benchmark the performance of the non-contact sensor within an EEG brain-computer interface application. Compared to dry and wet contact electrodes, the non-contact electrode exhibited more noise, but was successfully utilized for brain-computer control (~2x lower throughput), even placed on top of dry hair. To our knowledge, this level of performance has never been demonstrated before. [Presented in Appendix as "Dry and Non-contact Biopotential Sensors"].

2. **Erica Andreozzi** (Advisor: Angelique Louie), UC Davis

Multimodal Imaging Probes for the Diagnosis of Traumatic Brain Injury

As a result of the improved protective equipment that enables soldiers to survive bomb blasts that would have before been fatal, there is an apparent increase in the incidence of Traumatic Brain Injury (TBI) of the war in Iraq and Afghanistan, as compared with previous wars. This emphasizes the need to study the pathology underlying mild TBI for ensuring proper diagnoses and effective treatments. We use a novel, multimodal imaging probe targeted to activated microglia (immune cells of the brain) as a means of non-invasively diagnosing TBI with PET and MRI before the onset of cognitive deficits. Focusing on the key role of microglia in TBI pathology, we use multimodality imaging of microglia to detect mild TBI early and characterize the associated neuro-degeneration in order to guide appropriate therapy. Our lab has developed a multimodal imaging probe, malBSA-DOTA(Gd+3/64Cu), that is targeted to microglia through SR-A type scavenger receptors which are overexpressed on activated microglia. The multimodal probe to be used in our multimodal imaging approach consists of maleylated (mal) bovine serum albumin (BSA) coupled to gadolinium (Gd3+) and 64Cu chelates (DOTA), allowing the use of MRI and PET modalities (Fig. 1).9 Mal-BSA serves as the ligand for SR-A scavenger receptors overexpressed on activated microglia. In previous work, we have confirmed the targeting and specificity of malBSA to activated microglia. We have also initiated the chemical modifications necessary for optimizing our probe design. First, we completed studies for optimizing the amount of probe ligand (maleyl groups) since maleylation is what gives the BSA molecule its SR-A targeting capability. Although our multimodal probe cannot readily cross a healthy blood brain barrier (BBB) due to its size and charge, it can transport across the BBB compromised in the lateral fluid percussion (LFP) model of TBI. We are working to confirm that LFP opens up the BBB and to identify the specific 'time window' for BBB opening, Once the time window of BBB permeability can be identified for this LFP model of TBI, then our multimodal imaging probe, malBSA-DOTA(Gd+3/64Cu), can be

appropriately administered for in vivo investigation of activated microglia following TBI. Overall, we anticipate that our SR-A targeted probe will be taken up more effectively in the TBI rat versus the Sham rat.

3. **Foad Mashayekhi**, Yin T. Chiu, Daniel T. Kamei, Alexander Le, Felix C. Chao (Advisor: Benjamin M. Wu), UCLA

Enhancing Rapid In-Field Detection of Biological Warfare Agents via Aqueous Two-Phase Systems

Biological warfare agents (BWAs), such as Ebola virus and ricin toxin, present great danger to the front line military personnel. Therefore, it is essential to provide the front line military personnel with a means to rapidly detect BWAs in-field before advancing into hostile territories. Due to the unique circumstances that the deployed military personnel operate under, the detection device needs to be light, small, and require minimal power. One approach that meets these requirements is the lateral-flow immunoassay (LFA), which has previously been used for detection of BWAs. LFA is an immunoassay that utilizes a test strip that collects a sample through lateral flow, and detects the presence of a target molecule through its specific antibody bound to a color indicator. Although LFA is an attractive option for rapid in-field detection of BWAs, the detection limit of LFA is still inferior to lab-based assays, such as the enzyme-linked immunosorbent assay (ELISA), and needs to be improved. One approach to achieve a higher sensitivity for LFA is to improve the assay itself. Another approach is to concentrate the target molecule prior to the detection step. In this project, we have focused on the latter approach. However, for the detection assay to still be implementable in-field, it is essential for the concentration step to also be implementable in-field, meaning it must be simple to perform, and require minimal training and power and no laboratory equipment. One approach that meets these criteria is liquid-liquid extraction using aqueous two-phase systems, such as aqueous two-phase micellar systems. Aqueous two-phase systems typically exhibit a homogeneous, isotropic phase at low temperatures. Upon increasing the temperature, the solution undergoes a macroscopic phase separation to yield two phases, one more hydrophobic than the other. Biomolecules would then distribute, or partition, unevenly between the two phases based on their physico-chemical characteristics, such as hydrophobicity and size. Our results showed that concentrating proteins, such as protein toxins, prior to a detection step via LFA may improve the detection limit of the immunoassay. The improved LFA could then be used in-field to rapidly and more reliably detect BWAs, such as ricin toxin. In the first part of this study, we successfully developed an LFA for

