



# Pedi Press



A Quarterly Publication of the Department of Pediatrics  
Baylor College of Medicine

**Volume 9, Issue 3, Part II**

**Summer 2020**





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## PART II

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**Dr. Gordon Schutze, Interim Editor-in-Chief**  
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**Julie O'Brien Anderson, Copy and Content Editor**  
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## DEPARTMENT NEWS

### FACULTY, FELLOWS, RESIDENTS, & STAFF

#### COVID-19 Vaccine Licensed

**Drs. Peter Hotez and Maria Bottazzi** (pictured above) have been co-leading a research team focused on developing a coronavirus vaccine. The vaccine now has a licensing agreement with India-based Biological E. Limited. The recombinant protein vaccine candidate has been licensed through negotiations with the BCM Ventures team, a part of BCM, based on discussion about BCM's technology and how it could be effective in producing a vaccine to answer the current global pandemic. The company, founded in 1953, has supplied other vaccines to more than 100 countries, so it will apply that experience to globalize the vaccine once it is completed. A major target will be India, which has reported nearly 24 million total COVID-19 cases, with more than 650,000 active cases, 1.7 million hospital discharges, and more than 47,000 deaths (according to the country's Minister of Health and Family Welfare). Dr. Hotez commented, "This week's information that India has become the third-leading nation in terms of COVID-19 cases has sparked concern that COVID-19 will become widespread and a serious and deadly infection across the crowded urban areas of South Asia. This is why this agreement is timely." (see page 7)

## In Memoriam Dr. Peter Kazembe

*"Dr. Kazembe was a dedicated husband, father, leader, advocate, mentor, clinician educator, teacher, and friend. I'm deeply saddened by his loss but know his legacy will live on in the work of many."*

*Michael Mizwa, BIPAI Chief Executive Officer*



On August 18, 2020, Dr. Gordon Schutze, Interim Chairman, shared the sad news with the department that Dr. Peter Kazembe had passed away the previous Tuesday. Below are Dr. Schutze's words of recognition:

*Dr. Peter Kazembe, often considered the "grandfather of pediatrics" in Malawi, made monumental contributions to the health of children and families in Malawi and beyond over his decades long career. Although many physicians leave Malawi to pursue their training in the UK, very few ever return. Dr. Kazembe was one that did. One of the best things BIPAI ever did was partner with Dr. Kazembe when we were looking to work in Malawi. Under his leadership, Baylor College of Medicine Children's Foundation-Malawi in a public private partnership with the Government of Malawi and Abbott Fund, built and operated the first stand-alone pediatric HIV clinic in Malawi and was the first non-government organization to provide antiretroviral therapy for children in Malawi, fast becoming the country's largest provider of pediatric HIV care.*

*Dr. Kazembe's contributions span clinical care, research, advocacy, policy, and education – and cross pediatric HIV, TB, malaria, neonatology, maternal and child health. Throughout his career, he developed long-lasting partnerships and deep friendships around the world that have blossomed and prospered and will continue to benefit the people of Malawi. He was a dedicated husband, father, leader, advocate, mentor, clinician educator, teacher and friend. He was the kind of physician we all dream of being.*

*Dr. Peter Kazembe was recently selected by the American Academy of Pediatrics Section on Global Health to receive the prestigious 2020 Hillman Olness Award for lifetime service and lasting contributions to global child health. Established in 2011 in honor of the late Liz Hillman, the late Donald Hillman, and Karen Olness, the award recognizes individuals who have devoted their careers to advancing global child health. The award will be presented posthumously to Dr. Kazembe on October 4, 2020 as part of the AAP National Conference & Exhibition.*

## Regional Chair of Pediatrics CHofSA Announced

It has been a distinct pleasure working with Dr. Appachi in my current role and I know the incoming Chair will have the same experience.

-- Dr. Gordon Schutze, Interim Chair



Dr. Gordon Schutze, Professor and Interim Chair, announced that **Dr. Elumalai Appachi**, Assoc. Professor, accepted the role of Regional Chair of Pediatrics in the Children's Hospital of San Antonio (CHofSA). Dr. Appachi will also serve as a Vice Chair in the overall Department of Pediatrics representing our physicians in San Antonio. Dr. Appachi was one of the earliest faculty recruited to CHofSA and has served as the Interim Regional Chair of Pediatrics since January 2019. Since his arrival in San Antonio, he has not only built an outstanding Pediatric Intensive Care Unit team but has also been a wonderful ambassador for Baylor College of Medicine.

