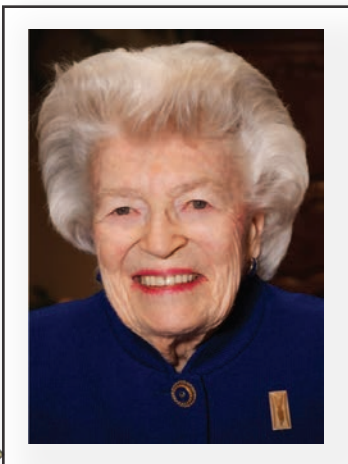


Wilkinson and Colleagues USE A LEADING-EDGE TECHNIQUE TO MORE PRECISELY DEFINE THE CELL TYPES PRESENT IN BOTH NEWBORN AND ADULT HUMAN TESTES. THE RESULTS OPEN A PATH FOR NEW STRATEGIES TO TREAT MALE INFERTILITY WITH STEM CELLS

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◆ CHAMPION OF WOMEN'S HEALTH AND EDUCATION, PALLIATIVE CARE PIONEER,
Doris A. Howell (1923-2018)

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DEPARTMENT AMONG THE BEST FOR POST-DOCTORAL FELLOWS,
 PAM MELLON RECOGNIZED BY UCSD FOR MENTORSHIP: PAGE 2

Letter from the Chair



Dear Colleagues,

Happy 2019.

Welcome to our second quarterly Department Newsletter, which comes with the Lunar New Year. The quarter reflects a busy time, with labs and clinics buzzing across the department and many grants being submitted. Despite a little bit of rain, we continue to enjoy some of the best weather in the country. The rain promises a spectacular green spring for the region. Even our collaborators in Northern California may be envious.

Not long after our last FQ was published, we lost Dr. Doris Howell, a long-time local champion and advocate for women's health in San Diego. Dr. Howell acted in this role for decades. Prior to her passing, the Doris A. Howell Foundation was started in her honor. It has been an important source of research funding for Women's Health Issues across San Diego. Within our department, this includes a key funding mechanism for our undergraduate research trainees. Learn more about Dr. Howell as well as the Howell Foundation in our Milestones Section on page 6.

Investigator-initiated trials are key pillars that support, and bridge, our research and clinical enterprises. We congratulate Sanjay Agarwal who has just been awarded funding for a new trial of *Anakinra* in endometriosis, as well as our other recent awardees.

In this edition, our *Bench to Bedside* section will focus on the most recent studies of the Wilkinson Lab, which provides us with a new and unprecedented understanding of male fertility. In this case, Miles and his colleagues use single cell sequencing to begin to understand patterns of gene expression among the different cells present in male spermatogonia. There are some surprising findings that are likely to impact the male component of infertility in the future.

In the *At the Frontier* section, we again feature some of our recent research and clinical publications. These come from the middle of November into early February. We also continue to meet new faculty members in our growing department, this time talking to Gillian "Jill" Mackay and Jerry Ballas. We have a trend of rapid adaption to San Diego among our new recruited physicians. This continues to be true, with Jill and Jerry noting their family's appreciation of the mild winters and amenities such as bilingual schools for their children.

However, in addition to the continuing content in *Fimbria Quarterly*, we look forward to introducing new elements to the next issue. We'll have new articles on our clinical practice and educational missions.

Hope you enjoy this and find it informative. Please forward it on to colleagues if you do.

Charles Nager, MD

CHARLES NAGER
Distinguished Professor and Samuel Yen Chair
 Department of Obstetrics, Gynecology
 & Reproductive Sciences

DEPARTMENT OF OBSTETRICS, GYNECOLOGY
 & REPRODUCTIVE SCIENCES DIVISION CHIEFS

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News & New Arrivals

Pamela Mellon Recognized for Career-long Excellence in Developing Scientists

In November of 2018, our own Pamela L. Mellon, Ph.D., Distinguished Professor of OB/GYN and Reproductive Sciences was awarded the inaugural

Excellence in Mentoring Award

Pam stands out among a cadre of well recognized mentors within the UCSD health science faculty as the first ever recipient of this award. This reflects her tireless contributions to the development of student, post-doctoral and junior faculty members. She shared the honor with Victor Nizet from the Department of Pediatrics. The award was announced at the Health Sciences Excellence in Mentoring Celebration on November 14, 2018, where the Chair of Obstetrics, Gynecology and Reproductive Sciences, Dr. Charles Nager, introduced her.

