# CONGENITAL CARDIOLOGY TODAY

Timely News and Information for BC/BE Congenital/Structural Cardiologists and Surgeons

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### **CONGENITAL** CARDIOLOGY TODAY

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### THE 4TH ADVANCED COURSE IN PEDIATRIC CARDIOVASCULAR MR

Toronto, Ontario, Canada December 13-14, 2008 ~ See ad on page 7 ~

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### Treating Severe Pulmonary Regurgitation with Moderate Right Ventricular Outflow Tract (RVOT) Stenosis

By Peter Ewert, MD, PhD and Felix Berger, MD, PhD

### Synopsis

To treat severe pulmonary regurgitation with moderate right ventricular outflow tract (RVOT) stenosis, we chose the Medtronic Melody<sup>®</sup> Trans-catheter Valve.

With a minimally invasive femoral vein puncture, we could position and deploy the valve under angiographic guidance.

Following implantation of the valve, there was immediate and complete relief of conduit stenosis and no detectable pulmonary regurgitation. There was also no detectable regurgitation at the six-month follow-up.

### Rationale

Pulmonary regurgitation can lead to severe right ventricular dysfunction, which reduces exercise tolerance, promotes dysrythmia and, if left untreated, is fatal.

Replacing the pulmonary valve to abolish regurgitation improves the patient's clinical condition and life expectancy.

Until recently a surgical approach was the only method to replace a diseased heart valve. With the development of transcatheter heart valves, providing certain ana-



[A] Medtronic Melody<sup>®</sup> Trans-catheter Valve Ensemble delivery system, and [B] Medtronic Melody<sup>®</sup> Trans-catheter Valve.





# Tri-City Pediatric Cardiology

### **Pediatric Cardiologist Needed in Tricities, Tennessee**

Exciting opportunity for a pediatric cardiologist to join a mature 3-physician private group in Tricities, Tennessee. Come and enjoy an excellent work environment as well as an attractive, affordable lifestyle.

### Practice Description:

- The ideal candidate should be: well trained, BE/BC, skilled in general pediatric cardiology (all aspects of noninvasive diagnostic modalities including transthoracic, transesophageal and fetal Echo) and have a liking/training in diagnostic and interventional cardiac catheterization and cardiac MRI.
- The physician will share equal call with minimal inpatient responsibilities and 80% of time spent in one of our 3 offices which are all equipped with state-of-the-art Echo machines and staffed with pediatric trained Echo techs.
- The group is committed to getting a fully digital Echo lab and EMR in the near future.
- The referral base consists of 1.5 million people throughout Northeast Tennessee, Southwest Virginia and Eastern Kentucky.
- He/she should have excellent interpersonal skills, good work ethic and interact well with peers and community physicians.
- The position offers an attractive compensation package including relocation expenses, competitive salary based on experience and comprehensive benefits package. There is a potential for partnership track for the ideal candidate.

### About Tricities, Tennessee:

- Tricities, comprised of Johnson City, Kingsport and Bristol, is nestled in the mountains in Northeast Tennessee, surrounded by lakes, and is close to the Great Smoky and Blue Ridge Mountains.
- It is the home of ETSU (East Tennessee State University) with a medical school in town.
- The progressive Tricities region has a metropolitan statistical area (MSA) of 450,000 people, giving it the attributes of a cosmopolitan area, but with the atmosphere and charm of a small town.
- The area offers a wonderful blend of cultural and recreational activity, low crime, affordable and upscale living and an excellent public school system rated in the top 5% nationwide.
- Four distinct seasons offer immense outdoor activities including: water skiing, hiking, cycling, water rafting, and ski-slopes within 30-60 miles.



E-mail/fax CV for immediate consideration: Ashish Madhok, MD, FACC (423) 610-1166 (Fax) ashishdoc1973@yahoo.com amadhok@pedscardiogy.com www.pedscardiology.com

### CONGENITAL CARDIOLOGY TODAY



### Figure 1.

tomical criteria are met, it is possible to replace the pulmonary valve using a trans-catheter technique. Using this approach it is possible to significantly reduce the re-operation rate in this group of patients.

