BIOGRAPHICAL SKETCH

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NAME:	Jaime E. Ramirez-Vick
eRA COMMONS USER NAME:	JVICK62
POSITION TITLE:	Professor of Biomedical Engineering

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Puerto Rico – Mayaguez	BS/MS	1985/89	Chemical Engineering
Arizona State University – Tempe	PhD	1997	Chemical Engineering
Lawrence Berkeley National Lab, Berkeley, CA	Post Doc	1998	Cancer Genetics
UCSF Cancer Center, San Francisco, CA	Post Doc	1999	Cancer Genetics

A. Personal Statement

The objective of the proposed project is to develop a nanomedical formulation that offers a treatment option to docetaxel (DTX)-resistant prostate cancer (PCa) using the combination of siRNA and DTX therapeutics through a multifunctional system capable of simultaneous targeting and sequential drug delivery. This formulation is based on the use on biomimetic reconstituted high-density lipoproteins (rHDL) nanoparticles, which consist of a poly(lactic-co-glycolic acid) hydrophobic core with dispersed DTX, and a shell of cholesterol-conjugated siRNAs, amphiphilic phospholipids and apolipoproteins. Selective targeting will be achieved through the interaction between the apolipoprotein on the rHDL and the SR-B1 receptor on the PCa. This method of time-staggered siRNA/DTX delivery combines the RNAi technique to inhibit the drug-resistance genes, which then allows normal chemotherapy using DTX. The silencing of the genes opens a window of time, in which the resistant cells become sensitized to the anti-cancer drug, which is slowly released from the erodible core of the rHDL.

Targeting and treatment efficacy will be assessed using a 3D in vitro model consisting of human DTX-resistant PCa spheroids, normal prostate epithelial cells and fibroblasts, embedded in a self-assembled peptide hydrogel with tumor-equivalent stiffness. I have considerable experience in the three key areas of this project: 1) synthesis and characterization of nanostructures including, lipid nanoparticles and its derivatives, 2) the development of conjugation chemistries to immobilize biomolecules, 3) the analysis of nanostructure cytotoxicity towards cancer cells, and 4) analysis of gene expression data as it pertains to cytotoxic response. To provide support in the siRNA knockdown experiments we will consult with Dr. Kate Excoffon who is my collaborator and the resident expert in RNAi technologies at Wright State. All the necessary methods required for the proposed project are working and at hand. I am confident that my previously acquired expertise will enable me to effectively lead and manage the proposed project ultimately resulting in the emergence of insights for the development of novel nanomedicine formulations for cancer treatment.

As my past research and educational accomplishments demonstrate, I am highly motivated to continue developing an academic career Wright State, an institution with an emerging capacity in biomedical research. Under my supervision I have always had a good-sized interdisciplinary group of graduate and undergraduate students from many of the engineering and life sciences departments. For instance, I have graduated 9 graduate students, have advised 17

undergraduate research project and 6 post-MS practical training projects. I currently supervise 8 graduate and 5 undergraduate students from Biology, Physics, Biomedical and Mechanical Engineering. All undergraduate and graduate student names are underlined in all citations.

1. BD Arya, S Mittal, AK Pandey, JE Ramirez-Vick, SP Singh, “Graphene oxide-chloroquine nanoconjugate induced necroptotic death of lung cancer cells through autophagy modulation,” Nanomedicine (Lond) 13(18):2261-2282 (2018).
2. S Verma, A Singh, A Shukla, J Kaswan, K Arora, JE Ramirez-Vick, P Singh, SP Singh, “AuNPs–rGO nanocomposite as immunosensing platform for non-invasive electrochemical detection of oral cancer biomarker IL8,” ACS App Mater Inter, 9(33):27462–27474 (2017).
3. X Narváez-Pita, C Ortega-Zuniga, CY Acevedo-Morantes, B Pastrana, J Olivero-Verbel, JE Ramírez-Vick, E Meléndez, "Water soluble molybdenocene complexes: Synthesis, cytotoxic activity and binding studies to ubiquitin by fluorescence spectroscopy, circular dichroism and molecular modeling "J Inorg Biochem, 132(3):77-91 (2014).
4. CY Acevedo-Morantes, E Meléndez, SP Singh, JE Ramírez-Vick, "Cytotoxic effect of Ferrocene and Ferrocenium Ions on MCF7 Breast Cancer Cells," J Cancer Sci Ther, 4(9):271-275 (2012).

