BIOGRAPHICAL SKETCH

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NAME: Rena Feinman, PhD

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

POSITION TITLE: Associate Scientist (equivalent to Associate Professor), Department of Biomedical Research

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 Toronto, Toronto, Canada	BS	1981	Microbiology
Hebrew University-Hadassah Medical School, Jerusalem, Israel	MS	1983	Microbiology
Sackler Institute of Basic Science New York University School of Medicine, New York, NY	PhD	1988	Microbiology
Memorial Sloan-Kettering Cancer Center, New York, NY	Postdoctoral Fellow	1992	Laboratory of Biochemical Genetics

A. Personal Statement

Over the last 22 years, my research has transitioned from identifying nuclear factor kappa B (NFκB) as an underlying factor for primary drug resistance in multiple myeloma (MM) to understanding how ischemia and inflamed gut acts as a motor in the development of the systemic inflammatory response syndrome and acute respiratory distress syndrome. Since 2003, I have been fortunate to have a productive collaboration with Dr. Deitch, who pioneered the gut-origin hypothesis of sepsis and multiple organ failure and Dr. Semenza, a leading expert in the biology of hypoxia-inducible factor (HIF). As a PI and co-investigator on NIH and non-NIH funded grants, my research has primarily focused on delineating the mechanisms underlying the maladaptive HIF-1 and TLR4 mediated responses in abdominal trauma-shock animal models.

My research investigating how mucosal insults drive systemic inflammation and multiple organ failure has provided me with the insight, versatility and expertise needed for defining the pathogenic mechanisms of intestinal GVHD from the “gut” perspective. In 2013, I was recruited by Dr. Korngold, Chairman of the Department of Biomedical Research, to identify gut-protective and reparative strategies to limit early, conditioning- and graft-versus-host disease (GVHD)-induced intestinal injuries that culminate in the development of systemic GVHD. The recent discoveries that gut bacteria relay their signals distally and shape anti-tumor immunosurveillance has captivated us to question the impact of the gut microbiome in modulating response in high-risk MM patients treated with consolidation immunotherapy in the post-transplant setting.

Our proposed translational studies are being done in collaboration with Dr. Biran and Dr. Siegel, leaders in the development of novel, cutting-edge immunotherapies for MM patients and management of one of the largest MM clinics in the US. In parallel, our mechanistic studies are being done in collaboration with Dr. Korngold, an expert in T cell biology and Dr. Ericsson, Director of the University of Missouri Metagenomics Center (Colombia MO) and a leading expert in mouse models for fecal microbiota transplantation studies.

Selected References

1. Feinman R, Koury J, Thames M, Barlogie B, Epstein, J, Siegel DS. 1998. Role of NF-κB in the rescue of multiple myeloma cells from glucocorticoid-induced apoptosis by Bcl-2. Blood 93:3044-3052. PMID: 10216101. (Corresponding and senior author)
2. Koury J, Deitch EA, Homma H, Abungu B, Gangurde P, Condon MR, Lu Q, Xu DZ, Feinman R. 2004. Persistent HIF-1α activation in gut ischemia / reperfusion injury: potential role of enteric bacteria. Shock 22(3):270-277. PMID: 15316398.
3. Feinman R, Deitch EA, Watkins AC, Abungu B, Colorado I, Kannan KB, Sheth S, Caputo FJ, Lu Q, Ramanathan M, Attan S, Badami CJ, Doucet D, Barlos D, Bosch-Marce M, Semenza GL, Xu DZ. HIF-1 mediates pathogenic inflammatory responses to intestinal ischemia reperfusion injury. 2010. Am J Physiol Gastrointest Liver Physiol. 299(4):G833-843. PMID:20689059. (Corresponding and senior author)
4. Kannan KB, Colorado I, Reino D, Palange D, Lu Q, Qin X, Abungu B, Watkins A, Caputo FJ, Xu DZ, Semenza GL, Deitch EA, Feinman R. Hypoxia-inducible factor plays a gut-injurious role in intestinal ischemia reperfusion injury. 2011. Am J Physiol Gastrointest Liver Physiol. 300(5):G853-861. PMID:21183660.
5. Reino DC, Pisarenko V, Palange D, Doucet D, Bonitz RP, Lu Q, Colorado I, Sheth SU, Chandler B, Kannan KB, Ramanathan M, Xu DZ, Deitch EA, Feinman R. 2011. Trauma hemorrhagic shock-induced lung injury involves a gut-lymph-induced TLR4 pathway in mice. PLoS One. 6(8):e14829. PMID:21829592

