Drugs on Target

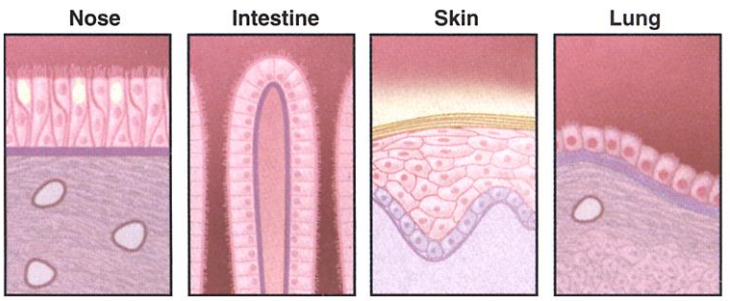
Robert Langer

The field of drug delivery is advancing rapidly. By controlling the precise level and/or location of drug in the body, side effects are reduced, lower doses are often needed, and new therapies are possible (*1*).

The past few years have seen several firsts, for example, the clinical introduction and regulatory approval of the first controlled-release system for local delivery of an anticancer drug, Gliadel, and the first controlled-release system for the systemic delivery of a protein, Nutropin Depot. The former is used to treat brain cancer, and the latter continuously releases human growth hormone for several weeks to treat pituitary dwarfism. Oral controlled-release Ritalin systems with a novel osmotic pump formulation, Concerta, can produce a release profile optimized to the needs of children with attention deficit hyperactivity disorder. Interferons that can circulate in the bloodstream for up to a week have been created by linking them to polyethylene glycol. Systems for delivery of macromolecules such as heparin orally and insulin through the lungs are in final stage clinical trials.

As a result of these and other advances, sales of advanced drug delivery systems (*1*) in the United States are approaching $20 billion annually. Nonetheless, substantial challenges remain. For example, safe and effective nonviral delivery systems for gene therapy need to be developed.

To succeed, we need materials that can condense or package DNA to small sizes so that it can be taken up by cells, stabilize DNA before and after cellular uptake, bypass or escape the cell's endocytic pathways, deliver the DNA to the cells nucleus, and unpackage DNA by releasing it in active form (*2*). In addition, one difficulty thus far in developing polymers for gene therapy delivery has been toxicity. Two of the most widely used polymers, polyethyleneimine and polylysine, can be toxic in mammals. One must also ensure that polymer-DNA or lipid-DNA complexes do not aggregate upon injection because of salts or serum.

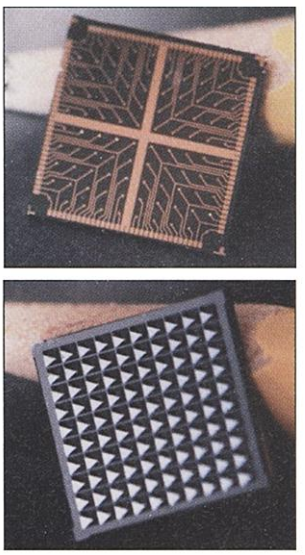


Crossing the barrier. In the case of the nose, intestine, and skin, the cellular barrier is difficult to cross for some drug molecules. In the case of the lung, the main difficulty lies in getting a drug to the deep lung. Epithelial cells, dark pink; basement membrane, purple; blood vessels, red; stratum corneum of skin, yellow.

To address the problem of gene therapy delivery, cationic β-cyclodextrin–based polymers have been synthesized that complex DNA and can safely transfect cells (*3*). Another approach is based on a "terplex," a combination of stearyl-polylysine, low-density lipoprotein (LDL), and DNA (*4*). The potential advantage of the terplex is that one molecule, stearyl-polylysine, can be used to complex DNA while a second molecule, LDL, can be used to target the DNA to a desired location, such as the myocardium. A number of cationic polymers (*5*) and novel lipids (*6*) are being studied for safety and efficacy. To create effective nonviral delivery systems, their lifetime in the circulation may also need to be improved, and approaches for targeting specific cells may need to be developed.

