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A Message From PharmaNet

PharmaNet has been conducting clinical studies for oncology products since 1996. In the past five years alone, innovative pharmaceutical, biotechnology, generic drug and medical device companies have entrusted us with 200 local, regional and global oncology clinical trials. Most recently, PharmaNet entered into a collaboration with the Cancer Immunotherapy Trials Network (CITN), a premier group of clinical investigators, institutions and thought leaders in the area of cancer immunotherapies and vaccines. This collaboration will help identify trials with immunotherapy agents prioritized by the CITN as having high potential as cancer therapeutics.

This breadth of involvement provides PharmaNet a distinct perspective on a variety of developments in the field of oncology. In this issue of FOCUS, we introduce you to some of the companies and individuals who are making a difference in oncology today.


- **Eutropics Pharmaceuticals**: A new biomarker/companion diagnostic aims to help bring to the market a novel targeted therapy for treating multiple myeloma and other cancers.

- **Principal Investigator – South Africa**: Conducting clinical trials is just one way Daniel A. Vorobiof, MD, director of Sandton Oncology Centre in Johannesburg is bringing advances in cancer care to sub-Saharan Africa.

- **Principal Investigator – Taiwan**: A look inside hepatocellular carcinoma clinical trials with Shi-Ming Lin, MD, of Chang-Gung Memorial Hospital and University.

- **Lymphedema Rehabilitation and Prevention**: University of Pennsylvania/Abramson Cancer Center’s Dr. Kathryn Schmitz revolutionizes treatment and prevention of lymphedema in breast cancer survivors.

We thank our contributors for their participation in this issue of FOCUS.
In 2011, after successful completion of Phase II trials for head and neck cancer, CEL-SCI Corporation – a biotech company founded in 1983 and based in Vienna, Va. – is now moving its drug Multikine® forward into Phase III trials in nine countries on three continents. CEL-SCI, whose interest in Multikine traces to research done in the late 1970s, knows only too well that the lengthy process of drug development is as much about tribulations as it is about trials. CEL-SCI overcame matters of funding and the fickleness of financial markets, manufacturing and the selection of targets. But perhaps all that CEL-SCI has endured is testimony to how forward-looking company founder and President Maximilian de Clara’s vision really was – that the human immune system was the key to treating and fighting cancer – and that it was something worth the perseverance.
Multikine (Leukocyte Interleukin, Injection) is a complex biological product that contains a mixture of naturally derived and naturally occurring human cytokines with immunomodulatory activity. Multikine belongs to a new drug class called combination immunotherapy, because it has both active and passive immune activity; it both attacks the tumor and, at the same time, stimulates immune antitumor responses in the cancer patient. The broad-spectrum therapy cytokine mixture includes interleukins, interferons, chemokines, and colony stimulating factors, all of which augment the body's healthy immune response.

Initial research was followed by clinical trials, the first of which were conducted in the early and mid-1980s in England by Dr. Dudley Dumonde – who coined the term cytokine. The early trials involved patients with a variety of cancers: malignant melanoma, breast cancer, colon cancer, and other solid tumor types. The trials demonstrated safety and showed signs of potential efficacy. However, it took time – and money – before CEL-SCI could refine its approach, both in how and when Multikine is administered to patients, and what cancer indication to target.

“You must remember that we only learned in the late 1970s that leukocytes contained T-cells and B-cells,” said Dr. Eyal Talor, chief scientific officer of CEL-SCI. “Dr. Dumonde and his colleagues were very much pioneers.” Dr. Talor also pointed out that the cell culture manufacturing technology – not a recombinant process – necessary to manufacture Multikine as a biological drug product on a scale sufficient to supply widespread studies only became available in the mid-1990s when CEL-SCI first built a pilot-scale plant.

An Unmet Need
Selecting the best indication to pursue for development was critical for CEL-SCI’s progress. Head and neck cancer possesses several characteristics that made it an excellent candidate for a Multikine trial. The main subtype within head and neck cancer is squamous cell carcinoma. The current, universal standard of care (SOC) for oral squamous cell carcinoma, recommended in the National Comprehensive Cancer Network (NCCN) guidelines for treatment, calls for initial surgical treatment followed by, depending on degree of tumor tissue remaining, either radiotherapy or chemoradiotherapy. The current SOC (also adopted by the NCCN guidelines for head and neck cancer) was established from studies conducted and published in 2004 (New England Journal of Medicine) by the Radiation Therapy Oncology Group (RTOG) and the European Organisation for Research and Treatment of Cancer (EORTC).

Each year there are an estimated 600,000 new cases of head and neck cancer worldwide, approximately 150,000 – along with 50,000 deaths – in the United States and European Union. As many as 66 percent to 80 percent of head and neck cancer patients present on first visit with (locally – not metastatic) advanced disease and no prior treatment. The five-year survival rate is between 30 percent and 40 percent, a rate that has not materially improved over the last several decades, according to Dr. Talor.

“Within 18 to 24 months of treatment, approximately 50 percent of cases recur – and we don’t know which 50 percent that is going to be,” said Dr. Talor. “And those with recurrence die within a year or two no matter what aggressive treatment they receive. No new treatments that significantly improve overall survival have been developed in more than 40 to 50 years for newly diagnosed – yet untreated - head and neck cancer patients. There clearly is an ‘unmet need’ here for a new therapy of head and neck cancers.”

CEL-SCI has received orphan drug designation from the U.S. Food and Drug Administration (FDA), which imparts significant benefits to the company, including seven years marketing exclusivity from the date of approval or licensing; potentially expedited or accelerated approval; possible grants up to $350,000 per year for three years; and significant tax incentives for the product’s development.

Multikine Treatment for Head and Neck Cancer
CEL-SCI has focused its present development efforts for Multikine on previously untreated patients with advanced primary squamous cell carcinoma of the head and neck. Cancers of the oral cavity (lip, tongue,
cheek, and floor of mouth), in particular, represent 65 percent of all such cancers.

A critical aspect of Multikine therapy is that it is a first-line treatment. In the CEL-SCI trial protocol, patients receive Multikine before any other treatment, even before the standard of care surgery or radiation or chemotherapy. The theory is to stimulate the immune system and attack cancer before the immune system is weakened or disabled by other treatment and before the “highways” of the immune system, the lymphatics, are destroyed (or removed) by surgery.

The potential validity of this strategy is suggested by results of the Multikine Phase II study. There was complete tumor destruction in 12 percent of the patients after only three weeks of dosing five times per week. There was also a 33 percent increase in 3.5-year overall survival after treatment with Multikine followed by standard of care procedures compared with after treatment with standard of care only.