the detection of Tf in-solution, and established a detection limit of approximately 0.5 μg/mL for the immunoassay. In the second and final part of this project (which will be described in the final report), we will investigate the concentration of Tf using the aqueous two-phase Triton X-114 micellar system prior to its detection via LFA to investigate the effect of the concentration step on the detection limit of LFA.

4. **Jessica A. DeQuach**, Amar Miglani, Diane Hu (Advisor: Karen L. Christman) UCSD
An Injectable Decellularized Muscle Matrix for Skeletal Muscle Tissue Engineering

The aim of this study was to assess an injectable form of decellularized skeletal muscle matrix as a scaffold for skeletal muscle tissue engineering, and to determine the cellular influx into the scaffold in a hindlimb ischemia model. The skeletal muscle matrix was injected intramuscularly to determine gelation properties and compared to a collagen scaffold. Skeletal muscle matrix material was derived through decellularization of porcine skeletal muscle tissue using detergents, similarly to a previously published protocol from our lab. After complete decellularization, the skeletal muscle matrix was frozen, sectioned and stained using H&E to confirm removal of nuclear content. The matrix was characterized for protein content, glycosaminoglycan content, and protein composition was identified using mass spectrometry. Using a proliferation assay, both skeletal muscle progenitor cell and smooth muscle cell were found to increase proliferation when cultured with the skeletal muscle matrix added to the media when compared to the collagen. Scanning Electron Microscopy (SEM) demonstrated that the self-assembled skeletal muscle matrix forms a porous, fibrous scaffold that is composed of fibers both on the nano- and micro-scale. The harvested tissue was sectioned and stained for specific markers that would demonstrate whether the skeletal muscle matrix would serve as a better scaffold for skeletal muscle tissue engineering. Muscle cell infiltration was measured using antibodies to stain for desmin as well as MyoD. The desmin positive cells were also co-stained for Ki67 to quantify whether the cells were additionally proliferating, as Ki67 is a known proliferation marker. The skeletal muscle matrix recruited more desmin-positive cells when compared to the collagen matrix. Additionally, the majority of cells expressing desmin also were Ki67 positive, indicating proliferating muscle cells were infiltrating the injection region. MyoD positive cells would indicate the recruitment of activated satellite cells. It was found that there were a low number of MyoD positive cells that were recruited into either injection region, but there were more MyoD cells in the skeletal muscle matrix, especially at earlier time points. Finally, endothelial cell staining was also

studied, as early capillary formation could be potentially important for bringing blood flow back to the ischemic region. It was found that endothelial cell staining was similar in both materials, with an increase in the skeletal muscle matrix at days 3 and 5. As endothelial cell staining may demonstrate capillary formation, it is well known that capillaries can retract if not utilized, and it is not as indicative of a marker of blood flow regeneration compared to arteriole formation. Neovascularization was measured in the skeletal muscle matrix and compared to collagen injection regions by staining for smooth muscle actin and quantifying arteriole density. Vessels with a lumen > 10 μm were quantified and normalized to the injection site. It was found that arteriole density was much greater in the skeletal muscle matrix injection region than collagen, and that many of the vessels had an average diameter greater than 25 μm. The larger vessels found in the skeletal muscle matrix suggest that the vessels that formed were mature, and more likely to be permanent. To briefly summarize, The skeletal muscle matrix can be relyophilized, stored long term at -80^{o}C, so that sterile water is needed prior to resuspension and injection, making the material an off-the-shelf treatment and more clinically relevant. After resuspension, the skeletal muscle matrix is able to self-assemble and form a gel in vivo after injection into a rat hindlimb ischemia model. There was high cellular infiltration into the skeletal muscle matrix when compared to collagen, with more muscle cells recruited into the injection region. Additionally, arteriole density was much greater in the skeletal muscle matrix injection sites at earlier time points when compared to collagen, however it must be noted that at 2 weeks, the injection site was difficult to locate due to extensive extracellular matrix degradation and remodeling. The increase vessel formation is promising, as bringing blood flow to the ischemic region could help preserve the tissue after damage.

