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THE NUCLEUS

February 2006 *Vol. LXXXIV, No. 6*

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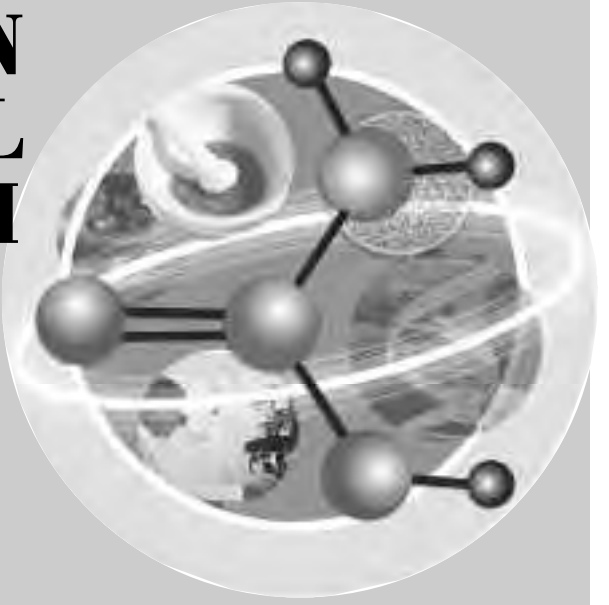
"Synthesis of Indole and Oxindole Derivatives of Glutathione as Potential Inhibitors of Glyoxylase II"

2006 EASTERN ANALYTICAL SYMPOSIUM

Call for Papers



November 13-16, 2006

Garden State Exhibit Center

Somerset, NJ

Deadline – April 15, 2006

Celebrating the Diversity of Science

The Eastern Analytical Symposium is the second largest meeting in the United States dedicated to the needs of analytical chemists and those in the allied sciences. Please help us to make the 2006 EAS the best ever–be a part of the program by contributing your own papers for inclusion in the oral or poster sessions.

We invite you to submit a contributed presentation for the 2006 EAS Technical Program. Please submit abstracts through our web site at www.eas.org, after March 1, and follow the instructions for preliminary abstract submission. **Invited speakers should not submit preliminary abstracts to EAS, although your session organizer may request one for his/her use.** All preliminary abstracts must be submitted electronically via the EAS web site at www.eas.org. The abstract submission deadline is April 15, 2006. Please visit our web site for a list of session topic areas.

Please carefully review the following information:

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2. The title of the presentation and the list of authors that you submit are final, and may not be changed.
3. The preliminary abstract that you submit will be considered to be your final abstract for use in the abstract book for the 2006 Eastern Analytical Symposium.
4. All preliminary abstracts will be acknowledged via e-mail.
5. Presenting authors of contributed submissions will be notified in June 2006 of the status of the abstract and its session assignment.

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Deadlines: *April Issue: February 10, 2006*
May Issue: March 17, 2006

THE NUCLEUS

The Nucleus is distributed to the members of the Northeastern Section of the American Chemical Society, to the secretaries of the Local Sections, and to editors of all local A.C.S. Section publications. Forms close for advertising on the 1st of the month of the preceding issue. Text must be received by the editor six weeks before the date of issue.

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Stephen Lippard

by Amy Kallmerten

In the study of chemistry, the research you do, the people you meet, the next generation you influence and the breakthroughs you make all have an impact on your life and career. Dr. Stephen Lippard, recent recipient of the National Medal of Science, said "If on a Friday night at 5pm you have your most creative idea, you need to be willing to stay that night or even that weekend to try out the idea in the labs." As an undergraduate chemistry major at Northeastern University in Boston, I was thrilled at the opportunity to talk with Dr. Lippard. I was even more impressed by what he had to say.

The first question I had for Dr Lippard was about his work. All students, regardless of major, wonder where they are going and which path their life will follow. What in his career and schooling led this man to his specific lines of research? I learned quickly that Dr. Lippard, like many of us, had different interests when he was young. He had fancied the idea of being a brain surgeon when he was a teenager. Starting out at Haverford College as a pre-med student, while working towards an English degree, he was required to take many chemistry classes. There, he says, wonderful professors, as well as the multitude of visitors through the Phillips Lecturer program, influenced him greatly. As a junior he toyed with the idea of medical school, graduate school in English, as well as the possibility of attending graduate school studying chemistry. Ultimately, he chose chemistry. His thesis while pursuing his PhD at the Massachusetts Institute of Technology was mostly pure inorganic chemistry, as opposed to the bioinorganic which would be his later focus. He said that when he began his independent career at Columbia University, his early interest in medicine inspired some of his first research themes. These early projects, including the attachment of heavy-atom labels to DNA, would eventually evolve to studies of the structural and mechanistic properties of platinum anticancer drugs. Overall, he believes, it is the people who influenced him who led him to be where he is today.

Upon learning how much the professors and visitors had influenced Dr. Lippard early on, I wondered next, in his opinion, how important was undergraduate research. He said to me, "I like to think of professors as professional students." He believes that you learn from everything: professors from students as well as students from professors. He has, in some cases, had high school students work in his laboratory. He said that regardless of where your chemistry degree takes you, to medical school, law school, synthetic chemistry or anywhere else, undergraduate research can be a very important experience on the path.

