

## The Next Quarter Century

*Immunity* celebrates its 25th anniversary at an exciting time in immunology, marked by the advent of new, door-opening approaches and a deeper understanding of the centrality of the immune system to both health and disease. We asked 25 investigators to look forward and share a vision of the next quarter century of immunology research.

### A Wolf in Sheep's Clothing



**Andrea Ablasser**  
 École Polytechnique Fédérale de Lausanne,  
 Switzerland

I feel a bit overwhelmed reflecting upon big challenges of immunity research for the future years to come. Looking back at the scientific development within my “comfort zone,” the area of innate pattern recognition, I am fascinated by how much progress there had been made within a relatively short period of time. Most notable to me is the emergence of a new perspective of the role of innate immune sensors—one that made innate immunity breach its “traditional” borders with important relevance for various fields of biology and medicine. It is the notion that the same immune receptors and molecules that launch protective immune responses during infection can likewise be detrimental to the host, underlying the pathogenesis of a range of non-communicable diseases, including cancer, cardiovascular disease, or neurodegenerative disorders—potentially even promoting the natural aging process itself. While recognizing the importance of the well-ordered functioning of innate immunity’s receptor repertoire for human health, a significant challenge is how to safely intercept it in a state of disease. Tackling this critical question will require a more complete understanding of pattern-recognition immunity as a whole. This includes advancing basic knowledge on the functioning of known sensing systems at a molecular, cellular, and organismal level. It also includes the consideration of yet-to-be-identified receptors and molecules and their specific beneficial or detrimental effects on the host. Achieving this level of knowledge on pattern recognition will be critical for the development of safe therapeutics for the prevention and treatment of inflammatory diseases. Even more exciting—it will offer novel insight into the fascinating mechanisms that rule one of the most fundamental aspects of immunity.

### Nature and Nurture



**Luis Barreiro**  
 University of Chicago, USA

Susceptibility to infections, sensitivity to inflammatory disorders, and response to vaccinations are highly variable from one individual to another. Yet, we still do not know the underlying genetic and environmental determinants that impact the host response to immune stressors. Understanding the factors that contribute to immune response heterogeneity among humans is essential to establish the basis for the development of personalized immune-based diagnostic and prognostic clinical tests. It is crucial that we place more emphasis on human studies if we are to realize the potential health benefits of immunological research in their entirety. With the explosion of genomic tools that allow us to profile the immune system at single-cell resolution, engineer the genome, and edit the epigenome, we are now able to dissect human immunity in ways that were historically impossible. Graduate programs in immunology must be the first to embrace the human immunogenomics movement through the incorporation of computational biology and statistics training in their core curriculums. Twenty-five years from now—hopefully from a beach in Portugal—I hope to be able to describe: (1) the key genetic variants that control host immune response variation to infection, (2) the long-lasting effects of particular environmental factors (and their interaction with genetics) in influencing human immunity, and (3) the role played by past selective events on shaping current population differences in immune function and susceptibility to disease.

### Uniqueness Breeds Complexity



**Karin E. de Visser**  
 The Netherlands Cancer Institute, The Netherlands

The recent clinical successes of cancer immunotherapy are a prime example of how fundamental research can change clinical practice. However, we have reached a stage where new immunomodulatory drugs are being rushed into clinical trials, without a clear scientific rationale for the selected patient group or therapeutic combination partner. To maximize the successes of immunomodulatory drugs, it will be critical to return to the bench to gain deeper mechanistic insights into the complex crosstalk between the immune system and cancer. A key challenge that needs to be addressed is the profound unexplained inter-patient heterogeneity in the composition and functional state of the immune system, as well as in the response to immunotherapy. Understanding the biology behind this inter-patient heterogeneity will help to (1) select the right patients for the right immune intervention strategy, and (2) uncover novel actionable pathways that can be exploited to convert tumor-supportive immune landscapes into those that favor anti-tumor immunity. There is emerging evidence that—besides the (sub)type, stage, and mutational load of the tumor, as well as age, treatment history, and the gut microbiome of the patient—the genetic makeup of cancer cells dictates immune composition and functionality. Molecular insights into causal tumor-genotype/immunophenotype relationships will facilitate the design of immunomodulatory strategies tailored to the genetic makeup of individual tumors and thus set the stage for personalized immune intervention strategies for cancer patients in the next 25 years.



