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FOCUS ON PEDIATRIC CARDIOLOGY & CARDIAC SURGERY

Affiliated with Columbia University College of Physicians and Surgeons and Weill Cornell Medical College

A Window to the Heart

It may be hard to believe by looking at it, but the clear plastic model sitting in the palm of the doctor's hand held the key to a tiny and fragile child's future. The three-dimensional model of the newborn's heart changed the entire course of his care.

When Baby S. was 20 weeks into his fetal development, his mother's doctors diagnosed a complex constellation of abnormalities in his heart. He appeared to have double outlet right ventricle with a posterior ventricular septal defect. His aorta looked to be to the right of the pulmonary artery, and it appeared small and potentially obstructed. "Doctors at multiple centers had told the parents that the lesion was very complex, and may not be able to be repaired completely and in one surgery," explains Anjali Chelliah, MD, Attending Physician at NewYork-Presbyterian/Morgan Stanley Children's Hospital and Assistant Professor of Pediatrics at Columbia University College of Physicians and Surgeons, who specializes in fetal and pediatric cardiologic imaging.

When his mother reached the 35th week of her pregnancy, she came to NYP/Morgan Stanley Children's Hospital, and Baby S. was born there in July 2014. Dr. Chelliah performed a very low-radiation CT scan of his heart when he was one day old and sent the digital data to a Midwestern vendor called Materialise. Using an advanced 3D printer and software called HeartPrint®, Materialise created the 3D model of the baby's heart and delivered it to the pediatric cardiac surgeons to help plan the infant's surgery.

Thanks to this 3D heart model, cardiac surgeons could plan an infant's operation before stepping into the OR.

While CT and MRI scanning generate useful information

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Supporting Young Lungs and Hearts

The 14-year-old patient was struggling with status asthmaticus in a New Jersey community hospital. His blood pH dropped precipitously as he progressed toward respiratory failure. His doctors knew drastic measures would be necessary to save him. That's when they called for ECMO transport.

ECMO — extracorporeal membrane oxygenation — is a device that functions as an artificial lung that can support a patient's own failing lungs. The ECMO circuit pumps a patient's blood through a gas-exchange device, allowing for the delivery of oxygen and removal of carbon dioxide. For the asthmatic patient, it meant he could receive supportive care en route to NewYork-Presbyterian/Morgan Stanley Children's Hospital, the only hospital in the New York City area offering ECMO transport for pediatric patients. The Pediatric ECMO Program is directed by William Middlesworth, MD, Associate Professor of Surgery in Pediatrics at Columbia University College of Physicians and Surgeons.

NewYork-Presbyterian Hospital/Columbia University Medical Center has extensive experience transporting adults with respiratory and cardiac failure with ECMO support.

NewYork-Presbyterian Hospital's Mobile ECMO Transport Team. The service is now available for young patients.

Our ECMO program is the largest in the United States, and we are now able to extend these services to pediatric patients. Mobile ECMO transport via ambulance can be arranged for pediatric patients within a 150-mile radius by calling **1-800-NYP-STAT (1-800-697-7828)**, 24 hours a day. For patients outside of this radius, aeromedical ECMO transport may be arranged.

"We want physicians to know that if they're seeking ECMO transport for young patients, we're open for business," says Erika

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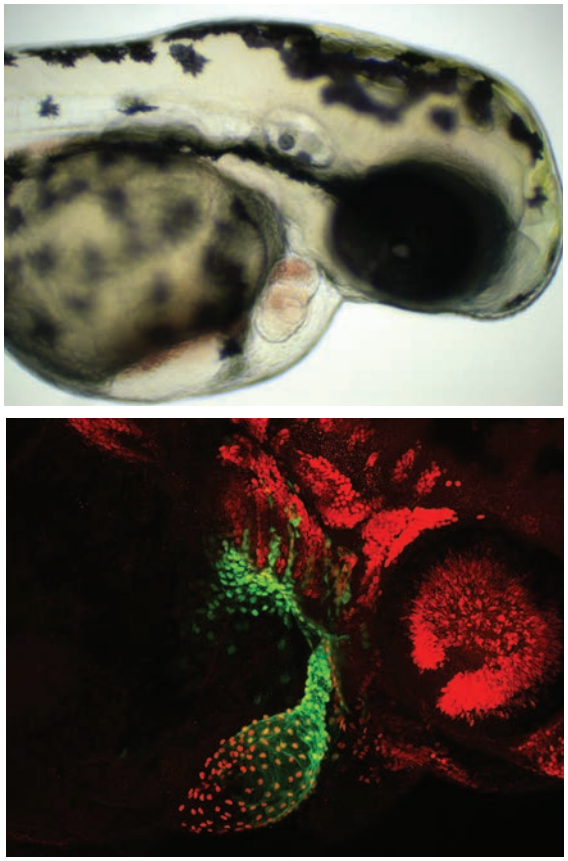
A Fish Earns Its Stripes

What does a zebrafish embryo have to do with congenital heart disease? Everything, according to pediatric cardiologist and developmental biologist Kimara Targoff, MD.

