Imagine treating a disease whose site, characteristics, and biological behavior are unknown. Without this knowledge, there is little basis for developing a rational treatment plan or assessing its outcome. But a small group of physicians at The University of Texas M. D. Anderson Cancer Center are slowly learning to overcome that uncertainty: they are responsible for the care of the 200 to 300 patients who come to M. D. Anderson each year with unknown primary tumor, a form of cancer that first presents as the metastasis typical of late-stage cancer. About five percent of all cancers are unknown primary tumors.

A typical cancer patient presents with signs and symptoms of one tumor whose type and site can be ascertained. Determining the site of a tumor provides the physician with a large body of knowledge that allows prediction of the tumor’s behavior and the patient’s prognosis and thus development of a treatment strategy. Unknown primary tumors, on the other hand, provide too few clues for the physician to make these predictions.

“Unknown primary tumor” is a disquieting diagnosis to patients and physicians alike. It seems an enigma that could be “known” if only the right test were performed. Martin N. Raber, M.D., chairman of the Department of Clinical Investigations, conceded that “physicians who are trained to base diagnosis and treatment on established patterns of natural history have uneasy about unknown primary tumors because these tumors are not only unpredictable but are notoriously heterogeneous among patients.”

Until 1987, when the Unknown Primary Tumor Clinic was founded at M. D. Anderson, little attempt had been made to classify these patients or to develop a treatment strategy for their disease. Now, Raber and the other physicians of the clinic, James L. Abbruzzese, M.D., chief of the Section of General Oncology, and Renato Lenzi, M.D., assistant professor in the Section of General Oncology, examine biological processes in these patients and design individualized treatment strategies to outwit the disease.

M. D. Anderson has built a database of the more than 1000 patients seen in the Unknown Primary Tumor Clinic, and the physicians who treat these patients have begun to construct the natural histories of unknown primary disease. Abbruzzese reported that an understanding of the prognostic factors of unknown primaries is developing as the clinic identifies subsets of patients who have responded similarly to treatments.

Raber explained that patients with unknown primary tumor have neither a uniform prognosis nor a uniform treatment course. Quite the contrary, they have extremely varied outcomes, and for that reason a major goal of the Unknown Primary Tumor Clinic is to sort patients. “There is danger,” Raber emphasized, “in thinking that because the group of patients having unknown primaries has a poor prognosis that the individual does.” Although patients with unknown primary tumors survive an average of eight months from diagnosis, some survive as long as five years. Physicians at the clinic thus try to identify favorable subsets of patients who have diseases known to respond to certain treatments.

Although the amount of time that should be spent searching for the site of the primary tumor is controversial, Raber pointed out that the time is minimized at M. D. Anderson because multidisciplinary evaluation by specialists in every field of oncology is readily available; a complete, thorough clinical evaluation requires only two to three days. “As in many situations,” commented Raber, “physicians who specialize in a disease have a different view than do physicians who see it only rarely.” All patients in the Unknown Primary Tumor Clinic continued on page 2
"There is danger in thinking that because the group of patients having unknown primaries has a poor prognosis that the individual does.

undergo a physical examination, chest x-ray, computed tomographic scan of the abdomen and pelvis, and routine screening for hematological and biological tumor markers. Gastrointestinal imaging, thyroid screening, and specific tests are performed if indicated by the findings of the first round of tests or by patient complaints. Occasionally, pathologic tests—light microscopy, immunohistochemistry, and electron microscopy—on a tissue specimen reveal a diagnosis that has previously been overlooked. Lenzi added that the diagnosis of “undifferentiated carcinoma” is never accepted at M. D. Anderson: “When a referring institution indicates this diagnosis, we then perform various tests that help in making an accurate diagnosis and in detecting tumors that are potentially curable or responsive to treatment, such as lymphomas and sarcomas.”

For 75% of patients with unknown primaries, tests are unable to detect the primary tumor. Although both the patient and the physician are more comfortable with a specific diagnosis, researchers at M. D. Anderson found that exhaustive searching for the primary tumor does not guarantee a more desirable outcome. In a study of 927 patients that examined the value of each diagnostic test, the investigators concluded that barium enemas and upper gastrointestinal scans have a low yield in finding primary tumors. To spare the patient unnecessary discomfort and expense, these tests are no longer routine but are performed only for specific indications.

