discover >> develop >> translate >> commercialize

CENTER FOR
BIOTECHNOLOGY
*A NYSTAR Center For Advanced Technology*

# President's Remarks

The opportunity to harness the tremendous resources of our academic enterprise to accelerate the discovery, development, and commercialization of life-enhancing technologies has never been greater. At Stony Brook University we are committed to ensuring that the ground-breaking biomedical research that takes place on our campus ultimately reaches patients.

The Center for Biotechnology has been central to this mission. As described in the following pages, they have contributed to the development of more than a dozen commercially available products with cumulative sales approaching $1B. More importantly, these products are helping to advance science and improve human health.

The Center has also been a leader of our State's bioscience agenda, having participated in the founding of the Long Island High Technology Incubator, the New York Biotechnology Association, the Long Island Life Sciences Initiative, and the New York Bioscience Council. These organizations provide a framework by which our State's bioscience industry can continue to grow.

This is, of course, just the beginning. In looking forward, it is true that the challenges in biomedicine are daunting, but the opportunities are infinite. Together, as academia and the bioscience industry join forces, new discoveries, new diagnostics and new treatments are on the horizon. I look forward to the continued success of the Center for Biotechnology, and applaud the many advances in the biomedical sector that it has fostered.

Samuel L. Stanley, Jr., M.D.
President
Stony Brook University

# Mint Condition | *Anti-cavity technology*

Israel Kleinberg, D.D.S., Ph.D., D.Sc., F.R.C.D.(c), Distinguished Professor, Chair, Department of Oral Biology and Pathology

Candies, chocolates and cookies that prevent cavities? No, you're not dreaming. In the not-too-distant future, sweet treats may become a delectable part of daily dental care for kids, and happily, for adults. The tooth-friendly treats are actually sugarless confections infused with CaviStat®, a novel anti-cavity agent developed by Dr. Kleinberg and his research team. The technology mimics the natural protective action of saliva by neutralizing harmful acid-producing oral bacteria while protecting the teeth against destructive acid demineralization. It is available in a commercial product called BasicMint™.

Two clinical studies have confirmed CaviStat® efficacy. In one with 200 children, those who received twice daily doses of BasicMint™, had up to 75% reduction in dental caries compared to their controls. In another study with 726 children, CaviStat® incorporated into toothpaste cut cavities by more than half compared to a fluoride dentifrice.

"CaviStat® technology should mean substantial reduction in cavities and big reduction in treatment costs," says Dr. Kleinberg. And, if CaviStat® is applied to teeth before caries is visibly detectable, such pre-caries lesions can be repaired by re-mineralization treatment, thereby avoiding dreaded drilling and filling.

Dr. Kleinberg's lab is a fertile breeding ground of ideas and inventions. His team is currently involved in 16 projects in various development and marketing stages. Besides CaviStat® for dental caries, these include two products that reduce dentinal sensitivity: DenClude® for home use and ProClude® for professional use. Both resulted from licensing to Ortek Therapeutics on Long Island and sub-licensing subsequently to one of the world's largest dental consumer companies for world-wide marketing. A mouthwash that eliminates halitosis has also been developed and is being marketed by another start-up company. An electronic caries explorer, yet unnamed, has reached the manufacturing stage. It is capable of detecting cavities long before they are present visually.

Based on his decades of research into the complex oral ecosystem, Dr. Kleinberg is now examining the metabolisms of the under-arm, between-toes, vaginal, nares (nose) and colon microbial communities. "These investigations have given us a broad understanding of how mixed bacteria become unbalanced and cause disease" says Dr. Kleinberg. "We now know how to correct microbial community imbalances and are building a significant pipeline of novel health care products and treatments based thereon."

"CaviStat® incorporated into toothpaste cut cavities by more than half compared to a fluoride dentifrice."

## Under Construction
### *Hyaluronic Acid Hydrogels*

Glenn Prestwich, Ph.D., Presidential Professor, Director, Center for Therapeutic Biomaterials, Special Presidential Assistant for Faculty Entrepreneurism, Department of Medicinal Chemistry, University of Utah

In the laboratory as in life, a minor makeover can make a big difference. While at Stony Brook University in the early 90's, Glenn Prestwich and his research team found a way to transform hyaluronic acid, or HA (perhaps best known today as a cosmetic facial filler or injectable for arthritis), from a shapeless "goo" into a functional, customizable biomaterial with a multitude of applications.

