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Exposing T Cell Secrets Inside and Outside the Thymus

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Abstract

I've had serious misgivings about writing this article, because from living the experience day by day, it's hard to believe my accomplishments merit the attention. To skirt this roadblock, I forced myself to pretend I was in a conversation with my trainees, trying to distill the central driving forces of my career in science. The below chronicles my evolution from would-be astronaut/ballerina to budding developmental biologist to devoted T cell immunologist. It traces my work from a focus on intrathymic events that mold developing T cells into self–major histocompatibility complex (MHC)-restricted lymphocytes to extrathymic events that fine-tune the T cell receptor (TCR) repertoire and impose the finishing touches on T cell maturation. It is a story of a few personal attributes multiplied by generous mentors, good luck, hard work, perseverance, and knowing when to step down.

IMAGINING MY FUTURE

I was born in Dodge City, Kansas, a town dead center in the country that many people I've encountered have assumed is a fictitious setting for a much beloved TV show. I have no stories of tense gunfights between Marshal Dillon and the bad guys to relay from what was a happy and sheltered childhood devised by loving parents and shared with two intelligent and accomplished sisters. And lots of cats. I spent most of my childhood in Kansas City and was educated in the excellent public school system. Looking back, I am a little surprised that, despite growing up in a conservative community, we three girls assumed we'd excel in school, earn graduate degrees, and forge independent careers. But that is what happened. My interest in science was first sparked in high school by inspiring biology, chemistry, and math instructors, mentors I'm certain, as a typical teenager, I never adequately thanked. Despite the fact that both of my parents were in the medical field—my mother was a nurse and my father a pathologist—I never saw myself as providing patient care. I knew I was too prone to overempathy to provide sick people the dispassionate advice they needed. I loved working with my hands and really took to the methodical process of lab work. Despite this early meshing of my skills and intellectual interests, many more years elapsed before I zeroed in on research as a career path.

As a child of the 1950s and '60s, my first answer to the perennial question "What do you want to be when you grow up?" was "An astronaut." The moon landing had captured the imagination of many kids in my era, even those who were clearly unsuited for this glamorous profession. And by unsuited, I don't mean female; I mean so prone to motion sickness that watching a home video involved an unscheduled trip to the bathroom. To their credit, my parents didn't dissuade me from this delusion. An article on the training required to become an astronaut popped this particular bubble. Being from a landlocked state, my second dream focused on experiencing the romance of the sea by becoming a marine biologist. These hopes were dashed by my growing understanding that time spent performing meticulous chores on a rocking boat was not in my future (see above). My third dream was more tenacious. I wanted to become a ballerina. I studied classical dance throughout my childhood (a financial burden for my middle-class family) and even joined the Kansas City Civic Ballet. My merely modest talent helped put the kibosh on this particular career path, but not until I entered college.

MINING THE VIRTUES OF A LARGE MIDWESTERN STATE SCHOOL

I'm fairly certain that when it came time to head to college, I would have chosen a small "prestigious" school in the east if my family could have afforded it. Fortuitously, these tight finances (coupled with the desire to enter the same program as Bob Proctor, my first serious boyfriend) helped funnel me instead into a large Midwestern university. Indiana University (IU) had world-class music and dance programs, fantastic swimming (think Mark Spitz) and basketball (think Bobby Knight), and a famous bicycle race (think *Breaking Away*). It also had an excellent four-year honors biology program, in which a small cohort of students tracked with each other through demanding semester-long lab and lecture courses in genetics, physiology, microbiology, developmental biology, and ecology. Together, these courses covered nearly every lab technique and biology-based topic imaginable at the time (altogether dodging immunology, however), and they were taught by accomplished scientists and communicators. IU was one of the few universities in the country that could foster my joint interests in biological research and classical dance. Without understanding how lucky I was, I tapped into the advantages of a university with a student body larger than 30,000 while soaking up everything a small, focused program could deliver. The tricky logistics of balancing five-hour labs with equally grueling dance rehearsals

finally forced me to reassess my dual goals. While it was the most wrenching decision I had to make in my first quarter century, it wasn't much of a gamble to allow biology to win that battle.