5. **Yiqian Eugene Zhu**, Aijun Wang, Shyam Patel (Advisor: Song Li), UC Berkeley
Peripheral Nerve and Spinal Cord Regeneration Using Nanofibrous Scaffolds and Neural Crest Stem Cells

Spinal cord injury (SCI) remains a major challenge for regenerative medicine. Following SCI, axon growth inhibitors and other inflammatory responses prevent functional recovery. Previous studies have demonstrated that rolipram, an anti-inflammatory and cAMP preserving small molecule, improves spinal cord regeneration when delivered systemically. However, there is evidence that rolipram has toxic effects on spinal cord repair. Here, we developed a drug-delivery platform for the local delivery of rolipram into the spinal cord. Impressively, drug-eluting nanofibrous patches continuously delivered rolipram for 7 days

in vitro. After C5 hemisections, athymic rats were treated with patches loaded with low and high doses of rolipram. Animals treated with low-dose rolipram experienced greater functional and anatomical recovery relative to all other groups. Outcomes from the high-dose rolipram treatment were similar to those with no treatment. In addition, high-dose treated animals experienced reduced survival rates suggesting that systemic toxicity was reached. With the ability to control the release of drug doses directly into the spinal cord, drug-eluting nanofibrous patches demonstrate the importance of appropriate local release-kinetics, proving their usefulness as a therapeutic platform for the study and repair of SCI. A high-efficiency protocol has been developed to derive neural crest stem cells (NCSCs) from human induced pluripotent stem cells (iPSCs), which had been reprogrammed from adult human somatic cells. After characterization in adherent 2D and neurosphere 3D cultures and following electrospinning, the NCSCs were transplanted in conduit of sciatic nerve that had been disrupted in mice. The transplanted NCSCs can develop into multipotent-peripheral neurons and Schwann cells, thus improving nerve regeneration in vivo. This is evidenced by the enhanced electrophysiological recovery and improved nerve regeneration (axonal regeneration and myelination). Thus, this approach provides a great potential of using NCSCs for tissue regeneration, especially the NCSCs derived from patient-specific iPSCs; this would obviate immunological problems associated with non-self iPSCs.
[Presented in the Appendix as "Drug-Eluting Microfibrous Patches for the Local Delivery of Rolipram in Spinal Cord Repair" by Timothy L. Downing, Aijun Wang, Zhi-Qiang, Yan Yvette Nout, Andy L. Lee, Michael S. Beattie, Jacqueline C. Bresnahan, Diana L. Farmer, and Song Li.]

BIC/UC Santa Barbara Grand Challenge Competition in 2011

As mentioned above, although there was no funding from TATRC for a new round of Grand Challenge Competition at the 12th System-wide Symposium at Santa Barbara, the meeting organizers were successful in organizing a session on Grand Challenge Competition with a greatly reduced budget. Out of twenty-five applicants, nine semi-finalists were chosen to give presentation in the afternoon of June 13, immediately before the TATRC Grand Challenge session mentioned above in a session chaired by Dr. Samir Mitragotri of UC Santa Barbara. The nine students made superb presentations that stirred many meaningful discussions. Following rigorous review using the guidelines established at the 11th System‐wide Symposium, three winners were chosen, with Timothy Downing

of UC Berkeley receiving the top prize. The names of the presenters, their topics, and campus of origin are shown below:

Sandeep Bhat, Michael Liebling, UC Santa Barbara: Improving Specificity in BrightField Microscopy Images of the Beating Embryonic Heart Via MotionBased Separation.

