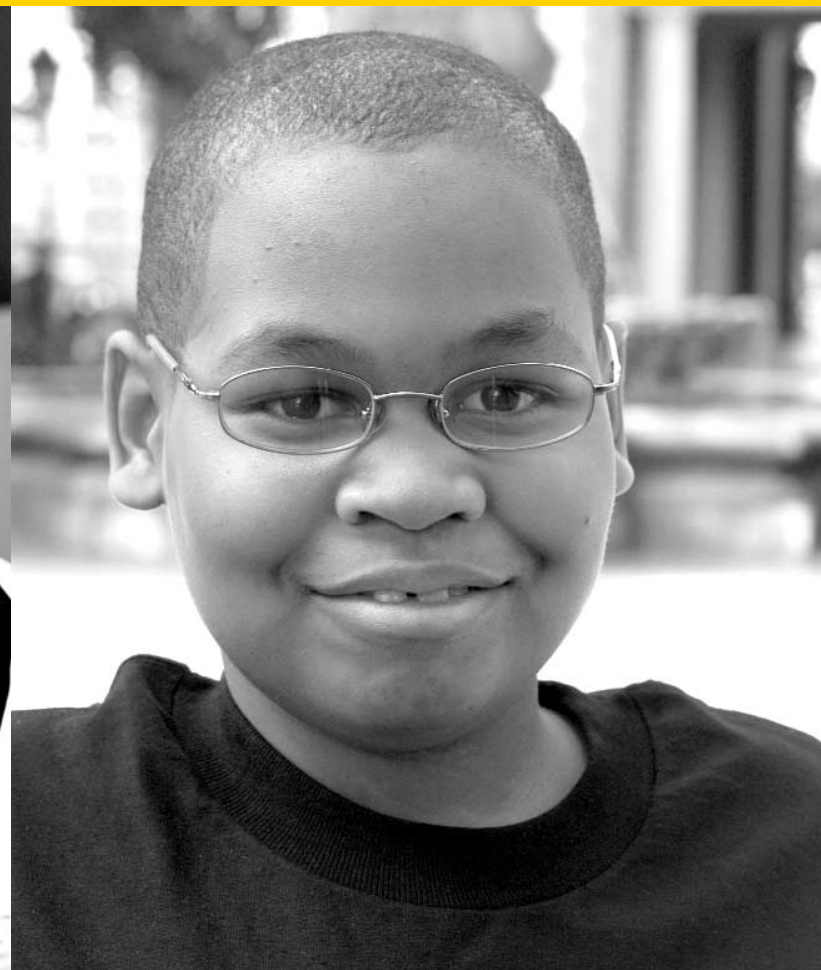




**Lance Armstrong Foundation
Advancing Research**
2004 Overview - Individual Grant Awards



The Lance Armstrong Foundation (LAF) exists to enhance the quality of life for those living with, through and beyond cancer. Founded in 1997 by cancer survivor and champion cyclist Lance Armstrong, the LAF seeks to promote the optimal physical, psychological, and social recovery and care of cancer survivors and their loved ones. The LAF works to define, refine and improve services for cancer survivors and to facilitate the delivery of those services — with a large dose of hope — to patients, their families and other loved ones touched by the disease.

Issues of Cancer Survivorship

Survivorship means facing the ongoing challenges of cancer, every day, starting from the moment of diagnosis. The LAF awards grants to study issues of survivorship, including a myriad of physical and psychosocial issues facing survivors and their families before, during and after cancer diagnosis and treatment.

Basic and Clinical Science of Testicular Cancer

Testicular cancer remains a leading cause of cancer morbidity and mortality for young men. The biology of the disease, the epidemiology of the increasing prevalence, the psychosocial impact, and the realm of clinical investigations make testicular cancer a paradigm for aggressive but treatable malignancies. The LAF supports cutting-edge research of testicular cancer in basic science, basic science translated to clinical issues, and purely clinical investigations.

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The groundbreaking research supported by the Lance Armstrong Foundation is as impressive in its variety as it is in its scope. From a study of memory loss after chemotherapy, to the study of the benefits of exercise for cancer patients, to the identification of specific genes causing testicular cancer, these research projects are charting new scientific territory, and the LAF is proud to help lead the way.

By supporting cutting-edge research from extremely talented researchers, the LAF hopes to gain a better understanding of the many issues of cancer survivorship and the biology of testicular cancer in order to enhance the quality of life for those living with, through and beyond cancer.

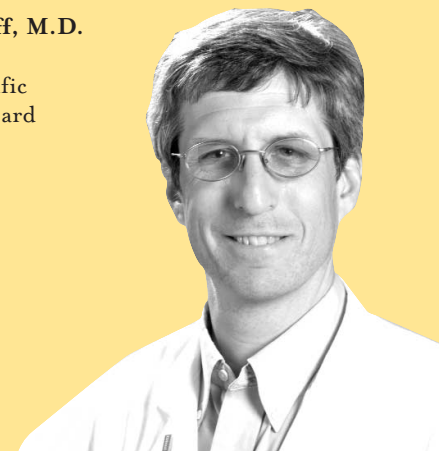
Since 1997, the LAF has awarded more than \$6.4 million for 55 medical and scientific research grants on the study of testicular cancer and survivorship issues. In 2003 alone, the LAF funded 22 new one- to three-year research projects. The LAF has also funded two groundbreaking survivorship clinics, the Cook Children's Hospital *Life After Cancer Program* and the University of Pennsylvania's *Living Well After Cancer Program*.

These awards are made possible by assistance from members of the LAF Scientific Advisory Board, leaders in medicine and science who guide the Foundation's research programs. This group personally reviews each of the grant applications we receive each year and selects only those found to be meritorious to warrant LAF funding. This process carefully ensures that financial contributions to the LAF make the greatest possible impact.

Each of the innovative projects funded by the LAF—and the dedicated researchers, doctors, and scientists leading them—is highlighted in the following pages. We know you'll enjoy learning about them, their work, and the difference they are making in the lives of millions of cancer survivors.

Steven Wolff, M.D.

Chairman,
LAF Scientific
Advisory Board





Building Strength

LAF Research Spotlight: Carolyn Kaelin, M.D., M.P.H., F.A.C.S.

Dr. Carolyn Kaelin understands how greatly cancer can affect quality of life. As the director of the Comprehensive Breast Health Center at Brigham & Women's Hospital in Boston, a surgical oncologist at the Dana-Farber Cancer Institute, and an assistant professor in surgery at Harvard Medical School, Kaelin has treated thousands of cancer patients. But even her years of experience as a surgical oncologist could not prepare her for her own breast cancer diagnosis in July of 2003.

"Since becoming a patient myself, I've developed a much longer list of quality of life parameters that are affected by treatment," says Kaelin. "The key is being able to address those issues so that one can start a 'new' life—and I say 'new' because life is never the same as it was before cancer."

Kaelin, who has long focused her research on exercise and quality of life, received a three-year grant from the LAF in 2002 to pursue an innovative study of the effects of rigorous upper-body exercise in breast cancer patients' recovery. The inspiration for the study began with one of her patients, a skilled rower who underwent a mastectomy, breast reconstruction, radiation, and chemo-therapy. The patient introduced Kaelin to Olympic gold medalist rower Holly Metcalf, founder of the Row As One Institute in Newton, Massachusetts. (See pg. 8)

After meeting Metcalf, Kaelin saw the perfect opportunity to challenge the common belief that breast cancer patients should decrease their exercise levels. "To lower the risk of lymphedema, the long-standing dogma has been to tell patients who have had axillary lymph nodes surgically removed to avoid upper body exercise, like rowing," explains Kaelin. Lymphedema, or swelling in the arm, occurs when lymph fluid is not able to travel from the arm through the underarm lymphatic drainage channels and back into the body. The swelling predisposes to infection of the arm and hand.

"The recommendation to avoid vigorous exercise seemed to be counterintuitive to protecting a patient's long-term health," says Kaelin, "given that exercise decreases the risk of other health conditions such as cardiovascular disease, diabetes, hypercholesterolemia, hypertension, osteoporosis, and colon cancer. It also improves mental and emotional health." In addition, for women who exercise, there may be a lower risk of breast cancer recurrence, asthma, and Alzheimer's disease.

Rowing is a popular sport in the Boston area, and neither Kaelin nor her oncology colleagues had ever seen lymphedema occur as a result of rowing. "This led to the question: does exercise actually minimize the chance of lymphedema?" Kaelin hypothesized that a controlled stress to the arm in the form of resistance weight training may enable the lymphatic channels in the axilla and collateral channels around the shoulder to dilate, and thus to accommodate an increased flow of lymph fluid during times of stress, such as an infection to the arm.

Kaelin began studying the effects of rowing on the recovery of breast cancer survivors in a collaboration with The Row As One Institute and its *WeCanRow Program* (Women Enduring Cancer Row). *WeCanRow*, which received a 2003 community grant from the LAF, is a free wellness program that uses rowing to increase strength, flexibility, and overall fitness in a team environment that builds a positive support system. Participants in *WeCanRow*, who meet once a week in a year-long rowing program, include women currently undergoing treatment to those who are 12 years past treatment.

The *WeCanRow* participants comprise part of the study's data; Kaelin and her research team, including Holly Metcalf and the Row As One Institute, have also

made the rounds of the national rowing meets to survey a population of more than 400 rowers with and without breast cancer. Study participants each completed a questionnaire and were measured for grip strength, arm circumference, and shoulder range of motion. The normative data accrued will form a knowledge base for a prospective trial of breast cancer survivors who begin a rowing program.

Of course, says Kaelin, not every breast cancer patient should immediately enroll in a rowing boot camp. "Exercise must be paced differently based on a patient's pre-treatment condition," she says, "but we hope the results of this study will be used to improve communication between physicians and breast cancer survivors regarding the extent to which a woman can safely participate in vigorous exercise after surgery and treatment." An avid cyclist herself, Kaelin intends to resume bicycling and join the *WeCanRow* program as soon as her own post-treatment physical therapy allows.

Kaelin's interest in medicine began at Smith College, when a stint working on medical laws in the State Assembly intrigued her. She switched from pre-law to pre-med and went on to receive her M.D. from The Johns Hopkins University School of Medicine and an M.P.H. from the Harvard School of Public Health. While she initially intended to practice obstetrics/gynecology, a medical school rotation with a team of surgical oncologists impressed her so much that she decided to pursue the field. "I liked the fact that taking care of a patient in surgical oncology is not a one-time event, like an appendectomy," says Kaelin. "It involves a long-term relationship with the patient, and with the patient's family and friends." She completed an internship and residency in surgery at the Tufts University New England Medical Center.

Kaelin particularly enjoys focusing on women's health and studying how cancer treatment affects quality of life differently among pre-menopausal and post-menopausal women. "Traditional breast cancer research funding has looked, appropriately so, at survival issues," says Kaelin. "Now treatment has become so successful that we are at the point where the majority of the breast cancer survivors outlive their cancer, so quality of life becomes extremely important. For the LAF to focus on the parameters that ultimately benefit long-term survival is visionary. They are truly leading the way."

Issues of Cancer Survivorship New Grants



Jill Bennett, Ph.D.

Oregon Health & Science University
Portland, Oregon
\$97,048 (2)
2003

Does Walking Work? A Study of Cancer Survivors

Many cancer survivors suffer persistent symptoms or treatment side effects that impede their quality of life and pursuit of health following treatment. One of these is fatigue, a debilitating symptom that often persists well beyond the treatment period. The presence of long-term fatigue can initiate a downward spiral that is difficult to stop. It can encourage cancer survivors to decrease their level of activity, which can lead to muscle deconditioning and the onset of chronic conditions such as obesity, heart disease, or diabetes.