**Multikine Mechanism of Action**

Multikine is injected percutaneously with one-half the dose delivered peritumorally – around the tumor – and the other half dose perilymphatically – in the region of the local/regional draining lymph nodes. The Multikine mode of effect results from the cascade of events induced by the combined activity of the different cytokines present in the unique and proprietary composition of Multikine. It contains, among other components, three major “families” of bioactive molecules:

1. Tumoricidal/tumoristatic cytokines that kill tumor cells, inhibit tumor growth, and block initiation and promotion of tumorigenesis

2. Chemotactic cytokines and chemokines that direct/attract killer and other cells to targets

3. Lymphoproliferative and pro-inflammatory cytokines that recruit and expand tumor-specific immune cells to destroy identifiable tumor targets

The mechanism of action of the local/regional injection of Multikine mixed interleukins overcomes local immune suppression induced by the tumor, breaks tumor tolerance to tumor antigens, changes tumor cellular immune infiltrate (from a preponderance of ineffective CD8 T cells to CD4 T cells) and affects the tumor microenvironment allowing for an effective and sustainable local antitumor immune response. The mechanism by which Multikine (LI) causes immune augmentation is schematically reproduced in Figure 1.
The National Institutes of Health was very interested in this Phase III trial and we have a material transfer agreement with them to provide tumor microenvironment genetic information from materials obtained from the Phase III study patients. Together we can determine which type of genes are being activated in patients treated with Multikine and what mRNA is present, a second-tier step that allows proteins to be made.

Without Multikine, CD8+ T-cells and NK cells are “blocked” by the tumor. Therefore they are unable to kill the tumor.

The Phase III Study

CEL-SCI started the Phase III trial with the objective of enrolling 880 patients in North America, Europe, the Middle and Far East, and Asia, making it the largest ever study in head and neck cancer.

Study Summary: A pivotal Phase III, open-label, randomized, controlled, multi-center global study of the effects of Multikine plus standard of care (Surgery + Radiotherapy or Surgery + Concurrent Chemoradiotherapy) in subjects with advanced primary squamous cell carcinoma of the oral cavity versus standard of care only.

Objectives: The primary objective is to determine the efficacy of peritumoral and perilymphatic injection of Multikine given prior to standard of care as measured by overall survival. The secondary objectives are to evaluate the effects of Multikine treatment on the cumulative incidence of local-regional control, progression-free survival, tumor response, tumor histopathology, and quality of life, while confirming Multikine safety.

Desired Outcome: To show a 10 percent overall survival advantage to Multikine plus SOC treatment, over that which can be achieved with SOC alone.
Using mRNA as a marker for gene activation, we know that not just the gene is going to be activated but that the product — the protein (in this case, cytokines) is going to be made. That knowledge will allow us to determine what proteins are needed to activate a cytokine cascade required to reject a tumor. Of note is the fact that many of the same cytokines which we know are needed for tumor rejection are already present in the Multikine preparation,” said Dr. Talor.

With Multikine administration, tumor-specific activated CD4+ helper T cells “rescue” and activate tumor residing NK cells, which then kill the tumor.

Multikine Phase III schematic:
Randomization and Treatment of Enrolled Patients

- **Group 1**: Multikine 5X/week X 3 weeks + CI\(\text{Z}^*\)
- **Group 2**: Multikine 5X/week X 3 weeks (No CI\(\text{Z}\))
- **Group 3**: Standard of Care

- RT\(x\)**: Radiotherapy (60-70 Gy, 30-35 fractions over 6-7 Weeks)
  OR

- CRT\(x\)**: Concurrent radiochemotherapy (60 – 70) Gy, 30-35 fractions, over 6-7 weeks + IV cisplatin (Dose 100 mg/m²)
  1X per week on first day of weeks 1, 4, 7 of RT\(x\)

- **\(\text{CI}\text{Z}^*\)**: Cyclophosphamide 300 mg/m² (x1.IV, day -3); Indomethacin 25mg tid, po (day 1 to 24 hrs prior to surgery) + 15-45mg Zinc (as Multivitamin) i.d., p.o.

- **Surgery**: complete surgical resection of primary tumor and any positive lymph nodes.

- **Higher Risk** patients are defined as those with: positive surgical margins, 2 or more clinically positive nodes, or extra capsular nodal spread (any or all of the above).
**Multikine Manufacturing**

Before the FDA would approve CEL-SCI’s plan for Phase III trials, they required CEL-SCI to demonstrate that it could manufacture sufficient quantities of Multikine to supply both the trials as well as patients should Multikine receive approval to market. Although CEL-SCI’s pilot-scale plant was adequate for smaller-scale trials, it would not suffice for later-stage trials or commercial-scale manufacturing. (Outside contract manufacturing capabilities with appropriate technology were not available and the method of Multikine manufacture is a trade secret.)

CEL-SCI’s new $25 million Good Manufacturing Practice (GMP) plant outside of Baltimore, which successfully produced and filled its first lot of Multikine in August 2010, has an annual capacity to make 20,000 treatments of Multikine and can be expanded to 60,000 treatments per year. The plant was designed to fill biologics in true cold conditions of 4 degrees Celsius, which averts any loss of biological activity.

In December 2010, CEL-SCI announced that a European Union Qualified Person (QP) had completed an audit of its Multikine manufacturing plant and laboratories and found them to be in a high level of compliance with the GMP Directives of the International Conference on Harmonization (ICH). The QP’s finding clears the way for CEL-SCI to export Multikine to the European Union (EU) for use in the Phase III clinical trial.

To ensure the product’s safety for Phase III studies, the EU – unlike other countries in CEL-SCI’s Phase III trial – requires that a non-EU drug developer have a QP release every lot or batch of medicinal product intended for use in a clinical trial being conducted within its member states. Each QP must be certified individually by the EU regulatory body to become a QP and needs to have extensive training and an in-depth critical understanding of all the aspects associated with manufacturing and distribution of drug products. The audit report also commended the CEL-SCI facilities and the Multikine product for being in compliance with the requirement of GMP for the safety, quality and efficacy of the product.

**CEL-SCI – the Next Step**

In the world of biotech startups, it is not uncommon that both the company and its investigational new drug fail to survive clinical trials. CEL-SCI has demonstrated extraordinary persistence and commitment to the concept behind Multikine to reach the Phase III trials. “With facilities in place, and strong Phase III partners, we are positioned to take Multikine through this pivotal trial,” said CEL-SCI CEO Geert R. Kersten. “What has kept us going through to this stage was a deep-seated belief that the immune system has to be the key to defeating cancer, and you have to administer an immune system drug before any other therapy. And that treatment for the disease has to be something very complex that approximates nature.”

