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The Barbara Ann Karmanos Cancer Institute (KCI) is dedicated to training young scientists for careers in research. The intent of this application is to broaden the number of students that can participate in KCI's undergraduate summer training program by creating a focused program utilizing the established Breast Cancer Program of our Comprehensive Cancer Center. It is our intent to recruit promising undergraduate science majors, give them the opportunity to take part in breast cancer research and impress them with the excitement of contributing to the cure/prevention of this dread disease. This summer research fellowship will reflect KCI's conviction that elucidation of the biological basis of human cancer and the application of results from basic research in the clinic requires knowledge and training in many disciplines including biochemistry, pathology, molecular biology, immunology, therapeutics, pharmacology and chemistry. The goal of this training program will be to develop within each student the approach to critical scientific thought needed to pursue independent research, stimulating the student's desire for a future career in breast cancer research.

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Introduction

- The initial summer fellowships supported by this undergraduate training program were awarded to 8 outstanding students from 5 universities. Depending on the date the various universities completed their academic year, the trainees began their research experience in May and June of 2002 and completed 10 weeks of training in August and September.
- The 8 fellows were mentored by 8 individual faculty members during their training and conducted investigations in a variety of different topics concerned with breast cancer.
- Studies were carried out in cell signaling, estrogen receptor, chemotherapy, DNA repair, free radical damage of DNA, transformation, metastasis and cell cycle.
- During their training, fellows interacted not only with their mentor but had the opportunity to work with predoctoral students and postdoctoral fellows in their laboratory. Furthermore, the group of undergraduate fellows had the opportunity to discuss their research project with each other and attend institutional seminars and grand rounds, giving the trainees some feeling of the broad areas which cancer research encompasses.
- At the end of the training period, the fellows gave a poster presentation of their individual projects to the Karmanos Cancer Institute/Wayne State University faculty and students.

Body of Report

1. Recruiting

a. An attractive color brochure describing the Undergraduate Summer Fellowships in Breast Cancer Research has been prepared (please see Appendix). Contents include a description of Wayne State University, Karmanos Cancer Institute, the city and the area. Other sections deal with the fellowships and their support, housing, the breast cancer program, resources, the faculty and their individual research programs. Finally, the application procedure is delineated.

b. Three hundred brochures were printed and 75 were sent to science departments of colleges and universities in Michigan, Ohio, Indiana and Illinois on November 10, 2002. It is expected that faculty visits will be made to selected departments this spring. Nine applications to our second summer (2003) training program have been received to date.

2. Initiation of Program

Last year (Summer 2002), we received 12 applications for the summer undergraduate fellowships. These applicants learned of the program by "word of mouth" prior to our advertising the DOD fellowship programs. Applicants sent letters indicating their interest in breast cancer research, their curriculum vitae and a description of their research accomplishments. Applications were screened by a 3-member recruiting committee and the materials for 8 top rated applicants were distributed to the 11 faculty of the training staff for consideration. At a subsequent meeting of the faculty, the 8 fellows were matched with faculty having similar research interests.

The successful applicants were notified in early May and fellowships starting dates arranged.

3. Training Program

The Fellows were assembled for an orientation on May 8, 2002 in which an overview of the program was presented and they were familiarized with laboratory and personnel procedures. At this time, most of the fellows met with their mentors. Due to the variation in the academic year of the undergraduate universities of each fellow, start dates for the fellowships were adjusted to meet the student's requirements.

The fellows selected for the program are listed in Table 1 along with their undergraduate universities, mentors and title of their research project (poster).

During the summer program, the progress of each student was monitored by the Director of the program. As each fellow reached the end of his/her 10-week training, instructions were given on preparation of posters with which to present their accomplishments. A "Poster Day" was held on August 15, 2002, during which the fellows presented their research to the body of fellows, the training faculty and the staff of the Karmanos Cancer Institute. Each fellow was presented with a certificate denoting their successful participation in the program.

4. Evaluation of the Program and Modifications

Since this was the first year of the program, the training faculty paid close attention to the progress of each fellow. Furthermore, students were routinely queried regarding what they expected from the experience and how this related to the training they were receiving. Each found the fellowship beyond their expectations. This feeling persisted through the poster presentations.

Faculty evaluation was carried out after the training had been finished. Overall the mentors were excited about the students and their performance. It was felt, however, that the group experience should be tighter. For example, every effort should be expended to start all fellows at the same time (try to overcome the problem of later starts for students from universities in which their academic year terminates in June, e.g. start the entire group later). In addition, it was felt that weekly meetings of the 8 fellows in which they would alternate in the presentation of their research progress to each other and members of the faculty would be beneficial.

Follow-up questionnaires will be sent to the fellows this April to determine how they evaluate the fellowship after reflection and to ascertain how the research experience affected their educational goals and possible career choices.

Table I
Undergraduate Summer Fellows in Breast Cancer Research (2002)

Fellows	Undergraduate Institution	Mentor	Poster Title
1. Jason Chien	University of Michigan	K. Reddy, Ph.D.	Suppression of N-CoR and SMART corepressors and its effects on estrogen receptor signaling
2. Justin Goodwin	Michigan State University	D. Skafar, Ph.D.	The construction of two double mutants of the human estrogen receptor alpha
3. Robert Grignon*	University of Michigan	F. Sarkar, Ph.D.	Genistein potentially synergizes the effects of chemotherapeutic agents in breast cancer cell lines
4. Dorothy Ho	Yale University	M. Shekhar, Ph.D.	Rad6 overexpression induces alterations in expression of genes associated with adherens junctions and cell polarity
5. Matthew Hornik*	Michigan State University	Z. Djuric, Ph.D.	Detection of 8-oxoguanine in DNA
6. Laura Jakubik*	Wayne State University	F. Miller, Ph.D.	The effects of various dietary compounds and drugs on gap-junctional communication in human premalignant breast cancer cells as measured by two functional assays
7. Ari Konheim	University of Michigan	R. Fridman, Ph.D.	Structural and Functional studies of membrane Type 1- Matrix metallo-proteinase (MT1-mmp)
8. Michael Sasack	Kalamazoo College	W-Z Wei, Ph.D.	Functions and interactions of the protein ATR (a DNA damage sensor) at several cell cycle check points

***Publications/grant applications dervied from fellowship**

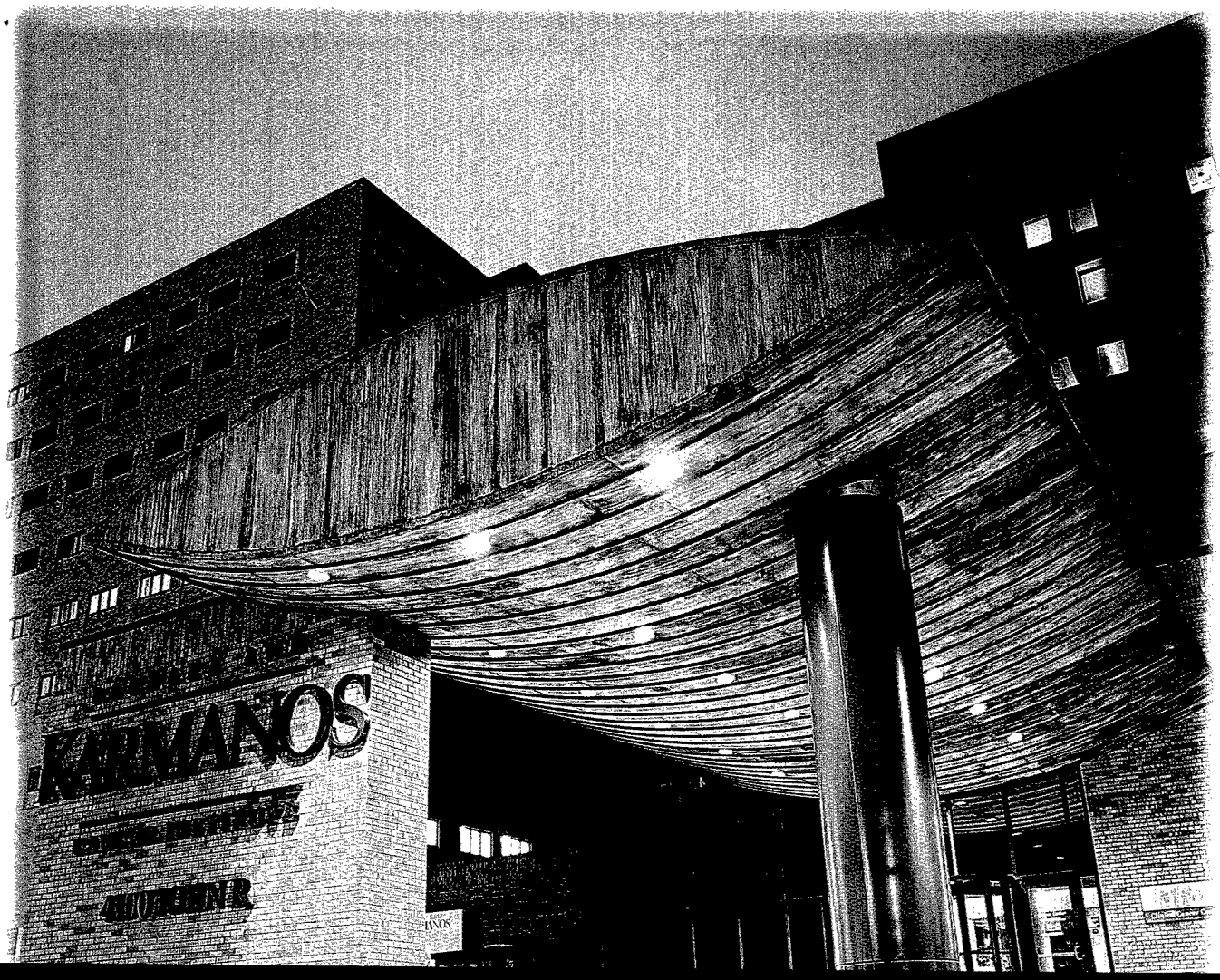
a. Robert Grignon perfected a method which was used in a publication "Suppresion of human prostate cancer cell growth by ciprofloxacin is associated with cell cycle arrest and apoptosis" Aranha, O., Grignon, R., Fernandes, N. McDonnell, T. J., Wood, D. P. and Sarkar, F. H. Int. J. Oncol. (in press, 2003)

b. Matthew Hornik's data used in R01 grant applications "Weight loss in breast cancer survivors", PI Z. Djuric

c. Larua Jakubik's data used in R01 grant application, "Gap junction modifiers in breast cancer prevention", F. Miller, PI

