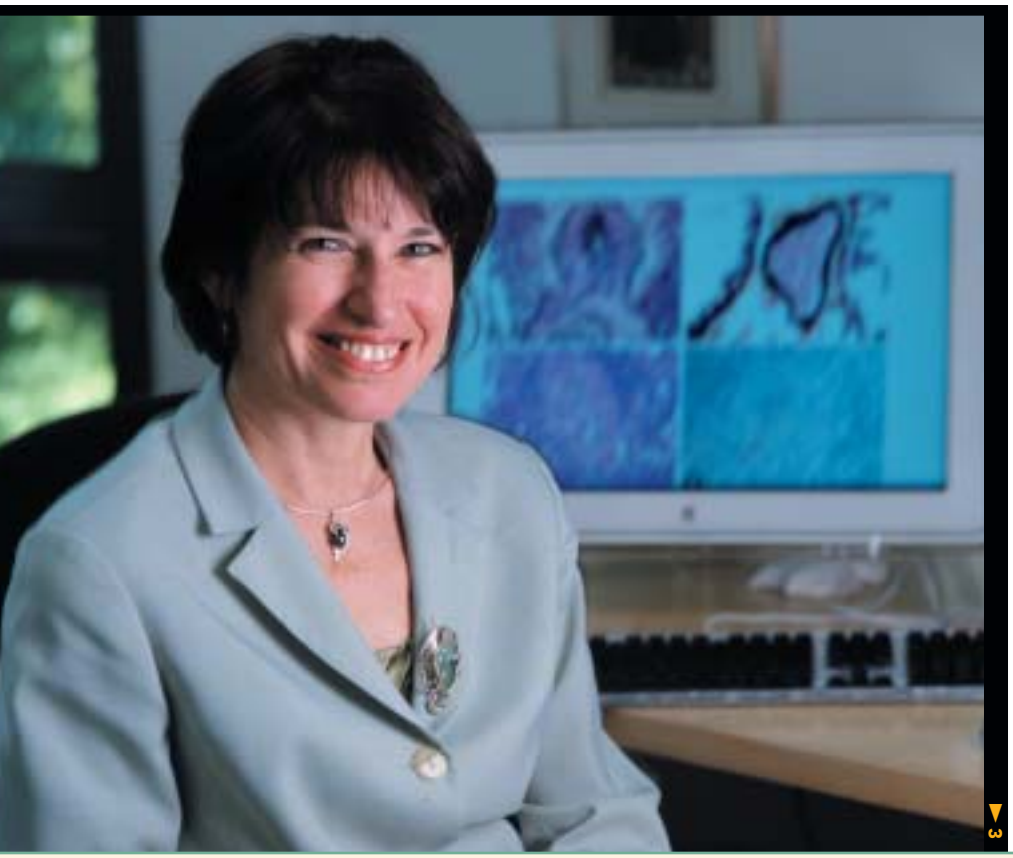
Research

Preventing the unpreventable – discovering new treatments for pediatric heart problems

Packard Children's Hospital has earned a reputation as a place that brings hope and healing to kids who cannot find help anywhere else. The future of pediatric medicine, however, lies in being able to prevent disorders that are as yet unpreventable, and to find treatments to contain or reverse conditions that are now irreversible. The paths to discovering these new treatments start in basic medical research. Packard Children's Hospital, Stanford University, and Silicon Valley offer a uniquely rich environment for such medical research, one that has attracted bright medical scientists from research universities throughout the country.



Researcher Marlene Rabinovitch, M.D., Ph.D., brings to Packard her expertise in understanding the molecular biology of cardiopulmonary disorders in children.

Understanding Cardiopulmonary Disorders

One of the prize recruits to Packard this year is Marlene Rabinovitch, M.D., Ph.D., formerly head of cardiovascular research at The Hospital for Sick Children in Toronto. Rabinovitch brings with her a strong program of research in the molecular and cellular underpinnings of cardiopulmonary disorders in children.

Rabinovitch's laboratory has demonstrated how damage to blood vessels from inflammation, toxins, low oxygen, or high

Defining State-of-the-Heart *(continued)*

The day after Aubrey arrived at Packard, Reddy operated. Using only his hands and magnifying goggles, Reddy was working with a heart the size of the tip of his thumb, cutting and sewing until he put in a new valve and closed a hole between her two ventricles. Even more than with older children, heart surgery with such tiny babies requires special training and experience. Anesthesia must be administered exactly, and surgeons have an even smaller margin for error than they would in larger children or adults. Earlier this year, Reddy had successfully corrected a heart defect in a premature baby weighing just over one pound – the youngest and smallest baby in the world to undergo open-heart surgery.

