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PEOPLE & IDEAS

Akiko Iwasaki: Women in STEM

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Akiko Iwasaki is a Waldemar Von Zedtwitz Professor of Immunobiology, a Professor of Molecular and Cellular and Developmental Biology at Yale, and an Investigator at the Howard Hughes Medical Institute. Her laboratory works on a wide variety of topics, from mucosal immunology to viruses, and recently she published a pioneering paper showing how the meningeal lymphatic vasculature can be manipulated with VEGF-C to promote an immune response to glioblastoma. She is the future president of the American Association of Immunologists, a *JEM* Advisory Editor, has been awarded numerous prizes, and is a true Twitter celebrity. I chatted with Akiko to find out about her career so far and about being a woman in STEM.

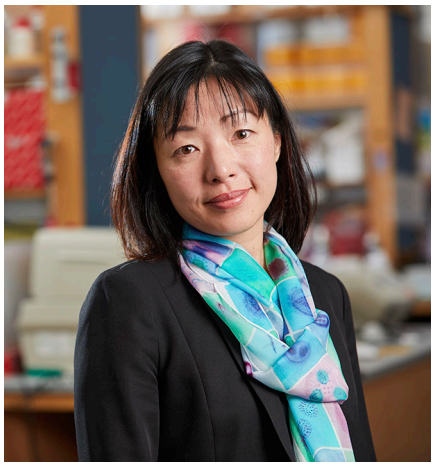
Where did you grow up?
I grew up in rural areas within the Kansai region of Japan.

When did your interest in science begin? What was your first experience of science?
My interest in science began when I discovered the joy of mathematics in ninth grade. I grew up in a society where girls were supposed to go into literature, and boys into science. While I still loved literature, I also became thrilled with math, and then physics. My interest in biology did not develop until later in college.

Where and with whom have you studied (undergraduate, graduate, postdoc)?
When I was thirteen, I went with my father and my sister to Maryland for 9 mo. My father is a physicist, and he was doing a sabbatical in University of Maryland College Park. My sister and I went to a local middle school with virtually no ability to speak or understand English. We felt so out of place! We had to quickly learn English and adjust to the American teenage culture of the 1980s. That was a formative period for me, as I was a naive teenage Japanese girl trying to figure out everything in my life on my own. Little did I know at the time that I would return to Maryland to do my postdoc years later.

My exposure to America made me bold. In the middle of high school, I went on a foreign exchange program, where I stayed with families in a small town a couple of hours outside of Toronto, Canada. After this experience, I did not want to go back to Japan, where a woman was expected to find a suitable husband and create a home for her family. That was not something I aspired to do. I saw no future for myself in Japan. That was when I decided to leave the country at the age of 16—alone. To really give myself a chance to do something I wanted to do: science. I applied to the University of Toronto and got into the undergraduate program. I did a biochemistry major and physics minor and took a lot of math courses, which I loved. In my senior year in college, I took an introductory course in immunology. I was blown away by the amazing nature of the immune system, how it interacts with various organs of the body, and how it provides protection against infectious agents. Vaccine lectures were my favorite! I fell in love with immunology, as it is a fascinating defense system against pathogens and is so relevant to human health and disease. The professor who taught the vaccine lectures was Brian Barber. I immediately asked him if I can join his laboratory—and I did a year later, as a graduate student in immunology at the University of Toronto.

As a graduate student in Prof. Barber's laboratory, I wanted to work on vaccines. Specifically, I wanted to understand how vaccines elicit protective immunity. Around this time (~1994), there was an exciting new vaccine strategy called DNA vaccines. The idea was simple and elegant. Instead of making attenuated pathogens or recombinant antigens, DNA vaccines use a plasmid DNA that encodes for an antigen of interest under a strong promoter. DNA can be injected into the muscle, and robust immune responses are elicited against the antigen. At that time, there was a notion that the muscle cells somehow become super antigen-presenting cells that stimulate T cells and are the basis for DNA vaccine's effectiveness. I wanted to test this notion using a technique I just learned in my lectures, namely, irradiation-induced bone marrow chimeric mice. This is a classic technique we



Akiko Iwasaki. Courtesy of Michael Marsland.

