Drug-delivery systems have had a growing influence on the clinical application of cancer therapeutics for several decades, and novel delivery systems now have been used by millions of patients. These delivery systems have enabled the development of new cancer therapies, have permitted cancer treatments with significantly reduced side effects, and have facilitated the development of more effective chemotherapeutic regimens using anticancer drugs that are already available.

In addition to their direct effects on treatments targeting tumor growth and progression, new drug delivery systems also have impacted the areas of cancer prevention and pain management associated with cancer chemotherapy.

In this article, we review some of the drug-delivery systems that are FDA-approved and in clinical use against a variety of cancers. These systems include controlled delivery of cancer drugs, local chemotherapy, polymer-drug conjugates, liposomal systems, and transdermal drug-delivery patches.

The possibility of delivering cancer drugs in a targeted manner with increased control has captured the imagination of scientists from a broad range of disciplines, including microelectronics, nanotechnology, material science, immunology, and human genomics, and their efforts have resulted in the development of the next generation of “smart” drug-delivery approaches.

Controlled Delivery Is Possible with Drug Diffusion from Polymers

A major factor limiting the use of biologically active peptides and polypeptides as therapeutics is their short in vivo half-lives. It is now widely appreciated that controlled drug-delivery systems have enabled the physical and biochemical protection of these drugs resulting in their successful use.

For many years, the delivery of such molecules was thought to be impossible due to difficulties associated with the diffusion of large molecules through the materials (polymers) of conventional drug delivery (controlled-release) systems. In 1976, Robert Langer and Judah Folkman solved this problem by showing that molecules could be physically embedded into polymers in a manner that created a complex network of interconnecting pores through which the drug could subsequently diffuse.

In fact, by controlling the pore structure and polymer composition, it was possible to design systems that release the drug at nearly any rate and for nearly any duration (e.g., days to years). This innovation resulted in the development of the first polymers for the sustained release of proteins and other macromolecules.

One of the earliest proof-of-principle studies used nondegradable polymers such as ethylene-vinyl acetate copolymer. Subsequently, lactic-glycolic acid copolymers were...
A variety of drug-delivery approaches are being used clinically or are in development for the treatment of human cancers. Systems in clinical use include polymer microspheres carrying anticancer peptides, used to treat advanced prostate carcinoma (the drug is released through diffusion or polymer degradation); polymer wafers embedded with the chemotherapeutic agent BCNU, used for the localized treatment of brain cancer; osmotic pumps delivering antiangiogenic and other drugs; and liposomal systems, used in the treatment of Kaposi’s sarcoma. Polymer-drug targeting moiety conjugates are being tested against a variety of human cancers, and controlled-release microchips are in various stages of preclinical development.

used to develop degradable polymer systems. As the polymer matrix degrades, drug is released slowly into surrounding tissues.

One example of the usefulness of this drug-delivery approach is in the treatment of advanced prostate cancer, in which analogs of luteinizing hormone-releasing hormone (LHRH), such as leuprolide acetate, are now delivered and released in this manner.

Years of work with the goal of developing a successful cancer treatment based on these drugs had met with limited success and huge challenges. For example, when the drug was initially administered orally or nasally, only 0.05% and 3% of the drug, respectively, was bioavailable in animals, not enough to achieve a positive therapeutic effect. In addition, blood levels of the drug proved to be inconsistent, and when the drugs were injected, their half-lives were extremely short, being only minutes long.
Drug Delivery Systems Currently Used for Cancer Treatment

