BIOGRAPHICAL SKETCH

NAME: Virumbrales-Muñoz, María

eRA COMMONS USER NAME: virumbralesm

POSITION TITLE: Assistant Professor, Department of Obstetrics and Gynecology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
University of Zaragoza, Spain.	B.S.	9/2006	9/2011	Biochemistry
University of Zaragoza, Spain.	M.S.	9/2011	9/2012	Cell and Molecular Biology
University of Zaragoza, Spain.	M.S.	9/2012	6/2013	Teaching
University of Zaragoza, Spain.	Ph.D.	5/2013	06/2017	Biomedical Engineering
University of Wisconsin, Madison, WI	Post-doc	7/2017	6/2022	Biomedical Engineering

A. Personal Statement

I have spent most of my career at the interface of cell biology and engineering, in developing new strategies to recapitulate cell and tissue environments in disease states. Specifically, my strengths lie **in multidimensional cancer biology**, which I define as the integration of all the different dimensions (e.g., 3D architecture, cellular crosstalk, extracellular environment) in biological studies. These additional dimensions are known to have a dramatic impact on cellular behavior and drug response. While traditional *in vitro* models find stark challenges to add these additional dimensions, microfluidic biomimetic are ideally suited for this task, as recently recognized by the NIH (RFA-CA-18-004, PAR-22-099) in specific funding calls and the FDA modernization act 2.0. During my graduate training, I worked on characterizing and applying new biomaterials for use in bioengineering research. This work was foundational to my post-doctoral focus in development of models and proof-of-concept applications for multidimensional cancer biology. These models are ideally suited for investigating the role of different dimensions as either cancer promotors or potential therapeutic targets against cancer. My science contributions in the field, which I have received awards for (e.g., **Midwest TME Young Investigator and Poster Blitz Awards**) include models recapitulating tumor progression in renal carcinoma (Virumbrales-Muñoz et al, **Biomaterials 2022**) using primary patient-derived endothelial cells (Virumbrales-Muñoz et al, **Lab on a Chip 2020**); and studying of the effects of ECM on lymphatic vessels (Lugo Cintron et al, **Lab Chip 2020**), patient-specific models of lymphangiogenesis in head and neck cancer (Lugo-Cintron et al, **eBiomedicine 2021**), in which I have had a senior author role. Finally, another application of my research lies in the use of multidimensional models to study the role of the **immune system** in biological environments, with the aim of using our newly acquired knowledge for therapeutic purposes (JM Ayuso et al, **Science Advances 2021**).

I currently have 31 accumulated publications in multidimensional model development and characterization: 13 as first (or co-first) author, 4 as co-last author. Thanks to my graduate and post-doctoral training I find myself in a unique position to take multidimensional vascular biology models **beyond proof-of-concept** applications and establish them as a key tool for biological research.

Breaks in research effort: leave for childbirth in 2020, 2023.

Ongoing project that I would like to highlight include:
1/1/2023-12/31/2024
772 / UnityPoint Meriter Foundation
Boeldt; PI
Vessel on a Chip: Novel approaches to combat vascular pathologies of Preeclampsia
Role: Co-I

B. Positions, Scientific Appointments

2023	Assistant Professor, OB-GYN Department, UW-Madison (Effective September 1st).
2022-present	Special issue editor in Biosensors (MDPI) and Frontiers in Medical Technology
2021-2023	Scientist I, Pathology, University of Wisconsin, Madison, WI (Advisor: David Beebe).
2020-	Guest editor in Micromachines (MDPI)
2019-	Member, Association for Spanish Researchers in the US (ECUSA)
2019-	Member, North American Vascular Biology Organization (NAVBO)
2017-2021	Postdoctoral Fellow, Biomedical Engineering, University of Wisconsin, Madison, WI (Advisor: David Beebe)
2016-	Member, European Association for Cancer Research (EACR)
2016	Three-month research visit to the Queen's Medical Center, University of Nottingham (UK). Advisor: Anna Grabowska.
2015	Three-month research visit to the University of Twente, MESA+ Institute (The Netherlands). Advisor: Séverine Le Gac.
2013-2017	Predoctoral Fellow, Biomedical Engineering, University of Zaragoza, Spain (Advisors: Manuel Doblaré, Ignacio Ochoa, Luis Fernández)
2012	Internship in clinical and forensic genetics company Citogen (3 months). Advisor: Maria Sánchez.
2010-2012	Undergraduate Research Fellow, Department of Biochemistry. University of Zaragoza, Spain (Advisors: Patricio Fernández-Silva, Pilar Bayona-Bafaluy).
2010	Undergraduate Research Assistant (3 months). Department of Infectious Diseases. Institute for Biomedical Investigation of La Rioja (Spain). Advisors: Carmen P. Pérez Matute, Jose A Oteo.

