CHAPTER 11.

DRUG TARGETING

WHAT IS TARGETING?

DRUG
TARGETING.

SIZE OF THE
TARGET

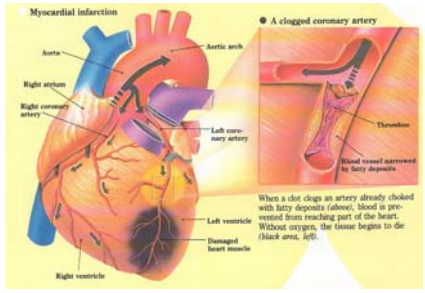
CUPID (Sam Cooke)

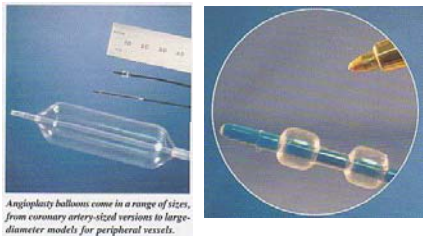
Cupid draw back your bow
And let your arrow go
Straight to my lover's heart for me
Cupid please hear my cry
And let your arrow fly
Straight to my lover's heart for me
Now I don't mean to bother you but I'm in a mess
There's danger of me losing all of my happiness
For I love a girl who doesn't know I exist
And this you can fix
So... Cupid draw back your bow
And let your arrow go
Straight to my lover's heart for me

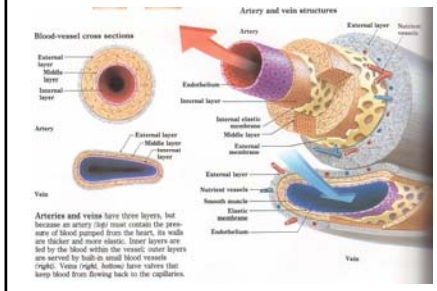
I. DRUG TARGETING BY LOCALIZED DELIVERY

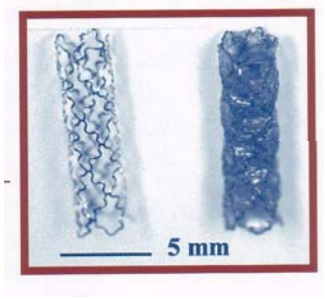
A. TARGETING TO SURROUNDING TISSUES FROM IMPLANTED SITES

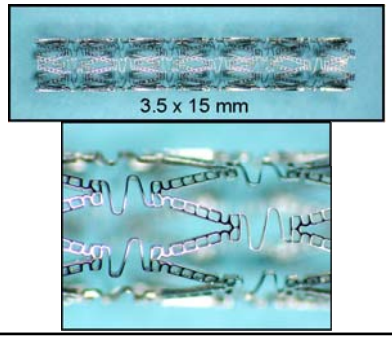
1. LOCAL DELIVERY FROM STENTS

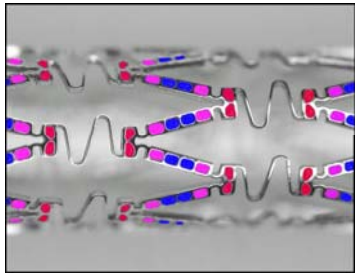



Angioplasty balloons come in a range of sizes, from coronary artery-sized versions to large-diameter models for peripheral vessels.



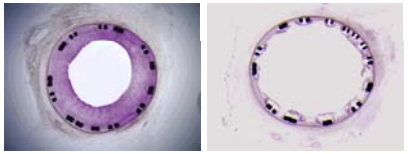


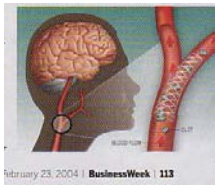




ARTERY LUMEN
AFTER 30-DAY IMPLANTATION IN PIGS

CONTROL **TEST**





STROKE ZONE

USING A TINY SIEVE TO DIVERT DEADLY BLOOD CLOTS

RESEARCHERS IN Israel believe they have hit on a solution to prevent many of the strokes caused by embolisms. By surgically inserting what look like miniature wire cones into arteries at both sides of the neck, they can reroute potentially fatal clots away from the brain and over to the face without interrupting blood flow. The face has a rich blood supply, so blockages there are far less damaging than those that might cause a total loss of oxygen to the brain.

