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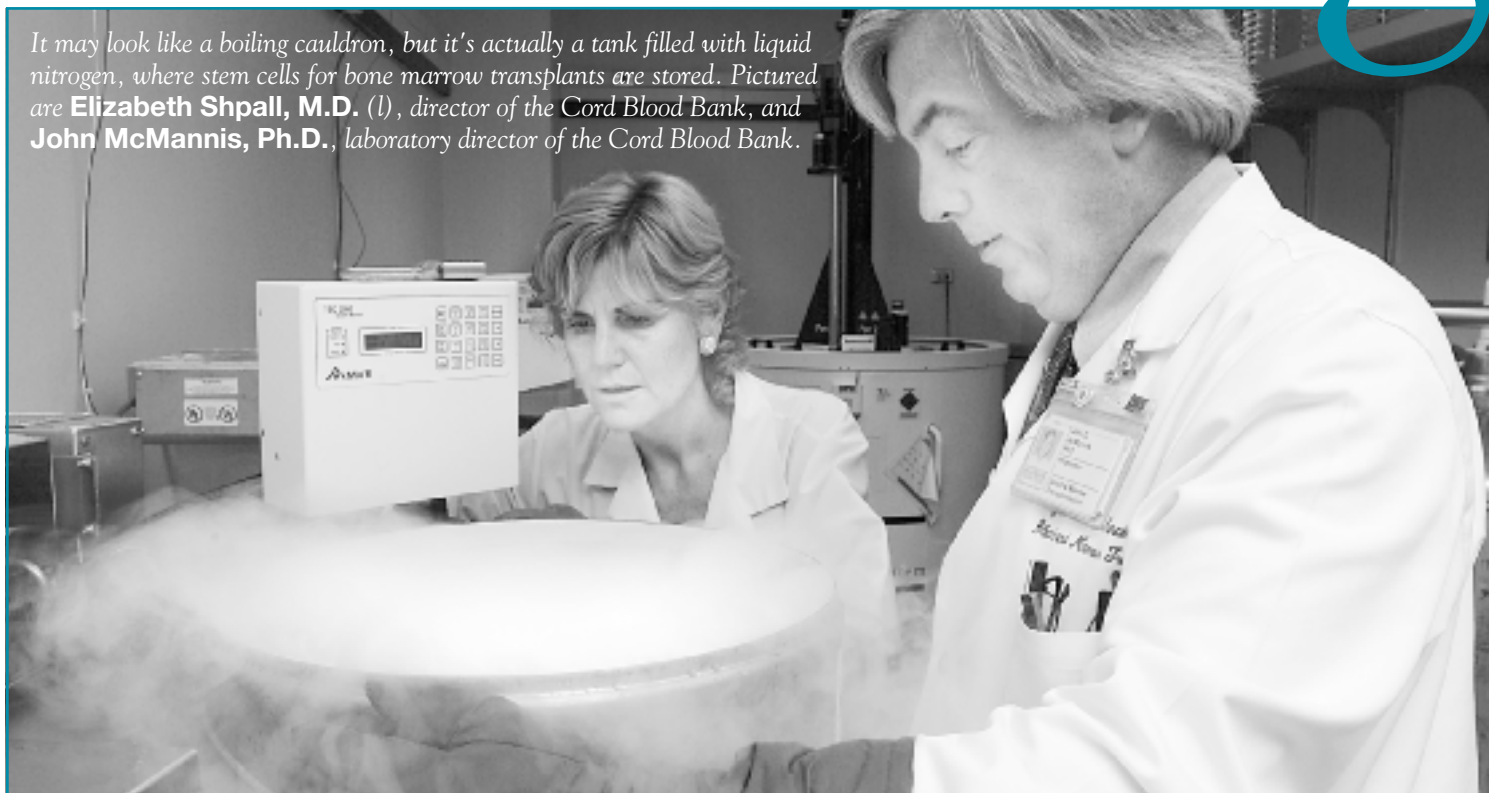


REPORT TO PHYSICIANS

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Oncology

It may look like a boiling cauldron, but it's actually a tank filled with liquid nitrogen, where stem cells for bone marrow transplants are stored. Pictured are Elizabeth Shpall, M.D. (l), director of the Cord Blood Bank, and John McMannis, Ph.D., laboratory director of the Cord Blood Bank.