One solution to reducing fatigue, and improving functional ability and health status, may be to increase daily physical activity. Dr. Jill Bennett, an assistant professor in the School of Nursing at the Oregon Health & Science University, will use funding from the LAF to test CHOICE (Choosing Healthy Options: I Can Exercise), a six-month intervention designed to increase walking exercise in people who are six months or more post-treatment for cancer. The study will be the first to employ motivational interviewing as a tool to help cancer

survivors reduce fatigue, improve functional ability, and improve health status. Dr. Bennett will measure specific participant outcomes (walking exercise, functional ability, fatigue, and health status) at the outset, three months, and six months and determine the efficacy of the CHOICE intervention. If CHOICE is successful in increasing walking exercise in cancer survivors in this pilot study, Dr. Bennett believes a larger efficacy trial in a clinic setting will be warranted. "If we can help people choose to change their physical activities, and offer support for those choices and encouragement to continue," says Dr. Bennett, "we may help people develop lifelong healthy activity habits."

Sharon Bober, Ph.D.

Dana-Farber Cancer Institute
Boston, Massachusetts
\$150,000 (3)
2003

Breast Cancer Risk After Hodgkin's Disease: Development of an Educational Intervention for Young Female Survivors



A number of recent studies show that at risk populations can significantly benefit from effective cancer risk education. Educational interventions can promote greater accuracy of cancer risk perceptions and provide increased knowledge about cancer. Dr. Sharon Bober will develop and pilot an educational intervention for young female Hodgkin's Disease (HD) survivors. Although the disease carries an excellent cure rate, female HD survivors have an exceedingly high risk for breast cancer (more than 30 to 50 times the normal risk) that is strongly associated with exposure to chest irradiation. In addition, female HD survivors are also at high risk for breast cancer at a young age. Recent research reveals that many female HD survivors are unaware of their increased breast cancer risk and are not engaging in risk management strategies such as

mammography and clinical breast exams, despite physician recommendations. "It is our goal to develop an educational intervention that may be easily implemented in a variety of settings and with a range of women, including those women who may have limited educational and financial resources," says Dr. Bober, an instructor in psychology at the Dana-Farber Cancer Institute. The intervention will inform HD survivors about breast cancer risk and risk reduction strategies while also helping them cope with the anxiety associated with increased awareness of breast cancer risk. Dr. Bober hopes that after further testing the intervention will be used across the country as an educational tool.

Robert Casey, Ph.D.

Yale University
New Haven, Connecticut
\$46,133 (1)
2003

An Evaluation of Summer Recreational Camps for Children Diagnosed with Cancer

For children diagnosed with a serious or chronic illness, the prospects of routine recreational activities, including summer camp, are often limited. Even when specialized programs are available, children and parents may have a range of concerns about attending. The Hole in the Wall Gang Camp and the Association of Hole in the Wall Camps have served more than 70,000 seriously ill children from 27 countries (free of charge). Anecdotal evidence suggests that such programs provide a valuable therapeutic intervention for children with chronic or life-threatening illnesses, but few research studies have evaluated the impact of a summer recreational camp experience on children diagnosed with cancer.



Dr. Robert Casey, the director of psychology training at the Yale School of Medicine, Child Study Center, will evaluate the physical and psychological impact of the Hole in the Wall Gang Camps on children with cancer and their siblings. The investigation will expand previous research conducted in Ireland by including camp programs in the United States. The study's qualitative measures will use open-ended questions to assess the experiences of children attending camp and their parents. Quantitative measures will assess the impact of camp participation on self-esteem, quality of life, and physical symptoms. The study, says Dr. Casey, could provide "a meaningful contribution to our understanding of effective intervention, and it would no doubt encourage a broader utilization of this approach."

Melinda Irwin, Ph.D.

Yale University
New Haven, Connecticut
\$150,000 (3)
2003

Physical Activity and Breast Cancer Survivorship

Surviving breast cancer usually means enduring medical treatments with side effects such as decreased physical activity, weight gain, and diminished quality of life. Dr. Melinda Irwin, an assistant professor in the Department of Epidemiology and Public Health at the Yale School of Medicine, recently reported that women diagnosed with

"A physical activity intervention aimed at favorably changing these factors in breast cancer survivors represents a novel approach to improving breast cancer survivorship, as well as reducing risks associated with other cancers and chronic diseases."

breast cancer were less physically active within their first year after diagnosis than they were one year before diagnosis. She reported that women who decrease their physical activity the most experience the greatest weight gain two years after diagnosis and that this weight gain is adversely associated with breast cancer recurrence and death. Physical inactivity and weight gain are also associated with a less favorable hormone profile, which can in turn promote tumor growth and breast cancer recurrence.

Dr. Irwin's new study, a physical activity intervention, will recruit newly diagnosed breast cancer survivors into a six-month randomized controlled exercise intervention. The study will examine the effect of exercise versus usual care on physical activity levels, body weight and fat, quality of life, and hormones. "A physical activity intervention aimed at favorably changing these factors in breast cancer survivors represents a novel approach to improving breast cancer survivorship, as well as reducing risks associated with other cancers and chronic diseases," says Dr. Irwin. "Results from such a behavioral intervention could influence the way men and women with cancer are managed in the future."

Jennifer Ligibel, M.D.

Dana-Farber Cancer Institute
Boston, Massachusetts
\$96,862 (2)
2003

Pilot Study of the Effects of an Exercise Intervention on Insulin Levels in Breast Cancer Survivors

More than 200,000 women in the U.S. are diagnosed with breast cancer each year. A significant number of these women will develop a recurrence of their breast cancer months to years later—and ultimately die of the disease. Recent research shows that obesity is a risk factor for breast cancer recurrence. Although the mechanism is not well understood, it is known that obese women have higher estrogen and insulin levels. A recent study demonstrated that breast cancer patients with higher fasting insulin levels at the time of diagnosis are also at increased risk of developing a breast cancer recurrence or dying than are patients with lower insulin levels.

Dr. Jennifer Ligibel, a physician at Dana-Farber Cancer Center and Faulkner Hospital in Boston, will look at the impact of a 16-week exercise intervention on fasting insulin levels in

"Most treatments for breast cancer have side effects. It is highly desirable to find additional ways to decrease breast cancer risk that are associated with less toxicity."

a group of nondiabetic breast cancer survivors. If a change in insulin levels is detected over the course of the exercise intervention, the findings would suggest that exercise can produce a change in insulin levels in breast cancer survivors and would lead to a larger trial designed to improve survival through exercise in women with breast cancer. "Most treatments for breast cancer have side effects," says Dr. Ligibel. "It is highly desirable to find additional ways to decrease breast cancer risk that are associated with less toxicity."



Alexander Ng, Ph.D.

Marquette University
Milwaukee, Wisconsin
\$149,444 (3)
2003

Mechanisms of Fatigue in Cancer

Symptomatic fatigue can occur regardless of cancer type, stage, or treatment and can persist well after treatment has ended. Most research to date on cancer fatigue research has focused on characterizing its psychosocial or neuropsychological aspects, while little is known about the actual physiological, or even psychological, mechanisms of fatigue in cancer patients.

Dr. Alexander Ng, an assistant professor in the Exercise Science Program at Marquette University, hypothesizes that altered muscle function or muscle fatigue could contribute to the overall symptom of fatigue in cancer patients and that altered muscle function could result primarily from the cancer (secondary to therapy or inactivity). Dr. Ng will investigate changes in muscle function as they relate to excessive muscle fatigue and general symptomatic fatigue. His study will assess cancer patients' neuromuscular mechanisms of fatigue, alterations in muscle oxidative metabolism, and mechanisms of muscle weakness. The study also will measure physical activity and assess fatigue, depression, and cognitive function.

Dr. Ng, a survivor of testicular cancer, hopes that a clearer understanding of fatigue in persons with cancer will lead to targeted interventions to combat fatigue and that knowledge of specific mechanisms of fatigue will lead to targeted pharmacological treatments.



Crystal Park, Ph.D.

University of Connecticut
Storrs Mansfield, Connecticut
\$99,751 (2)
2003

Predicting and Understanding Positive Life Changes in Young Adult Cancer Survivors

The experience of facing and surviving cancer may bring about transformative change in many areas of a survivor's life, including interpersonal relationships, life philosophies, goals, values, spirituality, and lifestyle. Young adults (those in their 20s, 30s, and 40s) may experience distress and more traumatic reactions to the cancer, given its unexpected and 'off-time' nature. However, Dr. Crystal Park, an associate professor of psychology at the University of Connecticut, believes that young adult survivors may also have more opportunities to make transformative changes in their lifestyles, attitudes, and psychosocial development.

Dr. Park will launch a study to examine positive changes in a group of 200 young adult cancer survivors. Assessments will be made via questionnaire at the beginning of the study and one year later to examine the extent and patterns of positive life changes following cancer and to examine the process and determinants of these positive changes over time. A particular focus is positive changes in health behaviors made in response to surviving cancer. The study aims include an examination of personal resources and coping processes as predictors of positive changes, relations of positive changes with indices of physical and psychological well-being, and the time course of positive changes. Results of this study will inform interventions for cancer survivors to facilitate positive life changes in relationships, coping skills, and health and lifestyle behaviors.

Bernardine Pinto, Ph.D.

The Miriam Hospital
Providence, Rhode Island
\$149,345 (3)
2003

Translating Research-based Physical Activity Promotion Among Young Cancer Survivors: A Pilot Study

With improvements in detection and treatment for cancer, the survivor population has grown, making secondary prevention increasingly important.

With improvements in detection and treatment for cancer, the survivor population has grown, making secondary prevention increasingly important. Many who have survived a cancer diagnosis and treatment are still plagued by health issues such as increased risk of cardiovascular disease and/or emotional distress. Studies in research settings have demonstrated that physical activity interventions among cancer survivors can improve their physical functioning, quality of life, mood, and level of fatigue.



Dr. Bernardine Pinto will launch a pilot study to examine the feasibility and effects of a telephone-based physical activity program offered by volunteers (specifically, Reach to Recovery volunteers of the local office of the American Cancer Society) to 25 breast cancer survivors. Dr. Pinto is an assistant professor in the Department of Psychiatry & Human Behavior at The Miriam Hospital and Brown University School of Medicine. The goals of the study are to determine the feasibility of volunteer delivery and effectiveness of this intervention on participants' level of physical activity. The secondary goals are to determine the effect of the intervention on mood, quality of life, physical functioning, and fatigue and to obtain both the volunteers' and the participants' evaluations of the intervention. If the study results are promising, community volunteers could offer this intervention to many more survivors.

Michel Henry-Amar, M.D., Ph.D
John Raemaekers, M.D., Ph.D
Centre Regional Francois Baclesse,
Service de Recherche Clinique
France
\$98,500 (2)
2003
**Long-term Survivorship of Hodgkin's
Lymphoma Patients Enrolled in
Successive Prospective EORTC
Lymphoma Group Trials**

While an increased awareness of emotional and socio-economical consequences of treatment for Hodgkin's lymphoma is emerging, a thorough study of long-term survivors that includes all these aspects has never been undertaken.

