BIOGRAPHICAL SKETCH

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NAME: Zavaleta, Cristina L.

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POSITION TITLE: Assistant Professor, University of Southern California

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Incarnate Word University	BS	05/2001	Nuclear Medicine
University of Texas Health Science Center at San Antonio	PhD	08/2006	Radiological Sciences/Nanotechnology
Stanford University	Postdoc	04/2012	Optical Imaging/Raman Spectroscopy

A. Personal Statement

My lab focuses on the development, assessment and clinical translation of new diagnostic strategies that include functional imaging capabilities to help clinicians detect cancers with better sensitivity and specificity. These tools are directed at: 1) Improving early cancer detection during routine screening techniques and 2) Helping surgeons identify and resect tumor margins with better sensitivity and specificity.

As a graduate student in the lab of Dr. Beth Goins, I focused on the fabrication and pharmacokinetic biodistribution of radiolabled liposomal nanoparticles for diagnostic and therapeutic application in preclinical tumor models using microPET and microSPECT/CT imaging. My dissertation involved utilizing a novel intraperitoneal delivery system to administer radiotherapeutic (^{186}Re) liposomes for the treatment of peritoneal ovarian metastases. Our ^{186}Re labeled liposomal formulation is currently undergoing clinical trials for intratumoral radiotherapeutic delivery during surgery.

In my postdoctoral fellowship at Stanford University with Dr. Sanjiv Gambhir, I spent considerable effort in developing an entirely new molecular imaging approach which involves the use of Raman spectroscopy in conjunction with tumor targeting contrast agents known as surface enhanced Raman scattering (SERS) nanoparticles. I also had the rare opportunity to work on the clinical translation of this new imaging technique—involving the development and fabrication of a novel endoscopic Raman probe in conjunction with tumor targeting Raman nanoparticles for the ultrasensitive detection of precancerous lesions in the colon. I have also played active role in working with various regulatory agencies such as the IRB and the FDA on matters of IDE and IND approval for our proposed device/drug combination product.

The current application builds logically on my prior research efforts to clinically translate an entirely new class of nanoparticle-based molecular imaging agents for tumor imaging. I have established strong ties with the biomedical community at USC making it possible to bring together a consortium of chemists, engineers, and clinicians to successfully move this project forward towards clinical translation. I realize the importance of maintaining continuous communication throughout the course of a collaborative project and the construction of realistic timelines to achieve the milestones set forth. I have also been working on the development of several new optical imaging devices that would be ideal to use in conjunction with the proposed tumor targeting optical imaging contrast agents we intend to develop. I have a considerable amount of experience in collaborating with a diverse group of scientists and clinicians, and as a result, we have produced several high impact peer-reviewed papers. My lab has a considerable amount of experience in developing novel nano-based imaging contrast agents and we routinely characterize their effectiveness in cell culture and in mouse tumor models. Our expertise in this area will ensure that the proposed work is successfully carried out with thoughtful experimental planning and execution.

B. Positions and Honors

Positions and Employment

2000-2001 Nuclear Medicine Technologist, Brook Army Medical Center, San Antonio, TX
2001-2006 Teaching Assistant, Radiology Department, University of Texas Health Science Center, San Antonio, TX
2001-2006 Research Assistant, Radiology Department, University of Texas Health Science Center, San Antonio, TX
2006-2012 NCI Postdoctoral Fellow, Stanford University, Stanford, CA
2012-2017 Instructor, Stanford University, Stanford, CA
2017-present Assistant Professor, University of Southern California

Other Experience and Professional Memberships

2002-2005 Member, American Association of Physicists in Medicine (AAPM)
2001-present Member, Society of Nuclear Medicine (SNM)
2004-present Member, World Molecular Imaging Congress (WMIC)
2009-present Member, Society of Photo-Optical Instrumentation Engineers (SPIE)

Honors

2001 Graduated Magna Cum Laude
2001 Amy Freeman Lee Service Award
2001 Sister Mary Fitzpatrick Award, Highest Ranking Graduate of Nuclear Medicine Program
2006 Academic Excellence Award presented by the 3rd Annual Conference on Ovarian Cancer Research
2007 Young Investigators Travel Award presented by the Joint Molecular Imaging Conference for top 1% scored abstract Providence, RI
2009 Young Investigators Travel Award presented by the World Molecular Imaging Congress, Montreal Canada
2009 Star of Excellence Award for 1st Place Podium Winner at NIH's CRCHD Professional Development Workshop, Rockville, MD
2009 First place poster winner at the CCNE Symposium, Stanford, CA
2018 Powell Foundation Award
2018 Carl Storm Award

C. Contribution to Science

Complete List of Published Work: www.zavaleta-lab.com/publications.
Publications below selected from 32 total.

