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Systems Immunology: Origins

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Fifteen years ago, human immunology was stagnating compared with the rapid pace of work with inbred mice. There was a desperate need for new strategies and methods that would allow us to leverage the advantages of immunology research in humans: the genetic and environmental diversity, the thousands of infectious diseases, and responses to clinically deployed treatments and vaccines. Development of the much-needed approaches led to a new field, systems immunology, with its emphasis on gathering as much information as possible from human blood samples, focusing on the cells and cytokines of the immune system, and organizing studies of vaccine responses in different human cohorts, including twins, the elderly, and children in high versus low pathogen environments. These types of studies have grown exponentially over the years, with great advances in technology and analysis, and have become an important way to understand the vast differences in human responses and what they can tell us about our own immune systems.

What follows is a personal account of the role that I and my colleagues played in the early days of systems immunology. For a more extensive treatment of the current state of the field, I recommend some recent reviews (1, 2). For my part, almost two decades ago, I became alarmed that human immunology seemed to be almost at a standstill while murine work was racing ahead. This struck me as unsustainable because if all we do is improve the health of mice, even if the science is wonderful, we will lose public support and become another obscure academic curiosity. Although our work on imaging T cells and understanding the intricacies of cell-cell interactions was going well, I thought this problem was so compelling that I decided to shift my laboratory's focus to human immunology and to help develop more effective technologies and strategies. Both were clearly needed better technologies, because most of what we do in mouse immunology is impossible or very limited in humans, forcing immunologists to use a relatively small set of tools. Moreover, we needed distinct strategies for human immunology, especially because, as far as I could tell, the main strategy in mice was to create or find a model of a disease with the hope of uncovering the key to the human equivalent. But this wasn't working in most cases: lots of interesting data to be sure, but typically falling short of something "translatable" or failing in clinical trials. Some years before we made the switch, my then colleague at Stanford, Alan Krensky, told me, "Mark, we've cured cancer and autoimmunity in mice many times." This suggested to me that we were not facing just a medical problem; there was important immunology we knew very little about.

But what should a new strategy look like? I thought it needed to be independent of mouse immunology, not because I think the immune systems of these two species are very different, but because if we wanted to understand why these models of disease or new

vaccines weren't working, we couldn't be directly dependent on mouse data, because it might obscure what was different. Also, the essence of a good strategy is to maximize the advantages of the system and minimize the disadvantages. So, what are the advantages of the "human model" (3)?

1. They come to hospitals-screening themselves for disease or dysfunctions of all kinds.
2. Humans are genetically diverse and outbred-key deficiencies of inbred mice. Inbreeding can dramatically reduce fitness, and immunity is likely a key part of fitness. Heterozygosity creates flexibility, and an ability to respond to changing conditions, both in real time and evolutionarily.
3. Humans are environmentally diverse, living in vastly different places in terms of climate, food, pathogens, and microbiomes.
4. Humans are treated with thousands of different immune modulatory procedures, vaccines, drugs, and surgeries.
5. The multitude of known infectious diseases in humans, each of which interact directly with a persons' immune system, sometimes more than once, likely tell a plethora of important immunology stories, only a few of which we know in any detail.
6. Humans can live a very long time, accumulating multiple immune modulating experiences.

Given these advantages, how does this inform our search for an adequate strategy? First and foremost, we had to address the issue of what immunologically relevant clinical material could be obtained relatively easily and from as many people as possible. Here, the obvious answer was blood samples, and particularly purified PBMCs and serum or plasma, which have the added advantage of being easily frozen and stored for years in liquid nitrogen. But blood cells are not a complete representation of the immune cells that one can easily harvest from spleens and lymph nodes of mice. However, at that time, these were the only clinical materials one could get from large numbers of people, with no practical alternatives. More recently, it has become clear that blood is a good representation of what is going on in a person's immune system at that moment, because recently activated immune cells usually circulate. As such, blood cells are excellent reporters of vaccine responses or other stimulations, with a much greater signal to noise than spleen or lymph nodes, which are repositories of many previous events. This was brought home to us in our work on regulatory $CD8^1$ T cells, which we could see surging in the blood of patients with celiac disease challenged with gluten (4) and in the blood of mice induced for experimental autoimmune encephalomyelitis, but not in the spleen or lymph node cells of those mice, likely because there were so many other cells there already (5).