Hodgkin's lymphoma is a malignant cancer that affects patients of all ages, particularly those between 18 and 40 years. The majority of patients with Hodgkin's lymphoma can be cured of their disease with current treatment strategies: chemotherapy, radiation therapy, or a combination of both. However, long-term survivors face numerous complications such as secondary cancers, cardiovascular events, pulmonary toxicity, infertility, hypothyroidism, neuropathies, fatigue, and others. While an increased awareness of emotional and socio-economical consequences of treatment for Hodgkin's lymphoma is emerging, a thorough study of long-term survivors that includes all these aspects has never been undertaken.

Dr. Michel Henry-Amar, Dr. John Raemaekers and the European Organization for Research and Treatment of Cancer (EORTC) Lymphoma Group will undertake a study of patients from previous clinical trials performed by the EORTC. Over 6,500 patients have been enrolled in nine consecutive randomized trials since 1964, and follow-up data of at least ten years is available for more than 3,000 patients (2,000 of whom are still alive). Data on survival status, relapse details, and long-term toxicities will be updated and documented in detail, and questionnaires concerning quality of life and lifestyle will be sent to all living patients for a cross-sectional analysis. Drs. Henry-Amar and Raemaekers believe the results of the study will aid in the development of strategies for prevention and intervention not only with Hodgkin's lymphoma but with other cancers as well.

Ian Thornley, M.D.
Children's Hospital Corporation
Boston, Massachusetts
\$150,000 (3)
2003
**TGF- β in Children and Adults with
Chronic Graft-Versus-Host Disease**

Allogeneic hematopoietic stem cell transplantation (HSCT)—high-dose radio-chemotherapy followed by the transplantation of blood or bone marrow cells from another person—is a therapy used for many children and adults with high-risk cancers of the blood and lymphatic tissues. Unfortunately, the donor immune system may attack normal body tissues in these individuals, resulting in graft-versus-host disease (GVHD). Chronic GVHD is the leading cause of death and disability in survivors of HSCT. An especially disabling form of chronic GVHD is the sclerodermatous variant (ScGVHD), in which the skin may become scarred and fixed, and movement at joints may become profoundly limited.

Dr. Ian Thornley, a pediatric bone marrow specialist at The Children's Hospital and Dana-Farber Cancer Institute in Boston, will test whether transforming growth factor β (TGF- β) generated in the course of regulatory immune cell activity plays an important role in the development of ScGVHD in human HSCT recipients. The study's objectives will be to determine if certain forms of the gene for TGF- β are more common in donor-derived cells from patients developing ScGVHD, and if TGF- β levels are increased in the skin and blood of affected individuals. Study participants are HSCT survivors, with and without chronic GVHD, followed in the pediatric and adult transplant programs at the Dana-Farber Cancer Institute. "This research path stems directly from my experience caring for children whose cancer survivorship has been seriously impacted by this disabling complication of transplant," says Dr. Thornley. "Better therapies are desperately needed."

Issues of Cancer Survivorship Current Grants

Smita Bhatia, M.D., M.P.H.
City of Hope National Medical Center
Duarte, California
\$150,000 (3)
2002
**Key Adverse Events After Childhood
Cancer: Follow-up of the Children's
Oncology Group Cohort**

The objective is to determine if patients who develop key adverse events have a genetic susceptibility to do so and if an interaction between genetic susceptibility and environment plays a role in the development of these events.

For most children diagnosed with cancer today, cure is a likely outcome. With this success comes a heightened recognition of the need to reduce long-term treatment effects and improve quality of life. While existing research has focused on demographic and treatment-related risk factors in late effects among childhood cancer survivors, Dr. Smita Bhatia's project will establish a mechanism to identify the genetic risk factors that contribute to key adverse events such as congestive heart failure, myocardial infarction, ischemic stroke, avascular necrosis, and subsequent malignant neoplasms. The study focuses on survivors registered with the Children's Oncology Group, which develops and coordinates cancer clinical trials at 238 member institutions. The project will explore gene-environment interactions using case (patients who have developed these outcomes) and control patients' DNA and RNA. The objective is to determine if patients who develop key adverse events have a genetic susceptibility to do so and if an interaction between genetic susceptibility and environment plays a role in the development of these events.

While the LAF-funded study is still in progress, Dr. Bhatia has published preliminary findings in the *British Journal of Haematology*. Dr. Bhatia has focused her entire research career on the health of cancer survivors, which she says has always been her primary interest.



Andrea Canada, Ph.D.

The University of Texas M.D. Anderson Cancer Center
Houston, Texas
\$98,152 (2)
2001

A Pilot Intervention to Enhance Psychosexual Development in Adolescents and Young Adults with Cancer

In the transition from youth to adulthood, every young person faces the challenges of developing the skills necessary to establish intimate relationships, integrating physiological changes that begin with puberty, and beginning to think about long-term relationships and parenthood. For the individual with cancer, these challenges are made even more complex by concerns about immediate and late effects from the disease and its treatment. Such concerns, if not addressed, may contribute to the negative sexual self-image of adolescent and young adulthood cancer survivors and lead to later difficulties with sexual self-esteem and sexual function.

Dr. Andrea Canada received a two-year grant from the LAF to develop and evaluate a brief counseling intervention that will facilitate healthy sexual development in adolescents and young adults with cancer. Project participants, age 15 to 25, are recruited from The University of Texas M.D. Anderson Cancer Center's Adolescent and Young Adult Program. Dr. Canada believes that participation in the intervention will increase the patients' cancer-specific knowledge regarding sexual issues, improve their body and self-image, lessen their sexual/relational concerns, and decrease their overall level of psychological distress. Should the pilot be successful, further research will involve the creation of an Internet-based, interactive version of the intervention.

Dr. Canada's graduate and post-graduate work focused on psychosocial oncology, and she has developed several interventions to help cancer patients reduce emotional stress, increase effective coping, and improve immune functioning.

Robert Ferguson, Ph.D.

Dartmouth Medical School
Lebanon, New Hampshire
\$189,791 (5)
2000

Behavioral Management of Cognitive Impairment Associated with Chemotherapy

Research shows that up to 40 percent of cancer patients demonstrate long-term decline in memory and attention function after chemotherapy. Given that approximately one million Americans undergo chemotherapy each year, a substantial number of people live with cognitive change following cancer treatment.

Dr. Robert Ferguson is leading a multi-phase research project designed to develop and evaluate the efficacy of a brief cognitive-behavioral treatment designed to help cancer survivors manage changes in memory function following



chemotherapy. If demonstrated to be effective, this treatment may provide a helpful, drug-free alternative to aid people's adaptation to survivorship and optimize daily memory function and quality of life. The overall goal of the project is to develop a user-friendly, brief, and practical cognitive-behavioral treatment that helps improve daily cognitive function and quality of life for all cancer survivors who experience memory problems after chemotherapy.

"The emphasis on a brief treatment package is made in order that dissemination to medical settings such as oncology and primary care can be a reality," says Dr. Ferguson, a licensed clinical psychologist and an assistant professor of psychiatry at Dartmouth Medical School in the Behavioral Medicine Section. "It is these settings where cancer survivors are most likely to hear about and find help for cognitive symptoms resulting from cancer treatment."

Sophie D. Fosså, Prof.Dr.med.

The Norwegian Radium Hospital
Oslo, Norway
\$150,000 (3)
2002

Post-treatment Fertility in Young Adult Former Cancer Patients

Dr. Sophie Fosså's project takes advantage of two existing national registries in Norway to determine and analyze the incidence of parenthood after cancer treatment. Her study documents post-treatment fertility in 19,980 former cancer patients who were less than 45 years old at diagnosis and treated at Norwegian Radium Hospital in Oslo, Norway during 1971 and 1998. By linking this information with the Medical Birth Registry of Norway, which contains medical information about each child born in Norway after 1967, the project will compare age- and gender-adjusted samples from the normal population to identify fertility statistics and pregnancy-related and perinatal problems among cancer survivors.

The study's findings will help increase oncologists' understanding and awareness of post-treatment infertility issues in cancer patients, indicate what modifications of treatment are possible to preserve fertility, and help promote early detection of expected problems in pregnant women with a previous cancer diagnosis. The research results will also be used to counsel new cancer patients on their chance of post-treatment parenthood.

Dr. Fosså has conducted clinical work at the Norwegian Radium Hospital since 1968 as a medical oncologist and radiotherapist and has received several national and international research awards. She is currently head of the NRH's section of long-term outcome in cancer patients.

Judith Jacobson, Dr.P.H.

Columbia University
New York, New York
\$146,048 (3)
2001

Complementary or Alternative Medicine (CAM) Outcomes in the Long Island Breast Cancer Study Project Follow-up

Many cancer patients use both conventional and complementary/alternative medicine (CAM) during their course of treatment. In fact, a recent survey found that nearly 40 percent of adults in the U.S. reported using CAM, which ranges from participation in support groups to the use of nutritional supplements.

Because the oncology community knows very little about the effects of commonly used CAM, Dr. Judith Jacobson proposes to assess the effects of CAM on breast cancer. Her three-year research project will study the predictors and outcomes of the use of CAM among breast cancer patients in the Long Island Breast Cancer Study Project case-control study.

The study will conduct detailed telephone interviews with approximately 1,500 breast cancer survivors to identify what CAM patients are actually using, the factors that lead to their use of CAM, and the outcomes that may be associated with CAM use. The study will also collect data on prognostic factors, treatment, and outcomes from patients' medical records.

"We hope that our research will encourage clinicians who care for cancer patients to ask them about their CAM use," says Dr. Jacobson, who currently serves as an assistant professor of clinical epidemiology at the Mailman School of Public Health at Columbia University. She also hopes the study findings "will identify CAM treatments that show safety and possible efficacy and may be worth studying further in clinical trials."

Carolyn Kaelin, M.D., M.P.H., F.A.C.S.

Dana-Farber Cancer Institute
Boston, Massachusetts
\$150,000 (3)
2002

The Evaluation of Lymphedema and Arm Symptoms in Rowers With and Without Breast Cancer

Exercise is proven to lower the risk of many medical conditions while improving mental health. However, breast cancer patients whose treatment includes surgical excision of the axillary lymph nodes are typically instructed to limit arm activity for fear of developing lymphedema (fluid backlogging in the arm causing swelling). Dr. Carolyn Kaelin believes that this long-standing directive, which is not data-driven, may in fact be counterproductive.

Dr. Kaelin's primary objective in this study is to assess lymphedema in survivors who have been treated for unilateral breast cancer with axillary surgery. Her hypothesis is that arm exercises enable an increase in arm lymphatic flow. The study seeks to build data on rates of lymphedema and arm symptoms among females with and without breast cancer who perform rigorous upper-body exercises. This information will form a knowledge base

for a trial of breast cancer survivors who begin a rowing program to determine if survivors can safely participate in a rigorous upper extremity exercise program. The results of the study will be used to improve recommendations made to breast cancer survivors after surgery.

Since being diagnosed at age 42 with breast cancer in July of 2003, Dr. Kaelin has made public appearances to discuss the disease and the positive impact of exercise on cancer recovery. She is director of the Comprehensive Breast Health Center at Brigham & Women's Hospital and an assistant professor in surgery at Harvard Medical School.

Alice Kornblith, Ph.D.

Dana-Farber Cancer Institute
Boston, Massachusetts
\$148,657 (3)
2001

Psychosocial Adjustment of the Older Survivor of Breast and Endometrial Cancer

The challenges faced by a 30-year-old testicular cancer survivor are quite likely very different than those faced by a 70-year-old breast cancer survivor. Yet despite the fact that 60 percent of cancer patients are 65 and older, little research exists on the specific issues facing older cancer patients. Dr. Alice Kornblith's study will serve to better understand the long-term impact of cancer treatments on older survivors' quality of life.

