More progress in cancer diagnosis and treatment

While there have been dramatic reductions in the incidence of certain cancers, the overall numbers have changed little during the past 40 years: Cancer remains the second leading cause of death in the U.S. However, "Cancer Progress," a conference sponsored by Communitech (Yorktown Heights, N.Y.) and held in New York City earlier this month, zeroed in on developments in cancer diagnosis and therapy, and delivery systems for cancer drugs. And in those areas, reported Robert C. Hickey, head of surgery at M. D. Anderson Hospital and Tumor Institute (Houston, Tex.), "progress is being made."

This year, it is estimated, 876,000 new cases of cancer will occur in the U.S. and 453,000 people will die of the disease. In addition, approximately 5 million patients now require monitoring—either for therapy or because they have had a malignancy that is in remission. Yet annual sales of *in vitro* cancer diagnostics, says Stephen Turner, president of Oncor (Gaithersburg, Md.), are less than $100 million. "Clearly," says Turner, "there's a need for new and unequivocal diagnostic tools."

On the horizon: Monoclonal antibodies that can identify specific tumor antigens

Diagnosis. An ideal approach to the definitive diagnosis of cancer, in the view of Nagesh S. Mhatre, president of Becton Dickinson Immunocytometry Systems (Mountain View, Calif.), would seem to require labeled monoclonal antibodies—antibodies that bind to a single antigen—that selectively and specifically react to tumor cells without reacting to such cells' nontumor counterparts—i.e., normal cells. But most tumors express the same cell surface antigens as expressed by normal cells. Few monoclonal antibodies, therefore, are truly tumor-specific, although some are tumor-associated and reasonably selective.

Thus, current applications generally use antibodies to antigens expressed on the tumor cell and the normal cell. Monoclonal antibodies targeted for leukemic cells offer a good example of how the system would function. Leukemia is a malignant disease of the blood-forming organs and is characterized by the distorted proliferation of derived leukocytes, or white blood cells. But there are many types of white blood cells and, therefore, many types of leukemia, each of which can behave differently and respond differently to treatment. However, since leukemic cells often retain the surface antigens associated with the normal cells from which they were derived, monoclonals specific for those antigens can be used to identify the type of leukemia. Such monoclonals, says Mhatre, may allow early diagnosis and better survival rates.

Other types of monoclonals that Mhatre says may be developed in the next few years:

- antibodies specific for major cancers of such organs as lungs, breasts and colons to help determine the origin of metastases;
- antibodies to determine whether a cell is malignant.

Agreeing with Mhatre, Allan M. Green, director of nuclear medicine at Boston University Medical Center, says that identification of tumor-associated antigens (TAA)—antigens specifically associated with tumor cells and not with normal cells—is the key to the success of monoclonals in diagnosis.

The difficulty in such identification, however, is illustrated by carcinoembryonic antigen (CEA), says Green. CEA is perhaps the best known and characterized TAA. And while CEA is clearly associated with colon tumors, it is also found on other tumors of the gastrointestinal (GI) tract and on such non-GI tumors as cancer of the breast. Further, it is associated with nonmalignant diseases such as acute hepatitis. This nonspecificity, says Green, hampers the use of CEA in the diagnosis of colon cancer.

Moreover, diagnosis of the exact location of colon tumors is impeded by the fact that CEA isn't firmly anchored to the tumor cell surface. Instead, it is shed into the bloodstream where it can interact with monoclonals far from the tumor site.

Other TAAs also are shed. And no TAA has yet been found that is present on all cells in a given tumor. "The fundamental diversity and entrepreneurial character of tumors," says Green, "means that there is enormous biochemical variability in their expression."

With an eye toward development of monoclonals for diagnosis, researchers are focusing on the biodistribution of intravenously administered antibodies to develop techniques that reduce their nonspecific distribution in the body. Efforts also are focused on increased delivery of monoclonals to microscopic tumor deposits in lymph nodes.