HA is a naturally occurring, gel-like substance found throughout the body that acts as a joint lubricant, a protective agent and helps maintain the shape of the eye.

"For researchers, the problem is that HA is rapidly turned over; in the body, it degrades and is remade all the time," says Dr. Prestwich. "At Stony Brook we found a way to modify the chemistry of HA, to make it last longer and to give it 'shape' – we controlled the composition and the stiffness of the gel – and then a whole range of commercial opportunities became evident."

Since then, the applications of HA have blossomed to include products for preventing post surgical adhesions, in ophthalmic surgery, to promote wound healing and tissue repair. Within the past several years, "we've been investigating HA as a cellular scaffold for tissue engineering, in other words, going beyond just repairing tissues to actually growing new tissues," says Dr Prestwich.

What started at Stony Brook has now been commercialized by five companies-Clear Solutions Biotech, Sentrx Surgical, Carbylan Biosurgery, Glycosan BioSystems and Sentrx Animal Care.

"HA... going beyond just repairing tissues to actually growing new tissues."

"In the war on cancer… a quest to identify and formulate tumor-specific drugs that are at once more potent and more merciful."

## Guided Molecular Missiles
### *Cancer Therapeutics*

Iwao Ojima, Ph.D., Distinguished Professor of Chemistry, Director, Institute for Chemical Biology and Drug Discovery

In the war on cancer, the ongoing challenge for researchers has been how to design drugs that destroy the enemy—the tumor cells—without damaging innocent bystanders—the healthy cells. Dr. Ojima and his team are on a quest to identify and formulate tumor-specific drugs that are at once more potent and more merciful.

Since the 1980's Dr. Ojima's research has focused on developing second-generation, more effective derivates of taxol (the anti-cancer drug derived from the Pacific Yew tree) and novel delivery systems that, in essence, trick tumor cells into welcoming the agents of their own destruction. It's no easy task: cancer cells often have ingenious methods to dispose of would-be executioners. Some cancers, for example, have an "efflux" pump, a mechanism that actually "boots out" certain drugs, while others, such as pancreatic cancer, are inherently drug-resistant.

But the good guys aren't retreating. "We're using second-generation taxoids as the warheads and omega-3 polyunsaturated fatty acids, monoclonal antibodies and vitamins as tumor-targeting molecules," says Dr. Ojima. These compounds exhibit a "higher potency (up to 1000 times) at lower doses against drug-sensitive and drug-resistant tumors and also display remarkable tumor specificity when used as tumor-targeting drug conjugates."

Dr. Ojima has an impressive 150 patent awards and/or patents pending. Two of his technologies have already been licensed to Sanofi-Aventis and Indena Pharmaceuticals.

# Oldies but Goodies
## *Chemically Modified Non Antibacterial Tetracycline Analogs*

Lorne M. Golub, D.M.D., M.Sc., M.D. (Honorary), Distinguished Professor, Department of Oral Biology and Pathology

The annals of medicine are filled with tales of serendipitous discoveries -- treasures tripped over while searching for something completely different. And not infrequently, what is discovered turns out to be more valuable than what was originally sought.

This is a scenario that Dr. Lorne Golub can relate to personally. In 1981, while trying to identify the biologic mechanisms by which diabetes increases the severity of periodontal disease ("gum" disease, the major cause of tooth loss in adults), Golub and his collaborators stumbled onto a previously unrecognized and totally new therapeutic use for an old family of drugs.

"We identified the ability of tetracyclines (TCs), by a mechanism completely unrelated to their antibiotic activity, to inhibit collagen- and tissue-destructive enzymes, such as those involved in periodontal disease," says Dr. Golub. The researchers immediately initiated the development of several non-antibiotic formulations of TCs. Over the years, these new chemical compositions and formulations have shown efficacy as inhibitors of collagen and connective tissue breakdown and bone resorption in vitro, in cell cultures, in animal models and in human studies.

