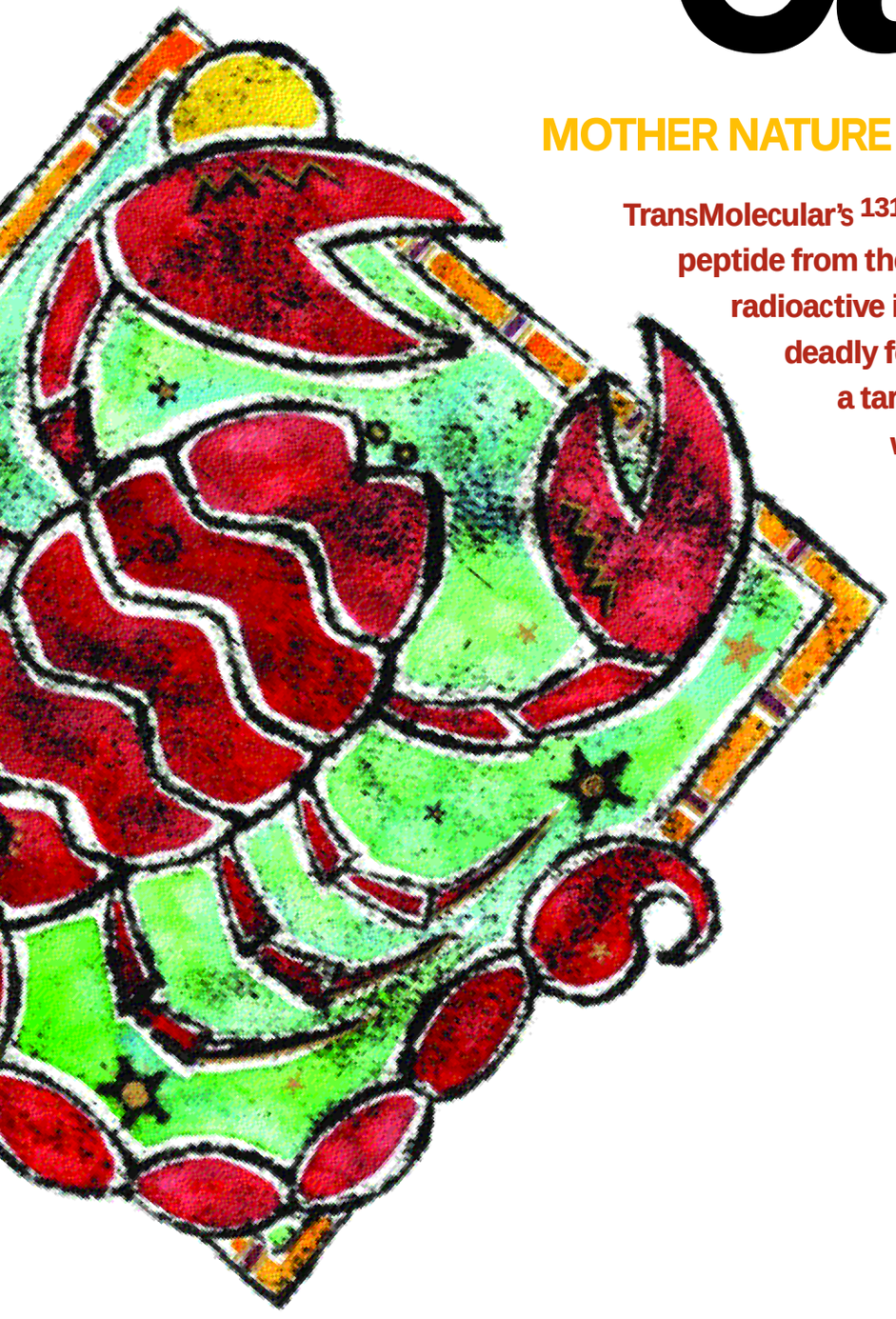
FROM Scorpion TO Cancer

BY DENISE MYSHKO



MOTHER NATURE BUILT IT, MAN IS IMPROVING IT.

