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Editorial

The Future of Drug Delivery

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Drug delivery technologies have been proven to improve treatment outcomes in many ways, including enhancing therapeutic efficacy, reducing toxicity, increasing patient compliance, and enabling entirely new medical treatments. As the therapeutic landscape has evolved from small-molecule drugs to a new generation of therapeutics including proteins, peptides, monoclonal antibodies, nucleic acids, and even live cells, drug delivery technologies have also evolved to meet their unique delivery needs. Starting from the advent of Spansule® sustained release technology in 1952,[1] a large amount of effort has been focused on extending the release of small-molecule-based drugs by entrapping them in dissolution-based formulations consisting of cellulose derivatives and cross-linked poly(acrylic acid) polymers; in biodegradable injectables based on poly(lactic-*co*-glycolic acid) (PLGA) and poly(lactic acid) (PLA); or in nondegradable implants based on poly(ethylenevinyl acetate), silicones, polyethylene, and other polymers.[2] These approaches have enabled the long-term delivery of small-molecule therapeutics over a period from several days to weeks or months, thereby reducing the dosing frequency and improving patient adherence and compliance. Such long-acting delivery systems have revolutionized the treatment and management of multiple conditions, including psychotic disorders, pain, and advanced prostate cancer.[3−5] Recent FDA approval of Apretude®—a long-acting injectable of cabotegravir, an antiretroviral—has also demonstrated the enormous potential of long-acting approaches for pre-exposure prophylaxis (PrEP) of HIV and other infectious diseases.[6] The use of long-acting systems for localized drug delivery has also been shown to improve the therapeutic outcome by changing the local pharmacokinetics (PK) of the drug. Zilretta®, a PLGA microsphere-based intra-articular formulation of a corticosteroid, resulted in significantly higher drug levels in the knee joint compared to the free drug during the first few weeks postinjection, which translated to improved therapeutic benefit.[7] In parallel, nanoparticles have also emerged as an effective method of altering the biodistribution of small-molecule drugs, prolonging the half-life in systemic circulation, and enhancing tissue targeting. Although a major focus for nanoparticles has been to achieve tumor-targeted delivery, the approved products Doxil® and Abraxane® were primarily focused on reducing side effects and extending circulation time rather than the superior efficacy of the drugs.[8] Drug delivery innovations over the past several decades also feature ambitious efforts to deliver macromolecules or biologics. Conjugating polyethylene glycol (PEG) to proteins increased their circulation time; about 20 PEGylated protein formulations have been developed to date.[9] In 2018, siRNA was successfully delivered to the liver using lipid nanoparticles (Onpattro®).[10] Subsequently, nanoparticle delivery technology laid the foundation for all-mRNA vaccines, which addressed the global COVID-19 pandemic.[11] Looking back, seven decades of effort have produced stunning drug delivery technologies to break down the barriers between new drug candidates and their targets in tissues and cells. Looking forward, the future of drug delivery is bright. The global pharmaceutical drug delivery market is projected to reach $2206.5 billion by 2026, exhibiting a compound annual growth rate (CAGR) of 5.9%.[12] While the overall goal for drug delivery technologies remains transporting and maintaining therapeutic concentrations of a drug at the target biological site, we envision that the future will focus on (i) enhancing targeting efficiency at both the tissue and cellular levels and increasing the delivery of molecules through barriers such as the brain, intestine, skin, lung, and vagina; (ii) developing next-generation long-acting delivery technologies to improve drug PK and achieve preprogrammed pulsatile release over a period of time; (iii) developing drug delivery technologies for personalized therapies; and (iv) merging advanced technologies, including machine learning, artificial intelligence (AI), wireless, and soft electronics, with drug delivery. Success in these directions will require concerted efforts from broad interdisciplinary groups of scientists and researchers and strong backing from funding agencies, investors, hospitals, clinical trial groups, and other key stakeholders.