Next I asked Dr. Lippard a slightly more personal question. I wanted to know what advice he could of fer someone like me. In response to my question, he said that people often make key decisions based on interactions they didn't anticipate or predict. Not all decisions should be made from intellectual reasoning; some have to be made from gut feelings.

A great thing to hear is that, despite his breakthroughs and his fantastic awards, Dr. Lippard considers his students to be his most important contribution to science. He feels it is rewarding to see his students go on and themselves be rewarded for their hard work and it is gratifying to see them using skills and knowledge learned while working in his group and in his lab.

Talking with Dr. Stephen Lippard was incredibly rewarding. If I could summarize what I learned from him it would be this: interactions are the number one influence on someone's life. If it hadn't been for several influential people, Dr. Lippard might not be where he is today. Secondly, you can't always predict what is going to happen. Sometimes you need to trust your gut feeling and go with it. Lastly, it is equally important to be influenced, as it is to influence others. Thank you, Dr. Lippard! Your advice is sure to be something I'll never forget.

Amy Kallmerten is President of the Northeastern University Student Affiliates (NUSAACS). She is a Junior majoring in chemistry and is originally from Gilford, New Hampshire. ◇

Monthly Meeting

The 867th Meeting of the Northeastern Section of the American Chemical Society

Thursday – February 16, 2006

Harvard Faculty Club,
20 Quincy St., Cambridge, MA.

5:30 pm Social Hour

6:30 pm Dinner

8:00 pm Evening Meeting, Dr. Pam Mabrouk, Chair, presiding

Prof. Paula Hammond, Associate Professor, Department of Chemical Engineering, Massachusetts Institute of Technology.

Exploration of Macromolecular Self-assembly in Thin Films: from Electrochemistry to Drug Delivery

Dinner reservations should be made no later than noon, Thursday, February 9, 2006. Please call or fax Marilou Cashman at 800-872-2054 or e-mail at Mcash0953(at)aol.com. Please specify vegetarian. Reservations not cancelled at least 24 hours in advance must be paid. Members, $28; Non-members, $30; Retirees, $15; Students, $10.

THE PUBLIC IS INVITED

Anyone who needs special services or transportation, please call Marilou Cashman a few days in advance so that suitable arrangements can be made. Free parking in the Broadway St. Garage (3rd level or higher), enter from Cambridge Street via Felton, St.

Abstract

Exploration of Macromolecular Self-Assembly in Thin Films: from Electrochemistry to Drug Delivery

Our research and educational program emphasizes the use of molecular aspects in the study and development of new materials and processes. Its basis is the molecular design and synthesis of self-assembling polymeric systems, and the understanding and use of secondary interactions to guide their assembly at surfaces as well as in the bulk and solution state. The research scope encompasses polyelectrolyte multilayers for biomaerials, power, sensor, and display applications; dendritic block copolymer assemblies for drug delivery; and hierarchically ordered copolymers for mechanical and actuator applications. In this presentation the focus will be on molecular self-assembly in thin films.

The alternating adsorption of oppositely charged molecular species, known as the electrostatic layer-by-layer (LBL) process, is a simple and elegant method of constructing highly tailored ultrathin polymer and organic-inorganic composite thin films. We have utilized this method to develop a number of functional ultrathin film systems, including materials that can be tailored for display, sensor and protective coating applications. New approaches in our group have involved the incorporation of hydrophilic polyelectrolyte systems to create highly ionically conductive multilayer thin films. These systems have allowed the formation of a range of electrochemical devices using multilayer assembly, including the use of conjugated polymers and inorganic nanoparticles for electrochromic displays, the formation of thin films as proton exchange membranes in fuel cells, and the use of these multilayers in other power and micropower devices. New explorations have also included the use of some of these unique redox active nanoscale systems as systematically deconstructible polymers in multilayers with potential uses as an electrochemical means of drug delivery. We discuss the application of these functional thin films toward a number of device systems at the interfaces between electroresponsive systems, nanoscience and biology.◇

Biography

Professor Paula T. Hammond is the Mark Hyman, Jr. Career Development Chair Associate Professor in the Department of Chemical Engineering at the Massachusetts Institute of Technology. Paula Hammond earned her S.B. in Chemical Engineering from the Massachusetts Institute of Technology in 1984, her M.S. degree from Georgia Institute of Technology in 1988, and her Ph.D. in Chemical Engineering in 1993 from the Massachusetts Institute of Technology.

In 2000, Professor Hammond was awarded the Bose Junior Faculty Award at MIT. She has also received the National Science Foundation Career Award, the Environmental Protection Agency Early Career Award, the DuPont Young Faculty Award, and the 3M Innovation Fund Award. She is on the Advisory Board of the journals *Advanced Materials* and *Chemistry of Materials*. She was recently a 2003 Radcliffe Fellow at Harvard University. Dr. Hammond was one of a core group of founding faculty members involved in the planning and development of the Institute for Soldier Nanotechnologies (ISN) at MIT, a program funded by the US Army and directed toward new technologies involving nanostructured materials for the protection of the soldier. ◇

Theodora Whatmough Greene

by Frederick D. Greene

Theodora W. Greene, author of *Protective Groups in Organic Synthesis*, died on July 14, 2005.

