

UConn Cancer

Dialogue

REMARKABLE CARE THROUGH RESEARCH AND EDUCATION



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A Message from Carolyn D. Runowicz, MD

Director, UConn Cancer Center;
2nd Vice President,
American Cancer Society



Dear Colleagues:

I am delighted to be authoring this article for the *Dialogue*. As the new director of the UConn Cancer Center, this is my

first opportunity to write about the vision that brought me to UConn, and communicate to you the goals that I seek for the Cancer Center.

Let me start where I will also end this article. I am dedicated to the vision that, over time, the Cancer Center will achieve NCI-designated status as a comprehensive cancer center. The Health Center's strength in basic and translational research, coupled with a very strong cancer-related curriculum, position us well for this goal. Every strategic decision that I will make will be framed in the context of whether it will take us a step closer to this important goal. While the funding obtained through achieving NCI status is clearly important, the imprimatur of the NCI in recognition of the excellence in patient care, research and education is the ultimate accomplishment. When achieved, members of the oncology community in the Health Center and partners in the State will look back with pride at a job well done. We then begin the challenging but critically important job of maintaining the designation, by continuing to deliver state-of-the-art treatment to our patients and through partnership with the basic scientists, whose research is translated into innovative treatments.

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A Message from Carolyn Runowicz, MD

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There are obviously many practical as well as strategic issues that need to be addressed in the coming months. Key among them is expanding the current collaborations between the community oncologists and the Cancer Center. There are exciting national models to guide us in building these bridges to the community. I look forward to developing mutually advantageous relationships with colleagues in the cancer community throughout Connecticut.

I am very pleased to bring my background and experience in oncology to the new Cancer Center. As many of you know, I have a deep and long-standing commitment to patient care, and translational research. I am an ardent advocate for bringing “bench to the bedside,” so that our patients receive innovative cancer therapies. However, I would be remiss in not acknowledging the clinical and translational research already in existence at the Cancer Center. The Clinical Research Program has several vaccine trials looking at vaccine therapy in melanoma, ovarian cancer, leukemia and renal cell cancer. My passion for cancer prevention will continue at the Cancer Center. There are already strong programs through the NIH cooperative groups, including the SELECT trial and the STAR trial. Many programs have already been developed in oral cancer, dermatology, bone and gastrointestinal cancers that will provide the backbone of our application for NCI comprehensive cancer center status.

In addition to developing a strong clinical and basic science center, it is important that we involve our community in the cancer efforts outside of the state of Connecticut. In my roles at the NCI and with the American Cancer Society, I will lead this effort. My current position as 2nd Vice President of the American Cancer Society will allow me to contribute to a national cancer agenda. As I ascend to President of the ACS over the next three years, I hope to integrate key members of our Cancer Center in this process.

Clearly, I will need and count on your support. I am sufficiently realistic to know that achieving major advances in any worthwhile endeavor cannot be accomplished single handedly. In addition, I know that change can be threatening to some stakeholders and challenging to everyone. Please know that I will do everything I can to build effective working relationships that will serve the collective good, with the cancer patient at the center of the model.

Thank you for this opportunity to be appointed as the newest member of the proud team at the Cancer Center. As I indicated at the beginning of this article, decisions of which I’ll be a part will be directed toward achieving the goal of NCI-designated comprehensive cancer center status. To that end, today’s successes will serve tomorrow’s legacy well. ■

The Multidisciplinary Program for the Treatment of Colorectal Cancer at UConn Health Center

By **Susan Tannenbaum, MD, Victor Moyo, MD, Wayne Frederick, MD, Robert Dowsett, MD, and Philip Jaffe, MD**

This summer brought many changes to the UConn Cancer Center including more resources for prevention, diagnosis and treatment of cancer. We are in the process of developing a multidisciplinary team for the management of gastrointestinal malignancies. These will include cancer of the esophagus, stomach, pancreas, liver, biliary tract, colon and rectum.