With my new focus, I cobbled together time to initiate a research project in Dr. John Richardson's lab in the Department of Chemistry, studying the elegant genetics and remarkable means of operon control in bacteriophage λ. Dr. Richardson was a patient mentor, even in the face of my rookie mistakes in the lab, and I was included as a middle author on my very first science publication (1). It was also at this point in my undergraduate training that I fell in love with developmental biology. I still remember the thrill of spending all night in the lab watching the process of gastrulation in frog eggs. Such beautiful choreography more than made up for the dance performances I was missing! Molecular and genetic tools were just then being applied to dissecting the mysteries of organismal development, and I was intrigued. My newly invigorated love of lab science also provided a much-needed distraction as I coped with the death of my too-young father. Being able to throw myself into these studies provided an essential outlet for my nervous energy and awareness of life's impermanence.

One final praiseworthy attribute of IU is its location in the lovely rolling hills surrounding Bloomington. There were beautiful old quarries and labyrinthine limestone caves to explore, a particular draw as Bob and I were avid spelunkers. I realize now I would later have refused permission for my kids to embark on many of my early adventures—rappelling off railway bridges and into caves, whitewater canoeing during flood stage, and bushwhacking with a cheap compass and zero experience in the Rockies. One of my last truly irresponsible youthful acts involved Bob, a leaky rubber raft, a massive downpour, and several hours clinging underground to the grate of a storm sewer as the floodwaters washed over us. Needless to say, neither of us ever told our parents about this particular near-death experience. It was clearly time to grow up and get serious.

FINDING THE THYMUS IN CAMBRIDGE

What better way to get serious than to enroll in the biology PhD program at the Massachusetts Institute of Technology (MIT)? In fact, it was so serious that our faculty advisor warned us at our orientation get-together that we would all likely need mental health support at some point during our tenure in the program. That was quite a rude awakening for a naive young woman from the nurturing Midwest! But it turned out that my classes at IU were excellent preparation for the rigors of MIT, and I gradually became comfortable rubbing elbows with my new classmates, many of whom could (and did) boast of degrees from highbrow institutions. I was part of a remarkable graduate student class at MIT, one that included Connie Cepko, Doug Koshland, Cliff Tabin, Ihor Lemischka, Tom Alber, Cynthia Kenyon, Mark Rose, Tom Gridley, and David Raulet, among others. I lived on a shoestring budget in a group house with multiple roommates, including law students, a musician, a science fiction writer, a photographer, a political scientist, and a flute maker. I was fortunate to learn as much outside of formal instruction from my classmates and roommates as I did during lectures from excellent professors. At MIT during my era, students selected thesis labs through an intensive monthlong exposure to each lab's research interests, driven by four or so hours of discussion led by each professor within the department. This was a magical month, and it was hard to narrow down my lab interests to select a PhD supervisor.

In the end, it was the work of a newly minted assistant professor and his focus on how T cells recognize antigen on cell surfaces that merged my love of developmental biology with the wide-open field of immunology. Michael Bevan had just joined the MIT faculty after a remarkably productive postdoctoral stint in Mel Cohn's lab at the Salk Institute, during which time he had discovered that cytotoxic T cells recognize minor histocompatibility antigens in a self–major histocompatibility complex (MHC)-restricted manner (2). His work also showed that which MHC a

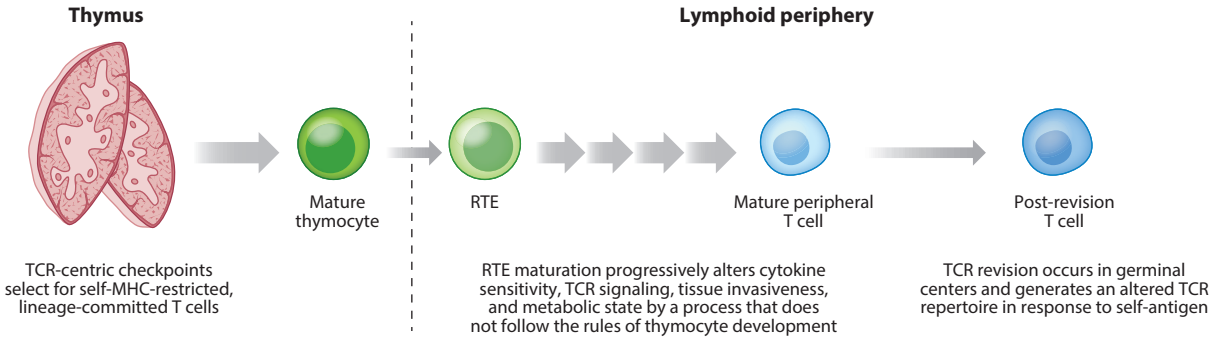

Figure 1

Generating functional T cells that are both useful and safe is a multistep, multisite process. T cell development in the thymus is a TCR-centric process that takes place in the absence of foreign antigen and yields self-MHC-restricted, lineage-committed T cells. Extrathymic events, including TCR revision (a rare process) and postthymic maturation of RTEs, do not follow the rules of thymocyte maturation. The latter processes have been dissected using a GFP reporter for initiation of *Rag* expression, denoted here by green. Abbreviations: GFP, green fluorescent protein; MHC, major histocompatibility complex; RTE, recent thymic emigrant; TCR, T cell receptor.

