Immunity

CellPress

Voices

AI and immunology

AI is rapidly becoming part of many aspects of daily life, with an impact that reaches all fields of research. We asked investigators to share their thoughts on how AI is changing immunology research, what is necessary to move forward, the potential and the pitfalls, and what will remain unchanged as the field journeys into a new era.

Ronald N. Germain
National Institute of Allergy and Infectious Diseases

Creativity

How does creative science happen? We have a reservoir of knowledge acquired over years based on reading and from lectures and attendance at conferences, our experimental findings, and discussions with colleagues. Through a combination of consciously directed thought and subconscious connections among all these data-points, an idea comes into our mind that we think provides some new insight.

How do emerging AI paradigms differ from this "human" process? When we examine the way in which unsupervised machine learning or neural network methods work, the similarities are striking. They accumulate "knowledge" from all the sources I mentioned other than unpublished data and collegial conversations. AI then looks for connections among the various data points, using in part existing mappings—published pathways or networks, summary diagrams in review articles, textbooks, and so on, as we do also. But where does the creativity come from? I posit that it would lie in phrasing the query to the AI tool—asking a question to be addressed that is itself informed by what we do know and yet is unanswered and is, at the moment, unanswerable using our personally limited knowledge and what is open in the field—or even better, not yet considered as an issue to address.

When looked at in this way, AI becomes a collaborator in the process of creative discovery. It helps us include much more than we can personally "know" in seeking to gain new insight into an old problem or to decide if there is a new problem at hand that is worth exploring.

Eliezer M. Van Allen
Parker Institute for Cancer Immunotherapy, Dana-Farber Cancer Institute

Building foundations

As the scientific convergence of AI and biology expands across many domains, the field of immunology in general—and cancer immunology in particular—is perhaps best positioned to reap the benefits of this intersection. Indeed, many points of progress already highlight how AI can advance immunology research, such as algorithms for antigen and neoantigen prediction, immune cell inference in space and time across tissues, and immunotherapeutic engineering. These efforts underscore a crucial point: the successful integration of AI in immunology research depends on collaborative team science between immunologists and computer scientists.

These advances also indicate key areas for further development at the AI-immunology interface. Biological interpretability of AI models, which allows investigators to understand why the AI works, remains an important goal as this would allow immunologic investigations to build directly upon hypotheses derived from AI. In addition, team science across disciplines would benefit from ongoing encouragement, both at the individual investigator level and among institutions and funding organizations to ensure the biggest challenges are taken head on collectively.

Most importantly, the field must critically consider the sources of data generated and used for AI-immunology pursuits. If the underlying foundations of data are not broadly representative, the resulting data absenteeism may lead to AI algorithms with biases—both seen and unseen—that do not generalize. These issues could propagate down troublesome paths, including development of immunology therapeutics that have underappreciated population-specific biases and suboptimal clinical impact. By addressing data absenteeism at the earliest steps, the fields of immunology and AI

could harmonize to maximize scientific impact that may also impact peoples' lives everywhere.

Gosia Trynka
Wellcome Sanger Institute

Integration and collaboration

At the cornerstone of a well-functioning immune system is its ability to mount an adequate response to a threat. This response is complex and requires coordination and tightly controlled immune cell-cell communication. However, this complexity usually forces a reductionist approach: studying individual genes and pathways or characterizing linear relationships. Yet, due to the immune system's importance in disease, there is a wealth of data—from immune profiling of blood and disease-relevant tissues to mechanistic insight into the function of immune cells in different disease settings. Studies in preclinical models have provided important *in vivo* context.

Accurate prediction of immune system regulation requires complex models that can incorporate non-linear relationships between genes and pathways across a range of immune cell types while accounting for cell-cell communication. There is great opportunity for collating in-depth immunology data with the breadth of immunogenomics data to develop and train AI models that will enable a deeper understanding of immune interactions. We may accurately predict the effects of regulating immune cell functions and design new or better drugs to prevent or revert autoimmune disease, infection, and cancer. This will require a community effort that brings together machine-learning scientists, immunologists, geneticists, and molecular biologists to harmonize, model, contextualize, and interpret the data. It will be an iterative process where the predictions will need to be benchmarked and improved by generating data in a targeted manner to enhance their accuracy. The scale of this effort, from biology through drug discovery to clinical intervention, is substantial, and developing a dynamic dialogue and close collaboration between academic, clinical, and industry researchers will be transformative to accelerating drug discovery with AI.