He received his medical degree from Stanley Medical College, Madras University, Madras, India. He completed his pediatric residency at the Institute of Child Health and Hospital for Children and completed a pediatric residency and pediatric clinical care fellowship at the Cleveland Clinic. A Fellow of the American Academy of Pediatrics, he has received numerous awards including the Excellence in Service Award for Clinical Practice from the Society of Critical Care Medicine and the Star Faculty Award from the Baylor College of Medicine.

## New Pediatrics Grand Rounds Director Named



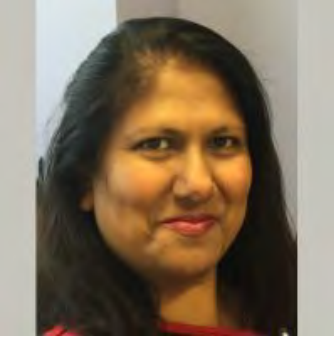
Dr. Mark Ward, Professor, announced in July that **Dr. Brian Rissmiller**, Asst. Professor, would be assuming the role of Pediatrics Grand Rounds Director. Dr. Rissmiller is also Associate Program Director of the Pediatric Residency Program and Deputy Director of Assessment, Evaluation and Quality for Pediatric Critical Care Fellowship program. His research interests focus on developing novel educational methods and tools for enhancing the acquisition of medical expertise by novice learners, thereby decreasing diagnostic errors. For the foreseeable future, grand rounds will be held virtually, via the Zoom platform.

## Section Chief Steps Down



**Dr. K. Suresh Gautham**, has stepped down as Section Chief and Section Head of Neonatology at Texas Children's Hospital and the Department of Pediatrics, Baylor College of Medicine. Dr. Gordon Schutze, Interim Chairman, and Dr. Jim Versalovic, Interim Physician-in-Chief, thanked him for his five years of service in those capacities. Dr. Gautham will remain an attending physician in the nurseries and a faculty member in the Department. Dr. Tammy Kang, Executive Vice-Chair of the Department of Pediatrics, will serve in an interim capacity in those roles until a permanent successor to Dr. Gautham is identified.

## Chief of Adolescent Psychiatry Announced



On October 6, 2020, Dr. Gordon Schutze, Interim Chair, Dr. Jim Versalovic, Interim Physician-Chief TCH, and Dr. Wayne Goodman, Chair of Psychiatry, announced the promotion of **Dr. Kirti Saxena**, Assoc. Professor, to Chief of the Section of Child and Adolescent Psychiatry at Baylor College of Medicine/Texas Children's Hospital. She received her medical degree from Albert Szent-Gyorgyi Medical University in Szeged, Hungary. She completed her residency at the University of Southern California/LA County Medical Center in 2000 and her fellowship in Child and Adolescent Psychiatry at Stanford University in 2002. Her work in anxiety and mood disorders has advanced the mission of TCH to create a healthier future for children and

adolescents. As interim Chief of Child and Adolescent Psychiatry since March 27, 2020, she has demonstrated strong leadership skills and has enabled Child and Adolescent Psychiatry at TCH to move forward during the COVID-19 pandemic. She is certified by the American Board of Psychiatry and Neurology, Psychiatry and the American Board of Psychiatry and Neurology, Child and Adolescent Psychiatry and is a Senior Associate Editor for *Child Psychiatry & Human Development*.

## Lifetime Achievement Award Presented



Only July 10, 2020, **Dr. Sherry Vinson** was presented the **Jan Goddard-Finegold Memorial Lifetime Achievement Award in Developmental Medicine Education**. Dr. Vinson was recognized for "her over two decades of unparalleled dedication to teaching Developmental Medicine to every BCM Pediatric resident, Neurodevelopmental Disabilities resident, and Developmental-Behavioral Pediatrics fellow, ALL other learners at the Meyer Center for Developmental Pediatrics and Texas Children's Hospital, and innumerable local, regional, national, and international clinicians, researchers, educators, and families of children with developmental disabilities."

## Faculty Submission Receives Recognition



**Dr. Adam Wolfe**, Asst. Professor, ChofSA, received recognition for his MedEdPORTAL submission, "Building a Local Research Symposium," as an exemplary resource. Only 16% of submissions are accepted by MedEdPORTAL, with even fewer identified as exemplary. Of note was that his submission was not an item that fits neatly into the MedEdPORTAL genre, so it was considered a somewhat risky way to share his scholarship, demonstrating how "thinking outside the box" can pay off (from Dr. Anne Gill). The editor of MedEdPORTAL, in congratulation Dr. Wolfe, said that "it compellingly described the challenge that community-based academics face, it provided the necessary and above-and-beyond details and communication templates for another institution to implement . . . it is extremely well

organized for such a complex event, and the evaluation was thoughtful and comprehensive, including high-level process outcomes."

