Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Cell

Embracing the Landscape of Therapeutics

Before there were pills, prosthetics, and biologics, there were potions, poultices, and herbal teas. Disease dogs all life, and the innate desire to preserve life and restore health has propelled humans to experiment with medicines and therapeutics since before written history. Yet, there was poor progress in understanding or treating our many ailments until the 19th century, which marked the age of modern medicine. Although people are living longer and healthier lives than 200 years ago, there is much farther to go to cure or treat all diseases. The same modern technologies that are giving us deep insights into the mechanisms of disease are also revealing the challenges of developing safe and effective therapeutics. Even so, there is reason to be hopeful: more than ever before, basic and clinical research are joining efforts and resources to understand and cure human diseases.

Therapeutic development and basic biological research propel each other forward in a mutually beneficial cycle. Basic research studies uncover how the body works by defining what is a healthy baseline but then also enable the dissection of what happens when things go wrong, leading to more rational approaches to therapeutic development. At the same time, fundamental biology has also benefited from the clinic: the results of clinical data and analyses can potentially reveal both conceptually new biological insights and knowledge gaps, either of which can inspire new avenues of scientific research.

Our goal at *Cell* is to foster the fluid exchange of information between basic and clinical research, as we strongly believe that the greatest advances will come by breaking down these silos. This is why, for example, *Cell* is both a home for clinical trials describing new approaches to enhance checkpoint blockade therapy and the fundamental mechanisms of genomic re-arrangements. This is also why we are excited to publish the Bench to Bedside format; these graphical articles boil down the disease context and biological mechanisms of exciting new therapeutics, providing essential information for bench researchers and clinicians alike. There are a lot of diseases, known and unknown. And disease affects us all, directly or indirectly. As *Cell* matures as a home for both translational and basic research, we wanted to take the opportunity to reflect on some exciting advances in therapeutic development; try to understand how basic research has helped shape those developments; and outline the fundamental challenges that bench, clinical, and biotech/pharmaceutical research will need to work together to solve in the coming decade.

In this Special Issue, we're excited to feature pieces that reflect the progress and challenges of the therapeutic landscape of today. In some instances, where there has been incredible success in understanding and treating disease, the focus now turns toward widening the spectrum of patients who can be treated. In others, we sufficiently understand the biological underpinnings of disease but lack the tools to correct them. And in some cases, the basic biological understanding needed to begin on the path to developing safe, effective therapeutics is still lacking. *Cell* aims to publish research that pushes through each of these bottlenecks. In thinking about the scope of therapeutic research today, and the direction it is heading, we see themes emerge that transcend the individual disease or therapeutic approach.

No One Can Whistle a Symphony

To develop therapeutics and bring them to the people who need them most, diverse stakeholders must be identified, engaged, and encouraged to collaborate. This is especially imperative for global health issues, such as the current threat of COVID-19, and diseases that disproportionately impact vulnerable populations, such as those in the developing world. In these instances, researchers, clinicians, and industry and public health officials may be separated by geography, language, and other barriers. At *Cell,* we strive to promote dialog among these groups, because we expect to see the greatest bursts of progress when people come together in new ways. As a breathtaking example of collaboration, the recently approved Ebola vaccine was developed initially by the Public Health Agency of Canada, was further developed by Merck, and was allowed for compassionate use in vaccinating over 200,000 people prior to official approval.

New and Not-So-New Sources of Inspiration

Expanding the circle of collaborators is one way to stimulate new ideas and solutions, but other approaches are needed, especially in cases where therapeutic progress has slowed or reversed.

Consider the antibiotics field. Not only has the discovery of new antibiotics stalled out in the past two decades, but microbes have begun to develop resistance to antibiotics that were once effective. To get past this crisis, innovative methods and approaches are needed to search for new molecules from other sources. What might an antibiotic look like? Where might it come from or be found?

In some cases, the best approach to finding a new therapeutic may be to dig back into the past. This could mean repurposing small molecules or reconsidering medicines that were abandoned for political or social reasons. For example, decades-old evidence shows that some psychedelic drugs can have beneficial effects for psychiatric disorders, such as depression. Yet, they have remained poorly explored as therapeutics because their rampant use as recreational drugs prompted heavy regulation. Renewed interest in their efficacy has led to the approval of a variant of ketamine as the first conceptually new antidepressant since the 1950s. Moreover, it has changed our understanding of the neurobiological basis of depression and opened new therapeutic avenues.

Finally, to develop the therapeutics of the future, we need to think beyond classical medicines. An effective therapeutic might be a pill of microbes or a small machine implanted into your spine; it could be a cell, pulled out of your body, modified, and put back in; or a therapy might start before birth, with the genome or mitochondria of an egg replaced or manipulated. It will be important to keep an open mind about what a therapeutic could be, as the future of medicine might look entirely different from what exists today.