APPENDIX

1. Brochure: "Undergraduate Summer Fellowships in BREAST CANCER RESEARCH" at the Barbara Ann Karmanos Cancer Institute of Wayne State University



Undergraduate Summer Fellowships in Breast Cancer Research at the Barbara Ann Karmanos Cancer Institute of Wayne State University

BARBARA ANN KARMANOS CANCER INSTITUTE

WAYNE STATE UNIVERSITY SCHOOL OF MEDICINE

•• This book was designed by Tiffany Richardson

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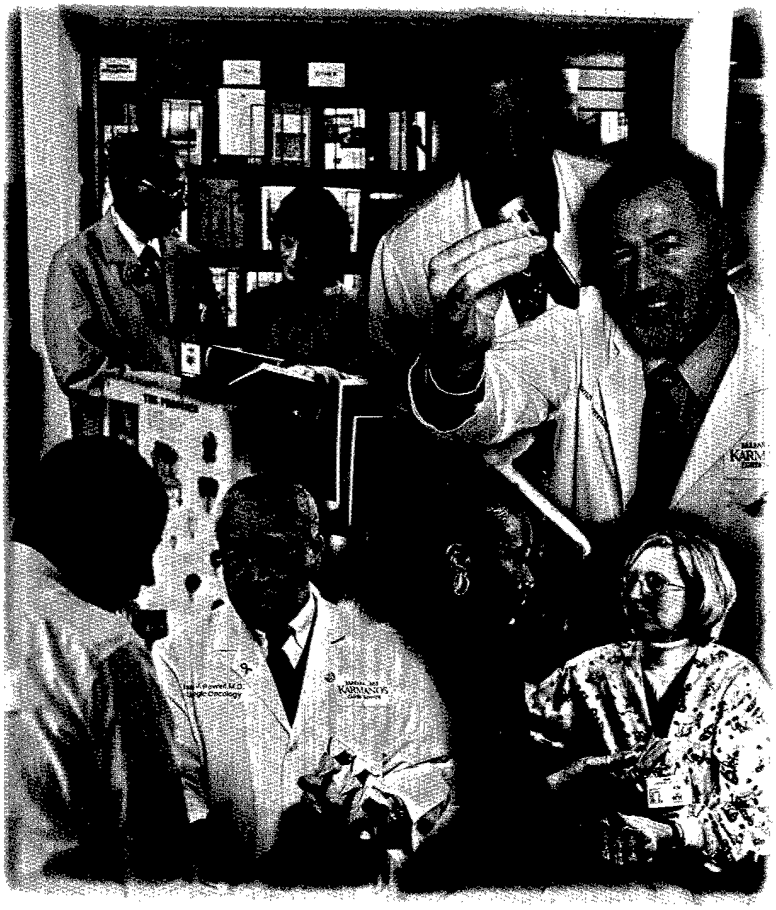
WSU: People working together to provide quality service
All Buildings, Structures and Vehicles at WSU are smoke free.
Wayne State University is an Affirmative Action/Equal Opportunity Employer.

11/02



To Prospective Undergraduate Fellows:

The Barbara Ann Karmanos Cancer Institute is responsible for the clinical and research cancer programs of the Detroit Medical Center and Wayne State University, as well as the community outreach and research activities of the former Michigan Cancer Foundation. It operates the Meyer L. Prentis Comprehensive Cancer Center of Metropolitan Detroit, which is a designation given by the National Cancer Institute (NCI) to institutions with excellent, broad-based cancer programs that span basic, translational and clinical research, clinical care and community-based education and prevention. The Institute is a site of one of the NCI sponsored SEER (Surveillance, Epidemiology and End Results) registries which collect and maintain data on the cancer incidence in specific geographic areas of the United States. Our area is the three counties (Wayne, Oakland, Macomb) of the Detroit Metropolitan region. We provide valuable data relative to ethnic, cultural, and occupational differences in cancer incidence and outcome. Laboratory research is focused on cancers of special significance to our community (breast, prostate and lung, among others), as well as on the basic mechanisms that underlie cancer development, progression and treatment. Cancer prevention is the goal of many of our laboratory and community programs.

The breadth and depth of research at Karmanos offer unique opportunities for summer fellowships. Whether their projects are focused on basic mechanisms in cancer or on new approaches to treatment or prevention, students are able to learn from, and contribute to, our collective efforts to eradicate cancer. Here is a place where you can make a difference while you are becoming familiar with breast cancer research, as well as developing research skills for the future.

We invite you to join us at this exciting, productive cancer center.

Sincerely,

Vainutis Vaitkevicius, MD
Interim Director, Cancer Institute
Wayne State University
School of Medicine

WAYNE STATE UNIVERSITY

Wayne State University is one of the three constitutionally autonomous major state universities in Michigan with annual research expenditures in excess of $80 million. The 180-acre campus is the academic meeting ground for the 31,000 students enrolled in its fourteen schools and colleges, making it the 18th largest university in the nation. In 1994, Wayne State University joined a select group of 87 other universities nationwide classified as "Research Universities I" by the Carnegie Foundation in recognition of its broad range of baccalaureate programs, commitment to graduate education and strong emphasis on research.

The University faculty number nearly 1,700 with more than 700 in the School of Medicine. In 2002, the total external funding for cancer research was more than $38 million. There is more than 500,000 square feet of laboratory space committed to teaching and research. A significant fraction of both faculty and research support (internal as well as external) is committed to cancer.

Recognized for the beauty and uniqueness of its architecture and highlighted by some of Minoru Yamasaki's best known buildings, the main campus of the university is located in the University Cultural Center of the City of Detroit, a region of leading museums, libraries, and other cultural institutions.

Adjacent to the University Cultural Center is the campus of Wayne State's School of Medicine, one of the largest single-campus medical schools in the United States. This campus, in turn, is contiguous with The Detroit Medical Center (DMC) which contains seven major hospitals specializing in gynecology and obstetrics, pediatrics, oncology, psychiatry, orthopedics and emergency medical treatment. This center includes a University Clinics Building.

Adjoining the main campus on the west is the Matthaei Physical Education and Recreation Building surrounded by 42 acres of recreational and athletic facilities. Housed within this complex are an eight-lane swimming pool, a diving pool, three large gymnasia, eight handball and six squash courts, various exercise rooms, 16 lighted tennis courts, a lighted baseball diamond, a track field, a football field and various utility fields. The new Wayne State University Recreation and Fitness Center is a state-of-the-art facility with full disabled access. It is conveniently located in the heart of the campus on Gullen Mall.

The university's outstanding theater program provides excellent entertainment opportunities for both students and faculty. The Hilberry Theatre, located on the main campus, features the country's only graduate repertory company which provides a continual calendar of classic and modern plays during the academic year. The Bonstelle Theatre, housed in a historical theater building adjacent to the medical campus, features undergraduate theater at its best. Another unique forum for free-ranging theatrical programs is provided by the Experimental Theatre. Additionally, frequent (and often free) concerts are given by the University's various performing musical organizations. Nearby, the Center for Creative Studies, which incorporates art, music and dance also provides numerous shows and performances in an academic setting.

The Detroit Public Library, which adjoins the main campus, contains more than two million volumes. This lovely and spacious building is distinguished for its Fine Arts Department with 500,000 prints, the famed Burton Historical Collection, and the world's largest automotive history collection. The Library also contains a complete set of scientific literature. It is a great place to study or temporarily escape academic pressures.

The magnificent Detroit Institute of Arts is the nation's fourth largest art museum housing some of the world's famous art treasures. The Art Institute cannot possibly be digested in a single visit, but since it is only one block from the main campus, students can enjoy the exhibits during lunch or research breaks. The Art Institute is more than just a museum, however: it is a complete cultural center presenting special programs on a regular basis.

Woodward Avenue is also the site of the renovated Orchestra Hall, home of the internationally acclaimed Detroit Symphony Orchestra. The Detroit Symphony Orchestra plays three to four concerts a week during the regular season (September to June) and other recitals and chamber concerts also utilize Orchestra Hall. The metro area offers numerous indoor and outdoor concert areas that draw large numbers of popular, jazz, and classical performances each year.

The International Institute with its ethnic displays and lunches, and the Merrill Palmer Institute, pioneering in the area of children's educational research are located to the north of the Art Institute. To the south is the magnificent Rackham Educational Building, housing both the University of Michigan's Extension Service and Engineering Society of Detroit. The African-American Museum is adjacent to the Science Center and has received national acclaim for its unique displays and architectural structure.

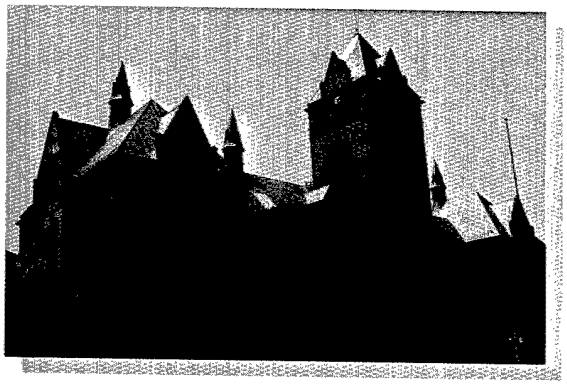
Adjacent to the library is the Detroit Historical Museum. There is always something different to be seen in the changing exhibit area, and a workshop program allows both young and old to experience life as it really was for early settlers.

A recent addition to this cultural complex is the expanded Detroit Science Center. Designed for people of all ages, the exhibits range from experiments with optics and sound to models of some of America's space achievements, including real space capsules.

Wayne State University offers more than 7,700 courses each year, which is one of the widest and most comprehensive academic programs among urban universities in the nation. A student may choose from 350 undergraduate programs and major areas of study. Graduate offerings include more than 138 different master's and 64 doctoral programs, as well as degrees in medicine and law. The university's schools and colleges are Business Administration, Engineering, Law, Medicine, Nursing, Pharmacy and Allied Health Professions, Graduate, Fine, Performing and Communication Arts, Liberal Arts, Science, Education, Social Work, Lifelong Learning and a College of Urban, Labor and Metropolitan Affairs.

Although the university and its adjoining medical and cultural complexes are important factors in the pursuit of research experience in Detroit, it is the internal components of faculty, students, laboratories and support which have the major impact on the quality of the experience.