Theo was born in Boston on November 19, 1931, the daughter of Professor and Mrs. Whatmough. She attended Bishop Strachan School in Toronto from 1942 to 1948, and received a BA degree from Radcliffe College in 1952. That fall she began graduate work at Harvard with Professor Louis F. Fieser, receiving the MA degree in 1953. In June, 1953 she married Frederick D. Greene. She stopped graduate work in 1954 to turn her full attention to a growing family.

In 1975, with the encouragement of her husband and Professor Leonard K. Nash (teacher of her first chemistry course at Harvard in the fall of 1948), she reapplied to Harvard and resumed graduate work, now with Professor E. J. Corey in his retrosynthetic analysis program for computer-assisted synthesis (LHASA). She received the Ph.D. on June 5, 1980 - her 27th wedding anniversary. In 1981 she published her work, Protective Groups in Organic Synthesis (John Wiley & Sons), a book that continues to be of great value to chemists involved in the construction of organic molecules. With Peter G. M. Wuts as co-author (suggested to her by Professor James A. Moore of the University of Delaware, a long-time friend of Theo and Fred), two further editions (1991 and 1999) and a Chinese edition (2004) were published. She was Assistant Editor with her husband (Editor) for the Journal of Organic Chemistry from 1960 to 1970, and she was Assistant Editor for the annual publication Organic Syntheses from 1980 -2002, working with Professor Jeremiah P. Freeman (University of Notre Dame) and the members of the Editorial Board of Organic Syntheses. From 1981 - 1995 she was Librarian at the Rowland Institute for Science (RIS), a research center founded in 1981 by Dr. Edwin H. Land before he retired from Polaroid Corporation. Her first task here was "to set up a science library from scratch."

In her personal life she was an active member in the First Congregational Church in Winchester, primarily with the choir and the handbells group - sources of great inspiration, pleasure, and friendship. After her retirement from RIS in 1995 she was a volunteer at the Winchester Hospital until 2002. All her life she enjoyed the outdoors - hiking, camping, nature. She was an avid reader (but rarely of fiction), and took up cross-stitching late in life.

She was devoted to her family, and is survived by her husband, four children, nine grandchildren, her brother, nieces and nephews. She died on July 14 - peacefully and surrounded by her family - after a long battle with cancer. During that time she continued to lead a serene and graceful life, albeit with decreasing energy. Her gentle spirit will always surround us. ◇

2006 Richards Medal

Awarded to Richard R. Schrock

Richard R. Schrock of the MIT Department of Chemistry has been selected by the committee as the recipient of the 2006 Theodore William Richards Award. The Richards Award dinner and award presentation has been tentatively scheduled for Thursday, March 9, 2006 at the Harvard Faculty Club. The dinner and award presentation will be followed by the Award Lecture in the Pfizer Lecture Hall in Mallinkrodt Laboratory.

C.E. Kolb ◇

Secondary School Chemistry Teacher Award

Request for Nominations for 2006

The New England Institute of Chemists (NEIC) is now seeking nominations for its annual **Secondary School Chemistry Teacher Award.** The award recognizes outstanding secondary school chemistry teachers in New England who have also fostered an interest in chemistry through outreach programs and extracurricular activities.

The candidate must be currently teaching chemistry in a secondary school in one of the six New England States. We are seeking teachers who have encouraged an interest in the field of chemistry through innovative and inspirational teaching, improved the image of chemists and chemistry, pro-

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Application of Genomics to Discovery and Development of Cancer Miracle Drugs

By Martin Freier

According to the American Cancer Society, 22.9 percent of all deaths in 2001 were attributed to cancer. Other than surgery, treatment for most cancers consists of toxic chemotherapeutic agents and/or radiation. A cure is achieved when the cancer cells in the affected body are destroyed by selectively interrupting their cellular processes relative to non-cancerous cells.

As a result of the successful treatment of chronic myeloid leukemia (CML), using the miracle drug Gleevec, scientists are modifying their drug discovery and development strategy to one that considers the patient's genes, without abandoning the more traditional arsenal of drugs.

The idea that genetics plays a major role in an individual's well-being has been with us for long time. However, Gleevec is the first drug that was designed to manipulate the proteins that are produced in response to malfunctioning genes by inhibiting the out-of-control tyrosine kinase enzymes in the body that typically play an important role in cell signaling events in growth and cell division.

The Gleevec development effort started in 1960. While examining certain blood cells of patients suffering CML, Medical Doctors Peter Nowell and David Hungerford at the University of Philadelphia discovered that one copy of a chromosome 22 (out of 23 chromosomes) was unusually short (1). It turned out that a whole chunk of DNA stored in that chromosome mysteriously disappeared. In 1973, Janet Rowley from the University of Chicago discovered that the missing chunk of DNA had been "translocated" to chromosome 9.

As for the principal cause of CML, it was attributed to the fusion of two broken DNA's in chromosomes 9 and 22, which led to the production of an abnormal Bcr-Abl protein (now known as one of the tyrosine kinases). The specific abnormal Bcr-Abl protein was sending out continuous messages throughout the cell that resulted in a massive increase in the number of white blood cells. In 1992 Dr. Druker reported that the Bcr-Abl protein caused the CML by interrupting the sequence of signaling events begun by growth factors outside the cell and permanently left that sequence switched on, a condition that led to rapid and unchecked cell division. This event was the first time that the product of a particular chromosomal defect had been conclusively identified as the cause of a specific form of leukemia (2).