In order to begin the process, we have chosen to develop our multidisciplinary program in the management of colorectal cancers. This was the fourth most frequently diagnosed cancer in the United States in 2002, and ranks only second to lung cancer in the number of yearly deaths.

Colorectal cancer prognosis and treatment depends in large part on the extent of the cancer at the time of presentation. Stage I disease is the earliest stage and carries a 90 percent chance of survival to five years while stage IV disease includes patients with metastatic or distant disease and carries an 8 percent five year survival. Clearly, early diagnosis as well as prevention is critical in saving lives related to this cancer. To this end, the gastrointestinal service at the Health Center has a focus on both basic research and clinical diagnosis of patients with these cancers. We are looking at novel ways to predict the formation of dangerous polyps and the prevention of this formation both at the molecular level as well as in animal models.

Once the cancer is diagnosed, it is imperative that a multidisciplinary approach is taken. The team is often composed of the three clinical management services involved in the decision making for the patient. These include the surgical oncologist, radiation oncologist and medical oncologist. These clinicians are dependent on the input of the gastroenterology service



for diagnosis of the disease and definition of the disease in terms of location. In rectal cancers, endoscopic ultrasound is performed on all patients. A small sound wave probe is placed into the rectum to accurately determine the extent of penetration of the tumor through the rectal wall and the involvement of lymph nodes. Radiologists and pathologists are essential to the formulation of tumor characteristics of prognostic importance as well as accurately defining the disease and stage of the patient.

All these features are critical and need to be discussed prior to the institution of any treatment. All cancer must be removed to enhance patient cure. In the instance of local disease, often the surgeon can remove it effectively, particularly with the use of new specialized techniques such as mesorectal excision, performed only at some centers like ours. As the disease progresses, we are more dependent on additional or adjunctive measures to cure the disease including radiation

and chemotherapy. At the Cancer Center, we have formed a multidisciplinary clinic so all patients can be seen by surgical, radiation and medical oncologists for optimal treatment decisions. The newer surgical techniques, combined with state-of-the-art radiation and chemotherapy modalities, can then be discussed with the patient and result in the best outcomes.

For more information and scheduling appointments, please contact the Cancer Center at (860) 679-2100. ■

Photo: The multidisciplinary team for colorectal cancer. Back row (standing from left): Philip Jaffe, MD, Gastroenterologist; Wayne Frederick, MD, Surgical Oncologist; Dana Ayer, APRN. Front row (seated from left): Susan Tannenbaum, MD, Medical Oncologist; Victor Moyo, MD, Medical Oncologist; Robert Dowsett, MD, Radiation Oncologist and Division Chief, Radiation Oncology.

Lipids and Cancer: The Good and the Bad

By **Timothy Hla, Ph.D.**, Professor of Cell Biology;
Director, Center for Vascular Biology

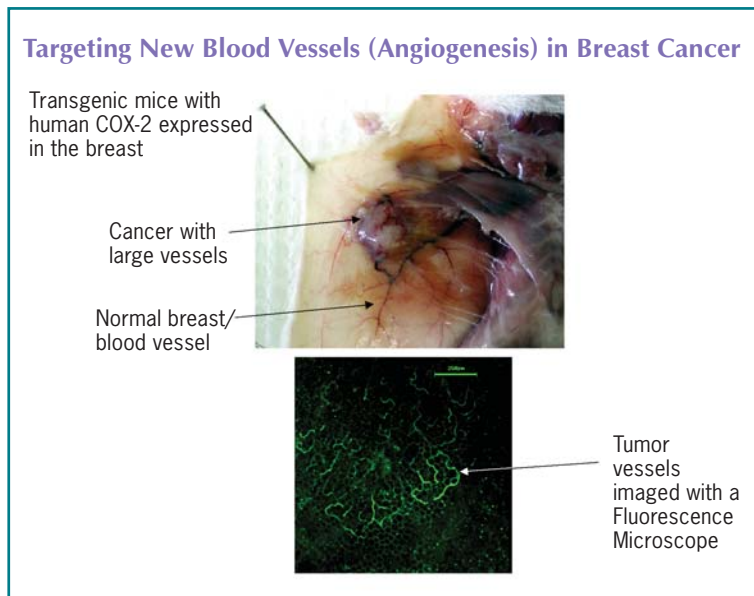


Figure 1. Tumor angiogenesis in the breast tissue of COX-2 transgenic mice.

