Cell
Leading Edge

Voices

Cell biology is…

50 years ago, cell biology was a nascent field. Today, it is a vast discipline whose principles and tools are also applied to other disciplines; vice versa, cell biologists are inspired by other fields. So, the question begs: what is cell biology? The answers are as diverse as the people who define it.

Julie A. Theriot
University of Washington and Howard Hughes Medical Institute, Seattle, WA, USA

Holding the secret of life

For me, cell biology is the study of the secret of life. Nothing smaller than a cell can really be said to be alive, and nothing bigger than a cell is any more alive than an individual cell. I delight in the knowledge that all cells come from other cells. That is, every single cell currently living on our planet had a mother cell, who had a mother cell, and so on in a continuous lineage back to the origins of cellular life on our planet, a common inheritance shared by cells in bacterial biofilms, in vampire squid, and in redwood trees. In addition, cell biology represents the most interesting scale for interdisciplinary science. Understanding the inner workings of a living cell demands that we embrace scientific disciplines and concepts ranging from metabolic biochemistry to fluid dynamics and from evolutionary theory to statistical mechanics. Being a cell biologist means always being ready to learn something new. For the past thirty-five years, my primary research tool has been live cell videomicroscopy, and I continue to be awed every day by the richness, complexity, and sheer beauty of cellular behavior. At this scale, our field has developed a wide array of precise, quantitative methods for both manipulating and measuring cell processes, with frequent technical breakthroughs continuously giving us new ways to explore. We do not yet fully understand how billions of nanometer-scale macromolecules are able to organize themselves into a living cell without a blueprint or an architect, but we are getting closer.

Anne Simonsen
University of Oslo, Oslo, Norway

Understanding the cellular society

During my education in general biology in the late 1980s, I became particularly interested in cell biology. I realized that understanding the various processes that occur within cells, the basic structural and functional units of all living organisms, is key to answering fundamental questions about life in general and disease development. I find it highly fascinating to think about every cell as an independent society, with its own rules (expressed genes), highways (cytoskeleton and vesicles), power plant (mitochondria), recycling (autolysosomes), and communication platforms (signaling and exocytosis). I decided to devote my career to deciphering the signals and mechanisms involved in vesicle biogenesis and transport during endocytosis and autophagy and trying to elucidate their link to disease development. It has indeed been an exciting journey, paralleled by the development of advanced technology and the genomic revolution that have led to the discovery of many new concepts in cell biology and new avenues for therapeutic interventions. Recent advancements in single-cell analysis revealed the importance of studying individual cells to fully understand biological processes. Yet, we are still far from knowing the role of every society member (protein) and how they cooperate to maintain cellular homeostasis in response to changes in the internal or external environment. It will also be important to understand how cells interact and work together to maintain overall cell health and organismal well-being. While different in scale, organization, and complexity, comparing cells to societies may help us appreciate the fundamental principles of cooperation that underlie the functioning of all living systems.

Iva Tolić
Ruđer Bošković Institute, Zagreb, Croatia

Decoding the rules of our existence

Functioning as the fundamental building blocks of life, every cell encapsulates a miniature universe within itself. Understanding the laws that govern this microcosm presents an immense and exciting challenge. The exploration of cellular inner workings not only enhances our understanding of cells and organisms but also serves as a foundation for developing treatments for a variety of diseases such as cancer, genetic disorders, infectious diseases, and neurodegenerative conditions.

When I first entered the world of cell biology, my dream was to shrink to the size of a macromolecule, dive into the cell, and watch what all the molecules are up to, trying to figure out how it all works. This dream has not left me ever since. The closest I can get to this in real life is through live-cell microscopy, which, growing more powerful with emerging technologies, becomes our lens into this fascinating show. It's about peering into the tiny cellular world, following our favorite proteins as they go about their business, and prodding them occasionally to see the cell's reaction and learn from it.

The most mind-blowing event in the life of a cell is cellular childbirth. I am fascinated by the elaborate choreography of cellular dynamics leading to the equal inheritance of the genome by the two daughter cells and by the various ways in which this can go wrong, contributing to cancer, infertility, and congenital disorders. In exploring cells, we appreciate the enormous complexity of life. In understanding cells, we decipher the rules of our own existence.