T cell considered "self" was defined not by a T cell's genetics but by its developmental history (3). T cell maturation provided a developmental system whose mysteries unfolded not just during the short window of embryonic development but throughout the lifetime of the organism (a mouse, in this case). This realization was an epiphany for a beginning graduate student with no prior background in immunology. Here was an accessible developmental system with genetic tools (multiple MHC congenic mouse strains expressing distinct minor histocompatibility antigens); brand-new monoclonal antibody reagents; and an elegant, quantitative assay for cytotoxic T cell activity. I was hooked.

Without at first realizing how fortunate I was, I joined the nascent Bevan lab as one of Mike's first graduate students (along with David Raulet). Mike's key interests at the time he established his lab at MIT were twofold: solving the paradox behind the foreign antigen–independent generation of T cells that are groomed to recognize foreign antigen in the context of self-MHC, and determining whether T cell recognition of antigen is mediated by a single receptor recognizing the interface of foreign antigen and self-MHC (Mike's favored altered-self hypothesis) or by dual receptors recognizing antigen and MHC as separate entities. As a postdoctoral fellow, Thomas Hünig tackled the latter problem and bolstered the altered-self hypothesis (4), while I began to focus on understanding how T cells learn which MHC to define as self. The spotlight immediately fell on the thymus, the organ in which T cells develop (**Figure 1**). To dissect the impact of the thymic microenvironment on T cell MHC restriction specificity, we needed to mix and match T cells, thymic tissue, and extrathymic environment from distinct genetic backgrounds. The generation of radiation chimeras, in which hematopoietic stem cells of one genotype are forced to differentiate into mature T cells (among other hematopoietic lineages) in a mouse of a distinct genotype, was a technique already well-used in the field of cellular immunology (in Reference 3, for example). As for the thymic component, I was lucky that Henry Wortis, at nearby Tufts University, offered to teach me how to remove the mouse thymus surgically and to implant fetal thymic lobes under the kidney capsule.

After mastering the finicky techniques required to tease apart the key aspects of T cell education I next needed to bolster my own thymic education. To strengthen my weak understanding of all things immunological, Mike generously funded my attendance at a Cold Spring Harbor basic

immunology course that offered a chance to learn from the greats in the field in a small, intense class setting. It was here that I was first exposed to the many competing hypotheses swirling around T cell function and began to feel a little more comfortable engaging in back-and-forth discussion with the likes of Pippa Marrack and Charlie Janeway. I was now better armed to tackle the goals of my thesis project, and over the next several years, together with Mike, I demonstrated that the MHC molecules expressed within the radioresistant thymic microenvironment defined self for developing cytotoxic and helper T cells (5, 6). Contrary to the assertions of others in the field (7, for example), our work also showed that this thymic preference was not absolute but was instead characterized by a 20-fold or greater preference for self-MHC versus nonself MHC that we felt revealed a molding of the T cell repertoire, rather than a rigid requirement (3, 5, 6).

