The Stony Brook Young Investigators Review

AN UNDERGRADUATE JOURNAL OF SCIENCE

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PROBING BIOLGICAL SYSTEMS ONE ATOM AT A TIME

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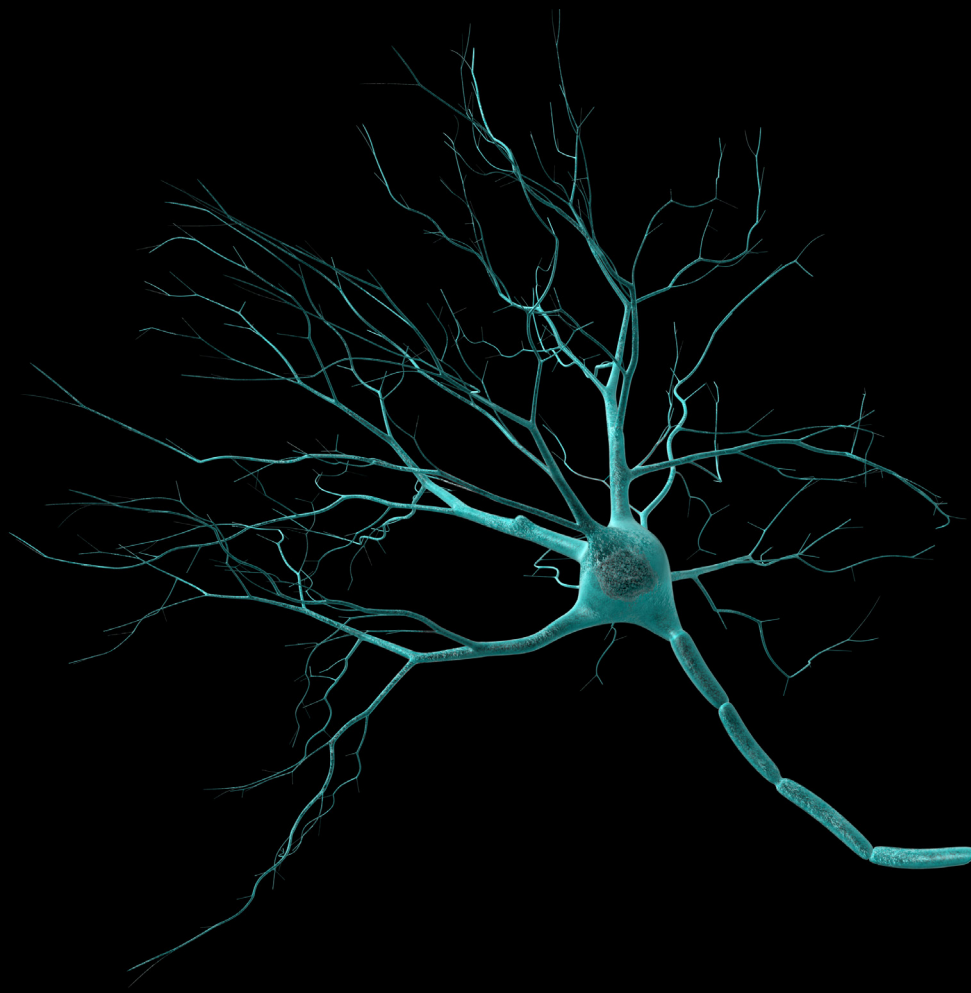

Battling Alzheimer's

STONY BROOK LEADS THE WAY

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The Stony Brook Young Investigators Review

CALL FOR ARTICLES & STAFF

Articles

YIR seeks original research articles from Stony Brook undergraduates conducting research in any natural or applied science.

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On the Cover

Alzheimer's Disease is a neurodegenerative disease that afflicts millions of older Americans. In this issue, Nadya Peresleni discusses what strides are being made at Stony Brook to find relief for those suffering from the disease. Pictured on the cover is a normal, healthy neuron. The accumulation of amyloid plaques in Alzheimer's sufferers causes healthy neurons like this one (left) to malfunction and eventually die.

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In This Issue

President's Message

On a Mission with the Stony Brook Young Investigators Review

Stony Brook University is well known for the prodigious research efforts that occur here. Indeed, many important discoveries have been made over the years by Stony Brook's expert faculty. The development of Magnetic Resonance Imaging (MRI) by the late Professor and Nobel Laureate Paul Lauterbaur immediately comes to mind, but there are many others: the discovery of the cause of Lyme disease and the first *de novo* synthesis of a virus, to name a few.

The reputation that Stony Brook's faculty have earned is well-deserved, but as anyone who spends even a few hours at Stony Brook knows, undergraduates are very much involved in the scientific efforts here as well. 'Doing research' is almost a rite of passage for many Stony Brook undergrads. After running their first western blots or synthesis reaction, one hears these students speak with great enthusiasm and satisfaction, as if they had just been initiated into an elite club. Yes, only at Stony Brook are the cool kids the ones who can say, "Oh, I work in so-and-so's lab."

Yet, despite the existence of this extensive population of undergraduate researchers, there are surprisingly few avenues for these students to share their efforts and discoveries with their peers and professors. This is not to say that there aren't any. The Undergraduate Research Education and Creative Activities (URECA) program's annual symposium is an excellent venue for Stony Brook undergrads to show off their work, but this event only takes place once a year in the spring. Some departments host symposia in which undergraduates can put their research on display, but the audience for these events is typically limited to people in the department and a few outsiders. Students and faculty in other departments around the campus are likely unaware that these events are even taking place.

This shortage of opportunities for undergraduates is regrettable because it means that student-researchers are not fully taking part in the scientific enterprise. Without some kind of forum in which to present their findings and open themselves and their work to criticism, undergrad researchers are being trained to become useful technicians but not the next generation of pioneering investigators.

Equally unfortunate is the fact that non-science majors are often left in the dark concerning the stellar strides that are made in basic science research at their own school by students and faculty alike. This not only makes it harder to achieve the important goal of educating a scientifically literate populace, but it also encourages the further balkanization of different kinds of knowledge and disciplines that is already a problem in academia. Making the scientific discoveries at Stony Brook accessible to the wider student body would do much to bridge the divide between science and non-science majors and would foster the kind of interdisciplinary exchanges that are increasingly characteristic of innovative academic work.

To address these issues, we have created the Stony Brook Young Investigators Review, or just YIR. Our mission is to provide an outlet for students through which they can share and discuss scientific ideas and information. In particular, we aim to highlight the efforts and discoveries made here at Stony Brook, by undergraduates and faculty alike. Moreover, we hope to increase awareness of and enthusiasm for science throughout the Stony Brook community.

In this inaugural issue, we present a collection of original articles, perspectives and scientific reviews encompassing a wide range of topics. In coming issues, we also hope to publish original research articles by undergraduates who have carried out significant work in any of the natural or applied sciences. We believe that in this regard, YIR offers a unique opportunity for undergraduate researchers to prevent their hard-earned findings from falling by the wayside after they leave the university. For example, the work that many graduating seniors do for their theses might not be complete enough to pass the rigors of a professional journal, but would be ideal for YIR. So, we invite them and all other students conducting research in the natural and applied sciences to consider submitting original work for our next issue. In the same vein, we warmly invite students to participate in the first annual Young Investigators Review symposium (see back cover for more information).

This first issue of the Young Investigators Review has been a long time coming, and is the product of much hard work and dedication from numerous people. I cannot thank enough our staff members, who stuck it out with us through some uncertain times, and who have produced the marvelous articles that make up this journal. Likewise, words are not enough to express my gratitude to the countless people who put their faith in a bunch of kids with big ambitions and only minimal experience. Their support, both financial and intellectual, has made YIR possible. And I can only hope that what we offer here leaves them feeling that their investment was a sound one.

So, I leave you to enjoy this first of hopefully many issues of the Stony Brook Young Investigators Review. When you're done, please let us know what you think. Your feedback will help us to better suit your interests and achieve our goals.

Sincerely,
Alexander Chamessian
President and Co-Founder
Stony Brook Young Investigators Review

Letter from the Editor

For undergraduates aspiring to careers in science and research, the road may seem to be filled with obstacles, distractions, set-backs, and uncertainty. Walking into your first general chemistry or biology class during your freshman year of college is only a small foreshadowing of what your future holds. The competitiveness fills the giant lecture halls, which are probably too small to seat all the students that show up for the first couple of lectures. However, the numbers of students that attend lectures begins to drop slowly but surly. After the midterms, faces that became somewhat familiar, either drop the class, or decide to switch their majors. What you have experienced is a simple and early filtering step. If you decide to stick to science and medicine, you will be faced with many more of those steps, which will continue to increase in difficulty, and the effort and work necessary to doge and out survive them exponentially grows. So is it all worth it? Is there light at the end of the tunnel? if so, how do you stay competitive and ahead of the curve?

"How to succeed in science: A concise guide for young biomedical scientists" by Jonathan W. Yewdell published in Nature Review, is a must read for any aspiring researcher. Yewdell begins his article with some very depressing and discouraging facts that I must share with you,

- A small number of those holding a Ph.D. degree will ever become principal investigators (PI) with the opportunity to direct their own research.

- The average age for receiving the first NIH research grant (R01) is 43.

- Applying for grants is continuing to become more and more competitive, and if you lose your grant, you might risk your job especially in your early years.

- By the time you become professor, you are doing much worse financially than your peers in other fields that put in the same amount of effort that you do.

There are two possible reactions to such news, the first and most effort free is to consider a change of career goals and field of work. The second is to find ways to become more competitive as an applicant to graduate schools, fellowships and post docs, and eventually grants and funding. Our true intentions ultimately determine the path we end up choosing. Only those that choose the field out of pure interest and natural curiosity will decide to endure the long pursuit. They will even begin to notice that they enjoy the journey as much as the ends. They enjoy juggling research and their undergraduate classes, or the long hours in the lab in their graduate years. Only then can somebody know for sure, that they made the correct decision.

The idea of starting an undergraduate journal here at Stony Brook began when I become more involved in research in a biochemistry lab. Reading journal articles, and going to scientific talks, I began to understand the importance of scientific writing in particular to the research process. I quickly began to realize its not something that you can just learn and become good it, but rather a process and a journey in by itself. I knew there was a need of a medium to practice such skills early on, and attempt to learn the arts of writing a scientific article, a scientific review, or simply communicate effectively scientific ideas and thoughts to members of our peers. The Young Investigators Review is our modest contribution to our eager peers to meet such need. Running a science magazine proved a lot more difficult that initially thought. As the Editor-in-Chief, my goal for YIR is for every issue of this magazine to be better in quality and scientific content than the one before. Since this is our first issue, I would ask all those that stumble upon it to give it a read, and to please give us some feedback on what to improve and how to become better. Feedback from fellow students, faculty, graduate student, and anybody with an opinion will be greatly appreciated and held in high esteem.

Finally, I would like to thank all those that gave us the support and initial push to put this first issue out. It is one thing to support an established idea, and a different thing to support an inchoate vision.

Sincerely,
Muath Bishawi
Editor-in-Chief and Co-Founder
Stony Brook Young Investigators Review

Chemical Biology Here, There, Everywhere

Alexander Chamessian '09

The 20th century, it is said, was the century of physics. Today, with many of the great problems of physics behind us, scientists are directing their efforts towards the numerous unsolved problems in biology and medicine, leading some to call the 21st the century of biology. One consequence of this mass shift in aims is the gradual erosion of the traditional divisions and barriers that once kept scientists in different arenas isolated. In step with this trend, whole new fields are emerging that draw on multiple fonts of knowledge to approach - and hopefully solve - the long-standing questions about life on earth. Chemical biology is one such emergent discipline that is breaking new ground and attracting much attention.

Chemical Biology in Principle

Discussions of chemical biology almost always begin with some attempt at defining this young field and distinguishing it from its predecessors. Critics of chemical biology claim that the new name is just a rebranding of established fields like biochemistry and biological chemistry, which have been applying chemistry to biology for a century or more. It doesn't help that even the chemical biology faithful sometimes have difficulty differentiating their craft from closely related fields like the ones already mentioned, and others, such as bio-organic chemistry, medicinal chemistry, molecular pharmacology and the like.

Nature Chemical Biology, the pre-eminent field journal, offers a simple but broad definition of chemical biology as "both the use of chemistry to advance a molecular understanding of biology and the harnessing of biology to advance chemistry.[1] " Other definitions are more explicit, such as this one: "Chemical biology is the science of small molecules in the context of living systems..." *(2).* In an article titled "Chemical Biology is..." Elizabeth Olster, a researcher at the University of Brighton, arrives at this important and unifying insight: "...a common underlying theme can be discerned; collaboration. Collaborative partnerships have made Chemical Biology into a subject in its own right" *(3).*

So chemical biology is small molecules, probing biological systems, the mutual advancement of chemistry and biology and it is collaboration. Got all that?

Chemical Biology in Practice

They say a picture is worth a thousand words, and so, where definitions of chemical biology still leave something to be desired, illustrations of the exciting work being done in the field can fill in those gaps.

Chemical Genetics

At the Broad Institute of Harvard-MIT, Stuart Schreiber, one of the pioneers of chemical biology and perhaps its most ardent spokesman, uses a combinatorial method called diversity-oriented synthesis to create vast libraries of small molecules which he then uses to elicit a biological phenotype or to interact with a particular gene product in live cells. In this way, Schreiber and his colleagues are seeking to characterize the tens of thousands of proteins that the Human Genome Project tells us are there, but whose roles in cellular processes and disease we know little about. This type of genetic study using small molecules is aptly called chemical genetics, and enthusiasm for it has spread from Cambridge to places such as the NIH and the Scripps Research Institute, where similar projects that screen chemical libraries in pursuit of gene and gene product characterization are well underway *(2).*

Signal Transduction

How cells communicate has fascinated biologists since the beginning, and over the last century, great leaps in our understanding of signal transduction have been made. But much remains to be learned about the way cells transmit information within and amongst themselves. In questions of cell signaling, the focus is often on protein kinases, of which there are more than 500 in humans *(4).*

Kevan Shokat, Professor of Cellular and Molecular Pharmacology at the University of California, San Francisco, spearheaded the application of a chemical modification strategy called the 'bump-hole' method to probe kinase function and activity *(5).* In brief, Shokat *et al.* have devised a method wherein they engineer specific mutations into the substrate binding site of a kinase whose substrate is unknown. The modified binding site is designed to only accept an ATP analog (kinases uses the γ-phosphate of ATP to phosphorylate their substrates). Because this analog bears a radioactive phosphate group, the tagged target protein can be tracked either *in vivo* or *in vitro.* This ingenious method, which uses tools and information from genetics, synthetic organic chemistry, enzymology and signal transduction, can be used in myriad applications, for example, in drug-target validation and signaling pathway elucidation.

No discussion of cell signaling is complete without mentioning calcium, the major second messenger of the cell. The work of Roger Y. Tsen, Professor of Chemistry and Biochemistry at the University of California, San Diego, and a 2008 Nobel Laureate in Chemistry, has contributed immensely to the understanding of calcium signaling through the study and creation of organic dyes that change color upon binding the Ca2+ ion *(6).* These calcium-binding dyes have allowed members of his group and of groups around the world to track the movement of calcium ions during key signaling events. True to the chemical biological form, Tsien has applied the powerful molecular tools of chemistry to gain insights into vital biological processes.

Protein Engineering

The structural biologists' favorite refrain, "structure determines function," has been taken to heart by some chemical biologists who seek to use structural and chemical insights to either create new proteins or modify existing ones to give them novel functions. The kinds of things one can do to various classes of proteins - antibodies, receptors, transmembrane proteins, enzymes, peptide pharmaceuticals - is limited by one's imagination, and perhaps more importantly, by the tools currently at one's disposal. Thankfully for researchers, their toolbox has been expanding substantially over the last decade.

Peter Schultz of The Skaggs Institute for Chemical Biology, part of the Scripps Research Institute in La Jolla, California has been one of the leaders not only in expanding that toolbox, but also in demonstrating creative applications for the new tricks. One of Schultz's salient achievements was the development of catalytic antibodies. Given the fact that enzymes often catalyze reactions by binding preferentially to the transition state, he and his coworkers took advantage of the chemical diversity of immunoglobins to develop antibodies specific for transition state analogs. For example, the use of phosphonate/phosphate transition state analogs allowed him and his group to discover highly efficient esterolytic antibodies. Using the principles of this early work by Schultz, other researchers have looked to directed evolution and powerful screening methods such as phage display to produce novel immunoglobins that serve as catalysts in a wide range of reactions *(7)*.

Nature is restricted to using the 20 natural amino acids, but that doesn't mean scientists have to be. In fact, there is a practically limitless number of α-amino acids that can be made, some having exotic side groups with diverse functionalities. The question is, however, how should one incorporate members of this greatly expanded synthetic repertoire into natural proteins? Here, Schultz again is responsible for leading the way with the development of an ingenious method called the 21st pair. In short, this method uses a bioorthogonal duo consisting of an evolved amino-acyl tRNA synthetase and accompanying tRNA to fool the cell's translational machinery into incorporating unnatural amino acids at specific sites. Remarkably, this actually works, and Schultz et al. have introduced a wide range of unnatural amino acids into proteins site-specifically, giving them new and interesting properties *(8)*.

Chemical Glycobiology

In the realm of glycobiology, which studies the structure, biosynthesis and biology of saccharides *(9)*, chemical biology has been making significant contributions. As in protein engineering, where the repertoire of amino acids has been expanded to include molecules with strange and unusual functionalities, chemical glycobiologists such as Carolyn Bertozzi, HHMI Investigator at UC Berkeley, have synthesized a host of unnatural sugars that bear useful functional groups. Bertozzi and others have demonstrated that these unnatural sugars, such as N-Azido Sialic acid (SiaNAz), which act as surrogates for natural substrates, are recognized and used by the cell's glycotransferase enzymes. This strategy, called metabolic engineering because it uses the cell's own metabolic pathways to introduce unnatural sugars into glycans and glycoproteins, has allowed Bertozzi and others to trace the fates of hard-to-study glycoproteins, and to glean valuable information about their structure and function. Importantly, Bertozzi, like her counterparts in the world of unnatural amino acids, makes heavy use of 'click chemistry,' a type of reaction in which alkynes link covalently and irreversibly to azides forming a stable nitrogenous heterocycle. And so, with the azido sugars, such as SiaNAz, Bertozzi has managed to 'click' countless classes of peptides, small molecules, chromophores, or therapeutic drugs to cell-surface glycoproteins for diverse purposes *(9)*.

One attractive use of unnatural sugars is the specific targeting of chemotherapeutics to cancer cells. Taking advantage of the fact that cancer cells display unique glycans on their surfaces, researchers have fed cancer cells unnatural sugars and then used the particular functionality on the sugar to attach a drug molecule. Here, as in so much of the chemistry that is being developed for in vivo use, bioorthogonality - meaning that the reaction doesn't affect the cell's own chemistry - is a crucial consideration, for if side reactions can occur, then delivery of the drug would be ineffective and most certainly deleterious. Fortunately, advancements in the chemistry side of chemical biology give researchers a large arsenal of bioorthogonal reactions to utilize in powerful ways, as is the case here in the development of cancer therapeutics *(9)*.

