scientific ANNUAL REPORT

OCTOBER 1, 2013 -
SEPTEMBER 30, 2014

Children's National™

Sheikh Zayed Institute
for Pediatric Surgical Innovation

Part of the Children's National Health System

OUR MISSION IS TO MAKE PEDIATRIC SURGERY **MORE PRECISE, LESS INVASIVE**, AND **PAIN FREE**.

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I am pleased to present the Sheikh Zayed Institute's third scientific report, highlighting the Institute's progress from October 1, 2013 through September 30, 2014. During the reporting period, we formed new collaborations and partnerships that open the way to complimentary and integrated expertise.

We continue to be driven by our mission to "make pediatric surgery more precise, less invasive, and pain free." We are keen to stimulate meaningful engagement among all stakeholders – patients and families, clinicians, researchers, engineers, business professionals, and policy makers – to improve children's health.

Innovation – We are committed to open innovation. In this past year, we opened two challenge competitions to innovators throughout the world to accelerate the advancement of pediatric surgical and device innovation. As a result, we awarded $325,000 to seven companies that develop pediatric devices. The awardees collaborate with us – and are now connected with each other, and with our network of experts – to promote best practices to accelerate the pediatric products' path to market.

Partnership and Collaboration - At our 2nd Annual Symposium on Pediatric Surgical Innovation, we brought together leaders and advocates of pediatric surgical and device innovation to form consensus and actionable tasks to accomplish one major goal: get pediatric products to children who need them. Through this annual event, we have created a venue to work together and collectively figure out how to come up with efficient paths to bring pediatric surgical and medical devices to market.

Path to Bedside – To close the gap that exists between our innovations and commercially viable technologies that enter the market, we rolled out the Entrepreneur In Residence (EIR) Program to ensure that the innovators receive the resources needed to transform the technology from ideation into a market ready product. This program is also designed to support the early stage start-ups that are spun out of the Institute.

Efficiency and Accountability – Through our Stage Gate process, we have been able to maximize the use of our scarce resources and funding. Moreover, programs are held accountable to milestones, deliverables, and Go/no-Go time points. This is in an effort to ensure promising programs receive the support they need to reach their goals, while those that fall short of their targets are redirected or closed. This demonstrates our commitment to responsible stewardship to maximize our donors' and investors' Return on Investment (ROI) and Return on Philanthropy (ROP). We constantly measure impact in terms of value to children and families whom we serve.

We continue the trust of our original sponsors in Abu Dhabi to translate our innovations to the bedside – for children everywhere.

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

a MESSAGE from our VICE PRESIDENT

SHEIKH ZAYED INSTITUTE **leadership**

VICE PRESIDENT	Peter C. W. Kim, MD, CM, PhD
EXECUTIVE DIRECTOR	Kolaleh Eskandanian, PhD, MBA, PMP

Catherine M. Bollard, MBChB, MD
Kevin Cleary, PhD
Julia Finkel, MD
Craig Peters, MD
Diego Preciado, MD, PhD
Zenaide Quezado, MD
Anthony Sandler, MD
Raymond Sze, MD

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

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Brian Duncan, MD, MBA, Medical Director, Sorin Group

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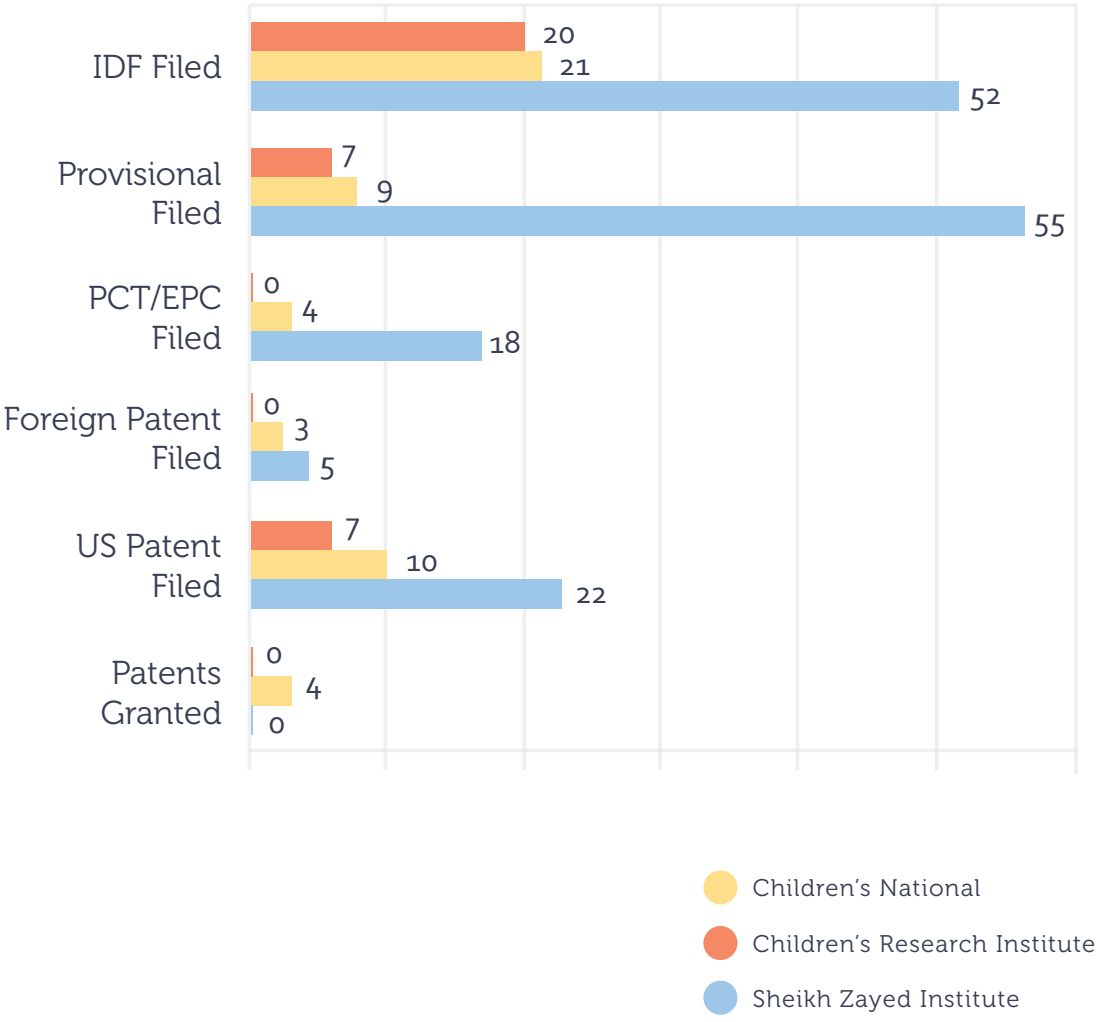
Josh Makower, MD, Partner, NEA

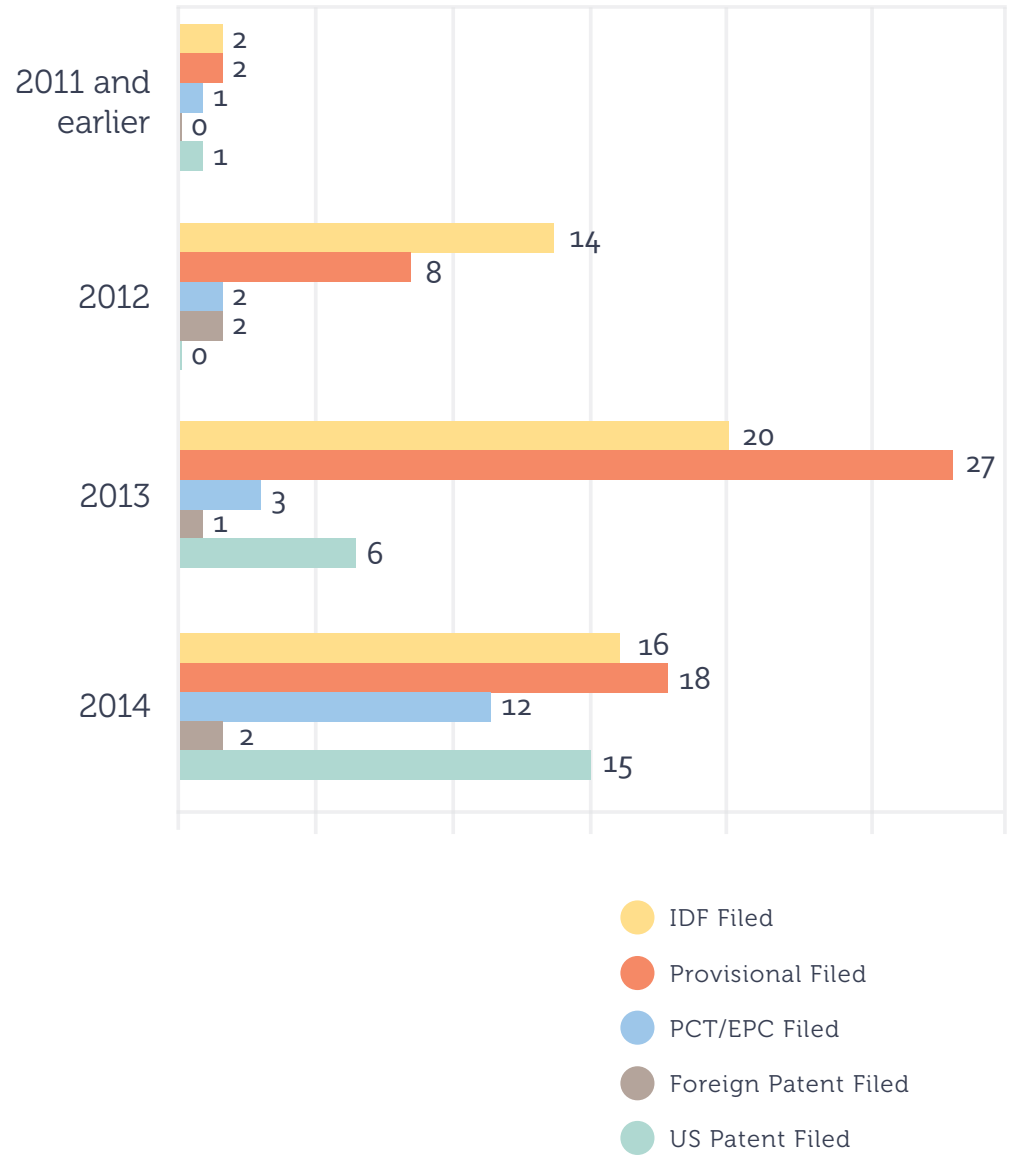
David Schlitz, JD, Partner, Baker Botts LLP

INTELLECTUAL PROPERTY **portfolio**

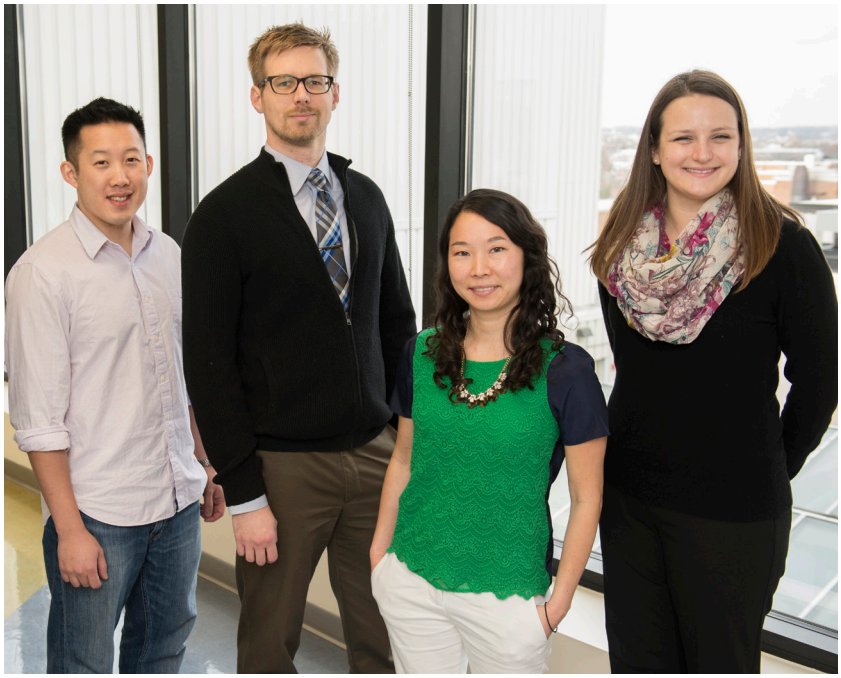
Intellectual Property Portfolio at Children's National Health System



Intellectual Property Portfolio at the Sheikh Zayed Institute for Pediatric Surigcal Innovation



EDUCATION intiatives



JOSEPH E. ROBERT, JR. FELLOWSHIP

This past year we welcomed the fourth class of Joseph E. Robert, Jr. fellows. In addition to partnering with the Institute's principal investigators in ongoing R&D projects, the fellows also participated in pre-clinical and clinical trials activities. Mentored by the Entrepreneurs In Residence, selected Robert fellows' projects were accepted into the NSF-funded DC I-Corps program, taught by successful technology entrepreneurs. Over the course of several weeks, the Robert fellows talked to approximately hundred customers, competitors, and other market stakeholders – all in order to validate their concept and probe if a product-market fit exists.

STUDENT INNOVATOR PROGRAM

In Summer 2014 the Institute welcomed over forty high school, college, and graduate students to spend the summer working side-by-side our leading biomedical researchers. The program covered a minimum of 6 weeks and placed the students across all our laboratories. In addition, students attended didactic courses on biomedical research, intellectual property, and commercialization. As a highlight of the program, the students participated in a hackathon, jointly organized by the Sheikh Zayed Institue, the Clinical and Translational Science Institue, and the Bear Institute. Concepts for a Neonatal Intensive Care Unit (NICU) dashboard, presented by the students, were later incorporated into a working product, currently being piloted by physicians and nurses of the NICU.

JOSEPH E. ROBERT, JR. **fellows**

TANYA DAVIS

Tanya Davis, MS, MD, joined the Institute in 2014 as a Joseph E. Robert, Jr., Fellow after completion of her residency in Urology at the Medical College of Wisconsin. She also is joining Children's National Health System's Division of Urology as a Pediatric Urology Fellow. She received her medical degree with a Distinction in Bioethics from Albany Medical College and an MS in Healthcare Management. Her clinical and research interests include translational research related to urinary tract infections in children with neurogenic bladders as well as pediatric urologic surgical device development and innovation. Within the institute, she also collaborates with pediatric cardiac surgery and cardiology on surgical device research and minimally invasive surgical technique development.

MATTHIEU DUMONT

Matthieu F. Dumont, PhD, is a chemist with a passion for nanomedicine. His work at the Sheikh Zayed Institute for Pediatric Surgical Innovation focuses on the design of new smart contrast agents designed to expand the power of MRI, allowing physicians to visualize diseases at the molecular level. Dr. Dumont's other area of interest are smart materials that can be dissolved on command or detected with special cameras. These materials are developed with Children's National surgical teams to improve on procedure outcomes and patient comfort. His work on nanomedicine and smart materials yielded multiple publications and pending patents. He received his PhD in Inorganic Chemistry from University of Florida where he studied materials science, nanotechnology, and MRI.

NORA LEE

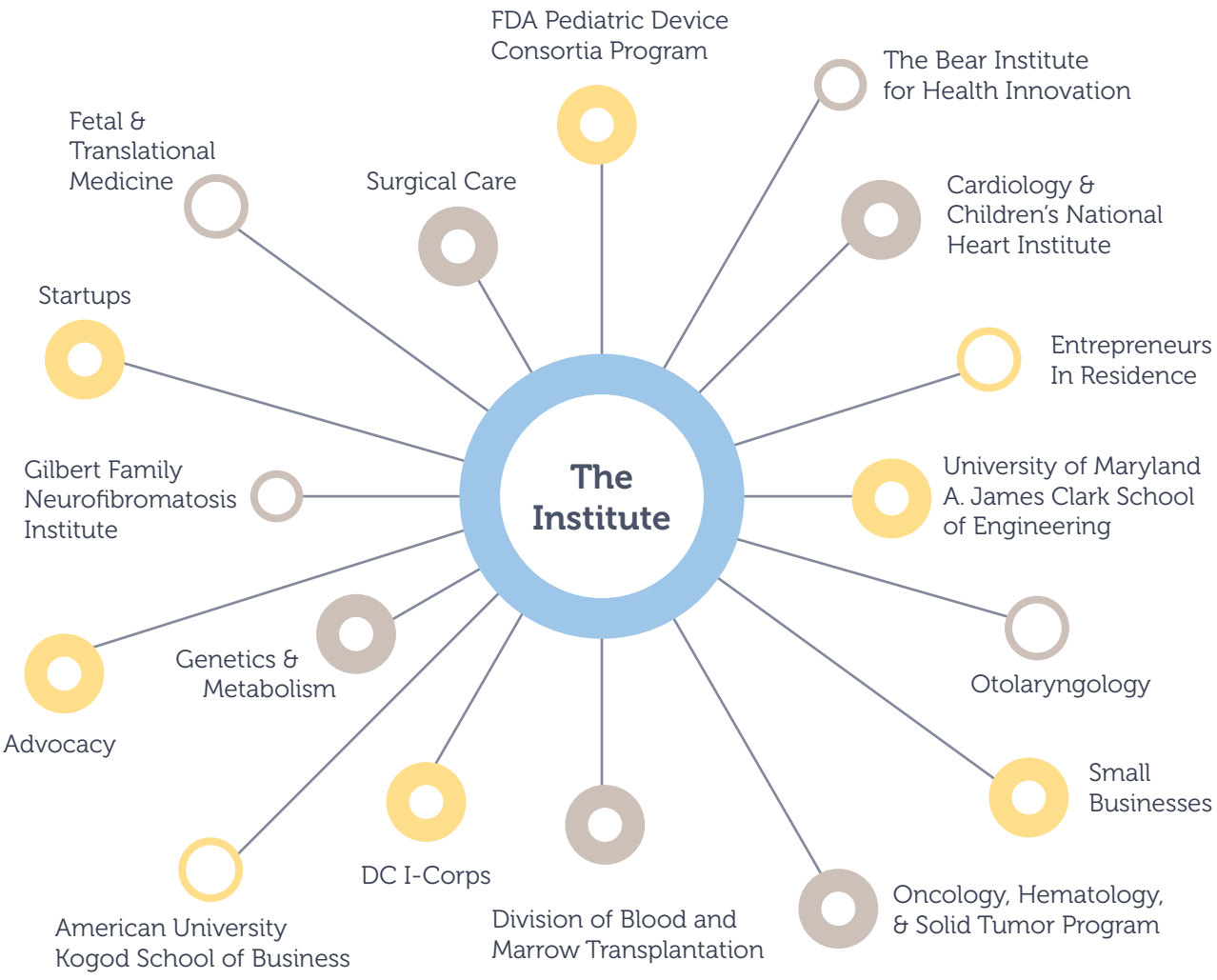
Nora Lee, MD, is a urologist with research interests in urinary biomarkers for congenital urinary obstruction, catheter associated urinary tract infections in pediatric institutions, and robotic surgery. She completed her MD degree at the University of Virginia in Charlottesville and completed a five-year urology residency at Boston University. She finished her clinical year of fellowship in pediatric urology Children's National and is currently working in the Sheikh Zayed Institute as a research fellow. Her current projects include 2D and 3D image analysis on ultrasonography to predict function and drainage of obstructed kidneys as well as novel use of a blow spin polymer as an agent for tissue repair.

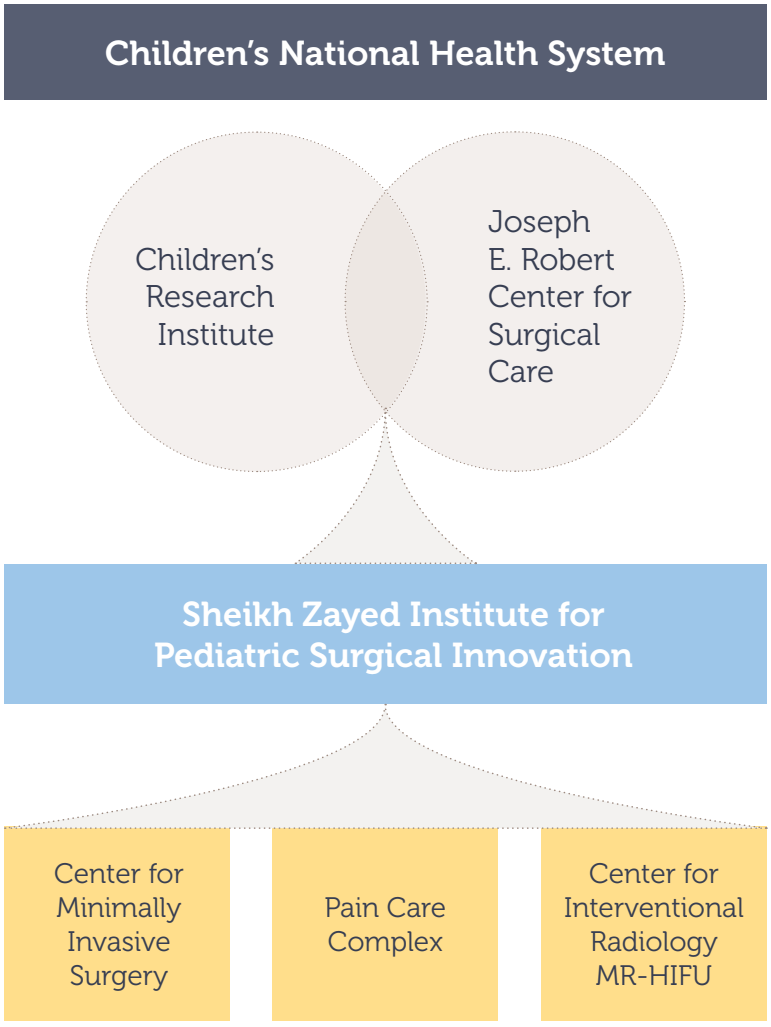
JONATHAN TAN

Jonathan Tan, MD, MPH, is a pediatric anesthesiologist and a Joseph E. Robert, Jr., Fellow. His research has focused on evaluating healthcare technology, data-driven medical decision-making, and the effectiveness and cost-effectiveness of innovative products and processes. Dr. Tan received his bachelor's degree in Biology as well as Health and Society from the University of Rochester, an MPH from the Yale University School of Epidemiology and Public Health with a focus on Health Policy and Administration, and a MD from SUNY Stony Brook School of Medicine. Dr. Tan completed his residency training in Anesthesiology at SUNY Stony Brook Medical Center where he was Chief Resident and completed his Pediatric Anesthesiology Fellowship at the Children's Hospital of Pittsburgh.

CREATIVE **connections**

NEW & ONGOING COLLABORATIVE INITIATIVES




Children's National Health System
Children's Research Institute
Joseph E. Robert Center for Surgical Care
Sheikh Zayed Institute for Pediatric Surgical Innovation
Center for Minimally Invasive Surgery
Pain Care Complex
Center for Interventional Radiology MR-HIFU

1 THE INSTITUTE + Advocacy

HILL DAY

On March 4, 2014, the Sheikh Zayed Institute's faculty and staff visited Capitol Hill and held an all-day event highlighting the latest in pediatric surgical innovation at the Rayburn House Office Building of United States House of Representatives. Members of the Congress and visitors were invited to stop by the Institute's stations to speak with experts about pediatric surgical innovations to improve children's health around the world.

> "A HIGH-PROFILE EVENT SUCH AS THIS **ALLOWS US TO DEMONSTRATE THE TRUE VALUE** OF THE GOVERNMENT OF ABU DHABI'S GENEROUS GIFT TO CHILDREN'S NATIONAL AND THE **WORLD-CLASS INNOVATION WE ARE ABLE TO PRODUCE** AT THE SHEIKH ZAYED INSTITUTE."
>
> **Peter Kim, MD, PhD**
> Vice President, Sheikh Zayed Institute


VFW
8766

SECOND ANNUAL SYMPSOSIUM ON PEDIATRIC SURGICAL INNOVATION

With the second annual symposium, held on October 24, 2014, the Sheikh Zayed Institute for Pediatric Surgical Innovation brought together key leaders from the National Institutes of Health, the Food and Drug Administration, medical device industry, law firms, pediatric societies and advocacy groups, along with scientists, engineers, clinicians and policy makers. The symposium's keynote address was delivered by Margaret A. Hamburg, MD, commissioner of the FDA. The event drew more than 230 attendees and was held at The Newseum in Washington, D.C. The program included panel discussions on the clinical and regulatory pathways for pediatric devices, lessons to be learned from pediatric drug development, growth capital for pediatric innovation and coverage reimbursement from the payor perspective.