**What Is Immunology?**

**Gerard Eberl**  
Pasteur Institute, France

Mainstream immunology has spent close to a hundred years understanding the nature of adaptive immunity, its specific memory, and the recognition of non-self from self. We are now at a point where these once-clear concepts become fuzzy: cells other than lymphocytes adapt and remember, and symbiotic microbes within us feel safe. In other words, walls between concepts and fields are falling. We live in an exhilarating time where immunology mingles with microbiology, metabolism, and neurosciences, just to mention three, letting us wonder what the immune system and immunology are really about. From its inception, immunology was about defense against pathogens, but now, it appears more fundamentally to be about homeostasis. So, the challenges of modern immunology, beyond the issues linked to big data, are to manage its morphing into a more diffuse discipline that allows for a holistic view of the organism and its interaction with the environment. In this view, the immunologist must think physiology to resolve long-standing and complex biomedical issues, such as chronic inflammatory pathologies and their consequences such as cancer and metabolic and mental disorders. We have also come to realize that the benefit of an immune response is contextual. For example, high IFN- $\gamma$  levels help control viruses and tumors but push a genetic susceptibility to type 1 diabetes into pathology. Here, the immunologist will contribute to precision medicine, and help define a healthy from a pathologic immune response, depending on the individual's complex background in time.

**Tearing Down the Wall**

**Eran Elinav**  
Weizmann Institute of Science, Israel, and German Cancer Research Center (DKFZ), Germany

A decade and a half ago, research at my department was focusing on the study of T and B cells, while innate immunology, studied by a single PI of 15, was still being shrugged off by many as “primitive” and non-specific. A decade and Nobel prizes later, innate immunology has assumed its central place across our field and is now studied by half the PIs at my department. Similarly, in the past 7 years, our recruitment committee supported the establishment of microbiome, single-cell transcriptomics, post-translation immune modifications, and immunotherapy labs, all utilizing approaches adopted from outside disciplines. While a few still refer to these new niches as “non-immunological,” “overly genomic,” or “too translational,” within just a few years they helped expand our understanding of immune regulation, and to utilize immune therapy as an effective treatment modality for a growing number of “non-immune” diseases. What makes such inclusiveness a success story? I believe that the answer spans more than just the identification of new technologies. The realization that immunology has no boundaries, enables its expansion into seemingly unrelated areas such as development, metabolic health, neurology, and aging. The willingness to re-visit the immune response and re-dissect its components, enables to deepen our understanding of cellular and organismal stress. But most importantly, the welcoming inclusion of bright new minds and of original and at times provocative new angles of thought enables to challenge existing dogmas in advancing our field towards new exciting directions.

**Big Data: Blessing or Curse?**

**Florent Ginhoux**  
A\*STAR, Singapore

Immunology has undergone a revolution: The high dimensional space, catapulting researchers into a new age of big data. For decades, immunologists have used flow cytometry to conduct multi-parameter analyses of single cells, aiming to add new dimensions to their data and fantasizing of unlimited parameters. It was a dream for all of us but without a clear understanding of the analytical implications. It is now a daily reality. Mass cytometry led the field, expanding the numbers of markers to test and force us to implement dimensional reduction approaches such as tSNE/UMAP that have revolutionized data analysis. In parallel, single-cell RNA-seq platforms have become established as new pipelines to characterize the immune landscape and discerning heterogeneity in both health and disease. It is now possible to assess hundreds of thousands, if not millions, of individual cells simultaneously, and these numbers are likely to increase rapidly. Ultimately, techniques that combine both protein, gene expression, and genomic and epigenetic parameters will gain prominence. High-dimensional imaging technologies are also progressing and will add spatial information to this evolving picture. Exciting times are ahead, but so are big challenges! We will need to make sense of these data and progress beyond descriptive mapping approaches to validate biologically this almost virtual descriptive dimensions of the immune system. It is fundamental to realize that big data will never replace the understanding of the biology underlying it and the need to go back to a simple question: what was the question?