Also showing great promise as diagnostic tools are DNA probes, reports Oncor's Turner. Such probes—small pieces of DNA that recognize specific genes or segments of DNA—can detect relocations of DNA sequences that relate to tumor development. An example is the rearrangement of a specific cell-surface receptor gene that occurs in two distinct types of immune system white blood cells—B and T lymphocytes—as they turn from normal to cancer cells. Probes developed by Oncor that detect this rearrangement, says Turner, can be used in the early identification of tumorous T and B cells in lymphoblastic leukemia. The probes, Turner says, can detect as little as 1-3% tumor

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cells in a mixed specimen.

Other Oncor probes also can detect oncogenic viruses. Those strains of human papilloma virus now closely associated with the onset of cervical cancer can be detected, as can human T lymphotropic virus III (HTLV-III), the virus closely linked to acquired immune deficiency syndrome (AIDS). DNA probes, says Turner, "provide the only current means to gauge active papilloma or HTLV-III infection."

Reorganize. What's more, says Turner, probe technology will "deliver a new kind of cancer patient data that will become mandatory for diagnostic accuracy." He adds that "over time it will reorganize the basis by which tumors are identified and classified."

Monoclonal antibodies also are gaining recognition in cancer therapy. Near term, their greatest potential, says Becton Dickinson's Mhatre, is in transplantation to treat bone marrow cancer. The rationale for such transplantation is that although it may be possible to kill all the tumor cells in bone marrow with a dose of radiation or chemotherapy, an adequate dose also would destroy the patient's immune system, which is generated by bone marrow.

Yet, if normal bone marrow could be injected into a cancer patient following high-dose therapy, such treatment could be successful. The problem is that bone marrow from another person—even if closely matched for histocompatibility—has immune system cells that will recognize the new host as foreign and will attack host tissues, a condition known as graft versus host (GVH) disease.

One approach that has worked well in mice and has been used with increasing success in people is to remove T cells—the cells that initiate GVH disease—from donor marrow before injection. Removal can be accomplished using monoclonals specific for T cells. Methods now being tested use such monoclonals conjugated to toxins and monoclonals attached to magnetic beads or columns. The best technique, says Mhatre, should be determined within the next two years.

The use of monoclonals for direct *in vivo* treatment of cancer—the "magic bullet" concept—has proved elusive, says Mhatre. The reason is the same difficulty that has hindered monoclonal antibodies in diagnosis: Truly tumor-specific monoclonals have been difficult to produce.

An estimate of new cancer cases and deaths in 1984

Lung	139,000	121,000	1
Colon-Rectum	130,000	59,000	2
Breast	116,000	38,000	3
Prostate	76,000	25,000	4
Pancreas	25,000	23,000	5
Kidney/Bladder	57,000	19,000	6
Leukemia	24,000	17,000	7
Ovary	16,000	12,000	8
Other	291,000	139,000	9

But if such monoclonals can be developed, several approaches could render them toxic to cancer cells. Monoclonals can be coupled to immunotoxins, such as ricin, to radioactive isotopes or to cancer drugs like daunomycin. In fact, ricin and daunomycin are now being used extensively in clinical trials. In addition, the naked monoclonal can mark tumor cells for destruction by the host immune system.

Probe technology will deliver a new kind of data 'mandatory for diagnostic accuracy'

However, work with monoclonals for *in vivo* therapy "is mostly in its infancy," says Mhatre. He adds that the most promising approaches will not be determined for several years.

Another potential cancer therapeutic agent, the human protein tumor necrosis factor (TNF), is being explored by a host of firms active in genetic engineering. Timothy E. O'Connor, associate institute director for scientific affairs at Roswell Park Memorial Institute (Buffalo, N. Y.), says that TNF presents a different set of problems. Although nontoxic to a wide range of human cells, the compound can destroy a number of the most lethal human and rodent tumors, including melanoma, lung carcinoma, colon carcinoma and breast carcinoma. At the same time, TNF is not effective against other cancers, including other breast carcinomas, bladder carcinoma and erythroleukemias. But it is toxic to the intraerythrocyte parasite of malaria and to microorganisms of the genera *Klebsiella* and *Listeria*.