In the quest for better drug delivery, nearly every part of the body is being explored, either to deliver drugs to that part directly or as a portal for noninvasive delivery of drugs to the systemic circulation. In many cases, the challenge for systemic drug delivery is to get through a difficult-to-cross cellular barrier. This is the case, for example, in the nose, intestine, and skin (see the first figure). In other cases, for example, the lung, the cellular barrier may be less difficult to cross (see the first figure). Here, the difficulty lies in getting the drug to the desired region, in this case the deep lung.

Oral delivery of proteins has been particularly challenging. Generally, it is important to use an enteric coating, which enables the protein to pass though the stomach unharmed, and protease inhibitors, which prevent the protein from being destroyed by digestive enzymes. The biggest challenge, however, is to enable the drug to pass through the gastrointestinal tract into the systemic circulation. To do so, a variety of approaches are being studied, including incorporating the proteins into micro- or nanostructured bioadhesive systems that can penetrate the epithelium through and between cells, producing protein-containing vesicles such as liposomes or polymer microspheres, which may be targeted to the Peyers patches (oval lumps of lymphoid tissue in the small intestine), coupling the proteins to ligands that target specific receptors in the gastrointestinal tract, or using permeation enhancers (*1*, *7*, *8*).



Drugs on chips. (**Top**) Front side of controlled release microchip showing an array of 100 gold reservoir caps and their associated electrodes (the tip of a pencil in the background is shown for scale). (**Bottom**) Back side of same microchip showing 100 reservoirs each containing a different drug or a different dose of the same drug or any combination thereof. These microchips measure 1 cm by 1 cm by 0.53 cm. Each reservoir has a volume of 150 nl.

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In pulmonary delivery, recent advances in inhaler design enable larger drug amounts to be delivered to the lung. Drugs may even be delivered in response to the patients' breathing patterns. Novel aerosols are also being developed. These aerosols are larger and much more porous compared with conventional small nonporous aerosols, enabling them to enter the deep lung. Furthermore, the larger particle size leads to decreased surface area and thus less aerosol aggregation as well as decreased phagocytosis by lung macrophages. This enables not only more efficient delivery and much smaller inhalers but also sustained release (*9*).

In the future, the intersection between nanotechnology and drug delivery may see exciting developments. Approaches involv-

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ing microelectrical mechanical systems (MEMS) or microchips are being studied. For example, microchips containing nanosized drug reservoirs might be able to deliver pharmaceuticals for long time periods in a controlled manner (see the second figure), ultimately by placing a microprocessor, power source, and biosensor in a chip. An implantable system that can deliver drug and respond to specific regulatory in vivo molecules may one day be possible (*10*).

Numerous other challenges exist. Targeting drugs to specific cells, the creation of novel vaccine delivery approaches, and the development of cell-based delivery systems are but a few examples. Recent advances point to a future where drugs are delivered only to the place where they are needed and at the levels they are required, with major benefits to patients.

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PERSPECTIVES: PALEOCLIMATE

Ice Ages, the California Current, and Devils Hole

David W. Lea

It is tempting to assume that key climate events in the past—the extent of continental ice sheets during glaciation, the coldest ocean temperatures, the response of the biosphere—occurred at the same time. But evidence is emerging from studies of marine sediments that ocean temperatures in some regions began to warm thousands of years before the melting of continental ice sheets. Inferred previously for the Subantarctic Indian Ocean (*1*), new proxies of sea surface temperature indicate that this early warming characterized the end of glacial periods in the tropics (*2–4*), the Southern Ocean (*5*), and, as Herbert *et al.* report on page 71 in this issue, on the California Margin (*6*). The temperature leads in the California Current were as large as 10,000 to 15,000 years, which implies warming during the coldest part of the ice ages; they varied spatially up and down the margin, and they are supported by diverse terrestrial evidence.