Researchers Alex Matter and Nicholas Lydon at Ciba-Geigy (forerunner of Novartis) in Basel, Switzerland, used that information to develop inhibitors for the Bcr-Abl protein out-of-control behavior. Together with colleagues including Jürg Zimmermann (medicinal chemist) and Elisabeth Buchdunger (cell biologist), the group quickly identified phenylamino pyrimidines as potential kinase inhibitors.

In 1993, Lydon and Druker demonstrated that STI571 (one of the

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Martin Freier is a consultant specializing in technical management, technical strategies and training strategies. He holds a BS in Chemistry from Brooklyn College and an MS degree in Engineering and Management Science from Worcester Polytechnic Institute. He is a member of the ACS, Northeastern Section.

Miracle Drugs

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potential drug candidates) suppressed the proliferation of Bcr-Abl expressing cells in vitro and in vivo, without affecting normal cells. Because they realized that the patients would need to continue treatment over extended periods, they developed this drug in a more convenient pill form (patented as Gleevec) (3).

In May 2001, the US Food and Drug Administration (FDA) approved Gleevec (matinib mesylate) for CML therapy. European approval followed in November. The interim phase III drug trials were so successful that the Independent Data Monitoring Board recommended a change in the protocol that allowed patients on the standard therapy to switch to Gleevec if their current treatment was not effective. The first publication of the 12-month trial results showed that Gleevec was four times more effective at eliciting major cytogenetic responses than the standard therapy, with 75 per cent fewer patients progressing to end stage CML.8 (4).

At some point in the late 90's, some of the information from the Human Genome, which is a map of the human genes contained in Deoxyribonucleic Acid (DNA) as well as the sequence of its more than 3 billion base pairs, was being made available to the scientists around the world. As a result, genomics, which is the study of genes and their functions, became a credible scientific tool.

In 1990, the Whitehead Institute/MIT Center for Genome Research (WICGR) was founded, and it soon became an international leader in the field of genomics and a flagship of the Human Genome Project. As early as 1995, WICGR scientists recognized the need to bring the power of genomics to the understanding of human disease. WICGR launched pilot projects in genomic medicine and became an unofficial collaborative network among young scientists who pioneered new approaches to cancer and human genetics. In parallel in 1998, Harvard Medical School-based scientists established the Institute of Chemistry and Cell Biology (ICCB).

In May 2004, the Broad Institute was founded. It merged within it the former WICGR and ICCB, as well as many new people, projects and activities to apply the tools of the Human Genome. The Broad Institute's mission is to construct new powerful tools for genomic medicine, to make them accessible to the global scientific community, and to apply them to the understanding and treatment of disease.

Using the Human Genome, scientists who became knowledgeable in the sequencing of DNA and genes of various species have recently begun to show that some of the cancers are caused by genetic mistakes that direct the production of dysfunctional proteins. Because proteins carry out the instructions from the genes located on the DNA, dysfunctional proteins (such as the kinases) deliver the wrong message to the cells, making them cancerous. When these proteins are inhibited, the progression of the cancer is likewise inhibited.

For this article, I interviewed Dr. Matthew Meyerson, an assistant professor of Medical Oncology at the Dana Farber Cancer Institute (DFCI). DFCI is a founding member of the Dana-Farber/Harvard Cancer Center (DF/HCC), designated a comprehensive cancer center by the National Cancer Institute. Meyerson is also an Associate Member of the Broad Institute. He is involved in genomics and its application toward cancer drug discovery.

After graduating from Harvard University with an undergraduate science degree (chemistry/physics), Meyerson received his M.D. in 1993 and Ph.D. in 1994 from Harvard University. He was inspired to pursue research in biology and chemistry by the potential of the combination of both to facilitate new treatments for human disease. He did his residency in clinical pathology at Massachusetts General Hospital, obtained a research fellowship with Dr. Robert Weinberg at the Whitehead Institute (MIT), and joined DFCI in 1998. At that time Meyerson's colleagues and mentors were mapping the genomes of several different species at the WICGR (now the Broad Institute). As to why Dr. Meyerson chose to continue work with genomics and cancer at

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Miracle Drugs

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DFCI, he answered, "For me, the challenge is irresistible. And then there is always the possibility that I might be involved in the discovery of a Gleevec."

One of the more frustrating problems in cancer therapy is that patients' cancerous cells can mutate and develop resistance to virtually any drug and at any time. That means the ultimate success of the treatment is not assured, unless there is a way of monitoring the mutation status. While this kind of problem was not encountered in CML patients originally with the early form of the disease, later studies showed that all of a sudden mutations were in progress.

Dr. Mercedes E. Gorre and her colleagues evaluated nine cases of patients with advanced disease who had developed resistance to Gleevec. They found that in each case resistance was associated with reactivation of the causal oncogene (gene that controls cell growth). In some cases, the oncogene had mutated in such a way as to alter the enzyme's ability to bind to Gleevec. In other cases, the oncogene mutated to produce even higher levels of the kinase enzyme (5).