After surgery, Aubrey continued to need the assistance of pediatric heart specialists. In the cardiac intensive care unit, her heart began to race, beating so fast that finally she suffered cardiac arrest and had to be resuscitated. Aubrey also

blood pressure can cause structural changes that narrow arteries. "When certain vascular tissues are disrupted, the natural reaction of muscle cells surrounding the artery is to try to repair the damage by multiplying, which constricts the arteries," Rabinovitch says.

Narrowed arteries can create yet higher blood pressure, causing further damage and creating the basis for a progressive degenerative disease. When this occurs in the lungs, the result is pulmonary hypertension. Although pulmonary hypertension is rare in children, it can be devastating for kids and their families.

"Our focus is on trying to understand the basic mechanisms of pulmonary hypertension so that we can identify it better and reverse it more effectively," Rabinovitch says.

She has shown that researchers may be able to block certain molecular events that lead to pulmonary hypertension. Research by Rabinovitch and her colleagues could result in a new class of drugs that will stop or reverse the multiplication of muscle cells that narrow arteries, a development that could have implications far beyond pulmonary hypertension.

"Many of the enzymes we study also play a part in organ rejection after heart transplantation and other cardiovascular diseases," Rabinovitch says. She and

(continued)

Wall Center and Children's Heart Center Combine Research and Clinical Expertise

The Children's Heart Center is one of the six Centers of Excellence designated in the Campaign for Lucile Packard Children's Hospital. By establishing the Heart Center as a focus of fundraising efforts, Packard has been able to greatly enhance its expertise in pediatric cardiac surgery and cardiology.

The Hospital also is at the forefront of basic research efforts to understand the fundamental causes and mechanisms of heart problems in children, thanks in large part to the newly established Vera Moulton Wall Center for Pulmonary Vascular Disease at Stanford. The Wall Center was created in 2001 as the result of a $40 million anonymous gift to create a leading center for the investigation and treatment of heart and lung diseases in adults and children.

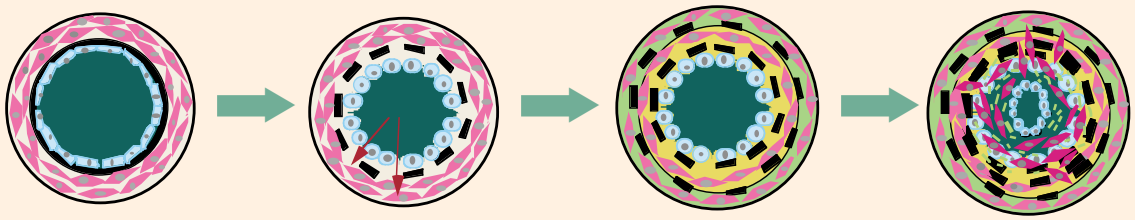
This spring, Marlene Rabinovitch, M.D., Ph.D., considered one of the world's leading researchers in vascular biology, was recruited from Toronto to Packard as a key player in the Wall Center team. Rabinovitch joins the Center as the first Dwight and Vera Dunlevie Professor in Pediatric Cardiology.

suffered from high blood pressure, which could damage her lungs or other organs. Cardiologists were crucial in finding medications that could control these conditions. Nurses and physicians with training in pediatric intensive care were important for monitoring Aubrey's progress and finding signs of trouble.

After just over a month, Aubrey was released to go home, but she continues coming back to Packard so that her condition and her response to medications can be monitored. "She is on the road to recovery, and she still has a way to go," says Beth Klemm, "but we feel good about how she's been treated and the expertise we've found here at Packard." ●

Using only his hands and magnifying goggles, Reddy was working with a heart the size of the tip of his thumb...

Pulmonary Vascular Disease



When blood vessels are traumatized, muscle cells surrounding the artery try to repair the damage by multiplying. As a result the artery is constricted, which can lead to pulmonary hypertension.

her colleagues are now studying the effectiveness of these compounds in the lab and setting the stage for future human trials.

When researchers such as Rabinovitch develop new drugs they often face another challenge: how to deliver the drugs to the correct tissues and to release those drugs into the tissue at a steady rate. Stanford scientists are developing new devices that can be implanted via catheter to deliver the right dosage of a drug over months, keeping children away from the hospital for a longer period of time. For cases in which effective drugs don't yet exist, Stanford researchers are investigating genetic therapies that will allow kids' bodies to make their own missing or therapeutic proteins.

"Our focus is on trying to understand the basic mechanisms of pulmonary hypertension so that we can identify it better and reverse it more effectively."