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The use of predictive and prognostic biomarkers paired with targeted cancer therapies is believed by many to hold the key to reducing drug development time, improving drug efficacy and guiding clinical decision making. Eutropics Pharmaceuticals is using a new biomarker/companion diagnostic to help bring a novel targeted therapy to the market. The biomarker provides a unique understanding of cancer cells that is important in the pre-clinical development and will be important in the later stages of development of our therapeutic. The biomarker is also being tested as a predictive diagnostic assay for therapies currently in use to treat multiple myeloma.
Though there are clearly outstanding new treatments for cancer, it remains that chemotherapy is in general inefficient and limited in effectiveness, frequently showing low response rates. Many believe that a key reason for the generally poor performance of chemotherapy is that often the treatment is not closely matched to the individual patient being treated. There is growing acceptance that a personalized medicine approach that couples precise diagnostics with therapeutics, especially targeted therapeutics, will alleviate this problem.

In March of 2004 the U.S. Food and Drug Administration (FDA) issued a Critical Path Initiative that identified the use of companion diagnostics as important for improved success of drug development. The goal was to encourage the discovery and development of tools that would help deliver safer and more effective therapies for treating cancer. Since then many of the major pharmaceutical companies have embraced the idea and are developing companion diagnostic tests both for experimental and approved targeted therapies. Some well-documented cases demonstrate the promise in this approach, for example, the HercepTest™ (Dako) guiding trastuzumab (Genentech’s Herceptin®) use, KRAS test guiding anti-EGFR monoclonal antibody drugs panitumumab (Amgen’s Vectibix®) and cetuximab (ImClone’s Erbitux®), and EGFR mutation tests (Genzyme, QIAGEN) guiding use of EGFR inhibitors erlotinib (OSI Pharmaceutical’s Tarceva®) and gefitinib (AstraZeneca’s Iressa®). These tests have proven to be predictive of patient response and are contributing to improved benefit of these treatments. Some of the drugs mentioned would have limited use, or none at all, if not for the rescue by the companion test.

**New Class of Therapeutic That Targets the Mitochondria**

Our approach to treating and predicting response to cancer treatment is based on detecting and controlling a particular mitochondrial function. Why the mitochondria? In addition to being the energy-producing center of the cell, the mitochondrion is the key node in the proogramed cell death (apoptosis) signaling pathway. It is generally accepted that cancer cells survive because they elude the instruction to undergo apoptosis. It is also widely believed that most cancer therapies are effective because they elicit apoptosis through the mitochondrial signaling pathway (Figure 1).

**Co-development of Therapeutic and Companion Diagnostic**

Eutropics was founded with the purpose of co-developing a novel targeted therapy/companion test for treating multiple myeloma and other cancers. Our approach relies on a novel technology that provides a biomarker that shows when our lead candidate compounds are working precisely on target.
Extensive research carried out over the last twenty years has described the events that occur at the mitochondrial surface as key determinants of apoptosis. These events are known to occur differently in cancer cells versus normal healthy cells, and this difference is thought to determine if cancer cells will respond or not respond to therapy. Our strategy is to target the proteins that regulate apoptosis signaling at the mitochondrial surface in a way that will selectively induce or restore responsiveness to apoptosis signaling in cancer cells.

The Bcl-2 family proteins have been identified as the principle players in the mitochondrial apoptosis-signaling pathway. Pharmacological inhibition of certain of these proteins with small molecules is regarded as a promising approach to inducing apoptosis and treating cancer. Eutropics’ therapeutic lead compound targets the Bcl-2 family protein myeloid cell factor-1 (Mcl-1), a protein believed to be important in multiple myeloma as well as other cancers and is considered a high value target. Our work to develop this targeted therapeutic is supported by grants from the National Cancer Institute’s Small Business Innovation Research (NCI SBIR) program, and by the Massachusetts Life Science Center Accelerator Program.

Identifying When Cancer Cells Will Respond to Treatment
We have approached the drug discovery and development challenge with the understanding that cancer cells are often more susceptible to treatment than non-cancer cells, but not always. The cancer cells that either never respond or lose sensitivity to treatment become the problem and result in poor clinical response. Knowing when and how certain cancer cells lose their sensitivity to treatment would increase the odds of successfully developing and using chemotherapies, including our therapy if that process involved our target protein. We asked if we could measure the ability of cancer cells to respond robustly, partially respond, or not respond at all to our therapy, or to any chemotherapy prior to applying the treatment.

Five years ago I met our co-founder Tony Letai at a Cold Spring Harbor apoptosis meeting and we discussed how one could make such measurements. Tony had developed a method to determine if a cancer cell is, or is not, “pre-set” to respond to apoptosis signals that are usually induced by cancer therapies. The method, called BH3 profiling, provided a test that could in theory predict cancer patient response
to such apoptosis inducing therapies. As such, it held potential to be an important predictive test for a number of chemotherapies. We agreed then that this technology could also be very important in guiding the development and use of Mcl-1 or Bcl-2 targeted therapies. The papers published from the Letai Laboratory at Dana-Farber Cancer Institute over the next few years demonstrated in experimental systems that this would very likely be the case. Work done at Eutropics corroborated this. Eutropics has exclusively licensed the technology from Dana-Farber and is now routinely using the assay.

The underlying principle of the assay is that as a result of aberrant phenotypes, cancer cells develop blocks in apoptosis signaling pathways. These blocks make cancer cells resistant to chemotherapy, but surprisingly, can also result in the cancer cells becoming hypersensitive to chemotherapy. At some point cells that initially rely on the block for survival can become hyper-dependent, and more vulnerable to treatment (Figure 2).

The concept of “oncogene addiction” describes the phenomena of cancer cells’ acquired dependence on, or addiction to, particular proteins for survival. BH3 profiling determines if such a dependence on any of the Bcl-2 family proteins occurs in given cancer cells, and identifies which one. This understanding provides a unique insight to the best course of treatment, the one that will kill the addicted cell much more effectively than the non-addicted cell by affecting the dependent apoptosis regulating oncogene.

Figure 2: Apoptosis signaling thresholds at the mitochondrial surface
In practice, the assay simultaneously measures the functionality of the roughly dozen Bcl-2 family proteins in question. The novelty and advantage of the BH3 profiling assay is that it examines the precise function of the protein or combination of these proteins in the disease state. This capability along with the fact that the assay is run on freshly extracted, or time-zero, tumor cell samples without expansion, makes the assay unique (Figure 3).

In essence the BH3 profiling assay provides an understanding of how or if particular Bcl-2 family proteins can function in response to a drug-induced apoptosis signal. This understanding then translates to a predictive understanding of the cancer cell response and, in turn, the patient response to treatment.

**Providing an Important Diagnostic Test to the Clinical Community**

We are now in the process of achieving clinical validation of BH3 profiling for guiding the use of marketed therapies for treating multiple myeloma in preparation for eventual clinical development. In particular we are looking at samples from patients treated with Takeda/Millennium’s bortezomib in combination with other established and experimental drugs. The work is being supported by an NCI SBIR Contract.

