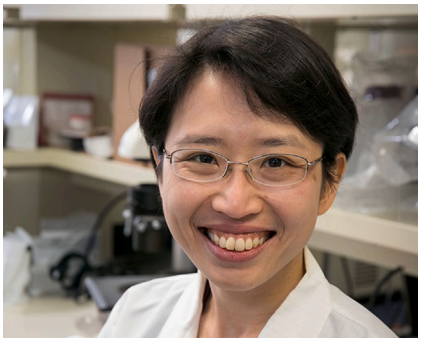
Cell
Leading Edge

Voices

What tool or method do you wish existed?

We asked researchers from a range of disciplines across biology, engineering, and medicine to describe a current technological need. The goal is to provide a sample of the various technological gaps that exist and inspire future research projects.



Yvonne Y. Chen
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Real-time reporting of cell-based immunotherapies in action

Cell-based immunotherapies have transformed the treatment landscape for some hematological malignancies, but their efficacy against solid tumors remains limited. CRISPR screens have generated a long and growing list of target genes whose manipulation may promote the proliferation and/or function of immune cells. Similarly, library screens of receptor designs have identified components such as signaling domains that could significantly enhance activity. However, such screens are typically performed either *in vitro* or with *in vivo* assays that rely on a single readout—i.e., the number of cells bearing a certain design—to identify hits. While cell persistence and proliferation can contribute to efficacy, they are not a direct assessment of anti-tumor activity. For example, it is quite plausible that the CAR T cell clones that survive and expand the most in a screen are not the same clones that did the hard work of eliminating tumor cells.

Ideally, one would like the ability to quantitatively assess cellular composition and function in the tumor microenvironment (TME) in real time. Parameters of interest include where a cell is located relative to the tumor and to other immune cells, what the cell is doing (degranulating, secreting cytokines, etc.), and how many copies of a particular clone are present in the TME and how its population size changes over time. A technology platform that combines intravital imaging with multiplex and repeatable assessment of protein and/or mRNA transcripts could dramatically enhance our ability to develop next-generation cell-based therapies.

Charles L. Evavold
Ragon Institute and Harvard Medical School, Cambridge, MA, USA

New perturbation analysis tools for the innate immune system

Early in my scientific investigations, I trained in observational astrophysics—a field that left me unsatisfied with the inability to perturb systems. I transitioned into microbiology and immunology, and today, my group aims to create datasets and an exploration platform for myeloid cells that integrate genome-wide perturbations with high-dimensional phenotypes for mechanistic insights. Expanding upon the premise of existing data browsers, such as ImmGen, that have provided valuable gene expression and regulation data to build hypotheses, we hope to catalog defined perturbations to their complex phenotypes within important cell types of the innate immune system.

An iteration of this tool could use Perturb-seq approaches to perform genome-wide perturbations in primary cell types coupled with single-cell transcriptome analysis. The most impactful version of this tool would involve gene activation and inactivation in several cell states of a primary cell type of interest. Various biological fields could adapt this technology and analysis framework to other cell types or phenotypes beyond transcriptomes, such as high-content imaging.

Current challenges include technical hurdles, resource intensive computation, and the high cost of single-cell transcriptomics. Increasing efficiency in targeting primary cells and reducing perturbation library sizes to a subset of the best validated sgRNAs

will enable the creation of cell-type-specific perturb-omes for *in silico* screening and hypothesis generation.

Matthias Mann
Max Planck Institute of Biochemistry, Planegg, Germany

Universal mass spectrometry-based blood tests with AI integration

As a scientist dedicated to the field of mass spectrometry (MS) and proteomics, I envision a groundbreaking tool: a universal MS-based blood test. This instrument would be highly standardized, fully automated, and integrated with AI, particularly large language models. This test would be conducted every 6 months for all individuals while also being applied to oncology and dermatological tissue samples. To reach this massive scale, the LC-MS system needs to be super robust and process 100 samples per day at a marginal cost of about $10.

Early detection and precise monitoring are pivotal in managing diseases, yet current diagnostic methods are often fragmented and reactive. A universal blood test would allow for the comprehensive analysis of a person's health status, identifying biomarkers for a wide range of conditions long before clinical symptoms appear. The incorporation of AI would ensure real-time data interpretation and personalized insights, enhancing diagnostic accuracy and therapeutic decision-making.

This tool would revolutionize healthcare by making comprehensive health monitoring widely accessible on a routine and economical basis. It would benefit patients, clinicians, and researchers alike, providing a continuous stream of detailed health data to drive personalized medicine and early intervention strategies. The main barriers to its development are the current technological limits in MS standardization and AI integration. However, with ongoing advances and interdisciplinary collaboration, this vision is within reach.