ENHANCING TARGETING EFFICIENCY AT BOTH THE TISSUE AND CELLULAR LEVELS AND INCREASING THE DELIVERY OF MOLECULES THROUGH BARRIERS

With our increasing understanding of disease biology, aberrant gene expressions and novel targets continue to be uncovered. However, therapeutics against these targets often fail in later stages of development due to poor targeting efficiency.[13] To overcome biological barriers and achieve targeted delivery at both the tissue and cellular levels, we need a deeper understanding of how drug delivery materials interact with the extracellular matrix and the vast array of cell types in the target tissue and on the route, including cells that comprise the mononuclear phagocyte system (MPS) and endothelial

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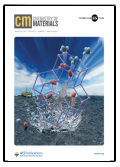

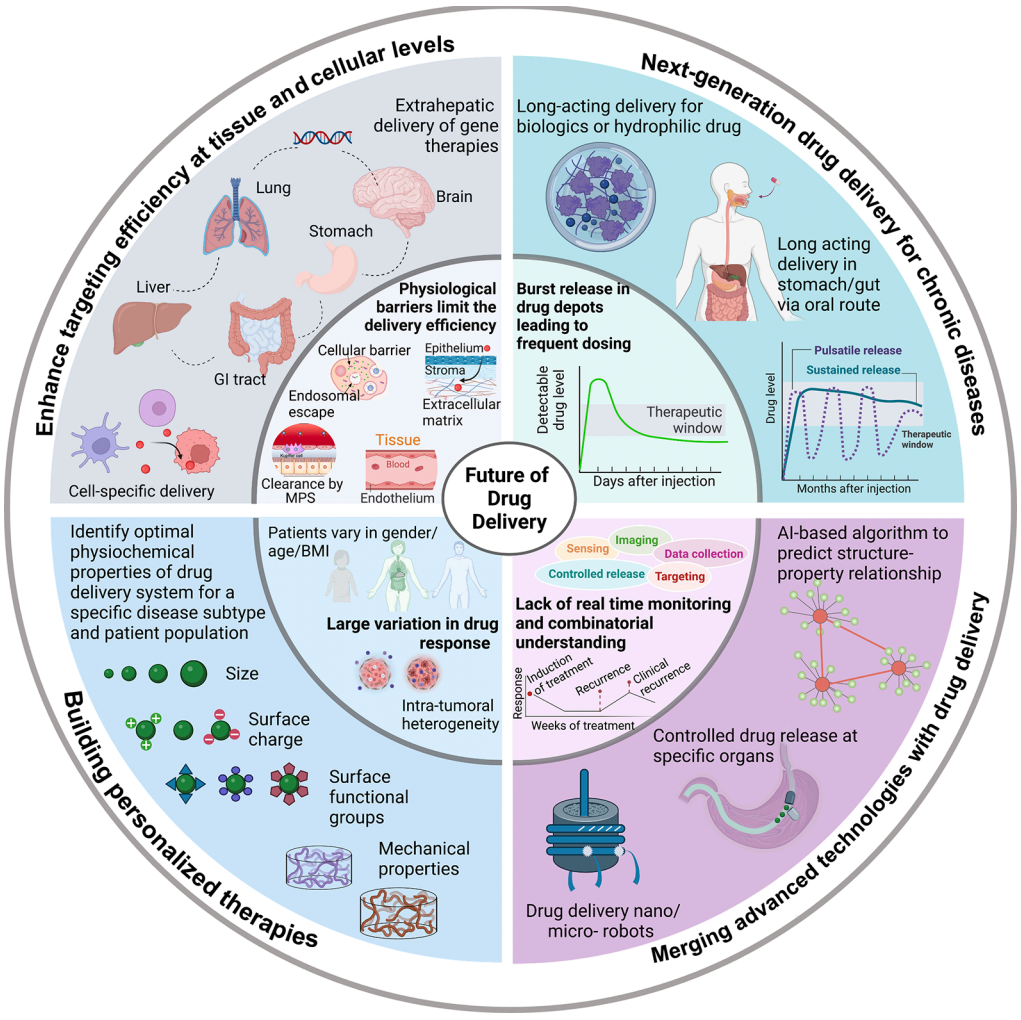

Figure 1. Challenges and the future of drug delivery.

barriers. Local administration offers the simplest way to deliver drugs to diseased tissue; however, it is limited to organs that are easy to reach, and we still have not been able to fully overcome the physiological and anatomical barriers in the local tissues. For example, the mucus in lungs and the intestines poses a huge barrier that greatly impacts the delivery of inhaled and orally ingested particles, respectively.[15] The extracellular matrix and stroma in the tumor microenvironment limit the penetration of delivery systems, thereby limiting the efficacy of promising immunotherapies.[16,17] Innovative approaches are required to overcome such barriers. For example, an orally ingestible and robotic drug delivery capsule (RoboCap) was recently developed to clear the mucus layer in the intestine and enhance luminal mixing for the topical deposition of the drug payload, resulting in increased absorption.[14]

