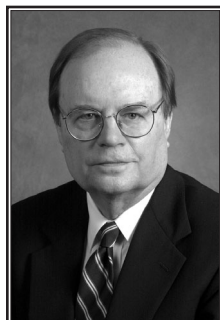


DIRECTOR'S MESSAGE

JOHN S. KOVACH, MD



THE IMPORTANCE OF TRANSLATIONAL RESEARCH

Translational research in medicine is scientific investigation involving the application of basic research to problems of human disease. Equally important is the reverse pathway by which the clinician takes medical problems to the laboratory scientist looking for greater understanding of causation and mechanisms underlying

disease so as to be able to improve methods of diagnosis, estimation of prognosis, prevention, and treatment.

All the National Institutes of Health are emphasizing the importance of translational research. In particular, the National Cancer Institute encourages the coming together of clinical and basic research scientists to bridge gaps in communication. The aim is to turn observations made in fundamental laboratories into testable hypotheses for evaluation in clinical trials.

Translational research in all fields of medicine has been given a tremendous impetus by new insights into mechanisms of disease stemming from advances in genetics and cell biology. Once the specific pathways that drive growth of cancer cells are identified, translational scientists, particularly medicinal chemists and pharmacologists, can use their expertise to create drugs to attack specific biochemical pathways. It is also now possible to screen tens to hundreds of thousands of compounds existing in "libraries" of chemicals at many pharmaceutical houses for activity against a single biochemical pathway in a matter of days to weeks.

Perhaps the most dramatic example of anti-cancer drug development in recent years is that of "Gleevec®", a rationally designed molecule that when given by mouth to patients with chronic lymphocytic leukemia inhibits a specific enzyme reaction unique to the cancer cell. Remarkably, oral Gleevec® is associated with very few side effects yet leads to complete or striking remission of this leukemia in almost every patient.

This kind of dramatic success is spurring intensive translational research throughout the academic and commercial research communities. Critical elements to this process are the ability to synthesize molecules targeted against specific molecular defects in the cancer cell and then to determine efficacy and safety in animal models and finally, in the clinic.

Two Stony Brook Programs Spur Research in Translational Cancer Pharmacology

The Long Island Cancer Center (LICC) is fortunate in having a well organized clinical trials program led for many years by Dr Stefan Madajewicz. Collaboration between Dr Madajewicz and Dr Louis Peña, a pharmacologist at Brookhaven National Laboratory, has merged clinical with pharmacological expertise providing for state-of-the-art evaluation of new drugs. They are establishing a collaboration with a major international pharmaceutical company to bring promising new anti-cancer agents through clinical evaluation on campus (see *article page 3*).

Anti-cancer drug development on campus has been given a big boost by the creation of an Institute for Chemical Biology and Drug Discovery by Distinguished Professor Iwao Ojima, Department of Chemistry. Dr Ojima is a world respected chemist who sparks a team working closely with structural and cellular biologists in the rational design of drugs targeted to specific biochemical processes (see *'Focus On' insert*). These new developments bring excellence in translational cancer pharmacology research to the LICC programs.

The opportunities for translational research at Stony Brook, however, are not limited to cancer pharmacology. The basic science departments of the School of Medicine and in the University, as well as Brookhaven National Laboratory, are conducting investigations at the forefront of understanding the basic life processes that regulate life of the cell and life of the cell within complex tissue such as in the breast or prostate or brain.

Particularly relevant to translational cancer research is the depth of research at Stony Brook in developmental biology. The processes by which the cells of organisms multiply and differentiate and the perturbations of those processes that lie at the heart of uncontrolled cancerous growth are fertile areas for translational research. As in many fields of discovery, the major path to converting fundamental knowledge to applied benefits is communications between disparate cultures. Our opportunity is to facilitate frequent exchange of ideas across scientific disciplines so that excellence in translational research becomes the hallmark of the LICC.

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SEPTEMBER HAPPENINGS

Sep 15 **First Annual Long Island OCEANS
"Wave of Hope Gala"**
Begins 6:30 PM
Giorgio's Restaurant & Catering
Baiting Hollow
Honoring: Eva Chalas, MD;
Robert Cox, Esq.; Joan Cox
Contact: 631-878-7080

Long Island OCEANS (Ovarian Cancer Education Advocacy Networking Support) is a non profit support group for women living with gynecological cancers. Together with the community and Stony Brook University Hospital, Long Island OCEANS is committed to finding early detection tests to improve survival rates.