Manuel D. Leonetti
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Enabled by the power of imaging

When I think "cell biology," I immediately think of Albert Claude, Christian de Duve, and George Palade, whose Nobel Prize, just like *Cell*, celebrates its 50th birthday this year. Their work exemplifies the power of imaging cellular structure to understand cellular functions; the "small particulate component" seen in Palade's micrographs led to the discovery of ribosomes. Their discoveries also illustrate how our understanding gets transformed by complementary technologies (in this case, cell fractionation and electron microcopy) that unlock new levels of observation. I can't wait to see what we will discover next by observing cells and their structures through the lens of recent transformative technologies. New methods such as volume electron microscopy and cryo-tomography will bridge molecular and cellular scales. Advances in live imaging, from adaptive optics light-sheet microscopy to super-resolution, will enable us to map cellular dynamics with unprecedented resolution in space and time. Comprehensive labeling of cellular components, for example using CRISPR engineering, will pave the way for a description of how different parts of the cell interact to build a complex system. Finally, machine learning and computational methods will revolutionize our capacity to extract and interpret mechanistic information from images or movies. "Looking" at cells is a central pillar of cell biology. I will bet that cells are not done surprising us.

Satyajit Mayor
National Center for Biological Sciences, Tata Institute for Fundamental Research, Bangalore, India

Entering the dawn of a new era

As the fundamental unit of all life forms, understanding how the cell functions is key to our ability to study how a living system is put together, and it is truly an amazing time to be able to be a cell biologist. Today we have an unprecedented grasp of the composition of a living cell as it is situated in its micro-environment and phylogenetic locale. This is made possible by the tools of metabolomics, proteomics, and lipidomics becoming available almost all at the single-cell level, intersecting with spatial-omics from complex tissues and diverse evolutionary branches in the Tree of Life. While this level of description is data-rich and available for the avalanche of statistical methods available today, active matter physics is providing a new window into understanding the properties of biological materials in their native non-equilibrium environments. This has been enabled by the development of powerful imaging methods to study biological systems in their living state from the molecular scale to the scale of multi-cellular organisms. There is also a growing appreciation of the role of mechanical forces and the geometry of the system at every scale of biological organization. These developments have hugely influenced my own research into the structure, function, and evolution of the cell membrane.

From the perspective of cellular interfaces, where the cell engages with the outside world and connects to its innards, I can only say, "You Ain't Seen Nothin' Yet."

Patricia Bassereau
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Inspiration for soft matter physicists

Physics and biology have successfully cross-fertilized for a long time, and it is particularly true for cell biology and soft matter physics in the last two decades. In the middle of the nineties, I transitioned, like some others, from soft matter physics toward "cell-biology-inspired physics." At that time, soft matter had established solid conceptual bases about membranes, polymers, colloids, gels, and liquid crystals, as well as adhesion, wetting, condensed matter physics, and phase transitions or critical phenomena. This science has now been shown to be instrumental in unveiling operating principles for, e.g., molecular motors, cell sub-compartments, chromosomes, cells, tissues, or embryos in healthy or unhealthy conditions. This is particularly clear with cellular condensates that have been recently discovered. Importantly, the physical models had to evolve to integrate the intrinsic non-equilibrium nature of living systems and their complexity. While the physics of living systems was developing, it inspired in return soft matter physicists; "active soft matter" became a bustling field on its own. In addition, cell biology is an endless source of inspiration for engineering new bioinspired/biomimetic systems, for building up synthetic cells, or for progressing toward understanding the origin of life. We can be certain that with more technological developments that will reveal new aspects of cells and tissues, cell biologists and soft matter physicists will continue to reciprocally benefit from these fruitful exchanges.

Ewa K. Paluch
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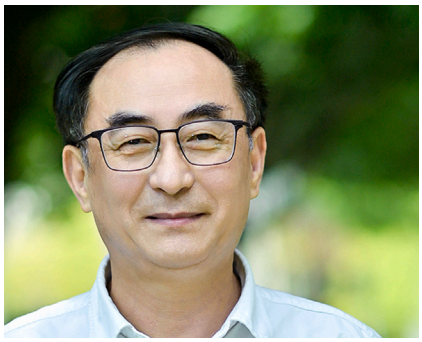
Where biology meets physics

My mentor Michel Bornens used to say, "a discipline is defined by the questions it asks." As a physicist turned cell biologist, I am fascinated by the integration of questions from physics into cell biology. Cells are physical in nature and function in a world governed by the laws of physics. They must obey force balance and the laws of thermodynamics, which profoundly impact what a cell can and cannot do.