The central theme of my scientific research has been the development, assessment and clinical translation of novel nano-based molecular imaging approaches that have the potential to provide important functional information about various cancers.

1. My earliest work focused on developing novel delivery approaches for therapeutic liposomal nanoparticles. It was here that I was introduced to the field of biomedical nanotechnology research, which encompassed everything from the basic fabrication of liposomal nanoparticles, to their chemical modification with radioactive isotopes, and their eventual diagnostic/therapeutic application/utility in small animal models, while utilizing various preclinical molecular imaging modalities (SPECT/PET/CT) to monitor their localization. The focus of my earliest work involved developing a novel intraperitoneal delivery system to administer radiotherapeutic (^{186}Re) liposomes for the treatment of peritoneal ovarian metastases. Since ^{186}Re has both beta and gamma emissions, we were able to effectively treat the ovarian cancer and simultaneously monitor the localization of the administered liposomes noninvasively using SPECT. Much of the work published below with our ^{186}Re liposomes was recently used in an IND application to the FDA, where a phase 1 clinical trial is currently underway entitled: Maximum Tolerated Dose, Safety, and Efficacy of Rhenium Nanoliposomes in Recurrent Glioblastoma. This is the first step in the clinical translation of our liposomal nanoformulation.

a. **Zavaleta, C.L**., Goins, B.A., Bao, A., McManus, L.M., McMahan, C.A. & Phillips, W.T. Imaging of 186Re-liposome therapy in ovarian cancer xenograft model of peritoneal carcinomatosis. *J Drug Target* **16**, 626-637 (2008).
b. **Zavaleta, C.L.**, Phillips, W.T., Soundararajan, A. & Goins, B.A. Use of avidin/biotin-liposome system for enhanced peritoneal drug delivery in an ovarian cancer model. *Int J Pharm* **337**, 316-328 (2007).
c. **Zavaleta, C.L.**, Phillips, W.T., Bradley, Y.C., McManus, L.M., Jerabek, P.A. & Goins, B.A. Characterization of an intraperitoneal ovarian cancer xenograft model in nude rats using noninvasive microPET imaging. *Int J Gynecol Cancer* **17**, 407-417 (2007).
d. Bao, A., Phillips, W.T., Goins, B., Zheng, X., Sabour, S., Natarajan, M., Ross Woolley, F., **Zavaleta, C.** & Otto, R.A. Potential use of drug carried-liposomes for cancer therapy via direct intratumoral injection. *Int J Pharm* **316**, 162-169 (2006).

2. I have also contributed to the development of an entirely new preclinical optical-based molecular imaging strategy that utilizes nano-based contrast agents to localize cancer in conjunction with Raman spectroscopy. Raman imaging is a new molecular imaging strategy that offers unsurpassed sensitivity and multiplexing capabilities. Our work resulted in a patent entitled "Raman Imaging Devices and Methods of Molecular Imaging", filed with the United States Patent and Trademark Office on March 9, 2010, and assigned Serial No. 61/311,840. This work also received a significant amount of press coverage from: The San Francisco Chronicle, The Atlantic, ABC7 News, and several online magazines like Science Daily. As a result, several groups around the world are now working toward the clinical translation of this novel molecular imaging strategy, including my own lab.