Most of us are aware that excess intake of dietary fats (lipids) leads to heart disease. It is true that excessive intake of certain foods rich in animal fats and trans-saturated fatty acids is not conducive to cardiovascular health. However, a less understood aspect is the connection between dietary fats and cancer.

Lipids are important essential components of all cells. We know that lipids are high in calories, and therefore, animals and humans store them for use when food intake is limited. From biology classes, we may even remember that all cells are covered by membranes made of lipids. But that's not all; as animals evolved, new functions of lipids were incorporated as important processes in animal physiology. For example, lipids in cell membranes served as reservoirs of potent "lipid mediators." These are molecules that cells secrete to communicate with other cells, either in close proximity or at distant sites. Lipid mediators bind to specific molecules called "receptors" to relay their signals to the recipient cells. Some receptors are found on cell membranes, but others are found inside the cells, such as in the cytoplasm or the nucleus¹.

My laboratory is interested in angiogenesis, a process by which new blood vessels grow in tissues. Tumors need excessive angiogenesis to grow and spread (metastasis), and blocking angiogenesis is expected to inhibit tumor growth. Therefore, we have been looking for new molecules that influence angiogenesis. From our studies conducted in the late 1980s, we discovered two families of lipid mediators as modulators of blood vessel growth.

The first is the prostaglandin family, potent, ubiquitous and short-lived molecules that induce tumor cell proliferation, metastasis and angiogenesis. We found that an enzyme called cyclooxygenase (COX)-2 is over-expressed in many tumor cells and produces high levels of prostaglandins². We also found that a particular lipid, called prostaglandin E₂ is likely to be the culprit. Most importantly, we showed that if COX-2 is over-expressed in specific tissues, for example the breast tissue of transgenic mice, such mice develop breast cancer³. It turns out that this prostaglandin acts on specific membrane receptors called EP₂ and EP₄ receptors to induce a

growth factor specific for endothelial cells, called vascular endothelial growth factor (VEGF). This causes tumor vessels to become leaky and proliferate abnormally, contributing to tumor growth and spread. Since COX-2 can be effectively inhibited by drugs called the "Coxibs" (for example, CelebrexTM and VioxxTM), this work has led to new thinking about breast cancer prevention and treatment strategies. Moreover, this mechanism is not specific to breast cancer; COX-2 involvement has been shown in many human cancers, including colon, lung, liver, ovary, bladder, among others.

The second family of lipid mediators that we study is called sphingolipids¹. These are some of the least understood lipids, and they were named after the mythical Egyptian creature, the Sphinx, to reflect their enigmatic nature. We found that a specific sphingolipid, called sphingosine 1-phosphate (S1P), profoundly regulates blood vessels, again, acting as a messenger that activates specific receptors⁴. S1P treatment blocks blood vessel permeability (or leakage) and matures the new blood vessels into bigger arteries and veins. Thus, early in tumor growth, S1P may inhibit the VEGF action and may inhibit angiogenesis⁵. However, later in tumor spread and growth, it may be required to sustain blood vessel maturation, which is needed for efficient tumor growth. There are no drugs available to block or stimulate the S1P system, however, basic research in this area is prompting many companies to develop new drugs to harness this enigmatic lipid system in our favor to control tumor angiogenesis.

Recent research like these studies have illustrated the double-edged nature of lipids and cancer. Although they are needed for normal blood vessel function (the good), when cancer develops, some mediators play crucial roles in sustaining and making tumors deadly (the bad). Only by better knowledge of how these lipids function, can we design intelligent tools to control cancer.