### **Case Study**

A seventeen year old patient with Tetralogy of Fallot had undergone three previous heart operations. These included: reconstruction of the right ventricular outflow tract in 1992 and implantation of a homograft in 1996.

Cardiological investigations showed a marked reduction in exercise capacity. Echocardiography and Magnetic resonance imaging of the heart showed severe pulmonary regurgitation with an ejection fraction of 22%, and moderate RVOT conduit stenosis.

### The Cardiac Catheter Procedure

The cardiac catheter procedure was performed under local anaesthetic and intravenous sedation.

Vital signs were monitored constantly including E.C.G., blood pressure and oxygen saturation.



#### Figure 2.

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The femoral vein and artery were both punctured, and introducer sheaths were placed insitu. Heparin 5000 iu was given.

Pressure measurements were made in the right ventricle, pulmonary artery and aortic positions.

Angiographic cine pictures were made of the RVOT in Lateral and AP. planes (Figures 1 and 2).

"With the development of trans-catheter heart valves, providing certain anatomical criteria are met, it is possible to replace the pulmonary valve using a trans-catheter technique."





Working Together to Develop a Better Tomorrow

### PEDIATRIC CARDIOLOGIST

The Division of Pediatric Cardiology of Sanger Clinic and Levine Children's Hospital in Charlotte, N.C. is recruiting a board certified pediatric cardiologist with sub-specialty expertise in electrophysiology (EP). The candidate should be clinically excellent, have superior interpersonal skills and be willing to develop and grow a successful local and regional EP program. The successful applicant will join a rapidly growing practice of eight pediatric cardiologists and two cardiothoracic surgeons. The Sanger Clinic also has a large and busy adult congenital practice with a large volume of adult congenital patients. Electrophysiology cases will be performed in one of two biplane catheterization laboratories including a new biplane laboratory which will be completed in the first quarter of 2009.

The Sanger Clinic is the premier congenital heart center in North Carolina performing over three hundred surgeries and cardiac catheterizations per year. The practice is affiliated with Carolinas Healthcare System, the third largest hospital authority in the country, but operates much like a private practice with very competitive compensation and benefits. The hospital authority just opened Levine Children's Hospital in the fall of 2007, an eighty-five million dollar, 240 bed state-of-the-art facility. Charlotte, NC is a friendly, thriving metropolis with excellent arts (symphony, theatre, and museums), entertainment (US National Whitewater Center), professional sports (Panthers, Bobcats, NASCAR) and wonderful restaurants (Johnson and Wales College of Culinary Arts). The city is only two hours from the mountains and three and one half hours to the coast. Interested applicants should fax or e-mail their CVs to Dr. Stern.

Herbert J. Stern, MD, FACC Director, Division of Pediatric Cardiology Sanger Clinic and Levine Children's Hospital herbert.stern@carolinashealthcare.org fax # 704-543-0018



We also used some cranial tilt on our a.p. projections for this case.

The coronary arteries are identified under angiography to exclude any possibility of occlusion when the valve is deployed.

The decision is then made whether to proceed with implantation.

#### Criteria Include:

- Objective evidence of conduit dysfunction
  - Moderate or severe regurgitation
  - RV to PA conduit stenosis
- Consensus with cardiac surgery team
- Clinical indication for surgical intervention
  - Weight ≥30 kg
- Favorable RVOT morphology
  - Amenable to stent anchorage
  - Sizing balloon (waist) diameter ≥ 14 mm and ≤ 20 mm

### Contraindications to trans-catheter valve implantation:

- Active endocarditis
- Conduits smaller than 16 mm and greater than 22 mm
- No calcification in the conduit.

Once criteria to continue were confirmed, the valve was prepared.

The Melody<sup>®</sup> valve is a bovine jugular valve within a platinum iridium stent. Being biological tissue, it is stored in gluteralderhyde solution which must be rinsed thoroughly before implantation.