Sep 20 **Cancer Education Program:**
Sep 27 **Sponsored by the Department of
Social Work Services at Stony
Brook University**
7 PM to 9 PM
Holiday Inn Express
Stony Brook
Contact: HealthConnect®
at 631-444-4000

This educational series provides cancer patients and their families with a variety of information and resources regarding treatment, support services, and issues related to care of disease.
September sessions: Communicating with your Health Care Team (Sep 20), and Managing Side Effects of Treatment (Sep 27).

Sep 18 **12th Annual "Walk for Beauty...
in a Beautiful Place"**
Registration Opens 8 AM
Walk Begins 9:30 AM
Stony Brook Village Center
Contact: HealthConnect®
at 631-444-4000



The Walk for Beauty, which follows a scenic route through historic Stony Brook, raises thousands of dollars annually for breast and prostate cancer research at Stony Brook University. The walk remains one of the university's most successful fundraising and community events. Last year nearly 2,000 people participated in the walk.

SEVEN LICC PHYSICIANS NAMED TO "BEST DOCTORS" LIST

New York Magazine's "Best Doctors in New York" list for 2005 includes seven physicians who practice at the Long Island Cancer Center (LICC) at Stony Brook University Hospital (SBUH). A total of 27 physicians from SBUH received this honor. The selection process for this annual mid-year listing is based on answers to questionnaires from approximately 16,000 top physicians in the Greater New York Metropolitan Area. Each "best doctor" was selected from more than 50,000 physicians practicing in this region.

The LICC physicians chosen as "the best" provide a wide range of clinical expertise, including surgery for breast, head and neck, thyroid, ovarian, colorectal and other gastrointestinal cancers, and neurological and pediatric cancers. Most of these physicians are active in investigating

cancer prevention, early detection, and clinical trials of promising experimental treatments.

The seven selected as among "the best" in New York in cancer care are: Eva Chalas, MD, Gynecologic Oncology; Raphael P. Davis, MD, Neurological Surgery; Dorothy S. Lane, MD, Preventive Medicine; Brian J. O'Hea, MD, Director and Chief Surgeon, Carol M. Baldwin Breast Care Center; Martin S. Karpeh, MD, Chief, Surgical Oncology; Robert I. Parker, Director, Pediatric Hematology/Oncology, and Maisie L. Shindo, MD, Director, Head and Neck Oncology.

Physicians were rated in a multitude of categories with emphasis on education, training, clinical skills, board certification, professional reputation and interpersonal skills.

News & Views

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Stony Brook University Hospital and Health Sciences Center
7547 SUNY
Stony Brook, NY 11794-7547
Phone: 631-444-9348
LICC website: Stonybrookhospital.com/licc



Send comments about News & Views to:
Editor: Greg Filiano
Phone: 631-444-9343
E-mail: gfiliano@notes.cc.sunysb.edu

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ANTI-CANCER DRUG EVALUATION PROGRAM: COLLABORATION WITH BROOKHAVEN NATIONAL LABORATORY SCIENTIST JUMPSTARTS PROCESS

Stefan Madajewicz, MD, PhD, a medical oncologist at the Long Island Cancer Center (LICC) at Stony Brook University Hospital (SBUH), is teaming up with Louis A. Peña, PhD, radiobiologist and pharmacologist, and Associate Scientist, Medical Department, Brookhaven National Laboratory (BNL), to evaluate the biological mechanisms of new drugs that show potential as anti-cancer agents. This important collaboration could potentially bring new molecularly based anti-cancer drugs directly into the SBUH therapeutic pipeline.

This drug development program includes laboratory testing in animal and human cell cultures and in animal models of human disease. If a drug appears effective against a particular type of cancer, Dr Madajewicz, the director of clinical trials program, will consider that drug for evaluation in a therapeutic study by the LICC. He is in discussions with several drug companies to test their products in therapeutic approaches with laboratory animals.