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New 'State-of-the-Art' Breast Reconstruction Helps Maintain An Active Lifestyle

By **Rajiv Chandawarkar, MD**
Assistant Professor, Division of Plastic Surgery

Introduction: Muscle-Sparing Breast Reconstruction

Reconstructive breast surgery restores surgically removed breast tissue with tissue that closely resembles the anatomic form and physical characteristics of a normal breast. It is well-accepted that autologous tissue breast reconstruction (using one's own tissue) is an excellent and reliable method to reconstruct the breast after mastectomy. It surpasses implants in terms of durability, shape, form and long-term complication rates.

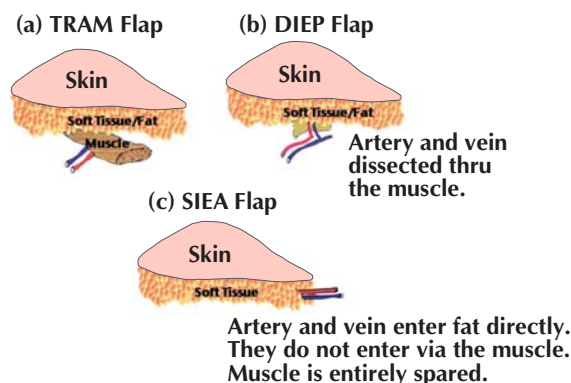
Customarily, breast reconstruction procedures transfer skin, fat and muscle. The recovery time is longer, and physically some limitations arise because the abdominal rectus muscle is disrupted. For example, the traditional TRAM flap, cuts into the abdominal muscle (Figure 1a), disrupting the counterbalance that is vital for maintaining certain activities.

We now offer two new breast reconstruction procedures at the Cancer Center—the superficial inferior epigastric artery (**SIEA**) flap, and the deep inferior epigastric perforator (**DIEP**) flap.

Both of these flaps use a woman's lower abdominal skin and tissue without sacrificing muscle, allowing patients faster recovery and the ability to maintain active lifestyles. Briefly, skin and fat are transferred from the abdomen to the newly reconstructed breast, with the blood supply coming from feeder blood vessels. Using this technique, the abdominal muscle is not needed and is left intact. Ideal for physically active women who want to preserve their athletic lifestyle, these procedures provide the best alternatives^{1 2 3}.

Both are performed using microsurgery. This significantly improves aesthetics of the reconstructed breast

Figure 1: Comparison of amount and type of tissue sacrificed



by reducing complications such as fat necrosis.

However, microvascular autologous reconstruction is surgically more complex and requires special training to be performed satisfactorily.

Historical background: The DIEP and SIEA flaps are well-established and time-tested.

First performed in 1989, the DIEP and SIEA flaps have become steadily more popular in the United States. The short and long-term results of the procedure are excellent. Patients have a relatively short hospital stay of four to five days and can return to normal daily activities in about two to three weeks, while being able to resume exercise and lifting in 6 weeks.

Insurance Coverage

All breast reconstruction and breast symmetry procedures, including the SIEA and DIEP flaps, are covered by insurance, as legislated in 1998.

Advantages

Advances in microsurgery have brought breast restoration to a new era. It enables us to restore a woman's breast through a much less invasive surgical procedure, resulting in a natural, soft breast with the

potential for return of sensation. After the recovery period, women can remain physically active; this state-of-the-art technique allows them to feel good about themselves despite the traumatic experience of the disfigurement caused by mastectomy. We counsel women on all the options available to them if a mastectomy is needed, and emphasize less invasive more natural breast restoration options.