“I […] APPLAUD THE CHILDREN’S NATIONAL HEALTH SYSTEM’S SHEIKH ZAYED INSTITUTE FOR PEDIATRIC SURGICAL INNOVATION BECAUSE IT LAYS OUT A SET OF AMBITIOUS GOALS FOR MAKING PEDIATRIC SURGERY MORE PRECISE, LESS INVASIVE, AND PAIN FREE. CERTAINLY HOW YOU’VE GONE ABOUT TRYING TO ACHIEVE THIS GOAL IS A MODEL TO EMULATE. BESIDES **BRINGING TOGETHER** A CRITICAL MASS OF **TALENTED EXPERTS**, YOU’VE RECOGNIZED THAT **SIGNIFICANT HEALTHCARE ADVANCES** ALSO **REQUIRE CREATIVE CONNECTIONS** WITH PATIENTS AND FAMILIES, CLINICAL, ACADEMIC, GOVERNMENT, AND CORPORATE PARTNERS IN WASHINGTON, THE NATION, AND THE WORLD.”

Margaret Hamburg, MD
FDA Commissioner

SECOND ANNUAL SHEIKH ZAYED PRIZE IN PEDIATRIC DEVICE INNOVATION

As part of the Symposium, in a competition, two pediatric medical device innovators, Velano Vascular and REBIScan, were selected from eight finalists to each receive a $50,000 Sheikh Zayed Award in Pediatric Device Innovation. A total of 56 submissions from five countries were received for the competition. The finalists each made five-minute presentations to the symposium audience and then responded to judges' questions.

Sharing their device for the first time in a public forum, the team from Velano Vascular, of Philadelphia and San Francisco, presented a novel innovation that enables safe, effective needle-free blood draws for hospitalized children. Award-winner REBIScan, of Cambridge, Mass., presented a handheld vision scanner for the eradication of amblyopia ("lazy eye").

SHEIKH ZAYED PRIZE WINNERS

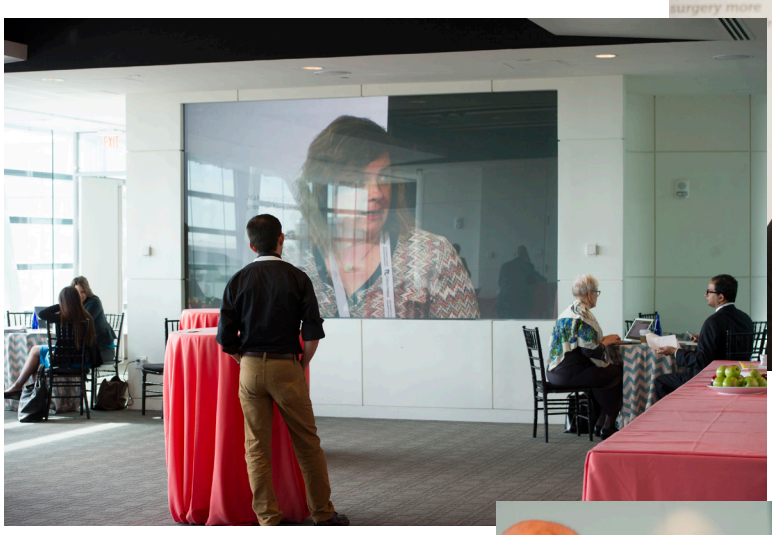
"The competition's esteemed judges and the caliber of fellow presenters makes winning this prize even more validating as we make this technology a reality for our children."

Eric Stone, Co-Founder, Velano Vascular

"This prize has a deep impact because it will enable us to transition from the regulatory phase into manufacturing so that we can get our device into the hands of clinicians."

Justin Shaka, CEO and Co-Founder, REBIScan


Children's National
Sheikh Zayed Institute
for Pediatric Surgical Innovation



2 THE INSTITUTE + FDA Pediatric Device Consortia Program

NATIONAL CAPITAL CONSORTIUM FOR PEDIATRIC DEVICE INNOVATION: INAUGURAL YEAR IN REVIEW

Funded through US Food and Drug Administration's Pediatric Device Consortia Grant Program in 2013, the National Capital Consortium for Pediatric Device Innovation (NCC-PDI) is a partnership of the Sheikh Zayed Institute for Pediatric Surgical Innovation at Children's National Health System and the A. James Clark School of Engineering at the University of Maryland.

The Consortium supports pediatric medical device development throughout the development lifecycle—concept formation, prototyping, preclinical, clinical, manufacturing, marketing, and commercialization.

Support from NCC-PDI includes:

1. FUNDING TO DIRECTLY ADVANCE QUALIFIED PEDIATRIC DEVICE PROJECTS
2. EXPERT CONSULTATION ON:
   - Business planning for pediatric device development
   - Securing funding from dilutive and non-dilutive sources
   - Preparing for FDA pre-submission meetings and deficiency meetings
   - Preparation and submission of IDE, HUD/HDE, 510(k), PMA applications
   - Scientific and engineering aspects of pediatric device development
   - Clinical research with pediatric population
   - Legal and intellectual property

National Capital Consortium for Pediatric Device Innovation

Children's National
Sheikh Zayed Institute for Pediatric Surgical Innovation
Part of the Children's National Health System

University of Maryland 1856
A. James Clark School of Engineering

FDA

In addition to seed funding, in its first year, the NCC-PDI **provided consultation to 36 projects** at different stages of device development lifecycle. These consultations included expert advice in the following:

Patent Applications Filed:
20

Initial Prototypes Generated:
18

Advanced Prototypes Generated:
18

Licenses or Option Agreements Executed:
3

Animal Studies Advised:
15

Other Preclinical Studies:
16

Human Studies Advised:
15

HDE/HUD:
5

IDEs Advised:
5

510(k) Applications Advised:
7

National Capital Consortium
for Pediatric Device Innovation

The **NCC-PDI FUNDED 5** teams/companies as part of the **1st Annual Pediatric Device Innovation Competition** held on April 3, 2014.

TOTAL AMOUNT AWARDED AT COMPETITION:
$225,000

FIRST YEAR OF OPERATION

WINNING TEAMS / COMPANIES

Vittamed Corporation
AWARD $50,000
Non-Invasive Intracranial Pressure (ICP) Meter Head Frame Modification for Children
PI: Remis Bistras, PhD, MBA

Vasoptic Medical, Inc. & University of Maryland Baltimore
AWARD $50,000
Development of Laser Speckle Contrast Imaging as a Non-Invasive Diagnostic for Retinopathy of Prematurity
PIs: Janet Alexander, MD &
Jason Brooke, MSE, JD

Procyrion, Inc
AWARD $50,000
Development of a Novel Catheter-Deployed Cavopulmonary Support Device for Management of Single Ventricle Physiologies Associated with the Fontan Procedure
PIs: Omar Benavides, PhD &
Jason Heuring, PhD

Otomagnetics LLC & Children's National Health System
AWARD $50,000
Magnetic System to Direct Therapy to Middle Ear Infections in Children
PIs: Benjamin Shapiro, PhD &
Diego Preciado, MD, PhD

University of Maryland Baltimore, Centerfor Advanced Sensor Technology
AWARD $25,000
Engineering Optimization of a Low-Cost Multifunctional Incubator
PI: Govind Rao, PhD

The chief challenge [in pediatric device development] is the small market size, which makes it unattractive for venture funding and large device companies to include pediatric medical devices in their R&D portfolio. That said, less competition means a company can have an edge in this niche market.

Kolaleh Eskandanian, PhD, MBA, PMP
Executive Director of the Sheikh Zayed Institute,
in an interview with AAMI News, December 2014

3 THE INSTITUTE
+ Entrepreneurs In Residence

The gap between innovations and commercially viable technologies that enter the market is not an unfamiliar concept. The Sheikh Zayed Institute, in consultation with its Business Advisory Council, partially attributed this gap to the absence of resources such as resident entrepreneurs. In order to facilitate the movement of the technology along the commercialization path, the Institute rolled out the Entrepreneur In Residence (EIR) Program to ensure that the innovators receive the resources required to transform the technology from ideation into a commercially viable product, ultimately to have a positive impact on children's health. In addition to backing the innovators, the program is designed also to support the early stage start-ups that are formed. The initial two EIRs are Tim Moran and Mark Chandler.

> "We are thrilled to strengthen the innovation hub of the hospital with Mark, Tim, and their collective experience in bringing ideas to market."
>
> **Kolaleh Eskandanian, PhD, MBA, PMP**
> Executive Director of the Sheikh Zayed Institute

"We are confident that our EIRs, Mark Chandler and Tim Moran, will continue to accelerate the growth of our ideas from conception to market. Both are serial entrepreneurs who have gone through the start-up process, launched medical products to market, and maintain solid relationships among the regulatory, intellectual property law, industry, and investor communities."

Peter C.W. Kim, MD, CM, PhD
Vice President of the Sheikh Zayed Institute

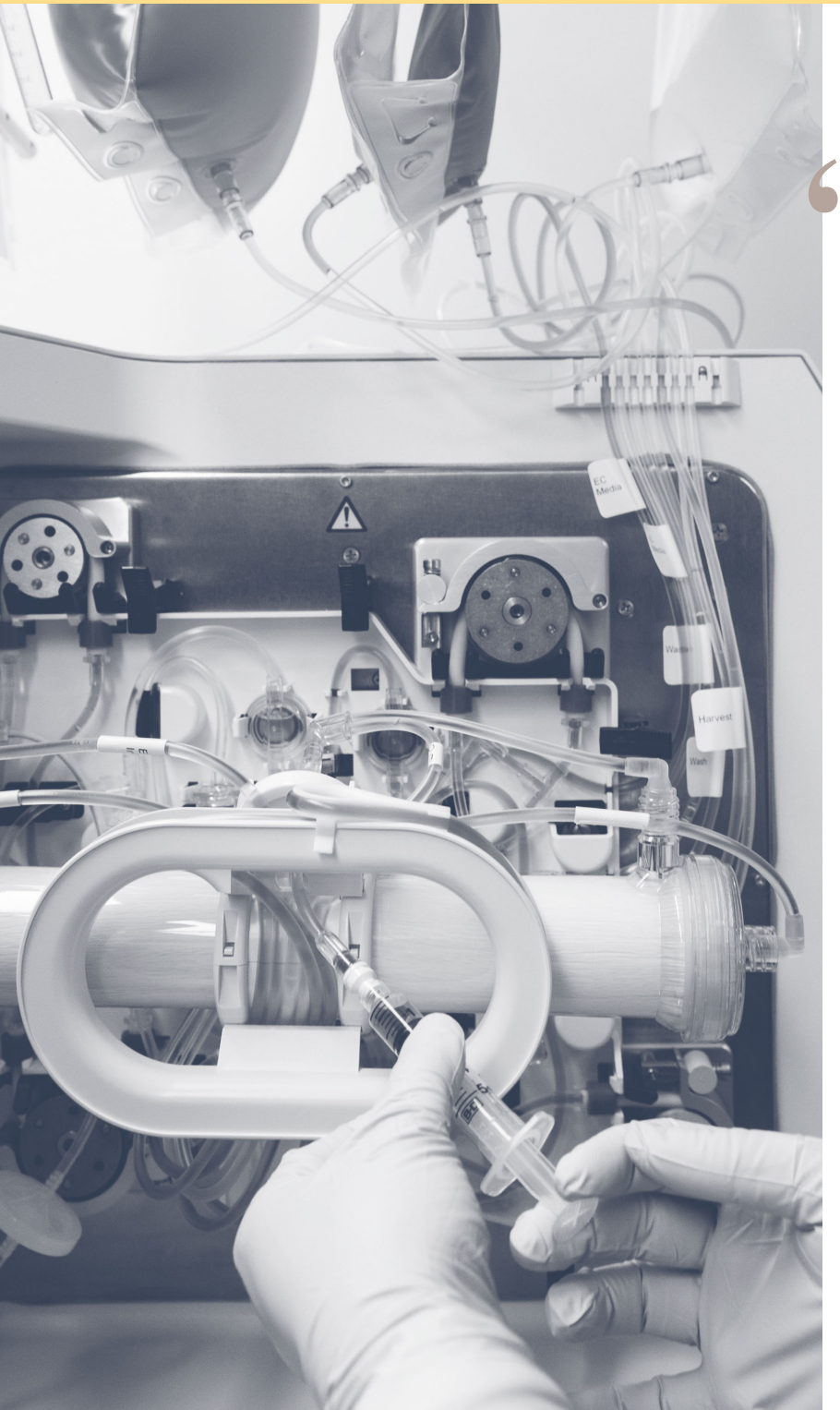
MARK CHANDLER

Mark Chandler, MBA is Managing Director of Upstream Partners, where he provides advisory and transaction services in the areas of intellectual property and finance. Active for over 20 years in technology and intellectual property (IP) commercialization, Mark has helped early-stage ventures, universities, research institutes, companies of all sizes, and independent inventors value, develop, and commercialize their technology. Mark is also Chief Executive Officer of TAO Life Sciences Inc., an early stage medical device investment and development company that invests its capital and expertise to develop prototypes, demonstrate clinical proof of concept, and secure financial exits for its innovations. Mark managed a $60 million early-stage corporate venture capital fund for BTG plc and also helped form Primaxis Technology Ventures, Inc., a $50 million Canadian early-stage venture fund, for which he also served on the Board of Directors. He has also served on the Board of Directors for several early-stage venture-backed companies. Mark completed his undergraduate studies in Electrical Engineering (BSEE, Bucknell University) and continued his technical education in Physics while working at the Johns Hopkins Applied Physics Lab. He practiced as a researcher building the world's most accurate atomic clocks and implantable medical devices, and then obtained his MBA from the Wharton School of the University of Pennsylvania.

TIM MORAN

Tim Moran, MBA is Founder and CEO of PediaVascular and Founder and Executive Director of PediaWorks. Motivated by an experience with his premature daughter, Tim Moran formed PediaWorks to improve pediatric clinical outcomes by developing medical devices specifically for children. As a 501(c)(3) non-profit, PediaWorks selects projects based on clinical impact rather than sales or profit potential. In 2010, PediaWorks assembled a team of over 50 pediatric interventional cardiologists to identify device needs in their field. It then formed a social venture, PediaVascular, along with an international manufacturer, to co-develop and market many of the identified devices. To date PediaVascular offers the only angiography catheters and introducer sheaths the FDA has cleared for pediatric use. PediaWorks is currently developing several devices in interventional cardiology and applying its needs-based approach to other pediatric specialties. In addition to managing its own projects, PediaWorks has also provided pro bono commercialization assistance to clinicians and researchers at select institutions. Tim obtained his MBA from Northwestern University Kellogg School of Management.

4 THE INSTITUTE + Division of Blood and Marrow Transplantation

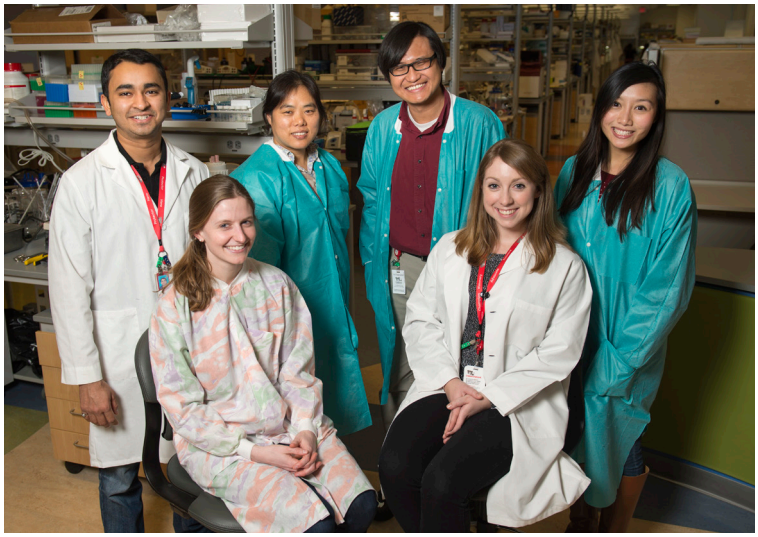


"As a leader in the area of immunology/ immunotherapy, Dr. Bollard's work will be an asset to strengthening programs within Children's Research Institute, the Sheikh Zayed Institute for Pediatric Surgical Innovation, and the Blood and Marrow Transplantation Division."

Mark Batshaw, MD
Physician-in-Chief &
Chief Academic Officer,
Children's National

"It's extremely important, offering a novel therapeutic that's not available at the majority of hospitals worldwide."

Catherine M. Bollard, MD
Director, Program for Cell Enhancement
& Technologies for Immunotherapy, Children's National



In this reporting period, Catherine M. Bollard, MD, Russell Cruz, MD, PhD, and Patrick Hanley, PhD joined the Immunology team of the Sheikh Zayed Institute. Dr. Bollard is a senior scientist and a member of the Division of the Blood and Marrow Transplantation and co-directs the Immunology Initiative of the Sheikh Zayed Institute for Pediatric Surgical Innovation.

Under Drs. Bollard and Hanley's direction, Children's National established a specialized research team dedicated exclusively to cellular therapy, working in an advanced, sophisticated cGMP facility. The facility adheres to FDA-enforced regulations. The team has rolled out the Program for Cell Enhancement and Technologies for Immunotherapy (CETI), and has performed the hospital's first treatment using T-cell therapy for a six-month-old patient with congenital immune deficiency and a life-threatening virus infection.

Dr. Bollard's research interests focus on different areas including developing cell and gene therapies for (i) patients with cancer, (ii) underlying immune deficiencies and (iii) inflammatory disorders/ autoimmune conditions. Dr. Bollard is also head of the non-Hodgkin's lymphoma committee of the Children's Oncology group.

5 THE INSTITUTE + Cardiology & Children's National Heart Institute

INTERVENTIONAL CARDIAC MAGNETIC RESONANCE (ICMR) PROGRAM

Congenital heart defects are the most common birth defect. About one percent of newborns are born with a heart condition. The Heart Institute at Children's National assesses and/or treats thousands of babies, children, and young adults each year. The Heart Institute includes a robust cardiac fetal imaging program with specialized care for newborns diagnosed in utero. Identifying and repairing heart defects in children or infants requires overcoming unique challenges, such as working on a smaller and more delicate heart, the difficulty in having children lie still or hold their breath for imaging procedures, increased sensitivity to radiation damage from x-rays, and the need for supportive devices like incubators.

> The ICMR collaboration means patients and families now have access to the finest cardiology imaging available in the world, which will enhance diagnosis and treatment. Ultimately, we hope to perform radiation-free procedures in children who are still developing and thus particularly vulnerable. At Children's National, we always strive to make assessment and treatment more precise and less invasive, and this partnership further advances that mission.

Gerard Martin, MD
Senior Vice President, The Center for Heart, Lung, & Kidney Disease, Children's National

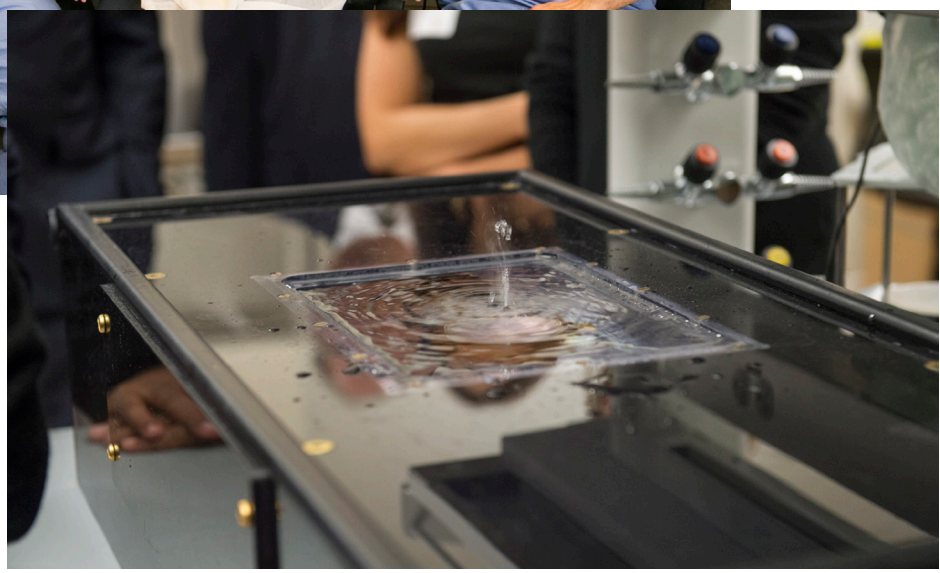
Dr. Kanishka Ratnayaka and Dr. Charles Berul, members of the Sheikh Zayed Institute, and their team successfully renewed their NIH National Heart, Lung, and Blood Institute (NHLBI) Interventional Cardiac Magnetic Resonance (ICMR) contract. This program contributes to the advancement of diagnostic and interventional cardiac magnetic resonance imaging techniques in pediatric cardiology and adults with congenital heart disease. The ICMR program brings together researchers, clinicians, engineers, and physicists to provide more precise and less invasive diagnostics and treatment. The ICMR team's work translates to more streamlined use of magnetic resonance imaging (MRI), which is radiation-free. The initiative seeks to enhance the speed and quality of MRI machines and reduce the need to sedate children getting an MRI; increasing the capability of MRI to take fetal images; developing better, pediatric-specific catheters for probing the heart and blood vessels; and incorporating an incubator into an MRI scanner to enable procedures on premature babies.

Children's National™
Heart Institute
Part of the Children's National Health System

NIH
National Heart, Lung, and Blood Institute

6 THE INSTITUTE + Oncology, Hematology, & Solid Tumor Program

From left to right: Peter Kim, MD, PhD, Pavel Yarmolenko, PhD, Aerang Kim, MD, and Haydar Celik, PhD.



A collaboration of the Sheikh Zayed Institute and the Oncology group at Children's National, the Image-Guided Non-Invasive Therapeutic Energy (IGNITE) program aims to improve the quality of life and outcomes for pediatric patients through the development and clinical introduction of novel minimally invasive and noninvasive surgery technologies and combination therapy approaches. The program focuses on the full integration of efficacious minimally invasive and noninvasive treatments in pediatric surgery and oncology.

The program consists of a high intensity focused ultrasound (HIFU) team of experts in oncology, developmental therapeutics, interventional radiology, immunology, anesthesiology, surgery, and bioengineering from Children's National and the National Institutes of Health. Collectively, the team supports and coordinates all HIFU activities from regulatory approval to subject recruitment to data management, capitalizing on a strong partnership with Philips Healthcare. The MR-HIFU system used in trials is manufactured by Philips, who supports the technical and regulatory requirements for the clinical components at both Children's National and NIH.

7 THE INSTITUTE + The Bear Institute for Health Innovation

> This novel dashboard will provide us with earlier and clearer means of identifying red flags in our practice, and thus continuously **improve the quality and safety of care for our babies**.

Lamia Soghier, MD
Neonatologist, Children's National

Brian Jacobs, MD, Chief Information Officer, Children's National and Kevin Cleary, PhD, Technical Director of Bioengineering, Sheikh Zayed Institute for Pediatric Surgical Innovation.

The Bear Institute is a first-of-its-kind health information technology institute dedicated to improving clinical pediatric outcomes. It is a collaboration of Children's National Health System and Cerner, with the goal of utilizing innovation in electronic health information technology to further evidence-based pediatric care, research, and education.

Challenging the 2014 Summer Innovator students, the Sheikh Zayed Institute, the Bear Institute, and the Clinical and Translational Science Institute at Children's National held a Hackathon to develop a dashboard for the Neonatal Intensive Care Unit (NICU). The goal set for this challenge was to come up with a design to help improve patient care quality and safety by providing real-time status of key indicators across the NICU.