Dr. Nager noted in the nomination letter that mentoring junior faculty is an essential responsibility in the Health Sciences. Dr. Mellon not only recognized this as a key role early in her career, but proceeded to fulfill that role spectacularly. Her dedication and skills at mentoring are exceptional and her approaches successful. She has given her time and focus generously to junior faculty, nurturing their careers carefully and providing key support for their development into successful future leaders of our Health Sciences faculty.



Dr. Mellon is a past awardee of the post-doctoral mentoring award (pictured above), and co-directs our department's junior faculty mentoring program with Dr. Christine Miller, M.D. The program provides structure and leadership for the important endeavor of developing successful careers of our junior faculty.

Postdoctoral Trainees in Obstetrics, Gynecology and Reproductive Sciences among the most satisfied in San Diego

The UC San Diego Office of Postdoctoral and Visiting Scholar Affairs recently conducted a survey of postdoctoral fellows appointed during the 2018-2019 academic year in order to assess their overall satisfaction with their environment and training. The survey included 40+ departments and research units across the UC San Diego main campus, The Scripps Institute of Oceanography, and the School of Medicine. Postdocs within Obstetrics, Gynecology and Reproductive Sciences ranked second in the Medical School and fourth overall in satisfaction.

The Postdocs ranked the department with a mean score of 4.32 on a 5 point scale across 54 questions. Department strengths included the physical work environment, mentor support, opportunities to share work, understanding the mentor's research mission, and the ability of postdocs to make recommendations without (negative) consequence. Over 1200 Postdocs and visiting scholars are present on campus - among the largest across the entire UC system. The results were noted by Mark Lawson, the UCSD Faculty Director for Postdoctoral Training and Education. Lawson's role is to improve postdoctoral training practices and support training program directors in developing or improving their programs with support from the Office of Research Affairs.

In Funding news...

We congratulate **Varykina Thackray** who was awarded an R01 grant to study the Role of the Gut Microbiome in Polycystic Ovary Syndrome. **Sanjay Agarwal** received SOBI funding for a PI-Initiated Clinical Trial Pilot study of the IL-1 antagonist Anakinra for endometriosis. **David Schlaepfer** and **Dwayne Stupack** just received a Department of Defense Pilot award for their continuing research on Ovarian Cancer Immune Evasion, and **Sheila Mody** received a Doris A. Howell Foundation Community Engagement Initiative Award.

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Bench & Bedside

How Men Continually Produce Sperm — and How that Discovery Could Help Treat Infertility

The production of sperm — otherwise known as spermatogenesis — generates more than 1,000 sperm per second in normal males. This productivity comes, in part, from a special cell type called the spermatogonial stem cell. The staying power of this stem cell has allowed men, and most famously celebrities such as Robert DeNiro and Pablo Picasso, to father children after the age of 65.

Yet spermatogonial stem cells have not been well studied in humans, and attempts to grow them in the lab for clinical purposes have had limited success. Now, researchers at University of California San Diego School of Medicine used a technique called single-cell RNA sequencing to develop a clearer picture of human spermatogonial stem cells and how sperm are formed. They also developed tools to better isolate these stem cells, making the technique possible. The study was published February 5th in *Cell Reports* (1).

This advance opens the possibility that spermatogonial stem cell transplants could be developed to treat male infertility, an issue that affects more than 100 million men worldwide.

“Single-cell RNA sequencing determines the activity of hundreds of genes in the genomes of single cells,” said senior author Miles Wilkinson, PhD, professor in the Department of Obstetrics, Gynecology and Reproductive Sciences at UC San Diego School of Medicine. “Because each cell type has a different combination of active genes, this technique allows new cell types to be identified. Applying this approach to the testis, we uncovered many different stages of sperm precursor cells in human testes.”

