Chapter 4

INTO THE FUTURE

In 1981, the College of Pharmacy moved into what was then called simply Unit F. The building is now known as Weaver-Densford Hall, in part to honor the deans who were the driving force in getting it built. But instead of this milestone marking the onset of a period of stability and manageable development, the 1980s would, like the preceding decade, be a time of transition and turmoil, not just for the department but for the University as a whole.

One of the sources of that turmoil was financial. The same year the College moved into its new facilities, the American economy took a nosedive into the worst recession to hit the country since the end of World War II.

Accompanying the recession was the inauguration of President Ronald Reagan and the rapid ascent of a new—or even radically different—conception of the proper relationship between the private and public sectors. President Reagan was a champion of a specific form of free market capitalism and shared that philosophy with Margaret Thatcher, who was elected Prime Minister in the United Kingdom at about the same time: the belief that anything government can do, private enterprise can do better. This led, not surprisingly, to a nationwide emphasis on privatization—the shifting of responsibility to private entities not only for implementing the tasks previously assigned to the public sector but for funding those tasks as well.

In higher education, that shift meant steep reductions in federal support, followed in time by reductions in state funding. In short order, a combination of a shrinking tax base caused by the recession and sharp increases in military spending led to mushrooming federal deficits that made the impulse to reduce funding from Washington even more urgent. In the five years ending in 1983, state funding for the University dropped almost 20 percent while federal funding shrank by an alarming 56.7 percent during the same period.

These cutbacks led to mandatory budget reductions throughout the University,

including the College of Pharmacy, which had to find ways to reduce expenditures (Anderson & Pennigton, 2005, 153-4).

The cuts led to suggestions by Dean Lawrence Weaver to merge the Department of Medicinal Chemistry with Pharmacognosy, folding the smaller program into the larger medicinal chemistry program—a suggestion that ultimately was carried out, though only several years later. Less predictably, the belt-tightening also led to a reversal of the previous decade's most radical innovation: de-departmentalization of the College.

De-departmentalization had never sat well with faculty, particularly for the faculty in medicinal chemistry with its long history of strong departmental identity and autonomy.

The return to a department structure had been broached in faculty meetings with the dean as early as 1981. Although efforts by several faculty groups to convince Dean Weaver about the need for departmentalization were not well received, he eventually appointed a committee that year, with Mahmoud Abdel-Monem as chairperson and Yusuf Abul-Hajj representing the medicinal chemistry/pharmacognosy faculty. The committee addressed the issues of reorganization and the reestablishment of academic departments and submitted its recommendation to Weaver late in 1982. In March 1983, he announced plans to reinstate departments, in order to better achieve targeted cuts and assign clear lines of accountability for cost-containment and spending. By the following fall, the College had four formal units: pharamceutics; pharmacy practice; social, administrative, and hospital pharmacy; and medicinal chemistry and pharmacognosy, headed by Abdel-Monem.

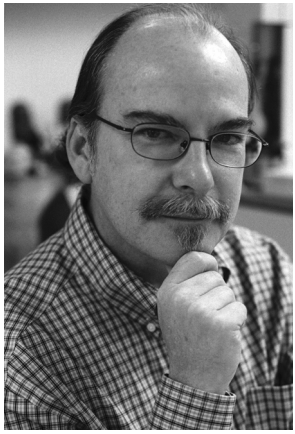
Although the former departments of medicinal chemistry and pharmacognosy were administratively one unit, the professional pharmacy curriculum was integrated and the graduate programs were completely autonomous and had their own curriculum and director of graduate studies.

The move was significant but not quite the return to the autonomy previously enjoyed by faculty over the governance of their departments. Under the new plan, the four new units would be run by department heads rather than department chairpersons. The department heads, meanwhile, would be appointed by the College dean, rather than elected by faculty with voting rights within the departments. That structure, however, was offset to some degree by the establishment of a permanent advisory council of faculty, also created by Weaver, which would include elected members as well as those appointed by the dean (Abdel-Monem, interview, 2011).

Dean Weaver did not have much time to place his personal stamp on the new order of things. At a faculty meeting early in 1984, he announced that he was resigning at the end of June to become vice president of what is now the Pharmaceutical Research and Manufacturers of America (Anderson & Pennigton, 2005, 156-7).

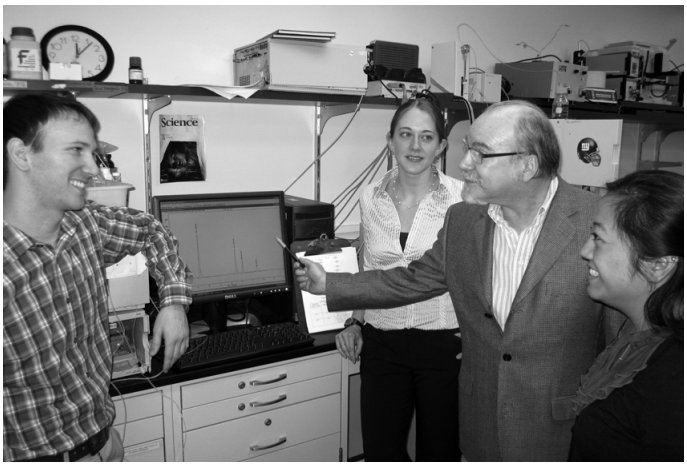
Weaver left before a permanent replacement could be found. Upon his departure, Abdel-Monem, recently appointed head of the Department of Medicinal Chemistry and Pharmacognosy, was made interim dean. During his year in the position, Abdel-Monem was able to unite the faculty and maintain the momentum for continued progress.

The search for a permanent replacement was a long process, and it was not until early in 1985 that the College announced that Gilbert Banker had been chosen to take over as the new dean (Anderson & Pennigton, 2005, 116). Abdel-Monem was appointed Associate Dean for Academic Affairs, a position he held until 1987 when he left Minnesota to assume the position of Dean of Pharmacy at Washington State University.