Using breast and endometrial cancer (the most prevalent cancers in women) as paradigms for the types of issues older women cancer survivors face, Dr.

Kornblith will identify both the strengths and problems that affect their adjustment, particularly as compared to younger survivors. The study will use telephone interviews to identify the factors that increase older cancer survivors' vulnerability to the stress of having cancer, as well as the factors that buffer the effects of these stresses.

Dr. Kornblith predicts that her research findings will enable the development of interventions that more effectively meet the psychosocial and medical needs of the older breast and endometrial cancer survivor. "Greater knowledge in this area should lead to more enlightened understanding and treatment of survivors, both medically and psychologically," says Dr. Kornblith, who serves as both director of Psycho-Oncology Research in the Women's Cancers Program at the Dana-Farber Cancer Institute as well as a senior research scientist in the Harvard School of Public Health.

Ann C. Mertens, Ph.D.

University of Minnesota
Minneapolis, Minnesota
2002
\$149,984 (3)

Radiation Dosimetry for Childhood Cancer Survivors

Dr. Ann Mertens and her research team are conducting state-of-the-art radiation dosimetry (measuring the dose of radiation a patient receives and where in their body they receive it) in childhood cancer survivors to quantify the risk of secondary cancers associated with radiation dose. The project will focus on two nested case/control studies of participants in the Childhood Cancer Survivor Study (CCSS), a cohort of over 14,000 survivors of childhood and adolescent cancer who were diagnosed at one of 25 institutions in the U.S. or Canada. It will quantify the risk of secondary breast cancer associated with radiation dose to specific sites/regions of the breast, considering additional characteristics such as age at exposure, chemotherapy, and hormonal-related factors. It will also quantify the risk of subsequent thyroid cancers in relation to radiation dose to the thyroid gland.

As an associate professor in the Department of Pediatrics at the University of Minnesota and project director of the Childhood Cancer Survivor Study, Dr. Mertens has an especially strong interest in childhood cancer survivors. She hopes that the study's findings will help the oncology community better understand the long-term effects of radiation therapy and make it possible to identify individuals at risk for these effects.

Kevin C. Oeffinger, M.D.

The University of Texas Southwestern
Medical Center
Dallas, Texas
\$100,000 (2)
2002

Feasibility Study for Project VISION: A Virtual Center for Survivors

A significant percentage of childhood cancer survivors are at risk for a wide array of late effects related to their previous cancer therapy. Risk-based health care attempts to mitigate these effects through techniques developed with the survivors' specific risk factors in mind. Unfortunately, most survivors do not receive risk-based health care for a variety of reasons, including lack of awareness of risks and need for follow-up; lack of knowledge on the part of primary health care providers; lack of programs serving

adult survivors; and lack of communication between the cancer center, the survivor, and the primary health care provider.

Dr. Kevin Oeffinger hopes to address this issue with the Survivor Virtual Information Center, a source of ongoing communication and information for adult cancer survivors. The LAF grant will help Dr. Oeffinger determine the feasibility of the Center, which would bring together the expertise of physicians, nurse practitioners, and social workers and provide information to survivors and health care providers via a website and a toll-free telephone number.

"Studies to enhance survivor health care and understand methods to effectively communicate with survivors are critically important," says Dr. Oeffinger, a professor of family practice and pediatrics at The University of Texas Southwestern Medical School. "This study begins to lay the foundation for future work in this area."

Christopher Recklitis, Ph.D., M.P.H.

Dana-Farber Cancer Institute
Boston, Massachusetts
\$150,000 (3)
2000

Detecting Psychological Late Effects in the Cancer Survivor Clinic: Development of a Universal Screening Program

The impact of cancer and cancer treatment on the psychological functioning of survivors is an area that is widely acknowledged as important, but there are very few tests that have been adapted to the problems faced by cancer survivors. In an extension to a grant awarded by the LAF in 2000, Dr. Christopher Recklitis



will continue to develop a Computer Assisted Survivor Screening (CASS) program designed to take standard measures of physical and mental health functioning and adapt them for screening adult survivors of childhood cancers.

The current project aims to refine the CASS by screening a large sample of adult

survivors of childhood cancer using standardized measures of psychological functioning. Dr. Recklitis will use the results of this initial screening to develop a more concise computerized screening, which will be pilot tested in three survivor clinics to determine its validity and reliability. The successful development of the screening process will serve as the basis of a national cooperative group trial to be made available as universal screening to all medical providers serving childhood cancer survivors. Preliminary results of the study have been published in the *Journal of Clinical Oncology*.

Dr. Recklitis is chief psychologist for the David B. Perini, Jr., Quality of Life Clinic at the Dana-Farber Cancer Institute and a clinical instructor of psychology at Harvard Medical School.

Eileen Shinn, Ph.D.

The University of Texas M.D. Anderson Cancer Center
Houston, Texas
\$150,000 (3)
2002

Depression Treatment of Ovarian Cancer Patients

Depressive disorders are the most common psychiatric disorder in cancer patients, affecting between 20 to 50 percent of all patients. Untreated major depression is a critical hurdle in cancer patient care and survivorship, as it can undermine symptom management, heighten pain, reduce adherence to treatment, and compromise immune functioning. Yet despite the availability of effective treatments, treatment rates for depressed cancer patients are low. In many cases, cancer patients who are most in need of treatment for depression have the most difficulty accessing treatment due to problems with pain, physical and social functioning, and disease progression.

Dr. Eileen Shinn will develop and evaluate a pilot in-home psychotherapy intervention for depressed ovarian cancer patients using telephone therapy and a structured cognitive behavioral journal. The goals of the project are to improve patient depressive symptom level and to evaluate the feasibility and acceptability of the intervention to patients.

Dr. Shinn is a clinical psychologist and an instructor at The University of Texas M.D. Anderson Cancer Center. "I have been struck with the insidious nature of depression and the dramatic change that

occurs once a person's depression is effectively treated," she says. "Our intervention has the potential to provide a cost-effective, easily disseminated, and accessible means for treating depression in patients who may otherwise not be able to receive treatment."

Kenneth Tercyak, Ph.D.

Georgetown University
Washington, D.C.
\$150,000 (3)
2001

Promoting Health Behaviors Among Pediatric Cancer Survivors

"Very few, if any, programs take a comprehensive look at behavior and lifestyle in children who have survived cancer," explains Dr. Kenneth Tercyak, assistant professor of oncology and pediatrics at the Lombardi Comprehensive Cancer Center at Georgetown University. "We know very little about the most effective ways of promoting healthy behaviors in this vulnerable population."

"Our project is designed to change the way that children who have survived cancer take care of themselves on an everyday basis — from what they eat, to how they exercise, to not smoking — to help them live a healthier lifestyle."

With a three-year grant from the LAF, Dr. Tercyak will help fill this information void by developing and pilot testing a psycho-educational group intervention to promote healthy behavior among adolescent survivors of cancer and determining the intervention's effectiveness on the outcomes of interest. The intervention will focus on healthy behaviors such as sunscreen use, physical activity, medical check-up, and proper nutrition while will also addressing negative behaviors such as experimentation/use of tobacco and alcohol, excessive sun exposure, and high-fat diet.

"Our project is designed to change the way that children who have survived cancer take care of themselves on an everyday basis—from what they eat, to how they exercise, to not smoking—to help them live a healthier lifestyle," says Dr. Tercyak. If the intervention is successful, Dr. Tercyak will develop and test a method to improve survivorship in adolescents that could prove to be widely applicable in other programs.

John R. Wingard, M.D.

University of Florida College of Medicine
Gainesville, Florida
\$50,000 (1)
2002

Unexamined Issues for Survivors and Their Spouses After Blood and Marrow Transplantation

The intense, often life-threatening experience of blood or marrow transplantation (BMT) can impact patients and their families significantly at every conceivable level, but there are a number of important BMT survivorship issues that have yet to be investigated. Dr. John Wingard and his team are conducting research into five areas: 1) the effect of the BMT experience on the preventive health behaviors of survivors and spouses post-BMT; 2) the relationship between psychological growth and spirituality post-BMT; 3) the marital quality of spouses and survivors, and how it relates to overall quality of life; 4) the perceived value survivors place on life with various health conditions following BMT; and 5) using findings to create an empirically validated "toolbox" for QOL assessment in future studies.

The results will contribute to the design of future interventions to increase physical, psychological, marital, and spiritual well-being post-transplant.

The current study is an outgrowth of work completed by Dr. Wingard and funded by the National Cancer Institute. The five aforementioned areas of study were not included in the original NCI grant proposal, so the LAF is providing funding for analysis planning, data management, and statistical analyses to answer these important questions. Dr. Wingard believes the results will contribute to the design of future interventions to increase physical, psychological, marital, and spiritual well-being post-transplant.

Dr. Wingard is professor of medicine, professor of pediatrics, director of the Blood and Bone Marrow Transplantation Program, and associate director of clinical and translational research at the University of Florida College of Medicine and Shands Cancer Center.

Diane Wright, Ph.D.

Massachusetts General Hospital
Boston, Massachusetts
\$100,000 (2)
2003

Microinjection of Sugars: A Novel System for Long-term Preservation of Human Oocytes

Current statistics suggest that one in 52 females under the age of 40 is diagnosed with cancer.

Current statistics suggest that one in 52 females under the age of 40 is diagnosed with cancer. The acute toxicity of anticancer treatments has one dramatic and common side effect: injury to the reproductive system. Although young men often experience successful gamete preservation prior to cancer treatment, women are still facing the challenge of attempting reproduction after treatment. A successful method to prevent damage to the oocytes, cryopreservation (freezing) prior to treatment, could alleviate the emotional consequences of cancer therapy for women afflicted not only with a malignant disease but also the possible impairment of their reproductive potential as well.

A procedure developed by Massachusetts General Hospital (MGH) fertility researchers involves the microinjection of a sugar found in nature, trehalose, into the oocyte prior to cryopreservation. Dr. Diane Wright hypothesizes that sugars introduced into oocytes can stabilize the oocytes and protect them against the stresses associated with freezing; her current study aims to develop long-term cryopreservation techniques for human oocytes. The specific objectives are to determine the optimal thermodynamic conditions that will permit successful freezing, storage, and subsequent recovery of viable oocytes and to demonstrate the success of combining the most effective sugar condition with the cryopreservation technique and development of offspring. Dr. Wright is director of the Vincent IVF Embryology Laboratory at MGH.

Lonnie Zeltzer, M.D.

Brad Zebrack, Ph.D.
University of California Los Angeles
Los Angeles, California
\$149,778 (3)
2001

Psychosocial, Behavioral and Pain Outcomes in Long-term Survivors of Childhood Cancer

Thanks to advances in diagnostic and treatment technologies and the coordination of childhood cancer treatment protocols via clinical trials, three of every four children and adolescents diagnosed and treated for cancer will be cured. This medical progress presses scholars, clinicians, and social service organizations to consider the quality of life of those young people who have successfully completed treatment.

The research being conducted by Dr. Lonnie Zeltzer and Dr. Brad Zebrack makes use of the Childhood Cancer Survivor Study (CCSS), the largest epidemiological cohort of childhood cancer survivors and sibling controls known to date. The project's goal is to provide greater understanding of the prevalence, characteristics, and predictors of the psychosocial health status, health risk behaviors, and pain sequelae among long-term survivors of childhood cancer. "This work represents an effort to understand and respond to the needs of childhood cancer survivors," says Dr. Zeltzer, "and will have significant implications for the development of appropriate health programs, policies, and practices that support the quality of life and survival of these individuals." Articles relating to the ongoing study are in progress, in review, and published.

