Charlene Susan Dezzutti (1964–2018) Virologist with a Passion for HIV Prevention

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EVERYONE HAS A FAMILY. Some people are lucky enough to have a second family—the family of people who you see and talk with every day at work. For those of us who worked with Charlene Dezzutti, she was like a sister. Charlene could be blunt. She could be impatient. She could make you laugh when you really needed a laugh—with her own broad smile and a beautiful dimple in her cheek. She absolutely loved what she did at work—having a passion for her research that made the rest of us more passionate about what we did every day. Charlene told us the truth even when we may not have wanted to hear it. Dr. Charlene Dezzutti, our friend and colleague, passed away on March 15, 2018 at the age of 53 after a brief but fierce battle with cancer.

Charlene was a native of Pittsburgh and earned her degree in Microbiology and Biochemistry from the University of Pittsburgh in 1986. After graduating, she moved to Columbus, Ohio, to start graduate studies in Veterinary Pathology and Cell Biology. Like many people who were drawn to work in the HIV field, Charlene saw firsthand what HIV can do to those we love. Her favorite uncle, August Pusateri (Uncle Buzz), was diagnosed with AIDS that year, and Charlene rushed back to Pittsburgh for what she thought was a death vigil at his hospital bed. Fortunately, Uncle Buzz survived that and several subsequent rounds of AIDS-related illnesses. In fact, Uncle Buzz is still with us today, one of the longest survivors participating in the Pitt Men's Study, a one-man tribute to the astonishing progress realized in the treatment of HIV. Charlene's early exposure to the impact of HIV through her uncle's journey led her to change her own career trajectory.

Charlene switched from veterinary pathology to the study of retroviruses in 1986, earned her PhD in 1989 from The

Ohio State University, and then completed a postdoctoral fellowship at Ohio State. In 1993, she joined the National Center for HIV, STD, and TB Prevention at the U.S. Centers for Disease Control and Prevention (CDC) where she worked for 13 years. She was a senior research microbiologist in the Division of HIV/AIDS Prevention—Laboratory Branch.

James Cummins, who was one of her trainees at the CDC said, “Her complexity as a person is what drew so

many of us to her—her tenacity, incredible work ethic, sharp wit, and infectious laugh. I think what cemented the bond with us was a life touched by HIV at the most personal level—myself having an HIV positive partner and Charlene a close family member; though we didn't dwell on it or spend that much time talking about it—at its core we fundamentally knew that we had committed ourselves toward developing tools to prevent HIV infections—to end this horrible disease.”

Working with James and others at the CDC, Charlene developed the polarized human ectocervical and colonic explant model systems. She and many other investigators have used these tools to gain a better understanding of how HIV infects genital and colonic tissues, and how antiretroviral drugs can disrupt infection. In 2004, Dr. Dezzutti wrote a seminal article on the comparative analysis of microbicide products in which she established some of the first benchmarks for the preclinical evaluation of agents being considered for use as topical microbicides. Before this publication, there was no established algorithm for rigorously testing microbicide products, and the article has served as a guide to the field. The article was the first to assess product safety by evaluating the impact of microbicide products on epithelial integrity and expanding testing to a broader range of HIV-1 clades from Africa and Asia.

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In 2005, to expand research supporting the development and evaluation of HIV prevention products, we recruited Charlene to the University of Pittsburgh School of Medicine and the Magee-Womens Research Institute (MWRI). She joined the University of Pittsburgh School of Medicine in the Department of Obstetrics, Gynecology, and Reproductive Sciences as an associate professor in September 2005, was awarded tenure in 2012, and was promoted to professor in 2018. She was also a member of the Graduate School of Public Health, Infectious Diseases and Microbiology (GSPH/IDM).

The major focus of Dr. Dezzutti's research at the University of Pittsburgh was the evaluation of the safety and activity of promising biomedical HIV prevention products. She was the principal investigator for the Microbicide Trials Network (MTN) Laboratory Center from its inception in 2006 until her death in 2018. In that role, she provided leadership for the work conducted in her own laboratory (product evaluation and pharmacodynamics) and six laboratories that included pharmacology (Craig Hendrix, Johns Hopkins University; Peter Anderson, University of Colorado) and others at the University of Pittsburgh, including virology (John Mellors and Urvi Parikh), mucosal immunology (Ian McGowan), pharmaceuticals (Lisa Rohan), and site support and diagnostics (Sharon Hillier).

