

Regenerative Medicine Minnesota Progress Report

Grant Title: Graduate Scholar in Regenerative Medicine

Grant Number: MRM 2015 GSCH 003

Requester: Saranya P. Wyles

Project Timeline: May 1, 2015 – April 30, 2016

Brief description: (please describe your course of study or research project)

Globally, the pandemic of heart disease predicts a significant increase in the incidence and prevalence of heart failure, with cardiovascular diseases projected to be the leading cause of death worldwide in the upcoming decades. This project focused on understanding how the heart muscle acquires disease in the setting of an inherited cause known as familial dilated cardiomyopathy, the leading indication for heart transplantation. By bioengineering stem cells from the patient's body, this study characterized the ability of stem cells to differentiate into heart muscle and identify the initial point of divergence from normal heart development. Our laboratory sought to determine whether dysfunctional cardiogenesis, a disruption in the natural process of cardiovascular development, due to a mutation in the patient's gene could play a role in structural and functional maturation of their heart cells. The information gained from these studies could allow us to target molecular therapy at the root cause of familial dilated cardiomyopathy and determine initial defects to better anticipate disease progression.

Outcome: (In 2-3 paragraphs, please explain how the RMM funds impacted your course of study, research project, and/or career path.)

My overall career goal is to work in an academic medical center as a physician scientist with 80% protected research time in stem cell and regenerative biology. There are currently very few female leaders in clinical regenerative medicine in the United States. I hope to add to this number and in doing so, help to lead translation of discoveries using bioengineered stem cell platforms into the clinic while promoting other female scientists to pursue this rewarding career path. The education and experience gained from my thesis research here at Mayo Clinic with mentorship from Dr. Timothy Nelson as well as guidance from Dr. Andre Terzic, Dr. Timothy Olson, Dr. Grazia Isaya and members of our laboratory, has prepared me well for development toward a career as an independent investigator. I look forward to integrating my research experience into the clinical setting and serving as an intermediary between basic science investigation of disease processes and clinical problems that need solutions.

This graduate scholar fellowship was an excellent first step toward becoming a productive independent investigator. Under this training fellowship, I expanded my knowledge in cardiology and stem cell biology as well as gain experience with research collaborations and communicate my work in various settings. My training has allowed me to learn important laboratory techniques and become experienced with the human iPSC model system, and pair this with relevant coursework to complete a clinically relevant research project. Accomplishing these goals has positioned me well for a successful career in translational research.

Please list any of the following that have resulted from your Regenerative Medicine Minnesota grant funding:

MD/PhD Candidate – Thesis Defense, August 2015: Bioengineered Stem Cell-Based Disease Modeling and Therapeutic Approaches for Familial Dilated Cardiomyopathy

Publications and/or manuscripts submitted for publication

1. **Wyles, S.P.**, Li, X., Hrstka, S.C., Reyes, S., Oommen, S., Edwards, J., Terzic, A., Olson, T.M., Nelson, T.J. (2015) Modeling structural and functional deficiencies of *RBM20* familial dilated cardiomyopathy using human induced pluripotent stem cells. (2015) Human Molecular Genetics. PMID: 26604136.
2. Faustino R.S., Behfar A., Groenendyk J., **Wyles S.P.**, Niederlander N., Reyes S., Puceat M., Michalak M., Terzic A., Perez-Terzic C. Calreticulin secures calcium-dependent nuclear pore competency required for cardiogenesis. (2016) Journal of Molecular and Cellular Cardiology. PMID: 26826378.
3. **Wyles, S.P.**, Hrstka, S.C., Reyes, S., Terzic, A., Nelson, T.J. Pharmacological Modulation of Calcium Homeostasis in Familial Dilated Cardiomyopathy: An In Vitro Analysis From an *RBM20* Patient-Derived iPSC Model. (2016) Clinical and Translational Sciences. PMID: 27105042.
4. **Wyles, S.P.**, Terzic, A., Nelson, T.J. Insights from human induced pluripotent stem cell models of cardiovascular disease. (2016) Journal of Cardiovascular Translational Research (in preparation).

Presentations

1. **Wyles SP.** 2015. Patient-specific pluripotent stem cells as tools for cardiovascular disease modeling and drug repurposing. Mayo Clinic-Karolinska Institutet 21st Annual Meeting. Stockholm, Sweden. (Oral Presentation)
2. **Wyles SP,** Hrstka S, Reyes S, Terzic A, Olson TM, Nelson TJ. 2015. Pharmacological modulation of calcium overload in familial dilated cardiomyopathy using human induced pluripotent stem cells. World Stem Cell Summit, Atlanta, GA. (Poster Presentation)

Other grant applications and/or awards

- 2016 **Alumnae Association of Barnard College Fellowship for Graduate Study**
- 2015 **American Association for the Advancement of Science: Excellence in Science** – Nomination by Mayo Clinic Graduate School
- 2016 **Regenerative Medicine Minnesota – Education Program:** Minnesota Medical Student Guide to Proficiency in Regenerative Medicine and Surgery

Responsible Spending:

Please let us know how you spent the money. Any unspent funds must be returned.

Funding was utilized as outlined in the grant (included below). Specifically, the budget covered MD/PhD training stipend and tuition costs. It also supplemented educational expenses including conference travel (World Stem Cell Summit 2015) and medical school testing preparation (National Board of Medical Examination).

	Principal Investigator:	Saranya Wyles	
GRANT TITLE	Utilizing patient-specific stem cells for heart disease modeling		
		START DATE	END DATE
		4/1/2015	3/31/2016
PERSONNEL			
NAME	ROLE ON PROJECT	Year 1	TOTALS
Saranya Wyles	PI/PD	35,150	\$ 35,150
Personnel Subtotal		35,150	
	SUBTOTAL		\$ 35,150
CONSULTANT COSTS			
EQUIPMENT			
SUPPLIES			
TRAVEL			
OTHER EXPENSES			
Tuition		9,850	\$ 9,850
SUBTOTAL DIRECT COSTS		\$ 45,000	\$ 45,000
FACILITIES AND ADMINISTRATIVE COSTS		0%	\$0
TOTAL COSTS		\$45,000	\$ 45,000