2004 Cottrell Scholar Award: Seth M. Cohen, Department of Chemistry and Biochemistry, University of California, San Diego: *A Bioinorganic Approach to Designing Improved Matrix Metalloproteinase Inhibitors*

Statement of Problem and Significance. An important goal in chemical education is attracting students to pursue chemistry as an undergraduate major and a career.[1] At large institutions such as U.C. San Diego, where introductory chemistry classes typically enroll more than 300 students per section, it can be challenging to transform the 'routine' chemistry curriculum into an exciting educational and potentially career-directing experience. It is often difficult to convey the importance of chemistry and chemical principles to 'everyday' experiences, which may help to attract young scientists to the field. However, recent developments in popular culture and broadcast television have shown that chemistry, placed in an appropriate context, can be extremely intriguing to a broad audience, while maintaining the integrity and quality of the science. Specifically, the use of forensic science as a means to introduce chemical concepts, methodologies, and the experimental process is proposed to increase interest and enthusiasm for the pursuit of chemical careers early in the undergraduate curricula. As will be discussed below, preliminary results with this approach have been extremely encouraging and the proposed program seeks to expand on these successes. It is anticipated that the development of an undergraduate course in forensic chemistry will aid in increasing the interest and enrollment of students in chemistry and biochemistry majors, as well as help direct students into socially conscious chemical careers through the establishment of summer internships at local crime laboratories.

Plan of Procedure. In order to attract students to the chemistry major early in their career, a new class entitled "Chemistry of the Crime Scene" will be offered during the Fall quarter of 2004 (approximately late September to mid December) for undergraduate students of sophomore level standing or higher. Limiting enrollment to upperclass students will target undergraduates that have not yet declared a major (~40% of undergraduate students at U.C. San Diego are 'undeclared' by the end of their sophomore year), but will ensure that the students have some basic chemistry background to undertake the subject material (general freshman chemistry will be required as a prerequisite). In addition, by having exposure to introductory chemistry courses, the utility of the seemingly 'generic' subjects of general chemistry will be revealed in the 'real world.'[2-4]

As a testing ground for the aforementioned course, I taught a class in the Winter quarter of 2003 entitled "Crime Scene Investigation: Fact and Fiction." The class was offered as a one-unit course as part of a new freshman seminar program at U.C. San Diego. The class involved ten one-hour lectures on various topics in forensic science including drug analysis, explosives and firearms, ballistics, fingerprinting, and DNA analysis. Class lectures were based on a popular forensic text[5] and augmented with demonstrations of various chemical analyses (e.g. color tests for illegal drugs). A guest lecturer from a local crime laboratory also participated in the course, giving seminars in her area of expertise. The final examination for the class was performed in two parts. The first part involved a critical analysis of a crime novel by popular forensic author Patricia Cornwell.[6] The second part of the final was a screening of an episode of the popular television program "CSI: Crime Scene Investigation."

Although this freshman seminar was only a simplified version of the proposed teaching plan, the course illustrates several instructive points. First, the class was extremely popular; of the more than 100 freshman seminars offered, "Crime Scene Investigation: Fact and Fiction" was among the first three to attain full enrollment (indeed, several students, including upperclassmen, had to

be turned away). Secondly, a variety of chemical principles including chemical structure and synthesis, chemical reactivity, and analytical instrumentation techniques were successfully introduced and played a central role in the class curriculum. Third, students in the course developed the ability to think critically about chemical analysis. During the viewing of "CSI: Crime Scene Investigation" students successfully pointed out consistencies as well as inaccuracies in the scientific process and chemical methodsto a simulated experimental scenario. Finally, the course succeeded in the ultimate goal of encouraging enrollment in the chemistry major, with a number of students commenting on an interest in majoring in chemistry and pursuing careers as forensic chemists.

