# Heart Institute

## RESEARCH AND TRAINING DETAILS

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
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<tbody>
<tr>
<td>Faculty</td>
<td>67</td>
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<tr>
<td>Joint Appointment Faculty</td>
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<tr>
<td>Research Fellows</td>
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<tr>
<td>Research Students</td>
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<tr>
<td>Support Personnel</td>
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</tr>
<tr>
<td>Direct Annual Grant Support</td>
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<td>Direct Annual Industry Support</td>
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<tr>
<td>Peer Reviewed Publications</td>
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## CLINICAL ACTIVITIES AND TRAINING

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<thead>
<tr>
<th>Category</th>
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<td>Clinical Staff</td>
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<td>Staff Physicians</td>
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<tr>
<td>Clinical Fellows</td>
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<td>Other Students</td>
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<tr>
<td>Inpatient Encounters</td>
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<td>Outpatient Encounters</td>
<td>19,397</td>
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</table>
Division Publications


Congenital Heart disease - International Study (APPROACH-IS): rationale, design, and methods. *Int J Cardiol.* 2015; 179:334-42.


problematic TnT staining. J Mol Cell Cardiol. 2014;64:45-54.


149. Sawyer JE, Chamberlain AR, Cooper DS. **Pharmacogenomics.** In: R Munoz, EM da Cruz, VL Vetter, DS Cooper,


187. Whiteside W, Christensen J, Zampi JD. Three-dimensional magnetic resonance imaging overlay to assist with percutaneous transhepatic access at the time of cardiac catheterization. Ann Pediatr Cardiol. 2015; 8:150-2.


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Division Publications


Nash D, Neath SX, Nathan M.

Duchenne muscular dystrophy carriers current and future landscape of urinary thromboxane testing to evaluate atherothrombotic risk associated with outcomes after the Norwood procedure SR.


150. Schmidt MR, Redington A, Botker HE. Remote conditioning the heart overview: translatability and mechanism. *Br


MYPN Mutations Affect Medication Effectiveness for Children with Restrictive Cardiomyopathy

particularly in children, restrictive cardiomyopathy (RCM) has the poorest prognosis among heart muscle diseases. The condition can lead to heart failure, arrhythmias and sudden cardiac death, with a 5-year mortality rate exceeding 70 percent.

To date, no medications have proven effective against RCM, which has left heart transplantation as the sole definitive treatment option. Now, fresh clues for finding new therapeutic targets are emerging thanks to a study led by Enkhsaikhan Purevjaj, MD, PhD, a former researcher with the Heart Institute at Cincinnati Children’s who recently moved to the University of Tennessee Health Science Center.

Purevjaj and former research fellow Anne-Cecile Huby, PhD, report that mutations in the myopalladin (MYPN) gene cause diverse cardiomyopathic phenotypes within a critical “final common pathway.” These mutations could explain why ACE inhibitors, beta-blockers and angiotensin receptor blockers are ineffective in patients with RCM. Their findings were published Dec. 30, 2014, in the Journal of the American College of Cardiology.

The study involved developing “knock-in” mice to carry mutations of the murine Mypn gene that would be homologous to the human MYPN-Q529X mutation. At six weeks, signs of restrictive physiology (RP) were detected in the mice carrying the mutation. At 12 weeks, the mice showed signs of impaired diastolic filling of the left ventricle, decreased T-wave duration, and other RCM symptoms.

“From these data, we hypothesize that the RCM phenotype results from persistence of dysfunctional truncated MypnQ526X protein and consequent multiple pathological ‘hits,’ ” Purevjaj says.

MYPN is one of several genes that appear to be involved in RCM. These findings suggest that further studies on time-dependent expression changes in CARP, MLP, DES, and ERK1/2 proteins in patients with RCM may provide useful information for discovering diagnostic and therapeutic targets.
Electrocardiography in WT (A) and mutant (B-D) mice. MypnWT/Q526X mice display arrhythmias (arrows), including (B) premature atrial contractions, (C) premature ventricular contractions, and secondary atrioventricular block (D; 1:7 Wenkebach).

M-mode images of mitral valve (MV) movement (top) indicate an increase of early and late diastolic velocities (E/A) ratios in myopalladin (Mypn) WT/Q526X mice compared with wild-type (WT) mice or homozygotes, which became significant in 12-week-old heterozygote mutants compared with WT and homozygote mice. Cardiac magnetic resonance images (left) demonstrate enlarged left atria in MypnWT/Q526X mice (middle columns) compared with WT (left columns) and MypnQ526X (right columns) mice.
Even with the many advances in surgical repair of complex congenital heart malformations, total anomalous pulmonary venous connection (TAPVC) repair in patients with heterotaxy syndrome carries a high mortality risk, particularly with functionally univentricular physiology.

Some of the most complex heart defects occur in children born with heterotaxy syndrome, in which abdominal organs form on the opposite side of the body. The cardiac lesions that result, which are almost always multiple, can vary widely in severity and potential outcome. An analysis led by David Morales, MD, and colleagues, published April 23, 2015, in the *Annals of Thoracic Surgery* is the first to provide national-level data on the mortality risks that certain patient populations face when receiving TAPVC repairs.

The study examined 261 operations for TAPVC repair in 258 patients from 65 medical centers. Overall, mortality was 38 percent. Heterotaxy patients undergoing TAPVC repair and requiring postcardiotomy ECMO had still higher operative mortality rates.

