BIOGRAPHICAL SKETCH

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NAME: Renato J. Aguilera

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

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
University of Texas at El Paso	B.S.	1981	Microbiology
University of Texas at El Paso	M. S.	1982	Biology
University of California at Berkeley	Ph.D.	1982-1987	Immunology
University of California at Berkeley	Postdoctoral	1987-1989	Immunology

A. Personal Statement: I have extensive experience in immunology, cancer research, molecular and cell biology, and drug screening. As the director of the Research Infrastructure Core and the Cellular Characterization and Biorepository Facility of the Border Biomedical Research Center (BBRC), I oversee the biomedical research facilities that provide support to over 200 faculty, staff and students. Over the past decade, my research group has developed high-throughput assays for screening of chemical libraries on a variety of human cancer cells and pathogens (1). The recent screening of >5,000 compounds on a human triple-negative breast cancer cell line resulted in the detection of novel lead compounds with potent anti-cancer activity. Secondary screens revealed that the most promising compound, a pyrazole-3-carbohydrazide compound (named P3C) induces apoptosis and is cytotoxic to the majority of breast cancer cell lines at sub-micromolar concentrations (a provisional patent has been recently submitted). Our research has also focused on the effects of repurposed drugs with potential anticancer activities. One such drug is Pyronaridine that is a potent anti-malarial drug that we determined has significant anticancer activity (patent pending; 2). In addition, in collaboration with other local researchers at Texas Tech Health Science Center, our groups determined that a well-known blood pressure medication propranolol exhibits anticancer activity and induces apoptosis in breast cancer cells (3, 4). The following are recent publications describing distinct anti-cancer projects:

(1) Lema, C., Varela-Ramirez, A., and Aguilera, R.J. (2011). Differential nuclear staining assay for high-throughput screening to identify cytotoxic compounds Curr.Cell.Biochem. 1, (2011) 1-14. PMC4816492.

(2) Villanueva, P., Martinez, A., Baca, S.T., Gutierrez, D.A., Varela-Ramirez, A., Aguilera, R.J. (2018). Pyronaridine exerts potent cytotoxicity on human breast and hematological cancer cells through induction of apoptosis. PLoS ONE Nov. 5; 13(11):e0206467. PMC6218039

(3) Montoya, A., Amaya, C.N., Belmont, A., Diab, N., Trevino, R., Villanueva, G., Rains, S., Sanchez, LA, Badri, N, Otoukesh, S, Khammanivong, A, Liss, D, Baca, S.T., Aguilera, R.J., Dickerson, E.B., Torabi, A., Dwivedi, A.K., Abbas, A., Chambers, K., Bryan, B.A., Nahleh Z. (2017). Use of non-selective beta-blockers is associated with decreased tumor proliferative indices in early stage breast cancer. Oncotarget; (8) 6446-6460. PMC5351644

(4) Montoya, A., Varela-Ramirez, A., Dickerson, E.B., Pasquier, E., Torabi, A., Aguilera, R.J., Nahleh, Z., and Bryan, B.A. (2019). The beta adrenergic receptor antagonist propranolol alters mitogenic and apoptotic signaling in late stage breast cancer. Biomedical J. 42(3):155-165. PMC6717753

B. Positions and Honors

Positions:

1978-1980	MBRS Undergraduate Trainee Department of Biological Sciences, University of Texas at El Paso.
1980-1982	MBRS MS Graduate Fellow, Department of Biological Sciences, University of Texas at El Paso.
1982-1985	NSF-Predoctoral Fellow, Department of Immunology, University of California at Berkeley
1984-1987	Ford Foundation Dissertation Fellow, University of California at Berkeley.
1987-1989	University of California President's Postdoctoral Fellow, Department of Molecular and Cellular Biology, Division of Immunology, University of California at Berkeley.
1989-2002	Assistant/Associate Professor, Department of Molecular, Cell and Developmental Biology, University of California at Los Angeles
1998-2002	Director of the Minority Access to Research Careers Program (MARC U*STAR) at UCLA.
2002-	Professor, Department of Biological Sciences, The University of Texas at El Paso.
2002-2005	Deputy Director of the Border Biomedical Research Center (RCMI) at UTEP.
2004-2008	Board of Scientific Counselors of the National Institute of Environmental Health Sciences (NIEHS).
2005-2011	Director of the SCORE Institutional Program at UTEP.
2010-2015	Chair of Minority Affairs Committee (MAC) of the American Society of Cell Biology.
2002-	Professor, Department of Biological Sciences, The University of Texas at El Paso.
2002-	Director of Graduate Program in Biology, The University of Texas at El Paso.
2004-	Director of the Research Initiative for Scientific Enhancement (RISE) Program at UTEP
2007-2019	Director of the Cytometry, Screening and Imaging Core, Border Biomed. Res. Ctr. (BBRC)
2012-2019	Program Director of the BBRC at UTEP.
2019-	Deputy Research Director and Director of the Research Infrastructure Core of the BBRC
2019-	Director of the Cellular Characterization and Biorepository Facility of the BBRC

Honors:

1995	Departmental Distinguished Teaching Award, UCLA
2007	College of Science (UTEP) Distinguished Teaching Award
2010	American Society for Microbiology, William A. Hinton Research Training Award
2013	Triumphant Hispanic (Hispanos Triunfadores) Award
2013	Society for the Advancement of Chicanos and Native Americans in Science (SACNAS) Distinguished Research Mentor Award
2017	Selected as a Lifetime Fellow of the American Society for Cell Biology
2019	SACNAS Distinguished Research Scientist Award

C. Contribution to Science

1. The work initiated during my Ph.D. research involved the characterization of factors involved in normal and abnormal immunoglobulin (Ig) gene recombination in murine lymphomas. During this period a lymphocyte-specific DNA binding factor was characterized that interacted with the Ig recombination signals (1). This work resulted in the first description of DNA binding proteins with specificity for the Ig signals and led to the subsequent cloning of the gene by another group. In addition to this work, I co-authored work describing the identification of a nuclease activity that cleaved at the Ig recombination signals (2). In related work, my group cloned and characterized the transcriptional regulatory regions of the Recombinase Activating Genes 1 and 2 (*rag-1* and *rag-2*). This work resulted in the identification of key tissue-specific and non-specific transcription factors that regulate *rag* gene expression (3-4). These diverse projects provided me with the training and confidence to pursue research in a variety of areas from basic cell and molecular biology to biochemistry in various model systems.

(1) Aguilera, R.J., Akira, S., Okazaki, K., and Sakano, H. (1987). A pre-B nuclear protein which specifically interacts with the immunoglobulin V-J recombination sequences. Cell 51, 909-917.

(2) Hope, T.J., Aguilera, R.J., Minie, M., Sakano, H. (1986). Endonucleolytic activity that cleaves immunoglobulin recombination sequences. Science 231, 1141-1145.

(3) Miranda, G. A., Villalvazo, M., Galic, Z., Alva, J., Abrines, R., Yates, Y., Evans, C.J. and Aguilera, R.J. (2002). Combinatorial regulation of the murine RAG-2 Promoter by Sp1 and distinct lymphocyte-specific transcription factors. Molecular Immunology 38:1151-1159.

(4) Brown, S. T., Miranda, G., Galic, Z., Hartman, I.Z. Lyon, C. and Aguilera, R.J. (1997). Regulation of the RAG-1 promoter by the NF-Y transcription factor. J. Immunology 158: 5071-5074

2. During our search for enzymes involved in antibody gene recombination, we detected a nuclease activity in plasmacytoma extracts that cleaved precisely at the G-rich antibody switch region that are commonly involved in normal and abnormal gene rearrangements. This nuclease activity was further characterized by my group and the gene was cloned (1) resulting in one patent (US Patent # 6,455,250). The cloning and further characterization of this gene resulted in the realization that the gene encoded DNase II, an enzyme involved in phagocyte-mediated DNA degradation. Mutation of this gene in *Drosophila melanogaster* was subsequently found to result in the inability of flies to fend of bacterial infection (2). Subsequent genome-wide gene expression microarray analyses of DNase II mutant flies resulted in the discovery of a novel nuclease that we named Stress Induced DNase (SID) that was found to be induced by bacterial infection and oxidative stress (3). SID appears to be induced to protect the host from excessive DNA in the environment in the absence of DNase II. After many years of frustrating work trying to purify DNase II to determine its structure, the structure of DNase II was finally solved by purifying a recombinant microbial enzyme expressed in *E. coli.* This work resulted in the novel discovery that DNase II behaves as a dimmer with a unique structure not previously reported for a nuclease (4).

(1) Lyon, C.J., Evans, C.J., Bill, B.R., Otsuka, A.J. and Aguilera, R.J. (2000). The C. elegans apoptotic nuclease Nuc-1 is related in sequence and activity to mammalian DNase II. Gene 252:147–154.

(2) Seong, C., Varela-Ramirez, A., and Aguilera, R.J. (2006). DNase II deficiency impairs innate immune function in Drosophila. Cellular Immunology, 240:5-13. PMC2430755

(3) Seong, C., Varela-Ramirez, A., Tang, X., Anchondo, B., Magallanes D. and Aguilera, R.J. (2014). Cloning and Characterization of a Novel Drosophila Stress Induced DNase. PLoS One 9(8):e103564; PMC411890055.

(4) Varela-Ramirez, A., Abendroth,J., Mejia, A.A., Phan, I.Q., Lorimer, D.D., Edwards,T.E., Aguilera, R.J. (2017). Structure of acid deoxyribonuclease. Nucleic Acids Research 45(10):6217-6227. PMC5449587

3. During our search for new anticancer drugs, we noticed that some compounds were more active against cancers derived from male patients. These results corroborate the long held belief that distinct compounds could have gender-dependent differences in their mode of action or activity (1). In work recently completed by our group, we discovered that a highly effective anti-malarial drug, pyronaridine (PND), has anticancer activity that is in part mediated by DNA intercalation (2). As a potent antimalarial, PND has been used for over 30 years worldwide and exhibits little if any negative side-effects in patients. Ruthenium-based compounds have also been shown to have potent antimalarial activity and we also determined that two such compounds induced apoptosis in lymphoma and prostate cancer cell lines (3). Arsenic contamination of well water in the Southwest region of the US has the potential to lead to significant health problems in the foreseeable future and for this reason, we collaborated with other investigators to determine the effects of arsenic on human keratinocytes (4). Our results revealed that several microRNAs that have been implicated in the genesis of melanoma were differentially expressed after arsenic exposure (4).