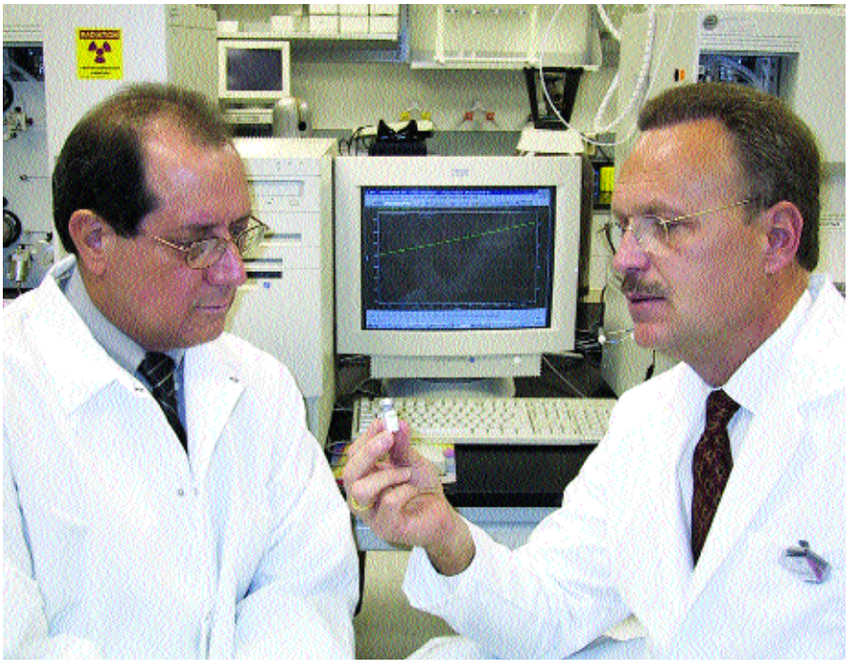
TransMolecular's ^{131}I-TM-601 is a synthetic version of a peptide from the venom of scorpions combined with a radioactive iodine. In Phase I/II trials to treat glioma, a deadly form of brain cancer, the product can deliver a targeted dose of radiation to cancerous cells without affecting normal tissue.

^{131}I-TM-601 Timeline

SEPTEMBER 2002. TransMolecular receives patents to protect composition of matter and methods of treating cancer retaining all rights to chlorotoxin and its use in treating cancer in humans. Chlorotoxin is a substance derived from scorpion venom, and is the lead compound in the company's investigational new drug — ^{131}I-TM-601, currently in Phase I/II clinical trials for the treatment of glioma.

JUNE 2002. FDA grants TransMolecular orphan drug designation for ^{131}I-TM-601 for use by glioma patients.

JUNE 2002. TransMolecular begins multi-center clinical study to evaluate the safety and tolerability of a single dose of ^{131}I-TM-601, as well as overall tumor response rate in an initial study group of 18 patients. In preclinical studies, TransMolecular scientists determined that ^{131}I-TM-601 was able to extend survival in a mouse model that mimicked human brain tumors.



DR. VERNON ALVAREZ AND DR. MATTHEW GONDA

TransMolecular is developing a synthetic version of chlorotoxin, a component of scorpion venom, called TM-601. TM-601 is being used as a drug-delivery vehicle that binds specifically to a receptor found on primary brain tumors or gliomas, but not normal tissues.

Patients diagnosed with glioma, especially primary high-grade forms of the disease, often die not long after diagnosis. And the quality of life after diagnosis is quite poor. Standard treatment, surgery followed by radiation, is not effective and, in most cases, the cancer will recur.

Now, a poisonous venom from a scorpion holds hope as an effective treatment for this deadly form of brain cancer. TransMolecular Inc., a neuroscience biotechnology company, is developing a synthetic version of chlorotoxin, a component of venom obtained from the giant yellow Israeli scorpion, *Leiurus quinquestriatus*, called TM-601. TM-601 is being used as a drug-delivery vehicle that binds specifically to a receptor found on primary brain tumors, or gliomas, but not normal tissues. TM-601 is a very small, stable, and versatile peptide that can cross the blood brain and tissue barriers. ^{131}I-TM-601 is a radiopharmaceutical that combines TM-601 with a medical radioisotope, 131I.