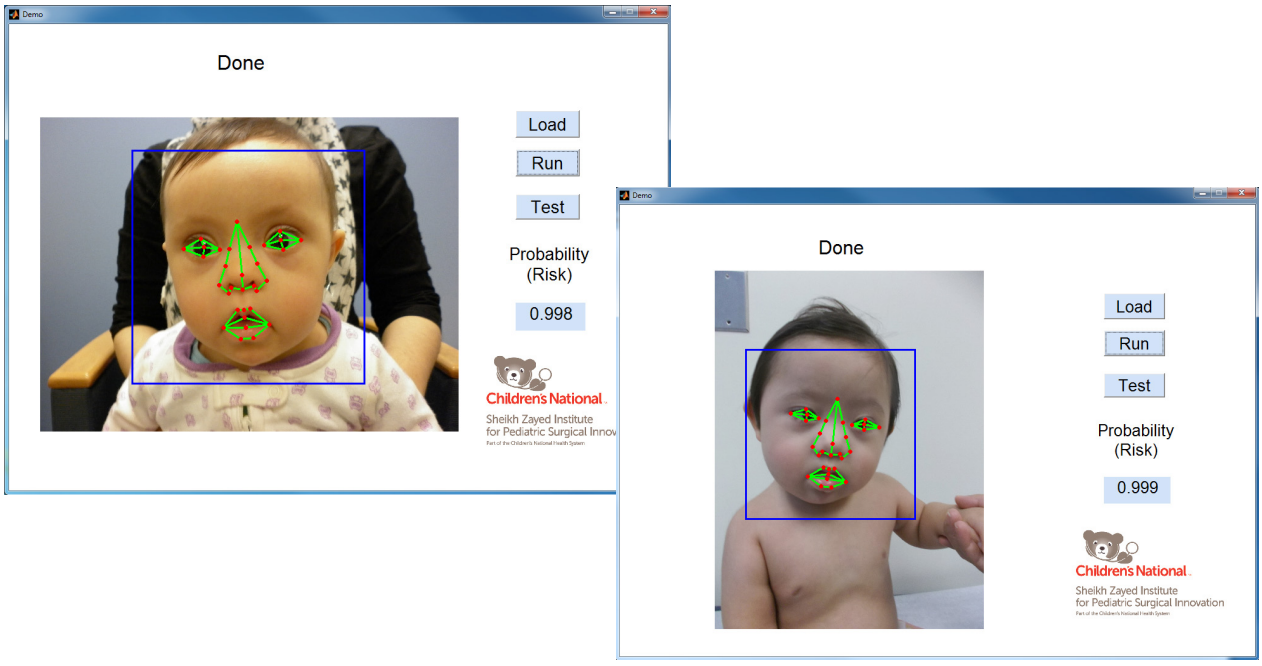
The students were given project background by NICU nurses and physicians. An expert from the University of Maryland gave an overview of the human factors engineering. The students then broke into six teams of four to five students each and developed design concepts for the dashboard. These concepts were then presented to a panel of judges and experts from Cerner, the NICU, and the Sheikh Zayed Institute. The best concepts were selected to develop a "best of breed" final solution. The Cerner software developers used the concepts and developed the first iteration of the software that is in pilot production at the NICU.

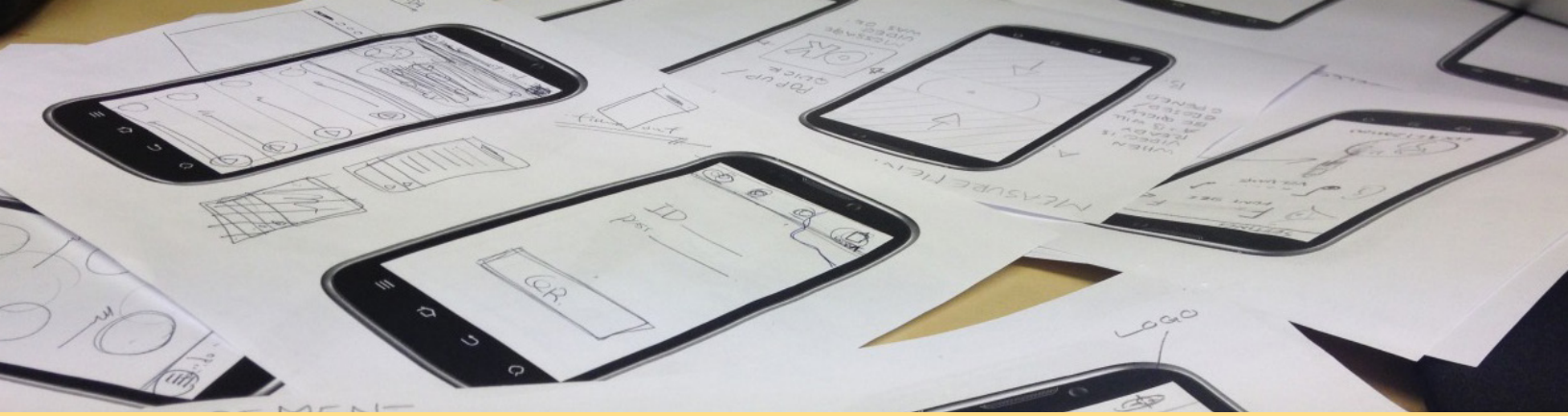
8 THE INSTITUTE + Genetics & Metabolism

Dr. Marshall Summar, Chief of Genetics and Metabolism with Dr. Marius Linguraru, Prinicipal Investigator at the Sheikh Zayed Institute.

DIGITAL FACIAL DYSMORPHOLOGY FOR GENETIC SCREENING

Down syndrome, the most common single cause of human birth defects, produces alterations in physical growth and mental retardation. If missed before birth, the early detection of Down syndrome is crucial for the management of patients and disease. However, the diagnostic accuracy for pediatricians prior to cytogenetic results is moderate and the access to specialists is limited in many social and low-economic areas. Researchers at the Sheikh Zayed Institute and clinicians at the division of Genetics and Metabolism are developing a simple, non-invasive, and automated framework for Down syndrome detection based on disease-specific facial patterns. This method has currently been validated in a pre-clinical setting, on a dataset with mixed genetic syndromes. A clinical trial is open for recruitment to further validate the concept.





9 THE INSTITUTE + American University Kogod School of Business

RIGHT BRAIN + LEFT BRAIN: MBAs, DESIGNERS, CLINICIANS PARTNER TO CREATE A PEDIATRIC MEDICAL DEVICE PROTOTYPE - THE PUPILLOMETER

The Sheikh Zayed Institute collaborated with full-time MBA students from American University Kogod School of Business and students from the International Design Business Management (IDBM) program at Finland's Aalto University to develop the concept and prototype for a medical device to collect data from the pupil and send diagnostic information to a smart phone. Beyond developing a useful tool to aid in diagnosing children, the pupillometer project has provided the opportunity for all involved to stretch beyond professional comfort zones.

While the business students were learning to see beyond spreadsheets, the design students were getting a crash course in more left-brained activities, and the clinicians were guiding the scientific aspects beyond the concept. In addition to two in-person team meetings – one in Helsinki in October 2013 and one in D.C. in February 2014 – the teams held weekly Skype calls and maintained an internal blog to share progress throughout the project. Together, the three teams created a device prototype that has now entered clinical trials to be validated for clinical use.

The primary market for the pupillometer will be medical professionals in a hospital setting; it is hoped that the product will also be a useful field diagnostic tool for first responders and medical volunteers with less formal training.

Children's National

Sheikh Zayed Institute for Pediatric Surgical Innovation

Part of the Children's National Health System

Kogod School of Business

American University • Washington, DC

Aalto University

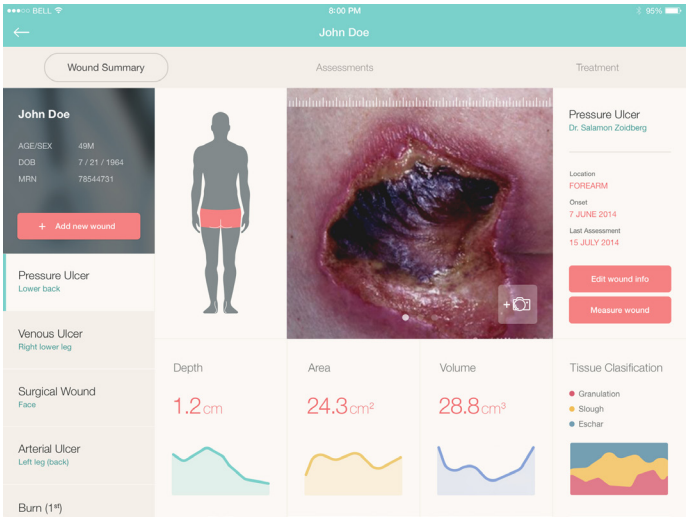
School of Arts, Design and Architecture

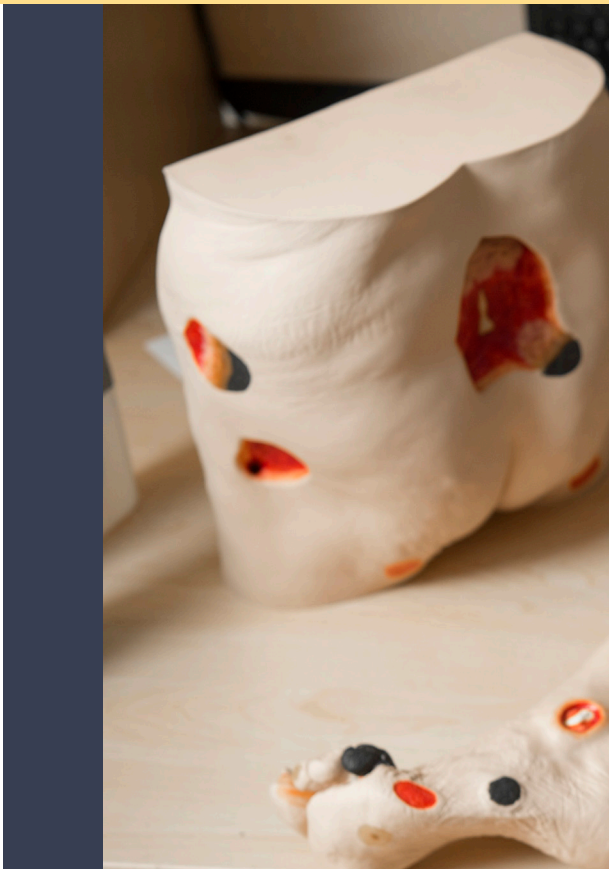
> Projects like this are an incredible opportunity for our students and our partners... A successful collaboration produces good fruit for all involved and really shows our students what kind of professional partnership to strive for.

Mark Clark, PhD
Faculty Program Director for the Full-time MBA,
American University Kogod School of Business

10 THE INSTITUTE + Startups

The Sheikh Zayed Institute's raison d'être is to translate its research and discoveries to the patients. As stewards of government and donor funds, the Sheikh Zayed Institute is committed to being responsive to market forces by promoting entrepreneurial efforts of its researchers, clinicians, and engineering staff. In the past 18 months, spinoff startup companies were formed to commercialize Sheikh Zayed Institute's inventions that are subject to the intellectual property polices of Children's National.





STARTUPS:

eKare | Wound Management

Omniboros | Surgery Smart Tools

MIRA Medical | Robotics & Rehabilitation

featuring **eKARE**

Sheikh Zayed Institute's spinoff, eKare, combines the latest computer vision and sensor technologies to bring wound measurement to a new level. The solution is a simple 1-2-3 step process. Visit **www.ekareinc.com** for more info.

1. Capture Data - Capture 2D and 3D data instantaneously like how you would normally use your smartphone or tablet camera.

2. Use Automated Process - Automatically obtain 3D wound dimensions and tissue classification through intelligent computer vision algorithms.

3. Review Results - See results anywhere with any device via cloud-based wound management platform. Content instantly syncs in cloud.

11 THE INSTITUTE + Gilbert Family Neurofibromatosis Institute

The Sheikh Zayed Institute's investigators collaborate with the Gilbert Family Neurofibromatosis Institute, one of the largest neurofibromatosis programs in the world that leads the medical field in diagnosis, evaluation, and treatment of children and adults with all the conditions that relate to this disorder. Research projects jointly funded by the Neurofibromatosis Institute and the Sheikh Zayed Institute are:

Biofunctionalized Prussian Blue Nanoparticles for Multimodal, Molecular Imaging
Applications led by Rohan Fernandes, PhD, and Laurie Conklin, MD

Quantitative Volumetric Analysis of Optic Pathway Gliomas in Children with NF1led
Led by Marius Linguraru, DPhil, and Robert Avery, MD

12 THE INSTITUTE + Small Businesses

In this reporting period, in collaboration with its small businesses partners, the Sheikh Zayed Institute was the recipient of the following three additional SBIR/STTR Phase I funding.

Project: **Evaluation of VBP15 as a Dissociative Steroidal Analogue on Pain and Inflammation**

Principal Investigators: Zenaide Quezado, MD (Sheikh Zayed Institute), Jesse Damsker, PhD (ReveraGen Biopharma, Inc.)

Funding Institute: NIH National Institute on Minority Health and Health Disparities

Project: **Image-Guided Planning System for Skull Correction in Children with Craniosynostos**

Principal Investigators: Marius Linguraru, DPhil (Sheikh Zayed Institute), and Andinet Enquobahrie, PhD (Kitware, Inc.)

Funding Institute: NIH National Institute of Child Health and Human Development

Project: **Clinical Translation of Augmented Reality Visualization for Laparoscopic Surgery**

Principal Investigators: Raj Shekhar, PhD (Sheikh Zayed Institute), and William Plishker, PhD (IGI Technologies, Inc.)

Funding Institute: NIH National Cancer Institute

13 THE INSTITUTE + University of Maryland A. James Clark School of Engineering

The seed funding program to boost collaboration between researchers at the University of Maryland A. James Clark School of Engineering and the Sheikh Zayed Institute for Pediatric Surgical Innovation, established in 2013, led to over ten joint intellectual property fillings, and an impressive number of joint publications and grant submissions. As but one example of this inter-institutional collaboration, in collaboration with the Fischell Department of Bioengineering, the Sheikh Zayed Institute formed a joint program in pediatric tissue engineering and regenerative medicine (PTERM). The goal of this program is to combine the existing tissue engineering expertise of the Fischell Department with the pediatric medicine and research expertise of the Sheikh Zayed Institute to build a world-class translational program in PTERM. The program is led by Dr. John Fisher and Dr. Peter Kim.

14 THE INSTITUTE + DC I-Corps

DC I-Corps is a National Science Foundation-funded regional program designed to foster, grow, and nurture an innovation ecosystem in the mid-Atlantic region with a strong focus on Washington, DC, metropolitan area. The program is jointly run by the University of Maryland College Park, George Washington University, Virginia Tech, and Johns Hopkins University. It provides real world, hands-on training on how to successfully incorporate innovations into successful products. The program's ultimate goal is to help participants create a new venture or land a licensing opportunity.

For the second year in a row, Sheikh Zayed Institute entrepreneurs got accepted into the I-Corps program and benefited from a curriculum taught by successful technology entrepreneurs. Each participating team talked to a minimum of one hundred customers, partners, competitors, and other market stakeholders.

I-Corps Projects

Clinical Translation of Augmented Reality Visualization for Laparoscopic Surgery
Raj Shekhar, PhD (PI), Children's National
William Plishker, PhD (C-Level Executive), University of Maryland
Mark Chandler, MBA (Industry Expert), Upstream Partners, Inc.

iUFlow – A home uroflowmetry device and voiding diary implemented on a mobile platform
Tanya Davis, MD, Children's National
Guy Hidas, MD, Hadassah Hebrew University Medical Center, Jerusalem, Israel
Gil Hidas, BBus BIS, CEO of Kesem Solutions

Dissolvable On-Command Ear Tubes
Brian Reilly, MD (PI), Children's National
Matthieu Dumont, PhD, Children's National
Nora Lee, MD, Children's National
Patrick Cheng, MS, MBA, Children's National
Carolyn Cochenour, Children's National

15 THE INSTITUTE + Fetal & Translational Medicine

Dr. Adre du Plessis, Chief of Fetal and Transitional Medicine at Children's National joined the Sheikh Zayed Institute to develop non-invasive continuous neuromonitoring techniques and validate novel biomarkers of imminent brain injury.

Brain injury is a dreaded, often devastating complication of critical illness, and its impact on the quality of long-term survival offsets the advances made in the mortality of critical care. Prevention of brain injury in this population remains impeded by delayed detection of emerging brain insults until well after the window for effective intervention has closed. The results of Dr. du Plessis's research will address this unmet medical need.

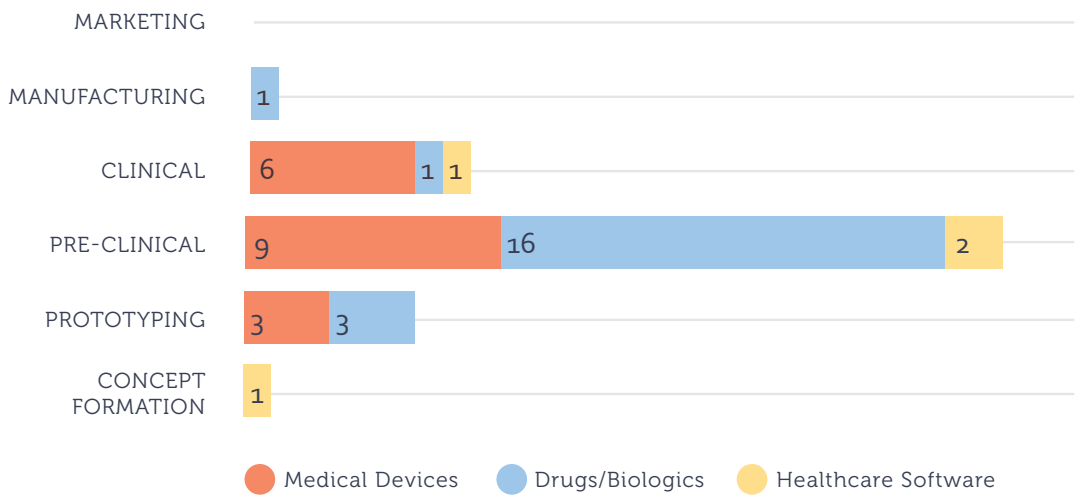
16 THE INSTITUTE + Otolaryngology

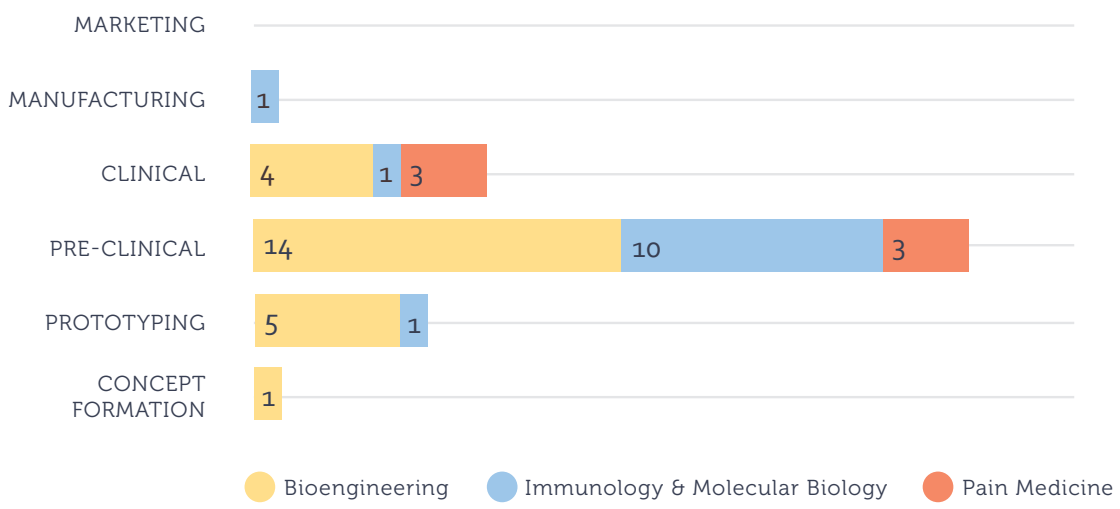
Dr. Brian Reilly of Otolaryngology, a new member of the Institute, is working with the Sheikh Zayed Institute's engineers to develop an ear tube made of a biocompatible material that can retain its form and function in physiological conditions and quickly dissolve on contact with uniquely formulated ear drops. This new approach will reduce follow up surgeries for removing ear tubes.

THE RESEARCH FUNDING FROM THE GOVERNMENT OF ABU DHABI HAS PLAYED A CRITICAL ROLE IN ADVANCING BIOMEDICAL RESEARCH AT CHILDREN'S NATIONAL TO **IMPROVE HEALTH OF CHILDREN - EVERYWHERE**

PROJECT **portfolio**

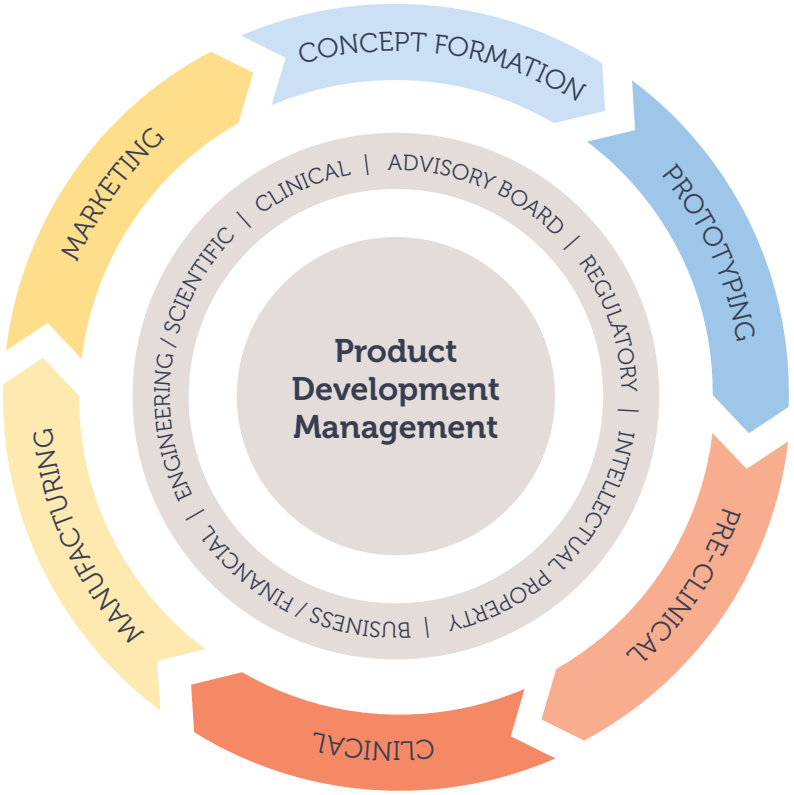
Project Portfolio at the Sheikh Zayed Institute for Pediatric Surigcal Innovation