A New Source of Stem Cells

Umbilical cord blood is expanding the options for bone marrow transplants.

by Don Norwood

A bone marrow transplant can mean new hope for life for someone with leukemia or another serious blood disease. But each year, many people who need a transplant aren't able to have one because a matching donor can't be found.

However, a new source of stem cells has become an emerging source of hope for such patients: umbilical cord blood. Once discarded, the umbilical cord is now prized for its wealth of stem cells that can be used in bone marrow transplants. The University of Texas M. D. Anderson Cancer Center is now on the frontline in the collection and use of cord blood with the establishment of the M. D. Anderson Cord Blood Bank.

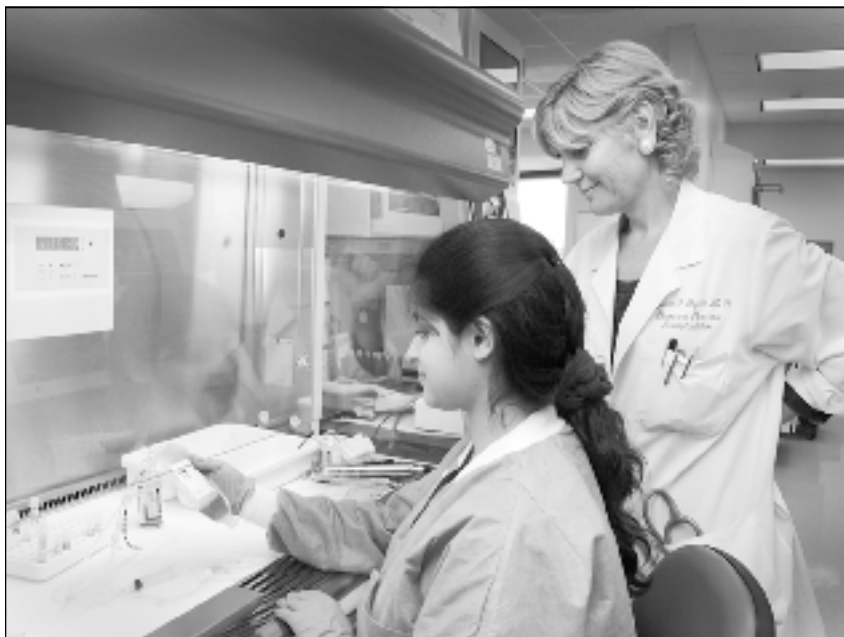
M. D. Anderson has the largest stem cell transplantation program in the world, so establishing a Cord Blood Bank was a logical step, according to Elizabeth Shpall, M.D., a professor in

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A New Source of Stem Cells

(Continued from page 1)



Dr. Elizabeth Shpall (standing, r) looks on as **Sufira Kiran**, a laboratory technologist, processes blood extracted from an umbilical cord, and then stores it in the Cord Blood Bank's fully automated storage tank.

the Department of Blood and Marrow Transplantation and director of the Cord Blood Bank. Officially in operation since April, the still-new Cord Blood Bank collects umbilical cords from consenting maternity patients at selected hospitals in the Houston area. The cords are collected just after birth, and the blood is extracted, processed, frozen, and inventoried. It is then made available to transplant centers worldwide.

"We take the cords from the hospital, and we bring them here and test them for everything that we would test in a normal donor," said Dr. Shpall. "When they're found to be good, we freeze them and put them in our bank, and they are ready to go as a source of stem cells."

Upon accreditation, which is pending, the M. D. Anderson Cord Blood Bank will join a number of transplant registries, starting with the National Marrow Donor Program. The bank is currently a member of NETCORD, which maintains a worldwide cord blood database. Through these registries, the human leukocyte antigen (HLA) types of the cord blood specimens will be made available around the world.

