

Physician

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Since 1992, the National Cancer Institute (NCI)'s Specialized Programs of Research Excellence (SPORE) grants have promoted collaborations among physician and basic researchers to move new discoveries quickly and efficiently from the laboratory to the clinic. The NCI intends SPORE grant research to reduce cancer incidence and mortality, as well as to improve the well-being and survival of cancer patients.

Minnesota is on the SPORE map in several areas. Out of 55 grants in 14 organ sites, Mayo Clinic has gained SPORE support to study five cancers—brain, breast, lymphoma (shared with the University of Iowa), prostate, and pancreas. Additionally, Mayo Clinic is collaborating on a multiple myeloma grant awarded to Dana Farber Cancer Institute.

While there are several ongoing projects within each SPORE, the following sections highlight just a few to give a flavor of the studies at the Mayo Clinic.

Brain cancer

More than 120 different types of brain tumors have been described in patients.

Researchers on the cutting edge

Moving discoveries from lab to clinic

By Brian Patrick O'Neill, M.D.

While brain tumors generally do not cause death due to metastasis, their development poses a significant threat to the individuals who have them. Of the approximately 18,500 new cases that occur in the United States each year, almost 13,000 result in death.

The Mayo brain cancer SPORE program seeks to develop more effective treatments for gliomas in adults. Gliomas, which originate in the brain and spinal cord, are the most common form of brain tumors. Novel treatments that are less toxic than existing conventional chemo and radiation therapies are urgently needed. Mayo Clinic was awarded \$10.8 million for five years of research that started in 2004.

In a manner typical of SPORE projects, Mayo's brain cancer collaborators are converging on the biology of brain tumors from four distinct directions. One

study is targeting tumor cells with inhibitors of the epidermal growth factor receptors (EGFR), a cell-surface protein that drives growth and aggressiveness of glioblastomas. A second study is evaluating the action of the Pyk2 protein in glioblastomas to determine whether inhibiting the protein will be a safe and effective treatment, as well as a marker of glioma invasiveness.

A third major focus is the identification of genetic factors that lead to glioma development and subsequent response to treatment and survival. This project, which is being done in collaboration with SPORE researchers at Duke University School of Medicine, highlights another unique aspect of the SPORE program: facilitating interactions between SPORE institutions.

In a fourth project, Mayo investigators are applying a unique measles

virus gene-delivery system for treating glioblastomas. Mayo Clinic Cancer Center researchers discovered some time ago that the measles virus kills many solid tumor cancer cells while inflicting minimal damage on healthy tissue. Current studies aim to discern the impact on cancer cells of measles virus that has been genetically modified to carry genes with cancer-killing properties. Studies defining toxicity limits of the modified measles virus are completed, and we hope to commence a Phase I trial in patients with recurrent glioblastoma multiforme later this year.

Breast cancer

More patients are diagnosed with breast cancer every year in the United States than with any other type of cancer except the more benign, non-melanoma types of skin cancer. About 211,000 invasive breast cancers were diagnosed last year, and 40,000 women died from the disease. One of every eight women will develop breast cancer during her lifetime.

Mayo researchers working to combat this prolific cancer have received a \$11.6 million,

five-year SPORE award. This SPORE, led by James Ingle, M.D., includes two projects on vaccine therapy; studies of pathways involved with development of breast cancer; examination of the clinical value of mammographic breast density; and research into novel approaches to therapy, including the use of viruses (virotherapy).

One of these projects is identifying ways to tell whether or not a woman who has a certain type of BRCA1 or BRCA2 mutation (called a "missense" mutation) has an increased risk of breast cancer. Thus far, this information has been determined for over 50 missense mutations. Given that over 10,000 women in the U.S. alone carry these so-called BRCA1 unclassified variants and that patients who have them cannot be given effective cancer risk counseling, it is clear that this is an important clinical issue for many women and their health care providers.

Other researchers are working on determining the roles of the CHFR gene in cancer cell division; determining the sensitivity of cancer cells to taxane treatment; and developing a vaccine against a carbohydrate-laden protein, MUC1, which is overexpressed in more than 90 percent of breast cancers.