Similar to many large metropolitan areas, the faculty and students of WSU live throughout the metro area. Each suburb has its own unique features and many have central regions for shopping and entertainment, giving them more of a small-town atmosphere.



BARBARA ANN KARMANOS CANCER INSTITUTE

The Institution

For more than half a century, the Barbara Ann Karmanos Cancer Institute (BAKCI) (formerly the Michigan Cancer Foundation) has actively carried out basic research as well as served the cancer control, education and information needs of southeastern Michigan. Basic research laboratories are housed in the Prentis Building, a modern, 125,904 square foot building located at Warren Avenue and John R in Detroit, adjacent to the Wayne State University campus and The Detroit Medical Center and in the recently completed Hudson-Webber Cancer Research Center (5 floors, 100,000 square foot) adjacent to Harper Hospital. These laboratories are dedicated to translational cancer research.

The BAKCI receives competitive external funding in a yearly amount of $30 million, with additional support derived from the United Foundation of Metropolitan Detroit, the American Cancer Society, private trusts and foundations, and from generous donors led by a dedicated cadre of local philanthropists.

Research at the BAKCI is done alongside programs dedicated to alleviating the burden of cancer to patients, their families and the community as a whole. In addition to scientists, technicians and support personnel, BAKCI's staff includes social workers, nurses, and physicians. It provides home and outpatient health care and rehabilitation, as well as many other social services to cancer patients and their families. Health education, early detection and cancer control programs bring to the public the latest information and techniques, kept up-to-date by close collaboration with the BAKCI's Research Division. Our Cancer Information System now covers the states of Michigan, Ohio and Indiana.

The Research Division

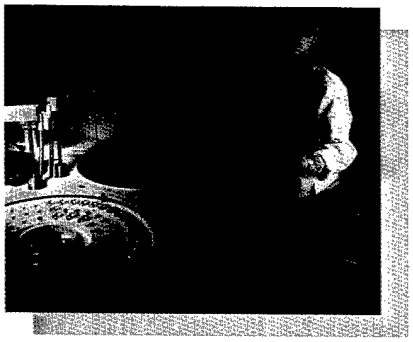
BAKCI's research program include basic laboratory research and epidemiological research as well as "translational research" which seeks to interface laboratory scientists at BAKCI with bedside physicians and clinical researchers in our neighboring medical institutions.

BAKCI's scientific leadership emphasizes creative, multidisciplinary approaches to cancer investigative work, based on fundamental and applied peer reviewed research. BAKCI's senior scientific staff is actively encouraged to engage in inter-institutional research projects, to travel to scientific meetings and symposia, and to participate in professional societies and organizations.

The BAKCI's established laboratories - in breast cancer research, chemistry, chemical carcinogenesis and immunology were augmented during the last few years by the recruitment of scientific teams in molecular biology, developmental therapeutics, metastasis research, drug resistance, and genetics. The aim of this recruitment program was to develop a more comprehensive laboratory research effort representing various specialized fields in biology and chemistry, all working on fundamental aspects of the cancer problem.

BAKCI's research programs in Epidemiology are focused on the industrial and racial diversity of metropolitan Detroit. An important local and national resource for cancer research is maintained by the Epidemiology program: the population-based Metropolitan Detroit Cancer Surveillance System. This cancer reporting system has provided information about the occurrence of new cancers and about changing cancer patterns in Detroit's tri-county population since 1969. It is a founding participant in the National Cancer Institute's cancer reporting system for the United States - the SEER program. BAKCI's local cancer surveillance system provides nearly half the national data on cancer in the African-American population and covers the largest industrial complex in the national program. Sixty-seven hospitals and more than 5,000 physicians in the tri-county area participate in this cancer surveillance system.

Future Research Program plans are oriented toward the development of studies integrating the work of laboratory research staff and the research staff in Epidemiology with clinical patient care and research at The Detroit Medical Center and other state, national and international clinical cancer research programs. New methods are being developed to measure exposure to specific cancer-causing agents and to measure genetic susceptibility to cancer. Similarly, laboratory methods are being developed to detect markers and modulate mechanisms associated with resistance of tumors to drugs and radiation therapy. As these become available for application to studies in human populations, the combined expertise of the research staff in carcinogenesis, molecular biology, genetics, epidemiology, developmental therapeutics and biostatistics will be applied to research into the causes, prevention and cure of cancer. Our community outreach program provides conduits to special population groups who are at highest risk of developing cancer and therefore provide opportunities to extend research findings to true prevention programs. The BAKCI is one of few institutions in the United States with the diversified research staff required for developing and applying these new methods of research to large, ethnically diverse populations.



THE CITY - AN AMERICAN RENAISSANCE

Symbolic of the new Detroit is the Renaissance Center, a towering glass and steel complex standing beside the Detroit River in the heart of the city. This futuristic structure, larger than New York's Rockefeller Center, is the focus of a riverfront development that has become a bustling convention center and a gathering place for Detroiters. In this area are Ford Auditorium, Joe Louis Arena (the home of the Detroit Red Wings), Cobo Arena, and Cobo Hall (site of major exhibitions and conventions). Also on the river-front, Hart Plaza is a summertime refuge for office workers on their lunch hour and a wintertime haven for ice skaters. As if these activities were not enough, the Detroit River is the scene of major international hydroplane races. What else is the new Detroit?

Detroit is music - classical, jazz and popular. The Detroit Symphony Orchestra plays in Orchestra Hall during the winter and at Meadowbrook in the summer. Open rehearsals are free, and low-priced season tickets are available to students. Moreover, it is a Detroit tradition that season-ticket holders, unable to attend a particular concert, call the box office prior to curtain-time to make tickets available to students. Detroit has always been a mecca for jazz. A continual flow of top-flight jazz artists perform in the city. The Montreux-Detroit Jazz Festival has become a well attended weeklong affair which is eagerly awaited by all. The birthplace of Motown, Detroit continues to produce excellent local musicians, and top popular artists and groups appear regularly at Joe Louis Arena and at the open-air summer arenas at DTE Energy Music Theatre and Meadowbrook.

Detroit is theater - The Fisher Theatre (just north of the WSU campus) presents extravagant productions including many pre-Broadway and post-Broadway hits featuring their original casts. "Fiddler on the Roof" and "Hello Dolly" began their runs at the Fisher. Detroit's Michigan Opera Theater presents its spring operas at the Detroit Opera House. The Masonic Temple Auditorium, adjacent to the medical campus, also presents touring shows and is the home of Michigan Opera Theater's spring productions. There is the Detroit Music Hall, which features a wide variety of live entertainment year-round. In November, 1988, Detroit's venerable Fox Theatre re-opened its doors following a multi-million dollar year-long renovation program. The 4,500-seat theater, built in 1927 at a cost of more than $6 million, is truly one of the most breathtaking performing arts and historical attractions in the United States. Today, the Fox is host to live theatre productions, Las-Vegas type extravaganzas, and entertainers representing virtually every musical taste. Detroit's Attic Theatre presents off-Broadway contemporary plays and musicals, featuring the works of new playwrights, performed by a highly acclaimed professional company. And there's much, much more. The semi-professional Windsor Light Opera Company excels in its Gilbert and Sullivan productions. In addition to Wayne State's Hilberry and Bonstelle theaters, strong college programs abound at the University of Detroit, Mercy and Marygrove College. Added to this are the Detroit Repertory Theatre and more than 100 other community and professional groups.

Detroit is museums - In addition to the Detroit Institute of Arts, the Detroit Science Center, the Museum of African-American History and the other museums in the University Cultural Center, the Detroit area has Greenfield Village and the adjoining Henry Ford Museum, national treasures assembled by auto pioneer Henry Ford. The museum is an immense collection of the history of technology - from light bulbs to locomotives. The village is a remarkable collection of fully restored historical buildings and includes such gems as the Wright Brother's cycle shop, Stephen Foster's home and Thomas Edison's laboratory. Greenfield Village craftsmen demonstrate revived traditional skills while weekly events such as antique car gatherings, musket shoots, and pottery festivals spice the season.

Detroit is restaurants - Esquire and Holiday rate it as one of the 10 best restaurant towns in the U.S. There are the usual fine steak and seafood establishments plus dozens of small ethnic restaurants where the menus have to be printed in two languages. Greektown cuisine is fantastic and within a student's budget! Also reasonably priced and convenient to campus are several excellent Mexican restaurants and the cafes in the Warehouse District down by the river.

Detroit is parks - Belle Isle, a 982-acre island park, stands in the Detroit River one and a half miles upstream from the heart of downtown. The park offers a variety of activities for a pleasant afternoon including frequent free concerts, canoeing on lagoons, biking and running on wooded trials, a children's zoo, a nature center, an aquarium, the Dossin Great Lakes Museum, a conservatory, greenhouses, and a vast picnic area. On Belle Isle, you can glimpse the herd of deer that run free in the woods or watch the steady stream of ships passing by on the Detroit River, one of the busiest inland waterways in the world. Other parks are scattered along the river and throughout the city.

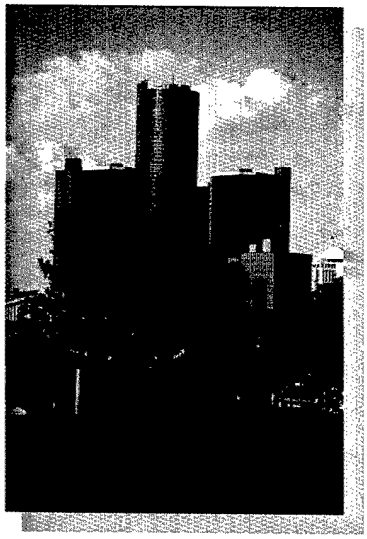
Detroit is neighborhoods - Detroit has the lowest population density of any major city. A great percentage of the houses

Detroit is neighborhoods - Detroit has the lowest population density of any major city. A great percentage of the houses are single family dwellings, and a great many of them are finely built brick homes, with stained glass windows and well-kept lawns. Each neighborhood has its own identity (often formalized with a name) and a sense of community.

Detroit is commerce - As the center of the U.S. automotive industry, Detroit is home to many of the companies that supply the industry as well as the Big Three automakers. Because of the city's importance as a commercial center, the Economic Club of Detroit is an influential forum for leading businessmen, economists and political figures.

