# BIOGRAPHICAL SKETCH

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NAME: Mangino, Martin J.

eRA COMMONS USER NAME (agency login): mangino

POSITION TITLE: Professor of Surgery

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

| INSTITUTION AND LOCATION | DEGREE (if applicable) | Completion Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Michigan State University, E. Lansing, MI | BS | 06/1981 | Physiology |
| Michigan State University, E. Lansing, MI | PHD | 06/1985 | Physiology and Pharmacology |
| Washington University School Medicine, St. Louis, MO | Postdoctoral Fellow | 06/1987 | Biochemistry (John Turk) |
| Washington University School Medicine, St. Louis , MO | Postdoctoral Fellow | 06/1987 | Transplantation Biology (C.B. Anderson) |

## A. PERSONAL STATEMENT

My laboratory studies the molecular mechanisms of ischemia and reperfusion injury in two major clinical manifestations: 1.) Organ preservation for transplantation and 2.) Trauma, Shock, resuscitation injury, and critical illness. We use the entire spectrum of tools from cell and molecular biology to pre-clinical models and clinical studies including everything in between. This recent program began 8 years ago from ideas, principles, and concepts that were mastered in organ preservation but applied to severe hemorrhagic shock and resuscitation. Specifically, we determined that lethal cell swelling and its resolution through the use of simple ideal cell impermeants was a crucial component of organ preservation injury. I then added various cell impermeants to low volume I.V. resuscitation solutions to test this mechanism in ischemia during low volume shock states since most cell impermeants are nontoxic. Our labs remarkable success in this area has led to the hypothesis that ischemia-induced cell and tissue swelling and the secondary microvascular effects are as important in shock as in preservation injury of transplanted organs. This study explores these mechanisms in detail to validate the pharmacological and physiological attributes of these impermeant agents in severe hypovolemic shock and how best to deploy them in the field. My lab is most qualified to accomplish this project because of my training in ischemia and microcirculation, contributions and understanding of similar volume control mechanisms in organ preservation injury, and because of the dramatic results and significance of our foundational studies and background data. Finally, my network of colleagues at VCU with state-of-the-art technology and training in intravital microscopy and spectroscopy, and in experimental MR Imaging will be key to understanding these proposed mechanisms and testing the hypothesis.


1. Lee CY, Mangino MJ. Preservation methods for kidney and liver. Organogenesis. 2009 Jul;5(3):105-12. PubMed PMID: 20046672; PubMed Central PMCID: PMC2781089.
2. Arora TK, Malhotra AK, Ivatury R, Mangino MJ. L-arginine infusion during resuscitation for hemorrhagic shock: impact and mechanism. J Trauma Acute Care Surg. 2012 Feb;72(2):397-402. PubMed PMID: 22439203; PubMed Central PMCID: PMC3752159.
3. Parrish D, Lindell SL, Reichstetter H, Aboutanos M, Mangino MJ. Cell Impermeant-Based Low-Volume Resuscitation in Hemorrhagic Shock. Annals of Surgery, 2015 Apr 24. [Epub ahead of print]; PMID: 25915911
4. Parrish D, Plant V, Lindell SL, Limkemann A, Reichstetter H, et al. New Low Volume Resuscitation Solutions Containing PEG-20k. J Trauma Acute Care Surg, 2015 Jan;79(1):22-9; PMID: 26091310

## B. POSITIONS AND HONORS

### Positions and Employment

| | |
|---|---|
| 1987 - 1989 | Instructor, Washington University, School Medicine, St. Louis , MO |
| 1989 - 1994 | Assistant Professor, Washington University , School of Medicine, St. Louis, MO |
| 1994 - 1999 | Director of Research, Miami Children's Hospital, Department of Critical Care Medicine, Miami, FL |
| 1999 - 2000 | Associate Professor, Mt. Sinai Medical Center and Miami Heart Institute, Department of Research, Miami Beach, FL |
| 2000 - 2005 | Senior Scientist and Research Professor, University of Wisconsin, Department of Organ Transplantation, Medical School, Madison, WI |
| 2005 - | Professor, Virginia Commonwealth University, Medical College of Virginia Campus, Richmond, VA |