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The M. D. Anderson Cord Blood Bank currently has a partnership with the Women's Hospital of Texas and is negotiating another with Ben Taub General Hospital, both of which are near M. D. Anderson. These partnerships guarantee not only a large source of cord blood but also cord blood from a very diverse population, increasing the chances that an appropriate match can be found for a given patient.

The first transplantation choice for someone with leukemia is always bone marrow from a sibling. However, only one patient in three or four has a sibling who is a match. The next option is the

National Marrow Donor Program, which finds HLA matches for about 65% of applicants. This avenue offers less hope for minorities because most of the donors in the registries are white and of Western European descent. In comparison, cord blood specimens are collected from a more diverse group of donors, creating options for people who might otherwise have had little hope of finding a matched donor.

Furthermore, patients who receive stem cells from cord blood are less likely to develop graft-versus-host disease than those who receive stem cells from bone marrow, because of the naïveté of cord blood. Stem cells from cord blood also seem to work particularly well in conjunction with fludarabine when compared with other chemotherapeutic agents. Yet another advantage of cord blood stem cell transplants is that they can be used for immune deficiency and genetic diseases. In particular, these transplants have been shown to correct neurological deficits in patients with Krabbe's disease, Dr. Shpall said.

Cord blood does have its disadvantages. Namely, it has fewer stem cells than bone marrow and peripheral blood, making for a longer engraftment period.

However, two recent studies published in *The New England Journal of Medicine* report similar survival rates in a comparison of cord blood transplants with transplants using marrow from unrelated donors. Also, researchers at M. D. Anderson are working to counteract the long engraftment period.

“The patient is especially at risk during engraftment,” said Dr. Shpall. “So, our laboratory has been focused for a decade on trying to expand the stem cells from cords ex vivo before implanting them. We have trials looking at two different expansion strategies, and we’re about to embark on a third, which we think is the most promising.

“Basically, we take an umbilical cord and we pull out the stem cells and combine them in the lab with vitamins and growth factors, expanding 100-fold the stem cells we think are necessary to engraft. We then infuse the expanded cells instead of unmanipulated cells. It’s still too early to know for sure whether it’s working, but we’re encouraged by our preliminary findings.”

Because the number one risk before engraftment is life-threatening infection, researchers in the Department of Blood and Marrow Transplantation have expanded their study of cord blood to the T cells also contained in it. Dr. Shpall said this will be a major focus of future research in the department.

“We’re doing a lot of work to try to reduce infections in transplant patients, so another whole area of research in our laboratory is expanding the T cells from cord blood. We take a fraction of the umbilical cord and expand the T cells. Once we confirm in the laboratory that those T cells have the potential to be effective, we plan to infuse them into the patient separately to bolster the immune system, in hopes it will recover more quickly after transplant. That’s a critical area, which if successful, will lead to major improvements in outcomes for cord blood transplant patients.” ●

FOR MORE INFORMATION, contact Dr. Shpall at (713) 745-2161.

PROTOCOLS

Current and upcoming stem cell transplant and cellular therapy trials at M. D. Anderson Cancer Center include the following:

- Ex-vivo cord blood expansion with a copper chelator for hematologic malignancies (02-455). **Physician: Elizabeth Shpall, M.D.**
- Randomized trial of unmanipulated versus expanded cord blood for hematologic malignancies (02-407). **Physician: Marcos de Lima, M.D.**
- RhG-CSF treatment of severe epithelial/endothelial or solid organ-specific tissue damage in stem cell transplant recipients (02-300). **Physician: Martin Korbling, M.D.**
- Mesenchymal stem cells secreting interferon-beta in patients with metastatic breast cancer (04-0836). **Physician: Michael Andreeff, M.D.**
- Ex-vivo cultured mesenchymal stem cells for GVHD in allotransplant patients (05-0168). **Physician: Partow Kebriaei, M.D.**
- Alloreactive NK cells with allergenic stem cell transplantation for AML and MDS (05-0508). **Physician: Richard Champlin, M.D.**
- Active immunization of sibling stem cell transplant donors against purified myeloma protein of the stem cell recipient with multiple myeloma (04-0434). **Physician: Sergio Giral, M.D.**
- Treatment with AMD 3100 in multiple myeloma patients to mobilize peripheral blood progenitor cells for collection and for transplantation (2004-0708). **Physician: Chitra Hosing, M.D.**
- Nonablative allergenic blood stem cell transplantation for indolent lymphoid malignancies (99-035). **Physician: Issa F. Khouri, M.D.**
- PR1-specific cytotoxic T-lymphocyte infusion for patients with recurrent CML after allogeneic hematopoietic transplantation (03-0564). **Physicians: Muzaffar Qazilbash, M.D. and Jeffrey Moldrem, M.D.**
- Allogeneic stem cell transplantation using suicidal lymphocytes (03-0080). **Physician: Steven M. Kornblau, M.D.**
- Unrelated bone marrow versus peripheral blood transplantation (03-1010). **Physician: Paolo Anderlini, M.D.**
- Mini-allogeneic peripheral blood progenitor cell transplantation for recurrent or metastatic breast cancer (97-268). **Physician: Naoto Ueno, M.D., Ph.D.**
- Stem cell transplantation for ovarian cancer (98-363). **Physician: Richard Champlin, M.D.**
- Autologous purged hematopoietic stem cell transplantation for chronic myelogenous leukemia (2003-0710). **Physician: Marcos de Lima, M.D.**

FOR MORE INFORMATION about these trials, call the M. D. Anderson Information Line at (800) 392-1611 or (713) 792-3245. For a broader list of clinical trials at M. D. Anderson, visit www.clinicaltrials.org.

Phase I Cancer Findings Under-Reported

Phase I cancer studies are under-reported in peer-reviewed journals—a trend that could ultimately delay scientific progress and negatively affect patient care, say researchers at M. D. Anderson in a new study published online in *Cancer* on August 22, 2005.

Over the last decade, greater understanding of cancer at the molecular and cellular levels has resulted in the development of numerous potential anticancer agents. An excellent indication of this progress, said Luis Camacho, M.D., assistant professor in M. D. Anderson's Phase I Clinical Trials Program, is the 10-fold increase in the number of Investigational New Drug applications for oncology agents filed with the Food and Drug Administration—from 100 compounds in 1980 to over 1,000 in 1998.

"With all this new knowledge, the need to share information is paramount, now more than ever before," said Dr. Camacho, the study's first author. "We, as clinicians and researchers, have a tremendous responsibility to not only investigate and discover new agents but also to disseminate our discoveries—good and bad—to the medical community at large, to ensure the safety and well-being of our patients.

"Obviously, if a phase I agent proves too toxic, we need to ensure that information is shared within the cancer medical community, so as to not put patients in harm's way," Dr. Camacho said. "Of course, if phase I studies are promising, publishing can encourage further investigation of these potential therapeutic agents."

In unique cases, Dr. Camacho said, positive phase I results can have an immediate impact on clinical care. "Phase I studies are not necessarily first-in-human trials—they also can investigate combinations of already approved drugs," he added. "If those combinations prove relatively nontoxic and show some effect,

that combination can potentially be moved forward to phase II trials and, in selected cases, used to treat patients almost immediately."

"Developmental Reprogramming" Could Explain Cancer Risk

Researchers at M. D. Anderson Cancer Center may have uncovered the reason why some people who are genetically predisposed to hormone-dependent cancers develop the disease as an adult, while others who are similarly susceptible do not.

In a study published in the June 14, 2005, issue of the *Proceedings of the National Academy of Sciences USA*, the researchers showed, for the first time, that exposure to a pharmaceutical estrogen during fetal development can permanently "reprogram" tissue in a way that determines whether tumors will develop in adulthood.