Prostate cancer

Approximately 230,000 new cases of prostate cancer were diagnosed and over 30,000 deaths from prostate cancer occurred in the U.S. last year. Prostate cancer is the most prevalent form of cancer and the second-leading cause of cancer deaths among men in the U.S. A quarter of all men aged 50, and one in two men aged 80, may harbor cancerous cells in their

prostate gland.

Led by Donald Tindall, Ph.D., the Mayo team is examining the genetic, proteomic, immunotherapeutic, and gene therapeutic aspects of this disease. Six projects, supported with \$12 million in SPORE funding, include:

- Gene susceptibility in prostate cancer;
- Evaluation of kallikreins as novel markers for prostate cancer;
- Determining the significance of amplification of 8q24 genetic information in prostate cancer progression;
- Development of immunotherapeutic approaches for treating prostate cancer; and
- Use of fusogenic membrane glycoproteins for gene therapy for prostate cancer.

One of the most cutting-edge developments in these SPORE projects is in the area of prostate cancer-directed gene therapy using radioiodine. The team seeks to adapt strategies that are successful in treating thyroid cancer. By transferring into prostate cancer cells the gene called NIS, which facilitates the trapping of radioactive iodide inside thyroid cells, researchers aim to selectively increase the concentration of cancer cell-killing radiotherapy in prostate tumors. A Phase I clinical trial examining the efficacy of this therapy in men with recurrent prostate cancer in the prostate gland will commence this fall.

Pancreatic cancer

Pancreatic cancer is the fifth-leading cause of cancer death in the U.S. The disease has a very poor prognosis, with a five-year survival rate at about 4 percent. More than 32,000 people will die from pancreatic

cancer this year, and one-fifth of them will be younger than 60 years old.

Gloria Petersen, Ph.D., is the principal investigator for the Mayo pancreatic cancer SPORE, which has a grant of \$10.7 million over five years to support studies on molecular epidemiology of pancreatic cancer and on the interactions of proteins that exacerbate the spread of pancreatic cancer.

The team is also evaluating the role of the DNA repair gene BRCA2 in the development of pancreatic cancer, and is looking at the mechanism of VAV1-mediated pancreatic cancer cell growth. One key project is research on the VAV1 proto-oncogene and the protein it encodes that transforms normal cells into cancerous cells. The project seeks to determine the extent to which VAV1 contributes to pancreatic tumor cell growth and to study approaches for controlling VAV1 in tumor cells.

Hematologic malignancies

Mayo Clinic investigators also collaborate on SPORE projects with other institutions. In a joint grant to the University of Iowa and Mayo Clinic, we received \$5.25 million to support three projects led by Mayo Clinic scientists. Those efforts, directed by Thomas Witzig, M.D., include developing imaging tools that will enable us to understand, monitor, and evaluate anti-lymphoma therapies; enhancing lymphoma radioimmunotherapy by CpG ODN to target non-Hodgkin lymphoma; and determining the connections between genetic variations in immune function and overall survival.


Mayo's hematologic malignancies program, led by Philip Greipp, M.D., also collaborates on the Dana

Farber multiple myeloma SPORE. Mayo researchers oversee several projects, which are supported by \$1.5 million of the grant, including using novel therapeutics to target genetic abnormalities in multiple myeloma. The researchers are also trying to pinpoint molecular markers that will indicate eventual evolution from MGUS (monoclonal gammopathy of unknown significance) to multiple myeloma.

Collaboration drives research successes

The SPORE approach to promoting research productivity complements Mayo Clinic's medical model, which places patients first and is built on teamwork and the synergy of minds conducting research and education to discover the best ways of improving and delivering health care to people.

In these projects, as well as our other cancer research at Mayo Clinic, we collaborate not only internally among our three sites in Arizona, Florida, and Minnesota, but also externally with institutions across the country and around the world. These collaborations, which include many with the University of Minnesota and other Minnesota health care partners, are a necessary component of research that enables us to grow closer to prevention, control, and, ultimately, cures for cancers.

More information about the National Cancer Institute's SPOREs is available at <http://spores.nci.nih.gov>. 

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