Ask Big Questions, Find Big Answers

The research community is collecting more data, and more distinct types of data, than ever before.

With the appreciation that many, if not most, diseases are incredibly complex has come the equal appreciation that a lot of data, and many types of data, are needed to understand and treat such complexity. Multidimensional datasets are beginning to be collected and analyzed for individual patients, including the genetic, proteomic, and metabolic features of their disease. Such data collection is not limited to the clinic; in the future, wearable, implanted, and smart-home devices could be used to monitor disease progression and therapeutic response. The hope would be that a physician could use these data to alter and personalize the therapeutic course for maximum efficacy while minimizing side effects. However, extracting knowledge from such large and complex data is challenging.

Machine learning algorithms aimed at helping make sense of these data are being rapidly developed. However, these algorithms must be trained on a large base of ''ground truth'' data, and such datasets have lagged in biology compared to other fields. To address this, a foundation is being built from basic research through the collection and synthesis of multidimensional data on healthy and diseased tissues. At *Cell*, we believe in the value of foundational datasets as well as the sophisticated machine learning algorithms that use them to inform biomedicine.

Other types of big data are making a big impact on therapeutics development. For example, advances in cryoelectron microscopy have increased the volume of data and analytical capabilities of this approach. As a result, structural information has now become both abundant and easily obtainable, such that it is beginning to inform the design of drugs targeting clinically relevant proteins in HIV, cardiovascular disease, neurodegeneration, neuropsychiatric disorders, and other diseases.

Get Personal

While stratification can group patients together in ways that inform treatment options, ultimately, diseases affect individuals.

Although the principles behind a therapeutic approach may be sound, many variables can impact whether a particular patient will respond to a therapy. Understanding the molecular basis for their disease will be important, but treatment and efficacy may need to incorporate the broader context of their lifestyle, environment, and overall genetic landscape. For example, emerging data suggest that gut microbiome composition may impact the metabolism of a drug, potentially explaining inter-individual differences in efficacy. In the context of autoimmune diseases, the diverse etiology and presentation of these diseases have stymied efforts to develop truly targeted therapeutics. To move past treating symptoms and truly treat the root causes of these diseases, an understanding of who will respond to each therapeutic is needed.

Understanding the impact on the individual can drive therapeutic research in other ways. Meeting people impacted by a disease can be a driving motivational force for the basic researchers, regulatory officials, and funders working on that disease. Creating opportunities for these personal interactions is especially important for rare diseases, where having a well-connected network of stakeholders can mean the difference between a fully enrolled, successful clinical trial and one that never begins.

Get to the Source

Even if the mechanistic basis of a disease is understood, it is still often challenging to fix the source of the problem.

Even when diseases are caused by a single mutation, it is still a struggle to correct these errors *in vivo*. The major challenges have been in creating tools to safely manipulate the genome without off-target mutations and targeting delivery specifically to the affected tissues. While progress is being made on the former, the latter remains a challenge both for genome editing and for therapeutics more broadly.

In some cases, targeting a therapeutic to a specific location can be achieved by directly implanting it at that location, such as with neuromodulatory devices. However, these devices have their own set of challenges to becoming therapeutically viable on a broad scale. For example, features that are compatible with ordinary human life, such as being wireless, soft, and flexible, are challenging to engineer.

The Changing Therapeutics Landscape

Medicine and therapeutics have become incredibly sophisticated. Today's therapeutics are dominated by small molecules, nucleic acids, antibodies, and increasingly, cellular therapies. Tomorrow's therapeutics may add an even more diverse set of modalities, including gene editing machinery, nanodevices, microbes, mitochondria, and lab-grown organs or tissues. More than ever before, medical breakthroughs are fueled by deep biological understanding of the mechanistic basis of disease, whether derived from massive multi-omic datasets on patient tissues, sophisticated machine learning algorithms, complex animal or cell culture models, or a combination of all these.

However, to leverage this understanding into new therapeutics, communication between clinicians, basic researchers, commercial entities, regulatory agencies, and—especially—the patients and their loved ones is needed. This communication will blur the existing boundaries between the research bench, pharmaceutical lab, clinic, hospital, and the patient's home. The result will be a smarter, faster trajectory toward treating patients, and the path there may involve new kinds of clinical trials, increased use of fast-track status, and more instances of compassionate use.

We at *Cell* are thrilled to bring you this Special Issue highlighting some of the exciting recent advances and the emerging

frontiers in therapeutic development. While curing or treating the spectrum of human disease is still a daunting goal, it no longer seems as impossible as it once did. As a journal, we are proud of the part we play in accomplishing this goal by being the home for research, reviews, and commentary that push therapeutic development and the future of medicine in new directions. We hope that you will find within these pages many reasons for hope and excitement for the future of therapeutics.

The *Cell* Editorial Team

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