Currently there is no test that has proven to be predictive for patient responsiveness to bortezomib or any other multiple myeloma therapy presently on the market. This deficiency may have future implications for sales and reimbursement of such therapies, as it has most notably affected the use of bortezomib in the United Kingdom.

In developing the BH3 profiling assay for use with marketed therapies we are learning how to best use the companion diagnostic with our Mcl-1 inhibiting drug when that comes to the clinic.
What’s Next for Eutropics?
Eutropics’ goal is to provide a predictive and prognostic test for multiple myeloma patient responsiveness to current and new chemotherapies. The assay is likely to have utility in other disease areas as well, including follicular lymphoma, acute lymphoblastic leukemia, chronic lymphocytic leukemia and non-Hodgkin lymphoma, and is also potentially applicable to several solid tumors, especially those that are affected by aberrant Mcl-1 activity, including non-small lung cell carcinoma and melanoma. The guidance of treatment by BH3 profiling, and its benefits to the drug development process, should contribute significantly to the fulfillment of the promise of paired diagnostics with therapeutics.

We have seen that the BH3 profiling assay provides an important advantage in de-risking the development of our Mcl-1 inhibiting compound.

Based on results in experimental systems we are envisioning that the BH3 profiling assay will also be useful to a range of therapies that induce apoptosis. The published studies indicate that those could include vincristine, flavopyridol, the Bcl-2 inhibitor from Abbott Laboratories (ABT-263) and others.

We envision that appropriately designed iterations of the BH3 profiling assay will accompany a number of drug candidates into and beyond the clinic and help speed their delivery to patients and improve drug efficacy by identifying responsive patients.

About the Author and Eutropics Pharmaceuticals Inc.

Michael Cardone’s experience includes over 10 years of scientific and business management at private biotech companies, working with founding teams to develop operating plans, IP portfolios, and building next level operating teams. He received his undergraduate degree in Biology from San Francisco State University, and a PhD in Cell Biology from the University of California San Francisco. He completed postdoctoral studies at the Burnham Institute in La Jolla, CA, where he studied apoptosis signaling.

Eutropics Pharmaceuticals was founded on research and technology originating from the Dana-Farber Cancer Institute (DFCI) to enable delivery of personalized medicines to patients suffering from cancer. They seek to displace current treatment paradigms by developing novel therapies tailored to an individual’s cancer profile identified by their proprietary diagnostic technology. Eutropics indicates that this personalized approach utilizing unique diagnostics and therapeutics should result in more effective treatments and reduce unnecessary suffering.

References
Consultants’ Perspectives

Dr. Daniel A. Vorobiof was born in Argentina and received his medical degree at the University of Cordoba before immigrating to Israel in 1973, the year of Juan Peron’s return from exile. He completed his internal medicine residency at Ben-Gurion University Medical School’s teaching hospital, Soroka Medical Center, in Beersheba. However, Dr. Vorobiof’s interest in medical oncology eventually led him in 1980 to South Africa.
“Truth is, there was very little medical oncology in the whole of Israel because it mainly followed the English system with its emphasis on radiotherapy,” said Dr. Vorobiof. “Being a physician, I was mainly interested in the medical oncology part and not in the radiation part. And at that time I received a letter of invitation from the University of Pretoria, which had a very strong department in medical oncology.”

There he served his fellowship under Professor Geoffrey Falkson, the pioneer of medical oncology in South Africa and founder of the university’s department. Particularly valuable for Dr. Vorobiof was the department’s relationship with the Eastern Cooperative Oncology Group (ECOG) and the Cancer and Leukemia Group B (CALGB) in the United States.

“I started my oncology career and research mainly being involved with the American cooperative groups,” said Dr. Vorobiof.

**Sandton Oncology Centre**

In 1991, Dr. Vorobiof moved to Johannesburg, where he founded Sandton Oncology Centre (SOC). The private outpatient center combines under one roof radiation therapy, chemotherapy and clinical research, as well as supportive care and services for both patients and their families. It was the first such center in South Africa.

Today, as SOC’s director, Dr. Vorobiof is part of a team of three medical oncologists, five radiation oncologists and supporting staff including oncology nurses, clinical research assistants, radiologists, oncology pharmacists, a social worker, an in-house counselor and massage therapists, as well as the administrative personnel.

“When we started SOC, we felt that patients required additional help to heal and strengthen themselves and their families. This approach is now referred to as an integrative medicine,” said Dr. Vorobiof.

SOC treats approximately 50 radiotherapy and 30 chemotherapy patients daily, in addition to patients coming for clinical visits, examinations, observations or diagnoses. The Centre does not offer surgery on premises but works with a network of surgeons with a special interest in oncology. In a nearby hospital, a dedicated oncology ward is available for those patients requiring in hospital treatments, therapy for side effects, and palliative care.

**Clinical Trials**

Dr. Vorobiof still works with international and national cooperative groups as well as with pharmaceutical company-sponsored clinical trials.

He has been active in clinical research with the International Breast Cancer Study Group, the Breast International Group, the World Health Organization’s Melanoma Group, the Swiss Group for Clinical Cancer Research (SAKK), and the European Organization for Research and Treatment of Cancer (EORTC).

"In addition to breast cancer, melanoma and lymphomas, because of our patients’ varied pathologies, we also conduct clinical trials in many other types of solid tumors such as malignant

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“South Africa is a good place for sponsors to conduct clinical research, according to Dr. Vorobiof. The country’s medical facilities, both public and private, have good technology – CTs, MRIs and linear accelerators – and can perform electronic data capture to facilitate sponsor work.”
mesothelioma, lung, ovary, prostate and colorectal cancers,” said Dr. Vorobiof.

Dr. Vorobiof has noticed a shift in the sources of clinical research. Studies used to originate with the cooperative groups but he would estimate that some 70 percent of all studies over the past 10 to 12 years have come from pharmaceutical sponsors. Plus, many of the current cooperative group studies are done together with the support of pharmaceutical sponsors, as cost of research has increased dramatically so that it is difficult to do proper research without a corporate sponsor.

South Africa is a good place for sponsors to conduct clinical research, according to Dr. Vorobiof. The country’s medical facilities, both public and private, have good technology – CTs, MRIs and linear accelerators – and can perform electronic data capture to facilitate sponsor work.

“The same happens with pathology diagnosis and investigation,” said Dr. Vorobiof. “The large pathology departments (private and public) can perform molecular pathology for a number of cancers as well as genetic profiling for breast cancers. All those tests are becoming more available.”

Dr. Vorobiof considers South Africa’s excellent medical training, advanced technology, and up-to-date medical therapies and practices as main reasons patients come for appropriate diagnosis and treatment from other countries. SOC, he added, receives many patients who work for multinationals and international organizations in countries such as Zimbabwe, Kenya, Nigeria, Zambia, Angola, Mozambique and elsewhere.

