SPECIAL ARTICLE

An Evolving Story of Translational Research: A Decade after the Jacobson Promising Investigator Award

Mark Puder, MD, PhD, FACS

The Third Joan L and Julius H Jacobson Promising Investigator Awardee, Mark Puder, MD, PhD, FACS

In 2005, the Surgical Research Committee (SRC) of the American College of Surgeons was tasked with selecting the recipient of a newly established award, "The Joan L and Julius H Jacobson Promising Investigator Award." According to the Jacobsons, the award, funded by Dr Jacobson, should be given at least once every 2 years to a surgeon investigator at "the tipping point," who can demonstrate that his or her research shows the promise of leading to a significant contribution to the practice of surgery and patient safety.

Every year, the SRC receives many excellent nominations and has the difficult task of selecting 1 awardee. The first awardee was Michael Longaker, MD, FACS, who, 10 years later, reflected on the award and the impact it had on his career.[1] This year, Mark Puder, MD, PhD FACS, the third Jacobson awardee, reflects on his 10-year journey after receiving the award. Dr Puder is now a national and international figure in the field of intestinal failure-associated liver disease and has studied the effect of intravenous lipid emulsions on the etiology and treatment of a once fatal disease in children.

Kamal MF Itani, MD, FACS and Brian S Zuckerbraun, MD, FACS,
on behalf of the Research Committee of the American College of Surgeons.

I am extremely proud to have been the recipient of the Jacobson Promising Investigator Award in 2007. I completed my college education at Midwestern State University and my medical school education at Vanderbilt University School of Medicine. I spent 2 years at Yale-New Haven Hospital training in pediatrics, before changing fields and completing my general surgery residency at what is now Beth Israel Deaconess Medical Center. This program mandated time for research and at first I was reluctant to embrace it. However, with the support of several strong mentors, my passion for research flourished and I not only fulfilled the required research expectations but also pursued a PhD from Harvard University. On completion of the general surgery residency, I went on to a pediatric surgery fellowship at Boston Children's Hospital (BCH). From there I was mentored by Dr M Judah Folkman, and under his tutelage, I developed 2 areas of interest: intestinal failure-associated liver disease (IFALD) and the role of angiogenesis in organ regeneration and compensatory organ growth.

As a pediatric resident, I saw first hand how the death of a child can destroy a family. During my pediatric surgery fellowship, several infants died of IFALD, and this motivated me to help this vulnerable group. At that time, infants with intestinal failure, with long-term parenteral nutrition (PN) dependence, had high mortality from sepsis and liver failure, with liver transplantation required for survival. In fact, IFALD was one of the leading indications for liver transplantation in children under 4 years of age.[2,3] It was a slow death, and we became attached to the families and staff who were dealing with this on a daily basis. Several nurses who cared for these children transferred to other nursing units to escape the helplessness they felt knowing that, unless the child was able to wean off PN or get a liver transplant, he or she would ultimately die, usually bleeding to death from fulminant hepatic failure. In 2001, when I completed my surgical fellowship at Boston City Hospital,

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Abbreviations and Acronyms

BCH = Boston City Hospital
DHA = docosahexaenoic acid
EFAD = essential fatty acid deficiency
FOLE = fish oil-based lipid emulsion
IFALD = intestinal failure-associated liver disease
PN = parenteral nutrition
PNALD = parenteral nutrition-associated liver disease

I was in the position to mentor a young surgical research fellow who was facing the same dilemma. During 1 summer, several infants died from IFALD. She was determined to solve the problem and was challenged by my own mentor, Dr Folkman, to repeat his earlier experiments in creating a rodent model of PN-induced liver disease.[4] His hypothesis was that there was deficiency or toxicity in the dextrose-amino acid portion of the PN, and he hoped she would dialyze out the toxin in question. When I assumed my role as her mentor, we revisited the model and noticed that the steatosis that developed in the mice was due to de novo lipogenesis from receiving fat-free PN, not necessarily from PN-induced injury. However, when we repeated the experiments with and without intravenous lipid emulsion, we observed the same phenomenon: the mice developed hepatosteatosis and liver injury. This supported the commonly held belief at the time that the role of lipid emulsions in the development of parenteral nutrition-associated liver disease (PNALD) was minimal because the disease occurred with or without lipid provision.

We then approached the problem in a different way, this time providing the lipid through different routes of administration. We determined that the liver disease occurred only when the standard lipid (Intralipid, Baxter) was given intravenously and not through the oral route.[5] Subsequently, our PN pharmacist, Dr Kathleen M Gura, who had also worked with Dr Folkman on the earlier rodent experiments, joined the group. She had insight into the formulas he had used and extensive clinical experience in PN therapy. The next step in our animal studies was to substitute soybean oil with the only soy-free lipid emulsion available in the world—one comprised solely of fish oil (Omegaven, Fresenius Kabi, Bad Homburg, Germany).[6] Due to a series of serendipitous events, Dr Gura had successfully used this fish oil-based lipid emulsion (FOLE) at that time to treat essential fatty acid deficiency (EFAD) in a young bone marrow transplant patient who had a soy allergy.[7] This clinical insight prompted us to repeat the experiment, this time using FOLE, which yielded dramatically different results. Regardless of the route of administration, the liver histology remained normal when FOLE was provided. We then sought to understand the mechanism behind this exciting finding and attempted to secure the necessary funding for additional animal work. On each grant application, our summary statement remained the same, "if we can demonstrate the use of FOLE in treating IFALD in an animal model, we plan on translating our findings to studies in humans."

Interestingly, the response from our colleagues regarding our findings was tepid at best. Those with extensive experience in clinical nutrition dismissed it, citing, "everyone knows it is not the lipids." Even the manufacturer of the FOLE did not see value in these findings and refused to provide any support. Grant applications from many of the leading nutrition organizations responded in a similar fashion. Fortunately, the Surgical Foundation at BCH saw value in this work and continued to fund it. Intestinal failure-associated liver disease continued to occur at a frightening pace at our institution and for the second year, we had multiple children who were listed for liver transplantation or who lost their battle with grieving families left behind. One such patient was Charlie. Luckily for Charlie, he had a surgeon, Dr Russell Jennings, and parents who refused to give up. Charlie had progressive liver disease on liver biopsy and persistent hyperbilirubinemia, but he was too small to undergo transplantation and too sick to keep waiting. We were approached by Dr Jennings to use our "mouse protocol" on Charlie to buy him time to gain weight, and grow, until transplantation would be possible. His parents were interested in the experimental therapy, but insisted that if successful, the therapy be made available to any qualifying child at BCH, regardless of Charlie's final outcome. It was risky and I was very hesitant, but Charlie had run out of options and was running out of time. Because we had previous experience treating the soy-allergic patient with Omegaven, the FDA quickly issued an emergency investigative new drug allowance, and approval from our Institutional Review Board allowed us to begin treatment. In September 2004, we began treating Charlie with intravenous FOLE and after 6 weeks, his jaundice resolved and his bilirubin levels normalized. Response from colleagues continued to be tepid, now with many saying it was not the use of fish oil that was responsible for Charlie's amazing recovery but rather, the dose. Others saw hope at BCH and would contact us when a child developed IFALD and hoped that we could repeat what we did for Charlie. Starting in February 2005, patients with IFALD were treated with Omegaven, using the Innovative Therapy Pathway of the Institutional Review Board, but the effort was entirely paid for by our department of surgery.