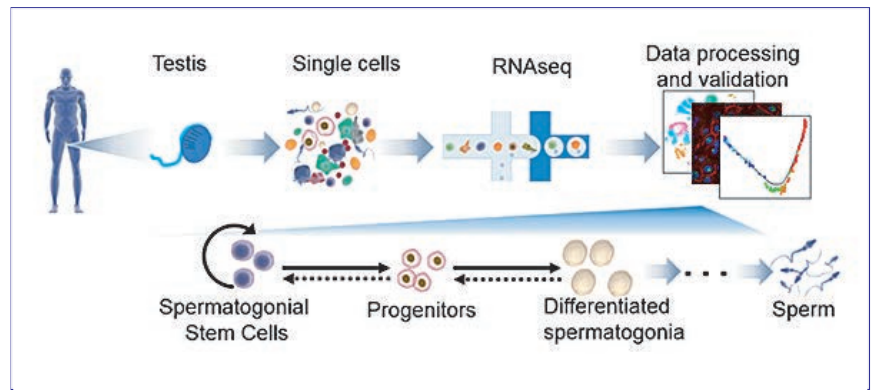
1. [https://www.cell.com/cell-reports/fulltext/S2211-1247\(19\)30063-4](https://www.cell.com/cell-reports/fulltext/S2211-1247(19)30063-4)

Fimbria
QUARTERLY

In adult human testes, the researchers identified several cell subtypes that likely include the spermatogonial stem cells. They also found cells that displayed characteristics of spermatogonial stem cells present in human newborns.

“Given that spermatogonial stem cells are not necessary for generating sperm until puberty, this finding in newborns raises the possibility that these cells perform as-of-yet unknown functions in infants and young children,” Wilkinson said.

Their study also identified many unique molecules — biomarkers — that define spermatogonial stem cells. These new biomarkers, which they detected with specific antibodies, allowed the researchers to efficiently capture human spermatogonial stem cells.



Wilkinson’s team also identified the genes active in other cells that support spermatogonial stem cells. The finding may help researchers develop protein cocktails that drive spermatogonial stem cell proliferation in the laboratory, and allow them to scale up enough of the cells for clinical applications. “This was a proof-of-principal for future clinical studies to use spermatogonial stem cell therapy as a means to treat men suffering from infertility, including cancer patients rendered infertile by chemotherapy,” said Wilkinson.

The co-authors of this international study include: Abhishek Sohni, Kun Tan, Hye-Won Song, Dana Burow, Louise Laurent, Tung-Chin Hsieh who are also from UC San Diego; American collaborators Saher Sue Hammoud of University of Michigan Medical School and Raja Rabah of Michigan Medicine CS Mott and Von Voigtlander Women’s Hospitals; Dirk G. de Rooij of Utrecht University in the Netherlands; and Elena Vicini of the Sapienza University of Rome in Italy.

—H. Buschman.

New Faculty

Jerry Ballas & Gillian Mackay

The department continues to grow! *Fimbria Quarterly* (FQ) recently talked with two of the newer clinical faculty, Jill Mackay of Obstetrics and Gynecology, and Jerry Ballas from Maternal Fetal Medicine.



FQ: You were both born pretty far from San Diego?

GM: I was born in Edinburgh, Scotland and lived in Lebanon until I was almost a year old after which my parents moved back to Scotland. When I was five years old my parents moved to England where I spent the rest of my childhood in places with proper English names, like Hertfordshire and Hampshire.

JB: I was born in New York City. Not as far as Scotland, but my family moved upstate to the small town of Warwick, also a proper English name and also when I was five years old. I grew up with cows and cornfields within commuting distance to the city, so I feel as if I got the best of both worlds. When it was time for college, however, I knew it was time to leave the countryside for good and I headed to Boston for college. I completed medical school at SUNY Downstate in Brooklyn, NY, then I did my OB/GYN Residency at SUNY Stony Brook in Long Island. I may look familiar to folks because I completed my MFM Fellowship here at UCSD in 2013, then went on a 4 and half year adventure to Houston where I was faculty at Baylor College of Medicine before returning to UCSD last January.

FQ: Gillian, your path was different?

GM: I attended University College London Medical School and did some initial house officer training at the Whittington Hospital and Kings College Hospital in London. Then, in 2003 I moved to Boston and completed residency at Tufts Medical Center. Since graduating from residency I have worked at various academic centers (Massachusetts General Hospital, UCLA, Oklahoma University and University of Basel, Switzerland).

FQ: And the academic environment attracted you to UCSD?

GM: Yes. I wanted to continue to provide care in an academic center, to manage more complex patients, and to continue to be involved in resident and student teaching.

JB: Exactly. The skills and experienced I gained during my MFM Fellowship here, and the faculty and staff I met, were second to none. Having worked and trained in departments both large and small, in inner cities and outer suburbs, from one coast to the other (and Texas in between), I came to realize UCSD offered me the size, flexibility, teaching environment and professional pathway I was looking for at this point in my career.