A part of cell biology where physics brings key insights is cell shape. In the "pre-molecular era," much of cell biology focused on morphology as an essential feature defining cell function. All animal cells come from a round-ish egg, yet differentiated cells display a variety of shapes, duty-bound to function. Since shape is determined by force balance at the cell surface, investigators of cell morphogenesis must measure and understand cellular forces. The past 20 years have seen the development of multiple methods to measure these forces: AFM, traction force microscopy, and laser ablation, to name a few. Combined with physical modeling, investigating forces in cell biology has brought immense insight into understanding shape, movement, mechanosensing, and tissue morphogenesis. One frontier I find particularly exciting is the integration of morphogenesis and cell-state studies. The latest imaging capabilities enable the inclusion of shape analysis in studies that traditionally focus on multi-omics data. This will allow simultaneous interrogation of what a cell looks like and what it does with unprecedented mathematical precision, ultimately illuminating cell identity from both a molecular and a physical perspective.



Jiahuai Han
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The core of life science

Textbooks tell us that cell biology is a branch of biology. As a cell is embedded in processes of all living behaviors of organisms, including unicellular and multicellular ones, cell biology is immersed in the whole field of biology. Cell biology to me is the center of life science.

The discovery of cells resulted from the invention of the microscope. Along with the recent rapid development of science and technology, new inventions dramatically revolutionized research tools in cell biology. A notable example is the capability to conduct single-cell-level studies not only on cell ultrastructures but also on cellular contents (transcriptomics and proteomics) and chemical reactions (metabolomics). Revealing large numbers of previously unknown cell subtypes/statues by single-cell analysis could define a physiological/pathological process by cell populations. With additional *in situ* information of the single cells, it enables the modeling of a biological process with a spatiotemporal resolution. Systemic homeostasis is the fundamental requirement for the life of any given organism, of which cellular homeostasis is the base and cellular stress responses that maintain cell homeostasis are indispensable. Single-cell analysis and subcellular analysis have revolutionized the ways to discover mechanisms of cellular responses, enabling the discovery of the coordinated cellular stress response across tissues, organs, and the whole organism for maladaptation.

Markus W. Covert
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A quantitative discipline

In recent years, we have seen a transformative change in the way that experiments are performed and interpreted in cell biology, due largely to a substantial influx of intellectually ambidextrous trainees who are equally fluent in biology, mathematics, statistics, physics, chemistry, engineering, and computation. Their scientific contributions have opened vast frontiers in both fundamental science and biomedical applications. Significantly, the integration of these disciplines was premeditated, and here I have to shout out the Whitaker Foundation, which spent hundreds of millions of dollars in the 90s and early 2000s to build up bioengineering programs in the United States. Whitaker's unique "spend-it-all" philosophy gave a major jump start to burgeoning programs across the country just when it was most needed, funding the creation of dozens of new departments as well as many hundreds of graduate students and young faculty. No less importantly, it raised the profile of the endeavor, attracting follow-on interest and funding from other initiatives, both governmental and private. I never received funding from the Whitaker Foundation, and yet I was its beneficiary in many ways. Now, as I consider the future of cell biology and the most pressing challenges of our time—the health of our planet comes first to mind—I wonder: which fledgling fields in interdisciplinary science would now benefit the most from a similar infusion of philanthropic support and enthusiasm, and who are the individuals and groups with the courage and vision to catapult these fields to the future?

Noboru Mizushima
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Generality and specificity

Cell biology is a science of both generality and specificity. Many cellular functions are common across cell types and organisms. This allows us to learn universal principles from model organisms such as yeasts, worms, flies, fish, plants, and mice. For example, most cells maintain homeostasis and flexibly adapt to their environment by not only synthesizing their own components but also degrading them (intracellular degradation, especially autophagy, is my area of expertise). Cell differentiation and development often involve both synthesis and degradation. I believe that this general principle might even apply to extraterrestrial organisms, should they ever be discovered (I am really looking forward to seeing them!). At the same time, what makes cell biology so fascinating is the fact that cellular functions are remarkably specialized for each organism and cell type—the result of evolution over a long period of time. Budding yeast, for example, is often thought of as a simple model organism, but based on my own experience with yeast and mammalian cells, yeast is just as amazingly specialized as cells such as neurons and hepatocytes. Unraveling the questions of cell biology, both general and specific, will be a fun and rewarding experience.