So now, with a focus on blood cells, we could explore all kinds of situations that humans find themselves in, but what should the focus be? For one, it should be methods that collect as much information as possible, which, back in 2007, meant gene arrays and FACS cell phenotype analysis, as well as cytokine levels in the blood. We aimed to acquire as much

data as possible to rapidly build a database that was independent from mice but also because individual cells and cytokines are the heart of how the immune system functions.

This last point is very important because it was clear that it would require a systems biology type of approach, almost the opposite of what has been the major focus in mouse immunology, which extols the importance of hypothesis-driven and mechanistic studies and is entirely justified in a mature field. But I thought that this would be premature for human immunology, because any hypothesis would necessarily be dependent on mouse immunology. I also felt that we should start from scratch to see novel mechanisms, should they emerge from the data. An important aspect of our strategies was to consider what should be the focus system-wise. The original efforts with systems biology in yeast had focused on signaling pathways, as had some pioneering work with lymphocytes by Alan Aderem (6). But although the intricacies of decision making in signaling path-ways are a worthy endeavor, I didn't think this was the way to go, because the main pathways in multicellular organisms are interchangeable. What's important is that different immune cells vary in their inputs (receptors) and outputs (cytokines, chemokines, effector functions).

Also critical is the fact that immune cells are largely autonomous. They make decisions individually, based on signals they receive. A strong set of signals may activate many cells of a given type anda weaker one just a few. We publisheda vivid example of this in 2013, when Jun Huang found that naive, memory, and activated CD4 T cells all had the same sensitivity —one peptide-MHC ligand—but varied greatly in their response times (7). Additionally, multiple ligands didn't change their sensitivities, but instead a T cell response could be scaled up only by triggering more T cells, each with their own specificity. My conclusion was that the heart of immune function was a series of specialized cell types that talk to each other via cytokines and chemokines and that rapidly assaying cell types, activation states, and chemokines/cytokines may not be the whole story but was a good starting point for understanding human immunology.

A great help at this juncture, 2006–2007, was my collaboration with Ann Arvin, Harry Greenberg, and Corry Dekker at Stanford, who had already established and received funding from the National Institute of Allergy and Infectious Diseases (NIAID) to begin a series of influenza vaccine studies. This was important because the first thing needed for maximum value in a systems immunology study is to have a safe, straightforward way to stimulate an immune response in different individuals. Influenza vaccination is ideal because the vaccine can be administered to almost anyone, but it's not a very good vaccine, so there are many nonresponders! The other problem we faced was "who was going to do all of these FACS, gene expression, and multiplex cytokine assays?" We needed to analyze three separate blood draws (prevaccination, then 7 and 28 days post-vaccination, to capture the T, B, and Ab responses) for dozens or hundreds of subjects. The vaccinations and blood draws could all be handled by Dr. Dekker, an expert vaccinologist, and her team, but what about the assay work? The standard academic solution was to put postdocs and students on this, but this seemed inappropriate, because they should not be spending most of their time doing repetitive assays. So, the solution was to establish a new facility, now known as the Human Immune Monitoring Center, originally founded by David Hirschberg but since 2009 headed by Professor Holden Maeker. This center employs skilled technicians and staff

fellows who handle the throughput required and create an almost automatic data stream for what started out as a small study of fewer than 30 subjects but soon blossomed to the analysis of hundreds of subjects each year. Not only was it key to our own studies, but it has become a magnet for dozens of other projects as well, because there is an escalating need for sophisticated immunological data. It also became a mechanism for those of us developing new technologies, such as Bendall et al. with cytometry by time of flight (8) or my own laboratory with our single T cell analysis (9) methods. We could transfer these approaches to the facility and make them widely available to others.

Key help in seed funding and getting the center started was provided by Garry Fathman and Bill Robinson, also at Stanford. Once we had this working for a small number of subjects, we became more ambitious and developed cohorts focused on aging: the first longitudinal study with a primary immune focus, now in its 15th year (10–14). There was also a study of twins, which showed that most of immune variation is not genetically driven, and thus environmental influences are key (15). Another novel finding was that young adults infected with CMV had better influenza vaccine responses than CMV-negative individuals and that this transient effect was even more pronounced in mice (16). But going back to those early days, after our first encouraging data in 2007, I was increasingly convinced that this was the way forward and began giving talks describing what we hoped to learn. An editor from *Immunity* heard one of these talks and asked me to write an essay about it, which came out in late 2008, titled “A Prescription for Human Immunology” (17). In it, I described the problem as I saw it and proposed the systems approach described above. At around this same time, Bali Pulendran and Rafik Sekaly published the first data papers showing that they had reached a similar conclusion, although using the yellow fever vaccine as the stimulant (18, 19). Thus, the field of systems immunology was launched!