Even so, physicians at M. D. Anderson agree that cancer can be managed on the basis of its metastasized location. Lenzi observed, “Single-site cancer requires regional surgery and radiotherapy whether it is a primary site or a metastasized site, and widespread disease requires systemic chemotherapy regardless of its point of origin.” The histologic subtype of the disease and the metastasized site of presentation are important criteria in determining treatment. Raber, concurring, voiced the most essential questions: “What kind of cancer is it? What are its pathologic characteristics?”

Patients whose primaries have not been determined are offered a chemotherapeutic protocol developed for patients with unknown primary tumors, explained Raber. In developing the protocol, consideration was given to the relative frequencies of different sites in which unknown primaries are thought to occur. At M. D. Anderson, the rate of response to the regimen cisplatin plus 5-fluorouracil plus leucovorin is about 30%. Cisplatin was selected because it is effective in ovarian and lung cancers, 5-fluorouracil and leucovorin because they are effective in cancers of the gastrointestinal tract. Because the new agent paclitaxel (Taxol) is thought to be effective in breast, ovarian, and lung tumors that are refractory to cisplatin, physicians at the clinic have recently added it to the protocol.

Biological Investigations

A research team led by Menashe Bar-Eli, Ph.D., assistant professor of the Department of Cell Biology, hopes to describe the properties of the late-stage metastatic cancers they find in patients with unknown primary tumors. To explain the rapid spread of the disease, the clinic is testing the hypothesis that unknown primary tumors are unique and behave differently from known primary tumors. Abbruzzese said, “Studies with mice indicate that unknown primary tumors grow much more independently than do known primaries, suggesting that these unknown tumors are much more ‘malignant’ in their ability to grow unrestrained and independently of their host.” Abbruzzese said that this postulate fits with the aggressive cancers and widespread metastases found in patients with unknown primaries. Although some institutions have reported that the path of metastasis in unknown primaries is abnormal and that these cancers do not spread in the same manner as known primaries, researchers at M. D. Anderson have not found this to be so. According to Lenzi, clinical studies show that the spread of unknown primaries is similar to that of known primaries—just faster.

The clinic has developed a number of cell lines from patients with unknown primary tumors. Using these and other cancer cell lines, Bar-Eli is able to compare the occurrences of common oncogenes, thought to participate in the process of converting normal cells into cancer cells, and tumor suppressor genes (anti-oncogenes), thought to control the growth and differentiation of tumors, in known and unknown primary tumors. Bar-Eli said that his goal

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Molecular technologies allow development of biological agents

**Biological response modifiers promising adjuvants to cancer therapy**

Physicians who look for new and better ways to treat cancer patients have long recognized that the body's natural immune system is a powerful fighter of disease. Lacking the tools to harness that power, they have relied largely on three treatment modalities: surgery, radiotherapy, and chemotherapy. Although these treatments, either alone or in combinations, are effective in many patients, other patients have little if any response to them. In addition, some forms produce uncomfortable or even unacceptably severe side effects or complications.

Today, however, new research tools have spawned a vast new field of cancer therapy research. Biological therapy is a broad term encompassing the use of various agents, most of them naturally occurring, to induce or enhance the patient's own immune responses to disease. A few of these agents, or biological response modifiers, have been so clearly shown effective in treating specific diseases that they have already been approved by the U.S. Food and Drug Administration for those applications. Most of these agents, however, are still considered experimental.

Recombinant DNA technology ignites research

One of the most important of these tools is recombinant DNA technology. This technique fuses a gene that encodes a protein to a strand of DNA from another organism; the DNA enables the gene to make many copies of the protein, allowing mass production of a relatively pure form of the protein. The sudden availability of large amounts of many bodily proteins fueled the explosion in molecular biology and molecular genetics that has dominated medicine for the last 15 years. As understanding of the often multiple roles of these proteins in the body grew, cancer researchers began to develop strategies for using them therapeutically, for example, to boost or substitute for the immune system. The field has moved rapidly: new models and agents are being introduced ever more quickly, and the strategies become more specific and more complex, utilizing combinations of agents and combinations of biological therapies with other modalities. Recent figures show that the number of biological therapies under investigation has exceeded the number of conventional chemotherapeutic drugs under investigation.