Detroit is international - Together with Windsor, Ontario, Canada, it represents by far the largest metropolitan area on any international border in the world. Surprisingly, approximately one-third of all U.S.-Canadian border crossings take place here. Each summer, the two cities join in the Freedom Festival, a joint celebration of Canada's Dominion Day and our Independence Day. Detroit is also a melting pot, home to at least 67 designated ethnic communities. This ethnic mosaic is celebrated throughout the summer by the weekly Ethnic Festivals held in Hart Plaza. Each week, a different ethnic group presents a free, three-day affair featuring food, dance and entertainment.

Detroit, the oldest city in the Midwest, is metropolitan, with something for everyone. No matter what interests you, you can find it here.



THE AREA - SOMETHING FOR EVERYBODY

The recreational and cultural activities of the surrounding surburban communities play an important role in the lives of members of the Wayne State community.

The vast Metro Park system is always popular with students and faculty. There are 10 large parks located throughout a five-county region of southeastern Michigan circling the Detroit area. Attractions include nature study centers, swimming beaches, boating and sailing centers, picnic facilities, camping areas and winter sport activities. The admission fee is nominal and the parks are well maintained. If one chooses to "escape" for a day, the Metro Parks offer that opportunity.

For the sports fan, the Detroit area boasts Lions Football, Pistons Basketball, Red Wings Hockey, Tigers Baseball, Rockers Soccer, and horse-racing. New football and baseball stadiums have recently been completed near the DMC.

Meadow Brook Theatre on the Oakland University campus in Rochester offers fine theatrical productions as well as an outdoor summer concert program. DTE Energy Music Theatre, in Clarkston, also offers music under the stars. All varieties of music are offered through these two music theaters: symphony, rock, country, pop, jazz and music from every decade of the last 100 years. Big name performers find Detroit audiences among the largest and most enthusiastic in their tours across the country.

The Cranbrook Institute of Science and Academy of Art Museum in Bloomfield Hills provides an excellent family learning and entertainment environment in a beautiful wooded setting. Cranbrook's public planetarium offers star shows throughout the year. Likewise, the Detroit Zoological Park in Royal Oak is an extensive and ever popular attraction. The Detroit Zoo is one of the largest in the country in terms of acreage and is open year-round. It was among the first to exhibit its animals in natural settings with moats instead of behind bars and fences.

Windsor, Ontario, Canada, is but five minutes away via either the Ambassador Bridge or the Detroit-Windsor tunnel. The relationship between the two cities is warm and friendly. Windsor is an excellent place for shopping and dining, and its lovely riverfront park is the ideal site from which to enjoy the beauty of Detroit's downtown skyline.

Windsor is also a stepping stone to additional Canadian attractions including historic Amherstberg, the world-famous Jack Miner Bird Sanctuary, the Stratford Skakespearean Festival, and the northern shore of Lake Erie. An outstanding attraction for Detroit-area birdwatchers and naturalists is Point Pelee National Park, a scenic peninsula with marshlands, woodlands, and beaches which swarm with migrating birds in spring and fall.

UNDERGRADUATE SUMMER FELLOWSHIPS IN BREAST CANCER RESEARCH

Background. Breast cancer mortality rates have remained essentially unchanged for the past 50 years. Indeed, there has been an increase in breast cancer incidence. Whereas some cancers have yielded dramatically to treatment (lymphoma, testicular cancer and childhood leukemia), breast cancer overall has not displayed spectacular responses. It will be necessary to continue research into breast cancer prevention, control and treatment for many years to come. It is therefore essential that promising young scientists be trained and motivated to dedicate their research careers to conquering this dread disease. A summer fellowship in breast cancer research directed toward outstanding undergraduate science majors will impress these students at a time when they are about to make the important decision regarding their research careers. Not only will this training guarantee continuation of the investigation of breast cancer, but bright young scientists will undoubtedly contribute new ideas and new techniques to the search for the prevention or cure of breast cancer.

The Barbara Ann Karmanos Cancer Institute of Wayne State University has had a long-standing interest in the training of scientists for careers in cancer research. This interest culminated in the extension of a NCI sponsored training grant into a Graduate Program in Cancer Biology in 1989. Throughout this period, the KCI and its predecessor, MCF, have actively recruited high school and college students for summer research fellowships. These programs were initiated and became successful due to the variety of basic, clinical and translational research carried out by an expert faculty who have consistently been dedicated to the training of young scientists. Whereas the funds to support the training of undergraduates have been derived from local philanthropy, the Institute has recently been awarded funds by the U.S. Army Medical Research and Material Command to supplement this training, especially in the area of breast cancer research.

Objective. The objective of this training program is to inform outstanding college science majors of the realities of scientific research and to aid them to envision and prepare for careers in breast cancer research.

Specific Aims. Specifically, this program is designed to; 1) increase the number of trainees experiencing the gratification and excitement of participating in breast cancer research, 2) facilitate the interaction of students with a broad segment of our faculty in the KCI Breast Cancer Program, and 3) instruct students in research data handling and presentation.

Study Design/Training Plan. The eight undergraduate students admitted to this program will be assigned to one of eleven faculty with funded breast cancer research projects. Each student will carry out a specific research assignment which is designed to yield new data and findings within the allotted time (10 weeks, May-August). Through lab meetings, seminars and Grand Rounds, students will interact with numerous faculty. At the end of the summer experience, each student will prepare and deliver a poster describing his/her work in an organized "Poster Day" together with other summer cancer research fellows.

Relevance. This summer training program will acquaint outstanding undergraduate science majors with the gratification and excitement of breast cancer research. Experience shows that young scientists, who have been given similar opportunities to participate in research at this point in their life, will be stimulated to pursue careers in scientific investigation.

Application. Application for the Undergraduate Summer Fellowships in Breast Cancer Research consists of a letter stating the applicants interest in cancer research accompanied by a personal resume describing college courses completed, community service participated in, honors received, as well as extracurricular activities while at college/university. Applications should be received by March 1st and sent to: Dr. S. C. Brooks, Department of Biochemistry and Molecular Biology, Wayne State University School of Medicine, 540 E. Canfield, Detroit, MI 48201

FINANCIAL SUPPORT

The financial support for this training program is derived from a grant to Wayne State University from the U.S. Army Medical Research and Material Command. A stipend of $4,000 is awarded to each of the selected undergraduate trainees. Each of the trainees is expected to commit 10 weeks during the summer to their laboratory training.

HOUSING

The university currently operates eight housing facilities certain of which are available to summer undergraduate fellows. There are several older apartment complexes and halls plus two newer apartment towers on campus. The DeRoy, Forest and University Towers apartment buildings each contain modern efficiency and one bedroom apartments. These buildings are maintained by WSU personnel and provide convenient, secure housing on the main campus. On the medical campus there is also available a housing complex of one-bedroom apartments.

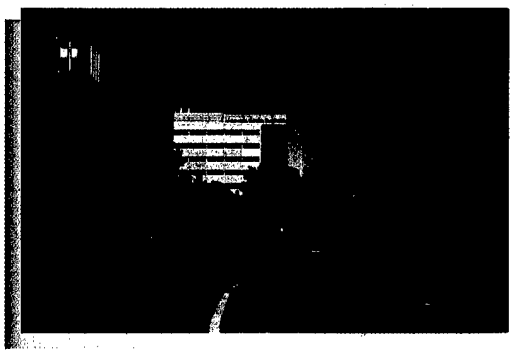
Housing is also available in a number of privately owned apartments near the campus. In addition, the convenient location of WSU at the confluence of four major metropolitan expressways provides easy access to other residential areas in the city or surrounding suburbs.

CAMPUS SAFETY

The 180-acre WSU campus and the nearby areas encompassing The Detroit Medical Center and BAKCI represent one of the safest urban locales in the state of Michigan. And, the university's record of safety compares favorable with other large universities in the country.

Much of the credit belongs to Wayne State University's Public Safety Department. The complement of 39 police officers (each possessing at least a bacalaureate degree), 16 cadets and 12 support personnel provide a full range of police services to the university community 24 hours a day.

Safety at WSU is more than just perception, it is a hard fact. The latest annual FBI statistics show that violent crime on our campus is less than one-tenth of that for the entire state of Michigan.



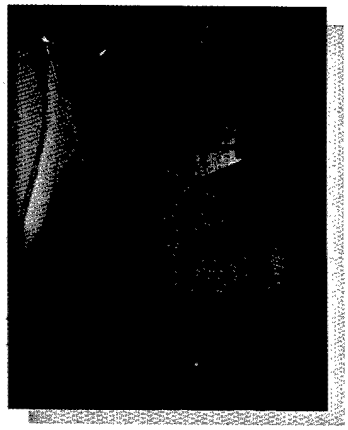
BREAST CANCER PROGRAM

The Breast Cancer Research Program has been an established focus of investigation in the BAKCI for more than 28 years. This program integrates basic breast cancer biology with clinical programs in early detection and prevention.

Scientists at the BAKCI established the first, long-term breast cancer cell line, known as MCF-7, in the 1970's. This line has been distributed all over the world and is used in basic studies on, for example, the endocrine control of breast cancer, as well as in work directed toward development of new anticancer drugs.

Currently within the program there are laboratories involved in a wide variety of basic and clinical studies. Newly established laboratories are carrying out molecular, genetic and cytogenetic characterizations of both human and experimental cancers. Special emphasis is placed on research into the early events in breast cancer development and in experimental systems for studying preneoplastic events. A recent advance is the development of a human breast epithelial line, known as MCF10AT, that grows in nude beige mice and mimics the histological picture of proliferative breast disease seen in women at high risk of developing breast cancer. These proliferative lesions develop into carcinoma upon prolonged growth in the mice. Administration of estrogen accelerates the process. Other laboratories are concerned with the later stage processes in breast cancer — the factors that influence metastasis as well as the emergence of hormone independence and drug resistance. An additional theme is the role of the host in mammary tumor development and in metastasis, both on the level of tissue interactions between mammary epithelium and stroma, as well as inflammatory and immune response effects.

Basic studies on the biology of breast cancer are complemented by several large clinical resources. The BAKCI maintains a repository of tissues and serum from more than 1,200 breast cancer patients whose clinical course is being closely monitored. Wayne State University and Harper Hospital have established a Breast Cancer Prevention Clinic in which women at high risk of developing breast cancer participate in a variety of studies aimed, ultimately, at early detection and prevention of the disease. The BAKCI houses the Walt Comprehensive Breast Center which combines mammography, physical examination and health education approaches to early detection. Each of these resources offer opportunities for a wide variety of research into breast cancer problems — be they at the basic, clinical or cancer control levels.