B. Positions and Honors

Positions and Employment

1988-1992	Postdoctoral Fellow, Laboratory of Biochemical Genetics, Memorial Sloan-Kettering Cancer Center, New York, NY
1992-1995	Research Associate, Laboratory of Biochemical Genetics, Memorial Sloan-Kettering Cancer Center, New York, NY
1995-1998	Assistant Professor, Department of Medicine, Myeloma and Transplantation Research Center, University of Arkansas for Medical Sciences, Little Rock, AR
1999- 2000	Adjunct Assistant Professor, Department of Surgery, UMDNJ-New Jersey Medical School, Newark, NJ
2000-2009	Assistant Professor, Department of Surgery, UMDNJ-New Jersey Medical School, Newark, NJ
2009-2013	Associate Professor, Department of Surgery, UMDNJ-New Jersey Medical School, Newark, NJ
2013-Pres	Volunteer Associate Professor, Department of Surgery, Rutgers University-New Jersey Medical School, Newark, NJ
2013-Pres	Associate Scientist, Department of Biomedical Research, Hackensack Meridian Health, Hackensack, NJ
2017-Pres	Member, Experimental Therapeutics, Lombardi Comprehensive Cancer Center, Georgetown University School of Medicine
2018-Pres	Associate Professor, Department of Medical Sciences, Hackensack Meridian School of Medicine at Seton Hall University, Nutley, NJ
2018-Pres	Adjunct Associate Professor, Department of Oncology, Georgetown University School of Medicine, Georgetown, DC

Honors and Awards

1983	Hebrew University-Hadassah Medical School, M.S with distinction
1986	First Annual Graduate Student Research Presentation Competition, New York City Branch, American Society of Microbiology-Second Prize
1986-1988	National Institutes of Health Training Grant, Predoctoral Fellowship
1988-1991	American Cancer Society, Postdoctoral Fellowship
1991-1992	Leopold Schepp Foundation Award
1993-1995	The New York Community Trust, Grant for Blood Diseases (PI)
1996-1997	International Myeloma Foundation, Brian D. Novis Research Grant for Multiple Myeloma (PI)
2000	Dr. Ira Wolmer Multiple Myeloma Foundation of the Fidelity Investments Charitable Gift Fund
2000-2003	NIH/NCI R01CA85604 (PI)
2001-2003	State of New Jersey Commission of Cancer Research (Co-Inv)

2002-2005 NIH/NCI (Co-Inv)
2003-2004 UMDNJ Foundation Award (PI)
2004-2007 Celgene Corporation (Co-I)
2004-2008 NIH/NIGMS R01GM59841 (Co-Inv)
2006-2012 NIH/NIGMS P50 GM069790 (PI, Project IV)
2009-2013 NIH/NIGMS R01GM59841 (Co-Inv)

Scholarly and Teaching Activities

2001-2013 Department of Surgery, Rutgers-New Jersey Medical School, Newark, NJ
Research Training of surgical residents (12 PGY3s), postdoctoral fellows (2), medical students (6), graduate students (1) and undergraduate students (2).

2013-Pres Department of Biomedical Research, Hackensack University Medical Center, Hackensack, NJ
Research Training of medical students (1), undergraduate students (3), MSc thesis student from Stevens Institute of Technology, Hoboken NJ.

2007-Pres Ad Hoc Reviewer for PNAS, J. Immunol, Frontiers in Tumor Immunity, J Mol Med, Crit Care Med and Shock.