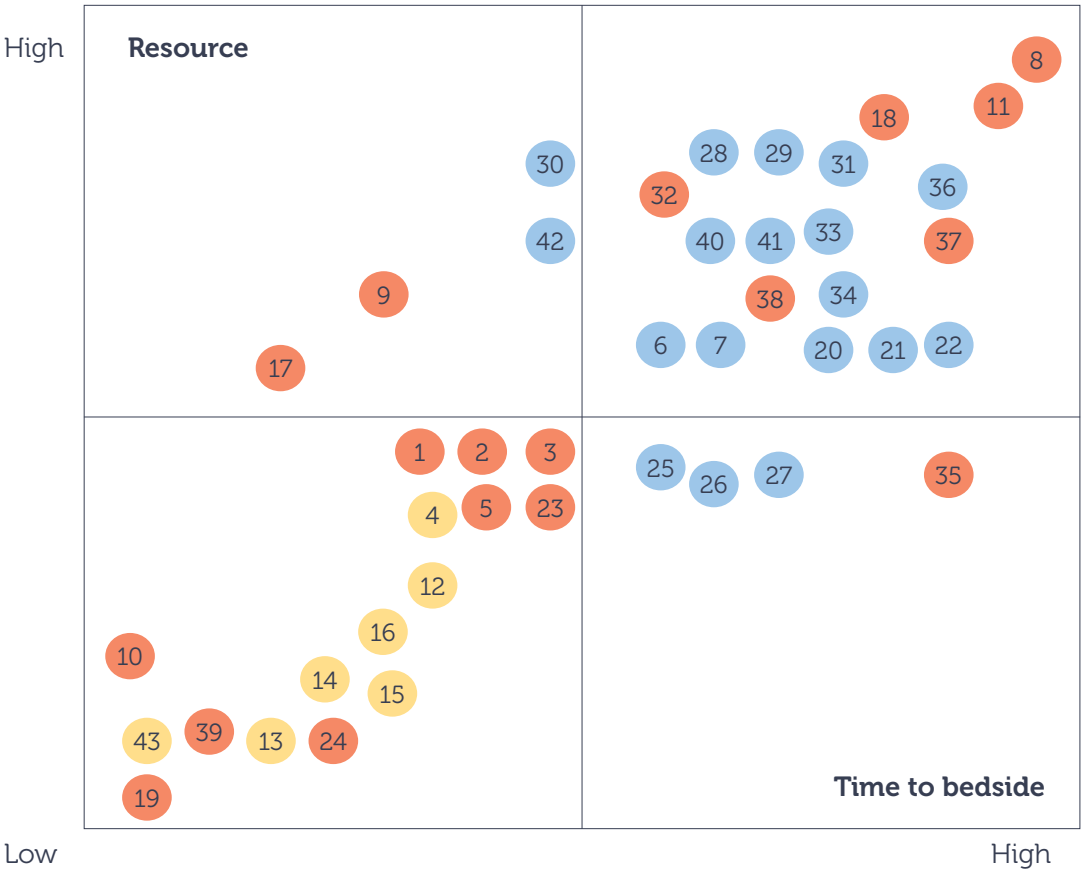


SCIENTIFIC highlights

medical devices	18 projects
drugs/ biologics	18 projects
healthcare software	7 projects



Product Development Maturity Quadrant



1. IGNITE: Non-Invasive Growth Plate Ablation Treatment
2. IGNITE: Safety and Feasibility of MR-HIFU Ablation of Pediatric Solid Tumors
3. IGNITE: Safety and Feasibility of MR-HIFU Ablation of Osteoid Osteoma
4. IGNITE: Optimization of Treatment Planning of Non-Invasive Therapy with MR-HIFU
5. Body-Mounted MRI-Compatible Robot for Percutaneous Needle Procedures
6. Biofunctionalized Prussian Blue Nanoparticles for Multimodal Molecular Imaging of Pediatric Diseases
7. Engineered Prussian Blue Nanoparticles for Photothermal Therapy of Pediatric Tumors
8. Smart Tissue Anastomosis Robot (STAR)
9. EndoPyloric Tool
10. Cardiac 3D Printing
11. 3D Printed Vascular Grafts
12. Non-Invasive Kidney Quantification for Hydronephrosis: Computer-Aided Diagnosis Tool (KidCAD)

key:

- Medical Devices
- Drugs/Biologics
- Healthcare Software

- 13. Digital Dysmorphology: Automated Early Detection of Genetic Syndromes from Photography
- 14. Quantitative Volumetric Analysis of Optic Pathway Gliomas in Children with NF1
- 15. Quantitative MR Enterography Markers of Inflammatory Bowel Diseases via Radiology-Pathology Fusion
- 16. Image-Guided Planning System for Skull Correction in Children with Craniosynostosis
- 17. Stereoscopic Augmented Reality Visualization for Laparoscopic Surgery
- 18. Minimally-Invasive Pacemaker/Defibrillator
- 19. Treadmill Stress Test for Toddlers
- 20. Tissue Engineered Model of Preeclampsia
- 21. Modern Lymph Node for Perfusion Bioreactor Culture
- 22. Tissue Engineered Trachea
- 23. Development of Non-Invasive Continuous Neuromonitoring Validating Novel Biomarkers of Imminent Brain Injury
- 24. On-Demand Dissolvable Ear Tube
- 25. Program: Immunotherapy for Targeting Pathogens
- 26. Program: Immunotherapy for Eliminating Cancer
- 27. Program: Immunotherapy for Controlling Inflammation
- 28. Vaccine Therapy for Cancer: Id2KD Attenuated Whole Tumor Cell Therapeutic Vaccination
- 29. Reversible Adaptive Plasticity: Cancer Cell Biology
- 30. Microfluidic Nanoparticle Therapy
- 31. Genetic Studies of Necrotizing Enterocolitis
- 32. Blow Spin Polymer for Surgical Applications
- 33. TGF-beta in the Pathogenesis of Experimental Biliary Atresia
- 34. Adipocyte Exosomes in the Pathogenesis of Non-Alcoholic Fatty Liver Disease
- 35. An Anchored Non-Spherical Obesity Balloon
- 36. Proteomic Networks of MUC5B Infectious/Inflammatory Induction in Otitis Media
- 37. Magnetic Delivery of Drugs to the Middle Ear
- 38. Algometer
- 39. Pupillometer
- 40. Pathobiology and Novel Therapeutic Approaches for Pain in Sickle Cell Disease
- 41. The Role of VBP-15 a Dissociative Steroid on the Sickle Cell Disease Pain
- 42. Development of a Nanoliposomal Transdermal Drug Delivery System
- 43. SCD-PROMIS- An App for Outpatient Monitoring and Treatment of Sickle Cell Pain

Bioengineering

medical devices — 13 projects

drugs/ biologics — 5 projects

healthcare software — 6 projects

Kevin Cleary, PhD
Peter Kim, MD, PhD
Raymond Sze, MD
Fahad Alfares, MD
Bamshad Azizi, MS
Juliana Cano-Mejia, MS
Haydar Celik, PhD
Juan Cerrolaza, PhD
Carolyn Cochenour
Ryan Decker, MS
Adre du Plessis, MBChB
Avinash Eranki
Rohan Fernandes, PhD
John Fisher, PhD
Oezguer Gueler, PhD
Timothy Kane, MD
Sukryool Kang, PhD
Joshua Kanter, MD
AeRang Kim, MD, PhD
Axel Krieger, PhD
Che-Ying (Vincent) Kuo, MS, PhD Candidate
Simon Leonard, PhD
Marius Linguraru, DPhil
Xinyang Liu, PhD
Awais Mansoor, PhD
James McConnaughey
Christopher Meyer
Reza Monfaredi, PhD
Dilip Nath, MD
Matthew Oetgen, MD
Laura Olivieri, MD
Justin Opfermann, MS
Craig Peters, MD
Jin Qi, PhD
Lauren Querido
Kanishka Ratnayaka, MD
Brian Reilly, MD
Azad Shademan, PhD
Karun Sharma, MD, PhD
Raj Shekhar, PhD
Elizabeth Sweeney, PhD
Emmanuel Wilson, MS
Pavel Yarmolenko, PhD

TO HARNESS THE FULL POWER OF SCIENCE AND TECHNOLOGY TO MAKE TREATMENT AS PRECISE AS IT CAN POSSIBLY BE

1. **IGNITE: Non-Invasive Growth Plate Ablation Treatment**

CATEGORY	MEDICAL DEVICES	STAGE OF DEVELOPMENT	PRE-CLINICAL
FUNDING SOURCE	Clinical and Translational Science Institute at Children's National (CTSI-CN) Pilot Program Award		

KEY PERSONNEL

Matthew Oetgen, MD
Pavel Yarmolenko, PhD
Haydar Celik, PhD
Peter Kim, MD, PhD

Harry Kim, MD

FINDINGS / ACCOMPLISHMENTS

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 1cm into the physis. Having completed preliminary phantom and animal studies (specific aim 1) we are currently scheduling the animal studies that will allow us to complete the study in the second quarter of 2015.

SYNOPSIS

Discrepancy in lower limb lengths in children is a common condition, with as many as 40% of children affected. If untreated, in approximately 8% of all children, the condition may lead to a noticeable limping, lower back pain, scoliosis, poor posture, osteoarthritis of the hip and spine, lower extremity stress fractures and other conditions that require surgery. Traditionally, surgery (epiphyseodesis) has been used to equalize the limb lengths by ablating one or more growth plates (physes) in the longer limb if the discrepancy is projected to exceed 2.5cm at skeletal maturity. Reliance of current treatment options on incisions and physical physeal destruction or use of surgical implants exposes the patient to risks of infection, intra-articular damage, post-operative fracture and pain, joint stiffness, and the need for protected weight-bearing.

This project explores use of magnetic resonance-guided high intensity focused ultrasound (MR-HIFU) for epiphysiodesis due to the advantages offered by its noninvasive 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) to develop and optimize an MR-HIFU heating algorithm and associated MR imaging and mathematical modeling in ex-vivo phantoms, and (2) to determine safety and feasibility of MR-HIFU epiphysiodesis in a preclinical, large animal model.

2. IGNITE: Safety and Feasibility of MR-HIFU Ablation of Pediatric Solid Tumors

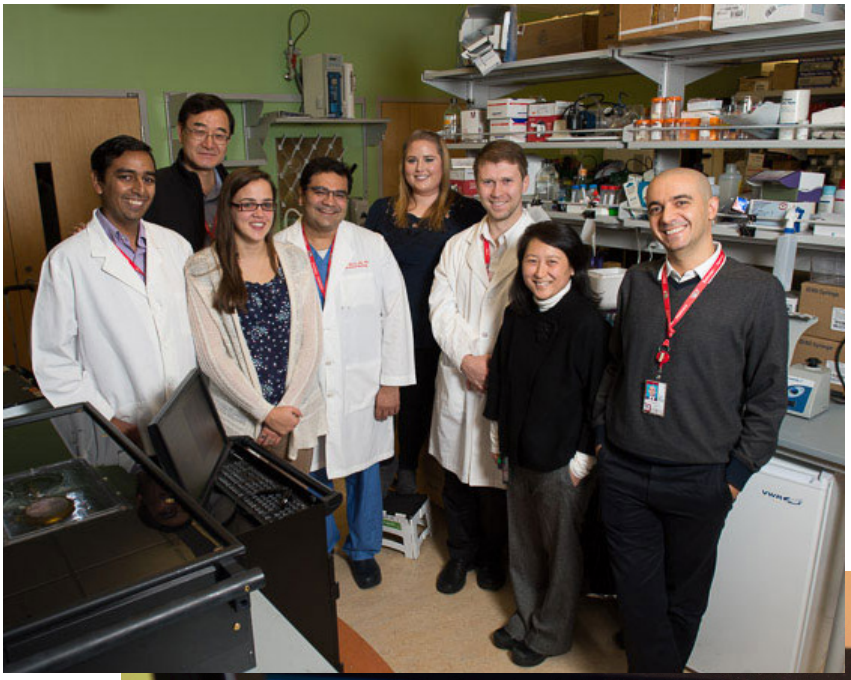
CATEGORY	MEDICAL DEVICES	STAGE OF DEVELOPMENT	CLINICAL TRIALS
FUNDING SOURCE	Sheikh Zayed Institute Hyundai Hope On Wheels		

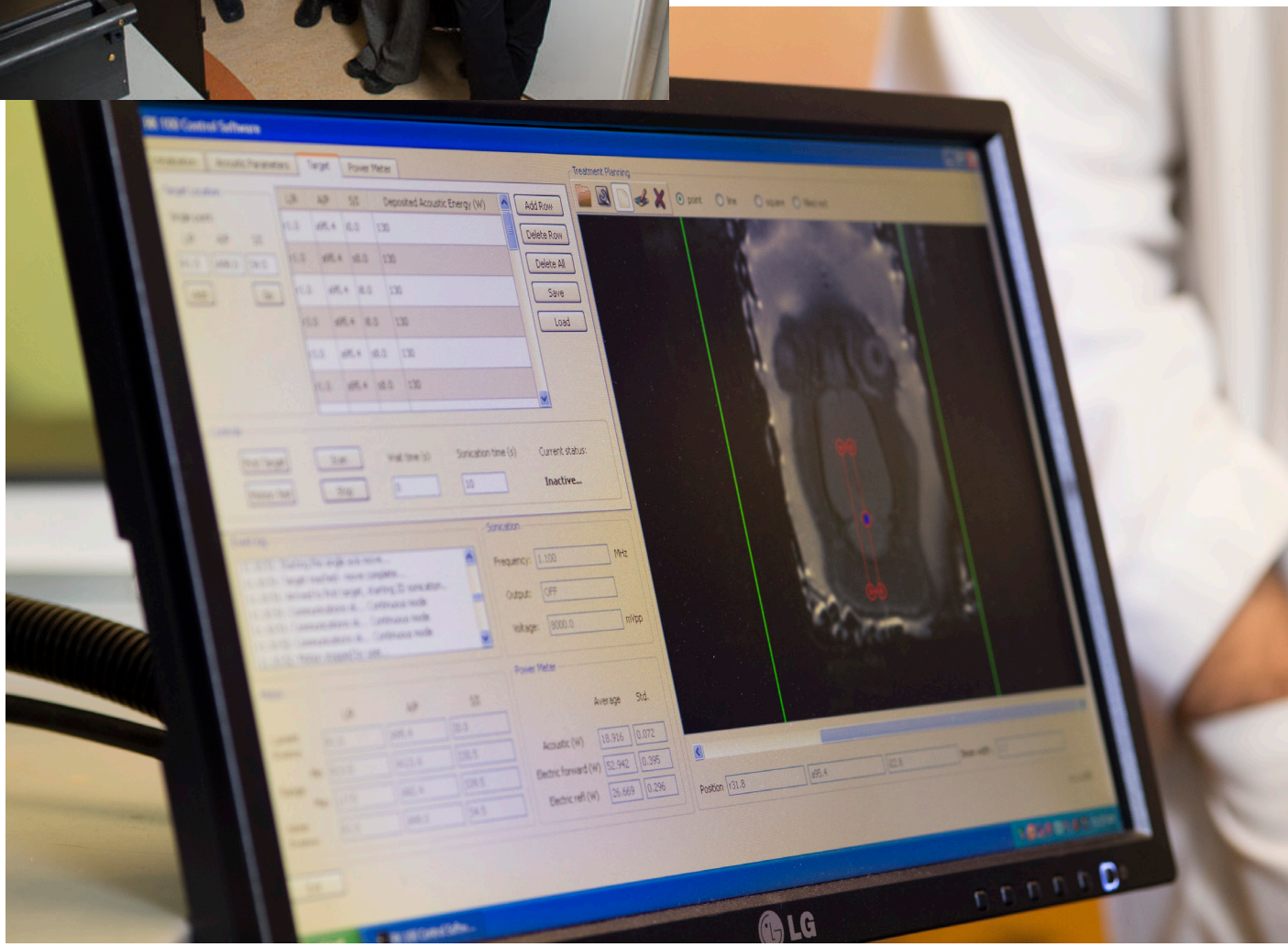
KEY PERSONNEL

Aerang Kim, MD, PhD
Pavel Yarmolenko, PhD
Haydar Celik, PhD
Peter Kim, MD, PhD

SYNOPSIS

Cure rate for pediatric cancer has dramatically improved over the past several decades. However, this improvement came at a cost of substantial acute toxicities and late effects of current multi-modal therapy. In addition, prognosis remains poor for many pediatric cancers such as those with solid tumors that present with overt metastatic disease. Thus, a clear need exists for less traumatic and more efficacious therapeutic approaches for pediatric malignancies. To begin addressing this challenge, our group is investigating safety and feasibility of a non-invasive treatment approach to treating solid pediatric tumors: ablation with externally focused beam of ultrasound under MRI guidance (MR-HIFU). We have reviewed several possible candidates for the study and we are continuing to recruit patients. Following completion of this clinical trial, our group plans to continue with the next phase of clinical evaluation of this technology.

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Output:
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Power Meter
Average
Std.
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3. **IGNITE: Safety and Feasibility of MR-HIFU Ablation of Osteoid Osteoma**

CATEGORY	**MEDICAL DEVICES**	STAGE OF DEVELOPMENT	**CLINICAL TRIALS**
FUNDING SOURCE	Sheikh Zayed Institute Hyundai Hope On Wheels		

KEY PERSONNEL

Karun Sharma, MD, PhD
Pavel Yarmolenko, PhD
Haydar Celik, PhD
Aerang Kim, MD, PhD
Peter Kim, MD, PhD

SYNOPSIS

Osteoid Osteoma (OO) is a benign, but painful, bone tumor commonly occurring in children and young adults. Common treatment options are surgical excision or, more recently, CT-guided radiofrequency ablation (RFA). RFA is less invasive, but it still requires drilling from the skin through muscle and soft tissue into bone. It also exposes the patient and operator to ionizing radiation.

Magnetic resonance-guided high intensity focused ultrasound (MR-HIFU) provides precise and controlled delivery of focused ultrasound energy inside a lesion using an external applicator, without the need for a scalpel or needle. MR-HIFU has been successfully used to treat painful bone metastases in adult clinical trials and one recent report suggests that it can also be used to treat OO.

MR-HIFU ablation of OO may provide a better alternative to surgical resection or RFA as it is completely non-invasive and does not require ionizing radiation. These two qualities of MR-HIFU are especially beneficial in growing children and young adults. Furthermore, MR-HIFU OO ablation is quick, with expected total procedure time of less than two hours. Such short treatments offer additional safety benefits from reduced anesthesia/sedation requirement compared with surgery and RFA.

4. **IGNITE: Optimization of Treatment Planning of Non-Invasive Therapy with MR-HIFU**

CATEGORY	HEALTHCARE SOFTWARE	STAGE OF DEVELOPMENT	PROTOTYPING
FUNDING SOURCE	Sheikh Zayed Institute Hyundai Hope On Wheels		

KEY PERSONNEL

Pavel Yarmolenko, PhD
Haydar Celik, PhD
Karun Sharma, MD, PhD
Aerang Kim, MD, PhD
Matthew Oetgen, MD
Peter Kim, MD, PhD

SYNOPSIS

This project aims to address a clearly identified need to improve patient positioning and pre-planning of treatment with magnetic resonance-guided high intensity focused ultrasound (MR-HIFU). Current clinical trials of MR-HIFU treatments typically rely on approximate patient positioning based on the general location of the disease to be targeted. Our review of imaging data of pediatric patients with solid tumors revealed that such coarse approaches to patient positioning are not sufficient to allow for treatment of the entire lesion.

Repositioning the patient is a time-consuming process that involves not only re-positioning, but 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 min for every avoided patient repositioning) 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 patient positioning that relies on multimodal (any of the available: MRI/CT/US/PET) imaging data as well as physician input. 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 will work closely with our industrial partners to integrate the results of this work into the next iteration of clinical MR-HIFU instruments.


PHILIPS

5. **Body-Mounted MRI-Compatible Robot for Percutaneous Needle Procedures**

CATEGORY	MEDICAL DEVICES	STAGE OF DEVELOPMENT	PROTOTYPING
FUNDING SOURCE	NIH National Cancer Institute Sheikh Zayed Institute		

KEY PERSONNEL

Kevin Cleary, PhD
Karun Sharma, MD, PhD
Raymond Sze, MD
Reza Monfaredi, PhD
Bamshad Azizi, MS
Emmanuel Wilson, MS

SYNOPSIS

The goal of this research program in MRI compatible robotics is to offer radiation-free, minimally invasive procedures to our pediatric patients. Minimally invasive procedures such as biopsy, drainage, or ablation are typically done under x-ray imaging to enable the Interventional Radiologist to target the anatomy of interest. In keeping with our general goal of minimizing dose whenever possible, if we could move these procedures to the MRI environment we could eliminate the radiation dose.

However, patient access in a standard closed bore MRI scanner can be difficult and the MRI environment presents several challenges. Therefore, we have been developing a body-mounted needle-positioning robot that is MRI compatible with the goal of enabling MRI-guided interventions. The first clinical application we have focused on is shoulder arthrography.

Arthrography is the evaluation of joint condition using imaging modalities such as magnetic resonance imaging (MRI). Currently, this test requires two separate stages, an intra-articular contrast injection typically guided by fluoroscopy followed by an MRI. The current two-step workflow can result in anxiety for the patient, prolonged sedation time when sedation is needed, radiation exposure from the fluoroscopic imaging, and may increase cost due to the use of both the fluoroscopy and MRI suite.

FINDINGS / ACCOMPLISHMENTS

A 4-degree of freedom patient mounted robot was developed to enable procedures in the MRI environment. The prototype robot has been constructed using a rapid prototyping machine (Objet 500, Stratasys) and ABS material. Preliminary results in the MRI environment shows the distortion profile introduced by the robot is minimal.

6. **Biofunctionalized Prussian Blue Nanoparticles for Multimodal Molecular Imaging of Pediatric Diseases**

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PRE-CLINICAL
FUNDING SOURCE	Sheikh Zayed Institute Gilbert Family Neurofibromatosis Institute Award		

KEY PERSONNEL

Rohan Fernandes, PhD
Raymond Sze, MD
Elizabeth E. Sweeney, PhD
Jennifer M. Vojtech
Erin F. McCaffrey
Xuefei (Angelina) Nou
Shraddha Kale
Laurie S. Conklin, MD
Javad Nazarian, PhD
Yuan Zhu, PhD

FINDINGS / ACCOMPLISHMENTS

The team demonstrated that the biofunctionalized Prussian blue nanoparticles yields 9-times the MRI signal compared with the medically used Magnevist® while simultaneously enabling fluorescence imaging, a novel imaging modality. This results in more sensitive and specific imaging of eosinophilic esophagitis in vitro and pediatric brain tumors in vivo.

SYNOPSIS

Molecular imaging agents enable the visualization of phenomena with cellular and sub-cellular level resolutions and therefore have enormous potential in improving disease diagnosis and therapy assessment. Multimodal imaging involves the combination of two or more imaging modalities where the combination leverages the strengths of the individual imaging techniques, while compensating for their limitations. Despite these advantages, there are no clinically approved, multimodal molecular imaging agents. This project fills this need by synthesizing biofunctionalized Prussian blue nanoparticles as a novel class of multimodal, molecular imaging agents for improved visualization of pediatric diseases. The novel biofunctionalized Prussian blue nanoparticles have a simple core-shell design and combine the advantages of MRI and fluorescence imaging. Our rationale for combining fluorescence imaging with MRI is because fluorescence imaging provides high sensitivity but lower spatial resolution, while MRI provides high spatial resolution, depth of penetration but lower sensitivity. The MRI relaxivities of our novel nanoparticles are nearly nine times those observed for the clinically used MRI contrast agent Magnevist®. The biofunctionalization of the nanoparticles with a layer of fluorescently-labeled avidin enables fluorescence imaging and serves as a platform for attaching biotinylated ligands that target disease-specific markers. Over the past year, we have demonstrated the use of our novel nanoparticles as multimodal, molecular imaging agents in an in vitro model of eosinophilic esophagitis – an inflammatory disease of the upper GI tract. In these studies, we demonstrated the specific targeting of eosinophils in a mixture of "disease-specific" eosinophilic cells and "normal" squamous epithelial cells. In later studies, we built on these promising results by demonstrating our nanoparticles for multimodal, molecular imaging of pediatric brain tumors in a mouse model. These studies demonstrate the potential for translating our nanoparticles to the clinic as novel, multimodal, molecular imaging agents.