DIEP Flaps

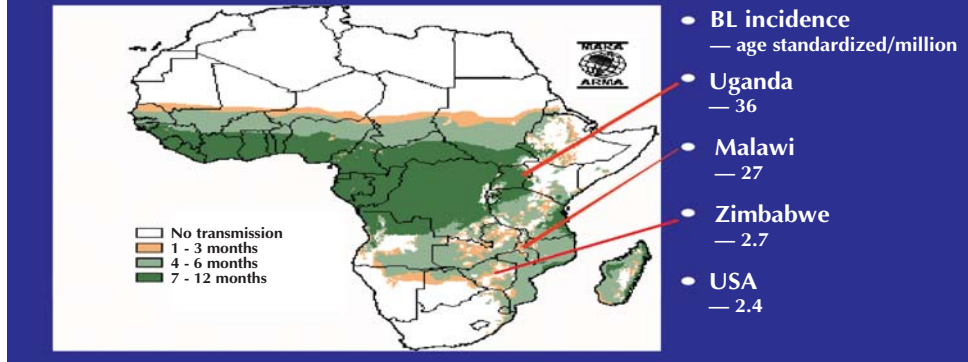
The DIEP flap breast reconstruction uses the abdominal and subcutaneous fat by cutting through, but not sacrificing the abdominal muscle, namely the rectus abdominis muscle. The blood supply to the skin is from perforating blood vessels from the deep inferior epigastric artery (DIEP). The flap is transferred to the chest for breast reconstruction by attaching the blood vessels to the blood vessels in the chest (internal mammary) or in the axilla (thoracodorsal). A schematic of the cross section of a DIEP flap is presented in Figure 1b. Notice the absence of the rectus muscle and fascia. The procedure is technically more complex and is performed in centers that routinely perform microsurgery.

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Burkitt Lymphoma and Malaria: Revisiting an Old Story

By **Victor Moyo, MD**,
Assistant Professor of Medicine

Figure 1. BL with Malaria transmission



Burkitt Lymphoma (BL) is a rapidly proliferating non Hodgkin's B cell lymphoma with predilection for the jaw and abdomen. This was first described by Dennis Burkitt in young African children¹. The malignancy has a worldwide distribution and it is sub-classified into (i) the endemic form, (ii) an immunodeficiency associated form, and (iii) the sporadic form².

The endemic form is the primary focus of this article and three characteristic features will be described. These are (i) its geographic restriction to areas endemic for malaria, (ii) association with the Epstein Barr Virus (EBV) and (iii) translocations involving the MYC gene. In this article, I will attempt to generate a hypothesis based on these observations.

Geographic distribution of BL

BL in Africa appears to be confined to areas that are holoendemic for malaria. The incidence appears to parallel decreasing malaria transmission rates (Figure 1). Uganda is holoendemic for malaria and has the highest recorded incidence for BL whereas Zimbabwe, a country where malaria transmission rates are much lower, has an incidence of BL similar to that noted in the United States. Within each of these countries

such as Kenya, there may also be variation that reflects malaria transmission rates within the population that demonstrate this phenomenon.

BL and EBV

In endemic areas where children are invariably infected with EBV by the first year of life², the EBV genome is present in the majority of neoplastic BL cells³. EBV lies dormant as an episome in the nuclei of an infected B-cell expressing a limited genetic profile i.e. EBNA1 Epstein Barr Nuclear Antigen 1 as well as EBER (EBV encoded RNA). EBER functions include IL-10 production, B-cell proliferation and suppression of cytotoxic T-cell activity while counteracting some pro-apoptotic features of unmutated MYC. EBNA is associated with immune evasion⁴.

Translocations involving the MYC gene

The most common translocation is the [t(8;14)] resulting from translocation of chromosome 8q24 the MYC gene to the 14q32 locus of immunoglobulin heavy chain. The process appears to be an aberration of the physiological process of hypermutation seen in normal B-cell development and is termed somatic hypermutation₄. This