Justin Lee, Eyal Dassau, Howard Zisser, Lois Jovanovic, and Francis J. Doyle III, UC Santa Barbara: Semi-automated Artificial Pancreas using prandial inhaled insulin and Zone Model Predictive Control.

Carolyn Schutt, Michael Benchimol, Mark Hsu, Sadik Esener, UCSD: Ultrasound Modulated Fluorescent Contrast Agent for Optical Detection of Cancer Lesions in Deep Tissue.

Jiawen Li, Jiehen Yi, Xiang Li, Joe Jing, David Mukai, Sari Mahon, Ahmad Edrisd, Khiet Hoang, K. Kirk Shung, Matthew Brenner, Jagat Narula, Qifa Zhou, and Zhongping Chen, UC Irvine: Miniature Integrated Optical Coherence Tomography (OCT) ultrasound (US) probe for intravascular imaging.

Seung Soo Oh, Minseon Cho, H. Tom Soh, UC Santa Barbara: Structure‐switching Aptamer Array for Reagentless, Label-Free Multiplexed Detection of Proteins in Clinical Samples.

Ting Wei Su, Anthony Erlinger, Derek Tseng, and Aydogan Ozcan, UC Riverside: Lensless On chip Microscope as a Portable Semen Analysis Device.

Timothy L. Downing, Aijun Wang, Zhi Qiang Yan, Andy Lee, Song Li, UC Berkeley: Drug Eluting Nanofibrous Patches Demonstrate Importance of Release Kinetics in Spinal Cord Repair.

Pasha Hadidi, Kyriacos Athanasiou, UC Davis: Lysophosphatidic Acid: A Novel Biochemical Agent for Tissue Engineering Fibrocartilage.

Key Research Accomplishments

The key research accomplishments are:

A. Successful follow-up of the *Meeting of TATRC* Sponsored *"Grand Challenge" in Military Medicine Research.*

B. Successful planning of the BIC / UC Davis / UC Santa Barbara Sponsored Meetings of *"Grand Challenge" in Military Medicine Research*.

C. Increase of awareness of military-specific interests and requirements among members of the University of California (UC) research community.

D. Enhancement of the exposure of the research community to the needs of the military and to DoD funding opportunities.

E. Encouragement of researchers to address key problems in military medicine, and to adopt an applied, product-oriented approach to research.

F. Successful generation of many excellent applications to the Grand Challenge and the successful selection of outstanding winners by a rigorous process.

Reportable Outcome

The activities and follow-up of the System-wide Symposia held in 2010-2012 have summed up the outstanding research on bioengineering foundation and therapeutic approaches to diseases that inflict military and civilian patients, as well as the processes of innovation and how to address this in research and development, especially for students. These activities also generated extensive interactions of UC with industry and government that led to facilitation of student career development in addressing problems of importance to military and civilian medicine. The superb presentations and discussions of the TATRC Grand Challenge winners from 2010 and the Grand Challenge semi-finalists in 2011, as well as their follow-ups (including one that has been planned for December 11, 2012, at UC San Diego), were made possible by the valuable support by TATRC that allowed the winners to further pursue their promising projects and give their progress reports.

Conclusions

The *Meetings of TATRC Grand Challenge in Military Medicine Research* held at the UC System-wide Symposia at Davis and Santa Barbara, with their follow-up, has been great successes. They accomplished the specific aims of the Meeting to: increase the awareness of military-specific interests and requirements among members of the UC research community, to enhance the exposure of the research community to the needs of the military and to DoD funding opportunities, to encourage researchers to address key problems in military medicine, and to encourage an applied, product-oriented approach to research.

The Grand Challenge led to outstanding presentations on the bioengineering basis and therapeutic approaches for diseases that inflict military and civilian patients and on research and development relevant to innovation. It synergized the activities of faculty and students of the UC campuses and their interactions with industry and government and facilitated student career development in addressing problems of importance to military and civilian medicine.

The outstanding research studies carried out by the five 2010 Challenge Award winners and by the eight 2011 finalists were the most important outcomes that underscore the full realization of the goals of the TATRC grant.