The first experimental drug being evaluated, developed by a global pharmaceutical company, is being tested against brain cancer in rats. Dr Peña is using a brain tumor model (glioblastoma) that he developed in his laboratory several years ago. He induces cancer by transplanting tumor cells into the brain. Once the tumors are established, Drs Peña and Madajewicz work together to evaluate tumor growth, drug toxicity, and the ability of the agent to penetrate the tumor.

"Glioblastoma in the rat is similar to the glioblastoma disease process in humans," says Dr Madajewicz, noting the primary reason for testing the drug against this form of cancer. He points out specifically that Dr Peña's expertise as a translational scientist and

pharmacologist, along with his extensive experience in working with brain tumors in rat and mouse models makes him an ideal partner in this collaborative research.

A Model to Build On

Their expertise, combined with the molecular research facilities of Stony Brook University and BNL, he adds, provides the foundation for a variety of studies for each cancer model created and potential drug tested. Access to BNL's high-powered small animal magnetic resonance imaging (MRI) and positron emission tomography (PET) systems is a powerful aspect of this collaboration. These instruments provide an accurate and non-invasive method for following changes in the tumor and in animals.

Much evaluation and testing of the drug's effectiveness and safety in animals must be done before a clinical trial in humans can be developed. Preliminary results show that the agent effectively shrinks the tumors in rodents, but this does not mean it will be effective against brain tumors in humans.

The research team believes that as the drug development program gains momentum, the Stony Brook University / BNL partnership should prove to be a fruitful one. In combination, the institutions bring together outstanding clinical and pharmacologic expertise combined with advanced instrumentation that is necessary for this research. The team is expanding their focus beyond brain tumors to metastatic breast cancer and cancers of the lung and gastrointestinal tract.

TARGETED RESEARCH OPPORTUNITIES NEARLY \$500,000 AWARDED TO CANCER INVESTIGATORS

Ongoing philanthropic support from the community is giving nine Stony Brook University cancer researchers an opportunity to advance their work in breast, prostate, lung, thyroid and other types of cancers. Each of the Targeted Research Opportunity (TRO) Awards, sponsored by Stony Brook University's School of Medicine and the Office of the Vice President for Research, totals \$30,000 annually and most last for a period of two years.

Announced this summer, the TRO Awards include five supported by the Carol M. Baldwin Foundation for Breast Cancer Research. This research involves investigation on the molecular basis of breast cancer that could lead to earlier detection and targeted therapies.

The awardees are Dafna Bar-Sagi, PhD, Department of Molecular Genetics & Microbiology; Edward Chan, MD, Department of Pediatrics; Janice Lu, MD, PhD, Department of Medicine / Hematology Oncology; W. Todd Miller, PhD, Department of Physiology & Biophysics, and Ken-Icchi Takemaru,

PhD, Department of Pharmacological Sciences.

Two newly recruited Long Island Cancer Center physicians, Ted Gabig, MD, Head of the Division of Hematology/Oncology, and Kopal Patel, MD, Assistant Professor, Division of Surgical Oncology (see *article page 4*), received the Catacosinos Cancer Translational Researcher Award. Dr Gabig is leading a project investigating molecular markers for chemoprevention of lung cancer, and Dr Patel is studying the role of a gene (MUC1) in the pathogenesis of thyroid cancer.

Two other 2005 TRO Awards involving cancer research are supported by the Ward Melville Heritage Organization's Walk for Beauty Foundation. One is for breast cancer and the other for prostate cancer.

Deborah Brown, PhD, Department of Biochemistry & Cell Biology, is investigating how a certain anti-tumor antibiotic drug affects a gene specifically implicated in breast cancer; and Gayle Vaday, PhD, Department of Medicine, is studying a specific protein signal (chemokine) involved in prostate cancer.

NEWLY FORMED ICB & DD POOLS STONY BROOK UNIVERSITY'S RESEARCH STRENGTHS TO TACKLE DISEASE

By Greg Filiano

The unraveling of the human genome that has sparked rapid and continuing advancement in human molecular genetics and advances in chemical biology prompted Iwao Ojima, PhD, Distinguished Professor, Department of Chemistry, to establish an interdisciplinary organization of Stony Brook University researchers that integrates basic and clinical sciences with medicinal chemistry. The goal of the Institute for Chemical Biology & Drug Discovery (ICB & DD) is to design novel therapeutic drugs, including anti-cancer agents. The institute maximizes the existing strengths of Stony Brook's many science disciplines and adds outside expertise to explore drug development.