MindGuard Medical Devices developed the so-called Diverter as an alternative to risky blood-thinning drugs. The company, based in Caesarea Industrial Park, just south of Haifa, claims it has the potential to lower by 60% the incidence of stroke—the No. 3 cause of death in the U.S. The devices have already been implanted in one high-risk patient in Germany, and clinical trials are under way in both Germany and Italy. MindGuard founder and Chief Marketing Officer Dr. Ofer Yodfat intends to market the Diverter in Europe within two years. The company is uncertain when it will be ready to meet tougher U.S. standards.

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CAROTID STENTING PREVENTS STROKE IN HIGH-RISK PATIENTS

A new study indicates that high-risk diabetic patients who underwent carotid stenting had far fewer heart attacks and significantly fewer major adverse events overall after a year than those who underwent carotid endarterectomy surgery

The finding stems from the diabetic arm of the Sapphire trial, a Cordis-sponsored prospective trial at 29 U.S. centers comparing the safety and efficacy of stenting carotid arteries to prevent stroke.

The stenting group had a 2.4 percent incidence of heart attacks compared with 18.4 percent of the surgery group. The major adverse event rate, including death, stroke, and heart attack, was 4.8 for the stent group versus 25 percent for the surgery patients.

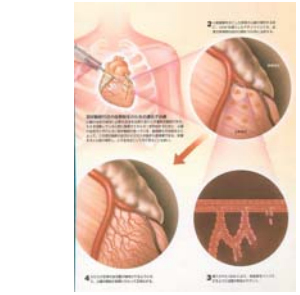
Science & Technology

TISSUE ENGINEERING

CAN THIS NEW SURGERY ACTUALLY REVIVE A DYING HEART?

Optimist Bodnar's complete cell-transfer procedure offers hope against America's No. 1 killer

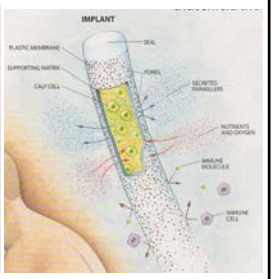
FROM THIGH TO HEART



» PAIN ZAPPER

Doctors sometimes let patients suffering from chronic pain self-administer prescribed doses of intravenous drugs. But those patients have always had to be tethered to an IV and drug bag. The first fully implantable drug pump could change all that. Here's how it works: morphine is stored in a pager-size pump just under the skin of the abdomen. A plastic catheter runs from the pump to the fluid-filled space outside the spinal cord, where pain signals travel. When the patient presses a handheld remote, the pump sends a measured dose of morphine directly to the spine. According to its maker, the SynchroMed works better and requires much smaller doses of medication than intravenous methods because it intercepts pain signals on their way to the brain.

- **INVENTOR** Medtronic
- **AVAILABILITY** In 2003, for $1,500
- **TO LEARN MORE** Visit medtronic.com; click on "Patient Information" and then "Pain"



CYTOTHERAPEUTICS

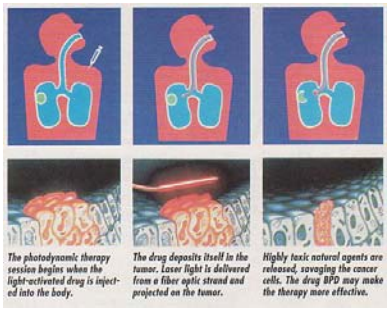
Enlarged, cutaway view of an empty tubular implant reveals the membrane's foamlike structure.

