Hong Lab Highlights!

Merging drug discovery, stem cells, and chemical genetics under one lab

The major theme of the research in the Hong laboratory is chemical biology of vertebrate development and stem cell differentiation. In a manner analogous to the classic forward mutagenesis screens, we conduct high-throughput chemical screens in zebrafish for small molecules that specifically perturb embryonic pattern formation. Since some of these compounds will function by promoting development of specific tissue types, an important goal of our research is to develop chemical tools for stem cell research and regenerative medicine. Moreover, since aberrant activities of many developmental pathways play a major role in pathogenesis of variety of postnatal diseases, such as cancer, compounds that modulate them show promise as lead compounds for treatment of variety of human diseases. Using this interdisciplinary approach, we have thus far discovered potent and selective chemical modifiers of bone morphogenetic protein (BMP), Wnt, NF-kB, innate immunity and Hedgehog pathways.

The Hong lab has 3 major areas of basic research: Fellows or graduate students are sought in any of these areas.

**Drug Discovery:** We discovered the world’s first BMP inhibitor, which we named dorsomorphin. Dorsomorphin and its structural
analogs has been successfully used to evaluate the therapeutic potential of BMP inhibitors for anemia of chronic inflammation, a purported billion dollars a year market, and fibrodysplasia ossificans progressiva, a devastating inherited disorder in which affected children become progressively encaged in a “prison of bone.” To develop better drug leads, we conducted one of the first large-scale structure activity relationship (SAR) study in live vertebrates. We are also exploring the potential of novel hedgehog inhibitors as future treatments for chemotherapy resistant medulloblastomas and pancreatic cancers. For this goal, we work very closely with the synthetic chemistry colleagues in the Vanderbilt Program for Drug Discovery.

Directed differentiation of cardiomyocytes from pluripotent stem cells: Using our novel small molecules, we find that we can massively induce formation of cardiac cells in tissue culture. Interestingly, we find that distinct compounds induce cardiac cells in distinct ways. We are using our methods as a platform to study the elusive and diverse nature of progenitor cells that give rise to cardiac cells.

To dissect the mechanism of vertebrate axis formation using chemical genetic approaches: Following high-throughput screening to discover novel small molecules that specifically modulate embryonic patterning, we then utilize the principals of “chemical genetic linkage analysis” to identify molecular targets of these compounds. In addition to discovering novel drugs that target BMP, Wnt, NF-κB and Hedgehog signaling, we hope to discover important new insights into the signaling events involved in the establishment of body axis. Indeed, we have identified novel signaling components that appear to be critical for the establishment of the embryonic body axis.

Translational Projects available in Hong Lab for Fellows or Post-Doc Students

In vitro characterization of cardiac cells engineered from patients with inherited heart diseases. We hypothesize that the revolutionary new advances in genetic reprogramming of adult somatic tissues to make induced pluripotent stem cells (iPSCs) will advance our understanding of human cardiomyopathies by making patient derived-heart tissues accessible to detailed studies. We are currently working on devising robust methods to induce cardiomyocytes from human iPSCs in a rational and consistent manner.

Phenotyping and genotyping of patients with inherited cardiomyopathies. Through our work in the Center for Inherited Heart Disease, we have acquired an impressive list of blood samples from patients with inherited heart conditions. In cases where causal mutation is not found through routine genetic screening, we plan to conduct whole exome Next Generation sequencing to look for novel mutations that cause heart failure. We will utilize our family cohorts as both negative and positive controls, and validate our findings in a larger population using the BioVU.

Heart Tissue Core. Finally, we have generated a sizable collection of heart tissue samples from explanted hearts and congenital heart surgeries. This collection, now maintained by the Division’s Translational Research Core, is available to future research to look for endogenous progenitor cells and for expression profiling, etc.

Cardiovascular Research Day

The second annual cardiovascular research day will be held on April 20th. Do not miss out on a chance to highlight your research and projects. Abstracts for ongoing studies and case reports are due April 14th.

Instructions are found on the cardiology website: http://www.vanderbilthealth.com/cardiovascular/25063
Clinical Research Getting the Flow Down

Have you ever wondered if your patient qualifies for a research study?

Thanks to the help of Dr. Dan Lenihan, Bobbye Wieman, and all the clinical research personnel, clinical research flow-charts will now be posted in clinical areas to heighten awareness about the breadth of clinical research opportunities at VHVI. These flow diagrams are broken down into broad research groups: General Cardiology, Heart Failure, Atrial Fibrillation, Devices, and Interventional/Surgery.

The flow-charts contain the essential inclusion criteria and important contact information (principal investigator and study coordinator). Regular updates will be made to keep the charts up-to-date with active studies. Future plans are to post charts electronically for easy viewing access.

See following pages for flow-charts.

