NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING

Drug Delivery Systems

Getting Drugs to Their Targets in a Controlled Manner

National Institutes of Health

What are drug delivery systems?

Drug delivery systems are engineered technologies for the targeted delivery and/or controlled release of therapeutic agents.

Drugs have long been used to improve health and extend lives. The practice of drug delivery has changed dramatically in the past few decades and further changes are anticipated in the near future. Biomedical engineers have contributed substantially to our understanding of the physiological barriers to efficient drug delivery, such as transport in the circulatory system and drug movement through cells and tissues; they have also contributed to the development of a number of new modes of drug delivery that have entered clinical practice.

Yet, with all of this progress, many drugs, even those discovered using the most advanced molecular biology strategies, have unacceptable side effects due to the drug interacting with parts of the body that are not the target of the drug. Side effects limit our ability to design optimal medications for many diseases such as cancer, neurodegenerative diseases, and infectious diseases.

Drug delivery systems control the release rate and the location in the body where a drug is released. Some systems can control both.

How are drug delivery systems used in current medical practice?

Clinicians historically have tried to direct their interventions to areas of the body at risk or affected by a disease. Depending on the medication, delivery method, and how our bodies respond, side effects sometimes occur. These side effects can vary greatly from person to person in type and severity. For example, an oral drug for seasonal allergies may cause unwanted drowsiness or an upset stomach.

Administering drugs locally rather than systemically (affecting the whole body) is a common way to decrease side effects and drug toxicity while maximizing a treatment's impact. A topical (used on the skin) antibacterial ointment for a localized infection or a cortisone injection of a painful joint can avoid some of the systemic side effects of these medications. There are other ways to achieve targeted drug delivery, but some medications can only be given systemically.

Microneedle patch for influenza vaccine delivery.
Source: Dr. Mark Prausnitz, Georgia Institute of Technology

What technologies are NIBIB-funded researchers developing for drug delivery?

Current research on drug delivery systems can be described in four broad categories: routes of delivery, delivery vehicles, cargo, and targeting strategies.

Routes of Delivery

Medications can be taken in a variety of ways—by swallowing, by inhalation, by absorption through the skin, or by intravenous injection. Each method has advantages and disadvantages, and not all methods can be used for every medication. Improving current delivery methods or designing new ones can enhance the use of existing medications.

Microneedle arrays are one example of a new method to deliver medications through the skin. In these arrays, dozens of microscopic needles, each far thinner than a strand of hair, can be fabricated to contain a medicine. The needles are so small that, although they penetrate the skin, they don't reach nerves in the skin, thus delivering medications painlessly.

NIBIB-funded scientists are developing such a patch with an array of disolvable microneedles for vaccine delivery. These patches are easy to use and do not require refrigeration or special disposal methods, so they could be used by patients themselves at home. This technology could be especially helpful in low-resource communities that may not have many health care providers or adequate storage facilities for traditional, refrigerated medicines.

Delivery Vehicles

Biotechnology advances are leading to improved medications that can target diseases more effectively and precisely. Researchers have begun to reformulate drugs so they may be more safely used in specific conditions. The more targeted a drug us, the lower its chance of triggering drug resistance, which is a cautionary concern surrounding the use of broad-spectrum antibiotics.

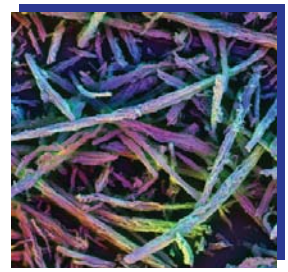
Nanotechnology is opening up new avenues for drug delivery vehicles. NIBIB-funded researchers have reported promising results in developing a treatment for glioblastoma, a devastating brain cancer. In rat models of the disease, they have shown that tumors can be penetrated and shrunken when injected with nanoparticles. The nanoparticles target the tumor by delivering an altered gene, or suicide gene, that is programmed for cell death. The nanoparticle method replaces a type of gene therapy using viruses, which can have unpredictable outcomes.