RESEARCH RESOURCES

Present day cancer research requires sophisticated, advanced research facilities. The following core facilities are part of the Cancer Center and presently available to all faculty and students. A number of these facilities are briefly described below.

Analytical Instrumentation

An extensive, professionally staffed instrumentation facility within the Department of Chemistry provides state-of-the-art technology for cancer investigators. It contains mass spectrometers with fast atom bombardment, GC/MS capabilities and high resolution analysis. Nuclear magnetic resonance spectroscopy can be done at high field (600 MHz) or wide-bore multinuclear studies. A third instrument provides for in vivo surface coil studies. Another area of emphasis is molecular structure determination with advanced computer-supported x-ray diffractometers. Other instruments encompass the range of spectrometers (FT-IR, UV-Vis, Raman and fluorescent).

Analytical Cytometry

The Ben Kasle Flow Cytometry Facility has been recently expanded with the acquisition of new instruments and by consolidating facilities at both Harper Hospital (4th Floor Hudson) and BAKCI Prentis Building (Ground Floor).

BAKCI has a BD FACScan 5-parameter flow cytometer and a Coulter Epics 753 dual dye laser unit with the ancillary data acquisition and analysis hard and software. The enhanced UV capabilities of the Epics unit make it valuable for studies on calcium flux and other UV excitable fluorochromes. Also, BD FACStar single laser cell sorter offers the advantage of analog sort control, essentially increasing cell sorting speeds. Harper Hospital (Hudson 4th Floor) has a BD FACScan flow cytometer.

Supporting these instruments is an extensive array of computer systems to facilitate complex analyses and publication graphics. HP9000 series systems serve as the principle computers for the FACScans and the FACStar. Also available are several automated acquisition and analysis packages (AUTOCOMP, AUTOMATE, CELLFIT) along with networking capabilities (FACSNET) for remote analysis. The Coulter Epics system is connected to a MDADS and Easy-88 data acquisition and analysis system.

Besides the flow cytometers, the BAKCI core lab has several other analytical instruments (e.g. fluorescent microscopes) available for automated cell analysis.

Histology, electron microscopy, immunohisto-(cyto-)chemistry and limited dark room services are offered by the BAKCI Analytical Cytometry Core Lab located at BAKCI Prentis Building. The electron microscopy unit includes scanning (ETEC Autoscan) transmission (Zeiss, 10C) with STEM, goniometric and video reproduction capabilities.

Computing Facilities

The Computing and Information Technologies (C&IT) resource of WSU is an especially versatile and user-oriented facility emphasizing interactivity. The C&IT operates two computing systems: An Amdahl 470 V/8 under MTS and an Amdahl 470 V/6 under VM/MVS. MTS (Michigan Terminal System) is the main research and academic system. A number of computing systems are devoted to oncology research and service. These include:

Two VAX 4000's, supporting Cancer Center Administration and Clinical Trials.
Two VAX 4000's and three Sun stations supporting magnetic resonance imaging and spectroscopy.

Three Dec Station 5000's supporting radiation therapy treatment planning, picture archiving and communications, clinical research and radiation oncology department management.

Numerous dedicated computers for scientific instrumentation are scattered throughout the research and patient care areas. All systems are linked through high speed FDDI and Ethernet connections; all are on the Internet.

Macromolecular Core Facility

This facility provides four analytical and synthetic capabilities for the local research community: Quantitative amino acid analysis, Edman N-terminal sequence analysis, solid-phase oligonucleotide synthesis (both RNA and DNA), and solid-phase peptide synthesis. In addition, users receive assistance in the interpretation of data and advice on how to prepare samples properly for amino acid analysis and Edman N-terminal sequencing. Major instrumentation in the facility, which is housed within the Department of Biochemistry in Scott Hall, includes a Waters Pico-Tag Amino Acid Analyzer, an Applied Biosystems 470A Gas-Phase Sequencer (includes a Model 120 PTH Analyzer and a 900A Data Analysis Module), two Applied Biosystems Oligonucleotide Synthesizers (a four-column Model 394 and a three column Model 380B with a Large Bottle update), a Beckman Model 990 Peptide Synthesizer, and a Waters Gradient HPLC System.

Animal and Human Tumor Resource

The Animal and Human Tumor Resource facility is responsible for the acquisition and distribution of tumor cell culture and xenograft models most commonly used by investigators in chemotherapeutic, biochemical and biological studies. Quality control of tumor stocks includes MAP testing for viral contamination; determination of bacterial contamination; histology; and biologic behavior. In addition, staff of the faculty provide protocol design assistance, demonstration of techniques, data analysis methodology, and technical assistance as required.

Cell Lines Resource

The Karmanos Cancer Institute has developed a number of unique cell line resources. In particular, a number of lines are maintained and distributed by the investigators in the Breast Cancer Program with special expertise in their development. The MCF-7 breast cancer line is a major research resource generated from this facility. A more recent resource is a set of immortalized lines, designated MCF-10 and MCF-12 derivatives, that provide models of non-malignant human breast epithelium. One of these derivatives, MCF-10AneoT, is of special interest for studies on the development of human breast cancer.

Confocal Imaging Core Facility

The Confocal Imaging Core Facility became partially operational in November of 1992 and fully operational approximately six months later. The facility includes a Zeiss LSM 310 microscope and associated Silicon Graphics workstation. With recent upgrades to the microscope and computer, the Confocal Imaging Core Facility offers state-of-the-art technology for the evaluation of up to three fluorophores in a single specimen. Two lasers can be used for simultaneous analysis and the uv laser can be used for an additional analysis within seconds of the lasers within the visible range. Both fixed and live specimens can be analyzed, with the live specimens able to be analyzed at temperatures ranging from 15 to 65oC. Optical slices of images can be reconstructed in three dimensions on the Silicon Graphics workstation. The image recording systems allow one to obtain publication quality prints, as well as slides, from either the Zeiss Monitor or the Silicon Graphics monitor. Therefore, images for publications, grant

applications and presentations are available immediately without having to go to outside image processing facilities. An important advantage of the Zeiss LSM 310, in comparison to other confocal microscopes, is its user friendliness. After initial training, individual investigators are capable of operating the microscope with minimal technical assistance.

Pharmacokinetics and Metabolism Core Facility

The Pharmacokinetics and Metabolism Core Facility provides expertise and equipment to perform pharmacokinetic studies as well as studies on drug metabolism in vivo and in vitro. In addition to the capability to perform studies on plasma pharmacokinetics in either human or murine models, the kinetics of anti-cancer drugs can be monitored in tumors and major organs in the murine models. The facility also has the capability to analyze drugs and metabolites in urinary and fecal excretions and to measure the amount of free drug in the serum. Cellular pharmacokinetics and assessment of drug uptake into tumor cells and in vitro studies on tissue culture lines are also available. In addition, the facility has the capability of analyzing drug metabolism tumors in vitro, in tissue culture lines of sensitive tumors, using tissue homogenates, subcellular fractions such as microsomes or even purified enzymes. Methods of analyses which are routinely available through the facility include high performance liquid chromatography (HPLC) and gas chromatography (GC).

The capability of this core is currently being enhanced by a collaboration with the Institute for Chemical Toxicology, which maintains a series of cell lines that have been genetically engineered to express specific cytochrome P450 cDNAs. These lines allow identification of the specific enzymes that contribute to the metabolic disposition of a particular compound. Both cytotoxic and genotoxic assays are performed routinely.

Quantitative Image Processing Systems Core Facility

A quantitative image processing system (QUIPS) for fluorescence microscopy consists of an epifluorescence microscope interfaced to a computer equipped with appropriate software to allow for the acquisition and quantitative analysis of multicolor fluorescence images. This system allows performance of comparative genomic hybridization (CGH), physical mapping of probes (Flpter analysis), and various other techniques including metaphase finding for translocation analysis and cell-based phenotype/genotype analyses. This system is useful to any investigator interested in using the tools of modern molecular cytogenetics as they apply to many disease processes.

Molecular Genetics Core Facility

The new Molecular Genetics Core Facility will serve two primary functions for KCI members: (1) The core will provide molecular genetic services (DNA sequencing, genomic and cDNA library screening, mutation detection, gene array) at a fee to KCI members; and (2) will provide free-of-charge consultative services to KCI members. The core will also provide training opportunities in specific molecular techniques to interested researchers on a fee-for-service basis.

Libraries

WSU's extensive library system includes the David Adamany Undergraduate Library, the Purdy/Kresge Library, the Neef Law Library, the Science and Engineering Library, and the Shiffman Medical Library. The latter two maintain substantial collections and services in support of cancer biology research. The libraries of the BAKCI and The Detroit Medical Center (DMC) hospitals are also available for student use. Collectively, these libraries offer well over two million books and journals applicable to cancer research and care.

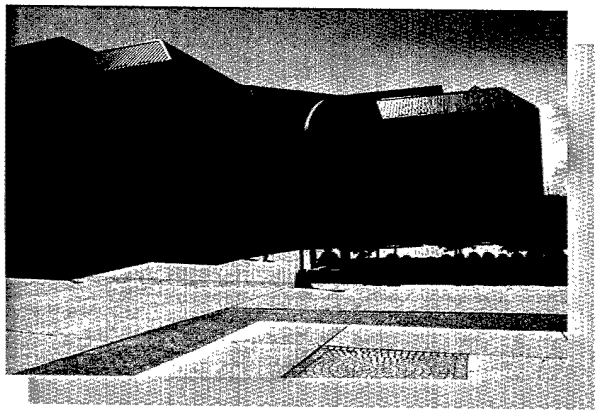
The Shiffman Medical Library, conveniently located on the DMC campus adjacent to the School of Medicine, maintains collections of more than 250,000 volumes and 2,970 journal subscriptions. Outstanding services in support of biomedical research and study include: Seven-day per week reference and online information services; access to the complete Medline database from the library, offices, laboratories and homes; on-site access to full-text databases in the health sciences and subsidized or no-charge access to all databases at the National Cancer Institute, National Library of Medicine, National Center for Biotechnology Information and prominent national research sites. Microcomputers are available for student use within the library. Instructional programs in support of health sciences information management are a growing part of the mission of the Shiffman Library.

All information resources needed for graduate study can be accessed through the University Libraries' Detroit Area Library Network (DALNET), a fully-computerized library system, and the Shiffman Library's membership in the National Network of Libraries of Medicine which extends the graduate student's access to the collections of all academic health sciences center libraries.