Drug Discovery

With its emphasis on understanding biological systems at an atomic level, chemical biology is naturally poised to play an important role in the discovery of new drugs. In fact, many of the hits that come up from chemical genetic screens of small molecule libraries are often used as lead molecules in further development of a marketable drug.

The National Institutes of Health (NIH) in Bethesda, MD, has been integral in advancing this effort to understand the roles of certain genes in disease and to find potential therapeutics against those diseases. For example, at the NIH Chemical Genomics Center recent screens have produced nearly 60 lead candidates for potential drug development against diseases that have not garnered much attention from Big Pharma. This past spring the group published a paper in *Nature Medicine* describ-

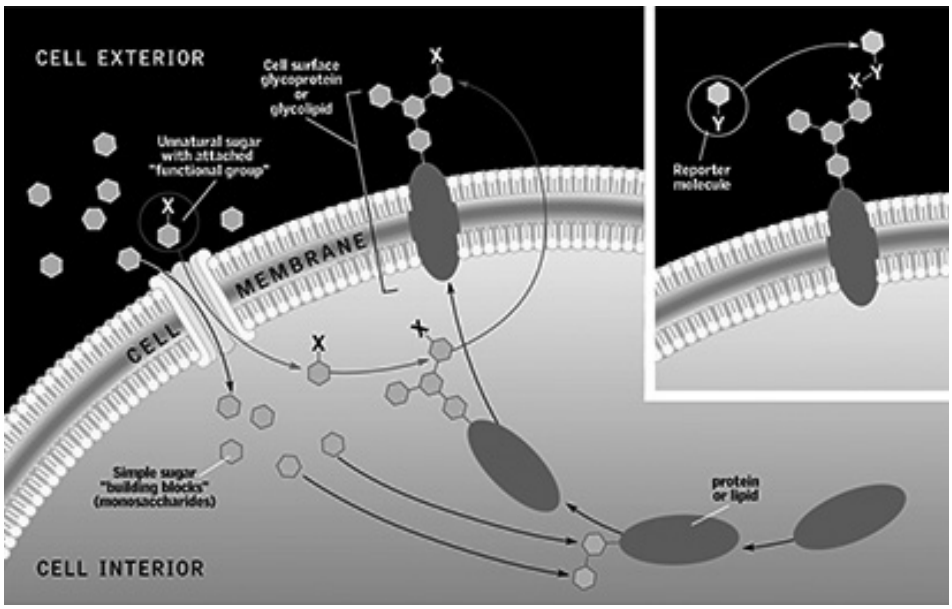


Figure 1. Metabolic Engineering: Unnatural sugars are recognized by the cell's biosynthetic enzymes, leading to their incorporation in lipids, proteins and glycans. Novel functionality on these sugars can be exploited in numerous ways. Here an unnatural sugar is displayed on a cell-surface glycoprotein where it is amenable to linkage to a receptor molecule. Source: HHMI Bulletin, Winter 2005.

ing their finding that the parasitic disease schistosomiasis is amenable to treatment with oxadiazoles *(10)*. Before that, the group had reported numerous hits against classical drug targets, such as G-protein coupled receptors, tyrosine kinases, phosphodiesterases, and topoisomerases. To be sure, massive library screens have been going on in industry for several decades, but what makes the NIH program unique is that the results for any molecule are accessible to the public through the newly established NCBI database, PubChem, which means that researchers around the world can now take advantage of this prohibitively expensive discovery technique.

Using the success of this and similar ventures as grounds for extending the project, the NIH just this September dedicated $280 million to developing a nationwide chemical biology network at nine academic institutions to find new drug leads or probes. With this initiative, the collaborative aspect of chemical biology is evident, as is the optimism with which scientists and policy makers are looking to this burgeoning field.

Chemical Biology at Stony Brook

It shouldn't come as any surprise that, Stony Brook University, a research institution recognized for its numerous scientific achievements, has many faculty doing work at the interface of chemistry and biology. What might come as a surprise, however, is that chemical biology may have been born right here nearly three decades ago.

According to Francis Johnson, Professor in the Departments of Chemistry and Pharmacology, "we started talking about chemical biology in the late 1970's before anyone else." By 'we' Johnson means he and Arthur Grollman. Dr. Grollman is director of the Leo and Judy Zickler Laboratory of Chemical Biology located in the Health Sciences Center. Together, says Johnson, "we were some of the first ones to study a biological system using an analogous chemical model." Specifically, he and Grollman overcame one of the major obstacles of studying DNA repair —the inherent instability of abasic deoxy sugars — by substituting the deoxy sugar for a more stable structural analog. This simple chemical modification, they reported, "makes it possible to study these lesions with respect to their postulated role in DNA repair" *(11)*. "At the time everybody said we were crazy," jested Johnson in a phone interview. He can say this laughingly now only because his break with scientific orthodoxy thirty years ago paid big dividends. Today, it would be unthinkable to study DNA repair without using some of the chemical methods that people like Johnson and Grollman pioneered.

Orlando Schärer, associate professor in the Departments of Chemistry and Pharmacological Sciences, would agree. An organic chemist by training, Schärer's work on DNA damage and repair relies heavily on modified nucleotides and other small molecules to understand the ways that cells mend the lesions created by physiological and environmental insults. His research reflects the attitude of many younger scientists trained in the last decade who are much more comfortable applying the tools of chemistry to biological systems than were researchers in the days when Johnson and Grollman undertook their study of DNA repair.

A New Class of Chemical Biologist
Professor Isaac Carrico, Dept. of Chemistry, Stony Brook University

Two other such researchers are Isaac Carrico and Elizabeth Boon, who came to Stony Brook after completing post-doctoral work at Berkeley in 2006. With them they brought excellent credentials and, like Schärer, a decidedly interdisciplinary outlook to research. Both assistant professors in the Department of Chemistry, Carrico and Boon received formal training in chemistry, but had a keen interest in biology from the beginning. Lucky for them, they went to graduate school just as the ex-

Perspectives

Chemical Biology
with Elizabeth Boon

YIR: How would you define chemical biology?
Boon: There is no one answer to this question, but f you want to draw distinctions, it is the use of chemical tools in biological systems in a more holistic sense than traditional biochemistry, ie., more cell based assays than purified components in a test tube. Chemical biologists attempt to answer biological questions by directly probing living systems at the chemical level.

YIR: What sparked your interest in chemical biology?

Boon: As a chemist that has always been interested in biology, it is a natural fit. The real answer (to a slightly different question) is that I am a hypothesis-driven scientist interested in cellular signaling pathways, with training in chemistry and biochemistry, and I am willing to use any tool at my disposal to test my hypotheses. So... in a way my interests have simply landed me in chemical biology territory, as opposed to me specifically pursing chemical biology as a field.

YIR: What is the major focus of your work?
Boon: We are interested in gas-based signaling processes in bacteria, nitric oxide (NO) in particular.

YIR: What specific advantages does SB offer chemical biologists, and what could it do to improve research in this area?

Boon: SBU's main advantage is that we have a department full of people interested in this field and an on-campus research Medical School. We have access to lots of equipment, centers, resources, expertise, etc. For example, through the IBC&DD, the chemistry department has a MALDI-TOF/TOF, which is a top-of-the line mass spectrometer, a huge resource for chemical biologist. Furthermore, the medical school has a proteomics facility, a DNA synthesis and sequencing facility, the list goes on.

citement for chemical biology was starting, and as it was becoming commonplace for chemists and biologists to cross into each other's territory.

Carrico's research interests are quintessentially chemical biology. Reflecting his stints with Carolyn Bertozzi of UC Berkeley and David Tirrell at Caltech, Carrico uses unnatural sugars and amino acids in a plethora of contexts. One promising application is the use of unnatural sugars tagged to viral coat proteins for use in gene therapy. Another is an immunoproteomics project in which unnatural amino acids are incorporated into antigenic proteins and then displayed on the cell surface. Retrieval of the surface-presented antigen by linkage to the unnatural acid's chemical handle can reveal valuable information about what parts of proteins are recognized by the immune system.

As to why he chose the path he did, Carrico says, "I love chemistry and really enjoy the steep learning curve chemists have to climb to impact biology. In addition, as chemical biology is a less defined area, it often requires more creativity when approaching target problems and areas, which I really enjoy."

Boon's work focuses on another important area for chemical biologists: cell signaling. While well-established in eukaryotes, the role of nitric oxide (NO) is uncertain in bacteria. Here, Boon hopes to shed some light on the question by using "any tool at my disposal to test my hypotheses." (To learn more about Professor Boon's research, see side box).

To attract such a talented cadre of young scientists, the intellectual and funding environments at Stony Brook must as good or better than those of competing institutions. Moreover, there must a commitment on the part of the faculty and university to support and encourage the interdisciplinary approach required by chemical biology. Carrico says Stony Brook's got that. "We have wonderful people in this area. These scientists are nationally recognized and very well funded —even in this dismal funding environment. Despite the fact that Stony Brook scientists who fit the vein of Chemical Biology are in a variety of departments (Chemistry, Pharmacology, Biochemistry, Biomedical Engineering, etc.), we are well networked and have generated many collaborative projects."

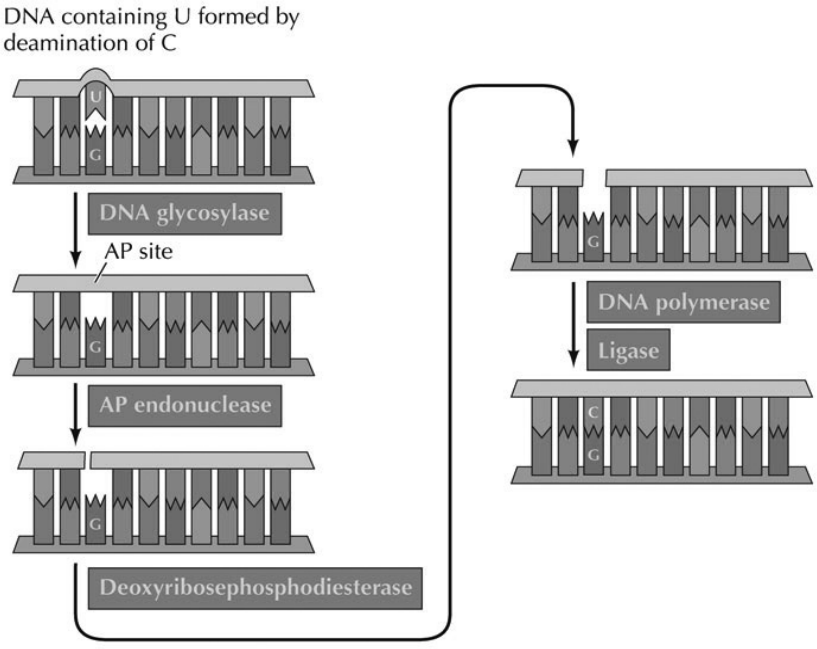


Figure 2. DNA Repair: Base excision repair is one mechanism that cells use to repair DNA lesions. In this scheme, a damaged base is removed by a specific DNA glycosylase. AP endonuclease cleaves the phosphodiester backbone and the abasic sugar is removed. The vacant position is then filled with the correct base and the DNA polymer is re-linked by DNA ligase. Studying this mechanism has been made possible by the use synthetic model systems, such as those employed by Johnson, Grollman, and Scharer. Source: Cooper, G.M, and Hausman, R.E. *The Cell: A Molecular Approach, 4 ed.*

Peter Tonge, also a Professor in the Department of Chemistry, shares Carrico's sentiments but adds that, "We also have the ICB&DD, which serves as a focal point for chemical biology research on campus."

The ICB&DD, or Institute for Chemical Biology and Drug Discovery, to which Tonge refers was created in 2005 with the primary objective of "establish[ing] a world-class 'Center of Excellence' in chemical biology and drug discovery at Stony Brook University"*(12)*. The ICB&DD is headed by Professor of Chemistry, Iwao Ojima, and is composed of faculty from multiple departments whose expertise lends to the specific goals of the institute. The "ICB&DD will complement Stony Brook's Centers for Molecular Medicine (CMM) and significantly contribute to the establishment of a truly comprehensive biomedical research enterprise from molecular science to clinic at Stony Brook," says Ojima.

In this message, Ojima reminds us of another very important aspect of chemical biology: the furthering of our understanding of disease and the rapid development of translational therapies. Indeed, the ICB&DD, as Ojima says, was created in part for this purpose, and so the work done by many of its project member reflects this. One notable example is Nicole Sampson, Professor in the Department of Chemistry and a project member of the ICB&DD. Sampson says the aim of her lab is "to understand the relationship between protein structure and function and to synthesize chemical tools to probe and control biological function." As is true for many chemical biologists, Sampson works across diverse areas to realize her goal. For example, her lab studies steroid degradation pathways in M. *tuberculosis*, sperm-egg interactions in mammalian fertilization and the function of the matrix metalloprotease hemopexin domain in cell migration. Admittedly, Sampson's primary motivation is not clinical, but herein lies the utility of the ICB&DD. Because of its collaborative bridges, clinicians who deal with infectious disease, fertility and cancer, for example, stand to benefit much from her work, whether or not it was intended for those purposes.

Lest one think chemical biology at Stony Brook is a one-way street, it is worth mentioning one of the many notable researchers in the ICB&DD whose

background and interests are primarily biological. Galina Botchkina is an associate professor in the Department of Surgery and Surgical oncology. Dr. Botchkina studies cancer stem cells, which are thought to be the immortal progenitors of bulk tumor cells. Her work aims to find unique features on cancer stem cells that allow them to be identified amongst bulk tumor cells. In addition to looking for distinguishing molecular markers, Dr. Botchkina is collaborating with the the Ojima group through an ICB&DD partnership to develop drugs specific for cancer stem cells. Because of this partnership, the two groups can carry out work that neither alone has the expertise or resources to do. This is the essence of chemical biology at Stony Brook and elsewhere.

Training Chemical Biologists at Stony Brook

Elizabeth Boon admits that she "picked up" biology in between her chemistry courses as a graduate student. Hers is not an uncommon story. In fact, most chemists who work with cells or whole organisms will tell you that on the biological end of things, they mostly taught themselves or picked up skills by watching others in the lab. On the other hand, many biologists openly eschew any kind of chemistry (often, that's the reason they went into biology in the first place). Perhaps this worked in the past, but the days of the autodidactic chemistry student and the lone biology student with a penchant for drawing curved arrows must soon come to an end if chemical biology is to grow and advance in the coming years. Students must gain a thorough grounding in both chemistry and biology from their first days as undergraduates and not have to wait until graduate school to really start their education.

A few schools such as UC Berkeley have created an undergraduate major in chemical biology. Most other schools don't have a chemical biology major but do have biological chemistry tracks within the chemistry major that allow interested students to supplement their chemistry courses with some biology.

Stony Brook falls into this latter category, offering a biological chemistry track within the chemistry major, as well as biochemistry and pharmacology majors for those so inclined. While not terrible, Stony Brook's options for students who want to study chemical biology are not optimal either. For both the biological chemistry track and the biochemistry major the central problem is that there is little to no integration of the two underlying disciplines.

In the chemistry track, students take a smattering of biology courses, such as introductory cell and molecular biology and biochemistry. For biochemistry students, there is organic chemistry and the one-semester physical chemistry course. In both cases, chemistry is taught in isolation of biology, and biology in complete disregard for chemistry. In the biochemistry course itself, one sees lots of chemical structures and is forced to memorize them in the context of metabolic pathways, but there is not one mention of a molecular orbital or any discussion of bio-organic mechanism beyond a passing remark about SN2s. Similarly, in cell biology, a required course for both groups, one could go the entire semester studying the fundamental unit of life without any concern for the chemistry that makes that life possible. Clearly something is amiss. In chemistry courses, such as Organic II and Inorganic, things are a little better, with instructors making genuine but too infrequent efforts to show the biological relevance of a particular reaction or mechanism.

To be fair, what the courses do teach they teach very well, so it is understandable that the instructors should want to focus on what they know best and not risk venturing into areas where they are not expert. Moreover, with the exception of those few universities where undergraduate chemical biology programs have been developed, Stony Brook's offerings are no worse than those at most other institutions. But that is not a reason to rest contentedly. Rather, Stony Brook should lead the way toward excellence in the teaching of chemical biology to undergraduates as much as toward excellence in research.

So what would a satisfactory chemical biology program look like? A chemical biology curriculum "must preserve the rigor of a traditional chemistry major, yet provide a serious in-depth exposure to biology," says Tadgh Begley, a noted chemical biologist and professor at Cornell University *(13)*. Under Begley's leadership Cornell has taken steps to create an undergraduate curriculum suitable to the specific needs of chemical biology. Importantly, the curriculum includes an introductory and advanced course on chemical biology that "describes the organic chemistry of biomolecules with numerous examples drawn from biology as well as methods for studying the cell that involve organic chemistry." "The final part of the course," emphasizes Begley, "integrates the information from the first two parts in a chemical and biological description of selected cellular subsystems."