<table>
<thead>
<tr>
<th>Delivery Name</th>
<th>Drug</th>
<th>Cancer Treatment</th>
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<tbody>
<tr>
<td><strong>Injectable Polymer Rod/Microsphere</strong></td>
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<tr>
<td>Zoladex*</td>
<td>LHRH analog</td>
<td>Advanced prostate cancer</td>
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<tr>
<td>Lyron depot †</td>
<td>LHRH analog</td>
<td>Advanced prostate cancer</td>
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<tr>
<td>Decapeptyl †</td>
<td>LHRH analog</td>
<td>Advanced prostate cancer</td>
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<td><strong>Implantable Wafer</strong></td>
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<td>Gliadel</td>
<td>Carmustine</td>
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<td><strong>Liposomes</strong></td>
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<tr>
<td>Doxil</td>
<td>Doxorubicin</td>
<td>Ovarian cancer, AIDS-related Kaposi's sarcoma</td>
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<tr>
<td>AmBisome</td>
<td>Amphotericin</td>
<td>Fungal infections in chemotherapy patients</td>
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<tr>
<td>Daunoxome</td>
<td>Daunorubicin</td>
<td>AIDS-related Kaposi's sarcoma</td>
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<td><strong>Polymer-Drug Complex</strong></td>
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<tr>
<td>SMANCS–lipiodol emulsion</td>
<td>Zinostatin stimalamer †</td>
<td>Hepatocellular carcinoma</td>
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<td><strong>PEGylated Drug</strong></td>
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<td>Oncaspar</td>
<td>L-Asparaginase</td>
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<td>PEG Intron</td>
<td>™-Interferon</td>
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<td>Neulasta</td>
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<tr>
<td><strong>Transdermal Patch</strong></td>
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<tr>
<td>Duagesic</td>
<td>Fentanyl</td>
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<td>Habitrol</td>
<td>Nicotine</td>
<td>Smoking cessation (cancer prevention)</td>
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<td>Nicotrol</td>
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<td>Nicoderm</td>
<td>Nicotine</td>
<td>Smoking cessation (cancer prevention)</td>
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<tr>
<td>Prostep</td>
<td>Nicotine</td>
<td>Smoking cessation (cancer prevention)</td>
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<tr>
<td><strong>Lipid Depot in CSF</strong></td>
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<tr>
<td>Depoctye</td>
<td>Cytarabine</td>
<td>Carcinomatous meningitis</td>
</tr>
</tbody>
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* Injectable polymer rod; † Injectable polymer microsphere; ‡ SMANCS; adapted from Moses et al: Cancer Cell 4:337-341, Nov 2003.

These problems were resolved by physically embedding the drugs into polymers, where they were released by a combination of diffusion through pores as well as polymer matrix degradation. This approach is the basis for the currently available injectable delivery systems (Lupron®, Zoladex®, Decapeptyl®) that now last from 1 to 4 months and are used successfully by hundreds of thousands of patients with prostate cancer.

Another effective method to extend drug lifetimes is by chemically binding the drug of interest to

The copolymer ethylene-vinyl acetate, shown in cross-section, reveals the presence of pores left behind where released proteins had been.
**Polymer delivery systems.** In basic polymer systems, drug diffuses through the outside polymer rim, either through pores or a permeable membrane. Examples of this system include Norplant, Ocasert, and others. In the degradable matrix system, drug is evenly distributed and released by diffusion through the polymer or by a combination of diffusion and polymer erosion. In the osmotic system, the membrane is permeable to water but impermeable to drug; the movement of water through the membrane by osmosis, due to the presence of the drug itself or salts that have been encapsulated with the drug, then pumps the drug out through a tiny hole in the membrane. In polymer-drug conjugates, a polymer (curved line) is connected to a drug via bonds that can be cleaved once inside the body. Some of these conjugates contain a targeting (T) moiety as well.

Water-soluble polymers, such as polyethylene glycol (PEG). This approach can decrease immunogenicity and extend the biological lifetime of the drug. Such systems have been used for the delivery of asparaginase, interferon, and granulocyte colony-stimulating growth factor (G-CSF).

**Drug-Impregnated Wafers Enable Localized Chemotherapy**

Most commonly used cancer chemotherapy agents induce significant toxicity that ranges in severity from uncomfortable to life-threatening. To avoid this problem, approaches have been developed to deliver these drugs locally, with the goal of improving both their safety and efficacy. Local delivery guarantees higher local drug concentrations when compared to those obtained with traditional systemic delivery methods.

Delivery of a polymer-drug conjugate during cancer surgery would have the advantage of enhancing the benefit of surgery while minimizing the systemic toxicity that is usually associated with standard drug treatments.

This approach has now been successfully exploited, most notably in brain cancer surgery. The ability to deliver chemotherapeutic drugs to this organ via traditional systemic routes is severely restricted by the presence of the blood-brain barrier, which limits transport to this organ. Novel polymers, such as polyanhydrides in the form of wafers, have now been used to deliver chemotherapeutic drugs, such as carmustine (BCNU), locally to treat brain cancer.