Dr. Zeltzer is currently a professor of Pediatrics, Anesthesiology, Psychiatry and Behavioral Sciences at the David Geffen School of Medicine at UCLA. Dr. Zebrack is an assistant professor at the USC School of Social Work.



Issues of Cancer Survivorship Completed Grants

Craig Earle, M.D.

Dana-Farber Cancer Institute
Boston, Massachusetts
\$95,287 (2)
2000

Colorectal Cancer Survivors: Assessing Health Service Utilization

Research shows that a major determinant of outcomes for cancer survivors is the competing risk from other medical conditions. The objective of Dr. Craig Earle's two-year study was to examine the interactions between cancer survivors and the health care system in order to better understand survivors' medical needs and use of health resources, and whether there is any discrimination against survivors in the delivery of preventive services.

The project analyzed the Medicare claims



of more than 14,000 five-year colon cancer survivors and compared the quality of health care they received to that of non-cancer patients. The study found that survivors were consistently less likely to receive recommended interventions for both acute and chronic non-cancer-related medical conditions, suggesting that the cancer diagnosis may divert attention from other important health problems. In addition, some cancer survivors appear to use specialists as their primary physicians, although research shows that these providers may be less interested in providing increasingly complex primary care. "Whether due to patient or physician factors or both, cancer survivors appear to be a vulnerable patient population as their cancer diagnosis may shift attention away from important non-cancer problems and

providers," says Dr. Earle, an assistant professor of medicine at Harvard Medical School and a board-certified oncologist at the Dana-Farber Cancer Institute and Brigham & Women's Hospital. An abstract of his research was presented at the annual meeting of the American Society of Clinical Oncology in 2002.

R. Brian Giesler, Ph.D.

Indiana University
Indianapolis, Indiana
\$97,071 (2)
1999

Long-term Quality of Life of Testicular Cancer Survivors and their Spouses Following Chemotherapy

Although cisplatin-based chemotherapy has dramatically increased survival rates in men diagnosed with testicular cancer, concern has been raised over the long-term impact of the disease and treatment on quality of life. Prior research on this topic has often produced contradictory or incomplete findings.

Dr. R. Brian Giesler set out to evaluate quality of life of testicular cancer survivors and their spouses following chemotherapy. The objectives of the study were to compare testicular cancer survivors treated with chemotherapy and their spouse/partners to age-matched control groups on disease-specific and generic measures of quality of life; to determine whether and to what extent disease- and treatment-related morbidity predicts quality of life of testicular cancer survivors and their spouse/partners; and to assess the psychometric properties of quality of life scales modified for use with testicular cancer populations.

Dr. Giesler recruited testicular cancer patients treated with chemotherapy in full remission for at least three years and their spouse/partners from patients served by the Indiana University Medical Center. He also recruited age-matched, healthy controls for survivors and spouses using an acquaintance-identification procedure.

Dr. Giesler intends data and observations resulting from this study to contribute to the design of interventional therapies to address survivorship issues. "Without a comprehensive understanding of quality of life in survivors and their spouse/partners," he says, "health care professionals will be unable to provide effective interventions to relieve the long-term physical and psychological burdens that can occur after chemotherapy."

Ellen Gritz, Ph.D.

The University of Texas M.D. Anderson Cancer Center
Houston, Texas
\$205,539 (5)
1998

Neurocognitive Function and Quality of Life after Testicular Cancer Treatment

Such findings can be used to better inform treating oncologists, as well as testicular cancer patients, about the potential important consequences of treatment regimens.

Cognitive decline or dysfunction after chemotherapy may be a by-product of the treatment itself, a symptom of depression or anxiety, or a result of other quality of life difficulties. Dr. Ellen Gritz is spearheading a study focusing on the effects of chemotherapy on neurocognitive function and quality of life in testicular cancer patients. The extended five-year study will characterize neurocognitive functioning (e.g. memory, attention, concentration, oral fluency, and dexterity) and quality of life in this patient population and will examine the dose-response relationship between neurocognitive functioning and dose chemotherapy. Patients are studied before and after chemotherapy treatments, and men treated only with surgery for testicular cancer are studied for comparison.

"The findings will have substantial preventive implications if specific curative chemotherapeutic combinations are found to be associated with increased risk of cognitive decline, or if men at the highest risk of neurocognitive loss can be identified earlier after diagnosis," says Dr. Gritz. Such findings can be used to better inform treating oncologists, as well as testicular cancer patients, about the potential important consequences of treatment regimens. Dr. Gritz is professor and chair of the Department of Behavioral Science and Frank T. McGraw Memorial Chair in the Study of Cancer at The University of Texas M.D. Anderson Cancer Center.

Derek Raghavan, M.D., Ph.D.

Cleveland Clinic
Taussig Cancer Center
Cleveland, Ohio
\$100,000 (2)
2000

Long-term Follow Up of Treatment of Testis Cancer

Dr. Derek Raghavan and his research team turned to the LAF for funding to complete an important program to determine the incidence of late complications of patients treated for testicular cancer. The program hypothesized that patients cured of metastatic germ cell tumors and treated with cisplatin-based chemotherapy were more likely to develop major late complications of chemotherapy, including higher rates of cardiovascular and cerebrovascular disease, pulmonary and neurological complications, psycho-social dysfunction, and second malignancies.

“This is the first population-based survey to illustrate the costs of successful, curative treatment of advanced testis cancer and will form the basis for future recommendations for post-treatment surveillance and follow-up.”

The research team used the records of the Los Angeles Tumor Registry to identify patients treated in Los Angeles County for a ten-year period until 1985. They then sent letters to the physician of record, followed by requests to identified patients for information about a broad range of demographic, treatment-related, and psychosocial issues. Patients were asked to provide a case-control: a friend of approximately the same age who was known to the patient before the diagnosis and not known to have a history of testis cancer. Even as the first surveys were returned, Dr. Raghavan and his team began to see preliminary evidence to support their hypothesis, including multiple cases of cardiovascular disease, known history of hypercholesterolemia, cisplatin-related long-term toxicities, malignant melanoma, and evidence of psychosocial disruption. “This is the first population-based survey to illustrate the costs of successful, curative treatment of

advanced testis cancer and will form the basis for future recommendations for post-treatment surveillance and follow-up,” says Dr. Raghavan, the newly appointed director of the Cleveland Clinic Taussig Cancer Center in Cleveland, Ohio. Raghavan served as chief of oncology at USC’s Norris Comprehensive Cancer Center when he received the LAF grant.

Mary Rourke, Ph.D.

Children’s Hospital of Philadelphia
Philadelphia, Pennsylvania
\$146,664 (3)
2000

Promoting the Successful Adaptation of Young Adult Cancer Survivors: An Intervention Study

“Our ultimate goal is to disseminate a standardized treatment protocol that can be widely used, therefore improving the quality of life of survivors and maximizing their appropriate participation in health care activities.”

Post-traumatic stress disorder among young adult cancer survivors occurs at four times the rate seen in younger survivors and includes symptoms such as reliving difficult moments of treatment and becoming nervous, agitated, or excessively worried when reminded of cancer and treatment. These distressing psychological symptoms may impede young adults’ developmental progress toward independence as well as their participation in ongoing health care. Unfortunately, there is no existing research on effective ways to treat these symptoms.

Dr. Mary Rourke received funding from the LAF to develop and pilot test an intervention to reduce post-traumatic stress in young adult survivors of childhood cancer. After a successful pilot test, her team conducted a randomized clinical trial of the intervention in order to demonstrate its effectiveness in reducing post-traumatic stress disorder. “Our ultimate goal is to disseminate a standardized treatment protocol that can be widely used, therefore improving the quality of life of survivors and maximizing their appropriate participation in health care activities,” says Dr. Rourke.

Dr. Rourke is a psychologist in the departments of Oncology and Psychology at The Children’s Hospital of Philadelphia.



Flora van Leeuwen, Ph.D.

Netherlands Cancer Institute
Amsterdam, Netherlands
\$141,790 (3)
2000

Long-term Risk of Second Cancers and Cardiovascular Disease Following Treatment of Testicular Cancer

“Now that curative treatment is available for a substantial group of cancer patients, it is increasingly important to evaluate how the occurrence of late complications after primary treatment affects patients’ long-term survival,” says Dr. Flora van Leeuwen, head of the department of epidemiology at the Netherlands Cancer Institute and consulting epidemiologist to the Comprehensive Cancer Center of Amsterdam.

Dr. van Leeuwen’s three-year study evaluated the risk of second cancers in five-year survivors of testicular cancer (over a period of up to 35 years after primary treatment) to determine for which second cancer types risk is increased as compared with the incidence in the general population. It also evaluated the morbidity and mortality from cardiovascular disease in five-year survivors of testicular cancer and examined whether risk varies by follow-up interval, treatment modality, age at first treatment, and calendar period of first treatment.

Results of this study may be used to improve long-term management and follow-up of cancer patients at increased risk of second cancer and cardiovascular disease. Dr. van Leeuwen also hopes the study’s findings will help in the search for alternative treatment options that are as effective as existing therapies but associated with a lower risk of second cancer.

“If our hypothesis proves correct, this study will provide information on a novel pathway involved in testicular tumor development and progression. It has the potential to lead to improved strategies for both diagnosis and treatment of these cancers.”

Knockout Science

LAF Research Spotlight: Toni Antalis, Ph.D.

Dr. Toni Antalis spends a large part of each day in the company of exceptional mice. Little do they know it, but these mice are playing an important role in researching the causes of testicular cancer.

A senior scientist at the Jerome H. Holland Laboratory of the American Red Cross in Rockville, Maryland, Antalis developed an interest in proteases and their involvement in cancers when she joined the Queensland Institute of Medical Research in Brisbane, Australia. In 1998, while a senior scientist at the Institute, her work led to the discovery of a gene that she named Testisin. Her laboratory cloned and characterized the gene and published the results in *Cancer Research* in 1999.

Antalis hypothesized that the loss of Testisin increases the susceptibility of germ cells to tumor development. With the help of a research grant from the LAF, Antalis and her lab developed a Testisin-deficient mouse to determine the impact of Testisin deficiency on the whole animal and on the initiation of testicular tumorigenesis. Using a technique called homologous recombination, she and her research team successfully created the Testisin 'knockout' mouse by manipulating DNA in mouse embryonic stem cells and implanting the cells in pregnant female mice. (See pg. 16)

The team discovered that methylation (modification) of specific DNA sequences in the Testisin gene plays a key role in silencing Testisin gene expression in testicular tumors. Because absence of Testisin is a feature of human testicular tumors, the research has significant implications for the study of human testicular cancer, explains Antalis.

“If our hypothesis proves correct, this study will provide information on a novel pathway involved in testicular tumor development and progression,” says Antalis “It has the potential to lead to improved strategies for both diagnosis and treatment of these cancers.”

More specifically, Antalis hopes the results of this study will assist in the development of sensitive techniques for monitoring tumor development, clinical aggressiveness, and tumor recurrence. The animal model may further provide a unique laboratory reagent for assessing the efficacy of drug treatments for spermatocytic tumors.