### Defining “Self”



**Shohei Hori**  
The University of Tokyo, Japan

One of the central questions in immunology will continue to be immunological self-tolerance, a deep understanding of which should be instrumental in developing strategies for specific prevention and treatment of many diseases including autoimmune diseases, allergy, and cancer. Over the past 25 years, our view has been radically transformed from a recessive (cell-intrinsic) to dominant (cell-extrinsic) tolerance view, from a refusal to acknowledgment of self-recognition, and from a negative to positive definition of immunological “self.” Thus, the question of immunological self-tolerance cannot be understood at the level of individual self-reactive lymphocyte clones but has to focus on the complex web of reciprocal interactions among a diverse repertoire of such clones (including pathogenic and regulatory ones), other cells in the body, and the external environment. The fundamental question is therefore to elucidate the principle that governs the dynamic behavior of this whole complex system. What would be the key to this broad question then? Given that the antigenic universe of “self” is influenced by both the immune repertoires and the functional phenotypes of each lymphocyte clone, it will be important to understand how these genetic and phenotypic layers of immune heterogeneity are appropriately coupled, how this coupling is shaped by the interclonal interactions, how it develops adaptively in response to changes in the internal and external environments, and how it goes wrong in diseases. The time is ripe for tackling these challenges in the next 25 years.

### The Neuroimmune Collective



**Elaine Y. Hsiao**  
University of California Los Angeles, USA

We live in an exciting era of immunology where cells are functionally profiled with unprecedented resolution, imaged with high spatiotemporal control, and engineered to fight immunological diseases with extraordinary specificity. While the field continues to translate knowledge from basic research to clinical treatments, the future holds the opportunity to expand the frontiers of immunology to illuminate the breadth of immune interactions with diverse biological systems. Of particular interest is the intersection of immunology and neuroscience across the lifespan, wherein immune cells and factors exhibit novel roles during early development, guiding circuit wiring and neuronal identity, and during aging, influencing neural activity, degeneration, and cognitive behavior. Many questions remain to be answered: What are the mechanisms by which specific immune cells signal and respond to neurons in the central nervous system and in the periphery? How does the functional diversity of the immune system vary across different developmental states and environmental contexts? Can alterations in neuroimmune communication contribute to the many neurodevelopmental, neuropsychiatric, and neurodegenerative disorders that are associated with immune dysregulation? Broadly, such interdisciplinary research will help uncover that the immune system is integrated with other physiological systems to perform complex biological processes that impact health and disease.

### Immunity in Spacetime



**Wolfgang Kastenmüller**  
University of Würzburg, Germany

The last 25 years of studying the immune system have been guided by the pursuit of understanding how the immune system perceives signals and translates them to functional outputs. Major discoveries include the identification of how cytokines, chemokines, and a vast range of receptors guide immune cell differentiation, function, and positioning. Critical future challenges are to exactly quantify, localize, and understand how these various signals are integrated into a robust response from a single cell to population and organismal level over time. Only with this information will we be able to predict immune responses and understand when they are efficient and when they go astray. To this end, imaging-based approaches will be particularly important because they provide information that spans across biological scales. Imaging delivers data of molecules within a cell, of cells within an organ, or even a whole organism, and thereby information in its natural context across orders of magnitude. To bring imaging-based approaches to the next level, we will need to transform ourselves from mere observers to active, interventional researchers by developing optogenetic tools that help us to precisely regulate information exchange *in situ*. We will further need to refine our models to allow for localized cell-specific genetic manipulation, optimally in a time-resolved manner. After an era of elucidation of signaling events and pathways we are looking into a future that aims at reconstructing immunity from single molecules, cellular elements, and multicellular niches into a spatiotemporal system.

