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October 2009
Volume 3, Issue 7

The CARE Newsletter



The Cardiovascular and Research Education Newsletter

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Faculty Spotlight

David McManus, MD

Dr. David McManus is a cardiologist and cardiac electro physiologist with broad clinical interests in atrial fibrillation (AF), heart failure, and device and ablative anti-arrhythmic therapies.

Dr. McManus' primary research interest lies in identifying factors influencing atrial structural remodeling as they pertain to risk of AF. He has partnered with Dr. Vasan

Ramachandran of the Framingham Heart Study to examine the clinical correlates of atrial remodeling during adulthood. Dr. McManus has recently had first-author manuscripts accepted examining the relation of kidney disease to risk of AF as well as describing the incidence and prognosis of AF after acute myocardial infarction. He has collaborated with Dr. Lawrence Rosenthal in authoring a chapter on AF treatment and was recently awarded an extramural grant to establish an outcomes registry for patients undergoing catheter-based AF ablation at the University

Campus.

Most recently, Dr. McManus has begun several investigations into adipocytokines (fat-secreted proteins) as potential mediators of cardiac remodeling in obesity and he is partnering with Dr. Robert Goldberg in an effort to examine the relationship between obesity and AF. Dr. McManus is currently pursuing a Masters in Clinical Investigation through the University's Center for Clinical and Translational Sciences.

Recent Publications:

McManus D, Pipkin S, Whooley M. A two-item screen for depression in patients with coronary artery disease: data from the Heart and Soul Study. *Am J Cardiol.* 2005; 96:1076-1081.

McManus D, Aurigemma G. Clinical Advances in Diastolic Heart Failure. *Minerva Cardioangiol.* 2006; 6:695-713.

Hsue PY, McManus D, Selby V, et al. Cardiac arrest in patients who smoke crack cocaine. *Am J Cardiol.* 2007; 99(6): 822-824.

Blauwet LA, Hayes SN, McManus DD, et al. Low rate of sex-specific result reporting in cardiovascular trials. *Mayo Clin Proc.* 2007; 82(2):166-170.

McManus D, Shlipak M, Ix J, et al. Association of cystatin C with poor exercise capacity and heart rate recovery: the heart and soul study. *Am J Kidney Dis.* 2007; 49(3):365-372.

McManus DD, Ockene IS. Brief supported lifestyle counseling: modest interventions yield modest effects. *Arch Intern Med.* 2008; 168(2):129-130.

McManus DD, Mattei ML, Rose K, et al. Inadvertent Lead Placement in the Left Ventricle: A Case Report and Brief Review. *Indian Pacing Electrophysiol J.* 2009; 9(4):224-228

McManus DD, Shah SJ, Fabi MR, et al. Prognostic value of left ventricular end-systolic volume index as a predictor of heart failure hospitalization in stable coronary artery disease: data from the Heart and Soul study. *J Am Soc Echocardiogr.* 2009; 22(2):190-197.

Turakhia MP, McManus DD, Whooley MA, et al. Increase in end-systolic volume after exercise independently predicts mortality in patients with coronary heart disease: data from the Heart and Soul Study. *Eur Heart J.* 2009 Jul 3. [Epub ahead of print].

McManus DD, Rosenthal LS, Robotis DA. Inappropriate shock from nonphysiologic noise during implantation of a Boston Scientific Cognis N119 biventricular implantable cardioverter defibrillator (CRT-D). *Heart Rhythm.* 2009; Epub Feb 12.

Rosenthal L, McManus DD. Atrial Fibrillation. *eMedicine* from WebMD. Updated November 21, 2008. Available at: <http://www.emedicine.com/med/topic184.htm>.

McManus DD, Corteville DC, Shlipak MG, et al. Relation of kidney function and albuminuria with atrial fibrillation (from the Heart and Soul Study). *Am J Cardiol.* 2009; In Press.



Timothy Fitzgibbons,
MD



Dr. Fitzgibbons is a research fellow in the Millenium MD/PhD Program who is conducting research under the mentorship of Dr. Keaney and Dr. Michael Czech. Dr. Czech's laboratory has recently discovered an oral system of siRNA delivery (*Aouadi M et al. Nature Vol 458: 1180-1185, 2009*) that was shown to be effective in

suppressing systemic inflammation. The lab is now using this technology to study its' efficacy in a variety of systemic inflammatory diseases. Dr. Fitzgibbons will be studying the application of this technology to ameliorate atherosclerosis in both *in vitro* and *in vivo* models of disease, specifically the *Apoe*^{-/-} mouse.

Recent Publications:

Fitzgibbons TP, Hardy OT, Lessard D, Gore JM, Yarzebski J, Goldberg RJ. Body Mass Index, Treatment Practices, and Mortality in Patients With Acute Heart Failure. *Coronary Artery Dis* (In Press).