“I have always been fascinated by life and curious about how cells in the body work together to make life as we know it,” says Antalis, who traces her love of biochemistry to a high school chemistry class. She received a bachelor’s degree in chemistry from Furman University, in Greenville, South Carolina and her Ph.D. in biochemistry from Rice University in Houston, Texas. After a postdoctoral period in the Cell Biology Department at Baylor College of Medicine, she moved to Sydney, Australia and then to the Queensland Institute of Medical Research Brisbane. After 20 years in Australia, she relocated her laboratory to the Jerome H. Holland Laboratory of the American Red Cross in 2001. She is a professor in the Department of Biochemistry and Molecular Biology at George Washington University and currently serves on the editorial board of the *Journal of Biological Chemistry*. Antalis is the recipient of numerous awards and honors, and her work has been widely published in scientific journals.

The LAF recently extended the original four-year grant by one year, which will allow for comprehensive breeding studies to further determine the role of Testisin in testicular cancer. Antalis believes that while her research focuses on biology at its most basic level, her findings could apply to the treatment of human testicular cancer within five to ten years. “When you study basic biology,” she says, “you often find things that are quite unexpected that lead you in a new direction. Ultimately, it is highly possible that those directions will prove very important in the study of human fertility.”

Testicular Cancer New Grants

Robert Blelloch, M.D., Ph.D.

Brigham & Women's Hospital
Boston, Massachusetts
\$50,000 (1)

2003

Reprogramming the Embryonic Cancer Cell

Cancer develops from a combination of genetic and non-genetic changes in the material of previously normal cells. Testicular cancers are caused predominantly by germ cell tumors, which can be separated into two types: seminomas and non-seminomas. Non-seminomas can consist of differentiated cells representing various adult tissue types as well as the malignant tumor-forming or embryonic carcinoma cells. The non-seminoma tumor type can be artificially derived in the mouse model by transplanting early germ cells to an abnormal environment, suggesting that this tumor might be predominantly the result of non-genetic or environmental rather than genetic factors. Consistent with this notion, embryonic carcinoma cells transplanted back into the early mouse embryo can occasionally revert to an embryonic stem cell-like phenotype and partially

"It is our hope, that these studies will contribute to a better understanding of molecular parameters that distinguish malignant from normal cells and thus may help to devise rational strategies for reversing the malignant state."

contribute to normal mouse development. Dr. Robert Blelloch and his team will conduct experiments to further characterize the role of non-genetic modifications in germ cell tumor growth and development. Dr. Blelloch, a post-doctoral fellow at the Whitehead Institute for Biomedical Research, proposes to use nuclear cloning to discover whether and to what extent a nucleus from a tumor cell can be reprogrammed, first to a stem cell and then to fully differentiated tissues. "It is our hope," he says, "that these studies will contribute to a better understanding of molecular parameters that distinguish malignant from normal cells and thus may help to devise rational strategies for reversing the malignant state."

Diego Castrillon, M.D., Ph.D.

The University of Texas Southwestern
Medical Center
Dallas, Texas
\$150,000 (3)
2003

Genetic Models of Testicular Cancer



Testicular cancer arises from germ cells that reside within the testis and whose function is unique: the production of male gametes, or spermatozoa. Often, the genes mutated in cancers are the ones important for the normal development of the very cells that give rise to that cancer type. This is especially true for testicular cancer. For this reason, an understanding of development at the molecular genetic level is crucial, but most testicular cancer genes remain unidentified, and the specific genes responsible for testicular cancer growth are unknown.

"Progress in our understanding of testicular cancer is in large part impeded by the lack of an optimal genetic toolkit useful for studies of normal germ cell biology and transformation," says Dr. Diego Castrillon, an assistant professor in the Department of Pathology at The University of Texas Southwestern Medical School. Because germ cell development is similar in mice and humans, Dr. Castrillon will generate new mouse lines and use them to explore a molecular pathway of central importance in testicular cancer growth and development. Dr. Castrillon hopes the research will lead to the creation of useful genetic tools to understand the contribution of individual genetic alterations that drive the malignant progression of germ cells.

Barbara Cohn, Ph.D.

Public Health Institute
Berkeley, California
\$50,000 (1)

2003

Exposure to DDT, DDE, and PCBs Before Birth and Human Testicular Cancer: A Prospective Study Based on Archived Pregnancy Samples Collected Before DDT Was Banned

Testicular cancer incidence rose dramatically worldwide among birth cohorts born after 1945. The widespread introduction of DDT during the same period may have contributed to this increase. Dr. Barbara Cohn's research is the first human study to investigate whether in-utero exposure to DDT, DDE, or certain PCBs increase the risk of testicular cancer. This pilot study will be a prospective, nested case-control study in a 40-year follow-up of 20,000 pregnancies: The Child Health and Development Studies (CHDS). Dr. Cohn is the director of the CHDS and the director of the Center for Research on Women's and Children's Health at the Public Health Institute in Berkeley.

This finding would have important implications for the treatment, and ultimately the prevention, of testicular cancer.

For Dr. Cohn's study, serum that was drawn from mothers one to three days after delivery will be used to measure exposure to endocrine disruptors in the womb for 16 cases of testicular cancer and 48 controls among their sons. If an association between prenatal exposure to endocrine-active chemicals and testicular cancer is found, this study will add direct evidence to current speculation that the increase in testicular cancer, particularly in men born after World War II, is due to the introduction of endocrine-active environmental compounds. This finding would have important implications for the treatment, and ultimately the prevention, of testicular cancer. Even though DDT has been banned in many countries (including the U.S. in 1972), there are many other endocrine-active substances currently in use.

Dezhong Liao, M.D., Ph.D.

Wayne State University
 Detroit, Michigan
 \$50,000 (1)

2003

The Role of X Chromosome in Testicular Cancer

Although the origin of testicular cancer is still largely obscure, genetic factors seem to play an important role; a much higher incidence has been observed among brothers, twins, and members of the same family. The fact that the risk of brothers having testicular cancer is twice as high as the risk of father or son suggests an X chromosome linkage. Dr. Dezhong Liao, an assistant professor of pathology at the Wayne State University Medical Center, hypothesizes that X-linked tumor suppressor genes may escape the X-inactivation in normal male germ cells, but they may be inactivated in testicular cancer. Moreover, the cancer-causing genes may be reactivated and overexpressed. Dr. Liao's project will test these hypotheses by studying the mRNA and protein expression of these tumor suppressor genes and cancer-causing/growth stimulatory genes in human testicular cancers and their adjacent normal testicular tissue.

"This specific objective is unique since very few studies have been focused on the role of sex chromosomes in testicular cancer. Identification of the role of the X chromosome in this cancer will contribute to our understanding and may help identify the high-risk population," says Dr. Liao. If the study successfully demonstrates that X-linked tumor suppressor genes are significantly involved in testicular cancer development and progression, these genes may also be used as the targets for the development of therapeutic drugs.

Vasco Liberal, Ph.D.

Scripps Research Institute
 La Jolla, California
 \$50,000 (1)

2003

The Involvement of Cyclin E in Testicular Cancer Development and Progression

Testicular germ cell tumors are the most common solid cancers among young men. While there is some evidence for genetic predisposition, the genetic control of the susceptibility remains poorly understood. During the past few years, significant evidence has been found suggesting the involvement of cyclin E, a crucial component of the cell cycle

regulatory machinery, in tumor development. This evidence suggests that deregulation of cyclin E might affect the cell cycle and generate instability, accelerating the loss of tumor suppressors and the accumulation of cancer-causing genes.

Dr. Vasco Liberal, a research associate in the Department of Molecular Biology at the Scripps Research Institute, will conduct a study to clarify the role of cyclin E deregulation on testicular cancer by generating mouse models of the disease. The mouse models have degradation-resistant human cyclin E in testicular germ cells and are expected to develop testicular tumors. "The characterization of the mice, as well as cell lines established from developed tumors, will provide precious information about the effect of cell cycle deregulation in the development of testicular cancer," says Dr. Liberal. "This model will help us test this hypothesis as well as generate a valuable tool for better understanding testicular cancer development and progression."

Howard Lieberman, Ph.D.

Columbia University
 New York, New York
 \$50,000 (1)

2003

Genetic Control of Testicular Cancer

It is estimated that in the year 2003 there were 7,600 new cases of testicular cancer diagnosed. Although much is known about the pathology of testicular cancer, very little is understood about its molecular mechanistic underpinnings. Dr. Howard Lieberman, a professor of radiation oncology at Columbia University's College of Physicians & Surgeons, has discovered a gene, called HRAD9B, that is highly related to another gene already known to control genomic stability, resistance to DNA damage, and cell cycle progression. In their work, Dr. Lieberman and his team discovered that expression of HRAD9B is limited primarily to normal testis, but very low in or absent from testicular cancers. Dr. Lieberman's current study will

continue his genetic research and address whether HRAD9B is a tumor suppressor directly related to testicular cancer; the study will focus on defining the link between HRAD9B and testicular cancer in detail. Dr. Lieberman's work will determine if HRAD9B plays a role in transformation of testicular cells and tumor growth and development and will analyze normal and cancerous human tissues to determine exactly which type of testicular cells express HRAD9B. The work is directed toward understanding the molecular basis of the disease, as well as ultimately developing HRAD9B as a prognostic, diagnostic, and therapeutic tool.

Bin Teh, M.D., Ph.D.

Van Andel Research Institute
 Grand Rapids, Michigan
 \$150,000 (3)

2003

Molecular Mechanisms for Chemo-Resistance in Testicular Cancer Patients

Testicular cancer is the most common cancer in males between the ages of 15 to 34 years. While the majority of testicular cancer patients can be cured, approximately three percent of patients develop late relapse (defined as recurrence two or more years after initial successful therapy); these cases are resistant to chemotherapy and usually carry a very poor prognosis. These differences in chemosensitivity and survival are most likely related to the underlying genetic and biological profiles of the patients.

Based on preliminary microarray gene expression profiling (in collaboration with Indiana University), Dr. Bin Teh and his team have identified a set of genes that can distinguish between chemo-sensitive (early relapse) and chemo-resistant (late relapse) cases of testicular cancer. Dr. Teh is the senior principal investigator in the Laboratory of Cancer Genetics and the head of Sequencing and Cytogenetics Core Facilities at the Van Andel Research Institute. In their current study, Dr. Teh and his team will validate their findings in a larger number of patients with the ultimate aim of using the genetic markers to identify chemo-resistant cases. "Our proposed studies will allow us to identify this subgroup of patients prior to their relapse so that additional intervention measures can be applied," says Dr. Teh. "Furthermore, these studies will allow us to understand the molecular mechanisms underlying their chemo-resistance and provide novel drug targets for chemo-resistant testicular cancer."

Gail Vance, M.D.

Indiana University
Indianapolis, Indiana
\$100,000 (2)
2003

Expression Profiling in Germ Cell Tumors

Germ cell tumors are among the most highly curable of human cancers. Advances in chemotherapeutic regimens over the last two decades now cure approximately 85 percent of patients with germ cell tumors, and several clinical prognostic factors have been identified that help define which patients have the best probability of cure. However, there are a minority of germ cell tumors that remain resistant to therapy.

Dr. Gail Vance hypothesizes that there are molecular differences between incurable versus curable germ cell tumors and that these molecular 'signatures' may define clinical outcome. The goal of her project is to identify and distinguish the molecular signatures of curable and incurable germ cell tumors by gene expression profiling using microarray technology. Dr. Vance is the director of the Genetics Laboratories in the Department of Medical and Molecular Genetics and the Indiana University School of Medicine.