In 1998, the first offspring of their research, Periostat®, received FDA approval. Over a decade later, it is still the only systemically-administered drug for the treatment of periodontal disease approved by the FDA (and approved by regulatory agencies in Canada and a number of European countries). More recently, another offspring, Oracea®, received FDA approval for rosacea, a chronic inflammatory skin disease. Both drugs contain small non-antimicrobial amounts of doxycycline, a TC derivative. The doses were designed to be weak enough to prevent antibiotic side-effects yet strong enough to inhibit the collagen-destructive enzymes and to treat periodontal and chronic inflammatory skin disease.

Today, Periostat® is in clinical practice in both periodontics and dermatology and has recently shown evidence of efficacy in humans as a treatment for other diseases like rheumatoid arthritis, as well as local bone loss (periodontitis) and mild systemic bone loss (osteopenia) in post-menopausal women. Moreover, several human clinical trials indicate that Periostat® can reduce risk factors of cardiovascular disease.

Dr. Golub and his team aren't resting on their laurels. "We also developed a series of chemically-modified TC analogues that in high doses have shown efficacy in suppressing blood vessel lesions (angiogenesis) in patients with a type of cancer, Kaposi's sarcoma," he says, "And a higher dose regimen has also been very effective in a clinically-relevant animal model of acute respiratory distress syndrome, a fatal disease in 40% of patients and for which there is no FDA-approved drug."

"Over a decade later, (Periostat®) is **still the only** systemically-administered drug for the treatment of periodontal disease **approved** by the FDA."

## Protein Matchmaker

### *Genetic System to Detect Protein-Protein Interactions (Yeast Two-Hybrid System)*

Stanley Fields, Ph.D., Professor, Genome Sciences, Medicine, Adjunct Professor of Microbiology, University of Washington School of Medicine, Investigator, Howard Hughes Medical Institute

In 1989, long before Internet dating became the rage, Dr. Fields pioneered a high-tech matchmaking method for proteins. The technique, which came to be known as the yeast two-hybrid system, was a major breakthrough for researchers, making it easier and significantly speedier for scientists to identify complex protein-protein interactions.

Proteins are essential components of all living cells. In the molecular hierarchy, they are the worker bees, performing countless essential tasks, from ferrying other proteins to cellular repair and communications. And like bees, they work in colonies, often forming complex, elaborate structures that fit together with "exquisite precision," says Dr. Fields. And identifying protein interactions is one of the keys to demystifying disease processes from cancer to diabetes to heart disease.

Twenty years ago, before the two-hybrid system, identifying protein-protein interactions was a long biochemical process that could take anywhere from weeks to months to years. By contrast, the two-hybrid assay takes a mere week or two to do the same thing.

Since 1994, when Fields' process was patented, it has been licensed nonexclusively to more than 100 pharmaceutical and biotechnology companies. Dr. Fields offers a poetic explanation for his invention's popularity: "It addresses one of life's fundamental questions: how to find a meaningful partner."

"… identifying protein interactions is one of the keys to demystifying disease processes."

"the first drug ever developed by a SUNY institution that was approved for sale by the FDA."

## Crowd Control

### *Antiplatelet drug development*

Barry Coller, M.D, Vice President, Medical Affairs, Physician-in-Chief, Allen and Frances Adler Laboratory of Blood and Vascular Biology, The Rockefeller University

The lifespan of human platelets is fleeting –about ten days, on average. But during their brief sojourn in the human body, these cells play a critical role. They patrol the vascular system looking for any tear or leak in a blood vessel in need of repair. The first platelets on scene stick to the vessel wall to stem the bleeding. When reinforcements arrive, the platelets crowd together creating a kind of cellular superglue in a process called aggregation.

At least, that's how it should work. For reasons that are not always clear, platelets can overreact, forming clots in blood vessels constricted and damaged by atherosclerosis (plaque build-up). These clots can block the flow of blood leading to a heart attack or stroke.

In the 1970s and 80s, while researching the cellular mechanism of aggregation at Stony Brook University, Dr. Coller developed a monoclonal antibody that inhibits the action of a key protein receptor involved in platelet aggregation. His discovery and his subsequent collaboration with scientists at Centocor led to the creation of abciximab, a drug that effectively prevents platelets from closing off blood vessels.

