CHAPTER TWO

# Challenges and opportunities in targeted delivery

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## 1. Introduction

Human history is marked by a series of wars among tribes and nations. Typically, invincible armies invaded other countries to conquer them, often destroying villages in the process. Historical figures such as Julius Caesar, Alexander the Great, Napoléon Bonaparte, and Genghis Khan exemplify the use of brutal force to expand territories. However, imagine an alternative strategy: by thoroughly understanding the enemy and identifying their weaknesses, a small team of highly trained elite soldiers could infiltrate enemy territory to destabilize and paralyze their response. This approach results in significantly less collateral damage. Sun Tzu's book, "*The Art of War,*" is particularly relevant for today's drug delivery scientists who are engaged in a battle against diseases. The supreme art of war is to subdue the enemy without fighting. If scientists can discover ways to strengthen our bodies, diseases can be cured without reliance on drugs. The next best method for winning the war begins with a thorough understanding of both the enemy and ourselves. Once we grasp the strengths and weaknesses of the enemy, we can devise our strategies according to our capabilities and limitations. If scientists can comprehend the nature of diseases, they will undoubtedly find cures more effectively than through brute-force trial-and-error methods. Many difficulties we encounter in treating various diseases stem from a lack of clear understanding of their underlying causes. Even when disease mechanisms are known, drug delivery remains a significant challenge.

The goal of drug delivery has remained the same since the introduction of pill medications, i.e., to provide an effective dosage while minimizing harm to the body. In clinical studies, a drug formulation is considered effective if it outperforms a placebo. No drug is effective for all patients. Consequently, not all drugs and formulations yield the same results for every patient. As illustrated in Fig. 2.1, the changes in the drug concentration as a function of time, or pharmacokinetic profiles, are utilized since the drug concentration in the target area is in equilibrium with the bloodstream. A drug becomes effective when its concentration in the blood exceeds the minimum effective

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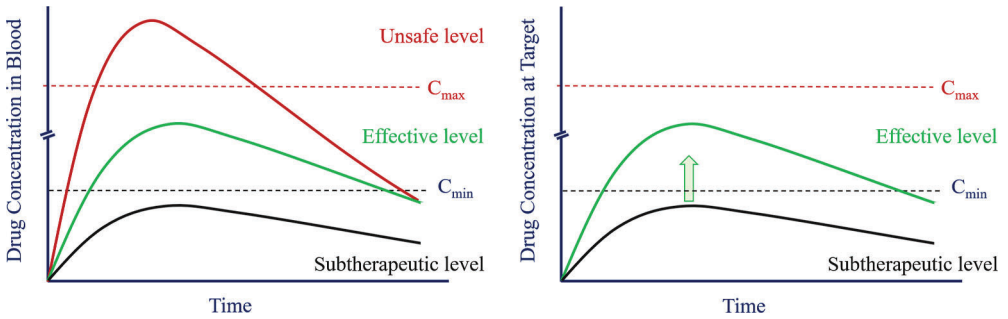


**Figure 2.1** Pharmacokinetic profiles displaying drug concentrations in the blood (A) and at the target site (B). The drug concentrations in the toxic (*red*), effective (*green*), and subtherapeutic (*black*) ranges are shown.

concentration and is safe below the toxic threshold. The drug concentration at the target site may be increased when specialized delivery systems are employed, allowing the drug to accumulate beyond equilibrium levels. For a drug that is ineffective, e.g., a drug at a subtherapeutic level in Fig. 2.1, a slight increase in the concentration at the target site can make it effective. This is where targeted delivery can be particularly beneficial. The targeted drug delivery here means an improved delivery to make the drug effective and does not mean that all or most of the administered drug only goes to the target site (more on this below).

## 2. Targeted drug delivery

Attempting to treat a disease without a clear understanding of its underlying mechanisms is akin to indiscriminately bombing an entire village, reminiscent of tactics used during the Vietnam War. Once the core of a disease is identified, a precise strike, similar to a cruise missile, can effectively eliminate the target. Our approach to treating diseases has evolved from carpet bombing to more strategic bombing methods. However, we still lack drug delivery systems that can be considered equivalent to strategic strikes. We still mostly rely on the indiscriminate distribution of drugs throughout the body.