Cancer in South Africa
South Africa’s population of approximately 42 million is divided into four racial groups: black, white, mixed and Asian/Indian. And the demographics of cancer tell a story of the races. It must be noted, though, that compiling accurate cancer statistics has been hindered by the lack of funding to the National Cancer Registry of South Africa over the previous eight years, but Dr. Vorobiof cited some overall trends that he believes hold true since 2002 data appeared. He added that “A recent change in the legislation will make cancer a reportable disease by all physicians, enhancing the existing pathology based registry while developing population based registries.”

Breast cancer is the most prevalent cancer among white and Asian/Indian women (who total approximately 16 percent of the population); whereas cervical cancer is the most prevalent among black and mixed race women, with breast cancer second. Cervical cancer is potentially preventable through improved access to screening and early detection. On the other hand, increased breast cancer incidence has been tied to Westernized diets, higher in meat and fats.

In the overall male population, prostate cancer is most prevalent, followed by lung, esophagus and colorectal. In the white male segment, colorectal cancer ranks first, followed by prostate cancer. Melanoma in South Africa is a significant problem in the white population, as it is in Australia – another country nearer equatorial latitude, with a large northern European immigrant population.
Healthcare System
Hospitals and healthcare facilities in South Africa are either public or private. Approximately 15 percent of the population maintains private health insurance coverage and uses private primary care and private hospitals. Another 20 percent uses private primary care paid out-of-pocket and the public hospital system. The remaining 65 percent uses public clinics and hospitals. Considerable support for healthcare could come in the form of national health insurance, which is currently under discussion by the South African government with the objective of instituting a system by 2015.

“For cancer patients, although the tertiary public institutions may have the proper equipment, the availability of treatments is not always what it should be because the facilities are highly constrained financially.”

Responding to the Challenges
Beyond providing oncology care to patients through the Sandton Oncology Centre, Dr. Vorobiof is committed to advancing the state of oncology practice in, and introducing the latest advances to, both South Africa and sub-Saharan Africa. He has devoted himself to professional education and establishing a South African professional society infrastructure to disseminate ideas.

“One of my main areas of interest has been the education of fellow colleagues in countries that have relatively poor access to data from international meetings and to bring to them the latest information,” said Dr. Vorobiof.

Dr. Vorobiof is a founder member, and has twice served as chairman, of the South African Society of Medical Oncology. Because of his interest in the particular problems presented by melanoma in South Africa, he founded the South Africa Melanoma Advisory Board. He was a member of the American Society of Clinical Oncology (ASCO) International Committee (1998 to 2001) and also a member of the ASCO International Strategic Planning Task Force (2001), as well as representative for sub-Saharan Africa of the European...
Society of Medical Oncology (ESMO)(2004 to 2011) and member of ESMO’s Developing Countries Task Force (2004 to 2007). He has recently become involved with the Breast Global Health Initiative for low- and middle-income countries.

With the help of the European School of Oncology he was the Convenor of three educational meetings in South Africa during 2002, 2004 and 2006.

Dr. Vorobiof also serves as associate editor of the Annals of Oncology, Europe’s largest medical oncology journal, from which he also edits excerpts five times a year, publishing and distributing them through a local publisher to sub-Saharan countries. He serves as well on the editorial board of several international cancer related journals.

Patient education and advocacy groups are not as well established in South Africa as in Europe or the United States but are gaining momentum, according to Dr. Vorobiof.

He was until recently a director for the Prostate Cancer Foundation of South Africa.

A Wish List

Asked what he would change about oncology research if he could, Dr. Vorobiof wished there were a more uniform way of treating cancer patients in South Africa.

“We also have a problem with some – but not all – medical insurers,” said Dr. Vorobiof. “The moment they know that an insured patient is accrued into a clinical trial, they are unwilling to pay for anything related to the treatment of the patient while on the clinical trial. Suddenly standard procedures are not covered. This is also another restraint on cooperative groups or pharmaceutical companies that want to do research here.”

In a situation not unique to South Africa, obtaining regulatory approval is a time consuming process he would like to see streamlined. In South Africa, the national Medicine Control Council must first approve a trial. Then regional ethical review boards and committees must provide their approval. The process has been, in Dr. Vorobiof’s opinion too time consuming – anywhere from six to eight or nine months. But there is hope here too: a current review of procedures seeks to reduce review time from between six to nine months to between three to four months.

Now that, plus national health coverage – and a system that would allow more patients to participate in clinical trials – says Dr. Vorobiof will be “a big step in the right direction to providing up to date treatment to most cancer patients in South Africa.”

“In clinical trials they receive the same, uniform treatment, but that is a small portion of the patient population – maybe 5 percent to 6 percent,” said Dr. Vorobiof. “If you’re really pushy you might be able to recruit up to 10 percent of your patients into clinical trials, but that is a high percentage to achieve.”

He also finds that the research process is becoming increasingly dominated by rules and regimentation. Even small but important steps that are directed to attract poor rural patients, such as requirements that sponsors provide travel costs and food allowances, strike Dr. Vorobiof as a potential discouragement for sponsors.
Taiwan has many qualities that make it an excellent location to conduct clinical trials. The technical literacy of its people and the country’s advanced medical and technical infrastructure easily support electronic data capture, clinical trial management systems and communications for sponsors. The professional population and medical staff are well educated and trained. The country is also one of the more densely populated nations in the world – comparable to squeezing the population of Florida into an area the size of Vermont. The majority of the Taiwanese population resides in urban areas, easily within reach of medical centers and clinical trial sites. The Taiwanese people, with a heritage of traditional Chinese medicine, are relatively new to participation in clinical trials utilizing conventional pharmaceuticals, but willingly participate in such studies. All of these factors can contribute to timely enrollment of patients.
Even the country’s health insurance system cooperates. “There is no conflict between clinical trials and National Health Insurance in Taiwan,” said Dr. Lin. “This insurance system can cover some additional examinations, usually for the medical issues unrelated to clinical trials, such as MRI, CT or blood tests even in a trial if necessary.”

Established in 1995, after studying healthcare systems of the world’s leading countries, National Health Insurance (NHI) is a single-payer coverage system that resembles Medicare in the United States, except that it covers the entire population, not just the elderly, and offers more benefits.

“In general, there are no financial barriers – except certain expensive examinations or medications that are not covered by the NHI – or typical financial thresholds for recruiting patients for trials here,” said Dr. Lin.

CHANG GUNG MEMORIAL HOSPITAL

In 1976 the Chairman of Formosa Plastics Group, a $4 billion company, Yung-Ching Wang and its President, Yung-Tsai Wang founded the hospital in Taipei in memory of their father, Chang-Gung, to introduce modern medicine and medical technologies to Taiwan and to meet the growing medical needs of the people of Taiwan. Since then, Chang-Gung has added hospitals in five other cities: at Keelung, Linkou (also site of the specialty Chang Gung Children’s Hospital) and Taoyuan in northern Taiwan and at Chaiyi and Kaohsiung in southern Taiwan. Together, the seven hospitals have a capacity of 6,800 beds and serve a total of 27,000 outpatients. The hospital is a vital research institution and also publishes its own research journal, Chang Gung Medical Journal.

