

## 2nd Annual Dunlevie Lecture in Pediatric Cardiopulmonary Medicine - May 10, 2002

### *Reversing Pulmonary Hypertension in the 21st Century*

Marlene Rabinovitch, MD

Professor of Pediatrics of Laboratory Medicine & Pathobiology, and Medicine

University of Toronto

Director, Cardiovascular Research at the Hospital for Sick Children, Toronto

At the second annual Dunlevie Lecture in Pediatric Cardiology on May 10, 2002 the Wall Center's new Director of Research, Dr. Marlene Rabinovitch presented a constellation of exciting new findings that reveal what causes obliterative changes in pulmonary arteries due to excessive growth of cells, and point the way to new drug therapies that can control or even reverse such growth.

Dr. Rabinovitch began her talk by remarking that she had just been to the 400<sup>th</sup> anniversary celebration of William Harvey's graduation from the University of Padua. "We have come a long way from viewing the circulatory system as simply branching pathways and blood elements, to where we now can talk about the circulatory system in terms of regulation of specific genes," Dr. Rabinovitch said. Furthermore, she noted, "we will soon have the profile for every protein and every gene in each of the blood vessel cells under all kinds of conditions that lead to disease". With this information comes the responsibility that we can do better for our patients in terms of finding new treatments for vascular disease especially pulmonary hypertension.

#### **A Problem of Cell Growth**

Dr. Rabinovitch's research focus has been to understand how the behaviour of the cells of the vessel wall changes when there is high blood pressure in the lung and how this leads to thickening and occlusion of the vessel lumen, raising pulmonary blood pressure even further and leading to more damage.

Searching for clues, Dr. Rabinovitch and her colleagues studied the inner surface of a hypertensive pulmonary artery using an electron microscope. What they found was not the neat ridges of a healthy endothelial surface, but one full of interlocking, jumbled bumps and gullies, "We also could see that the layer of elastin that normally separates endothelial cells from underlying muscle cells seemed to have broken down," Dr. Rabinovitch said. Since a disruption of elastin stimulates tissue remodeling during wound healing, they suspected that cell growth in the hypertensive vessels might be related to release of an elastolytic enzyme, which would break down the elastin layer. In theory, an increase in blood pressure or flow would lead to leakage of serum factors through the endothelial cells, causing increased production of elastolytic enzymes breakdown in elastin and new tissue growth. "Once the elastic layer is disrupted", according to Dr. Rabinovitch, "it signals the cell that, 'the foundation is falling apart, we need reinforcement's." The reinforcements arrive in the form of growth-promoting molecules.

Following this line of reasoning, Dr. Rabinovitch and her colleagues showed that rats exposed to low oxygen pressure, high oxygen pressure, or a toxin that damages endothelial cells, exhibit an increase in elastolytic enzyme activity in blood vessels. These rats also later developed narrowing of the blood vessels due to muscle cell growth.

This finding suggested that inhibiting elastolytic enzyme activity might protect against such blood vessel damage, which is what Dr. Rabinovitch and her colleagues found in her next set of experiments. Mice that were treated with elastase inhibitors (or were genetically engineered to increase their own production of elastase inhibitors) showed very little structural change in pulmonary vessels under experimental stresses that would ordinarily produce pulmonary hypertension.

## **Reversing the Damage**

In subsequent studies Dr. Rabinovitch and her team figured out a way to not only prevent the abnormal growth of cells in blood vessel with inhibitors of the elastase enzyme but also to reverse the process and return the diseased blood vessel to its normal state. They showed that dividing cells receiving growth signals from degraded collagen go into reverse and die off after the collagen that supports them is no longer degraded by the elastase enzyme.

Dr. Rabinovitch and her team thought that this effect could be exploited. “Can we take a very abnormal thick-walled vessel, put the excessive cells into reverse and into a death mode?” The next set of experiments showed that a thickened vessel wall under a pressure load, continually degrades elastin and collagen and maintains its thickened state even in culture, but when the load on the vessel is relaxed, the cells can no longer degrade elastin and collagen, there is cell death and the vessel wall shrinks.

Since that time, Dr. Rabinovitch’s group has shown in rats with severe pulmonary hypertension that unloading the blood pressure on thick walled vessels does indeed lead to a reversal of pulmonary hypertension. Since it is not always possible to offload the pressure, they used oral elastase inhibitors in experimental animals with advanced pulmonary hypertension to prevent the degradation of elastin and collagen and achieve the same result as pressure offloading. Thus the same treatment that prevents disease, i.e., elastase inhibitors, can also be used to reverse the disease.

“What we found was that the animals with no treatment all died of their pulmonary hypertension within 30 days,” Dr. Rabinovitch said. “But with treatment we got 90 percent survival—they were back to normal after two weeks of therapy.” She and her colleagues also showed that other compounds may accomplish the same result.

The real key to not just understanding pulmonary hypertension, but treating it, lies in deciphering the molecular signals that lead to thickening of the vessel wall, Dr. Rabinovitch said. “As you understand these mechanisms in greater depth, you get new insights into ways to block the disease process.” Such insights might well also apply to other disease, she notes. “This might also be useful for systemic vascular disease like restenosis or arteriosclerosis.”

Remarking on how pleased she was to be giving the Dunlevie Lecture, Dr. Rabinovitch made note of the Dunlevie family’s commitment to fostering research in pulmonary hypertension “This is a family that really wants to make a difference,” Dr. Rabinovitch said. “Not only for their own child, who was eventually cured of her condition, but for other patients and other families.”

Dr. Rabinovitch herself has long had a commitment to making a difference in children’s lives. After graduating from McGill University Medical School, she took pediatric cardiology training and research at Boston Children’s Hospital before joining the Hospital for Sick Children (HSC) in Toronto. There she became professor of pediatrics as well as the director of the Cardiovascular Research Program. She joined the Stanford Faculty in July, 2002.