Pulling It All Together

Hundreds of pathways, thousands of cell types, tens of thousands of molecules, megabytes of data, and seemingly infinite biological networks—the study of life has perhaps never been more daunting. What ever happened to the explanation from Miller-Urey's experiment on life's origins, involving just four compounds, or the simple (okay, merely seemingly simple) unidirectional flow from DNA→RNA→protein? One can hardly study biology within the confines of a single textbook anymore, owing to its vast stratifications and marriage with multiple other disciplines. Each field seems to be paving its own frontier explaining what it takes to be a living organism. Is this trend in any way fragmenting the biological community or diminishing our unity of purpose?

In thinking about the diversification of biology, we're reminded of *Cell*'s own editorial journey. *Cell* was launched forty years ago in 1974, in a period during which exciting biology was synonymous with molecular biology. But if the early 1970s were the heyday of classic molecular biology, the later 70s and 80s marked the rapid confluence of molecular biology with other fields such cell biology, physiology, genetics, immunology, developmental biology, and neuroscience. Through the 90s to the present day, molecular biology has become intertwined with the era of big data, genomics, and medicine. So while it seems that this massive expansion of biology is a recent event, in truth, the currents of diversification have been running through the field all along, with *Cell's* own scope evolving and broadening along with the evolution of biology as a whole.

That these trends are long-standing is comforting to realize, but does that help us make sense of it all? Are there common threads, weaving through seemingly dissimilar fields, integrating and perhaps even explaining some of the most pressing questions about the processes that define a living organism? Looking at the landscape of biological discovery today, we indeed find that this ocean of divergence and dissimilarity isn't necessarily what it appears to be. In this special review issue, as part of our anniversary celebration, we are excited to present eight themes that we hope will serve as a prism through which to view emerging trends that bridge the various biological disciplines. Each theme is exemplified by a series of reviews by eminent scientists around the world who share our vision and sport theme-tinted glasses. Though by no means exclusive or exhaustive, these eight themes have allowed us to appreciate forty years of exhilarating discoveries and to use our unique view as editors across the whole scope of biology to identify and extract some hopefully useful conceptual threads that cast a new light and help tie things together. We hope that you are left with the same awe and admiration that we've felt.

We open with The Power of One (page 3). In a field in which the n number is paramount, what could be more paradigm changing than putting the emphasis on the just "one" unit? The Power of One explores the idea that a wealth of spatial, molecular, and functional information can be gleaned from studying a single molecule or a single cell. The reverse extrapolation from one to many can in fact yield surprising discoveries into aspects of molecular or cellular function that may have been lost in "averaging," such as discovering new parameters to measure DNA function or clues into cellular migration, the stochastic nature of gene expression, and the importance of noise in biological systems.

If much of the understanding over the last forty years has been centered on the "how" or the "what" of a process, looking at all levels of analysis, we see that there is a convergence of appreciation for a new paradigm, the "where." Adding a whole new dimension to biological processes, Location Matters (page 12) explores the concept of how the location of a process—be it subcellular or systemic—defines its function and purpose. After all, how many times have we thought about our favorite protein and wondered, "What on earth is it doing there?"

Within all of us, there's a rebellious streak that revels in thrill and excitement when breaking what was once called a rule. In the section Breaking Old Rules, Defining New Ones (page 76), we explore established rules laid down decades ago, which have since been broken (or at the very least needed a complete rewrite). Some of these new rules have led to the discovery of entirely new fields, such as epigenetics.

Most of us grew up learning that "bugs are bad for you." In Redefining the Enemy (page 120), we learn that there's much to discover from microbes within and around us. There is an emerging appreciation of the organismal ecosystem—the sum of bacteria, viruses, and fungi that together make up microbiomes and how they impact multiple aspects of host form and function. Meanwhile, our ability to modify microbes has enormous potential for medical and environmental applications.

From replication to transcription to translation, much of the science in *Cell*'s early history was heavily focused on the science of synthesis—in learning how molecules, cells, and tissues were made. But the cell isn't a mere assembly line of mass production. It is imperative to get rid of material that is neither critical nor functional. In Taking Out the Trash (page 51), we highlight an emerging focus across fields on the mechanisms that help biological systems remove, recycle, and even refurbish their own materials to maintain a homeostatic zen and keep going. Be it sick neighbors, proteins that are out of shape or in the wrong place or wrong time, or distress signals from distal tissues, cells need to know when it's time to go, even when it comes to making the ultimate self-sacrifice.

Perhaps no other part of the human body is more befitting the moniker "final frontier" than the brain. Over the last forty years, *Cell* has witnessed and shared exciting developments at the very forefront of neuroscience research. In this era of connectomics and optogenetics, it seems that we finally have the approaches and tools to decipher the most mysterious part of the human body. In Decoding the Brain (page 162), we recognize the processes that underlie learning and memory and explore the biology of emotion and prospects for treating psychiatric illness.

Who are we, and where did we come from? In the early days of *Cell*, discoveries made using powerful genetically tractable organisms provided us with a glimmer into our own inner workings. While these systems continue to fuel all aspects of research, including basic and translational, today we're equipped with the tools and the knowledge base to begin considering humans as a potential model system. Uniquely Human Biology (page 215) explores the idea that there's a level of complexity in function, in physiology and disease, that is uniquely human and, even more so, unique to each individual. The tools of molecular biology and genomics are opening up the world of personalized medicine and are also allowing us to peer back in time to our origins as a species.

Where does this all leave us? We wouldn't blame you if, like us, you're thinking "this is all so complex." Herein lies the final theme, a super theme even: Finding Meaning in Complexity (page 254). In this era of high-throughput analyses, big data, and systems biology, the challenge lies in unraveling a core set of modules—a series of key patterns that may help to provide mechanistic and functional clues into a process. To find meaning in complexity, one needs to amalgamate the space-station view with the microscopic one and mold together layers of information. With this paradigm in mind, hopefully we'll be able to accurately triangulate new and meaningful insights into how biology really works, and perhaps this may even provide inklings of themes yet to emerge.

Exploring the themes illuminating forty years of exciting biology could only have been made possible through the vision and contributions of authors and reviewers not just to this special issue, but to all of the science in the history of *Cell*. We continue to be inspired and exhilarated by the emergence of new themes and big concepts. In a way, we have come full circle in conceding that the study of life is indeed complex, and yet, never has it been more exciting.

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