BIOGRAPHICAL SKETCH - SSR-VEC Rising Stars

NAME: Laronda, Monica M.

POSITION TITLE: Assistant Professor, Department of Pediatrics, Division of Endocrinology, Division of Pediatric Surgery, Ann & Robert H. Lurie Children's Hospital of Chicago

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Bridgewater State University, Bridgewater, MA	B.S.	05/2004	Biology Major, Chemistry Minor
Northwestern University, Chicago, IL	Ph.D.	06/2011	Life Sciences, Endocrinology
Northwestern University, Chicago, IL	Postdoctoral	02/2013	Female Reproductive Biology
Northwestern University, Chicago, IL (NU)	Postdoctoral	07/2016	Oncofertility

A. Personal Statement

My interest in reproductive biology began when I worked as the undergraduate Research Assistant for the Frontiers in Reproduction Course at the Marine Biological Labs. This interest in basic reproductive biology and endocrinology was solidified during my Ph.D. at NU and continues to be my research passion. My independent research laboratory at the Stanley Manne Children's Research Institute at the Ann & Robert H Lurie Children's Hospital of Chicago, and the Feinberg School of Medicine at Northwestern University strives to understand how the ovarian microenvironment maintains and promotes gametogenesis; to use this information to generate *in vitro* models and implantable bioprosthetic ovaries as a regenerative means to support endocrine function and gamete production in endocrine deficient and infertile patients, and to engineer endocrine organs that support sex hormone production. **I have contributed innovative perspectives to the reproductive biology field by:** (1) investigating mechanisms of progenitor cell differentiation in reproductive organs, (2) developing methods for preserving and supporting human folliculogenesis, (3) establishing unique resources to understand differences in sex development, (4) engineering the ovarian follicle niche to restore function, and (5) mapping the ovarian microenvironment.

I received the Burroughs Wellcome Fund Career Award at the Scientific Interface, a **transition toward independence grant**, that supported the work for bioengineering an ovarian transplant at the end of my postdoc with Dr. Teresa Woodruff (primary mentor) and Dr. Ramille Shah (co-mentor) and jump-started my independent research projects. I was able to turn the results of this transition award into published and preliminary data for a recently awarded **R01** (NIH/NICHD). The **long-term goal of my lab** is to improve options for fertility and hormone restoration in patients with ovarian insufficiency. I have previously developed the bioprosthetic ovary, that supports *in vitro* follicle maturation and once transplanted, restores fertility and hormone function, which was published as a proof-of-concept in mice in *Nature Communications 2017* (4c). My lab has also recently published a matrisome map that identified variations in protein density, content, and expression within different ovarian compartments, which included variations in structural proteins and signaling molecules, in *Scientific Reports* 2019 (5a). We are currently investigating the roles of candidate matrisome proteins that may influence primordial follicle activation, the rate-limiting step in folliculogenesis that can influence the longevity of a transplant and is the first step in *in vitro* growth and maturation.

In August 2016, I began as an Assistant Professor and co-director of the Fertility & Hormone Preservation & Restoration (FHPR) Program at Lurie Children's Hospital, with Erin Rowell, MD, a pediatric surgeon. We earned recognition as one of two accelerated research initiatives (chosen from 13 proposals) for the Lurie Children's 2025 Vision campaign. This program bridges foundational reproductive endocrine research with immediate and near-future development of clinical best practice techniques as we improve fertility and hormone preservation and restoration for our patients. Therefore, **I understand first-hand** the current fertility preservation needs of our cancer patients and, importantly, the current processes for cryopreservation and potential restoration opportunities.

I have been a member of the Society for the Study of Reproduction (SSR) since 2006, currently serve on the Development Committee, and have presented at annual meetings as a trainee, fellow and faculty member. I am thrilled to share this society with my own trainees and was honored to watch my first graduate student, Nathaniel Henning, give poster presentations and flash talks. SSR is one of my favorite societies and the annual meeting is where (my husband and) I reunite with long-standing colleagues, mentors, and friends. As a ***Rising Stars in Reproductive Biology*** speaker, I would offer a unique perspective as I describe recent and ongoing innovations in my lab that span foundational and translational reproductive research that would have broad appeal to the SSR membership and virtual guests.