The researchers and clinicians of the Department of Clinical Immunology and Biological Therapy at The University of Texas M. D. Anderson Cancer Center are charged with investigating these agents and incorporating them into therapeutic strategies. In this, the first of a series of two articles, the ongoing clinical trials of two important biological therapies will be discussed.

**Biological therapies ameliorate side effects of other therapies**

Saroj Vadhan-Raj, M.D., is looking for a way to incorporate biological therapy into supportive therapy, which aims to improve the effectiveness of primary therapies such as chemotherapy and radiotherapy while enhancing the comfort and safety of the patients receiving the therapy. Myelosuppression, the inhibition of the hematopoietic process of generation, maturation, and functioning of blood cells, is one of the most frequent and severe side effects of chemotherapy and is often the reason that chemotherapy dose is limited to a subtherapeutic level. Hematopoietic suppression in cancer patients may also be a response to internal disease processes. Myelosuppression may lead to depletions of platelets and neutrophils and is the principal reason patients receiving chemotherapy are especially prone to infections and their complications, bleeding problems, and anemia.

Vadhan-Raj and her colleagues have for several years studied the myeloprotective effects of hematopoietic growth factors, proteins that regulate hematopoiesis and may indirectly trigger the release of cytokines, which regulate communication between cells and the extracellular environment, mediating immune system responses. Vadhan-Raj recalled, “In early trials, two factors called G-CSF and GM-CSF were effective in accelerating neutrophil recovery from chemotherapy-induced myelosuppression, reducing the incidence of infections and their sequelae by about 50%. This improvement was enough to allow modest elevation of the

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Recent figures show that the number of biological therapies under investigation has exceeded the number of conventional chemotherapeutic drugs under investigation.

Chemotherapy dose, but not enough to have a really significant effect on tumor response. Nor did these agents have any effect on thrombocytopenia or anemia."

A more recent approach to myeloprotection has been the combination of hematopoietic growth factors. In this generation of trials, Vadhan-Raj and her colleagues have tried combinations of G-CSF and GM-CSF with several relatively newly discovered interleukins, substances that mediate immune responses and are known to increase production of platelets. These combinations have been more effective than the growth factors alone in reducing myelosuppression.

Fusion molecule PIXY321 combines the effects of two cytokines

The concept of combining cytokines has been refined by fusing GM-CSF and an interleukin, IL-3, in a molecule called PIXY321. The first phase I clinical trial of PIXY321 was conducted at M. D. Anderson, and Vadhan-Raj and her colleagues from the Department of Melanoma/Sarcoma Medical Oncology found that PIXY321 reduced the incidence and severity of not only neutropenia but also thrombocytopenia in patients with sarcoma who were receiving chemotherapy. In early trials, PIXY321 appeared to reduce not only the incidence and severity of myelosuppression, but also the incidence of infectious sequelae and the need for blood transfusions. Moreover, the technique used to produce the fusion molecule has opened the door to the development of customized combinations of factors and other proteins that may offer even greater therapeutic value. Vadhan-Raj hopes that this new agent will be an important addition to the array of therapies against myelosuppression. Phase II and III trials are being planned.

Hematopoietic growth factors are also being used to mobilize progenitor cells in peripheral blood, another approach to overcoming myelosuppression associated with high-dose chemotherapy. When administered after chemotherapy in combination with previously harvested and cryopreserved blood progenitor cells, the growth factors enhance hematopoietic recovery from the chemotherapy, allowing higher doses. Another therapeutic approach to myelosuppression is based on work carried out by Vadhan-Raj and her colleagues on the proliferative kinetics of hematopoietic progenitor cells. In these trials, growth factors are being used to stimulate cells to enter the cell cycle. When the therapy is suddenly stopped, the cells enter the quiescent phase of the cycle, which may protect them from the side effects of chemotherapy. This technique attempts to get as many cells as possible out of the S phase, that is, to reduce their vulnerability to killing by chemotherapy.

Vadhan-Raj and her colleagues are carrying on with their work, trying newer, earlier acting growth factors and techniques to prime target blood progenitor cells before treatment. These approaches have great promise in providing complete hematopoietic reconstitution, allowing doses of chemotherapy that may offer substantial clinical benefit to some patients.

