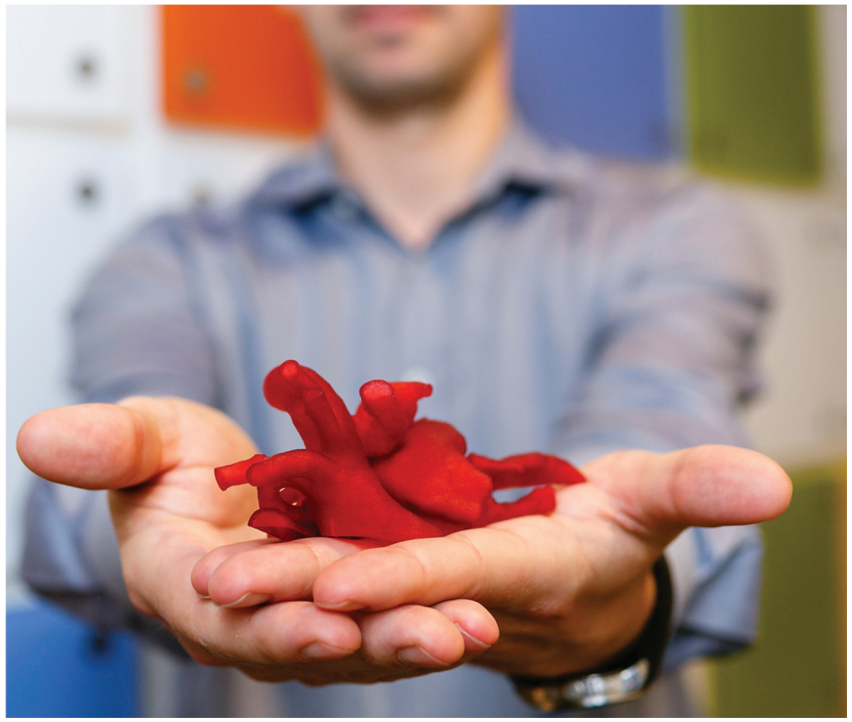

The Sheikh Zayed Institute for Pediatric Surgical Innovation

Annual Scientific Report 2012 – 2013

Children's National™

Sheikh Zayed Institute
for Pediatric Surgical Innovation

Part of the Children's National Health System

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EXECUTIVE SUMMARY

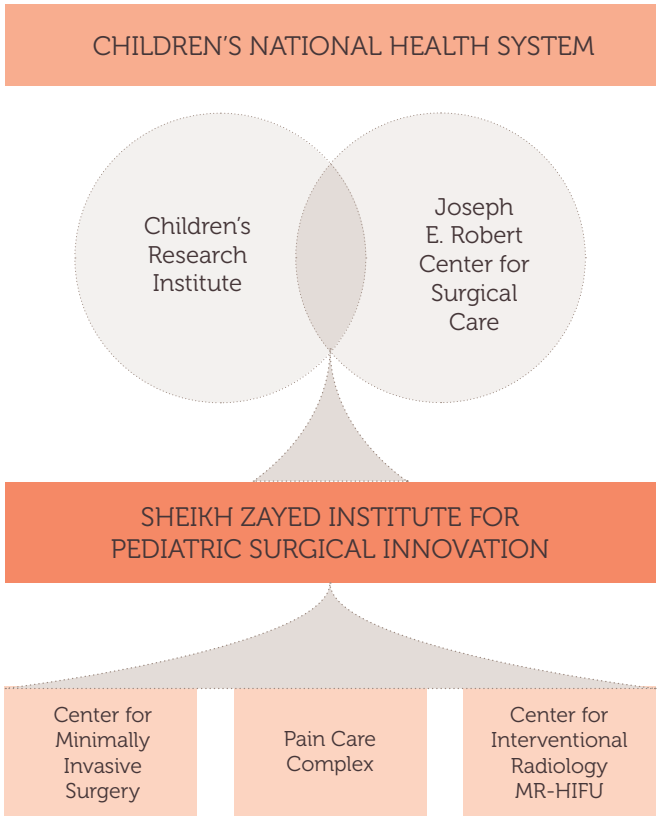
Our mission is to make pediatric surgery less invasive, more precise, and pain-free. We are agile and provide a research and development infrastructure for innovators who bring solutions to improve the health of children.

Each year, millions of newborns and children around the world undergo strenuous surgical procedures to improve their health and even save their lives. While pediatric surgery is advancing, new research-based solutions and products are necessary in order to help children thrive. Unfortunately, there remain formidable barriers to pediatric product development, which has historically lagged behind the adult medical research market. These barriers are characterized by the technical, business, testing, and regulatory complexities of research and development (R&D). In addition, there is a great need for broader support among the business community so that we can collectively bring pediatric products to market more quickly.

To address these challenges, the Sheikh Zayed Institute for Pediatric Surgical Innovation has galvanized leading experts from many industries to harness the most innovative thinking. Our multidisciplinary approach enables us to accelerate R&D to better support young lives. Through shared innovation and a spirit of collaboration, thought leaders spanning many industries—nonprofit, academia, corporate, advocacy, and healthcare—join forces to successfully support pediatric product development for children everywhere. The Institute's highly innovative team of physician-scientists, engineers, researchers, and business professionals work together to:

- Solve the problem of diagnosing and treating pain in children
- Promote technologies that enable surgeons to operate with more precision
- Develop non-invasive surgical solutions
- Teach a child's own immune system to fight illness
- Create educational opportunities to train the next generation of clinician-innovators and entrepreneurs

We are pleased to report that in this reporting period, the Sheikh Zayed Institute made great progress. Specifically, we further strengthened our internal and external partnerships, advanced many of our projects in all development phases, and attained highly prestigious external funding grants. The Sheikh Zayed Institute was made possible by a historic philanthropic gift from the Government of Abu Dhabi, which shares our vision to make surgery more precise, less invasive, and pain-free for children. As a leader of healthcare innovation in pediatrics, we work to translate groundbreaking ideas into lasting results for children, bringing solutions from the lab bench to the patient's bedside faster. By thinking differently and innovatively, we will continue to redefine what is possible in pediatric surgery so that children around the world can live healthy, vibrant lives.



A MESSAGE FROM THE VICE PRESIDENT

I am pleased to present the Sheikh Zayed Institute's second scientific report, highlighting the Institute's progress from October 1, 2012, through September 30, 2013. During the past year, we continued to re-imagine the way we care for vulnerable children around the world so that they can live healthy, vibrant lives. By fostering a robust culture of innovation, our team made significant achievements for children. In the following pages, you will read about our major accomplishments and a synopsis from each project.

As a young institute, we recognize that while innovative ideas are the lifeblood behind our work, without applying critical principles of discipline and practice, new ideas may never fully flourish. In order to harness ingenuity and make real strides, we rigorously applied business discipline to an innovation model by continuing to employ the stage-gate process, with participation from internal and external unbiased experts. In addition, we practiced various innovation techniques in order to determine what works best. Finally, we continued to enhance the culture of innovation at the Sheikh Zayed Institute by infusing principles of innovation and entrepreneurship into everything we do.

Being accountable to our major stakeholders, we understand that our innovation succeeds only if we can produce lasting results for children in need. Our cumulative returns must exceed the investment that was made in our Institute. As such, in the coming year, our innovators will continue to promote the **discipline**, **practice**, and **culture** of innovation that will ultimately bring new products to market for our children, and place the Institute in the highest national and international position of leadership in pediatric surgical innovation.

We continue the trust of our founders to make pediatric surgery more precise, less invasive, and pain-free for children around the world.

Peter C. W. Kim, MD, CM, PhD


Transforming Pediatric Surgery and Device
Innovation through the Discipline, Practice,
and Culture of Innovation
Children's National
SHEIKH ZAYED INSTITUTE for Pediatric Surgical Innovation


Children's National
Children's National

LEADERSHIP

VICE PRESIDENT
Peter C. W. Kim, MD, CM, PhD

EXECUTIVE DIRECTOR
Kolaleh Eskandanian, PhD, MBA, PMP

PAIN MEDICINE
Julia Finkel, MD
Zenaide Quezado, MD

BIOENGINEERING
Raymond Sze, MD
Kevin Cleary, PhD

IMMUNOLOGY AND SYSTEMS BIOLOGY
Anthony Sandler, MD
Peter C. W. Kim, MD, CM, PhD
Catherine M. Bollard, MBChB, MD

EDUCATION
Craig Peters, MD

LEADERSHIP

Executive Oversight Committee

Anthony Sandler, MD, Chair
Kurt Newman, MD, Voting Member
Mark Batshaw, MD, Voting Member
David Wessel, MD, Voting Member
Peter C. W. Kim, MD, CM, PhD, Voting Member
Raymond Sczudlo, JD, Ex Officio
Kolaleh Eskandanian, PhD, MBA, PMP, Ex Officio
Pam King Sams, CFRE, Ex Officio
Her Excellency Professor Maha Barakat, MB, PhD, Non-Voting Observer

Scientific Advisory Committee

Keith Georgeson, MD, Chair, Lead Physician of Procedural Services, Providence Medical Group
Brian Duncan, MD, MBA, VP, BioEnterprise
Nawal Al Kaabi, MBBS, ABP, FRCPC, Division Head, Pediatric Infectious Disease, Sheikh Khalifa Medical City
Mohamed Hamdan, MD, Head, Division of Pediatric Cardiology, Tawan Hospital
Bala Balachandran, PhD, Chair of Mechanical Engineering, University of Maryland
Tomer Kagan, CEO Quixey
Elliott McVeigh, PhD, Director, Dept of Biomedical Engineering, Johns Hopkins University School of Medicine
Hamid Rabb, MD, Vice Chairman, Johns Hopkins University School of Medicine
Benno Ure, MD, PhD, Vice Chief Executive Officer, Hannover Medical School

Business Advisory Council

Brian Duncan, MD, MBA, Co-Chair, VP, BioEnterprise
Maggie Kavalaris, JD, Co-Chair, Partner, Dentons US LLP
David Schlitz, JD, Partner, Baker Botts LLP
Nate Gross, MD, MBA, Medical Director, Rock Health
Steven Ferguson, CLP, Deputy Director, NIH Tech Transfer
Craig Dye, Director, Mtech Ventures
Ali Behbahani, MD, MBA, Principal, NEA
Martha Connolly, PhD, Director, Maryland Industrial Partnerships
Amanda Sammann, MD, MPH, Medical Director, IDEO
Josh Makower, MD, Partner, NEA

Research Advisory Committee

Mendel Tuchman, MD, Chair
Naomi Luban, MD
Mark Batshaw, MD
Peter Scheidt, MD
Patricio Ray, MD
Stephan Ladisch, MD

GROWTH MILESTONES

2009

SEPTEMBER
Announcement for the establishment of the Sheikh Zayed Institute for Pediatric Surgical Innovation, thanks to a gift pledge from the Government of Abu Dhabi

DECEMBER
Key faculty hires begin for each initiative

2010

MARCH
Construction begins for the home of the Institute at the top of Children's National

DECEMBER
The Sheikh Zayed Institute and University of Maryland A. James Clark School of Engineering jointly awarded seven pilot and exploratory projects to foster collaboration between the two institutions

1st

DECEMBER
First HIFU clinical research protocol

OCTOBER
First Leadership in Innovation Summit gathers leaders from Children's National and The George Washington University

OCTOBER
The First-in-Human clinical trial for the Pain Algometer begins

2013

JANUARY
The Pain Medicine Care Complex opens its doors

JANUARY
Charles Berul, MD, a cardiology expert joins the Institute

MAY
The Institute convenes its first Business Advisory Council

JUNE
The Institute hosts the first International Symposium on Pediatric Surgical Innovation

JUNE
The Institute presents its inaugural Sheikh Zayed Prize for Pediatric Surgical Innovation to Heung Bae Kim, MD, of Boston Children's Hospital

MARCH
The Institute's first patent filed for "Apparatus and Method for Human Algometry"

APRIL
Doors open to the Sheikh Zayed Institute for Pediatric Surgical Innovation

JULY
Peter C. W. Kim, MD, CM, PhD, is named Institute's Vice President

JULY
Inaugural Class of Robert Fellows and Student Innovators

OCTOBER
Institute's Investigator, Raj Shekhar, PhD, receives Institute's first STTR award from NIH

DECEMBER
First Scientific Advisory Committee meets

2011

SEPTEMBER
R21
The Institute's Investigator, Sarah Rebstock, MD, receives the Institute's first R21 award from NIH

SEPTEMBER
In collaboration with the Institute, Children's National opens new operating room with intraoperative MR capability that also allows for HIFU experiments

FEBRUARY
R01
Institute's Investigator, Diego Preciado, MD, PhD, receives the Institute's first R01 award from NIH

DECEMBER
Arrival of the da Vinci Robot with additional console for learning opportunities

2012

JULY
Catherine M. Bollard, MBChB, MD, an immunology expert, joined the Institute

JULY
The Institute hosts 31 Summer Student Innovators and implements the first Medical Hackathon

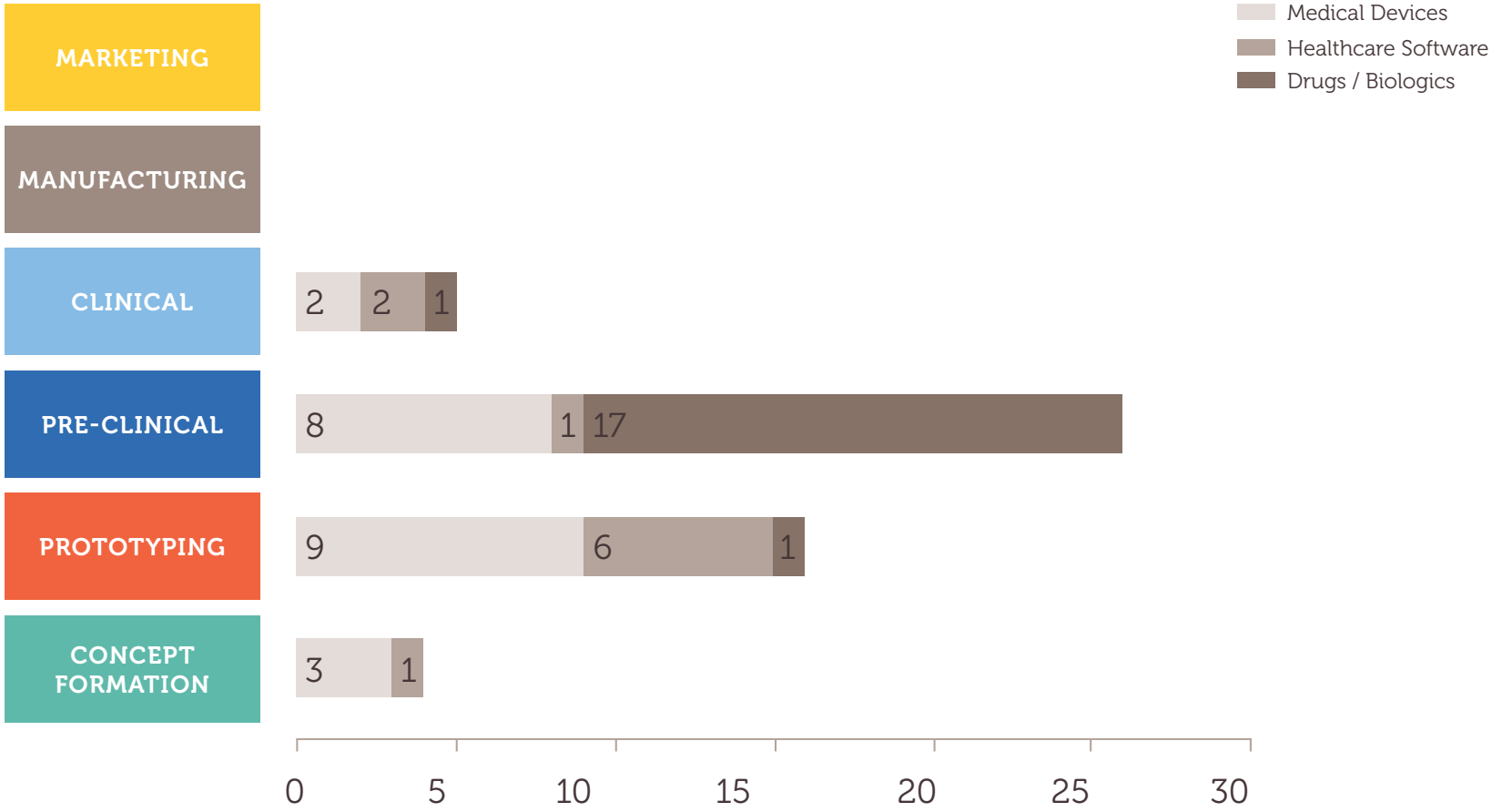
AUGUST
R01
Kevin Cleary, PhD, receives an R01 award from NIH National Cancer Institute