In addition to her leadership role within the MTN, she was a project or core leader on five U19 grants funded by the NIH/NIAID and an investigator on additional U19 and R01 grants. In the last year of her life, she was awarded an R01 grant to assess the impact of contraceptive hormones on susceptibility to HIV through use of her tissue models. In addition to awards from NIH, she received a grant from the Bill and Melinda Gates Foundation to understand the inherent variability of HIV replication in cervical and vaginal tissue *ex vivo*, and she supported the work on four other Bill and Melinda Gates Foundation grants.

Advances in HIV prevention have demonstrated that the use of oral pre-exposure prophylaxis (PrEP) can reduce HIV transmission in persons who are adherent to the PrEP regimen. Topical microbicides have provided similar evidence with those highly adherent to product use showing the greatest protection from HIV infection. Despite these advancements, it has been difficult to provide evidence early in product development that there would be a benefit in using a particular drug and/or delivery method, and thus rationalize product advancement and further testing in larger clinical trials. Consequently, the lack of surrogate markers of efficacy remains a daunting challenge for the HIV prevention field.

In HIV treatment, one of the early achievements was the finding that reductions in plasma viral load in response to antiretroviral treatment were a surrogate of clinical treatment success and survival. However, for HIV prevention, there have been no recognized surrogates of efficacy proven to be relevant in clinical trials. Many of the laboratory-based tests used to evaluate products for activity against HIV were shown to be poor predictors of effectiveness in HIV prevention trials.

Dr. Dezzutti developed a method that relies on tissue biopsies taken from living donors after they have used an HIV prevention product. By preserving the complex architecture of genital tissues, this method allows the tissue biopsies to be cultured and challenged *ex vivo* with HIV—providing a means to determine whether drug present in these tissues can inhibit HIV infection. This measure of efficacy after product use was termed the *ex vivo* biopsy challenge assay. She published the method in 2013 and

implemented the *ex vivo* biopsy challenge assay in six clinical trials in which topical drug delivery (gels, films, and vaginal rings) and systemic drug delivery (oral and injectable) were evaluated. Moreover, she shared her assay with several research groups in the United States and internationally so that HIV prevention products could be evaluated expeditiously.

Dr. Dezzutti spearheaded the preclinical evaluation of the 1% tenofovir gel, which showed that this product could block HIV infection of female genital tract tissues *ex vivo*. The findings in this article were born out by the first successful clinical trial of 1% tenofovir gel in July 2010, a study that demonstrated that women using this product had a significantly decreased acquisition of HIV. A second trial (MTN-003) further showed prevention of HIV infection in women who used the gel, including additional protection against HSV-2 acquisition. As already demonstrated, Charlene's body of work has helped shape the preclinical evaluation of topical microbicide products and has changed the paradigm of preclinical product testing.

One of the many ways that Charlene gave back to others in our field was through training and mentorship of the next generation of scientists. She loved to teach all kinds of students about what it meant to be a scientist, and why science was a distinguished career choice. Every summer, the MWRI opens its doors to host high school and college students. These programs expose young people to a possible career in science and allow them hands-on experience in laboratory or clinical research.

Dr. Dezzutti was the director of the MWRI College Program between 2006 and 2013. During this time, the number of applications increased from a low of 19 in 2006 to a high of 149 in 2013. Each student presented his or her work at the end of summer during a College Program Symposium. MWRI also included a "Lunch & Learn" series for the students. After stepping down as the head of the College Program, Dr. Dezzutti continued to participate in the Lunch & Learn series so that she could expose the students to a research environment and enrich their knowledge of HIV prevention research. She had arranged to host three more students in the coming summer, a testament that she was committed to training through the end of her life.

When we reflect on Charlene's life and career, we are reminded of those lessons that we have learned from our time with her:

- (1) Commit yourself to the work you're doing.
- (2) When necessary, be tenacious, have a strong voice to stand up for what you know and believe is right.
- (3) Find your inner creativity and don't be afraid to take a chance—it just may lead to a new chapter or success in your life.
- (4) And finally, at the end of one of those days when things just seem to not be going your way: (a) Find yourself some good food—preferably a good Italian dinner. (b) Pour yourself glass of excellent red wine (but keep the bottle close by). (c) Share a laugh or two with those you care most about.

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