Emily R. Davenport
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Microbiome spatial multi-omics

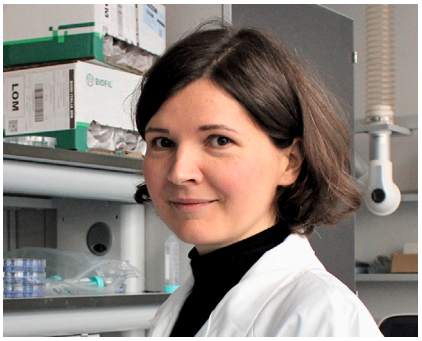
The advent of "next-generation" sequencing 20 years ago revolutionized microbiome research. It allowed scientists to transition from valuable but laborious studies of individual microbes to the high-throughput sequencing of entire microbial communities. However, current shotgun sequencing approaches leave us without crucial information, like which fragments of DNA came from the same genome, the 3D organization of microbes, and the heterogeneity of transcription within a population. These types of information are essential for identifying sources of mobile genetic elements (e.g., plasmids conferring antibiotic resistance), determining the spatial configuration of microbes (e.g., biogeography within biofilms), inferring species interactions (e.g., syntrophic relationships in soil), dissecting gene regulatory circuits (e.g., variability in transcriptional responses to stress), and more.

Development of spatial single-cell multi-omics for the microbiome would enable the next generation of microbiome research. While emerging methods like HiPR-FISH and MaPS-seq exist to characterize microbiome spatial organization at the taxonomic level, we still face limitations. We cannot yet collect spatial single-cell genomes, transcriptomes, metabolomes, proteomes, or multiple "-omics" features in a single experiment, as can be done for eukaryotic samples. I anticipate rapid advancements in this space over the next 5 to 10 years, in both technology development and data analysis techniques. These advances will enable us to address open questions on the spatial organization and heterogeneity of microbial ecosystems.

Margaret McFall-Ngai
Carnegie Institution for Science and California Institute of Technology, Pasadena, CA, USA

Tools to study microorganism signaling in real time

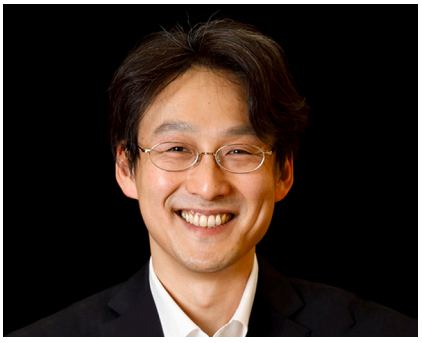
The application of technological breakthroughs in DNA sequencing over the last 20 years has revealed that microorganisms are foundational to the health of all corners of the biosphere. Concomitantly, we have learned that microbes are highly social organisms, communicating both among themselves and with a vast diversity of animal and plant partners. However, unlike animals and plants, for which we have the tools to observe the signaling that drives behavior and population/community ecology, we lack sufficient tools to study such interactions for microorganisms. The innovative tool we need is real-time microscopy with molecular-level resolution to define the molecules underlying signaling and observe their flow both between microbial cells and to and from their macrobiological hosts. Approaches to visualize, track, and/or identify this small-molecule flow, such as two-photon and cryoelectron microscopy and nanoSIMS, have provided game-changing insights. However, currently these techniques produce only snapshots in time. Exciting advancements are occurring in other methods, including photoacoustic microscopy, quantum imaging, nano-DESI, and MALDI. However, some of these may be too perturbing at the nanometer scale, and adapting them to probe molecular events will require the development of new hardware and software and the incorporation of AI. To invent such groundbreaking real-time technology is a tall order. However, this advance would be of exceptional value in understanding the language of microbes. It is a capability well worth dreaming about.



Magda Bienko
Human Technopole, Milan, Italy; Karolinska Institutet, Stockholm, Sweden

New methods to probe the 4D genome

Working in the field of genome organization, a major unmet need I see is having methods to probe the 4D genome—temporal changes in the 3D genome structure—across multiple timescales with genome-wide resolution. The 3D genome is a fundamental epigenetic trait that influences many nuclear processes, including DNA replication, repair, and transcription. Snapshots of the 3D genome obtained at various time points during embryonic development or cellular differentiation have indicated that it undergoes reorganization over time. However, the extent of 3D genome dynamics across different timescales remains underexplored. This is because current methods used to map the 3D genome typically operate on fixed cells. Approaches leveraging the CRISPR-Cas system have been developed to image selected DNA loci in living cells. However, these are difficult to scale up and often require genetic engineering, considerably limiting the number and size of DNA loci that can be visualized simultaneously. On the other hand, COMBO-FISH allows DNA FISH in living cells, yet only ~2% of the human genome can be imaged using this technique. We therefore need to develop innovative strategies enabling the visualization of large portions of the genome, with high genomic resolution, in living cells. The recent discovery of DNA-binding RNAs forming triple helices with DNA in a locus-specific manner, when combined with detection approaches such as Casilio, could provide a solution toward this goal.