Fitzgibbons TP, Madias C, Seth A, Bouchard JL, Kuvin JT, Patel AR, Pandian NG, Meyer TE, Aurigemma GP, Tighe DA. Right Ventricular Dysfunction in Transient Stress Cardiomyopathy: Prevalence and Clinical Characteristics. *Am J Cardiol*.104(1):133-6, 2009.

Fitzgibbons TP, Meyer TE, Aurigemma GP. Mortality in diastolic heart failure: an update. *Cardiol Rev*. 17(2): 51-55, 2009.

Research Study

Osiris Stem Cell Synopsis_V4

Title of Protocol: A Phase II, multi-center, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of PROCHYMAL® (*ex vivo* cultured adult human mesenchymal stem cells) intravenous infusion following acute myocardial infarction.

Phase: II

Route of Administration: I.V. Infusion

Number of patients planned: 220

Objectives: The objective of the present study is to establish the safety and efficacy of PROCHYMAL® following first acute myocardial infarction.

Study Design:

Approximately 220 subjects will receive a single intravenous infusion of PROCHYMAL® (200 million cells) or placebo for treatment within 7 days following first acute myocardial infarction.

Steven Ball, R.N.



Subjects will be evaluated on days 0 and months 1, 3, 6, 12, 18 and 24 months for efficacy. Safety data will be collected throughout.

Main Criteria for Inclusion:

1. Subject has experienced a first myocardial infarction within 7 days prior to randomization and drug infusion.
2. Subject has a global left ventricular systolic dysfunction with an ejection fraction of $\geq 30\% \leq 45\%$ on initial presentation as determined by quantitative echocardiography using the biplane, modified Simpsons

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- algorithm. LVEF values obtained after reperfusion by other methods can be utilized if quantitative echocardiogram was not performed after reperfusion. Otherwise, quantitative echocardiography will be performed at screening.
3. Subject is male or female ≥ 21 ≤ 85 years of age.
 4. Subject has a body mass between 45kg (100 lbs) and 150kg (330 lbs).
 5. Patient has a luminal diameter narrowing less than 50% and TIMI antegrade flow >1 demonstrated by coronary arteriogram. (Note: a subject who has had thrombolytic therapy or angioplasty/stent placement may be eligible).
 6. Presence of a peak estimation of >4 times upper limit of normal of troponin at any time during the first 72 hours after initial hospitalization for the index MI. If troponin is unavailable, then eligibility may be determined based on a similar elevation of CK-MB.
 7. Subject has been hemodynamically stable within 24 hours prior to randomization. Hemodynamic stability is defined as a 24-hour period in which:
 - a) Patient does NOT need parenteral inotropic support for the maintenance of mean arterial blood pressure ≥ 60 mmHg,
 - b) Patient has systolic blood pressure of ≥ 80 mmHg and can be lower for no longer than 20 minutes,
 - c) Resting heart rate of ≤ 110 beats per minute and can be greater for no longer than one hour,
 - d) Patient does NOT need mechanical ventilation at any time during the acute MI,
 - e) Patient does NOT need cardiopulmonary resuscitation,
 - f) Patient does NOT need intra-aortic balloon pump,
 8. Subject has adequate pulmonary function:
 - a) Forced expiratory volume in 1 second (FEV1) $>50\%$ of predicted,
 - b) Percentage of oxygen saturation in blood (SpO₂) of $\geq 97\%$ as measured by pulse oximetry. For patients requiring oxygen, the peripheral arterial oxygen saturation (SaO₂) should be $\geq 97\%$ when given a maximum of 2L/minute supplemental O₂ via nasal cannula.
- Main Criteria for Exclusion:**
1. Subject has any medical condition, which in the opinion of the Investigator renders his/her participation in this trial unsuitable.
 2. Prior clinical history of:
 - a) Myocardial infarction,
 - b) Cardiomyopathy,
 - c) Congestive heart failure,
 - d) Clinically significant valvular heart disease (this is defined as patients with moderate to severe structural stenosis in any of the left-sided cardiac valves as well as $>2+$ on $4+$ scale of mitral or aortic insufficiency),
 - e) Decompensated heart failure (NYHA Class IV),
 - f) Aortic dissection.
 3. Revascularization via a surgical coronary artery bypass procedure before randomization.
 4. Has or requires an implantable electronic defibrillator, pacemaker, or has other contraindication to MRI scanning.
 5. Evidence of a life-threatening arrhythmia on baseline ECG monitoring (including QTc interval of ≥ 550 ms) as determined by Investigator. Life-threatening arrhythmias include non-sustained ventricular tachycardia (defined as 3 or more consecutive beats arising below the atrioventricular node with a rate > 120 beats/min and lasting less than 30 s) and complete heart block with a pause of ≥ 2 seconds.
 6. Subject has eGFR of ≤ 60 ml/min/1.73m², as estimated by using MDRD4v equation.
 7. Patients who are Killip Class 4 (indicative of cardiogenic shock).
 8. Other Diseases or Conditions including:
 - a) Subject has active infection requiring systemic antibiotic therapy,
 - b) Also includes those with chronic conditions such as hepatitis B, hepatitis C, HIV, or TB. At randomization, HIV-2 tests must have been performed but the results can be pending,
 - c) Subject has significant active chronic inflammatory disease that requires immunosuppressive medication or high dose corticosteroids. This includes but is not limited to, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, scleroderma, sarcoidosis, inflammatory bowel disease, or asthma,
 - d) Evidence of active malignancy, or prior history of active malignancy that has not been in remission for at least 5 years (excluding

