BIOGRAPHICAL SKETCH

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NAME: Jason Mathew Butler

eRA COMMONS USER NAME (credential, e.g., agency login): JABUTLER

POSITION TITLE: Associate Scientist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Florida	B.S.	1999-2001	Zoology
University of Florida	M.S.	2001-2002	Molecular Genetics
University of Florida	Ph.D.	2002-2006	Stem Cell Biology
Weill Cornell Medical College	Postdoc	2006-2009	Stem/Vascular Biology
Weill Cornell Medical College	Instructor	2009-2011	Stem/Vascular Biology
Weill Cornell Medical College	Assistant Professor	2011-	Stem/Vascular Biology
Hackensack University Medical College	Associate Scientist	2018-	Regenerative Medicine

A. Personal Statement

My laboratory is dedicated to understanding the role of tissue-specific ECs in establishing unique instructive vascular niche cells that produce the correct milieu and stoichiometry of paracrine factors to direct organ regeneration, in particular within the BM microenvironment and in the context of aging and regeneration. We have assembled large transcriptional profiles from tissue-specific vascular niches that have revealed remarkable heterogeneity within the adult vasculature that is underscored by the production of tissue-specific paracrine factors which we believe are necessary for orchestrating the regeneration of their organ of origin. Based on these data, we are developing novel therapeutic applications and justification for the transplantation of genetically modified BMECs or other cellular sources that are directly reprogrammed into BMECs utilizing a unique set of transcription factors that establish BMEC identity to enhance the regeneration of the BM microenvironment. We hypothesize that reconstitution of hematopoiesis along with an increase in engrafted ECs will not only cooperatively augment both the stability and integrity of the newly formed vessels but also via an inductive mechanism to promote tissue repair and multi-organ regeneration. We expect that the knowledge gained from my laboratory's research goals will have a significant and positive impact on decreasing the morbidity and mortality associated with life threatening pancytopenia that is associated with hematopoietic dysfunction.

B. Positions and Honors

Postdoctoral Training

- December 2005 – July 2006
  Postdoctoral Associate in laboratory of Dr. Edward Scott at the University of Florida Shands Cancer Center

- August 2006 – August 2009
  Postdoctoral Associate in the laboratory of Dr. Shahin Rafii at Weill Cornell Medical College

Faculty Appointments

- September 2009 – September 2011
  Instructor of Genetic Medicine, Weill Cornell Medical College
  Faculty Mentor: Dr. Shahin Rafii

- October 2011– Present
  Assistant Professor of Medicine and the Ansary Stem Cell Institute, Weill Cornell Medical College

- March 2018 – Present
  Associate Scientist, Center for Discovery and Innovation, Hackensack University Medical Center
  Member, John Theuer Cancer Center

- March 2018 – Present
  Member, Lombardi Cancer Center

Honors/Awards/Extramural Activities

1. National Institutes of Health Loan Repayment Program Recipient 07/01/2011 - Present
2. American Society of Hematology Scholar 12/01/2013 - Present
3. American Federation on Aging Research Scholar 07/01/2014 - Present
4. Molecular Cellular Hematology Study Section 01/2017 - Present
5. Professional Memberships
   - American Society of Hematology 2011 - Present
   - International Society of Stem Cell Research 2012 - Present
   - International Society of Experimental Hematology 2012 - Present
   - North American Vascular Biology Organization 2015 - Present
6. Invited Lectures
   - Japanese Society of Hematology in Kyoto, Japan; October 24th, 2009. **Title: The role of the bone marrow microenvironment in normal and malignant hematopoiesis.**
   - Janssen Pharmaceuticals in Fukuoka, Japan; October 25th, 2009 **Title: Bone marrow vascular niche supports the initiation of leukemia and expansion of leukemia initiating cells.**
   - Keystone Symposia (D2) Hematopoiesis. March 28th, 2011. **Title: Inhibition of NFkB signaling in endothelial cells supports the expansion of hematopoietic stem cells.**
   - Cold Spring Harbor Laboratory; Stem Cells Meeting; July 27-August 5, 2012. **Title: Role of angiocrine factors in stem cell maintenance.**
   - National Institutes of Health; Earl Stadtman Lecture; December 11th, 2013. **Title: Vascular regulation of hematopoietic ontogeny.**
   - BMT Tandem Meetings, Plenary Session; February 27th, 2014. **Title: Endothelial cell transplantation for mitigation of radiation-induced hematopoietic suppression.**
   - American Society of Hematology, Niche Interactions, December 7th, 2015. **Title: Endothelial MAPK activation disrupts functional hematopoiesis.**
   - MD Anderson Emil J Freireich Leukemia Hematology Grand Rounds, November 11th, 2015. **Title: Maladaptive bone marrow endothelium and its role in leukemogenesis.**
   - University of Florida Pepper Center on Ageing Center Special Symposium, January 27th, 2016. **Title: The role of endothelium on the life cycle of hematopoietic stem cells.**
   - American Society of Gene and Cell Therapy, Plenary Session, May 5th, 2016. **Title: Vascular Niche Platform to enhance the ex vivo expansion of adult blood products.**