Hiroki R. Ueda
University of Tokyo, Tokyo, Japan

Next-generation genetics beyond *Drosophila*

Drosophila genetics has significantly advanced our understanding of evolutionarily conserved biological processes. However, if humans are indeed more intricate than *Drosophila*, then the genetics used to study us must be faster and more efficient than that for *Drosophila*.

To achieve this, technologies enabling next-generation genetics, which can be defined as genetics without the need for mating, and whole-organ cell analysis are crucial. Next-generation genetics allows rapid manipulation of genes, such as precise knockout or insertion, surpassing traditional genetics reliant on breeding. While we conceptualized this in 2010 and achieved knockouts with the Triple-CRISPR method in 2016 and knockins using the embryonic stem cell-derived mouse method in 2017, improvements are ongoing. If next-generation genetics becomes fully realized, it could unravel complex molecular networks within mammals.

Whole-body/-organ cell analysis comprehensively examines every cell within organs or organisms. Recent advancements in tissue clearing and light-sheet

microscopy have accelerated analysis at the individual cell level, enhancing understanding of cell types, states, interactions, and 3D arrangements. While we achieved whole-brain cell analysis in mice in 2018 and whole-body cell analysis in 2024, further refinement is needed. Integration of next-generation genetics and whole-cell analysis promises a new era in biology, potentially unlocking insights into complex biological phenomena, including consciousness, and paving the way for revolutionary disease treatments.

Nikki Tjahjono and Lin Tian
University of California Davis, Davis, CA, USA; Max Planck Florida Institute for Neuroscience, Jupiter, FL, USA

Highly specific tools to monitor and manipulate ion channel activity

Technological advances in optogenetics, high-density electrophysiology, large-scale imaging with highly optimized genetically encoded indicators, and high-dimensional quantitative behavior have revolutionized our ability to dissect the functional activity of neural circuits. These tools enable large-scale monitoring and manipulation of neuronal activity with cell-type and circuit specificity.

Neurons exhibit tremendous diversity in their electrical signaling due to the distinct collections of ion channels with unique expression patterns specific to cell types and circuits. These ion channels are attractive drug targets for neurological conditions like pain and neuropsychiatric disorders. However, the diversity of ion channels makes it difficult to precisely identify and control their activity at a systems level, thereby limiting our understanding of their physiological and pathological functions and hindering therapeutic discovery. There is a need to develop novel molecular tools to monitor and manipulate native ion channel activation in behaving animals with precise temporal, spatial, and cell-type and subtype specificity. These tools would allow us to understand how ion channels collectively integrate and transform diverse neurochemical inputs into the firing patterns of cells, shaping the outputs of neural circuits. The development of these next-generation tools will usher in a new era where neuroscientists gain unprecedented access to the chemical and molecular underpinnings of behavior and neural disorders, ultimately accelerating the development of new therapies for neurological diseases.

Polina Anikeeva
Massachusetts Institute of Technology, Cambridge, MA, USA

Expanded techniques to study the peripheral nervous system

Working at the intersection of neurotechnology development and its applications to study brain-body physiology, one can observe the stark difference in the number of tools developed for the brain versus the peripheral nervous system. While electrophysiology, optogenetics, and optical imaging in the brain are routine, they remain near intractable in the peripheral nerves and organs of behaving subjects. This is in part due to anatomical and physiological complexity of mobile and vascularized visceral organs. These challenges can be overcome through innovation in soft bioelectronics precisely tailored to organ anatomy. However, rapid evaluation of such platforms remains impeded by the challenges in delivering molecular tools such as opsins or fluorescent indicators to the organs of interest. Unlike brain neurotechnology that can be evaluated in wild-type rodents across many regions through stereotactic injections of viral vectors, peripheral neurotechnology targeting different organs (e.g., intestine and lung) has to be evaluated in distinct genetic models. Although indispensable for rigorous hypothesis testing, intersectional genetics demands financial and intellectual investment that may deter engineering contributions to peripheral neurotechnology. Novel promoters, enhancers, and viral vectors that can enable cell-type- and organ-specific delivery of molecular tools in wild-type animals would empower fundamental study of interoception, boost the deployment of peripheral neurotechnology, and attract new talent to the intellectual frontier of brain-body physiology.

Jun-Jie Gogo Liu
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Tools to reveal 3D hyperdynamics

Current methods for obtaining atomic structures of biomolecules, such as X-ray crystallography or cryoelectron microscopy, average signals from large populations and require a relatively homogeneous and stable target. They have limited tolerance for structural flexibility, especially for targets exhibiting continuous large-scale dynamics (hyperdynamics) like long noncoding RNAs, polysaccharides, and low-complexity proteins. These hyperdynamic structures play crucial biological roles.