# Researchers Enter Into Agreement to Produce COVID-19 Vaccine

Dr. Maria Bottazzi, Assoc. Dean of the National School of Tropical Medicine and Co-Director of the Texas Children's Center for Vaccine Development, and her team, including Dr. Peter Hotez, Professor and Dean of the National School of Tropical Medicine and Co-Director of the Texas Children's Center for Vaccine Development, have long worked on vaccines for SARS. They agreed that the outbreak of COVID-19 resembled that of SARS, which originated in China in 2002 and spread to 29 countries. A particularly virulent disease, it caused the deaths of 10 percent of the people who contracted it before it was contained.



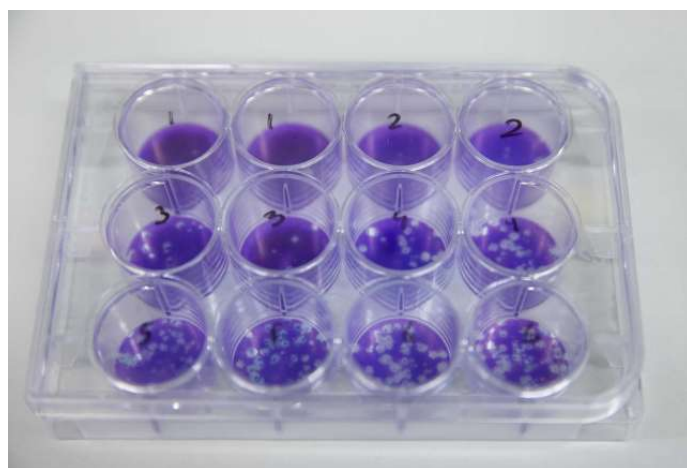
The two researchers immediately thought of a vaccine they had developed earlier using a government bioterrorism grant that had expired in 2016. They had applied for follow-up grants but had been unable to obtain funding. All of the 20,000 doses manufactured had remained viable because Dr. Bottazzi had stored them in a freezer in Houston.

The work on coronaviruses was a departure from their other work, which targets neglected tropical diseases, a term Dr. Hotez coined to describe debilitating poverty-related syndromes ignored by most in the medical field, as well as funding establishments.

When COVID-19 appeared, the two researchers realized it resembled the SARS virus, noting that the new virus shared 82 percent of its genes with SARS. They decided to proceed on two levels: first, develop a new vaccine specific to SARS2 and, second, push for a clinical trial to test the SARS vaccine they already had against the new virus.

They faced stiff competition, as Operation Warp Speed's beneficiaries, seven prosperous for-profit companies, were bankrolling efforts for their own researchers for at least \$1 billion in funds plus more they obtained from the Trump administration, which has reached more than \$11 billion added to their funds. At BCM/TCH, funding was only \$3.5 million, all from philanthropy.

Development of the new vaccine took only a few months, with the center's SARS2 vaccine as its best candidate, and they set to begin clinical trials in less than a month in India. The vaccine was developed quickly and in high quantities because the research team used a yeast-based expression technology commonly used in vaccine production. It is the same process used in manufacturing the hepatitis B vaccine, which Biological E. Limited, the company that has licensed the BCM/TCH vaccine, already produces en masse. BCM entered into a licensing agreement with Biological E Limited, a biotechnology company based in India, to develop the COVID-19 vaccine.



Dr. Bottazzi noted that "They very rapidly took it on and built on it. And we know that they can make it at a very low cost. Their hepatitis B vaccine probably sells for a dollar a dose...Even with COVID-19, they told us they could very easily make this vaccine to probably not cost more than a couple dollars a dose . . . There are so many underserved populations that may need something like a dollar-a-dose vaccine."

The work has also been funded by a recent \$1 million grant from Tito's Vodka, which enabled them to move forward initially and now see some fruition from that contribution.

## Faculty briefs . . .

**Dr. Maria Elena Bottazzi**, Professor and Assoc. Dean of the National School of Tropical Medicine, was named one of the 100 Most Powerful Women of 2020 by Forbes Centromérica. She's spotlighted in the August edition for her career in vaccine development and her work on a COVID-19 vaccine.