Various strategies have been developed to enhance drug delivery to specific targets. One notable approach is "targeted drug delivery," which ensures that a higher amount of drugs reaches the intended site compared to conventional methods. This improvement is a crucial element in achieving drug efficacy. However, targeted drug delivery has often been misunderstood and, consequently, misapplied in the literature. It is vital to grasp the true meaning and limitations of targeted drug delivery.

The concept of targeted drug delivery, commonly referred to as a "magic bullet," originated from Paul Ehrlich's observations that certain chemical molecules can bind to

specific pathogens without harming normal host cells. However, it is important to recognize that these drugs disperse throughout the body and bind to pathogens upon encounter, rather than specifically seeking out pathogens in particular organs or tissues. Consequently, the term "targeting" primarily refers to the binding or interaction of the drugs with pathogens and does not guarantee that the drugs will accumulate exclusively at the intended site (Park et al., 2024). Misunderstandings regarding targeted drug delivery have fostered the false expectation that drugs will selectively concentrate at the target site. Such misconceptions within the drug delivery community hinder advancements in treatment and underscore the need for a precise understanding of the concept of targeting.

In recent decades, the prevailing theme in the field of drug delivery has been "nanomedicine." This approach primarily focused on targeted drug delivery to tumors, leveraging the enhanced permeability and retention (EPR) effect. The convenient pairing of nanomedicine with the EPR effect emerged from a desire to present something innovative and appealing to the public (Bae and Park, 2011; Park, 2013, 2016, 2017). While the field of nanomedicine has produced tens of thousands of research articles, its actual impact on tumor treatment in patients has been modest at best. This provides a valuable lesson: substantial international attention and funding do not always lead to breakthrough formulations. Ultimately, it is not about the number of publications on a certain topic but rather the effective delivery of the right dosage of the drug that leads to successful treatment.

Regardless of the terminology used, the most important consideration is whether a new formulation effectively accomplishes its intended purpose, namely, curing a disease. For a drug to be effective, it is essential to recognize that we only need to deliver an amount to the target site sufficient for treatment, even though drug distribution throughout the body is unavoidable. Fig. 2.2 illustrates that achieving an effective concentration of the drug at the target site is crucial despite the fact that a significant portion may be distributed to other tissues. Ultimately, it is irrelevant whether 1% or 10% of the total administered drug reaches the target; as long as the amount delivered is effective.

## 2.1 Endogenous targeted drug delivery

Delivering the optimal amount of the drug to the target site is sufficient for efficacy. One effective strategy to achieve this is to utilize endogenous targeted drug delivery. The topic has been explored for decades already (Parayath and Amiji, 2017; Vyas and Sihorkar, 2000; Cook and Decuzzi, 2021), but there has been no reference source dedicated to the topic yet. This book presents careful alternatives for treating a variety of diseases, not limited to cancers, by harnessing endogenous mechanisms. There are notable overlaps between traditional and endogenous targeted drug delivery; however,

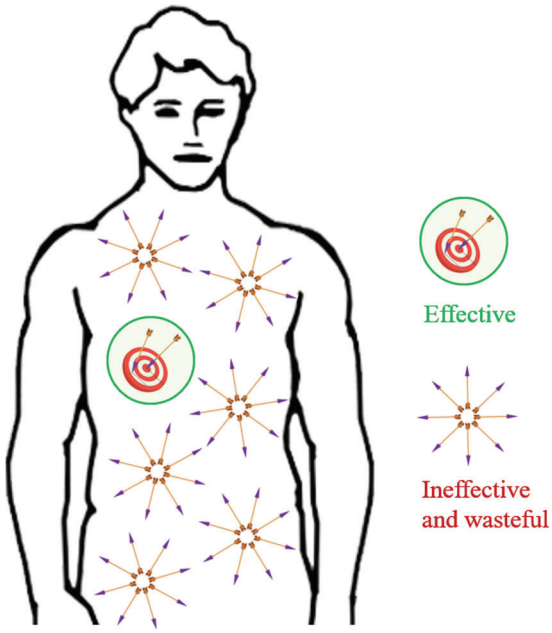


**Figure 2.2** Targeted drug delivery refers to the delivery of sufficient medication to the intended site, ensuring the drug is effective while minimizing severe side effects that may occur from accumulation in other areas of the body.