FQ: With your goal being?

JB: Building on the professional skills I've acquired since finishing fellowship and bringing some new knowledge and different perspectives to our department. Teaching has always been one of my main focuses and I look forward to contributing to student, resident and fellow education. Ultimately, I want to leverage the longstanding tradition of Maternal-Fetal Medicine at UCSD to help grow and expand our reach, both locally and nationally, through outreach, research and advocacy.

GM: Exactly. In short, to provide the best care possible to patients, while at the same time training the next generation of physicians.

New Faculty *con't*

FQ: Has your family adjusted to San Diego?

GM: My husband Alex is a reproductive endocrinologist working at Reproductive Partners in La Jolla. He is enjoying his work very much. He is originally from Germany. Our 6 year old twins, Ella and Sebastian have settled in well to life in San Diego. They attend the Albert Einstein Academy Charter School in South Park which is a German Bilingual School.

JB: My wife, Regina, finished her Child Neurology Fellowship in Houston this past October and is now faculty here at UCSD in the Department of Neurology and in the Division of Child Neurology at Rady Children's Hospital. Our three year old daughter, Violet, is adjusting to San Diego well. She loves the ocean, Balboa Park and the Zoo, and being able to ride her bike or scooter anytime she wants.

FQ: The city has been good for family activities?

JB: Not only family activities. I am a firm believer in coworker camaraderie both inside and outside the hospital. Bonds are also made outside of work, so I keep a look-out for social gatherings, happy hours, and any excuse to go out and get food or order in. I'm a huge fan of comic books, baseball and music, so if anyone is interested in Comic Con, a Padres game (especially if the Mets are in town) or catching a rock n' roll show, let me know.

FQ: We definitely will.

At the Frontier

Recent Publications:

Since November, Department members have been productive, including these 14 publications:

1. Design of a randomized controlled trial on the efficacy of a reproductive health survivorship care plan in young breast cancer survivors. Stark SS, Natarajan L, Chingos D, Ehren J, Gorman JR, Krychman M, Kwan B, Mao JJ, Myers E, Walpole T, Pierce JP, Su HI. *Contemp Clin Trials*. 2019 Feb;77:27-36. doi: 10.1016/j.cct.2018.12.002. Epub 2018 Dec 12. PMID: 30553078
2. Sex, Microbes, and Polycystic Ovary Syndrome. Thackray, VG. *Trends Endocrinol Metab*. 2019 Jan;30(1):54-65 .