This is done in 3 stages:

- 1. The valve is removed and placed in a sterile rinse bowl full of 500 mls of saline, after emptying out any residual solution left on the valve.
- 2. After 5 minutes of washing achieved by filling and emptying the valve, it is transferred into a second saline filled bowl.
- 3. After another 5 minutes wash time, the valve is placed into its third and final 5 minutes wash bowl.

The valve can remain in this third and final bowl until it is needed for implantation.

Whilst the valve was being rinsed the Ensemble<sup>®</sup> delivery system was prepared, the inner and outer balloons are de-aired with luer lock syringes filled with a mixture of radio-opaque contrast and saline.

The valve is crimped initially onto a 2 or 3 ml syringe before finally crimping onto the delivery system.

It is crucial that the valve is orientated correctly during mounting on the delivery system. This is confirmed by matching markers on the valve and delivery system: blue to blue and white to white.



Parent Heart Watch P.O. Box 237 Geneva, Ohio 44041 Contact Person: Linette Derminer linette@parentheartwatch.org 440-466-0417

The members of Parent Heart Watch advocate for awareness and change- all with the goal of protecting children from SCA

www.CongenitalCardiologyToday.com



Figure 3.



### Figure 4.

The delivery system was then introduced through the femoral vein over a stiff angiographic wire pre-positioned in the left P.A.

The system is passed through the right atrium and ventricle and up into the RVOT conduit under angiographic guidance.

The valve stent is clearly visible under angiography. (Usual projections are AP and lateral.)



### Pediatric Cardiology Of Southwest Louisiana, LLC

2005 Southwood Drive Lake Charles, LA 70605 337-562-2293

Due to rapid growth, Private Pediatric Cardiology office seeking two BC/BE pediatric cardiologists to join a primarily outpatient practice with inpatient consultations.

This practice was established in 1998 and is the sole provider of pediatric cardiology services in Southwest Louisiana. We provide consultation services for the area hospitals, two level III NICU units and a pediatric ICU. Patients are referred to Houston or New Orleans for open-heart surgery.

This position offers a competitive salary starting at 220K/ year, increasing \$10,000/year to a maximum of 250K/year guaranteed after 3 years and includes incentive pay once fully vested after 3 years. This is an opportunity to achieve financial compensation above national average. Vacation package offers 4 weeks of paid vacation and an additional week for CME. There is a generous benefit package, which includes, 401K plan, paid health, disability, life insurance, moving expenses, malpractice insurance, and CME allowances.

This practice is located in Southwest Louisiana with easy access to the metropolitan cities of Houston and nearby New Orleans. This region is an outdoorsman's paradise and offers a taste of Cajun Country with its year round celebration of food, music, and culture.

Will sponsor applicants with H-1 and J-1 Visa's.

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Any final position changes can be made before uncovering the valve from its protective sheath through which confirmatory angiograms can be made prior to deployment (Figure 3).

Once satisfied with position, the inner balloon is inflated. At this stage it is still possible to make minor changes in position of the delivery system. Inflating the outer balloon enables final deployment of the valve. The balloons are quickly deflated to restore pulmonary blood-flow (Figure 4).

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Figure 5.



Figure 6.

Competency of the valve is assessed by pulmonary artery angiography (see Figures 5 and 6).

Right ventricular, aortic and pulmonary artery pressures were recorded to assess gradients across the valve.

"There were no procedural complications and the Melody<sup>®</sup> valve was free from regurgitation both initially post op, and at the six-month follow-up."

E.C.G. is observed for any changes.

Femoral sheaths are removed and haemostasis is achieved with direct digital pressure.

Total procedure time in this case was just 62 minutes, with a fluoroscopy screening time of 9.1 minutes.

There were no procedural complications and the Melody $^{\!(\!8\!)}$  valve was free from regurgitation both initially post op and at the sixmonth follow-up.

The patient's exercise capacity remains similar to pre-op findings.

The patient is routinely able to cycle to work.