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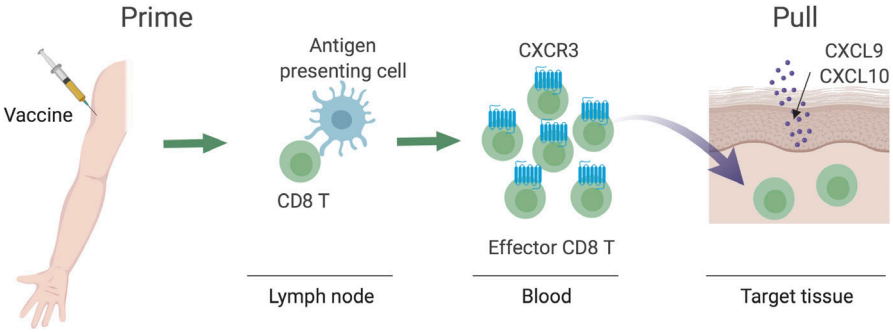

Schematic illustration of Prime and Pull vaccine strategy. The host is primed with a vaccine (in the periphery) that elicits CD8 T cell response to a desired antigen in the lymph node. Effector CD8 T cells exit the lymph node and enter systemic circulation. They express CXCR3. Once effector CD8 T cells sense chemokines (CXCL9 and CXCL10) applied to the mucosal surface in the target tissue, they exit circulation, enter the tissue, and establish tissue residency. They provide protective immunity upon viral challenge or reactivation within the target tissue. Image created with BioRender.

still use in my own laboratory, whereby we can separate the contributions of hematopoietic cells (of donor bone marrow origin) and the nonhematopoietic cells (of the host origin). By generating bone marrow chimeras with donors that lack MHC class I into wild-type hosts, I was able to show that, unlike what was believed at the time, it is the hematopoietic cells that prime CD8 T cell response upon DNA vaccination, not muscle cells (Iwasaki et al., 1997), and in collaboration with Dr. Ron Germain's laboratory at the National Institutes of Health, we showed a predominant role for directly transfected dendritic cells in antigen presentation after DNA vaccine.

At the end of my graduate studies, I became intrigued by the unknowns in the field. In particular, while most pathogens enter the host through mucosal surfaces, we knew very little about how such pathogens are taken up and presented to T cells for priming at the site of infection. I applied to a few laboratories that worked in dendritic cells and mucosal tissues and decided to join the laboratory of Dr. Brian Kelsall at the National Institutes of Health.

In Dr. Kelsall's laboratory, I decided to tackle dendritic cells in Peyer's patches, which are mucosa-associated lymphoid tissues that are found in the terminal ileum. I was fascinated by these cells, as they live on the edge between the host and the outside world (gut lumen). The first thing I wanted to do was isolate them from the rest of the cells in the Peyer's patch, so I could see how they behaved when they come in contact with T cells. For the first 6 mo of my postdoc, I spent night and day trying to isolate enough of these cells. I became friends with the technicians at the flow cytometry core, as I was there all the time. They would ask me, "Why don't you sort lymphocytes? There are many more than the cells you are interested in." I just smiled and kept putting them (lymphocytes) in the dump gate. One day, I obtained enough dendritic cells to culture them with T cells. I examined the secretion of various cytokines in the supernatant. I still remember Brian gasping in his office upon seeing my ELISA plate that dendritic cells from the Peyer's patches selectively induced type 2 immunity, while those from the spleen induced robust type 1 cytokines from cognate T cells (Iwasaki and Kelsall, 1999).

What interested you about your current area of study?

In my second year of postdoc, a colleague, Dr. Robert Seder, told me about a position opening at Yale University. They were recruiting a "mucosal immunologist." While it was still early in my postdoc training, I thought, "What is the harm in submitting an application?" After all, I felt ready and energized to start my own laboratory. In fact, I had felt that way since the middle of graduate school. By some miracle, I was offered a faculty position in the School of Public Health at Yale University, thanks to Dr. Nancy Ruddle. I started my laboratory in 2000. At this juncture, I wanted to shift my research to something more infectious disease oriented. I loved studying vaccines and dendritic cells, but in the end, they exist to do only one thing: fight pathogens. I also wanted to focus on mucosal tissues that were under-studied but were highly relevant to human infections. Thus, I decided to tackle vaginal mucosal immunity against herpes simplex virus 2 (HSV-2). There was a small problem: I had never cultured or titered viruses in my life. I wrote a letter to an expert in the field I found online, Prof. David Knipe. He kindly responded and agreed to show me the techniques needed to study this virus! I took three Amtrak train rides to Boston. On these trips, I learned about the virus, how to culture the virus, quantitate it, infect with it, and to collect vaginal tissues for analysis. I applied this knowledge to start a new program in my laboratory. I could not have done any of this without the generous help of Prof. Knipe, and I am forever grateful. I look back and think about the incredible generosity of Dr. Knipe—to respond to an email from a complete stranger (a no-name assistant professor) and to offer to meet and train her. This act of generosity has made my career, and also made me determine to pay it forward to help younger generation of scientists.