2014-Pres Member of American Society of Hematology

2015-Pres Member of Lombardi Comprehensive Cancer Center Clinical Research Committee

C. Contribution to Science

1. As a postdoctoral fellow and research associate in Dr. Ravetch's at Memorial Sloan Kettering Cancer Center, I investigated the molecular basis for myeloid-specific and interferon-γ (IFN-γ) inducible-gene transcription of the low- affinity Fc receptor for IgG (FcγRIII) and high-affinity Fc receptor for IgG (FcγRI). My work contributed to defining the first STAT transcriptional response element and DNA binding protein, namely the binding of STAT1 to the gamma-activating sequence (GAS) that induced FcγRI expression upon IFN-γ treatment. Since this discovery, there have been more than 6 other STATs described as transcriptional regulators of the cytokine response. I also identified a myeloid cell specific transcription factor, PU.1 that regulated FcγRIII expression in macrophages. PU.1 is now recognized as an essential transcriptional regulator of myeloid and B cell-specific genes involved in hematopoiesis.

- Luster AD, Weinshank RL, Feinman R, Ravetch JV. 1988. Molecular and biochemical characterization of a novel γ-interferon-inducible protein. J Biol Chem. 263;12036-12043. PMID: 3136170
- Pearse RN, Feinman R, Ravetch JV. 1991. Characterization of the promoter of the human gene encoding the high affinity IgG receptor: Transcriptional induction by gamma-interferon is mediated through common DNA response elements. Proc. Natl. Acad. Sci. USA 88:11305-11309. PMID: 1837149
- Pearse RN, Feinman R, Shuai K, Darnell JE Jr., Ravetch JV. 1993. Interferon-γ induced transcription of the high-affinity Fc receptor for IgG requires assembly of a complex that includes the 91-kDa subunit of transcription factor ISGF3. Proc. Natl. Acad. Sci. USA, 90; 4314-4318. PMID: 8483949
- Feinman R, Qui WQ, Pearse RN, Nikolaczyk BS, Sen R, Sheffery M, Ravetch JV. 1994. PU.1 and HLH family member contribute to the myeloid-specific transcription of the FcγRIIIA promoter. EMBO J., 13; 3852-60. PMID: 8070412

2. During my four years as an Assistant Professor at the Myeloma and Transplantation Research Center, University of Arkansas for Medical Sciences in Little Rock, my lab was among the first to describe the central role of NFκB in MM and the regulation of apoptosis. I identified NFκB as a clinically relevant therapeutic target and predictive factor in determining the patient's clinical response to glucocorticoid-based therapy. More importantly, this discovery led to the development of proteasome inhibitors in the treatment of MM patients. This research resulted in an award from the International Myeloma Foundation in 1997 and a NCI-funded R01 in 2000.

- Feinman R, Koury J, Thames M, Barlogie B, Epstein, J, Siegel DS. 1998 Role of NF-κB in the rescue of multiple myeloma cells from glucocorticoid-induced apoptosis by Bcl-2. Blood, 93; 3044-52. PMID: 10216101.
- Siegel DS, Zhang X, Feinman R, Teitz T, Zelenetz A, Richon VM, Rifkind RA, Marks PA, Michaeli J. 1998. Hexamethylene bisacetamide induces programmed cell death (apoptosis) and down-regulates Bcl-2 expression in human myeloma cells. Proc. Natl. Acad. Sci. USA, 95:162-6. PMID: 9419346.
- Feinman R, Siegel DS, Berenson J. 2004.Regulation of NF-κB in Multiple Myeloma: Therapeutic implications. Clin Adv Hematol Oncol. 2:162-166. PMID: 16166946

- Feinman R, Sawyer JR, Hardin J and Tricot G. (1997) Cytogenetics and molecular genetics in multiple myeloma. Hematol Oncol Clin North Am.11:1-25. PMID: 9081201

3. Having moved to New Jersey in 2000, I joined the Department of Surgery at UMDNJ-New Jersey Medical School in Newark, as an Assistant Professor. Not being a major site for MM research and having access to patient samples, I decided to make the transition to investigating the molecular basis of the intestinal mucosal response to gut ischemia reperfusion (I/R) injury. A major conceptual contribution to trauma research was that HIF-1 acted as a proximal signaling mediator in the induction of gut injury during I/R states and transduced the hemodynamic gut I/R insult into a systemic inflammatory state leading to acute lung injury. Additionally, we documented for the first time that bacteria and LPS induced the expression of HIF-1α in intestinal epithelial cells upon reoxygenation and the intestine upon reperfusion.