"...we need to open our eyes to the notion that cancer that develops in an adult may have been put in motion before the person was born."

While the study was conducted with rats that are susceptible to benign uterine tumors, the researchers say their conclusions likely have relevance for humans who inherit defective tumor suppressor genes that make them susceptible to a number of different cancers. The study could explain, for example, why some women who inherited BRCA1 or BRCA2 gene defects develop breast cancer as adults while other women with the same genes remain disease free.

"The kind of developmental reprogramming we see from this work could represent an important determinant of risk in people genetically susceptible to hormone-dependent

tumors, such as uterine, breast, and prostate cancer," said the study's principal investigator, Cheryl Walker, Ph.D., a professor in the Department of Carcinogenesis.

While more work is needed to make the case that some human cancers occur in the same way, "we need to open our eyes to the notion that cancer that develops in an adult may have been put in motion before the person was born," said the first author, Jennifer Cook, a graduate student who works with Dr. Walker.

An Alternative to Bone Marrow Biopsies?

New tests may soon be available that will allow physicians to diagnose and monitor disease activity in leukemia and lymphoma patients using blood samples. These tests could reduce the need for the uncomfortable bone marrow biopsies traditionally used.

"Our research has shown that testing for tumor constituents in the blood provides a more clinically useful assessment of disease status because it shows what is happening in the entire body, compared with a biopsy, which only provides information about a specific area," said Michael J. Keating, M.D., a professor in the Department of Leukemia at M. D. Anderson Cancer Center.

The new tests are designed to detect certain proteins that are expressed on the surface of tumor cells. The assays will look for the proteins CD3, CD4, CD8, CD19, CD20, CD33, and CD52, as well as tumor-specific DNA and RNA in blood plasma. Quest Diagnostics is developing the new tests based on technology developed at M. D. Anderson.

"The new blood tests may give us a less painful and more cost-effective way to monitor patients," said Dr. Keating. "As a result, oncologists may be able to assess patients more frequently and thus provide more clinically relevant monitoring of their progress." ●



Complementary and Alternative Medicine

Sorting through the Choices

When facing a diagnosis of a serious disease like cancer, it's natural to want to fight it in every way possible. According to one large study, close to 70% of cancer patients try at least one type of complementary and alternative medicine (CAM) as part of their cancer treatment.

Alternative medicine refers to therapeutic approaches used *in place of* traditional medicine to treat or ease the effects of disease. Complementary medicine, on the other hand, includes nontraditional approaches used *together with* conventional medicine.

One example of CAM is homeopathy, which uses non-detectable doses of substances made from plants, minerals, animals, or chemical drugs to trigger the body to heal itself. Traditional Chinese medicine views health as a balance in the body of two forces called yin and yang. Still another example of CAM is ayurvedic medicine, a system from India that emphasizes herbal medicine, physiotherapy, and diet. Naturopathy advocates treating one's mental, physical, and emotional states.

Will it help or hurt?

Studies show that most people do not discuss their use of CAM with their doctors, and this can be a mistake. While some forms of CAM have proven beneficial, others can interfere with cancer treatments and can even be harmful. For example, a study on the use of laetrile (another name for the chemical amygdalin, which is found in the pits of many fruits and in numerous plants) showed it ineffective or potentially harmful in treating cancer.

Some alternative approaches, however, have been shown to be useful in managing the symptoms of cancer. For instance, acupuncture, which involves stimulating specific anatomic points in the body by puncturing the skin with a needle, has been demonstrated to be effective in managing chemotherapy-associated nausea and vomiting and in controlling pain associated with surgery.

The jury is still out on many CAM treatments because there isn't enough scientific data yet. But much research is underway: both the National Center for Complementary and Alternative Medicine (NCCAM), the federal government's agency for research on CAM, and the National Cancer Institute (NCI) are funding research to evaluate the safety and effectiveness of many CAM therapies.