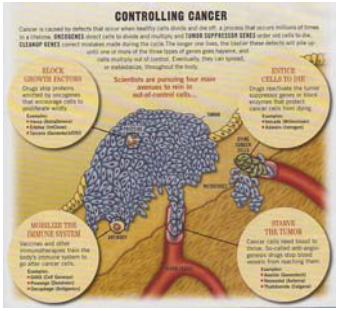
I. DRUG TARGETING BY LOCALIZED DELIVERY

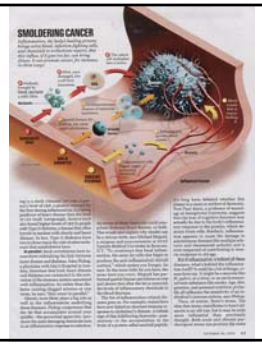
A. TARGETING TO SURROUNDING TISSUES FROM IMPLANTED SITES

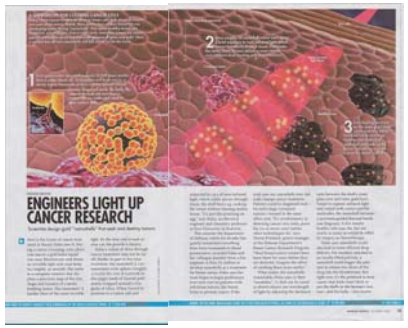
1. LOCAL DELIVERY FROM STENTS

B. DRUG ACTIVATION AT THE TARGET SITE









II. TARGETING IN BLOOD CIRCULATION

A. ACTIVE TARGETING

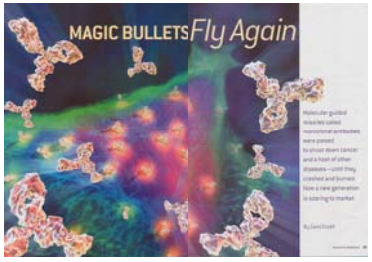
(TARGETING WITH HOMING DEVICES)

1. DRUG-HOMING DEVICE CONJUGATES

2. IMPROVEMENTS TO BE MADE IN CANCER CELL TARGETING

3. BLOCKING OF BLOOD VESSELS LEADING TO TUMORES

4. ANTIANGIOGENESIS

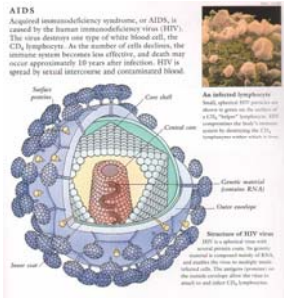


Nanodevices with a homing moiety (e.g., targeting to cancer cells)

Problem: Protein adsorption onto nanodevices

Partial solution: PEGylation

ABILITY TO DELIVER CARGO INTO THE CELLS



BIOTECHNOLOGY

AIDS VACCINE TRIAL RESULTS DISAPPOINT

Antibody-based strategy exhibits puzzling racial disparities

TARGETED

Researchers hoped antibodies would bind to the HIV surface protein gp120.

THE MUCH-ANTICIPATED RESULTS of the world's first Phase III clinical trial of an AIDS vaccine showed that it was statistically no better than a placebo in preventing HIV infections.

But there was also an unexpected result. According to an analysis of the data, released last week by the vaccine's developer, VaxGen, blacks had 78% fewer HIV infections than those receiving a placebo, and a group of nonwhites that included blacks and Asians had 67% fewer infections. Only a small percentage of blacks and nonwhites were enrolled in the study, however, raising the possibility of a statistical fluke.

Another ongoing Phase III trial of AIDSVAX, conducted on injecting-drug users in Thailand, will conclude in June. Results from that study, which will be released later this year, might shed light on the baffling results, researchers say.

The three-year study of AIDSVAX consisted of 5,009 volunteers, two-thirds of whom received injections of a genetically engineered version of the gp120 surface protein on the AIDS virus. It was hoped that the recombinant protein would stimulate production of antibodies that would then bind to gp120 on the virus, incapacitating it.

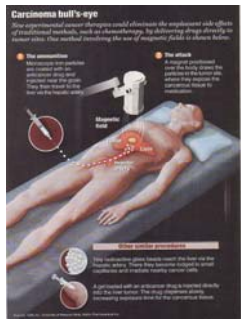
VaxGen Communications Director Jim Key notes that black and other nonwhite participants produced higher levels of vaccine-induced antibodies, a finding that VaxGen is continuing to analyze. "There's a possible correlation between that and protection," Key says.

As to what might possibly confer immunity on a separate racial group, Tom Coates, director of the University of California, San Francisco's Center for AIDS Prevention Studies, says he's hard-pressed to come up with a biologically plausible mechanism. "At this point, it defies explanation," he says. VaxGen will present a more complete analysis of its data later.