At present, Stony offers a tripartite

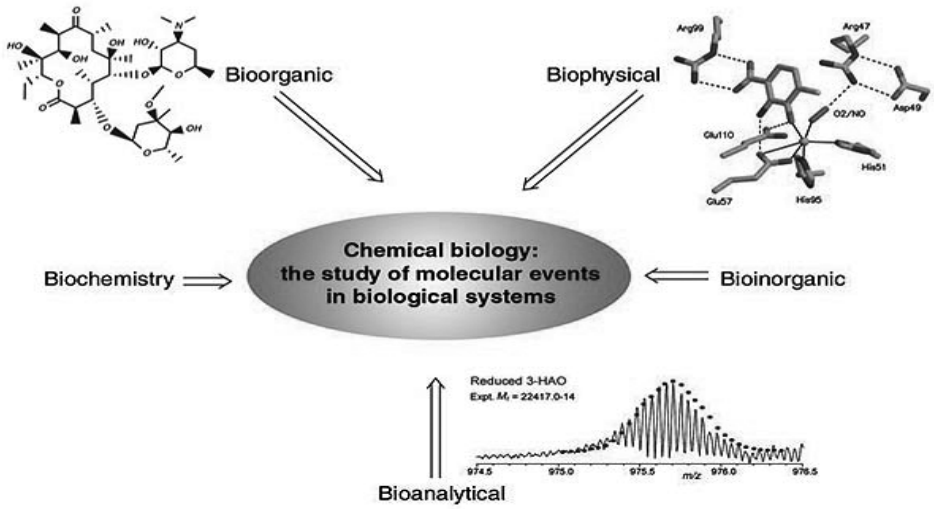
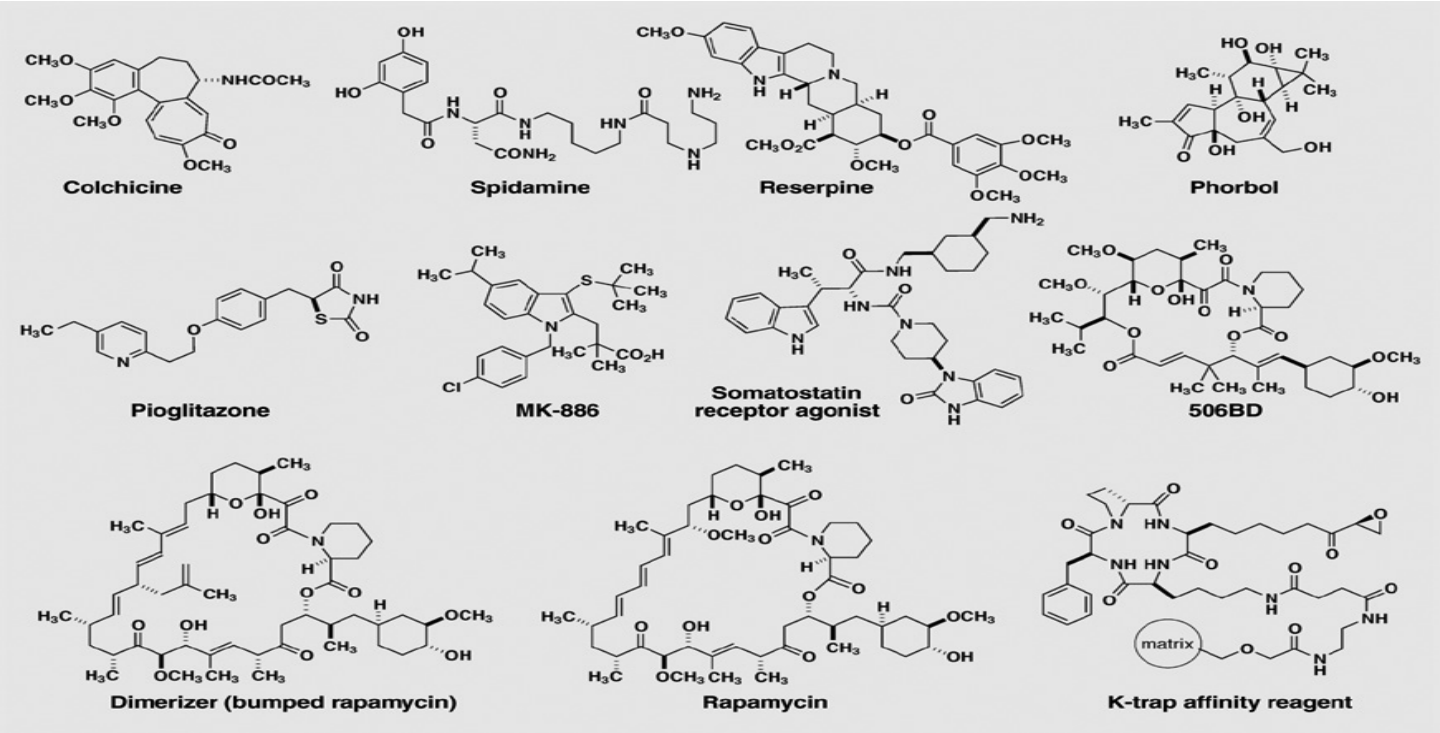


Figure 3. Chemical Biology - One Big Umbrella: Chemical biology brings together biochemical, bioorganic, biophysical, bioinorganic and bioanalytic methods to attack challlenging biological questions in new ways. To train the next generation of chemcial biologists, undergraduate programs should adapt the interdisciplinary nature of research in chemical biology to the classroom. Source: Bagley, T. *Nature Chemical Biology*, 1, 236. (2005)



Tools of The Trade: Small molecules figure prominently in toolbox of chemical biologists. Above: A collection of small molecules that have been employed widely in various contexts. For example, rapamycin has received much attention as a chemotherapeutic agent but also as a important player in chemical genetics studies of protein targets and as a chemical dimerizer.
Source: Schreiber, Stuart L. *Chemical & Engineering News,* Volume 81, Number 9. March 3, 2003.

course series focusing on biological chemistry (CHE 541, 542 and 543) but only for graduate students. If Stony Brook is serious about training the next generation of chemical biologists, it would do well to offer a similar series for its undergraduates, like the one at Cornell. Moreover, "the development of chemical biology laboratory courses in which students learn the key methodologies used for the characterization of macromolecules and cells in the context of chemistry," [13] would do much to reinforce the principles taught in that chemical biology course.

But beyond new offerings, the current courses that are common to students of chemistry and biology alike — general and organic chemistry, introductory molecular and cell biology, etc. — can be reshaped so as to emphasize the interdependence and complementarity of the two perspectives, making liberal use of examples and exercises that force students to bridge key concepts between disciplines. Instructors do try to do this already, but they must try harder and more frequently. All students, not just the ones who plan to pursue an advanced degree in chemical biology, would benefit from such pedagogical changes.

There is one area where Stony Brook need not change too much. Both in terms of quality and abundance, undergraduate research here is excellent. Chemical biology undergraduates, therefore, should have no difficulty finding research posts that would allow them to concretize concepts learned in their courses, and to acquire valuable critical and technical skills that will serve them throughout their careers as researchers or clinicians. Perhaps the opportunities for research in chemical biology could be publicized more effectively to underclassmen so as to get them started in the lab sooner, but that is a criticism applicable to all of the sciences at Stony Brook, not just chemical biology.

Conclusion

Chemical biology is an ascendant field that operates at the interface of chemistry and biology. Making full use of the tools and insights offered from these perspectives, chemical biology has contributed significantly to the advancement of countless areas of inquiry, and is poised to help unravel many of the remaining questions and problems of biomedicine in the 21st century. With its stellar researchers, collaborative conduits and abundant resources, it is certain that Stony Brook will play a leading role in the rapid and dynamic world of chemical biology. And, if it it makes some key changes in the curriculum, its future alumni will be certain to as well.

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The Applications and Obstacles Associated with Nanoparticles in Biomedicine

Taemee Pak '10

Nanotechnology is an extensive field that involves such materials as nanoparticles, nanorods, and nanotubes. Within the field of nanotechnology, the term "nanotubes" is generally understood to refer specifically to carbon nanotubes (CNTs) although inorganic nanotubes have been fabricated as well.*(3)* CNTs are a type of carbon allotrope; that is, they are made purely of specially-arranged carbon and, as such, exhibit certain characteristic properties. Other allotropes of carbon include diamond and graphite, both of which are made purely of carbon as well but are endowed with radically different properties. CNTs in their simplest form may be described as "one or several concentric graphite like layers" rolled into tubes (Figure 1). One-layer tubes have been coined as single-walled carbon nanotubes (SWCNTs) whereas having several concentric layers describes multi-walled carbon nanotubes (MWCNTs). The versatility of CNTs in terms of their properties make them a topic of great interest. Physically, they are the strongest material on Earth because they are incredibly resilient to tension and elasticity with an experimentally-determined tensile strength of 11-63 GPa and a Young's modulus ranging from 1-2 TPa in comparison to high-strength steel alloys' tensile strength of 2 GPa and modulus of 300-950 GPa (4). Electrically, they may function as a metal or a semiconductor depending on the way the original carbon sheet is wrapped; thermally, they are very good thermal conductors along the tube, able to carry high currents with negligible temperature fluctuations, but are also good insulators laterally (*1, 4, 5*).

Carbon nanotubes are the focus in applications such as non-cancerous drug delivery and sensing systems; however, in other areas of medicine such as oncology, the focus is re-directed from carbon nanotubes to quantum dots and nanoparticles. Quantum dots are nanocrystals of semiconductors such as cadmium selenide (CdSe) or cadmium telluride (CdTe) that exhibit strongly size-dependent optical and electrical properties. They are highly luminescent with easily tunable emission and absorption frequencies. *(6, 7, 8)* This intrinsic variability is caused by the high amount of restriction in their spatial excitation, which leads to dynamic properties based on size and allows for their manipulation in oncological diagnoses.8 A nanoparticle is a particle with a diameter ranging from 1-2500 nm that behave as a standalone, functioning unit. Colloidal gold (Au0) was found in the 1950s to bind to proteins while leaving protein activity unaltered; thereafter, functionalized gold colloid solutions began to be explored as a vehicle for novel cancerous drug delivery, along with biodegradable nanoparticles such as chitosan. *(9,10)*

Nanotechnology in Drug Delivery and Biomolecular Sensing

Recent research has been focusing on using carbon nanotubes as vehicles for drug delivery. Current postulated mechanisms include attaching the drug treatment to the tail of the CNT so it could be trailed behind and also encapsulating the drug inside the tube itself.11 Though the method of delivery is not wholly understood, the nanotubes gain entry into target cells either by passive diffusion – perfusing through the lipid bilayer – or by adsorption onto the external membrane with subsequent endocytosis. *(12)* Though CNT solubility has been and remains to be an issue to some extent, new syntheses have been discovered that attach polar groups such as carboxyl, hydroxyl, and amide groups to the tube surface to increase hydrophilicity (*13, 14, 15*). Other biomedical applications include using carbon nano-

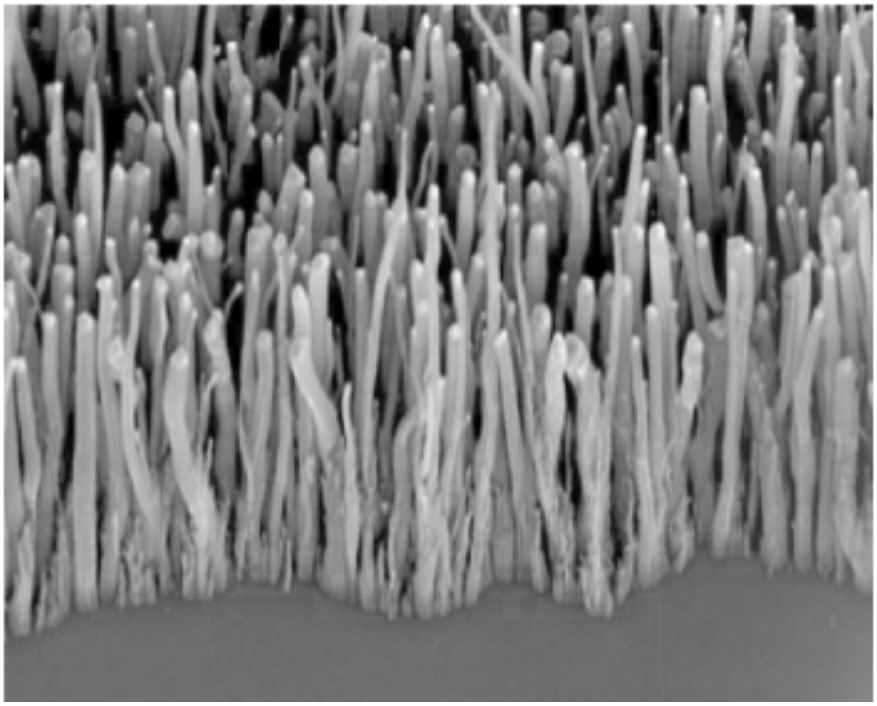

Figure 1. Scanning electron microscope (SEM) image of a nanotubes forest. Source: A.G. Mamalis, L.O.G. Vogtländer, A. Markopoulos, *Precision Engineering* 28, 16 (2004).

tubes as implantable biosensors that can selectively and sensitively read endogenous characteristics such as blood glucose levels for diabetic patients, perform routine diagnostics, or detect exogenous agents such as poison or biowarfare agents.*(2, 13, 16, 17)* As a distant goal, CNTs would be able to act as a DNA scanner via sequence-specific pairing interactions, detecting specific sequences that are linked to certain genetic diseases or cancers, and ultimately leading to high-throughput single nucleotide polymorphism analyses. *(13,18)* However, biocompatibility is a serious caveat to these medical applications: the long-term toxicological effects of CNTs in living systems is still unknown. A plethora of recent toxicology papers has reported carbon nanotubes as having a detrimental effect on biological matter, causing an increase in oxidative stress, cell apoptosis and tumor growth. *(12, 19)* In contrast, similar studies have shown no negative corollaries of CNTs on cellular function. *(20)* As such, there is still debate on this issue in the scientific community and toxicology research remains ongoing. Another caveat to consider is that these nanotubes easily become airborne and, being on the nanoscale in diameter and length, do not settle. One must also consider the health effects these carbon nanotubes could possibly have on both the researchers studying them and the industrial workers manufacturing them once they are inhaled, using the respiratory system as a portal of entry. *(11, 21, 22)*

Nanotechnology in Oncology

Oncological diagnosis and treatment is a prominent application of nanotechnology as well. Quantum dots are being developed for cancer diagnosis – these dots leak into tumor cells and glow when under ultraviolet light, allowing for sensitive tumor detection (Figure 3). For cancer treatment, stable gold nanoparticles (AuNPs) may be functionalized with anti-cancer treatments and antibodies that will guide them into tumor cells where they may deposit the drugs directly in the tumor, thereby maximizing drug efficiency. Another possible method of treatment is to attach superparamagnetic iron oxide nanoparticles to AuNPs and inject this colloidal solution into the patient at a tumor site. Using RF therapy to irradiate the area with radio waves cause the superparamagnetic particles to heat up quickly and to release this heat into their immediate surroundings, ultimately killing the cancer cells while keeping adjacent healthy cells viable. *(23, 24)* This method provides a way to tailor cancer treatments based on individual tumor dimensions. An active subset of research in this area is the mode by which these iron oxide-gold nanoparticles are synthesized, for the method dictates variation in the final nanoparticle shape which lends the overall structure flexibility in biofunctionalization (Figure 3). *(25, 26)*

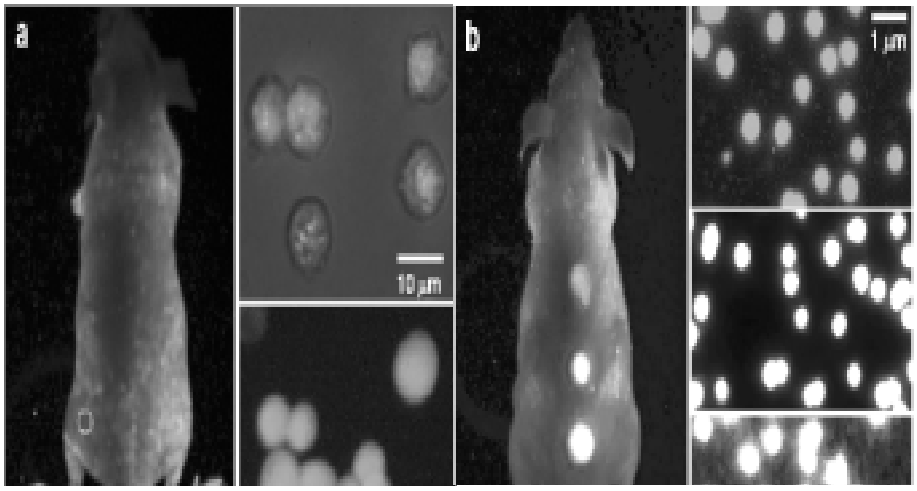

Figure 2 (A) Sensitivity comparison between quantum dot-tagged (orange, top) and green fluorescent protein-transfected cancer cells (green, bottom). ***(B)*** in vivo comparison of multicolored quantum dot-tagged beads.

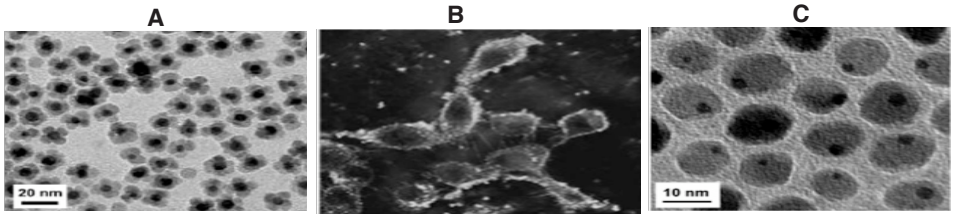

Figure 3 (A) A transmission electron microscope (TEM) image of flower-shaped Au-Fe3O4 nanoparticles. **(B)** A confocal microscope image showing double-lobed dumbell-shaped Au-Fe3O4 nanoparticles. The magnetite particles constitute the large lobes while the gold serves as the attachment point in the middle.25 **(C)** A TEM image of dumbbell-shaped Au-Fe3O4 nanoparticles.

Current Research in Biomedical Nanotechnology

There are several researchers at Stony Brook who conduct research in nanotechnology. Dr. Benjamin Hsiao (Chemistry) does research revolving around manipulating electrospun biopolymer nanofibers, another type of nanostructure, for a variety of different applications such as serving as tissue-building scaffolds. Antithetically, his lab is developing anti-tissue materials to prevent post-operational tissue adhesion that is usually induced during surgery. Moreover, the same piece of scaffold can simultaneously induce growth of a certain tissue while inhibiting growth of a different type through careful functionalization. Another application of his research involves fabricating a mask of nanofiber mesh for protection against biological agents – this may also be used as protection for scientists against aforementioned airborne CNTs if necessary. *(28)* Meanwhile, Dr. Nadine Pernodet (Chemical and Molecular Engineering) is concerned with characterizing the impact of nanostructures upon entrance into living cells in terms of cellular response to the foreign matter. She is also attempting to determine the range of tolerance in nanoparticle size that will not induce a negative physiological response. Dr. Gary Halada (Materials Science and Engineering) also focuses on toxicological work but is interested in manipulating functionalized carbon nanotubes to act as electrochemical sensors.

Nanotechnology research is a global effort; as such, it would be remiss of this article to not mention other researchers in

"Nanotechnology is anticipated to be the pre-eminent harbinger of a new generation of medical diagnostics and treatments. "

nanobiotechnology such as Dr. Carl Batt (Cornell University, Food Science) who is engineering gold nanosensors for biowarfare agents and food pathogens. Dr. Harold Craighead (Cornell University, Applied and Engineering Physics) is developing various devices such as cantilevers to detect a single microorganism. Dr. Craighead, in collaboration with Dr. Rob Ilic (Cornell Nanoscale Facility), was the first to successfully weigh the mass of a single virus (6.3 attograms, which is equivalent to 6.3 × 10-18 grams). Japan is prolific in their advancements in nanotechnology as well – Dr. Tomonobu Nakayama (University of Tsukuba) is constructing a microscope that makes use of carbon nanotube bundles attached to metal probes. These nanoprobes may be inserted into cells for electrical measurements and may be used to elucidate the "cell odyssey" for more efficient drug delivery.29 In Spain, Dr. Isabel Garcia (Parque Tecnológico de San Sebastian) is creating non-viral gene delivery vectors using superparamagnetic gold nanoparticles such as those previously described. *(30)*

Conclusion

Though this article mainly focused on introducing carbon nanotubes, nanoparticles, and their biomedical applications, there is still much research to be done with CNTs and nanotechnology in its entirety. There are many nanostructures that are currently being developed and manipulated on a global scale. This article is limited in the depth and breadth to which it describes the role of nanotechnology in medicine, for the field is immensely vast and overwhelming. However, the goal was to primarily impress the fact that nanotechnology has the innate capacity to have a profound effect on many public sectors, especially medicine and public health. Nanotechnology is anticipated to be the preeminent harbinger of a new generation of medical diagnostics and treatments.

