

BIOGRAPHICAL SKETCH

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NAME: **Cristel V. Camacho**

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

POSITION TITLE: **Assistant Professor, Cecil H. and Ida Green Center for Reproductive Biology Sciences**

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
Hardin-Simmons University, Abilene, TX	B.S.	05/2005	Biology/Biochemistry
University of Cambridge, UK			Biology
University of Texas Southwestern Medical Center, Dallas	Ph.D.	05/2012	Cancer Biology
University of Texas Southwestern Medical Center, Dallas	Postdoc	08/2012	Cancer Biology
St. Jude Children's Research Hospital, Memphis, TN	Postdoc	01/2017	Cancer Biology

A. Personal Statement

I am a trained cancer biologist with an expertise in animal modeling. The overarching theme of my research studies has focused on understanding key genetic events that lead to cancer in an effort to identify novel targets that will help improve current therapies. During my graduate studies, I exploited the use of animal models to study the role of stochastic radiation-induced DNA damage and its ability to cooperate with existing sensitizing mutations in driving brain cancer initiation. Similarly, my postdoctoral studies employed various animal models of DNA repair deficiency to elucidate the role of DNA ligases in the development of brain cancer. Currently, my research focuses on characterizing the molecular basis of breast cancer phenotypes with an emphasis on lncRNA and PARP biology.

B. Positions, Scientific Appointments, and Honors**Positions and Employment:**

12/20 to Present	Assistant Professor, Cecil H. and Ida Green Center for Reproductive Biology Sciences, University of Texas Southwestern Medical Center, Dallas.
09/19 to 12/20	Senior Research Scientist, Cecil H. and Ida Green Center for Reproductive Biology Sciences, University of Texas Southwestern Medical Center, Dallas (with Dr. W. Lee Kraus).
09/17 to 08/19	Research Scientist, Cecil H. and Ida Green Center for Reproductive Biology Sciences, University of Texas Southwestern Medical Center, Dallas (with Dr. W. Lee Kraus).
01/17 to 08/17	Senior Research Associate, Cecil H. and Ida Green Center for Reproductive Biology Sciences, University of Texas Southwestern Medical Center, Dallas (with Dr. W. Lee Kraus).

09/12 to 01/17	Postdoctoral Research Associate, Department of Genetics, St. Jude Children's Research Hospital, Memphis, TN (with Dr. Peter J. McKinnon).
05/12 to 08/12	Postdoctoral Research Fellow, Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas (with Dr. Sandeep Burma).

Awards and Honors:

2016	Hardin-Simmons University, Outstanding Young Alumni Award.
2013	Brookhaven National Laboratory, First Place RHIC & AGS Thesis Award.
2012	St. Jude Children's Research Hospital, selected to attend National Graduate Student Symposium.
2011	NASA Space Radiation Investigator's Workshop, First Place Graduate Student Poster Presentation Award.
2011	National Institutes of Health, selected to attend National Graduate Student Research Conference.
2009	International Workshop on Space Radiation Research, Young Scientist Oral Presentation Award.
2009	International Workshop on Space Radiation Research, Student Travel Award.
2008	NASA Space Radiation Investigator's Workshop, Third Place Graduate Student Poster Presentation Award.
2008	NASA Space Radiation Investigator's Workshop, Student Travel Award.
2007-2009	University of Texas Southwestern Medical Center, T32 Cancer Biology Program Training Grant, Ruth L. Kirschstein National Research Service Award.

C. Contributions to Science

My research over the past 14 years has contributed to our understanding of key genetic and regulatory events in the initiation, promotion and progression of cancer. Each of my studies has a clear translational aspect, revealing exciting new clinical applications to be explored.

Full publications list: <https://www.ncbi.nlm.nih.gov/myncbi/1b9Kt-s8txbQDF/bibliography/public/>

1) Genetic Events Underlying Radiation-Induced Gliomagenesis

My graduate research focused on understanding the possible carcinogenic consequences of prolonged exposure to ionizing radiation (IR). In this NASA funded work, using a combination of cell-based systems and mouse models, I was able to systematically show that heavy particles found in space, similar to those currently being used in the clinic for targeted cancer therapy, pose a significant cancer risk to astronauts. My studies showed that persistent DNA damage caused by heavy particles induce high levels of senescence by upregulation of the tumor suppressor p16/Ink4a. Abrogating this fail-safe mechanism using mouse models, I showed that cells are rapidly transformed in response to IR, resulting in the formation of *de novo* brain tumors. While radiation-induced DNA damage is stochastic, common recurrent mutational events were discovered that have important implications for IR-induced gliomagenesis and for the development of therapy-resistant recurrent tumors.