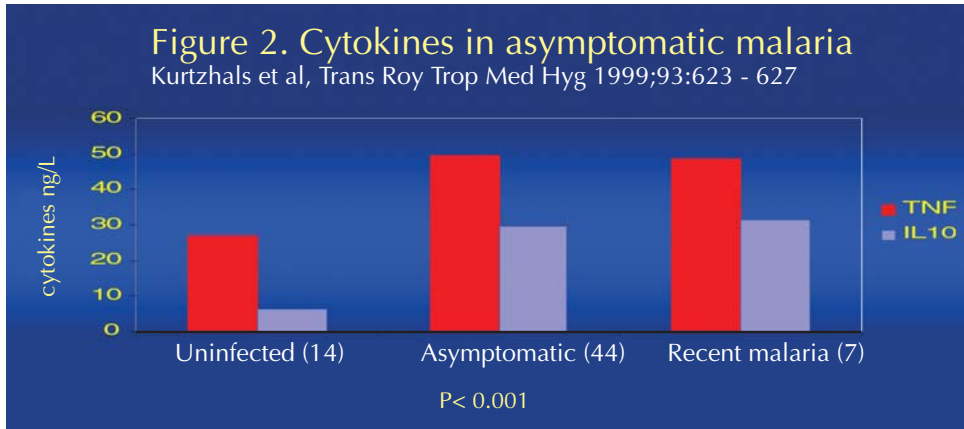
apparent deregulation of MYC has effects on proliferation and apoptosis that favor tumor growth.

Cytokine deregulation and malaria

In holoendemic areas, virtually all children may have asymptomatic parasitemia from malaria. These children have higher levels of Interleukin-10 (IL-10) and tumor necrosis factor alpha (TNF- α) compared to uninfected individuals (Figure 2). Both TNF- α and IL-10 have been implicated in lymphomagenesis. Paradoxically, higher levels of IL-10 seem to be protective from severe forms of malaria such as anemia. Severe malaria kills at least 2000 children a day in Africa alone!

Hypothesis

What, if anything, does BL have to do with malaria? The hypothesis is that there is positive selection for EBV infected clones of B-cells and clones of B-cells that may possess the MYC translocation in part because they confer some survival advantage to individuals living in areas that are endemic for malaria. Unfortunately, in a few individuals, this protective advantage lead to lymphomagenesis by chance. This is summarized in the model (Figure 3). EBV infection occurs

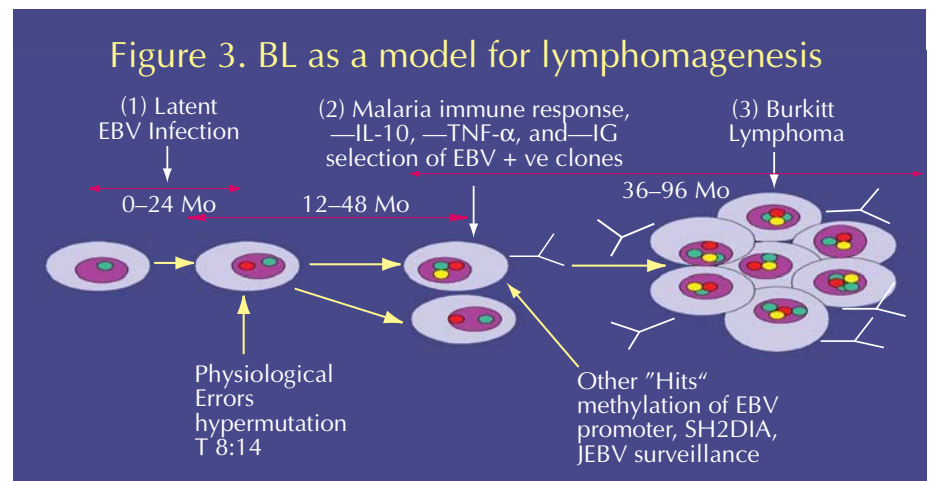


early on followed by the process of somatic hypermutation as B-cells mature in germinal centers of lymphoid follicles. These and other mutations may be selected on the basis of some functional advantage against severe malaria in that setting, which is crucial to survival against malaria.

The technological tools and expertise exist at the Health Center to elucidate this hypothesis further and show how the deadly infection of malaria possibly contributes to development of this malignancy. A better understanding of this process could lead to better therapeutic strategies for the treatment and prevention of this malignancy and possibly even malaria. ■

References

1. Burkitt DP (1958) A sarcoma involving the jaws in African children. *Brit J Surg.* 46:218-223.
2. de The G (1977) Is Burkitt's lymphoma related to perinatal infection by Epstein-Barr virus? *Lancet.* 1(8007):335-338.
3. Hecht JL, Aster JC (2000) Molecular biology of Burkitt's lymphoma. *J Clin Oncol.* 18(21):3707-3721.
4. Kuppers R (2003) B cells under influence: transformation of B cells by Epstein-Barr virus. *Nat Rev Immunol.* 3(10):801-812.