When I asked him how his research will help in dealing with such genetic mutations, Meyerson responded, "Gleevec is designed to deal with CML, a blood cancer. Our emphasis now is on genome-scale approaches that will help us discover chromosomal alterations and cancer-causing mutations in other types of cancer, such as solid tumors. We developed single-nucleotide polymorphism (SNP) arrays, helping us analyze loss-of heterozygosity (LOH) and copy number alterations in human cancer samples. We have since discovered multiple regions of LOH and copy number changes in human lung carcinomas. And that is a good beginning."

One reason for having two copies of each chromosome is so that they can back each other up. If one is mutated (making it not function properly), often the other one can compensate. Even though we have two of each chromosome, they are not identical sequences because mom and dad are not identical (like clones). Having two variants of the same gene is called heterozygosity. Loss of heterozygosity is a type of mutation that happens when one chromosome is lost, leaving us with only one working chromosome. If this single remaining copy becomes mutated, we no longer have a backup that is working properly. That kind of problem is catastrophic.

Changes in copy number occur when a chromosome—or even a part of a chromosome, like a gene—is deleted or amplified. For example, Down syndrome occurs when a person has an extra copy of chromosome 21, a condition called trisomy 21.

Identifying the handful of genes that are mutated, missing, or of which there are too many copies requires scientists to sift through something in the order of 3.1 billion molecules that make up our genome. This appears be a daunting task. But the search methods called chromosome copy number analysis and loss of heterozygosity analysis are generating promising new results rather quickly.

"Our next step is to characterize the genes in these potential target regions in detail to understand their role and whether they are cancer-causing or cancer-preventing genes," added Meyerson. But this is just one of many techniques that Meyerson's laboratory has pursued with success in collaboration with Sellers' Laboratory, headed by Associate Professor at DFCI William R. Sellers, now global head of oncology research at Novartis

This laboratory was also involved in re-sequencing the human genome to identify oncogenic mutations in cancer, with an initial focus on protein kinases. Another success story was the discovery of oncogenic mutations in the BRAF serine-threonine kinase and frequent mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase in human lung adenocarcinomas.

The results are a clear indication that, like blood cancers, solid cancers could also be treated with kinase inhibitors. The implication for lung cancer treatment is that patients with EGFR mutations could probably be treated with EGFR inhibitors such as

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Summer Research Scholar

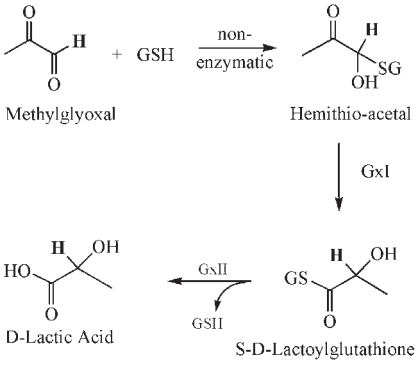
Synthesis of Indole and Oxindole Derivatives of Glutathione as Potential Inhibitors of Glyoxalase II

Alison N. Erbeck and Edward J. Brush, Department of Chemical Sciences, Bridgewater State College

Introduction

The glyoxalase system is found in the cytosol of all living organisms, where it plays a major role in cell growth and the detoxification of methylglyoxal, a cytotoxic metabolite of oxidative metabolism[1]. The system consists of two enzymes: Glyoxalase I (GxI) and Glyoxalase II (GxII). They convert methylglyoxal into lactic acid, using glutathione (GSH) as a co-substrate, Figure 1.

Figure 1



These enzymes are proposed to be involved in a variety of diseases, including cancer, diabetes, and Alzheimers, and are considered to be relevant therapeutic targets. Our hypothesis is that inhibition of GxII can kill cancer cells through a buildup of toxic metabolites and depletion of GSH. First, GxII inhibition will result in a build up of the product from the GxI reaction, S-lactoylglutathione (SLG), which is toxic to cells[2]. Second, inhibition of GxII prevents the release of glutathione from SLG, depleting its concentration for critical cellular processes. Furthermore, if glutathione is no longer available, the GxI reaction will stop and toxic methylglyoxal will build up and kill the cell.

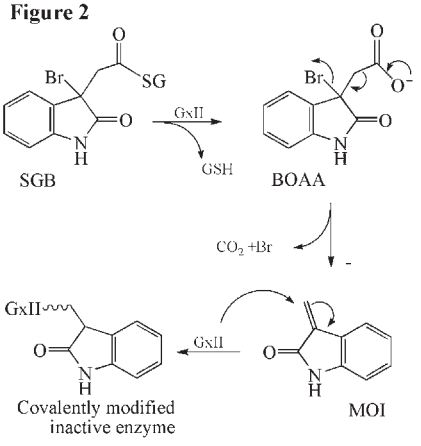
Several competitive GxII inhibitors have been studied as potential anti-tumor agents, but have limited therapeutic value[3]. These compounds have common structural features that include a small, non-polar aromatic molecule that is typically conjugated with glutathione. My work has focused on the synthesis of unique indole and oxindole conjugates of glutathione as potential reversible or irreversible inhibitors of GxII. Our design of these compounds is based on our success in designing similar inhibitors of GxI. The glutathione conjugates in this study include: S-glutathionyl-3-methyleneoxindole (GSMOI, Figure 5), S-glutathionyl-3-indole acetic acid (SGI, Figure 7), and S-glutathionyl-3-bromooxindole acetate (SGB, Figure 8).