SEPTEMBER
P50
The Institute receives Food and Drug Adminstration's prestigious P50 award to form the National Capital Consortium for Pediatric Device Innovation


Anthony D. Sandler, M.D.
Chief, Division of Surgery

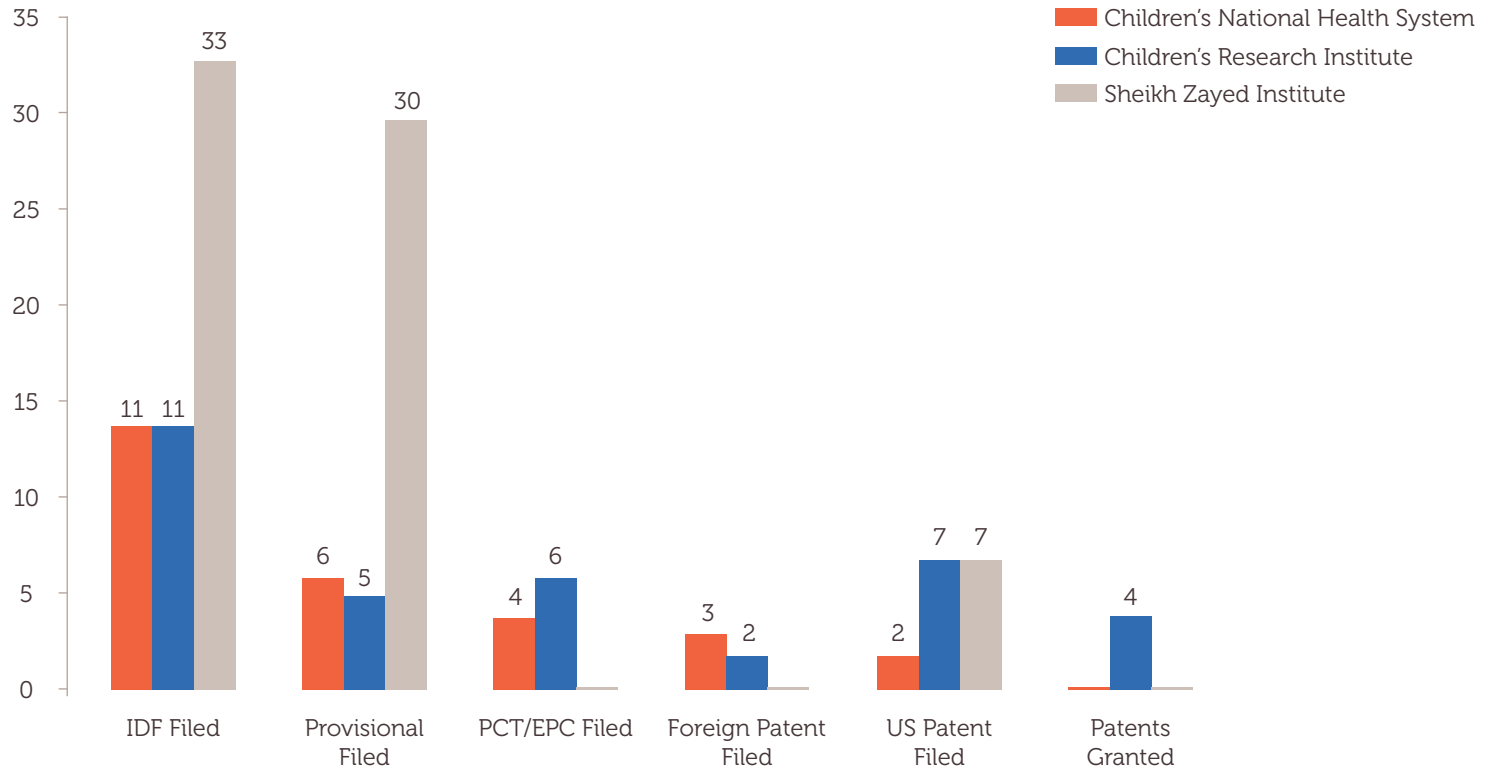

Children's National

PROJECT PORTFOLIO

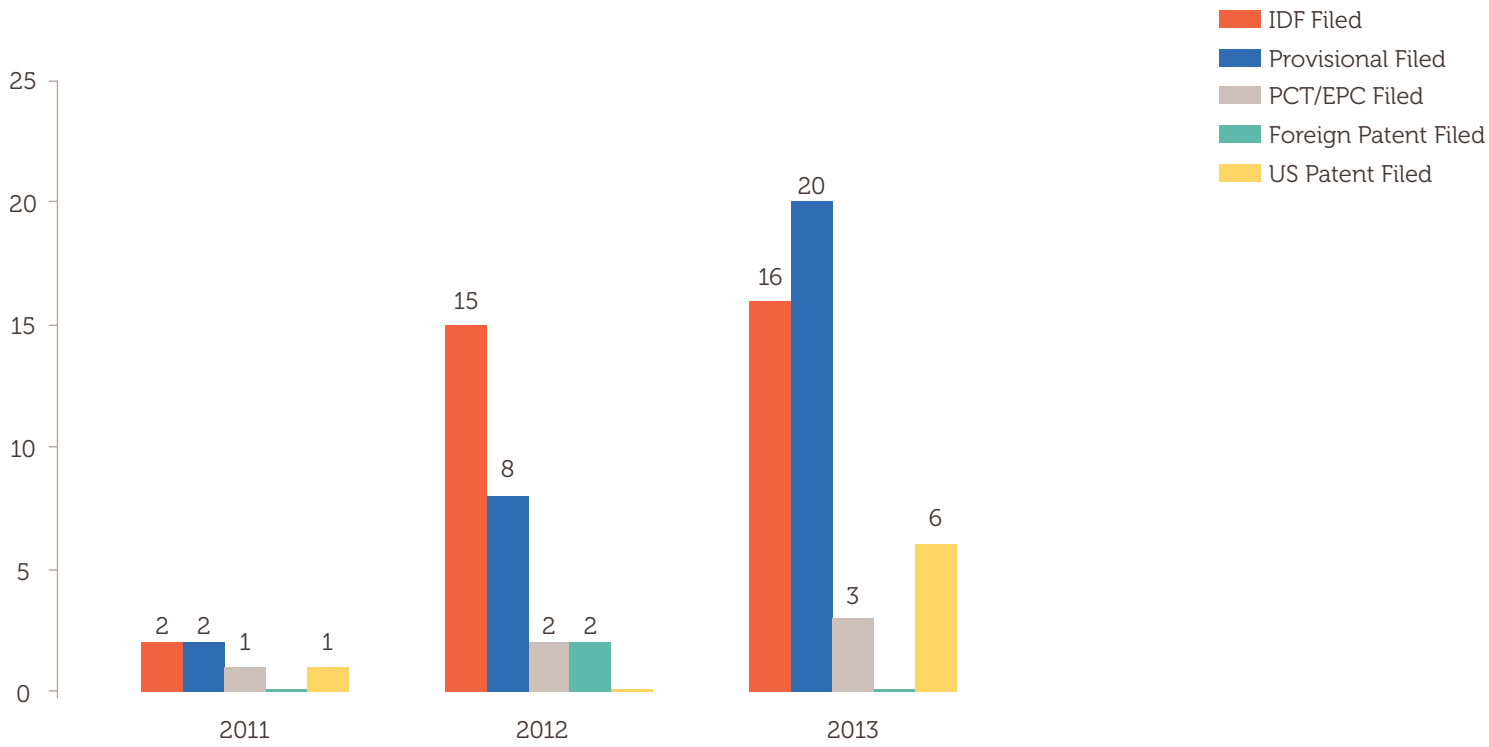


INTELLECTUAL PROPERTY PORTFOLIO

Intellectual Property Portfolio at Children's National Health System



Intellectual Property at the Sheikh Zayed Institute for Pediatric Surgical Innovation



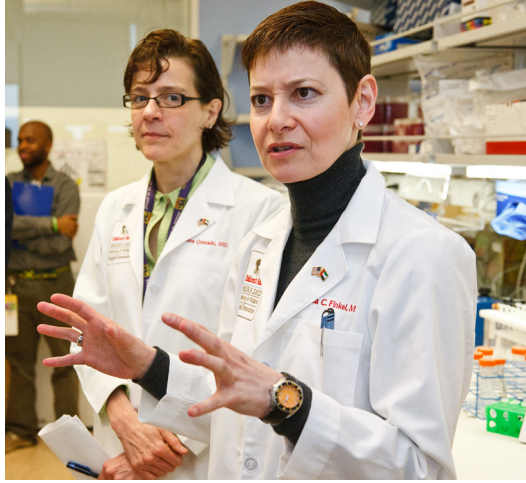
PROGRAM HIGHLIGHTS

The Institute Unveiled the New Pain Medicine Care Complex

In April 2013, the Institute opened the new Pain Medicine Care Complex, which aims to eliminate pain in children by addressing each patient's pain from every angle. The Pain Medicine Care Complex combines new treatment approaches with sophisticated data collection via novel gaming technology that fully engages young patients and also objectively measures their treatment progress over time.

The Institute's pain medicine program is the first of its kind to use unique video gaming therapy, holistic therapeutic tools, and digital data collection to enable short- and long-term measurement of patient progress. For the first time, physicians can quantitatively measure pain and assess treatment progress in pediatric patients – all within an environment that is specially designed for children and teens. The Complex features the following elements:

- **A Multi-Sensory Room (MSR)** in which a physical therapist uses video gaming therapy that distracts the patient, while simultaneously digitally measuring treatment progress through Kinect technology and a proprietary software application to gather patient data in realtime, which targets and tracks 24 musculoskeletal points in the body.
- **A high-tech, interactive POD bed** designed by renowned interior designer Alberto Frias that serves as a biofeedback environment, including heart-rate monitors, soothing lights and music, and tools to monitor a patient's response to therapy and reduce patient anxiety.
- **State-of-the-art teleconference and telemedicine technology** allows the pain medicine experts at Children's National to diagnose and treat patients around the world.



"Through a cost-effective, continuous loop where evidence drives clinical care, and clinical care drives research, we are advancing pediatric pain medical research to improve the lives of children and reduce healthcare costs. Using our unique approach – Distract, Measure, Treat – we can dramatically improve patient outcomes in the short term while simultaneously driving long-term research to transform how care is delivered to children..."

Julia Finkel, MD
Chief, Division of Pain Medicine

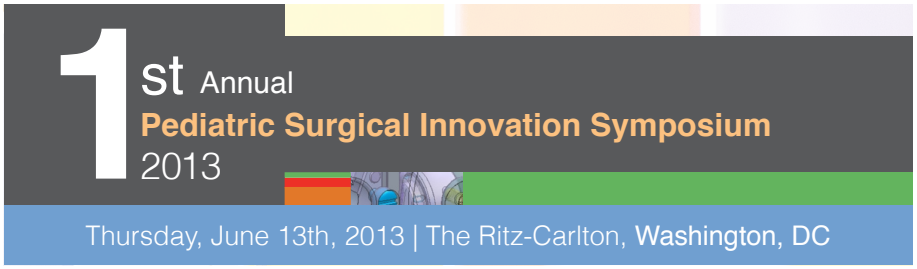
"Infants and children are not simply small adults-their physiology is different, and they experience rapid anatomical and physiological change. An improved regulatory framework for pediatric devices and surgical tools will reflect these substantial differences, keeping safety paramount while encouraging future innovation and investment."

Mark Batshaw, MD

Physician-In-Chief & Chief Academic Officer | Children's National Health System

Building Consensus around Challenges to Pediatric Surgical Innovation and Medical Device Development

On June 13, 2013, the Institute held the First International Symposium on Pediatric Surgical Innovation to discuss the current status and challenges to pediatric surgical innovation and medical device development. The Institute drew nearly 250 high-level participants, including representatives from the U.S. Food and Drug Administration (FDA), European Medicines Agency, Japan's Pharmaceuticals and Medical Devices Agency, U.S. National Institutes of Health (NIH), American Academy of Pediatrics, American Pediatric Surgical Association, World Federation of Associations of Pediatric Surgeons, children's hospitals, pediatric device consortia, device makers, and experts in intellectual property and regulatory science. The symposium included discussions such as strategies for seeking regulatory approval in the top-three medical device markets – the United States, the European Union, and Japan. Following the day-long symposium, the Institute held a closed session with key opinion leaders and speakers from the conference to begin the formation of the white paper, which will be published in the last quarter of 2013. This document will outline a consensus from world-renowned thought leaders on recommended priorities and changes to address current challenges and to speed advances in pediatric surgical innovation and device development.



The Institute Received the FDA P50 Grant to Form the National Capital Consortium for Pediatric Device Innovation (NCC-PDI)

The Institute received the prestigious U.S. Food and Drug Adiministration (FDA) grant for $700,000 for FY2013, as part of an anticipated five-year award. The NCC-PDI will be a collaboration of Children's National Health System with the University of Maryland A. James Clark School of Engineering and its flagship institute, the Maryland Technology Enterprise Institute (Mtech). The partnership will also involve the university's Fischell Department of Bioengineering, chaired by Fischell Distinguished Professor and Co-PI William Bentley, and the Maryland Industrial Partnerships (MIPS).

For-profit, academic, and medical association partners in the consortium include Arent Fox, Oblon Spivak, Medical Murray, Key Tech, Philips Healthcare, Cook Medical, Medtronic, QUASAR, Root3 Labs, Weinberg Medical Physics, JustRight Surgical, Georgetown University Medical Center, The George Washington University School of Business and School of Medicine and Health Sciences, George Mason University, Howard University College of Medicine, Anne Arundel Medical Center, Howard Hughes Medical Institute, Virginia Tech, Vanderbilt University, Johns Hopkins University, Sickkids Toronto, Texas Scottish Rite Hospital for Children, American University Kogod School of Business, National Institutes of Health/Clinical Center, Medical Device Manufacturers Association (MDMA), The World Federation of Associations of Pediatric Surgeons (WOFAPS), and American Pediatric Surgical Association (APSA).

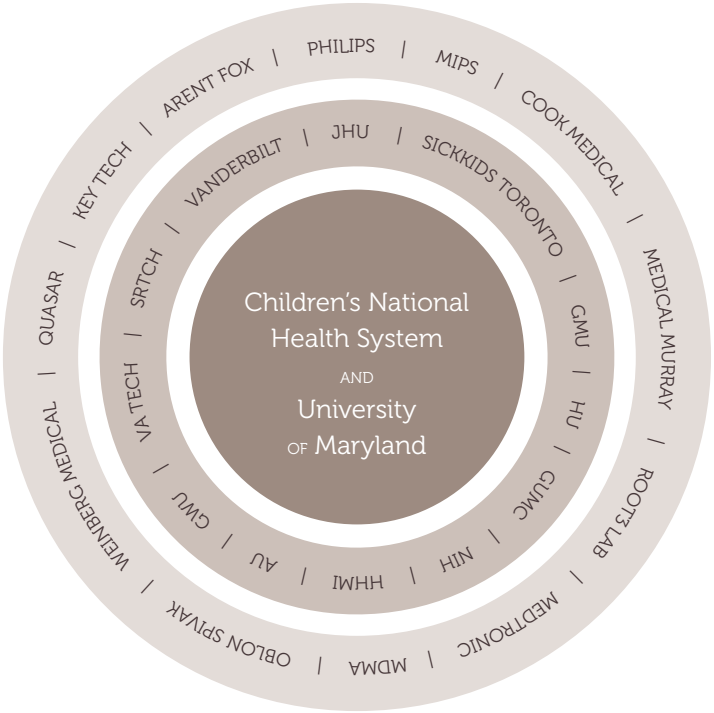
The grant was awarded by the FDA's Office of Orphan Products Development in its third round of funding since 2009 to consortia that advance the development of pediatric medical devices. The 2013 grants were awarded to consortia that brought together teams with excellence and expertise in delivering business, regulatory, legal, scientific, engineering, and clinical services for children. All consortia work collaboratively with the FDA to help innovators effectively navigate existing laws, regulations, and agency guidance to protect the health and safety of children.