7. Engineered Prussian Blue Nanoparticles for Photothermal Therapy of Pediatric Tumors

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PRE-CLINICAL
FUNDING SOURCE	Sheikh Zayed Institute, Clinical and Translational Science Institute at Children's National (CTSI-CN) Pilot Program Award		

KEY PERSONNEL

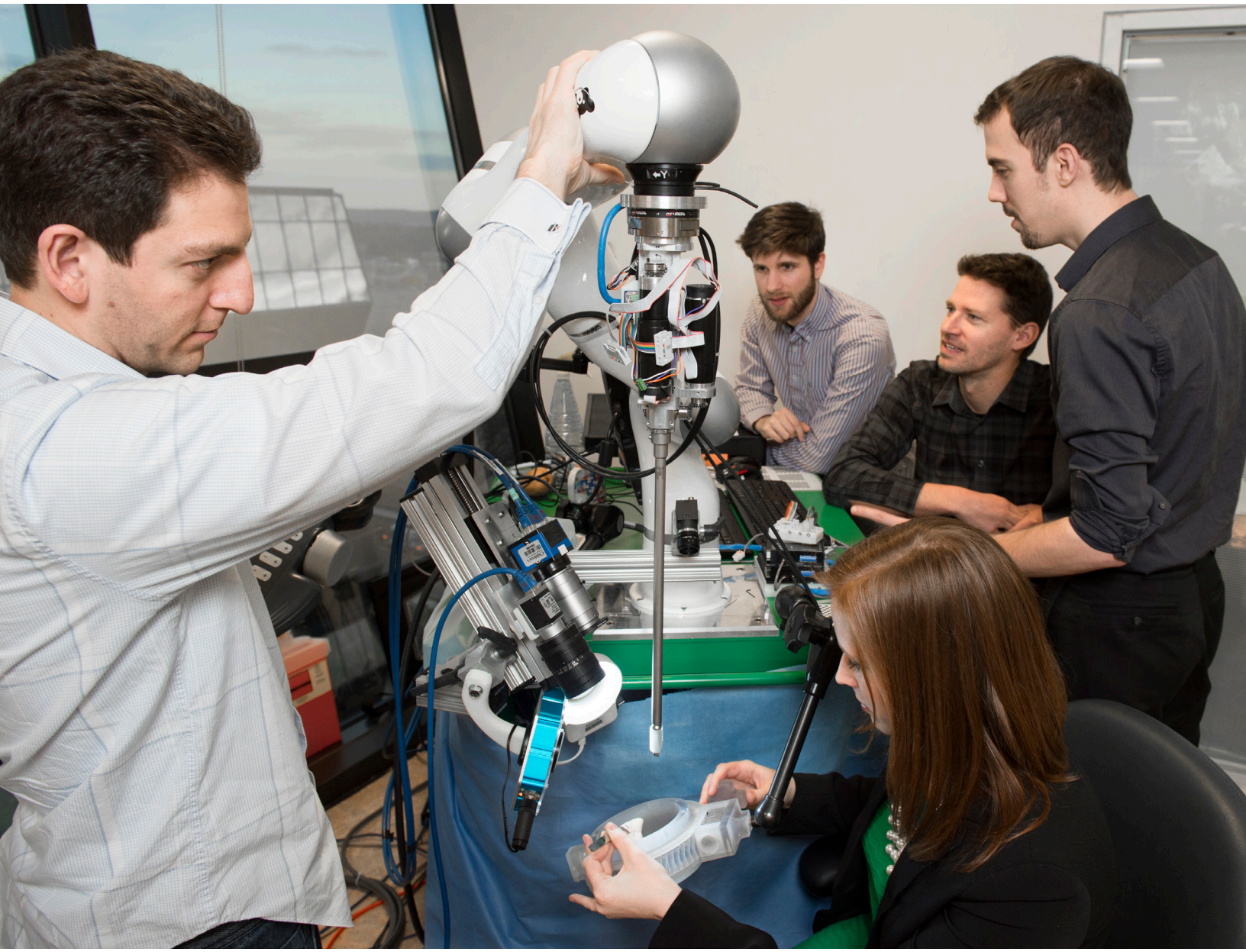
Rohan Fernandes, PhD
Raymond Sze, MD
Elizabeth E. Sweeney, PhD
Juliana Cano-Mejia
Rachel Burga
Russell Cruz, MD, PhD
Anthony Sandler, MD
Lina Chakrabarti, PhD

FINDINGS / ACCOMPLISHMENTS

Through proof-of-principle studies, the team demonstrated that laser-induced, photothermal therapy of neuroblastomas using the engineered Prussian blue nanoparticles results in an increased number of tumor-free days, decreased tumor growth rates, and improved survival in an animal model.

SYNOPSIS

Surgery is one of the mainstays of cancer therapy. It is an efficient and widely-used intervention for removing cancerous lesions from the body consequently reducing tumor burden on a patient. However, surgery has associated risks – it can be invasive, cannot be used for cancerous lesions adjacent to vital tissue, and can result in debilitating loss of function. Motivated by the need for lesser invasive interventions for cancer therapy as alternatives to surgery, we are engineering Prussian blue nanoparticles for photothermal therapy of pediatric tumors. In photothermal therapy, precisely directed near infrared light absorbing nanoparticles within a tumor are irradiated by a low intensity near infrared laser resulting in non-invasive, precise, rapid heating and ablation of the tumor. Since the human body exhibits low absorbance at near infrared wavelengths, the heating effect is minimal when using the low power laser alone. Our engineered Prussian blue nanoparticles exhibit higher photothermal conversion efficiencies when compared with most nanoparticles and similar to that of gold nanorods. In contrast with gold nanorods, the Prussian blue nanoparticles are biodegradable mitigating concerns associated with the long-term fate and associated toxicity of the nanoparticles within the body. In the past year, we have successfully demonstrated ablation of primary neuroblastoma tumors in a mouse model. Mice treated with Prussian blue nanoparticle-based photothermal therapy exhibited lower tumor growth rates and increased survival relative to untreated mice. Ongoing studies are investigating the immune response to photothermal therapy with the goal of biofunctionalizing our nanoparticles with immune adjuvants that prime a robust antitumor immune response. These studies demonstrate the potential of our Prussian blue nanoparticle for photothermal therapy as a novel alternative therapy to surgery for tumor therapy.



8. **Smart Tissue Anastomosis Robot (STAR)**

CATEGORY	MEDICAL DEVICES	STAGE OF DEVELOPMENT	PRE-CLINICAL
FUNDING SOURCE	Sheikh Zayed Institute		

KEY PERSONNEL

Axel Krieger, PhD
Peter Kim, MD, PhD
Simon Leonard, PhD
Justin Opfermann, MS
Azad Shademan, PhD
Ryan Decker, MS

Hanh Le, PhD Candidate, (JHU)
Jin Kang, PhD, (JHU)

SYNOPSIS

The goal of the 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.

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% 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: (i) Novel end effector that incorporates and simplifies current surgical technique; (ii) New visual modality that allows tracking of mobile deformable soft tissue targets; and (iii) Collaborative decision support for surgical tasks between the surgeon and smart tools based on real-time target information.

This paradigm of "intelligent tools" exemplifies the next generation of surgical tools that will enhance function and outcome of surgical tasks such as anastomosis.

FINDINGS / ACCOMPLISHMENTS

An accuracy study of the STAR prototype demonstrated a positional accuracy of 0.5mm. 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 with manual mode demonstrated more consistent bite size and suture spacing in autonomous mode. The team successfully demonstrated leak-free anastomoses in initial preclinical studies.

9. EndoPyloric Tool

	CATEGORY	MEDICAL DEVICES	STAGE OF DEVELOPMENT	PRE-CLINICAL
	FUNDING SOURCE	Sheikh Zayed Institute, Atlanta Pediatric Device Consortium, Joseph E. Robert, Jr. Endowment Award		

KEY PERSONNEL

Axel Krieger, PhD
Carolyn Cochenour
Timothy Kane, MD
Peter Kim, MD, PhD

SYNOPSIS

EndoPyloric Tool (EPL) project aims at 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% circumferentially. We hypothesized that a similar outcome can be accomplished effectively with an endoluminal balloon tool.

FINDINGS / ACCOMPLISHMENTS

The team designed a new endopyloric catheter-based balloon dilation tool and evaluated the tool in in vivo preclinical studies using a rabbit model. The device safely dilated the rabbit pylori as there was no indication of perforation or damage to the pylorus and surrounding anatomy. The team is currently conducting further preclinical testing and preparing for clinical studies.

10. **Cardiac 3D Printing**

CATEGORY	MEDICAL DEVICES	STAGE OF DEVELOPMENT	CLINICAL TRIALS
FUNDING SOURCE	Sheikh Zayed Institute Children's National Board of Visitors (BOV) Award		

KEY PERSONNEL

Axel Krieger, PhD
Laura Olivieri, MD
Dilip Nath, MD
Peter Kim, MD, PhD
Lilian Su, MD
Fahad Alfares, MD

SYNOPSIS

Congenital heart disease (CHD) is the most common type of birth defect with an incidence of 75 per 1,000 live births for all lesions and 6 per 1,000 live births for moderate to severe lesions. Accurate display of the defect is critically important for clinical care, decision making, and surgical planning. The defect can be imaged using magnetic resonance imaging (MRI), computed tomography (CT), or echocardiograph (echo) images. The image quality and resolution of all three modalities have advanced significantly in recent years to where detailed three-dimensional (3D) information can be acquired. Despite the rich 3D information provided by cardiac imaging, the display of this information is still largely constrained to viewing multiple contiguous two-dimensional (2D) slices of the 3D scan, which is sub-optimal.

We hypothesize that the efficiency and quality of (i) preoperative decision-making and (ii) surgical preparation prior to surgical correction for structural and congenital heart defects can be improved using 3D printed replicas of patient's heart anatomy.

FINDINGS / ACCOMPLISHMENTS

To date, thirty MRI and 3D echo datasets have been obtained, converted to DICOM format, segmented, and successfully printed. The team obtained IRB approval and is currently evaluating the impact of these models on clinical care. The team is also evaluating the use of 3D printed heart models in simulation and training of the Cardiac Intensive Care Unit (CICU) care team to successfully anticipate/manage postoperative course. The team is 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.

11. **3D Printed Vascular Grafts**

CATEGORY	MEDICAL DEVICES	STAGE OF DEVELOPMENT	PRE-CLINICAL
FUNDING SOURCE	Sheikh Zayed Institute, University of Maryland A. James Clark School of Engineering, Center for Accelerated Innovations at Cleveland Clinic, funded through NIH National Heart, Lung, and Blood Institute		

KEY PERSONNEL

Axel Krieger, PhD
Carolyn Cochenour
Justin Opfermann, MS

John Fisher, PhD, (UMD)
Anthony Melchiorri, PhD Candidate, (UMD)
Narutoshi Hibino MD, (NCH)

SYNOPSIS

Congenital heart disease (CHD) is among the leading causes of death associated with congenital anomalies in the newborn period. Approximately 25% of babies born with CHD require invasive treatment, where often a connection must be established using a graft conduit. Complications of current grafts include progressive obstruction, lack of growth potential, and thromboembolic complications. Tissue engineered vascular grafts (TEVGs) offer a potential strategy for overcoming the complications of commercially available grafts by providing a scaffold for the patient's own cells to proliferate. Still, current TEVG strategies may not address the diversity in graft shape necessary for each patient. Recent progress in imaging technologies provides detailed, three-dimensional (3D) views of complex cardiac and vascular anatomy before surgery. 3D images obtained from patients can be modified into a computer model to design optimal patient-specific TEVGs.

The goal of this project is to develop a new category of patient-specific TEVGs utilizing 3D printing technology based on 3D imaging of the patient. 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 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, vascular grafts that recruit endothelial cells and recapitulate the native mechanical properties.

FINDINGS / ACCOMPLISHMENTS

An in vivo study in a mouse model demonstrated long-term patency of the grafts. The team is preparing for further pre-clinical testing using the grafts.

12. **Non-Invasive Kidney Quantification for Hydronephrosis: Computer-Aided Diagnosis Tool (KidCAD)**

CATEGORY	HEALTHCARE SOFTWARE	STAGE OF DEVELOPMENT	PROTOTYPING
FUNDING SOURCE	Sheikh Zayed Institute		

KEY PERSONNEL

Marius Linguraru, DPhil
Juan Cerrolaza, PhD
Craig Peters, MD
Nabile Safdar, MD

SYNOPSIS

The most common pediatric ultrasound studies are of the kidney (10-30 cases daily at Children's National); the most common abnormal finding in these studies is hydronephrosis (2-2.5% of children). Ultrasound is the mainstay of imaging for pediatric hydronephrosis, yet is limited by its subjective assessment, absence of a consistently interpreted grading system, and apparent lack of correlation with functional imaging modalities. When hydronephrosis is found with ultrasound, the patient is often required to undertake a diuretic renogram, an invasive and ionizing exam to determine the severity of hydronephrosis.

The goal of our project is to characterize hydronephrosis more precisely, non-invasively and without radiation, and permit the routine adoption (at our center and others) of a quantitative, robust and reproducible ultrasound-based technique to evaluate and follow hydronephrosis. For this purpose, we have developed new ultrasound-based quantitative imaging biomarkers of pediatric hydronephrosis in order to limit the need for diuretic renograms in young patients. The underlying hypothesis of the study is that renal morphology can be quantitatively correlated with the severity of obstruction and possibly with renal function. The project has shown positive bench test results on 2D ultrasound data from routine clinical examinations. Further pre-clinical evaluations are ongoing while also transitioning to 3D image data in collaboration with Philips Healthcare.

FINDINGS / ACCOMPLISHMENTS

The study has demonstrated the feasibility of developing reliable and objective imaging biomarkers to support the routine clinical evaluation of kidneys from non-invasive ultrasound. In preliminary results from 2D ultrasound scans, we identified 100% of the critical hydronephrotic cases and indicated that diuretic renograms could likely be avoided in a majority (62-85%) of non-critical cases. The technology has the potential to non-invasively assess renal obstructive severity, minimize the use of ionizing radiation tests on children with hydronephrosis, and reduce clinical cost.

13. **Digital Dysmorphology: Automated Early Detection of Genetic Syndromes from Photography**

CATEGORY	MEDICAL DEVICES/ SOFTWARE	STAGE OF DEVELOPMENT	PROTOTYPING/ PRE-CLINICAL
FUNDING SOURCE	Sheikh Zayed Institute		

KEY PERSONNEL

Marius Linguraru, DPhil
Qian Zhao, PhD
Marshall Summar, MD
Ken Rosenbaum, MD
Tim Moran, MBA

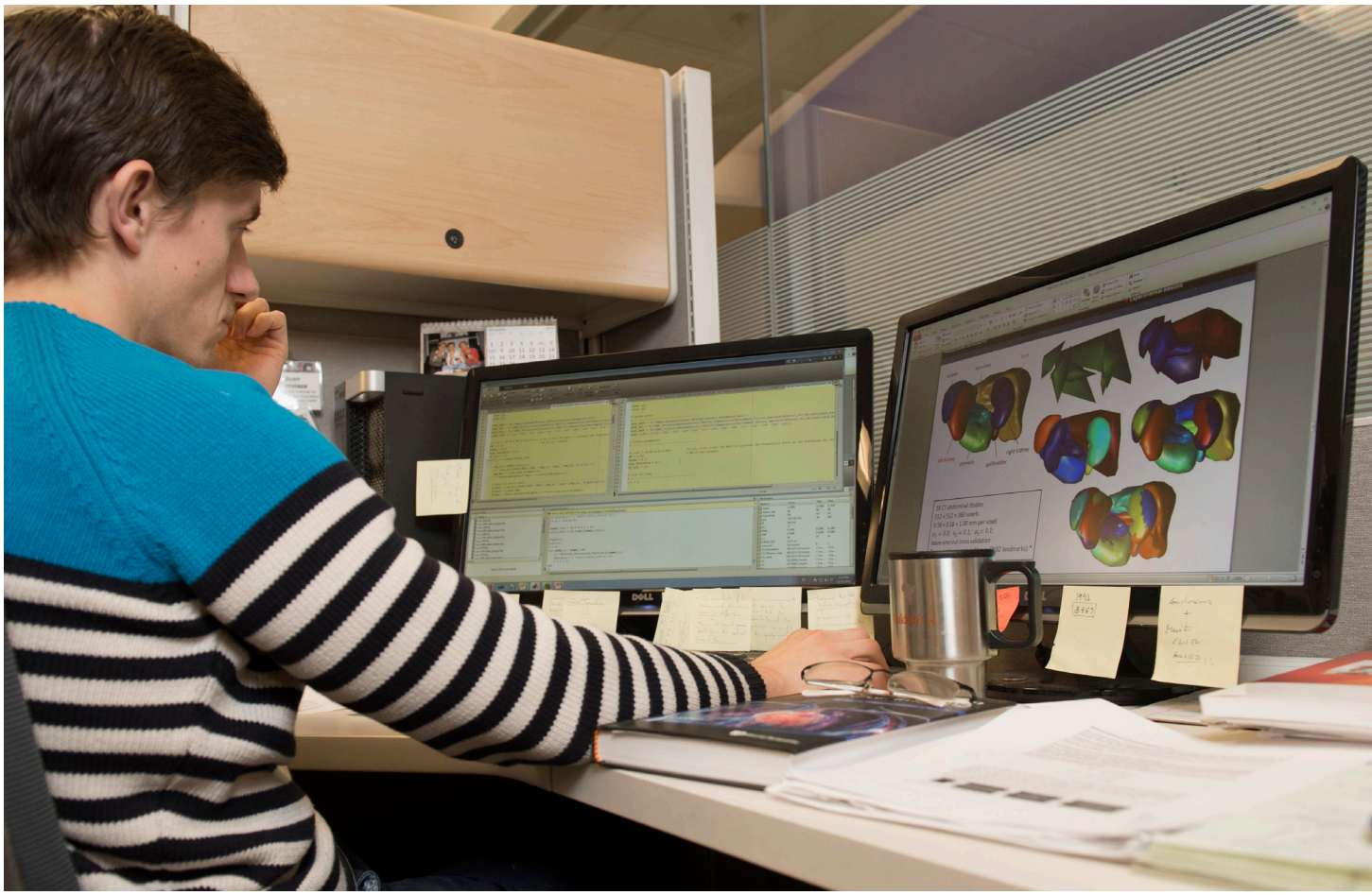
SYNOPSIS

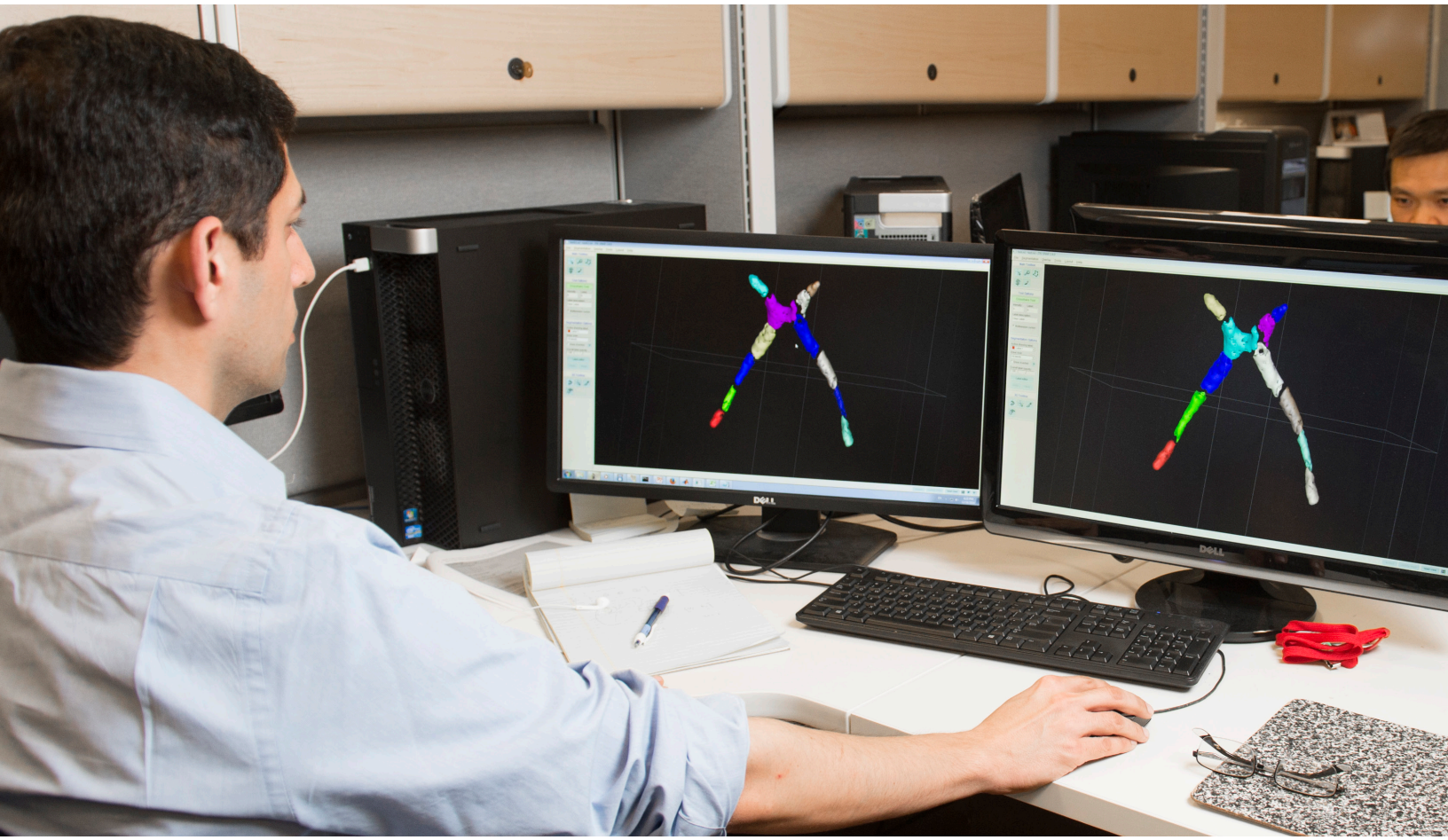
One in 150 children in U.S. is born with a chromosomal condition, including Down syndrome. The result is over 1 million children born worldwide every year with an undiagnosed genetic syndrome, the cause of 15% to 53% of hospital admissions and 20-30% of childhood deaths. These children have high incidence of serious medical complications (cardiac, pulmonary, motor) and intellectual disability that require treatment and usually surgery. Because of these related complications, it is critical to detect genetic syndromes early. While the number of patients with genetic syndromes increases worldwide, the number of geneticists remains flat and genetic tests and medical costs are very expensive. Thus, current dysmorphology services are often overwhelmed and inefficient.

We developed a software technology that can assess a child immediately after he or she is born, without the need for blood tests or specialized clinics. This noninvasive test uses automated facial recognition as a screening tool and can make the detection of genetics syndromes as easy as a snapshot. An early prototype of the technology is already available with a graphic-user-interface to allow the easy analysis of photographic data on a laptop. After successful preclinical test results, we are preparing for extensive clinical validation and looking for partners for commercialization.

FINDINGS / ACCOMPLISHMENTS

The accuracy of this technology is > 96%; other genetic syndromes with facial dysmorphology can be detected in a similar way. The technology could bring sophisticated and rare genetic expertise to isolated areas without access to specialized services or even to basic clinical care. These improvements in the current clinical management of genetic disorders, together with lower clinical costs, have a lifesaving potential especially for children whose condition is only subtly apparent in physical terms.





14. **Quantitative Volumetric Analysis of Optic Pathway Gliomas in Children with NF1**

CATEGORY	MEDICAL DEVICES/ SOFTWARE	STAGE OF DEVELOPMENT	CONCEPT FORMATION
FUNDING SOURCE	Gilbert Family Neurofibromatosis Institute		

KEY PERSONNEL

Marius Linguraru, DPhil
Awais Mansoor, PhD
Robert Avery, DO
Gilbert Vezina, MD

SYNOPSIS

Nearly 20% of children with Neurofibromatosis Type 1 (NF1) will develop an optic pathway glioma (OPG). OPGs can cause permanent vision loss ranging from a mild decline in visual acuity to complete blindness. About 50% of children with OPGs will experience vision loss from their tumor, typically between 1 to 8 years of age, which has a significant impact on a child's quality of life. However, identifying which children will lose vision remains elusive and frequently results in unnecessary treatment in some and delayed treatment in others. Risk stratification of vision loss using an objective quantitative marker could significantly improve the care of children with NF1-OPG. We hypothesize that by developing and validating automated quantitative magnetic resonance imaging (MRI) analysis of the optic nerve in children with NF1-OPG, we will: (i) establish standardized criteria of OPG diagnosis and thus reduce inappropriate diagnosis, imaging, treatment, and inherent costs; (ii) provide an objective and quantitative understanding of tumor growth and response to treatment for personalized clinical management of NF1-OPG; and (iii) ultimately be able to stratify patients based on their MRI assessment into a low versus high risk of vision loss, and thus improve clinical decision making.

FINDINGS / ACCOMPLISHMENTS

While the project is still in an early stage, we have constructed a computational model of the variability of the healthy optic pathway, in which local shape variability is captured to accommodate pathological morphological changes, such as OPGs. The model is very accurate to allow the automatic segmentation of the optic pathway from routine MRI scans with an average root mean squared symmetric surface distance of 0.59mm.