THE BREAST CANCER RESEARCH FACULTY

The superb faculty of the Cancer Center represent the central factor in a student's consideration of our program for training in cancer research. The faculty's distinguished record of research and teaching provides the basis for the intellectual stimulation necessary for the training of undergraduates in breast cancer research. There are eleven outstanding investigators carrying out investigations concerned with the understanding, prevention and treatment of breast cancer. The faculty is listed below. Individual faculty write-ups will be found in the following pages.

Dr. Sam C. Brooks, Director
Dr. Zora Djuric
Dr. Joseph A. Fontana
Dr. Rafael Fridman
Dr. Fred R. Miller
Dr. Robert J. Pauley
Dr. Kaladhar B. Reddy
Dr. Fazlul Sarkar
Dr. Malathy Shekhar
Dr. Debra F. Skafar
Dr. Wei-Zen Wei



Sam C. Brooks, Ph.D.

Breast Cancer
Ph.D., University of Wisconsin, 1957

Two of the most important gene regulatory proteins in breast cancer, the estrogen receptor (ERa) and the tumor suppressor p53, are transcription factors. ERa is required for hormone dependent growth of some ER+ breast tumors and is the target for tamoxifen based breast cancer therapy. The transcriptional and growth activity of ERa is regulated by the hormone estradiol (E2). Mysteries still remain regarding this gene regulatory factor. The biological activities of the tumor suppressor p53 are mainly attributed to its ability to control the expression of various cell regulatory genes which are involved in cell growth, DNA damage repair and programmed cell death. The activity of p53 is feed-back regulated and the cellular level of this factor is controlled by the oncoprotein mdm2. In response to DNA damage, p53 is protected from mdm2 dependent down regulation. Interestingly, p53 represses the transcription of certain genes, such as TPA, c-fos, c-jun and bcl-2, which contain estrogen response elements and are thus potential targets for activation by the estrogen receptor. How p53 suppresses the expression of ERa responsive genes is not clear. In preliminary studies conducted in this laboratory, we have recently found that the ERa protein can physically interact with both p53 and mdm2 proteins. Functional assays show that the ERa-p53 interaction leads, on one hand, to suppression of estrogen induced expression of certain ER-dependent genes, while, on the other hand, this interplay leads to protection of p53 activity against mdm2 induced deactivation. These findings indicate that the interaction between ERa and p53 is biologically significant, representing an important process in breast cancer cells. In order to learn more about this phenomenon, we have hypothesized that the ERa-p53-mdm2 interactions may hold the key to the above questions. Information pertaining to this premise will be obtained by examining the specifics of the ERa-p53 binding interaction and determining the biological consequences of ERa-p53 interaction in breast cancer cells. In addition, we are investigating the possibility that selective ERa expression may be a method of cellular regulation of p53. Finally, the functional consequences of the ERa-mdm2 interaction are being examined. Information gained in these studies will further the understanding of ERa-p53 cross-talk in breast cancer cells, shed light on how ERa is regulated, as well as point to unconventional roles for ERa. New concepts which will arise may lead to a more precise determination of breast cancer prognosis and reveal novel areas for chemotherapeutic interventions in this disease.

Selected Publications

Schwartz, J.A. and Brooks, S.C. Changes in the structure of the ligand or substitutions to AFZ resides in the estrogen receptor make independent contributions to coactivator sensitivity by SRC-1. J. Steroid Biochem. Mol. Biol. 67: 223-232, 1998.

Schwartz, J.A. and Brooks, S.C. Genistein – mediated altenuation of tamoxifen-induced antagonism from estrogen receptor-regulated genes. Biochem Biophys Res Comm. 253: 38-43, 1998.

Davis, M.D., VanderKuur, J. A. and Brooks, S.C. Ligand Structure influences autologous down-regulation of estrogen receptor-alpha messenger RNA J. Steriod Biochem. Mol. Biol. 70: 27-37, 1999.

Liu, G., Schwartz, J.A. and Brooks, S.C. p53 down regulates ER responsive genes by inteferring with the binding of ER to ERE. Biochem Biophys Res Comm. 264: 359-364, 1999.

Liu, G., Schwartz, J.A. and Brooks, S. C. Estrogen receptor protects p53 from being deactivated by hdm2. Cancer Research, 60: 1810-1814, 2000.

Zora Djuric, Ph.D.

Breast Cancer
Ph.D., University of Michigan, 1983

Lifestyle interventions to reduce cancer incidence hold great promise for reducing the burden of cancer in our society. These interventions may be especially important in persons who are at increased risk for the disease. One aspect of the research in this laboratory concerns examining the relationship between risk of breast cancer and levels of oxidative stress. Oxidative stress is caused by oxygen free radicals from both endogenous and exogenous sources. This results in damage to DNA, lipids and proteins. Such damage may well play a role in carcinogenesis and might be elevated in persons at increased cancer risk. We are interested in understanding the mechanisms that lead to oxidative damage and the biological significance of different kinds of damage. In addition, we are interested in developing new biomarkers of oxidative stress. This has involved biochemical, cellular and animal experiments. Markers of oxidative stress have relevance to clinical studies in which lifestyle changes are tested for possible beneficial effects. The lifestyle interventions that we have been studying all appear to exert their beneficial effects, at least in part, via a decrease in oxidative damage levels. One area of emphasis currently is on weight loss in obese breast cancer survivors to decrease risk of recurrence. This involves both behavioral and basic research. In other studies we are examining specific dietary factors that can contribute to cancer prevention using intermediate markers of risk as endpoints. For example, high fruit and vegetable diets are of interest since many of the carotenoids and flavonoids present in those foods have antioxidant effects. The metabolism of those compounds, however, is complex and their effects on cellular oxidative damage levels does not appear to be straightforward. In clinical studies, many variables can affect the results. The biomarker data we obtain is interpreted taking into account dietary data, anthropometric measurements and demographic characteristics of the subjects. The relationships between different biomarkers also is investigated. Interesting relationships that are uncovered can then be explored in the laboratory for mechanistic links.

Selected Publications

Djuric, Z., Heilbrun, L.K., Lababidi, S., Berzinkas, E., Simon, M.S. and Kosir, M.A.. Levels of 5-hydroxymethyl-2'-deoxyuridine in DNA from blood of women scheduled for breast biopsy, Cancer Epidemiol. Biomarkers Prev., 10: 147-149, 2001.

Chen, G. and Djuric, Z.. Carotenoids are oxidized but do not protect lipids from peroxidation in unilamellar liposomes. FEBS Letters, 505:151-154, 2001.

Djuric, Z., Chen, G., Doerge, D., Heilbrun, L.K. and Kucuk, O. Effect of soy isoflavone supplementation on markers of oxidative stress in men and women, Cancer Letters, 172:1-6, 2001.

Djuric, Z., Heilbrun, L.K., Lababidi, S., Depper, J.B., Poore, K.M. and Uhley, V.E. Effect of low-fat and/or calorie restricted diets on anthropometric measures in pre-menopausal women. J. Amer. Coll. Nutr., 2001, in press.

Joseph A. Fontana MD, Ph.D.

Breast Cancer
Ph.D., Johns Hopkins University, 1969
MD, University of Pennsylvania, 1975

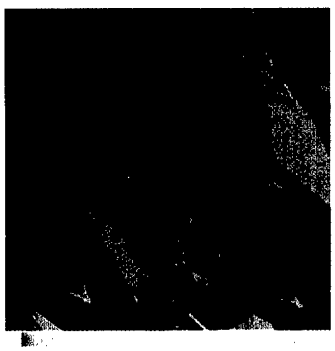
The major thrust of our laboratory is the development of a novel class of retinoid analogs as potential therapeutic agents in the treatment of malignant diseases. We are examining the underlying mechanism(s) by which this unique class of compounds induces apoptosis in malignant leukemia/prostate and breast carcinoma cells. Our studies are now concerned with the identification of the nuclear receptor for this class of compounds and the mechanism(s) involved by which this receptor activates a number of genes as well as protein kinases.

Selected Publications

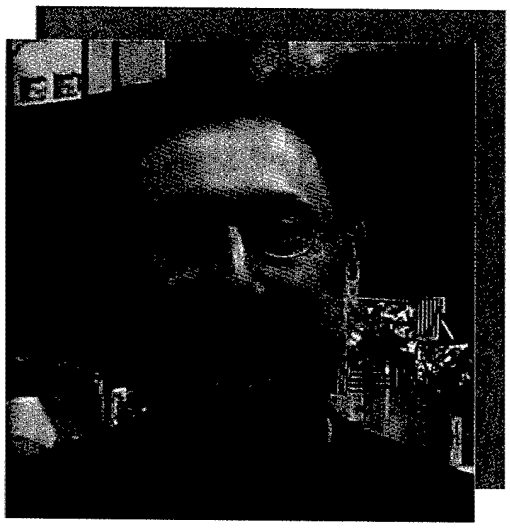
Zhang Y, Rishi AK, Dawson MI, Tschang R, Farhana L, Boyanapalli M, Reichert U, Shroot B, Van Buren EC and Fontana JA. S Phase Arrest and Apoptosis Induced in Normal Mammary Cells by a Novel Retinoid. Cancer Res 60:2025-2032, 2000.

Dawson MI, Hobbs PD, Peterson VJ, Leid M, Lange CW Feng K-C, Chen Q-q ,Gu J, Li H, Kolluri K, Zhang X-K, Zhang Y and Fontana JA. Apoptosis induction in cancer cell, by a novel analog of 6 - [3-(1-Adamantyl) - 4- hydroxyphenyl] - 2 – naphthalene carboxylic acid lacking retinoid receptor transcriptional activity. Cancer Res 61: 4723-4730, 2001.

Zhang Y, Mohammad R, Rishi AK, Farhana L, Dawson MI, Feng K-C, Leid M, Peterson V, Zhang XK, Edelstein M,Eilender D, Biggar S, Wall N, Reichert U, and Fontana JA. Induction of Apoptosis of human B-CLL and ALL cell by a novel retinoid and its non-retinoidal analog. Blood (in press)



Rafael Fridman, Ph.D.