Packaging and Replicating Proof of Concept Program to accelerate the translation of University discoveries with application of military medicine

Introduction

In the first Wireless Health Technology Acceleration Program focused in Southern California, the von Liebig Entrepreneurism Center, TATRC and Qualcomm sought to leverage the unique combination of established telecommunications, medical device, and life sciences innovation clusters in Southern California to accelerate the translation of mobile healthcare from universities and research institutes to meet the medical needs of the soldier and their families. The following were the specific objectives of this pilot program:

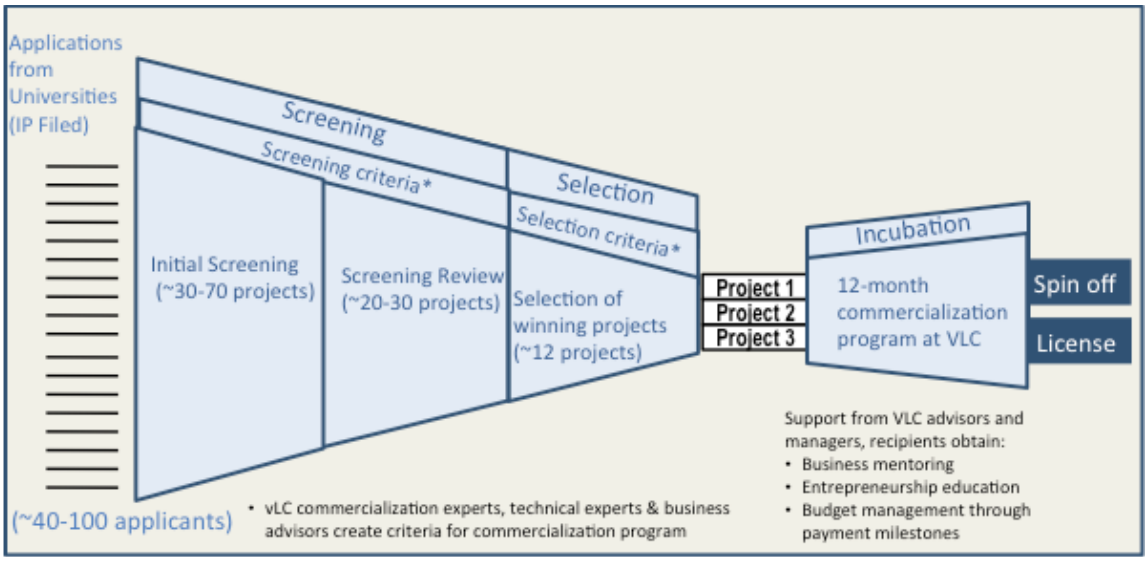
1. Develop a methodology to conduct regional proof of concept programs that is available to multiple universities and research institutes in a broad geographical region.
2. Test methodology in the form of a pilot TAP focused on wireless health and that includes
universities and research institutes in Southern California.
3. Package and adapt this program into regional innovation challenges that under TATRC leadership can be duplicated in other regions in the country.

Throughout the year, the PI working with the team of technology and business advisors, MBA students, and technical experts, has been focused on ensuring that all three projects completed successfully their goals by the project end date of September 2012. Funding from TATRC allowed the PI working with strategy business advisors and higher education leaders, to define package, the vlC model to be replicated the TAP program for accelerating basic research from regional universities.

Body

Methodology Development and Pilot Challenge Implementation

The von Liebig Entrepreneurism Center modified and streamlined its processes and procedures to facilitate the application and implementation of the regional Wireless Health Technology Acceleration Program. This included identification of best processes to reach faculty/student teams from multiple institutions, provision of virtual mentoring services, application process, program monitoring and intellectual property issues. Funding provided by TATRC and Qualcomm allowed for three innovation teams of faculty/student researchers to receive up to $90,000 in proof of concept grants, along with extensive commercialization-directed advisory services from the von Liebig Center, for one year. Successes were made in institutionalizing the process of fund transfer amongst the von Liebig Center, the Henry Jackson Foundation and the awardees' universities. The Technology Acceleration Program Process has been defined and packaged for efficient screening, selection and incubation of highly commercially-viable university discoveries (Figure 1).