RORY P. REMMEL
B.Sc. 1976, University of Wyoming-Laramie
Ph.D. 1982, University of Washington
Assistant Professor 1984-91; Associate Professor 1991-98; Professor 1998-present, University of Minnesota
Born, Colorado Springs, Colorado, 1954.
Awards
- Award for Outstanding Contributions for Professional and Graduate Education, 2010

Although Abdel-Monem continued teaching, his increased administrative responsibilities made it difficult for him to continue his courses. Dean Banker, therefore, approached the department and requested the appointment of Rory Remmel as an assistant professor to assume Abdel-Monem's teaching responsibilities. At that time, Remmel was working as a postdoctoral research associate with Abdel-Monem and was already giving a few lectures to pharmacy students. Remmel brought a wealth of experience to the department in the use of modern analytical techniques for identification and measurement of drugs and their metabolites in small quantities of biological fluids. He spearheaded a departmental initiative in acquiring state-of-the-art instruments including gas chromatography, high pressure liquid chromatography, and mass spectrometry. Remmel's research included investigations on the metabolism and chemical mechanisms of hepatotoxicity of antifungals and antiviral agents, the mechanisms of metabolic interactions between investigational antiepileptics and standard antiepileptic drugs using *in vitro* and *in vivo* animal models, and the role of glucuronidation and cytochrome P450 enzymes in drug-drug inter-



Rory Remmel discusses HPLC results with graduate students Aaron Teitelbaum, Kathy Nelson, and Amy Doan.

actions. In collaboration with Robert Vince, Remmel and Cheryl Zimmerman conducted the first animal pharmacokinetic studies on (±)-carbovir and (-)-carbovir in rats, leading to a National Institutes of Health (NIH) grant on prodrugs of carbovir.

From 1992 to 2002, Remmel and Courtney Fletcher from the Department of Pharmacy Practice were co-investigators on a National Institute on Allergy and Infectious Diseases (NIAID) contract as one of five national sites for a combined pediatric and Adult AIDS Clinical Trials Group (ACTG) Laboratory that supported multi-site clinical trials of AIDS drugs. Remmel directed the analytical laboratory and several novel assays, including one of the first simultaneous assays for protease inhibitors were developed and validated. In collaboration with several surgeons and chemical engineering professors at the University, Remmel was instrumental in the development of a bioartificial liver utilizing collagen-entrapped hepatocytes in a hollow-fiber reactor. This effort was begun by Frank Cerra, a critical care surgeon, and Wei-Shou Hu, a faculty member in the Department of Chemical Engineering. The result was a licensing agreement with Regenerex.

Remmel also excelled as a teacher and was the recipient of several teaching recognitions including the semester and teacher of the year awards. He also was recognized in 2010 with the Award for Outstanding Contributions for Professional and Graduate Education from the Academy of Distinguished Teachers. In the same year, he was awarded the first Outstanding Faculty Award from the Council of Graduate Students.

At the collegiate level, the administration's philosophical break with Weaver following the new dean's appointment was distinct. Banker, who'd received his doctorate from Purdue University where he went on to serve as a faculty member in pharmaceutics, came to the University of Minnesota with a formidable record in research and writing, including a book he authored, *Pharmaceutics and Pharmacy Practice*. At his very first meeting with College faculty he made it clear that one of his top priorities would be to increase efforts to garner external funding, principally

through research grants, and to strengthen the departments, which now would have chairpersons rather than department heads. He also announced that he planned to have monthly meetings with the faculty.

In the meantime, Banker's inclination toward strong departments and enhanced research was reinforced by implementation of a new University-wide initiative called "Commitment to Focus," introduced by Kenneth Keller, who took over as president of the University of Minnesota only a few months before Banker was appointed dean of the College of Pharmacy.

As part of this new University-wide effort, each unit at the University identified internal goals. For the College of Pharmacy one such goal was to double outside research funding by the end of the 1980s. At the time, the majority of federal research money, principally from the NIH, was coming to medicinal chemistry and pharmacognosy—a little less than $1 million per year at the time Commitment to Focus was launched. In response to the ambitious goal to double that figure, the department more than doubled the amount of outside research funding in just four years, reaching a total of $2.3 million by 1989, with average funding per faculty member rising from $78,000 to $193,000 during that time. The increase, in turn, reflected trends already at work within medicinal chemistry, such as the acquisition of increasingly sophisticated equipment and techniques like NMR (nuclear magnetic resonance) and molecular modeling (Anderson & Pennington, 2005, 156-69).

The emphasis on research and funding in Commitment to Focus, as well as Dean Banker's own research orientation, proved beneficial to medicinal chemistry with its long tradition of research orientation and strong departmental identity. In 1984, when Abdel-Monem was appointed interim dean, Abul-Hajj was appointed interim department chairperson. With Banker in the driver's seat, Abul-Hajj was offered the job on a permanent basis. Abul-Hajj seized the opportunity as a chance to put the department's fiscal house in order.