During my formative years, in the late 1970s, I benefited enormously from the support of key mentors, beginning with Mike. As his subsequent students and postdocs can attest, Mike has a remarkable ability to define fundamental (yet answerable) questions in immunology and to nudge his trainees into addressing them in a critical manner. Mike endorsed intellectual independence in the lab and was happy to entertain dissenting views, but his trainees learned early on that they'd better be ready and able to defend those views fearlessly. It was at this point that I began to understand there is little difficulty in generating copious data if you have good hands and a solid work ethic, but generating useful data from precisely designed experiments is another matter entirely. Learning to explain my work in-house to an intense and accomplished audience of scientists with little knowledge of basic immunology was daunting, but it forced me to become a much better communicator. It was also fortuitous that at the time, David Baltimore was just beginning to focus more of his neighboring lab's energy on B cell development. His always insightful probing into the hows and whys of T cell biology kept me on my toes. I was also perfectly placed to take advantage of the fantastic immunology coming out of the greater Boston/Cambridge area, and I regularly attended very lively (and, not coincidentally, entirely unplugged) off-campus journal clubs and thought-provoking seminars with Harvard and Tufts groups. During one memorable seminar at Harvard Medical School, in an auditorium filled with the usual white men in white lab coats, one visiting speaker began his talk on the nature of the as yet unidentified T cell receptor (TCR) with a slide of Renoir's *Female Nude Lying on a Bed*, saying something along the lines of, "Here is one type of beautiful receptor, and I work on another." My indignation at the assumption that the pictured woman was nothing more than a passive receptor has stuck with me all these decades. Only much later did I realize the speaker was more accurate than he deserved to be, given what we now know about how the TCR not only receives signals but also orchestrates much of the complex downstream response to these signals. I did end up analyzing the TCR at the molecular level several years later, but it would be a stretch to say this irritation drove me to do so.

EMBRACING CALIFORNIA MELLOW

By the time I finished graduate school, and despite our best efforts to avoid this complication, Mike had become more than a thesis advisor to me. I decided it would be important for me to move some distance away temporarily to test our relationship and to prove I could succeed as a postdoctoral fellow away from Mike's notable sphere of influence. I chose to focus on my interest in thymobiology and joined Irv Weissman's lab at Stanford. Irv had a very large lab that he managed with little hands-on mentoring but that he imbued with his creativity and his seemingly boundless optimism and excitement for all things immunological. I struggled mightily with severe culture shock (there is a ritzy shopping mall on Stanford's campus!), the lack of diversity (why does everyone look like me?), and the laid-back lab culture (where *is* everybody?). But, as I gradually came to understand, at least the latter observation was more apparent than actual. My new

Figure 2

Discussing the thymus, California style, with Jon Sprent. 1984 photo by Mike Bevan.

labmates worked consistently and efficiently but didn't feel the need to advertise their long hours as we were wont to do in graduate school. This is an aspect of West Coast science that I've tried to mimic since (**Figure 2**). However, despite the gradual mitigation of cultural whiplash and a very beneficial collaboration with Bruno Kyewski (a postdoctoral fellow in the neighboring Kaplan lab), I decided less than two years later to move down to Scripps, where Mike had recently taken a position. Irv was gracious and empathetic, and with his support, I completed a set of marathon experiments using the state-of-the-art Herzenberg cell sorter at Stanford, flying with my freshly sorted thymocyte subpopulations from the Bay Area to San Diego, where in the wee hours I plated the cells in limiting dilution to assess their immunocompetence (8). Airport security was obviously a bit more lax in those days!

I enjoyed a very productive and happy stint in Mike's lab at Scripps (**Figure 3**), continuing to collaborate with Irv on the recirculation to the thymus of mature peripheral T cells (9) and with Bruno on the unique biology of thymic nurse cells (10). At that time, I also began to analyze the function of T cells that block cytolytic activity directed against their own self-antigens, cells we later named veto cells (11, 12). Mike's lab at that time comprised a remarkable set of postdoctoral fellows, including Frank Carbone; John Klein; Leo Lefrançois; and Hans-Georg Rammensee, who was also exploring veto cell function (13), which fostered a fruitful intralab collaboration (14–16). However, I still felt the need to diversify my work from Mike's, and I jumped at the chance to join Steve Hedrick's lab at the University of California, San Diego, where he had just arrived, fresh from having famously cloned the TCR β chain genes with Mark Davis at the National Institutes of Health (NIH) (17, 18). I benefited from being Steve's first postdoctoral fellow, as Steve himself exposed me to the ins and outs of TCR gene cloning and the byzantine world of the mouse CD4 T cell response to pigeon and moth cytochromes *c* (19). We published the first structure/function analysis of the αβ TCR, in *Nature* (20), a herculean task given that I was racing as a neophyte against very capable molecular biologists. Our work showed that the CD4 T cell response to pigeon cytochrome *c* in B10.A mice is primarily limited to the use of Vβ3 and the Vα11 family genes (20). We further demonstrated that this limited germline diversity is offset by mechanisms generating combinatorial and junctional diversity, but not by somatic mutation (20–22). Subsequent work focused on the selective processes that distinguish alloreactive from MHC-restricted T cell clones (23) and the roles of positive and negative selection in the thymus in shaping the TCR repertoire to this model antigen (24). I also took careful mental notes

Figure 3

In San Diego with Mike Bevan. Circa 1984 photo by Bruno Kyewski.

as Steve worked through the bureaucracy to equip a research lab at a state university. My years in the Hedrick lab were productive both scientifically and personally—Mike and I now had a new baby boy, so new in fact that I was revising the *Nature* article with Steve while on maternity leave.