This research is looking into issues such as the effect of massage on cancer-related pain, the use of acupuncture for symptom control, the effectiveness of ginger in reducing chemotherapy-induced nausea and vomiting, and the effect of spiritual healing on survival time and loss of function in patients with a certain type of brain cancer.



Seek trustworthy advice

Cancer patients who are considering CAM should ask their doctors about the possible benefits, risks, and side effects to ensure the approach won't interfere with their treatment. Even some seemingly harmless herbs and vitamins may cause anticancer drugs to work less effectively. High doses of vitamins, for example, may affect how radiation and chemotherapy work, and the herb St. John's wort, often used for treating depression, may make some cancer medications less powerful.


While there is a lot of information available about CAM, it's important to get guidance from trustworthy sources

Cancer patients who are considering a complementary or alternative therapy should ask their doctors about the possible benefits, risks, and side effects.

such as your physician, reputable public agencies, or academic institutions. One example is M. D. Anderson's Web site on complementary/integrative medicine education resources (www.mdanderson.org/cimer), which provides evidence-based reviews of therapies as well as links to authoritative resources, such as NCCAM (<http://nccam.nih.gov>) and NCI's Office of Cancer Complementary and Alternative Medicine (www.cancer.gov/cam). The Directory of Information Resources Online (<http://dirline.nlm.nih.gov>) includes information about a number of health organizations that focus on CAM. Additionally, Medline Plus (<http://medlineplus.gov>) provides access to reliable health information. Useful free publications from the NCCAM Clearinghouse (1-888-644-6226) include "Are You Considering Using Complementary and Alternative Medicine?" and "Selecting a Complementary and Alternative Medicine Practitioner." ●

For more information, contact your physician or contact the M. D. Anderson Information Line:

 **(800) 392-1611, Option 3,**
within the United States, or

 **(713) 792-3245** in Houston
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DiaLog

Risks and Benefits of Phase I Oncology Trials

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Phase I trials are closely scrutinized and their ethics debated, because of the many unknown factors participants face.

An often-repeated misconception is that the sole function of phase I trials is to find the right dose and to assess toxicity—that evaluation of clinical responses is not an objective. It is true that the design of phase I trials generally precludes the statistical assessment of response rates, but we think that describing responses is important. Indeed, almost all new anticancer agents approved in recent years by the FDA brought about objective clinical responses among patients in phase I trials. Even so, the ethics associated with phase I trials have been questioned, in part because the prospect for improvement is perceived as low.

A recent article by Horstmann et al.,¹ however, shows that the chance of benefit is higher than previously reported. Indeed, 10.6% of patients with advanced cancer, for whom conventional options offered no hope, achieved a complete or partial remission; an additional 34.1% had either stable disease or a “less-than-partial”

response. From this perspective, then, 44.7% of participants derived a benefit, since all patients had to have progressive cancer to qualify for a phase I trial. In addition, these trials have an impressive safety record, with less than 0.5% of the close to 12,000 participants dying of what could be drug-related toxicity.

Our clinical experience with patients with metastatic cancer who seek out clinical trials suggests that they want highly experimental therapy, even if the chances of a response are small, because their quality of life is improved by “not giving up.” Lobbying efforts for earlier access to experimental therapies for AIDS and breast cancer are further evidence that patients facing inevitable death may be less risk-averse than is the regulatory community. Indeed, one trial that allowed fully informed patients to choose among doses of a therapeutic agent, 28% chose the highest available dose.

Phase I trials are crucial for the development of new cancer therapies. Several phase I trials have proved so pivotal that they have changed the landscape of cancer therapy. Perhaps the most striking example is the phase I trial of imatinib mesylate for the treatment of chronic myelogenous leukemia, which yielded a 93% response rate. For most phase I studies, the response rate is considerably lower, but the benefit-versus-risk ratio is, nevertheless, favorable. ●

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¹Horstmann E, McCabe MS, Grochow L, et al. Risks and benefits of phase I oncology trials, 1991 through 2002. N Engl J Med 2005;352:895-904.

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