### References

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# THE 4TH ADVANCED COURSE IN PEDIATRIC CARDIOVASCULAR MR

### DECEMBER 13-14, 2008; TORONTO ONTARIO, CANADA



The Society for Pediatric Radiology (SPR) and the Hospital for Sick Children in Toronto, Canada are pleased to co-sponsor the 4th Advanced Course in Pediatric Cardiovascular MR. Organized by the Departments of Diagnostic Imaging at the Hospital for Sick Children (HSC) in Toronto and the Children's Hospital & Research Center Oakland (CHRCO), the Symposium will be held in the Hospital for Sick Children, December 13th and 14th, 2008. This is a two-day course whose aim is to review advanced utilization of MR for heart diseases in children. The course will consist of didactic lectures and a free communication session. For registration forms and questions about the symposium, please contract Ms. Vicki Corris (vicki.corris@sickkids.ca), or visit the web site: http://www.pedrad.org. We look forward to having a highly educational and productive symposium in coming December in Toronto!

ORGANIZERS: Andrew Redington and Paul Babyn (HSC) and Ronald Cohen (CHRCO) PROGRAM DIRECTORS: Shi-Joon Yoo, MD (HSC) and Taylor Chung, MD (CHRCO)

### LEARNING OBJECTIVES:

- · Discuss the MR utilization in patients with pulmonary regurgitation or aortic regurgitation / stenosis.
- Define when and how pulmonary and aortic regurgitation should be intervened.
- Discuss the MR utilization in patients with functionally single ventricle.
- · Update the knowledge regarding MR-guided or directed procedures in pediatric cardiology.
- Update the new MR technologies and applications.
- Update the new developments in CT, PET CT and echocardiography.
- Exchange cardiovascular MR experience among attendees and faculties.

SPEAKERS: L Benson, T Bradley, F Chan, M Charron, T Chung, A Dick, M Fogel, L Grosse-Wortmann, WA Helbing, KJ Lee, C Macgowan, L Mertens, A Powell, P Radau, R Razavi, A Redington, A Taylor, SJ Yoo

LOCATION: Hollywood Theater, 1st Floor, Elm Wing, the Hospital for Sick Children, Toronto CME: 12.25 Category 1 Credits REGISTRATION FEE: US \$200 REGISTRATION DEADLINE: November 15, 2008

### WWW.PEDRAD.ORG/



### Work of Heart

By Janet LaPlante, Freelancer Writer and Speaker

When you read the stories, look at the pictures and meet the families of someone with a congenital heart defect, you want to be involved. Five years ago, four "heart moms" held the first fundraising event for Children's Heart Institute at Rady Children's Hospital – San Diego. Their group, now called CHI Fund, sponsors annual fundraisers, as well as offers support to those afflicted with heart defects and their families.

Money raised is used to purchase and update medical equipment and provide research that is vital to understanding and treating congenital heart defects. Donations of goods and services are also accepted.

Rady Children's Heart Institute is one of the top pediatric cardiac programs in the nation. It serves not only San Diego and Imperial counties, but also accepting referrals from Orange and Riverside counties, New Mexico, Arizona, Hawaii and the Pacific Rim Island states, including military personnel stationed there. Satellite sites of the Children's Heart Institute are located throughout Southern California.

Research studies specific to the testing of drugs for children are a main priority of the Heart Institute, along with its partner, UCSD. The Institute also coordinates research and education programs of cardiology and cardiovascular surgery, as well as studies on interventional devices. Other projects include: a grant to study Marfan Syndrome, and a study of a new drug developed for adults with high blood pressure that possibly could be used for children with enlarged aortic root.

More importantly, a pediatric heart transplant program is under development for the Institute, which would enhance today's existing programs, says Dr. John Lamberti,



Lego Heart Model. The Lego heart is a work of art, and will be auctioned to raise money to support care and research in congenital heart disease. Photo courtesy of brickartist.com.

the Eugene and Joyce Klein Director of the Heart Institute at Rady Children's.

On Saturday, November 1, 2008, CHI Fund will host its annual Gala, Helping Little Hearts Heal "Work of Heart," at the Hyatt Regency La Jolla at Aventine. Deadline for submission of original works of art for the silent auction is October 15th.