"Drug discovery is often left out of fundamental biological research, yet it is one of the most important and beneficial scientific contributions to society," says Dr Ojima, Director, ICB & DD. He believes the scientific community's growing understanding of the molecular bases of many kinds of diseases is a catalyst for new drug development. Dr Ojima adds that this new era of molecular medicine sets the stage at academic medical institutions for prime opportunities for collaborative research to develop more effective targeted therapies against disease.

The ICB & DD bridges chemical biology to areas such as immunology, infectious diseases and oncology. An essential element of the collaborative work is translational research, which involves basic and clinical researchers investigating the molecular bases of diseases and connecting these findings to targeted therapies. This involves interdisciplinary collaboration at many levels where the drug is tested, including examining drug actions and resistance, first in animal disease models then in human disease.

Researchers from the ICB & DD are working in conjunction with the Long Island Cancer Center (LICC). The LICC's resources in human molecular genetics and the creation of a frozen tumor bank in the Department of Pathology will enable translational research scientists to increase the molecular understanding of human cancers. Such knowledge is needed by synthetic and medicinal chemists at the ICB & DD to design new, more specific, and less toxic treatments.

Scope of the ICB & DD

Officially formed in 2004, the ICB & DD is comprised of nearly 30 faculty members from the departments of Biochemistry and Cell Biology, Molecular Genetics and Microbiology, Pharmacological Sciences, Physiology and Biophysics, the

Centers of Molecular Medicine, and The Institute for the Conservation of Tropical Environments. Outside members include scientists from other universities, Brookhaven National Laboratory, and major pharmaceutical firms. This grouping of researchers forms a dynamic institute that has drawn attention and support within Stony Brook University and outside the university.

This ICB & DD was launched with support from each of Stony Brook's vice presidential offices -- Academic Affairs, Research, and Health Sciences. The New York State Office of Science, Technology, and Academic Research has also contributed substantially to the formation of the institute. Dr Ojima, who has worked with many international pharmaceutical companies to develop new drugs, expects significant financial support from the pharmaceutical and biotechnology industries and grants from the National Institute of Health as collaborative projects take hold.

Projects in Anti-Cancer Drug Development

The goal of the cancer arm of the ICB & DD is to develop new chemotherapeutic agents with improved tumor specificity. One of the first collaborative efforts in developing such agents involves testing a derivative of Taxol®, an anti-cancer agent used



Iwao Ojima, PhD

"Drug discovery is often left out of fundamental biological research, yet it is one of the most important and beneficial scientific contributions to society."

to treat breast, ovarian and non small-cell lung cancer.

While taxol has a unique mechanism of action and is effective on some tumors, the drug lacks tumor specificity and tumor cells often become resistant to the drug. Dr Ojima has developed a new generation of taxoid agents that he patented. They have additional molecular mechanisms to deal with tumor specificity and drug resistance.

"A problem with the current drug is that some cancer cells have 'efflux pumps' that push taxol out of the cell, deteriorating

the drug's effectiveness," explains Dr Ojima. He says that his class of taxoids has a built-in mechanism that moderates the cells efflux pumps so that the agent can stay in the cancer cell and kill it.

Dr Ojima's taxol derivative is effective against breast, ovarian, and colon cancers in animal models, and the institute's researchers are in the process of evaluating and refining the drug in a variety of ways. One approach is to deliver the new taxoid as conjugates to certain unsaturated fatty acids. Given in this way, the drug conjugate stays within cancers and releases the active taxoid for a much longer time (10 days) compared to the conventional administration of the drug.

The new taxoid also has the potential to be given orally. This could be advantageous to patients who would then not require intravenous administration of the drug, which is often associated with acute toxicity. Dr Ojima expects a prototype of the drug for human trials can be developed within two years.