But despite the vaccine's apparent failure, "we now have a vaccine trial where we've got real data on real people, and we can examine those data to see what might have happened," Coates says. "In the main, this advances the field of vaccine research for HIV." —ELIZABETH WILSON

II. TARGETING IN BLOOD CIRCULATION

A. PASSIVE AND PHYSICAL TARGETING



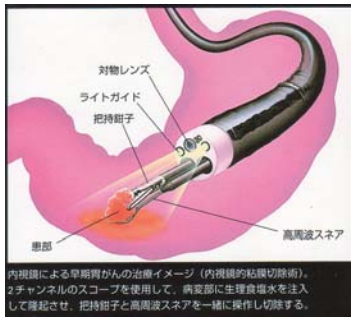
III. TARGETING IN THE GI TRACT

A. TARGETING TO STOMACH

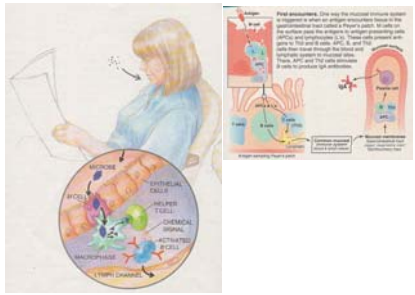
B. TARGETING TO SMALL INTESTINE

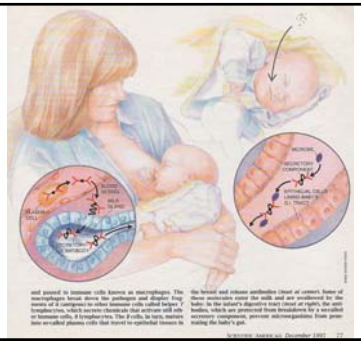
1. ORAL VACCINATION
2. ORAL VACCINATION USING EDIBLE VACCINES

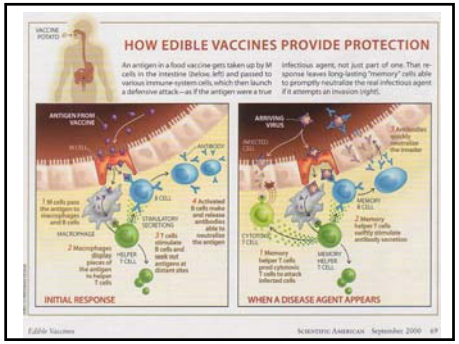
C. TARGETING TO COLON



内視鏡による早期胃がんの治療イメージ（内視鏡的粘膜切除術）。2チャンネルのスコープを使用して、病変部に生理食塩水を注入して隆起させ、把持鉗子と高周波スネアを一緒に操作し切除する。







IV. GENE DELIVERY

A. VIRAL VECTORS

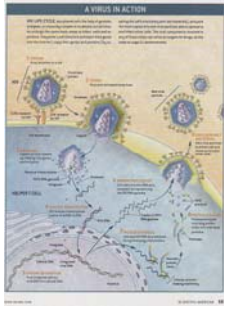
HIGH TRANSFECTION EFFICIENCY

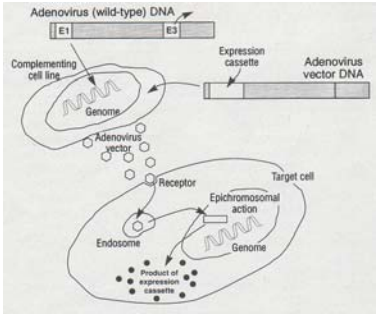
HIGH RISK (VIRUS IS VIRUS)

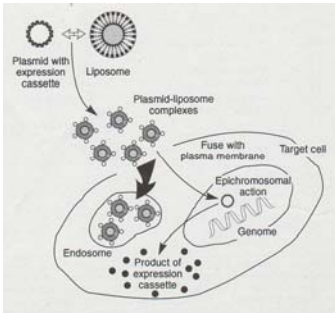
B. NON-VIRAL VECTORS

LOW TRANSFECTION EFFICIENCY

LOW RISK





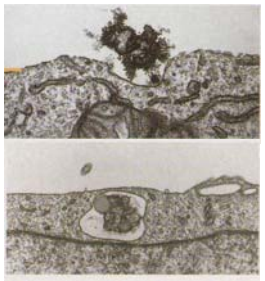


IDEAL GENE CARRIER

1. **THERAPEUTIC DNA**
2. **DNA-CONDENSING AGENT**
   (POLYLYSINE, POLYETHYLENEIMINE, CHITOSAN)
3. **CELL TARGETING MOIETY**
4. **ENDOSOMAL DISRUPTING MOIETY**
5. **NUCLEAR TRANSLOCATION MOIETY**

MOST IMPORTANT STEP:

4. **ESCAPE FROM ENDOSOME**



VECTORS ALSO PROTECT THE DNA CARGO.