The findings suggest that early outcomes of TAPVC repair are significantly worse when patients with heterotaxy are in high-risk subgroups such as those who have functionally univentricular physiology.

“It is clear that TAPVC heterotaxy patients are very rare and present with extremely complicated anatomy and physiology that varies with patients, and therefore their care has to be individualized,” Morales says. “However, there are centers that have achieved higher levels of success treating these patients such as ours. The key next steps will be to understand and share best patient management practices, so that through education they can be spread throughout the country to improve outcomes for all of these children.”
Early outcomes of TAPVC repair are significantly worse when patients with heterotaxy are in high-risk subgroups, such as those who have functionally univentricular physiology. This table details outcomes from 261 operations for TAPVC repair involving 258 patients at 65 medical centers.

### OPERATIVE MORTALITY AMONG HIGH-RISK SUBGROUPS IN TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION HETEROTAXY PATIENTS

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Mortality With Risk Factor, n (%)</th>
<th>Mortality Without Risk Factor, n (%)</th>
<th>P Value</th>
<th>Single Ventricle Mortality, n (%)</th>
<th>Non Single Ventricle Mortality, n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic-to-pulmonary artery shunt</td>
<td>38/84 (45)</td>
<td>62/177 (35)</td>
<td>0.134</td>
<td>33/71 (46)</td>
<td>5/13 (38)</td>
<td>0.764</td>
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<tr>
<td>Pulmonary atresia</td>
<td>26/64 (41)</td>
<td>74/197 (38)</td>
<td>0.660</td>
<td>24/51 (47)</td>
<td>2/13 (15)</td>
<td>0.057</td>
</tr>
<tr>
<td>Age at surgery of ≤48 hours</td>
<td>20/54 (37)</td>
<td>80/207 (39)</td>
<td>0.876</td>
<td>17/38 (45)</td>
<td>3/16 (19)</td>
<td>0.122</td>
</tr>
<tr>
<td>Weight at surgery &lt;2.5 kg</td>
<td>13/31 (42)</td>
<td>87/230 (38)</td>
<td>0.696</td>
<td>10/21 (48)</td>
<td>3/10 (30)</td>
<td>0.452</td>
</tr>
<tr>
<td>Infracardiac TAPVC type</td>
<td>24/59 (41)</td>
<td>76/202 (38)</td>
<td>0.761</td>
<td>20/44 (45)</td>
<td>4/15 (27)</td>
<td>0.238</td>
</tr>
<tr>
<td>Postcardiotomy ECMO</td>
<td>13/20 (65)</td>
<td>87/241 (36)</td>
<td>0.015</td>
<td>10/13 (77)</td>
<td>3/7 (43)</td>
<td>0.174</td>
</tr>
<tr>
<td>Concomitant Norwood/DKS procedure</td>
<td>3/3 (100)</td>
<td>97/258 (38)</td>
<td>0.055</td>
<td>3/3 (100)</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

DKS = Damus-Kaye-Stansel; ECMO = extracorporeal membrane oxygenation; TAPVC = total anomalous pulmonary venous connection.

- **a** — Comparison between patients with and without particular risk factor.
- **b** — Comparison between single ventricle and non-single ventricle groups.
A new scientist at Cincinnati Children’s is beginning to unlock the genetic secrets of muscle cell fusion, an advance that could have extensive implications for health.

While working as a post-doctoral fellow at the University of Texas Southwestern in Dallas, Doug Millay, PhD, and his mentor found the only muscle-specific protein known to be essential for fusion of embryonic and adult myoblasts. In a paper published in 2013 in *Nature*, they dubbed the gene “myomaker.” Then in a more recent paper in *Genes and Development*, the team showed that myomaker also is necessary for normal adult muscle cell regeneration.

Their work shows that myogenic basic helix-loop-helix (bHLH) transcription factors induce myomaker expression in satellite cells during acute and chronic muscle regeneration. Moreover, genetic deletion of myomaker in adult satellite cells completely abolishes muscle regeneration, resulting in severe muscle destruction after injury.

The ability of myomaker to promote fusion to adult muscle fibers and muscle regeneration suggests opportunities to enhance muscle repair through myomaker-directed cell-cell fusion. In mice, the myomaker gene can be expressed in non-muscle cells, which then allows these cells to fuse to skeletal muscle. This implies that myomaker might be useful as a delivery vehicle for future therapies to address muscle loss in Duchenne muscular dystrophy, cancer, AIDS, and COPD.

“In all of these conditions, restoring muscle cell growth may likely do even more than impact quality of life,” Millay says. “It could also slow the progression of the disease itself.”

Millay is one of two scientists at Cincinnati Children’s to be named Pew Scholars in 2015. He is continuing his work to more fully understand the machinery of muscle cell development.
This confocal microscopic image shows that expression of the myomaker gene in fibroblasts (green) induces fusion with myoblasts (red) resulting in yellow/orange chimeric myotubes. Recent research shows that myomaker is necessary to promote fusion in skeletal muscle cells during prenatal development and later during the muscle repair process. In mice, myomaker also can be expressed in non-muscle cells, which implies that myomaker could serve as a delivery vehicle for future therapies to address muscle loss in conditions such as Duchenne muscular dystrophy and cancer.