   a. **Zavaleta, C.L.**, Smith, B.R., Walton, I., Doering, W., Davis, G., Shojaei, B., Natan, M.J. & Gambhir, S.S. Multiplexed imaging of surface enhanced Raman scattering nanotags in living mice using noninvasive Raman spectroscopy. *Proc Natl Acad Sci U S A* **106**, 13511-13516 (2009).
   b. **Zavaleta, C.**, de la Zerda, A., Liu, Z., Keren, S., Cheng, Z., Schipper, M., Chen, X., Dai, H. & Gambhir, S.S. Noninvasive Raman spectroscopy in living mice for evaluation of tumor targeting with carbon nanotubes. *Nano Lett* **8**, 2800-2805 (2008).
   c. **Zavaleta, C.*,** Keren, S.*, Cheng, Z., de la Zerda, A., Gheysens, O. & Gambhir, S.S. Noninvasive molecular imaging of small living subjects using Raman spectroscopy. *Proc Natl Acad Sci U S A* **105**, 5844-5849 (2008). *co-first authors.
   d. Bohndiek, S.E., Wagadarikar, A., **Zavaleta, C.L.**, Van de Sompel, D., Garai, E., Jokerst, J.V., Yazdanfar, S. & Gambhir, S.S. A small animal Raman instrument for rapid, wide-area, spectroscopic imaging. *Proc Natl Acad Sci U S A* **110**, 12408-12413 (2013).

3. Another optical-based imaging area I have contributed to is the development of one of the first preclinical photoacoustic imaging systems. We have also had success in developing a multimodal strategy that combines, Raman spectroscopy, Photoacoustic imaging and MRI imaging to localize glioblastoma in preclinical mouse models. More recently, I have been actively involved in the development of a novel strategy that involves the use of a new clinical-ready fluorescence wide-field imaging endoscope in conjunction with activatable fluorescence contrast agents.

   a. De la Zerda, A., **Zavaleta, C.**, Keren, S., Vaithilingam, S., Bodapati, S., Liu, Z., Levi, J., Smith, B.R., Ma, T.J., Oralkan, O., Cheng, Z., Chen, X., Dai, H., Khuri-Yakub, B.T. & Gambhir, S.S. Carbon nanotubes as photoacoustic molecular imaging agents in living mice. *Nat Nanotechnol* **3**, 557-562 (2008).
   b. Kircher, M.F., de la Zerda, A., Jokerst, J.V., **Zavaleta, C.L**., Kempen, P.J., Mittra, E., Pitter, K., Huang, R., Campos, C., Habte, F., Sinclair, R., Brennan, C.W., Mellinghoff, I.K., Holland, E.C. & Gambhir, S.S. A brain tumor molecular imaging strategy using a new triple-modality MRI-photoacoustic-Raman nanoparticle. *Nat Med* **18**, 829-834 (2012).

c. **Zavaleta, C.***, Sensarn, S.*, Ehud, S., Rogalla, S., Lee, W., Gambhir, S.S., Bogyo, M., Contag, C.H., A clinical wide-field fluorescence endoscopic device for molecular imaging demonstrating cathepsin protease activity in colon cancer. *Mol. Imaging Biol.* **18**(6): 820-829.(2016) *co-first authors.

4. An additional facet of my work, has been evaluating the biodistribution, targeting efficiency and toxicity effects of various imaging contrast agents. In working with the FDA to clinically translate some of our molecular imaging strategies, it became apparent just how important it was to assess these parameters with great care and precision. These published studies have no doubt paved the way towards gaining regulatory approval of our unique contrast agents as well as aiding others within the community.

   a. Campbell, J. L., SoRelle, E. D., Ilovich, O., Liba, O., James M. L., Qiu, Z., Perez, V., Chan, C. T., de la Zerda, A. and **Zavaleta, C.** Multimodal assessment of SERS nanoparticle biodistribution post ingestion reveals new potential for clinical translation of Raman imaging. *Biomaterials* 135: 42-52 (2017).
   b. **Zavaleta, C.**, Hartman, K.B., Miao, Z., James, M.L., Kempen, P., Thakor, A.S., Nielsen, C.H., Sinclair, R., Cheng, Z. & Gambhir, S.S. Preclinical evaluation of Raman nanoparticle biodistribution for their potential use in clinical endoscopy imaging. *Small* **7**, 2232-2240 (2011).
   c. Thakor, A.S., Luong, R., Paulmurugan, R., Lin, F.I., Kempen, P., **Zavaleta, C.**, Chu, P., Massoud, T.F., Sinclair, R. & Gambhir, S.S. The fate and toxicity of Raman-active silica-gold nanoparticles in mice. *Sci Transl Med* **3**, 79ra33 (2011).
   d. Smith, B.R., **Zavaleta, C.**, Rosenberg, J., Tong, R., Ramunas, J., Liu, Z., Dai, H. & Gambhir, S.S. High-resolution, serial intravital microscopic imaging of nanoparticle delivery and targeting in a small animal tumor model. *Nano Today* **8** (2013).