Honors

2023	Centennial Scholars Program Awardee, UW-Madison.
2023	TOP Program (Faculty diversity initiative) Awardee, UW-Madison
2021	Chester B. Martin Graduate Training Program Mentorship Award (Student's choice). OB-GYN Department, UW-Madison.
2020	Young Investigator Award and Travel Grant. 7th Midwest Tumor Microenvironment Meeting.
2020	Best poster award. Online μTAS Conference.
2016	Three-minute PhD Blitz talk Prize Finalist. G9 University Consortium, Spain.
2015	EACR best poster Award. University of Castilla la Mancha, Spain.
2017	Invited talk at the Institute for Bioengineering of Catalonia (IBEC), Spain.
2017	Best poster award. G9 University Consortium Graduate Student Meeting, Spain.
2016	Best talk Award, I Conference of Young Researchers in Biomedicine, Spain.

C. Contributions to Science

1. Use of 3D models for elucidating and targeting breast cancer metastasis: Breast cancer affects 1 in 8 women, with metastasis of breast cancer cells to other organs being responsible for 90% of breast cancer-related deaths. Currently, treatments after metastasis are ineffective, arguably due to our poor understanding of the metastatic process. Metastasis is a complex multi-step process where the different dimensions (e.g., cell signaling, biomechanical stimuli, 3D ECM architecture) of the tumor niche play crucial roles in the metastatic initiation and dissemination. Through my unique graduate and post-doctoral training, I have positioned myself as one of the leaders in studying breast cancer metastasis from a multidimensional perspective, specifically focused on the role of the vasculature in this cascade.

a. H Humayun, JM Ayuso, RA Brenneke, **M Virumbrales-Muñoz,** S Kerr, SM Ponik, and DJ Beebe. "Elucidating cancer-vascular paracrine signaling using a human organotypic breast cancer cell extravasation model." Biomaterials (2021), Volume 270, 120640. PMID: 33592387.

b. KM Lugo-Cintrón, MM Gong, JM Ayuso, L Tomko, DJ Beebe, **M Virumbrales-Muñoz**, SM Ponik. (2020). "Breast Fibroblasts and ECM Components Modulate Breast Cancer Cell Migration Through the Secretion of MMPs in a 3D Microfluidic Co-Culture Model." Cancers 12(5): 1173.

c. KM Lugo-Cintron, MM Gong, JM Ayuso, L Tomko, DJ Beebe, **M Virumbrales-Muñoz***, and SM Ponik*. "Matrix density drives 3D organotypic lymphatic vessel activation in a microfluidic model of the breast tumor microenvironment." Lab on a Chip (2020) 20 (9), 1586-1600. PMID: 32297896. (***Co-last authors)**

2. Microfluidic modeling of renal cell carcinoma to evaluate therapeutic effectiveness and resistance: Renal cell carcinoma is one of the most common genitourinary cancers. It is characterized by large, highly heterogeneous, and highly vascularized tumors. The high heterogeneity of these tumors results in resistance to conventional chemotherapy. Anti-angiogenic therapies, which are at the frontline of renal cell carcinoma treatment, result in highly variable among different patients. With no effective predictive biomarkers to guide treatment decision, the need for better stratification of renal carcinoma patients has recently been established in the field. Existing angiogenesis models are unable to reproduce sprouting angiogenesis in a patient-specific manner. During my post-doctoral training, I have positioned myself as a leader in using patient-specific patient-derived models to model treatment response. These models reproduce the response/resistance behaviors observed in the clinic and can be used to screen potential pharmacological therapies to inform patient treatment decisions. The predictive value of these models is currently being evaluated. This is an unparalleled effort that may result in the discovery of specific predictive biomarkers or the implementation of the technology in clinical settings to inform patient treatment decisions.