Mukherjee, B., **C. V. Camacho**, N. Tomimatsu, J. Miller and S. Burma (2008) Modulation of the DNA-damage response to HZE particles by shielding. *DNA Repair (Amst)* 7(10): 1717-1730. PMID: 18672098

Camacho, C. V., B. Mukherjee, B. McEllin, L. H. Ding, B. Hu, A. A. Habib, X. J. Xie, C. S. Nirodi, D. Saha, M. D. Story, A. S. Balajee, R. M. Bachoo, D. A. Boothman and S. Burma (2010) Loss of p15/Ink4b accompanies tumorigenesis triggered by complex DNA double-strand breaks. *Carcinogenesis* 31(10): 1889-1896. PMID: 20663777

Camacho, C. V., P. K. Todorova, M. C. Hardebeck, N. Tomimatsu, C. R. Gil del Alcazar, M. Ilcheva, B. Mukherjee, B. McEllin, V. Vemireddy, K. Hatanpaa, M. D. Story, A. A. Habib, V. V. Murty, R. Bachoo and S. Burma (2015) DNA double-strand breaks cooperate with loss of Ink4 and Arf tumor suppressors to generate glioblastomas with frequent Met amplification. *Oncogene* 34(8): 1064-1072. PMID: 24632607

2) Glioblastoma in the Clinic: Novel Implications for Therapy

Glioblastoma is highly resistant to IR and chemotherapy, making it one of the deadliest types of cancer. During my graduate work I participated in studies aimed at elucidating the genetic basis of this radioresistance. Our results showed that a key glioma-specific mutant EGFRvIII receptor confers radioresistance through its

modulation of the DNA repair enzyme DNA-PKcs, accelerating the rate of DNA double-strand break (DSB) repair. Further studies showed that NVP-BEZ235, a potent dual PI3K/mTOR inhibitor, could also inhibit DNA-PKcs. Using mouse xenografts, we showed that NVP-BEZ235 could significantly attenuate DSB repair *in vivo*, conferring an extreme degree of radiosensitization. We also uncovered a novel potential use of PARP inhibitors by showing that PTEN-null astrocytes are deficient in homologous recombination, rendering cells sensitive to PARP inhibition due to synthetic lethality. These studies presented important implications for the informed and rational design of much needed clinical trials using drugs that target DNA-repair pathways exploited by this highly resistant tumor type.

Mukherjee, B., B. McEllin, **C. V. Camacho**, N. Tomimatsu, S. Sirasanagandala, S. Nannepaga, K. J. Hatanpaa, B. Mickey, C. Madden, E. Maher, D. A. Boothman, F. Furnari, W. K. Cavenee, R. M. Bachoo and S. Burma (2009) EGFRvIII and DNA double-strand break repair: a molecular mechanism for radioresistance in glioblastoma. *Cancer Research* 69(10): 4252-4259. PMID: 19435898

McEllin, B., **C. V. Camacho**, B. Mukherjee, B. Hahm, N. Tomimatsu, R. M. Bachoo and S. Burma (2010) PTEN loss compromises homologous recombination repair in astrocytes: implications for glioblastoma therapy with temozolomide or poly(ADP-ribose) polymerase inhibitors. *Cancer Research* 70(13): 5457-5464. PMID: 20530668

Mukherjee, B., N. Tomimatsu, K. Amancherla, **C. V. Camacho**, N. Pichamoorthy and S. Burma (2012) The dual PI3K/mTOR inhibitor NVP-BEZ235 is a potent inhibitor of ATM- and DNA-PKcs-mediated DNA damage responses. *Neoplasia* 14(1): 34-43. PMID: 22355272

Tomimatsu, N., B. Mukherjee, M. Catherine Hardebeck, M. Ilcheva, **C. V. Camacho**, J. Louise Harris, M. Porteus, B. Llorente, K. K. Khanna and S. Burma (2014) Phosphorylation of EXO1 by CDKs 1 and 2 regulates DNA end resection and repair pathway choice. *Nature Communications* 5: 3561. PMID: 24705021