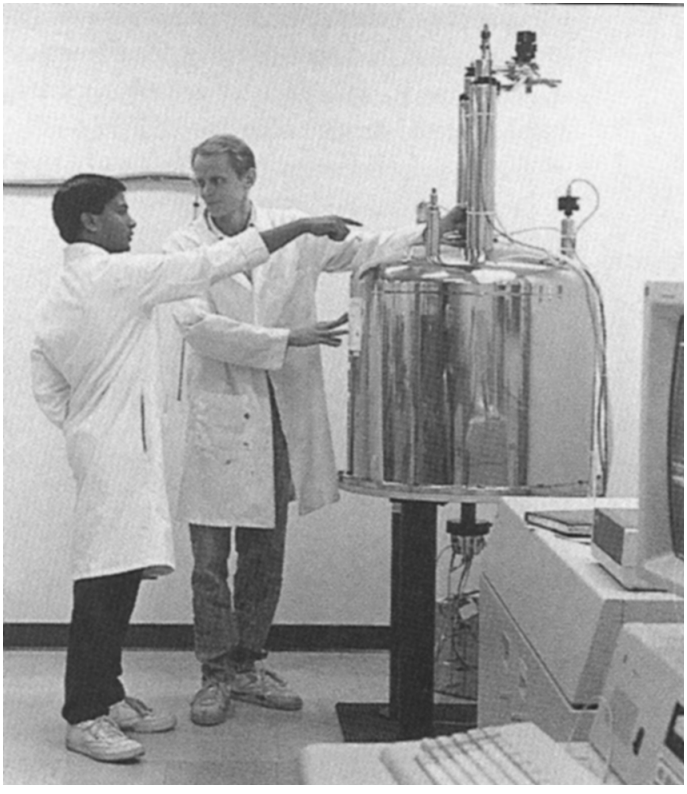
According to observers, at the time the College of Pharmacy was, for a variety of reasons, in a shambles financially. Funding allocated by the College to the four departments was not sufficient to meet expenses, and the Department of Medicinal Chemistry had been running a deficit for several years. One of the conditions that Abul-Hajj outlined for accepting the job of department chair was that the structure by which the departments were funded be changed. Banker, in consultation with Abdel-Monem, concurred and the necessary reforms were implemented.

When Abul-Hajj became the department chair, the dean's office under Weaver was keeping 100 percent of the indirect cost recovery (ICR) funds that faculty in medicinal chemistry were awarded as part of their federal research funding; no faculty outside the department was bringing in any ICR at that time. To make matters seem even less fair, Weaver refused to approve any grant application that did not seek ICR. If he was going to run the department, Abul-Hajj stipulated that this par-

ticular inequity would have to be rectified as would salary offsets—another chunk of indirect savings coming in by way of research grants. When Banker came on board the dean's office was keeping the savings in salary from faculty in medicinal chemistry who were winning outside funding. That, too, would have to change.

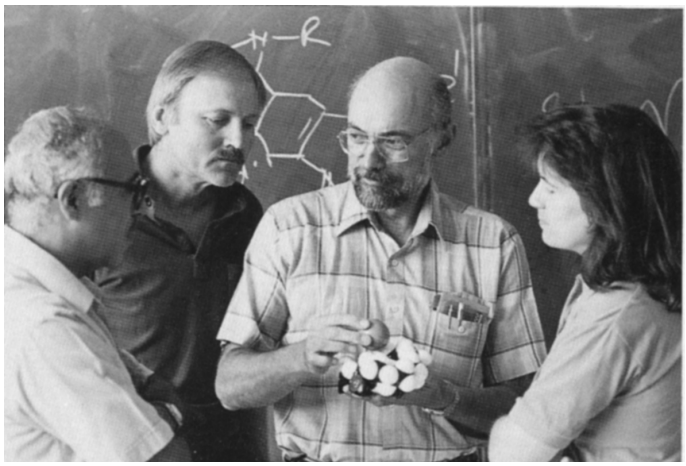
In a major signal of the new era ushered in by Dean Banker and the University's Commitment to Focus, the College acceded to Abul-Hajj's requests. Banker agreed to pass on 80 percent of the ICR and salary offset money to medicinal chemistry, with the College holding the balance.

Suddenly, the department, which had been operating in the red, now had abundant resources with which to proceed. Abul-Hajj approached the medicinal chemistry and pharmacognosy faculty to gather their ideas on how best to use the funds. For his part, he proposed that all of it be used over the next few years to build the department's infrastructure and acquire instrumentation. Because of the faculty's success in more than doubling the amount of research funding coming to medicinal chemistry, the department began to build up a reserve within only a couple of years. Abul-Hajj and the faculty agreed to a plan in which individual researchers would now receive half of the ICR and salary offset money grants generated.



Graduate student Mike Genin helps another student on the proper use of the GE 300 MHz NMR spectrometer.

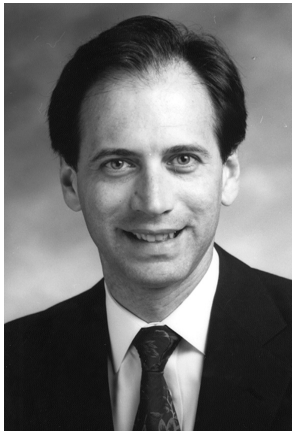
In retrospect this transformation from a resource-starved to resource-rich department marked a turning point in the history of the department, at least in modern times. With the new departmental structure, medicinal chemistry regained its autonomy over coursework. With the new financial policies, it gained a high degree of autonomy over resources as well. By the end of the 1980s as the department reserve kept build-



Philip Portoghese discusses the interaction between ligand and a receptor model with Yusuf Abul-Hajj, Dennis Larson, and graduate student Eileen Larkin, 1985.

ing, eventually 75 percent and finally 100 percent of the ICR and salary-offset money was reverted to individual faculty. For example, 80 percent of Philip Portoghese's salary came from outside the University, a situation that allowed him to place the funds he would have received from the University into a reserve fund to underwrite future research projects.