a. **M Virumbrales-Muñoz**, J Chen, JM Ayuso, MH Lee, EJ Abel, DJ Beebe "Organotypic primary blood vessel models of clear cell renal cell carcinoma for single-patient clinical trials." Lab on a Chip (2020). 4420-4432. PMID: 33103699

b. JA Jimenez-Torres*, **M Virumbrales-Muñoz***, KE Sung, MH Lee, EJ Abel, DJ Beebe. "Patient-Specific Organotypic Blood Vessels as an in Vitro Model for Anti-Angiogenic Drug Response Testing in Renal Cell Carcinoma." EBioMedicine 42 (Apr 2019): 408-19. PMID: 30902740. (***Co-first authors)**

c. **M Virumbrales-Muñoz,** JM Ayuso, JR Loken, KM Denecke, SR Rehman, MC Skala, EJ Abel, DJ Beebe. "Microphysiological model of renal cell carcinoma to inform anti-angiogenic therapy" Biomaterials. 2022 Mar 11;283:121454.

3. Microfluidic modeling to elucidate the role of lymphatic vasculature in cancer: Although lymphatic vessels are a preferential route for metastasis in many cancers (e.g., breast cancer), their role in the metastatic cascade remains largely understudied. This literature gap was largely due to the lack of specific lymphatic markers, which have been characterized in the last few years. Therefore, there is great opportunity and reward in understanding the biology of lymphatic vasculature and its role in disease. During my post-doctoral training as a multi-dimensional biologist, I have pioneered 3D lymphatic and lymphangiogenesis modeling. In my work, I have investigated and targeted the process of lymphangiogenesis in head and neck cancer and elucidated the impact of ECM density in tumor-lymphatic signaling.

a. **M Virumbrales-Muñoz,** JM Ayuso, MM Gong, M Humayun, MK Livingston, KM Lugo-Cintron, PH McMinn, YR Alvarez-Garcia, DJ Beebe. "Microfluidic Lumen-Based Systems for Advancing Tubular Organ Modeling." Chem Soc Rev 49, no. 17 (Sep 1 2020): 6402-42. PMID: 32760967.

b. KM Lugo-Cintron, JM Ayuso, BR White, PM Harari, SM Ponik, DJ Beebe*, MM Gong*, and **M Virumbrales-Muñoz***. "Matrix density drives 3D organotypic lymphatic vessel activation in a microfluidic model of the breast tumor microenvironment." Lab on a Chip (2020). 20 (9), 1586-1600. PMID: 32297896 **(*Co-corresponding authors)**

c. KM Lugo-Cintrón, JM Ayuso, M Humayun, MM Gong, SC Kerr, SM Ponik, PM Harari, **M Virumbrales-Muñoz***, and DJ Beebe*. "Primary head and neck tumour-derived fibroblasts promote lymphangiogenesis in a lymphatic organotypic co-culture model." EBioMedicine 73 (2021): 103634. PMID: 34673450. **(*Co-corresponding authors)**

d. GS Simitian*, **M Virumbrales-Muñoz***, C Sanchez-de-Diego*, DJ Beebe, D Kosoff. "The emerging role of microfluidic technologies in angiogenesis *in vitro* research: at the interface of biology, biomedicine, and engineering" Lab on a Chip. (***Co-first authors**)

4. Use of 3D microfluidic models to study the role of immune cells in cancer and the biology behind their therapeutic potential: The tumor niche is a complex system where biochemical gradients (e.g., oxygen,

nutrients, waste products) are prevalent and highly influence cancer cell activity, proliferation, and response to therapies. 3D microfluidic models confer the user with a high degree of control to establish and investigate the effects of these gradients. One area where biochemical gradients are of high interest is in cell-mediated immunotherapies, due to their deep impact on immune cell cytotoxic effects. Therefore, in a project spanning from my graduate work to my post-doc years, I have worked on developing 3D microfluidic models that recapitulate complex biological scenarios, such as tumor niches, and evaluate their effects in the immune system and therapeutic potential.