C. Contribution to Science

1. ***Role of Endothelial Cells in Hematopoietic Regulation:*** The long-term goal of my research program is to unravel the mechanisms by which supportive niche cells promote organ regeneration in the hope of translating these therapeutic modalities to repair injured organs. My laboratory has focused on enhancing regeneration of the hematopoietic system in the context of hematological injuries (e.g. myelosuppression) and aging. Our commitment to studying the hematopoietic system is based on the discoveries by our group demonstrating that bone marrow endothelial cells (BMECs) serve as instructive niche cells that are essential for the reconstitution of the hematopoietic system following radiation injury. Our approach

proved that the cellular cross talk between the BM vascular niche and hematopoietic stem cells (HSCs) is largely dependent on the activation state of the ECs. These innovative concepts have lead to a paradigm shift in vascular biology, demonstrating that BMECs are not only essential for the delivery of oxygen, nutrients, and waste disposal, but also function as a specialized vascular niche that, upon proper activation, can instructively support the maintenance and reconstitution of normal HSCs. The concept that ECs provide an instructive fertile niche for maintenance of functional HSCs opens up new avenues for many aspects in stem cell biology and can be applied to multiple biosystems.

a) Poulos MG, Ramalingam P, Gutkin MC, Llanos P, Gilleran K, Rabbaby S, ***Butler JM***. Endothelial transplantation rejuvenates aged hematopoietic stem cell function. *The Journal of Clinical Investigation.* 2017 Nov 1;127(11):4163-4178. doi: 10.1172/JCI93940.
b) Poulos MG, Ramalingam P, Gutkin MC, Kleppe M, Ginsberg M, Crowley MJ, Elemento O, Levine RL, Rafii S, Kitajewski J, Greenblatt MB, Shim JH, ***Butler JM***. Endothelial-specific inhibition of NF-κB enhances functional haematopoiesis. *Nature communications.* 2016; 7:13829.
c) ***Butler JM***, Nolan DJ, Vertes EL, Varnum-Finney B, Hooper AT, White IA, Seandel M, Kobayashi H, Kobayashi M, Falciatori I, Lui B, Zhu Z, Witte L, May C, Shawber C, Kimura Y, Kitajewski J, Rosenwaks Z, Bernstein ID, and Shahin Rafii. Endothelial cells are essential for the self-renewal and repopulation of Notch-dependent hematopoetic stem cells. *Cell Stem Cell.* 6:251-64, 2010.
d) ***Butler JM***, Kobayashi H, O'Donnell R, Kobayashi M, Ding B, Bonner BR, Chiu VK, Nolan DJ, Shido K, Benjamin L, and Rafii S. Angiocrine factors from Akt-activated endothelial cells balance self-renewal and differentiation of haematopoietic stem cells. *Nature Cell Biology.* 12:1046-56, 2010.