At the Frontier *con't*

3. A microRNA cluster in the Fragile-X region expressed during spermatogenesis targets FMR1. Ramaiah M, Tan K, Plank TM, Song HW, Dumdie JN, Jones S, Shum EY, Sheridan SD, Peterson KJ, Gromoll J, Haggarty SJ, Cook-Andersen H, Wilkinson MF. *EMBO Rep*. 2019 Feb;20(2). pii: e46566. doi: 10.15252/embr.201846566. Epub 2018 Dec 20. PMID: 30573526
4. Nonsense-mediated RNA decay in the brain: emerging modulator of neural development and disease. Jaffrey SR, Wilkinson MF. *Nat Rev Neurosci*. 2018 Dec;19(12):715-728. doi: 10.1038/s41583-018-0079-z. Review. PMID: 30410025
5. Urinary symptoms are associated with certain urinary microbes in urogynecologic surgical patients. Fok CS, Gao X, Lin H, Thomas-White KJ, Mueller ER, Wolfe AJ, Dong Q, Brubaker L. *Int Urogynecol J*. 2018 Dec;29(12):1765-1771. doi: 10.1007/s00192-018-3732-1. PMID: 30116843
6. Reduced Uteroplacental Perfusion Pressure (RUPP) causes altered trophoblast differentiation and pericyte reduction in the mouse placenta labyrinth. Natale BV, Mehta P, Vu P, Schweitzer C, Gustin K, Kotadia R, Natale DRC. *Sci Rep*. 2018 Nov 21;8(1):17162. doi: 10.1038/s41598-018-35606-x. PMID: 30464252
7. Haploinsufficiency of SIX3 Abolishes Male Reproductive Behavior Through Disrupted Olfactory Development, and Impairs Female Fertility Through Disrupted GnRH Neuron Migration. Pandolfi EC, Hoffmann HM, Schoeller EL, Gorman MR, Mellon PL. *Mol Neurobiol*. 2018 Nov;55(11):8709-8727. doi: 10.1007/s12035-018-1013-0. PMID: 29589282
8. CD44ICD promotes breast cancer stemness via PFKFB4-mediated glucose metabolism. Gao R, Li D, Xun J, Zhou W, Li J, Wang J, Liu C, Li X, Shen W, Qiao H, Stupack DG, Luo N. *Theranostics*. 2018 Nov 29;8(22):6248-6262. doi: 10.7150/thno.28721. PMID: 30613295
9. Lipophilic statins inhibit growth and reduce invasiveness of human endometrial stromal cells. Sokalska A, Hawkins AB, Yamaguchi T, Duleba AJ. *J Assist Reprod Genet*. 2018 Dec doi: 10.1007/s10815-018-1352-9. PMID: 30554393
10. The mysteries of menopause and urogynecologic health: clinical and scientific gaps. Alperin M, Burnett L, Lukacz ES, Brubaker L. *Journal of The North American Menopause Society*. 2018;26(1): 103-111. DOI 10.1097/GME0000000000001209. PMID:30300297
11. Nonsense shielding: protecting RNA from decay leads to cancer. Wilkinson MF, Cook-Andersen H. *EMBO J*. 2019 Feb 1;38(3). pii: e101417. doi: 10.15252/emj.2018101417. PMID: 30679197.
12. Year in Review 2018: Microbiome Urobiome Updates: Advances in Urinary Microbiome Research. Alan Wolfe and Linda Brubaker *Nature International Journal of Science*. <https://www.nature.com/articles/s41585-018-0127-5>.
13. The Neonatal and Adult Human Testis Defined at the Single-Cell Level. Sohni A, Tan K, Song HW, Burow D, de Rooij DG, Laurent L, Hsieh TC, Rabah R, Hammoud SS, Vicini E, Wilkinson MF. *Cell Rep*. 2019 Feb 5;26(6):1501-1517.e4. doi: 10.1016/j.celrep.2019.01.045. PMID: 30726734.
14. The Prevention of Lower Urinary Tract Symptoms (PLUS) in girls and women: Developing a conceptual framework for a prevention research agenda. Brady SS, Bavendam TG, Berry A, Fok CS, Gahagan S, Goode PS, Hardacker CT, Hebert-Beirne J, Lewis CE, Lewis JB, Kane Low L, Lowder JL, Palmer MH, Wyman JF, Lukacz ES; Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium. *Neurourol Urodyn*. 2018 Nov;37(8):2951-2964. doi: 10.1002/nau.23787. PMID: 30136299

Milestones

Doris Howell 1923-2018

Doris A. Howell Foundation for Women's Health.

Doris A. Howell, M.D., initially trained as a Pediatric Hematologist/Oncologist, but in time would become a pre-eminent, internationally renowned leader in pediatrics and hospice care. A graduate of McGill University, Dr. Howell held faculty positions at both the Harvard and Duke Schools of Medicine prior to becoming chair of the Department of Pediatrics at the Medical College of Pennsylvania. In 1974, she joined the faculty at UCSD Medical School as chair of the the Department of Community and Family Medicine.

Dr. Howell immediately embraced the hospice concept as a radical departure from the established way of dealing with the dying and their families. Her reputation as a hospice pioneer followed her when she moved to UCSD. Serving on the San Diego Hospice Board of Directors since its inception, she was a driving force for San Diego Hospice, now a model recognized throughout the nation. She was elected Director Emerita in 1989, and received national awards for leadership and service. Among others, Dr. Howell received Service awards from the American Academy of Pediatrics, and the Humanism in Medicine Award from the Health Care Foundation of New Jersey. She has been further honored by the Rotary of San Diego, MacLaggen Award; the Salvation Army Woman of Distinction Award; the Elderhelp Essence of Life Award; and the Soroptimists International of La Jolla Woman of Distinction Award.

Following her formal retirement, Dr. Howell next focused upon the need to improve women's health care, research and education. With members of Soroptimist International of La Jolla, she began awarding research grants to young scholars. The Soroptimists honored Dr. Howell by establishing the Doris A. Howell Foundation for Research in Women's Health, an independent nonprofit foundation, in 1995. Grants have been awarded for research and service at each of the major San Diego County institutions, including UCSD, SDSU, and USD as well as CSU San Marcos. Dr. Howell was a driving and vital force in both the selection and the realization of these goals.