the primary distinction is that endogenous targeted delivery enhances drug efficacy without causing side effects. As mentioned earlier, administered drugs are distributed throughout the body, and endogenous delivery can direct certain drugs to their targets, increasing their effectiveness, as shown by the arrow in Fig. 2.1.

The drug delivery systems must penetrate the body's natural biological barriers, which serve as its defense mechanisms. Due to our limited understanding of how to effectively overcome these barriers, the outcomes can appear unpredictable. In other words, the butterfly effect is prevalent in drug delivery; we cannot always anticipate which small, seemingly unrelated factors might influence the result. These topics are thoroughly addressed in this well-organized book. Section 2 of this book describes delivery barriers, including the blood–brain, blood-tumor, ocular, pulmonary, gastrointestinal, and cellular and intracellular barriers, followed by a discussion of endogenous targeting strategies in Section 3. Sections 4 through 9 explore various methods for achieving endogenous delivery through drug conjugates, protein corona, different body cells, cellular backpacks, extracellular vesicles, and viral particles.

Endogenous targeted drug delivery is designed to align with the human body's natural biochemical pathways, thereby enhancing the effectiveness of treatments while

minimizing side effects. It is important to remind that the two key criteria for effective treatment are safety and efficacy. These criteria are clearly examined in Chapter 9, titled "Overview of Endogenous Targeted Delivery Strategies." A significant challenge faced by many newly developed formulations is "poor accumulation at target sites or excessive off-target effects." Endogenous processes represent the optimized outcomes of millions of years of evolution, and our bodies have developed innate capabilities to facilitate communication and transport. Therefore, it makes sense for us to utilize these mechanisms to enhance the delivery of therapeutic agents to targeted areas within the body. Chapter 9 offers a comprehensive overview of these endogenous mechanisms, discussing the roles of the protein corona, extracellular vesicles, cell-based targeting strategies, and viral vectors, along with their potential applications in drug delivery. Other chapters of Section 2 deal with specific endogenous mechanisms, such as pH, hypoxia, redox, nutrients, and glycans.

The protein corona can be utilized to attract endogenous proteins that specifically bind to their corresponding receptors, which are often overexpressed in target tissues. Chapter 18 in Section 5, focusing on the protein corona, is particularly pertinent to both current and future strategies in targeted drug delivery. When a drug delivery system, typically at the nanoscale, is injected into the bloodstream, it encounters various biomolecules present in the blood. Many of these molecules adhere to the surface of the drug delivery system, largely due to the abundance of proteins, forming a layer known as the protein corona. This protein corona effectively creates an interface that influences the interactions of the drug delivery system with cells and tissues. The initial soft corona is subsequently replaced by a hard corona because of the Vroman effect. Consequently, the body recognizes the "cloaking" protein corona instead of the unprotected drug delivery systems. Therefore, harnessing the protein corona offers new opportunities for optimizing the fate of administered nanosized drug delivery systems (as elaborated in Chapter 19). However, analyzing and identifying the composition of the protein corona remain a significant challenge. Naturally, this complexity makes controlling the protein corona's composition for enhanced targeted delivery one of the highest priorities in this field.

Viruses have been repurposed as vectors for therapeutic delivery. There are numerous exciting possibilities for utilizing endogenous mechanisms, including mesenchymal stem cells, large peritoneal macrophages, leukocytes, neutrophils, erythrocytes, and platelets (Section 6). Cell-based drug delivery can enhance circulation time and improve the specific tissue-homing capabilities of drug-carrying cellular agents. This approach often involves the use of "cellular backpacks," also known as hitchhiking, which refers to the attachment of nano-to microscale cargos to the exterior surfaces of cells (Section 7).