"That's key — ^{131}I-TM-601 targets the tumor cells, but not normal cells," says Matthew A. Gonda, Ph.D., president, CEO, and director of TransMolecular, a privately held and venture-capital backed company founded in 1996. "^{131}I-TM-601 takes the radioactivity right to the tumor cells."

In preclinical studies, ^{131}I-TM-601 has shown significant capacity to increase survival in human tumor xenograft mouse models of brain cancer and to image tumors *in vivo*.

Glioma is highly invasive, sending cancerous cells throughout the brain and spinal cord. Surgical techniques fail to eradicate the tumor

JANUARY 2002. FDA approves TransMolecular's IND application to begin Phase I/II clinical study of the drug in humans.

SEPTEMBER 2000. TransMolecular completes a $9 million round of financing. The company is using the funds to advance its programs in cancer and neuropathic pain, as well as drug manufacturing and preclinical and clinical development of its lead compounds for primary brain cancers.

SEPTEMBER 2000. TransMolecular is awarded two Phase I Small Business Innovation Grants. It receives $131,702 for the study of peptide and recombinant toxin therapies based on the peptide chlorotoxin for glioma, and $128,351 for the development of a novel sodium ion channel as a target for pain drug discovery.

JANUARY 1999. Matthew A. Gonda, Ph.D., joins the company as president and CEO and serves on the board of directors.

JULY 1996. TransMolecular is founded by Dr. Stephen G. Waxman of Yale University and Dr. Harald W. Sontheimer of the University of Alabama at Birmingham Medical Center. The company is targeting two diseases applicable to its technology platforms — cancer and neuropathic pain.

and other adjunct therapies are inadequate.

"What makes this such a critical effort is the fact that there currently is no effective therapy," says Lyle Hohnke, Ph.D., general partner at Tullis-Dickerson & Co. Inc. "Diagnosis of glioblastoma is essentially a death sentence for most people."

The five-year relative survival rate for all people with brain cancer varies with age, according to The American Cancer Society. For adults between the ages of 15 and 44, it is 55%. For those between the ages of 45 and 64, it is 16%, and for adults over 65, it is 5%.

Despite advances in chemotherapy and radiation, survival rates for gliomas have remained unchanged during the last 20 years. This is believed to be because of their high resistance to radiation and chemotherapy, but also to their ability to invade healthy brain tissue.

THE SCORPION'S VENOM

Dr. Gonda emphasizes that ^{131}I-TM-601 represents unique targeting technology. It is not an antibody, he says, but a peptide derived from the venom of scorpions. Although this scorpion's venom is a neurotoxin to invertebrates, it does not appear to be toxic to animals or people.

TM-601 is similar in size and targeting specificity to single-chain antibodies made by recombinant DNA methods.

"Mother Nature already built this into TM-601," Dr. Gonda says. "It wasn't designed by the scorpion to go after tumor cells, it just so happens that human tumor cells share a receptor found in the central nervous system of invertebrates. But in humans, the receptor only is expressed on tumor cells.

"Human antibodies, cytokines, and polypeptides have a specific targeting nature similar to TM-601, but their receptors, unlike that for TM-601, are found on many other normal tissues throughout the body as well, which could complicate tumor-specific therapy," he says.

"It was known that scorpion venom contains peptides that bind to receptors involved in ion transport found on certain brain cancer cells," says Vernon Alvarez, Ph.D., VP of research and development at TransMolecular. "Researchers involved with ion transport essentially used the scorpion venom as a resource to test brain cells for a totally different purpose. That purpose was to study the electrophysiology of those cells. That's the study of the natural transport of ions that allows brain cells to interact with each other and balance cell processes. But then it turned out that normal cells did bind chlorotoxin, suggesting that they did not have this particular signal. With further analysis, it was determined that chlorotoxin bound only to the tumor cells and not to normal cells. We thought we could use those sequences to identify tumor cells and then perhaps ultimately to deliver therapeutic payloads to them."