2. ***Role of Endothelial Cells in Specifying Definitive HSCs:*** My laboratory is currently aiming to identify relevant paracrine factors and metabolites found within the BM vascular niche cells that modulate self-renewal and expansion of adult HSCs and to develop strategies to enhance hematopoietic reconstitution in the clinical arena. In addition to studying the role of the ECs in regulating adult hematopoiesis, we are interrogating the ability of embryonic vascular niches to induce and expand definitive HSCs from pluripotent stem cell (PSC) sources *(collaboration with Irwin Bernstein at the Fred Hutchinson Cancer Research Center)*. In order to determine the optimal embryonic vascular niche for the induction and expansion of embryonic-stage hematopoietic stem/progenitor cells (HSPCs), we have developed methods to isolate and culture ECs from numerous fetal (e.g. E11 AGM, E10.5 placenta, E13.5 fetal liver) and adult (e.g. bone marrow) hematopoietic tissues. Furthermore, we have developed an effective, novel platform to expand adult BM macaque CD34+ LT-HSCs and iPSC-HSPCs on human ECs that have high levels of engraftment in NSG mice *(collaboration with Hans-Peter Kiem at the Fred Hutchinson Cancer Research Center)*. This evidence substantiates our novel approach to enhance definitive HSPCs through direct contact cultures with pro-hematopoietic signals unique to ECs. It is our long-term goal to deconstruct the critical stage-specific signal pathways differentially required for induction and expansion of HSCs from embryonic sources as well as enabling the use of patient-specific cells to safely treat their hematological deficiencies.

a) Lis R, Karrasch CC, Poulos MG, Kunar B, Redmond D, Duran JGB, Badwe CR, Schachterle W, Ginsberg M, Xiang J, Tabrizi AR, Shido K, Rosenwaks Z, Elemento O, Speck NA, ***Butler JM***, Scandura JM, Rafii S. Conversion of adult endothelium to immunocompetent haematopoietic stem cells. *Nature.* 2017 May 17. doi: 10.1038/nature22326.
b) Gori JL, ***Butler JM***, Kunar B, Poulos MG, Ginsberg M, Nolan DJ, Norgaard ZK, Adair JE, Rafii S, Kiem HP. Endothelial Cells Promote Expansion of Long-Term Engrafting Marrow Hematopoietic Stem and Progenitor Cells in Primates. *Stem Cells Transl Med.* 2017 Mar;6(3):864-876.
c) Gori JL, ***Butler JM***, Chan YY, Chandrasekaran D, Poulos MG, Ginsberg M, Nolan DJ, Elemento O, Wood BL, Adair JE, Rafii S, Kiem HP. Vascular niche promotes hematopoietic multipotent progenitor formation from pluripotent stem cells. *J Clin Invest.* 2015 Feb 9. pii: 79328. doi: 10.1172/JCI79328.

d) Sandler, V.M., Lis, R., Liu, Y., Kedem, A., James, D., Elemento, O., ***Butler, J.M.***, Scandura, J.M., & Rafii, S. Reprogramming human endothelial cells to haematopoietic cells requires vascular induction. *Nature.* 2014 July 2. doi:10.1038/nature13547.

3. Role of SDF-1 in Aberrant Neovascularization: In December 2005, I received my PhD from the University of Florida's Interdisciplinary Program in Biomedical Sciences, specializing in the hematopoietic stem cell and its role in regenerative medicine. Under the tutelage of Dr. Edward Scott we developed a unique mouse model that mimicked the pathology seen in diabetic retinopathy. Using this model, we found that the adult hematopoietic stem cell could give rise to a subset of cells, known as endothelial progenitor cells (EPCs), which were necessary for the pathological angiogenesis seen in diabetic retinopathy. We explored the role of the stromal cell-derived factor 1 (SDF-1)/CXCR4 axis in promoting the recruitment of bone marrow-derived EPCs to the retina and found that if we block this axis we were able to ameliorate and block the aberrant angiogenesis. Additionally, I explored the role of BM-derived EPC in promoting the initiation and progression of solid tumors. Using SDF-1 as a therapeutic target, we found that not all tumors were dependent on the SDF-1/CXCR4 axis. However, tumors that were dependent on SDF-1 were effectively targeted when SDF-1 was neutralized by treatments.

a) ***Butler JM***, Guthrie SM, Koc M, Afzal A, Caballero S, Brooks HL, Mames RN, Segal MS, Grant MB, Scott EW. SDF-1 is both necessary and sufficient to promote proliferative retinopathy. *Journal of Clinical Investigation. 115:86-93, 2005.*
b) ***Butler JM***, Madlambayan GJ, Hosada K, Fu D, Guthrie SM, Shenoy AK, Brank A, Russel KJ, Otero J, Siemann DW, Scott EW, and Cogle CR. Bone marrow stem and progenitor cell contribution to neovasculogenesis is dependent on model system with SDF-1 as a permissive trigger. *Blood.* 114:4310-9, 2009.
c) Sengupta N, Caballero S, Mames RN, ***Butler JM***, Scott EW, Grant MB. The role of adult bone marrow-derived stem cells in choroidal neovascularization. *IVOS.* 44: 4908-13, 2003.