Ongoing and recently completed research projects include:

NIH/NICHD R01HD104683
Laronda (PI)
05/01/21– 04/30/26
Title: *Defining the microenvironment that will enable a long-term bioprosthetic ovary transplant*
The goal of this study is to define the microenvironment of the bank of potential eggs in order to develop an engineered ovarian transplant that restores safe, effective and long-term function for cancer survivors.
Role: ***Principal Investigator***

Burroughs Wellcome Fund #1014568
Laronda (PI)
07/01/15–12/30/20
Title: *Engineering an artificial ovary to restore fertility and endocrine function in cancer survivors*
The mentored portion of this grant focuses on creating the components necessary for developing an artificial ovary using human induced pluripotent stem cells and intelligently designed 3D printed scaffolds. As an independent investigator, the endocrine organ will be assembled and tested in animal models of primary ovarian insufficiency.
Role: ***Principal Investigator / Postdoctoral Research Fellow (1 year) to Tenure-Track Faculty (4+ years)***

NIH/NICHD P50HD076188
Woodruff (PI); Role: Contributor, Postdoctoral Research Fellow
04/01/15–03/31/19
Title: *Measuring and Modifying the Human Follicle Environment to Improve Infertility*
Our aims are to develop new ways to support human in vitro follicle growth and to test egg quality with the goal of inventing methods that provide reliable ways to obtain high quality female gametes.
Role: ***Contributor, Postdoctoral Research Fellow***

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021-	Course co-Director (with Kara Goldman, MD), *Translational Topics in Fertility Preservation and Oncofertility* (REPR-SCI_430-0), Master's in Reproductive Science and Medicine, NU
2016-	**Assistant Professor**, Department of Pediatrics, Divisions of Endocrinology and Pediatric Surgery, Feinberg School of Medicine, NU
2016-	**Investigator**, Stanley Manne Children's Research Institute, Ann & Robert H. Lurie Children's Hospital of Chicago
2016-	**Director** of Basic and Translational Research, Fertility & Hormone Preservation and Restoration Program, Ann & Robert H. Lurie Children's Hospital of Chicago
2015,2016	Teacher – Women's Health Science Program, High school students and undergraduate research mentors, NU
2014	Postdoc Student Leader –Tissue Engineering and Regenerative Medicine Course, The Center for Talent Development, Equinox 2014 Summer Program
2010-2014	Faculty – Oncofertility Saturday Academy, Women's Health Research Institute, NU
2009	Science Writer – Clinical and Translational Research Working Group, Office of Research on Women's Health, NIH
2008-2010	Teacher's Assistant – Medical Microbiology Laboratory, Feinberg School of Medicine, NU
2004	Research Assistant – Frontiers in Reproduction, Marine Biological Labs, Woods Hole, MA
2003	Senior Scientist – BSC CityLab, Bridgewater State College, Bridgewater, MA

2003 Course Assistant – Undergraduate Biology for Non-Majors, Bridgewater State University, Bridgewater, MA

Honors (selection)

2019 Early Investigator Award, Endocrine Society
2016- Warren & Eloise Batts Scholar (yearly endowment)
2016 TEDx NorthwesternU Speaker: Beyond Boundaries
2015-2020 Burroughs Wellcome Fund: Career Awards at the Scientific Interface
2015 Office of Postdoctoral Research Scholarship Award, Kellogg School of Management Course: Business for Scientists and Engineers
2015,2016 John and Lillian Mathews Regenerative Medicine Endowment Fund
2014 Constance Campbell Memorial Research Award, Platform Presentation at the 33rd Annual Minisymposium on Reproductive Biology
2013 Marine Biological Laboratory Scholarship, *Frontiers in Stem Cells & Regeneration* Course
2012 Lalor Merit Award, Society for the Study of Reproduction 45th Annual Meeting
2004 Beta Beta Beta, National Biological Honor Society
2004 *Magnum cum laude*, Bridgewater State College
2004 Adrian Tinsley Program for Undergraduate Research Grant Recipient
2003 Prof. L.C. Stearns Memorial Scholarship Award Recipient, Bridgewater State College
2002-2004 Departmental Honors Program Completed, Bridgewater State College

C. Contributions to Science

1. ***Mechanisms of progenitor cell differentiation within reproductive organs:***