Monoclonal antibodies attack tumors directly

James Lee Murray, M.D., is taking a more direct approach: rather than providing supportive care for a conventional treatment modality, he is using biological agents called monoclonal antibodies to attack tumors directly.

The concept of directing antibodies, either alone or coupled to various toxic substances, as "magic bullets" to tumor cells was first proposed in the early 1900s. Because of the difficulties in obtaining large enough quantities of these antibodies in a pure enough form, little work was done to test this concept until the mid-1970s, when the then-new hybridoma technology, the fusion of normal mouse lymphocytes and tumor cells, made it possible to mass produce extremely pure mouse antibodies derived from a single tumor cell, or clone. This technology fueled the development of a group of biological response modifiers known as monoclonal antibodies, each of which targets a specific antigen.

Antibodies were first administered in their native, unaltered form to cancer patients. Many of the antibodies are known to have their own immunologic activity: they not only "find" the tumor cells in the body, but several of them directly mediate killing of the cells. Despite the intuitive attractiveness of the approach, monoclonal antibodies have
not yet found an established niche as anticancer therapy. Murray recalled, "In the early 1980s, researchers began to realize that monoclonal antibodies administered alone were unlikely to eradicate bulky tumors. They began designing studies that combined antibodies with other biological response modifiers or chemotherapeutic agents to enhance their effects."

Conjugated antibodies effective in some solid tumors
Monoclonal antibodies have been successfully conjugated to substances known to kill tumors, such as drugs, toxins, and radioisotopes. Radioisotope-antibody conjugates were the first to be used in the clinic because they were the first conjugates that did not lose the antibody's binding affinity for the antigen. In early clinical trials, some of them at M. D. Anderson, radionlabeled antibodies were shown to effectively image tumor deposits. One such antibody, Oncoscint™, has been approved by the Food and Drug Administration to image ovarian or colon cancer.

Various isotopes of higher radioactivities than those used for imaging have been coupled to other antibodies for use as radioimmunotherapy for cancer. Although these conjugates have yielded complete response rates as high as 70% in human lymphomas, they have been less effective in other solid tumors, mainly because the radioactivities needed to achieve the desired therapeutic effects cannot be used because they are toxic to the bone marrow. Researchers are looking at refinements of radioconjugates that could deliver more radiation to tumor sites while sparing normal organs.

Besides radioisotopes, both plant (ricin) and bacterial (Pseudomonas) toxins have been used in antibody conjugates. The most encouraging results have been in leukemias or lymphomas: monoclonal antibodies coupled to ricin have yielded response rates of 40% to 50%.

Many investigators have been working primarily with drug conjugates, the linking of a chemotherapeutic agent such as doxorubicin or vincristine to the antibody. They have encountered a significant problem: the linkers employed to connect the antibody to the drug reduce the potency of the antibody, the drug, or both. Moreover, the antibodies that are produced from mouse cells, which include most of those now in use, often stimulate the production of antimouse antibodies in patients. These antibodies may form immune complexes that continue on page 7

Unknown Primary Tumors
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...is to recognize a pattern of oncogene and anti-oncogene abnormalities that will allow speculation about where an unknown primary tumor arose.

Bar- Eli also used these cell lines to study the frequency of mutations in the tumor suppressor p53 gene in various tumor types. Because changes in p53 usually occur in the late stages of many common adult primary cancers, just before they begin to spread, it was expected that the highly metastatic and advanced unknown primaries would have a high incidence of p53 mutations. These mutations, however, were found in only 26% of unknown primaries, whereas they were found in 50% to 75% of known primaries arising in the lung, breast, pancreas, and gastrointestinal tract—sites frequently found to be the origin of tumors initially considered to be unknown primaries. Bar- Eli concluded that p53 mutations do not play a major role in the development and progression of these tumors.

Bar- Eli said, “This low frequency of mutations in the p53 gene seemed to indicate that many unknown primary tumor cells progress to malignancy through unique molecular changes.” Bar- Eli and Abbruzzese posited that although unknown primary tumors arise from a variety of primary sites typical of known primary tumors, their highly aggressive biology suggests a unique series of molecular and biochemical events.

Because p53 mutations do not appear to play a major role in the metastases of unknown primaries, M. D. Anderson investigators are searching for other molecular markers that might explain the rapid metastasis. The clinic has begun screening patient tumors for K-ras, another gene mutated in many cancers.