Breast Cancer
Ph.D., Hebrew University, Jerusalem, 1986

Our research focuses in understanding the molecular mechanisms involved in tumor cell invasion and metastasis. To invade tissue barriers, metastatic tumor cells utilize proteases capable of degrading extracellular matrix components. An important group of enzymes associated with tumor invasion and metastasis are the matrix metalloproteinases (MMPs). To study the role and function of MMPs in malignancy, we utilize a comprehensive approach involving molecular biology, cell biology and biochemical techniques. We have characterized the biochemical properties of several members of the MMP family and their mechanism of activation and inhibition in tumor cells. One important group of MMPs is the membrane-anchored MMPs, known as MT-MMPs, which by their surface localization they are major mediators of pericellular proteolysis. We have shown that the activity of MT-MMPs on the cell surface is regulated by specific interactions of the enzymes with TIMPs, specific protein MMP inhibitors. As membrane-anchored proteases, the MT-MMPs are regulated by a complex process of turnover involving shedding of the enzyme ectodomain, which regulate surface and extracellular activity. Structure-function relationship studies using mutant enzymes are addressing how processing of MT-MMPs alter the ability of cells to control pericellular proteolysis and invasive behavior. We have also various active collaborations aimed at developing specific MMP inhibitors and at investigating the role of MMPs in various models of human cancer.

Selected Publications

Hernandez-Barrantes, S., Toth, M., Bernardo, M.M., Yurkova, M., Gervasi, D.C., Raz, Y., Sang, Q-X. A., and Fridman, R. Binding of active (57 kDa) membrane type 1-matrix metalloproteinase (MT1-MMP) to tissue inhibitor of metalloproteinase (TIMP)-2 regulates MT1 MMP processing and pro-MMP-2 activation. J. Biol. Chem., 275, 12080-12089, 2000.

Toth, M., Gervasi, D.C., Bernardo, M.M., Soloway, P.D., Wang, Z., Bigg, H.F., Overall, C.M., DeClerck, Y.A., Tschesche, H., Cher, M., Brown, S., Mobashery, S., and Fridman, R. TIMP-2 acts synergistically with synthetic MMP inhibitors but not with TIMP-4 to enhance the MT1-MMP-dependent activation of pro-MMP-2. J. Biol. Chem., 275, 41415-41423, 2000.

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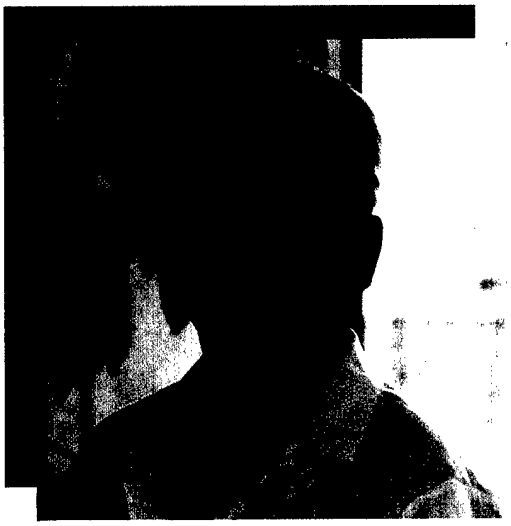
Dong, Z., Nemeth, J.A, Cher, M.L., Palmer, K.C., Bright, R.C., and Fridman R. Differential regulation of matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1 (TIMP-1) and TIMP-2 expression in co-cultures of prostate cancer and stromal cells. Int. J. Cancer. 93: 507-515, 2001.

Nemeth, J.A., Yousif, R, Herzog, M., Che, M., Upadhyay, J., Shekarriz, B., Bhagat, S., Mullins, C., Fridman, R., and Cher, M.L. Matrix metalloproteinase activity, bone matrix turnover, and tumor cell proliferation in prostate cancer bone metastasis. J. Natl. Cancer Inst. 94: 17-25, 2002.

Bernardo, M.M., Brown, S., Li, Z-H., Fridman, R. and Mobashery, S. Design, synthesis and characterization of potent, slow binding inhibitors that are selective for gelatinases. J. Biol. Chem., in press, 2002.



Fred R. Miller, Ph.D.

Breast Cancer
Ph.D., University of Wisconsin-Madison, 1976

We are developing the MCF10 xenograft model of human breast disease as 1) a tool to elucidate genetic alterations occurring with progression, 2) a tool to screen possible chemopreventive agents, and 3) a tool to detect breast carcinogenic/promoter activity. At present the model consists of MCF10AT premalignant cell lines, MCF10DCIS.com which represents the more advanced carcinoma in situ stage of disease, and MCF10CA1 variants which are fully malignant. We also have developed a unique panel of closely-related mouse mammary tumor subpopulations, some metastatic but by different routes, and some non-metastatic but with deficiencies at different steps of metastasis. One of the subpopulations metastasizes widely to lung, liver, bone, and brain.

Selected Publications

Lelakis, M., Moseley, J.M., Martin, T.J., Hards, D., Williams, E., Ho, P., Lowen, D., Javni, J., Miller, F.R., Slavin, J., and Anderson, R.L. A novel orthotopic model of breast cancer metastasis to bone. Clinical and Experimental Metastasis 17:163-170, 1999.

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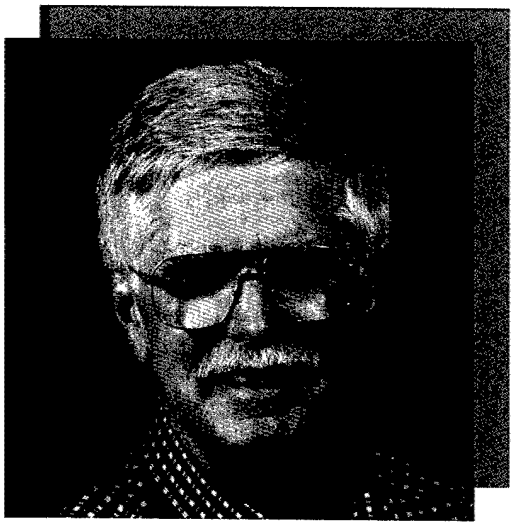
Tao,K., Li, J., Warner, J., MacLeod, K., Miller, F.R., Sahagian, G.G. Multiple lysosomal trafficking phenotypes in metastatic mouse mammary tumor cell lines. International Journal of Oncology (In Press).

Robert J. Pauley, Ph.D.



Breast Cancer
Ph.D., Marquette University, 1975

Normal development and differentiation of breast tissue require complex interactions between epithelial cells within the parenchyma and both fibroblasts and myofibroblasts within the stroma. Changes in the structural organization and function of parenchymal epithelial cells and stromal fibroblasts characterizes breast neoplasia. Our research has focused upon the establishment and characterization of key parenchymal and stromal cellular components, as well as to evaluate these for properties important to normal development and neoplasia. Our studies demonstrate that breast stromal cells in vitro synthesize estrogens by the rate limiting aromatase enzyme, and that CYP19/aromatase gene regulation involves multiple alternative transcription initiation sites that are differentially regulated by hormones and growth factors in stromal myofibroblasts from normal, benign and tumor breast tissues. Breast parenchymal epithelial cells have been propagated from breast reduction mammoplasty tissue and demonstrated to exhibit properties of differentiated breast epithelial cells in vitro including homotypic cell-cell interactions and to acquire a neoplastic phenotype upon transfection. Ongoing studies concern three-dimensional in vitro homotypic and heterotypic cell-cell interactions between breast epithelial cells and fibroblasts to model breast tissue differentiation and neoplastic development, and parallel to in vivo studies including a recently developed cell line that forms in xenografts lesions features of ductal carcinoma in situ, an established human preneoplastic condition for breast cancer, as well as comedo/apoptotic differentiation.

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Pauley, R.J., Soule, H.D., Tait, L., Miller, F.R., Wolman, S.R., Dawson, P.J., Heppner, G.H. The MCF10 Family of Spontaneously Immortalized Human Breast Epithelial Cell Lines: Models of Neoplastic Progression. European Journal of Cancer Prevention, 2:67-76, 1993.

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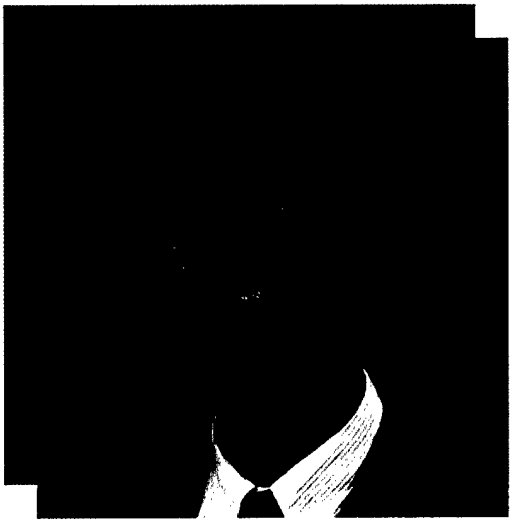

Kaladhar B. Reddy, Ph.D.

Breast Cancer
Ph.D., Osmania University, 1984

A major goal of our research is to understand how phosphorylation controls cell signal transduction, by identifying protein kinases and phosphatases that are controlled by growth factors and examining their mechanisms of regulation. Second goal is to understand role of cross-talk between peptide growth factor and estrogen receptor signaling pathways and its effect on tumor progression and anti-estrogen treatment. Our aim is to understand the regulation of MEK and its role in cell motility and invasion in breast cancer cells. We have identified several phosphorylation sites on this enzyme, and are examining their contributions to kinase activation. Mutants of MEK that are either constitutively active or catalytically inactive were designed, which, upon transfection into cultured mammalian cells respectively, enhance or block signal transduction through the MAP kinase pathway. Overexpression of constitutively active MEK mutants led to enhanced cell motility. Interestingly, expression of constitutively active MEK mutants activates estrogen receptor by cross-talk and this enhanced estrogen mediated signaling and tumor growth. We are currently examining downstream cellular targets of MAP kinase and MEK to explain how the same pathway can control such different cellular responses.

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Visscher, D.W., Sarkar, F.H., Kasunic, T.C. and Reddy, K.B. Clinicopatholigic analysis of Amphiregulin and Heregulin immunostaining in breast neoplasia. Breast Cancer Res. Treat., 45:75-80,1997.

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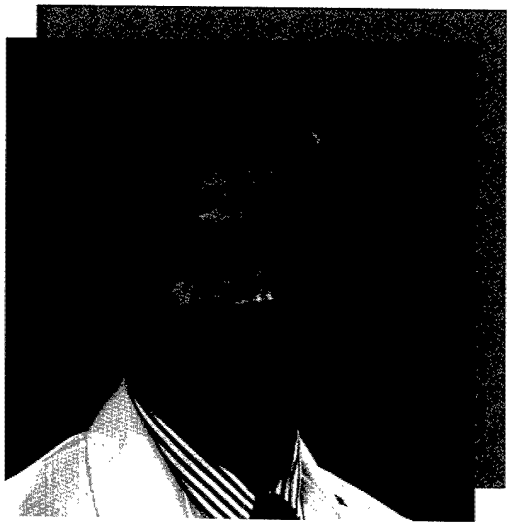
Fazlul H. Sarkar, Ph.D.