Undifferentiated or progenitor cells are influenced by their niche environment, and I have been intrigued by these mechanisms in reproductive organs. First as a graduate student, I established key aspects of the first wave of spermatogenesis in neonatal murine pups. I discovered that *Sox3* is necessary for spermatogonial differentiation and without intrinsic expression of this gene, the cells were held at the transitional signal from the Sertoli cells. This caused a failure in the first wave of germ cells to differentiate and caused disrupted spermatogenesis in adult animals (1a). While working toward my Ph.D., I collaborated with other investigators on the transcriptional regulation of non-classical estrogen signaling in cells and the impact of these signals on male fertility (1b). I expanded my training in reproductive biology with a postdoctoral appointment in the Department of Obstetrics and Gynecology, by exploring the effects of diethylstilbestrol, a synthetic estrogen prescribed to pregnant women until the 1970s, on vaginal epithelium and cervicovaginal adenosis development in fetal and prenatal mice (1c). This work demonstrated the essential TGF-β signaling cascades toward transcriptional regulation that are necessary for pliable cell fate decisions. I broke down the molecular mechanism from the signal of the vaginal mesenchyme to the progenitor Müllerian duct epithelium and identified the point that was disrupted by diethylstilbestrol that leads to vaginal adenosis (1d). This training has influenced research on the effect of the ovarian microenvironment and TGF-β signaling cascades that control primordial follicle activation that is ongoing in my independent lab.

a. **Laronda MM**, Jameson JL. Sox3 Functions in a Cell-Autonomous Manner to Regulate Spermatogonial Differentiation in Mice. ***Endocrinology***. 2011; 152(4):1606-15. PMCID: PMC3060639.
b. Weiss J, Bernhardt ML, **Laronda MM**, Hurley LA, Glidewell-Kenney C, Pillai S, Tong M, Korach KS, Jameson JL. Estrogen Actions in the Male Reproductive System Involve Estrogen Response Element-Independent Pathways. ***Endocrinology*** 2008 Dec; 149(12): 6198–6206. PMCID: PMC2613049
c. **Laronda MM,** Unno K, Ishi K, Serna VA, Butler LM, Mills AA, Orvis GD, Behringer RR, Deng C, Kurita T. Diethylstilbestrol induces vaginal adenosis by disrupting SMAD/RUNX1-mediated cell fate decision in the Müllerian duct epithelium. ***Developmental Biology***. 2013; 381, 5–16. PMCID: PMC3947918.
d. **Laronda MM**, Unno K, Butler LM, Kurita T. The development of cervical and vaginal adenosis as a result of diethylstilbestrol exposure in utero. ***Differentiation***. 2012; 84, 252-60. PMCID: PMC3060639.

2. ***Development of methods for preserving and supporting human folliculogenesis:***

I expanded my research acumen to develop modalities in preserving and restoring female fertility by utilizing ovarian cortical tissue pieces processed for cryopreservation. This research was supported by the Oncofertility Consortium, a collective established to preserve and restore fertility and endocrine function in patients whose treatments cause off-target, toxic effects in the ovary. Under Professor Teresa Woodruff's mentorship, I led collaborative groups on successful research projects that advance *ex vivo* culture in this field. Current standard preservation procedures include removing the cortical region of one ovary, where the follicle reserve resides.

These strips can be preserved for future use in restoring fertility through transplantation. I developed a clinical-grade kit for vitrifying these cortical strip tissues, a potential improvement over the slow-freezing method currently performed (2a). Additionally, I contributed to some fundamental guidelines for transporting ovarian tissue, identifying cortical strip tissue that contained follicles without disrupting their environment and culturing these follicles to support *ex vivo* folliculogenesis. We found that over six weeks, all patient strips cultured were able to undergo folliculogenesis, secreted estradiol, and that the strips contained all classes of follicles (2b). At this point the secondary follicles could be isolated and matured *in vitro* through alginate encapsulation protocols. My primary research focus remains in fertility preservation and Oncofertility and I hope to insight this passion into the next generation of scientists as co-Director of the first graduate-level course at NU, titled *Translational Topics in Fertility Preservation and Oncofertility*. This is also apparent in my role as co-Director of the FHPR program at Lurie Children's, where I have published several papers on using laparoscopic surgeries for ovarian procurement for fertility preservation (2c,d), and voiced opinions about current OTC procedures (***Fertility and Sterility Dialog***. 2020; Mar 26, 2020).