Research Meetings

CV/VHVI Research Meeting
1st Wed. of the mo. 5-6 PM 5053 MCE

HF Research
2nd Tues. of the mo. 12-1 5181 MCE

General Cardiology Research
2nd Tues. of the mo. 12-1 317 PRB

Arrhythmia / Device Research
3rd Fri. of the mo. 7-8 AM CRC conf room 3 MCN

Interventional Research
4th Fri. of the mo. 7-8 AM MCN 5053

Imaging Research
Pending new time and date

Upcoming Fellow Events

March 7th
Bosco’s Dinner with the Applicants

March 8th
2nd Interview Day

April 3rd
Bosco’s Dinner with the Applicants

April 4th
3rd Interview Day

April 15th Book Club
Sawyer House
“Man’s Search For Meaning” by Viktor Frankl

Friesinger Society Meeting
Nashville, TN
April 16-18th
Keynote speaker Sen. Bill Frist
Saturday 17th Hutton Hotel
contact Denise Leveque at 6-3762 to register

What is the Vanderbilt Physician Scientist Development (VPSD) Program?

Vanderbilt has increasingly recognized the formidable challenges facing the career development of successful physician scientists. In particular, the institution has identified the reduced quantity and quality of postdoctoral research training available to junior faculty physician scientists (even M.D./Ph.D.) in comparison to full-time Ph.D. basic scientists who hold the same academic rank. As a means to augment physician scientist career development in the junior faculty years, Vanderbilt has established a Physician Scientist Development (VPSD) Awards Program. The VPSD program is designed to provide an enriching scientific environment and salary support to allow newly-appointed Assistant Professor physicians with significant research experience to receive additional mentored investigative training. Vanderbilt has extensive mentoring resources for physician scientists interested in broad areas of basic science and patient-oriented research.

For more information, check out the website: https://medschool.mc.vanderbilt.edu/vpsd/ DUE DATE March 15th
Diagnosed Heart Failure

- **Energy Starvation Study**
  - To employ PET and CMR to evaluate several determinants of myocardial "energy starvation" in patients with HF due to nonischemic dilated cardiomyopathies
  - PI: Kronenberg
  - SC: White/Nagy

- **ATMOSPHERE**
  - A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of both aliskiren monotherapy and aliskiren/enalapril combination therapy compared to enalapril monotherapy, on morbidity and mortality in patients with chronic heart failure (NYHA Class II - IV)
  - PI: Geisberg
  - SC: Geisberg

- **Walk Study**
  - A prospective, placebo controlled, randomized, pilot study examining the effect of exercise in heart failure patients
  - PI: Geisberg
  - SC: Geisberg

- **FOCUS**
  - Randomized, controlled, phase II, double-blind trial of intramyocardial injection of autologous bone marrow mononuclear stem cells under electromechanical guidance for patients with chronic ischemic heart disease and left ventricular dysfunction
  - PI: Zhao
  - SC: Bowman/Francescon

- **TOPCAT**
  - A multicenter, international, randomized, double-blind placebo-controlled trial of the aldosterone antagonist, spironolactone, in adults with heart failure and left ventricular ejection fraction of at least 45%
  - PI: Naftilan
  - SC: Nagy/White

Preventing Heart Failure

- **Breast Cancer**
  - Patients being treated with Anthracyclines or Her2+

- **Predicting Effects of HF in Breast CA**
  - Predicting HF in patients with breast cancer by levels of early progenitor cells at baseline
  - PI: Sawyer/Geisberg
  - SC: White/Nagy

If you have a patient who may qualify, please contact Study Coordinator (SC) Contact Numbers:
- Sherry Bowman, RN – 615.403.3039
- Rachel Criswell, MS – 615.936.191
- Judy Francescon, RN – 615.403.3880
- Sarah Nagy, RN – 615.343.6238
- Brenda White, RN – 615.936.2458
- PI/SC – Carrie Geisberg, MD - 615.299.6610
Inplanted Device

**Flow chart**

### ICD/CRT/PACEMAKER

**PROVIDE**
- Randomized to specific settings to prevent or prolong time to first shock
- PI – Whalen
- SC/DT – Hale/White

**SC/DT – Hale/White**

**PI – Whalen**

**VHVI Main Heart Registry**
- PI – McPherson
- SC – Criswell/ALL

**ORE-Registry**
- Medical product longevity and performance registry
- PI – Rottman
- SC/DT – Hale/Nagy

**PACEMAKER Study**
- Modulation of QT Interval by Rapid Atrial Pacing in Patients with Dual Chamber Pacemakers
- PI – Darbar
- SC – Richardson
- DT – Hale

**PACEMAKER**

**ICD**

**CRT**

**No CAD/CHF**

**SSS only**

**QT Change with Rapid Pacing**

If you have a patient who may qualify, please contact Study Coordinator (SC) Contact Numbers:
- Rachel Criswell, MS - 615.936.7191
- Leslie Hale (Device Tech) - 615.818.8011
- Sarah Nagy, RN - 615.343.6238
- Rachael Richardson, RN - 615.322.3173
- Brenda White, RN - 615.936.2458
Atrial Fibrillation (AF)

VHVI Main Heart Registry
PI – McPherson
SC – Criswell / ALL

Maze Procedure: Chronic AF

Paroxysmal AFib

No Amiodarone

Registry (Hybrid Procedures)

CABANA
Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation
PI – Darbar
SC – Nagy/White
DT - Hale