Legendary artist Nathan Sawaya constructed a larger than life, anatomically correct heart using the child-friendly toy LEGO<sup>®</sup>, to be auctioned as one of the signature sculptures of the upcoming gala. Besides being a beautiful piece of artwork, it will also assist physicians in talking to young patients about their hearts through a medium they understand. See more of his creations at www.brickartist.com. "On Saturday, November 1, 2008, CHI Fund will host its annual Gala – Helping Little Hearts Heal 'Work of Heart'- at the Hyatt Regency La Jolla at Aventine."

"CHI Fund reaches out to the San Diego community for support to ensure the best care continues to be available for these little hearts," said Wendy Robinson, a heart mom and chair of the evening. The ticket price is \$150 per person, with many levels of underwriting and corporate seating available.

For more information please visit www.chifund.org or contact Wendy Robinson at: wendy@chifund.org or call: 760-402-4011.

Janet LaPlante is a freelance writer and speaker, whose focus is the topics of relationships, spirituality and finding balance in our lives. She writes from her strong beliefs of the human experience in her Tattler newspaper column "Joy from Janet." She freelances for the *Arizona Republic*, *Catholic Sun* and various magazines, including *Canticle* and *Grand* magazine. Janet's grandson has HPLH, and she has just completed a children's book, *Scars on My Tummy*, to help children who have undergone heart surgeries.

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Janet LaPlante, Freelancer Writer & Speaker



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### Medical News, Products and Information

### Patient Reports Can Add to Efforts to Identify, Reduce Adverse Events in Hospitals

Hospitals' efforts to improve patient safety rely on several methods of monitoring and evaluating the occurrence of adverse events: including incident reports from members of the health care team, automated surveillance of clinical data, and review of medical records. A group of Massachusetts researchers report in the July 15, 2008, Annals of Internal Medicine that surveying patients about their experiences can provide additional important information. They found that nearly 23% of patients reported experiencing a complication during or immediately after their hospital stay, compared with about 11% of patients whose adverse events were identified through medical record review.

"Every approach to monitoring adverse events or complications has its limitations, even record review, which has been regarded as the 'gold standard,'" says lead author Joel Weissman, PhD, of the Massachusetts General Hospital (MGH) Institute for Health Policy. "Our research demonstrates that patients themselves can be a valuable source of information about unexpected complications that occur as a result of medical care, both during their hospital stay, and after they are discharged."

While many hospitals regularly survey patients after discharge, those surveys are usually focused on patients' satisfaction with their care, and not on whether they experienced injuries or complications. The current study was designed to: evaluate whether patients can accurately report adverse events they experienced, the types of events patients were most likely to report, and how well patient reports matched what is in the medical record. It consisted of two primary phases: a telephone survey of patients admitted to 16 Massachusetts hospitals during six months in 2003, and a review of the medical records of survey participants who gave written permission for the review.

Weissman explains, "Adverse events are complications or injuries to patients some of which may be due to preventable errors, and some which are neither preventable nor error-related. For example, an allergic reaction to a drug is an adverse drug event. If the allergy was known, administering that drug was a preventable error. But if the allergy was unknown, it was not preventable, although still an adverse event. Patients may be more likely to know about complications than about errors in their care."

About 2,600 patients participated in the telephone survey, which took place 6 to 12 months after hospital discharge. The 20-minute interview assessed several aspects of their clinical care and specifically asked about any negative effects, complications or injuries they had experienced during or after their hospitalization. Event s patients reported were subsequently reviewed by two physician coauthors, who evaluated and scored them by severity and preventability.

A medical records review, approved by almost 1,000 patients, was conducted by nurses trained to identify adverse events according to specific criteria. Two different physician reviewers classified and scored the medical record events.

The study identified 381 patients who experienced some sort of adverse event - 2 29 were identified in the interview and 105 in the medical record, but only 53 were noted by both sources. Less than 10% of events identified by either method were serious or life-threatening, and under a third were determined to be proba-



We also treat the human spirit.\*

### PEDIATRIC CARDIOLOGY Loyola University Health System

The Division of Pediatric Cardiology at Loyola University Chicago (LUC) Stritch School of Medicine's Department of Pediatrics is seeking three pediatric cardiologists to join their growing practice. The positions require excellent clinical skills in general pediatric cardiology. Subspecialty interest or training is desired but not required. The ideal candidates should be board-certified in pediatric cardiology with expertise in general Echocardiography, Fetal Echo, TEE etc., as well as other noninvasive procedures. Faculty will also have important roles in pediatric student and resident education and have the opportunity to conduct research.