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Alzheimer's Research at Stony Brook

Nadya Peresleni '11

Today, the dilemma that faces about 4.5 million Americans is that they cannot stop the slow but inevitable progression of a disease that will eventually change their lives and those of their families forever. It may begin with not being able to find their way back home; it may end with irreversible personality change and complete dependence on caregivers. This is Alzheimer's Disease, a neurodegenerative disorder first described by Dr. Alois Alzheimer, a German physician, after studying the brain of a deceased woman in 1906. AD is characterized by an accumulation of amyloid plaques, containing a protein called amyloid β, and neurofibrillary tangles made of a protein called tau. The most common form, known as late onset AD, affects those 65 and older. Early onset, however, which is usually linked to family history, can affect people even younger than 65.

The main culprit of the plaque formation is amyloid β, a protein that appears after the proteolysis of the Amyloid Precursor Protein (APP) by an enzyme called β-secretase. In the healthy brain, APP is a transmembrane protein that is normally made by neurons. It gets cut up by enzymes such as β-secretase, which creates differently sized amyloid fragments. This process can create two forms of amyloid: Aβ40 and Aβ42. The latter, Aβ42, is known to be more deleterious and is a characteristic of AD. All forms of amyloid β, however, are normally present at certain levels in our bodies. They get transferred across the blood-brain barrier into the circulatory system without any abnormal accretion. The blood brain barrier is a succession of endothelial cells that function together to protect the organ's pristine environment by being extremely selective in admitting molecules wanting to pass through. Only certain transport molecules that attach to amyloid β can cross the barrier into the circulatory system, preventing the brain parenchyma – the tissue between the blood vessels – from accumulating amyloid β. This accumulation, if it happens, is a hallmark of AD. It is caused by a disorder in the structure of amyloid β that makes the protein polymerize, i.e. to come together and create fibrillar dimers, trimers, tetramers, etc. that become insoluble aggregates. These clumps are too big to be transported, so they remain indefinitely, eventually causing an extremely dangerous condition: chronic inflammation. The chronic nature of the condition is the result of the continual activation of the immune cells of the central nervous system, such as the microglia. They recognize the abnormal accumulation of amyloid but are only able to recognize the problem without being able to engulf the agent as they usually would. Chronic inflammation will eventually lead to tissue atrophy and a decrease in size of certain brain regions, mainly the cerebral cortex. This leads to the cognitive impairment characteristic of AD patients *(1)*.

Here at Stony Brook, researchers have been studying the mechanisms of amyloid β accumulation for over fifteen years. Under the leadership of Professor Van Nostrand, a Stony Brook alumni and distinguished research faculty member, scientists have been studying the formation of fibrillous amyloid β specifically in the blood vessels of the brain. Their goal is to find how this vascular amyloid contributes to senile plaques. In order to study this process, Prof. Van Nostrand and his team developed a unique transgenic mouse model called the Tg-SwDI. This model, developed in 2004, contains three mutations that are known to occur in the Amyloid Precursor Protein: the Swedish, Dutch, and Iowa mutations *(2)*. Out of these three mutations, only the Swedish is a risk factor for developing Alzheimer's. The Dutch and the Iowa, however, are also very useful in creating a model that exaggerates the mechanism of amyloid β vascular accumulation. In collaboration with John Robinson, Associate Professor in Biopsychology at Stony Brook, Prof. Van Nostrand and his team developed a set of behavioral tests for these transgenic mice that examines their learning and memory patterns.

In a current study, Prof. Van Nostrand and his lab have continued their research on a protein involved in fibrillar amyloid βaccumulation – Apolipoprotein (Apo) E. ApoE is unique because it carries an allele, known as APOE4, that has been shown to increase the risk of AD and decrease the age of its onset *(3)*. It is not, however, the only gene on ApoE that has been studied in relation to AD. For example, there is the most common allele on the protein, APOE3, which has no such definite effect on AD pathogenesis *(4)*. The protein itself has been just recently shown to assist in the proteolysis of amyloid β *(5)*.

In order to study the effect of ApoE alleles on vascular amyloid, Prof. Van Nostrand and his group, using their transgenic mice model, crossed transgenic mice carriers of human APOE3 and 4 with mice carrying their endogenous alleles. They discovered that the expression of both alleles in the new generation dramatically influenced the spatial deposition of amyloid β in the mouse brain. The new generation displayed lower levels of microvascular fibrillar amyloid and, surprisingly, increased levels of parenchymal amyloid as compared to the brains of mice with endogenous ApoE 2. "This was a very unexpected finding," said Prof. Van Nostrand, referring to this result of the study. There was also a significant redistribution of activated microglia, which further defines the interaction between fibrillar amyloid β and the neuroinflammatory response *(2)*. Ultimately, these mechanisms provide possible targets for future therapeutic drugs.

In the light of amyloid β, there is currently an ongoing epidemiological research on Alzheimer's, known as the Nun Study, which has provided a new perspective on Alzheimer's and the amyloid β theory. Led by Dr. Snowdon, Professor of Neurology at the University of Kentucky, this study, begun in 1986, has focused on 678 nuns, aged 75 to 107, living and teaching in seven convents in various states belonging to the order of the School Sisters of Notre Dame. Nuns were chosen to be studied because of their similar, stable lifestyles – they do not smoke or drink and experience little illness.

Such a stable way of life makes it easier for scientists to rule out certain factors that could influence the pathogenesis of AD. Thus, with their consent, the nuns were monitored through special behavioral and

memory tests that would diagnose them with dementia or AD. They also agreed to donate their brains after death for, as they said themselves, the good of science *(6)*. Thus, the scientists were able to track individual mental states and afterwards, if it was possible, draw conclusions from brain autopsies. These findings revealed certain exceptions to the amyloid plaque and neurofibrillary tangle explanation of AD. For example, a nun known as Sister Bernadette was genetically predisposed to develop AD and an autopsy revealed high levels of neurofibrillary tangles and plaques. Surprisingly, she did not have AD, suffered none of the characteristic symptoms of the disease and was lucid until her death at the age of 85. She showed a remarkable resistance to the effects of the lesions in her neocortex *(7)*. Her extreme example was a fascinating exception to the theory behind an intensely complicated disease and stands out as a signal that AD remains one of the enigmas in the medical world today.

The other conclusions of the study were made possible by the researchers' access to old autobiographical essays written by the nuns on their entry into the order, when still in their twenties. This led scientists to draw parallels between language skills and the onset of dementia much later in life. For example, Dr. Snowdon concluded that the nuns who wrote much more complex autobiographies, with high "idea density" per sentence, were less likely to develop AD *(8)*.

Looking at another possible factor in AD pathogenesis, a group of scientists from both the US and Canada have recently shown the connection between oxidative stress and the formation of senile plaques and neurofibrillary tangles *(9)*. In the brain, which consumes about 20% of the body's oxygen, oxidative stress is normally the result of daily metabolic activities in cells that release reactive oxygen species *(10)*. These free radicals react with molecules such as DNA, proteins, and lipids that accumulate and diminish the function of the elderly brain *(11)*. Just recently, oxidative stress in AD has been linked to amyloid β through its role in increasing the levels of the proteolytic enzyme that cuts the APP *(12)*.

The research focused on the enzyme called GST, glutathione-S-transferase, which has been shown to be a defense against oxidative stress *(13)*. There are many enzymes associated with GST, but the one that was the focus of the research was GSTM3. It was chosen because a previous study showed that it accumulates in the senile plaques and neurofibrillary tangles which are the hallmark of AD *(14)*. In the new study, scientists studied a polymorphism in GSTM3 and found that its presence decreased the amount of the enzymes in the AD brain . Since GSTM3 plays a role in defense against oxidative stress, its absence could expose other molecules to harm. Thus, it can be concluded that this enzyme may work simultaneously, although in very different ways, with the APOE4 allele in the pathogenesis of AD.

Research has gone a long way in the past two decades in AD research, but no magic bullet has yet been found that would cure this debilitating disorder. Perhaps the problem is that people are waiting and looking to the future for a panacea instead of learning what can be done today. As Professor Van Nostrand said, "The problem is that we're looking at patients who already have the disease. It's the result of decades of accumulation." Once the AD is diagnosed, it is often too late to be able to do anything. And so it all boils down to that one piece of advice that comes from the lips of every physician: lead a healthy lifestyle. It is recommended to exercise, eat a healthy diet and avoid head trauma, which could cause the formation of small infarcts in the brain that have been shown to be present in the AD brain *(7)*. In some studies, folic acid has been shown to increase the functional activity, memory storage and information processing in the elderly if taken for three years daily in 800mcg doses *(15)*. But any definite solution with either folic acid or vitamin, therapy, or vaccine that could treat AD has not yet been found. Therefore, since there is no magic bullet yet, prevention is the key.

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Lost in the DARC: The Undefined Role of an Anti-Malarial Mutation in HIV Infection

Zachary Kurtz, '09

Over the last 25 years, research into the AIDS epidemic and HIV has yielded insight into medical biology and, surprisingly, evolution as well. Understanding how pathogens interact with their human hosts, on an evolutionary scale, has provided important clues of pathogenesis mechanism and designing new anti-HIV drugs. Recent research into these mechanisms might also be able to provide a genetic explanation of why the AIDS epidemic is more prevalent in Sub-Saharan Africa than anywhere else in the world.

Traditionally, the scientific consensus has chalked this up to anachronistic, cultural and socioeconomic reasons. However, given that nearly two-thirds of AIDS patients live in Sub-Saharan Africa, it is important to consider the recently characterized physiological factors as well. Weijing He and his colleagues from the University of Texas Health Science Centre have published in the journal of Cell Host & Microbe their discovery of a genetic variation which is common in people of African heritage *(1)*. The study shows that this mutation increases susceptibility to and prolongs the dormant stage of HIV. This widespread mutation in a population in Africa in which HIV is more virulent and, because symptoms are delayed, AIDS is more easily spread.

The genetic variation is in a gene which codes for the "Duffy Antigen Receptor for Chemokines" (DARC)*(2)*. This protein cell receptor is expressed on the cell surface of reticulocytes, immature red blood cells, erythrocytes and some tissue specific endothelial cells. In the normal state, DARC binds to and adsorbs multiple specific chemokines, to control the local plasma concentration of the pro-inflammatory chemicals. When bound to other lymphocyte transmembrane receptors, these cytokines recruit leukocytes to inflamed areas. In effect, DARC controls chemokine concentration in its capacity as a red blood cell surface molecule by retaining and scavenging chemokines and transporting them throughout the circulatory system.

However, a single point mutation in the promoter region of DARC causes 50% less transcription of the receptor protein by altering transcription factor binding. Another common point mutation downstream in the coding region causes an amino acid substitution which destabilizes the protein. These mutations have evolved in Africa over the course of evolutionary history, occurring at a frequency exceeding 90% in populations, but only in about 3.5% of Caucasians.

The most likely explanation for this high frequency of the DARC-negative allele lies in its role in malaria. The human malarial parasites Plasmodium vivax and Plasmodium knowlesi can use DARC as a receptor for the invasion of erythrocytes. Over the last 10,000 years, the time in which malaria has been known to exist in areas like Sub-Saharan Africa, there has been strong selection pressure towards the mutation of human proteins which limit parasite infection. This has happened regardless of the resulting trade-offs, one of which is the well characterized sickle cell anemia.

For a relatively newly emergent pathogen, like HIV, the trade-off would never have even been considered when selecting for the Duffy-negative phenotype. However, extrapolating from their data, Dr. He et al predicted that around 11% of the HIV cases, 2.5 million individuals, could now blame this once favorable mutation for their particularly virulent form of AIDS.

The study itself was conducted over a 22-year period among US Air Force pilots of mixed descent. The correlation between 1,200 HIV positive African-American males who were Duffy-negative and the increased, but delayed, virulence of AIDS was statistically significant; the single nucleotide polymorphism on the DARC promoter, by itself, is associated with a 40% increase in the occurrence of HIV infection. The tricky part, of course, is understanding the physiology behind this correlation, which is turning out to be a complex relationship between multiple biological mechanisms.

Normally, HIV binds to the wild type Duffy receptor, and uses the red blood cells as a "stepping stone" for CD4+ T-cell infection. In an apparent reprisal of its role in controlling chemokine concentration, the abundant DARC molecule is exploited by HIV as a means of transportation, survival and persistence *(3)*. By binding to DARC as an intermediate to T cell infection, HIV could increase its vigor and serve as a kind of reservoir for infection. Given this assumption, which is based on previous in vitro and genetics findings, a study that shows a negative DARC phenotype actually increases HIV virulence is even more suprising and serves to demonstrate the complexity of in vivo systems and the sometimes difficulty of translating in vitro results.

The absence of DARC could explain delayed infection because if HIV has evolved to rely on the DARC pathway, infection could be slowed because HIV's normal route has been blocked. In this case, it would actually be advantageous for HIV to prolong infection because it could be transmitted to a new host before symptoms begin to show, thereby increasing the likelihood of transmission. However, even if this does explain delayed infection, its not so obvious why the missing receptor would cause an increase in the strength of virulence.

Knowing the mechanism by which HIV is passed from the DARC to T-cells, it would be expected that a DARC deletion would reduce this transmission and decrease incidence of infection. Clearly, there is a missing piece to this puzzle, which is mirrored by an incomplete picture of DARC as a competitive-binding chemokine receptor; it is not clear how the absence of DARC may affect chemokine homeostasis. One possible answer is that the absence of DARC may result in a shift in chemokine concentration in a way which reduces immune activation in response to certain types of infection. We are presented

with two different scenarios: the DARC+ phenotype resulting in HIV in competitive binding with immune-activating chemokines which quickens disease progession but reduces virulence, or a DARC- state which could result in decreased immune system activation, but a slowing of disease progression because of the decreased viral load on red blood cells.Another factor, which was discussed by Walton and Jones may complicate the picture; the DARC-negative state may additionally affect HIV pathogenesis indirectly. Recent studies show that the systemic translocation of bacterial products, such as lipopolysaccharides from gastrointensinal bacteria, play a role in HIV-related immune activation *(4)*. If the DARC-negative state decreases the availability of proinflammatory chemokines, this may increase the effect of these bacterial products to enhance HIV pathogenesis. Therefore, it may be the case that HIV benefits more from the presence of bacterial products than it does from using DARC as a gateway to CD4+ T cells.

If, as it seems, HIV infection is related to chemokine concentration, additional studies should be launched to elucidate the exact nature of this relationship, whether it is due to direct competition, the lack in the DARC negative case or if its related through some intermediate process related to bacterial products. This, together with the continued discovery of complexity in areas of HIV pathogenesis has important implications to medicine and to the millions suffering from AIDS. It is a fascinating discovery for its scientific implications and could be another clue as to why an HIV vaccine remains beyond our grasp.

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Development of an Animal Model of Autism

Timothy Aiello '09

Animal research has many advantages when trying to understand a disorder, especially one as complicated as autism. First and foremost, it is decidedly unethical to induce brain damage or sickness in human beings. Regardless of confidence in a certain drug's effect, or a procedure's chance of success, the possibility of being wrong outweighs any positive results. Research guidelines require that animal model be tested as a subject first, to make researchers that much more confident that the effects on humans will not be life threatening.

Another advantage that is less well known is that some animals, such as rats and mice, are readily available and have a short gestational period. This means that rats and mice can be bred to have the same genotype. This is a critical factor in research because using too few subjects allows for the chance that confounding variables could affect the results. In other words, there are many outside influences that could affect the behavior of any one animal, such as smelling the researcher, or even being agitated by the researcher's clothing. However, if many animals show the same behavior, the chance that all of them were agitated by a subtle environmental cue seems less plausible. Thus, change in the behavior of one animal as a consequence of a drug or brain damage is not nearly as powerful as a change in many animals. Animals with the same genome make deviations from the mean behavior seem that much more due to the variable effect than by chance. Thus, the fact that all animals started with the same genes increases confidence in the credibility of the model.

Animal models do have some disadvantages. One very important factor to remember when analyzing the competency of an animal model is that animals such as mice and rats are not humans. So, no matter how closely changes in an animal's behavior correlate to those seen in the human disorder, or how successful a study seems to be, we cannot be certain that the disorder has been figured out. Much more testing must be done to confirm results, replicate them and ignite further research.

Almost all disorders have animal models associated with them, including schizophrenia, Down syndrome, autism and ADHD, to name a few. Each disorder attracts numerous researchers, many of which have different theories as to what causes the disorder. Thus, there are many animal models that all try to show significant effects associated with various theories as to its cause. Animal models of psychiatric disorders are constantly being created, each with the same hope that they will incorporate the most commonalities with the actual disorder seen in humans. One of these disorders, autism, has gained more research attention than most, in recent years.

It is no secret that autism has grown into a worldwide epidemic. Rates are on the rise and there seems to be no leading theory as to what causes it. As a result, many scientists are studying the perplexing disorder and many are creating models of autism in animals to try and crack the mystery behind its debilitating effects. Stony Brook University has headed the call to crack the autism mystery as well. Many of Stony Brook's professors and staff, including Dr. Whitaker, have worked to create animal models of autism.

How is an animal model of autism created?

It is no easy feat coming up with an idea for an animal model. The proposed mechanism has to exist and able to be affected in an appriopriate animal. The plausibility of the model must be rigorously tested and peer-reviewed.

A model of autism should express phenotypical symptoms similar to those found in the human disorder. Thus, a good model of autism should try to illicit the same behavioral deficits and excesses similar to those in autistic individuals, such as social avoidance, lack of bonding to caregivers and systemization.

A good model would not, however, want to show conflicting behaviors in addition to phenotypical behaviors, such as increased attachment to caregivers, in the case of autism. This type of conflict would only serve to diminish the reliability of the model.

In addition to behavior tests aimed to substantiate a model of autism, it is advantageous to search for brain abnormalities in the animals that coincide with brain abnormalities found in the human disorder. There would include, but not be limited to, enlarged cortical regions, and hypothalamic region irregularities. There are, of course, many other brain regions that have been implicated in dysfunctional or irregular activity in autistic individuals, but some of these are less substantiated then others. The best bet is to search for those that are the most established.

Finally, it is important to note that when trying to develop an animal model, some level of ambiguity is inherent. By this it is meant that mice are not humans, so it is unlikely that an animal model will overlap the human condition perfectly. Thus, discretion is left to the investigator to determine why certain behaviors or abnormalities that should not have been there, are, and why the model can still be considered credible. At the base of this idea is the scientific method itself. It is up to scientists to look at a problem objectively, come up with an explanation, and let other scientists help substantiate findings.

