BIOGRAPHICAL SKETCH

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NAME: Pranela Rameshwar

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

POSITION TITLE: Professor

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
Univ of Wisconsin-Madison, WI	B.S.	1985	Medical Microbiology
Rutgers University	Ph.D.	1993	Biology
New Jersey Medical School	Post Doc	1993-1995	Hematopoiesis

A. Personal Statement

I have a multi-disciplinary background that covers stem cell biology, hematopoiesis, immunology, aging and breast cancer. Beginning with my doctoral thesis, I studied bone marrow biology and hematopoietic dysfunction, and along with my mentors, coined the term neural-hematopoiesis axis. I applied my scientific background to investigate how breast cancer cells survive as dormant cells in the bone marrow and then determine what causes the dormant breast cancer cells to resurge as metastatic cancer. Our main conclusions are: i) Acquired dormancy occurs when breast cancer cells dedifferentiate into cancer stem cells (CSCs), which is facilitated by bone marrow niche cells. A main mechanism by which this occurs is the release of microvesicles from mesenchymal stem cells (MSCs). Based on these findings, we surmised that tissue niche conducts similar effects to facilitate breast cancer dormancy in other organs; ii) 3D bioprinting of a structure/organoid of the bone marrow using different cell types, including breast cancer cells, indicated cell-autonomous method by which the cancer cells dedifferentiated into CSCs; iii) Examine how epigenes can be interrogated to chemosensitize dormant breast cancer cells. In my quest to target CSCs, I developed a preclinical model to show how combination of NFκB (Bortezomib) and DMNT (azacytidine) inhibitors can succeed. In order to use MSCs in the clinic, I have focused on their immune response and to show their effectiveness as cellular vehicle of drugs including crossing the blood brain barrier. I have leveraged my expertise in hematopoiesis to identify methods to reverse the aging hematopoietic system in humanized mice. This technology has now proved to be effective in humans. I have applied my seminal research on neural-hematopoietic axis to understand how secretome from glioblastoma influence the bone marrow for their survival.

I have a long history of mentoring post-doctoral fellows; students in the MD/Ph.D., Ph.D. and Masters of Science programs; undergraduate students from colleges and medical students; high school students; residents; clinical fellows and junior faculty. Several of the trainees from my lab are principal investigators at academic centers including Universities, Biotechnology and Pharmaceutical Companies. More than >90% of the trainees remain in science.

Ongoing active projects that I would like to highlight include:

Av Regen
Rameshwar (PI)
2012-2023
“Restoration of aged stem cells”
The goal is to study the mechanisms by which cellular interactions could cause functional changes in aged hematopoietic stem cells.

National Academy of Science
Rameshwar (PI)
2018-2023
Engineered mesenchymal stem cells as a therapeutic strategy in glioblastoma for targeting the initiating stem cells

WR II Biotech
2020-2024
Rameshwar (PI)
Immuno-aging research

R25-HL150544
2020-2025
Multi-PI: Rameshwar, Fitzhugh & Fraidenraich
Multidisciplinary Summer Research Education Program for Health Professional Students

METAvivor
Rameshwar (PI)
2021-2023
"Preventing epigenetic-mediated DNA repair induced by bone marrow niche cells to prevent drug resistance"

Rameshwar (PI)
2022-2024
"Towards precise treatment for metastatic breast cancer in black patients"

Citations:

- Potian JA, Aviv H, Ponzio NM, Harrison JS, **Rameshwar P**. Veto-like activated of mesenchymal stem cells (MSC): Functional discrimination between cellular responses to alloantigen and recall antigens. *J Immunol* 171:3426-34, 2003. PMID:14500637
- Munoz JL, Bliss SA, Greco SJ, Ramkissoon SH, Ligon KL, **Rameshwar P**. Delivery of functional anti-miRNA-9 by mesenchymal stem cells-derived exosomes to Glioblastoma Multiforme conferred chemosensitivity. *Mol Ther - Nucleic Acids* 2:e126, 2013. PMID: 24084846
- Sherman LS, Shyam A. Patel SA, Marianne D. Castillo MD, Rachel Unkovic R, Marcelo Taborga M, Gergues M, Patterson S, Etchegaray J-P, Jaloudi M, Nehra A, Kra J, Rojas DP, Victor T. Chang VT, **Rameshwar P**. NFκB targeting in bone marrow mesenchymal stem cell-mediated support of age-linked hematological malignancies. *Stem Cell Rev Reports* 17:2178-2192, 2021. PMID:34410592
- Greco SJ, Ayer S, Guiro K, Sinha G, Donnelly RJ, El-Far MH, Sherman LS, Kenfack Y, Pamarthi SH, Gergues M, Sandiford OA, Schonning MJ, Etchegaray J-P, **Rameshwar P**. Restoration of aged hematopoietic cells by their young counterparts through instructive microvesicle release. *Aging* 13:23981-24016, 2021. PMID:34762598