From 2000-2013, I had a productive collaboration with Dr. Deitch, Chairman of the Department of Surgery, that shed light on potential mechanisms linking intestinal injury to the development of acute lung injury. Our work implicated toll-like receptor-4 (TLR4) and nitric oxide signaling pathways in the development of lung injury in response to circulating factors in the mesenteric lymphatics after gut I/R injury. Additionally, my work with Dr. Harrison, from 2001-2006, as a co-investigator, identified NFκB as a therapeutic target in the treatment of colon cancer cells with differentiation inducers. As a PI and co-investigator, my research was supported by both NIH and non-NIH funds as well as funds from the Pharma sector. In 2009, I was promoted to Associate Professor of Surgery.

I have also been fortunate to contribute in the mentoring of surgical residents and postdoctoral fellows in my lab and Department of Surgery. Several lab residents had oral presentations and received awards for their research at national and international trauma and shock society meetings. Additionally, I have mentored numerous medical and graduate students.

- Koury J, Deitch EA, Homma H, Abungu B, Gangurde P, Condon MR, Lu Q, Xu DZ, Feinman R. 2004. Persistent HIF-1α activation in gut ischemia / reperfusion injury: potential role of enteric bacteria. Shock 22(3):270-277. PMID: 15316398
- Feinman R, Deitch EA, Watkins AC, Abungu B, Colorado I, Kannan KB, Sheth S, Caputo FJ, Lu Q, Ramanathan M, Attan S, Badami CJ, Doucet D, Barlos D, Bosch-Marce M, Semenza GL, Xu DZ. HIF-1 mediates pathogenic inflammatory responses to intestinal ischemia reperfusion injury. 2010. Am J Physiol Gastrointest Liver Physiol. 299(4):G833-843. PMID:20689059
- Kannan KB, Colorado I, Reino D, Palange D, Lu Q, Qin X, Abungu B, Watkins A, Caputo FJ, Xu DZ, Semenza GL, Deitch EA, Feinman R. Hypoxia-inducible factor plays a gut-injurious role in intestinal ischemia reperfusion injury. 2011. Am J Physiol Gastrointest Liver Physiol. 300(5):G853-861. PMID:21183660
- Reino DC, Pisarenko V, Palange D, Doucet D, Bonitz RP, Lu Q, Colorado I, Sheth SU, Chandler B, Kannan KB, Ramanathan M, Xu DZ, Deitch EA, Feinman R. 2011. Trauma hemorrhagic shock-induced lung injury involves a gut-lymph-induced TLR4 pathway in mice. PLoS One. 6(8):e14829. PMID:21829592
- Reino DC, Palange D, Feketeova E, Bonitz RP, Xu da Z, Lu Q, Sheth SU, Peña G, Ulloa L, De Maio A, Feinman R, Deitch EA. 2012. Activation of toll-like receptor 4 is necessary for trauma hemorrhagic shock-induced gut injury and polymorphonuclear neutrophil priming. Shock 38 (1):107-114. PMID:22575992

4. In 2013, I joined the Department of Biomedical Research at Hackensack University Medical Center. Given my expertise in the biology of HIF, mucosal immunology and systemic inflammation, our lab sought to determine if the inability of the gut to regenerate drives the local and systemic deleterious effects of GVHD. We began to investigate whether HIF-1 and HIF-2 play gut-protective roles in limiting conditioning- and alloreactive T cell-induced gut damage in allogeneic BMT mouse models. Using both genetic and pharmacologic approaches, we observed that epithelial HIF-1 and HIF-2 protected the intestinal stem cell niche from GVHD-induced injury and mitigated systemic GVHD. The discovery that intestinal stem cells (ISC) are instrumental in repairing and regenerating a damaged gut and the successful generation of “mini-gut” organoid cultures have prompted us to hypothesize that transplantation of a BMT recipient with ISCs from a related donor would repair conditioning-induced gut damage and mitigate GVHD severity. Our current studies suggest that mice administered with “mini-gut” organoid cultures from a mismatched donor post-BMT were able to engraft in the colon and mitigate the early stages of acute GVHD.