We have used the mouse model of genital herpes to demonstrate the role of innate sensors, various dendritic cell subsets, lymphocyte recruitment and retention mechanisms, and the role of tissue-resident T cells in protection and enabling antibody access to neural tissues. More importantly, we have leveraged our insights from these basic studies to develop a vaccine strategy called Prime and Pull. This strategy is a two-step immunization protocol in which T cells are generated by a conventional vaccine (Prime), followed by their recruitment to the tissue of interest by application of chemokines or chemokine-inducing agents (Pull). Using animal models, we showed that Prime and Pull can be used to confer

Recent photograph of the Iwasaki laboratory at the holiday party (December 2019).

protection as prophylactic (Shin and Iwasaki, 2012) and therapeutic vaccines against genital herpes. We have since expanded our scope of viruses to respiratory infections (rhinoviruses, influenza viruses) and other sexually transmitted viruses (human papillomavirus, Zika virus, HIV-1), mostly driven by fantastic colleagues who joined my laboratory with relevant expertise and interests.

What are you currently working on? What is up next for you?

I could literally go on about the current work and fill up this entire interview! I am so excited about our ongoing studies. Roughly, they are divided into four areas: viral pathogenesis, endogenous retroelements, tissue-resident memory lymphocytes, and antitumor immunity. In the area of viral pathogenesis, we have shown unexpected links between temperature and the common cold (how host immune response is dampened by cold temperature), between chronic constipation and genital herpes infection, and the key role of type I interferons in fetal demise following Zika virus infection in pregnancy. The second program, endogenous retroelements, was something we started ∼6 yr ago, when I became fascinated by how a large portion of our genome is occupied by endogenous retroviruses and retroelements, but we know little what they do! Maria Tokuyama (postdoc) started this whole field of study in my laboratory. First, she realized that there was no great database that annotates human endogenous retrovirus (ERV) loci in our genome, or a good way to map RNA sequencing reads to a specific ERV locus. To solve this problem, she created ERVmap (see https://www.ervmap.com for free access), a tool used to assign RNA sequencing reads to specific ERV loci in human genome (Tokuyama et al., 2018). This opened the door to understanding ERV expression pattern across individuals and across cell types. Around the same time, we began asking how ERVs are regulated at the genomic level and discovered two host restriction factors, Snerv-1 and Snerv-2, which are next to each other on chromosome 13 encoding KRAB-ZFP. We made the serendipitous observation that a very closely related mouse substrain, C57BL/6N mice, but not C57BL6/J mice, had elevated expression of ERVs belonging to the nonecotropic ERV loci. Rebecca Treger, a fantastic Medical Scientist Training Program student, took this finding and applied rigorous genetics approaches to figure out the genes responsible for this observation. The bonus was that she found that these exact genes are also responsible for the autoantigen gp70 (envelope protein from ERV) expression found in lupus prone mice and NZB and NZW strains (Treger et al., 2019). Now we are following up on whether there is a link between ERV expression, ERV antigens, and lupus in human patients.

As a third area of study, we continue to explore the role of tissue memory cells. Recently, we showed that recruited memory B cells serve as a source for antibodies secreted into the vaginal lumen upon HSV-2 infection. In collaboration with Drs. Alessandro Santin and Sangini Sheth, we are almost at the end of our first phase 2 clinical trial to test whether Prime and Pull vaccines can be used to prevent progression of cervical intraepithelial neoplasia from becoming cancerous in HPV-infected women. It is so gratifying to see that our basic discovery can be used to help women who otherwise have to undergo invasive surgical procedures to remove part of their cervix, which can interfere with future pregnancies.