My Bibliography for complete publication list:
http://www.ncbi.nlm.nih.gov/sites/myncbi/125NJi8P3K0QL/bibliograpahy/47556296/public/?sort=date&direction=ascending

D. Research Support

Current Research Support

1) Sponsored Research Agreement 8/1/2013 -7/31/2020
Principle Investigator: Butler, JM Angiocrine Bioscience
Project Goal: Organ-specific vascular niches maintain their tissue-resident stem cells.

2) Tri-Institutional Stem Cell Initiative 8/1/2014 – 7/31/2019
Principal Investigator: Butler, JM
Project Goal: Endothelial mTOR signaling regulates hematopoietic stem cell aging.
The overall goal of this research project is to determine if disruption of the Akt/mTOR signaling axis in ECs will deprive the hematopoietic system of proper EC-derived instructive signals that maintain the hematopoietic system.

3) Leukemia and Lymphoma Society Quest For Cures 7/1/2017 – 9/1/2019
Principle Investigator: Butler, JM
Project Goal: Rejuvenation of vascular niches to treat age-related hematopoietic malignancies.
The long-term objective of this LLS Quest for Cures proposal is to determine if age-related alterations in the bone marrow vascular niche promotes the development of myeloid leukemia.

4) Consortia to Accelerate Therapeutic Applications of Stem Cells 6/1/2015– 5/31/2019
(PI: Rafii/Sadelain; NYSTEM): Co-PI Butler, JM
Project Goal: The overarching goal of this proposal is to breach current obstacles to the cure of SCD using a novel vascular niche platform to expand genetically-modified, autologous long-term hematopoietic stem cells (LT-HSCs) on a clinically relevant scale.

5) 1R01CA204308-01 04/01/16-03/31/21
Principal Investigator: Butler, JM
Project Goals: Modulating signaling pathways in endothelial cells to abate leukemic progression.
The overall goal of this research project is to determine how physiological aging of the bone marrow (BM) vascular niche results in a dysregulation of signaling pathways that leads to the disruption of the cellular cross talk between the BM vascular niche and the hematopoietic stem cell. In this proposal, we aim to define the mechanisms by which age-related alterations to the BM vascular niche can enhance the progression of hematopoietic malignancies.

6) 1R01HL133021-01 09/01/16—08/31/20
Principal Investigator: Butler, JM
Project Goal: Modulating endothelial-specific signaling to enhance functional hematopoiesis.
The major goal of this research proposal is to study the role of NF-kB signaling in bone marrow endothelial cells BMECs ***1)*** protects the HSC from radiation induced DNA and cellular damage, ***2)*** helps maintain and restore the proper metabolic profile during hematopoietic regeneration, ***3)*** rejuvenates the BM vascular niche and hematopoietic system by transplanting properly activated BMECs, and ***4)*** enhances the expression of novel pro-hematopoietic factors that promote homeostatic and regenerative hematopoiesis.

7) Tri-Institutional Stem Cell Initiative 8/1/2017 – 7/31/2019
Role: Principal Investigator
Project Goal: Alterations in Endothelial-Mitochondrial UPR Signaling Drives Hematopoietic Stem Cell Aging.
The overall goal of this research project is to determine if aged ECs have altered mitochondria that leads to the improper release of pro-HSC EC-derived instructive signals.

Completed Research

1) Tri-Institutional Stem Cell Initiative 8/1/2013 – 6/30/2015
Principal Investigator: Tri-SCI Institute

2) NHLBI PCBC–Ancillary Projects/U01HL099997-8496 8/1/2013 – 6/31/2015
Co-Investigator (PI: Michael Terrin): National Institutes of Health

3) American Federation for Aging Research 7/1/2014 – 6/30/2015
Principal Investigator: AFAR

4) Junior Faculty Scholar Award 7/1/2014– 6/30/2016
Principal Investigator: American Society of Hematology