- Oral Presentation at 56th ASH Annual Meeting, Dec 2014. Feinman R, Colorado I, Zilberberg J, Sreedhar A, Dziopa E, Dzipoa L, Yang Z and Korngold R. Intestinal Epithelial HIF-1 Plays a Protective Role in Gut Graft Versus Host Disease. Blood 2014, 124:539

- Zilberberg J, Feinman R, Korngold R. 2014. Strategies for the Identification of T Cell Recognized Tumor Antigens in Hematological Malignancies for Improved Graft-versus-Tumor Responses Following Allogeneic Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 21(6): 1000-1007. PMID:254559643
- Poster Presentation at 58th ASH Annual Meeting, Dec 2016. Feinman R, Colorado I, Wang K, Dzopia E, Flynn MA, Peters K, Pecora AL and Korngold R. Inhibition of HIF Prolyl Hydroxylases Mitigate Gut Graft-Versus-Host Disease. Blood 2016, 128:3349

5. A major focus in our lab is to identify novel microbiota-associated immunomodulatory biomarkers that predict response to combination therapy, disease-free survival and overall survival. We are investigating whether heterogeneity of progression-free survival and overall survival in MM patients treated with various immunotherapies relate to differences in the composition of the gut microbiome. Longitudinal analysis of the gut microbiome is being performed on stool samples collected from MM patients prior to transplant, at engraftment, during treatment, follow-up and at relapse. In parallel, we seek to understand how gut microbiota modulate tumor burden and survival in response to various immunotherapies in several preclinical MM mouse models. We are currently funded to investigate the impact of the gut microbiome on modulating pathologic complete response in triple negative breast cancer patients treated with standard of care neoadjuvant chemotherapy.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1x9esg6M4B7AZ/bibliograpahy/47563745/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

Breast Cancer Research Foundation 10/01/2018-9/30/19
"Gut and Intratumoral Microbiome Effect on the Neoadjuvant Chemotherapy-induced Immunosurveillance in Triple Negative Breast Cancer"
Main Goal: Determine whether differences in the gut and intratumoral microbial composition contribute to the heterogeneity of anti-tumor T cell adaptive response in triple negative breast cancer patients receiving neoadjuvant chemotherapy.
Role: PI
Co-PI: Leslie Montgomery

Breast Cancer Research Foundation 04/01/2017-9/30/18
"Gut Microbiome Effect on Neoadjuvant Chemotherapy-Induced Immunosurveillance in Triple Negative Breast Cancer"
Main Goal: Determine whether differences in the gut microbial composition contribute to the heterogeneity of anti-tumor T cell adaptive response in triple negative breast cancer patients receiving neoadjuvant chemotherapy.
Role: PI
Co-PI: Leslie Montgomery

Completed Research (Past 5 years)

Georgetown Lombardi & John Theurer Cancer Center RACIIT Funding N Biran (PI) 02/01/17-1/31/18
"Microbiome Effect on Immunotherapeutic Responses in High-Risk Multiple Myeloma"
Main Goal: Determine whether correlation between gut microbiota and improved response is predictive for the resolution of T cell exhaustion in the post-transplant consolidation setting.
Role: Co-Investigator

Georgetown Lombardi and John Theurer Cancer Center "CaRe Initiative" Award 02/01/16-01/31/17
"Intestinal stem cell therapy for gut graft-versus-host disease"
Main Goal: Determine if ISCs from the donor will repair gut GVHD and mitigate systemic GVHD severity in allogeneic BMT mouse models.
Role: PI
Co-PI: Steven Singer

NCI R01 CA154244-10 R Korngold (PI) 04/01/13-05/31/15
"T cell repertoire of graft-versus-host disease and graft-versus-leukemia effects"
Main Goal: To delineate the mechanisms of donor T cell-mediated immunopathology of the gut in relation after manipulation of extracellular matrix proteins.
Role: Co-Investigator