Loyola's Ronald McDonald Children's Hospital, located in Loyola University Hospital, is a "hospital-within-ahospital" and is comprised of 36 general inpatient, 20 newborn nursery, 14 pediatric intensive care, and 50 neonatal intensive care beds. The hospital is staffed by a full complement of pediatric subspecialty services and a 46-member residency program.

Please send CV's to: Dr. Marc Levine, Division Director, Pediatric Cardiology, c/o Holly Nandan, **Director of Physician Recruitment**, Loyola University Physician Foundation, Two Westbrook Corporate Center #600, Westchester, IL 60154; hnandan@lumc.edu.

The Loyola University Care Health System is an affirmative action/equal opportunity educator and employer. The University undertakes affirmative action to assure equal employment opportunity for underrepresented minorities, women, and person with disabilities.



A BOARD REVIEW COURSE PRESENTED BY UIC University of Illinois at Chicago College of Medicine in collaboration with • Society of Pediatric Cardiology Training Program Directors Children's Memorial Hospital (Chicago) www.conferences.uiuc.edu/PedCardReview

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bly or definitely preventable. Most of the events that took place after patients were discharged from the hospital were related to their care but did not become evident until they left the hospital.

"This study shows very clearly that additional tools can and should be added to hospitals' efforts to evaluate patient safety," says study co-author Nancy Ridley, MS, of the Massachusetts Department of Public Health. "Patient involvement plays an important role in the safety and delivery of health care services, and we encourage hospitals to enlist patients in these efforts wherever possible."

Adds Saul Weingart, MD, PhD, of Dana-Farber Cancer Institute, a study co-author and one of the physicians who reviewed patient-reported events, "We need to learn more about how patients can help clinicians ensure safe care in the hospital and in ambulatory settings. It's pretty clear that they can teach us important things about improving patient safety, if we only ask them."

While conducting the kind of telephone surveys used in this study might be costly, the researchers note, so is medical record review. Adding safety-oriented questions to existing satisfactionfocused patient questionnaires might be a first step, but utilizing multiple methods to track adverse events will probably give the most accurate results. "What is most important is to learn from our mistakes and determine how to prevent them in the future," Weissman says. "We hope that our research will give patient safety advocates another tool to accomplish that aim."

An associate professor of Medicine at Harvard Medical School, Weissman is currently on leave from his MGH position and working as a senior health policy advisor in the Massachusetts Executive Office of Health and Human Services. He is also a professor of Family and Community Medicine at the University of Massachusetts Medical School.

Additional co-authors of the Annals report are Eric C. Schneider, MD, MSc, and Arnold M. Epstein, MD, MA, Harvard School of Public Health; Jo Ann David-Kasdan, RN, MS, and Sandra Feibelmann, MPH, MGH; and Constantine Gatsonis, PhD, Brown University. At the time the study was conducted, coauthors Catherine Annas, JD, and Leslie Kirle, MPH, were with the Mass. Department of Public Health and the Massachusetts Hospital Association, respectively. The study was supported by a Cooperative Agreement from the Agency for Healthcare Research and Quality to the Mass. Department of Public Health.

### Gene Directs Stem Cells to Build the Heart

Researchers at the Washington University School of Medicine in St. Louis, have shown that they can put mouse embryonic stem cells to work building the heart, potentially moving medical science a significant step closer to a new generation of heart disease treatments that use human stem cells.





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Scientists at Washington University School of Medicine in St. Louis report in *Cell Stem Cell* that the Mesp1 gene locks mouse embryonic stem cells into becoming heart parts and gets them moving to the area where the heart forms. Researchers are now testing if stem cells exposed to Mesp1 can help fix damaged mouse hearts.