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References

1. Hla T, Lee MJ, Ancellin N, Paik J H, Kluk MJ (2001) Lysophospholipids—receptor revelations. *Science* 294, 1875-1878.
2. Sano H, Kawahito Y, Wilder RL, Hashiramoto A, Mukai S, Asai K, Kimura S, Kato H, Kondo M and Hla T (1995) Expression of cyclooxygenase-1 and -2 in colorectal cancer. *Cancer Res* 55, 3785-3789.
3. Liu CH, Chang Sung-Hee, Trifan OC, Narko K, Smith E, Haudenschild C, Lane TF and Hla T (2001) Over-expression of cyclooxygenase (Cox)-2 gene is sufficient to induce tumorigenesis in transgenic mice. *J Biol Chem* 276, 18563-18569.
4. Lee M, Thangada S, Claffey KP, Ancellin N, Liu CH, Kluk M, Volpi M, Sha'afi RI and Hla T (1999) Vascular endothelial cell adherens junction assembly and morphogenesis induced by sphingosine-1-phosphate. *Cell* 99 (3), 301-312.
5. Sanchez T, Estrada-Hernandez T, Paik JH, Wu M, Venkataraman K, Brinkmann V, Claffey K, Hla T (2003) Phosphorylation and action of the immunomodulator FTY720 inhibits VEGF-induced vascular permeability. *J Biol Chem* 2003 Sept 3 [epub ahead of print] IN PRESS.

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SIEA Flaps

As seen in the Figure 1c, the SIEA flap uses the abdominal skin and soft

tissue but completely spares any incisions whatsoever into the rectus sheath and muscle. The flap circulation comes from the superficial inferior epigastric artery and vein (SIEA)—a robust vascular system that only traverses subcutaneous fat of the lower abdominal skin⁴. In addition there is a potential of restoring touch and pressure sensation to the reconstructed breast.

In 40 percent of these women, the arteries are large enough to be amenable to this procedure. Not all patients have adequate size of superficial system vessels, and are therefore not candidates for this procedure. At the Health Center, we have evolved a technique wherein we test the size of these vessels beforehand to help guide the selection process. For women who do not have a large size vessel, we offer the DIEP flap as described above.

Patient Selection: Customized Approach

The unique circumstances of each specific patient define the choice of breast reconstruction⁵. No single technique is applicable to all patients. Consultation with a microsurgeon is required to determine if a patient is a

candidate for autologous reconstruction with a TRAM, DIEP or SIEA flap. Although technically more complex, the potential benefits of DIEP and SIEA flaps are significant, and morbidity is significantly lower.

For more information and to schedule an appointment, please contact the Cancer Center at (860) 679-2100. ■

References

1. Grotting JC, Beckenstein MS, Arkoulakis NS. The art and science of autologous breast reconstruction. *Breast J*. 2003; 9(5):350-60.
2. Allen R, Guarda H, Wall F, Dupin C, Glass C. Free flap breast reconstruction: the LSU experience (1984-1996). *J La State Med Soc*. 1997;149(10):388-92.
3. Craigie JE, Allen RJ, DellaCroce FJ, Sullivan SK. Autogenous breast reconstruction with the deep inferior epigastric perforator flap. *Clin Plast Surg*. 2003; 30(3):359-69. Review.
4. Arnez ZM, Khan U, Pogorelec D, Planinsek F. Breast reconstruction using the free superficial inferior epigastric artery (SIEA) flap. *Br J Plast Surg*. 1999; 52(4):276-9.
5. Arnez ZM, Khan U, Pogorelec D, Planinsek F. Rational selection of flaps from the abdomen in breast reconstruction to reduce donor site morbidity. *Br J Plast Surg*. 1999; 52(5):351-4.



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