B. Positions and Honors

Positions and Employment

2015-Pres Professor, Biomedical, Industrial & Human Factors Engineering, Wright State University, Dayton, OH
2007-2015 Professor, Engineering Sciences & Materials Department, University of Puerto Rico, Mayagüez, PR
2002-2007 Associate Professor, Engineering Sciences & Materials Department, University of Puerto Rico, Mayagüez, PR
2001-2006 President, Daedalus BioTechnologies, Berkeley, CA
1999-2001 Director of Technology, Iris Biotechnologies, Inc., Santa Clara, CA
1998-1999 Postdoctoral Fellow, Cancer Center, University of California, San Francisco, CA
1997-1998 Lawrence Postdoctoral Fellow, Lawrence Berkeley National Lab, Berkeley, CA

Other Experience and Professional Memberships

Fellow, American Institute Medical and Biological Engineering (AIMBE)
Member, Research Advisory Council, Wright State Research Institute
Board Member, Simman Wound Care & Fellowships Foundation
Member, Council of Chairs in Bioengineering and Biomedical Engineering
Academic Council Member, American Institute for Medical and Biological Engineering
Member, Council of Industrial Engineering Academic Department Heads, IISE
Editorial Board – Adv Sci Eng Med, Adv Biosens Bioelectron, Austin J Biomed Eng, Front Sensors, J Biosens Bioelectron, JSM Biotechnol & Biomed Eng.
Editor – ACS Appl Mater Interfaces, App Surf Sci, Bioengineering, Biomed Eng Online, Biomed Mater Eng, BioNanoScience J, Bioorganic & Med Chem Lett, Biotechnol Prog, Bone, Chem Cent J, Colloids Surf B Biointerfaces, Drug Deliv, Euro J Med Chem, Euro J Nanomed, Int J Nanotechnol, J Nanosci Nanotech, J Organometal Chem, Macromolec Biosci, Materials, Med Chem Res, Nanomaterials Nanomedicine, Nature Cell Death Dis, Sensors, Stem Cells Int.
NIH Peer Review Panel – Ad Hoc Member of the Biomaterials and Biointerfaces Study Section

C. Contributions to Science

1. Nanoscaffolds to Enhance Osteogenic Stem Cell Functions

The lack of suitable high-throughput assays is particularly problematic in the field of biomaterials research where a wide range of specialized tests are required. Examples of key biomaterial properties include surface protein adsorption, rate and mechanism of degradation, specific biological responses of cells contacting the material surface, cytotoxicity, and degree of biocompatibility in vivo. Each of the above-mentioned properties must be explored through rather

tedious experiments. This is a critical bottleneck in the implementation of a combinatorial biomaterial discovery process. We developed high-throughput methods for selecting metal oxide combinations for yielding optimal osseointegration when used in bone prosthetics. In this process we found that all these combinations had unique nanostructured topographic features and that these promoted osseointegration by allowing to adsorb more serum proteins, which then unfold exposing their cell-binding motifs.

a. DM Rivera-Chacon, L Polo-Corrales, SP Singh, JE Ramirez-Vick, "Osteoblastic Differentiation of Mesenchymal Stem Cells on Metal Oxide Nanoscaffolds," Acta Biomater, Accepted (2020).
b. L Polo-Corrales, M Latorre-Esteves, JE Ramirez-Vick, "Scaffold design for bone regeneration," J Nanosci Nanotech, 14(1):1-42 (2014).
c. M Alvarado-Velez, DM Rivera-Chacon, CY Acevedo-Morantes, SP Singh, E Gultepe, D Nagesha, S Sridhar, JE Ramirez-Vick, "Effect of fibronectin and vitronectin on human fetal osteoblast cell attachment, and proliferation on nanostructured titanium surfaces," J Biomed Nanotechnol, 9(6)1-6 (2013).
d. CY Acevedo-Morantes, PG Caceres-Valencia, RA Irizarry-Ortiz, SP Singh, JE Ramirez-Vick, "Combinatorial Metal Oxide Nanoscaffolds and its Influence in Osteoblast Cell Adhesion," J Applied Physics, 111(10):102810-102817 (2012).

2. Electrochemical Biosensors for Cancer Biomarkers

Biomarkers are described as characteristics that provide information about biological conditions whether normal or pathological. Detection of biomarkers at the earliest stage of the cancer is of utmost importance for clinical diagnosis. Electrochemical biosensors allow detecting low levels of specific analytes in blood, urine or saliva and providing a sensitive approach for direct measurement of cancer biomarker detection. Moreover, the integration of electrochemical devices with nanomaterials, such as carbon nanotubes, gold and magnetic particles offer amplification and multiplexing capabilities for simultaneous measurements of cancer biomarkers very sensitively. Our main goal was to improve sensitivity and signal to noise ratio without using mediators. We combine materials, first to detect analytes and improve enzymatic reactions. Finally, we developed highly-sensitive electrodes using nanostructured materials and used for the first time double stranded DNA for the detection of transcription factors.