(1) Villanueva, P., Martinez, A., Baca, S.T., Gutierrez, D.A., Varela-Ramirez, A., Aguilera, R.J. (2018). Pyronaridine exerts potent cytotoxicity on human breast and hematological cancer cells through induction of apoptosis. PLoS ONE Nov. 5; 13(11):e0206467. PMC6218039

(2) Nunes, L.M., Robles-Escajeda, E., Santiago-Vazquez, Y., Ortega N.M., Lema, C., Muro, A., Almodovar, G., Das, U., Das,S., Dimmock, J. R., Aguilera, R. J., and Varela-Ramirez, A. (2014). The gender of cell lines matters when screening for novel anti-cancer drugs. Amer. Assoc. Pharm. Sci. May 30. PMC407025751

(3) Robles-Escajeda, E., Martínez, A., Varela-Ramirez, A., Sánchez-Delgado, R. A. Aguilera, R.J. (2013). Analysis of the cytotoxic effects of ruthenium-ketoconazole and ruthenium-clotrimazole complexes on cancer cells. Cell Biol.and Tox. 29(6):431-43. PMC4207122

(4) Gonzalez, H., Lema, C., Kirken, R.A., Maldonado, R.A., Varela-Ramirez, A., and Aguilera, R.J. (2015). Arsenic-exposed keratinocytes exhibit differential microRNAs expression profile; potential implication of miR-21, miR-200a and miR-141 in melanoma pathway. Clinical Cancer Drugs 2:138-147. PMC4819983

4. Our prior work with lymphomas resulted in a logical move to discover novel therapeutics against these malignancies. In collaboration with various synthetic chemists, we were able to develop a robust high-content screening assay to detect and characterize novel anti-cancer compounds. Using this high–content screening assay, we recently identified several potent anti-lymphoma compounds in a small library of compounds (1) and recently determined that these compounds elicit cell death *via* proteasome inhibition (2). In addition, a small subset of the anti-lymphoma compounds induced cell death via apoptosis on triple-negative breast cancer cell lines after increasing exposure to the compounds (3). Our search for novel anticancer compounds has also

resulted in the identification of a novel family of pyridazinones that induces apoptosis on a variety of cancer types including lymphoma and breast cancer cell lines (4)

(1) Nunes, L.M., Hossain, M., Varela-Ramirez, A. Das, U., Dimmock, J. R., and Aguilera, R. J. (2016). A novel class of piperidones exhibit potent, selective and pro-apoptotic anti-leukemia properties. Oncology Letters 11(6) 3842-3848. PMC4888252

(2) Contreras, L., Calderon, R.I., Varela-Ramirez, A., Zhang, H.Y., Quan, Y., Das, U., Dimmock, J.R, Skouta, R., Aguilera, R.J. (2018). Induction of apoptosis via proteasome inhibition in leukemia/ lymphoma cells by two potent piperidones. Cell. Oncol. 41(6):623-636. PMC6241245

(3) Robles-Escajeda, E., Das,U., Ortega N.M., Parra, K., Francia, G., Y., Dimmock, J. R., Varela-Ramirez, A., and Aguilera, R. J. (2016). A novel curcumin-like dienone induces apoptosis in triple-negative breast cancer cells. Cell. Oncol. 39(3):265-277. PMC4899127

(4) Gutierrez, D.A., DeJesus, R.E., Contreras, L., Rodriguez-Palomares, I.A., Villanueva, P., Balderrama, K.S., Monterroza, L., Larragoity, M., Varela-Ramirez, A., Aguilera, R.J. (2019). A new pyridazinone exhibits potent cytotoxicity on human cancer cells via apoptosis and poly-ubiquitinated protein accumulation. Cell Biol Toxicol. doi: 10.1007/s10565-019-09466-8. PMID: 30825052

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1HuC4twIcokku/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

NIMHD 2U54MD007592 4/01/19-3/30/24
(PI: R. Kirken)
Border Biomedical Research Center
Roles: Research Deputy Director and Director of the Research Infrastructure Core

1R25 GM069621-13 (Aguilera) 4/01/17-5/31/22
NIGMS
Title: RISE Scholars Program at UTEP
The RISE training grant assists minority students to transition to graduate/ academic careers.
Role: Program Director

Pending: none

Completed Research Support

1SC3GM103713-03
NIGMS SCORE SC3 (Aguilera) 7/01/13-1/31/18
Title: Characterization of novel anti-lymphoma compounds with selective toxicity.
The goal of this project is to characterize several anti-lymphoma compounds detected by drug screening
Role: Principal Investigator