Need for Cardioversion

QT Variability Study
Assessing biomarkers of QT variability pre & post AF cardioversion
PI – Darbar
SC – Richardson
DT - Hale

Atrial Fibrillation (AF)

Recurrent AF either treated or not documented Arrhythmia

Fish Oil Study
Randomized placebo controlled trial to see if Fish Oil decreases AF recurrence
PI – Stein
SC – Sullenger

Genetic AF Registry
To study genetics of AF
PI-Darbar
SC-Kucera/Stubblefield

If you have a patient who may qualify, please contact Study Coordinator (SC) Contact Numbers:
Rachel Criswell, MS – 615.936.7191
Leslie Hale, Device Tech - 615.818.8011
Gayle Kucera, RN – 615.936.6069
Sarah Nagy, RN - 615.343.6238
Rachel Richardson, RN – 615.322.3173
Tonya Stubblefield, RN - 615.936.1984
Valerie Sullenger, RN – 615.343.7065
Brenda White, RN – 615.936.2458

2/24/2010
If you have a patient who may qualify, please contact

Study Coordinator (SC) Contact Numbers:
- Lynn Blair-Anton, RN – 615.484.3657
- Sherry Bowman, RN – 615.403.3039
- Michelle Clark, RN – 615.322.9349
- Rachel Criswell, MS – 615.936.7191
- Kim Crum, RN – 615.343.9071
- Mary Gordon, RN – 615.936.8377
- Judy Francescon, RN – 615.403.3880
- Christa LaFontaine – 615.936.6991
- Sarah Nagy, RN – 615.343.6238
- Tami Neal, RN – 615.260.1330
- Brenda White, RN – 615.936.2458

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**Interventional/Surgery Studies**

**Cardiac Catheterization**

**VHVI Main Heart Registry**
- PI – McPherson
- SC – Crum/Clark

**MI/ACS**

**1st Time MI/Non-ST**
- EF 20-45%, no CABG Hx

**1st ST Elevation MI**
- EF ≤ 45%

**Cardiac Surgery**

**CABG (on Pump)**

**BNP Study**
- To measure levels of NPs in the cardiac chambers/vessels
- PI-Monahan
- SC – Blair-Anton

**PREDICT**
- Female, Non-DM-no prior hx of CAD
- One time blood draw to detect genetic factors
- PI-McPherson
- SC – Crum/Clark

**GRAVITAS**
- Gauging Responsiveness with a Verify Now Assay - Impact on Thrombosis and Safety
- 6-Month
- Single or double dose Plavix with a point of care device used to detect platelet inhibition
- PI-Robbin
- SC -Clark/Crum

**DAPT Registries**
- Dual anti-platelet therapy post-stent
- PI – McPherson
- SC – LaFontaine/Clark

**TRACER**
- Randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of a thrombin inhibitor vs standard of care in subjects with ACS
- PI – Cleator
- SC – Gordon/Blair-Anton

**PROCHYMAL**
- Allogeneic cultured adult human mesenchymal stem cells to improve LV dysfunction after MI
- PI-Zhao
- SC – Blair-Anton

**TIME (3-7 days) or Late-Time (14 days)**
- Autologous bone marrow stem cells post MI to prevent/improve LV function
- PI – Zhao
- SC – Francescon/Bowman

**REDCABG**
- AcaDesine vs. placebo to prevent reperfusion ischemia injury during cardioplegia
- PI – McPherson
- SC – Gordon/Blair-Anton

**DETERMINE**
- ICD vs. Usual Care for post MI; EF >35% (>10% scar by MRI)
- PI – Saavedra
- SC – Nagy/Neal
If you have a patient who may qualify, please contact Study Coordinator (SC) Contact Numbers:
Lynn Blair-Anton, RN – 615.484.3657
Rachel Criswell, MS – 615.936.7191
Mary Gordon, RN – 615.936.8377
Beth Meador, NP – 615.936.1641
Sarah Nagy, RN – 615.343.6238
Tami Neal, RN – 615.260.1330

**General Cardiology**

**VHVI Main Heart Registry**
PI – McPherson
SC - Criswell

**Patent Foramen Ovale**

**Hypercholesterolemia**

**Hypertension**
(Systolic bp ≥ 140 and/or diastolic bp of ≥ 90, or on antihypertensives)

**Initiating Warfarin Therapy**

**RESPECT Study**
Randomized evaluation of recurrent stroke comparing PFO closure to established standard of care treatment
PI – Piana
SC – Gordon/Blair-Anton

**ISIS-Extension Study**
An open-label extension study to assess the long-term safety and efficacy of phosphorothioate oligonucleotide in subjects with familial or severe hypercholesterolemia
PI – Linton
SC – Meador

**ALISKIREN**
The effects of renin inhibition on fibrinolytic balance and endothelial function
PI – Muldowney
SC – Neal/Nagy

**COAG Study**
A randomized, multicenter, double-blind clinical trial to evaluate efficacy in the use of clinical plus genetic information to guide warfarin therapy initiation and improve anticoagulation control for patients
PI – Muldowney
SC – Neal/Nagy