a. M Choudhary, P Yadav, A Singh, S Kaur, JE Ramirez-Vick, P Chandra, K Arora, SP Singh, "CD 59 targeted ultrasensitive electrochemical immunosensor for fast and noninvasive diagnosis of oral cancer," Electroanalysis, 28:1-11 (2016)
b. WI Perez, Y Soto, JE Ramirez-Vick, E Melendez, "Nanostructured gold dsDNA sensor for early detection of breast cancer by beta protein 1 (BP1)," J Electroanal Chem, 751:49-56 (2015).
c. N Palomera, JL Vera, E Meléndez, JE Ramirez-Vick, M Tomar, SK Arya, SP Singh, "Redox Active Poly(pyrrole-N-ferrocene-pyrrole) Copolymer-Based Mediator-Free Biosensors," J Electroanal Chem, 658(1-2):33-37 (2011).
d. N Palomera, M Balaguera, SK Arya, S Hernandez, M Tomar, JE Ramirez-Vick, SP Singh, "Zinc Oxide Nanorods Modified Indium Tin Oxide Surface Based Amperometric Urea Biosensor," J Nanosci Nanotech, 11(8):6683- 6689 (2011).

3. Nanostructured Therapeutics for Cancer

Cancer continues to be one of the most difficult global healthcare problems. Although there is a large library of drugs that can be used in cancer treatment, the problem is selectively killing all the cancer cells while reducing collateral toxicity to healthy cells. Our initial focus had been on the creation of multifunctional drug delivery formulations that considering the drug mechanism of action. We then included specific targeting molecules to these formulations, starting with antibodies and ligands, and eventually moving towards highly-specific aptamers. Additional considerations for the formulation included the nanoparticle uptake mechanisms to optimize drug delivery and targeting. We have varied our formulations from metals and semiconductors to

biomimetic HDL nanoparticles. In addition, we have developed formulations for the co-delivery of therapeutics that can be delivered in a time-staggered manner.

a. BD Arya, S Mittal, AK Pandey, JE Ramirez-Vick, SP Singh, “Graphene oxide-chloroquine nanoconjugate induced necroptotic death of lung cancer cells through autophagy modulation,” Nanomedicine (Lond) 13(18):2261-2282 (2018).
b. X Narváez-Pita, C Ortega-Zuniga, CY Acevedo-Morantes, B Pastrana, J Olivero-Verbel, JE Ramírez-Vick, E Meléndez, "Water soluble molybdenocene complexes: Synthesis, cytotoxic activity and binding studies to ubiquitin by fluorescence spectroscopy, circular dichroism and molecular modeling "J Inorg Biochem, 132(3):77-91 (2014).
c. CY Acevedo-Morantes, MT Acevedo-Morantes, D Suleiman-Rosado, JE Ramírez-Vick, "Evaluation of the Cytotoxic Effect of Camptothecin Solid Lipid Nanoparticles on MCF7 cells," Drug Delivery, 20(8):338-48 (2013).
d. P Joshi, S Chakraborti, P Chakrabarti, ZA Ansari, JE Ramirez-Vick, SP Singh, and V Shanker, “The anticancer activity of chloroquine-gold nanoparticles against MCF-7 breast cancer cells,” Colloids Surf B Biointerfaces, 95:195-200 (2012).

4. Dimensionality in Growth and Differentiation of Mesenchymal Stem Cells

Human mesenchymal stem cells (MSCs) are considered a promising cell source for regenerative medicine because they have the potential to differentiate into a variety of lineages among which are the mesoderm-derived lineages such chondrocytes (cartilage), adipocytes (fat) and osteoblasts (bone). We hypothesize that a supportive three-dimensional (3D) structure provides MSCs an environment that more closely mimics the *in vivo* environment. We studied the chondrogenic, lipogenic and osteogenic differentiation capability of MSCs in 3D cultures and compared it the chondrogenic, lipogenic and osteogenic potential of MSCs in conventional monolayer (2D) cultures. In addition to proliferative and morphological changes, we measured temporal gene expression, focusing of the principal transcription factors involved in bonde development. This analysis allowed us to monitor cartilage and bone-relevant markers to compare the monolayer and 3D environment in their induction capacity of the chondrocytic, lipocytic or osteocytic phenotype.