The new class to be developed, "Chemistry of the Crime Scene," will be a full three-unit elective in the chemistry major (target enrollment 50-75 students). The course will utilize a popular forensic textbook entitled 'Criminalistics'[4] and this broad-based text will be augmented by case study texts[6] and more detailed chemical discussions presented in the form of class handouts. These handouts will be prepared from the large number of educational resources readily available in the chemical literature for demonstrating forensic methods.[7-9] Also, a host of online resources are available through the websites associated with dramatic programming such as "CSI: Crime Scene Investigation", as well as other 'nonfiction' programs that are focused on the forensic sciences such as the Discovery Channel's "The New Detectives" and "The FBI Files."[10] Additional online[11] and printed resources[12] are available from major government agencies such as the Federal Bureau of Investigations (FBI) that provide information on their forensic operations.

The course syllabus will involve a comprehensive overview of the forensic sciences: Subjects will include (corresponding chapters in text[4] and chemical concepts are also listed):

1. Crime scene processing – chapters 1-2
2. Organic analysis – chapter 5 – chromatography, spectroscopy, mass spectrometry
3. Inorganic analysis – chapter 6 – atomic emission, X-ray diffraction
4. Trace evidence – chapter 8 – transmission spectroscopy, gas chromatography
5. Drug analysis – chapter 9 – infrared spectroscopy, capillary electrophoresis
6. Explosives and arson – chapter 11 – gas chromatography, chemical reactivity
7. DNA and serology – chapters 12-13 – restriction analysis, antigenic bioassay
8. Fingerprint analysis – chapter 14 – chemical reactivity

Despite the broad range of topics, nearly all of these lectures will involve understanding chemical concepts (as listed above), such as chemical tests, spectroscopic methods (IR), chromatography and mass spectrometry (GC-MS),[9] polymerase chain reaction (PCR), and antibody-antigen interactions. While at this time no laboratory component to the class is proposed, lectures will be enhanced by the use of demonstrations, for which this topic is very conducive. Demonstrations on the use of drug color tests, chemical lifting of latent fingerprints,[7] and instrumental analysis of toxins[8,13] can all be safely and vividly illustrated in front of the lecture hall. To develop a more rigorous course than the freshman seminar already devised, the class will be tested through problem sets and written examinations. However, to ensure that a sense of chemical understanding is being cultivated, exams will include 'case study' questions. Again, forensic science is particularly suited for case study questions that require an understanding of fundamental chemical principles, analytical reasoning, and examination of chemical evidence to successfully solve. A final project involving groups of students analyzing 'evidence' to solve a crime will be part of the course requirements. This project will culminate in a final report and oral presentation to exhibit the case findings; this will serve as a means to develop communication skills, both written and public speaking, that are an essential tool for all

scientists.[14] Finally, a critique of an episode of the television program "CSI: Crime Scene Investigation" will be retained for one lecture to maintain enthusiasm for the subject material and to further develop the critical thinking skills of the class in an engaging setting.

The course structure as outlined above should provide for a comprehensive introduction to the field of forensic chemistry and the broadly applicable chemical principles that underline this important field of study. To further enhance the value of the program, other features of the course will be designed to encourage participation in undergraduate research. Research at the undergraduate level is a critical experience that I strongly support (vide infra) and can be a tremendous device for fostering careers in chemistry. To provide exposure to a real laboratory experience, visits to local crime labs will be arranged. The San Diego Police Department and San Diego County Sheriffs' Department both maintain forensic laboratories within 20 miles of the U.C. San Diego campus. In addition, the Southwest Laboratory of the Drug Enforcement Administration (DEA) is located just 30 miles north of U.C. San Diego. The DEA laboratory has recently built an expansive, modern facility (opened in February 2003) that serves the forensic needs for all analytical operations in the southwest United States, Hawaii, Guam, and American Samoa These resources offer a tremendous opportunity for students to share in the excitement of a chemical career and to interact directly with active professionals in the field. If visits to local forensic laboratories prove complicated due to large class sizes, then practicing forensic chemists will be scheduled to visit the class.