B. Positions, Scientific Appointments, and Honors

Positions and Employment

1995-2001 Assistant Professor, Rutgers (formerly UMDNJ), New Jersey Med. Sch, Dept. of Medicine-Hem/Onc, Newark, NJ.
2001-2007 Associate Professor (tenure), Rutgers, New Jersey Med Sch, Dept of Medicine-Hem/Onc, Newark, NJ.
2007- Professor, Rutgers, New Jersey Med. Sch, Dept of Medicine-Hem/Onc, Newark, NJ.
2014- Member, Rutgers Cancer Institute of New Jersey
2016- Adjunct Professor, Dept of Biomedical Science, New Jersey Institute of Technology, Newark, NJ.
2018- Appointment, East Orange Veteran's Hospital, Div of Hematology/Oncology

Honors

1983-1985 World Health Scholar
1984 Phi Beta Kappa, Univ of Wisconsin-Madison, WI
1990 Walter Russel Award, Rutgers Univ, Newark, NJ
2005 Rutgers (formerly UMDNJ) Master Educator
2006 Faculty of the Year Award, Rutgers New Jersey Medical School
2015 Mentor of the Year Award, Rutgers New Jersey Medical School
2018 Outstanding Scientist, Edward J. Ill Excellence in Medicine, NJ

2020 Distinguished Career Award, Faculty Org, Rutgers, New Jersey Medical School

Other Experience and Professional Membership

2000- Member, Rutgers School of Graduate Studies
2003- Member, Rutgers-New Jersey Institute of Technology Combined Grad Program in Biomed Eng.
2/02-2010 Member, Rutgers Integrative Neuroscience Graduate Program.
2004- Member, Institutional Animal Care and Use Committee, New Jersey Medical School.
2007- Research Integrity Committee Member, Newark Campus.

Scientific Societies: Am Assoc of Immunol; Am Soc of Hematol; Am Assoc for Cancer Res

Grant Reviewer: >20 International Study Sections (including on site reviews for European Scientific Foundation, Strausbourg, France); Institutional Grants; NIH; Susan G. Komen Breast Cancer Foundation; California Breast Cancer Res Program; HHMI Fellow Program; American Heart Assoc; DOD Breast Cancer Program; Am Instit Biol Sci-Stem Cell Characterization

Key Opinion Leader: Roche (for stem cell)

Scientific Advisory Boards (Current): New Amsterdam Sci; Celvive; ImmuTrix

Editor in Chief: Breast Cancer – Targets and Therapy**;** Intl J Stem Cell Res and Transpl; J Cancer Stem Cell

Senior Editorial Board: Am J Cancer Research; Hematology/Leukemia

Series Editor: Research and Business Chronicles: Biotechnology & Medicine

Editorial Boards: >35 International/Peer-reviewed Journals

C. Contributions to Science

1. Developing neural-hematopoiesis axis: I started my scientific career and continue to investigate the role of tachykinins and their receptors in mediating the neural-hematopoietic axis (a term coined by my mentor and me). This expanded the field of neuroendocrine-immune axis with the addition of hematopoiesis. Publications from these studies are consider to be seminal for the field. Along with other research projects on bone marrow failure (myelofibrosis and aplastic anemia), I have developed a strong understanding of the bone marrow microenvironment, resulting in a new area of research to reverse the aged hematopoietic system.