If large-scale ocean warming preceded ice sheet melting, it suggests that the oceans were responding to an external factor independent of the ice sheets. Furthermore, the early warming of the oceans is likely to have played a role in the melting of the ice sheets. In contrast, some previous scenarios have assumed that climate variability caused by the presence of the ice sheets (such as changes in the thermohaline ocean circulation) dictated oceanic conditions. The geographic distribution of the timing of change (see the figure) may help establish the regional and global patterns of climate change associated with global warming at the end of glacial periods.

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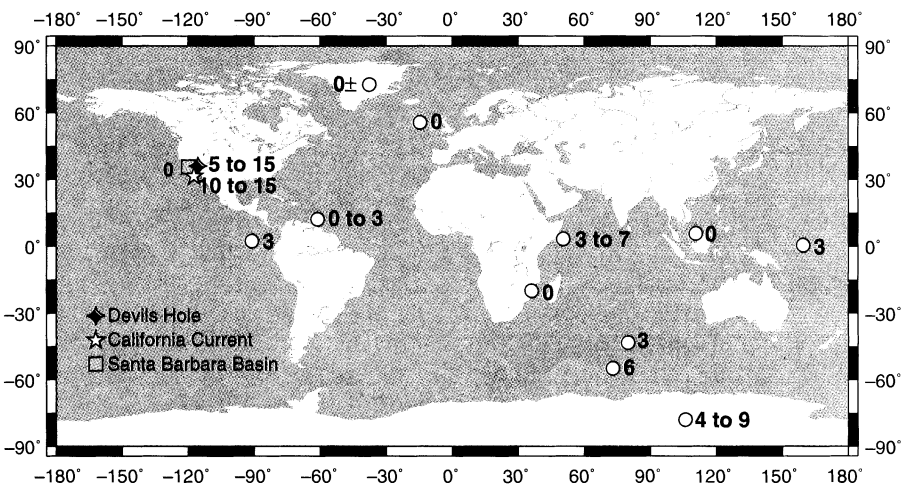
Strong support for the ocean temperature lead comes from air temperature records preserved in polar ice sheets. Proxies in an ice core from Vostok, Antarctica, show that local atmospheric warming led ice volume (the amount of continental ice) changes by 4000 to 9000 years at glacial terminations (*7*). The ice core data suggest that the temperature lead is not a purely oceanic or regional phenomenon. Rather, it reflects a large-scale response to a climate forcing, such as atmospheric greenhouse gases, which also changed before ice volume but at the same time as temperature (*7*). There is, however, ample evidence that the temperature lead was not uniform across the globe (see the figure). Sea surface temperatures in the North Atlantic, the region most directly linked to the Northern Hemisphere ice sheets, do not show a lead (*8*). Temperatures in some parts of the tropics seem to have changed at the same time as ice volume and Greenland temperatures (*2*, *9*), and the Greenland ice cap itself has an air temperature history that can be interpreted both as leading or lagging ice volume (*10*).

In their study, Herbert *et al.* exploit the fact that the number of double bonds in long-chain, unsaturated ketones (alkenones) produced by certain marine algae is correlated with the ambient temperature at the time of synthesis. Their measurements of alkenone unsaturation indices in the California Current indicate much larger temperature leads than have been observed in other oceanic records (10,000 to 15,000 years versus ~3000 years). Some proxies of California Current temperature, such as faunal abundance and oxygen isotopes in planktonic



What happens at the end of an ice age? The map shows key oceanic, continental, and ice core sites where the timing of temperature versus ice volume change at glacial terminations has been established. Lead in units of 1000 years. One of Herbert *et al.*'s California Current sites (*6*), the Santa Barbara Basin core (*11*), and Devils Hole (*13*) are indicated. The data that are mapped (*1–11*, *13*) are a composite of the last five glacial terminations, which occurred between 10,000 and 500,000 years before present and differ substantially in their orbital characteristics (*1*).