Current Stony Brook research on autism models

Stony Brook University has been the birthplace of many models of disorders, including autism. Currently, a model is being created that hopes to implicate the actions of prenatal estradiol as having a negative impact on brain development in utero and causing brain damage and behaviors similar to those found in the human condition. This particular study is being conducted in Dr. Whitaker's laboratory in the biopsychology department.

The basis behind this model is that excesses of estradiol, a hormone produced by the mother that plays a major role in brain development, has the ability to cause damages similar to those found in autistic individuals. What is essential to this theory is that there is a natural influx of estradiol during pregnancy and that autism is four times more likely in males then in females,

implying a decreased susceptibility in females.

During the three trimesters, estradiol increases dramatically, reaching levels much greater then that of normal somatic conditions. The presumed reason is that estradiol has many functions as a neurodevelopmental agent and thus, normal development relies on sufficient amounts. However, given the vital role of the drug, it is plausible to believe that fluctuation in blood serum levels of the hormone could disrupt normal brain development. In fact, this has been found to occur in many brain regions under various conditions.

Because autism is four times more likely to occur in males then females, a good model of the disorder should allow for sufficient explanation of this ratio. In the estradiol model of autism, the ratio can be accounted for. In rats, and presumably in humans, a protein called alpha-fetoprotein is known to bind to estradiol thus making it nonreactive. What is most interesting here is that this protein is found only in the developing female, leaving the developing male rat much more vulnerable to the effects of the hormone. Thus, the increased ratio of males that develop autism may be accounted for using the estradiol model.

Methods

In this particular study, four behavior tests, which include "return to dam", "huddling behavior", "response to a novel object" and "social behavior test", were used. Each of these tests is designed to assess specific behaviors related to autism.

The return to dam test is meant to show differences in how pups from different treatment groups interact with their mother. Of course, this behavior is one of the most well known in the human condition and thus, it can be very persuasive if replicated in animal models. In this test, each pup was separated from its mother by a wire mesh screen. The total time spent within a body length of the screen during a three minute time interval was recorded and group means were compared.

The huddling behavior test shows how closely each litter huddled together during a 15 minute time interval. Because huddling behavior has been shown to be directly affected by oxytocin and oxytocin is known to be in deficit in autistic individuals, changes in behavior due to estradiol would show an indirect route as to how oxytocin levels may be affected. To observe huddling behavior, animal litters were placed in a custom made box and allowed to huddle freely. A camera was suspended at a known distance from the play area and a snapshot of the litter was taken each minute. The pictures were then analyzed, and, using a screen tracing program, litter areas were determined. The mean litter areas of the treated and control groups over that 15 minute time interval were compared for significant differences.

To measure each group's response to a novel object, toilet paper rolls were added to the cages of each animal. After a day (24 hours) the roll was removed and weighed. The final weight was subtracted from the initial weight and the mean differences across groups were compared. This test is meant to show if the drug affect could be a cause of variation in the pup's interest in novel stimuli. Rats naturally chew on objects of interest, so by measuring differences in weight after the test, it can be determined how much the rats chewed. The behavior toward novel stimuli has shown variability in autism. On one hand, many autistic individuals oppose change in their environment while others show reduced fear toward situations that may normally cause concern. There is a fine line here as to what behavior is actually being measured by the animal tests, but this is a normal occurrence in animal models.

How can a promising model be substantiated further?

If behavioral results concurrent with a theory are found, it is important to link behaviors to brain abnormalities that coincide with those found in the disorder. Finding structural or neural system abnormalities that can be linked to deviated behaviors will help to show that the observed behavioral changes are likely not explainable by chance or some other confounding variable. As well as substantiating behavioral data, finding brain abnormalities in a model that have been implicated in the human condition can link phenotypical behaviors and brain abnormalities to a proposed mechanism. The more a model can explain and show similar deficits and exclude behavior and abnormalities absent in the human condition, the better the model.

The aforementioned model, being created at Stony Brook, will search the oxytocin system, dendritic and synaptic networks and cortical tissues in the hope of linking the observed behaviors to brain deficits. The value of finding deficits in these areas is that each can be linked to the human condition.

The oxytocin neuropeptide has been implicated in playing a major role in the social deficits and lack of bonding to caregivers that are frequently observed in Autistic individuals. In fact, recent research has determined that autistic people have less oxytocin in their blood as compared to those without the disorder. Furthermore, finding variation in huddling behaviors due to the drugs affect, and linking that to observed brain structures is critical.

Dendritic and synaptic networks may also help to explain abnormalities in the oxytocin system as well as those found in cortical tissues of Autistic individuals.

One of the affects of estradiol is the up regulation of glutamate production, which can cause dendritic spine proliferation and synaptogenisis. If this occurs in excess in the oxytocin system as a direct result of the drug, deficits in functioning are certainly possible. The same holds true for cortical tissues. Again, finding structural abnormalities will further substantiate behavior test findings, such as in the huddling behavior, return to dam tests and response to novel objects tests.

Building a model of a disorder requires intense planning along with a strong helping of creativity. Not only should a model of autism be reliable, but it should also resemble the human condition as much as possible, without any unexplainable attributions. A strong model can certainly help to inspire further research and ultimately bring the scientific community closer to finding a cause of the disorder.

Zinc Finger Nucleases: Nature's Scissors

Michael Hagler '11

Zinc Finger Nucleases (ZFN) are a system of novel transcription factors are providing insight in new ways to silence genes. The technique was developed by Sir Aaron Klug of the Laboratory of Molecular Biology in Cambridge as a radically new method to permanently silence genes. There are currently several drugs in the pipeline that take advantage of ZFN's. One such therapeutic approach that I will highlight was in the field of HIV research and was conducted at the University of Pennsylvania in collaboration with Sangamo Biosciences, the industry leader in the field.

Gene targeting has shown to be an important part of a researcher's toolkit for genome manipulation. Traditionally, it involves insertion of exogenous DNA via homologous recombination. This technique has assisted in the development of transgenic animals and cell lines. Additionally, gene targeting has the potential to aid in the treatment of several diseases such as Huntington's, hemophilia, and cystic fibrosis. Problems with the current approach lie in the inherently low frequency of success, the need to introduce manipulations in culture rather than into the entire host organism at once and the reliance on viral vectors. These carrying agents often produce immunological reactions to the virus used, insertion mutations, and long term silencing of an inappropriate gene. Additionally there have been several attempts at gene silencing via viral vectors in the clinical sector which have resulted in poor clinical results.

Why are Zinc Finger Nucleases' Different?

ZFN's are a radical new type of restriction enzymes, and provide an alternative solution to current approaches to reengineering existing meganucleases, because they can be designed to digest a specific sequence of DNA with a high frequency of success with a low risk of insertion mutagenesis. Mechanistically, ZFN's are able to introduce a specific double bond break in any given point in a specified locus. At that point, homologous recombination can repair the break with the proper code supplied from an endogenous chromosome or previously introduced exogenous DNA. This is done by designing ZFN's that combine the non-specific cleavage domain (N) of FokI endonuclease. This ZFN-plasmid technique avoids many of the potential problems that viral vector gene therapy has faced. Additionally, ZFN's can simply disable an allele by causing a double strand break in the DNA and then allowing the cell to repair itself via non-homologous end joining, thereby simply excising that piece of DNA.

Use of ZFN's in HIV Research

Elena Perez and her colleagues in the June Lab at the Abramson Family Cancer Research Institute at the University of Pennsylvania in collaboration with re-

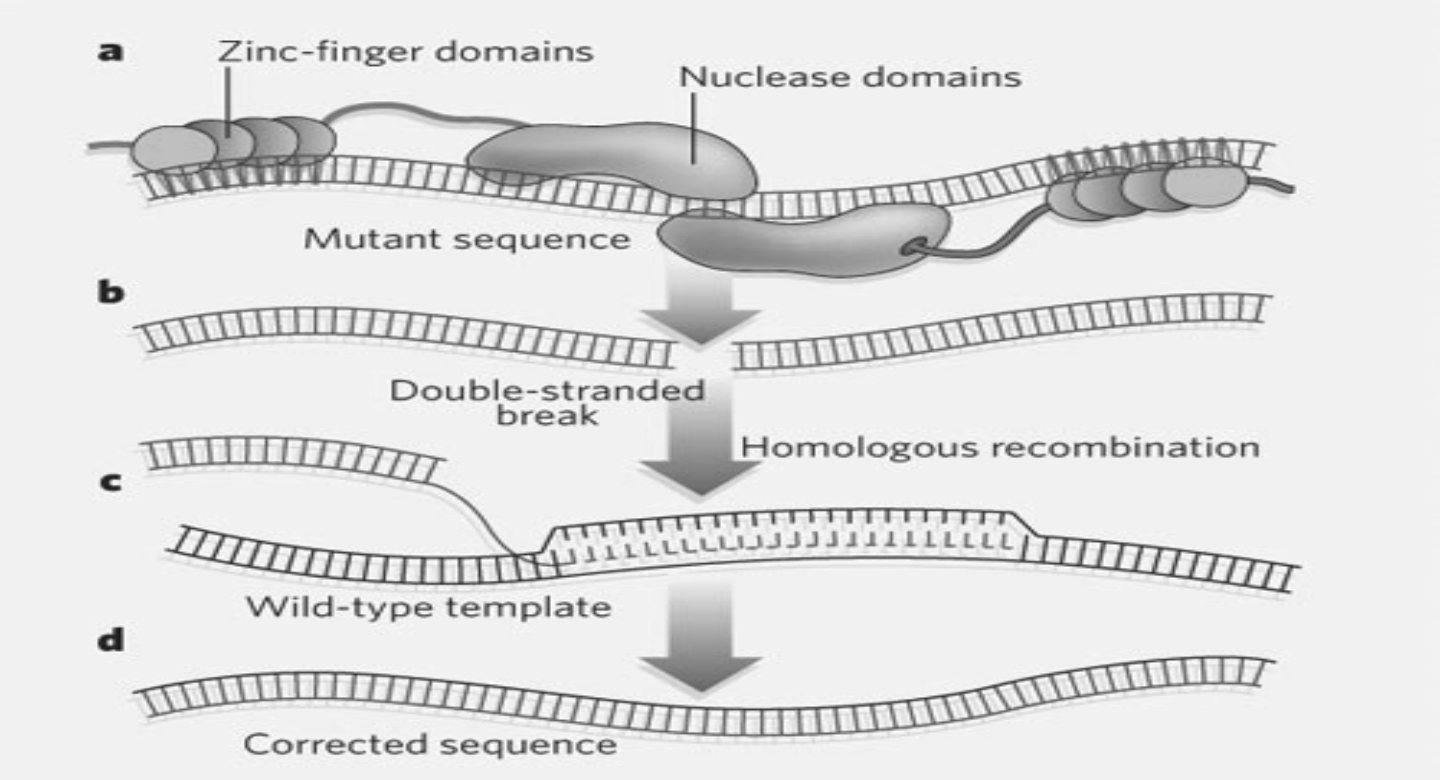

Fig 1. General Schematic of ZFN induced double strand breaks and subsequent repair by homologous recombination. Source: High K. The Moving Finger. *Nature*. 2005 June 435:437-439

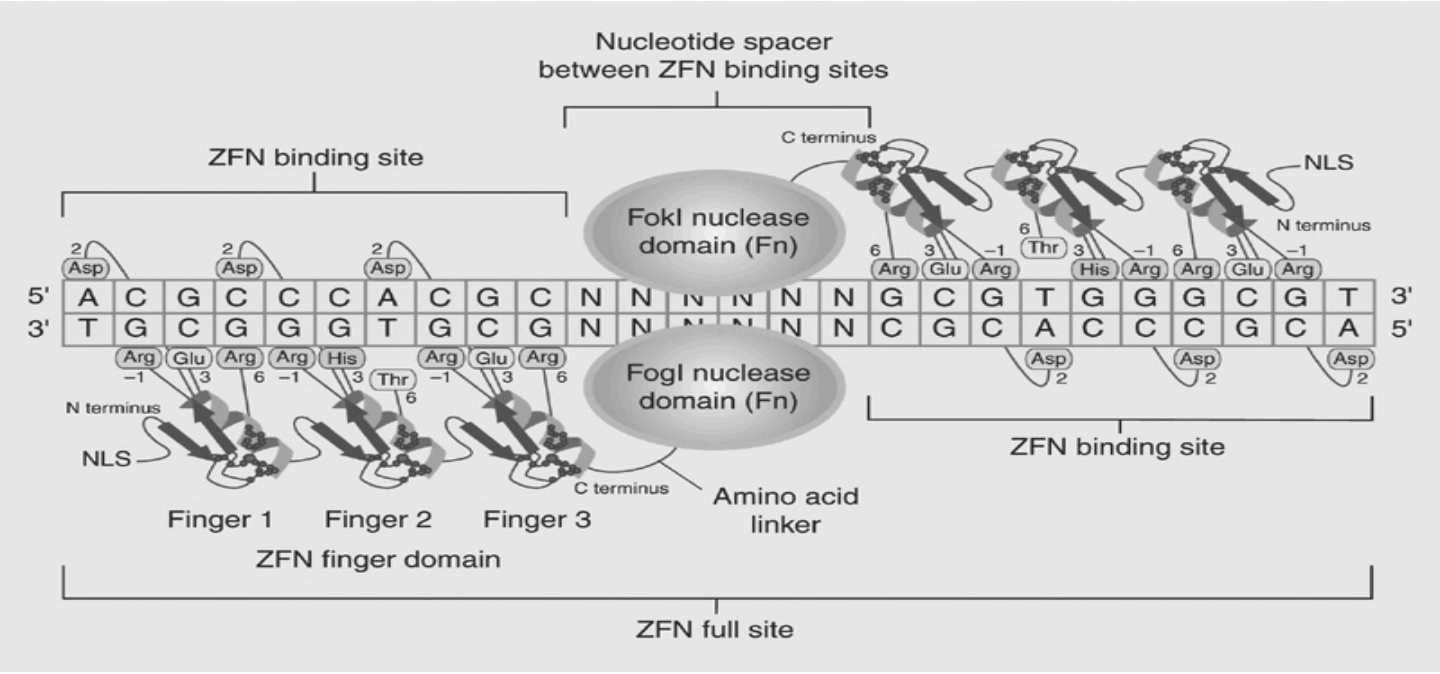

Figure 2. Mechanism of action for double strand breaks by ZFN's.
Source: Porteus M Carroll D. Gene Targeting using Zinc Finger Nucleases. *Nature Biotechnology.* 2005 Aug:23(8):967-973

searchers at Sangamo Biosciences recently published an article in Nature Biotechnology that is one of the biggest breakthroughs in ZFN research to date. In the study, researchers aimed to modify an HIV infected individuals T-cells to achieve increased anti-HIV activity. The study titled Establishment of HIV-1 resistance in CD4+ T cells by genome editing using zinc-finger nucleases focused on CCR5, a transmembrane chemokine receptor used as the principal receptor for HIV-1 entry. Previously, researchers had discovered patients with a Δ32 deletion on CCR5 had increased resistance to infection, and as such CCR5 is a novel therapeutic target. In this study the goal was to introduce the Δ32 phenotype into CD4+ T cells (the primary target of HIV pathology) using ZFN's. By designing a ZFN to bind to the DNA sequence coding for the first trans-membrane domain of the CCR5 receptor they were able to alter a highly specific segment of the genome that would resemble naturally occurring defects in the Δ32 region of CCR5.

To test the efficiency of their gene targeting, researchers infected CD4+ T cells with R5-tropic HIV which uses CCR5 to enter cells. They found that the ZFN treated cells proliferated in culture with the virus, indicating a higher level of resistance compared to untreated cells. Furthermore, they discovered that they only needed to treat the cells once to gain sufficient efficiency for HIV resistance. At this point, the study transitioned into animal models where the researchers utilized mice whose immune systems were modified to accept human cells. The researchers infused ZFN treated cells into the mice and saw that the treated cells proliferated at a rate two to three times greater in HIV infected mice. Additionally, mice given ZFN modified cells had higher levels of CD4 cells and a reduced viral load that mice treated with control cells. This indicates that the HIV infected mice infused with ZFN modified cells gained significant protection from HIV infection. It is also worth noting that ZFN treated cells showed a heritable resistance to HIV resistance in progeny cells, indicating that it is feasible to introduce the Δ32 CCR5 phenotype in humans.

Conclusion

This study demonstrated one of the first successful attempts at utilizing ZFN's for gene targeting, and preparations for a clinical trial are currently underway. This new tool for researchers opens up many doors not previously available for investigation and should generate a significant amount of breakthroughs in the years to come as more researchers gain experience designing custom ZFN's for a wide variety of both therapeutic and experimental purposes.

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Important Things Often Come in Small Packages: The Power of RNA interference

Farzan Gorgani '09

What if I told you that recently scientists made a discovery that is so surprising and so powerful, not only are we about to know much, much more about how all these diseases work [alzheimer's, asthma, arthritis, cancer, HIV, hepatitis C&B, ALS, muscular dystrophy, cystic fibrosis, small pox, SARS, macular degeneration, and influenza], there's a chance, a real chance, that we can treat these diseases much more effectively all because of this one discovery called RNAi." *(8)*

RNA interference (RNAi) is a new tool used in molecular biology that may be one of the most important discoveries of our time. Independently discovered throughout the 1990s by many molecular biologists, most notably plant scientists David Baulcombe of Cambridge University and Richard Jorgensen of the University of Arizona, who were perplexed upon its first observation, RNAi today is a common and effective means in which gene products are silenced. Unfortunately, at the time of the first discovery of these RNA molecules, research in molecular biology was not taken seriously when performed on lowly plant cells and was overlooked. *(7)* Little did these researchers know, these experiments with these puzzling RNAs would lead to Science magazine's Breakthrough of the Year award in 2002.