The goals of NCC-PDI are to:

- Provide a platform of experienced regulatory, business planning, and device development services (such as intellectual property counsel, prototyping, engineering, laboratory and animal testing, grant writing, and clinical trial design) to foster the advance of medical devices for pediatric patients;
- Bring together individuals and institutions that can support pediatric medical device progression through all stages of development – ideation, concept formation, prototyping, preclinical, clinical, manufacturing, marketing, and commercialization;
- Support a mix of projects at all stages of development, particularly the later stages of clinical, manufacturing, and marketing; and
- Provide counsel on accessing various Federal and non-Federal funding resources while assessing the scientific and medical merit of proposed pediatric device projects.

"We are excited to unite within this consortium the diverse strengths of our distinguished partners and collaborators to bring important advances to medical devices for children."

Peter C. W. Kim, MD, CM, PhD, Vice President
Sheikh Zayed Institute for Pediatric Surgical Innovation



Partnerships

The Institute Convened its First Business Advisory Council

"Presenting before and meeting with the BAC committee was an invaluable experience. Their continued advice and guidance helped me form a practical business strategy for the pediatric medical device we are developing."

Carolyn Cochenour, BS
Staff Engineer | Sheikh Zayed Institute

Since the Institute moved to its new home, its innovators have made tremendous progress towards establishing product pipelines that include therapeutics and devices as well as information technology applications. While the projects are focused on pediatrics, they are all scalable and applicable to the adult population. On May 10, 2013, the Institute hosted its first Business Advisory Council (BAC), comprised of members of the venture capital, legal, business, and intellectual property communities to evaluate the projects on the product development path. The day-long meeting led to valuable recommendations for each project/company on whether their progress is on the right track, needs change in direction, or should be placed on hold.

"ChronoKair™ is an excellent example of why the Sheikh Zayed Institute is a leader in pediatric care innovation. Dr. Kelly Swords has created a tablet-based software application that facilitates comprehensive communication and decision-making during doctor hand-off of patients, daily rounds, and when responding to patient care phone calls remotely. A simple, elegant solution to a complex problem."

Craig W. Dye | Director, Mtech Ventures

Joseph E. Robert, Jr., Fellow Alumna Formed a Maryland-Based Company, ChronoKair™

Medical errors are devastating in every aspect. Injury to patients takes physical, emotional, and economic tolls for families and hospitals. Adverse events and near-misses are routinely linked to communication between all types of practitioners and also between patients and practitioners, and it has been demonstrated that the most important patient information is not communicated at least 60 percent of the time. Kelly Swords, MD, developed ChronoKair™, a mobile phone and tablet application, that provides a comprehensive and visual summary of the patient's hospital course and/or treatment as well as their projected trajectory in one screen. ChronoKair™ allows providers to navigate smoothly to specific moments in time and track real-time patient data.

ChronoKair™ facilitates and reinforces the communication and decisions made during patient sign-out, daily rounding, patient care phone calls, and other telemedicine.

ChronoKair™

"The seed grant funding allowed us to successfully merge our expertise in 3D printing and biomaterials to develop patient specific bioabsorbable vascular grafts, which are customized for a child's congenital heart defect surgery. We were able to successfully develop and test prototypes, leading to two provisional patent applications and a major collaborative grant submission."

Axel Krieger, PhD
Principal Investigator, Sheikh Zayed Institute

The Sheikh Zayed Institute and University of Maryland A. James Clark School of Engineering Provide Seed Funding to Seven Collaborative Projects

In early 2012, the Sheikh Zayed Institute and A. James Clark School of Engineering's (UMD-Clark) faculty and professionals held a half-day workshop at the Sheikh Zayed Institute for Pediatric Surgical Innovation at Children's National. At this initial meeting, the Institute innovators presented their projects in an effort to begin identifying potential areas for collaboration. A tour of the selected clinical units and the Institute was arranged. The second of this series of workshops took place at the Clark School of Engineering at University of Maryland for a full day. At this workshop, the Institute's innovators had the opportunity of learning more about UMD-Clark and its flagship programs Maryland Industrial Partnerships (MIPS) and Maryland Technology Enterprise Institute (Mtech). Based on the first workshop at the Institute, the following topics were selected for breakout sessions as potential areas for collaboration: (1) Medical Devices and Robotics, (2) Human Factors Engineering, (3) Imaging and Image-Guided Technology, and (4) Biomaterials and Tissue Engineering. The breakout sessions led to the identification of specific projects for pediatric surgical innovation and pediatric device development. The partners, the Sheikh Zayed Institute and UMD-Clark, committed to provide $100,000 each in seed funding for a total of $200,000, and released an RFA to solicit joint collaborative multiple-PI proposals. Fourteen well-presented proposals were received and seven were funded. The Sheikh Zayed Institute and the University of Maryland collaboration provides critical mass for clinical, regulatory, business, scientific, and engineering expertise, as well as geographical proximity of only six miles. This collaboration was instrumental in attaining the prestigious FDA P50 grant.

"I learned that a simple idea can make a difference. Don't underestimate yourself, you too can be creative. You don't have to be an expert to help."

Eiman Alhmoudi
2013 Student Innovator
Khalifa University

The Institute's Student Innovators Presented their Creations at the 2013 Medical Hackathon

The Institute hosted the first Medical Hackathon on June 19-21, 2013, to challenge the student participants to design a mobile app or tool that effectively addresses childhood obesity. This was a hands-on experience that highlighted various aspects of the development process, e.g., working in teams, creativity, and the innovation process. Twelve faculty and subject matter experts presented on the topic and served in the judging panel. After two days, five app concepts were presented to the judges, four individual and team prizes were given, and two teams decided to continue their project past the summer program.

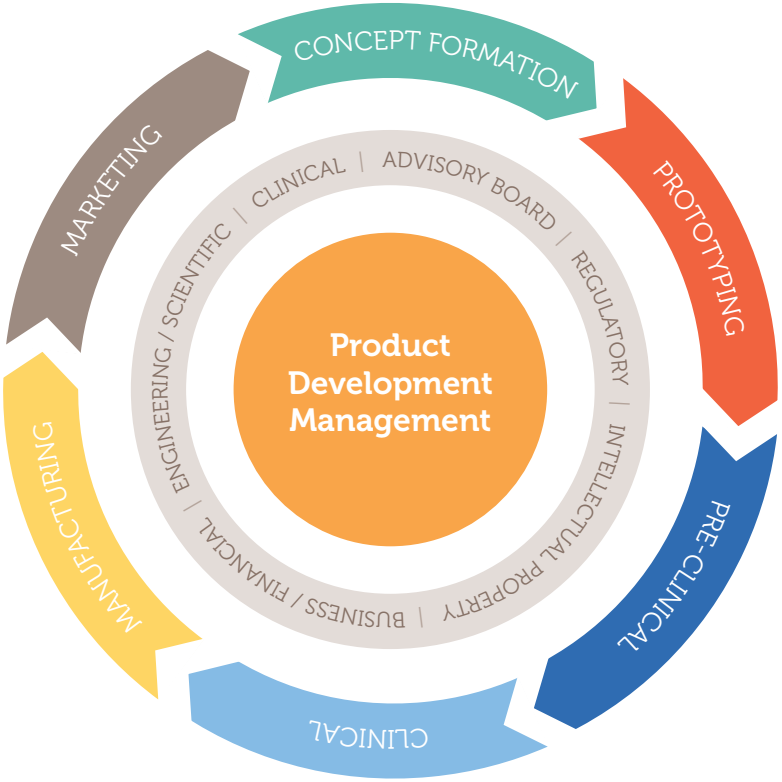
"I thought [the students] were amazing – I was very impressed with their ability to quickly pick up on the subject matter, and get a unique perspective by digging deep, and doing their research…this design challenge was a great way to effectively apply their conceptual understanding of the hospital, and their skill-sets…they came up with viable solutions in a short period of time, that they could then apply directly to actual issues."

Ivor Horn, MD, MPH, Technology and Innovation Advisor
Center for Translational Science | Children's National Health System


PRISMACOLOR

SCIENTIFIC HIGHLIGHTS

Our Product Development Methodology



Types of Institute Projects:

MEDICAL DEVICES

HEALTHCARE SOFTWARE

DRUGS / BIOLOGICS

Bioengineering's Initiatives

Kevin Cleary, PhD
Raymond Sze, MD
Bamshad Azizi, MS
Juan Cerrolaza, PhD
Matthieu Dumont, PhD
Rohan Fernandes, PhD
Renhui Gong, PhD
Ozgur Guler, PhD
Hilary Hoffman, BS
Timothy Kane, MD
Xin Kang, PhD
Rahul Khare, PhD
Wen Li, PhD
Marius George Linguraru, DPhil
Reza Monfaredi, PhD
Emmarie Myers, BS
Jihun Oh, PhD
Craig Peters, MD
Celeste Poley, BS
Nabile Safdar, MD, MPH
Karun Sharma, MD, PhD
Raj Shekhar, PhD
Emmanuel Wilson, MS
Ziv Yaniv, PhD
Anlin Zhang, MS
Qian Zhao, PhD

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PROTOTYPING

PROJECT: Augmented reality visualization for higher-precision laparoscopic surgeries

PROGRAM: Fusion

TEAM: RAJ SHEKHAR, PhD | TIMOTHY KANE, MD | CRAIG PETERS, MD | XIN KANG, PhD | JIHUN OH, PhD

FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: Visual information is critical to safe and effective surgical outcomes, particularly in laparoscopic procedures where haptic feedback is limited. Traditional laparoscopes provide a flat representation of the 3D operative field and are incapable of visualizing internal structures located beneath visible organ surfaces.

Using real-time stereoscopic camera technology now available for conventional laparoscopic surgeries, we have developed a novel visualization capability called stereoscopic augmented reality (AR). The stereoscopic AR system merges live laparoscopic ultrasound images with stereoscopic laparoscopic video. Stereoscopic AR visualization provides minimally invasive surgeons with two new visual cues: (1) Perception of true depth and improved understanding of 3D spatial relationship among anatomical structures; and (2) Visualization of critical internal structures such as blood vessels, bile ducts, and surgical targets such as tumors, along with a more comprehensive visualization of the operative field.

We have completed the development of the initial prototype, tested it in phantoms and animals, and begun its human testing. The experience of OR use and the feedback of laparoscopic surgeons gathered through clinical testing will shape future development and commercialization efforts associated with this project.

PROJECT: Development of a low-cost hardware accelerator for 3D image registration

PROGRAM: Fusion

TEAM: RAJ SHEKHAR, PhD | NABILE SAFDAR, MD, MPH | WEN LI, PhD

FUNDING SOURCE: National Institutes of Health

SYNOPSIS: Image registration is a fundamental need in modern medicine a need that remains unmet. It is the necessary first step before images with complementary information can be fused or images taken at different times can be subtracted to quantify anatomic/physiologic changes. It is also essential when creating a population-based atlas from images of many subjects. Image registration has numerous other applications, including the registration of pre- and intra-operative images in a host of emerging minimally invasive, image-guided interventions.

The overall goal of this multi-center project is to develop a novel computing solution for automatic and accurate registration (spatial alignment) of 3D medical images of any modality and any anatomy (rigid or deformable) in one minute or less. Existing image registration solutions have limited accuracy and/or limited applicability, preventing wide and routine clinical use. The current efforts are focused on developing high-impact applications of the technology in diagnostic radiology, interventional radiology, and radiation oncology. This project is expected to lead to a clinically viable and tested multi-purpose image registration computing technology.

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PROTOTYPING

PROJECT: A fluorescence imaging approach to visualizing PICCs / novel polymer composites for in situ visualization of PICCs

PROGRAM: Fusion

TEAM: RAJ SHEKHAR, PhD | TIMOTHY KANE, MD | CRAIG PETERS, MD | XIN KANG, PhD | JIHUN OH, PhD

FUNDING SOURCE: Sheikh Zayed Institute, Clinical and Translational Science Institute at Children's National (with Virginia Tech)

SYNOPSIS: The use of peripherally inserted central catheters (PICCs) for administering nutrition, blood, and medication, and for blood sampling is common in pediatric medicine. An estimated 120,000 to 320,000 PICCs are placed annually in the U.S., and the length of their implantation can be several months. Over time, the natural movement and growth of the child may displace the PICC. Frequent verification of the catheter position (especially the catheter tip) inside the body is critical because a malpositioned PICC can cause serious complications, including death. Currently, X-ray imaging is primarily used to confirm catheter tip location, but the associated cost and use of radiation prevent frequent inspection, making early detection difficult in the event of catheter migration from the intended position. Furthermore, radiation exposure is particularly undesirable in children due to its associated health risks.

The overall goal of this project is to develop novel polymer composites for making PICCs that can be visualized easily and frequently at the patient bedside without the use of ionizing radiation. Following the current approach of adding radio-opaque substances into the catheter material for enhanced X-ray imaging contrast, our hypothesis is that catheters can be constructed from a polymeric composite with optical or acoustic contrast materials that can then be visualized using near-infrared fluorescence or ultrasound imaging methods, respectively. The current efforts are directed toward proving the underlying imaging concepts and establishing the feasibility of fabricating "imageable" catheters.

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PROJECT: Automated renal ultrasound

PROGRAM: Joseph E. Robert, Jr., Fellowship in Pediatric Surgical Innovation
TEAM: REZA SEIFABADI, PhD | BAMSHAD AZIZI, MSC | NABILE SAFDAR, MD, MPH | KEVIN CLEARY, PhD
FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: Diagnostic renal ultrasound is the most common abdominal procedure that requires scanning the bladder and right and left kidneys. Every year, more than 12 million procedures are performed only in the U.S. At Children's National Health System alone, almost 3,000 cases were performed in 2012 (20 percent of all cases). The diagnosis is mostly based upon a couple of solid 2D images acquired by a skilled sonographer.

This procedure however has some problems: 1) There is always some degree of diagnosis uncertainty because a) these 2D images miss some information of the 3D structure of kidneys and bladder, and b) the image quality is highly dependent on sonographer's skills; 2) It is a challenging task for sonographers because a) it is hard to find the kidney and bladder, and b) small motion of the probe makes a big difference in terms of finding/missing the organs; 3) The procedure takes an average of 20 minutes which is long; and 4) It is yet costly (> $500/procedure).

We propose a supervised automated machine that sweeps the ultrasound probe over the patient's abdomen and acquires a lot of 2D images. Since the coordinates of these images are known from the machine sensors, a computer automatically puts together these images and reconstructs a 3D image of the organs. Each sweeps takes two to three minutes, and the operator repeats it few times until the image quality is satisfactory.

Due to the provided 3D volume (instead of some 2D images) and less independency of the output images of sonographer's skills, diagnosis certainty would improve. The procedure would be made easier for the sonographer by resolving the challenge of finding the organs and tiny motion of the probe thanks to sweeping a larger area of the body. The procedure would be quicker and less costly by increasing the number of patient visits which was otherwise difficult.

CONCEPT FORMATION

PROTOTYPING

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

CONCEPT FORMATION

PROJECT: Safe surgical drain

PROGRAM: Joseph E. Robert, Jr., Fellowship in Pediatric Surgical Innovation
TEAM: JOHNNY COSTELLO, MD
FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: A surgical drain that is safer for patients and providers during the process of emptying the drain as part of routine, post-operative drain care. Patients who have undergone abdominal, pelvic, joint, or soft-tissue surgery for numerous indications often have drains placed in the operating room at the time of surgery to allow for the evacuation of fluid that collects in various tissue spaces as a result of inflammation from surgical manipulation. Bedside care providers (including nurses, patient care technicians, and physicians) subsequently empty these drains twice or more per day for patients under their care. Given the current design of these drains, there is the potential for the biohazardous fluid contained within the drain to splash out of the drain and come into contact with the care provider, resulting in a significant occupational safety risk.

The approach to solving this problem is to address the safety concern from a systems-based perspective and re-design these highly utilized drains to incorporate numerous aspects of safety and ease of use. The goals of this project are to secure intellectual property related to drain design, develop a functional prototype for laboratory testing, and eventually market the drain for potential clinical use, given the enhanced safety profile of the new drain.