a. **Laronda MM**, McKinnon KE, Ting AY, Le Fever AV, Zelinski MB, Woodruff TK. Good manufacturing practice requirements for the production of tissue vitrification and warming and recovery kits for clinical research. ***JARG***. 2017; 34, 291-300. PMCID: PMC5306410
b. **Laronda MM**, Duncan FE, Hornick JE, Pahnke J, Whelan KA, Shea LD, Woodruff TK. Alginate encapsulation supports the growth and differentiation of human primordial follicles within ovarian cortical tissue. ***JARG.*** 2014; 31, 1013-1028. PMCID: PMC4130945. ***** Relative Citation Ratio (as of 3/25/2021) 3.64
c. Corkum KS, **Laronda MM** & Rowell EE. A review of reported surgical techniques in fertility preservation for prepubertal and adolescent females facing a fertility threatening diagnosis or treatment. ***Am J Surg*** 2017; 214(4), 695–700. PMCID: PMC6003699
d. Rowell EE, Corkum KS, Even KA, **Laronda MM**. Ovarian tissue health after laparoscopic unilateral oophorectomy: A porcine model for establishing optimized fertility preservation techniques in children. ***J Pediatric Surgery***. 2020;S0022-3468(19)30899-1. doi:10.1016/j.jpedsurg.2019.12.014 PMID: 31983401

3. ***Establish unique resources to understand differences in sex development:***

As part of our collaborative effort in FHPR, we have established the first (and currently only) IRB protocol for gonadal tissue cryopreservation in patients with Differences in Sex Development (DSD, 3a,b). I established the processing standard operating procedure and worked with the Gender and Sex Development program to identify health challenges for this diverse patient population. Dr. Courtney Finlayson and I co-mentor students, including one that was supported by the Endocrine Society Summer Fellowship to perform *Efforts in advancing fertility restoration options for Turner Syndrome patients*, to be presented at ENDO2022. By collecting research specimens within the GTPS and DSD clinics, we have established a bank of peripheral blood mononuclear cells with unique DSD mutations. My lab has created the first human induced pluripotent stem cell (iPSC) lines from patient specimens at Lurie Children's and the manuscript describing the first two lines from a patient with Complete Androgen Insensitivity Syndrome was recently accepted (3c). My lab has also developed an iPSC protocol to create granulosa-like cells that produce estradiol. These advancements could lead to personalized hormone replacement therapies (*research ongoing,* 3d).

a. Harris, CJ, Corkum KS, Finlayson C, Rowell EE, **Laronda MM,** Reimann MB, Yerkes EB, Cheng EY, Johnson EK, Establishing an Institutional Gonadal Tissue Cryopreservation Protocol for Patients with Differences of Sex Development. ***J Urology*****.** 2020; 204(5):1054-1061
b. Johnson EK, Finlayson C, Finney EL, Harris CJ, Tan SY, **Laronda MM**, Lockhart BA, Chen D, Rowell EE, Yerkes EB. Gonadal Tissue Cryopreservation for Children with Differences of Sex Development. ***Hormone Research Paediatics*** 2019; 92(2):84-91
c. Schwartz, GB, Kubo H, **Laronda MM**. Generation of two induced pluripotent stem cell lines to study complete androgen insensitivity syndrome. ***Stem Cell Research*** 2021 *accepted 6/20/2021*
d. Kubo H, Even KA, Henning NFC, **Laronda MM**. *Characterization and generation of ovarian follicle support cells.* ***Illinois Symposium on Reproductive Medicine*** 2019; Chicago, IL, *poster presentation*

4. ***Engineering the ovarian follicle niche to restore function:***

I have initiated puberty in ovariectomized mice with a decellularized ovary scaffold and primary granulosa cells. This environment also supported folliculogenesis, from denuded or primordial follicles to large antral follicles, and established hierarchy within the implant (4a). I used similar ECM-based materials to extend cultures of human and Rhesus macaque ovaries which produced estradiol for 8 weeks (4b). Additionally, I have investigated several architectural designs to determine a functional niche for murine follicles to differentiate and produce

fertilizable eggs *in vitro* and as an implant. This bioprosthetic ovary restored folliculogenesis, hormone cyclicity, fertility and lactation in a mouse whose ovaries were removed (4b). This scaffold is scalable, as it is made with a 3D printer, and gelatin. Therefore, this 3D printed bioprosthetic ovary is poised for translation into larger animal models and clinical applications and has received immense recognition from many news outlets, including NPR, Scientific American and TIME. This work also resulted in an issued patent (4d). The independent continuation of this project expanded in my lab into stem cell-based regenerative medicine (section 3) and mapping the ovarian microenvironment (section 5).