A key component for promoting undergraduate research will be the re-establishment of a summer internship program with the Southwest DEA laboratory and U.C. San Diego. The chemistry department at U.C. San Diego has previously maintained a co-op program that routinely sent students to the DEA for research experience. The program is presently inactive, but in direct conversations with the director of the DEA Southwest Laboratory there is strong interest to revive the program.[15] With this relationship in place, students in "Chemistry of the Crime Scene" will be afforded a unique opportunity to apply to a rejuvenated internship program. Students will be informed of the internship at the beginning of the course and academic performance in the class will be one of several criteria by which applicants to the program will be selected. By holding the class in the Fall quarter, sufficient time will be available for a background screening to be performed on selected candidates (required for all DEA employees). Ultimately, the DEA internship will be an exceptional mechanism for students to begin a career in chemistry and it is anticipated that similar programs will be developed with other crime laboratories in the San Diego area.

Teaching Background and Activities. I have a strong commitment to student learning and during the last two years at U.C. San Diego, I have developed three new courses that enhance the curricula at both the graduate and undergraduate level. I have taught a new class in bioinorganic chemistry that is a combined course for both advanced undergraduate and graduate students (Chemistry 124/225). A similar course had been offered intermittently at U.C. San Diego, but as two separate courses and only on a semi-regular basis. The course material was completely redesigned with extensive lecture notes devised. A concerted effort was made to keep the class extremely topical by integrating reading of the primary literature (some articles were less than one month old) and a final examination where students presented a recent paper from the literature to the entire class. The bioinorganic course has been extremely well received by students at both the undergraduate and graduate level and will be renewed for a third consecutive year in Spring of 2004. The second course I have taught at U.C. San Diego is a graduate course entitled "Supramolecular Coordination Chemistry". This class was designed to replace a generalized advanced inorganic course and therefore covered a broad range of subjects from fundamental coordination chemistry and ligand field theory, to supramolecular-self assembly and

quantum dots. Although listed as a graduate course (Chemistry 229), several undergraduates were also enrolled in the class and in the Winter of 2004 the course will be offered as a combined advanced undergraduate elective as well as a graduate course (analogous to the bioinorganic course described above). In addition to these classes, I have also taught a one-unit freshman seminar entitled "Crime Scene Investigation: Fact and Fiction" (Chemistry 87) that served as a test case for the proposed curriculum development and is described in detail above.

As a dedicated advocate of undergraduate research, I try to prepare students for their future beyond the bachelor's degree, regardless of their career goals. I believe working in the laboratory provides an environment to nurture professional and personal skills such as chemical experimentation, critical thinking, personal responsibility, and teamwork. The first undergraduate student I sponsored, [***], was part of the UCSD Faculty Mentor Program (FMP), which pairs up students with faculty in order to perform laboratory research on an independent project. [***] later completed an internship at Pfizer and will start pharmacy school this fall at the University of Southern California. Last summer (June – August 2002) three undergraduate students joined our group. Two undergraduate students, ([***]), were supported by the Minority Access to Science, Engineering, and Math fund as part of the UCSD Summer Training Academy for Research in the Sciences (STARS). The third undergraduate, [***], was supported by a Howard Hughes Undergraduate Fellowship. Many of the students will be co-authors on peer-reviewed publications. In addition to mentoring these students, I have also volunteered as a moderator for symposia associated with the FMP and STARS programs, where students from across the University of California system present the results of their internships. Ba Tran, a medicinal chemistry major at U.C. San Diego, recently joined our group (July 2003); he will be working on the project described in the Research Proposal section of this application. This summer, Prof. [***] has joined our laboratory as part of a sabbatical leave. [***] is a talented organic chemist that will fulfill the role of both mentor and scientific resource to the graduate and undergraduate students in the laboratory.

Note: [***] denotes names/information deleted.