Mattel Children's Hospital UCLA

UCLA researchers pursue personalized treatments for pediatric GI conditions

Intestinal stem cells developed from skin fibroblasts of a patient with a congenial diarrheal disorder

A key component of UCLA's Division of Pediatric Gastroenterology is its research mission, including laboratory, translational and clinical research. The division has active programs in numerous clinical and basic science areas, including two research initiatives funded by the National Institutes of Health (NIH) and the California Institute for Regenerative Medicine (CIRM) focused on intestinal stem cells and the genetics of intestinal failure in children, and *H. pylori* signaling systems and pathogenesis.

Patients seen in our clinics often have the opportunity to participate in clinical trials. Taking part in research studies can improve patient care and has allowed the division to emerge as an international leader in pediatric GI translational research.

Total exome sequencing

In recent years, clinicians have made significant strides in the understanding, prevention and treatment of intestinal failure. One avenue of research at UCLA focuses on the genetic underpinnings of GI disease through the use of whole exome sequencing. With technological advances, it is now possible to sequence as many as 35,000 genes at one time. The information obtained through whole exome sequencing has revealed the possible causes of some forms of intestinal failure and provides insights for improved therapies.

A new paradigm in pediatric GI disease research

"UCLA is taking research in a new direction by focusing on the mechanisms involved in severe pediatric gastrointestinal conditions," says Martín Gabriel Martín, MD, MPP, professor of pediatrics.

"The field has been stagnant for many years, with very few new drugs available," Dr. Martín says. "At UCLA, we are taking our research in the direction of personalized medicine. With our focus on mechanisms of disease, we are in a position to better understand these disorders and begin looking at novel approaches to treating them."

By making clinical studies available to patients, UCLA can offer excellent care while also permitting critically needed translational research to illuminate disease processes.

"Families are incredibly grateful that we are pursuing research to improve the lives of children with these conditions," Dr. Martín explains. "These disorders have a significant impact on society, including an economic burden due to the cost of treatment and an emotional burden to the child and the family."

Intestinal stem cell development

Genomic discoveries are frequently studied further using intestinal stem cells obtained from children with intestinal failure. Cells from skin biopsies are reprogrammed into intestinal stem cells, which are maintained in culture. Moreover, grants from the NIH and CIRM have paved the way for the development of methods to produce abundant stem cells developed from intestinal cells obtained from endoscopic biopsies.

These cells are the basis for further studies illuminating the genesis of intestinal failure and potential gene therapies. Research on intestinal stem cell transplantation is under way in mice and pigs. The goal of this research is to develop personalized therapies to dramatically improve outcomes. Knowledge gained about these severe conditions will also contribute to an enhanced understanding of more common GI conditions.

Novel research on *H. pylori*

Helicobacter pylori (H. pylori) is extremely prevalent, with infection rates of more than 50 percent worldwide. The infection is typically acquired in childhood although the symptoms of advanced disease, such as gastric cancer or duodenal and gastric ulcers, usually appear in adults. While many children and adults are asymptomatic, *H. pylori* infection always causes inflammation in the stomach.

At UCLA, scientists are exploring the interaction between the bacteria and their human host in order to identify which infected individuals are at risk for developing advanced disease. A model system that uses stomach surface barrier cells and acidic pH allows for the study of the bacteria in an environment similar to what is seen in the stomach. Researchers are investigating the effect of the bacteria and the stomach acid on cell connections, which are compromised during the progression to ulcers or cancer. Changes in inflammatory response to bacteria with or without suspected virulence factors are also being studied.

Progression of gastritis

Developing insights on the progression of gastritis to ulcers and cancer and on how the bacteria live in acid environments are also major objectives of the pediatric GI basic sciences program. Investigators are exploring the urea channel, a crucial component of the mechanism that allows the bacteria to live in stomach acid. Future interventions may consist of targeting the urea channel or the proteins that interact with the channel so that bacteria can no longer survive in acid.

Antibiotic resistance and patient noncompliance are the two major reasons for treatment failure. Discovery of a non-antibiotic target for treatment or a regimen that allows for fewer antibiotics would help slow the development of antibiotic resistance in *H. pylori* and other pathogens affecting children.

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