S-glutathionyl-3-bromooxindole acetate (SGB) is unique when compared to known competitive GxII inhibitors, because SGB is a potential mechanism-based irreversible inhibitor of the enzyme. We propose that GxII may activate SGB through hydrolysis of the GSH-ester producing 3-bromooxindole-3-acetic acid (BOAA). Under physiological conditions BOAA will undergo spontaneous decarboxylation with bromide elimination producing the potent alkylating agent MOI[4]. We propose that MOI will covalently bond to the enzyme's active site through Michael addition of a nucleophilic residue, irreversibly inactivating the enzyme, Figure 2.

Synthesis of Potential Glyoxalase II Inhibitors.

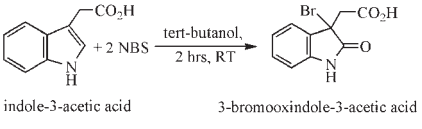
I. 3-Bromooxindole-3-acetic acid (BOAA, Figure 3). BOAA is a key synthetic intermediate for preparation of the proposed inhibitors, and was synthesized by bromination of indole-3-acetic acid with two equivalents of N-bromosuccinimide (NBS) in tert-butanol[5]. BOAA was obtained in 60% yield following recrystallization from toluene/ethylacetate, with a melting

Figure 2



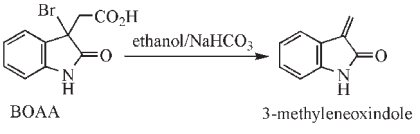
point of 154°C (lit. 152-153°C). H^1 NMR confirmed that the product was BOAA as indicated by the classic pair of doublets at 3.5 ppm for the diastereotopic methylene protons.

Figure 3



II. 3-Methyleneoxindole (MOI, Figure 4). MOI was prepared by modification of a literature procedure[6] in greater than 90% yield by the base-mediated decarboxylation of BOAA with elimination of bromide. The bright yellow solid has a melting point of 227-240°C(d) (lit. 218-232°C). The non-equivalent vinyl protons were observed as singlets at 6.2 ppm.

Figure 4



III. S-glutathionyl-3-methyleneoxindole (GSMOI, Figure 5). GSMOI was prepared by Michael addition of glutathione to 3-methyleneoxindole in

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Summer Scholar

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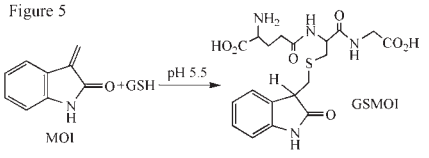
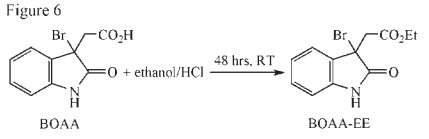
50% methanol/water, pH 5.5. Following extraction of unreacted MOI with ether and lyophilization, GSMOI was obtained in 85% yield as a white powder. The H^1 NMR spectrum is complex due to the presence of diastereomers, with the α-proton of the cysteine residue at 4.1-4.4 ppm (coupled to the adjacent diastereotopic methylene protons). The broad signal for the acidic C-3 oxindole proton at 3.8 ppm slowly disappears as it exchanges with the D_2O solvent.

Figure 5



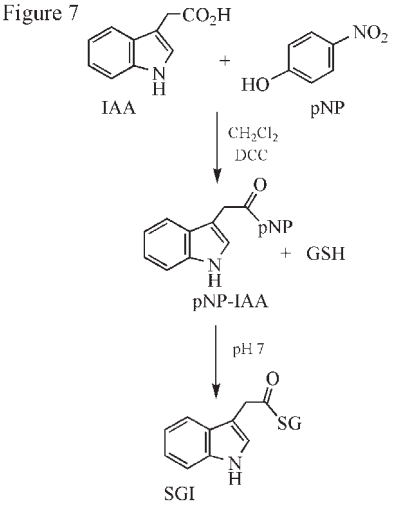
IV. Ethyl-3-bromooxindole acetate (BOAA-EE, Figure 6). BOAA-EE was prepared by acid-catalyzed esterification of BOAA in 2M ethanolic HCl, stirring for two days at room temperature, and monitoring the reaction progress by TLC (ethylacetate:acetic acid, 95:5). The solvent was removed on a rotavap, the yellow residue suspended in ethylacetate and extracted with 10% sodium bicarbonate, the ethylacetate solution dried with $MgSO_4$, and purified by flash chromatography on a Redisep silica column. BOAA-EE was obtained as a low-melting yellow solid in 34% yield. Analysis of the product by H^1 NMR was consistent with the structure of the ethyl ester of BOAA, with characteristic splitting patterns for the diasteriotopic methylene protons of BOAA (3.5 ppm) and the ethyl ester functional group (4 ppm), easily observed.

Figure 6



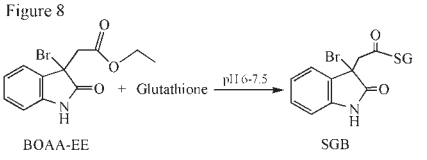
V. S-Glutathionyl-indole-3-acetate (SGI, Figure 7). Our attempted preparation of SGI involved ester exchange between glutathione and the para-nitrophenyl ester of indole acetic acid (pNP-IAA). pNP-IAA was prepared by DCC-mediated condensation of IAA and p-nitrophenol in methylene chloride[7]. Attempted ester exchange between glutathione and pNP-IAA was done in 25% methanol/water, pH 7. The reaction mixture was stirred overnight, centrifuged to remove precipitated p-nitrophenol, concentrated, and filtered to remove additional precipitate. Following lyophilization, the yellow powder was washed with ether, and dried under argon to give crude SGI. The H^1 NMR spectrum of the crude product was generally consistent with that of glutathione-indole conjugates, although contaminating free glutathione was also observed. Although not pure, this sample was used for preliminary inhibition assays.