To further develop Taiwan’s medical infrastructure, the hospital program created the Chang Gung Institute of Nursing and Chang Gung University. In addition to its medical school, the University has established with Arizona State University an international Biosignatures Center, co-directed by Arizona State’s Nobel Laureate, Leland Hartwell, PhD. The center’s aims are the prevention, early detection, diagnosis, and treatment of cancer and other diseases.
Inside the Clinic
It is in this environment that Dr. Lin, who received his medical degree from the National Taiwan University and served a fellowship at the Chang Gung Memorial Hospital in Linkou, spends some 80 percent of his time involved in clinical cancer research at the Chang Gung Memorial Hospital and Chang Gung University in the capital city of Taipei (see "Chang Gung Memorial Hospital").

The hospital has a clinical research center, medical research department and committee, which handle all oncologic and non-oncologic trials. Dr. Lin has a staff of three dedicated to working on trials. About one-quarter of his research time is spent on pure research; and three-quarters, on clinical trials and studies. Dr. Lin is honored to have as a colleague at both Chang Gung University and Memorial Hospital the international scholar and pioneer in hepatitis B study and treatment, Professor Yun-Fan Liaw, MD, who has also been a teacher and mentor who greatly influenced his decision to enter the profession of medicine and the field of clinical liver cancer research.

Four of the five clinical trials for which Dr. Lin has served, or now serves, as principal investigator have been sponsored by North American companies. The one exception is a Phase II study for Microbio Co. Ltd., a Taiwanese biopharmaceutical firm, that tests the ability of the firm’s MS-20 therapy to improve quality of life for liver cancer patients, hopefully by enhancing natural killer (NK) cells in cancer patients. Two Phase III studies for Bristol-Myers Squibb involve the firm’s brivanib: one compares outcomes in patients treated with brivanib with those in patients treated with sorafenib (Bayer AG’s Nexavar®); the other, use of brivanib with patients following TACE (transarterial chemoembolization), which blocks the flow of blood to a tumor prior to introducing chemotherapy. A Phase III “HEAT” study for Celsion explored administration of percutaneous ethanol injection (PEI) into liver tumors in conjunction with radiofrequency ablation. A Phase IV study involving Nexavar® for Bayer Healthcare and Onyx Pharmaceuticals is ongoing.

"Because of more novel approaches in global trials, I personally prefer international trials to national ones," said Dr. Lin.
The HEAT trial was especially aligned with Dr. Lin’s primary interests within oncology research. “First it involved possessing a mature technique for percutaneous radiofrequency ablation (RFA) but using novel RFA equipment. This required long-term experience of using RFA with intermediate or large-sized hepatomas. The next step is to test the combination therapies with intravenous administration of thermo-doxorubicin before RFA.

A Look at Patients

Dr. Lin’s other main areas of interest are secondary and tertiary prevention of hepatoma. At the secondary level, that involves treating the hepatitis B or C before the development of hepatoma. At the tertiary level, the challenge is to reduce the recurrence of hepatoma after percutaneous curative ablation therapies such as ethanol injection or radiofrequency ablation. Other than administering a cure these are, in Dr. Lin’s opinion, the best ways an oncologist can help patients.

Dr. Lin breaks down the types of patients with hepatoma who come see him into three stages: Early, Intermediate and Advanced. The therapeutic approach differs for patients in each stage. “For the early stage patients, we seek to prevent hepatocellular recurrence after initial curative therapy. At the intermediate stage, we combine novel locoregional therapies and novel target therapies like the HEAT trial’s use of RFA in combination with intravenous injection of thermo-doxorubicin before RFA.

In advanced stages, we must move directly into novel targeted therapies or chemotherapies,” explained Dr. Lin.

Looking forward

When describing how he sees medical research changing in coming years in Taiwan – and, for that matter, globally – Dr. Lin believes that clinical or pre-clinical medical research and clinical trials will become more closely allied. In particular, he sees the need for joint efforts in research on liver cancer related to the presence of the hepatitis B virus. Hepatitis B is endemic in many countries in Asia, infecting a far larger proportion of the population than in Europe or the United States. Chronic hepatitis B infection may lead to cirrhosis (chronic damage that diminishes the function of the liver) and to hepatocellular carcinoma, a disease with a poor treatment outcome for most patients. Dr. Lin feels that a better understanding of the relationship between hepatitis B and hepatocellular carcinoma may improve the treatment algorithm for patients with intermediate and advanced stages of that disease.

If he could change one thing about how oncology research is currently conducted, Dr. Lin said: “Focus my time to finish the trial or research as soon as possible because changing the current hepatoma treatment algorithms always requires advanced clinical studies or trials, and the results will improve the outcomes of liver cancer.”
As a graduate student I was interested in the cardiovascular and metabolic effects of exercise. And in a post-doctoral fellowship in cardiovascular epidemiology, I was basically looking at a career of focusing on exercise and issues related to obesity prevention and metabolism and cardiovascular disease. The great leaps about exercise and these topics had been made decades ago. Not that there isn’t more good work to do in this area, but I was facing down a career of incremental science.

“Then, a single paper that I read influenced me to take a very sharp turn in my career. That paper was ‘A Call to Action’ by Dr. Anne McTiernan of the Fred Hutchinson Cancer Research Center. In the paper McTiernan suggested that we could use the program of research on exercise and heart disease as a model for a program of research on exercise and cancer 

How many of us can recall a precise moment that completely changed the direction of our careers? Kathryn Schmitz, PhD, MPH, can. And that change has had a profound impact on the well-being of breast cancer survivors who have lymphedema and those who fear what it might do to their lives. The associate professor of Epidemiology and Biostatistics at the University of Pennsylvania School of Medicine and member of Penn’s Abramson Cancer Center tells the story best:
across the cancer control continuum – which
is to say, all the way from primordial prevention in
children to rehabilitation and, in the case of cancer,
potentially palliative care as well. Those of us who
were trained in the area of cardiovascular disease
and exercise could retool ourselves quite easily to
work on this brave new frontier.

“I said, ‘Sign me up.’ ”

What followed after Dr. Schmitz wrote Dr. McTiernan
was an open communication, a mentoring relationship,
and a career direction that led Dr. Schmitz to initiate a
series of pilot and clinical trials on exercise intervention
with breast cancer patients.

Science is Fickle

However, what Dr. Schmitz learned from her first
study in her new field was not exactly what she had
expected. The large pilot study was designed to
examine the effects of resistance training on breast
cancer biomarkers. It was the first time anyone had
studied resistance exercise – lifting weights – instead
of aerobic exercise in breast cancer survivors. The
exercise intervention she hoped would reduce growth
factors, insulin and potentially the risk for recurrence
of breast cancer turned out instead to be particularly
useful in reducing a persistent, adverse effect of breast
cancer treatment that women fear: lymphedema.