15. **Quantitative MR Enterography Markers of Inflammatory Bowel Diseases via Radiology-Pathology Fusion**

CATEGORY	HEALTHCARE SOFTWARE	STAGE OF DEVELOPMENT	PROTOTYPING
FUNDING SOURCE	Sheikh Zayed Institute		

KEY PERSONNEL

Marius Linguraru, DPhil
Juan Cerrolazza, PhD
Nabile Safdar, MD
Ray Sze, MD
Laurie Conklin, MD

SYNOPSIS

It is estimated that approximately 1.4 million Americans suffer from inflammatory bowel diseases with over 550,000 affected by Crohn's disease, the incidence and prevalence of which has been increasing over time. Crohn's disease presents most commonly between the ages of 15 to 30 and for many, this condition requires lifelong care with medical titration and often surgery. Clinical identification of Crohn's disease is performed based on clinical symptoms (which are largely subjective), with confirmation using an endoscopy and/or colonoscopy with tissue biopsy. However, these techniques have limited access to areas of the small bowel, carry a risk of perforation, and do not provide an accurate assessment of disease severity. Since Crohn's may cause serious complications, an effective, non-invasive method for identifying disease location and severity and monitoring disease activity is greatly needed to guide treatment. In response to this clinical need, we have developed a software technology that quantifies small bowel peristalsis in mm/s from dynamic magnetic resonance enterography sequences. This functional activity map of the small bowel is then fused with the structural information from additional imaging sequences to evaluate and follow Crohn's disease. At the next stage, we will investigate how imaging biomarkers can assess the severity of Crohn's disease in the small bowel.

FINDINGS / ACCOMPLISHMENTS

In a pilot study, small bowel areas presenting finding consistent with Crohn's disease (wall thickening, or luminal narrowing) were successfully identified with regions with reduced motility (< 1.2mm/s). A relative improvement in the motility of the affected areas (from < 1mm/s to 1.5mm/s) was observed for the patients who exhibited a positive response to treatment over time. A decrease in the overall motility of the small bowel (from >2.7mm/s to < 1.6mm/s) was observed for those patients with an interval progression of Crohn's disease. Thus, the developed technology has the potential to facilitate the accurate and objective longitudinal follow up of patients with small bowel Crohn's disease. The technology also provides important functional information about proximal small bowel disease.

16. **Image-Guided Planning System for Skull Correction in Children with Craniosynostosis**

CATEGORY	HEALTHCARE SOFTWARE	STAGE OF DEVELOPMENT	PROTOTYPING/ PRE-CLINICAL
FUNDING SOURCE	NIH National Institute of Child Health and Human Development		

KEY PERSONNEL

Marius Linguraru, DPhil
Jin Qi, PhD
Nabile Sfadar, MD
Benjamin Wood, MD

Gary Rogers, MD
Andinet Enquobahrie, PhD
Ricardo Ortiz, PhD,
Kitware, Inc.

SYNOPSIS

Craniosynostosis is the premature fusion of cranial sutures and occurs in approximately one in 2,000 live births. It results in cranial malformation that can lead to elevated intra-cranial pressure, brain growth impairment, and developmental deficiency. The most common treatment option for craniosynostosis is surgery. However, the surgical treatment planning of craniosynostosis is currently qualitative, subjective, and irreproducible, and the remodeling of the cranial vault is guided solely by the surgeon's experience.

To address these challenges, we are creating a software technology for treatment planning and evaluation of craniosynostosis through quantitative, robust, accurate, and reproducible methods to assess cranial shape. The potential impact of our technology is reduced perioperative morbidity and lower treatment costs. The technology will also enable the precise, quantitative comparison of measurements before and after cranial vault reconstruction to determine the efficacy and durability of specific reconstructive techniques. At this stage we have developed the first generation of a software technology for comprehensive cranial shape analysis and obtained positive bench tests for the accurate diagnosis of metopic craniosynostosis. At the next stage, we will develop and evaluate a software planning system for cranial remodeling. The project is a coordinated effort between Children's National Health System and Kitware Inc.

FINDINGS / ACCOMPLISHMENTS

In the first preclinical study, we evaluated our new method to identify the closest normal cranial shape to patients with craniosynostosis and compute automatically local bone deformations to guide surgical planning. The method was evaluated for the diagnosis of types of craniosynostosis. The accuracy (correct classification rate) obtained was 0.957 using a database of 141 cases (90 normal controls and 51 cases of different types of craniosynostosis). The development of quantitative and robust tools for personalized interventions could provide precise and reproducible techniques to guide cranial vault remodeling and leverage surgical expertise. Its impact will be decreased operative time and blood loss, thereby reduced perioperative morbidity and lower treatment costs, while facilitating an optimized and more durable long-term outcome.

17. Stereoscopic Augmented Reality Visualization for Laparoscopic Surgery

CATEGORY	MEDICAL DEVICES	STAGE OF DEVELOPMENT	CLINICAL
FUNDING SOURCE	Sheikh Zayed Institute NIH National Cancer Institute		

KEY PERSONNEL

Raj Shekhar, PhD
Timothy Kane, MD
Craig Peters, MD
Xinyang Liu, PhD
Sukryool Kang, PhD
James McConnaughey

SYNOPSIS

The overall goal of this project is to develop and commercialize a technology that gives minimally invasive surgeons enhanced view of the surgical anatomy for improved safety, precision, and efficiency. The two new visual cues we introduce are (1) perception of true depth and improved understanding of 3D spatial relationship among anatomical structures, and (2) visualization of critical internal structures along with a more comprehensive visualization of the operative field. This is accomplished by integrating two real-time surgical imaging modalities: (i) newly emerged 3D laparoscopic camera technology that allows visualizing the surgical anatomy with the highest image quality currently available and perception of true depth, and (ii) laparoscopic ultrasound capable of visualizing hidden structures. We call the resulting visualization capability stereoscopic augmented reality, in which stereoscopic laparoscopic video (the reality) is augmented with ultrasound findings, especially the blood vessels, ducts and tumors. For accurate spatial registration between the two types of images, the 3D location and orientation of the imaging devices are continuously tracked. A fully functioning prototype that has been tested in the laboratory and through animal studies is currently being tested in humans under an IRB-approved protocol. The human testing is generating critical data for technology improvement and product design and assessment of clinical benefits.

FINDINGS / ACCOMPLISHMENTS

The preliminary data led to a small-business technology transfer (STTR) Phase I grant from the NIH National Cancer Institute. This funding also led to the project team's selection to participate in the pilot NIH I-Corps program.

18. **Minimally-Invasive Pacemaker/Defibrillator**

	CATEGORY	**MEDICAL DEVICES**	STAGE OF DEVELOPMENT	**PROTOTYPING/ PRE-CLINICAL**
	FUNDING SOURCE	Medtronic, Inc.		

KEY PERSONNEL

Charles Berul, MD
Justin Opfermann, MS
Bradley Clark, MD
Tanya Davis, MD
Axel Krieger, PhD

SYNOPSIS

In children and patients with complex congenital heart disease, standard transvenous pacemaker and defibrillator placement is not a viable option. The only currently-available alternative is open-chest placement of pacing leads directly on the heart, which is a significantly more invasive procedure. Major device manufacturers do not have a business model or incentive to develop a pediatric-specific pacemaker or defibrillator device or implantation application. The goal of the present work is to develop minimally-invasive percutaneous lead delivery tools and techniques for implanting pacemaker and defibrillator leads via a pericardiocentesis needle to access the heart, specifically designed for pediatric and congenital heart applications. Using an infant piglet model, preclinical testing is demonstrating the feasibility of the technique, and development of specific tools for access is currently ongoing.

Tim Kane, MD and Raj Shekhar, PhD, members of the Sheikh Zayed Institute for Pediatric Surgical Innovation.

19. **Treadmill Stress Test for Toddlers**

CATEGORY	MEDICAL DEVICES	STAGE OF DEVELOPMENT	PROTOTYPING
FUNDING SOURCE	Sheikh Zayed Institute		

KEY PERSONNEL

Charles Berul, MD
Megan Yeigh
Justin Opfermann, MS
Axel Krieger, PhD
Megan Smith

SYNOPSIS

Presently, exercise stress testing is designed for older children and adults, using bicycle or graded treadmill exercise. The equipment currently available is too small for toddlers and young children to safely utilize. There is not a current commercially-available product for use in children under age 6 years, although there remains a clinical need for exercise stress testing at any age. Therefore, we designed and developed a prototype apparatus for young children, ages 2-6 years to perform graded exercise stress testing. A safety harness feature was incorporated for patient safety and comfort. An age-appropriate video motivational program with movement sensors (using Microsoft Wii technology) was integrated into the system to encourage participation by children in this age group. Clinical trials in children ages 2.5-5 years with normal hearts, followed next by clinical testing in young children with structural congenital or inherited electrical heart diseases, are planned to begin in 2015 under IRB approval.

20. **Tissue Engineered Model of Preeclampsia**

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PRE-CLINICAL/ PROTOTYPING
FUNDING SOURCE	Sheikh Zayed Institute University of Maryland A. James Clark School of Engineering		

KEY PERSONNEL

John Fisher, PhD
Che-Ying (Vincent) Kuo, MS, PhD Candidate
Peter Kim, MD, PhD

SYNOPSIS

Preeclampsia (PE) is the leading cause of maternal and fetal morbidity and mortality, affecting 5% of all pregnancies. PE is caused by hypoxia in the placenta due to improper trophoblastic invasion after the implantation of blastocyst. However, there is a lack of treatment options and understanding of PE compare to other multifactorial diseases such as heart diseases and kidney diseases. This is partly due to the lack of appropriate experimental models for treatment development. For example, the animal models used to study PE can be misleading, as the placentation process in humans is very different from other mammals. Human tests are often unfeasible due to ethical and regulatory constraints. Therefore significant efforts are spent on developing in vitro models to study and develop treatments for PE. However, current in vitro models do not capture the essential elements of the uterine wall, such as the unique spiral maternal vasculature. Additionally, these models often lack the heterogeneous cell, ECM, and chemical signals that are present in the natural endometrium structures. These limitations are particularly noteworthy since the spiral arteries, the heterogeneous cell populations, and the different layers of the uterine wall are all important in the pathology of PE. Using 3D printing technologies, we hypothesize that we can fabricate a vascularized tissue model with heterogeneous ECM, growth factor composition/concentration, and cellular compositions to develop in vitro models for disease such as PE. We will test our hypothesis by the following specific aims: (1) Identify the appropriate printing parameters and biomaterials/cells to develop a 3D tissue engineered model of placenta; (2) Place the placenta model under dynamic culture conditions and evaluate the effect of soluble factors on the morphologies, viabilities, and phenotypes of human villous trophoblast, endothelial cells, and epithelial cells; (3) Demonstrate the potential of the tissue engineered invasion model as a drug-screening and disease-modeling tool by applying the strategy to preeclampsia.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Craig Peters, MD
Chief, Division of Surgical Innovation,
Technology and Translation

21. **Modern Lymph Node for Perfusion Bioreactor Culture**

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PRE-CLINICAL/ PROTOTYPING
FUNDING SOURCE	Sheikh Zayed Institute University of Maryland A. James Clark School of Engineering		

KEY PERSONNEL

Russell Cruz, MD, PhD
John Fisher, PhD
Che-Ying (Vincent) Kuo, PhD Candidate
Jesse Kenneth Placone, PhD

SYNOPSIS

Congenital heart disease (CHD) is the most common birth defect in the world. To treat CHD, surgeons must often craft a graft device for a patient while the patient is on the operating table. Additionally, these devices do no grow with the patient and these devices are expected to fail within 10-15 years after implantation. Researchers seeking to minimize these complications are turning to tissue engineering. This approach can be combined with the advantages of 3D printing. Our work utilizes these concepts to print custom vascular grafts of poly(propylene fumarate) (PPF). PPF is a biodegradable, biocompatible polymer. However, in order to ensure the success of our 3D printed, tailor-made graft approach, we must ensure that the grafts support expedited and sufficient tissue growth and infiltration. We investigated a strategy of encouraging endothelial (EC) and endothelial progenitor cell (EPC) mobilization, migration, attachment, and proliferation. We hypothesize that we can encourage these behaviors through a combinatorial graft surface modification strategy via the immobilization of vascular endothelial growth factor (VEGF) and anti-CD34 antibody (CD34Ab). To improve cell migration and attachment, we investigated the effects of various concentrations of VEGF and CD34Ab in vitro and tested our tuned graft modification strategies with 3D printed grafts in vivo utilizing a mouse model. Our in vitro results demonstrated increased EC and EPC attachment on grafts incubated with VEGF concentrations of 1 ng/ml and CD34Ab concentrations of 10 ng/ml. Initial in vivo tests demonstrated good endothelial coverage and function on the 3D printed grafts, as well.

22. **Tissue Engineered Trachea**

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PRE-CLINICAL/ PROTOTYPING
FUNDING SOURCE	Sheikh Zayed Institute University of Maryland A. James Clark School of Engineering		

KEY PERSONNEL

Diego Preciado, MD, PhD
Joshua Bedwell, MD, PhD
John Fisher, PhD

Ting Guo, MS

SYNOPSIS

The objective of this project is to use a biocompatible material that has similar mechanical properties to cartilage and use this material to replace the damaged trachea in a mouse model. Based upon a poly-(lactic-co-glycolic acid) (PLGA) mesh we have successfully fabricated scaffolds of the desired dimensions and mechanical properties. Initial studies have focused on the short-term viability of chondrocytes. These studies demonstrated that we can successfully fabricate scaffolds that are conducive for cell survival; however, the attachment efficiencies were lower than expected. We hypothesize that we can enhance the cell survival and attachment rate by modifying the PLGA scaffolds by providing cell adhesion motifs. To investigate this hypothesis we will 1) fabricate PLGA scaffolds with a fibronectin coating (alternative coating and binding motifs such as RGD residues will be investigated if needed); 2) assess adhesion and cell survival with Live/Dead assays; 3) ensure long-term survival (>2 weeks); and 4) assess protein production and gene expression of the seeded cells. These four aims will be used to gain an insight into the survival, proliferation, and functionality of chondrocytes and airway epithelial cells. Upon the successful completion of these aims, we can move forward with in vivo testing.

23. **Development of Non-Invasive Continuous Neuromonitoring | Validating Novel Biomarkers of Imminent Brain Injury**

CATEGORY	MEDICAL DEVICES	STAGE OF DEVELOPMENT	PRE-CLINICAL/ PROTOTYPING
FUNDING SOURCE	Sheikh Zayed Institute Fetal and Translational Medicine at Children's National		

KEY PERSONNEL

Adre du Plessis, MBChB
Rathinaswamy Govindan, PhD

SYNOPSIS

Brain injury is a dreaded, often devastating complication of critical illness, and its impact on the quality of long-term survival off-sets the advances made in the mortality of critical care. Prevention of brain injury in this population remains impeded by delayed detection of emerging brain insults until well after the window for effective intervention has closed. Such delay is due to (i) the subtlety or absence of bedside neurologic signs during critical illness, and (ii) the ongoing lack of continuous neuromonitoring capable of detecting emerging brain insults with sufficient lead-time for meaningful neuroprotective intervention.

The overarching goal of this project is the prevention of irreversible brain injury in critically ill patients. A pivotal step in pursuit of this goal is the development of a non-invasive bedside brain-monitoring device that reliably identifies the antecedents of brain injury with sufficient lead-time to institute preventive neuroprotection responses. Given the current lack of reliable bedside neurodiagnostic techniques, the progression from insult to brain injury usually proceeds undetected through the critical period when neuroprotective intervention is likely to most effective. Both interventions to minimize insult, as well as emerging neuroprotective agents to minimize injury, have a limited therapeutic window beyond which efficacy rapidly wanes. We have developed a multimodal neuromonitoring device capable of detecting early failure of intrinsic brain compensatory systems well before the onset of irreversible brain injury. The team is currently testing the validity of the non-invasive neuromonitoring device against invasive gold standard techniques in an animal model. If successful, this device will facilitate truly informed preventive neuroprotection, and will become an important tool for reducing neurological morbidity in the growing population of critical care survivors.

24. **On-Demand Dissolvable Ear Tube**

CATEGORY	MEDICAL DEVICES	STAGE OF DEVELOPMENT	PRE-CLINICAL/ PROTOTYPING
FUNDING SOURCE	Sheikh Zayed Institute Clinical and Translational Science Institute at Children's National (CTSI-CN)		

KEY PERSONNEL

Brian Reilly, MD
Matthieu Dumont, PhD

SYNOPSIS

Ear tube insertion, also known as tympanostomy or myringotomy tube insertion, is the placement of a pressure equalizer tube into the tympanic membrane of the middle ear. In the United States, ear tube insertion is the most commonly performed surgical procedure in children. Each year, 667,000 children younger than 15 years receive tympanostomy tubes, accounting for more than 20% of all ambulatory surgery in this group.

Although the current generation of tubes is beneficial for the treatment of otitis media, there are 4 major complications with this procedure:

- Failure of the ear tube to extrude within 24 months of insertion requiring a procedure under general anesthesia to remove the tube safely;
- Permanent perforation of the ear drum from extended presence of the tube;
- Persistent and refractory ear drainage despite antibiotic drops requiring removal of the tube; and
- Displacement, medialization or malposition of the tympanostomy tube into the middle ear space, behind the tympanic membrane.

Researchers found that 21,446 ear tubes needed to be removed surgically in 2006, or roughly 3.8% of tubes placed. Thus, there is a clear unmet need for an ear tube that can be removed safely, eliminating the need for a second surgery, while maintaining integrity throughout the duration of the desired implant lifetime.

We have created an ear tube using a biocompatible material that can retain its form and function for up to two years under physiological conditions and dissolve shortly on contact with our uniquely engineered ear drops. This novel design will eliminate the need for secondary surgeries to remove ear tubes that are no longer medically necessary, as well as reduce ear perforations and secondary hearing loss from tympanostomy tubes.

Immunology & Molecular Biology

medical devices — 3 projects

drugs/ biologics — 10 projects

Catherine Bollard, MD
Anthony Sandler, MD
Evan Nadler, MD
Diego Preciado, MD, PhD
Allistair Abraham, MD
Cecilia Barese, PhD
Lina Chakrabarti, PhD
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Russell Cruz, MD, PhD
Hema Dave, MD
Ashanti Franklin, MD
Patrick Hanley, PhD
Fahmida Hoq, PhD
Tatiana Iordanskaia, PhD
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Neha Joshi
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Maria Martin Manso, PhD
Renuka Miller, PhD
Kathy Mintz
Cliff Morgan
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Bahey Salem, MD
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Stéphanie Val, PhD
Kirsten Williams, MD
Kaylor Wright

TO USE A CHILD'S
OWN IMMUNE SYSTEM
TO FIGHT ILLNESS AND
CURE DISEASE - WITHOUT
THE NEED FOR SURGERY
AND TO INVESTIGATE THE
PROTEIN AND GENETIC
CHARACTERISTICS OF
PEDIATRIC DISEASES
IN ORDER TO DEVELOP
INNOVATIVE MOLECULAR
THERAPEUTICS

25. **Program: Immunotherapy for Targeting Pathogens**

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PRE-CLINICAL
FUNDING SOURCE	Grant Funding (total funding approximately $400K per year): P01 CA148600-01A1 (Bollard/Shpall), U01 HL10894 (Bollard), R01 AI106574-01 (Kimata/Bollard), DC-CFAR (Bollard), Modell (Keller/Bollard)		

KEY PERSONNEL

Michael Keller, MD
Maria Manso, PhD
Russell Cruz, MD, PhD
Swaroop Bose
Patrick Hanley, PhD
Sharon Lam
Sarah McCormack
Kaylor Wright
Hema Dave, MD
Catherine Bollard, MD

EJ Shpall, MD (MDACC)
David Margolis, MD (UNC)
Douglas Nixon, MD, PhD (GWU)

SYNOPSIS

Infections are a major cause of morbidity and mortality after hematopoietic cell transplantation (HCT), as well as in an increasing number of immunocompromised patients. T-Cell immunotherapy directed against viruses has been shown to be effective in restoring antiviral immunity and preventing or controlling viral infections such as adenovirus, CMV, or EBV following transplant. These T-Cells are expanded from different donor sources (peripheral blood versus cord blood, autologous versus allogeneic, seronegative versus seropositive) and are able to specifically recognize and lyse cells that have been infected by the mentioned viruses through the proteins expressed on their surface in the context of MHC molecules. We have previously shown that we can robustly generate these cells in a good manufacturing practice (GMP) lab setting and administer them to patients without severe adverse events, and observe prevention and treatment of adenovirus, CMV, or EBV that are often significant sources of morbidity and mortality post transplant. We have now set up a bench-to-bedside translational research workflow at Children's National that aims to (i) evaluate the use of antiviral T-Cells in different clinical settings including post cord blood transplant and outside the context of HCT, (ii) improve upon current manufacturing processes used in the generation of clinical grade antiviral T-Cells in the GMP including the expansion of virus specific T-Cells from virus naïve donors, and (iii) develop highly novel cellular therapies in combination with new technologies to eliminate other pathogens like HIV and invasive fungal disease.

FINDINGS / ACCOMPLISHMENTS

T-Cell immunotherapies have shown great success in the prevention and treatment of viral infections (most particularly EBV, adenovirus, and CMV) post hematopoietic stem cell transplant with no major adverse events. Infused patients have shown decreases in viral load corresponding to increases in circulating virus-specific T-Cells post infusion. Efforts are underway to expand the viral antigens targeted (e.g. extend to HPV, HHV6, BKV, HIV) and the immune compromised patients eligible to receive these products (through third party T-cell banking, generating cells from naïve donors).

26. **Program: Immunotherapy for Eliminating Cancer**

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PRE-CLINICAL/ CLINICAL TRIAL
FUNDING SOURCE	Grant Funding (total funding approximately $300K per year): Hyundai Hope On Wheels (Williams/Bollard), Clinical and Translational Science Institute at Children's National Pilot Program Award, Brain Tumor Internal Funds (Cruz/Bollard), SCOR/LLS (Bollard), U10CA098543 FP00013087 (Bollard), St. Baldrick's Foundation (Bollard)		

KEY PERSONNEL

Renuka Miller, PhD
Catherine Bollard, MD
Kaylor Wright
Swaroop Bose
Russell Cruz, MD, PhD
Rohan Fernandes, PhD
Anthony Sandler, MD
Lauren McLaughlin, MD
Michael Keller, MD
Cecilia Barese, MD,PhD
Kirsten Williams, MD
Maria Martin Manso, PhD

FINDINGS / ACCOMPLISHMENTS

We have demonstrated that we can effectively prevent lymphoma relapse in the post transplant setting, particularly for lymphomas that express EBV antigens on their surface. We now plan to extend this therapy for patients with solid tumors and non-virus-associated malignancies.

SYNOPSIS

T-Cells have shown great ability to recognize and respond to malignanT-Cells. In particular, both virus-specific T-Cells that target viral antigens expressed by virus-associated malignancies (like EBV-positive Hodgkin's lymphoma and non-Hodgkin's lymphoma) as well as chimeric antigen receptors whose T-Cell recognition is redirected to surface molecules like CD19 (by genetic modification: antibody recognition spliced onto an intracellular T-Cell and costimulatory molecule signaling domains) in B cell malignancies have shown great promise in the clinics. T-Cell therapies have been heralded as an important component of Science's Breakthrough of the Year for 2013. Their ability to home to the site of disease, orchestrate immune responses via cytokine secretion, mediate directed lysis of their targets, and potentially confer lifelong protection against tumors have made their use extremely attractive. Over the last several years, different studies from various centers have shown that these cells are capable of treating cancers that have been otherwise refractory to standard therapies with measurable efficacy. We have previously shown that we can robustly generate these cells in a good manufacturing practice (GMP) lab setting, administer them to patients without severe adverse events, and observe complete and partial remissions. We have now set up a bench-to-bedside translational research workflow at Children's National that aims to: (i) evaluate the use of additional immune cells (like NK cells and dendritic cells) and how we can combine them into potent antitumor therapies, (ii) improve upon current manufacturing processes used in the generation of clinical grade antitumor T-Cells in the GMP, (iii) target more antigens in a single culture platform, and (iv) develop highly novel cellular therapies either in combination with other drugs (like epigenetic modifying drugs or immunomodulatory drugs) or via genetic modification – to increase targeting, resistance against immunosuppressive microenvironments, persistence, and function.