A Phase I/II study of ^{131}I-TM-601 is ongoing at two research centers — City of Hope in Los Angeles and the University of Alabama at Birmingham — to evaluate the safety and tolerability of ^{131}I-TM-601 and to evaluate overall tumor response rate in adults with recurrent high-grade glioma. The study currently has completed its first dosing panel, and will enroll an additional 12 patients. This first study is anticipated to be completed by the end of the second quarter of the year. The company expects to begin an expanded Phase II trial in the second half of this year.

"Therapy using ^{131}I-TM-601 is like molecular surgery," Dr. Gonda says. "The chlorotoxin sequences in TM-601 are the guidance system that delivers a radioactive payload to its target, precisely killing the tumor cells."

The compound is to be used after surgery to deliver a targeted burst of radiation directly to the cancer cells — binding directly to

BRAIN CANCER FACTS

- Cancers of the brain and spinal cord are among the **MOST DIFFICULT AND EXPENSIVE CANCERS TO TREAT**. The outlook for survival is dim, and there are few treatment options. This type of cancer accounts for about 1.4% of all cancers in both adults and children and 2.4% of all cancer-related deaths.
- The American Cancer Society estimates that each year 17,000 primary malignant tumors of the brain or spinal cord are diagnosed in the U.S. About **13,100 PEOPLE WILL DIE** from these malignant tumors.
- The **FIVE-YEAR RELATIVE SURVIVAL RATE** for all people with brain cancer varies with age. For adults between the ages of 15 and 44, it is 55%. For those between the ages of 45 and 64, it is 16%, and for adults over 65, it is 5%.
- Prognosis and treatment depend on the location of the tumor within the central nervous system and on the type of cell in which the cancer developed. In **ADULTS OLDER THAN 45, 90% OF BRAIN TUMORS ARE GLIOMAS**, a general category of cancers that start in the three types of glial cells:astrocytes, oligodendrocytes, and ependymal cells that line the ventricles.
- **GLIOMA IS HIGHLY INVASIVE**. This cancer is almost impossible to completely remove with surgery; the cancer cells continue to grow and eventually cause death. Average survival time for patients with low-grade astrocytomas or oligodendrogliomas is about 6 years to 8 years. Average survival for patients with anaplastic astrocytomas is about 3 years. Average survival for patients with glioblastomas is about 12 months.
- Most tumors that arise within the brain itself start in brain cells called astrocytes. These tumors are called astrocytomas. **MOST ASTROCYTOMAS CANNOT BE CURED** because they spread widely throughout the surrounding normal brain tissue. Sometimes astrocytomas spread along the cerebrospinal fluid pathways.
- Researchers do not fully understand the causes of brain cancer. The majority of brain tumors are not associated with any risk factors. **MANY CNS TUMORS HAVE BEEN FOUND TO HAVE GENETIC ABNORMALITIES.** Mutations have occurred with p53, p16, cdk4, and RB protein,amplification or over-expression of epidermal growth factor.
- Although brain tumors can occur at any age, research indicates that they are **MOST COMMON IN TWO AGE GROUPS**. The first group is children **3 TO 12 YEARS OLD**; the second is adults **40 TO 70 YEARS OLD**, according to the National Cancer Institute.
- Some brain cancers — meningiomas, some ependymomas, gangliomas, and cerebellar astrocytomas — can be removed through surgery. But tumors such as anaplastic astrocytomas or glioblastomas are not cured by surgery because cells from the cancer invade surrounding brain tissue. When possible, **SURGERY CAN LIMIT RADIATION AND CHEMOTHERAPY** and may relieve some symptoms.

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a receptor on a tumor, but leaving normal cells unaffected. The therapy has several advantages, Dr. Alvarez says. First, the peptide is stable, so it won't break apart. ^{131}I-TM-601's small size — with a molecular weight of less than 4,000 daltons — means it can filter through normal cells to find the smaller cancer cells that may have infiltrated into normal tissue.