Samara Reck-Peterson
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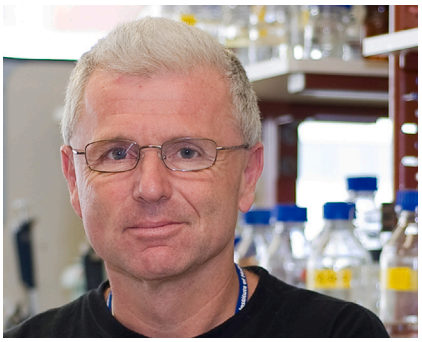
Viewing life through the lens of technology

Cell biology has been inextricably linked to advances in technology. Modern cell biology was arguably born under the beam of a transmission electron microscope in the 1940s and then propelled in the following decades by the complementary approaches of genetics and *in vitro* reconstitution. My own journey as a cell biologist was inspired and shaped by those same factors.

My decision to become a cell biologist began with a seminar taught by Lew Tilney in 1994. We discussed the discovery of gamma tubulin in *Aspergillus nidulans* by Liz and Berl Oakley (1989), the use of optical trapping to observe kinesin stepping by Karol Svoboda, Steve Block, and colleagues (1993), and the structure of myosin II by Ivan Rayment and colleagues (1993). Those landmark papers and my first exposure to experimental cell biology at the MBL Physiology course directed by Mark Mooseker (1994) sparked my interest in understanding intracellular transport across scales.

The combination of artificial intelligence, technological advances in experimental science, and broadening our view of what is important for human health will shape cell biology in the coming decades. Our dream of visualizing entire cells at molecular and even atomic resolutions in 4D is within reach. As our climate changes, cell biology is also in a unique position to understand how animals, plants, fungi, bacteria, and viruses respond and adapt to climate change and how those adaptations impact human health. I am excited to be a part of these efforts and to share the joy of being a cell biologist that my mentors instilled in me.



Andreas Strasser
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Key to promoting health

The development, division, differentiation, and death of cells underpins the proper functioning of all organs and is thus central for all aspects of multicellular as well as unicellular life forms. I am passionate about investigating the mechanisms that control the cellular processes that underpin health and uncovering the nature of the defects that subvert these processes to cause diverse diseases. Discoveries from these investigations will provide a solid foundation of understanding that can be exploited in translational research efforts that will promote better health and lead to the development of therapeutic strategies, including new drugs, to treat diseases. In particular, I am interested in deciphering how mutations in oncogenes and tumor suppressor genes deregulate the normal control of cell division, differentiation, and death to drive tumor development. It is anticipated that this will identify vulnerabilities, an "Achilles heel," engendered by these abnormalities in cellular processes that can be harnessed for developing novel targeted cancer therapeutics.

Iain Cheeseman
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Truly awesome

As a first-year graduate student 26 years ago, I attended my first lab meeting eager to learn about cell biology. I left having taken only a single sentence of notes that read "The cytoskeleton is boring." As someone who now deeply loves diverse aspects of cellular function, including the cytoskeleton, I frequently reflect on that moment and how wrong I was. My own cell biology education was often taught as a collection of facts to be memorized, whether it be the stages of mitosis, that the mitochondria is the "powerhouse of the cell," or the lists of proteins that comprise the cytoskeleton and other cellular structures. However, the beauty of cell biology is the elegant concepts and principles that govern this fundamental unit of life. Cells are not bags of proteins but are intricately spatially organized. Cells are not static but instead highly dynamic, constantly moving, changing, and generating incredible force. Cellular function must also be precisely controlled through rich regulatory mechanisms. For my own work, I aspire to understand these key cellular features and how they are altered across diverse physiological contexts. Cell biology is often defined by the ability to visualize cells in their amazing beauty, but cell biology is not simply descriptive, necessitating a deep molecular and

mechanistic understanding. Achieving this understanding requires combined approaches and concepts from across disciplines, from the angstrom scale to the organismal level. Ultimately, I believe that everyone whose work touches biology is a cell biologist at heart.

DECLARATION OF INTERESTS

The authors declare no competing interests.