Xianghong Wang, Ph.D.

Department of Anatomy, The University of Hong Kong
Hong Kong
\$50,000 (1)
2003

The Role of MAD2 in Overcoming Cisplatin Resistance in Testicular Germ Cell Tumors

Although cisplatin-based chemotherapy treatment for testicular cancer have achieved five-year survival rates of over 85 percent, significant numbers of patients still relapse and die each year because of the development of resistance to cisplatin.

One of the mechanisms thought to be responsible for cisplatin resistance is increased DNA repair ability (and therefore reduced cisplatin-induced DNA damage.) Dr. Xianghong Wang, an assistant research professor in the Department of Anatomy at The University of Hong Kong, found that reduced responsiveness of MAD2 (Mitotic Arrest Deficient 2), a key factor in the division of cells, is a common event in human cancer and is associated with resistance to cisplatin. Since the majority

of testicular germ cell tumors are sensitive to cisplatin, Dr. Wang hypothesizes that a small percentage of tumors express low levels of MAD2 protein and are thus resistant to cisplatin. The aim of her study is to reveal a novel strategy to overcome cisplatin resistance in these cells through laboratory expression of MAD2 and to explore the molecular basis of the mechanisms responsible for MAD2-induced sensitization to cisplatin in the cells. Dr. Wang hopes the results will shed light on a possible application in overcoming cisplatin resistance in human cancers in general.

Testicular Cancer Current Grants

Toni Antalis, Ph.D.

Jerome H. Holland Laboratory for the Biomedical Sciences, American Red Cross Rockville, Maryland
\$200,000 (4)
2000

The Role of Testisin, a Putative Type II Tumor Suppressor Gene, in the Testis

Testicular tumors arise largely as a consequence of disrupted programs in testicular development. Dr. Toni Antalis identified a novel membrane-anchored serine protease, Testisin, found specifically in testicular germ cells. Dr. Antalis hypothesizes that Testisin functions as a type II tumor suppressor in the testis and that loss of Testisin increases the susceptibility of germ cells to tumor development. As part of a study funded by the LAF in 2000, Dr. Antalis and her lab successfully developed a Testisin-deficient mouse for use in evaluating Testisin's role in the growth of testicular tumors.

As an extension of the 2000 grant, Dr. Antalis will explore the role of Testisin and the consequences of the absence of this gene in the development of testis cancer. The study will provide information on testicular tumor development and progression and has potential to lead to improved strategies for both diagnosis and treatment of these cancers.

"A better understanding of cell function will enable a better understanding of the origins of cancer. Cancer is a major cause of death in our population, and research in this area will allow development of more directed and specific ways of managing tumors, as well as provide

cures," Dr. Antalis says. Dr. Antalis is a senior scientist at the Holland Laboratory and professor in the Department of Biochemistry and Molecular Biology at George Washington University.

James Brooks, M.D.

Stanford University
Stanford, California
\$150,000 (3)
2001

Gene Expression Profiles of Testicular Tumors

Current understanding of the molecular genetic events that lead to testicular cancer is very limited. Dr. James Brooks and his team are using gene expression profiling with DNA microarrays to investigate which genes are turned on and off in testicular cancer development. Microarray technology allows the study of thousands of gene DNA, pasted onto a small glass slide, to be studied at one time using sophisticated computer software. The goals of the study are to profile gene expression in testicular cancer, identify genes deregulated in testicular cancer, and validate and test these genes in a separate set of testicular cancers.

"Improved understanding of the underlying genetic changes in testicular cancer could lead to new markers to diagnose these cancers or follow patients after therapy."

"Improved understanding of the underlying genetic changes in testicular cancer could lead to new markers to diagnose these cancers or follow patients after therapy," says Dr. Brooks, an assistant professor at Stanford University. Thus far, Dr. Brooks and his team have performed gene expression profiling on a set of testicular tumors and identified genes that are associated with each tumor type and are in the process of identifying and testing some of these genetic markers. In collaboration with Jamie Thompson in Wisconsin, the researchers have compared the gene expression profiles of the tumors to those from embryonic stem cells and have tentatively identified the cell type of origin for testicular cancers. Preliminary results have been published and work is continuing.

Marie-Claude Hofmann, Ph.D.

University of Dayton Research Institute
Dayton, Ohio
\$49,860 (1)
2002

Gene Expression Profile of Experimental Seminoma Compared to its Normal Cellular Counterpart

Testicular germ cell tumors are the most common malignant neoplasm of the testes and affect young men between 15 and 45 years. However, the molecular basis of the malignant transformation is still unknown. Dr. Marie-Claude Hofmann's study aims to identify genes involved in the origin of seminoma, which account for 50 percent of testicular germ cell tumors, and provide targets for gene therapy or novel anti-cancer drugs. Using a mouse model and a cell isolation technique recently developed in Dr. Hofmann's lab, the study aims specifically to isolate Apaired spermatogonia and to use these cells as a baseline to study differential gene expression in their malignant counterpart.

"While studies using microarray analysis have already compared gene expression of testicular germ cell tumors to normal testicular tissue, none have tried to compare seminoma to a specific spermatogonial cell type," says Dr. Hofmann. "This study will allow us to define which genes are involved in the transformation process." Work on the study, an extension of a previous grant from the LAF, is continuing. Dr. Hofmann is currently an associate professor in the Department of Biology at the University of Dayton.

Vundavalli V.V.S. Murty, Ph.D.

Columbia University
New York, New York
\$150,000 (3)
2001

Epigenetic Gene Inactivation in Male Germ Cell Tumors

Male germ cell tumors are highly curable malignancies that show exquisite sensitivity to cisplatin treatment. However, 20 to 30 percent of metastatic tumors remain resistant to this treatment. Dr. Vundavalli Murty is leading a study to examine the role of epigenetic (affecting multiple genes) changes in germ cell tumors. The project aims to identify gene-specific pathways that may play a role in tumor response to treatment. Identification of these pathways may allow for the creation of treatments to target resistant tumors.



Dr. Murty's ongoing studies examine the role of promoter hypermethylation and inactivation of specific genes. The studies have shown that the promoter methylation of certain genes is associated with resistance to treatment, and that the promoter methylation of another gene is commonly seen in a majority of tumors. Dr. Murty hypothesizes that these epigenetic alterations play a major role in determining a tumor's response to cisplatin. The value of such studies is to help understand the genetic basis for the development of testicular cancer, which could lead to treatment with novel anti-cancer drugs. Dr. Murty is director of the Cancer Cytogenetic Laboratory, director of molecular pathology, and an assistant professor of pathology at the College of Physicians and Surgeons of Columbia University.

Katherine L. Nathanson, M.D.

University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania
\$50,000 (1)
2002

Variants in Androgen Metabolism Genes and Testicular Cancer Susceptibility

The increase in the incidence rate of testicular cancer in the past 40 years suggests that environmental exposures as well as genetic factors play a significant role in the occurrence of testicular cancer. Dr. Katherine Nathanson's project is designed to characterize the differences between a set of testicular cancer cases and matched controls by 1) examining variants in the genes that encode proteins involved in determining exposure to testosterone, and 2) evaluating questionnaires completed by each case and control about risk factors

both known and hypothesized to be associated with testicular cancer. Dr. Nathanson hypothesized that variants that are associated with a greater exposure to testosterone will be found less frequently in the testicular cancer cases than in the matched controls.

The findings from the research "have the potential to assist in stratifying men at increased risk of testicular cancer," says Dr. Nathanson. "We have novel preliminary data that will be of interest to the oncology community and may influence how people think about testicular cancer biology." Based on their findings, Dr. Nathanson and her team now hypothesize that prostate and testicular cancer are at the two ends of the testosterone-estrogen balance spectrum. Research is ongoing, and preliminary results support the hypothesis. Dr. Nathanson is an assistant professor at The University of Pennsylvania School of Medicine.

John Richburg, Ph.D.

The University of Texas
Austin, Texas
\$150,000 (3)
2001

Cisplatin and Mechanism of Testicular Germ Cell Apoptosis

Cisplatin produces cellular changes that trigger apoptosis (cell death) pathways and thus eliminates dividing germ cells. However, cisplatin also causes the death of a number of "normal" testicular cells and in some cases may render the testicular cancer patient infertile.

Dr. John Richburg is leading a study to evaluate the manner by which cisplatin initiates apoptosis of both normal and tumorigenic germ cells. The key finding of the study to date has been a new understanding that the long-term loss of germ cells may be more closely aligned with the cisplatin-induced irreversible damage to the supportive cells rather than to the germ cells themselves. This new understanding has led Dr. Richburg and his team to rethink the possible mechanisms by which cisplatin may induce long-term infertility.

Work on the project continues; findings have been published and additional manuscripts have been submitted. Dr. Richburg is an associate professor (adjunct) in the Department of Carcinogenesis at The University of Texas M.D. Anderson Cancer Center.

Gary G. Schwartz, Ph.D., M.P.H.

Wake Forest University
Winston-Salem, North Carolina
\$50,000 (1)
2002

Fetal Exposure to Ochratoxin A: A Murine Model for Testicular Cancer



Little is known about the causes or origins of testicular cancer. Epidemiologic data points to a carcinogenic exposure in early life or in utero, but the nature of the exposure is unknown. Dr. Gary Schwartz and his team are conducting an investigation to discover whether in utero exposure to Ochratoxin A, a naturally-occurring contaminant of cereals, pork, and other foods, is a cause of testicular cancer; they hypothesize that consumption of foods contaminated with Ochratoxin A during pregnancy and/or childhood induces lesions in testicular DNA and that puberty promotes these lesions to testicular cancer. "If we are able to induce testicular cancers using Ochratoxin A, this would be a milestone in testis cancer research because it would establish a model system with which to study the prevention of testicular cancer," says Dr. Schwartz, an associate professor in the departments of Cancer Biology and Public Health Services (Epidemiology) at the Wake Forest University School of Medicine.

The specific goal of the project is to attempt to induce testicular cancer in the male offspring of female mice by exposing the pregnant females to Ochratoxin A. "This exposure is known to induce kidney cancer in mice and rats. Because during embryogenesis, the testis is formed from the fetal kidney, it is not unreasonable to expect that an agent known to induce kidney cancer may also induce testicular cancer," says Dr. Schwartz.

Janet Shipley, Ph.D.

The Institute of Cancer Research: Royal Cancer Hospital
Sutton, England
\$137,109 (3)
2002

Identification of Genes Involved with Testicular Cancer

Few genes have been implicated in the development of testicular germ cell tumors. The purpose of Dr. Janet Shipley's three-year study is to gain a better understanding of testicular germ cell tumor development and to identify potential targets for new therapies. Over the course of the project, Dr. Shipley and her team aim to identify key genomic regions of differential gene expression using a novel approach they developed for global expression profiling. The project focuses on identifying genes from regions involved in particular pathologies or associated with failure to respond to therapy and then assessing the involvement of these genes in tumor development.

Analysis to date has highlighted several genomic regions of frequent differential expression. Some of these regions are consistent with previous chromosomal changes, but others are novel and have defined small regions containing genes that may be important in testicular germ cell tumor development. Dr. Shipley, a team leader of the Molecular Cytogenetics Laboratory at the Institute of Cancer Research, plans to report her findings in scientific journals, increase understanding of testicular germ cell tumors, and identify potential targets for novel therapies.

Paul Turek, M.D.