**The Physician-Scientist Niche**

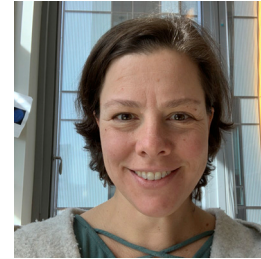
**Douglas S. Kwon**  
Harvard University, USA

In the past 25 years, advances in our understanding of the immune system have led to transformational new therapies for a wide range of diseases. Key to these successes have been the contributions of physician-scientists, who play a unique role in the medical research ecosystem by enabling the rapid incorporation of insights gained from patients into guiding principles of basic science research, and then translating these insights back to patients. This requires the perspective of individuals who understand the nuances of caring for patients as well as the potential of emerging scientific technologies to diagnose and treat disease. And yet, since former director of the National Institutes of Health James Wyngaarden declared physician-scientists an “endangered species” almost 40 years ago, the landscape has only become more challenging for their survival. Every year the number of physician-scientists declines and their average age increases, with projections from the American Association of Medical Colleges indicating that only half of the workforce needs for physician-scientists will be met in the coming years. In the next 25 years, physician-scientists will be a critical component of the vanguard needed to sustain and enhance the power of the immune system to impact patient lives. However, it will take more than just reports identifying the endangered nature of this species. It will demand concrete actions to meaningfully invest in this career path, providing specific support to ensure we continue to maintain the ecological niche for these keystone researchers.

**Is Tissue Residency Special?**

**Laura K. Mackay**  
Walter and Eliza Hall Institute, Australia

In recent years there has been increasing focus on lymphocyte populations that reside in tissues, ranging from classical T cells to subsets of ILC. What remains unclear is the relationship between permanently resident and migratory populations. Are resident lymphocytes simply a trapped version of their circulating counterparts or do they represent lineage-distinct populations? Whilst transcription factors such as *Hobit* appear to be unique drivers of lymphocyte residency, whether these are master regulators akin to *Foxp3* in Tregs remains to be shown. Resident lymphocyte functionality has largely been viewed through the prism of their circulating cousins, such as CD8 killer T cells eliminating virus-infected cells. But is functionality nuanced by tissue residency? For example, emerging evidence suggests that resident T cells contain rather than eliminate occult tumor cells, and resident subsets are known to suppress reactivation by herpesviruses; infections that are contained but not eliminated. A striking feature of peripheral residency is the expression of checkpoint molecules such as CTLA4, Tim3, and Nr4a receptors. Are these molecules simply activation dampeners as found in exhausted T cells or, rather, are they intimately tied to resident T cell functionality; for example, by favoring containment to minimize collateral tissue damage? Possibly the big unknown is how resident T cells can be harnessed to ameliorate disease. The answer to this likely requires an understanding of functionality that is unclouded by preconceived notions drawn from the circulating populations.

**Unite Against Infection!**

**Marion Pepper**  
University of Washington, USA

Vaccination, or intentional generation of immune memory, is arguably humanity's most important medical breakthrough. Vaccines have saved millions of lives—5 million annually from the smallpox vaccine alone. Yet the number of successful vaccines are few, and no licensed vaccines exist for any parasitic or fungal disease. The number of immunomodulatory therapies directed against infection is even less. This is in sharp contrast to the remarkable progress and Nobel-prize-winning breakthroughs that harness the immune system to fight cancer. Why this disparity? One can postulate: antibiotics have created a false sense of security, researchers focusing on host-pathogen interactions (innate/adaptive immunology, microbiology, vaccinology) remain steadfastly siloed, and financial incentives to support such research are low. Yet over the next 25 years, humanity will be challenged by new pathogens, emergence of drug resistance in old scourges, and altered distribution of disease vectors due to climate change. These challenges will require a new urgency within the research community. We must tackle infection with the same transformative, intensive efforts used to develop immunomodulatory strategies against cancer. We need meetings that bring together multiple aspects of infectious disease research, collaborative funding mechanisms, open access to publications across disciplines, and increased financial support. The process will be immensely challenging, but it is necessary to fully realize the potential of immune manipulation to prevent and treat infectious diseases and save lives.