In 1994, the drug, marketed as ReoPro® won FDA approval to prevent platelets from sticking together and causing blood clots following coronary angioplasty. The drug, which has been administered to an estimated 3 million people worldwide, has the distinction of being the first drug ever developed by a SUNY institution that was approved for sale by the FDA.

## (Not) Cutting the Cord
### *Collagenase*

Lawrence Hurst, M.D., Professor, Chair and Marie A. Badalamente, Ph.D, Professor, Department of Orthopedics

In most medical specialties, treatment is trending away from surgery towards less invasive interventions to treat diseases. But for "orphan diseases" those that affect only a small percentage of the population-and therefore have a limited market - identifying and developing such alternatives is more difficult. One example: Dupuytren's Contracture, a disorder in which excess collagen accumulation in the palm and fingers causes thick, inflexible cords to form triggering a progressive and permanent curling up of the fingers.

Historically, the standard of care has been surgery to cut the cords. But now, thanks to the investigational research begun in the mid '90s by Drs. Badalamente and Hurst, a non-surgical treatment may soon receive FDA approval. The treatment consists of injections of Clostridial collagenase - a highly purified form of a common bacterium - into the affected cords. Collagenase breaks up the cords and relieves the flexion. In clinical trials, it has been shown to be "well tolerated and effective in the treatment of Dupuytren's disease," says Dr. Badalamente. "And the FDA has convened an advisory committee to review collagenase for new drug approval for the Dupuytren's indication."

In addition, with Edward Wang, M.D., Associate Professor of Orthopedics at Stony Brook, Dr. Badalamente is studying injectable collagenase as a treatment for frozen shoulder (adhesive capsulitis), a condition in which scar tissue forms around the shoulder joint, restricting movement. Licensed to Malvern, Pa.-based Auxilium Pharmaceuticals, Inc., this application is in clinical trials.

And in a lighter vein, Clostridial collagenase just may turn out to be a silver bullet for a condition that is the scourge of women everywhere: cellulite. In 2006, Dr. Badalamente and a colleague conducted a small study. "The results," she says, "were very promising."

"thanks to the investigational research by Drs. Badalamente and Hurst, a non-surgical treatment may soon receive FDA approval."

## It's Lights Out for Cancer Cells
### *Altered Energy Metabolism–Directed Cancer Therapeutics*

Paul M. Bingham, Ph.D., Associate Professor, Department of Biochemistry and Cell Biology,
Zuzana Zachar, Ph.D., Research Assistant Professor, Department of Biochemistry and Cell Biology

In living organisms, normal cells have a shelf life, an expiration date of sorts. So when their time is up they go quietly. Cancer cells, on the other hand, are driven to multiply and reproduce. "It's what makes them malignant," says Dr. Bingham.

While scientists have long known that the energy metabolism of tumor cells differs dramatically from normal cells, over the past few years they've learned a great deal about how and why it differs. "We now understand that in cancer cells, there's a shift from energy production to cell manufacture," says Dr. Bingham.

That understanding led Drs. Bingham and Zachar to develop "the first successful drug to attack this fundamental metabolic difference between normal and tumor cells," says Dr. Bingham. The technology consists of chemically altered versions of lipoic acid (lipoate), a molecule that generates signals used to regulate energy metabolism.

The drug treatment, "apparently messes up the tumor cells' metabolism triggering programmed self-destruction while leaving normal cells unaffected," says Dr. Bingham.

"We are just beginning clinical trials in pancreatic cancer patients," explains Dr. Bingham. "But given the novel mechanism of our drugs and their performance in laboratory models, we hope to have a significant impact on treatments for all cancers. And down the line, "we can reasonably hope that our drugs will be effective as single agents, perhaps even superseding some earlier therapies," says Dr. Bingham. "Moreover, our drugs are very attractive anchors for multi-drug cocktail development in the future."

"a significant impact on treatments for all cancers. "

"the diagnostic tool that not only allows earlier disease diagnosis but also helps assess the efficacy of cancer therapies during treatment."