**Dr. Yi-Chun Carol**, Asst. Professor, was selected as the 2020-2021 chair-elect of the American Academy of Otolaryngology Young Physician Section. She previously served as secretary for the section.

**Dr. Hsiao-Tuan Chao**, Asst. Professor, has been honored with the Philip R. Dodge Young Investigator Award by the Child Neurology Society for her promising translational research in neurodevelopmental disorders such as intellectual disability, epilepsy and autism. She will present the Dodge Lecture at the CNS-ICNA Conjoint Meeting in October.

**Dr. Teresa Davis**, Professor, received two awards from the American Society for Animal Science: (1) the Fellow Award recognizes distinguished service to animal science and the livestock industry over a long period of time and (2) the Morrison Award recognizes outstanding recent research that has been of direct importance in livestock production.

**Dr. Jenny Despotovic**, Asst. Professor, was recently recognized as an Expertscape World Expert in idiopathic thrombocytopenic purpura (ITP), the most common immune hematologic disorder.

**Dr. Nick Ettinger**, Asst. Professor

- received a grant from the Texas Chapter of the Society of Critical Care Medicine to support his work with the Texas Children's Cancer and Hematology Center's Global HOPE Program partnership with Bristol-Myers Squibb to expand pediatric cancer care in sub-Saharan Africa. Through the grant he will undertake a project, "Teaching Critical Care Skills Remotely in a Resource Limited Setting: A Pilot Study."
- was re-elected to a second three-year term on the American Academy of Pediatrics Section of Critical Care Executive Committee. This group represents pediatric critical care providers, advocates for important issues in the field, contributes to national practice guidelines, and provides mentorship to trainees.
- is the lead author on a revision of the "Guidelines for Admission to Pediatric Intermediate Care."

**Dr. Peter Hotez**, Professor

- delivered numerous key lectures, including a pediatric Grand Rounds at Cook Children's Hospital
- participated in an hour-long town hall meeting with Rep. Sarah Davis
- served on the World Vaccine Congress "Panel on COVID19" and the BCM Congressional Briefing
- was named Hospital Hero by the *U.S. News and World Report*, coinciding with the release of the new hospital rankings.
- presented the Martin Kleiman Lecture, Pediatric Grand Rounds, Indiana University School of Medicine and Riley Children's Hospital: "Preventing the Next Pandemic: Vaccine Diplomacy in an Age of Antiscience"

**Dr. Faith Ihekweazu**, Asst. Professor, has been appointed to serve on the Harris County S.A.F.E. Elections Medical Advisory Committee. Harris County is prioritizing the S.A.F.E. initiatives to ensure that the November 3 election is safe, secure, accessible, fair and efficient, even in a pandemic.

**Dr. Joseph Lubega**, Asst. Professor

- has been selected to serve on the U. S. Pharmacopeia Healthcare Safety & Quality Expert Committee through 2025. He plans to focus on issues relating to appropriateness, safety, and access to pharmaceutical products for children in the U.S. and around the world.
- received the Award of Achievement in Educational Innovation by Texas Children's Hospital

**Dr. Bhukumusa Lukhele**, Executive Director of Baylor-Eswatini, was appointed as a member of the Eswatini Human Health Research Review Board by the Hon. Minister of Health.

**Dr. Poplack**, Professor, received the Alex's Lemonade Stand Foundation's Lifetime Achievement Award.





## DEPARTMENT NEWS RESEARCH & PATIENT CARE

### **Child Recovers from Cancer After Participating in Trial Study Using CAR T Cell Immunotherapy**

“This child’s cancer was considered high risk because it had not responded to standard chemotherapy. As a result, this child was a candidate to receive a promising new CAR T cell therapy, a personalized form of immunotherapy that redirects the patient’s own immune T cells to recognize and fight the tumor.”