Screening Phase / Project Intake / Pre-award phase Screening Process
During the screening process, applications from universities and research institutions in the Southern California Region were collected through outreach from the von Liebig Center. Applicants were first required to submit a statement of intent (SOI), including an overview of the technology and proposed application, its relevance for military medical applications and commercial potential. SOIs guided recruitment of a suitable panel of independent expert judges and facilitated the initial screening of applicants based on eligibility, stage of development, and program fit. Following a secondary screening, invitations were administered to submit a full proposal. One of the requirements of this process was that the inventor files at least a provisional patent with their institution's patent office. During this period, the vLC Center received 45 Statement of Intents (SOIs) from 13 different institutions (universities and research institutions) and 26 different departments from universities in Southern California.

Screening Criteria
The eligibility of incoming projects were:
• Candidate projects must involve technologies directed toward the field of "Wireless Healthcare" applications. These include:
  - Tools for behavioral health management (e.g., mechanisms for secure social networking to support behavioral health patients, or anger management tools for patients suffering from post-traumatic stress syndrome)
  - Tools for the management of chronic diseases, smoking cessation, etc.
  - Tools to aid rehabilitation of motor skills and balance
  - Technologies to enable remote clinical consultation
  - Physiological sensing (e.g., for home monitoring applications, or the integration of bodyworn sensors that use Bluetooth in civilian environments, but ultra-wideband (UWB) for short-range communications between "mobile devices" and sensor in deployed environments)
  - Patient education (e.g., health and wellness information)
• Participating faculty and researchers must have a current affiliation with a university or

research institute located in Southern California
• The PI must be a faculty member, or a graduate student affiliated with a faculty member who is an active participant in the project
• The technologies (inventions) should be protected, minimally by provisional patents filed in collaboration with the inventor's respective technology transfer office

Selection Process
Experts from the community, funders and vLC staff conducted the next phase, the selection of suitable projects. Of the 45 statements of intent (SOIs), 12 highly-competitive projects were selected to submit full proposals, with an additional 3 selected as alternates in the case that one of the original 12 was unable to complete their proposal. These top twelve candidates were assigned a business advisor who worked with them for 4 weeks to prepare for a presentation to an expert panel of reviewers composed of experts from TATRC and subject matter experts.

Summary
The von Liebig Center for Entrepreneurism and Technology advancement has successfully completed the Wireless Health Technology Acceleration Program supported by grants from TATRC and Qualcomm. This pilot program aimed to catalyze the translation of wireless health technologies from Universities and Research Institutes in Southern California. Three projects from a pool of 45 applications representing 13 institutions in the region were selected to receive a total of $275,000 in proof of concept funding and business mentoring. All three awardees worked with an assigned von Liebig Business Advisor that helped them put together a milestone-based development plan that was to be implemented during a 12 month period.
Strong mentorship and due diligence led to significant technical progress and commercialization plans that have resulted in the creation of three startup companies that will continue the commercialization of the TATRC/Qualcomm funded technologies beyond the funded period:
1. Farus, out of UC Los Angeles
2. Fluid Synchrony, out of University of Southern California
3. Nanovision Bioscience, out of UC San Diego
All projects have been able to successfully receive follow-up funding for their next steps in the commercialization process, encompassing a variety of funding types (angel funding, NSF grant, and SBIR funding). Funding from the TATRC/Qualcomm innovation challenge allowed the vLC to expand its TAP (Technology Acceleration Program) model to the Southern California Region and secure additional funding from the California Healthcare Foundation, Booz Allen Hamilton and the Robert Wood Johnson Foundation to conduct another regional program focused on identifying technologies that will lower the cost of delivering healthcare to underserved populations. The outcomes of these two programs are documented : Ochoa R, et al. Accelerating the Commercialization of University Technologies for Military Healthcare Applications: the Role of the Proof of Concept Process. SPIE Defense, Security, & Sensing and Accelerating Commercialization of Cost-Saving Health Technologies. May 2012 (White Paper)
The following are recent highlights of the projects funded by this program:

1. Auxiliary Haptic Feedback on Gait Training & Activities of Daily Living
team led by Dr. Warren Grundfest, Bioengineering, UCLA, von Liebig Business Advisors: Steve Flaim and Hal DeLong
Based on a haptic technology platform previously developed for providing tactile feedback in robotic surgery, the team has developed a portable haptic feedback system for conveying plantar pressure information to patients with sensory impairments by means of pneumatic silicone balloon actuators placed against the skin of the patient's thigh. The purpose of this project, therefore, was to develop and validate a platform whereby wireless patient activity monitoring technology may be used to evaluate the ongoing effects of haptic feedback on the gait and mobility of patients with lower limb sensory deficits throughout the course of daily life.

Main Technical Accomplishments
Collection of biomechanical gait data using both optical motion tracking technology and MDAWN sensors proved to successfully show integration through a clinical study at the Naval Medical Center, San Diego (NMCSD). The MDAWN sensors provide reliable data that can be used for accurate gait analysis. This finding serves to validate the use of MDAWN sensors for future work to evaluate the effects of haptic feedback on prosthetic gait outside of the gait lab environment, throughout the course of activities of daily living. The packaging and ergonomics of the haptic system components included the improvement of the actuator design for half its thickness and expanded on the sensors' analytical capabilities for increased usage time. A dual haptic feedback system has been developed for bilateral neuropathy patient, using an alternative system configuration that takes sensor inputs from two sensorized shoe insoles and gives tactile feedback to two tactile interfaces – one worn on each leg. They remain active in their patient recruitment and data collection and analysis efforts. With both NMCSD and UCLA collaborators, they have successfully established an agreement that all new patients that meet their inclusion criteria will be referred for their study.

Commercialization Outcomes
Former UCLA students from Dr. Grundfest have formed a startup company named FARUS LLC, to commercialize the haptic feedback technology. This company has already received a phase II SBIR and is in the process of licensing the technology from UCLA. Jacqueline Glynn, a Rady School of Management MBA led a team of MBA students that developed a business plan for the technology. This plan was shared with Farus LLC and discussions were held to explore potential partnership to facilitate further engagement to accelerate commercialization of the technology.

2. Wireless Electronic Drug Infusion Pumps for Telemedicine
team lead by Ellis Meng, Ph.D., Biomedical and Electrical Engineering, USC, von Liebig Business Advisor: Mike Krupp, Ph.D.
The project made significant progress toward the development of a high-performance drug delivery micropump with a high level of accuracy capable of delivering a diverse assortment of drugs at the right dose, to the right tissue, and at the right time over the entire course of treatment.

Main Technical Accomplishments
A just-in-time drug delivery micropump has been developed with an electrolysis actuator, refillable reservoir with flexible cannula, a microfluidic catheter flow regulation and valving and integrated microsensors. The unique implantable device has a much smaller form factor than commercially-available alternative and contains a wireless power source and connectivity. The pump mechanism has been improved for higher accuracy, an adjustable dosing scheme and reduced power and low heat. Along with perfecting the 2-way data transmission technology and prototyped electronics for integration into their proprietary pump platform, they have demonstrated a completely wireless-operated drug delivery system with unprecedented high performance, wide range of flow rates, and on-demand electronic control. These technical advancement allow for a high level of accuracy capable of delivering a diverse assortment of drugs at the right dose, to the right tissue, and at the right time over the entire course of treatment.

Commercialization Outcomes
Dr. Ellis Meng and her team have founded Fluid Synchrony LLC focused on the commercialization of the wireless pump technology. The company is currently negotiating with the USC technology transfer office the exclusive license of the technology and creating a website for the company. They have been able to secure an NSF iCORP grant to ensure the commercialization viability of the product and their start-up company. Dr. Meng is also actively seeing funding from investors and SBIR for further technology development.