### Other Experience and Professional Memberships

| | |
|---|---|
| 1983 - 1985 | NIH Pre-Doctoral Fellow, Michigan State University |
| 1987 - | Regular Member, American Physiological Society (Cardiovascular, GI, and Renal Sections) |
| 1990 - 1994 | Member, American Heart Association (Council of Basic Cardiovascular Sciences) |
| 1990 - 1994 | Member, American Chemical Society (Biological Chemistry Section) |
| 2003 - | Editorial Board Member, Transplantation |
| 2003 - | Regular Member, American Society of Transplantation |
| 2003 - | Reviewer, NIH Study Section (ad hoc): Bioengineering CPR (BMRP) |
| 2006 - | Reviewer, NIH Study Section-Physiology NIGMS SCORE Program |
| 2009 - | Director, VCU Initiative for Organ Donation and Organ Preservation |
| 2009 - | Reviewer, US Army Grant CDMRP |
| 2009 - | Reviewer, Swiss Academy of Sciences Grant Program |
| 2010 - | Reviewer, NIH Study Section (Special Emphasis Panel) Comparative Effectiveness Research to Optimize Prevention and Healthcare Management for the Complex Patient |
| 2010 - | Regular Member, American Society of Transplant Surgeons (ASTS) |
| 2011 - | Director, Division of Acute Injury and Repair, Virginia Commonwealth University Reanimation Engineering Sciences Center (VCURES) |
| 2013 - | Director of Research, VCU Trauma Center and Division of Acute Care Surgery |
| 2014 - | Associate Member, Eastern Association for the Surgery of Trauma (EAST). |

### Honors

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|---|---|
| 1983 | Awardee, American Gastroenterological Association (AGA) Research Award, Awardee |
| 1987 | American College of Angiology, Fellow (FACA) |

## C. Contribution to Science

1. MEDIATORS OF INTESTINAL ISCHEMIA: It is my hypothesis that splanchnic ischemia and reperfusion injury drives secondary ailments of circulatory shock including decompensated irreversible shock, sepsis, and critical illness in post-trauma surgical ICU patients. The most compelling evidence for this comes from patients and animals that recover from lethal hemorrhagic shock after bowel extirpation or after intraluminal oxygenation of the gut. Early on, I sought to elucidate a biochemical mechanism that drove reperfusion injury in ischemic gut. A comprehensive evaluation of lipid mediator metabolism in intestinal ischemia and in mononuclear cells infiltrating severely injured bowel was accomplished. 5-lipoxygenase products of arachidonate metabolism were found to be key mediators. This work also led to the characterization and discovery of both a high and a low affinity class of platelet activating receptors on the surface of T-Lymphocytes, which serve as late effectors in mucosal reperfusion injury. The ultimate goal is to increase

the bowel tolerance to ischemic injury during shock by understanding the biochemical mediators causing it to facilitate recovery at resuscitation.

a. Mangino MJ, Anderson CB, Murphy MK, Brunt E, Turk J. Mucosal arachidonate metabolism and intestinal ischemia-reperfusion injury. Am J Physiol. 1989 Aug;257(2 Pt 1):G299-307. PubMed PMID: 2504053.

b. Turk J, Bohrer A, Stump WT, Ramanadham S, Mangino MJ. Quantification of distinct molecular species of the 2-lyso metabolite of platelet-activating factor by gas chromatography-negative-ion chemical ionization mass spectrometry. J Chromatogr. 1992 Mar 27;575(2):183-96. PubMed PMID: 1629294.

c. Mangino MJ, Murphy MK, Weiss A, Anderson CB. Characterization of platelet-activating factor receptors on canine T lymphocytes. J Immunol. 1993 Nov 15;151(10):5310-8. PubMed PMID: 8228226.

d. Mangino MJ, Murphy MK, Anderson CB. Effects of the arachidonate 5-lipoxygenase synthesis inhibitor A-64077 in intestinal ischemia-reperfusion injury. J Pharmacol Exp Ther. 1994 Apr;269(1):75-81. PubMed PMID: 8169854.