Systemic targeting via nanoparticles also remains challenging due to nanoparticle clearance by the reticuloendothelial system (RES) and their accumulation in the liver.[18] Although the conjugation of targeting ligands to small-molecule drugs is a proven approach to achieve systemic targeting that resulted in clinically successful antibody−drug conjugates such as trastuzumab, similar active targeting strategies are rendered ineffective for nanoparticles due to protein corona deposition.[8] This has also posed a major hurdle toward achieving efficient gene delivery in extra-hepatic tissues. Conjugation of hydrophobic moieties including cholesterol and α-tocopherol to DNA/RNA heteroduplex oligonucleotides has been shown to enhance their penetration across the blood brain barrier after subcutaneous or intravenous administration in mice and rats.[19] Orally dosed milli-injector capsules have enabled nucleic acid delivery to swine stomachs.[20] More efforts toward the development of such novel delivery approaches are required for targeted gene delivery to extra-hepatic tissues, including those in the brain, intestine, lung, and vagina. Future approaches should also focus on controlling the local distribution of the delivery system at the cellular level within the target tissue, which would be critical to enhance the efficiency of gene therapies.

NEXT-GENERATION DRUG DELIVERY FOR CHRONIC DISEASES

Poor adherence to pharmaceutical drugs is a long-standing challenge in the healthcare community and is now recognized as a public health crisis, resulting in approximately 125 000 deaths per year and an estimated healthcare cost of $100 billion annually.[21] Long-acting drug delivery formulations that enable sustained drug release are critical for chronic diseases that require treatment over years or for patients in low-resource settings that have limited access to healthcare.[22] Currently, there are 63 FDA-approved long-acting drug products on the market. Among these, 22 products are based

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on biodegradable formulations.[2] While nondegradable implants usually enable controlled drug release for longer periods as compared to biodegradable injectables and implants, they require surgical removal after use, which could pose challenges in low-resource settings.[23] Biodegradable injectable formulations are ideal; however, they often exhibit high burst release,[24] which could be an issue for drugs with a narrow therapeutic window and can shorten the longevity of the formulation. Injectable long-acting formulations are also not suitable for hydrophilic drugs or biologics due to their rapid release.[25] Future research should focus on developing new long-acting injectable formulations that minimize burst release and are amenable to the delivery of hydrophilic drugs and biologics. Long-acting delivery has also begun to advance via the oral route. Once-a-week ingestible capsules for antiretroviral drugs[26] and a stellate pill for memantine or risperidone ER successfully demonstrate long-acting drug delivery through oral ingestion.[27] Next-generation long-acting delivery systems will also enable precise control over the release kinetics rather than merely achieving sustained release at a steady rate. Such systems will be uniquely advantageous for diseases including asthma, diabetes, and hypercholesterolemia that have predictable cyclic rhythms where the timing of the medication is critical to improve the therapeutic outcomes. Marketed technologies such as Pulsincap, Diffucaps, CODAS, OROS, and PULSYSTM have demonstrated pulsatile release but are limited to small-molecule drugs.[28] Recent works have reported microparticles that could provide multiple doses of a vaccine over an extended time period with just one injection.[29,30] Such approaches could be useful for most vaccines that require multiple shots, such as measles or COVID-19, and can greatly benefit people who do not have frequent access to medical care. We envision that similar pulsatile drug delivery systems will enable long-term release matching the rhythms of different chronic diseases.