Physicians who desire additional information may write Dr. Raber, Department of Clinical Investigations, or Dr. Abbruzzese, Department of Gastrointestinal Medical Oncology and Digestive Diseases, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, or call (713) 792-7765 (Raber) or 792-2828 (Abbruzzese).
the virus from binding to the receptors and penetrating the cell. Sastry is credited with creating R15K and discovering its inhibitory effects. He likened the V3 loop to a key: when HIV, using the V3 loop (the key), tries to enter a cell via a receptor (the keyhole), it is unsuccessful because the entrance is already blocked by R15K. "The theory behind the peptide strategy is that the peptide and the HIV V3 loop compete for cell-surface receptors, and the peptide wins," explained Sastry. "We are not certain exactly how the peptide blocks infection, but we believe it occupies all the sites on the surface of the cell that the V3 loop might otherwise use to allow the virus to enter the cell," he continued.

A very important step in the spread of HIV infection is destruction of T cells by a process called syncytium formation. In this process, an HIV-infected cell combines with several healthy T cells to form a giant, multinuclear mass or syncytium. The syncytia quickly die, killing the T cells. Sastry found that the R15K peptide can effectively block syncytium formation and prevent T cell loss.

**R15K as treatment**

Published studies suggest that at the time of transmission and for a variable period afterwards, HIV exists largely in nonsyncytial form and is relatively harmless to the body's natural immune system. It is believed that, during this phase, T cells generated by the immune system keep the virus in check. As the virus evolves, however, the immune system becomes less able to combat the virus. The result is the emergence of the syncytial form of HIV and the onset of the illness phase, the point at which the patient begins to develop AIDS.

The researchers anticipate that R15K's infection-inhibiting activity could be used therapeutically to slow down or even stop the progression from HIV infection to AIDS. Most therapeutic strategies today employ reagents such as zidovudine (AZT) to inhibit HIV once it has entered cells, but the injection of R15K into an HIV-infected individual would significantly slow down the virus's evolutionary cycles, prolonging the patient's disease-free phase. "Our studies imply that R15K acts as an adjunct to the immune system, allowing T cells to be more effective longer and delaying the onset of AIDS," Arlinghaus commented.

**R15K as vaccine**

The M. D. Anderson team developed a new vaccine approach that challenges the accepted strategy and takes into consideration the unique characteristics and behavior of HIV. "Traditional thought dictates that antibody immunity is needed to combat viruses," Arlinghaus stated. "But we think HIV is structurally different from other viruses and that it reacts differently in the body. We believe that to prevent HIV infection in humans, you have to induce a cellular immunity, a killer T-cell immunity, without inducing anti-HIV antibodies."

Arlinghaus believes that the team's novel strategy points to a breakthrough in HIV research. "The vaccine community at large would probably still consider this a 'dark horse' strategy, one that could succeed but is by no means mainstream. However, support for our hypothesis is increasing. Several key figures in the field of HIV vaccine research are beginning to seriously question the value of antibody immunity for HIV."

While investigating the preventive and therapeutic effects of R15K, Sastry discovered that R15K has a significant third effect: it can induce a killer T-cell response, a natural immune response that would destroy cells already infected with HIV. Very little is known about this effect, however. "This effect has only been tested in mice. We have no data that suggest that this response will occur in humans, but we will continue to investigate this possibility," said Sastry.
The next step: human trials

Two questions remain to be answered about the effectiveness of R15K: Will the peptide work in humans and, if so, can HIV, which is a shrewd culprit, find another way to enter healthy cells? To answer these questions, Sastry and his team will test the effectiveness and safety of R15K in clinical trials using human volunteers who are in the early stages of HIV infection. Before conducting human trials, tests will be conducted in animals to identify any toxic effects the peptide may produce. The M. D. Anderson research team will work with researchers at The University of Texas Medical School at Houston to obtain permission from the U.S. Food and Drug Administration to conduct the clinical trials. That approval could be granted within 12 months.

Arlinghaus added that if the peptide is successful in treating HIV-infected humans, it may eventually have a direct impact on cancers, such as B-cell lymphoma and Kaposi’s sarcoma, often found in AIDS patients.