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cutaneous basal cell and squamous cell carcinoma).

9. Other Medications or Procedures:

- a) Previous autologous or allogeneic bone marrow transplant, peripheral stem cell transplant or solid organ transplantation,
- b) Subject has received an investigational drug or device for any indication within 30 days of randomization,
- c) Undergone major surgical procedure or major trauma within 14 days prior to randomization,
- d) Subject is currently using mechanical ventilation or has required mechanical ventilation at any time after the MI,
- e) Subject is taking immunosuppressive medication (e.g. azathioprine, 6-mercaptopurine, methotrexate) that has not been at a stable dose for at least 8 weeks prior to screening.

10. Allergies:

- a. Allergies to bovine or porcine products,
- b. Hypersensitivity to dimethyl sulfoxide (DMSO),
- c. Allergies to gadolinium contrast agent.

11. Others exclusion criteria:

- a. A female subject who is breast-feeding, pregnant or intends to become pregnant during the study,
- b. Subject is a man or a woman of child-bearing potential, who refuses to use an acceptable form of contraception,
- c. Subject who has any medical condition that prevents him/her from performing the exercise test on the treadmill,
- d. Subject has a history of alcohol or recreational drug abuse within 6 months prior to randomization,
- e. Subject or legally acceptable representative who will not consent to subject's participation in study.

Duration of Treatment:

Subjects enrolled in the study will be evaluated for safety and efficacy for 24 months following the first infusion. For this adaptive trial, a blinded interim review of the standard deviation calculated from the change in ESV from baseline to 3 months will be performed, after

the 100th patient is evaluated at 3 months, to evaluate the suitability of the sample size for this trial. Interim study reports will be prepared after 6 and 12 months to evaluate safety and efficacy. Subjects will be evaluated for safety and efficacy until death, withdrawal, or 2 years after first Investigational Agent (IA) infusion, whichever occurs first.

- e) Includes those with chronic conditions such as hepatitis B, hepatitis C, HIV, or TB. At randomization, HIV-2 tests must have been performed but the results can be pending,
- f) Subject has significant active chronic inflammatory disease that requires immunosuppressive medication or high dose corticosteroids.

Criteria for Evaluation:

Primary Efficacy Endpoints:

- Left ventricular end systolic volume (ESV) at 3 months

Secondary Efficacy Endpoints:

- Left ventricular end systolic volume at 6 months
- Infarct size as % LV, at 3 and 6 months
- Left ventricular ejection fraction (LVEF) at 3 and 6 months
- Left ventricular end diastolic volume at 3 and 6 months
- Incidence of ventricular arrhythmias at 3, 12 and 24 months
- Physician Global Assessment at 6, 12, and 24 months
- Cardiovascular disease-specific quality of life (DASI) assessment at 6, 12, and 24 months
- NYHA congestive heart failure classification status at 6, 12 and 24 months
- Maximal symptom-limited exercise test (treadmill) at 6 and 12 months
- Time to rehospitalization and hospitalization rates at 6, 12 and 24 months
- MACE endpoints at 6, 12, and 24 months
- BNP at 6, 12 and 24 months

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We're on the Web!

See us at:

www.umassmed.edu/cardio

Safety endpoints:

- Adverse events
- Infusional toxicity

Study Contacts:

Principal Investigator: Daniel Fisher, MD
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Study Coordinator: Steven Ball, RN
Pager # 8357

Cardiovascular Working Group Meeting Schedule

Tuesdays at 5:00 PM, Faculty Conference Room S1-342 University Campus

Date	Speaker	Topic
Oct. 20, 2009	Marcus Cooper, M.D.	Mechanisms and metabolic implications of mitochondria in NAFLD
Nov.10, 2009	Nathan Lawson, M.D.	"Role of microRNAs and flow in shaping the vascular system"