Figure 7



VI. S-Glutathionyl-3-bromooxindole-3-acetate (SGB, Figure 8). The attempted synthesis of SGB involved ester exchange of glutathione with ethyl-3-bromooxindole acetate (BOAA-EE, Figure 6). This was done in 25% methanol/water, pH 6-7.5, and the reaction progress monitored by reverse-phase HPLC and UV-Vis spectroscopy where a new absorbance band at 250 nm formed, consistent with glutathione thioesters. The aqueous reaction mixture was lyophilized to give a hygroscopic powder of crude SGB. Analysis by H^1 NMR indicated the presence of conjugated and free glutathione, and a complex signal for the diasteriotopic methylene protons of BOAA at 3.5 ppm. This sample was used, without further purification, for preliminary inhibition assays.

Figure 8



Evaluation of indoles and oxindoles as potential inhibitors of Glyoxalase II. Preliminary kinetic assays of the synthetic compounds as potential inhibitors of glyoxalase II (Sigma) were conducted in 100 mM MOPS buffer (pH 7.2), containing 0.9 mM S-D-lactoylglutathione, and appropriate concentration of inhibitor in DMSO. Assays were conducted spectrophotometrically at 25°C, monitoring the hydrolysis of lactoylglutathione either directly at 240 nm, or coupled to the formation of free glutathione using 0.2 mM 5,5'-dithiobis(2-nitrobenzoate) (DTNB) at 412 nm. These preliminary results are presented in Table 1.

Table 1. Preliminary Evaluation of Glyoxalase II Inhibitors

Compound	Concentration	% inhibition
DMSO (control)	1 mM	0%
GSH (control)	1 mM	34%
IAA (control)	1 mM	19%
MOI	1 mM	58%
GSMOI	0.5 mM	15%
BOAA-EE	1 mM	92%
SGI	0.1 mM	31%
SGB	0.1 mM	7%

These preliminary data are promising as all potential inhibitors are at least weak inhibitors of glyoxalase II at the concentrations tested. The strong inhibition by BOAA-EE is interesting, possibly suggesting that GxII is catalyzing hydrolysis of the ester to BOAA, which subsequently forms the potent alkylating agent, MOI, Figure 2. Consistent with this idea is the strong inhibition also observed with 1 mM MOI. Weaker inhibition was observed by both SGI and SGB, due to the low concentrations necessary in the spec-

Continued on page 12

October 2005 Meeting

Pictures Courtesy of Ms. Ying Wei

Charles E. Kolb receiving the Henry Hill Award from Michael Strem

Jin Li and Medicinal Chemistry Chair, Liming Shao.

Mrs. Henry Hill and Anthony Cromwell Hill

50-Year Member, Louis Hantman

NESACS Chair Amy Tapper with 50-Year Member Joseph P. Flannery and Mrs. Flannery

50-Year Member, Wallace Gleekman

Summer Scholar

Continued from page 11

trophotometric assays and the low purity of each compound. Complete characterization of these compounds is not possible at this time due to their high absorbance at 240 nm and chemical interference with the DTNB assay at 412 nm. An alternative HPLC assay is being developed.

Conclusion

We have synthesized a series of novel indole and oxindole derivatives, and present preliminary evidence that these compounds are inhibitors of the anti-cancer target enzyme, glyoxalase II. Continuing studies will focus on the complete purification and characterization of S-glutathionyl-indole-3-acetate (SGI, Figure 7), and S-glutathionyl-3-bromooxindole-3-acetate (SGB, Figure 8). We are also developing an alternative assay for glyoxalase II using reverse phase HPLC. This will allow us to completely characterize all inhibitors synthesized in this study through their K_I and k_{inact} kinetic constants.

Acknowledgements

This research was supported by a James Flack Norris/Theodore William Richards Summer Research Scholarship, and the Bridgewater State College Adrian Tinsley Program for Undergraduate Research.

Literature Cited

1. Ayoub, F., Zaman, M., Thornalley, P., and Masters, J. (1993) *AntiCancer Res.* 13, 151-156.
2. Burg, D. and Mulder, G.J. (2002) *Drug Metab. Rev.* 34, 821-863.
3. Zang, T.M., Hollman, D.A., Crawford, P.A., Crowder, M.W., and Makaroff, C.A. (2001) *J. Biol. Chem.* 276, 4788-4795.
4. Petrounia, I.P., Goldberg, J., and Brush, E.J. (1994) *Biochemistry* 33, 2891-2899.
5. Hinman, R.L. and Bauman, C.P. (1964) *J. Org. Chem.* 29, 1206-1215.
6. Hinman, R.L. and Bauman, C.P. (1964) *J. Org. Chem.* 29, 2431-2437.
7. Pfeiffer, M.J. and Hanna, S.B. (1993) *J. Org. Chem.* 58, 735-740. ◇

Miracle Drugs

Continued from page 9

Iressa™ (gefitinib) or Tarceva™ (erlotinib) as part of the treatment, if the patients respond to such treatment or if there is evidence of cancer-causing mutations at any point during the more traditional treatment. Such treatment should especially be considered where the patient cannot tolerate other debilitating forms of treatment.