“I had been told that lymphedema happens in so
few women that we were not going to have to deal
with it,” said Dr. Schmitz. “I included it in the study
only as a nuisance variable. Well, this was in 2001.
It’s 2011 and I’m continuing to hear the same
dismissal of lymphedema’s significance and I’m
continuing to have no difficulty recruiting women
who have lymphedema for our studies. So there is
some kind of interesting disconnect. Lymphedema
was something that the women themselves told
me they feared tremendously. So you have to ask
yourself why, if lymphedema is supposedly that
rare, is there a waiting list at every lymphedema
clinic across the country – I had to deal with this.”

For the pilot study, Dr. Schmitz had assigned the topic
of writing up the ‘nuisance variable’ of lymphedema
to her doctoral student. It turned out to be the most
important result of the study and the doctoral student
became the first author of the article that appeared in
the *Journal of Clinical Oncology* in 2006. Then *The
New York Times* wrote an article about it. Science
is fickle.

The PAL Study

Following the pilot study, Dr. Schmitz conducted
the larger-scale, two-part Physical Activity and
Lymphedema (PAL) trial to determine the effect of
lifting weights, first on 141 breast cancer survivors
with lymphedema and second on 154 breast cancer
survivors who had been free of lymphedema within
five years of breast cancer treatment. The PAL study,
a one year randomized controlled exercise intervention
trial funded by the National Cancer Institute, has been
the largest to date on this sometimes debilitating,
icurable disease. The results have been dramatic.

“The large pilot study was designed to examine the
effects of resistance training on breast cancer biomarkers.
It was the first time anyone had studied resistance
exercise – lifting weights – instead of aerobic
exercise in breast cancer survivors.”
In the first part of PAL, 53 percent fewer women in the exercise treatment group than in the control group experienced lymphedema exacerbations that required treatment from a physical therapist. The percentage of women who experienced a 5 percent or more increase in limb swelling was similar in both groups.

In the year-long second part of PAL, the slowly progressive weightlifting regimen cut the risk of developing lymphedema by 35 percent. Among women who had five or more lymph nodes removed, there was a nearly 70 percent risk reduction. (Previous studies have shown that following surgery to remove multiple lymph nodes as many as 47 percent of patients develop lymphedema.)

Participants in the study also showed improved strength, improved body image and reduced body fat.

Because the participants were not necessarily within easy commuting distance to University of Pennsylvania facilities, the PAL program provided participants one-year memberships to a community fitness center near their homes – typically a YMCA – and 13 weeks of supervised twice weekly small group training. The program trained physical therapists at these facilities, which served the dual purpose of increasing the number of trained therapists available for future support of breast cancer survivors in the general population.

Dr. Schmitz cautions that women who have lymphedema, or are at risk of the condition, should speak with their doctors and seek guidance from a certified fitness professional to learn safe weightlifting techniques, many of which – with proper equipment – can even be practiced at home. Women with lymphedema should also wear a well-fitting compression garment during all exercise sessions.

**Countering Conventional Wisdom**

Perhaps the study’s most significant accomplishment is to have turned on its head the traditional advice given breast cancer patients on how to avoid lymphedema. In the past, women have been told not to lift anything over 15 pounds with an arm affected by breast cancer treatment. For many women this meant not picking up their children, carrying groceries or suitcases.

“I don’t know for sure where or when such strictures were first formulated,” said Dr. Schmitz. “But overuse of the arm is associated with lymphedema, and there is probably the connection between patients with complaints about lymphedema and doctors hearing responses to their inquiries like ‘I did a lot of gardening’ or ‘I did a lot of Christmas shopping.’”

This is where Dr. Schmitz saw the potential for the lessons of cardiovascular epidemiology to make significant contributions to the care of cancer survivors. At one time, treatment of heart patients dictated that they not get out of bed to avoid potential further damage. But, in fact, to improve a damaged system’s ability to tolerate stressing – such as the
occasional events of daily life – you have to exercise that system gradually to tolerate incrementally larger stresses. Ultimately, you increase its ability to function under something approaching more normal physical stress levels.

“We’ve known this about the cardiovascular system for a long time now,” said Dr. Schmitz. “The lymph system is also a vascular system. In fact, the textbooks refer to it as ‘the second circulation.’ All I’ve done is applied the same logic we used for cardiovascular rehabilitation to the lymph system after cancer.”

**Recruiting for the PAL Study**

Recruiting patients for the study also did not go the way Dr. Schmitz – or anyone else – assumed it would.

“They would think that most of my women would have come from recruitment through our clinics. That was not the case at all. In fact, it was very difficult to recruit for this study through the clinic.”

One of the challenges is that patients come to a cancer center for a variety of reasons related to referral patterns, because of insurance, because of location, or because of the reputation of the institution. For the Abramson Cancer Center, patients come not only from throughout the Philadelphia area and nearby New Jersey, but also from around the country and even internationally.

It took Dr. Schmitz and her colleagues essentially five months to arrive at the most successful recruitment method. In cooperation with the state cancer registries of Pennsylvania and New Jersey, the team mailed some 28,000 letters to patients with up to 15 years after their breast cancer diagnosis. From roughly 3,000 responses, they assessed about 2,000 for eligibility and 295 eventually consented.

**Follow-On Studies**

There are currently two studies in the works, following up on the initial PAL trial studies. The first, which began in April of this year, focuses on dissemination of the lessons from the PAL trial and offers a one-hour educational class to teach breast cancer patients about the risks of lymphedema. In addition to the
class, patients will be offered the option to enroll in a scaled-down version of the exercise intervention from PAL, which will consist of a physical evaluation for safety and four physical therapy group sessions. The physical therapy evaluation will be by patient co-pay. Dr. Schmitz is working with billing and administrative experts at Penn to determine whether the group physical therapy sessions will be billed to insurance or ‘self-pay’.

“We hope that this program will prove to be affordable for women,” said Dr. Schmitz. “The study will also evaluate the effectiveness of different means of advertising to the breast cancer patient community, as well as different ways to generate referrals to the class and program. For example, we’re going to conduct training for the Abramson clinicians on how the referral process works so that they can do it quickly and efficiently. Then we’ll see how many patients clinicians could refer compared with how many they actually did refer. And we’ll measure physical therapists the same way. We’re also going to evaluate the safety and efficacy of this revised version of the PAL intervention. If it works, we will seek funding to evaluate it as a model of a breast cancer rehabilitation approach for multiple cancer centers across the country.”