When she's not caring for young patients at NewYork-Presbyterian/Morgan Stanley Children's Hospital, Dr. Targoff can be found in her laboratory, scrutinizing the intricacies of zebrafish embryos to glean insights into cardiac morphogenesis. What makes a cell become a cardiac cell, and then differentiate to become part of an atrium or a ventricle? And what goes awry at the molecular level to cause a cell to die or to become another type of cell — causing a fetal heart to develop improperly, as in the case of hypoplastic left heart syndrome?

"Cardiac morphogenesis is a carefully orchestrated process representing the first organogenesis milestone in developing vertebrate embryos. The establishment of specific characteristics of two major cardiac chambers, a ventricle and an atrium, is crucial to the formation of a functional heart," explains Dr. Targoff, Assisting Attending Physician at NYP/Morgan Stanley Children's and Assistant Professor of Pediatrics at Columbia University College of Physicians and Surgeons. "Using the zebrafish as a model, we can uncover the basic mechanisms underlying the development of heart disease, since alterations in these basic cellular processes can lead to problems."



Top: The transparent zebrafish embryo provides a window to embryonic development. Bottom: Isl1 immunostaining (red) in embryos carrying a transgene that permits visualization of *NKX2.5*-expressing cells (green).

The zebrafish offers a host of features that make it widely popular for studying morphogenesis:

- Its eggs are externally fertilized at the one-cell stage, making the embryos easy to access.
- The fish lay as many as 150 eggs at a time.
- The chorion of the embryo is transparent, as is the embryo itself, providing a window to embryonic development. Organ development, right down to the beating of a developing heart, can be visualized under a microscope.
- Zebrafish do not require a functional cardiovascular system for survival until well after cardiac chamber formation is complete.
- The embryos are easy to manipulate genetically.

"The large volume of embryos that are readily obtained in the laboratory provides us with a powerful tool for genetic analysis," says Dr. Targoff. She and her team knock down or overexpress particular genes to observe the effects on heart development. They've centered their studies on a cardiac-specific transcription factor called *NKX2.5,* which is known to cause different types of heart defects.

The investigators are exploring the role of *NKX* genes on chamber identity. Using the zebrafish model, they showed that ventricular cardiomyocytes transdifferentiate into atrial cardiomyocytes when the *NKX* genes are not functioning. These studies suggest that *NKX2.5* may have the potential to guide stem cell differentiation to generate more ventricular cardiomyocytes. "We learned that for a cell to retain ventricular identity, it needs to express *NKX2.5,"* Dr. Targoff notes.

The findings may not only have relevance to children with congenital heart defects like hypoplastic left heart syndrome, but also to adults who have suffered cardiac muscle damage from a myocardial infarction. "In the long term, these studies could shed light on the etiologies of fetal and neonatal cardiac pathology as well as drive innovation in regenerative medicine," Dr. Targoff concluded. "The more we understand how normal cardiac development happens *in vivo,* the more we can understand what goes wrong in congenital and acquired heart disease. We could potentially use this information to identify new therapeutic targets."

The Center for Single Ventricle Care

NewYork-Presbyterian/Morgan Stanley Children's Hospital has long been a world leader in pediatric congenital heart disease management. The Center for Single Ventricle Care coordinates the care of children with hypoplastic left heart syndrome and offers the following services:

- Management of single ventricle defects in children, even before birth, using advanced technologies to accurately assess heart anatomy and function.
- Creation of a roadmap outlining a staged program of care, including a series of corrective surgeries that begin shortly after birth.
- Monitoring of children to support their health and optimal development till adulthood.

For more information or to refer a patient, call (212) 305-8509.