The Undergraduate Research Initiative

The Foundation's most important goal has been to fund undergraduate research scholarships focused on Women's Health. To date, the Howell Foundation has provided 241 scholarships and has contributed over \$680,725 towards boosting undergraduate student research efforts. Students are chosen according to a strict protocol, with a focus on both the quality of the students' scholarship application as well as the quality of supervision they will receive during their research. This supervision has become known as the "Mentor Program" and is the lifeline to the program's success. Each student must have a qualified mentor to direct and guide them.

The research subjects encompass basic life sciences, such as cell biology, to clinical problems such as creating vaccines and testing altered immune reactions. The results of the student's research may be presented at professional conferences or published in peer-reviewed journals. In addition to financial support, the student's education and career goals are enhanced, the cutting edge of scientific knowledge is advanced, and a positive contribution is made to the community and the future of the nation.

Four scholarships were available in 2018-2019. All were awarded to UCSD undergraduate students working within the Department of Gynecology, Obstetrics and Reproductive Sciences. The awardees were:

Annie Chen (UCSD)

"Exploring the Effects of Prolonged Letrozole Treatment on Metabolic Dysfunction in a PCOS Mouse Model" **Mentor:** Varykina Thackray, OGRS

Hoejeong Kim (UCSD)

"Characterization of Ly6A+ trophoblast cells in the mouse placenta" **Mentor:** David Natale, OGRS

Allison Kramer (UCSD)

"Intervening on cancer genetic counseling in young breast cancer survivors" **Mentor:** Irene Su, OGRS

Rachel Sebastian (UCSD)

"Using Placental Explants to Examine Alterations in exRNAs to varying glucose levels" **Mentor:** Louise Laurent, OGRS

Awardees (L-R) *Annie, Hoejeong, Rachel, Allison*



The back page Howell Foundation, con't

Community Engagement Initiative

The Howell Foundation made a commitment to fund research partnerships between academic and community-based organizations in 2012.



The goal of the Community Engagement Initiative (CEI) has been to support these partnerships working collaboratively to develop and evaluate programs designed to improve women's health. A priority is to ensure the development of evidence informed projects that address relevant issues affecting women's health within the greater San Diego community, with an emphasis on underserved and "at-risk" women.

To date, the Howell Foundation has awarded 6 CEI grants totaling \$100,000. Two of these have been received by members of the Department of Gynecology, Obstetrics and Reproductive Sciences.

The 2018 recipient was Dr. Sheila Moday (MD, MPH), who is the director of the Division of Family Planning. The funded project "Partnering with Refugee Women to Inform Culturally Appropriate Patient-Centered Reproductive Healthcare," is a research collaboration between the Department of Obstetrics, Gynecology and Reproductive Sciences at University of California, San Diego (UCSD), the Refugee Health Unit at the UCSD Center for Community Health, and United Women of East Africa Support Team (UWEAST).

The purpose of this collaborative study is to explore patient-provider interactions in reproductive health and adapt patient-centered reproductive health-counseling tools so that they are accessible, culturally sensitive, and appropriate for refugee women. If successful, the project has the potential to dramatically improve reproductive healthcare within this population.

Dr. Mody's project continues prior success by her departmental colleague Dr. Irene Su, who received the award in 2015. Dr. Su was then an Assistant Professor in the Division of Reproductive Endocrinology and Infertility.

Dr. Su's project, Developing a Reproductive Health Intervention for Adolescent and Young Adult Cancer Survivors, focused on the initial development and delivery of a web-based survivorship care plan with the goal of improving reproductive health issues such as fertility and pregnancy for adolescent and young adult women who have had cancer. Dr. Su also partnered with a community organization, Stupid Cancer, and worked with patient advocates and other UC San Diego cancer research and clinical faculty to conduct this study, and to pilot test the platform.

For more information on these and other activities of the Doris A Howell Foundation, please visit:

<http://www.howellfoundation.org>



Upcoming Event

1st CMI International Microbiome Meeting

jointly held with

1st Urobiome Meeting

February 26-28, 2019

University of California, San Diego

On behalf of Linda Brubaker, MD, Clinical Professor in the UC San Diego Department of Obstetrics, Gynecology, and Reproductive Sciences, we announce the 1st annual Urobiome Meeting.

Researchers will present on the emerging science of the Urobiome and its recently discovered implications for human health, including common conditions such as urinary tract infection, urinary incontinence, and bladder overactivity.