Extracellular vesicles (in Section 8) are diverse structures encased in lipid bilayer membranes with two primary subtypes: exosomes and ectosomes. Cells actively release these vesicles for intercellular communication under both physiological and pathological

conditions. Their roles in pathological processes have garnered significant interest from formulation scientists. Extracellular vesicles have demonstrated considerable potential in delivering nucleic acids, proteins, and small molecules. One of the unique advantages of extracellular vesicles over synthetic alternatives is their superior ability to permeate physiological barriers, positioning them as promising therapeutic tools.

Genome editing has become a standard procedure in gene delivery. Its success largely hinges on the availability of vehicles for transient delivery, a topic explored in Chapter 36 of Section 9. Rapid advancements in RNA and DNA delivery necessitate delivery systems that surpass the current reliance on lipid nanoparticles, which tend to be unstable during storage. Virus-like particles have been utilized for the targeted delivery of RNA and ribonucleoproteins, and ongoing innovations will enhance the efficiency of endogenous targeted delivery.

While there are many opportunities to utilize endogenous targeting for more efficient drug delivery, promising and theoretically sound approaches often encounter substantial challenges when it comes to translating them into clinical practice. Drug delivery scientists are encouraged to prioritize the translational aspects of novel drug delivery systems to ensure that their innovations become practical solutions. The translation of a new drug delivery technology starts with the development of a candidate formulation that adheres to current Good Manufacturing Practices (cGMP). cGMP manufacturing guarantees the quality of drug products, which is elaborated in detail in Chapter 38. This chapter offers valuable insights into the critical factors necessary for successfully transitioning from the laboratory to the bench knowledge that all researchers in drug delivery should be aware of.

## 3. Future

The future of drug delivery systems aims to enhance targeted drug delivery while minimizing individual variations. Achieving the ultimate targeted drug delivery, i.e., delivery only to the target site, will require the development of self-powered vehicles that, once injected into the bloodstream, can navigate through the blood vessels and self-direct toward the target tissues and cells. None of the existing drug delivery systems come even remotely close to the vehicle depicted in the 1966 science fiction film "Fantastic Voyage." In this film, a renowned scientist named Dr. Benes, who discovered a way to miniaturize objects for 1 hour, fell into a coma due to a severe blood clot in his brain. To rescue his crucial information, the government miniaturized a nuclear submarine and its crew to a microscopic size and injected them into Dr. Benes's body to carry out a delicate surgery to remove the clot. While traversing the bloodstream, the crew encounters various obstacles posed by blood components, including various blood cells and sticky proteins. Yet, they ultimately succeed in their mission by using a specialized laser ray,

restoring Dr. Benes's health and unlocking his secrets. This story from 6 decades ago provides a clear benchmark for achieving the ultimate targeted drug delivery. The miniaturized submarine serves as a model for nanovehicles that the field of drug delivery has been developing. A good example of such efforts is the development of nanorobots with self-propelled nanomotors (Mao et al., 2025). Imagine a scenario where "Fantastic Voyage" intersects with Michael Crichton's novel "Prey." In "Prey," self-replicating nanobots evolve into a sophisticated and lethal predatory swarm, hunting and eliminating everything in their path. These nanobots, which can communicate with each other, are designed to adapt and learn from their environment, making them increasingly intelligent. Such cognitive development is becoming plausible in reality, thanks to remarkable advancements in artificial intelligence (AI). While endogenous targeted drug delivery, extensively discussed in this book, may not yet have reached the nanobot level, it can be developed to incorporate the ability to adapt to its environment and learn how to overcome obstacles to reach its target.