The department's research muscle was further enhanced by faculty hires during this period. Immediately following his appointment as dean, Banker discovered that the College had no program in radiopharmacy. Coming from Purdue University,

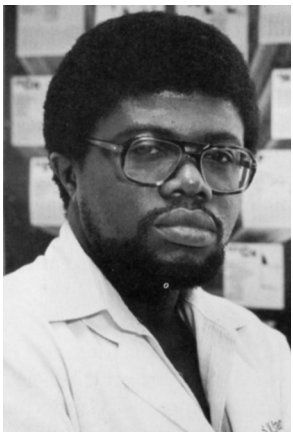


MARK A. GREEN
B.Sc. 1978, Rose-Hulman Institute of Technology
Ph.D. 1982, Indiana University-Bloomington
Assistant Professor 1985-88, University of Minnesota
Born, Sidney, Ohio, 1956.

which had a strong research and teaching focus in radiopharmacy and radiochemistry, Banker arranged with the department to hire a faculty member with a joint appointment in radiology and medicinal chemistry. Following a national search, Mark Green was hired with 90 percent of his appointment in radiology and 10 percent in medicinal chemistry.

Green brought a strong background in organometallics with a primary focus

on the use of metal radionuclides in imaging with positron emission tomography (PET). He conducted research on gallium and copper PET radiopharmaceuticals for mapping perfusion in the heart, brain, and kidneys, as well as the application of gamma imaging techniques in the evaluation of novel therapeutic dosage forms. His stay in Minnesota, however, was cut short after accepting a faculty position in 1988 at Purdue University.



SIMON MBUA NGALE EFANGE

B.A. 1979, State University College Geneseo, New York

Ph. D. 1984, State University of New York at Buffalo.

Assistant Professor 1988-93; Associate Professor 1993-99; Professor 1999-2003, University of Minnesota

Born, Nigeria, 1952.

Following Green's departure, Banker pressed for an immediate replacement, which led to the hiring of Simon Efange. Trained as a medicinal chemist with a focus on biochemical pharmacology, Efange used his synthetic chemistry skills, preparing novel receptor specific activity agents aimed at regional mapping of the living brain and their involvement with the cholinergic systems. These studies were designed to better understand neurological disorders in AIDS, Parkinson's, and Alzheimer's diseases. After spending 14 years at Minnesota, Efange decided to go back to his native Cameroon to help in building that country's educational institutions.

New Directions

Even while resources were opening up for the department, the College continued to move toward implementing Commitment to Focus. At a meeting with college deans, President Keller announced that one of the goals of the new initiative would be to phase out smaller departments. Since both medicinal chemistry and pharmacognosy were relatively small departments, their viability suddenly became an issue. Unless one or both could be made to grow, each would lose faculty lines, especially since the curriculum of the two programs at both the undergraduate and graduate level had significant overlap. Although he'd been hired as a faculty member in pharmacognosy, Abul-Hajj came to the painful conclusion that the best solution

for meeting the Commitment to Focus objectives was to fold pharmcognosy into a single enlarged and strengthened Department of Medicinal Chemistry.

Initially the faculty in medicinal chemistry and pharmacognosy wanted nothing to do with the proposed merger. At a meeting shortly after Abul-Hajj announced his intentions, the faculty rejected all three options he presented. To avoid an impasse—and any appearance of high-handedness—Abul-Hajj appointed a committee composed of two members each from medicinal chemistry (Philip Portoghese and Rodney Johnson) and pharmacognosy (John Staba and Thomas Shier) and charged it with studying the dilemma and returning a recommendation. Three months later, the committee returned its verdict. The proposal to merge the departments was the best, albeit, painful solution. In 1987, the name pharmacognosy was dropped, and there would only be one combined entity operating under the name of Department of Medicinal Chemistry.

Transformation Continues

The late 1980s were a period of transformation in other areas as well.

During the 1960s and 1970s the discipline of medicinal chemistry was grounded in synthetic organic chemistry guided primarily by *in vitro* and *in vivo* pharmacological testing to generate "hand-crafted" molecules that provided the knowledge base for the advancement of medicinal chemistry. However, the 1980s brought new advances in molecular biology and computational sciences, which helped to focus medicinal chemistry. These advances provided an increased awareness of structure-activity relationships, greater inputs from target structures and *in silico* modeling, new discovery techniques, as well as the necessity to integrate pharmacokinetics, metabolic, and toxicological considerations into molecule design and synthesis. They also brought about an ever-more detailed knowledge of disease mechanisms and pathologies. Furthermore, as synthetic chemistry was itself increasingly influenced by the paradigms of molecular biology—diversity, evolution, replication, and self-organization—the medicinal chemist had become increasingly linked with molecular- and cell-based biological disciplines.

All these changes at the interface between chemistry, biology, and disease necessitated a closer look at the new requirements for educating and training future medicinal chemists. The combined impetus of Dean Banker's appointment and President Keller's Commitment to Focus led the College of Pharmacy to begin the process of long-range planning, requiring each department, in turn, to develop a strategic plan.

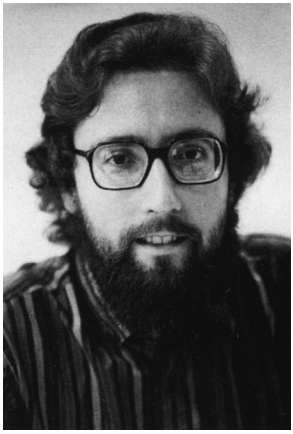
Through intense faculty discussion, the Department of Medicinal Chemistry adopted an ambitious strategic plan that won strong support from the College administration. The plan called for strategic hires over the following five years to

support the trends focusing medicinal chemistry research on structure-based drug design. Although the plan was lauded by the College administration, no funds were made available to support appropriate hires.

In the meantime, Portoghese was offered an endowed professorship in 1986 at the University of Tennessee that would provide him with considerable space as well as new faculty hires in computational chemistry and substantial resources for research. He was seriously thinking about accepting the offer, but was willing to consider remaining at Minnesota if the College hired a computational chemist; Portoghese's research program required such skills. Abul-Hajj, with the help of Associate Dean Abdel-Monem, worked hard to convince Banker to make a counter-offer and provide the necessary funds for retention of Portoghese. Funds from the College, Graduate School, and the office of Vice President for Health Sciences were committed and were sufficient to convince Portoghese to stay.