PROJECT: Navigation system for pediatric cardiac interventions to minimize fluoroscopy

PROGRAM: Minimally Invasive Therapy

TEAM: JOSHUA KANTER, MD | ZIV YANIV, PhD | REN HUI GONG, PhD | OZGUR GULER, PhD

FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: The specific aims for this project are to (1) develop a navigation system that combines pre-procedure MRI images for guidance in interventional cardiology with electromagnetic tracking and an augmented reality display of the catheter position. The navigation system will be based on our previously developed open source software package the IGSTK, and (2) evaluate the system in the cardiac catheter lab on a novel heart phantom. System evaluation includes navigation accuracy, required to be 5 mm or better, and reduction in fluoroscopic exposure as compared to the standard approach.

Congenital heart defects are the most common birth defect in newborn children. According to the Centers for Disease Control and Prevention, 40,000 children are born with congenital heart defects each year. Interventional cardiology procedures are widely used in the treatment of congenital heart defects. Current technology for interventional cardiology procedures employs fluoroscopy to image the heart and associated vascular structures. However, fluoroscopy uses X-rays that are known to be damaging to the patient, the physician, and the support staff. Extended exposure to fluoroscopy may result in an increased likelihood of developing cancer, and is dose dependent. In addition, as a patient undergoes multiple procedures, the chance of developing cancer increases. By developing an image-guidance and navigation system, we will minimize the use of fluoroscopy while enhancing 3D visualization during interventional cardiology procedures. This will be achieved by combining pre-procedure MRI imaging, electromagnetic tracking, and minimal X-ray fluoroscopy in a way that limits ionizing radiation while maintaining the highest levels of image quality, catheter tracking, and procedural accuracy. While our system will be applicable for a variety of interventional cardiology procedures, we focus on two challenging procedures: ventricular septal defects and biopsy of the endomyocardium.

PROTOTYPING

PROJECT: X-ray / MR registration for physeal-sparing ACL reconstruction

PROGRAM: Minimally Invasive Therapy

TEAM: JOHN LOVEJOY, MD | ZIV YANIV, PhD | REN HUI GONG, PhD | OZGUR GULER, PhD

FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: The specific aims for this project are to (1) develop a clinically viable intra-operative approach for X-ray/MR registration. Use 2-4 intraoperative X-ray images to align the preoperative MR with the patient, (2) develop an image-guided navigation system for ACL reconstruction. During the surgery, optically tracked tools and bone models will be displayed in 3D with the physeas and planned trajectories clearly indicated. A customized targeting view will be used to guide the surgeon so that the planned tunnel trajectory and drill trajectory are aligned. System will be based on the Image-Guided Surgical Toolkit (IGSTK), (3) evaluate the registration algorithm and navigation system using anthropomorphic phantoms. Accuracy of the registration, whole system, and tunnel placement will be evaluated using 10 phantoms.

With the growing clinical trend towards minimally invasive procedures, orthopedic surgeons rely more heavily on intraoperative imaging, primarily 2D X-rays. This imaging modality exposes the patient to ionizing radiation. In addition, when using 2D images the outcome is highly dependent upon the physician's ability to mentally reconstruct a 3D scene from one or more projections. This is the case with physeal-sparing ACL reconstruction. Repair of the ACL in skeletally immature patients is more challenging than in adults due to increased risk of iatrogenic bone-growth disturbance when using the standard arthroscopic technique. In children, the application of the standard technique would involve drilling across the growth plates, which can potentially lead to devastating complications such as deformities due to growth disturbance or even growth arrest.

By developing a multi-body, 2D-to-3D registration (alignment of the pre-operative image to the patient) algorithm we will enable 3D navigation guidance. Our guidance system will replace a mental roadmap with a concrete one, data derived from diagnostic images with dynamically overlaid tool locations. We hypothesize that this form of guidance will increase the procedure accuracy, and reduce complications and the use of ionizing radiation.

PRE-CLINICAL

PROJECT: Biofunctionalized prussian blue nanoparticles for multimodal molecular imaging of eosinophilic esophagitis

PROGRAM: Pediatric Molecular Imaging and Intervention

TEAM: ROHAN FERNANDES, PhD | LAURIE CONKLIN, MD | RAYMOND SZE, MD | JESSE DAMSKER, PhD | MATTHIEU DUMONT, PhD | HILARY HOFFMAN, BS

FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: Eosinophilic esophagitis (EoE) is an inflammatory disorder of the upper GI tract with a strong link to food/air allergies. EoE is marked by the striking infiltration of eosinophils into the esophageal epithelium. EoE presents in patients as difficulty eating, failure to thrive, chest/abdominal pain, dysphagia, and food impaction, and its annual prevalence has been rising and approaches one in 1000. Currently, diagnosis and follow-up of EoE is via endoscopy with random pinch biopsies for histologic analysis. Diagnosis requires demonstration of ≥15 eosinophils/high-power-field by endoscopy with biopsies, after exclusion of gastroesophageal reflux disease. This upper endoscopy/biopsy method of EoE diagnosis is invasive and causes patient discomfort, and, in extreme cases, can cause esophageal tearing. Further, the patchy distribution of eosinophils in EoE makes targeting of biopsies difficult for the endoscopist. Therefore, there exists a need to augment the current standard for the diagnosis of EoE and devise techniques that 1) improve the sensitivity of the biopsies by highlighting suspicious regions within the esophagus to aid the endoscopist, or 2) enable non-invasive imaging of EoE using techniques such as MRI to reduce the need for repeated endoscopies.

Our overall goal is to synthesize biofunctionalized Prussian blue nanoparticles which, upon oral administration to EoE patients, bind to the eosinophils or EoE-specific markers in the esophagus and enable 1) fluorescent imaging (for improved biopsy sensitivity) and 2) MRI (for non-invasive imaging) of EoE, compared with normal patients. Preliminary data in vitro shows that our nanoparticles can selectively detect eosinophilic cells in a mixture of eosinophilic cells and squamous epithelial cells via fluorescence and MRI. We are currently developing a mouse model of EoE to test our nanoparticles for multimodal imaging. If successful, our studies will yield an orally administered agent that enables more sensitive biopsies and non-invasive imaging of EoE.

PRE-CLINICAL

PROJECT: Prussian blue nanoconstructs for theranostics of aggressive pediatric brain tumors

PROGRAM: Pediatric Molecular Imaging and Intervention

TEAM: RAYMOND SZE, MD | ROHAN FERNANDES, PhD | JAVAD NAZARIAN, PhD | MATTHIEU DUMONT, PhD | SRIDEVI YADAVILLI, PhD | HILARY HOFFMAN, BS | MADHURI KAMBHAMPATI, BS

FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: Pediatric brain tumors (PBTs) are the most common type of solid tumor in children, and one of the leading causes of cancer-related deaths in children. Aggressive PBTs are one of the hardest brain tumors to treat with median survivals times of approximately one year. This is largely because drug delivery to aggressive PBTs remains a huge challenge and requires a therapy to cross the blood-brain barrier, penetrate brain tissue, and distribute within the tumor. Our goal is to fill this need by developing Prussian blue nanoconstructs that can be used for theranostics (therapy and diagnostics) of aggressive PBTs. Specifically, we are developing the Prussian blue nanoconstructs that can be used for tumor-site activate fluorescence imaging, molecular MRI and enzyme-based prodrug therapy in aggressive PBTs.

Preliminary data demonstrate that feasibility of our non-toxic nanoconstructs for molecularly targeting tumor cells, optical imaging and MRI of mice brains, and enabling site-activated killing of tumor cells. The nanoconstructs are being tested in a well-characterized mouse model of aggressive PBTs. The proposed project, if successful, will yield a nanoconstruct that enables dual-mode imaging and therapy for PBTs. Tumor site-activated fluorescence imaging sensitively outlines the margins of the PBT, which are critical in planning surgical interventions for PBTs. Molecular MRI enables real-time, molecularly-specific diagnosis, monitoring, and follow-up of PBTs. Enzyme-activated pro-drug therapy enables tumor site-activated therapy for PBTs. We will leverage the results of this project to advance our Prussian blue nanoconstructs closer to clinical trials. These developments will be important for improving the dismal prognosis of children with aggressive PBTs.

PROJECT: Anatomical and functional models: hydronephrosis from ultrasound of the kidney

PROGRAM: Quantitative Imaging

TEAM: CRAIG PETERS, MD | NABILE SAFDAR, MD, MPH | MARIUS GEORGE LINGURARU, DPhil | QIAN ZHAO, PhD | EMMARIE MYERS, BS

INDUSTRIAL PARTNER: PHILIPS HEALTHCARE

FUNDING SOURCE: Sheikh Zayed Institute with additional support from Philips Healthcare

SYNOPSIS: The most common pediatric ultrasound studies are of the kidney (10 to 30 cases daily at Children's National); the most common abnormal finding in these studies is hydronephrosis (2-2.5 percent of children). Hydronephrosis, or the dilation of the renal collecting system with distortion of the renal parenchyma, is present in a wide spectrum of severity. Currently, hydronephrosis is evaluated by diuretic renogram (i.e., MAG-3 scan), an invasive study that involves bladder catheterization and ionizing radiation exposure. Diagnostic renal ultrasound, while non-invasive and non-ionizing, currently offers only subjective and qualitative descriptors of the severity of hydronephrosis. These assessments can be inaccurate due to inter-observer and intra-observer variation and do not correlate with the degree of hydronephrosis severity and renal functional obstruction.

The goal of this study is to characterize hydronephrosis more precisely and permit the routine adoption (at our center and others) of a quantitative, accurate, and reproducible ultrasound-based technology to evaluate and follow hydronephrosis. Children's National has partnered with Philips Healthcare, which provided its newest 3D ultrasound equipment for the volumetric analysis kidneys. From modeling renal anatomy across normal and abnormal populations, shape analysis, and machine learning, the spectrum of hydronephrosis may now be defined with unprecedented precision. Our strategy is to (1) provide highly reproducible, quantitative descriptors of kidneys from ultrasound, (2) identify for the first time the relationship between such descriptors and renal function, and (3) reduce the number of invasive ionizing studies performed on patients with hydronephrosis. Initial results promise a reduction of the number of unnecessary, invasive, and ionizing tests by over 75 percent.

MEDICAL DEVICES | **HEALTHCARE SOFTWARE** | DRUGS / BIOLOGICS

PROTOTYPING

PRE-CLINICAL

PROJECT: Digital dysmorphology: automated early detection of genetic syndromes from photography

PROGRAM: Quantitative Imaging

TEAM: MARSHALL SUMMAR, MD | KENNETH ROSENBAUM, MD | RAYMOND SZE, MD | MARIUS GEORGE LINGURARU, DPhil | QIAN ZHAO, PHD | LINDSAY KEHOE, MS

FUNDING SOURCE: Sheikh Zayed Institute with additional support from the Division of Genetics & Metabolism at Children's National

SYNOPSIS: Each year, one in every 1,100 babies worldwide is born with Down syndrome. In some regions of the world, the rate is as high as one in 350. Children with the disorder have a high incidence of serious medical complications and intellectual disability that require treatment and usually surgery. Because of these related complications, it's critical that doctors detect Down syndrome as early as possible. It is estimated that the accuracy of pediatricians to detect Down syndrome on a newborn is between 50 to 60 percent. Moreover, access to genetic testing is limited by geography, cost, and physician access. Even when testing is available, blood analysis of chromosomes is expensive and is performed only if the child is suspected to have a genetic disorder, leaving many newborns with Down syndrome without adequate clinical care.

Our team has developed a new software program that can assess a child immediately after he or she is born, without the need for blood tests or specialized analysis. This simple and non-invasive test uses sophisticated automated facial recognition as a screening tool and can make the detection of Down syndrome as simple as a quick snapshot. A local doctor could upload a photo of the child's face to the software program and be told immediately if a child has Down syndrome. All this could be done remotely via the Internet today and possibly through smartphone applications, which would bring the expertise of specially trained doctors to people around the world for a fraction of the cost of modern tests. Children identified with Down syndrome can then be referred to expert geneticists for follow-up and comprehensive clinical care. The accuracy of our system to detect Down syndrome is already 96 percent. Ultimately, this software will do more than detect Down syndrome. This software will make sophisticated genetic expertise widely and affordably available.

PROJECT: Multimodal image and motion analysis: inflammatory bowel diseases

PROGRAM: Quantitative Imaging

TEAM: LAURIE CONKLIN, MD | RAYMOND SZE, MD | NABILE SAFDAR, MD MPH | MARIUS GEORGE LINGURARU, DPhil | JUAN CERROLAZA, PhD

FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: Crohn's disease affects between 3.1 and 14.6 cases per 100,000 person-years in North America with an observed an increase in the incidence of inflammatory bowel diseases (IBD) at a global level. While diagnosis of the small bowel by colonoscopy is unfeasible, recent technological advances have led to the clinical implementation of magnetic resonance enterography (MRE) imaging as the mainstay in the evaluation of IBD. The non-invasive, non-radiating nature of MRE makes it particularly suitable for patients who require serial imaging. However, the remarkable structural complexity of the small bowel, respiratory motion, as well as the variability of peristalsis, make the study and analysis of these images a very difficult task even for the expert eye. In particular, the evaluation of response to treatment is variable and can be unreliable, as current clinical practice relies purely on the qualitative assessment of the small bowel.

To address these clinical challenges, we are developing a new tool to enhance the clinical diagnosis and follow-up of patients with IBD. Using sophisticated image analysis, we remove respiratory motion and create quantitative peristaltic maps in mm/s from Fast Imaging Employing Steady-State Acquisition (FIESTA) sequences. By projecting these activity maps on the Single-Shot Fast Spin Echo (SSFSE) images, we create a new set of clinical images that provides personalized structural and functional information of the patient simultaneously. In the next steps we will develop methods for the automated structural analysis of the bowel and define quantitative measures of IBD from our new imaging biomarkers. The quantitative analysis of abnormal motility and structure in the small bowel will enhance the detection of IDB, improve treatment decisions and allow monitoring clinical outcomes. We are currently designing a pre-clinical study comparing clinical performance with versus without the new imaging biomarkers.

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PROTOTYPING

PROJECT: Safe and efficient devices: minimally-invasive surgical correction of pectus excavatum

PROGRAM: Quantitative Imaging

TEAM: ANTHONY SANDLER, MD | NABILE SAFDAR, MD, MPH | MARIUS GEORGE LINGURARU, DPhil | KEVIN CLEARY, PhD | QIAN ZHAO, PhD

INDUSTRIAL PARTNER: Kitware Inc.

FUNDING SOURCE: Sheikh Zayed Institute with additional support from the Department of Surgery at Children's National

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SYNOPSIS: Pectus Excavatum (PE) is a deformity of the chest wall with an estimated incidence of one in 400 to 1,000 live births. This defect causes chest pain, exercise intolerance, shortness of breath, and poor endurance in children. The standard surgical correction techniques are associated with significant pain and surgical failure, resulting in prolonged hospitalization and costs.

We are aiming to develop a novel device that uses compression springs and electromagnetic actuators that can be programmed to assume the desired chest shape to provide an optimal treatment (iPECT). The device is intended to provide an optimal PE correction with minimal risk and pain, akin to orthodontic treatment using dental braces. The device will use a software planning system for the surgical correction of PE. The system will identify the desired post-treatment shape/anatomy for every patient, and optimize and minimize the deformation required during treatment, therefore increasing the objectivity and decreasing the invasiveness and morbidity of the current surgical procedure in PE correction. The additional analysis of the biomechanical properties of the osseous and cartilaginous structures in the chest will permit us to simulate progressive deformations and compute and control the forces to apply to the patient's chest.

The project will first improve and personalize the current practice for PE surgical correction by providing objective and quantitative information to the surgeon that is not available from just the visual inspection of radiological data. Secondly, this work will lay the groundwork for a new paradigm in PE correction in a controlled setting using the novel correction device. Ultimately, iPECT will improve current pediatric surgical practice by alleviating pain and reducing surgical failure.

PROJECT: Asthma monitoring project

PROGRAM: Robotics
TEAM: IVOR HORN, MD | KEVIN CLEARY, PhD | KEVIN GARY, PhD (Arizona State University)
FUNDING SOURCE: Clinical and Translational Science Institute at Children's National

SYNOPSIS: The specific aims for this project are to (1) develop a tablet-based asthma home monitoring prototype using an iterative design process to incorporate user input, and (2) conduct a mixed-methods pilot study of the mHealth asthma home monitoring system to determine feasibility in the target population.