— Dr. Meenakshi Hegde, Asst. Professor

The child, who had rhabdomyosarcoma that had spread to the bone marrow, was treated with a new protocol in a trial called HEROS 2.0. Dr. Sujith Joseph, Senior Scientist at BCM’s Center for Cell and Gene Therapy, who conducted the evaluation of the patient’s immune response, noted, “It is fascinating to see remodeling of the patient’s T cell compartment and development of antibodies directed against proteins implicated in tumor survival and metastasis during the course of treatment in this child. The immune activation mechanisms and associated tumor targets unfolded during the acquired response, could inform novel approaches to fight difficult-to-treat cancers. “

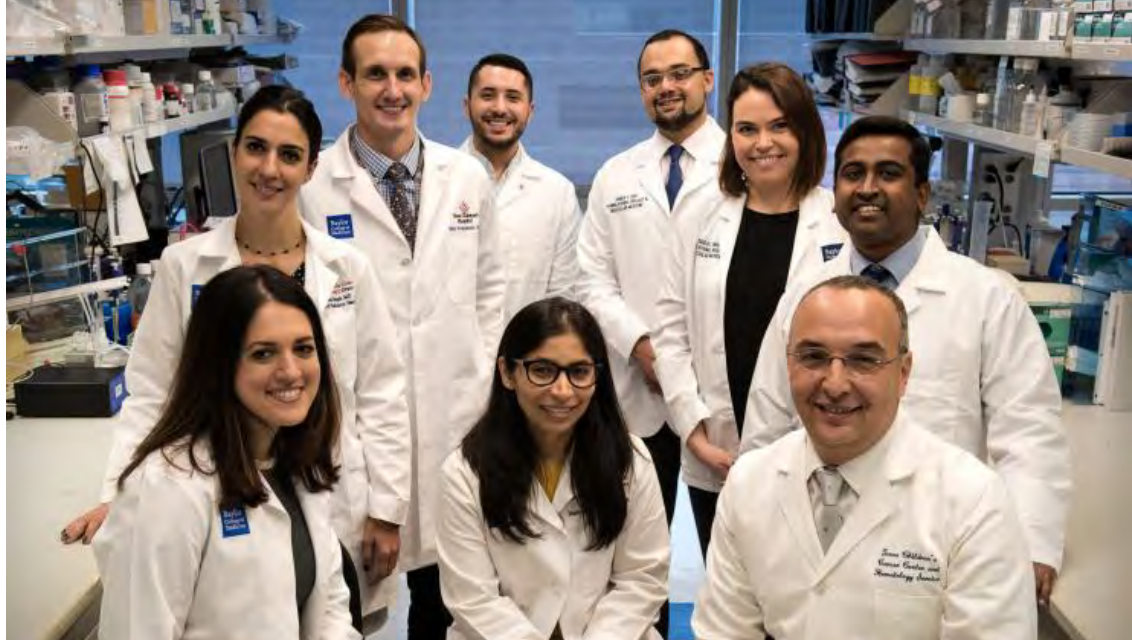
(the study is described on page 10)

Continued from page 9

**Dr. Meenakshi Hegde**, Asst. Professor, and her colleagues recently reported a case of a child with rhabdomyosarcoma, a form of muscle cancer, that had spread to the bone marrow. The child was part of a clinical trial evaluating a novel immunotherapy option for cancer treatment. When 75 percent of the child's tumor cells were shown to display the HER2 protein on their surfaces, the researchers reprogrammed the T cells to target the HER2 protein by genetically engineering them to express CAR molecules that recognize the HER2-expressing (HER2+) cancer cells. Following treatment with chimeric antigen receptor (CAR) T cells engineered to target the HER2 protein on the surface of the cancer cells, the child showed no detectable cancer.

Earlier CAR T cell treatment benefited only a small subset of patients but failed to eradicate their tumors. Dr. Hegde explained that from the earlier trial they learned that the HER2-CAR T cells expanded but did not persist in the patients, perhaps explaining the lack of anti-tumor responses. To obviate this hurdle, she and her colleagues added successive HER2-CAR T cell infusions along with low-dose chemotherapy to delete the normal T cells. The strategy was to improve the expansion and persistence of the infused HER2-CAR T cells. The lymphodepleting chemotherapy given to the patient before transferring HER2-CAR T eliminated the patient's existing immune cells, thereby forming a space for the engineered CAR T cells to expand.

After the first treatment, the child had a lasting response to HER2-CAR T cells, with no tumor detected, but cancer returned six months after the T cell infusions were stopped. A second remission after retreatment with HER2-CAR T cells resulted in remission; and the child has now been off T cell treatment for more than 19 months and remains cancer free.



Dr. Hegde noted that they found evidence suggesting that after the HER2-specific CAR T cells were infused, the patient's immune system was recruited to act against the tumor, which might account for the durable complete response. The team plans to conduct more detailed experiments with a larger group of patients treated with HER2 CAR T cells to gain a better understanding of the role played by the patient's immune system in eliminating the cancer.