Portoghese's need for computational science assistance was also fulfilled. Following a national search for an assistant professor in computational modeling, an offer was made to Terry Lybrand in July 1986 to join the Department of Medicinal Chemistry, which he decided not to accept on the grounds that the start-up package offered by the College was insufficient to establish a strong research effort in computer modeling and computer-assisted drug design.

Later that year Lybrand informed Abul-Hajj that he received a National Science Foundation Young Investigator Award, which required matching funds from industry. Abdel-Monem, Portoghese, and Abul-Hajj put a request for matching funds ($137,500) into the Riker-3M company to set up and support the equipment needs for a computer-assisted molecular modeling center to be housed in Weaver-Densford Hall. With these funds in hand, Lybrand accepted an offer to join the department in April 1987 as assistant professor of medicinal chemistry and was also appointed as a fellow of the University's Supercomputer Institute. In addition, he set up a computer-modeling center in Weaver-Densford Hall equipped with silicon



TERRY P. LYBRAND

B.Sc. 1980, University of South Carolina-Columbia

Ph.D. 1984, University of California-San Francisco.

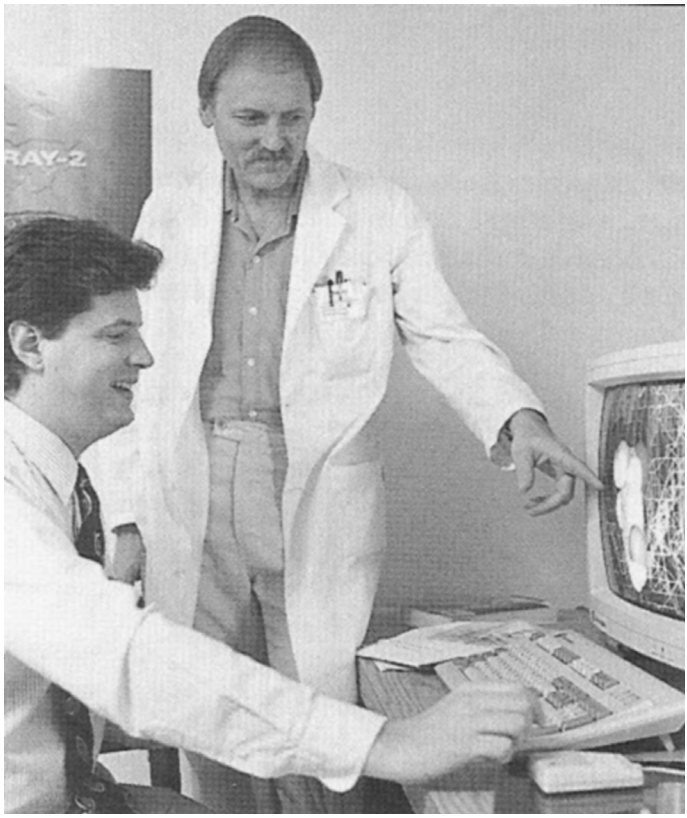
Assistant Professor 1986-90, University of Minnesota

Born, Fort Gordon, Georgia, 1957.

graphics and other computers to carry out molecular modeling and dynamics studies.

Although Lybrand was on his way to establishing a highly visible and productive program in molecular dynamics and computational chemistry, he decided to leave the University in 1990 to accept a position at the University of Washington. Following his departure, it was agreed during discussions between Banker, Abul-Hajj, Portoghese, and Leo Furcht, head of the Department of Laboratory Medicine and Pathology, that not only would medicinal chemistry hire a replacement for Lybrand but, in addition, Furcht would hire a technical support person, with both positions to be housed in Unit F. Furcht, however, decided instead to hire his own computational scientist.

Abul-Hajj then negotiated with Donald Truhlar, director of the Supercomputer Institute, to provide an annual budget to support the acquisition of software and hardware as well as funds for a 50 percent appointment of a technical support staff person. This ultimately led to the establishment of a visualization and computer-modeling center as a satellite of the Supercomputer Institute. It was housed in Weaver-Densford Hall where it served the computational needs for scientists in the Academic Health Center plus the engineering and chemistry departments. The center was instrumental in helping many research staff begin to learn and apply the techniques of molecular modeling and dynamics to advance studies in the design of molecules that would have better binding with their target protein. The center is cur-



The Center for Simulations and Visualization was initially equipped with three interactive Silicon Graphics 4D/30 TG and a 4D/310 VGX workstations and one 240 S supercomputing server. Faculty member Dennis Larson and graduate student Scott Moe run a molecular dynamic simulation experiment.

rently housed in a building at 717 Delaware Street Southeast and is still supported in part by the Supercomputer Institute.

In addition to Lybrand, there were several other strategic hires in the closing days of Banker's tenure as dean of the College.

With the acquisition of a new 500 MHz NMR instrument by biochemistry, the Department of Medicinal Chemistry hired Deborah Kallick in 1991 to establish and develop the area of drug design using high resolution NMR spectroscopy.

Kallick was the first of several high-resolution NMR specialists at the University to develop the art of drug design using high resolution NMR spectroscopy. During the next few years the University acquired several high resolution NMR spectrometers including the 600 and 800 MHz instruments. Kallick used these instruments to look at biomolecules, especially proteins and DNA, and to investigate the interaction of ligands with the macromolecules. Kallick left the university in 1999 for a position at Incyte Genomics.