a) **Rameshwar P**, Ganea D, Gascón P. *In vitro* stimulatory effect of substance P on hematopoiesis. *Blood* 81:391-8, 1993. PMID:7678516
b) **Rameshwar P**, Gascón P. Substance P (SP) mediates production of stem cell factor and interleukin-1 in bone marrow stroma: Potential autoregulatory role for these cytokines in SP receptor expression and induction *Blood* 86:482-90, 1995. PMID:7541664
c) **Rameshwar P**, Joshi DD, Yadav P, Gascón P, Qian J, Chang VT, Anjaria A, Harrison JS, Xiaosong S. Mimicry between neurokinin-1 and fibronectin may explain the transport and stability of increased substance P-immunoreactivity in patients with bone marrow fibrosis. *Blood* 97: 3025-31, 2001. PMID:11342427
d) Gergues M, Nagula V, Bliss SA, Eljarrah A, Ayer S, Gnanavel N, Sinha G, Wu Q, Yehia G, Greco SJ, Qian J, **Rameshwar P**. Neuroimmune/Hematopoietic axis with distinct regulation by the High Mobility Group Box 1 in association with tachykinin peptides. *J Immunol* 204:879-891, 2020. PMID:31924647

2. Adult Stem Cell-Derived Neurons: In order to understand the molecular interaction between bone marrow and the neural system, it was necessary to develop an *in vitro* model to represent both organs. This led to other studies to generate functional neurons from adult human mesenchymal stem cells (MSCs). These studies began early (2001) during the `infancy' period of MSC biology. We have continued these studies with the goal of identifying small molecules for endogenous neuronal development.

a) Greco SJ, **Rameshwar P**. Enhancing effect of IL-1α on neurogenesis from adult human mesenchymal stem cells: Implication for inflammatory mediators in regenerative medicine. *J Immunol* 179:3342-50, 2007. PMID:17709551
b) Trzaska KA, Kuzhikandathil EV, **Rameshwar P**. Specification of a dopaminergic phenotype from adult human mesenchymal stem cells. *Stem Cells* 25:2797-808, 2007. PMID:17656644
c) Greco SJ, **Rameshwar P**. MiRNAs regulate synthesis of the neurotransmitter substance P in human mesenchymal stem cell-derived neuronal cells. *Proc Natl Acad Sci USA* (Track II) 104:15484-9. 2007. PMID:17855557
d) Patel N, Klassert TE, Greco SJ, Patel SA, Munoz JL, Reddy BY, Bryan M, Campbell N, Kokorina N, Sabaawy HE, **Rameshwar P**. Developmental regulation of *TAC1* in peptidergic-induced human

mesenchymal stem cells: Implication for spinal cord injury in zebrafish. *Stem Cell Dev* 21:308-320, 2012. PMID:21671725

3. Breast Cancer Dormancy in Bone Marrow: My experience in bone marrow biology led to other studies in the laboratory to develop appropriate models of breast cancer dormancy in the bone marrow.

a) Singh D, Joshi DD, Hameed M, Qian J, Gascón P, Maloof PB, Mosenthal A, **Rameshwar P**. Increased expression of preprotachykinin-I and neurokinin receptors in human breast cancer cells. Implications for bone marrow metastasis. *Proc. Nat'l Acad. Sci. USA* (Track II) 97:388-93, 2000. PMID: 10618428
b) Rao G, Patel PS, Idler SP, Maloof P, Gascon P, Potian JA, **Rameshwar P**. Facilitating role of preprotachykinin-I gene in the integration of breast cancer cells within the stromal compartment of the bone marrow: A model of early cancer progression. *Cancer Res* 64: 2874-81, 2004. PMID: 15087406
c) Patel H, Ramkissoon SH, Patel PS, **Rameshwar P**. Transformation of breast cells by truncated neurokinin-1 receptor is secondary to activation by preprotachykinin-I peptides. *Proc Natl Acad Sci USA* (Track II) 102:17436-41, 2005. PMID: 10618428
d) Moharita AL, Taborga M, Corcoran KE, Bryan M, Patel PS, **Rameshwar P**. SDF-1α regulation in breast cancer cells contacting bone marrow stroma is critical for normal hematopoiesis. *Blood* 108:3245-52, 2006. PMID:16857992

4. Bone marrow microenvironment in Breast Cancer Dormancy: In order to understand breast cancer dormancy in the bone marrow, I studied the role of MSCs because these cells are located throughout the bone marrow and they can influence immune functions to facilitate the survival of dormant breast cancer cells. Also, an understanding of the immune property of MSCs is significant to develop treatment such as treating inflammatory diseases and as cellular vehicle for drug delivery, including brain tumors. More recent studies showed a link between MSCs and macrophages in support of dormancy/resurgence of breast cancer.