"In addition, manufacturing of our peptide derivative is scaleable," Dr. Alvarez says. "^{131}I-TM-601 is so potent; not much is needed. As a matter of fact, in our first dose level, we're giving 250 micrograms, about the size of four grains of salt."

Additionally, ^{131}I-TM-601 is non-immunogenic, meaning that the body does not develop an immune response to it.

"It's well-tolerated compared with other chemicals and at this dose of radiation therapy it doesn't appear to make the animals or patients sick," Dr. Alvarez says. "In addition, ^{131}I-TM-601 is relatively easy to manufacture with a lower cost of goods."

HUGE MARKET POTENTIAL

Dr. Gonda says the company will conduct research beyond the glioma indication to use ^{131}I-TM-601 as an imaging agent.

"We are developing a therapy first and then we will work to provide it as an imaging agent so that physicians can better manage the disease process; that is, they will be able to diagnose, treat, and follow the cancer," he says.

The receptor for TM-601 is found on a variety of other solid tumors, including metastatic brain cancers, expanding the application of its technology.

Research by TransMolecular estimates that the market for diagnostics and therapies for glioma and metastatic brain cancers could exceed $1 billion in the U.S. alone.

"The market for glioma products alone is about $500 million," Dr. Gonda says. "Primary gliomas are a niche market. We have orphan drug status for this compound."

TransMolecular received orphan drug designation from the FDA for ^{131}I-TM-601 in June 2002.

"We are extremely pleased by the FDA's action in granting orphan drug designation for ^{131}I-TM-601 as in important step in bringing this drug to market," Dr. Gonda says. "Orphan drug designation could greatly assist us in maintaining our exclusivity in marketing our new drug candidate for patients suffering from this devastating and deadly disease."

Longer term, TransMolecular plans to study the interaction of TM-601 with other chemotherapeutic agents and to work on the treatment of other solid tumors.

"These studies are in the research phase of development but have shown very promising results," Dr. Gonda says. "Cocktails are becoming the favored form of therapy. Patients tend not to develop drug resistance as fast and more of the tumor can be knocked out. But, cocktails have higher degree of toxicity associated with them. In the case of our drug, we have not observed any toxicity in our animal studies."

Although the company expects to file a marketing application in late 2006, Dr. Hohnke says there could be pressure on the company and on the FDA to get this product to the market faster.

"If the clinical results are robust, the company might be able to approach the FDA for early marketing approval given the fact that there is no current therapy on the market," Dr. Hohnke says.

Increasingly, radiopharmaceuticals are being researched as therapeutics. These products often consist of radiolabeled isotopes attached to a carrier molecule, which can be used to deliver therapeutic radiation to treat specific diseases. These differ from the diagnostics in the type of radiation that is emitted.

The therapeutic radiopharmaceuticals market generated revenue of about $56 million in 2001, a 7.5% increase over 2000, according to a May 2002 report by Frost & Sullivan. But researchers at Frost say they expect the market to increase dramatically as novel products become approved beginning in 2003 and beyond. Many of these newer products are anticipated to spur double-digit growth rates through the end of the decade. ❖

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Experts on this topic

VERNON ALVAREZ, PH.D. VP, research and development, TransMolecular Inc., Birmingham, Ala.; TransMolecular, founded in 1996, is a privately held and venture-capital backed biotechnology company that is developing products to diagnose and treat diseases of the central nervous system. For more information, visit transmolecular.com.

MATTHEW A. GONDA, PH.D. President, CEO, and director, TransMolecular Inc., Birmingham, Ala.; TransMolecular, founded in 1996, is a privately held and venture-capital backed biotechnology company that is developing products to diagnose and treat diseases of the central nervous system. For more information, visit transmolecular.com.

LYLE HOHNKE, PH.D. General partner, Tullis-Dickerson & Co. Inc., Greenwich, Conn.; Tullis-Dickerson is a private equity group providing capital to small- and midsize healthcare companies. For more information, visit tullisdickerson.com.