The overall objective of this project is to develop and test a novel mHealth system that incorporates indoor environmental monitoring and asthma self-management reminders (i.e., peak flow measurement and medication adherence) to improve asthma outcomes for at-risk urban, minority children. As part of an iterative design process, we will utilize qualitative methods (focus groups) to integrate feedback from the target population (parents/caregivers and their children with asthma in an urban metropolitan area – Washington, DC). At the completion of this project, we will have developed a mHealth system incorporating a mobile-device software application (app), a digital spirometer for measuring lung function, and a particulate monitor for measuring indoor air quality. The application, designed for a tablet PC, will prompt the child to record peak flow using the spirometer in addition to storing continuously-measured air quality data (e.g., particulate matter). The air quality and peak flow data will provide families with real-time monitoring of risk for asthma exacerbation and the ability to proactively manage their childrens's asthma more effectively.

PROTOTYPING

PROJECT: MRI compatible robot for bone biopsy

PROGRAM: Robotics

TEAM: RAYMOND SZE, MD | KEVIN CLEARY, PhD | BAMSHAD AZIZI, MS | DAN STOIANOVICI, PhD (Johns Hopkins University) | STAN FRICKE, PhD | AXEL KRIEGER, PhD

FUNDING SOURCE: NIH R01 for three years

SYNOPSIS: The specific aims for this project are to (1) design, construct, and evaluate a pneumatic, MRI-compatible robotic-assistant system for long bone biopsy in pediatric patients. The robot will be placed along the limb of the child in the MRI scanner and will precisely orient a needle-guide for biopsy based on the images. The physician will perform the biopsy manually through the needle-guide, (2) develop a path planning workstation for image-to-robot registration, selecting the location of the target, navigation and targeting based on the images, and means of trajectory verification before manual needle insertion for biopsy, and (3) integrate the robot with the planning workstation and evaluate the system in the MRI environment using custom anthropomorphic pediatric phantoms and goat legs obtained from a local butcher. The physician will modify the system as needed and repeat the evaluations to validate the system in-vitro.

The goal of this project is to develop and evaluate an innovative MRI-compatible robot for improved bone biopsy in pediatrics. The robot will enable a new paradigm for rapidly evaluating suspicious bone lesions through image-guided biopsy. This will enable a novel clinical workflow defined with the goal of minimizing trauma and radiation exposure. The robot would have important applications in diagnosing and distinguishing bone cancers and bone infections, greatly facilitating clinical decision-making and therapy management.

Malignant bone cancers are the third most common pediatric solid tumors after lymphoma and brain cancers and include osteosarcoma and Ewing sarcoma, with thousands of cases in the U.S. alone. Accurate histologic diagnosis is critical for the planning and initiation of surgery, chemotherapy, and radiation therapy. Osteomyelitis is a bone infection, with over 50 percent of reported cases seen in pre-school-age children. Accurate diagnosis of the presence of bone infection and the infecting organism is critical for optimal therapy. Importantly, the imaging appearance of neoplastic and infectious pathology can be indistinguishable, making targeted and rapid tissue sampling key to clinical management.

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PROJECT: Robotically assisted ureteroscopy

PROGRAM: Robotics

TEAM: CRAIG PETERS, MD | KEVIN CLEARY, PhD | RAHUL KHARE, PhD | ANLIN ZHANG, MS | EMMANUEL WILSON, MS

FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: The overall objective of this project is to develop mechanical assistance and an image-guided navigation system to enhance the precision and ease of use of flexible endoscopy. While the concepts developed will be broadly applicable, our focus is on ureteroscopy for kidney interventions, a procedure that is increasingly being performed. Ureteroscopy is a common procedure for examination of the upper urinary tract by passing the instrument through the urethra, bladder, and then directly into the ureter and kidney. The procedure is useful in the diagnosis and the treatment of disorders such as kidney stones, urothelial malignancies, and some obstructive conditions. Flexible endoscopy is a ubiquitous means of diagnosis and therapy in medicine. Endoscopic systems from the major manufacturers are similar, with controls based on simple flexion of the tip of the endoscope, rotational control, and translational movement. These three movements are controlled by the operator at the head of the instrument and are all distinct, making control difficult to learn and perform. Efficient and safe control could be enhanced by a control interface that permits intuitive movements with faithful visual feedback. Because of the complexity of movements needed for many endoscopic procedures, integration of a navigation system with the instrument has the potential to greatly enhance the safety, efficacy, and efficiency of these instruments.

While physicians who do endoscopy every day become skilled at the contortions needed for effective placement of the instrument tip, the shortcomings of the current approach extend the time required for procedures, increase user fatigue, can result in considerable radiation exposure, and have the potential to increase the frequency of errors. For physicians who perform endoscopy occasionally, the need for a more user-friendly and intuitive means of control becomes even more pronounced.

PROTOTYPING

PRE-CLINICAL

Immunology's Initiatives

Anthony Sandler, MD
Lina Chakrabarti, PhD
Ashanti Franklin, MD
Tatiana Iordanskaia, PhD
Hope Jackson, MD
Jennifer Ma, PhD
Clifford Morgan, BS
Sasa Radoja, PhD
Priya Srinivasan, PhD
Zoreh Tatari, PhD, MBA
Sarah Tostanoski, BS
Stanislav Vukmanovic, MD, PhD

PRE-CLINICAL

PROJECT: Micro-fluidic multifunctional nanoparticles

PROGRAM: Cancer Research
TEAM: ANTHONY SANDLER, MD | DON DEVOE, PhD (University of Maryland)
FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: Nanoparticle delivery systems can enhance the therapeutic index of anti-cancer agents by increasing drug concentration in tumor cells, due to enhanced nanoparticle permeability and retention in tumor tissues. Liposomal drugs have met considerable success for cancer treatment, and represent the most clinically advanced class of drug delivery nanoparticles. A key challenge facing liposomal drugs remains control over vesicle size. The ideal size for liposomal nanomedicines is commonly believed to be approximately 100 nm, large enough to provide a high drug payload volume while small enough to pass through leaky endothelial junctions in tumor tissues. This view ignores the increasing use of liposomes for lipophilic drugs where loading efficiency scales inversely with liposome size, and also ignores the impact of vesicle size on cellular uptake, cellular fate, and overall biodistribution. Relationships between these key characteristics and liposome size are poorly understood for nanoparticles below 100 nm, in large part because bulk synthesis yields large and polydisperse liposomes that render detailed size-dependent studies difficult.

Our novel microfluidic technology will overcome these limitations, and apply the technology to the development of a new multi-agent targeted liposomal drug for pediatric neuroblastoma. The microfluidic technique will be developed for achieving uniquely small and uniform liposomes over the range of 20 nm to 300 nm with population variance below 5 percent. The technique will be extended to a full "pharmacy-on-a-chip" for on-demand formation of targeted multi-agent liposomal drugs. We will use microfluidic-enabled liposomes to elucidate, for the first time, the impact of vesicle size on cell uptake, cell fate, clearance rate, and tissue distribution over a wide size range (20-300 nm) with fine size resolution (5 nm) using a combination of in-vitro and in-vivo experiments. The optimized microfluidic platform will be applied to a pre-clinical study of pediatric neuroblastoma using a combination treatment, comprising an amphipathic chemotherapeutic (doxorubicin), a lipophilic EGFR inhibitor (erlotinib), and a lipophilic FGFR inhibitor (PD-173074).

CLINICAL

PROJECT: Neuroblastoma: a novel paradigm for reversible adaptive plasticity

PROGRAM: Cancer Research

TEAM: ANTHONY SANDLER, MD | LINA CHAKRABARTI, PHD | STANISLAV VUKMANOVIC, MD, PhD

FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: Using a neuroblastoma model we have described a novel paradigm in solid tumor biology as reversible adaptive plasticity (RAP) that allows tumor cells to transition between highly proliferative anchorage dependent (AD) and slow growing anoikis resistant, anchorage independent (AI) phenotypes. Gene array analysis of mouse neuroblastoma cells revealed remarkable differences between the two phenotypes and elucidated the molecular pathways associated with each phenotype. Inhibitor of differentiation protein 2 (Id2) is identified as a key molecule modulating phenotypic transition in neuroblastoma cells that functions as a negative regulator of TGFß/Smad and plays an important role in phenotypic transition. The reversible adaptive plasticity and differential expression of Id2 in various cancer cells including rhabdoid, melanoma, rhabdomyosarcoma and pancreatic cancers were also observed suggesting there may be common molecular pathway(s) between the cancer cells regulating phenotypic transition. Thus, we propose a detailed investigation to delineate the mechanism of reversible adaptive plasticity in a variety of mouse and human cancer cell lines in order to develop less toxic and rational treatment strategies that will simultaneously target key transitional phenotypes irrespective of cancer type. Using molecular biology techniques we will verify the role of Id2-TGFß crosstalk in mediating the switch between the two phenotypes in various tumor cell lines. For in vivo proof of concept, we will test the ability of primary human tumor samples to undergo reversible adaptive plasticity. Furthermore, we will test in vitro and in vivo the efficacy of a variety of inhibitors and antagonists either alone or in combination on the various tumor cell lines. We will address toxicity and bioavailability by developing varied microparticle enclosed drug formulations for treating mouse models of neuroblastoma, melanoma, rhabdomyocarcoma and rhabdoid tumors. The detailed mechanistic studies and treatment strategies proposed will elucidate the phenomenon of reversible adaptive plasticity in various cancer types and will provide the molecular and pharmacological rationale for translational therapy in cancer patients.

PRE-CLINICAL

PROJECT: Approach to characterize premature infants at risk for developing necrotizing enterocolitis

PROGRAM: Inflammatory Diseases

TEAM: ANTHONY SANDLER, MD | ZOHREH TATARI CALDERONE, PhD, MBA | STANISLAV VUKMANOVIC, MD, PhD

FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: Necrotizing Enterocolitis (NEC) is the most common acute intestinal emergency occurring in premature infants. The incidence of NEC in the U.S. ranges between 3 percent and 28 percent, with up to 30 percent of affected infants dying of the disease. Survivors of NEC are at risk for sequelae including: intestinal stricture, partial bowel obstruction, short bowel syndrome, and neurodevelopmental delay. This disease not only significantly contributes to infant morbidity and mortality, but also remains quite challenging to manage, thereby constituting a real public health concern.

Despite advances in neonatal care and significant clinical and basic science investigations, the etiology of the disease remains incompletely understood. Pro-inflammatory cytokines, such as an increased level of IL-1 TNFα IL-6 and IL-8 have been reported to be an important factor in the development of NEC. Recent evidence has also shed light on an emerging role for Toll-like receptors of the innate immune system as a central player in the pathways that signal in response to enteric bacteria resulting in the development of NEC.

Our central hypothesis is that genetic variation(s) are the basis of differential immune responsiveness, thus predisposing some infants to developing NEC in its various forms of intensity. The goal of this project is to define the ("risk group (responders") who are susceptible to developing NEC based on their genetic variations or susceptibility. We will use Whole Exome Sequencing (WES – a new approach to large-scale identification of human genetic variation detecting rare mutations in the coding regions of the genome) complemented with Single Nucleotide Polymorphisms (SNPs) association analysis. Our preliminary results suggest that a rare variant SNP located in the promoter of TNF-α gene may be a marker of intestinal perforation, a serious complication of NEC. This approach has the benefit and potential for translating research findings into improved clinical practice by identification of the genetic biomarkers of NEC.

PRE-CLINICAL

PROJECT: Genetics of early childhood immune responsiveness and tolerance induction

PROGRAM: Inflammatory Diseases
TEAM: STANISLAV VUKMANOVIC, MD, PhD
FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: Infants and children under five years of age respond to antigens differently than the adults. Children either respond less efficiently or induce tolerance. Knowing the factors that control immune responsiveness in children is important for development of vaccines and other biologics (e.g., factor VIII in hemophylia), but are largely unknown due to scarcity of relevant experimental in vivo models. We study alloimmunization, the production of antibodies to red blood cell (RBC) antigens following RBC transfusion in patients with Sickle Cell Disease (SCD). We found a statistically significant association of a single nucleotide polymorphism in the regulatory region of the Ro52 gene, and development of tolerance to RBC antigens in early childhood. This finding is important given the relevance of inflammation for alloimmunization and the anti-inflammatory effects of Ro52 in a mouse model. Therefore, we hypothesize that genetic variation in Ro52 (and possibly other genes that control inflammation) predicts the induction of tolerance to RBC antigens in SCD patients before the age of five. To test this hypothesis, we will determine the association of genetic variation in Ro52, and elsewhere in the genome, with the development of tolerance to RBC antigens in young children with SCD. We will also examine the antigen exposure of SCD patients receiving RBC transfusions, and evaluate the association between Ro52 gene expression levels and tolerance induction to RBC antigens. Our findings will have important consequences for transfusion medicine. Thus, we predict identification of a significant subset of SCD patients who will no longer need costly molecular and/or serological matching, due to their established tolerance RBC antigens. In addition, identifying a molecular target(s) for potential therapeutic intervention (e.g., Ro52) will suggest future approaches for allowing the advent of alloimmunization-free RBC transfusions. This will be applicable also in a broader context, in design of therapeutical approaches to other biologics (vaccines, recombinant protein, antibody treatments, and so on).

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PRE-CLINICAL

PROJECT: A novel forward imaging probe for needle-based interventions

PROGRAM: Inflammatory Diseases

TEAM: ANTHONY SANDLER, MD | YU CHEN, PhD (University of Maryland)

FUNDING SOURCE: Clinical and Translational Science Institute at Children's National, Sheikh Zayed Institute

SYNOPSIS: Needle-based interventions are procedures that require a minimally invasive approach to gain access to tissue structures of interest. Each year, more than 30 million of these interventions are performed in the U.S. (excluding peripheral IV), comprising a multi-billion dollar industry. Due to the lack of visual feedback guiding navigation, up to 33 percent of needle-based interventions are associated with complications, incurring significant human and economic costs.

The goal of this proposal is to develop a novel device that will enable image-guided, needle-based navigation. Using optical coherent tomography (OCT) with Doppler capability (DOCT), we will create a miniaturized probe that would provide detailed real-time imaging of tissue structures ahead of the needle. The central hypothesis of this proposal is that OCT/DOCT needle probes and the miniaturized accompanying instrumentation will provide visual and audio feedback that will guide needle-based interventions for enhanced results. Our lab has developed miniaturized (0.7 mm in diameter, 22 Gauge) forward-imaging needle probes based on OCT/DOCT. In this proposal, we will demonstrate the pre-clinical applicability of the prototype device followed by miniaturization of the instruments to allow ergonomic handling. We will then conduct a comparative pre-clinical study validating device performance and comparing it to conventional navigation methods. The results from the proposed studies will pave the way towards subsequent clinical trials. The ultimate goal is to bring an innovative solution that will make needle-based interventions safer, easier, and faster.

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PRE-CLINICAL

PROJECT: A novel multifunctional fiber-optic sensor for real-time patient monitoring

PROGRAM: Inflammatory Diseases

TEAM: ANTHONY SANDLER, MD | KEVIN CLEARY, PHD | MIAO LU, PhD (University of Maryland)

FUNDING SOURCE: Sheikh Zayed Institute, University of Maryland

SYNOPSIS: The overall objective of this project is to develop and evaluate a novel multifunctional fiber-optic sensor for real-time measurement and monitoring of multiple physiological parameters, specifically blood pressure, glucose, and temperature. While our research team is focused on pediatric patients, the sensor will be applicable to all age groups. Pressure, glucose, and temperature monitoring are essential clinical needs, for which current methods can be invasive, bulky, and cumbersome. We aim to develop an ultra-miniature sensor probe that can be inserted into a vascular structure (or interstitial tissue compartment) through a small catheter in a minimally invasive fashion and simply secured with tape. Our goal is to validate this technology in a swine animal model of arterial and venous physiology monitoring. Accurate measurement and monitoring of physiologic parameters are vital to clinical care of surgical and critically ill patients. This information is used to guide informed decisions regarding administration of IV fluids, blood products, medications, and nutritional requirements.

Although both non-invasive and invasive methods currently exist, these suffer from significant shortcomings, especially in pediatric patients. We believe there is an absolute need for development of the ultra-miniature physiologic sensors proposed. We will develop a multifunctional fiber-optic sensor and evaluate it in the laboratory setting. Subsequently, we will evaluate the sensor operation in-vivo in a swine animal study. This is a proof-of-concept project that will result in a novel miniature sensor for real-time physiology monitoring. If successful, the proposed work will position us for a clinical trial in the next phase of the research. In addition, the sensor can be expanded to include additional measurement capabilities such as hydration status, oxygen content, etc., and development of a clinically relevant device will be pursued.