**Dr. Nabil Ahmed**, Assoc. Professor, noted that, "This study shows that CAR T cells could perhaps act as vaccines by exposing cancer proteins to the patient's immune system. With more understanding and further refinement of their design, CAR T cells could be effective against some incurable malignancies." Dr. Ahmed was senior author on the article, with Dr. Hegde as first author, which was published in the journal *Nature Communications*.

Other authors who also contributed to this work include Farzana Pashankar, Christopher DeRenzo, Khaled Sanber, Shoba Navai, Tiara T. Byrd, John Hicks, Mina Xu, Claudia Gerken, Mamta Kalra, Catherine Robertson, Huimin Zhang, Ankita Shree, Birju Mehta, Olga Dakhova, Vita S. Salsman, Bambi Grilley, Adrian Gee, Gianpietro Dotti, Helen E. Heslop, Malcolm K. Brenner, Winfried S. Wels and Stephen Gottschalk. The authors are affiliated with one or more of the following institutions: Baylor College of Medicine, Texas Children's Hospital, Houston Methodist Hospital, Yale University School of Medicine, Frankfurt's Institute for Tumor Biology and Experimental Therapy, German Cancer Consortium and Goethe University, St. Jude's Children's Hospital.

# Study Helps Understand Cancer Risk in Children with Birth Defects

“When we looked at the cancer stage at diagnosis, we found that, for the most part, there was no trend toward earlier stage at diagnosis in children with birth defects. This suggests that increased medical surveillance alone does not explain the earlier age at diagnosis in children with birth defects.”

-- Dr. Jeremy Schraw



“We hope that this research can inform future studies that will help us better understand cancer risk in children with birth defects. However, it should be noted that while children with birth defects are more likely to develop cancer, their overall risk remains low.”

--Dr. Philip Lupo



“If we understand better the link between birth defects and cancer, we might be able to identify which of these children have a unique high risk of cancer and need surveillance.”

-- Dr. Sharon Plon



The association between cancer and birth defects has long been a challenge, with some research indicating that birth defects pose a risk factor. However, whether the type of cancer, the age at which the patient is diagnosed, or the extent of the cancer at the time of diagnosis is different for children with birth defects compared with those without them has remained a question. To answer those questions, researchers at BCM/TCH and other institutions used data from population-based registries in four U.S. states and compared 13,111 children with cancer and no birth defects with 1616 children with cancer and one or more birth defects. The latter group did not include children with syndromes caused by chromosomal or single-gene alterations. The results were published in an article by **Drs. Jeremy Schraw, Philip Lupo, and Sharon Plon**, and colleagues.

The study revealed that acute lymphoblastic leukemia (ALL), the most common childhood cancer in the general population, accounted for a smaller proportion of diagnoses among children with birth defects. Instead, a larger number of tumors were of embryonic origin and included neuroblastoma and hepatoblastoma. Age also made a difference: children with birth defects were diagnosed 1 to 2 years earlier than children without birth defects. To determine if the difference was attributable to children with birth defects getting more medical attention due to their conditions, the researchers looked at the stage of the cancer at the time of diagnosis, which would be expected to be an earlier stage. Instead, no trend toward earlier stage at diagnosis was found in the children with birth defects.

Other contributors to this work include Tania Desrosiers, Wendy Nembhard, Peter Langlois, Robert Meyer, Mark Canfield, Sonja Rasmussen, Tiffany Chambers and Logan Spector. The authors are affiliated with one or more of the following institutions: Baylor College of Medicine, Texas Children’s Hospital, University of North Carolina, University of Arkansas for Medical Sciences, Texas Department of State Health Services, North Carolina Division of Public Health, University of Florida College of Medicine and University of Minnesota. This research was supported by Alex’s Lemonade Stand Foundation (Epidemiology Award), the Cancer Prevention and Research Institute of Texas (RP140258, RP170071, RP160097) and the National Cancer Institute (3P30CA125123-0851).

## Researchers Report on Lipid Emulsions to Prevent Liver Disease in Preterm Infants

Premature infants often require parenteral or intravenous nutrition because their digestive systems are immature and unable to digest certain nutrients. Prolonged administration of parenteral nutrition, however, has been associated with numerous complications, including cholestasis, which leads to accumulation of bile acids and injury to the liver. Although studies have found that cholestasis can be prevented by parenteral administration of oil emulsions, the mechanism(s) mediating this effect have remained unknown.