### Beyond Linear Mechanics



**Hai Qi**  
Tsinghua University, China

Advances in immunology have often been heralded by holistic theories and enabled by tools that expand the immunological observables. Intravital imaging enables real-time observation of immune cells functioning in native tissue environment and has led to vastly increased appreciation of the importance of cellular motility and interaction dynamics for an operating immune system. In the next 25 years, intravital imaging will be seamlessly integrated with cell function-state reporters, spatiotemporal control of cell manipulation (e.g., light-inducible gene ablation, cell labeling), and cell-history-recording device to break old and uncover new causalities. Dynamic imaging has already revealed profound heterogeneity of even the most well-defined cell populations and stochasticity of even events that must happen within a defined period of time. Heterogeneity and stochasticity, coupled with non-linear feedback and feedforward processes that emerge at all levels of biology, challenge the mechanic logic in our approach to immunological causalities that intellectually derives from the linear central dogma of molecular biology. We will have to explain how systemic order and certainty emerge from dynamics and stochasticity of individual cells or molecules at a lower level. This philosophical question, posed to every fundamental immunological inquiry, will lead to new holistic understanding of immunology. Given the virtue of diversity in the immune system, it is also fitting to expect more contributions to such understanding from scientists of more diverse gender and cultural backgrounds.

### V(D)J for the Future



**Gabriel A. Rabinovich**  
National Council for Science and Technology (CONICET), Argentina

What if the key to the future of immunology is hidden in one of the most celebrated discoveries of the past? We are familiar with V(D)J recombination, the process by which variable (V), diversity (D), and joining (J) gene segments are rearranged to generate the antigen-binding sequences of immunoglobulins and T-cell receptors, leading to immunologic novelty. However, the term “variable” also implies novelty in a broader sense, as it can be used to describe dynamic, flexible, and evolving processes. All important new discoveries require flexibility and open minds to cope with the turbulence of the creative process, while preserving scientific rigor. The second key term is “diversity,” meaning appreciation of distinctive talents, especially from newcomers eager for interdisciplinary exploration. Finally, we will only move forward by “joining” together, breaking through laboratory walls and crossing geographical borders. New scientific endeavors will be enriched by global collaborations that are critical to tackle unresolved problems, to formulate new questions and to accelerate development of novel therapies. This also applies to governmental, non-profit and private organizations, which should join in the effort to support research all over the world. The benefits of decades of basic research are now being realized at an amazing pace, having a profound impact in almost every aspect of public health including vaccination, cancer immunotherapy, and treatment of autoimmune diseases. Given the progress made, I ask everyone to support the promise of variability, diversity, and joining.

### The Devil Is in the Details



**Chiara Romagnani**  
Charité Universitätsmedizin and Deutsches Rheuma Forschungszentrum, Germany

As graduate student, I was confronted with the central question “what shall be the focus of my research?” In one of his essays, P.B. Medawar reminds us that “who wants to make important discoveries must study important problems,” but what is left for young immunologists, once what we currently perceive as the fundamental themes have been tackled? Throughout my training, I was exposed to the concepts of synergy and redundancy embodied by the plethora of NK cell activating and inhibitory receptors. The “rheostat” principle (Brodin et al., 2009) governing NK cell recognition and education seemed frivolous but more resourceful and tuneable compared to the monist or dualist activation system of T cells. We are now copiously aware of the large spectrum of receptors regulating T cell responses. The main lesson we learned from targeting the PD-1/PD-L1 axis is that modulating a rheostat likely yields a more compliant anti-tumor strategy than finding the Holy Grail of the on/off-switch. There is further room for tuning, as shown by new potential checkpoints, including some NK receptors, which are undergoing exploration in clinical trials.

Single-cell technologies and big data inevitably drive immunology towards details, leaving us often with the impression that we are dealing with redundancy and losing sight of the essential. My suggestion for the future is to dive into the “tunable” non-essential: if the devil is in the details, that is where we will find our best clues to tune the immune system and develop new therapies against tumors and chronic inflammatory disorders.