In 1987, Henry Brem and colleagues inserted these drug-impregnated wafers, layered at the surface of the brain, into the tumor resection cavity following tumor removal. The drug is slowly released from these wafers for approximately 3 weeks to destroy any residual tumor. Because the drug is delivered locally, rather than systemically, harmful side effects that normally occur with carmustine were minimized.

Results from one of a number of clinical trials showed that 31% of the patients treated in this manner were alive after 2 years, in comparison to only 6% of patients receiving standard brain tumor therapies.

In 1996, this therapy was approved by the U.S. FDA for patients with recurrent glioblastoma, the first new brain cancer therapy...
Polymer implants containing carmustine are inserted into a human brain, lining the tumor resection cavity, where the loaded drug is gradually released as the polymer wafers dissolve.

approved in over 20 years. In 2003, the FDA extended its approval to include initial surgery for malignant glioma, based on two additional randomized prospective studies that demonstrated improved survival and safety.

Experimental brain metastases and invasive pituitary adenomas also have been treated successfully by this approach. Carcinomatous meningitis likewise has been treated using long-lasting, implantable lipid formulations to deliver cancer drugs to spinal fluid.

Polymer-Drug Conjugates Allow Targeted Cancer Drug Delivery

Cancer drug targeting is a rapidly developing research discipline that has recently yielded a number of different drug-delivery approaches. One such strategy has been to couple small-molecular-weight cancer drugs to polymers. This coupling results in an altered biodistribution of the drugs following intravenous administration that favors concentration of the drug in tumors.

Normally, low-molecular-weight anticancer drugs will nonselectively penetrate most tissues, because they pass rapidly through cell membranes. This results in a relatively rapid distribution of the drug with no tumor selectivity.

In the case of polymer-drug conjugates, however, the polymer-drug linkages are designed to be stable in the bloodstream. This feature, along with the fact that the higher-molecular-weight polymer-drug can only gain entry into cells via endocytosis, results in circulation of the polymer-drug for a longer period than with the drug alone. Because most normal tissues have nonleaky microvasculatures, the polymer-drug accumulates more in tumor tissue, which has a notoriously leaky vascular supply.

In one example of this approach, Ruth Duncan and her colleagues developed a conjugate of the polymer N-(2-hydroxypropyl) methacrylamide (HPMA copolymer) to doxorubicin that could be cleaved by specific enzymes in lysosomes, resulting in the selective release of the drug. This approach resulted in the concentration of approximately 70 times more doxorubicin in mouse melanoma tumors than in normal tissues. Importantly, this approach also increased the maximum tolerated dose of the polymer-drug by up to 10 times that of the free drug.

Tumor-specific polymer-drug conjugates can also be created by adding specific targeting moieties to the polymer to aid in treatment of specific tumors (e.g., adding galactosamine to target hepatocellular carcinoma). There are currently 10 different polymer-drug systems at various stages of clinical trials.

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The use of small lipid vesicles called liposomes also has been investigated as a means of using drug delivery to alter drug distribution. In this case, drugs are encapsulated inside liposomes, which circulate freely in the bloodstream. The drug is emitted via diffusion through the liposome or by liposomal degradation.

Encapsulation of the drug in a liposome reduces many of the side-effects associated with certain anticancer agents, such as cardiac toxicity, by preventing release of the drug at undesirably high concentrations as would occur with simple injection. A significantly high drug-carrying capacity also can be achieved using liposomes as opposed to attaching a drug to a single polymer chain. One area of active research involves the attachment of cancer cell-targeting ligands to liposomes in order to direct the liposomal drugs preferentially to cancer cells.

Several key issues must be resolved before the full promise of liposome-based delivery can be realized. One of these is the prevention of liposomes from accumulating and being cleared by phagocytic cells. Among the approaches being investigated to prevent this involves attaching polyethylene glycol to the liposomes (PEGylated liposomes).

Liposomal drug-carrier systems with daunorubicin and doxorubicin have now been approved for the treatment of HIV-associated Kaposi's sarcoma, and liposomal amphotericin B has been approved for the treatment of fungal infections in cancer.

Transdermal Systems Provide Sustained Systemic Drug Delivery

Small lipophilic drugs have shown to have the ability to cross the skin quite efficiently. A variety of transdermal patches have now been developed, tested, and approved for several different drugs and conditions. These patches are composed of polymers impregnated with drug that diffuse through the polymer and skin to reach the systemic circulation.