PRE-CLINICAL

PROJECT: Promotion of Tr1 regulatory T cells with multilayer films to combat autoimmune disease

PROGRAM: Inflammatory Diseases

TEAM: STANISLAV VUKMANOVIC, MD, PhD | CHRIS JEWELL, PhD (University of Maryland)

FUNDING SOURCE: Sheikh Zayed Institute, University of Maryland Clark School of Engineering

SYNOPSIS: Autoimmune diseases such as multiple sclerosis (MS) are conditions in which "self" molecules are recognized as foreign, causing a detrimental attack by the immune system. In MS, myelin-derived molecules in the brain are incorrectly recognized as foreign, resulting in inflammation and neurodegeneration. MS treatments often involve immunosuppressive drugs that non-specifically block immune function, but this approach does not halt MS and leads to immunocompromised patients. A new experimental treatment is "reverse" vaccination. In this approach, patients are vaccinated with self-antigen to induce regulatory T cells that control attacks against self-antigens (i.e., tolerance). The most promising vaccines induce tolerance by co-administration of immune cues (e.g., cytokines, drugs) along with myelin antigens (e.g., MOG). These cues modulate autoimmune response away from inflammatory pathways and toward beneficial regulatory function. This idea – tuning immune response – is termed "immunomodulation", and the action of immunomodulatory agents depends intimately on combination and dose.

Recent observations underscore the ability of IL-10 (a regulatory cytokine) and chronic T cell receptor stimulation to promote Tr1 differentiation, and the shortage of this type of cells in patients with MS. We will investigate Polyelectrolyte multilayer (PEM) films as a new reverse vaccine platform for generating type 1 regulatory T cells (Tr1). PEM films are assembled through layer-by-layer electrostatic interactions of oppositely-charged polyelectrolytes, enabling controlled "chronic" delivery of the cargo. Films will be constructed from negatively charged DNA encoding IL-10 and multiple antigen peptides (MAP) that link repeated copies of myelin self-antigen. These MAPs will also contain a block of cationic amino acids that "anchor" each peptide layer to each DNA layer. Ultimately, this idea could help address challenges facing therapeutic vaccines for diseases like MS, Type I diabetes, allergies, lupus, rheumatoid arthritis, and others.

Pain Medicine's Initiatives

Julia Finkel, MD
Zenaide Quezado, MD
Luis Almeida, MD, PhD
Christina Baxter, MSN, MHA, RN, CPN
Elizabeth Bettini, APRN, PCNS-BC
Gabriela Calhoun, MD
Angela Fletcher, PsyD
Mariana Junqueira, MD
Sayuri Kamimura, BTPS
Rochelle Kane, MS
Nicholas Kenyon, BS
Alfia Khaibullina, PhD
Lashon Middleton, ALAT
Sarah Rebstock, MD, PhD
Katie Salamon, PhD
Kathy Sheehy, MSN, APRN, PCNS-BC
Li Wang, MD, PhD

PROJECT: Algometer

PROGRAM: Pain Diagnostics
TEAM: JULIA FINKEL, MD | ZENAIDE QUEZADO, MD | PATRICK CHENG, MBA
FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: The project started in March 2010. The Algometer is a device and method that measures pain intensity and type and can guide analgesic drug delivery in verbal and non-verbal patients. The device integrates a neurospecific neurostimulator and near-infrared spectroscopy signal responses (NIRS) over the somatosensory, frontal, and occipital cortices to determine a composite cortical pain response index (CCPRI). While the alpha prototype was delivered in 2012, the commercially available optodes precluded use through hair. We are collaborating on a solution with Chester Wildly of MRRA. He manufactures "brushed" optodes that sample easily through hair and increase the sensitivity 10-fold over the regular fiber bundle. We anticipate determining which vendor to engage by the end of Q1.

Our preliminary results using a regular fiber bundle are very encouraging:

- The cortical activation in the somatosensory cortex is clearly detected with a sub-threshold C-fiber specific neurostimulation
- There is significant NIRS response at very weak stimulation current, and the data suggest there is a linear dose-response relationship between stimulation and the NIRS signal

To bring this device to market, we have three phases planned moving forward:

- Phase I: Pilot Trial. Demonstrating feasibility and developing diagnostic protocol and algorithm;
- Phase II: Pivotal Trial. Showing efficacy data in a large-scale clinical trial;
- Phase III: Product Launch. Obtain FDA clearance and market device.

In this plan, we will focus on how we plan to implement and execute the Phase I using a stepwise approach to manage R&D risks.

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PROTOTYPING

PROJECT: Pupillometer

PROGRAM: Pain Diagnostics

TEAM: JULIA FINKEL, MD | CAROLYN COCHENOUR, BS | MARIANA JUNQUEIRA, MD | GABRIELA CALHOUN, MD | JUSTIN OPFERMAN, MS | JIHEEN OH, PHD

FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: This project's goal is to develop pupillary response detection applications, utilizing smart phone technology. Control of the pupil is a complex physiology that involves multiple neuronal pathways, and pupillary behavior is the reflexion of the integrity and functionality of these neurological circuits. Measurement of pupil size and dynamic response to light can reflect alterations or abnormalities in the metabolism or the structure of the central nervous system.

SmartPupillometer is a device that combines the PupilCam, an infra-red camera contained in a chamber attachment to a smart phone, with applications that will enable objective measurement of pupil size and dynamic behavior in the clinical setting. The PupilCam attachment will be adaptable to fit the patient's face to facilitate accurate pupil assessment by a ubiquitous device. The device will be a screening tool, and specific applications will contain algorithms developed to address different clinical situations.

This device is both an application for smart phones and hardware (chamber to adapt the smart phone to the patient's face). Pupillometers have been used in ophthalmology and many other medical fields to evaluate the pupil's size and reactivity. The devices currently available have not gained broader clinical use because they are expensive, stand-alone devices that provide raw data without interpretation, so they require a trained professional to evaluate the readings, synthesize the information and guide appropriate interventions.

This device will enable clinicians and healthcare professionals to assess, precisely and objectively, pupil dynamic measurements and compare these parameters over time using different algorithms specific to different clinical situations. The application format on the smart phone will also enable objective generation of comparative information to facilitate the understanding of the data generated. The device also will permit certain, limited assessments by laypersons to determine the need for further medical intervention.

PROJECT: Studies of nociception and behavior in animal models of developmental disabilities

PROGRAM: Pain Genetics

TEAM: ZENAIDE QUEZADO, MD | JULIA FINKEL, MD | GABRIELA CALHOUN, MD

FUNDING SOURCE: Clinical and Translational Science Institute at Children's National, Sheikh Zayed Institute

SYNOPSIS: Converging lines of evidence support the hypothesis that mutations in genes that regulate synapse formation and function underlie autism spectrum disorder (ASD). Given such evidence, clinical observations, and parent reporting that autistic patients have altered pain perception, we hypothesize that nociception is altered in autism. One of the best current models for understanding the brain abnormalities in ASD is Fragile X Syndrome (FXS). FXS is a single gene neurodevelopmental disorder that results from a lack of expression of the mRNA binding protein-encoding Fmr1 gene and the leading known genetic cause of autism. Another well-studied model of ASD is the BTBR mouse. The BTBR mouse exhibits several symptoms of ASD including reduced social interactions, impaired play, low exploratory behavior, unusual vocalizations, and high anxiety as compared to other inbred strains. Therefore, although most cases of ASD likely involve interactions between multiple genetic pathways, the behavioral similarities and involvement of overlapping brain regions indicates that the study of FXS and the BTBR mouse are well suited for the study of nociception in ASD and will contribute significantly to understanding the developmental alterations that impact on alteration of nociception in ASD. In collaboration with Carolyn Beebe-Smith at the intramural NIMH program and Joshua Corbin from the Center for Neuroscience here at Children's National, we have ongoing studies of nociception and behavior in these two models of ASD.

Our preliminary findings do suggest that nociception is indeed altered both in the BTBR and FXS mice. In these animals known to recapitulate features of human ASD, sensitivity to noxious cold and heat is altered, and current vocalization threshold in response to electrical stimulation of sensory nerve fibers is also altered in the BTBR but not in fragile-X mice.

PRE-CLINICAL

PROJECT: Studies of nociception in sickle cell disease

PROGRAM: Pain Genetics

TEAM: ZENAIDE QUEZADO, MD | JULIA FINKEL, MD | GABRIELA CALHOUN, MD

FUNDING SOURCE: Clinical and Translational Science Institute at Children's National, Sheikh Zayed Institute

SYNOPSIS: Our goal is to improve pain management for sickle cell disease (SCD) patients. The mechanisms of the pain associated with SCD remain poorly understood. Subjective pain scales to assess analgesic efficacy have proven unreliable to evaluate the adequacy of analgesic therapy. Studies link manifestations of SCD, including pain, to altered bioavailability of the vasodilator nitric oxide (NO) and uncoupling of the enzyme NO synthase (NOS). Substantial evidence suggests that NO and NOSs are involved in nociception during basal conditions and in acute and chronic pain. We are working to identify objective pain measurements to serve as clinical endpoints to test efficacy of novel analgesic agents, mechanistic studies in mouse models to understand, a pre-clinical screen of potential therapeutic agents able to reduce SCD pain, and planning for clinical trials focused on alleviation of pain. Our hypothesis is that that, in SCD, pain is associated with increased sensitization resulting from recurrent episodes of vasooclusive crisis and associated inflammation, with altered NO bioavailability and uncoupling of NOSs playing key mechanistic roles. To study the role of nitric oxide in sickle cell pain, we collaborate with the NIH intramural program at NIDDK (Schecther) and NHLBI (Kato) for studies of the role of nitric oxide in sickle cell disease-associated pain. In addition, we have active collaborations with our hematology colleagues (Luban, Luchtman-Jones, Meier, and Darbari) here at Children's National and have ongoing studies in sickle cell pain in our patients. Further, we have also ongoing collaborations with the Center for Genetic Medicine (Hoffman, Ragaraju, and Damsker) studying the effect of VBP15 in sickle cell pain.

Since the inception of the laboratory, we have initiated breeding and have well-established colonies of two strains of humanized sickle cell mice (BERK and Townes). We are equipped to maintain the colonies and established robust breeding maintenance and animal tracking systems.

PRE-CLINICAL

PROJECT: Dexmedetomidine and neuropathic pain

PROGRAM: Pain Therapeutics

TEAM: ZENAIDE QUEZADO, MD | JULIA FINKEL, MD | GABRIELA CALHOUN, MD

FUNDING SOURCE: Sheikh Zayed Institute, University of Maryland Clark School of Engineering

SYNOPSIS: Neuropathic pain is a chronic pain condition that is estimated to affect 10 percent of the U.S. adult population. Current treatment is based on oral/systemic medications with modest effectiveness whose use can be limited by adverse effects and drug interactions. More than 50 percent of these patients cannot adequately control pain using only one drug for treatment. The basic aim of this project is to elaborate a new drug delivery system for neuropathic pain treatment using the microfluidic technique to produce enhanced performance drug-delivering liposomes, in conjunction with a novel application of the drug dexmedetomidine. By changing the delivery route of the drug and better controlling its bioavailability, we intend to increase efficacy and decrease side effects of this new treatment, contributing to better care of patients with neuropathic pain.

In partnership with the mechanical engineer group from the University of Maryland, headed by Dr. DeVoe, we are able to manufacture liposomes using a microfluidic technique producing precise and homogeneous sizes of liposomes (Nanosome), completely distinct from other techniques. This manufacturing precision allows control of the range of envelope sizes permitting tailoring of size to delivery route, a critical factor in drug bioavailability. Liposomal encapsulation improves efficacy and safety for each drug over various administration routes.

The first product in the pipeline is liposomal dexmedetomidine. Dexmedetomidine is a highly selective $\alpha 2$ adrenergic receptor agonist, administered intravenously for sedation and analgesia. However, the drug has been used off-label as an adjuvant to improve anesthesia quality and duration. Initially, we plan to develop a formulation of liposomal dexmedetomidine. This is a topical formulation for local pain relief in neuropathic pain. Initial evidence indicates that the encapsulation in liposomal spheres will allow the drug to penetrate through the skin and reach the affected nerves in the dermis. The second formulation will be used for systemic delivery, also through a transdermal route.

PROJECT: Dexmedetomidine pediatric drug program

PROGRAM: Pain Therapeutics
TEAM: JULIA FINKEL, MD | ZENAIDE QUEZADO, MD
FUNDING SOURCE: Industry (Hospira)

CLINICAL

SYNOPSIS: We are conducting clinical trials to improve the treatment of pain during the perioperative period. Our first trial addressed pain after tonsillectomy, the most commonly performed pediatric surgical procedure in North America and Europe. In the U.S. alone, approximately one in 154 children undergoes the procedure every year. The procedure can be associated with significant postoperative pain, and opioids are the drugs most commonly used to treat post-tonsillectomy pain. As opioids can be associated with respiratory depression, otolaryngologists and anesthesiologists alike must reconcile adequacy of pain control with the risk of respiratory complications after tonsillectomy. This is particularly important because agents without respiratory depressant effects, such as non-steroidal anti-inflammatory drugs, acetaminophen, and local anesthetics, while used, are often inadequate to treat postoperative tonsillectomy pain. In 2011, we published the results of a seminal randomized double-blinded clinical trial of dexmedetomidine, a selective $\alpha 2$ adrenoreceptor agonist that has analgesic and sedative properties. Our study showed that dexmedetomidine decreases opioid requirements and prolongs opioid-free interval after tonsillectomy. Our patients are more comfortable and safer after tonsillectomies than ever before. This work has been cited over 20 times since its publication and has changed the practice of treating post-tonsillectomy pain in our hospital and around the nation.

PROJECT: Nano-liposomes for topical drug delivery

PROGRAM: Pain Therapeutics

TEAM: ZENAIDE QUEZADO, MD | JULIA FINKEL, MD | GABRIELA CALHOUN, MD

FUNDING SOURCE: Sheikh Zayed Institute, University of Maryland Clark School of Engineering

SYNOPSIS: Through seed funding from the Sheikh Zayed Insitutute and Clark School of Engineering at the University of Maryland, our teams are developing a new transdermal drug-delivery technology. Our first drug to be encapsulated is dexmedetomidine, an alpha 2 agonist labeled for use as a sedative. By creating a transdermal preparation, we stand to give this drug a new profile in that it can work at a different receptor system (HCN), which is thought to be active in neuropathic pain.

There is accumulating evidence that nanoparticles within the range of 20-40 nm can successfully penetrate the primary dermal barrier. However, this size range is not accessible to traditional liposomes, where bulk preparation methods including alcohol injection, membrane extrusion, detergent dialysis, and sonication produce vesicles that are both too large (typically >80 nm) and polydisperse, with typical populations exhibiting high variance in size and with distributions skewed toward larger diameters. We believe this is a central reason for the poor performance of traditional liposomes for dermal drug delivery. By forming liposomes with diameters below 40 nm in the proposed effort, efficient transport of intact drug-laden liposomes through the SC is anticipated, enabling controlled delivery of both hydrophilic and lipophilic compounds with a high drug-to-lipid ratio. To explore this concept for topical application of liposomal anesthetic drugs, we propose to leverage a unique microfluidic platform that offers on-demand liposome formation and drug encapsulation. The microfluidic technique will provide the ability to generate nearly monodisperse populations of drug-encapsulating liposomes with tunable mean diameters below 40 nm in single-step continuous-flow process that will open the door to a new paradigm for point-of-care preparation of next-generation topical anesthetics.