Our approach was very controversial at the time, because many people convinced themselves that mouse immunology is all we need to know. Peter Lee, the editor of *Immunity*, told me that my essay triggered the most discussion of anything they had ever published, hinting that not all of it was laudatory. But this is how things change. If you think you have something new to advocate for, of course there will be resistance and denial that change is needed. But the great thing about science is that it is not democratic: Ultimately, something stands the test of time or it doesn’t; what people want to believe isn’t important. So, I think that, currently, and surely with the con- sequences of the pandemic, ever more sophisticated human immunology and systems immunology approaches have been used to produce an ever-increasing array of important insights. We are still searching for unique human mechanisms, but what we have learned has already enriched our understanding of basic immunology. The *Immunity* essay (17) also triggered one of the most memorable phone calls of my life. A little over 1 month after it appeared, I got a call from Daniel Rotrosen, head of the Division of Allergy, Immunology, and Transplantation at the NIAID, who told me that they had just had a strategy retreat and were very impressed by my essay and the work of Pulendran and Sekaly and were going to put $100 million into a consortium of groups to foster this new field of systems immunology. Now known as the Human Immunology Project Consortium, it has been a major driver of this type of work. I was, of course, floored by this news, because I never imagined that I could have such influence. But it was my first hint that although scientists can be very resistant to taking on

new ideas, some funding agencies, such as the NIAID (way ahead of the pack!), who were thinking about the bigger picture, were eager to see progress on human immunology.

I think the field of systems immunology is still in its early stages, but there is clearly a great deal of momentum building, especially with an ever-growing set of powerful tools and a realization that this is an important, and sometimes the only, way to understand the complexities of human diseases and vaccine responses. But despite the many interesting results that have emerged, human immunology remains largely descriptive, and going further typically involves taking specific observations into inbred mice. Although this has worked well in many cases, it does not when human responses differ from those of mice, as we have already seen in numerous examples (2). Here, our best hope lies in the development of immune organoids (20), where tonsils or spleen cells can be reconstituted in vitro to reproduce key immunological mechanisms, such as specific B and T cell induction, affinity maturation, and class switching. Being in vitro means that many more aspects of an immune response can be captured and manipulated, ideal for systems immunology and modeling an immune response. Even more important is that these systems allow one to test hypotheses and pursue mechanisms in an entirely human system. Although we are still in the early days of understanding what these new systems can and can't do, I am optimistic that they will be critical to understanding what is unique in human immune responses.

Biography

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References

1. Pulendran B, and Davis MM 2020. The science and medicine of human immunology. Science 369: eaay4014. [PubMed: 32973003]
2. Medetgul-Ernar K, and Davis MM 2022. Standing on the shoulders of mice. Immunity 55: 1343–1353. [PubMed: 35947979]
3. Casanova JL, and Abel L 2002. Genetic dissection of immunity to mycobacteria: the human model. Annu. Rev. Immunol. 20: 581–620. [PubMed: 11861613]
4. Han A, Newell EW, Glanville J, Fernandez-Becker N, Khosla C, Chien YH, and Davis MM 2013. Dietary gluten triggers concomitant activation of CD4^1 and CD8^1 *ab* T cells and *cd* T cells in celiac disease. Proc. Natl. Acad. Sci. USA 110: 13073–13078. [PubMed: 23878218]
5. Saligrama N, Zhao F, Sikora MJ, Serratelli WS, Fernandes RA, Louis DM, Yao W, Ji X, Idoyaga J, Mahajan VB, et al. 2019. Opposing T cell responses in experimental autoimmune encephalomyelitis. Nature 572: 481–487. [PubMed: 31391585]
6. Gilchrist M, Thorsson V, Li B, Rust AG, Korb M, Roach JC, Kennedy K, Hai T, Bolouri H, and Aderem A 2006. Systems biology approaches identify ATF3 as a negative regulator of Toll-like

receptor 4. [Published erratum appears in 2008 Nature 451: 1022.] Nature 441: 173–178. [PubMed: 16688168]