BUILDING PERSONALIZED THERAPIES

Treatment regimens for multiple diseases do not follow the "one size fits all" approach. Disease heterogeneity among patients combined with differences in patient physiology necessitates personalized treatment decisions. For example, not all patients with type 2 inflammation asthma or inflammatory bowel disease respond to the same biologic therapy.[29,30] Similarly, tumor heterogeneity across patients renders therapies ineffective in a subset of the patient population. Future therapies are being developed to create a personalized plan based on the individual patient's need. The development of future drug delivery systems for personalized therapeutics must also consider patient-to-patient variabilities. Some of the critical factors include whether the treatment is for a child, adult, or elderly patient; whether it needs to be a sustained-release or pulsative-release formulation; the patient's lifestyle; and addressing the changes in biological barriers among different patients. Machine learning and proteograph were recently used to dissect the contribution of engineered nanoparticles to the composition of protein coronas for deep and large-scale plasma proteomics, which helped identify protein variants across patients.[31] Future drug delivery systems need to be thoroughly evaluated to better understand how physical and chemical properties impact the crossing of biological barriers in a specific disease subtype as well as a specific patient population to develop a personalized plan for drug delivery. For example, vascular physiology varies between patients, which can greatly influence the distribution and delivery of systemically administered nanoparticles.[32] Similarly, the mechanical loading in knee joints can impact an intra-articular drug delivery system, but it varies between patients with early or late-stage osteoarthritis due to differences in their level of physical activity.[33] Design criteria for developing future drug delivery systems should consider such heterogeneities. Ultimately, modular drug delivery systems that match specific therapies to patient subtypes are needed.

MERGING ADVANCED TECHNOLOGIES WITH DRUG DELIVERY

As AI and machine learning techniques impact biomedical research, they provide new potential to boost drug delivery. AI can be a robust tool to establish structure−function relationships between formulation parameters and release kinetics and can help tune a drug delivery system for optimal performance.[34] For example, a cascade computer model was designed to predict drug diffusivity from different mucoadhesive formulations.[35] Despite its potential to transform drug delivery, AI still has a long way to go in real-world applications. Future efforts to improve interpretability, provide guidance on machine learning model selection, and improve the quality of the data collected are critical to fully realize the potential of AI in drug delivery. Another exciting direction is combining drug delivery with soft-electronics, sensors, chips, an internal or external power supply, and micro-or nano- robots. For example, IntelliCap (AAPS)—an ingestible wirelessly transmitting device—includes a motor to enable drug release, a microprocessor to control the pump, and pH and temperature sensors.[36] Another example is a liquid autoinjector-based robotic pill that has been shown to improve the bioavailability of biologics, including a peptide or protein, by up to 80% upon oral administration.[37] Introducing chip-to-cloud technology with secure energy-efficient microchips into long-acting drug delivery platforms could enable continual access to data, allowing the doctor and the patient to monitor the release profile and adjust as needed.[38] For example, a computer-based programmer communicated wirelessly to confirm the proper operation of a drug delivery microchip, which was designed to delivered microgram quantities of an antiosteoporosis drug once daily for up to three weeks.[39] We also expect to see an increase in the use of mobile devices and apps to capture data that may help identify critical trends, for example adherence to treatment regimens, thereby improving the overall efficacy. Although it is exciting to combine these advanced technologies with drug delivery, their advancement toward clinical use would require a deeper understanding of the biological processes, the interactions of robots with organs and cells and their mechanisms of movement, and algorithms for controlling against environmental perturbations.

CONCLUDING REMARKS

The field of drug delivery has a bright and exciting future. As the current therapeutic landscape shifts from small molecules to biologics, drug delivery systems continue to evolve. We expect to see breakthrough technologies that can enhance the encapsulation and stability of biologics, enable their sustained release over a long period of time, and efficiently deliver them across complex physiological barriers. We also envision future drug delivery systems that utilize materials that more efficiently and effectively target specific biology, are programmable and

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responsive to biological cues, and yet can be integrated with simplicity to ease clinical translation. The future technologies will also impact healthcare globally by not only increasing the precision and efficacy of therapies but also making them more affordable and easier to use. Currently, most of the novel treatments, although curative, are only available to those who can afford them. Lowering the healthcare cost of new pharmaceutical treatments instead of waiting for lower cost generic versions will be of great significance for the public, especially for people who do not have easy access to medical resources. A series of innovations and combined efforts in drug delivery technologies and highly automated low-cost manufacturing platforms will provide great momentum toward this goal, thereby creating health equity.

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Notes

Views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

J.M.K. is a paid consultant and or equity holder for multiple biotechnology companies (see https://www.karplab.net/team/jeff-karp) and holds multiple patents on drug delivery. The interests of J.M.K. were reviewed and are subject to a management plan overseen by his institutions in accordance with its conflict of interest policies. N.J. holds multiple patents on drug delivery and is an equity holder and a paid consultant for a biotech company (Akita Biosciences). R.L. is a paid consultant and or equity holder for multiple biotechnology companies (see www.dropbox.com/s/yc3xqb5s8s94v7x/Rev%20Langer%20COI.pdf?dl=0) and holds multiple patents on drug delivery.

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