Now, as the fourth and newest area of our research, we are tackling basic questions in cancer immunity. Does it exist? If so, how are cancers recognized by the innate immune system? What makes some cancers more immunogenic than others? What cells are involved in early detection and control of tumors? How does cancer impact the immune system in general? The great success of immunooncology has given the entire field of immunology a boost of interest and resources. However, we still understand some fundamental aspects of antitumor immunity very little. We are chipping away at these questions using our expertise and understanding from viral immunity.

What kind of approach do you bring to your work?

My approach is quite trainee-centric! When someone joins my laboratory, I discuss with them the areas of interest we have in the laboratory, and I listen to their research interest to find a common ground. I always ask them to spend 2–3 mo thinking and honing in on the important questions in the field of their interest. I tell them not to touch a pipette or mouse for these periods, because it is so important to read the existing literature and truly identify the important gaps in the field. After discussions back and forth, we agree on a question or two. We discuss the best approach to address such questions, and the tools needed. Sometimes, we have to generate the tools de novo. This may take a while, and I discuss the pros and cons of such approach. Other times, we can use existing tools. My job is to ensure that such tools are made available to my trainees in a timely manner. More than half of my trainees are postdocs, and many of them want to pursue a career in academia. I want to ensure they develop a project of interest so they can take that away with them when they leave. I see no need to hang on to any of these projects—the postdocs need them more than I do. And, because there are so many important questions to address in immunology!

What did you learn during your PhD and postdoc that helped prepare you for being a group leader? What were you unprepared for?

My PhD and postdoc training was key in preparing me for becoming a PI. I observed the behavior and consequences of my own mentors and other professors around them. I learned a lot about what to do, but also what not to do, as a PI. I decided, if I ever become a PI, I will treat my trainees as equals, colleagues, with respect and kindness. I will honor their hopes and dreams, and help make them a reality. I will create an environment of collegiality and collaboration, a happy place to work. When people are disrespectful of others, no matter how capable they may be in techniques or intellect, they don't belong in my laboratory. This has worked well to develop and maintain a wonderful working environment in my laboratory over the years.

When I transitioned to a PI position from postdoc, I was pretty much unprepared for everything! I did not know how to put together an animal protocol, human investigation protocol, write an R01, hire and fire people, or even simple things like how to order equipment versus reagents. In the first few years, I learned to do these things with the help of more senior colleagues. The best thing I ever did was to hire a spectacular technician, who later became my laboratory manager and my right hand, Melissa Linehan. She has been with me since the

beginning. Without her, I would not be here. She handles everything in my laboratory so I can focus on science and teaching.

What has been the biggest challenge in your career so far?

The biggest challenge in my career so far is to find a good balance between my family life and science career (Iwasaki, 2015). I gave birth to two children since I started my own laboratory. This is the best thing that ever happened to me. I love every minute of being a mother to my wonderful children. I am so blessed to have them in my life, and to share joy and struggles with them. However, at the same time, everything about being a mother brings challenges to my career life. Being pregnant and feeling ill, childbirth and the aftermath health issues, caring for newborns and infants, toddlers, and then children. Dropping everything and caring for them when they are sick. Not having childcare close to work and having to commute several times a day between childcare and work. Shuffling their doctor's and dentist's appointments, dance practice, girl scout meets, etc., while trying to meet deadlines for grants, reviews, papers, teaching, and travel. I remember crying in the car one day driving 80 mph on the highway, for the third time that day, because my little daughter refused to drink milk from the bottle and I had to rush over to breastfeed her. I came very close to quitting science that day. Now that they are older, things have gotten easier in some ways but more difficult in others. I have decided to stop feeling guilty about missing work or meetings if I need to be with my children when they are sick. It makes no sense to feel guilty about taking care of your family over missing something at work. The latter can always wait.

What is the best advice you have been given?

The best advice I got was from my husband, Ruslan Medzhitov, when I was having lots of doubt as to my future in science as an assistant professor at the stage when I had no R01, no paper, no recognition. Others were telling me to "follow the money" and apply for whatever funding was available, and "go for the low hanging fruit" and publish something quick. He told me that I should not worry about such things as grants and papers, but to focus on asking fundamental questions in immunology. He told me never to pursue science only because there is funding available if I am not interested in the question. He assured me that grants and papers will follow if I keep making important discoveries. At the time I actually did not believe him entirely (I thought he was just trying to make me feel better). But looking back, I am so glad I followed his advice! I now give my postdocs the same advice before they leave my laboratory to run their own laboratories.