Systems Biology's Initiatives

Diego Preciado, MD, PhD
Evan Nadler, MD
Monica Hubal, PhD
Matthew Barberio, PhD
Laurie Conklin, MD
Elangovan Gopal, PhD
Emily Koeck, MD
Samantha Sevilla, MFS
Stephanie Val, PhD

PROJECT: Tobacco smoke exposure effects on sinonasal mucosa

PROGRAM: Flight Attendants Medical Research Initiative (FAMRI)
TEAM: DIEGO PRECIADO, MD, PhD
FUNDING SOURCE: FAMRI

SYNOPSIS: Chronic rhinosinusitis (CRS) is a ubiquitous upper airway disease representing one of the most prevalent chronic conditions in the U.S. where it poses an enormous economic burden accounting for an estimated 4.3 billion dollars in yearly public health expenditures. Environmental tobacco smoke (ETS), e.g., direct and second-hand smoke exposure, has been postulated to be a significant risk factor in the development of CRS. In the lower airways, ETS is known to contribute to chronic disease through the induction of chronic inflammation, glandular hyperplasia, and mucin overproduction. Mucins are glycoproteins that play an important role in innate immunity host defense by providing a protective barrier to epithelium and contributing to mucociliary clearance. In the sinuses, chronic expression of mucins can lead to secretion hyperviscosity resulting in secretion stagnation and chronic infection. Previous data from our group have shown that glandular hyperplasia is the primary histopathologic feature of pediatric CRS. Our group has also shown that ETS activates pro-inflammatory mediators and mucin glycoproteins in middle ear epithelium. Finally, our group has recently established an in-vitro model of primary nasal epithelial cells grown in culture both in an air-liquid interface where epithelial differentiation occurs, and in a 3D matrix, where submucosal glands form. The overall hypothesis of this FAMRI proposal is that, much like in the lower airways, tobacco smoke exposure induces in-vitro sinonasal glandular hypertrophy as well as upregulation of mucin gene expression as central pathological events in tobacco smoke-induced CRS.

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PRE-CLINICAL

PROJECT: Adipocyte exosomes mediate TGFß signaling in airway epithelium

PROGRAM: Systems Biology

TEAM: DINESH PILLAI, PhD | MONICA HUBAL, PhD | EVAN NADLER, MD

FUNDING SOURCE: Clinical and Translational Science Institute at Children's National

SYNOPSIS: Two growing epidemics in children, obesity and asthma, appear connected for reasons that remain unclear. In fact, obesity in children is associated with higher rates of asthma. Obesity results in a systemic inflammatory state, and visceral adipocytes from obese patients can produce numerous mediators that boost T lymphocytes and macrophage function, which in turn may stimulate airway inflammation. Furthermore, global mRNA and microRNA (miRNA) expression patterns in adipocytes demonstrate a net increase in inflammation in obese patients, and these RNAs may act locally or be secreted in the form of exosomes or exosome-like vesicles (ELVs) into the blood stream to induce distant effects. Exosomal RNAs are functional and may influence the phenotypes of the recipient cell, and ELVs from adipocytes from obese patients can contribute to the development of insulin resistance. In addition, TGFß, a pro-inflammatory mediator in asthma, is increased in the systemic circulation of obese patients and may be a link between obesity and asthma via ELVs since some exosomal miRNAs, including miR-214, let-7b, and let-7e can regulate TGFß signaling. Our preliminary data demonstrated that 1) TGFß associated mRNAs are upregulated in obese visceral adipose tissue, and 2) differentiated asthmatic human bronchial epithelial cell culture (hBEC) intrinsically expresses TGFß associated proteins. To better understand the impact of adipocyte ELV miRNA on airway epithelium, we have recently isolated ELVs from visceral adipose depots (lean and obese). Our goals for this study were to demonstrate 1) adipocyte ELVs from obese patients exhibit differentially expressed miRNAs compared to lean patients, and 2) adipocyte ELV miRNAs increase TGFß signaling in asthmatic hBEC. We therefore hypothesized that visceral adipocyte ELVs from obese individuals increase TGFß signaling in primary differentiated human asthmatic airway epithelium compared with adipocyte ELVs from lean individuals. The study is underway.

PROJECT: Adipose-derived exosomes modulate skeletal muscle insulin signaling

PROGRAM: Systems Biology
TEAM: MONICA HUBAL, PhD | EVAN NADLER, MD
FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: A multitude of co-morbidities are associated with increased visceral fat accumulation in obesity, including skeletal muscle insulin resistance. Skeletal muscle insulin resistance is a hallmark of Type 2 diabetes development and is a precursor to cardiovascular disease. While epidemiological data clearly associate obesity and insulin resistance, the mechanism(s) by which increased adiposity results in insulin resistance in distant tissue such as skeletal muscle remains poorly understood. Recent work has demonstrated that adipose tissue secretes exosomes that can carry molecular signals (largely miRNAs) through the bloodstream to end organs such as skeletal muscle. We have preliminary data demonstrating that 1) adipose-derived exosomal miRNAs are modified by obesity, and 2) incubation of muscle cells with adipose-derived exosomes from obese donors causes dysregulated insulin signaling (decreased phosphorylation of key insulin signaling proteins Akt and AS160). Our data show that exosomes from obese subjects demonstrate higher expression of miRNAs related to key pathways known to impact insulin signaling in skeletal muscle. As such, we propose that a novel mechanism by which obesity drives skeletal muscle metabolic dysfunction via adipose-derived exosomes. The goal of the current project is to extend our preliminary data to delineate the specific mechanism(s) by which adipose-derived exosomes cause insulin resistance in skeletal muscle. Together, these data will reveal mechanisms by which increased adiposity can directly affect end organ health, such as skeletal muscle insulin sensitivity.

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PRE-CLINICAL

PROJECT: Age and ethnicity-related differences in adipose specific-inflammation

PROGRAM: Systems Biology

TEAM: MONICA HUBAL, PhD | EVAN NADLER, MD

FUNDING SOURCE: Sheikh Zayed Institute, International Pediatric Research Foundation

SYNOPSIS: Adipose tissue acts as an endocrine organ, secreting pro-inflammatory cytokines. The accumulation of anatomically distinct depots of adipose tissue has disparate effects on disease risks, where the accumulation of omental or visceral adipose tissue (VAT) is particularly associated with increased risk of cardiometabolic disease, while associations with amounts of subcutaneous adipose tissue (SAT) are less clear. The determination of body fat distribution, and thus disease risk, varies by age, sex, and ethnicity. Ethnic disparities in obesity-related diseases are common in the U.S., with African Americans and Hispanics having significantly higher rates of insulin resistance and diabetes than Caucasians. The current study seeks to understand mechanisms underlying ethnic disparities in obesity-related disease development by investigating molecular differences within adipose tissues. We also are exploring the role of age in molecular dysfunction development. We examined depot-specific methylation in lean and obese adult females to determine depot and obesity related epigenetic loci. These data were then integrated with the gene expression profiles to determine functionality and relevant molecular pathways. An important preliminary finding was that obesity drives methylation changes in one of the most central inflammatory pathways, the transforming growth factor beta (TGFß) pathway. The TGFß pathway plays a particularly significant role in liver inflammation, which shows ethnic disparities in disease. Analyses are ongoing.

PROJECT: Magnetic delivery of drugs to the middle ear without ear drum puncture

PROGRAM: Systems Biology
TEAM: DIEGO PRECIADO, MD, PhD | BENJAMIN SHAPIRO, PHD (University of Maryland)
FUNDING SOURCE: Sheikh Zayed Institute, University of Maryland Clark School of Engineering

SYNOPSIS: Acute Otitis Media (AOM, middle ear infection) is the leading cause of physician visits by children. In the U.S., there are an estimated 15 million cases per year of AOM in children younger than five years of age, with associated public health care costs reaching three to five billion dollars. Approximately 20 percent of patients with AOM develop chronic otitis media with effusion (COME). COME results as a long term sequelae of acute middle ear infection, and is characterized by secretory epithelial metaplasia and persistence of middle ear effusion, most frequently mucoid. COME is associated with hearing loss, delayed speech development, and the potential for permanent middle ear damage.

The standard-of-care for AOM is systemic antibiotic administration for select populations, which include children ≤ two years of age, patients with bilateral infection, and with severe disease. Currently 42 percent of all antibiotics prescribed in the U.S. are for the treatment of AOM. This pattern of systemic antibiotic use for AOM has contributed significantly to the appearance of resistant organisms, and to an increased incidence of antibiotic-related side effects. The magnetic injection system designed by Dr. Ben Shapiro's group at the University of Maryland was originally invented to direct therapy to the inner ear, a site that is difficult to reach because of the restrictive blood-labyrinth barrier. However, there is also a critical need to develop alternative and effective treatment strategies for middle ear diseases. Effective trans-tympanic drug delivery to the middle ear without first puncturing the ear drum, especially in infants and children, could prove revolutionary in the management of AOM and COME. It would replace systemic steroids and antibiotics with local drug delivery, retaining efficacy while reducing side effects such as psychosis, gastritis, hypertension for steroids, anaphylaxis, diarrhea, and a changing intestinal flora for antibiotics; and it could obviate the need for tympanostomies and tube insertions in recurrent and chronic otitis media. We are currently working in collaboration with Dr. Shapiro to develop such a system.

PRE-CLINICAL

PRE-CLINICAL

PROJECT: Obesity and Type 2 diabetes effects on the metabolome across age: Does central adiposity underlie increased diabetes rates in Emiratis?

PROGRAM: Systems Biology

TEAM: EVAN NADLER, MD | MONICA HUBAL, PhD

FUNDING SOURCE: Department of Surgery at Children's National

SYNOPSIS: Obesity and Type 2 diabetes are epidemic in many parts of the world including the U.S. and U.A.E. While rates of obesity are similar (approximately 33 percent) between these two countries, there is a disparately higher rate of Type 2 diabetes in Emeratis (approximately 20 percent vs <10 percent in the U.S.), suggesting an altered obesity/diabetes inter-relationship. While environmental differences in diet and activity can contribute significantly to ethnic differences in diabetes rates, we hypothesize that a major factor driving higher diabetes rates in Emiratis is an increased rate of central adiposity (a key diabetes risk factor). The current study will test dependent and intependent effects of obesity and Type 2 diabetic status on blood metabolome differences between Emeratis and European-descent Caucasians living in the U.A.E. Patients will be recruited in partnership with the Imperial College of London Diabetes Center and will include lean controls, obese non-diabetics and obese diabetics, with Emiratis and European-descent expatriates in each group. Dual-energy X-ray absorptiometry (DEXA) will quantify central adiposity. Clinical measures related to cardiometabolic disease will include fasting glucose, HbA1C, liver enzymes, blood pressure, height, weight, and BMI. Blood metabolomics will use a combination of mass spectroscopy techniques at a commercial site. Correlational analyses and group differences by ANOVA will be used to test main and interaction effects of obesity, diabetes, central adiposity, and age on clinical and metabolomic parameters.

PROJECT: Proteomic networks of MUC5B infectious/inflammatory induction in Otitis Media

PROGRAM: Systems Biology
TEAM: DIEGO PRECIADO, MD
FUNDING SOURCE: 5R01DC012377-02, Proteomics in Auditory Diseases, NIDCD

SYNOPSIS: Otitis Media (OM) is one of the most frequent disorders in children requiring physician visits. It is a disease of the middle ear space characterized by acute infectious injury and inflammation, acute OM (AOM), progressing to chronic epithelial mucoid fluid secretion, i.e., chronic OM (COM). In this application, using a proteomic profiling approach, we aim to interrogate how pathologically relevant acute infectious stimuli result in a cascade of inflammatory mediator upregulation, which in turn ultimately lead to middle ear epithelial metaplasia and inappropriate over-expression of mucins. Currently no medications exist to treat COM effectively. An understanding of the molecular mechanisms behind the progression of acute middle ear infection to chronic OM may radically change the way the disease is treated, especially if novel molecular targets are identified.

PROJECT: **Visceral adipocyte exosomes mediate functional changes in hepatocytes and hepatic stellate cells: a novel paradigm for non-alcoholic fatty liver disease pathogenesis**

PRE-CLINICAL

PROGRAM: Systems Biology

TEAM: EVAN NADLER, MD | MONICA HUBAL, PhD

FUNDING SOURCE: Surgery Department Start-Up Funds at Children's National

SYNOPSIS: Nonalcoholic fatty liver disease (NAFLD) ranges from simple steatosis to nonalcoholic steatohepatitis (NASH), and is strongly associated with obesity. NAFLD prevalence is increasing with the obesity epidemic, however there is disparate prevalence across ethnicities (Hispanics > Caucasians > African Americans). We have preliminary evidence that ethnic differences in the adipocyte exosomes may explain this difference. We have isolated and characterized micro RNA from adipocyte exosomes in lean and obese adolescents from the three major ethnic groups above, and found that obesity drives the variability across these cohorts. Most importantly, targeted pathway analysis suggests that miRNA that regulate the TGF-ß signaling pathway are differentially expressed between obese Hispanics and African Americans. Modifications in polymorphisms in TGF-ß pathway members have been implicated in ethnic disparities in liver steatosis after viral infection. We also have preliminary data showing that hepatocytes exposed to visceral adipocyte exosomes upregulate expression of TIMP-1, with concomitant downregulation of MMP-7 drastically shifting these normally homeostatic mediators towards a pro-fibrotic state. Thus, we propose that adipocyte exosomes mediate NAFLD by directly affecting the hepatic parenchyma and altering mRNA and protein expression in the liver. Herewith we propose a series of in-vivo and in-vitro experiments to precisely define the role of adipocyte exosomes in the pathogenesis of NAFLD in an attempt to explain the wide ethnic discrepancies in this disease, and to investigate whether inhibition of various mediators in the TGF-ß signaling pathway can ameliorate the disease processes initiated by adipocyte exosomes.

Vice President's Initiatives

Peter C. W. Kim, MD, CM, PhD
Charles Berul, MD
Haydar Celik, PhD
Patrick Cheng, MBA
Carolyn Cochenour, BS
AeRang Kim, MD
Yonjae Kim, BS
Axel Krieger, PhD
Simon Leonard, PhD
Matthew Oetgen, MD
Laura Olivieri, MD
Justin Opfermann, MS
Azad Shademan, PhD
Karun Sharma, MD, PhD
Kyle Wu, MD, MBA
Pavel Yarmolenko, PhD

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PROJECT: Non-invasive growth plate ablation treatment

PROGRAM: IGNITE

TEAM: PETER C. W. KIM, MD, CM, PhD | MATTHEW OETGEN, MD | HAYDAR CELIK, PhD | PAVEL YARMOLENKO, PhD

FUNDING SOURCE: Clinical and Translational Science Institute at Children's National

PRE-CLINICAL

CLINICAL

SYNOPSIS: Development of novel non-invasive growth plate ablation treatment for children with limb-length discrepancy using MR-guided high-intensity focused ultrasound. Untreated limb length discrepancy may lead to serious problems in ≈8 percent of all children, such as noticeable limping, lower back pain, scoliosis, poor posture, osteoarthritis of the hip and spine, lower extremity stress fractures, and other conditions that require surgery. While the traditional surgical epiphysiodesis is effective, its approaches entail surgical trauma, lengthy recovery, the potential for unreliable results, and the potential need for ionizing radiation for guidance of therapy. This project explores use of MR-HIFU for epiphysiodesis due to the advantages offered by its non-invasive nature and precision. These features have the potential to render the technology superior to conventional surgical methods, possibly allowing a greater number of children to benefit from it. The overall objective of this project is to evaluate feasibility of MR-HIFU treatment of limb length discrepancy in ex-vivo phantoms as well as in survival and non-survival experiments in animals. Our hypothesis is that MR-HIFU ablation of the physis will allow for non-invasive treatment of limb length discrepancy by decreasing the rate of limb growth at the treated physis. In order to test this hypothesis, we will proceed through the following specific aims: 1) Develop and optimize an MR-HIFU heating algorithm and associated MR imaging and mathematical modeling in ex-vivo phantoms, and 2) Determine safety and feasibility of MR-HIFU epiphysiodesis in a preclinical, large animal model.

Initial results indicate that MR-HIFU can be rapidly configured to aim into a small linear structure within a phantom that mimics the physis and surrounding bone and soft tissues. The heated area appears similar in size to the area currently ablated with surgical methods, extending approximately 1 cm into the physis. Having completed this preliminary study, our team is now poised to complete the first specific aim.

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PROJECT: Non-invasive permeabilization of blood-brain barrier with MR-HIFU for drug delivery

CONCEPT FORMATION

PROGRAM: IGNITE

TEAM: PETER C. W. KIM, MD, CM, PhD | ROHAN FERNANDES, PhD | HAYDAR CELIK, PhD | PAVEL YARMOLENKO, PhD

FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: Pediatric brain cancer is often an aggressive and lethal disease. It affects a significant portion of the pediatric oncology patients. The blood-brain barrier (BBB) restricts delivery of most drugs to the central nervous system. Permeabilization of the BBB using MR-HIFU and micro bubbles has been demonstrated with a wide variety of drug delivery applications and animal models of disease. This project focuses on a specific area of this research, where lack of knowledge hampers clinical translation: there is a need to quantify the extent to which the BBB can be permeabilized and to define a range of treatment parameters that ensure continued vascular function following treatment. Continued vascular function in the treated area is necessary to ensure optimal drug delivery and accumulation. To fill this need, our team will quantify both BBB permeability and flow using contrast agents of different size, and investigate drug delivery following treatment. This project will produce a set of treatment criteria that will be further investigated in a larger pre-clinical study.