7. Huang J, Brameshuber M, Zeng X, Xie J, Li QJ, Chien YH, Valitutti S, and Davis MM 2013. A single peptide-major histocompatibility complex ligand triggers digital cytokine secretion in CD41 T cells. Immunity 39: 846–857. [PubMed: 24120362]
8. Bendall SC, Simonds EF, Qiu P, Amir AD, Krutzik PO, Finck R, Bruggner RV, Melamed R, Trejo A, Ornatsky OI, et al. 2011. Single-cell mass cytometry of differential immune and drug responses across a human hematopoietic continuum. Science 332: 687–696. [PubMed: 21551058]
9. Han A, Glanville J, Hansmann L, and Davis MM 2014. Linking T-cell receptor sequence to functional phenotype at the single-cell level. [Published erratum appears in 2015 Nat. Biotechnol. 33: 210.] Nat. Biotechnol. 32: 684–692. [PubMed: 24952902]
10. Furman D, Jojic V, Kidd B, Shen-Orr S, Price J, Jarrell J, Tse T, Huang H, Lund P, Maecker HT, et al. 2013. Apoptosis and other immune biomarkers predict influenza vaccine responsiveness. Mol. Syst. Biol. 9: 659. [PubMed: 23591775]
11. Furman D, Hejblum BP, Simon N, Jojic V, Dekker CL, Thie R´baut RJ Tibshirani, and Davis. MM 2014. Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. Proc. Natl. Acad. Sci. USA 111: 869–874. [PubMed: 24367114]
12. Furman D, Chang J, Lartigue L, Bolen CR, Haddad F, Gaudilliere B, Ganio EA, Fragiadakis GK, Spitzer MH, Douchet I, et al. 2017. Expression of specific inflammasome gene modules stratifies older individuals into two extreme clinical and immunological states. Nat. Med. 23: 174–184. [PubMed: 28092664]
13. Shen-Orr SS, Furman D, Kidd BA, Hadad F, Lovelace P, Huang YW, Rosenberg-Hasson Y, Mackey S, Grisar FA, Pickman Y, et al. 2016. Defective signaling in the JAK-STAT pathway tracks with chronic inflammation and cardio-vascular risk in aging humans. Cell Syst. 3: 374–384.e4. [PubMed: 27746093]
14. Alpert A, Pickman Y, Leipold M, Rosenberg-Hasson Y, Ji X, Gaujoux R, Rabani H, Starosvetsky E, Kveler K, Schaffert S, et al. 2019. A clinically meaningful metric of immune age derived from high-dimensional longitudinal monitoring. Nat. Med. 25: 487–495. [PubMed: 30842675]
15. Brodin P, Jojic V, Gao T, Bhattacharya S, Angel CJL, Furman D, Shen-Orr S, Dekker CL, Swan GE, Butte AJ, et al. 2015. Variation in the human immune system is largely driven by non-heritable influences. Cell 160: 37–47. [PubMed: 25594173]
16. Furman D, Jojic V, Sharma S, Shen-Orr SS, Angel CJL, Onengut-Gumuscu S, Kidd BA, Maecker HT, Concannon P, Dekker CL, et al. 2015. Cytomeg-alovirus infection enhances the immune response to influenza. Sci. Transl. Med. 7: 281ra43.
17. Davis MM 2008. A prescription for human immunology. Immunity 29: 835–838. [PubMed: 19100694]
18. Gaucher D, Therrien R, Kettaf N, Angermann BR, Boucher G, Filali-Mouhim A, Moser JM, Mehta RS, Drake III DR, Castro E, et al. 2008. Yellow fever vaccine induces integrated multilineage and polyfunctional immune responses. J. Exp. Med. 205: 3119–3131. [PubMed: 19047440]
19. Querec TD, Akondy RS, Lee EK, Cao W, Nakaya HI, Teuwen D, Pirani A, Gernert K, Deng J, Marzolf B, et al. 2009. Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans. Nat. Immunol. 10: 116–125. [PubMed: 19029902]
20. Wagar LE, Salahudeen A, Constantz CM, Wendel BS, Lyons MM, Mallajosyula V, Jatt LP, Adamska JZ, Blum LK, Gupta N, et al. 2021. Modeling human adaptive immune responses with tonsil organoids. Nat. Med. 27: 125–135. [PubMed: 33432170]