Why is there such an emphasis of some of the research on the protein tyrosine kinases (PTKs)?

PTKs are involved in cellular signaling pathways and in regulating key cell functions such as proliferation, differentiation, anti-apoptotic signaling and neurite outgrowth. Unregulated activation of these enzymes, through mechanisms such as point mutations or over-expression, could produce cancer.

The Meyerson laboratory's work has already gained attention in the biotech and pharma scientific community. He and other genomics scientists believe that genome-wide screening methods should be used as powerful tools for discovering cancer-causing mutations prior to prescribing treatment as well as during clinical trials of new drugs. Once mutations have been found, this is a good time to try more aggressive genomics-based methods in the development of good alternative drugs for treating cancers, especially where no other drugs currently exist.

As for the future of chemists in genomics, Meyerson commented: "The role of the chemist today is just as important as ever. No matter what we do in the laboratory, our ultimate goal is to develop drugs. Without chemists, drugs just do not happen. organic chemists, biochemists, and analytical chemists play their usual roles. On the other hand, since genomics and proteomics are likely to play a major role in drug development, I would say that nowadays chemists must have a solid education in all sciences, in particular, biology."

References:

1. P. C. Nowell and D. A. Hungerford, Science, 1960, 132, 164.
2. N. B. L ydon et al, Oncogene Research., 1990, 5, 161
3. B. J. Druker and N. B. Lydon, J. Clinical Invest., 2000, 105, 3.
4. B. Druker, The American Society of Clinical Oncology Meeting, Florida 2002
5. M. E. Gorre, M. Mohammed, K. Ellwood, N. Hsu, R. Paquette, P. N. Rao, C. L. Sawyers, Science, 2001, 293, 5531, 876-880. ◇

Teacher Award

Continued from page 6

moted extracurricular activities relevant to chemistry, and offered opportunities to students who might otherwise miss the "chemistry" experience.

The awardee will receive a plaque and be honored at the annual NEIC Awards Dinner, which will be held this year at Boston College on Thursday, April 27, 2006. At the dinner the NEIC also presents the American Institute of Chemists Foundation Student Award to outstanding college seniors and graduate students at the departments of chemistry, chemical engineering, and biochemistry from New England colleges and universities.

To facilitate the nomination process, the nominator need only mail or fax a letter containing a paragraph describing why the candidate is deserving of the award and include the candidate's mailing address and telephone number. The NEIC will contact the candidate directly to obtain supporting bibliographic information. The NEIC State Council and its committee chairmen will select the awardee. Nominations are requested by **March 15, 2006.** The NEIC may, at its discretion, select one awardee from each New England state. The NEIC has limited funds available to offset out-of-pocket travel expenses to attend the dinner if the awardee is from outside the Boston area. Nominations should be mailed to Timothy L. Rose, Secretary NEIC, 97 Bartlett Hill Road, Concord, MA 01742-1801, faxed to (978) 369-9575, or sent by e-mail to teerose(at)worldnet.att.net. ◇

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Feb 1 and 2

Prof. Jonathan Ellman (Univ. of Calif., Berkeley)
George Buchi Lectures in Organic Chemistry
MIT, room 6-120, 4:00 pm

Feb 6

Dr. Russell Hemley (Carnegie Institute of Washington)
Physical Chemistry Seminar Series
MIT, room 56-114, 4:30 pm

Feb 7

Prof. Michael Krische (Univ. of Texas, Austin)
"Hydrogen-Mediated Carbon-Carbon Bond Formation: Discovery and Development"
Novartis Lecture Series, Part 3
Boston College, Merkert 130, 4:00 pm,

Feb 9

Prof. Sunney Xie (Harvard Univ.)
"Holding Single Molecules up to the Light: From in Vitro to in Vivo Studies"
Boston College, Merkert 130, 4:00 pm

Feb 10

Prof. Ron Weiss (Univ. of Princeton)
"Engineering Collaborative Behavior for Synthetic Multicellular Systems"
Brandeis Univ., Gerstenzang 122, 3:45 pm

Feb 13

Prof. Stephen L. Buchwald (MIT)
"Progress in Metal-Catalyzed C-C and C-Heteroatom Bond-Forming Reactions"
Brandeis Univ., Gerstenzang 122, 3:45 pm

Feb 14

Prof. Ana de Bettencourt-Dias (Syracuse Univ.)
Univ. New Hampshire, Room L103, 11:10 am

Feb. 21

Prof. Frank McDonald (Emory Univ.)
"Chemical Synthesis of Bioactive Natural Products: Methodology, Development, and Applications"
Univ. New Hampshire, Room L103, 11:10 am

Feb 22

Prof. Ken Caulton (Indiana Univ.)
Harvard/MIT Inorganic Chemistry Seminar Series
MIT, room 6-120, 4:00pm

Feb 28

Prof. Steven Rokita (Univ. of Maryland)
"Predicting and Controlling Selective Alkylation of DNA"
Boston College, Merkert 130, 4:00 pm,

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