Researchers from the CNRC and TCH, working with an international group, reported evidence that the protective effect of parenteral oil infusions is accompanied by changes in the levels of gut bile acids and in the gut microbiome.

In 2014, Dr. Burrin and his colleagues published their findings that pure fish oil and multicomponent oil lipid formulations can reduce cholestasis associated with long-term parenteral nutrition. However, the means for reducing cholestasis remained to be elucidated.

In this study, they expanded the original investigation and compared two oil emulsions (soybean oil and a combination of soy, olive, coconut, and fish oils) and a new experimental formulation that added DHA, an omega-3 fatty acid, and arachidonic acid. For reference, they used an additional experimental group of piglets fed infant formula through a feeding tube. They evaluated the effects of the different emulsions in preterm piglets by measuring cholestasis, gut bile acids pools, and

“The piglet model enables us to study parenteral nutrition-associated liver diseases, such as cholestasis, in a way that is clinically relevant. We treat preterm piglets similarly to how we treat preterm infants in the hospital and look at liver function and gene expression in the piglets to better understand the physiology.”

--Dr. Douglas Burrin



**Dr. Douglas Burrin**, Professor, was senior author on the study, which is the first to connect parenteral oil infusions, the microbiome, metabolism and health. It was published in the *Journal of Lipid Research*. First author on the report is **Dr. Lee Call**, who was a Translational Biology and Molecular Medicine graduate student in Dr. Burrin's laboratory during the development of the study. He is currently a postdoctoral fellow at the Department of Energy Joint Genome Institute at Lawrence Berkeley National Lab.

For some 45 years, the only parenteral lipid option used for preterm infants was based on one component, soybean oil. Concern that it could lead to complications including liver disease prompted the development of new lipid emulsions with several oil components to prevent or treat liver diseases associated with parenteral nutrition.

composition of microbial communities in the colon and the profiles of the microbes' metabolic products. The results confirmed that multicomponent emulsions can prevent cholestasis and restore bile flow in preterm piglets, as observed in the experimental group, and that cholestasis was associated with changes in the gut microbiome and the metabolite profiles.

Other contributors to this work include Tiffany Molina, Barbara Stoll, Greg Guthrie, Shaji Chacko, Jogchum Plat, Jason Robinson, Sen Lin, Caitlin Vonderohe, Mahmoud Mohammad, Dennis Kunichoff, Stephanie Cruz, Patricio Lau, Jon Nielsen, Zhengfeng Fang, Oluyinka Olutoye, Thomas Thymann, Robert Britton and Per Sangild. The authors are affiliated with one of more of the following institutions: Baylor College of Medicine; USDA-ARS Children's Nutrition Research Center; Maastricht University, Netherlands; Sichuan Agricultural University, China; University of Copenhagen, Denmark.

# PolyA-miner Reported to be Effective Means to Identify Alternative Polyadenylation

"APA is about modifying one of the ends, called the 3-prime end (3'end), of RNA strands that are transcribed from DNA. The modification consists of changing the length of a tail of adenosines, one of the RNA building blocks, at the 3'end before RNA is translated into proteins. This adenosine chain helps to determine how long the messenger RNA lasts in the cell, influencing how much protein is produced from it."

-- Dr. Hari Krishna Yalamanchili, Lead Author

"I think that the most exciting part of this new tool is that it enables us to precisely reflect gene-level 3' changes and to identify many more APA events than before. With other analytical approaches, we underestimate the effect and number of poly-adenylation events"

--Dr. Zhandong Liu, Senior Author



**Dr. Hari Krishna Yalamanchili**, Postdoctoral Associate (top), and **Dr. Zhandong Liu**, Assoc. Professor (bottom), and colleagues reported their findings in *Nucleic Acids Research*, showing that PolyA-



miner can significantly improve data analysis and help decode the underlying dynamics of alternative polyadenylation (APA). Most human genes undergo APA and generate mRNA transcripts that have various

lengths, usually of the 3' untranslated regions (UTR). APA is known to play a role in the development and cellular differentiation, and its dysregulation can cause neuropsychiatric diseases and increase the severity to cancer. Studies have demonstrated that APA plays a pivotal role in key biological processes, including gene regulation, mRNA localization, cell proliferation, differentiation, and senescence, as well as in the development and prognosis of various oncological, neurological, immunological, and endocrinal diseases.