27. **Program: Immunotherapy for Controlling Inflammation**

CATEGORY	**DRUGS/BIOLOGICS**	STAGE OF DEVELOPMENT	**MANUFACTURING**
FUNDING SOURCE	Grant Funding (total funding approximately $100K per year): Board of Visitors Grant (Bollard), Joseph E. Robert Jr. Endowment Award (Conklin), Sheikh Zayed Institute Investment (Bollard)		

KEY PERSONNEL

David Jacobsohn, MD
Patrick Hanley, PhD
Allistair Abraham, MD
Laurie Conklin, MD
Catherine Bollard, MD

Sawa Ito, MD (NIH)
John Barrett, MD (NIH)
Jacques Galipeau, MD (Emory)

SYNOPSIS

Anti-inflammatory mesenchymal stromal cells (MSCs) have shown great promise in modulating inflammatory syndromes, including graft versus host disease and inflammatory bowel disease. Their lack of expression of HLA Class II and co-stimulatory molecules allows their use in the third party setting with little rejection or immunogenicity. These properties make them ideal candidates for a bank of products that can be readily used by patients without need for extensive manufacturing lead times. One crucial element that has been identified in recent years is the need for generating younger cells that have undergone fewer proliferative cycles: this need, we hypothesize, is fulfilled by a rapid expansion quantum bioreactor, which places cells in tubes for increased air contact and surface area. The bioreactor also allows for automation and cell feeding via perfusion, which allows better reproducibility, scalability, and healthier cells. Preclinical experiments show their anti-inflammatory properties are enhanced using this expansion method. Our goal is to manufacture these anti-inflammatory cells using our rapid expansion system and use them for a variety of clinical indications. Our initial focus is graft versus host disease and inflammatory bowel disease, but ultimately we will explore the use of MSCs for muscular dystrophies, transfusion related lung injuries, and other immune mediated syndromes.

FINDINGS / ACCOMPLISHMENTS

We have successfully manufactured mesenchymal stromal cells using a rapid expansion system, the quantum bioreactor, and have shown reproducible function and phenotype of our clinical grade products. We are now validating the manufacturing process to ensure they will be able to perform their functions in vivo, in patients with GVHD and inflammatory bowel disease.

28. **Vaccine Therapy for Cancer: Id2KD Attenuated Whole Tumor Cell Therapeutic Vaccination**

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PRE-CLINICAL
FUNDING SOURCE	Sheikh Zayed Institute		

KEY PERSONNEL

Anthony Sandler, MD
Lina Chakrabarti, PhD
Priya Srinivasan, PhD
Clifford Morgan

SYNOPSIS

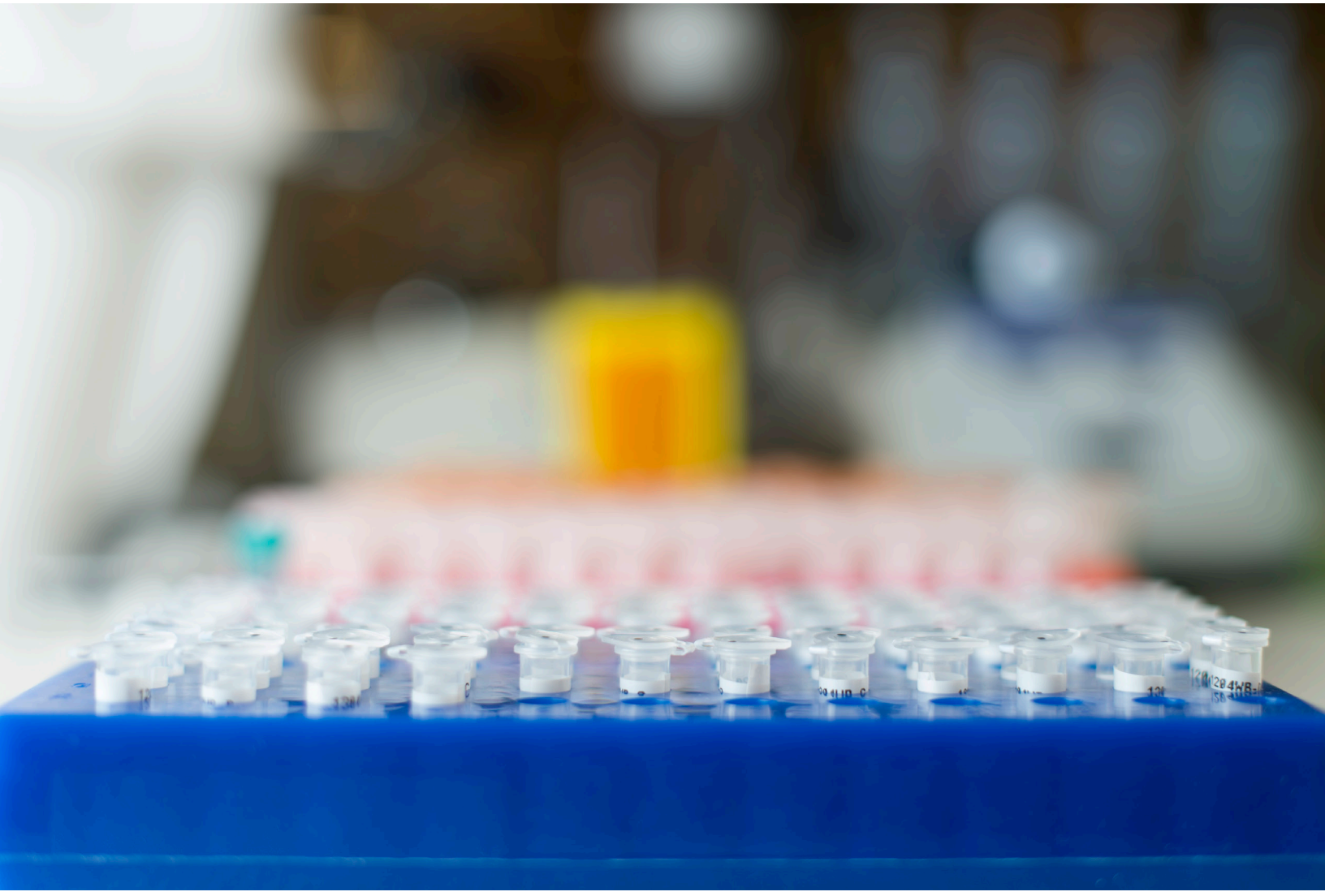
Tumor vaccines lack effect, primarily due to poor tumor antigen presentation and immuno-suppressive mechanisms exploited by the tumor itself. We explored the use of attenuated live tumor cells as a method for optimal tumor antigen presentation and determined the effectiveness of combining antigen presentation with an immune activating agent (checkpoint blockade).

The inhibitor of differentiation protein 2 (Id2) is found to be a key molecule modulating phenotypic transition in neuroblastoma. Immune-competent as well as immune-compromised mice were challenged with Id2 knockdown Neuro2a (Id2kd-N2a) and tumor growth was monitored for 4-6 weeks. Id2kd-N2a cells were subsequently used for vaccination with or without cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) blockade in a model of established neuroblastoma tumor.

Tumors failed to grow in immunologically competent mice challenged with viable Id2kd-N2a cells, and these mice subsequently developed immunity against further wild-type Neuro2a tumor challenge. Validating the immunologic effect, the Id2kd-N2a cells grew aggressively in SCID and nude immune-compromised hosts. Therapeutic vaccination with Id2kd-N2a cells alone suppressed tumor growth even in established neuroblastoma tumors, and when used in combination with CTLA-4 blockade, large established tumors were eradicated. Furthermore, an increased number of CD8+ T-cells and enhanced production of IFN-gamma was observed in the splenocytes of mice that were cured of tumor. More importantly, a massive infiltration of CD8+ T-cells was found in the shrinking tumors of vaccinated mice.

FINDINGS / ACCOMPLISHMENTS

Our findings suggest that down regulation of Id2 attenuated tumorigenicity in the mouse model and induced host immunity. When used in combination with CTLA-4 blockade, large established tumors were cured. The results also validate the role of T-cell immunity in this tumor vaccine strategy. These findings should enable translation into a therapeutic patient-specific vaccine for resistant neuroblastoma tumors. The results may also have implications for other high-risk aggressive tumors as well.



29. **Reversible Adaptive Plasticity: Cancer Cell Biology**

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PRE-CLINICAL
FUNDING SOURCE	Sheikh Zayed Institute		

KEY PERSONNEL

Anthony Sandler, MD
Lina Chakrabarti, PhD
Priya Srinivasan, PhD
Clifford Morgan

Don Devoe, PhD
(University of Maryland)

SYNOPSIS

Malignant rhabdoid tumors are extremely aggressive pediatric tumors that arise from the central nervous system, soft tissues, or kidneys. We have recently described a phenomenon of reversible adaptive plasticity (RAP) in neuroblastoma that allows tumor cells to switch their growth patterns between proliferative anchorage dependent (AD) or slow-growing anchorage independent (AI) phenotypes. This cellular plasticity and adaptation enables tumors to evade immune surveillance, survive unfavorable conditions, and/or escape therapy. Each cell type has a distinctive gene expression profile in which key differences define the cell types.

We sought to determine (i) whether RAP is a common feature of other aggressive pediatric solid tumors and (ii) if distinct gene expression patterns can predict drug sensitivity. Three human rhabdoid tumor cell lines were tested for phenotypic and molecular changes representing the phenomenon of reversible adaptive plasticity.

Two of the rhabdoid tumor cell lines tested exhibit reversible adaptive plasticity. The line that failed to transition is a chemo-sensitive proliferating cell line. Gene array analysis revealed striking differences between the AD and AI phenotypes of the two cell lines that transition. ID1, ID2, and ID3 genes are differentially expressed and up regulated in the AD phenotype, similar to that of the neuroblastoma cell lines. In addition, the two transitioning cell lines show a marked up regulation of STAT1, ISG15, and IFIT1 genes in the AI phenotype. These genes are characteristic of the interferon-related gene signature for DNA damage resistance (IRDS) observed in several other malignant tumor types. Other differences in gene expression include the MAP kinase signaling pathway, mTOR/PI3K-Akt signaling pathway and genes regulating cell cycle. The AD rhabdoid tumor cell phenotypes are sensitive to chemotherapy

SYNOPSIS cont.

while the AI phenotypes are less sensitive or completely resistant to even multi-drug combinations. However, the AI cells are more sensitive to drugs that target the Jak-Stat signaling pathway, a pathway identified by gene array analysis.

Aggressive rhabdoid tumors display reversible adaptive plasticity. The molecular mechanisms underlying RAP in rhabdoid and other highly malignant tumors are critical to their behavior. Defining these pathways will provide insight into developing effective treatment strategies and targets for these highly aggressive tumors.


APPROXIMATE VOLUMES
80
60
40
20

30. **Microfluidic Nanoparticle Therapy**

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PROTOTYPING/ PRE-CLINICAL
FUNDING SOURCE	Sheikh Zayed Institute University of Maryland A. James Clark School of Engineering		

KEY PERSONNEL

Anthony Sandler, MD
Lina Chakrabarti, PhD
Priya Srinivasan, PhD

Don Devoe, PhD (UMD)

FINDINGS / ACCOMPLISHMENTS

The team developed and tested micro-fluidic particles with tumor targeting properties. Pre-clinical studies are underway to determine efficacy of nano-particle drug constructs for tumor therapy.

SYNOPSIS

A novel technology is proposed for the encapsulation of therapeutic agents within nearly monodisperse liposome nanocapsules as a highly promising approach to next generation targeted drug delivery. By taking advantage of the unique microscale and nanoscale physiochemical interactions that occur at the boundary between two miscible solvent flows within a microfluidic system, liposomes with mean diameters as small as 20nm will be generated with exceptionally narrow distributions. The ability to form liposomes that are both smaller and more uniform than those previously explored for therapeutic applications has important implications for the safety and efficacy of drugs encapsulated using the microfluidic technique, and is expected to offer advantages over existing liposome production methods, including reduced toxicity and more cost-effective and agile production of liposomal drug formulations. Other benefits offered by the technology include high encapsulation efficiency with minimal reagent loss, and the ability to enable efficient in-line functionalization of liposome membranes with ligands for targeted drug delivery. Project goals include the optimization of the microfluidic liposome formation process to reduce size variations to below 5% of the mean vesicle diameter. By taking advantage of the tight control afforded over liposome size, detailed relationships between liposome size and biodistribution will be investigated for the first time using nearly-monodisperse liposomes smaller than 100nm. The microfluidic process will be extended to enable the encapsulation of hydrophilic, amphipathic, and lipophilic drug compounds. On-line decoration of the vesicles with cancer-targeting ligands will be demonstrated, together with on-line vesicle concentration and purification in a simple flow-through process. The optimized platform will be used for automated and on-demand preparation of a combination treatment, comprising an amphipathic chemotherapeutic (doxorubicin), a lipophilic EGFR inhibitor (erlotinib), and a lipophilic FGFR inhibitor (PD-173074), to be applied to a pre-clinical study of pediatric neuroblastoma.

31. Genetic Studies of Necrotizing Enterocolitis

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	CLINICAL TRIALS
FUNDING SOURCE	Sheikh Zayed Institute		

KEY PERSONNEL

Anthony Sandler, MD
Ashanti Franklin, MD
Mariam Said, MD
Joseph M. Devaney, PhD
Naomi C. Luban, MD
Khodayar Rais-Bahrami, MD

SYNOPSIS

Necrotizing enterocolitis (NEC) is a devastating gastrointestinal emergency that affects approximately 10% of premature neonates. The pathogenesis of NEC remains poorly understood. We hypothesize that some preterm infants exhibit an exaggerated inflammatory response, leading to the production of reactive oxygen species (ROS) and intestinal epithelial necrosis. The purpose of this study is to determine if (i) differences in redox homeostasis can be measured using metabolomic profiling and (ii) if functional single nucleotide polymorphisms (SNPs) in antioxidant enzymes are associated with NEC.

Institutional Review Board approval and parental/guardian consent was obtained. Buccal swabs for DNA extraction were collected from infants that were of the following clinical characteristics: ≤32 weeks gestation and/or a diagnosis of NEC. Patients with congenital heart disease (except PDA), major congenital anomalies, genetic disorders, and inherited blood/metabolic disorders were excluded. Controls consisted of infants ≤32 weeks gestation without NEC or spontaneous intestinal perforation. Metabolomic profiling was performed on plasma samples. A TaqMan allelic discrimination assay was used to determine alleles. Statistical analysis was completed using Welch's two-sample t-test and logistic regression.

FINDINGS / ACCOMPLISHMENTS

One hundred and thirty four African-American neonates were enrolled in this study, of which 46 had NEC. Metabolomic data from 30 enrolled subjects (10 control, 10 Stage III NEC, 10 NEC totalis) showed patients with NEC possessed reduced levels of oxidized glutathione and cysteine ($p=0.0379$, $q=0.09$) and depleted levels of anti-oxidants carnosine ($p=0.004$, $q=0.01$) and gamma-tocopherol ($p=0.01$, $q=0.03$). Utilizing a dominant model, Catalase (rs1001179) was associated with Stage III NEC in preterm African-American neonates ($p= 0.031$). Superoxide dismutase 2 (rs4880) trended toward an association with NEC totalis ($p= 0.0548$).

In patients with severe NEC an imbalance in redox homeostasis is noted, signifying increased ROS production and depletion of antioxidants. SNPs in antioxidant enzymes may be associated with severe NEC. This study suggests a predisposed genetic basis for the pathogenesis of NEC.

32. **Blow Spin Polymer for Surgical Applications**

CATEGORY	**MEDICAL DEVICES**	STAGE OF DEVELOPMENT	**PROTOTYPING/ PRE-CLINICAL**
FUNDING SOURCE	Sheikh Zayed Institute University of Maryland A. James Clark School of Engineering		

KEY PERSONNEL

Anthony Sandler, MD
Priya Srinivasan PhD
Lina Chakrabarti, PhD

Peter Kofinas, PhD (UMD)
Adam Behrens (UMD)

SYNOPSIS

While conventional suturing is still ubiquitous in surgery, tissue sealants that could improve usability, outcome, and patient comfort have great potential applications. Hence we have used solution blow spinning for the direct deposition of polymer fiber mats as surgical sealants. Solution blow spinning is a polymer fiber mat fabrication technique that requires only a simple apparatus, a concentrated polymer solution in a volatile solvent, and a high-pressure gas source. This technique does not have the high voltage and conductivity requirements of electrospinning and does not suffer from a slow deposition rate. This allows for direct deposition on any substrate including use in surgery. A commercially available airbrush (Master Airbrush, G222-SET gravitational feed) was used in all studies. Gas flow rate was varied using compressed carbon dioxide. SEM and optical microscopy were used to characterize morphology. Thermal transitions were characterized by DSC. Adhesive testing utilized an Instron mechanical tester with temperature control. Degradation was investigated by molecular weight change (GPC). In vitro biocompatibility was investigated with MTS assays. Pilot animal studies were used to illustrate potential applications. Through the use of biodegradable polymer blends and solution blow spinning, a method to conformally apply an adhesive surgical sealant was developed. Directly deposited fibers of certain polymer blends exhibit thermal responsive behavior at topical (32°C) and internal (37°C) temperature conditions. Upon reaching the phase transition, polymer fibers weld together, and the majority component becomes plasticized. In vitro cell viability showed no decrease of the direct deposition of fibers relative to the live control.

FINDINGS / ACCOMPLISHMENTS

A pilot animal study was done for liver resection and vascular injury. When used for intestinal anastomosis, burst pressure was significantly improved over suture alone. This technique showed ability to bridge mesenteric defects created during an anastomosis. Using blow spun polymers with different mechanical and chemical properties may transform surgical procedures.

33. **TGF-beta in the Pathogenesis of Experimental Biliary Atresia**

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PRE-CLINICAL
FUNDING SOURCE	NIH National Institute of Diabetes and Digestive and Kidney Diseases		

KEY PERSONNEL

Evan Nadler, MD
Tatiana Iordanskaia, PhD

SYNOPSIS

We have previously shown that pre-treatment with our novel cyclophilin (Cyp) inhibitor, MM284, could prevent disease in the animal model of biliary atresia (BA) by decreasing SMAD phosphorylation and TIMP-4 and MMP-7 expression. We hypothesized that MM284 treatment after viral infection would be similarly effective, and in vitro MM284 could prevent Cyp stimulation of hepatic stellate cells (HSCs). Newborn Balb/c mice were randomized to receive an intraperitoneal (i.p.) injection with saline control (n=5) or 1.5 x 106 fluorescence forming units (n=11) of rhesus rotavirus (RRV) within 24 hours of birth. Animals receiving RRV were further randomized to wreceive either 20mg/kg i.p of MM284 or control vehicle starting day of life 2, and then thrice weekly. Livers were harvested post-injection day 14. For the in vitro experiments, HSCs were cultured in supplemented Stellate Cell Medium. HSCs were treated with recombinant CypA (800 ng/ml) with or without MM284 (400ng/ml) and incubated for 72 hours. Liver homogenates were evaluated for RNA expression using quantitative real-time PCR. ELISA was used to evaluate SMAD2/3 phosphorylation in the HSCs. Statistical analysis was performed using ANOVA with statistical significance assigned to p-values < 0.05. Mice treated with MM284 were normal weight (7.9g$\pm$2.0 v 4.7$\pm$0.6, p=0.02), had an approximately 5-fold decrease in TIMP-4 (5.4$\pm$1.1, p<0.01) and a 10-fold decrease in MMP7 (9.9$\pm$ 0.7, p<0.01) mRNA expression when compared to RRV mice. SMAD2/3 phosphorylation in the HSC lysates revealed significant 1.5-fold increase after CypA treatment relative to untreated cells (1.4$\pm$0.09, p $\leq$ 0.01) which was completed abrogated by MM284. MM284 results in prevention of BA in the animal model after viral inoculation. Similarly, MM284 prevents SMAD2/3 phosphorlyation after CypA stimulation in HSCs. These findings suggest that Cyp blockade may be a novel treatment strategy in not only BA, but other liver diseases that are putatively mediated by HSC activation.

34. **Adipocyte Exosomes in the Pathogenesis of Non-Alcoholic Fatty Liver Disease**

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PRE-CLINICAL
FUNDING SOURCE	Sheikh Zayed Institute, Children's Research Institute Bridge Fund		

KEY PERSONNEL

Evan Nadler, MD
Tatiana Iordanskaia, PhD

SYNOPSIS

The pathogenesis of non-alcoholic fatty liver disease (NAFLD) has been attributed to increased systemic inflammation and insulin resistance mediated by visceral adipose tissue, although the exact mechanisms are undefined. Exosomes are membrane-derived vesicles containing mRNA, miRNA, and proteins, which have been implicated in cancer, neurodegenerative, and autoimmune diseases which we postulated may be involve in obesity-related diseases. We isolated exosomes from visceral adipose tissue (VAT), characterized their content, and identified their potential targets. Targets included the transforming growth factor beta (TGF-ß) pathway, which has been linked to NAFLD. We hypothesized that adipocyte exosomes would integrate into HepG2 and hepatic stellate cell (HSC) lines and cause dysregulation of the TGF-ß pathway. Exosomes from VAT from obese and lean patients were isolated and fluorescently labeled, then applied to cultured hepatic cell lines. After incubation, culture slides were imaged to detect exosome uptake. In separate experiments, exosomes were applied to cultured cells and incubated 48-hours. Gene expression of TGF-ß pathway mediators was analyzed by PCR, and compared with cells which were not exposed to exosomes. Fluorescent-labeled exosomes integrated into both cell types and deposited in a peri-nuclear distribution. Exosome exposure caused increased TIMP-1 and Integrin αvβ -5 expression, and decreased MMP-7 and PAI-1 expression in to HepG2 cells, and increased expression of TIMP-1, TIMP-4, Smad-3, Integrins αvβ-5 and αvβ -8, and MMP-9 in HSCs. Exosomes from VAT integrate into liver cells and induce dysregulation of TGF-ß pathway members in vitro, and offers an intriguing possibility for the pathogenesis of NAFLD.

FINDINGS / ACCOMPLISHMENTS

Targets included the TGF-ß pathway, which has been linked to NAFLD. We hypothesized that adipocyte exosomes would integrate into HepG2 and HSCs lines and cause dysregulation of the TGF-ß pathway. Exosomes from VAT from obese and lean patients were isolated and fluorescently labeled, then applied to cultured hepatic cell lines. After incubation, culture slides were imaged to detect exosome uptake. In separate experiments, exosomes were applied to cultured cells and incubated 48-hours. Gene expression of TGF-ß pathway mediators was analyzed by PCR, and compared to cells which were not exposed to exosomes. We found that fluorescent-labeled exosomes integrated into both cell types and deposited in a peri-nuclear distribution. Exosome exposure caused increased TIMP-1 and Integrin αvβ5 expression, and decreased MMP-7 and PAI-1 expression in to HepG2 cells, and increased expression of TIMP-1, TIMP-4, Smad-3, Integrins αvβ5 and αvβ8, and MMP-9 in the HSCs. We concluded that exosomes from VAT integrate into liver cells and induce dysregulation of TGF-ß pathway members in vitro, and offer an intriguing possibility for the pathogenesis of NAFLD.