5. Lastly, we have been working hard to clinically translate our newly developed molecular imaging strategy of utilizing Raman nano-based contrast agents in conjunction with Raman spectroscopy. Endoscopic imaging is an invaluable diagnostic tool allowing minimally invasive access to tissues deep within the body. However, conventional white-light endoscopy only offers physicians structural information without the biochemical information that would be advantageous for early detection or to help guide surgical resection, and is essential for molecular typing. To address this unmet need, we have developed two unique accessory, non-contact, fiber optic-based Raman spectroscopy devices that have the potential to provide real-time multiplexed, functional information. They have great potential to be used during routine endoscopy for early cancer detection and during surgery to help guide the resection of tumor margins. These new diagnostic tools are the first of their kind and have already generated quite a bit of interest within the imaging community.

   a. Davis, R.M.. Campbell, J.L., Burkitt, S., Qiu, Z.; Kang, S., Mehraein, M., Miyasato, D., Salinas, H., Liu, J.T.C., **Zavaleta, C.** A raman imaging approach using cd47 antibody-labeled sers nanoparticles for identifying breast cancer and its potential to guide surgical resection. *Nanomaterials* **2018**, *8*.
   b. **Zavaleta, C.L.**, Garai, E., Liu, J.T., Sensarn, S., Mandella, M.J., Van de Sompel, D., Friedland, S., Van Dam, J., Contag, C.H. & Gambhir, S.S. A Raman-based endoscopic strategy for multiplexed molecular imaging. *Proc Natl Acad Sci U S A* **110**, E2288-2297 (2013).
   c. Garai, E., Sensarn, S., **Zavaleta, C.L**., Van de Sompel, D., Loewke, N.O., Mandella, M.J., Gambhir, S.S. & Contag, C.H. High-sensitivity, real-time, ratiometric imaging of surface-enhanced Raman scattering nanoparticles with a clinically translatable Raman endoscope device. *J Biomed Opt* **18**, 096008 (2013).
   d. Garai, E., **C. L. Zavaleta**, S. Sensarn, N. O. Loewke, S. Rogalla, M. J. Mandella, S. A. Felt, S. Friedland, J. T. Liu, S. S. Gambhir and C. H. Contag. "A real-time clinical endoscopic system for intraluminal, multiplexed imaging of surface-enhanced Raman scattering nanoparticles." *PLoS One* **10**(4): (2015).

D. Research Support

Completed Research Support

R21 CA184608 (Zavaleta) 05/01/15-04/30/19
NIH/NCI
Role: Principle Investigator
Title: A New Raman-based Strategy to Identify Tumor Margins and Guide Surgical Resection in Breast Cancer

The research done in this proposal was instrumental in laying down the ground work for developing better nanoparticles to target breast cancer and help guide surgical resection. The nanoparticles used in this R21 proposal used gold/silica-based nanoparticles which we have come to learn are difficult for the body to eliminate and therefore harder to clinically translate from a regulatory perspective. As a result, in the proposed work for the current application, we are developing an entirely new imaging strategy where we administer the nanoparticles topically to the excised tissue and eliminating any contact within the patient, to avoid systemic toxicity all together and help accelerate approval by regulatory agencies for clinical translation.

K22 CA160834 (Zavaleta) 07/01/14-10/31/18
NIH/NCI
Role: Principal Investigator
Title: A New Strategy for Cancer Detection using Raman Spectroscopy with Nanoparticles

This proposal was a training grant that was instrumental in helping me to transition into an independent faculty position at USC. It was a mentored grant that gave me protected time to further develop my optical engineering skills as well as perform key experiments to understand nanoparticle physiology better. The results obtained in this grant will help us better direct our Raman nanoparticles toward targeting tumors.