Realizing I couldn't be a postdoctoral fellow forever (despite the obvious pluses), I was fortunate to be hired as an assistant member at Scripps Clinic and Research Foundation by Per Peterson. I was awarded my first R01NIH grant and set up my lab. The administrative hurdles to hiring and purchasing equipment were less onerous at a research institution than at a state university, and Per proved to be a very supportive mentor. This was a huge relief to me, as I delivered our second child

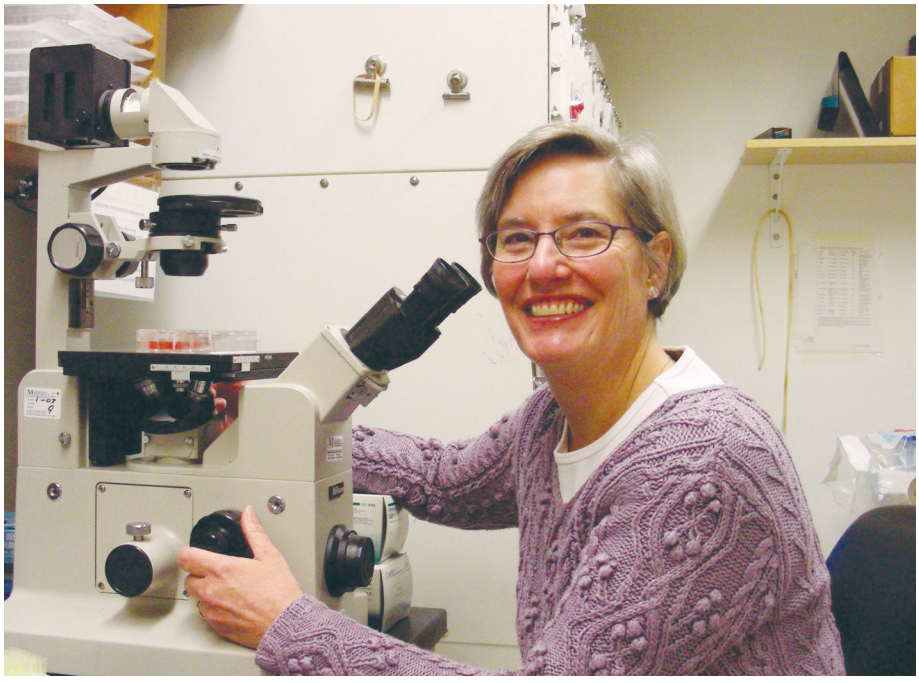

Figure 4

In my own lab at the University of Washington in 2000.

shortly after taking on this independent position. Although Mike and I left San Diego for Seattle less than two years later, I will always be grateful to Per for his mentorship and especially to the greater San Diego immunological community for their camaraderie. We were lucky to be a part of a close-knit community that included so many double-scientist couples, including Sue Webb and Jon Sprent, Suzy Swain and Dick Dutton, Ann Feeney and Don Mosier, Linda Sherman and Norm Klinman, and Antonella Vitiello and Franco Ferrari. When I had (frequent) doubts about how maintaining two research labs and raising kids could all possibly work out, I had to look no further than to my successful scientific friends for encouragement.

SEEKING INDEPENDENCE IN THE PACIFIC NORTHWEST

In 1990, Mike and I were recruited by Roger Perlmutter into the newly formed Department of Immunology at the University of Washington (UW). We two plus two kids, a dog, a cat, and a carload of houseplants all made our precarious way up Interstate 5 from San Diego to Seattle. We instantly fell in love with the Pacific Northwest, which catered to our love of the outdoors but also provided access to the big-city pleasures of fantastic restaurants, bookstores, theater, dance, and music. Having great colleagues and being able to help recruit into a nascent department were icing on the cake. I joined the department as an untenured assistant professor (**Figure 4**), while Mike joined as a full professor. Despite this gulf, I felt my contributions to the department were valued. I gradually came to understand that my strengths included teaching at the undergraduate and graduate levels, serving as an advisor to incoming graduate students, and helping devise our departmental curricula, in addition to tending to the pursuits of my own lab. This resulted in a smaller, less high-powered lab than that of my illustrious husband, but I gradually came to terms

with this assessment. My trainees were productive, were reasonably happy, and left the lab with a good publication record and secure, first-choice positions in hand. I learned early on that building on my strengths, rather than emulating the (mostly male) defined norms of success, was one key to promoting my long-term productivity and career satisfaction.