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PRE-CLINICAL

PROJECT: Optimization of combination of ablative and non-ablative hyperthermia and drug delivery for complete treatment of solid tumors in pediatric patients

PROGRAM: IGNITE

TEAM: AERANG KIM, MD | KARUN SHARMA, MD, PhD | PETER C. W. KIM, MD, CM, PhD | HAYDAR CELIK, PhD | PAVEL YARMOLENKO, PhD

FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: The phase I clinical trial of ablative treatment that will be conducted by our group is an important step towards establishing MR-HIFU. However, a significant portion of the pediatric population with such tumors may benefit more from a treatment that includes the use of local drug delivery with liposomes and mild, non-destructive heating of the tumor. This project will investigate this combination treatment and explore drug delivery and survival. We will use treatment planning algorithms and methods our group recently developed to optimally sub-divide tumors into regions that will be ablated and those that could only be treated with the combination of mild hyperthermia and drugs. Review of pediatric patient data strongly suggests that a significant portion of CNMC pediatric patients that suffer from solid tumors of extremities may benefit from this non-invasive treatment.

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PRE-CLINICAL

PROJECT: Optimization of treatment planning of non-invasive therapy with MR-HIFU

PROGRAM: IGNITE

TEAM: KARUN SHARMA, MD, PhD | PETER C. W. KIM, MD, CM, PhD | HAYDAR CELIK, PhD | PAVEL YARMOLENKO, PhD

FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: Repositioning the patient during the MR-HIFU treatment is a time-consuming process that involves not only re-positioning, but also re-planning of therapy. In addition, treatment following re-positioning requires knowledge of the portion of the lesion that has already been treated, and thus it is computationally intensive and potentially prone to error. We estimate that overall treatment time could be significantly reduced (by as much as 30 minutes for every avoided patient re-positioning) if the lesion geometry is taken into account during positioning of the patient. Thus, further development of non-invasive treatments with externally-focused MR-HIFU will benefit from optimized procedures and algorithms for patient positioning.

To address this challenge, our group has designed an approach to guiding the physician during patient positioning. This process relies on multi-modal (any of the available: MRI/CT/US/PET) imaging data as well as some physician input to provide the physician with visual cues. The resulting patient position is optimized for target geometry and patient anatomy as well as the geometry of areas that are critically important to avoid, such as motor nerves. This approach will be optimized using retrospective analysis of patient data and evaluated using an imaging study of healthy volunteers. We have also begun discussing these potential improvements with our industrial partners. We will work closely with them to integrate the results of this work into commercialization of MR-HIFU instruments.

PROJECT: Cardiac 3D printing

PROGRAM: Infor-Theranostics (Simulation)
TEAM: AXEL KRIEGER, PhD | LAURA OLIVIERI, MD | PETER C. W. KIM, MD, CM, PhD
FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: The use of 3D printing for the purpose of educating trainees and potentially incorporating into workflow to minimize complication and maximize effectiveness will be explored. Cardiac application is selected as a paradigm. In addition, we will use 3D printing to create potentially transplantable tissue in preclinical model for functional and anatomic improvements.

Congenital heart defects are the most common congenital defects and occur in 1-2 percent of the population. Infants and children with heart defects often require surgical or catheterization-based therapies early in life to help heal their hearts and improve their quality of life. We propose to utilize the newest advances in 3D MRI and echocardiography in conjunction with state-of-the-art image segmentation software to create printed 3D models of structural heart disease. To date, ten MRI and 3D echo datasets have been obtained, converted to DICOM format, segmented, and successfully printed. We obtained IRB approval and are currently evaluating the impact of these models on clinical care. We are spearheading a multi-center clinical study to determine the effect of printed models on surgical parameters (such as blood loss and bypass time) and outcomes.

In related works, we developed the capability to 3D print patient-specific biocompatible and bio-absorbable vascular grafts. We are currently evaluating this technology in pre-clinical tests.

PROJECT: Mobile apps – communication device for patients with cerebral palsy

CLINICAL

PROGRAM: Infor-Theranostics (Simulation)
TEAM: AXEL KRIEGER, PhD
FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: The goal of this project is to refine, test, and market a keyboard application for tablets, tailored to overcome the specific motor impairments of nonverbal or minimally verbal pediatric patients with cerebral palsy (CP). We hypothesize that the keyboard application improves speed and quality of communication for patients with cerebral palsy.

An estimated 500,000 people under the age of 18 in the U.S. are affected by cerebral palsy (CP). With 10,000 babies born each year developing CP, it is the most common cause of severe disability in childhood. CP is a group of movement disorders resulting from injury to the developing brain caused by lack of oxygen, infection, or other etiology. Motor planning, control, and coordination of fine motor movements are often impaired to a varying degree in individuals who have CP. Additionally, many individuals with CP may also have difficulties with control of facial muscles, resulting in impaired speech. Alternative and Augmentative Communication (AAC) devices have shown to improve quality of life and function in individuals with impaired language skills. The ability to communicate is essential to social development, learning, and autonomy. The current AAC devices on the market are complicated and difficult to use because they require fine motor control that are impaired in some children with cerebral palsy.

The team developed a fully functioning keyboard application on the Android platform and received IRB approval for a clinical comparison of efficiency and accuracy with the market leading AAC device.

PROJECT: Mobile apps – telemedicine – ostomy/wound management

PROGRAM: Infor-Theranostics (Simulation)
TEAM: PETER C. W. KIM, MD, CM, PhD | KYLE WU, MD | PATRICK CHENG, MBA
FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: This project aims at developing a telemedicine management platform incorporating mobile app and cloud computing to deliver an integrated healthcare model to improve patient experience, clinical outcome, and cost savings.

Each year, 150,000 Americans undergo ostomy surgeries where one end of the disconnected bowel is brought through the abdominal wall to re-establish passage of stool after bowel resection. Receiving an ostomy, whether planned or not, brings significant physical and psychosocial stress to the patient. They are especially vulnerable to adverse clinical outcomes. About 35 percent of these patients get re-admitted to hospital within 60 days after discharge, incurring a $9,000 cost per re-admission episode. However, studies have shown that a significant portion of readmissions can be prevented with adequate post-discharge monitoring. Currently, such interventions are costly and require intense human capital. Leveraging the latest image processing and mobile technology, we propose to streamline wound/ostomy post-dicharge care and monitoring through a tele-management platform.

Prototype of the tele-management platform is under development, including cloud infrastructure implementation, image processing and computer vision algorithm coding, and web portal designs. The preliminary clinical trial is expected in November 2013, with a plan for full scale multi-center clinical trial in the second quarter of 2014.

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PROTOTYPING

PROJECT: A new generation of tissue-engineered vascular grafts using 3D printing technology

PROGRAM: Infor-Theranostics (Simulation)

TEAM: AXEL KRIEGER, PhD | JOHN FISHER, PhD (University of Maryland) | CAROLYN COCHENOUR, BS | JOHN COSTELLO, MD

FUNDING SOURCE: Sheikh Zayed Institute, University of Maryland Clark School of Engineering

SYNOPSIS: Coronary artery disease accounted for approximately half of all heart disease related deaths in 2009 with more than 385,000 deaths out of 600,000 deaths associated with heart disease. One common treatment option available for coronary artery disease is a bypass surgery. To address current challenges and improve patient health, there has been a shift from traditional non-biodegradable grafts to biodegradable grafts, with the goal of promoting growth of native vessel tissue. We are using a biocompatible/biodegradable polymer such that we can adjust the mechanical properties of the graft and utilize topological cues to enhance the survival, proliferation, and migration of endothelial cells on our vascular grafts.

The end goal of this project is to develop a new category of tissue-engineered vascular grafts (TEVGs) utilizing 3D printing technology to precisely control topology and functionalize the surface for the manipulation of endothelial cell proliferation and survival, with the aim of reducing the risk of thrombosis and stenosis for small-diameter grafts. To accomplish our overall goal, we are approaching this problem using biological assays as well as mathematical modeling of our flow system in order to encourage endothelialization and minimize potential problems due to non-laminar flow.

The ability to successfully create these TEVGs will have a direct impact on what tools are available to surgeons and provide them with alternatives from current treatment options. This project will be the first step towards making patient-specific, small-diameter vascular grafts that recruit endothelial cells and recapitulate the native mechanical properties. The results of this work will have a broader impact on the design and fabrication of other more complex cardiovascular structures for implantation.

PROJECT: EndoPyloric tool

PROGRAM: SMART Tools

TEAM: AXEL KRIEGER, PhD | CAROLYN COCHENOUR, BS | TIMOTHY KANE, MD | PETER C. W. KIM, MD, CM, PhD

FUNDING SOURCE: Sheikh Zayed Institute

PRE-CLINICAL

SYNOPSIS: EndoPyloric Tool (EPL) is a device development project where we are changing the current open and minimally invasive surgical approach of treating pyloric stenosis in newborns to natural orifice-based balloon dilatation, obviating any incision.

Hypertrophic pyloric stenosis (HPS) is one of the most common reasons for infants to undergo surgery, occurring in approximately 10,000 births per year in the U.S. The pylorus is the muscle which separates the stomach from the duodenum, and in children with this condition, the muscular layers have become abnormally thickened. Correspondingly, the diameters of the pyloric canal and sphincter are reduced and thus do not permit normal passage of food. Laparoscopic and open pyloromyotomy offer definitive treatment for pyloric stenosis but are associated with complications, including perforation, incomplete myotomy, and infection. Effective pyloromyotomy enlarges the pyloric channel at most 30 percent circumferentially. We hypothesized that a similar outcome can be accomplished effectively with an endoluminal balloon tool.

We designed a new endopyloric catheter-based balloon dilation tool and evaluated the tool in cadaveric rabbit models. Effective dilatation was achieved (increase in normalized circumference, $2\varpi R$) of 63 percent in the rabbit pylorus (+/- 0.47, n=4) and 112 percent in the rabbit cervices (+/-0.23, n=4) resulting in a proportional increase in flow based on a normalized cross-sectional lumen area of 181 percent in rabbit pylorus (+/-1.58) and 354 percent in rabbit cervices (+/-1.25) (p=0.001). Histological examination demonstrated intact mucosa in all specimens. Balloon inflation up to three times the diameter of the pre-dilated pyloric lumen was determined to be safe with no tearing of the samples. This novel endopyloric tool has potential for less invasive surgical treatment of pyloric stenosis. Preclinical in-vivo testing of this non-invasive endoscopic approach and technique will be conducted.

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PRE-CLINICAL

PROJECT: Minimally invasive epicardial pacing

PROGRAM: SMART Tools

TEAM: CHARLES BERUL, MD | AXEL KRIEGER, PhD | JUSTIN OPFERMANN, MS | TIMOTHY KANE, MD | PETER C. W. KIM, MD, CM, PhD

FUNDING SOURCE: Sheikh Zayed Institute, University of Maryland Clark School of Engineering

SYNOPSIS: The goal of this project is to change the current paradigm of placing cardiac pacing wires from an open approach to a minimally invasive one, reducing collateral tissue injury and accelerating recovery. The team developed a minimally invasive epicardial pacemaker implantation method for infants and congenital heart disease (CHD) patients for whom a transvenous approach is contraindicated or impossible. The piglet is an ideal immature animal model for surgical technical development. This approach has not been reported in infants or infant-sized animal models.

In five piglets (4-5 kg), a needle was introduced via a subxiphoid approach under thoracoscopic guidance, and a wire was inserted into the pericardial space. With curved sheaths, pacing leads were affixed to the left ventricular (LV) free wall and left atrial appendage (LAA) under thoracoscopic visualization. After verifying functionality with atrial and ventricular pacing and sensing, the animals were euthanized. Pacemaker function was monitored daily for four days in the last animal.

With a minimally invasive pericardial approach, we fixated a pacing lead to the LV and LAA under direct visualization, with successful atrial and ventricular pacing. Coronary arteries and critical epicardial structures were easily visualized. One piglet experienced pneumothorax on the contralateral side resolving with needle decompression. No other acute adverse events occurred.

Minimally invasive epicardial pacemaker implantation in an infant-sized model is feasible and effective. This approach may shorten hospitalization and decrease pain, complications, and cost as opposed to sternotomy or thoracotomy. This innovation represents a new implant method, and may be of value for pacing and resynchronization in infants and CHD patients. Survival studies with permanent generator implantation are underway.

PROJECT: Natural Orifice Anastomosis Device

PROGRAM: SMART Tools

TEAM: AXEL KRIEGER, PhD | CAROLYN COCHENOUR, BS | PETER C. W. KIM, MD, CM, PhD

FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: Natural Orifice Anastomosis Device (NOAD), a catheter-based anastomosis device, provides the surgeon with a catheter-based, minimally invasive method by which to access a site for the anastomosis through a natural body orifice and reduce the associated trauma of the open or minimally invasive procedure. For the purposes of this project, we want to establish proof of concept by creating an esophageal anastomosis for the case of children born with esophageal atresia. NOAD differs from other catheter devices and methods for anastomosis by allowing anastomosis through the deployment of an expandable structure, with multiple arms containing engagement regions to join and secure body vessels. Before deployment, the catheter is advanced through the natural orifice to the most distal vessel. The distal vessel is engaged by deploying the expandable structure. The distal vessel is then brought into the proximal vessel by actuating the deployment system. The second or proximal section of the expandable structure is then deployed and engages with the proximal vessel wall as well as with the distal portion of the device. The device is secured in the deployed state, sealing the anastomosis through radial pressure and longitudinal tension. The device is then released from the deployment catheter, and the catheter is removed. The device remains at the anastomosis site, maintaining the anastomosis until the wound is healed. The device is made from biodegradable materials that are absorbed by the body.

The team filed a utility patent in April 2013 and has been working to build the prototypes for large-scale bench testing. The prototypes are made from plastics with similar properties to available biodegradable polymers. This is to simplify the test environment isolating the function of said structures. Bench testing will be conducted using synthetic esophagus tissue to test the holding strength of the device.

MEDICAL DEVICES | HEALTHCARE SOFTWARE | DRUGS / BIOLOGICS

PRE-CLINICAL

PROJECT: Smart Tissue Anastomosis Robot

PROGRAM: SMART Tools

TEAM: AXEL KRIEGER, PhD | PETER C. W. KIM, MD, CM, PhD | SIMON LEONARD, PhD | JUSTIN OPFERMANN, MS | AZAD SHADEMAN, PhD

FUNDING SOURCE: Sheikh Zayed Institute

SYNOPSIS: The goal of Smart Tissue Automation Robot (STAR) development is to create smart surgical tools that have the best practice and techniques of experienced surgeons, programmed into tools so that optimal efficiency, effectiveness, and safety are delivered consistently while enhancing access to the best practice.

Anastomosis is a critical surgical task performed millions of times each year for gastrointestinal (GI) and urologic conditions in the U.S. However, up to 30 percent of GI anastomoses are complicated by leakage, strictures, and stenosis, in part attributable to technical and technologic issues of surgical tools. Anastomosis remains one of the rate-limiting steps in broader adoption of minimally invasive surgery (MIS), particularly in children. We introduce three novel innovative technologies in STAR: (1) Novel end effector that incorporates and simplifies current surgical technique; (2) New visual modality that allows tracking of mobile deformable soft tissue targets which could not be done before; and (3) Collaborative decision support for surgical task decisions between the surgeon and smart tool based on real-time target information.

An accuracy study of our STAR prototype demonstrated a positional accuracy of 0.5 mm. A comparison study of efficiency and efficacy of STAR to state-of-the-art master-slave robotic (da Vinci) and manual laparoscopic techniques showed five- and nine-fold time reduction respectively and four times increased consistency in suturing planar suture phantoms with one knot and nine running sutures. A comparison study of efficacy for STAR in autonomous mode compared to manual mode demonstrated more consistent bite size and suture spacing in autonomous mode.

The team has filed several patents on this technology and is currently preparing for pre-clinical testing using STAR. This paradigm of "intelligent tools" exemplifies the next generation of surgical tools that will not only enhance function and outcome of surgical tasks such as anastomosis, but also enable and improve MIS procedures.

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