"This isn't the only gene we'll need to get stem cells to repair damaged hearts, but it's a key piece of the puzzle," says senior author Kenneth Murphy, MD, PhD, Professor of Pathology and Immunology and a Howard Hughes Medical Institute investigator. "This gene is like the first domino in a chain: the Mesp1 protein activates genes that make other important proteins, and these in turn activate other genes and so on. The end result of these falling genetic dominoes is your whole cardiovascular system."

Embryonic stem cells have created considerable excitement because of their potential to become almost any specialized cell type. Scientists hope to use stem cells to create new tissue for treatment of a wide range of diseases and injuries. But first they have to learn how to coax them into becoming specialized tissue types such as nerve cells, skin cells or heart cells.

"That's the challenge to realizing the potential of stem cells," says Murphy. "We know some things about how the early embryo develops, but we need to learn a great deal more about how factors like Mesp1 control the roles that stem cells assume."

Mesp1 was identified several years ago by other researchers, who found that it was essential for the development of the cardiovascular system but did not describe how the gene works in embryonic stem cells.

Using mouse embryonic stem cells, Murphy's lab showed that Mesp1 starts the development of the cardiovascular system. They learned the gene's protein helps generate an embryonic cell layer known as the mesoderm, from which the heart, blood and other tissues develop. In addition, Mesp1 triggers the creation of a type of cell embryologists recently recognized as the heart's precursor.

They also found that stem cells exposed to the Mesp1 protein are locked into becoming one of three cardiovascular cell types: endothelial cells, which line the interior of blood vessels; smooth muscle cells, which are part of the walls of arteries and veins; or cardiac cells, which make up the heart.

"After they are exposed to Mesp1, the stem cells don't make any decisions for several days as to which of the three cell types they're going to become," Murphy notes. "The cues that cause them to make those commitments come later, in the form of proteins from other genes."

Researchers already know a number of the genes that shape the heart later in its development. Murphy plans to start tracing Mesp1's effects from gene-to-gene, following the falling genetic dominoes, which branch out into the pathways that form the three cardiac cell types.

"If we can find gene combinations that only make endothelium or cardiac or smooth muscle, then that could be applied to tailoring embryonic stem cells for therapies later on," he says.

Lindsley RC, Gill JG, Murphy TL, Langer EM, Cai M, Mashayekhi M, Wang W, Niwa N, Nerbonne JM, Kyba M and Murphy KM. Mesp1 coordinately regulates cardiovascular fate restriction and epithelial-mesenchymal transition in differentiating ES cells. *Cell Stem Cell*, July 3, 2008. For more information: www.cellstemcell.com.

#### Improving Patient Care by "Personalizing" the Practice of Medicine Often Results from Studying Specific Drugs and Their Impact on Genetic Biomarkers

New research underway at George Washington University (GW) by Travis O'Brien, PhD, looks at the drug warfarin, an oral anticoagulant used to treat individuals with certain cardiovascular diseases. Warfarin accounts for several million prescriptions each year. With its narrow therapeutic index, warfarin may not be well tolerated by certain individuals because of their genetic makeup, says Dr. O'Brien, Associate Professor of Pharmacology and Physiology

O'Brien and a team of researchers hope to unlock the key to the personalization of warfarin therapy based on a patient's genetic biomarkers. The multidisciplinary research team also includes April Barbour, MD, Assistant Professor of Medicine, Linda Lesky, MD, Associate Professor of Medicine and Health Policy, and Perry Payne, Jr., MD, JD, MPP, Assistant Research Professor of Health Policy. In addition, the study will be conducted in collaboration with GW adjunct faculty, Arthur Harralson, PharmD, and Robert Kidd, PharmD, PhD, from Shenandoah University, Bernard J. Dunn School of Pharmacy.

As part of the study, samples will be collected by the Medical Faculty Associates. DNA from the samples will then be isolated and analyzed at the GW Pharmacogenomics Program laboratory, located at GW's Ashburn, Virginia campus. The analyzed samples will then be subject to DNA sequencing, which is undertaking in the Department of Pharmacology and Physiology's Core Sequencing Facility located in Ross Hall.