John S. Tsang
Yale University

Compressing dimensions

AI already has sizable footprints in immunology, some by way of its impacts on biology. Examples include predicting protein structure and molecular interactions, peptide-major histocompatibility complex (MHC) binding, cell state and function via models trained on cell atlases and images, and immune response quality and quantity to vaccines. Predicting antibody-epitope and T cell receptor-peptide-MHC interactions remains challenging, partly due to the paucity of data, but here technologies for massive data generation are not far off the horizon. What is left? These AI advances are confined largely to solving context specific problems, piecemeal. What is missing are holistic, causal models that cut across spatial and temporal scales to predict outputs of organismal immunity and its interaction with physiology. Such models can transform perturbations (e.g., to molecules, cells, and tissues) to outputs on health, disease, and organismal phenotypes. Data will help. Deep learning models are effective because they overcome high dimensionality by discovering representations that compress large configuration spaces down to smaller "embeddings" that capture relationships among the important players. Machine learning models can thus compress a person's vast immune and physiologic state space to reveal a relatively small number of essential entities and their relationships to measure and model for predicting and modulating outcomes. Such representation learning is extremely powerful but insufficient. AI capacities in scientific reasoning, experimental planning, and high-throughput experimental execution will likely be essential. Recent history of AI suggests that machine learning vastly outperforms logic and reasoning based approaches. Data are a must, but the jury is out on whether logic and human ingenuity can be spared.

Dominic Grün
Julius-Maximilians-Universität of Würzburg

From cells to tissues

The recent surge of novel AI tools for the analysis of single-cell genomics data has revolutionized our ability to integrate large collections of heterogeneous datasets for building tissue atlases and integrating data modalities such as chromatin accessibility and gene expression. At present, we are witnessing the emergence of single-cell resolution spatial data that reveal how cellular interactions affect tissue architecture and cell state responses driven by tissue niches. A key future challenge will be to move beyond cell-centered models and leverage generative AI to develop whole-tissue models that allow us to predict tissue responses to defined interventions at single-cell resolution. Such models will provide deeper insights into the cause and consequences of cellular perturbations in the tissue context. This goal demands further progress in the development of interpretable AI models. Although available approaches utilizing variational autoencoders or transformer models yield informative representations of multidimensional data as a basis for multimodal integration, mechanistic insights on gene regulation are limited by design. A promising avenue to overcome these limitations will be the design of AI agents that can be trained to actively learn causal actions subject to a generative task such as reconstructing the coupled ensemble of cell states in a tissue. Such agents could then explore the impact of defined interventions in individual cells on the entire tissue and massively expand our scope for a deeper understanding of the interplay between immune cells and their tissue context in health and disease. This would enable breakthrough applications such as *in silico* testing of the impact of immunotherapies on the tumor microenvironment.

Ashley L. Kiemen
Johns Hopkins University

Sharper vision

Through curation of exceptionally large datasets and rapidly improving computing power, modern AI models can generate high-quality text and images nearly instantaneously. These models screen large datasets to pinpoint relevant examples and generate accurate summaries. In cancer research, there has been rapid expansion of open-source AI algorithms and close collaborations between bench and data scientists. Spatial profiling has only highlighted the heterogeneity inherent to cancer.

Consider a 2 cm tumor comprising billions of cells, heterogeneous in their morphologic and molecular qualities and in interactions with the immune microenvironment. There may be a minority of cells capable of successfully migrating, surviving intravasation and circulation in the blood stream, and proliferating in a distant organ to form metastases. Random histologic sampling is likely to miss this population, instead capturing the more prevalent cancer cells that thrive within the primary tumor microenvironment. We utilize three-dimensional mapping of pathology specimens and AI screening for regions of interest containing rare, biologically significant events such as sites of immune response and transition from precancer to cancer.

Novel digital pathology workflows leveraging troves of historical clinical datasets have improved our ability to screen resected tumors for quantitative correlates of patient response. In the next decade, two shifts will drive widespread adoption of AI in pathology. First, massive digitization efforts will increase accessibility to historical pathology samples, enabling the training of large-scale deep learning models. Second, design of easy-to-use interfaces will enable non-experts to harness AI in the clinic. These advances will be key to new breakthroughs in understanding how cancer invades distant organs, evades immunity, and survives therapeutic interventions.

Yigong Shi
Westlake University

Reasoning and logic

The AI revolution exemplified by ChatGPT raises both excitement and concerns. Some are anxious about the future of learning and research. Others question the necessity of rigorous training in a research laboratory. Some worry about the future of structural biologists, because nearly all known proteins have had their three-dimensional structures predicted by AlphaFold, and in most cases, accurately. The excitement is warranted, but the concerns are unfounded.