35. **An Anchored Non-Spherical Obesity Balloon**

CATEGORY	MEDICAL DEVICES	STAGE OF DEVELOPMENT	PROTOTYPING
FUNDING SOURCE	Joseph E. Robert, Jr. Endowment Award Sheikh Zayed Institute		

KEY PERSONNEL

Evan Nadler, MD
Kevin Cleary, PhD
Anthony Sandler, MD

SYNOPSIS

The objective of this project is to develop and evaluate a novel low risk device for the treatment of morbid obesity. Obesity has become the world's most pressing healthcare issue, and the epidemic in the United States affects about 35% of the adult and 15% of the pediatric populations. The disease is associated with a myriad of physical and psychosocial conditions that negatively impact patients' health and quality of life. While lifestyle modification and patient education are important components of any weight management program, they alone have failed to demonstrate consistent durable weight loss results. Thus, bariatric (weight loss) surgery has gained acceptance as the most likely intervention to provide significant and sustainable weight loss for patients once they are morbidly obese. In this proposal, we intend to pursue a novel concept for a weight loss device that would completely eliminate risk of device migration. Our goal is to create a special-purpose balloon that would expand inside the stomach to reduce the luminal volume, however unlike other balloons being evaluated, this balloon is firmly anchored to eliminate migration risk. Furthermore the device will be designed to emulate the currently used surgical technique, the sleeve gastrectomy. By inflating longitudinally along the greater curvature of the stomach, and by being anchored in place, the balloon may prevent food from interacting with the proposed metabolically active cells in the fundus of the stomach. In the Phase I effort proposed here, we will develop a proof of concept balloon and evaluate the balloon in a swine animal model. Once we have demonstrated feasibility in Phase I, we will make any necessary device modifications in Phase II and complete a more extensive and longitudinal evaluation in swine. This will then position us for an initial clinical trial in patients.

Upon the completion of the first prototype, in early 2015, the team will perform swine experiments to obtain early product validation.

36. **Proteomic Networks of MUC5B Infectious/ Inflammatory Induction in Otitis Media**

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PRE-CLINICAL
FUNDING SOURCE	NIH National Institute on Deafness and Other Communication Disorders		

KEY PERSONNEL

Diego Preciado MD, PhD
Stephanie Val, PhD
Marian Poley
Mary Rose, PhD
Kristy Brown, PhD
Yetrib Hathout, PhD

SYNOPSIS

Otitis media (OM), the most prevalent chronic childhood disorder, is associated with staggering public healthcare costs. 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). The OM continuum from acute to chronic is triggered by infectious or noxious stimuli that result in thickening of middle ear epithelia (MEE) and leads to self-sustaining chronic inflammation and mucous hypersecretion. This in turn often leads to medical treatment failure, and the placement of surgical tympanostomy tubes – the most common surgical procedure of children. In published and preliminary data, we have begun to characterize the molecular progression of OM events. We have recently shown that the hyperviscous mucus in COM is characterized by an overabundance of MUC5B mucin, a major airway secreted mucin. Through a gene expression profiling approach in a mouse model of acute OM based on middle ear inoculation of Non-typeable Hemophilus Influenza (NTHi) (currently the most common human AOM pathogen), we identified the pro-inflammatory cytokine Cxcl2 as markedly and acutely upregulated. In this project we aim to use a proteomic and cytokine secretome profiling approach to determine the in vitro effects of NTHi on a middle ear epithelial pro-inflammatory response, gaining important information that would complement our preliminary in vivo data. Our findings should result in a better understanding of pathways in OM pathophysiology and are likely to reveal novel molecular therapeutic targets that when modulated may help abate progression of AOM to COM.

FINDINGS / ACCOMPLISHMENTS

MUC5B, the major predominant mucin in otitis media fluid, is activated by infection and inflammation and comprises an essential component of the middle ear's innate immune system.

37. **Magnetic Delivery of Drugs to the Middle Ear**

CATEGORY	MEDICAL DEVICES	STAGE OF DEVELOPMENT	PRE-CLINICAL
FUNDING SOURCE	Sheikh Zayed Institute, University of Maryland A. James Clark School of Engineering, National Capital Consortium for Pediatric Device Innovation		

KEY PERSONNEL

Diego Preciado, MD
Ben Shapiro, PhD
Didier Depireaux, PhD

SYNOPSIS

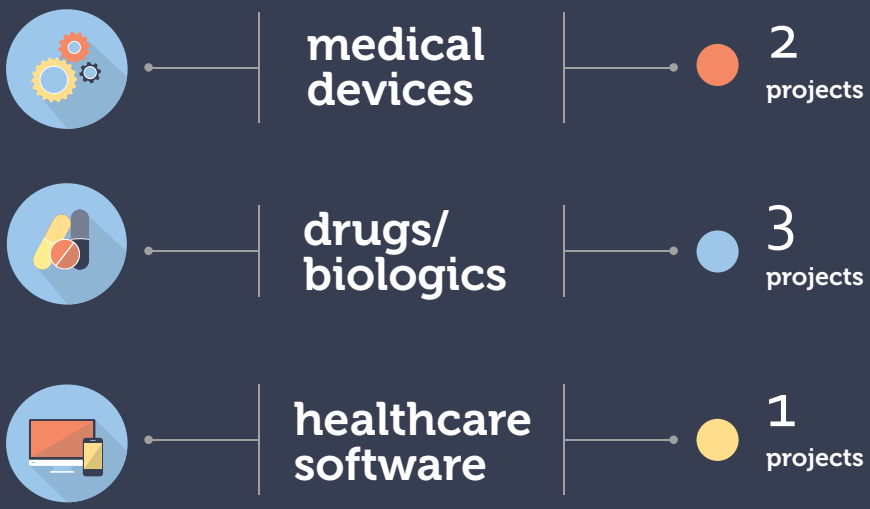
Acute otitis media (AOM) is the leading cause of physician visits by children. Currently, 42% of all antibiotics prescribed in the U.S. are for the treatment of AOM. Approximately 20% of children with AOM go on to develop chronic otitis media with effusion (COME). Although systemic antibiotics may reduce duration and severity of symptom burden and duration of AOM in children, they have no effect on the clearance of middle ear fluid. For this reason, tympanostomy tube placement under general anesthesia for treatment of recurrent AOM or COME is the most common pediatric surgical procedure requiring anesthesia in the U.S. There are no effective non-surgical treatments for COME, nor are there medical treatments that block the progression of AOM to COME. In collaboration with Children's National Health System, the Bioengineering group at the University of Maryland, led by Dr. Ben Shapiro, has developed a topical non-invasive middle-ear therapy delivery system that does not require systemic antibiotic administration, surgery, tympanic membrane puncture, or anesthesia. The system is based on the Dr. Shapiro's magnetic injection technology, which uses magnetic forces to transport bio-compatible nano-particles through the tympanic membrane into the middle ear. This technology has been validated in preliminary pre-clinical animal experiments, both for middle and inner ear delivery.

Phase I of this project focused on showing that we could magnetically deliver drugs to the middle ear without ear drum puncture (aim 1) and that the treatment was safe (no toxicity or hearing damage, aim 2). Both these aims were achieved in a rat animal model. In phase II, using an accepted rat animal model of middle ear infections, we will now show efficacy. We aim to demonstrate that magnetic delivery of sulfonamide, a front line antibiotic drug, is effective at clearing bacteria from a middle ear infection in the animals.

FINDINGS / ACCOMPLISHMENTS

The team established preliminary successful use of drug coated nanoparticles to treat acute otitis media in a rat model.

Pain Medicine



Julia Finkel, MD
Zenaide Quezado, MD
Sarah Albani, BS
Luis Almeida, MD, PhD
Sasha Gorham, BS
Sayuri Kamimura, MS
Nicholas Kenyon
Li Wang, MD, PhD

TO ALLEVIATE AND EVENTUALLY ELIMINATE PAIN IN CHILDREN

38. **Algometer**

CATEGORY	MEDICAL DEVICES	STAGE OF DEVELOPMENT	PROTOTYPING/ CLINICAL TRIALS
FUNDING SOURCE	Sheikh Zayed Institute		

KEY PERSONNEL

Julia Finkel, MD
Zenaide Quezado, MD
Patrick Cheng, MS, MBA
Jonathan Tan, MD, MPH

SYNOPSIS

The Algometer is a device and method that is designed to measure 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). The first prototype was delivered in 2012 and used the commercially available optodes, which precluded use through hair. The second, improved, prototype was designed in collaboration with a small business , MRRA. This company manufactures "brush" optodes that sample easily through hair and increase the sensitivity tenfold over the regular fiber bundle. Proof of concept studies using these brush optodes were conducted December 1st through December 16th, 2014.

FINDINGS / ACCOMPLISHMENTS

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 NIRS signal. Our very preliminary results from the experiments of December 2014, where we enrolled 35 subjects and used the brush optodes are encouraging. Here we sought to determine if we could discern an intensity response relationship using the newly constructed system. The initial preliminary analysis shows contralateral activations for both electrical stimulation and finger tapping, with corresponding smaller ipsilateral deactivations. The activations switch sides for left- versus right-handed subjects. These findings are consistent with the expected physiologic response.


SHEIKH ZAYED
Institute for Pediatric
Surgical Innovation
C. Finkel, MD

39. **Pupillometer**

CATEGORY	MEDICAL DEVICES/ SOFTWARE	STAGE OF DEVELOPMENT	PROTOTYPING/ CLINICAL TRIALS
FUNDING SOURCE	Sheikh Zayed Institute		

KEY PERSONNEL

Julia Finkel, MD
Zenaide Quezado, MD
Elizabeth Bettini, MSN, RN

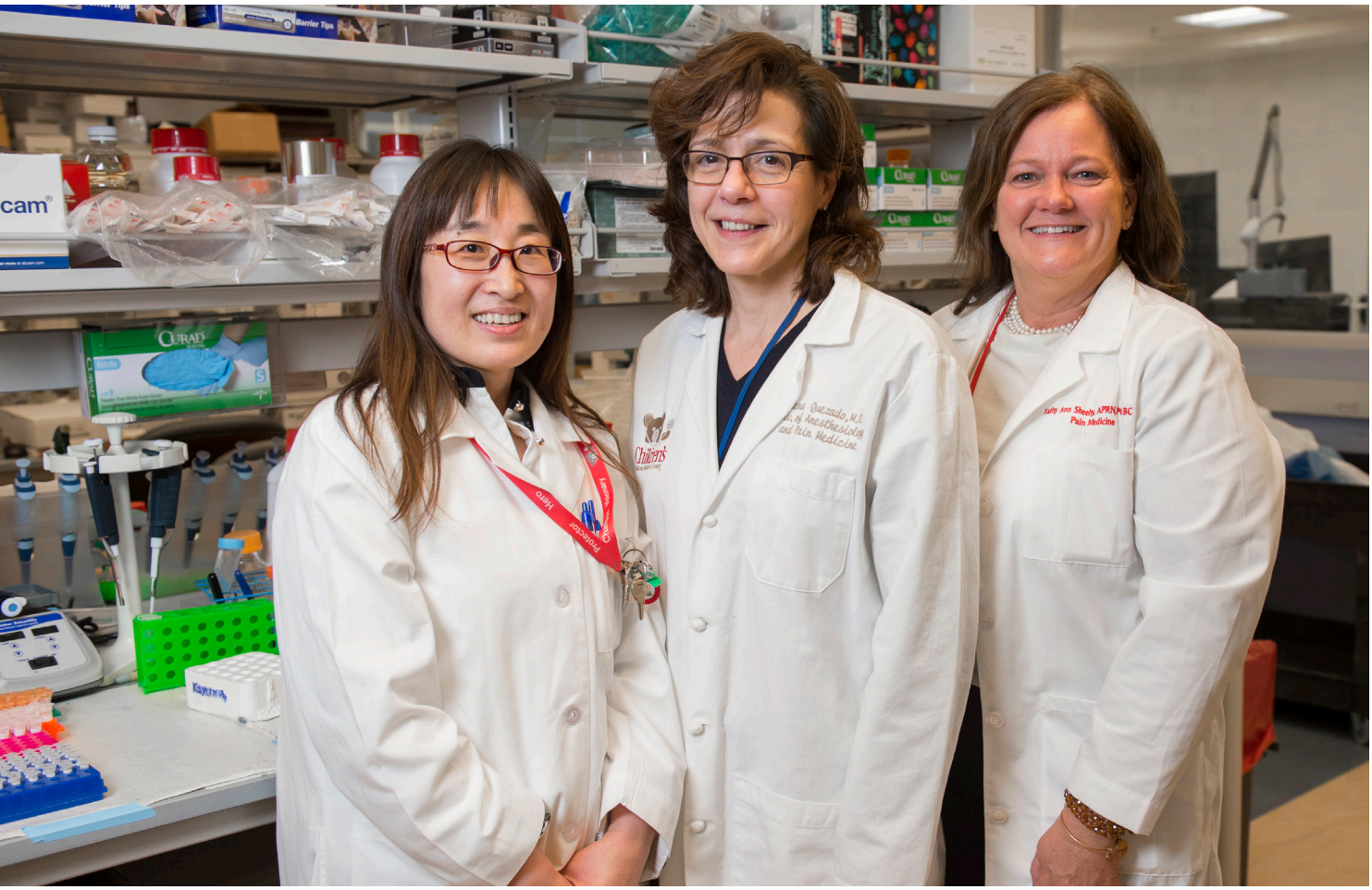
The concept formation and early prototyping phases were completed in collaboration with students from American University Kogod School of Business and International Design Business Management (IDBM) program at Finland's Aalto University.

SYNOPSIS

This project's goal is to develop pupillary response detection applications utilizing smart phone technology. Algorithms will be established that use the objective pupillometry measures in order to guide therapy. Control of the pupil is a complex physiology that involves multiple neuronal pathways, and pupillary behavior is the reflection 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. Such determinations are important in both experimental and clinical settings. 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. Applications include: a) opioid management; b) traumatic brain injury assessment; c) detection of diabetic neuropathy and dysautonomia before clinically overt symptoms appear; and d)phenotyping tool for the enzyme CYP2D6. The activity of this enzyme is important in the metabolism of many important analgesics.

FINDINGS / ACCOMPLISHMENTS

Pupillometry as a diagnostic and monitoring method for patients with postural orthostatic tachycardia syndrome study completed. POTS patients had a lower percent of constriction (CON) and a decreased constriction velocity (ACV) following light stimulus than healthy controls. We also found that the latency (LAT), which is the time the pupil takes to start constriction following the light stimulus, was longer in the POTS group. The only change under orthostatic stress noted in the control group was in the MIN by a margin of 4.7%. The magnitude of these differences were grossly significant ($p < 0.0003$). These data will be incorporated into an algorithm to screen for POTS and monitor therapeutic interventions.



Sheikh Zayed Institute members Li Wang, MD, PhD, Zenaide Quezado, MD, and Lisa Sheehy, CNS.

40. **Pathobiology and Novel Therapeutic Approaches for Pain in Sickle Cell Disease**

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PRE-CLINICAL
FUNDING SOURCE	Sheikh Zayed Institute		

KEY PERSONNEL

Luis Almeida MD, PhD
Alfia Khaibullina PhD
Sayuri Kamimura, MS
Li Wang, MD, PhD
Julia Finkel, MD
Zenaide Quezado, MD

SYNOPSIS

The spectrum of pain phenotypes in sickle cell disease (SCD) patients is highly variable. A small percentage of SCD patients experience many vaso-occlusive crises per year: 5% of patients account for over 30% of pain episodes, while 39% report few episodes of severe pain. Clearly, a better understanding of the pathobiology of SCD is needed to improve its therapy. Humanized sickle cell mice recapitulate several phenotypes of SCD patients and provide a model for the study of SCD pain. In a large cross-sectional study of SCD mice, we examined thermosensory response and sensory nerve fiber function using sine-wave electrical stimulation at 2000, 250, and 5Hz to preferentially stimulate Aβ, Aδ, and C sensory nerve fibers respectively. We used two strains of humanized SCD mice (BERKs and Townes) including one (Townes) with previously undescribed pain phenotype. These animals have been studied extensively and shown to display the hematologic abnormalities seen in SCD. We are now investigating the role of novel approaches to treat pain in SCD. Specifically we are examining the roles of the mTOR inhibitor rapamycin, which in erythroid precursor cells from normal human subjects has been shown to increase fetal hemoglobin. We are also evaluating the effect of an α2 adrenoreceptor agonist, dexmedetomidine in the nociception phenotype in animals with SCD.

FINDINGS / ACCOMPLISHMENTS

We found that BERK and Townes mice, compared to respective controls, had decreases in 2000, 250, and 5Hz current vocalization thresholds in patterns that suggest sensitization of a broad spectrum of sensory nerve fibers. In addition, the pattern and degree of sensitization of sensory fibers varied according to strain, sex, age, and genotype of the mice. In a similarly variable pattern, both Townes and BERKs also had significantly altered sensitivity to noxious thermal stimuli in agreement with what has been shown by others. In summary, the analysis of somatosensory function using sine-wave electrical stimulation in humanized sickle cell mice suggests that in SCD, both myelinated and unmyelinated, fibers are sensitized. The pattern of sensory fiber sensitization is distinct from that observed in pain models of neuropathic and inflammatory pain. These findings raise the possibility that sensitization of a broad spectrum of sensory fibers might contribute to the altered and variable nociception phenotype in SCD.

41. **The Role of VBP-15 a Dissociative Steroid on the Sickle Cell Disease Pain**

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PRE-CLINICAL
FUNDING SOURCE	NIH National Institute on Minority Health and Health Disparities		

KEY PERSONNEL

Luis Almeida MD, PhD
Alfia Khaibullina PhD
Sayuri Kamimura, MS
Li Wang, MD, PhD
Julia Finkel, MD
Zenaide Quezado, MD

SYNOPSIS

While the role of ongoing inflammation during vaso-oclusive crisis and pain is recognized, effective therapeutic interventions are lacking. Glucocorticoids, with their anti-inflammatory properties, in small clinical trials have been shown to reduce the duration of analgesic therapy in children with pain crisis and in SCD patients admitted with acute chest syndrome, a course of dexamethasone decreased hospitalization time. However, clinicians hesitate to prescribe steroids to treat steroid-responsive conditions in SCD patients because its use is associated with complications that include increased risk of hospital readmission, rebound pain, strokes, avascular necrosis, and acute chest syndrome. Further, some steroid-responsive conditions such as asthma have a high incidence in SCD, however, because of known side-effects, clinicians hesitate to use disease-altering therapy such as steroids in SCD patients. In turn, SCD patients who have steroid-responsive conditions may receive less than ideal treatment. VBP15 is a first-in-man dissociative steroid that has optimized sub-activities of more traditional glucocorticoids, with increased efficacy and reduced side effects. VBP15 retains NFkB inhibition (transrepression), increases membrane stabilization properties, and loses GRE-mediated transactivation activities associated with side effect profiles of clinically used steroids.

FINDINGS / ACCOMPLISHMENTS

Preliminary data shows that VBP15 has the potential to affect favorably the alterations in pain response and some hematologic and histopathologic alterations observed in a murine model of SCD. The goal of this STTR proposal is to carry out a pilot efficacy study of VBP15 to treat the altered pain response and to ameliorate the abnormal hematologic, biochemical, and inflammatory profiles in SCD mice.

42. **Development of a Nanoliposomal Transdermal Drug Delivery System**

CATEGORY	DRUGS/BIOLOGICS	STAGE OF DEVELOPMENT	PRE-CLINICAL
FUNDING SOURCE	Sheikh Zayed Institute University of Maryland A. James Clark School of Engineering		

KEY PERSONNEL

Don deVoe, PhD
Renee Hood, PhD
Luis Almeida, MD, PhD
Alfia Khaibullina, PhD
Sayuri Kamimura, MS
Li Wang, MD, PhD
Julia Finkel, MD
Zenaide Quezado, MD

SYNOPSIS

Transdermal drug administration holds great utility for pain-free and non-invasive drug delivery. In addition to obviating the need for injections, it has several advantages over the oral route. Transdermal drug delivery bypasses the liver first-pass effect that can prematurely metabolize drugs, is noninvasive, can be self-administered for longer periods of time, and greatly improves patient compliance. Transdermal delivery of free Dex is limited by poor transport across the structured lipid/protein matrix that comprises the stratum corneum (SC) layer, with reduced bioavailability due to the limited penetration of free drug through the skin. Nanoparticle-enhanced delivery offers a solution to this challenge. Organic and inorganic nanoparticles in the 20~40nm range can successfully traverse the SC and enter circulation for systemic drug delivery, but they suffer from high toxicity and low drug loading levels. In contrast, liposomal nanoparticles have low innate toxicity, support high drug payloads, and can extend a drug's period of action by significantly increasing blood circulation times and taking advantage of nanoparticle-controlled release of drug at the site of action. However, conventional liposomal particles either cannot traverse the SC in significant numbers or become lysed by the SC, negating their ability to extend duration of action through nanoparticle-mediated drug release. Here we propose the development of a unique nanoliposomal Dex/opioid polypharmaceutical enabling direct transdermal administration and extended duration of action, with Dex serving as an adjunct to opioid therapy.

FINDINGS / ACCOMPLISHMENTS

We have shown that small and nearly monodisperse nanoliposomes synthesized using a microfluidic flow-focusing technique can enhance transdermal penetration of liposomes by over two orders of magnitude while enabling passage of intact vesicles through the SC. By co-encapsulating the opioid and its adjuvant within each liposome, identical transdermal transport and release profiles will be maintained for both drugs. The nanoliposomal drug will enable non-invasive transdermal administration, significantly extended drug release profiles, and decreased opioid dose requirements. We identified drug candidates that will offer great antinociceptive potential and greatly add to armamentarium of analgesics. We are now optimizing the design of this nanomedicine construct using mouse models of nociceptive pain, and establish the feasibility of co-encapsulating Dex with fentanyl, a potent synthetic opioid, in a preparation that is to be administered transdermally.

43. SCD-PROMIS- An App for Outpatient Monitoring and Treatment of Sickle Cell Pain

CATEGORY	HEALTHCARE SOFTWARE	STAGE OF DEVELOPMENT	CLINICAL STUDIES
FUNDING SOURCE	Sheikh Zayed Institute, Joseph E. Robert, Jr. Endowment Award		

KEY PERSONNEL

Kevin Cleary, PhD
Kevin Gary, PhD
Zenaide Quezado, MD

FINDINGS / ACCOMPLISHMENTS

In a recent pilot study at Children's National Health System using a prototype mobile phone application, we found that weekly pain reporting is feasible, well accepted by SCD patients, and that it enables better patient monitoring.

SYNOPSIS

In the U.S., sickle cell disease (SCD) affects approximately 100,000, predominantly African-American individuals, who face a life-long challenge of living with pain that can be acute and chronic and is associated with decreases in quality of life and healthcare disparities. SCD-pain prompts approximately 180,000 emergency visits, 75,000 hospitalizations, and over $475 million in yearly hospital costs. When SCD patients are hospitalized because of intractable pain, often there can be little change in self-reported pain and the 30-day readmission rate is very high (17-50%). The most common reason for readmission is recurrent pain, which suggests that SCD pain is undertreated in the outpatient setting which in turn contributes to increased readmission. Other contributing factors for higher readmission rate for pain in SCD patients include the recurrent nature of vaso-occlusive crisis and poor patient compliance with therapeutic interventions and scheduled follow-up appointments. Feasibility studies have shown that web-based technology can help assess adherence to therapeutic interventions in SCD and other pain syndromes, improve self-efficacy, and decrease barriers to continuity of care (limited hospital access, travel difficulties). However, it is unclear whether this technology can improve monitoring of patients' clinical outcomes (pain, anxiety, fatigue, mobility), increase provider engagement, or lower readmission rates. We are developing a mobile phone-based application that uses rewards systems (badges, gift cards) to increase patient pain and therapy compliance reporting, identify worsening pain, and predict readmission. In this app, we are using validated NIH Patient Reported Outcomes Measurement Information System (PROMIS) measures to weekly monitor pain and associated outcomes (anxiety, fatigue, mobility) in SCD patients after hospital discharge. The next step is to develop an alert system (alerts, e-mails, text messages) and interventions to increase patient/provider engagement, to improve outpatient pain management, and to decrease hospital readmission. The long-term goal of this proposal is to improve outpatient monitoring and pain management and decrease readmission rates in SCD patients.

“IT IS IMMENSELY GRATIFYING TO SEE HOW DISCOVERIES IN THE LAB AT THE PROTEOMIC LEVEL HAVE PROFOUND TRANSLATIONAL IMPACT TO THE COMMON CONDITIONS WE TREAT. HOPEFULLY WE CAN TAKE OUR WORK FROM BENCH TO BEDSIDE THROUGH THE DEVELOPMENT OF INNOVATIVE THERAPIES ONLY MADE POSSIBLE BY THE INFRASTRUCTURE OF THE SHEIKH ZAYED INSTITUTE.”

Diego Preciado, MD, PhD
Principal Investigator, Otolaryngologist

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