What are the drugs of the future?

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Are small molecules or biologics the drugs of the future? Let's think about this... (Fig. 1). For many of us growing up in the 20th century, videotapes were fixtures of our childhoods. In the current entertainment industry, videotapes have completely become obsolete and been replaced by more complex and sophisticated Blu-ray Discs, which deliver ultra high-definition pictures and films to viewers. Technological change is inevitable in our society, which embraces innovations. Similarly, the pharmaceutical industry has been experiencing its own scientific revolution, as more and more novel biologic drugs continue to emerge. Are these biologics the Blu-ray Discs of the pharmaceutical industry? Will small-molecule drugs fade into history like videotapes did? In an attempt to address these questions, we will compare and contrast small-molecule and biologic drugs to assess what roles they will serve in our healthcare system in the future.

Small-molecule drugs

Small-molecule drugs are defined as compounds with low molecular weight that are capable of modulating biochemical processes to diagnose, treat, or prevent diseases. Small-molecule drugs include the aspirin, diphenhydramine, and other molecules that we typically have in our medicine cabinets. Small-molecule drugs, including natural products, have been the pillars of traditional medicine and played an important role in shaping the world we live in. A classic example is the wonder drug penicillin, which successfully reduced death rate by bacterial-related pneumonia to less than 1% during World War II.¹ Moreover, small molecules have been some of the biggest blockbusters in the history of the pharmaceutical industry. For example, atorvastatin (Lipitor) generated at least 9 billion dollars per year in revenue for Pfizer during its patent life from 2003–2011.² Despite the emergence of many bio-

Are small molecules or biologics the drugs of the future? Small-molecule drugs have historically been the pillars of traditional medicine. However, recently, we seem to be amidst a scientific revolution with the rise of many FDA-approved biologic drugs. This opinion article looks at the current state of small molecules and biologics and assesses what the future holds for these two broad classes of drugs.

logics, small-molecule drugs still remain highly prevalent on the latest WHO Model List of Essential Medicines in 2017.³

To healthcare providers and patients, small-molecule drugs remain attractive for several reasons. First, because of their relatively low molecular weight and simple chemical structures, their pharmacokinetics and pharmacodynamics are normally more predictable than those of biologics, which often lead to simpler dosing protocols. Second, the development of

Fig. 1 A cartoon representing how, in history, we are continuously faced with new scientific advancements that make us question what the future holds and whether what we currently have is still useful or should be replaced.

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small-molecule drugs often involves simpler manufacturing, characterizing, and regulatory processes. Additionally, many small molecules are highly stable and orally bioavailable, which further enhances patient compliance. Ultimately, because of all these reasons, small-molecule drugs are naturally relatively more affordable for patients and reimbursement bodies. On the other hand, from an inventor's perspective, the simplicity of small-molecule drugs exposes them to fierce generic competition, which negatively impacts profit gain after patent life. Because small molecules typically work by mimicking biological substrates or allosterically targeting hydrophobic pockets of proteins, certain biological targets may not be druggable. Many bacterial and cancer cells have developed resistance to small-molecule drugs through mechanisms such as chemoenzymatic modifications, efflux pumps, drug target mutations, *etc.*

Biologic drugs

Although small-molecule drugs have dominated the pharmaceutical industry since the beginning of modern medicine, we seem to be approaching the era of biologics. For instance, in 2016, 8 out of the top 10 global best-selling drugs were biologics.⁴ Most notably, adalimumab (Humira), a recombinant monoclonal antibody by AbbVie, is on pace to surpass atorvastatin and become the biggest blockbuster drug of all time. In the field of oncology, biologics continue to fill unmet clinical needs that small molecules cannot address. Many monoclonal antibodies such as trastuzumab (Herceptin) have become essential targeted therapies in many anticancer drug cocktails. Although antibodies, such as adalimumab and trastuzumab, make up a large class of biologics, as defined by the FDA, biologics also include other proteins, gene-based therapies, cellular products, vaccines, blood, *etc.* For decades, insulin has been an essential life-saving medicine for diabetic patients. 2017 was an exceptional year in terms of biologic approval by the U.S. Food & Drug Administration (FDA) with a total of 12 new approvals.⁵ Additionally, we also observed the first CAR T cell (Kymriah) and gene (Luxturna) therapies approved in 2017.

One of the factors that currently hinder the use of biologics is their exorbitant cost. Unlike small molecules, proteins contain variable complexes especially in terms of surface glycosylation and folding patterns making the manufacturing process incredibly complex.⁶ With our current technology, it is difficult to scale up biologics and maintain batch-to-batch equivalence. However, just like genome sequencing, which used to cost a fortune but now cost pennies, the price of biologics will surely decrease as more cost-effective preparation methods are discovered. Compared to small molecules, biologics are also much more fragile and sensitive to degradation by physical conditions or enzymes. Efforts to generate more stable biologics are currently ongoing. For example, one interesting strategy to limit degradation by protease is by generating D-amino acid analogues of FDA-approved drugs.⁷ Additionally, biologics are only avail-

able as intravenous injections, which adds burden to patient compliance and cost to hospitals. Lastly, one significant challenge in the development of biologics is that a number of patients can develop immune responses to the drugs leading to loss of effectiveness over time, and how fast this will happen is unknown.

Looking into the future

We believe that biologics are an important component of the drugs of the future. Biologics will continue to flourish and play significant roles in combating hard-to-treat diseases such as cancer, autoimmune diseases, and inheritable diseases. RNA interference and CRISPR-Cas9 are exciting gene editing tools that are arriving on the horizon and will continue to revolutionize medical research. With that said, small molecules are definitely not the “videotapes” of the pharmaceutical industry. Recent discoveries of small molecules that can modulate protein–protein interactions have further renewed interest and utilities of small-molecule drugs in many diseases.⁸ It is hard, actually almost impossible, to imagine a world without small-molecule drugs. Due to their size, small molecules can often easily cross the cell membrane allowing them to target intracellular proteins that biologics may not be able to target. Small molecules will always remain easier to synthesize and produce in large quantities, which will certainly keep their prominent roles in treating chronic diseases where patients need affordable medicines for long periods of time. In summary, a brighter future can only be envisioned with diversity and complementarity in a therapeutic armamentarium containing both small molecules and biologics.

Conflicts of interest

There are no conflicts to declare.

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