In his initial experiment where he first observed RNAi in action, Richard Jorgensen attempted to over-express an enzyme that lead to the production of a purple pigmented protein in petunias. He injected the plants with mRNA that carry the code for that enzyme, hoping that the flowers would turn out to be more purple. The results were unexpected; the pathway for the purple pigment was blocked and most of the flowers turned out either all white or with an alternating white and purple pattern. It was also seen that the mRNA production was reduced 50-fold. *(6)* These results were first credited to the fact that antisense RNA, RNA that is complementary to the mRNA, blocked ribosomes from translating the gene. However, when sense RNA, RNA with the same sequence as the mRNA, was injected in C. elegans, protein production was also blocked. Since the addition of exogenous RNA interferes with gene expression, the phenomenon is known as RNA interference. *(9)*

After a few years and many frustrating experiments, it was figured out that the exogenous mRNA induced a regulatory mechanism that down regulated both transcription of the gene and translation of the gene. Elucidating work done with C. elegans and Drosophila indicate that interfering RNA can occur in two ways: either naturally transcribed by the genome as microRNA (miRNA) or as short interfering RNA (siRNA) created from double stranded RNA invaders such as viral RNA9. Interfering RNA are short, single strands of RNA that can, with the help of certain enzymes, bind mRNA in the cytoplasm of the cell and prevent the ribosome from translating a gene. The general pathway is as follows: when double stranded RNA (dsRNA) is introduced into a cell, either by microinjection or through a virus, an enzyme known as Dicer comes along and chops up the RNA into siRNA, which are 21-23 nucleotides long with a 2 nucleotide overhang at its ends. After that, the siRNA is introduced to another enzyme, RNA-induced silencing complex (RISC), which creates single stranded siRNA and guides it to an mRNA with a complementary sequence. Once bound to an mRNA strand, RISC uses its endonuclease activity to cut the mRNA, which is subsequently degraded further by cellular nucleases, thus blocking translation. *(9)*

The human genome is estimated to have as many as 1,000 miRNA genes1 that block the production of about 30% of proteins4. RNAi is now known to occur in all eukaryotes presumably as a defense against viral dsRNA9. Endogenous miRNA can be transcribed in response to an over abundance of mRNA of a particular gene, adding on to the rigors of gene regulation. miRNA are transcribed as a ~70 nucleotide precursors with a hairpin structure containing an ~4-15 nucleotide loop. Studies show that miRNA hairpins function through translational suppression by hybridizing to the 3' untranslated region of mRNA. In contrast to the siRNA pathway, miRNA does not perfectly hybridize with the mRNA, having only 50-80% complementary base pairs. *(5)*

Because of its ability to specifically target protein-encoding mRNAs, many scientists and clinicians see great promise RNAi. "Any sort of disease that you can imagine becomes fair game. Cancer, HIV, for example…," says Dr. Greg Hannon of Cold Spring Harbor labs. Not so fast, say some critics, however. While RNAi might well be a powerful therapy someday for myriad diseases, the perennial problems of drug delivery and off-target effects need to be overcome before RNAi can find its way into the clinician's toolbox. Some clinical studies are underway right now that are using RNAi to treat diseases such as macular degeneration. Preliminary findings suggest that patients are receiving benefit from the RNAi-treatment and so the the prospect of RNAi finding wider use in medicine might not be so far off. But until all the kinks are worked out, RNAi will mostly find itself in the domain of basic science.

Research here at Stony Brook University, with associates at Cold Spring Harbor Laboratories, exemplifies many modern RNAi techniques. A particular experiment was conducted in the department of Pharmacology and the Developmental genetics. Du et. al reported an experiment in which they designed miRNA vectors, DNA carriers, which were inserted into specific introns of HeLa cells that were used to silence specific genes. The vectors took into consideration the post-transcriptional modifications of the miRNA by placing the miRNA cassettes inside synthetic introns. They first inserted an artificial firefly luciferase gene into the cells along with the miRNA vector; the knockdown of the gene was significant. They then inserted a vector to block the endogenous gene for phospholipase D2. Again, the expression of the gene was diminished considerably. Improvements on their design, as opposed to others, included a fluorescent marker and two inverted BsmB1, a restriction enzyme,

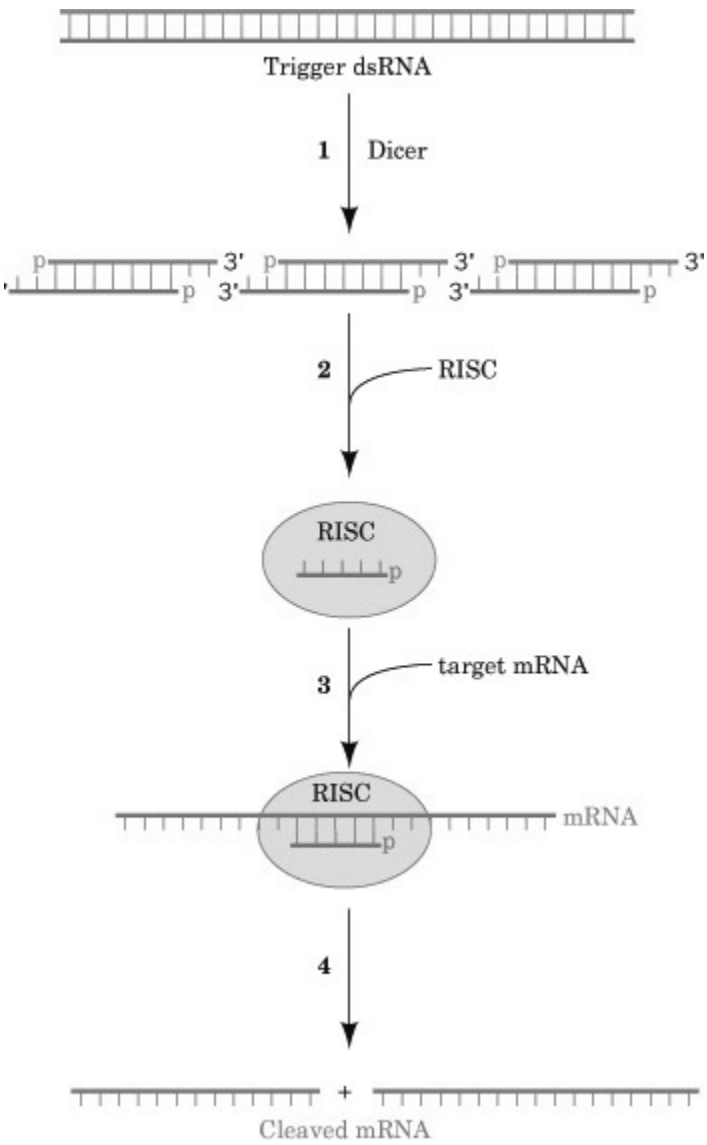

Figure 1. Mechanism of RNA Interference
Source: Voet, D., Voet, J.G., Pratt, C.W. 2006. *Fundamentals of Biochemistry: Life at the Molecular Level*, 2nd ed. John Wiley & Sons, inc., NJ, pp.1050-1053.

sites that were placed on the miRNA vectors so oligos used for cloning are shorter and the cost is reduced. These RNA vectors thus provided a new tool for gene suppression. *(2)*

In the lab of Dr. Gregory Hanon of Cold Spring Harbor Laboratory, researchers have recently implicated microRNAs in the p53 signaling network (3). p53 is the so called 'policeman' of the cell because of its anti-cancer features. It is a transcription factor that promotes genes involved in apoptosis (programmed cell death), cell cycle arrest and/or DNA repair; mutations in p53 are often connected with tumor growth. It has been seen that the miR-34 family of miRNA have a role in the p53 tumor suppression network and are produced, along with many other proteins involved in the network, when p53 is turned on. These all help knock down the production of cell cycle proteins and cell survival factors. The miRNA in particular use the properties of RNAi to block the production of the proteins on the translational level. The activation of p53 and, in turn, the transcription of those particular miRNAs is induced in times of DNA damage oncogene stress, telomere depletion, and/or hypoxia when oncogenesis is a looming threat. The main findings of this project were that when miR-34 is over-expressed, there is either apoptosis or cellular senescence, the loss of the ability for a cell division. However, when it is under-expressed, p53 mediated cell death is reduced and cells are allowed to proliferate; this is evident in several types of cancer. The pathway of oncogenesis inhibition is activated by p53 and along with many other proteins, the miR-34 family of miRNA helps knocks down the production of cell cycle proteins and cell survival factors. *(3)*

Conclusion

RNAi is a powerful tool used in vital research fields, most notably cancer research. miRNA regulates almost half of all human genes, and modifications in their activity could lead to many diseases. Interfering RNA now provides an extra tool for researchers to perform knock out experiments to test the response of a cell when that protein is missing. RNAi is also promising as a therapeutic agent to treat diseases. The discovery of these little molecules was overlooked at the initial time of observation, but is now known to be essential for cellular function. It is exciting to see where this new field will bring us in the future. There are indications that there are other types of small RNAs with different functions, signifying that we still may know only very little about non-coding RNAs and that our understanding of it has just begun.

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A Review of the The Micturition Reflex

Isaiah Schuster '10

Induced injury to the spinal cord can lead to very serious post-injury manifestations. Many individuals who suffer from this very serious injury have trouble urinating, and thus have to deal with catheterization procedures which are uncomfortable, in some cases ineffective, and often very painful. Stony Brook University's Professor William Collins has undertaken an effort to investigate the micturition, or voiding reflex, that is responsible for excreting urine out of the bladder by specifically exploring properties of motor neurons that innervate the external urethral sphincter. Principles of electrophysiology are central to Professor Collins' study of this reflex – using EUS-EMG technique to record electrical activity directly from the external urethral sphincter during bladder activity. In the long term, research in this area has prolific clinical consequences for individuals suffering from spinal cord injuries or for individuals suffering from other pathologies that may negatively impact voiding efficiency.

The micturition reflex recruits various components of both the Peripheral Nervous System, or PNS, and the Central Nervous System, or CNS (1). However, it is not simply the involvement of these two highly ordered and complex systems but the molecular interactions between the sympathetic, parasympathetic, and somatic nervous systems, with each playing a specific role in every step. This review article investigates the fundamental components of the reflex using the rat model, as well as provides information that is currently known about Spinal Cord Injury in terms of its effects on voiding.

The Urinary Tract: A Brief Overview

In order to appreciate the molecular subtleties of the reflex itself, it is important to understand the components that make up the urinary tract by looking at the path that the glomerular filtrate and urine take within the organism. Filtration of blood begins when it enters the Bowman's capsule in the glomerulus and furthers in the descending and ascending loop of Henle and is a function of osmotic pressure. This aids in the homeostatic maintenance of physiological pH, the osmolarity of ionic species, volume of the plasma, excretion, &c. After exiting the kidneys through the distal tubule, the fluid now considered as the urine enters the bladder, a smooth muscle known as the detrusor, via two ureters. After excitatory stimulation and contraction of the detrusor muscle, the urine passes through the bladder neck and enters the urethral sphincter – a structure that consists of smooth muscle, the internal urethral sphincter, and striated muscle, the external urethral sphincter. The synergy between the urethral sphincter and the bladder allows for the smooth excretion of urine through the urethra – a process that is mediated by postganglionic neuron release of neurotransmitters and their interaction with different receptor classes and subtypes both in the bladder and in the urethral sphincter.

The Reflex: Innervation and Bladder – Sphincter Activity

The Peripheral Nervous System, or PNS, can be divided into three main interrelated systems: the sympathetic and parasympathetic nervous systems, which comprise the autonomic nervous system, and the somatic nervous system. The accumulation of urine within the bladder at a rate that is a function of filtration in the kidney, acts to stimulate the reflex which is controlled by neurotransmitter release from postganglionic neurons– key components of the PNS. Sympathetic innervation of the lower urinary tract stems from a region in the spinal cord known as the thorocolumbar outflow, versus the parasympathetic innervation which arises from the sacral region of the spinal cord. (2) The bladder and the urethra contain an array of different receptor systems—mainly cholinergic and non-cholinergic (acetylcholine regulated), adrenergic and non-adrenergic systems (regulated by norepinephrine and/or epinephrine), as well as different receptor subtypes that are involved within these general system classes that have either excitatory or relaxing effects.

One important type of receptor is the purinergic receptor, which is located in the bladder, and is activated by ATP binding. These effects depend upon the location of the receptor and the sympathetic, parasympathetic, and/or somatic nerve innervating the region. (2) For instance, the hypogastric nerve synapses at the bladder (sympathetic innervation) and "activates adrenergic inhibitory receptors in the detrusor muscle to relax the bladder, adrenergic excitatory receptors in the urethra and the bladder neck, and α and β adrenergic receptors in [the] bladder ganglia." (2) Depending on the location and the receptor type, the same molecule may have completely different functions in the body.

Both efferent and afferent neurons are important in maintaining the integrity of the reflex and carry out a different function depending on where these neurons synapse. The terms efferent and afferent, when describing neurons in the nervous system, reflect the path that a signal takes. For instance, efferent neurons carry signals derived from the spinal cord to the tissue receiving the signal, and afferent neurons carry responsive signals back from the tissue to the spinal cord or the brain, the CNS.

Moreover, in order for all of these functions to properly work, something needs to be stimulated—something needs to communicate to the peripheral and central nervous systems that urine is present in the bladder and that one needs to void. This something is the bladder. The bladder as a whole acts as one giant stretch receptor that is activated by increases in pressure from within. If the bladder is full, and voiding is not possible as in some instances, such as when one has SCI, the bladder becomes distended. This giant receptor system is in reality made up of several layers which include the urothelium, myofibroblasts, and the detrusor which are all responsible for mediating the contraction and relaxation of the bladder through efferent and afferent neuronal pathways once urine has made its presence known to the bladder.

Scientists have unearthed a pattern unique to almost ever bladder voiding epi-

sode in terms of electrical activity in the urethral sphincter, which is a function of bladder pressure. Electrical recordings as well as pressure recordings, from the female rat, indicate that as the bladder fills with fluid, the pressure increases as well as the electrical activity. The increase in the EMG activity is the result of activation of the guarding reflex which prevents the urine from leaking prematurely. In general terms, once a threshold level has been reached, the bladder contracts while the external urethral sphincter relaxes, leading to voiding, and to a subsequent decrease in motor neuron activity in the urethral sphincter. Both the bladder and the sphincter function in the same way during voluntary voiding as well.

Spinal Cord Injury- what happens to voiding?

During spinal cord injury, patients often face the problem of not having proper communication between the sacral portion of the spinal cord and other areas of the Central Nervous System involved in the reflex, such as the Pontine Micturition Center, located in the brain. Immediately after one's injury, the bladder becomes fully areflexic and regains its function over the course of some time—although the once synchronous activity of both the sphincter and the bladder are now lost (3). This means that once urine accumulates in the bladder, the guarding reflex does not settle down once efferent stimuli are communicated to the bladder muscle. This bladder-sphincter dyssynergia causes one's inability to urinate when required to, a condition that may cause bladder distention and damage, if too much volume accumulates. Patients suffering from SCI and from other possible manifestations are subject to catheterization procedures, which involve the placement of a catheter into the urethra of the individual to facilitate the passage of urine.

Conclusion

Having a thorough understanding of the micturition reflex as well as its various components is critical in developing new treatment procedures for patients currently suffering from their inability to properly void. Faculty here at Stony Brook University have taken it to be their primary objective to advance the field of lower urinary tract dynamics, which may give insight as to how to improve current treatment methods for those suffering from some form of spinal cord injury.

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The Large Hadron Collider: An Overview

Simone Park '09

"I have no special talents. I am only passionately curious."
-Albert Einstein

I believe the majority of us are curious beings, wanting to know the answer to questions such as "Why is the sky blue?" or "Why do I have to brush my teeth?" Scientists are naturally curious beings, and their job descriptions include answering life's unanswered questions. Recently, a large collaboration of scientists have come together to build the world's largest particle collider, in hopes of answering the basic questions, such as where mass comes from, and to reveal more of nature's secrets. However, with such a large project comes controversy and worries, such as, Will the machine create a large black hole capable of sucking in the Earth? With such public worries, it's best to understand the whole story, including the scientists' motivations and answers to public concern. In this piece, I will attempt to explain the motivations for building such a large collider, its expected outcomes, and address public concern.

Background

Is there an elusive particle that gives matter its mass? Is nature really elegant and symmetrical in its deisgn? Particle physicists want to answer fundamental questions like these, and they hope the data extracted from the Large Hadron Collider (LHC) can assist them. The LHC is a circularly shaped collider (see figure 1) and is currently the world's largest particle accelerator, measuring close to 27 km in diameter (around 17 miles!). Built by the European Organization for Nuclear Research (CERN) and collaborative efforts from more than 10,000 scientists and engineers from over 100 countries, the LHC will collide ions at never-before attained high energies by man. The collider will consist of several projects aimed at the different inquiries, and ultimately uncover clues to assist physicists.

In order to understand what the LHC will actually accomplish (or hope to accomplish), I'll outline a basic understanding of the physics behind LHC's reasoning. First, we must realize that in this world, nothing travels faster than the speed of light. As particles reach this speed, abbreviated c, (where c=3.0E-10 m/s) they can only get closer and closer without surpassing this asymptotic value. As they approach c, since they can't pass this value, they just gain energy. The closer a particle gets to c, the more energy it gains. High-energy particle accelerators take advantage of this idea and boost particles such as electrons, protons, and other ions, to speeds closer and closer to c, thus driving them at higher and higher energies. The energy gained by such accelerations can be used in collisions such as those the LHC will do. Different particles emerge from collisions done at different energies. For example, two protons collided from opposite directions at a lower energy will produce different sets of subatomic particles than ones done at higher energies. The LHC hopes to accelerate its particles at 0.999999991 times the speed of light and then produce head-on collisions in order to simulate conditions similar to moments after the Big-Bang (10-25s after). The facility will bring particles to 14 TeV at collision (1 TeV = 1012 electron volts, and 1 eV is the amount of energy gained by an electron accelerated at a potential difference of 1 V), an amount never attained by any particle accelerator to date. The collisions will produce a vast array of sub-atomic particles that can be further analyzed and used as empirical data to confirm or discover theories.

Now that we know how the particles will collide, let's look at one of the motivations for building the LHC: finding the origin of mass. The current view of how the different forces hold matter and objects in place is called the Standard Model. This model explains how three of the four fundamental forces interact with particles that make up matter. These four fundamental forces are the Strong force, the Weak force, the Electromagnetic force, and the Gravitational force. The Strong and Weak forces are valid only in distances close to interatomic distances, and the gravitational force is the only one not accounted for in the Standard Model. According to this model, quarks make up protons, neutrons, and other hadrons (particles that feel the strong force) that make up matter. Furthermore, each force is carried by its respective force carrier. For example, the photon is the carrier particle for Electromagnetic force, i.e., light. Likewise, gluons are the carrier particles of the Strong force, W and Z bosons carry the Weak force, and the graviton carries the Gravitational force.

Another important component of the Standard Model is the theoretical existence of a Higgs field. Physicists theorize that moments after the Big Bang, the particles that emerged initially had no mass, but by interacting with the Higgs field, gathered mass. The mass of a particle was proportional to the amount of interaction with the Higgs field. This theory also then predicts the particle associated with the Higgs field, namely the Higgs boson. Physicists believe that the Higgs boson should be formed from the high-energy collisions done at the LHC. However, it's interesting to note that if the Higgs boson is not detected by the LHC after careful data analysis, the Standard Model will have to be re-examined or replaced by other theories. Thus, in either case, the experiments done at the LHC over a period of time will change our current beliefs about particle physics and the constituents that make up all matter.

Projects at the LHC

Now that we've explained the basic idea behind the workings of a collider and one of the motivations for building the LHC, we'll discuss the various projects that comprise the LHC and what each project's goals are.

The data produced by the collisions travel to the six detectors set up at the LHC, namely the ALICE, ATLAS, CMS, LHCb, LHCf, and TOTEM experiments (see images for the ALICE and ATLAS projects below).

A Large Ion Collider Experiment (ALICE) is a specialized detector that will analyze lead-ion collisions and study the quark-gluon plasma that is thought to have

existed just moments after the Big Bang. Quarks come together under the influence of gluons (remember, gluons are the carrier particles of the strong force) to make up hadrons, particles that experience the strong force, such as protons and neutrons. At very high temperatures and densities, the quarks are no longer bound to their hadrons and exist as plasma. Thus, ALICE will explore the properties of the lead-ion collisions and see if such quark-gluon plasmas existed. The ALICE experiment is located in France and includes collaborations from more than 1,500 people from 31 different countries.