a. **Laronda MM,** Jakus, AE, Whelan KA, Wertheim JA, Shah RN, Woodruff TK. Initiation of puberty in mice following decellularized ovary scaffold transplant. ***Biomaterials.*** 2015, 50, 20-29. PMCID: PMC4350019. *Relative Citation Ratio (as of 3/25/2021) 4.88 **Editor's Choice: Science Translational Medicine, 277, 27 (2015)*
b. Jakus AE, **Laronda MM**, Rashedi AE, Robinson CM, Lee C, Jordan SW, Orwig KE, Woodruff TK, Shah RN. "Tissue Papers" from Organ-Specific Decellularized Extracellular Matrices. ***Advanced Functional Materials***. 2017; 245 1-14. PMCID: PMC5665058. ***** Relative Citation Ratio (as of 3/25/2021) 4.36
c. **Laronda MM**, Rutz AL, Xiao S, Whelan KA, Duncan FE, Roth EW, Woodruff TK., Shah RN. A 3D printed bioprosthetic ovary restores function in sterilized mice. ***Nature Communications***. 2017; 8, 15261-15271 PMCID: PMC5440811 * Altmetric Score 2272, ranked 99th percentile (3/2021), *Relative Citation Ratio (as of 3/25/2021) 14.90
d. **Laronda MM**, Rutz AL, Shah RN, Woodruff TK. *Artificial Ovary*. (**U.S. Patent** 10,479,980 B2, issued Nov. 2019)

5. ***Mapping the ovarian microenvironment:***

The efficacy and longevity of an ovarian transplant depends on the number of primordial follicles that remain quiescent and the rate at which they activate, grow, and ovulate. There is an immediate spike of increased activation of primordial follicles upon transplantation of OTC tissue, which results in depletion of the oocyte pool (~80 % loss). This loss has been attributed in part to the disruption of the microenvironment and release of the primordial follicles from their stiff matrix during OTC processing. Additionally, healthy egg production over a women's lifespan is a bell-shaped curve where oocytes retrieved from women less than 22 years old have a decreased maturation rate and increased aneuploidy rate than those oocytes from women of the ideal reproductive age. Therefore, we must understand the mechanisms of how to regulate primordial follicle activation and define the necessary microenvironment that will support good quality eggs for the many pediatric and adolescent patients that use OTC or even ovarian stimulation for egg retrieval for fertility preservation. The follicular microenvironment is made up of biochemical and physical cues and a heterogeneous stromal cell population. We have mapped the extracellular matrix proteins across the porcine ovary (6a), confirmed patterns of critical proteins that may influence folliculogenesis in bovine and human ovaries, and have mapped the physical rigidity of bovine ovaries (4b). This ongoing research is supported by my NICHD/NIH *R01HD104683*. There is a need for the field to understand the ovarian microenvironment and to this end the NIH Working Group for Ovarian Anatomy Nomenclature was formed to define and expand as we make future spatial transcriptomics and proteomics discoveries. I am excited to lead the Sub-Anatomy Group and bring my unique perspective on ovarian biology transformations that occur through the pubertal transition, and perspective on matrisome protein localization, to create a pliable resilient ontology tool to serve as a blueprint for ovarian health and disease.

a. Henning NF, LeDuc RD, Even KA, **Laronda MM**. Proteomic analyses of decellularized porcine ovaries identified new matrisome proteins and spatial differences across and within ovarian compartments. ***Scientific Reports*****.** 2019;9(1):20001. PMCID: PMC6934504
b. Henning NFC, Schwartz GB, Kubo H, Tsui EL, Diaz AA, **Laronda MM**. *Defining the Contributions of the Matrisome to the Physical Properties of the Bovine Ovary to Support the Design of an Engineered Ovarian Environment.* ***Stanley Manne Research Institute. Research Scholar Day*** 2021; virtual

Publications can be obtained:

https://www.ncbi.nlm.nih.gov/sites/myncbi/monica.laronda.1/bibliography/48231129/public