a) Patel SA, Meyer J, Greco SJ, Corcoran KE, Bryan M, **Rameshwar P**. Mesenchymal stem cells protect breast cancer cells through regulatory T cells: Role of mesenchymal stem cell-derived TGF-β. *J Immunol* 184:5885 -5894, 2010. PMID:20382885
b) Walker ND, Elias M, Guiro K, Bhatia R, Greco SJ, Bryan M, Gergues M, Sandiford OA, Ponzio NM, Leibovich SJ, **Rameshwar P**. Exosomes from differentially activated macrophages influence dormancy or resurgence of breast cancer cells within bone marrow stroma. *Cell Death Dis* 10:59, 2019. PMID:30683851
c) Sandiford OA, Donnelly RJ, El-Far M, Williams LM, Sinha G, Pamarthi SH, Sherman LS, Ferrer AI, DeVore DE, Patel SA, Naaldijk Y, Alonso S, Barak P, Bryan M, Ponzio NM, Narayanan R, Etchegaray JP, Kumar R, **Rameshwar P**. Mesenchymal stem cell exosomes instruct breast cancer cells to undergo a stepwise dedifferentiation process towards dormancy at bone marrow perivascular region. 81:1567-1582, 2021. PMID:33500249
d) Sinha G, Ferrer AI, Ayer S, El-Far MH, Parmarthi SH, Naaldijk Y, Barak P, Sandiford OA, Bibber BM, Yehia G, Greco SJ, Jiang J-G, Bryan M, Kumar R, Ponzio NM, Etchegaray J-P, **Rameshwar P**. Specific N-cadherin-dependent pathways drive human breast cancer dormancy in bone marrow. *Life Sci Alliance* 4:e202000969, 2021. PMID:34078741

5. Stratification of Breast Cancer Cell Subsets & Bone Marrow Secretome in Dormancy: In order to understand breast cancer dormancy, I have developed methods to stratify breast cancer cells based on relative maturity, keeping in mind that these cells are transformed. I first selected subsets based on *Oct4A* expression. These studies were expanded to more robust stratification with single cell sequencing as well as the involvement of epigenes in cancer survival, including during dormancy. These studies have incorporated small non-coding microRNA and small microvesicles (exosomes).

a) Patel SA, Ramkissoon SH, Bryan M, Pliner LF, Dontu G, Patel PS, Amiri S, Pine SR, **Rameshwar P**. Delineation of breast cancer cell hierarchy identifies the subset responsible for dormancy. *Scientific Reports* 2, 906, 2012; PMID:23205268
b) Bliss SA, Paul S, Pobiarzyn PW, Ayer S, Sinha G, Pant S, Hilton H, Sharma N, Cunha MF, Engelberth DJ, Greco SJ, Bryan M, Kucia MJ, Kakar SS, Ratajczak MZ, **Rameshwar P**. Evaluation of a developmental hierarchy for breast cancer cells to assess risk-based patient selection for targeted treatment. *Sci Report* 8:367, 2018. PMID:29321622
c) Lim PK, Bliss SA, Patel SA, Taborga M, Dave MA, Gregory LA, Greco SJ, Bryan M, Patel PS, **Rameshwar P**. Gap junction-mediated import of microRNA from bone marrow stromal cells can elicit cell cycle quiescence in breast cancer cells. *Cancer Res* 71:1550-1560, 2011. PMID: 21343399

d) Bliss SA, Sinha G, Sandiford OA, Williams L, Engelberth DJ, Guiro K, Isenalumhe LL, Greco SJ, Ayer S, Bryan M, Kumar R, Ponzio NM, **Rameshwar P**. Mesenchymal stem cell-derived exosomes stimulates cycling quiescence and early breast cancer dormancy in bone marrow. *Cancer Res* 76;5832-5844, 2016. PMID:27569215

Complete List of Published Work in MyBibliograph:

https://www.ncbi.nlm.nih.gov/myncbi/pranela.rameshwar.1/bibliography/public/

My publications include 157 original articles, 23 Editorials/Perspectives/Commentaries, 51 Book Chapters, 68 Invited Reviews and edited/co-edited 6 books.