2. ARACHIDONIC ACID METABOLISM IN RENAL ALLOGRAFT REJECTION: The role of arachidonic acid derived lipid mediators of inflammation, especially 5-lipoxygenase products, were determined in cellular rejection of renal allografts.Stable isotope dilution mass spectrometry assays were developed to mesure lipoxygenase products of arachidonic acid metabolism in renal allograft tissue undergoing acute cellular rejection. These studies demonstrated increases in most lipoxygenase products, especially 5-lipoxygenase derived LTB4 and thiol ether leukotrienes. The functional effects of these metabolites were confirmed with non-selective and selective pharmacological inhibitor studies in rejecting renal allografts. Selective 5-lipoxygenase inhibition increased rejection times of renal allografts, which was attributable to inhibition of leukotriene synthesis. The goal was to identify selective pro-inflammatory mediator pathways upregulated during cellular rejection that could be amenable to pharmacological inhibition. The hypothesis was that downregulation of these pathways would potentiate the effectiveness of conventional immunosuppressive protocols in patients. Selective thromboxane inhibition unmasked a large vasoconstriction during cellular rejection that was not involved appreciably in either the rejection response or the functional decline during cellular rejection. Mixed lymphocyte reaction studies confirmed that 5-lipoxygenase metabolites and alkyl ether phospholipids (PAF) significantly activated T-lymphocyte function and DTH like responses.

a. Mangino MJ, Anderson CB, Deschryver K, Turk J. Arachidonate lipoxygenase products and renal allograft rejection in dogs. Transplantation. 1987 Dec;44(6):805-8. PubMed PMID: 2827351.

b. Mangino MJ, Jendrisak MD, Brunt E, Anderson CB. Eicosanoid synthesis inhibition and renal allograft function during acute rejection. Transplantation. 1988 May;45(5):902-7. PubMed PMID: 3130697.

c. Mangino MJ, Brunt EM, Von Doersten P, Anderson CB. Effects of the thromboxane synthesis inhibitor CGS-12970 on experimental acute renal allograft rejection. J Pharmacol Exp Ther. 1989 Jan;248(1):23-8. PubMed PMID: 2643702.

d. Jendrisak M, Mangino M, Peters S, Anderson C. Modulation of arachidonic acid metabolism and cytotoxic T lymphocyte function. Transplant Proc. 1989 Feb;21(1 Pt 1):174-7. PubMed PMID: 2784891.

3. IMMUNOLOGICAL CONTROL OF THE HEPATIC-PULMONARY MACROPHAGE AXIS IN CRITICAL ILLNESS: My collaborations with a transplant immunologist produced a series of works that describe the unique biochemical signaling of liver Kupffer cells during immunological challenge from gut derived stimuli such as LPS and enteric antigens. We studied the mechanisms of the unique suppressor role played by the Kupffer cell and how disarray of this system may result in secondary target organ injury (ARDS) following intestinal ischemia and shock. We introduced for the first time, the concept of the intestinal-hepatic-pulmonary tissue macrophage axis and its role in producing secondary injuries in shock and trauma, such as ARDS and critical illness due to a breach in the intestinal septic barrier. This work also describes a mechanistic basis for the development of critical illness in patients with liver failure, liver disease, or compromised liver function

a. Callery MP, Kamei T, Mangino MJ, Flye MW. Organ interactions in sepsis. Host defense and the hepatic-pulmonary macrophage axis. Arch Surg. 1991 Jan;126(1):28-32. PubMed PMID: 1985633.

b. Callery MP, Mangino MJ, Flye MW. A biologic basis for limited Kupffer cell reactivity to portal-derived endotoxin. Surgery. 1991 Aug;110(2):221-30. PubMed PMID: 1858031.

c. Roland CR, Goss JA, Mangino MJ, Hafenrichter D, Flye MW. Autoregulation by eicosanoids of human Kupffer cell secretory products. A study of interleukin-1, interleukin-6, tumor necrosis factor-alpha, transforming growth factor-beta, and nitric oxide. Ann Surg. 1994 Apr;219(4):389-99. PubMed PMID: 8161265; PubMed Central PMCID: PMC1243156.

d. Hafenrichter DG, Roland CR, Mangino MJ, Flye MW. The Kupffer cell in endotoxin tolerance: mechanisms of protection against lethal endotoxemia. Shock. 1994 Oct;2(4):251-6. PubMed PMID: 7757516.