Examination of TNF's "molecular mechanisms of action on tumor cells" will receive close attention in the coming year, says O'Connor. The compound, he adds, could "open new perspectives" on treatment of solid tumors.

Receiving equal billing with new diagnostic and therapeutic tools are new systems for delivering cancer drugs. Demetrious Papahadjoupoulos, chairman of the scientific advisory board for Liposome Technology (Menlo Park, Calif.), reported that liposome encapsulation of two highly toxic cancer drugs, Adriamycin doxorubicin hydrochloride and amphotericin B, drastically reduced adverse toxic effects. In both cases, says Papahadjoupoulos, animal experiments have shown promising results and clinical trials have begun.

When injected intramuscularly into the body, liposomes release a drug slowly and thus act as a molecular infusion pump. The vesicles consist of a thin lipid membrane that surrounds a central aqueous space that contains water-soluble drugs. The lipid membrane can carry lipid-soluble drugs. Moreover, liposomes can be made to interact with certain cells by attaching specific antibodies to their surface.

Other delivery systems were highlighted by Jeffrey H. Berg, vice-president of PA Technology (Hightstown, N. J.). Increasingly, says Berg, chemotherapy is being administered by such systems as external and implanted infusion pumps and vascular access ports.

Infusion pumps. Currently, about 30 companies produce external infusion pumps. Such pumps are based on two different infusion regimens. The closed-loop system regulates dosage by automatic sensing of physiological parameters. Open-loop devices operate on a preset flow rate or are programmable with a variable flow rate usually associated with a diurnal cycle. The pumps are used chiefly for delivering insulin but can be adapted to administer chemotherapeutic agents. However, only a few firms—including Deltec Systems, Autosyringe, Pancretec and Cormed—have focused on such adaptations.

Implanted infusion pumps, on the other hand, are being developed largely for cancer treatment. These pumps are generally placed in the abdominal wall or the subclavicular area. The rationale is that smaller total doses of toxic drugs are needed to achieve the same effect as with systemic infusion.

Infusaid (Sharon, Mass.) is the only company with Food and Drug Administration approval for the sale of such

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pumps and has sold about 14,000. Medtronic (Minneapolis) and Shiley (Irvine, Calif.) are clinically testing implanted pumps, as is Cordis in Europe. In addition, a number of leading pacemaker producers are developing these devices.

Use of the Infusaid pump in the treatment of liver cancer has been intensively studied. The pump continuously administers 5-fluorodeoxyuridine directly into the hepatic artery in patients with unresectable solid liver tumors. The method results in greater reduction in tumor mass, says Berg, and improved median survival rates relative to conventional intravenous therapy.

Vascular access ports also have become a popular infusion method for chemotherapy, says Berg. The ports, implanted under the skin, consist of a self-sealing injection port and a catheter

Drug delivery systems include self-sealing vascular access ports and implanted pumps

for drug delivery to selected sites. Infusaid, Pharmacia (Piscataway, N.J.) and Cormed are marketing products. Medtronic and Davol (Cranston, R.I.) are expected to enter the market.

More and more, says Berg, vascular access ports will be used in conjunction with external infusion pumps for drug delivery. In fact, manufacturers are now developing tubing and needle sets to interface the systems—a development that poses a "serious competitive threat" to the future of implantable infusion pumps, Berg says. The relative costs, he adds, are approximately $2,500 for the external pump/port system versus $8,000 for an implanted pump.

Controlled release. Moreover, vascular access ports may find use in controlled-release drug delivery, says Berg. For example, Pharmacia envisions using its system to deliver Spherex microspheres for treating liver cancer. The spheres are tiny starch beads that contain either *bis*-chloroethylnitrosourea or mitomycin C, which are released when the starch is broken down by amylase in the blood. The system is in clinical studies at the University of Michigan (Ann Arbor) and four other institutions.

The take-home message from the conference: Although progress appears to be painfully slow, continuous advances are being made. And some participants expressed considerable optimism. Green of Boston University Medical Center sums up: "The future, as Herbert Hoover observed, lies before us." □

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