## Tracking Cancer Cells
### *Cancer Invasiveness Analyzer*

Wen-Tien Chen, Ph.D., Research Professor of Medicine, Division of Hematology/Oncology, Director, Metastasis Research Laboratory

It's a medical mantra: the earlier cancer is diagnosed, the better the prognosis. A blood test technology developed by Dr. Chen and his lab could be the diagnostic tool that not only allows earlier disease diagnosis but also helps oncologists assess the efficacy of cancer therapies during treatment.

The tests—Vita-Assaytt™ and Vita-Cap ™—utilize proprietary Cell Adhesion Matrix technology (CAM)—a kind of Velcro for cancer cells—to detect the presence of rare, circulating tumor cells (CTCs) in the blood. Isolating CTCs from normal blood cells is the biological equivalent of looking for a needle in a field of haystacks. "We are talking about finding one cell in 100 million blood cells," says Dr. Chen. "CAM is proving to be 10 to 100 times better than existing methods," he adds. The technology led to the formation of Vitatex Inc., a biotech company focused on bringing this and other potentially revolutionary blood tests to market.

At present, these tests are used solely as a research tool but Dr. Chen believes that, eventually, CAM will play a vital role in identifying the primary source of a cancer. Dr. Chen and his team have also developed and patented several therapeutic monoclonal antibodies that prevent tumors from spreading to distinct organs and developing new blood vessels, an anti-cancer therapy known as antiangiogenesis. "Without a blood supply, tumors can't grow and spread," he says.

Starve a tumor. Save a life.

## Gut Instinct | *3-D Virtual Colonoscopy*

Arie Kaufman, Ph.D., Distinguished Professor, Chair, Department of Computer Science, Director, Center of Visual Computing, Chief Scientist, Center of Excellence in Wireless and Information Technology.

Although more than 90 percent of colorectal cancers are preventable, only 35 percent of us have regular screenings and a mere 20 percent proceed with recommended colonoscopies. Why?

"The prep for a traditional colonoscopy is so uncomfortable and unappealing that patients often disregard medical advice or delay the screening," says Dr. Kaufman, who developed 3-D virtual colonoscopy, a kinder, gentler approach.

Compared to traditional colonoscopy, the virtual variety requires no harsh prep, no lengthy latrine duty. While the exact prep protocol depends on where the test is done, at Stony Brook, patients follow a low residue diet the day before the procedure. Each meal is washed down with a banana and barium smoothie. The barium "tags" the food, allowing the computer to perform "electronic cleansing" and thus providing the doctors with a cleansed colon.

In a traditional, optical colonoscopy, sedation is required so the doctor can scope the length of the intestine. In a virtual colonoscopy, a non-invasive CT scanner takes pictures of the abdomen. The data is then processed into a 3-D image of the colon - that allows the doctor to do a virtual "fly" through the entire length of the colon in search of any polyps, the precursor of cancer. The screening takes less than 15 minutes and costs significantly less than a traditional procedure.

If polyps are found, an optical colonoscopy is needed to remove the growths. While this is considered problematic by some, Dr. Kaufman has a different view: virtual colonoscopy, he says, is a screening method, much like mammography, and less than 10 percent of those screened will have polyps for removal. "The goal is to increase compliance, find colon cancer earlier and save thousands of lives," says Dr. Kaufman.

Two large studies, including an Army study involving 1300 patients, proved the effectiveness of virtual colonoscopy which received FDA approval as a colon cancer screening in 2004. Based on Dr. Kaufman's work, Stony Brook, New York-based Viatronix, Inc. developed a commercial product which is now available all over the world. The 3-D virtual colonoscopy technology has been recently licensed by two CT manufacturers, including Siemens.

Dr. Kaufman and his team are currently developing 3-D imaging software to detect prostate cancer. "We are working on a mechanism to localize and visualize the cancer, so the oncologist or radiologist can actually look at it," says Dr. Kaufman. And that means a kinder, gentler diagnostic process. Men everywhere are breathing easier.

"Although more than 90% of colorectal cancers are preventable, only 35% of us have regular screenings…Why?"

## Boning Up
### *A non-drug therapy for osteoporosis and fracture healing*

Clinton Rubin, Ph.D., Distinguished Professor, Chair, Department of Biomedical Engineering, Director, Center for Biotechnology

By his own admission, Dr. Rubin is "a total bonehead." Rubin isn't suffering from low self-esteem; he is literally describing the focus of his research over the past 25 years.