a. JM Ayuso, S Rehman, **M Virumbrales-Muñoz M**, PH McMinn, P Geiger, C Fitzgerald, T Heaster, MC Skala, DJ Beebe. Microfluidic tumor-on-a-chip model to evaluate the role of tumor environmental stress on NK cell exhaustion. Science Advances. 2021;7(8):eabc2331.
b. JM Ayuso, R Truttschel, MM Gong, M Humayun, **M Virumbrales-Muñoz**, R Vitek, M Felder, S.D. Gillies, P Sondel, KB Wisinski, M Patankar, DJ Beebe, MC Skala. "Evaluating natural killer cell cytotoxicity against solid tumors using a microfluidic model". Oncoimmunology. 2019;8(3):1553477. PMID: 30723584.
c. JM Ayuso, **M Virumbrales-Muñoz**, A Lacueva, PM Lanuza, E Checa-Chavarria, P Botella, et al. Development and characterization of a microfluidic model of the tumour microenvironment. Sci Rep. 2016;6:36086.PMID: 27796335.

5. New biomaterial characterization and optimization for multidimensional modeling: Recapitulating the many dimensions of biology requires biomimetic environments capable of supporting cell function in an *in vivo*-like environment with no toxicity or cell activity downsides. Current biomaterials present limitations in biocompatibility, reproducibility, throughput, or interaction with biological substances, depending on the biological application for which they are needed. Therefore, new materials are always under development to overcome issues associated with each application. During my graduate training, and part of my post-doctoral training I have used different cell-based and mechanical assays, such as atomic force spectroscopy, to characterize new materials for biological applications. Specifically, one of my research focuses has been the characterization of different matrices for cell microencapsulation for implantable cell-based therapies, and their mechanical stability. Another application of this research has been the characterization of alternative materials for the development of microfluidic models integrating vascular components. The latter has focused on increasing reproducibility and throughput, while ensuring adequate cell function in the new microfluidic platforms. This line of research has been foundational for my post-doctoral bioengineering work.

a. **M Virumbrales-Muñoz***, MK Livingston*, M Farooqui, MC Skala, DJ Beebe, and JM Ayuso. "Development of a Microfluidic Array to Study Drug Response in Breast Cancer." Molecules (2019). 24, no. 23 (Nov 30 2019): 4385. PMID: 31801265. **(*Co-first authors)**
b. MK Livingston, MM Morgan, WT Daly, WL Murphy, BP Johnson, DJ Beebe*, and **M Virumbrales-Muñoz*.** "Evaluation of PEG-Based Hydrogel Influence on Estrogen Receptor Driven Responses in Mcf7 Breast Cancer Cells." ACS Biomater Sci Eng 5, no. 11 (2019): 6089-98. PMID: 31942444. **(*Co-corresponding authors)**
d. **M Virumbrales-Muñoz**, L Paz-Artigas, J Ciriza, C Alcaine, A Espona-Noguera, M Doblaré, L Sáenz del Burgo, K Ziani, JL Pedraz, L Fernández and I Ochoa. (2020). Force Spectroscopy Imaging and Constriction Assays Reveal the Effects of Graphene Oxide on the Mechanical Properties of Alginate Microcapsules. ACS Biomaterials Science & Engineering, 7(1).
e. **M Virumbrales-Muñoz**, JM Ayuso, M Olave, R Monge, D de Miguel, L Martinez-Lostao, S Le Gac, M Doblare, I Ochoa, LJ Fernandez. "Multiwell Capillarity-Based Microfluidic Device for the Study of 3d Tumour Tissue-2d Endothelium Interactions and Drug Screening in Co-Culture Models." Sci Rep 7, no. 1 (2017): 11998. PMID: 28931839.

Complete list of published work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/maria.virumbrales%20munoz.1/bibliography/public/