Recognition of the role APA plays in human health and diseases has encouraged the development of several 3' sequencing (3'Seq) techniques that provide means for precisely identifying APA sites, but research lacked having robust computational tools designed specifically to analyze 3'Seq data. Current analytical approaches have analyzed data using predominantly proximal-to-distal usage, but in the

approximately 50% of human genes that have more than two APA isoforms, these methods fail to capture the entirety of changes that APA undergoes and to account for non-proximal to non-distal changes.

This study sought to address key challenges, and proposed PolyA-miner, a novel *de novo* differential APA detection algorithm based on non-negative matrix factorization (NMF) and vector projections, as an option to accurately detect and assess differential APA, specifically from 3'Seq data. PolyA-miner accounted for all non-proximal to non-distal APA switches using vector projections and reflected precise gene-level 3' UTR changes. It also effectively identified novel APA sites that otherwise would have gone undetected with use of reference-based approaches. Evaluation of several data sets, including first-general MicroArray Quality Control brain and Universal Human Reference PolyA-seq data, recent glioblastoma cell line *NUDT21* knockdown Poly(A)-ClickSeq data, and the authors' own mouse hippocampal and human stem cell-derived neuron PAC-seq data, strongly supports the value of PolyA-miner and its protocol-independent applicability. A striking finding occurred in the glioblastoma cell line data: PolyA-miner identified more than twice the number of genes with APA changes than initially reported. The authors posited that "PolyA-miner can significantly improve data analysis and help decode the underlying APA dynamics."\*

Information extracted or quoted from: Yalamanchili HK, Alcott CE, Ji P, Wagner EJ, Zoghbi H, Liu Z. PolyA-miner: accurate assessment of differential alternative poly-adenylation from 3'Seq data using vector projections and non-negative matrix



## A Tribute

### “Ahead of the Times, Always Prepared, and Ever Present” Amy S. Arrington, M.D.



*Cholera, Ebola, Covid-19* are words that symbolize massive numbers of deaths and calls-to-action on the part of the healthcare system and society at large. In November of 2014, **Dr. Amy Arrington** was offered the challenge to organize the first pediatric Special Isolation Unit in the United

States to treat patients with highly contagious diseases. At the time, it was Ebola. The death rate reported in Africa was 50%, and two cases had been reported in the United States. It was imperative to meet this and other future enemies head on.

“Head on” is the way Dr. Arrington developed her career. After finishing her degree in Biology in 1995, she took a year off from school and, a little unsure of what her profession would be, she sat for LSAT, GRE, and the MCAT.

She decided to get a PhD in molecular virology and walked into the lab of Dr. Janet S. Butel, PhD, Chairman and Distinguished Service Professor in the Department of Molecular Virology and Microbiology at Baylor College of Medicine and asked if she could work with her. “I had no other way in,” says Dr. Arrington.

Her dissertation, *SV40 Pathogenesis in Humans and Animals*, gave her a deep understanding of the mechanisms of contagion, control, and prevention of infectious diseases. After completing medical school and a residency in Pediatrics, she faced an uncertainty similar to the one she experienced after college. She liked several disciplines such as nephrology, pathology, infectious diseases, and immunology, among others. She settled for intensive care because, as she says, “I could do a little bit of all of them.”



Between the SIU and the section of Critical Care, more than 250 critically ill children with COVID-19 related complications and more than 40 patients with MIS-C have been treated.

When the author of this writing asked her, "What are you the proudest of in your professional life?" "My team," she replied with a smile.

"[Dr. Arrington] is a dedicated scientist and compassionate expert, always available for her patients and her team."

-- Dr. Jeanine Graf

Chief Medical Officer, Texas Children's West Campus  
Member, Section of Critical Care



Dr. Arrington was on her second year as faculty member when she was asked to lead the brand-new Special Isolation Unit (SIU). Immediately thereafter, in 2016, she was appointed as Section Chief, Global Biologic Preparedness.

During the 21<sup>st</sup> century, there have been five pandemics, namely H1N1, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), EBOLA and COVID-19. The justification for the existence of a section and team of professionals to meet these challenges is self-evident, and it was put to the test when COVID-19 came to Texas.

The team of the SIU is composed of professionals with different levels of licensure and unique expertise in the care of patients with special isolation needs. Physicians, nurse practitioners, physician assistants, nurses, respiratory therapists, and pharmacists form a cohesive team under the leadership and collegial coordination of Dr. Arrington.



*Photo of Dr. Arrington, courtesy of Dr. Fernando Stein. All other photos are courtesy of Allan S. Kramer, Texas Children's Hospital.*