Dr. Rubin and his team advanced the use of biophysical stimuli (mechanical, electrical, temperature and acoustic) to both accelerate bone healing after fracture and to prevent, slow, and potentially reverse the age-related bone loss that leads to osteoporosis.

Although conventional wisdom correlated high-impact exercise with the most positive effect on bone, Dr. Rubin hypothesized that bone might actually respond more enthusiastically to subtle stimuli such as the tiny muscle contractions that occur when a person is standing or reaching for a cup of coffee. "Sometimes bigger isn't better," he explains.

To test their theory, the researchers came up with a high-frequency/low-magnitude oscillating platform that mimics those subtle muscle contractions. Animal tests and subsequent human studies confirmed that standing on a vibrating platform for 20 minutes a day improved bone health with minimal side effects. Additional NIH-funded studies are ongoing.

Juvent, a company that Dr. Rubin co-founded, is now marketing a version of the oscillating platform as treatment for osteoporosis in Canada, Europe, Australia and New Zealand. In the U.S., the Juvent 1000 will soon be sold as an exercise device pending future FDA studies.

Dr. Rubin and his colleagues also developed the Exogen Bone Healing System, the only FDA-approved device for the acceleration of fresh fracture healing. The Exogen system emits low-intensity, pulsed ultrasound waves that stimulate the bones' natural healing process, speeding up the healing process by an impressive 40 percent, says Dr. Rubin.

"Low-intensity, pulsed ultrasound waves… speeding up the healing process by an impressive 40%."

"Axons are filament-like extensions of neurons. They relay messages from one nerve cell to the next."

## Improved Communications
### *Monoclonal antibodies*

Joel M. Levine, Ph.D., Professor of Neurobiology, Department of Neurobiology and Behavior

In the early 1990s, Dr. Levine and his colleagues were starting to study spinal cord injury and axonal regeneration. Axons are filament-like extensions of neurons. Their job is communication: they relay messages from one nerve cell to the next.

Around the same time, neurobiologists became very interested in the potential role of certain complex molecules called proteoglycans (found in cartilage and other connective tissue) — in the regulation of axon growth and regeneration says Dr. Levine.

What the scientists lacked was a proper study tool. "At that time, there were few reagents available to study the location and functions of these complex molecules," says Dr. Levine.

So Dr. Levine embarked on a research project to develop monoclonal antibodies targeting those molecules involved in axon growth and regeneration. "It took about 16 months to develop and fully characterize the antibodies which were initially licensed to Chemicon Inc., in April of 1999," says Dr. Levine.

The antibodies allowed researchers to localize individual species of proteoglycans and to study their protein-protein interactions on the surfaces of neuronal cells. "This provided us with important information about the environment of the damaged brain and spinal cord," says Dr. Levine. For example, Neurocan, one of the species studied, prevents axonal regeneration, repair following brain or spinal cord injury, and is a factor in multiple sclerosis. "Therefore, it is important to

# ≫Technologies in Development

- Unique bioactive peptides with cosmetic and wound healing applications, as well as for the treatment of second and third degree burns
- Atrial fibrillation detection algorithms and wireless patient monitoring system
- Non-invasive, painless continuous glucose monitoring system
- New class of cancer therapeutics based on energy metabolism
- Novel biopolymers and hydrogel microspheres for drug and cell delivery, as well as hemostat and wound healing applications
- Non-invasive ultrasound medical device for the diagnosis of osteoporosis and other bone-related disorders
- Genetically-modified attenuated viral vaccines and virus-like particles
- Medical device for treatment of osteoporosis and the prevention of childhood obesity
- Non-invasive, painless allergy diagnostic testing
- Gene-based clinical diagnostic for infertility
- Novel compounds for the treatment of inflammatory diseases such as rheumatoid arthritis
- Nanofabricated membranes for drug and cell delivery, as well as tissue engineering applications
- New therapeutic approach for treating cardiovascular disease


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The Center for Biotechnology gratefully acknowledges the contributions
of the New York State Foundation for Science, Technology and Innovation (NYSTAR),

Produced with the generous support of Hoffmann & Baron, LLP, and Kenyon & Kenyon LLP