University of California, San Francisco
San Francisco, California
\$149,405 (3)
2000

Genetic Comparison of the Normal, Infertile and Cancerous Human Testes

The main objective of the study undertaken by Dr. Paul Turek and his team was to identify specific genes related to DNA repair that might be altered in testis cancer. The research goal was based on previously published work by the team that showed certain forms of severe male infertility to be associated with defective DNA repair. As the research proceeded, other findings led the team to change their focus and hypothesize that the three pluripotency genes on chromosome 12p (a "hotspot" for testis tumors) could play a role

in the development of testis malignancy. In a pilot study of seminomas, the team observed a seven- to nine-fold increase in expression of these three genes relative to normal testis, in agreement with their hypothesis. Continuing work on the project will include experiments to further confirm the relationship. If confirmed, overexpression or inappropriate expression of pluripotency genes likely represents a novel pathway for human cancer development.

The research findings, some of which have been published, will provide a greater understanding of the molecular biology of testis cancer. Dr. Turek also hopes the research will be used to predict which individuals are at risk for tumor development and possibly to provide genetically-based prevention or treatment strategies. Dr. Turek is an associate professor in the departments of Urology, Obstetrics-Gynecology, and Reproductive Sciences at The University of California San Francisco.

Debra J. Wolgemuth, Ph.D.

Columbia University
New York, New York
\$148,989 (3)
2002

Role of the A-type Cyclins in the Distinct Classes of Testicular Tumors

Germ cell tumors can be divided into two major groups: seminomas, which are very sensitive to treatment with radiation and chemotherapy, and non-seminomas, which are not. The molecular basis of the differences between seminomas and non-seminomas is not known, but the goal of Dr. Debra Wolgemuth's LAF-supported study was to provide new insight into the underlying mechanisms and thus to improve therapeutic approaches.

The hypothesis to be tested was that the atypical expression of the cell cycle-regulatory gene cyclin A1 is an important contributor to the properties of the germ cells that give rise to non-seminomas. Observations reported during the course of the project suggest that the misregulation of cyclin A1 can indeed lead to more serious forms of testicular cancer. The observations further suggest that inhibition of the gene's function might represent a target for therapeutic intervention. Results of the project were presented at the NAFA Annual Meeting in Norway in 2003. Dr. Wolgemuth is a professor in the Department of Genetics and Development at Columbia University.

Testicular Cancer Completed Grants

Sarah Freemantle, Ph.D.

Dartmouth Medical School
Hanover, New Hampshire
\$150,000 (3)

1999

Retinoid-mediated Differentiation of Germ Cell Tumors: Molecular Mechanisms and Therapeutic Implications

In human germ cell tumors an all-trans-retinoic acid (RA) signals growth arrest and maturation. By identifying and understanding the mechanisms by which retinoids act, Dr. Sarah Freemantle hopes to improve their clinical efficacy and identify other potential therapeutic targets. In the course of this project, Dr. Freemantle and her team have identified a cassette of regulatory genes whose expression is acutely altered during the initial events of RA-induced terminal differentiation of human embryonal carcinoma cells. The majority of the genes have not been previously implicated as RA targets. Dr. Freemantle proposes a role for these genes in mediating the differentiation, growth suppressive, and antitumorigenic effects of RA. In addition, the results of these in vitro studies may provide insight into normal human development and cancer.

"There is a need to understand the basic



biology of human testicular cancer," says Dr. Freemantle, who hopes this study will help define which events drive the formation of germ cell tumors and what can be done to revert them to normal cells.

"Ultimately we hope one of our discoveries will translate into the clinic," she says. Dr. Freemantle is currently an instructor in the Department of Pharmacology and Toxicology at Dartmouth Medical School. She has published several articles relating to this research since receiving the grant from the LAF.

Jane Houldsworth, Ph.D.

Memorial Sloan-Kettering Cancer Center
New York, New York
\$149,997 (3)

1999

Gene Amplification and Chemotherapy Resistance in Male Germ Cell Tumors

While adult male germ cell tumors are highly curable with cisplatin-based chemotherapy, there remains a portion of patients who will succumb to their disease. Dr. Jane Houldsworth's LAF-funded project was aimed at identifying genetic markers in germ cell tumor specimens indicating resistance to therapy that could potentially be used for predicting the outcome of the disease. The project also aimed to identify the responsible genes and determine how they contributed to resistance to therapy.

Over the course of their study, the research team has confirmed the sites of genomic amplification, has narrowed the regions of amplification, and has used expression profiling to identify candidate genes mapped to these regions. At the present time, research findings are still being concluded, but Dr. Houldsworth predicts that markers they have identified will be included in genetic assays performed on diagnostic specimens for evaluation of treatment outcome. In addition, Dr. Houldsworth now has available for study a large database of germ cell tumor specimens (both cured and not cured) with follow-up clinical data. "The ability to correlate genetic abnormalities with biologic features and clinical outcome is of importance in the study of these tumors," says Dr. Houldsworth.

Work on the project is still continuing, but findings have been published in several journals. Dr. Houldsworth is currently an associate laboratory member in the Sloan-Kettering Institute and associate attending geneticist in the Department of Medicine in the Memorial Sloan-Kettering Cancer Center.

Bonnie L. King, Ph.D.

Yale University School of Medicine
New Haven, Connecticut
\$50,000 (1)

1999

A New Approach for Finding a Testicular Cancer Gene: Looking for a Triplet Repeat Expansion

Dr. Bonnie King led a study to locate in testicular cancer patients a genetic abnormality found in patients with other disorders which, like testicular cancer, tend to

affect successive generations with an earlier onset and greater severity of the disease. The specific objectives of the study were to develop a new method for identifying genes containing a specific mutation (CAG triplet repeat expansion mutation) and to apply the method to identify a testicular cancer gene with the mutation. The project led to the successful development and application of a new method but has not yet led to the identification of a new gene.

The study's original observations have stimulated other investigators to examine their data regarding CAG repeat expansions, and Dr. King hopes the ongoing research will lead to new insights as to the cause of testicular cancer. Dr. King is currently an associate research scientist at the Yale Medical School.

Kent Robertson, M.D., Ph.D.

Indiana University
Indianapolis, Indiana
\$150,000 (3)

1999

AP Endonuclease (APE/ref-1) in Testicular Cancer

Treatment of testicular cancer and germ cell tumors has been one of the great success stories in oncology, with 80 percent of patients cured of their disease with chemotherapy. However, those patients with extra-gonadal primaries and relapsed or refractory disease do poorly, with disease-free survival rates of only 3 to 30 percent, regardless of treatment.

To study why some tumors respond completely to chemotherapy while other tumors do not, Dr. Kent Robertson undertook a study of an intracellular enzyme that repairs DNA damaged by chemotherapy. Preliminary data demonstrated that the DNA repair enzyme AP endonuclease (APE/ref-1) is elevated in testicular cancer/germ cell tumors and known to protect cells from cancer therapeutic agents (chemotherapy), so Dr. Robertson sought to determine whether high level expression of this repair enzyme is related to resistant disease, how the repair enzyme functions, and whether the level of the repair enzyme can be altered (functionally or quantitatively) to sensitize tumor cells to therapeutic agents. Dr. Robertson hopes that the study results will be applied to clinical trials and ultimately be used to improve the treatment of high risk testicular cancer. "Being able to predict patients with aggressive disease would allow us to treat these patients with more intense therapy up front to hopefully improve their outcome," says Dr. Robertson.

University of Pennsylvania Cancer Center Living Well After Cancer Program

Cancer has become a chronic illness, with the majority of patients living years past initial diagnosis. The increase in survival rates is a result of many treatment advances; however, these treatments can contribute to deleterious physiologic and psychological effects (called long-term or late effects of treatment), many of which may not arise until years after treatment has ended.

The LAF provided a grant to the University of Pennsylvania Cancer Center to support the establishment of its *Living Well After Cancer Program*. The program, developed as a model of care for adult survivors of cancer, is focused on clinical, research, and education efforts. The goals of the program are to improve the quality of life for cancer survivors by focusing on early intervention, prevention of disease, and education.

Patients come to the *Living Well After Cancer Program* for evaluations and recommendations regarding their personal risk factors for developing problems related to the treatment they have received. An initial clinical evaluation includes a comprehensive history and physical examination by an advanced practice nurse and oncologist. The evaluation concentrates on the assessment of physiologic and psychosocial issues related to cancer diagnosis and treatment. An individual risk profile is developed for each patient based on disease site, surgery performed, chemotherapy or radiation therapy received, and the individual's personal risk factors.

Ongoing program visits focus on health promotion and disease prevention, and patients receive diagnostic and lab tests and referrals for additional services based on risk assessment. The program's multidisciplinary team includes an advanced practice nurse, medical oncologists, a psychologist, social workers and other counselors, a nutrition counselor, and subspecialists, all of whom are kept up to date on the patient's progress.

The *Living Well After Cancer Program* strives to educate healthcare providers, as well as patients and their families, regarding the late effects of cancer treatment. Members of the program team have presented at educational programs for nurses, medical staff, patients, and families in a variety of forums to increase awareness of survivorship issues in the healthcare administration, nursing, and medical communities.

The program also conducts comprehensive research of its patient population, capturing demographic, diagnostic, and treatment information about all patients evaluated in the program. The analysis of this data enables the team to identify specific issues, areas of concern, and questions that ultimately will help determine the standard of care and improve the quality of life of this growing population of survivors.

Cook Children's Medical Center Life After Cancer Program

More than 12,000 children and adolescents younger than 20 years of age are diagnosed with cancer each year in the United States. Remarkably, childhood cancer survival rates have risen dramatically in the last four decades, from less than 30 percent in 1960 to approximately 80 percent in the current era. This amazing improvement is a result of improved chemotherapy regimens, supportive medical care, and participation of patients in cooperative clinical trials.

Nowhere does the term cancer survivorship apply more than the field of pediatric oncology. In the last two decades, it has become clear to pediatric oncologists that survivors of childhood cancer face the very real risk of developing a broad spectrum of late effects from their curative treatment. These include the development of second cancers, infertility, altered physical growth and development, organ dysfunction, impaired intellect, and difficulties with interpersonal relationships and employment. The cumulative number of future 'life years' for this ever-growing population is enormous, given that most will live for many years beyond their early life cancer experience.

In 2000, the Lance Armstrong Foundation partnered with the Hematology & Oncology Center of Cook Children's Medical Center (CCMC) in Fort Worth, Texas to create a flagship pediatric cancer survivorship program, the *Life After Cancer Program*. The program serves a large population of pediatric, adolescent, and young adult cancer survivors in North/Central/West Texas.

The goals of the *Life After Cancer Program* are to provide comprehensive survivor care, which encompasses neuropsychological assessment and intervention, socioeconomic evaluation and assistance, physical evaluations, participation in institutional research studies, intensive patient and family education, survivor social and emotional support groups, and unique social events for its participants. The program also collaborates with other pediatric survivorship programs and the NCI-sponsored Children's Oncology Group to further research in survivorship.

One component of *Life After Cancer* is the newly-launched Living Legacy program, which helps young men with cancer preserve their future fertility options through sperm cryopreservation. While it is generally recommended that newly-diagnosed adolescent males who decide to bank their sperm do so before cancer treatment, most insurance carriers do not cover this service even if the cancer therapy is practically guaranteed to cause sterility. Funds from the LAF will enable as many as 17 newly-diagnosed, economically disadvantaged young men to bank their sperm. The Living Legacy program is the first of its kind to provide financial assistance to economically disadvantaged patients, at a time of overwhelming emotional and financial stress, to ultimately give them the gift of life.



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