One approach to reveal hyperdynamics could be to combine experimental stable states with *in silico* intermediate states of the target. Integrating AI with scientists' understanding of molecular dynamics could help predict or simulate intermediate states. Alternatively, dissecting the target into multiple relatively stable subdomains and characterizing their dynamic interactions is promising. Despite its challenges, developing single-molecule, high-resolution imaging techniques will likely provide one of the ultimate solutions. This may involve pioneering new technologies like real-time observation of single biomolecules in solutions or living cells using electron microscopy to capture their atomic-resolution structures and changes at microsecond or nanosecond scales.

Analyzing hyperdynamic structures will generate vast amounts of data, necessitating new frameworks and approaches for data collection, storage, and analysis. Given the need to describe these hyperdynamic structures, new concepts such as atomic position probability distributions may offer insights distinct from the well-established PDB model of fixed atomic coordinates in 3D space.

Tara L. Deans
Georgia Institute of Technology, Atlanta, GA, USA

Technologies to spy on the central dogma

Over the last two decades, we have seen an explosion of technologies, ranging from highly multiplexed DNA synthesis and sequencing to enhanced methods for reprogramming cells with synthetic biology and improvements in automated super-resolution microscopy, to create large, feature-rich datasets. Developments in AI have made it possible to rapidly enhance the analysis of microscopy images by identifying complex patterns that can be used for predicting behaviors and complex outcomes. The intersection of these technological advances will likely radically accelerate the pace of scientific discovery.

A fantastic application for these unified approaches would be watching gene expression happen in real time with molecular resolution. This level of resolution could show how DNA is transcribed into RNA, the installation of post-translational modifications, how noncoding RNA moves and functions within the cytoplasm, and the translation of coding RNA into protein. AI will likely have a significant role in visualizing features that may go unnoticed or are inaccessible to the human eye. If this were possible, we could develop a fundamental understanding of how the central dogma is regulated in various dynamic cellular events, see the impact of dysregulation that causes disease, and study the effects of reprogramming on a cell. The intersection of these methods will empower a new frontier of science that can inform new approaches in cellular reprogramming, drug development, and the identification of new biomarkers.

Xiaohua Shen
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New eyes and new landscapes

Barbara McClintock once remarked, "With the tools and the knowledge, I could turn a developing snail's egg into an elephant." This highlights a profound truth: the genetic code within the DNA of a fertilized egg contains all information needed for vastly different organisms. How can the same linear DNA sequence create thousands of cell types and complexities of an organism? McClintock's bold assertion emphasizes the intricate regulation and timing of genetic expression.

Modern biology recognizes that noncoding sequences dominate mammalian genomes. These sequences, along with the inherent randomness of biomolecules and cells, challenge the deterministic view of genetic flow from gene to messenger RNA to protein in fully explaining biology. Just as quantum mechanics transformed physics by explaining phenomena like blackbody radiation and the photoelectric effect beyond Newtonian mechanics, biology is on the cusp of a similar paradigm shift.

To truly grasp life's complex phenomena, we need a new theoretical framework that goes beyond molecule-centered approaches and embraces nonlinearity. By combining

physical modeling of the nucleus with investigations into functional genome sequences of single nuclei, we can apply physical laws to interpret experimental observations and fundamental traits. This approach will help us understand noncoding genome regulation and uncover the algorithms governing information flow from DNA to cells and organisms. This evolving, holistic perspective offers hope, illuminating pathways through uncertainty and potentially fulfilling McClintock's vision.

DECLARATION OF INTERESTS

Y.Y.C. is an inventor of several patents related to CAR T cell therapies; is a founder of, holds equity in, and receives consulting fees from ImmPACT Bio; and is a member of the scientific advisory board of and holds stock options in Notch Therapeutics, Pluto Immunotherapeutics, Prime Medicine, Sonoma Biotherapeutics, Waypoint Bio, and AffyImmune.

M.M. is the director of the proteomics program at CPR, Faculty of Health and Medical Sciences, University of Copenhagen, and an indirect investor in Evosep.

H.R.U. is a co-inventor on a patent and patent applications covering the CUBIC reagents (PCT/JP2014/070618; PCT/JP2017/016410) and a cofounder of CUBICStars Inc.

M.M.-N. is chair of the Advisory Committee for the Max Planck Institute for Biology, Tuebingen, Germany, 2024–2027; a member of the Advisory Committee for NIH COBRE grant, U Hawaii, 2023–2028; a member of the Hypothesis Fund Advisory Committee, as of 2022; a member of the Burroughs Wellcome Fund's Climate Change & Human Health Advisory Committee, as of 2022; a member, of the advisory board for the Carl Woese Center for Genomics REsearcg, University of Illinois, Urbana-Champaign, as of 2020; and a member of the advisory board for the Collaborative Research Center, German Research Foundation, "Origin and Function of Metaorganisms," as of 2015.