Among the transdermal patches currently available are scopolamine for motion sickness, nitroglycerine for angina, fentanyl for pain, and clonidine for hypertension.

Transdermal delivery also has played an important role in both cancer therapy and prevention. Most compelling is the use of nicotine patches in preventing smoking and prolonging life.

As described by Henningfield in 1995, 2 years after they were on transdermal nicotine patches for Polymer-drug conjugates accumulate in tumor tissue due to the enhanced vascular permeability of tumors. Once in the tumor interstitium, polymer-drug conjugates enter cells via endocytosis. Drug is then cleaved from the polymer by lysosomal enzymes or in a pH-dependent process in endosomes, allowing the freed drug to interact with its therapeutic target.
**Growth and metastasis** in a solid tumor depend on angiogenesis, the formation of new capillaries from an existing vessel. The tumor will not grow to more than a few millimeters in diameter without being vascularized, and once vascularization occurs, tumor growth is often exponential. Metastasis may occur through direct extension or hematogenous spread, but angiogenesis also is required for metastases to become established as growing tumors.

12 weeks, four times as many patch wearers did not smoke as compared to those who received placebos. Based on these studies, it can be estimated that over one million smokers to date in the U.S. have given up smoking due to the use of these patches.

In addition, transdermal delivery systems for fentanyl are used to relieve pain in cancer patients. These systems last for 3 days and are used by hundreds of thousands of patients each year.

**Delivery Schedules and Vehicles Can Target Angiogenesis**

In the last several decades, the development and use of controlled-release polymers has enabled the design of bioassays for the in vivo identification and testing of angiogenesis inhibitors. This, in turn, has led to the introduction of a significant group of new cancer therapeutics, which target the new capillary growth that invades and nurtures developing tumors.

This antiangiogenic strategy to treat human cancer, pioneered by Judah Folkman, was recently validated in a large randomized clinical trial. In this trial, reported by Hurwitz and coworkers, bevacizumab (Avastin), a vascular endothelial growth factor (VEGF)/vascular permeability factor (VPF) antagonist, was administered along with conventional chemotherapy and significantly improved the survival of patients with metastatic colorectal cancer.

Bevacizumab, a recombinant humanized anti-VEGF monoclonal antibody, was given in combination with the standard chemotherapy of irinotecan, fluorouracil, and leucovorin (IFL) to a cohort of over 800 patients. Patients who received the combination therapy showed a median survival of 20.3 mos compared to 15.6 mos for the placebo group.

Studies aimed at achieving maximum therapeutic efficacy of some antiangiogenic drugs have led, ironically, to the development of what is now referred to as an
“antiangiogenic scheduling” of conventional chemotherapies. This regimen is able to circumvent the drug resistance induced by these same anticancer drugs delivered on the traditional chemotherapeutic schedule.

The first example of this phenomenon was seen in studies with the chemotherapeutic agent cyclophosphamide, when it was delivered on a low-dose, high-frequency schedule as opposed to standard bolus administration. This schedule resulted in effective control of tumor growth, with a concomitant lack of drug resistance in a number of tumor models. This delivery schedule, termed “low-dose metronomic chemotherapy” is currently being tested in clinical trials.

The unique vasculature of tumors, characterized by increased permeability and their complex 3-D architecture, has recently been exploited as an approach to deliver tumor-suppressing drugs with increased efficiency. By manipulating the physicochemical properties of liposomes, they can be made responsive to the specific physiologic features of a tumor (e.g., low pH), so that the liposomes release their carried drug selectively in tumor tissue. Liposome-mediated delivery of anticancer drugs has improved significantly with a concomitant increased accumulation of drug in tumor vessels.

**Targeted Drug Delivery Can Select Tumor Vasculature**

The tumor endothelium has proven to be an exciting target for anticancer drugs whose goal is to stop the angiogenesis required for tumor growth and progression. Many of the first-generation antiangiogenic proteins in clinical testing are delivered systemically and, for the most part, target active endothelium, such as that feeding a solid tumor, as opposed to the quiescent endothelium that supports normal, healthy tissues. If these angiogenesis inhibitors could be selectively targeted to the metabolically active endothelium of tumors, a much higher therapeutic index could be achieved.
“Angiogenic switch” refers to the stage at which a small, avascular, benign tumor acquires its own vasculature. This small thyroid tumor is shown before and after it has acquired the angiogenic phenotype. Tumors that have “switched on” angiogenesis are capable of rapid expansion and metastasis.