**Reversing Deconstruction**

**Carla Rothlin**  
Yale University, USA

Our predominant scientific approach is methodological reductionism. System diversity is increasingly being uncovered through unprecedented data acquisition enabled by outstanding technological advances. These data are hierarchically deconstructed using linear causality into a set of key components. For example, a biological process such as anti-tumor immunity becomes reduced to a function of checkpoint molecules, cellular subsets, or a certain microbiota. Notwithstanding its successes, this approach has its limitations. In quantum mechanics, the uncertainty principle preempts knowing everything about a system. Acquired data may be time- or context-dependent. For example, the immune signature identified may be specific to the type of tumor, to the site of tumor, or to a particular patient group and also a snapshot in time. Therefore, this preempts the derivation of a truly generalizable principle of anti-tumor immunity. Even knowing the complete set of components is not a guarantee for reconstructing system behavior. “The ability to reduce everything to simple fundamental laws does not imply the ability to start from those laws and reconstruct the universe” (Anderson, P.W. [1972]. More is different. *Science* 177, 393-396). Since we strive to engineer biological responses such as anti-tumor immunity, the challenge for the next 25 years will be to scale individual, deconstructed components back into systems, wherein the whole may be different than the sum of its parts. This may be achieved by defining second-order rules connecting the components, perhaps using rules of probabilistic causality. Reductionism will then be complemented by synthesis.

**Now Hear the Orchestra**

**Erica Ollmann Saphire**  
La Jolla Institute for Immunology, USA

The most exciting development on our horizon is the dramatic expansion of our technical toolbox. To fully understand disease and learn how to attack it, we must see it—in high resolution and in a biologically relevant state. For years, existing technology permitted study only of purified molecules and complexes, removed from their physiological context and separated from co-factors, and aiding and competing molecules with which they were designed to operate. Seeing a protein alone is like hearing only the solos in an orchestral piece: you can appreciate the music in isolation but miss understanding why it was written or how that player fits into the score. For example, Ebolavirus proteins change structure to change function in response to cues from the subcellular environment. Recognizing how this context influenced absolute structure necessitated our expansion into cryo-electron tomography to visualize structures inside cells. Further, because many important interactions are transient, weak, and additive, we need tools to image flexible, heterogeneous systems. With new instrumentation, we can restore information we previously had to strip away and study the molecular basis of immunity more completely and rapidly and in a more informed context. That’s why I’m spending this year building a facility that will help us achieve this goal. I expect that structural biology, freed from technical constraints, will no longer be a cloistered, inaccessible discipline understood by only a few. Roadmaps founded on structural insights will be more broadly available to all immunologists.

**\*Some Assembly Required**

**Alex K. Shalek**  
MIT, Ragon Institute, and Broad Institute, Cambridge

Our tissues represent evolved social contracts. Within each, distinct cell types have achieved specialized roles by relying on the complementary actions of their neighbors, yielding communities whose functionality far exceeds their parts. Over past decades, increasingly powerful molecular profiling methods have uncovered, at ever-finer granularity, a census of cellular community members. Still, the question remains: how does the whole emerge from the parts?

The next 25 years promise to bring a working knowledge of the rules that inform cellular communities. The immune system offers several unique angles from which to begin. Within our tissues, diverse immune, parenchymal, and stromal cell types must constantly collaborate to preserve physiologic function. This presents unique opportunities to examine how several immune cell types with common ontogenies successfully adapt to variable environments. Comparing multiple healthy tissue ecosystems enables exploration of underlying social mechanisms that stabilize against internal (genetics, age) and external (diet, pathogens) perturbations. Further, contrasting outliers of health and disease can reveal cellular features that enhance or diminish overall function. These can then be leveraged prophylactically, therapeutically, or diagnostically.

Codifying this information will define what constitutes health and drives disease. Considerable challenges and exciting opportunities lay ahead in developing and applying the experimental and computational toolkit necessary to describe how cells build their tissue communities comprehensively.