The "A large Toroidal LHC ApparatuS" (ATLAS) and "The Compact Muon Solenoid" (CMS) are general purpose detectors intended to cover a broad range of interests, including the search for the Higgs boson and finding extra dimensions. The two differ in design and location. ATLAS is in Switzerland while CMS is located in France. These two experiments collectively have around 4,000 members internationally.

The Large Hadron Collider beauty experiment (LHCb) will study slight asymmetry between matter and antimatter and will help answer why the universe is made up of matter. The Large Hadron Collider forward experiment (LHCf) will study cosmic-ray physics, and the "Total Cross Section, Elastic Scattering, and Diffraction Dissociation at the LHC" (TOTEM) will measure the total cross section, elastic scattering and diffractive processes at the LHC. These six experiments collectively span a broad range of topics of interest to particle physics and will help to understand and shape our current working knowledge of the field.

The LHC is a pseudo-circular ring made up of different kinds of magnets and insertion devices that help steer the beam of particles in its path and keep them in the bunches to maximize the concentration of particles colliding. Pseudo because the ring is not a perfect circle, it is made up of straight sections and curved sections that give the collider its properties. The magnets used for the LHC have to be cooled to superconducting (superconducting means that electricity can travel through the material with very little resistance) temperatures to provide and maintain the large energies attained. This cooling is done with liquid Helium in its superconducting phase, which will bring the LHC to -1.9K (-271.3 degrees C). This massive cooling of the entire system will take a few weeks to achieve, with three phases that will bring the LHC first to 4.5K, then finally 1.9K. The collider will have vacuum systems for the cryomagnets, the helium distribution lines, and the beam. The beam vacuum pressure will be at ultrahigh vacuum (10-13 atm) to avoid unwanted collisions with gas molecules present in the air.

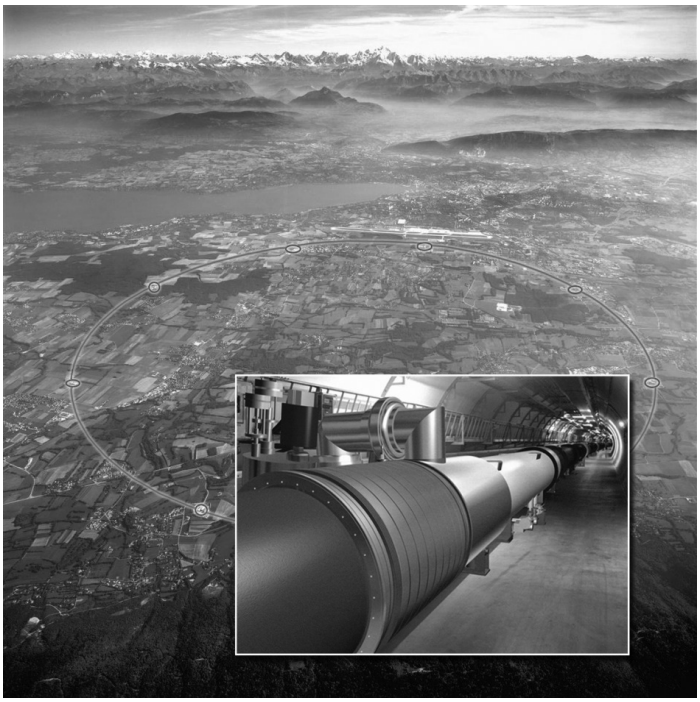

Figure 1. The LHC Collider Ring.
Source: Lawrence Berkeley Livermore National Lab News, http://www.lbl.gov/publicinfo/newscenter/features/08/06/12/AFRD-LHC.html

Safety concerns are important with a system producing large energies, and they are not overlooked by the scientists at the LHC. The official LHC guide outlines the safety issues such as unprecedented energy collisions, black holes, and radiation concerns, and compares them to natural processes that have yet to harm the Earth. With regards to the unprecedented energy collisions produced by the LHC, the guide compares these energies to cosmic rays formed from supernovae or the formation of black holes, and says that those energies are far greater than those that will be produced at the LHC. Since these cosmic rays that continue to hit the Earth's atmosphere have not destroyed the Earth, experiments done at the LHC should not either.

One publicly-made concern about the LHC was the possibility of a massive black hole, created during the high-energy collisions, that would destroy the Earth. A black hole is a condensed region of mass that gravitationally attracts surrounding matter. It is usually formed in outer space as massive stars collapse. The idea of the black hole is illustrated below, where we see this concentrated disc on the right pulling the planet-shaped mass in towards it. At the LHC, it is predicted that mini-black holes will be formed; however, since the strength of the black hole, or its ability to attract surrounding matter, is determined by its size, the microscopic black holes that could be formed at the LHC are too weak to pull in surrounding matter. These small black holes will disappear by emitting energy since they were small to begin with, and would exist only for short periods of time such that they could be detected only by their decay products. So, black holes, although they are seemingly dangerous, probably will not destroy Earth. High energy emits radiation, and we know that radiation can cause bodily damage. Since the LHC will collide high-energy particles, radiation exposure is a valid concern. The experts at CERN say that radiation exposure concerns are dealt with through monitoring radiation levels and following safe procedures to ensure the least amount of radiation exposure to the surrounding population. One obvious preventive measure is the underground location of the collider. It is estimated that the amount emitted to the public should be less than 10 micro-Seives a year. In comparison, the guide writes that a round-trip flight from Europe to Los Angeles exposes a person to around 100 micro-Sieves.

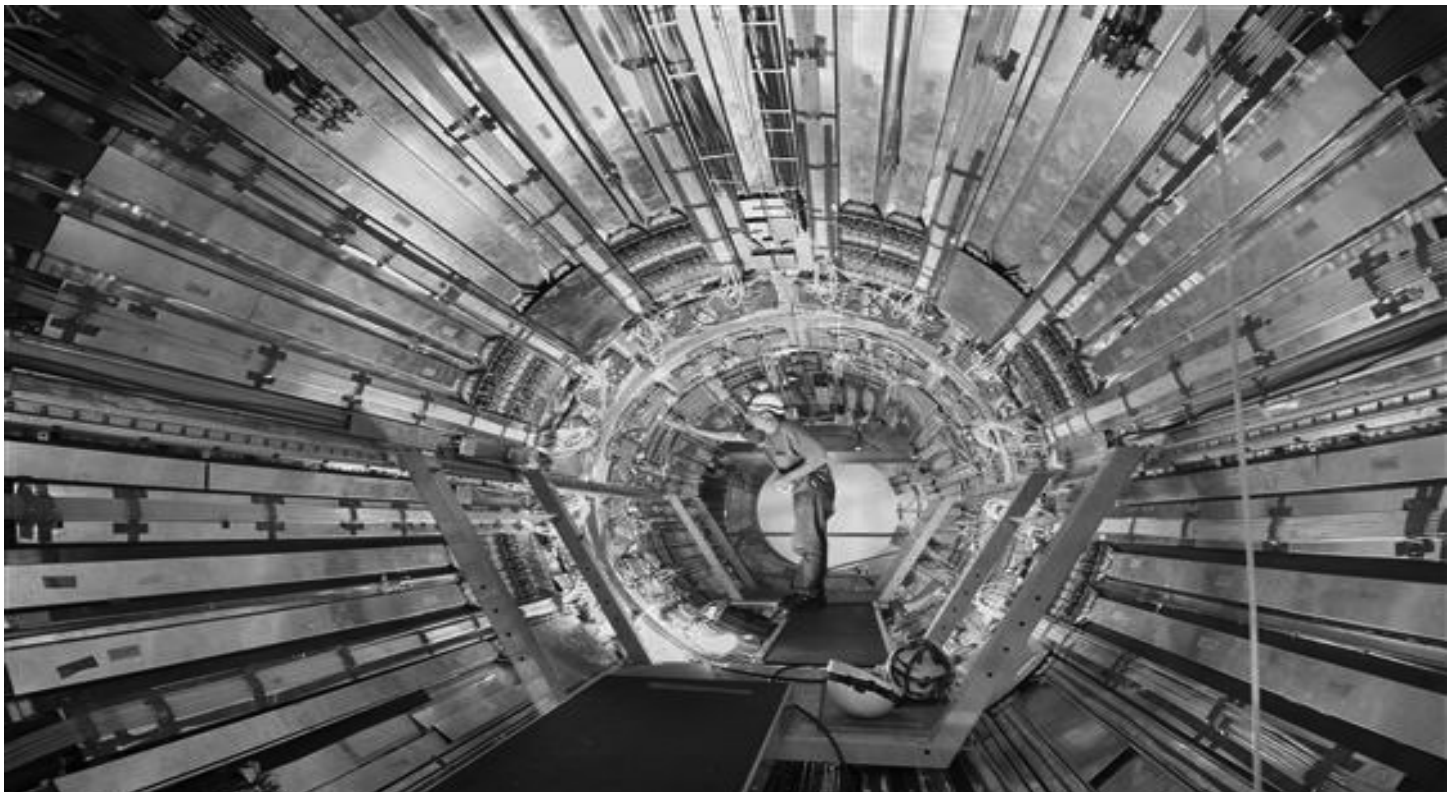

Figure 2. nside the ATLAS detector, another one of the six detectors part of the LHC complex.
Source: CERN, http://public.web.cern.ch/public/en/LHC/ATLAS-en.html

Computing Power

The data from the LHC experiments expected to produce around 600 million collisions per second will deliver about 700 Mega Bytes of data per second. This huge amount of data collected over time will take hundreds of thousands of computers to analyze. Thus, the LHC has put into place two filters that will successively filter out data and leave only the interesting collisions that scientists can analyze. The downside to this is that once data has been thrown away, it can't be recovered, and so it's important that the filtering algorithms are accurate. The remaining data, however, will be distributed around the world through the CERN Grid, a network similar to the internet, to distribute the load.

Conclusion

The completion of the Large Hadron Collider marks the beginning of a new set of powerful experiments that will undoubtedly change and shape our views of the world in a fundamental way. Whether success comes and we discover the long-awaited Higgs particle, recreate the quark-gluon plasma, explore symmetry principles, and discover extra dimensions, or fail to discover anything, science guarantees that the LHC will challenge our resources, technological power, and intelligence. The enormous technical challenges associated with building, transporting, cooling, and vacuuming such a large facility were taken on by the world's scientists; the sheer computing power that will have to be in place was met with by the creation of the CERN grid that allows scientists to share their processing power. This is not to say that particle physics is the only field that will benefit.

The computing power and technological tools developed through making of the LHC can help other fields with growing computing and probing demands. For example, biologists and protein crystallographers utilize synchrotrons, a circular particle accelerator that emits high intensity broad-band light, for high resolution imaging and X-ray diffraction techniques to study the structure of unknown biological materials at resolutions unattainable with common light sources.

In the end, the LHC has brought together the world's scientists in vast numbers and made us realize the common thread that holds these individual countries together: curiosity. This has led us to spend over 6 billion dollars on the largest particle accelerator the world has seen.

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Toward a Theory of Human Uniqueness

Molly McCann '10

The class BIO 358, The Biology of Human Social & Sexual Behavior, is a popular one here at Stony Brook University. This is partly because the class is taught by one of Stony Brook's most engaging and interesting professors and partly due to the fundamentally groundbreaking science taught in the course material. Professor of Biochemistry and Cell Biology, Paul M. Bingham has collaborated with course instructor Joanne Souza and economist Daijiro Okada, from Rutgers University, to develop a new theory of human evolution and human uniqueness. This theory will be described in a new book Bingham and Souza will publish early next year entitled Death From a Distance: The Birth of a Humane Universe. Together they have made vast contributions to the field of biology, the university, and most importantly, their students.

Professor Bingham and Joanne Souza research a new theory of human evolution which would help explain the source of human uniqueness. Humans beings, apart from all other animals, possess capabilities that have granted us unique success as a species. Our evolution from our pre-human ancestors, namely the primates, resulted in the development of certain muscles in the human body that enabled the action of what Bingham calls "elite throwing." The adaptation of our hip and upper arm muscles introduced the possibility of projecting "threat from a distance." As the only species that makes use of the force of throwing to kill a social outlier, humans have been able to limit the potential risk to individuals who threaten a socially non-cooperative individual.

Stopping a non-cooperative individual from benefiting from, without contributing to, a cooperative society has been one of the biggest unanswered questions in Game Theory. Without some means of solving the "free rider problem" the expression of altruism makes little sense in the context of a 'survival of the fittest' evolutionary model. Actions that benefit an individual's personal fitness, which is the potential of you and yours to reproduce, will get passed to the next generation, while behavior that results in altruistic cooperation would not confer increased fitness and should, theoretically speaking, be rare.

However, the complexity and pervasiveness of human societies tell us that the unlikely social cooperation has been quite successful. So where has the theory departed from reality? Until now, the mainstream of evolutionary biologists have chalked this up to the theory of reciprocal altruism. This is the idea that doing favors for others, whether or not your related, will be to your benefit when the favor is returned. However, Dr. Bingham rejects this theory because it does little to explain why large scale social cooperation is largely unique to humans. Furthermore, reciprocal altruism lacks an enforcement mechanism, so it would take only one lazy free loader to break the positive chain of reciprocal altruism.

Bingham's theory is a bit tidier. Being able to threaten free loaders became the first "inexpensive" form of violence. Complex human behavior, large human brains and complex societies, Bingham postulates, can only form when a society has a way to bring its citizens to a evolve a consensus of accpetable social behavior..

Killing from a distance has vanishingly small costs to the multiple members of a social group. Non-human animals do not possess this capability; thus, eliminating a social threat is usually done up close, and face to face. This can result in devastating costs to both individuals, each with an equal chance at insult and injury. Humans, however, can attack a social free loader by projecting violence not only from a distance, but in high numbers. This way, each member can use violence more effectively, sufficiently, and most of all, safely.

According to Bingham, this advanced human social cooperation has many consequences. One of the most interesting is the evolution of language. Language has allowed for the exchange of information between those within a close society. Problems of interests and such aspects of a civilization are easily discussed and handled based on this sharing of information. Free loaders who lie and misdirect must be cheaply ostracized for this exchange to be adaptively successful. Once again, the ability to remove these social outcasts, namely by remote killings, only adds to the overall success of the community. Language can also have a counter effect on the individual. For example, one would not lie or manipulate others to prevent being exiled from the society. Language has intensified the social cooperation of humans by allowing them to exchange vastly greater amounts of socially transmitted information than non-human animals – to have "culture" in the human sense.

Perhaps one of the most important questions Dr. Bingham asks himself is how to solidify his theories of human uniqueness. His first step was formally looking at the evidence provided to him already. Bingham advocates the "Front of the T-shirt" theory, states that any scientific theory should be able to be simple enough to be written on the front of a t-shirt. The purpose of science is not complication, but rather stripping away complexity and exposing the simplicity beneath.

While simplicity is the goal of science, doubt is its primary tool. Scientists seek to build theories that are simple enough to make very specific predictions. Such predictions are precise enough to be subjected to decisive test against the empirical evidence. In other words, scientists try to smash their theories on the facts, coming to believe only those theories that survive. Bingham and Souza suggest that this same practice of doubting, applied to ourselves, is how we seek personal wisdom.

One of the most defining aspects to Bingham's research occurred upon a family vacation in the Midwest. By examining local native archeological findings of the Mississippian peoples, Bingham had found evidence that would support his ideas. These ancient peoples had rich histories of large architecture that was designed before the European incursion into North America. Bingham discovered that local archaeologists knew that this Mississippian florescence followed the local introduction of a new capacity to project threat from a distance, the bow. This astonishing discovery tipped off Bingham to look into local publications of the Mississippian natives. Hoping to find conclusive evidence, these

"Our minds want to prove we are right, and that is a fundamental mistake."

publications had indeed told Bingham that he was headed in the right direction. Now all he had to do was link his evolutionary theories into a chronological series of events.

Many people tend to look past the idea that specific historical events are what can lead to such social accomplishments. The social stages in which we, as humans, have progressed throughout time is strong evidence for Bingham and Souza's theory of human uniqueness. As stated before, the first major step in the history of Homosapiens was the ability to throw and isolate our newly adapted muscles. This simple, yet defining, stage of human development sparked a cascade of events that would separate us from other species forever. Once humans could fully establish law enforcement and limit the coercions of free loaders on a larger scale, technological developments began to further social advancement. Each new adaptive revolution in our history resulted from the application of the same logic at a larger scale, always involving inexpensive law enforcement sustaining ever larger cooperative enterprises.

This theory of historical events was referred to by Bingham as the "adaptive staircase." Human social sophistication increases in discreet jumps or stages, and can figuratively resemble the motion of progressing up a flight of stairs. One event brings us to the next step, where we can plateau on for many years, or move directly onto the next, higher stage of ground. Bingham and Souza explain that each new "step" in historical evolution was the product of technological advancement of weaponry or defense from weaponry, the development of new means of social coercion. More than 10,000 years ago, the bow and arrow development allowed humans to reach a "next step" in social progression. The bow intensified the ability to project violence from a distance and on a much larger scale than elite throwing. And because of this, a new stage in human social cooperation was created.

The theory of the adaptive staircase reflects one of the most general theories of human history ever developed. However, even to this day Bingham, Souza, and their associates are constantly trying to improve their theories. Their tireless effort to try to ultimately prove themselves wrong has brought them to where they are today. They could have only achieved this by trial and error and with the scientific method.

This basic form of research and development has become a crucial aspect to any area of science. And as we all learned before, the overall reason for this process is to test a formulated hypothesis, or prediction about a scientific observation. Then through various experiments, the hypothesis is either supported or not. However, many believe that the scientific method proves a hypothesis to be true or correct. "Our minds want to prove we are right, and that is a fundamental mistake," says Souza. Falsification and doubt are the fundamental tools of science. A true scientist must always wear a "bull's eye" on his or her chest, inviting criticism, in hopes of constantly proving themselves wrong. By inviting in counterarguments and ideas, refinement of a theory can flourish. One needs to constantly doubt and try to falsify one's theory in order to truly make a recognizable theory. It is absolutely crucial for students today to understand this aspect of the scientific theory. Science is not built upon conclusive evidence, it is built upon doubt.

Please Meet Maggie, My Cadaver

The Experiences of a First Year Medical Student

Patricia Ng, Stony Brook Medical School '12

Approximately thirty white bags are laid out across the room, each containing a subject that every medical student will get to know all too well. I stand next to my assigned table, waiting anxiously in my dull blue scrubs and hoping that the stagnant formaldehyde stench won't seep too deeply into my skin. "You may open your bags," announces our instructor, and within seconds I was staring at a naked, elder female who I would be introduced to as "Maggie."