Other NIBIB-funded researchers are developing a system of drug delivery using a type of bacteria that has a two-part navigation system—magnetic and oxygen sensing. They have tested the delivery system in mice, achieving a remarkable success delivering drugs to tumors. The bacteria seek out oxygen-poor zones, which are a feature of tumors. Using a computer-programmed magnetic field to direct the bacteria to tumors, the researchers found that the bacteria were drawn deep into the oxygen starved tumors, away from healthy cells. This process could open the door for directing drug-laden bacteria to tumors deep in the body.address multi-drug resistant diseases.

Cargo
Perhaps the most obvious route to improving disease treatment would be to focus on the medications themselves. In addition to drugs and novel vaccines, researchers are also exploring the use of genes, proteins, and stem cells as treatments.

NIBIB-funded researchers are pursuing ways to improve the immune response against cancer and infection using nanovaccines that have unique structures and incorporate inorganic materials. In one study, they injected mice with a vaccine formulated with silica rods that assemble like a stack of match sticks. The scaffold of rods is capable of recruiting, housing, and manipulating immune cells to generate a powerful immune response. Researchers found that the nanovaccine could delay tumor growth in mice with lymphoma, a cancer affecting the infection-fighting cells of the immune system.

In another study, researchers prolonged survival for mice with melanoma by treating them with a nanovaccine that combines a bacterial DNA—programmed to trigger an immune response—and a nano-sized inorganic substance that helps the nanovaccine remain longer in the tumor environment. An injection of the nanovaccine forms complexes that resemble flower blossoms and are retained long enough in a tumor to be taken up by immune cells. There, they instruct the immune cells to recognize cancer cells as foreign and attack them.



Polychromatic scanning electron microscopy of 3-D vaccine consisting of microsized, porous silica rods
Source: James C Weaver, Wyss Institute

Targeting Strategies
Working backwards is sometimes an effective way to solve a problem. In drug delivery research, this means starting with a delivery method. The target may be whole organs (heart, lung, brain), tissue types (muscle, nerve), disease-specific structures (tumor cells), or structures inside of cells.

Using this reverse-engineering approach, NIBIB-funded researchers developed a plant virus nanoparticle that can target and attach itself to prostate cancer cells. When labeled with fluorescent dyes, the viral nanoparticles can show researchers whether cancer cells have spread into bone at earlier stages of the disease than with traditional bone scans.

Made from modified viruses, viral nanoparticles take advantage of the natural ways that viruses have developed to slip past immune defenses and enter cells. This means they do not need to be modified as much as other types of nanoparticles to behave in desired ways, and their actions within the human body are well understood. Plant-based viral nanoparticles are also biodegradable, harmless to humans, easy to use, and cheap to produce.

Further research aims to develop viral nanoparticles that can deliver chemotherapy drugs directly to tumors. Such an advance would reduce the severe side effects usually associated with cancer treatment.

What are some important areas for future research in drug delivery systems?

As scientists study how diseases develop and progress, they are also learning more about the different ways our bodies respond to illness and the influence of specific environmental or genetic cues. Coupled with advances in technology, this increased understanding suggests new approaches for drug delivery research. Key areas for future research include:

Crossing the Blood-Brain Barrier (BBB) in Brain Diseases and Disorders
When working properly, the various cells that comprise the BBB constantly regulate the transfer of essential substances between the bloodstream and the central nervous system as well as recognize and block entry of substances that may harm the brain. Delivering drugs into the brain is critical to the successful treatment of certain diseases such as brain tumors, Alzheimer's disease, and Parkinson's disease, but better methods are needed to cross or bypass the BBB. One method currently under study uses advanced ultrasound techniques that disrupt the BBB briefly and safely so medications can target brain tumors directly, with no surgery required.

Enhancing Targeted Intracellular Delivery
Just as our immune systems defend our bodies against disease, each of our cells also has internal processes to recognize and get rid of potentially harmful substances and foreign objects. These foreign objects may include drugs enclosed in targeted delivery vehicles. So as researchers work to develop reliable methods of delivering treatments to targeted cells, further engineering is still needed to ensure the treatments reach the correct structures inside cells. Ideally, future health care will incorporate smart delivery systems that can bypass cellular defenses, transport drugs to targeted intracellular sites, and release the drugs in response to specific molecular signals.

Combining Diagnosis and Treatment
The full potential of drug delivery systems extends beyond treatment. By using advanced imaging technologies with targeted delivery, doctors may someday be able to diagnose and treat diseases in one step, a new strategy called theranostics.

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