A big push of my new lab at UW, particularly through the early efforts of graduate students Stacey Dillon and Catherine Blish, was to understand the unusually leaky TCR β chain allelic exclusion in Vβ5 TCR transgenic mice originally generated by Frank Carbone and colleagues (25). With its Vα2 mate, this TCR β chain was world-famous as a class I–restricted, chicken ovalbumin–specific TCR (26), and it showed unusual ovalbumin reactivity even when paired with a diverse Vα repertoire (27). Surprisingly, Vβ5 expression among CD4 T cells in these mice decreased with age, under the influence of an *Mtv8/Mtv9*-encoded superantigen whose expression is limited to the lymphoid periphery (28–30). Over the course of two decades, my lab labored to establish that the expression of non-transgene-encoded TCR β chains in Vβ5 transgenic mice is the result of an extrathymic tolerance mechanism driven by RAG1- and RAG2-mediated TCR rearrangement in mature peripheral T cells (31). This age-dependent process, which we termed TCR revision (**Figure 1**), takes place within the confines of the germinal center (32–34), providing for a diverse, self-MHC-restricted, self-tolerant TCR repertoire (35–38). While all of my training led me to understand that these findings were heretical, I naively thought that careful, incremental lab work (performed by postdoctoral fellows Cathy McMahan and Cristie Cooper and graduate students Scott Hale and Lauren Higdon) and clearly written publications centered on well-supported conclusions would win the day. Not so. My lab had enormous difficulty publishing these papers and even more difficulty in getting our findings accepted by scientists in the field. I unwittingly exacerbated this situation by deciding early in my career to limit my travel to attend meetings and give seminars. This had seemed a prudent choice, given the difficulties of maintaining an even keel on the home front and spending as much time as possible with our young children. But the downside of this travel curtailment became obvious in later conversations with colleagues who did not believe our assertion of postthymic TCR rearrangement. When I asked what we needed to do to nail this down experimentally to their satisfaction, the answer was invariably to perform some set of experiments we had completed and published many years prior. These experiments included detection of T cell–specific TCR Vβ-to-DJβ recombination intermediates in revising T cells (31), demonstration that Cre-mediated loss of floxed *Rag2* alleles in peripheral T cells prevents TCR revision (39), and tracking the appearance of post-revision T cells in adoptively transferred populations of $RAG^+V\beta5^+$ mature peripheral T cells (39). It was clear to me only then that getting out and about to self-advertise is an essential component of being accepted into the scientific community.

After spending several years dissecting the costimulatory activity of Fas ligand in CD8 T cells through reverse signaling, made possible by the work of graduate students Ivy Suzuki and Mingyi Sun (40–44), I was eager to return to some of the developmental questions that had piqued my interest in immunology as a first-year graduate student. For this new line of research, postdoctoral fellows Tamar Boursalian, Lydia Makaroff, Qingyong Ji, and Cody Cunningham and graduate students Evan Houston, Deborah Hendricks, Amy Berkley, and Travis Friesen repurposed the green fluorescent protein (GFP) reporter mice developed by the Nussenzweig lab (45) that we had used to track the extrathymic *Rag* expression driving TCR revision (46). In these mice, GFP expression is driven by the *Rag2* promoter, such that thymocytes glow bright green upon *Rag* expression. While these mice faithfully report the on activity of the *Rag2* promoter, the slow decay of GFP relative to that of the RAG proteins (47) means that T cells remain detectably GFP^+ for up to three weeks after they extinguish *Rag* expression and exit the thymus (48). This provided a handy way to tag recent thymic emigrants (RTEs) as GFP^+ peripheral T cells and allow their

functional and phenotypic characterization as a population distinct from peripheral T cells that have resided in the lymphoid periphery for longer than three weeks. This straightforward and noninvasive tool allowed us to define a phase of postthymic T cell maturation (**Figure 1**) during which T cells alter their surface antigen phenotype (48–50), proliferative capacity (48, 50, 51), cytokine production (48–53), cytokine gene methylation status (54), cytolytic potential (48–50), tissue invasiveness (50, 52, 55), T helper polarization potential (52), TCR signaling capacity (50), sensitivity to low-affinity ligands (50), IL-2 sensitivity (53, 56), metabolic state (53, 56), sensitivity to regulatory T cell suppression (51), diabetogenic capacity (50, 51), and susceptibility to tolerance induction in the absence of inflammation (51). All of these maturational changes occur during a developmental process that requires thymic egress and access to secondary lymphoid organs (57).