Gross anatomy and its infamous cadaver lab is one of the most eye-opening experiences of medical school. For half a year, we medical students literally chop away for hours at a human body so that we can become experts on the organism that we will be examining for the rest of our lives. Day one of lab was not as stomach turning as second years made it out to be, but perhaps it was because we started with our cadavers lying prone. For the first week, we went through structures of the back, identifying muscles, finding nerves, and eventually chiseling through the spine. Yes, set aside at each table is a tool box that contains a chisel, saw, several hammers, and a flashlight, which we use to cut through bones. For the lumbar vertebrae, which are bones of the lower spine, we had to hack away rather diligently to reach the center spinal cord and it was impressive to see the resistance that these bones had against the force of tools that are normally used to cut wood. As we continued to slice and dice, the idea of dissecting an actual human being never really settled in. However when we reached week two, it was time to flip over our cadavers and it was then that Maggie became a person.

The patient information that we receive about our cadavers varies from each group and, unfortunately, my cadaver did not have a foot tag. We don't know her real name and calling her Maggie just seemed to suit her. All we know is that she died from pulmonary and cardiac arrest, and had suffered from Alzheimer's and dementia during her lifetime. Nevertheless, as I stared at her face, I saw that Maggie was someone. She was someone's daughter, someone's sister, someone's friend, and here we are snipping away, digging deep, and exploring her body as if she were an animal that we have never seen before. It is because of this desensitized attitude toward the deceased that many people believe that alternative methods for teaching anatomy should be considered. For example, with today's advancements in computer graphics and video, some argue that visual images should be sufficient and that the dead should be saved from being chopped to pieces. Although these computer programs are good resources for students, nothing can replace a cadaver dissection for learning anatomy. As we medical students work arduously at scraping away fat and fascia to find the smallest arteries and nerves, the anatomical facts become ingrained in our brains and we take that information with us forever. Thus if cadaver dissections were ever taken away, I think medical education would be at a great loss.

"I have become even more impressed with the complexities of our species and I'm excited to fully apply the knowledge that I gathered from undergrad to my medical education."

Furthermore, I believe that the anatomy lab has actually made me more sensitive toward the human body because I am so thankful for all the individuals in that room who have donated their bodies to science. To give oneself to facilitate the continuation of education is probably one of the greatest gifts that can ever be given. To some degree, these body donations are more valuable than any monetary gift that is given to the school and therefore I treat each cadaver with the utmost respect. In my opinion, consenting to a body donation is an extremely brave philanthropic act and I am honored that these people are assisting me with my medical training.

Now I've been in school for little over a month and I am in the midst of preparing for my first set of midterms. In five weeks, I have learned about everything that composes the trunk of the human body and have probably added over two hundred words to my vocabulary. In this short period, I have become even more impressed with the complexities of our species and I'm excited to fully apply the knowledge that I gathered from undergrad to my medical education. For example, when we dissected the thorax and studied the heart, I couldn't help but think about my days in Stony Brook University's BIO 203 course, when Professor Bill Collins taught us the flow of blood through the various chambers and vessels. Aortic and pulmonary semilunar valves do look like little half-moon cusps and the aorta really is a massive tube. This artery is probably 1.0 – 1.5 inches in diameter and I was amazed that I could wrap my hands around the vessel that is integral in distributing the oxygen and nutrients that our bodies thrive on. Without a doubt, as I continue to learn more about anatomy, I realize that my days of undergrad biology were not a waste. I am finally seeing the physiology that I learned come to life and I look forward to continuing my exploration of the human body.

Getting Involved in Research
It's Never Too Early To Start

Faye-Marie Vassel '11

This past summer I was part of an amazing ten-week Research Experience for Undergraduates (REU) program at Rice University. This particular summer research program was housed under the Rice Quantum Institute (RQI) and was one of several summer research programs at Rice. The RQI is geared towards individuals who are interested in research that crosses the interface of chemistry and physics. I interned with a group whose study of protein folding managed to encompass both sciences.

Having a defined interest in biophysical science was extremely helpful. My primary roadblock, so to speak, was the fact that I was applying to these programs as a freshman. I highlight this because I know there are many freshmen that are motivated and genuinely interested in doing research. However, many programs either only accept upperclassmen or take very few freshmen. I say this not to discourage driven freshmen, but to inform them that it may be a bit difficult to do research their freshman year, though not entirely impossible.

I took a systematic approach to researching various summer programs and, as I look back upon it now, I believe that this helped immensely. As I searched for internships, I kept several things in mind. First, I asked myself what type of lab I wanted to be affiliated with. This is crucial. Going into a lab that doesn't excite you may still turn out to be a worthwhile experience, but it is probable that this lack of interest will lead to lack of motivation in the work. Next, I asked myself if I would mind being in a situation where I would be placed with one or several other interns in the same lab. Finally, I considered whether I was interested in doing research at an institution other than Stony Brook.

Having a list of things you wish to gain out of your research experience is very helpful for it allows you to hone in and further define the aspects of your experience. After forming an idea of what I wanted to gain from my summer experience, I concluded that I would rather be in a small program, one with 10-20 students, being involved with research done at another institution definitely interested me and, most importantly, that I was seriously interested in working in a lab that conducted biophysics research. Consequently, I looked into quite a few NSF summer research programs falling under several broad categories (physics, chemistry, and biology), but all providing opportunities for biophysics research.

I eventually narrowed down my choices and applied to seven programs. As a part of my personal statement for most of the programs, I was asked to rank the labs listed in order of interest. After looking into the labs that were associated with the REU at Rice and those that conducted biophysics related research, I was most intrigued with the research done in Professor Cecilia Clementi's lab.

The Clementi group studies protein folding and dynamics. A large part of their research focuses on exploring the protein folding landscape using the coarse-grained protein model, a simulated protein model. This protein model uses molecular dynamics (MD) to represent groups of amino acid residues as effective interactive "beads." The Clementi model is very promising because past folding simulations have used contact energy potentials that limit the variability of residue-residue interactions, whereas this model corrects the issue. My ten-week REU experience gave me the opportunity to immerse myself in the group's research. By being assigned a particular task, my research project, I was able to feel like an integral member of the team.

The author, who attended an REU program this past summer at Rice University.

During my time in the Clementi lab I worked primarily with a graduate student. Everyday was a learning experience. To begin to understand critical concepts, such as why proteins fold spontaneously, I had to do a lot of independent work. No one explicitly advised me to do so, but the situation reinforced the need for me to be proactive. I realized that if I were to understand group literature and literature by others on protein folding, I would need to learn a lot on my own. However, the nature of the REU made it clear that we had the support of the program director as well as that of our respective lab groups if we ever encountered a roadblock or had pressing questions. In many ways this accessibility lessened my personal workload and gave me multiple sources of reference.

In the beginning I often felt like a fish out of water due to the amount of material I needed to absorb. Nevertheless, my efforts brought rewarding results. Whether it was my crash course in learning how to code using Python or just beginning to understand basic principles of statistical mechanics, I was amazed by my diligence. As a result of the time I invested I was able to follow group talks with more ease and make necessary connections. Also, being placed with an understanding and involved principal investigator helped my transition immensely. Even with Dr. Clementi's busy schedule, I was able to meet with her weekly to go over my progress and to discuss issues that required clarification.

My close interaction with graduate students allowed me in

"Stony Brook students should keep in mind that a variety of research opportunities are available to them."

turn to have immediate sources of guidance. The graduate students I worked with also encouraged me to challenge myself. They often refused to provided me with direct answers to my questions, just a foundation to bounce my own ideas off. Initially, I found this puzzling. Nevertheless, I believe that by encouraging me to dig to the roots of my questions allowed me to understand concepts better.

In addition, working daily with graduate students allowed me to see what is expected of them. I began to see a difference between the graduate and undergraduate experience. Not only are graduate students expected to focus on their research, but in many ways it is essential for them to read literature by other groups doing similar research and learn about the research of their lab cohorts.

The two months I spent in the Clementi lab provided me with a taste of graduate level research. It helped me see the immense need for motivation, patience and flexibility of ideas. The structured nature of the REU allowed me to learn about research that my peers were conducting and about research being conducted at Rice. It also gave me invaluable practice in writing a research paper and presenting my research at a colloquium highlighting graduate and undergraduate research. I chose Rice largely due to the fact that I was placed in the Clementi lab and it turned out to be a very rewarding experience.

In recent years, it has become increasingly important for undergraduates to get involved in research particular for students who plan to apply to graduate programs. Consequently, qualified candidates for research-centered graduate programs need to be involved in undergraduate research. Stony Brook students should keep in mind that a variety of research opportunities are available to them.

In the process of choosing a research internship many undergraduates decide on the first opportunity they find. By doing so, students neglect to take into account the abundance of opportunities available. Quite often it is the programs with the best publicity that attract students; however, there is no guarantee that such programs will offer an undergraduate student good research experience.

If you are a student with a burning desire to learn more about stem cells but you feel discouraged to contact labs because you are a freshman, it is important to keep in mind that getting involved in research as soon as you feel ready is strongly advised. This being the case, being aware of your options will make the process easier. There are two types of summer internships: independently arranged and organized internships. In deciding what type of research internship you want to be involved in, it is important be aware of both types and to then assess what it is that you want out of the experience.

Independently Arranged Research

In many ways independently arranged research is the best type of internship, whether here at Stony Brook or at another institution. However, it also requires the student to take the initiative and contact the principal investigator, convince them to take you on and, in some cases, get funding from them or another source. Nevertheless, independently arranged research also presents a host of opportunities. Obtaining an internship in such a manner allows you to choose a lab involved in amazing research in an area of your choice.

In particular, doing independently arranged research here at Stony Brook will allow you to visit individual labs, to meet the professors and lab members, and ultimately get a feel of the lab atmosphere. There is a large number of labs at Stony Brook and the University Medical Center. Medical school faculty may be very receptive to undergraduates interested in doing research because fewer undergraduates ask to work with them. This may be particularly helpful for freshmen and sophomores who typically have taken less advanced science courses but are interested in getting involved in research.

A good place to find information about labs at Stony Brook and at other institutions is through looking at department web pages. When looking into labs at Stony Brook it is also helpful to check out the Undergraduate Research & Creative Arts (URECA) website. It contains information on labs looking for undergraduates interested in research, links to department websites and information on how to obtain funding.

Once you have identified a handful of faculty with whom you are interested in working, you should contact them via email. It is quite helpful to pick several labs of interest as opposed to one to keep your options open. Quite often professors will email you back promptly and ask for you to meet with them. Prior to meeting with a professor you should do some background work on their research and be able to talk about why you would be interested in working in such a lab. It is advisable to be specific. It is also helpful to have a copy of your transcript and an organized CV/ academic resume on hand. Also, if you have worked in a lab previously, some professors may ask for a reference from your former principal investigator, so it is helpful to obtain one before hand. If you are offered a position in a lab you should come to an agreement with the professor on how many hours you plan on working in the lab and discuss how you will get funded.

Organized Internships

Quite a few universities, medical centers, national laboratories, and industries have organized summer research internship programs. Such programs can be viewed as samplers. Summer research internships allow institutions to bring outstanding undergraduates to their institutions often with hopes of attracting the best back for

graduate school. Top institutions often use summer internships as a tool to recruit the very best students to come and intern.

The standard procedure for such programs requires filling out an application, obtaining letters of recommendation, and writing a personal statement. The format of the personal statement depends on program requirements. The majority of these outfits provide funding and housing. Many organized internships have weekly seminars that allow summer interns to become more aware of on going research at the institution. In addition, such programs open channels for networking by bringing together undergraduates from different institutions.

While the organized nature of such programs is quite beneficial, you have very little say over where you will conduct your research. The method of lab placement varies. Some programs give you a list of labs affiliated with the program and ask you to write a brief proposal on the type of research you would like to pursue if placed in a particular lab. Other programs ask you to write a proposal in addition to ranking the labs listed in order of interest. Nevertheless, there is no guarantee that you will be placed in any of the labs you list. This being the case, it is very likely that you maybe involved in research you did not have in mind.

Whether you decide to pursue an independently arranged research internship or you become part of an organized summer program, looking into summer programs at Stony Brook is a great idea. Doing summer research here gives you the ability to continue your summer project the following academic year. Also, it is often possible to obtain course credit that may count towards your major. Foremost, starting research over the summer on campus gives you the opportunity to get adjusted to the lab.

When beginning work in a lab there is often a steep learning curve; therefore, having time to get adjusted is beneficial to everyone involved. Subsequently, starting research during the school year may hinder the amount of time you spend in the lab. However, by beginning research in the summer, you are generally bound to fewer outside obligations and therefore you are able to truly immerse yourself in the lab. It is far more worthwhile to stay in one lab for an extended period of time than to work in several labs and in the end gain very little.

Ultimately, being involved in research will give you the ability to look at your field of study in a new way; it will allow you to build upon current interests and gain new ones. Most importantly, it will allow you to have a concrete idea of what you may want out of a graduate program by allowing you to be an active participant and discover if a future in research is the career path you wish to pursue.

Summer Undergraduate Research Programs

1. Cold Spring Harbor Undergraduate Research Program

Location: Cold Spring Harbor, NY. Watson School of Biological Sciences.
Program Dates: June 7 - August 15, 2009
Website: http://www.cshl.edu/URP/
Areas of Study: Cancer Biology, Neuroscience, Plant Biology, Cellular and Molecular Biology, Genetics, Macromolecular structure, Bioinformatics
Stipend: $5500

2. Gerstner-Sloan Kettering Summer Undergraduate Research Program

Location: Gerstner Sloan-Kettering Graduate School, New York City
Program Dates: June-August
Website: http://sloankettering.edu
Areas of Study: Developmental biology and genetics, cellular signaling, drug development, chemical biology and structural biology, computational biology.
Stipend: $3500

3. Amgen Scholars

Location: Multiple sites: MIT, Columbia, UCSF, Harvard, and others.
Program Dates: June-August
Website: http://amgenscholars.com
Areas of Study: Biomedical research
Stipend: Variable

Stony Brook Summer Programs

4. URECA

Program Dates: June-August
Website: http://www.sunysb.edu/ureca
Areas of Study: All departments
Contact: Karen Kernan (karen.kernan@stonybrook.edu)
Stipend: $3500

5. HHMI Undergraduate Research Fellowship

Program Dates: June-August
Website: http://www.stonybrook.edu/cesame/
Areas of Study: Biomedical research
Contact: Judy Nimmo (cesame@stonybrook.edu)
Stipend: $3500

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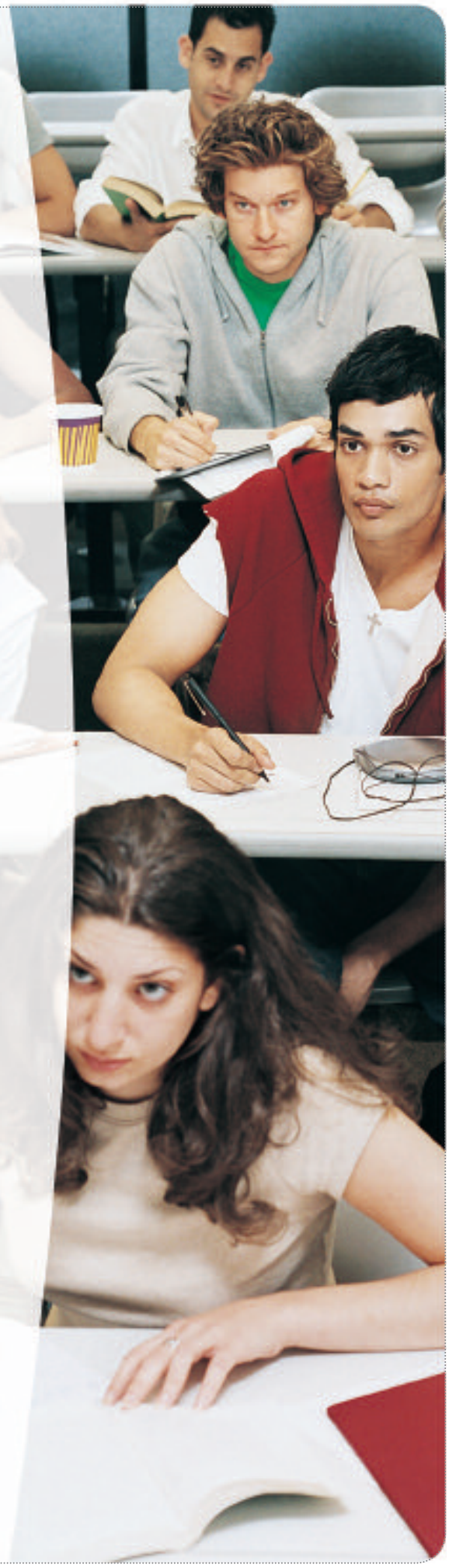

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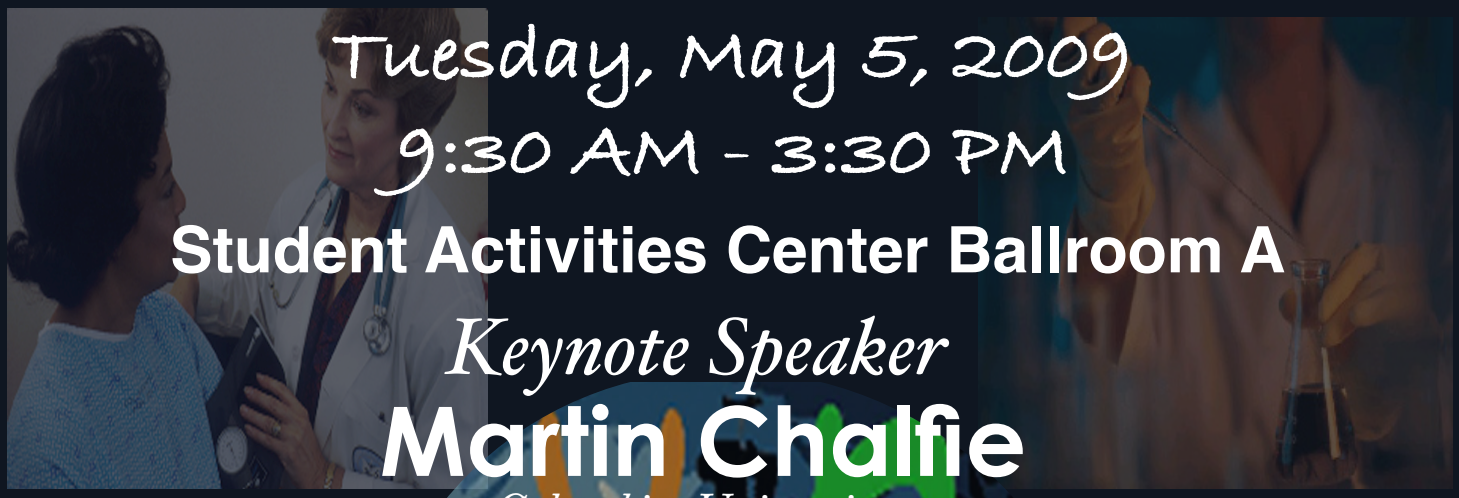

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