A Window to the Heart (continued from page 1)

about the anatomy of young hearts, it can be difficult to visualize intracardiac anatomy in detail, especially deep inside the hearts of children with doublet outlet right ventricle, L-transposition of the great vessels, and other disorders that require intracardiac surgical tunneling. "We used to have to wait until we were in the operating room to see what we were dealing with, and then execute the surgical procedure in a limited amount of time," says Emile Bacha, MD, Director of Congenital and Pediatric Cardiac Surgery at NewYork-Presbyterian Hospital and Calvin F. Barber Professor of Surgery at Columbia University. "With 3D printing, we can look at a heart in advance and plan the surgery. We can cut the model and look inside and decide what we need to do — where we need to place our sutures, patches, and so forth." Not only could he plan what to do surgically, but knowing the size and number of patches needed, he could cut them and have them ready before the operation began.

Customized 3D heart models give surgeons information about intracardiac anatomy that is useful for planning a surgery.

The 3D model showed that Baby S. had a hole between his two ventricles, and his aorta and pulmonary artery both branched off of the right ventricle. Not only did the heart model give Dr. Bacha vital information before stepping into the OR; it also gave him the visualization he needed to determine that the newborn needed only a single surgery, instead of three or four. "He went from a limited life span to a normal life expectancy with just one operation," says Dr. Bacha. He performed an arterial switch operation and tunneled the ventricular outflow to the aorta when Baby S. was just one week old.

The research behind the heart model was supported by a grant from *Matthew's Hearts of Hope* to postdoctoral clinical fellow Hannah Fraint, MD, who conducted a small pilot study to evaluate the utility of heart modeling in children with complex intracardiac defects. *Matthew's Heart of Hope* is a nonprofit organization that raises research funds for, as well as awareness of, congenital heart defects.

Three-dimensional organ modeling could have enormous applications for other surgeries, such as neurosurgical, urologic, and orthopedic procedures. "This approach is excellent for anyone who deals with three-dimensional structures," concludes Dr. Bacha. "For people like us in congenital heart surgery who deal with complex 3D anatomy, it's a huge advance. We don't have any more surprises — we can go into the operating room feeling confident about a heart's anatomy. And patients' outcomes will get even better as a result."

Supporting Young Lungs and Hearts (continued from page 1)

Berman Rosenzweig, MD, Associate Chief, Division of Pediatric Cardiology at NYP/Morgan Stanley Children's and Associate Professor of Pediatrics in Medicine at Columbia University. "We're implementing what we've learned from our adult program into the pediatric program, and can now transport children who may be too ill to be transferred by conventional ambulance."

ECMO is a device outside the body that directly oxygenates and removes carbon dioxide from the blood.

With most approaches to ECMO for respiratory failure, a catheter is placed in a central vein, usually near the heart. A mechanical pump draws blood from the vein into the circuit, where the blood passes through a membrane (an oxygenator or gas exchanger), providing an interface between the blood and freshly delivered oxygen. The blood may be warmed or cooled as needed, and is returned either to a central vein (veno-venous ECMO) or to an artery (veno-arterial ECMO). Veno-venous ECMO provides respiratory support alone, while veno-arterial ECMO provides both respiratory and cardiac support.

"We have a robust experience with ECMO transport but had limited it to adult patients until now," says Matthew Bacchetta, MD, Co-Director of the Center for Acute Respiratory Failure at NewYork-Presbyterian/Columbia. "We are leveraging our experience and our specially trained team to provide this service to patients of all ages."

The Mobile ECMO Transport Team includes a perfusionist, a surgeon, an ECMO fellow, and specially trained paramedics who are able to transport critically ill patients. The team's ambulance has advanced equipment such as a portable ECMO machine. The ECMO surgeon and fellow place the patient on ECMO support at the outside hospital. Once stabilized, the mobile ECMO transport team travels with the patient back to NYP/Morgan Stanley Children's for continued care. Once at NYP/Morgan Stanley Children's, patients on ECMO receive care from a pediatric medical-surgical team that includes surgeons, intensivists, cardiologists, perfusionists, and nurses with specialty training.

Physicians are encouraged to consider ECMO for patients with any serious cardiac or pulmonary disease that could be reversible. NYP/Morgan Stanley Children's also has extensive experience using ECMO to treat children with pulmonary hypertension and congenital heart disease.

Ambulatory ECMO is an option for some patients, enabling them to get out of bed and walk as their lungs heal. One patient with pulmonary hypertension and the flu was treated with ambulatory ECMO and was able to get out of bed and walk around the Pediatric Intensive Care Unit while recovering.

What happened to the patient with asthma? He was extubated a few days after being placed on ECMO and began his recovery. "There was a time when this patient never would have been transported and could easily have died," says Dr. Bacchetta. "Instead, he was able to walk out of the hospital."

NewYork-Presbyterian AMAZING THINGS ARE HAPPENING HERE FOR KIDS

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