### Fantastic Voyage



**Shannon Turley**  
Genentech Inc., USA

The immune system is a mobile network of diverse hematopoietic cells that works in a coordinated manner to protect tissues from pathogens and cancer. Migratory immune cells such as dendritic cells (DCs) and T cells must experience a mind-boggling number of physiological inputs as they traverse distinct tissue microenvironments. Understanding these events will unlock our ability to harness immune responses to prevent and treat disease. Being able to holistically and dynamically monitor the responses of immune cells to their tissue surroundings in normal or pathological states, and following therapeutic intervention, will eventually teach us how to better promote human health. Today we have the ability to capture data on the biological experience of single cells at snapshots in time. The next frontier will be monitoring complex physiological experiences of immune cells in real time, for example during the migration of a T cell from the spleen into an autoimmune or cancerous lesion, or a DC from a vaccine site into the lymph node. Nanoscale biosensors can provide the insight we need. Miniaturized sensors of intracellular processes that signify a cell's response to its microenvironment, such as phosphorylation, glycolytic flux, and lipogenesis could reveal what is happening inside the cell in situ. Such a technology would enable remote biometric monitoring of an individual immune cell's real-time experience of different tissue and pharmacologic milieus. Perhaps in the next 25 years, biosensors could be injected into patients to embark upon a fantastic voyage.

### The Fork in the Road



**Golnaz Vahedi**  
University of Pennsylvania, USA

Let's assume you as a taxpayer support government funding for further understanding of how our immune system protects us against infections and tumors. You read somewhere that latest improvements in imaging techniques have enabled biologists to probe cell function in previously unattainable resolution. You also learn about advances in sequencing technologies, which can provide unprecedented molecular details of the immune system one cell at a time. There is no doubt that discoveries require sifting through this deluge of data. Thanks to advances in machine learning and the lower-cost of computing, the big data can now be more accurately interpreted. Nonetheless, you are aware of the emphasis on hypothesis-driven research in government-funded proposals. Data-intensive research has been criticized for being nothing more than a "fishing expedition." In a hypothetical situation where you could choose how your money funds science, which of these options would be your choice: Would you prefer funding studies with preconceived notions that can be posed as testable hypotheses? Or would you favor scientific efforts incorporating an iterative mixture of capturing, curating, and analyzing large volumes of data, which can then generate unbiased hypotheses that guide reductionist and functional assessment of top ranked targets? This iterative process requires integrating quantitative and computational biology in training of the next generation of immunologists. I strongly believe that choosing between these two perspectives will shape the future of immunology over the next 25 years.

### Immunology Beyond Immunity



**Henrique Veiga-Fernandes**  
Champalimaud Centre for the Unknown, Portugal

The last decades have been largely dedicated to the study of the role of the immune system in immunity. This principle is perfectly reflected on our views of how host defense against pathogens and cancer is established. More recently, immune cells have been shown to integrate environmental cues in the absence of infection. For example, immune cells actively sense dietary, metabolic, and tissue-derived factors to control tissue physiology. Notably, neuronal and immune system interactions regulate homeostasis via tissue-restricted neuroimmune cell units, where immune and neuronal cells interact to steer local physiology. These findings are provoking a fundamental paradigm shift in our understanding of physiology and neuroimmune interactions. Exploring the broader neuroimmune crosstalk promises to be among the most exciting fields in biomedical research in the coming decades. Neuro-immune cell units drive local tissue homeostasis, but the existence of systemic neuroimmune circuits, which may ensure inter-organ communication and organismal physiology, remains vastly unexplored. For example, defining the architecture of neuroimmune circuits and how these link environmental cues to metabolism, cell fates, development, and homeostasis are major challenges ahead. Similarly, defining how brain activity and behavior shape neuroimmune signals is a critical endeavor to understand health and disease. In the next decades, deciphering the codes of neuroimmune interactions will unlock new horizons, transforming our understanding of organismal physiology and taking immunology beyond immunity.

**A Polyclonal Selection Theory**

**Gabriel Victora**  
The Rockefeller University, USA

The last 25 years have witnessed an explosion in our knowledge of the cellular and molecular cues that drive lymphocytes to clonally expand and acquire diverse effector and regulatory functions. Most of these studies (including many of our own) have largely ignored lymphocyte clonal diversity, either because they rely on monoclonal mice or because they treat polyclonal populations as homogeneous cohorts. In parallel, a second branch of immunology, built mostly on human studies, has tackled clonal diversity head-on. A prime example are efforts made by multiple labs to discover broadly-neutralizing antibodies to HIV and other recalcitrant pathogens. These studies have dissected the binding properties and evolution of antibody clones to unprecedented detail, while placing less emphasis on the cellular and molecular mechanisms that allowed these exceptional clones to arise, expand, and persist. The next 25 years should see a deepening of efforts by several labs to bridge these two branches. Fueled by the boom in single-cell technologies and ever more sophisticated mouse genetics, this work should ultimately reveal the rules that determine how individual lymphocyte clones wax and wane over time. From the B cell perspective, this knowledge may clarify the mechanisms of antibody immunodominance (and conversely, tell us how to coax B cells to target non-immunodominant epitopes) or define the rules that govern how B cell clones respond to repeated exposures to similar antigens. Insight from such studies may finally allow us to develop the vaccines we so desperately need.