Breast and Prostate Cancer
Ph.D., Banaras Hindu University, 1978

The process of cancer development and progression requires modulation of multiple genetic factors. Differential gene expression and regulation of specific genes appear to play an important role in the developmental cascade of cancer. Many oncogenes and tumor suppressor genes have been shown to be involved in such processes. Investigations are being pursued to study the differential expression of growth factor/growth factor receptor genes, oncogenes and tumor suppressor genes, in understanding the biology of human adenocarcinomas. Parallel investigations are also being pursued to understand the regulation of some key genes in the development and progression of breast and prostate cancer. The identification and characterization of novel transcription factors which regulate the transcription of some key genes may ultimately lead to the understanding of the effects of these genes in cellular growth, differentiation and programmed cell death (apoptosis). Since the development of a cancer mass is dependent upon the ratio of cellular proliferation and apoptotic cell death, molecular biological understanding of some of these genes (which are actively involved in the regulation of cell cycle and apoptotic processes) should yield information that will facilitate the development of novel preventive and therapeutic agents along with traditional treatment modalities for the management of human adenocarcinoma. The current research areas of focus include chemoprevention, molecular mechanism of action of novel agents, research on cellular signaling molecules, processes of cell growth inhibition and apoptosis and clinical translational research involving clinical trials.

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Sarkar FH, Li Y-W, Sakr W, Grignon DJ, Madan SS, Wood DP, Adsay NV. Relationship of p21WAF1 expression with disease-free survival and biochemical recurrence in prostate adenocarcinoma (PCa). The Prostate 40: 256-260, 1999.

Davis JN, Kucuk O, Sarkar FH. Genistein inhibits NF-kB activation in prostate cancer cells. Nutrition and Cancer 35(2): 167-174, 1999.

Li Y-W, Bhuiyan M, Sarkar FH. Induction of apoptosis and inhibition of c-erbB-2 in MDA-MB-435 cells by genistein. Int. J. Oncol. 15: 525-533, 1999.

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Davis JN, Kucuk O, Djuric Z, Sarkar FH. Soy isoflavone supplementation in healthy men prevents NF-_B activation by TNF-a in blood lymphocytes. Free Radical Biology and Medicine 30: 1293-1302, 2001.

Upadhyay S, Neburi M, Chinni SR, Alhasan S, Miller F, Sarkar FH. Differential sensitivity of normal and malignant breast epithelial cells to genistein is partly mediated by p21(WAF1). Clin. Cancer Res. 7: 1782-1789, 2001.

Prasad AS, Bao B, Beck FWJ, Sarkar FH. Zinc activates NF-kB in HUT-78 cells. Journal of Laboratory and Clinical Medicine 138: 250-256, 2001.

Malathy Shekhar, Ph.D.

Breast Cancer
Ph.D., Indian Institute of Science, 1985

Dr. Shekhar's research program focuses on the molecular and cellular aspects of breast cancer progression. A major aspect of Dr. Shekhar's research is concentrated on the role of estrogen in development of preneoplasia of the breast and mechanisms of hormone resistance. Using a model for human proliferative breast disease, Dr. Shekhar's group has identified the specific stages of morphological progression from hyperplasia to invasive cancer that is most susceptible to estrogen-induced progression and tamoxifen-mediated intervention. Recently, Dr. Shekhar's group has also shown that the growth and hormonal response of breast cancer cells is modulated in a dominant manner by the stromal microenvironment. Efforts are underway to determine the molecular changes induced by interactions with the stroma. Overexpression of Ha-ras is frequently observed in breast cancer. Dr. Shekhar's group has identified a novel hormone responsive transcriptional regulatory element in the intron-1 of the mouse Ha-ras gene. Using nuclear run off assays, her group has found distinct differences in the estrogen inducibility of Ha-ras expression between nonmetastatic and metastatic breast cancer cells: viz., estrogen-induced synthesis of Ha-ras mRNA in nonmetastatic mammary cells versus lack of sensitivity to estrogen in metastatic cells that constitutively overexpress Ha-ras mRNA. Such differences in hormonal inducibility of Ha-ras expression may play an important role in hormone-dependent and -independent phenotypes of breast cancer. Another major area of research is focussed on examining mechanisms that play a role in maintaining genomic integrity of breast cells. Dr. Shekhar's group has demonstrated that Rad6, a gene known to function in post-replication repair of DNA, is overexpressed in breast cancer cell lines and carcinomas. Constitutive overexpression of Rad6 in normal breast cells induces abnormal mitosis, aneuploidy, transformation and drug resistance. Current studies are focused on determining molecular mechanisms regulating Rad6 expression and structural/functional characterization Rad6.

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P.V.M. Shekhar, P. Nangia-Makker, S. Wolman, L. Tait, G.H. Heppner, and D.W.Visscher. Direct action of estrogen on sequence of progression of human preneoplastic breast disease. Amer. J. Pathol., 152: 1129-1132, 1998.

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Debra F. Skafar, Ph.D.

Breast Cancer
Ph.D., Vanderbilt University, 1983

The human estrogen receptor-alpha is succinctly described as a "ligand-activated transcription factor". It changes conformation in response to the binding of endogenous and exogenous ligands; the changes in conformation lead to changes in the interaction with coregulator proteins that lead to changes in the transcription of specific genes. Biologically, binding to this protein and subsequent changes in the activity of this protein is responsible for many of the physiological activities of the steroid hormone 17B-estradiol. Equally importantly, the estrogen receptor is a target for the anti-cancer drugs tamoxifen and raloxifene. My laboratory is focused on understanding the conformational changes of this important protein. By understanding the conformation changes of this protein and what drives the changes, drugs that produce the desired effects, but not the undesirable effects, can be designed. Our general approach is to identify areas likely to be involved in regulating the conformation of the protein, use site-directed mutagenesis to alter the identified areas, and finally test the functions of the mutants. We supplement our bench studies with molecular modeling of the wt and mutated receptors. We aim to provide information that will assist in the development of drugs that selectively block the growth-promoting effects of estradiol, while maintaining the beneficial effects of estrogen on bone density and the cardiovascular system.

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Yudt, M.R., Vorojeikina, D., Zhong, L ., Skafar, D.F., Sasson, S., Gasiewicz, T.A. and Notides, A.C. The function of estrogen receptor tyrosine 537 in hormone binding, DNA binding and transactivation. Biochemistry 38: 14146-14157, 1999.

Skafar, D.F. Formation of a powerful capping motif that corresponds to the start of "helix 12" in the agonist-bound estrogen receptor-alpha contributes to increased constitutive activity of the protein. Cell Biochemistry and Biophysics 33: 53-62, 2000.

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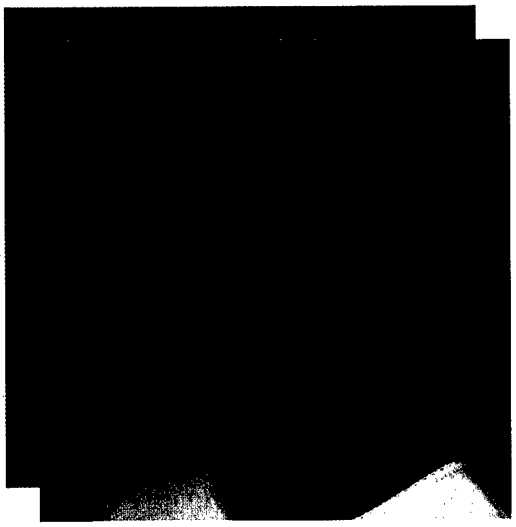

Wei-Zen Wei, Ph.D.

Breast Cancer
Ph.D., Brown University, 1978

The primary goal of this lab is to prevent cancer progression by immunological means. Recombinant erbB-2 (Her-2/neu) DNA vaccines and therapeutic pro-peptides are being developed to activate anti-tumor T cell responses. ErbB-2 is a transmembrane tyrosine kinase which mediates oncogenic activity and is over-expressed by several types of solid tumors including breast, ovarian, small cell lung cancer, etc. Over-expressed ErbB-2 is recognized by the immune system as a tumor associated antigen and is a target of active vaccination. ErbB-2 DNA vaccines have been generated to eliminate kinase activity, to expedite processing for T cell recognition and to contain adjuvant peptide for enhanced immunogenicity. ErbB-2 vaccines are administered as naked DNA, in Salmonella vector or as gene-modified antigen presenting cells, such that antigenic epitopes are generated in vivo by antigen presenting cells through the same pathways as natural antigens. Tolerance to ErbB-2, negative immune regulation and epitope spreading are studied in transgenic mice expressing human ErbB-2. Novel constructs to overcome tolerance and induce efficacious anti-tumor immunity are generated by students and post-doctoral fellows based on their individual hypothesis and design. The most efficacious constructs are translated to clinical trials. In another novel approach, we test the hypothesis that solid tumors can be eliminated by immunizing the patients with foreign peptides and by delivering to the lesions therapeutic peptides in the form of pro-peptides. A pro-peptide has been synthesized from a HLA-A2.1 restricted Influenza matrix peptide by conjugating glucuronic acid to the N-terminus of the peptide. Pro-peptides are inert because they lose the binding motif to MHC. Active peptides are released from the pro-peptides by enzymes secreted at the tumor sites. These locally released peptides mark the tumor cells or neighboring stromal cells for immune destruction. Based on this principle, novel peptides are developed and are candidate agents for cancer immunotherapy.

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Marie P. Piechocki, Shari A. Pilon and Wei-Zen Wei. Complementary anti-tumor immunity induced by plasmid DNA encoding secreted and cytoplasmic human ErbB-2. J. Immunol. 167: 3367-3374, 2001.

Wei-Zen Wei, Stuart Ratner, Terry Shibuya, George Yoo and Agnes Jani, Foreign antigenic peptides delivered to the tumor as targets of cytotoxic T cells. J. Immunol. Method. 258:141-150, 2001

Marie Piechocki, Shari A. Pilon and Wei-Zen Wei, Quantitative measurement of anti-ErbB-2 antibody by flow cytometry and ELISA., J. Immunol. Method. 259:33-42, 2002.

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