Our studies on RTEs revealed that T cell maturation is not complete at the time of thymic exit but continues in the lymphoid periphery, taking advantage of exposure to foreign antigen, inflammatory cytokines, and the general insults of life outside the protection of the thymic milieu. We originally adopted a thymocentric viewpoint and suspected that RTEs were mature T cell wannabes, moving on a conveyor belt from less to more immunocompetent (58). We now believe that RTEs are uniquely suited to providing protection under the conditions in which they predominate: the relatively T cell–lymphopenic environment in the newborn and the individual recovering from lymphoablation. RTEs are skewed toward effector cell differentiation, are more invasive, are less impacted by ligand affinity (and thus provide broadly cross-reactive protection), reside in a uniquely cytokine-sensitive poised metabolic state, and are prone to tolerance induction unless they encounter antigen in the context of inflammatory cytokines (59, 60).

Thus, my perspective has evolved considerably from the time I was a graduate student and a firm believer that the thymus was uniquely in charge of molding a useful but safe T cell population that was sent out into the real world as a fully formed protective force. As a new assistant professor, I began to accept that some events, such as TCR rearrangement, could take place under carefully controlled conditions outside the thymus, and as a professor, I began to appreciate that the lymphoid periphery also supplies essential hurdles newly emigrated T cells must surmount to prove they deserve to belong to the pool of recirculating mature lymphocytes. While intrathymic T cell development tests the T cell's capacity to be both useful and safe, employing a very TCR-centric process, the postthymic maturation of RTEs does not follow the rules of intrathymic T cell development. It requires neither IL-7 (61) nor, for CD4 RTEs, peripheral MHC class II expression (62) but instead tests the T cell's fitness to respond through a very metabolically focused process (60). Dissecting these two facets of T cell development has provided countless hours of pleasure in the lab!

FINDING SCIENTIFIC RELEVANCE OUTSIDE OF THE LAB

At some point in the career of most research scientists, there emerges a desire to exact influence outside the confines of one's own lab. Many people opt for administrative roles within their department or broader institution, an avenue that never appealed to me. Instead, I was honored to become the first female editor-in-chief of *The Journal of Immunology*, the journal of the American Association of Immunologists (AAI). I have always had a warm spot in my heart for *The JI*; I published my first paper there in 1979 (63) and found it a safe haven for my lab's work on TCR revision (32, 33, 36–39, 46). I appreciated the fact that all submitted papers are peer reviewed (protecting the review process from political contamination) and that, as stewards of a not-for-profit academic journal, editors of *The JI* feel no pressure to solicit sexy work or promote certain authors. Furthermore, *The JI* helps support the work of the AAI in advocating for science and scientists of all immunological stripes. This all struck the right note for me. My Midwestern sense

of fairness and love of writing and communicating ideas had found a good home, and I enjoyed a sense of satisfaction at having my horizons broadened beyond my concerns for the welfare of my lab and trainees. I enjoyed helping implement new avenues for the journal to explore, including organizing a podcast for the Pillars of Immunology commentaries, starting the Novel Immunological Methods and Systems Immunology sections of the table of contents, and publishing annual topical issues of Brief Reviews. I had the enviable chance to work with a remarkably talented and dedicated group of people, headed by AAI Executive Director Michele Hogan and Publications Director Kaylene Kenyon. Being able to lift the stigma cast by the absence of female editors-in-chief was a bonus, as was presiding over *The JI* during its 100th year of publication.

I've recently entered a new and unfamiliar phase of life—retirement. I've always felt that it is our duty to retire, both to provide breathing room for more-junior scientists and to explore other pathways that life has to offer. Mike and I both decided to quit while we were ahead and still had the health and energy to explore other activities. The ongoing COVID-19 (coronavirus disease 2019) pandemic has put a damper on many volunteer opportunities, but I've made headway in solitary activities, including sculling, reading, bird-watching, and needlepoint.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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