a. FT Zohora, N Nosoudi, SP Singh, JE Ramirez-Vick, “In Vitro Adipocytic Differentiation of Mesenchymal Stem Cells in 2D versus 3D,” Cells Tissues Organs, Editor's Choice: 208(3-4):113-133 (2019).
b. FT Zohora, N Nosoudi, SP Singh, **JE Ramirez-Vick**, “Chondrogenic gene expression profiling on 2D vs 3D human adipose stem cells,” Cells Tissues Organs, Accepted (2020)
c. RMIK Rony, BE Hull, K Excoffon, JE Ramirez-Vick, “Differential expression of PPARγ and CHOP-10 during adipogenic differentiation of human bone marrow derived mesenchymal stem cells,” FASEB J, 32(supp 1):lb17 (2018).
d. FT Zohora, N Nosoudi, PP Singh, JR Ramirez-Vick, “Dimensionality of *in vitro* growth environment and its effects on mesenchymal stem cell differentiation,” Biomedical Engineering Society Proceedings, October 17-20, 2018.

5. Biophysical Stimulation to Induce Mesenchymal Stem Cell Differentiation

The past decade has seen an unprecedented progress in the study and use of stem cells in cell replacement therapies and regenerative medicine. The advantage of these over pharmacological approaches for treating diseases can be seen by what they provide, with the former offering curative solutions while the latter merely providing palliative alternatives. For stem cell-based therapies to be able to be transferred from the bench to the bedside, a major challenge that needs to be overcome includes control over the stem cell differentiation towards specific lineages or tissues. Current differentiation induction involves the use of a variable set of biochemicals, which are not able to provide the necessary spatio-temporal dosage required by cGMP regulations. There is mounting evidence showing that changes in membrane potential (V_{MEM}) and intracellular Ca^{2+} can exert significant control over stem cell differentiation. Ideally the induction of stem cell

differentiation should be non-invasive and have spatio-temporal dosage control. The use of extremely-low frequency pulsed electromagnetic fields (pEMFs) as an adjuvant therapy for the treatment of bone and soft tissue wounds has been widely used since it was approved by the FDA almost four decades ago. This type of biophysical stimulation has been shown to induce these therapeutic outcomes by inducing stem cell differentiation through changes in ion fluxes and V_{MEM}, while providing the necessary dosage control in a non-invasive manner. Our approach has been to systematically study pEMF parameters as they promote human mesenchymal stem cell differentiation towards bone, cartilage and adipose tissue and to have a better understanding on the mechanisms involved in their development and regeneration.

a. Al Aldebs, FT Zohora, N Nosoudi, SP Singh, JE Ramirez-Vick, “Effect of Pulsed Electromagnetic Fields on the Human Mesenchymal Stem Cells using Magnetic Scaffolds,” Bioelectromagnetics, 41(3):175-187 (2020).
b. MA Larrick, N Nosoudi, Singh SP, JE Ramirez-Vick, “Physicochemical Properties of Nanoparticles and their effect on Transport across the Microvasculature,” J Ann Bioeng, 1(1):9-24 (2019).
c. L Polo-Corrales, J Ramirez-Vick, JJ Feria-Diaz, "Recent Advances in Biophysical Stimulation of MSC for Bone Regeneration," Indian J Sci Technol 11(16):1-41 (2018).
d. JE Ramirez-Vick, “Biophysical Stimulation for Bone Regeneration,” JSM Biotech Biomed Eng, 1(2):1014-1016 (2013).

D. Research Support

Ongoing Research Support

11234618 **Ramirez-Vick (PI)** **06/19-06/20**
DoD DURIP
Title: Low vacuum field emission scanning electron microscope (LVFESEM+ EBSD + STEM) and a low-angle X-ray diffraction instrument for core microstructural characterization.
Role: PI

Completed Research Support (Last 3 years)

1726095 **Sizemore (PI)** **09/17 – 08/19**
NSF MRI
Title: MRI: Acquisition of a CytoViva system for highly interdisciplinary research and education in nanoscience and nanotechnology.
Role: Co-PI

NRC-HQ-84-15-G-0032 **Ramirez-Vick (PI)** **09/15 – 08/18**
DoD NRC
Title: The University of Puerto Rico at Mayaguez Faculty Development Program: Structural Engineering for Nuclear Facilities – Experimental Research Initiative
Role: PI

1460704 **Cordova (PI)** **04/15 – 03/18**
NSF REU
Title: REU: Research Experiences for Undergraduates in Reconfigurable and Multifunctional Soft Materials at UPRM
Role: Co-PI

NRC-HQ-84-14-G-0057 **Ramirez-Vick (PI)** **08/14 – 07/17**
DoD NRC
Title: The University of Puerto Rico at Mayaguez Faculty Development Program in Structural Engineering for Nuclear Facilities
Role: PI