David Ferguson joined the department in 1991 after spending two years as a postdoctoral trainee in Peter Kollman's laboratory at University of California at San

DEBORAH A. KALLICK
B.A. 1980; Ph.D. 1986, University of Illinois-Chicago
Assistant Professor 1991-97; Associate Professor 1997-99, University of Minnesota

Francisco. During the 1990s, Ferguson focused his research program on employing quantum mechanics, molecular mechanics/dynamics, and computer graphics to look at structural models of opioid receptors in order to delineate the molecular basis for ligand binding, selectivity, and receptor activation. In recent years, Ferguson has focused his research on the design and discovery of new therapeutics, as anticancer and antiviral agents, using both traditional structure-based drug design methods and high throughput screening techniques.

To continue strengthening the department and consistent with the departmental strategic plans, the department convinced Banker to provide funds to hire a new faculty member with expertise in molecular biology and site-directed mutagenesis.

DAVID M. FERGUSON
B.Sc., Bucknell University
Ph.D. 1989, University of South Florida
Assistant Professor 1991-97; Associate Professor 1997-2007; Professor 2007-present; Director of Graduate Studies in Medicinal Chemistry 2011-present, University of Minnesota
Born, Philadelphia, Pennsylvania, 1961.

A national search led to the hiring of Carston Wagner.

Wagner came to the Department of Medicinal Chemistry in 1991 after completing a Ph.D. in chemistry at Duke University and an NIH Post-Doctoral Fellowship with Stephen J. Benkovic at Penn State University. Wagner was hired by the department in an effort to broaden and enrich the department with the techniques for recombinant protein expression, molecular biological analyses, and site-directed mutagenesis.

Wagner quickly started a program in targeted catalytic antibody nucleoside prodrug activation, which led him to discover that nucleoside phosphoramidates could be useful antiviral and anticancer agents. After further study, his laboratory in collaboration with Cheryl Zimmerman of the Department of Pharmaceutics determined that nucleoside phosphoramidates improved the pharmacokinetic parameters of nucleotides. Animal studies conducted in collaboration with Abul-Hajj showed that phosphoramidates of AZT were potent anti-breast cancer agents. Wagner continued to work on the mechanism of cellular uptake and metabolism, subsequently discovering phosphoramidases responsible for the bioactivation of nucleoside phosphoramidates.

David Ferguson asks John Goodell to purify the topoisomerase inhibitors.

In 2004, Wag-

CARSTON R. WAGNER
B.Sc. 1981, University of North Carolina-Chapel Hill
Ph.D. 1987, Duke University
Assistant Professor 1991-97; Associate Professor 1997-2004; Professor 2004-present; Director of Graduate Studies in Medicinal Chemistry 2002-09 & 2011, University of Minnesota
Born, Burlington, North Carolina, 1959.

ner began to branch out into a new area—the study and design of small molecules that are capable of dimerizing proteins. His laboratory discovered the first chemically directed method for the self-assembly of proteins to defined nanostructures. He has applied this approach to the design of unique nanostructures that have been fused to targeting single chain antibodies and peptides. These structures are being evaluated for their ability to carry out drug delivery and as tools to understand the behavior of cellular receptors.

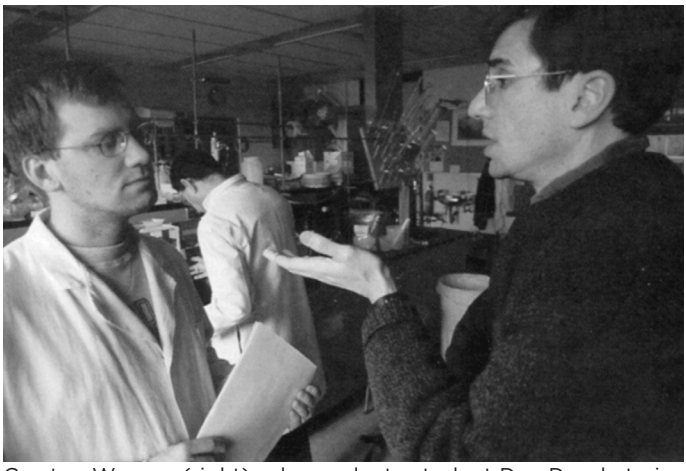
Wagner has been a highly collaborative researcher, engaging in projects with members of the department faculty, medical school, chemistry, mechanical engineering, and the University's Biotechnology Institute. In collaborations with Patrick Hanna and his long-standing interest in N-Arylamine acyltransferases (NAT), Wagner and Hanna cloned and developed the first recombinant expression systems for eukaryote NATs. They uncovered key features of their catalytic and kinetic mechanism as well as mapped their substrate specificities, especially for common environmental aryl amine carcinogens and established key features of their behavior in cells.

The Weisman Art Museum was designed by Frank Gehry and completed in 1993.

Wagner has had an impact on the department and the University in many other ways. Most importantly has been his interest

in developing interdisciplinary initiatives to facilitate research at the interface of chemistry, biology, and engineering. Early on, he recognized the value of bringing faculty, students, and researchers together from around the University who are working at the interface of chemistry and biology. After a year of study, he spearheaded the chemical biology initiative, which was initially funded by the Office of the Vice President for Research within the University. Wagner became the first director in 2003 and continues to serve in that position.

In this area, Wagner was also instrumental in championing the emerging area of bionanotechnology. With funds provided by the vice president of research, he and colleagues in the College of Science and Engineering and Medical School developed a Bionanotechnology Initiative (BI) that brought researchers from engineering, chemistry, developmental biology, medicinal chemistry, and medicine together to work on a number of projects. Most of these projects subsequently received substantial NIH funding. Wagner has served as associate director and director of the BI. In 2010 Purdue University offered Wagner an endowed professorship to head their emerging Nanotechnology Institute. Quickly, the department countered the offer by establishing a new endowed professorship in the department and offered Wagner the position as the first Medicinal Chemistry Endowed Professorship.