**Challenges in Vaccine Design**

**Hedda Wardemann**  
German Cancer Research Center (DKFZ), Germany

Vaccines have been highly successful in preventing and even eradicating global diseases. However, despite extensive efforts, highly efficacious vaccines against pathogens with sophisticated immune evasion strategies such as HIV or malaria parasites, where natural immunity is insufficient to mediate protection have not yet been developed. Antibody cloning strategies have shown that rare protective human monoclonal antibodies against these and other pathogens develop in some individuals and define their precise target epitopes. Many of the antibodies show prophylactic and therapeutic activity, suggesting that subunit vaccines that induce such potent antibodies will protect from the infection. However, humans harbor very diverse antibody repertoires. Efficacious vaccines will have to overcome this inter-individual diversity and induce potent antibody responses independent of genetic and environmental factors, age, and immune status. The current and future challenge is to gain a detailed understanding of the differences and similarities in human antibody repertoires at functional level. The most burning questions are whether everyone's immune system contains or can make rare protective antibodies. If so, how can the cells that produce them be reliably activated to dominate long-lasting responses? Can we design a universal vaccine, or do we need personalized solutions? Answering these fundamental questions will be key to designing rational vaccines against the most devastating infectious and non-infectious human diseases.

**Measuring Immune Health**

**E. John Wherry**  
University of Pennsylvania, USA

Immunology has a major opportunity looking forward to define what “immune health” means clinically. In the past 10 years, building on knowledge from infectious disease, vaccines, and other areas, immunologists have translated the potential of the immune system to treat and, in some cases, eradicate human cancer. Checkpoint blockades targeting CTLA-4 and PD-1 (re-)activate key immune cells including exhausted T cells resulting in dramatic and in some cases durable clinical responses. Rational engineering of immune cells and “synthetic biology” have generated CAR T cells—the first genetically engineered cellular drugs. Immune-based drugs, including cells and biologics, are changing the rules of drug treatment of disease. No longer are we just treating symptoms or diseased cells directly. We are directly or indirectly re-engineering immune cells to become new drugs. A critical question, however, is why some—seemingly similar—patients have dichotomous outcomes to these and other treatments. A major opportunity for immunology in the future will be to determine how to make clinical decisions based on measurements of our immune system. How can we turn high dimensional immune profiling and/or systems immunology, into actionable “immune health” information in the clinic? We are in the golden age of immunotherapy. It is now possible to readily capture science in patients as we treat with immunotherapies. A major opportunity may be to ask how we can turn these outstanding scientific advances into information upon which clinical decisions can be made in real time.



### A Perfect Fit



**Catherine J. Wu**  
Dana Farber Cancer Institute, USA

The major challenge facing cancer immunotherapy in the years to come is how to understand the basis for which patients respond or do not respond to therapy. We are witnessing amazing responses in the face of new agents that modulate immune responses, but we recognize that only a minority of patients benefit from these therapies. In parallel, we are also gaining powerful tools that now allow us for the first time to reliably dissect human biology at scale, and these include new sequencing approaches, single cell technologies, and new computational tools. Our hope is that we will be able to extract information from a single biopsy or blood test that can at once inform us as to the immunologic state of the host, while also guiding us to the most rational choices for therapy. In short, we are challenged to generate personalized approaches for cancer immunotherapy—a strategy that will allow us to gain maximal benefit from therapies while minimizing toxicity. Systematic analysis of the human immune system—of both its natural and diseased states—will serve to guide us down this important path and is a key launch point. Definitive understanding will require careful integration of genomic analyses, functional interrogation, and clinical information to this end.