—VICKIE J. WILLIAMS

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Biological Response Modifiers

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are cleared rapidly by the liver, deactivating the drug conjugate. After a concerted effort, researchers are now able to produce by recombinant molecular techniques humanized or chimeric (part mouse, part human) antibodies that can overcome or minimize the problem of immunogenicity.

BR96-doxorubicin conjugate in clinical trials

One of the new and improved monoclonal antibodies is BR96. Developed by Bristol-Myers, BR96 binds strongly to Lewis y, a carbohydrate antigen found in large quantities on a number of tumors, including carcinomas of the colon, breast, pancreas, and lung, some of the most prevalent and deadly cancers. The conjugate of BR96 and the chemotherapeutic agent doxorubicin is, once bound to the tumor cell, readily internalized. The antibody has been “chimerized,” that is, made part human, in an effort to diminish its immunogenicity.

In preclinical studies, BR96-doxorubicin significantly reduced the size of large solid tumors in mice and rats, often curing the animals. Murray and collaborators at M. D. Anderson and the University of Alabama Cancer Center are conducting a phase I clinical trial to determine the optimal dose, schedule, and route of administration and the safety and efficacy of the conjugate.

Although it is too early to report any results, Murray believes that this trial accurately reflects the direction monoclonal antibody research is taking: it uses an “improved” chimeric antibody to reduce antigenicity and increase the likelihood of the antibody conjugate penetrating the tumor. Although some researchers believe chimeric antibodies will solve the antigenicity problem, Murray expects to see antibodies further humanized—to about 98%, he estimated—nearly eliminating the chance of immunogenicity and increasing patient tolerance. This becomes especially important, explained Murray, when multiple doses are desired.

Murray also expects that monoclonal antibodies will become smaller as a way to improve penetrability and facilitate manufacture. “Antibody fragments offer hope in delivering more antibody to the tumor and delivering it to the core of the tumor where it can do the most good.” Finally, he anticipates that the antibodies will be manipulated to improve their targeting of and binding to the tumor antigen. “Right now,” Murray states, “we need to focus the majority of our research efforts on improving the therapeutic index of these antibodies, that is, on increasing their antitumor effects while causing less damage to normal tissues. It is only a matter of time before a new generation of antibodies will be ready for clinical testing.”

—KATHRYN L. HALE

Physicians who desire additional information may write to Drs. Vadhan-Raj or Murray at the Department of Clinical Immunology and Biological Therapy, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030, or call (713) 792-7966 (Vadhan-Raj) or 792-8189 (Murray).
New agent may have both preventive and therapeutic applications

Synthetic peptide effectively controls the spread of HIV in human cell cultures

Despite unprecedented biomedical research activity, a cure for the acquired immunodeficiency syndrome, or AIDS, eludes investigators. Like all infectious diseases, AIDS can be eradicated only by a successful two-pronged strategy: prevention for those who are likely to be exposed to the pathogen, the human immunodeficiency virus (HIV), and treatment for those who have already been infected. Many creative approaches to prevention and treatment have been tried, and although some have been successful in subpopulations of high-risk or infected persons, the deadly disease remains a major public health threat throughout the world.

Most experts agree that a fresh new approach is needed, and that is exactly what a group of researchers at The University of Texas M. D. Anderson Cancer Center have developed. The new approach is based on a synthetic peptide, a sequence of amino acids that is part of a protein, that effectively inhibits the spread of HIV in human cell cultures in the laboratory. Although test tubes are a far cry from human beings, the researchers are hopeful that the peptide, known as R15K, can be developed into both a vaccine that would prevent HIV infection and a drug that would prevent transmission of the infection.

Research on HIV began at M. D. Anderson Cancer Center six years ago. Leading the M. D. Anderson research team are Ralph Arlinghaus, Ph.D., professor and chairman, K. Jagannadha Sastry, Ph.D., assistant professor, and Pramod Nehete, Ph.D., research associate, all of the Department of Molecular Pathology.

Peptide blocks transmission of HIV

Infection occurs when HIV attaches to healthy cells at cell-surface receptors through which the virus is transmitted. Most researchers believe that a molecular component called the V3 loop on the outer coat of HIV plays a critical role in the infection process. The M. D. Anderson researchers believe that R15K, which is structurally similar to the V3 loop, mimics the V3 loop in a way that prevents continued on page 6