Accomplishments by Von Liebig Center
The vonLiebig Center demonstrated the extension of a regional TAP (Technology Acceleration Program) to the Southern California region. This allowed for the vonLiebig Center to become the thought leader on technology acceleration of university discoveries in a methodical and successful manner. The vonLiebig Center successfully screened 45 wireless healthcare technologies, selected the top12 for more screening by more experts, and picked 3 projects with highest potential for commercialization. This process decreased risk and increase rate of commercialization success by decreasing risk of funding many technologies in a specific functional area, increasing the development of a functional prototype of a need in wireless health, and increasing the success rate of university discoveries through giving gap funding and business advising to basic research innovations through their commercialization process. Within the one-year program, the vonLiebig Center was also able to coordinate the use of entrepreneurial experts. The vonLiebig Center successfully recruited a panel of experts and funders who selected 3 projects for commercialization assistance that showed the most promising need in the marketplace coupled with an excellent technical innovation and a powerful development team. Then, the vonLiebig Center successfully managed these 3 projects from discovery to prototypes through a robust milestone system. Both technical and business milestones were tracked and reviewed by business advisors and commercialization experts. Therefore, as a result of careful management, accountability, and expertise, the vonLiebig Center successfully assisted in the creation of 3 start-up companies.

REPORTABLE OUTCOMES

1. **Liu BJ,** A Knowledge-Based Imaging Informatics Approach for Managing Proton Beam Therapy Treatment of Cancer Patients, *Technology in Cancer Research and Treatment,* V. 6, No. 4 Supplement, pp. 77-84, 2007.
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3. Law, MYY, **Liu BJ,** Chan WC, An ePR-based Radiation Therapy Information System Utilizing the DICOM-RT Standard. *Radiographics,* V.29, No. 4, pp. 961-972, 2009.
4. Le A, Schulte R, Liu BJ, A Proton Therapy Electronic Patient Record Based on DICOM-RT and DICOM-RT-ION for Archiving, Distributing, and Visualizing Treatment Plans and Outcome Data, ASTRO 2009, Chicago, IL.
5. Le A, Documet J, Sullivan A, **Liu BJ**, A prototype of image-guided outcome analysis for prostate proton therapy patients based on DICOM-RT ePR, Proceedings of SPIE Medical Imaging 7264:72640L, 2009.
6. Accepted Oral Presentation at the SPIE Medical Imaging Conference, Feb 2010, San Diego, CA.
7. Ochoa R, et al. Accelerating the Commercialization of University Technologies for Military Healthcare Applications: the role of the proof of concept process. SPIE Defense, Security, & Sensing.
8. Accelerating Commercialization of Cost-Saving Health Technologies. May 2012 (White Paper)

CONCLUSION

Task 1:

As a first step towards the long-term research goals and objectives, initial data models and clinical workflow models for Proton Therapy were investigated to determine the impact of integrating these new RT objects into the ePR system. A medical imaging informatics approach was applied to Proton Therapy for treatment planning of cancer patients. This methodology was utilized for the design and development of and ePR system with standardized DICOM-RT-ION data. With the ePR system and standardized data, future quantified knowledge and decision-support tools can be developed and evaluated for outcomes analysis to ultimately improve the overall patient care utilizing Proton Therapy.

This methodology together with the DICOM-RT based ePR system can serve as a foundation for future decision-support research and outcomes research in a new frontier of Proton Therapy.

Task 2:

The HJF has provided its administrative, management and technical expertise to assist the USAMRMC/TATRC in the development of its long-term generation portfolio and investment strategy in this regional effort. The HJF's experience in facilitating medical research in support of the warfighter, as well as personnel strengths with local assets in

Southern California made its capabilities uniquely valuable in support of TATRC's expanding strategic research initiatives. HJF specialists have worked closely with USAMRMC/TATRC scientists and research managers evaluating the impact of regional management of coordinated research efforts.

Research efforts have focused on helping develop new, leading- edge research and development initiatives (e.g. embedded training) in the western US, including facilitating creation of robust, productive working relationships with nationally unique assets found only in the Pacific/West region (e.g. University of Southern California's Institute of Creative Technology). Additional military research investigations have focused on establishing proven and successful TATRC business practices, and developed new practices and methods as needed in the Pacific/West region, as well as creating a dynamic process through which to transition selected technologies from advanced research to advanced development.