Interindividual variability in drug response presents a considerable challenge in treatment approaches (Tatarūnas et al., 2024). Adapting drug delivery systems to this variability is crucial for their effectiveness. The pharmacokinetic profiles of drug formulations, illustrated in Fig. 2.1, typically represent averages derived from a large patient population. However, when assessing individual pharmacokinetics, these profiles can demonstrate a wide range of drug concentrations in the blood, encompassing both extremely high and extremely low levels. Such significant interindividual differences underscore the necessity for personalized treatment strategies. As previously mentioned, leveraging various endogenous mechanisms, such as the protein corona and extracellular vesicles, could be a promising approach to enhance targeted drug delivery. For this strategy to be effectively incorporated into personalized medicine, it is vital to develop assay methods capable of analyzing and identifying the composition of the protein corona in individual patients. Consequently, advancements in drug delivery must go hand in hand with improvements in analytical techniques. Fortunately, progress in analyzing and predicting protein corona composition is already underway (Huzar et al., 2025).

All future possibilities, many of which currently seem improbable, become attainable through the aspirations of scientists. Fifty years ago, when new drug delivery systems were first introduced beyond oral controlled release formulations, no one could have imagined the technological advancements we have today, such as mobile phones and AI, which have the potential to transcend international borders. Predicting what the world will look like in another 10 years—let alone 50—is a daunting task. However, one thing is certain: this book will inspire countless drug delivery scientists to develop innovative methods for treating various diseases more effectively through endogenous targeted drug delivery mechanisms.

## References

Bae, Y.H., Park, K., 2011. Targeted drug delivery to tumors: myths, reality and possibility. J. Contr. Release 153 (3), 198–205. www.elsevier.com/locate/jconrel. doi: 10.1016/j.jconrel.2011.06.001.

Cook, A.B., Decuzzi, P., 2021. Harnessing endogenous stimuli for responsive materials in theranostics. ACS Nano 15 (2), 2068–2098. https://doi.org/10.1021/acsnano.0c09115.

Huzar, J., Coreas, R., Landry, M.P., Tikhomirov, G., 2025. AI-based prediction of protein corona composition on DNA nanostructures. ACS Nano 19 (4), 4333–4345. https://doi.org/10.1021/acsnano.4c12259.

Mao, M., Wu, Y., He, Q., 2025. Breaking through physiological barriers: nanorobotic strategies for active drug delivery. Bioconjug. Chem 36 (1), 1–14. https://doi.org/10.1021/acs.bioconjchem.4c00480.

Parayath, N.N., Amiji, M.M., 2017. Therapeutic targeting strategies using endogenous cells and proteins. J. Contr. Release 258, 81–94. www.elsevier.com/locate/jconrel. doi: 10.1016/j.jconrel.2017.05.004.

Park, K., 2013. Facing the truth about nanotechnology in drug delivery. ACS Nano 7 (9), 7442–7447. https://doi.org/10.1021/nn404501g.

Park, K., 2016. Drug delivery of the future: chasing the invisible gorilla. J. Contr. Release 240, 2–8. https://doi.org/10.1016/j.jconrel.2015.10.048.

Park, K., 2017. The drug delivery field at the inflection point: time to fight its way out of the egg. J. Contr. Release 267, 2–14. https://doi.org/10.1016/j.jconrel.2017.07.030.

Park, K., Otte, A., Li, T., 2024. Bohemian rhapsody of future drug delivery systems: rational changes necessary for the next revolution. Mol. Pharm 21 (8), 3732–3742. https://doi.org/10.1021/acs.molpharmaceut.4c00550.

Tatarūnas, V., Čiapienė, I., Giedraitienė, A., 2024. Precise therapy using the selective endogenous encapsidation for cellular delivery vector system. Pharmaceutics 16 (2), 292. https://doi.org/10.3390/pharmaceutics16020292.

Vyas, S.P., Sihorkar, V., 2000. Endogenous carriers and ligands in non-immunogenic site-specific drug delivery. Adv. Drug Deliv. Rev 43 (2–3), 101–164. https://doi.org/10.1016/s0169-409x(00)00067-3.


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