What hobbies do you have?

I do yoga every morning before work. It puts my mind and body in the right place. Yoga is not just about stretching and relaxation; it can be a really great exercise if you make it. It provides me with necessary "me time." I also love to cook and eat; I try new recipes online and in books whenever I can. The benefit of this hobby is that we all get to enjoy eating afterwards. Finally, I love to read! I especially enjoy reading Japanese fiction books. It is both a guilty pleasure and my way of connecting back to my roots.

Any tips for a successful research career?

I think to be successful in anything, you have to enjoy it and enjoy yourself while doing it. Science does not provide instant gratification, but is a long-term commitment. Of course you need to work hard (but you want to, because you love science). This also means that you need to exercise self care and treat yourself to something you enjoy every once in a while. Otherwise you can burn out and be unproductive in the long run.

Another thing I think about is taking advantage of every failure and mistake. I feel like I have gained important life skills and developed emotional intelligence because I made mistakes and I failed. Every time this happens, instead of beating myself up about it (well, that may happen initially), I try to take advantage of it. I ask myself, how can I learn from this mistake so I do not make the same one in the future? How do I find a solution that is a win–win scenario for all parties involved? What are some alternative paths to recover from the failure? What opportunities are hidden in the aftermath? I think this growth mindset is very helpful for building a career in science.

Women in STEM

What are the biggest challenges you faced as a woman working in STEM?

Actually, the challenge we face as women is not one thing. A collection of challenges is hidden behind a veil of unconscious bias. Women are at a disadvantage with respect to their climb up the ladder at every step. Women's publications do not count similarly toward obtaining R01 as men's. Women are less likely to obtain R01. Women do not publish in top-tier journals even when corrected for the amount of funding they receive. Women do not have the same access to opportunities because they are outside the "network" of male faculty. Women do not get invited to give plenary talks as much as men. Women are nominated for fewer awards and prizes. Women are judged by their appearance instead of their ability by students and peers. Women have less time to devote to science because they tend to take on housework and childcare more than men. Women are paid less than men. Women are not promoted at the same rate as men. All of these disadvantages add up over time. Fortunately, while I faced these barriers during my scientific career, I had powerful allies who advocated for my science at various key stages of my career, which helped me overcome many of these obstacles.

What needs to change to encourage women to work (and stay) in academia?

There is a lot we need to do to change academia so women can unleash their full potential (watch out, guys!). A climate and culture that supports women in science, by providing an inclusive environment and sense of belonging, is important. What I am starting to realize after years of thinking and researching about this topic is that we need to fundamentally change the academic infrastructure at the institutional or at the national level to be able to bring about the change in climate and culture and to be successful in the long run. Providing affordable and accessible day care at academic centers is urgently important. The biggest loss of women in academia happens at the transition of postdoc to faculty. This also coincides with the childbearing age. Many women simply cannot afford to stay in science if they also want to start a family. This has to change! Another institutional change that can help women succeed is to build

strong mentorship programs for women and groom them for future leadership. Many men receive such mentorship and preparation because they are part of an established network. We need to enable women's access to similar supportive networks. We can even go one step beyond this and establish a provost-level position whose office is dedicated to identifying and nominating women for various awards, societies, and prizes. Finally, we need to hold those who harass or assault women accountable. There needs to be real consequences for professors who harass and bully their trainees and colleagues. Many of these people get away with a slap on the wrist, and they keep exhibiting the same behavior. They are bad for science, because they block and push away the very people who will become the next generation of scientists. We cannot keep exposing our young scientists to these toxic individuals.

Finally, even though I focused on issues women deal with (because of your question), all the same efforts should also be applied to increase the number of underrepresented minority scientists in academia.

What advice would you give to young women working in STEM today?

Personally, I feel so fortunate to be a scientist. I have the best job in the world—I get to do what I love and get paid for it. If you love science, keep going! Ignore the naysayers, as there are many. Find a supportive mentor who can guide you navigate through difficult situations. If you are with a toxic PI, leave as soon as possible. Find another laboratory. It is not worth "sticking it out." It will ruin your health and your career. Treat others and yourself with kindness. Take time to care for yourself. Science is a long-term commitment. Your wellbeing is key to success.

Disclosures: The author declares no competing interests exist.

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