■ Marlene Rabinovitch, M.D., Ph.D.

Bioengineering Missing Parts

One strong desire of pediatric cardiac surgeons is to be able to invent new materials to help in reconstruct cardiovascular malformations. "Cardiac defects in children are developmental, which usually means parts are missing," says surgeon Frank Hanley, M.D. "We can do reconstructive surgery, but we can't create a part if there's nothing there to work with." The interest in inventing artificial organs and tissues is the focus of the new children's surgical research program at Packard. This program fits well with Stanford's long history of innovation in other engineering and materials science programs, and with the school's record for moving those innovations from the laboratory to the world at large.

Ultimately, surgeons are interested in bioengineered parts that are grown from living cells and tissues. "Kids have special needs as heart patients because unlike adults they keep growing," Hanley says. "Now we use synthetic parts or those from cadavers, but they are not ideal because they degenerate or don't grow, meaning the child has to have multiple surgeries."

Flying Through the Heart

Using technology borrowed from Silicon Valley, Packard researchers are developing computerized medical imaging technologies to help surgeons repair heart defects in children. Images obtained with ultrasound, computed tomography (CT) scanners, or magnetic resonance imaging (MRI) are usually two-dimensional, but can be combined by computer into highly detailed 3-D images. "You can actually fly through the arteries and the heart's chambers, as if you were in a tiny airplane," says cardiologist Daniel Bernstein, M.D. "This lets the surgeon know exactly what he will see once he goes in."

Such imaging lets cardiologists construct a model of a child's cardiovascular system, recording blood velocity and pressure in a specific network of arteries and veins. Surgeons then can model the outcomes of various surgical interventions and choose the best one before surgery even begins.

It is precisely this combination of strengths in biomedical sciences and engineering that makes Stanford so productive in finding medical breakthroughs and delivering them to patients. "You can't find such a concentration of doctors, engineers, and private companies anywhere in the world," says Jeffrey Feinstein, M.D., an associate director of the pediatric cardiac catheterization lab and director of the Wall Center for Pulmonary Vascular Disease at Stanford (see sidebar, p. 13). "There's no doubt in our minds that we are going to be able to do things for children that can't be done anywhere else." ●

The Impact of Philanthropy

A number of donors have stepped forward to invest in the exciting work of the Children's Heart Center. Each gift has earned a match from the Campaign challenge grant.

We gratefully acknowledge:

The David and Lucile Packard Foundation

The Vera Moulton Wall Center

The Elkus Family

Montgomery Street Foundation

William and Patricia Wilson III

Paul Althouse

The Campaign

Children's Heart Center Gift Objectives

Several medical leadership positions already have been filled for the Children's Heart Center thanks to investment from the Campaign for Lucile Packard Children's Hospital. However, much remains to be funded if the Center's vision is to be fully realized. In addition to a program endowment required to support the Heart Center's expanding role, these remaining needs focus on facilities, including a specialized intensive care unit and surgical facilities, which currently do not exist at Packard Children's Hospital.

Phase I

Heart Center Naming Gift (program endowment) **$20 million**
Payout from this program endowment would sustain innovation and program development in perpetuity.

CVICU Facility Construction **$15 million**
A new Cardiovascular Intensive Care Unit (CVICU) will be built within remodeled space on the 2nd floor of the Hospital to care for the increased number of children having heart surgery.

Endowed Professorship in Pediatric Cardiovascular Surgery **$3 million**
Endowment of this chair would enable the School of Medicine to recruit and retain the most talented surgeons for the Children's Heart Center.

Endowed Director of Cardiovascular Surgery **$3 million**
A named endowed position would enable the Hospital to recruit a leading candidate to become the chief of the pediatric cardiovascular surgery division.

Endowed Director of CVICU **$3 million**
Packard seeks to recruit a Director of Cardiovascular Intensive Care to direct its state-of-the-art initiatives in children's heart care.

Endowed Fellowships in CV Surgery, Cardiology **$1 million each**
Named endowed fellowships support advanced clinical training for pediatric cardiologists and heart surgeons of the future, as part of the mission of an academic medical facility.

Endowed Program Support Fund **$4 million**
The Endowed Fund will support the ongoing needs of the Children's Heart Center, including annual staffing, equipment, and other resource needs. The minimum gift for a named endowed fund is $250,000.

Phase II

Cardiovascular Operating Rooms **$40 million**
As part of the Hospital's planned new surgical inpatient pavilion, the second phase of the Heart Center's investment includes dedicated operating rooms for pediatric cardiovascular surgery.