This goal recently was achieved with the development of a water-soluble polymer system used to deliver an antiangiogenic agent, TNP-470, to the tumor microvasculature. TNP-470, a low-molecular-weight analogue of fumagillin, was first shown to be antiangiogenic in 1990 by Ingber and colleagues.

More recently, when tested in clinical trials against a variety of tumors, TNP-470 treatment showed promising antitumor activity when used alone or in combination with conventional chemotherapy. However, the promise of this drug was significantly limited by neurotoxicity that occurred at the optimal anticancer dose.

Using an approach that combines a drug-polymer complex with targeted delivery to the neovasculature, Satchi-Fainaro and Folkman were able to achieve enhanced and prolonged activity of TNP-470 in a variety of in vivo models. They designed and synthesized a water-soluble conjugate of N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer, a Gly-Phe-Leu-Gly linker, and TNP-470.

This conjugate selectively accumulated in the tumor microvasculature due to the passive targeting phenomenon first described by Matsumura and Maeda. Called the enhanced permeability and retention (EPR) effect, this accumulation is attributed to the increased permeability and absence of effective lymphatic drainage in tumors.

The HPMA copolymer-TNP-470 conjugate, in addition to potently inhibiting tumor angiogenesis and subsequent tumor growth, did not cross the blood-brain barrier and did not induce neurotoxicity as did the unconjugated drug.

Approaches such as these hold significant promise for the development of new targeted antiangiogenic therapies as well as for the optimization of existing antiangiogenic drugs.

Current interest is focusing on an even earlier stage in tumor progression, the point at which a dormant, avascular tumor acquires the ability to grow and metastasize by “switching on” angiogenesis. As sensitive biomarkers and imaging systems capable of detecting the nascent microvasculature are developed, it is possible to imagine using a potent angiogenesis inhibitor that targets the first generation of angiogenic vessels developing in a tiny tumor lesion that is in the process of acquiring the angiogenic phenotype. Such an agent might be capable of maintaining the dormancy of that lesion indefinitely.

Much remains to be accomplished in our ability to target and deliver chemotherapeutic agents to a growing tumor. For example, successful localized delivery of drugs is still limited by less than optimal drug diffusion within cancerous tissues, as well as by

Danny Welch discusses Metastasis Suppressor Genes, in the August 2003 issue of Science & Medicine.
occasional undesirable interactions between drug and delivery vehicle.

Smarter drug delivery systems are being developed to address some of these challenges. A controlled-release microchip that stores and delivers on demand many different drugs (e.g., “pharmacy on a chip”) has recently been developed by John Santini and Robert Langer.

Such a system can eventually be preprogrammed or externally regulated to release drugs at any time, pattern, and rate. This ability would, in turn, facilitate the delivery of novel combination therapies, permitting the targeting of endothelial cells via the use of angiogenesis inhibitors, followed by suppression of the remaining tumor cells with chemotherapeutic drugs and subsequent maintenance on antiangiogenic therapy.

Ultimately, equal attention to the development of more potent and specific cancer chemotherapeutics, as well as to the optimal systems to deliver these drugs, will be necessary to guarantee that patients with cancer benefit from these advances.

**Implantable drug-releasing microchips** can deliver hundreds of doses over their lifetimes, lasting from months to years (Microchips, Inc., Bedford, MA). In some models, the various reservoirs can store one or multiple drugs, to be released on demand via a preprogrammed schedule or external control.

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Grant support has been provided by NIH CA52857 (HB), NIH RO1AT-00650 (RL, MAM), NIH CA83106 (MAM), NIH 2PO1CA455 (MAM), and NIH 5P50DK065298 (MAM). Under a licensing agreement between Guilford Pharmaceuticals and the Johns Hopkins University, Dr. Brem receives a royalty for products described in this paper. Dr. Brem and the University own Guilford Pharmaceuticals stock. Dr. Brem also is also a paid consultant to Guilford Pharmaceuticals. The terms of this arrangement are managed by the Johns Hopkins University in accordance with its conflict of interest policies.

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