The design of signal transduction enzyme inhibitors is another focus of the ICB & DD's anti-cancer therapeutics program. Signal transduction pathways control cell growth, differentiation, and survival by directing extracellular signals into the cell's interior. At Stony Brook University, approximately 25 laboratories are involved in signal transduction research, which involves the study of molecular targets and defined activities of enzymes and groups of enzymes.

The ICB & DD is fostering interdisciplinary research in several projects investigating use of enzyme inhibitors as potential anti-cancer treatments. Dr Ojima emphasizes that the results coming from collaborative research on novel signaling enzyme inhibitors with medicinal chemists is potentially a "gold mine" for discovery of new mechanism-based targeted anti-cancer agents.

Varied Expertise Necessary to Advance Discovery

The only way The ICB & DD at Stony Brook University can develop new and more effective anti-cancer agents is to continue building a team with a wide range of scientific expertise. Before any new cancer drug can be shown to be effective and safe, it needs to be evaluated within many segments of science.

An example of expertise critical to success is computational biology, or bioinformatics. This is the use of statistics and applied mathematics to understand biological problems such as gene expression and protein-protein interactions. Dr Ojima says that four new computational biologists recently hired by Stony Brook University will link basic research and fundamental biology to anti-cancer drug development.

Another essential component to the institute's interdisciplinary work is to incorporate expertise in pharmacokinetics, the science involved in studying the distribution of a drug in the body and in pharmacodynamics, the effects of the drug on the body. Experts in pharmacokinetics and pharmacodynamics flesh out important details about how to develop a new drug for a clinical trial.

Dr Ojima says that these disciplines are just a few of many specialized research areas that add to the core talents of researchers who have worked at Stony Brook University for years and are now part of the ICB & DD. He believes that by pooling their talents, and adding outside expertise from academia and industry in selected areas, the ICB & DD will flourish.



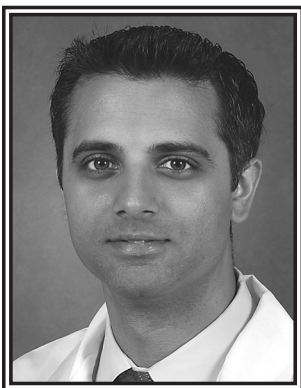
INSTITUTE FOR CHEMICAL BIOLOGY & DRUG DISCOVERY (ICB & DD)

FAST FACTS:

- The ICB & DD bridges chemical biology to areas such as immunology, infectious diseases and oncology.
- The ICB & DD is comprised of nearly 30 Stony Brook University faculty members from many branches of science.
- Researchers from the ICB & DD are working in conjunction with the Long Island Cancer Center.
- An essential element of the work is translational research investigating the molecular bases of diseases.
- The goal of the cancer arm of the ICB & DD is to develop new chemotherapeutic agents with improved tumor specificity.
- The design of signal transduction enzyme inhibitors is one focus of the institute's anti-cancer therapeutics program.
- Building a research team with a wide range of scientific expertise is key to the success of the institute.
- Adding outside scientific expertise from academia and industry will build the research strengths of the ICB & DD.

NEW SURGEON JOINS HEAD AND NECK ONCOLOGY

Kepal Patel, MD, a surgical oncologist whose primary clinical focus is the management of head and neck tumors, joined the Long Island Cancer Center (LICC) at Stony Brook University Hospital in July as Assistant Professor of Surgery, Division of Surgical Oncology.



Kepal Patel, MD

Dr Patel comes to the LICC from Memorial Sloan Kettering Cancer Center in Manhattan where he completed his fellowship training in head and neck oncology. He provides additional expertise for treating head and neck cancers at SBUH because of his special interest in

translational research in these types of tumors.

His clinical work falls within the Head and Neck Section of the Division of Otolaryngology, under the leadership of Maisie Shindo, MD, Director, Head and Neck Oncology, who is a nationally recognized expert in head and neck oncologic surgery and thyroid/parathyroid surgery.

In 2004, Dr Patel received the Young Investigator Award from the American Society of Clinical Oncology for his research on therapeutic targeting of a certain gene involved in aggressive thyroid cancer. He plans to continue this specific research and related investigation on genetic profiling in the progression of thyroid cancer. Dr Patel will collaborate with Dafna Bar-Sagi, PhD, Chair of the Department of Molecular Genetics and Microbiology, in these research efforts.