Abramson Cancer Center

The Abramson Cancer Center of the University of Pennsylvania has received continuous designation as a Comprehensive Cancer Center by the National Cancer Institute since 1973, one of 40 such Centers in the United States.

The Center is dedicated to innovative and compassionate cancer care. The clinical program, with its dedicated staff of physicians, nurse practitioners, nurses, social workers, physical therapists, nutritionists and patient care coordinators, currently sees over 70,000 outpatient visits and 9000 inpatient discharges, and provides more than 33,000 chemotherapy and 66,000 radiation treatments.

Not only is the Abramson Cancer Center dedicated to providing state-of-the-art cancer care, but also the latest forms of cancer prevention, diagnosis, and treatment are available to patients through clinical approaches developed to eliminate pain and suffering from cancer.

In addition, the Abramson Cancer Center is home to 400+ basic, translational and clinical scientists, working to determine the pathogenesis of cancer. Together with the faculty, they are committed to improving the prevention, diagnosis and treatment of cancer.
In addition to the assumption that patients will be able to afford the program, Dr. Schmitz hopes that donations such as the one recently received for 120 sets of dumbbells ranging from 1 pound to 33 pounds will help minimize cost burden to participants in need.

The second follow-on study is a larger clinical trial that essentially repeats the PAL trial to assess the cost-effectiveness of weightlifting intervention.

“My mission is that all two-and-a-half million breast cancer survivors know about access to appropriate weight training intervention so they can empower themselves not to fear lymphedema anymore,” said Dr. Schmitz.

**Funding Studies**

To date, Dr. Schmitz’s studies on lymphedema and breast cancer have been funded by the National Cancer Institute and the National Center for Research Resources. However, she is still seeking funding to study the effect of resistance exercise on lymphedema in lower limbs. Such lymphedema is linked mainly to treatment of melanoma, bladder cancer, and gynecological cancers (but not prostate cancer). Dr. Schmitz has already conducted a pilot study with 10 patients, and although there were signs of good results, two patients experienced adverse effects that may or may not have been related to the exercise. However, she has attempted three times to obtain funding for a larger study and has been unsuccessful. Funding ‘pay lines’ from the National Institutes of Health are low at the moment.

“People read the PAL study results and think lower limbs should respond the same, but we just don’t have the evidence,” said Dr. Schmitz. “I get asked about this weekly from some physical therapist somewhere in the country. This study desperately needs to get done.”

Dr. Schmitz hopes that one day pharmaceutical companies would be interested in funding studies to explore ways to relieve the adverse side effects of patients who undergo treatment for cancer – whether or not the side effects are related to their products.

**An Economic Epidemic**

According to Dr. Schmitz, it is not only studies that feel the financial pinch. Such pressures might also be costing cancer survivors their health. Dr. Schmitz has been struck by the fact that African American women are diagnosed with more aggressive forms of breast cancer and, as a result, are more likely to have axillary dissection (removal of underarm lymph nodes) – which increases lymphedema risk. They are also more likely to be obese, which is associated with the onset of lymphedema. And they are less likely to be insured well enough to manage their lymphedema care. One of the recommendations to come from the PAL study is that patients with lymphedema wear a compression garment during exercise. A custom fitting compression garment alone can cost $300 and is not always covered by insurance.

“I think there is a hidden health disparities epidemic in cancer survivorship,” said Dr. Schmitz. “I think that lower income individuals, lower-resourced individuals, lower education individuals are more likely to be diagnosed at higher stage and grade of breast cancer. Perhaps it’s because they have less access to screening – but it’s not entirely that, there might be some biological differences, we just don’t know. But if they have higher stage and grade, they have more intense treatments. And if they have more intense treatments, they have more side effects and late effects. And they don’t have the wherewithal to be asking for treatment for these side effects. Breast cancer survivors know they have symptoms and problems, like lymphedema, but they don’t know what to do about it.”

Dr. Schmitz hopes that her studies with weightlifting can lead to a proven, cost-effective intervention to help large numbers of breast cancer survivors overcome their fear and feelings of powerlessness against lymphedema.

**A Better Time for Cancer Survivors**

“We are living in very exciting times for cancer survivors,” said Dr. Schmitz. “Things are shifting dramatically and quickly. Thanks to earlier detection and more advanced treatments, cancer has largely
become a survivable or chronic disease. There are now about 12 million cancer survivors in the United States, about 4 percent of the population. And cancer survivors make up 16 percent of the population over age 65.”

The process of diagnosing and appropriately treating a cancer has required enough expertise that an entire medical profession and subset of specialties have been developed for that job. But how can these oncology experts now be expected to become experts in survivorship also?

“Breast, prostate and colon cancer – the three most prevalent cancers – are all survivable cancers with early diagnosis and treatment,” said Dr. Schmitz. “You have a brand new population with longer-term needs that studies like the PAL trial are revealing new ways to meet. This is how we can help the oncologists care for not only the patients’ diagnosis and treatment, but also their rehabilitation – in other words, their return as fully and as best they can to the lives they lived before cancer treatment.

“Good things are happening with guidelines being set and efforts being made to develop what are called ‘survivorship care plans’ – documents provided to patients that outline their continuing treatment, monitoring requirements, rehabilitation, counseling, broader care needs, and more integrative programs that help the patient live a fuller life. Gone are the days of ‘go home and live with your cancer now.’ ”

Dr. Schmitz and colleagues are able to glean lessons to be learned about cancer rehabilitation programs in various stages and modes of implementation in Nordic and European countries, which face cancer survivorship demographics similar to those in the United States. Delivery venues for rehabilitation run the gamut of public, private, national and local institutions. But what appears to be uniform is recognition for public policy guiding the nature and role of rehabilitation, that clear policy be supported by scientific data (clinical guidelines), and that multidisciplinary teams provide oversight and implementation. There is also a growing call for randomized trials to identify reasonable outcome indicators for the varieties of rehabilitation. And that is precisely where Dr. Schmitz has begun to direct her efforts.
About The University of Pennsylvania School of Medicine

The University of Pennsylvania School of Medicine — founded in 1765 as the nation’s first medical school — is consistently among the nation’s top recipients of funding from the National Institutes of Health, with $507.6 million awarded in the 2010 fiscal year.

The School of Medicine comprises 28 basic and clinical departments, and more than 1,800 faculty members and 2,200 students and trainees. Penn’s physicians and biomedical scientists engage in integrated research programs that employ an interdisciplinary approach to understand the fundamental mechanisms of disease and investigate new strategies for treatment.

In addition to the School of Medicine, Penn Medicine consists of the University of Pennsylvania Health System, which includes the Hospital of the University of Pennsylvania; Penn Presbyterian Medical Center; and Pennsylvania Hospital – the nation’s first hospital, founded in 1751. Penn Medicine also includes additional patient care facilities and services throughout the Philadelphia region. Penn Medicine is committed to improving lives and health through a variety of community-based programs and activities.