3) Gene Expression Regulation in Estrogen Receptor α -Positive Breast Cancer

In my current research I am interested in understanding the molecular mechanisms that drive ER α -regulated transcriptional responses. We have recently shown that the transcriptional coregulator BRD3 is recruited to and controls the activity of a subset of ER α transcriptional enhancers, regulating gene expression and breast cancer cell growth. Our recent studies also provide evidence that PARP-1 can regulate estrogen-dependent ER α and FoxA1 binding and gene expression. High PARP-1 correlates with poor survival and its inhibition can attenuate the estrogen-dependent growth of ER-positive breast cancer cells. Further, I have characterized the functions of lncRNA152, which is highly expressed in the luminal subtype of breast cancer that modulates angiogenesis and metastasis, and a novel lncRNA-derived peptide that is highly expressed in ER-positive tumors. Mechanistically, this novel peptide can regulate gene expression by modulating the activity of the histone demethylase KDM7B (manuscript in preparation). Collectively, these studies shed insight into the molecular basis of clinical cancer phenotypes and suggest novel therapeutic opportunities to target ER α -positive breast cancer in the clinic.

Camacho, C. V., R. Choudhari and S. S. Gadad (2018) Long noncoding RNAs and cancer, an overview. *Steroids* 133: 93-95. PMID: 29317255

Murakami, S., R. Li, A. Nagari, M. Chae, **C. V. Camacho** and W. L. Kraus (2019) Distinct Roles for BET Family Members in Estrogen Receptor alpha Enhancer Function and Gene Regulation in Breast Cancer Cells. *Molecular Cancer Research* 17(12): 2356-2368. PMID: 31551256

*Gadad, S.S., ***C.V. Camacho**, V. Malladi, C.R. Hutti, A. Nagari, and W.L. Kraus (2021) PARP-1 Regulates Estrogen-Dependent Gene Expression in Estrogen Receptor α -Positive Breast Cancer Cells. *Molecular Cancer Research* 19(10): 1688-1698. PMID: 34158394

*Kim D.S., ***C.V. Camacho**, R. Setlem, K. Kim, S. Malladi, T.Y. Hou, T. Nandu, S.S. Gadad, W.L. Kraus (2022). Functional Characterization of lncRNA152 as an Angiogenesis-Inhibiting Tumor Suppressor in Triple-Negative Breast Cancers. *Molecular Cancer Research* Epub ahead of print. PMID: 35997635.

4) PARPs: Biological Roles of ADP-ribosylation and Cancer

Historically, the study of PARPs focused heavily on their roles in DNA damage repair and genome maintenance. However, thousands of substrates of nuclear PARPs have been identified beyond proteins involved in these processes, suggesting alternative roles for PARP-1. In my current research, I have participated in studies that have outlined key roles for nuclear ADP-ribosylation by PARP-1 in fundamental physiological processes. In one such study, we showed that PARP-1 can promote enhanced ribosome biogenesis and cell

proliferation through modulation of DDX21. This research presents an exciting new mechanism of PARP-1 action that could broaden the utility of PARP inhibitors in the clinic. Further, we showed that PARP-1 mediated ADP-ribosylation of H2B modulates gene expression outcomes in breast cancer. ADP-ribosylation of histones is thus an important signaling modification that plays an important role in gene regulation. Finally, we show that PARP-16 mediated mono-ADP-ribosylation of ribosomes can inhibit translation and maintain protein proteostasis in ovarian cancer, which sheds light on a new potential therapeutic target.

Kim, D. S., **C. V. Camacho**, A. Nagari, V. S. Malladi, S. Challa and W. L. Kraus (2019) Activation of PARP-1 by snoRNAs Controls Ribosome Biogenesis and Cell Growth via the RNA Helicase DDX21. *Molecular Cell* 75(6): 1270-1285 e1214. PMID: 31351877

*Kim, D.S., ***C.V. Camacho**, W.L. Kraus (2021) Alternate therapeutic pathways for PARP inhibitors and potential mechanisms of resistance. *Exp Mol Med* 53(1):42-51. PMID:33487630

Challa, S., B.R. Khulpateea, T. Nandu, **C.V. Camacho**, K.W. Ryu, H. Chen, Y. Peng, J.S. Lea, and W. L. Kraus (2021) Ribosome ADP-ribosylation inhibits translation and maintains proteostasis in cancers. *Cell* 184(17):4531-4546. PMID: 34314702

Huang, D., **C. V. Camacho**, S. Martire, A. Nagari, R. Setlem, X. Gong, A. D. Edwards, S.P. Chiu, L. A. Banaszynski, and W. L. Kraus (2022) Oncohistone Mutations Occur at Functional Sites of Regulatory ADP-ribosylation. *Cancer Research* [Epub ahead of print]. PMID: 35472077