Genome sequencing fundamentally changed the course of traditional genetics but did not adversely affect geneticists. Quite the opposite, geneticists have enjoyed the full benefits of much faster research breakthroughs. Thanks to AI, a structural biologist like myself can now set sights on more complex principles of life, such as how the building blocks are assembled to orchestrate dynamic cellular life. The flow of research investigation in biology usually has followed the temporal order of genetics, cell biology, biochemistry, and structure. Now, the order may be reversed, because system-wide analysis of AI-predicted structures may uncover functions that await biochemical and cellular examination and genetic verification.

AI vastly accelerates just about any assigned task but only executes what it is told to do by humans. What remains unchanged is the analytical logic and fundamental principles behind each research project. My advice to trainees remains the same: go back to the bench and hone basic logic and skills—these will help you deal with future challenges, even in the era of AI. Critical thinking and analytical logic have weathered many transformative changes in scientific development—indeed, they have led these changes. Embrace AI, enjoy research!

Aimee Pugh Bernard
University of Colorado Anschutz Medical Campus

AI and education

Understanding and harnessing the power of AI is becoming increasingly important for immunology trainees and educators alike. To help navigate the complex landscape of immunological research and clinical applications, it is in our best interest to embrace all new technologies, including AI. Trainees should familiarize themselves with machine learning algorithms, data analysis techniques, and computational modeling to effectively interpret immunological data and derive meaningful insights. Educators should integrate AI into immunology curricula, teaching practices, and assessment to enhance learning and provide examples of appropriate use of this cutting-edge technology. We must also keep in mind that while AI can help us advance our knowledge, there are challenges, limitations, and ethical boundaries that surround the use of AI. Understanding that AI frequently "hallucinates"—producing content that is not factual or content that is biased—is essential. As educators, we must guide our trainees on the use of AI and provide the knowledge to enable review of AI output for biological meaning. To ensure our trainees understand ethical boundaries for the use of AI, we must work *with* students and postdocs to create guidelines and be aware that these may evolve as the technology changes. Expanding immunology training to incorporate the skills necessary to work with AI will require creativity, collaborative efforts with other disciplines, and support from university leadership and funding agencies. It will be challenging, but embracing and using innovative technologies wisely is something that we should strive to do together as a learning community composed of trainees and educators alike.

Garry P. Nolan
Stanford University School of Medicine

A wave of knowledge

We are entering a post-data world … shifting toward an inference universe. We are victims of our successes producing "big data"—surrounded yet paralyzed by riches. The infrastructure that methodically collects and analyzes the data is the foundational framework for an arising computational era in research and understanding. The corpus of human knowledge is being loaded into large language models (LLMs) that allow publications spanning decades of research to be readily interrogated with natural human language. You can "talk" to PDFs, upload the entirety of your own published papers—or that of any field—and have a focused discussion with an abstract entity that "represents" the thesis totality. Data live in concert with inference; witness AlphaFold's revolutionary protein structure predictions. My lab applies LLMs to contextualize any raw data type with stunning literature-based AI explanations of "why" that generate hypotheses and suggest experiments. Despite the enormous complexity of biology, the varied nature of cancers, or our present understandings of disease causality, the universe of possibilities is finite or often already extant *in* the literature. So why repeat what is done or that can be inferred from first principles? The next stage is learning how human intuition and reasoning, with the aid of custom LLMs, can exploit the richness of literature-embedded knowledge that can now be readily proffered via adroit harnessing of AI. As we face global challenges of various kinds, this expansion in understanding may enable meaningful progress. We surf a wave of extraordinary promise, and it couldn't come at a more opportune, or necessary, moment.

DECLARATION OF INTERESTS

E.M.V.A. declares the following interests in advisory/consulting: Enara Bio, Manifold Bio, Monte Rosa, Novartis Institute for Biomedical Research, Serinus Bio; research support: Novartis, BMS, Sanofi, NextPoint; equity: Tango Therapeutics, Genome Medical, Genomic Life, Enara Bio, Manifold Bio, Microsoft, Monte Rosa, Riva Therapeutics, Serinus Bio, Syapse; patents: institutional patents filed on chromatin mutations and immunotherapy response, and methods for clinical interpretation; intermittent legal consulting on patents for Foaley & Hoag; editorial boards: Science Advances. J.S.T. serves on the SAB of CytoReason Inc., Immunoscape Inc., and as the co-CSO on the the Human Immunome Project (non-profit). D.G. serves on the scientific advisory board of Gordian Biotechnology.