4. MECHANISMS OF ORGAN PRESERVATION INJURY: A significant contribution to science and interest is the molecular and cellular mechanisms of hypothermic preservation injury of donor organs recovered for transplantation. The main areas of interest have been in stress signaling pathways (ischemic preconditioning), the role of the allograft microenvironment in preservation injury of kidneys, machine perfusion preservation technology and engineering, and the role of the cytoskeletal system in causally mediating preservation injury in kidneys and livers during hypothermic preservation. Recent advances have shown that the sub-lamellar cytoskeletal system plays an important role in preservation injury of epithelial rich organs like kidney and liver. Moesin failure in liver seems to play a major role in liver preservation injury and possibly in ischemic cholangiopathy, which is a significant road block to using DCD donors. Programs to recover livers from uncontrolled DCD donors is also active by using novel cell impermeant treatment of donors immediately after death.
   a. Gilligan BJ, Woo HM, Kosieradzki M, Torrealba JR, Southard JH, et al. Prolonged hypothermia causes primary nonfunction in preserved canine renal allografts due to humoral rejection. Am J Transplant. 2004 Aug;4(8):1266-73. PubMed PMID: 15268727.

   b. Compagnon P, Lindell S, Ametani MS, Gilligan B, Wang HB, et al. Ischemic preconditioning and liver tolerance to warm or cold ischemia: experimental studies in large animals. Transplantation. 2005 May 27;79(10):1393-400. PubMed PMID: 15912109.

   c. Mangino MJ, Tian T, Ametani M, Lindell S, Southard JH. Cytoskeletal involvement in hypothermic renal preservation injury. Transplantation. 2008 Feb 15;85(3):427-36. PubMed PMID: 18301334.

   d. Tian T, Lindell SL, Kowalski C, Mangino MJ. Moesin functionality in hypothermic liver preservation injury. Cryobiology. 2014 Aug;69(1):34-40. PubMed PMID: 24836372;

5. CELL IMPERMEANTS AND LOW VOLUME RESUSCITATION, HEMORRHAGIC SHOCK, AND CRITICAL ILLNESS: Previous work in organ preservation describing the contribution of the components of UW solution discovered the significance of cell swelling as a major causal mechanism. The effectiveness of cell impermeant molecules to probe the derangement of energy dependent water movement during tissue ischemia conclusively demonstrated how important water accumulation was. Effective and simple preservation of organs from hypothermia or ischemia could be seen using simple solutions containing cell impermeant molecules that load into the interstitial space to pull water out of cells during ischemia-induced shut down of the Na/K ATPase. Since these agents are generally non-toic and biolchemically inert and since tissue ischemia suffered during hypovolemic shock should also cause cell swelling, I decided to use high concentrations of cell impermenats in low volume ressuscitation solutions to test the hypothesis that cell swelling is causally involved in low volume ischemia during shock in trauma patients. My laboratory has hence described in detail the huge therapeutic effects of various species of cell impermenats with unique and well described biophysical attributes. We are able to increase the golden hour after severe hypovolemic shock 10 fold with hybrid impermeant polymers, compared to saline or hetastarch controls. In addition to revolutionizing volume resuscitation in pre-hospital, Emergency Departments, and critical care ICU settings, the results force us to re-examine the major causal factors of shock and resuscitation injury to tissues and organs. We now must place much more weight to primary cell swelling and secondary effects on microcirculatory exchange function during the low flow state and after resuscitation.
   a. Parrish D, Lindell SL, Reichstetter H, Aboutanos M, Mangino MJ. Cell Impermeant-Based Low-Volume Resuscitation in Hemorrhagic Shock. Annals of Surgery, 2015 Apr 24. [Epub ahead of print]; PMID: 25915911

   b. Parrish D, Plant V, Lindell SL, Limkemann A, Reichstetter H, et al. New Low Volume Resuscitation Solutions Containing PEG-20k. J Trauma Acute Care Surg, 2015 Jan;79(1):22-9; PMID: 26091310

## D. RESEARCH SUPPORT

### Ongoing Research Support

2012/09/01-2015/08/30
W81XWH-12-1-0599, Department of Defense
Mangino, Martin J. (PI)
Low volume resuscitation with cell impermeants
This project explores the effects of cell impermenats used in low volume resuscitation solutions in severe hemorrhagic shock. This project led to the preliminary data for this proposal
Role: PI

2016/01/01 – 2018/12/31
Department of Defense
Renewal of W81XWH-12-1-0599
Mangino, Martin J. (PI)
Polyethylene glycol polymers in low volume resuscitation

### Completed Research Support

2010/09/01-2014/08/31
R01 DK087737, National Institutes of Health
Mangino, Martin J. (PI)
The cytoskeletal system in preservation injury
This project explores the role of the ERM system functionality in causally contributing to renal preservation injury in cellular, molecular, and whole organ models of hypothermic preservation injury.
Role: PI