Carston Wagner (right) asks graduate student Dan Dronle to interpret results.

Wagner has also been an active disciplinary leader, serving on several organizational boards for the ACS Medicinal Chemistry Division and as a founding editor of the American Chemical Society Journal of Molecular Pharmaceutics (Wagner, interview, 2011).

Changes Afoot

Although in many respects the 1980s ended and the following decade began with much promise for the department, difficult times lay ahead.

Challenges began in 1991 with the sudden announcement by Dean Banker—whose tenure at the College had been so beneficial to the Department of Medicinal Chemistry—that he planned to move to the University of Iowa as the dean of the College of Pharmacy. There followed a long and tumultuous period as the University struggled to find a suitable replacement. And once it did, a new wave of turbulence and hardship erupted with implementation of the re-engineering initiative in Academic Health Center (AHC).

Upon Banker's resignation, the AHC administration appointed Associate Professor Robert Cipolle, a faculty member in the Department of Pharmacy Practice, as interim dean to run the College while the University conducted a national search for Banker's replacement. More than a year after Banker resigned, the University offered the position to Craig Schnell, an applicant who was then serving as dean of the Graduate School at North Dakota State University. Schnell accepted the offer and then, a few days later, declined to take the job.

The reasons Schnell withdrew his acceptance have never been firmly established, but a rumor at the time—that a faculty member in pharmacy had contacted a state legislator to try to keep Schnell from being offered the position—symbolized to some a growing level of discord within the College of Pharmacy.

Whatever the case, Schnell's withdrawal set off a long period of uncertainty as University officials debated whether, given the large number of people who had already applied for the dean's position, a new national search would even succeed in turning up other candidates. The situation was made even worse because at the same time several other pharmacy colleges were also recruiting new deans.

A new internal search was undertaken and the job offered permanently to Cipolle, who not only turned down the offer but asked to be relieved as interim dean. Faced with the loss of its interim dean and with no permanent replacement in sight, the University asked Lawrence Weaver to come back and serve as interim dean at the beginning of 1994. That same year, Yusuf Abul-Hajj stepped down as department chairperson and was replaced by Rodney Johnson on an interim basis. Weaver then gave the department the green light to search for a new department chairperson. Following a national search, the faculty identified three qualified candidates to bring to campus. However, Weaver decided that these candidates should not be brought to campus for a formal interview until the new dean for the College had been selected.

Another search for a new dean ensued but took longer than anticipated when Marilyn Speedie finally took over as dean in September 1995.

Prior to joining the University of Minnesota, Speedie was head of the Department of Pharmaceutical Sciences at the University of Maryland and had an active research program in several areas, including enzymology and molecular biology of antibiotic biosynthesis, the expression and secretion of recombinant proteins in streptomyces, and the microbial biodegradation of pesticides and other pollutants.

However, the demanding administrative responsibilities of dean upon arrival precluded her from carrying on an active research program.

MARILYN K. SPEEDIE

B.S. 1970; Ph.D. 1973, Purdue University

Assistant professor 1973-75, Oregon State University

Assistant Professor 1975-80; Associate Professor 1980-88; Associate Professor and Chairperson, 1988-91; Professor and Chairperson, 1991-95, University of Maryland

Dean and Professor 1996-present, University of Minnesota

Awards

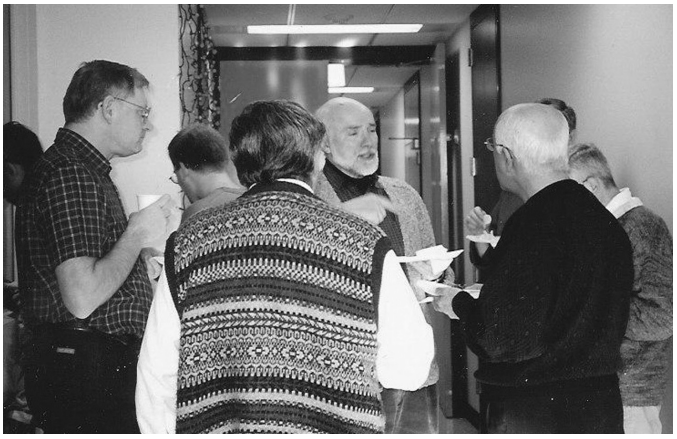
- Harold Popp Award, 2004
- Fellow, American Association for Pharmaceutical Scientists, 1996
- AACP Paul Dawson Biotechnology Award, 1994

But no sooner was she in her new position then yet another wave of turmoil engulfed the College. This one was even more disquieting than the prolonged search for a new dean. For one, faculty relations had reached a stage where, just prior to Speedie's arrival, faculty from each of the College's departments formed an ad hoc group dubbed the SOS (Save our School) committee, with Abul-Hajj representing the interests of medicinal chemistry. The committee surveyed College faculty about problems and possible solutions and came up with a report. In response, Speedie formed three task forces to address a range of issues.

The work of those task forces, however, was superseded by still another wrenching change—a second round of de-departmentalization.

This round of College reorganization was prompted by the actions of the new Academic Health Center Provost William Brody to re-engineer the AHC. Henceforth, the entire AHC would be organized into three functional units intended to serve "customers." Announced in January 1996, the re-engineering effort would lump individual departments and units into research, education, or clinical services groups.

Implementation of the effort was placed in the hands of 10 design teams charged with fitting the old departments and units into the new functional organization,



Monthly birthday parties were enjoyed by staff, students, and faculty.

which involved the establishment of centers and institutes and the elimination of departments and disciplines. At the College, Dean Speedie appointed a committee to oversee termination of the departmental structure.