"We believe that research aimed at decreasing the health care costs associated with stabilizing patients' wafarin dosing potentially can work as a preventative measure to decrease the inci-



dence of adverse drug reactions associated warfarin," Dr. O'Brien said.

### Most Newborns in ICUs Often Undergo Painful Procedures Without Pain Medication

An examination of newborn intensive care finds that newborns undergo numerous procedures that are associated with pain and stress, and that many of these procedures are performed without medication or therapy to relieve pain, according to a study in the July 2, 2008 issue of JAMA.

"Repeated invasive procedures occur routinely in neonates [a baby, from birth to four weeks] who require intensive care, causing pain at a time when it is developmentally unexpected. Neonates are more sensitive to pain than older infants, children, and adults, and this hypersensitivity is exacerbated in preterm neonates. Multiple lines of evidence suggest that repeated and prolonged pain exposure alters their subsequent pain processing, long-term development, and behavior. It is essential, therefore, to prevent or treat pain in neonates," the authors write. "Effective strategies to improve pain management in neonates require a better understanding of the epidemiology and management of procedural pain."

Ricardo Carbajal, MD, PhD, of the Hôpital d'enfants Armand Trousseau, Paris, and colleagues collected data on neonatal pain, based on direct bedside observations in intensive care units (ICUs) in the Paris region. The study, conducted between September 2005 and January 2006, included data on all painful and stressful procedures and corresponding analgesic (a medication used to relieve pain) therapy from the first 14 days of admission collected within a six-week period from 430 neonates admitted to tertiary care centers. The average gestational age was 33 weeks, and the average intensive care unit stay was 8.4 days.

During the study period, neonates experienced 60,969 firstattempt procedures, with 42,413 (69.6%) painful and 18,556 (30.4%) stressful procedures; 11,546 supplemental attempts were performed during procedures including 10,366 (89.8%) for painful and 1,180 (10.2%) for stressful procedures. Examples of painful procedures that were performed include nasal and tracheal aspiration (removal of fluid), heel stick and adhesive removal. The average number of all procedures per neonate was 141 and the average number of procedures per day of hospitalization was 16. Each neonate experienced a median (midpoint) of 115 procedures during the study period and 16 procedures per day of hospitalization. Of these, each neonate experienced a median of 75 painful procedures during the study period and 10 painful procedures per day of hospitalization.

Infants received specific analgesia for a median of 20% of the painful procedures performed during the study period. Of the 42,413 painful procedures, 907 (2.1%) were performed with



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### September 2008

pharmacological-only therapy, 7,734 (18.2%) with nonpharmacological-only therapy, 164 (0.4%) with both, and 33,608 (79.2%) without specific pre-procedural analgesia.

Further analysis indicated that prematurity, parental presence during procedures, neonates undergoing surgery, daytime performance (7 a.m. to 6 p.m.), and day of hospitalization (2-14 days) were associated with greater use of specific preprocedural analgesia, whereas mechanical ventilation, noninvasive ventilation, and the administration of nonspecific concurrent analgesia were associated with less frequent use of specific preprocedural analgesia.

"Advances in neonatal care in recent decades with increased survival of immature and sick neonates have led to an increased number of invasive procedures that may cause pain in these vulnerable neonates. The prevention of pain in critically ill neonates is not only an ethical obligation, but it also averts immediate and long-term adverse consequences," the researchers write. "....strategies to reduce the number of procedures in neonates are needed urgently. The American Academy of Pediatrics recently emphasized the need to incorporate a principle of minimizing the number of painful disruptions in neonatal care protocols. Such strategies would aim at bundling interventions, eliminating unnecessary laboratory or radiographic procedures, using transcutaneous measurements when possible, and minimizing the number of procedures performed after failed attempts."

"The knowledge that some vulnerable neonates underwent 153 tracheal aspirations or 95 heel sticks in a two-week period should elicit a thoughtful and relevant analysis on the necessity and the riskbenefit ratio of our clinical practices."

(JAMA. 2008;300[1]:60-70.



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