To address this new initiative, the medicinal chemistry faculty established three subcommittees to assess the viability of a Center for Drug Design (CDD). In April 1995 this led to a report calling for the establishment of such a center. Both Dean Speedie and Frank Cerra, the senior vice president of AHC, were supportive of the idea. Despite these efforts the CDD was not formally established until 2002, when a dispute over the royalties from Robert Vince's anti-AIDS drug, Zaigen, was finally settled with the company that had acquired the rights to produce it (Anderson & Pennington, 2005, 229-33).

With the dissolution of departments, Medicinal Chemistry spent almost three years confronting conditions similar to those that prevailed during Weaver's first term as dean. Decisions about resources, curriculum, space allocations, and funding—including the ICR and salary offsets so providentially gained only a few years earlier—went through the dean's office. A College executive committee was formed consisting of three associate deans and two faculty members—one from basic pharmaceutical sciences (Abul-Hajj), the other from clinical pharmacy (John Rotschafer). It held a series of contentious meetings. Salary increases for faculty in medicinal chemistry, which had ranked in the top third of the College, tumbled to the bottom third; it was perceived, in part, because all of the College's new associate deans—

who evaluated the pay structure—came from clinical pharmacy.

Once again, medicinal chemistry carried on as a shadow department, led this time by Abul-Hajj, in the same manner as it had in the mid-1970s. Delegations of department faculty held meetings with Dean Speedie that were described by some attendees as "intensive"—intense enough so that at one meeting the medicinal chemistry faculty informed her that they wanted to have their unit removed from the College of Pharmacy and moved into the Chemistry Department. The dean refused to consider the suggestion.

The Department has held an annual potluck holiday celebration for many years.

Faculty joining in the holiday festivities in 2004, including (left to right) Rodney Johnson, Patrick Hanna, Robert Fecik, and Thomas Shier.

Morale continued to sink, and faculty were up in arms—one even filed a grievance against the dean. But for the most part, the changes were met with passive resistance, and there were occasions on which Dean Speedie could not raise a quorum at faculty meetings when decisions needing faculty approval were pending on curriculum and other matters.

The standoff finally came to an end late in 1996 when Dean Speedie decided to

reinstitute the College's departmental structure. The move was made easier by the fact that Brody, the instigator of the re-engineering initiative, had unexpectedly left the AHC for a new position at Johns Hopkins University.

Brody was succeeded as provost of AHC by Frank Cerra. A new approach to internal College dissension was signaled by Dean Speedie's decision to hire outside consultants to gather input from faculty, staff, and administrators, and to recommend solutions. In September 1997, the consultants facilitated a two-day meeting. Nothing concrete came out of these gatherings, other than the observation that even as rancor within the College ran high, performance was just as high. In the end, all parties agreed to continue working on equitable solutions.

One of the organizations that was supposed to provide a forum for hammering out those solutions was the College's Constitution and By-Laws Committee, which now worked to develop an organizational structure that would meet with general approval.

In the end, however, the College's Executive Committee preempted the By-Laws Committee's deliberations by unilaterally deciding in April 1998 to move ahead with reinstating departmental structures, regardless of the outcomes reached by Constitution and By-Laws Committee. The plan proposed by the Executive Committee established a protocol in which all College faculty would have the chance to select membership in one of four departments: experimental and clinical pharmacology; pharmaceutics; pharmacy practice; or medicinal chemistry (ibid., 236-8).

The plan met with overwhelming faculty approval. Shortly thereafter, medicinal chemistry was reconstituted as a University department. At the time, there was no official head of medicinal chemistry and no money to hire anyone from outside the College. As part of her acceptance of the Executive Committee reorganization, Dean Speedie insisted that the new heads of each of the reconstituted departments had to have the backing of two-thirds of the faculty working in their units. Although Abul-Hajj, who previously led the department from 1984 until 1994, did not want to be named head of the newly reconstituted Department of Medicinal Chemistry, he reluctantly answered Speedie's request and was once again appointed department head.

FRANK CERRA
Senior Vice President for the University of Minnesota Academic Health Center, 1997-2011.

Control of funding was one of the principal forces driving the continued push for re-departmentalization. In a de-departmentalized College, royalties for drugs developed by a member of medicinal chemistry would go to the dean's office rather than having a portion of the money directed to the department, as would normally

be the case. At this time the anti-AIDS compounds discovered by Vince seemed likely to end up on the market, with potentially rich royalties accruing to the University. Unless the College was re-departmentalized, where that money went would be entirely up to the discretion of the dean. Meanwhile, the re-departmentalization plan also addressed structural issues that had vexed the College prior to the 1996 de-departmentalization—some of the issues that Dean Weaver was trying to address in his de-departmentalization in the mid-1970s.

Under the new plan, the curriculum would continue to fall under the purview of the College's Central Administration and the system of associate deans assigned to functional groupings within the institution would continue. Most important of all, the plan addressed—and eliminated—the source of some of the worst friction within the College, assigning to each department responsibility for tenure and promotion of faculty only within a respective department. For example, faculty from clinical pharmacy would no longer have a say in tenure and promotion of faculty in medicinal chemistry or vice versa.

Soon after Abul-Hajj assumed the head position, he tried to fill Deborah Kallick's vacancy, but Dean Speedie had already spent half of that position's salary line to support another faculty member in a different department and could not fund a new hire in medicinal chemistry.

About that time, the University Cancer Center hired Stephen Hecht to establish the division of carcinogenesis and chemoprevention and had funds for hiring several faculty in this newly created division. In turn, medicinal chemistry had a long-standing interest in carcinogenesis with Patrick Hanna, Rory Remmel, Herbert Nagasawa, and Yusuf Abul-Hajj carrying out investigations in several relevant areas of carcinogenesis/chemoprevention. In discussions with Hecht, Abul-Hajj indicated his willingness to have a joint hire between the cancer center and medicinal chemistry. Both Speedie and John Kersey, director of the cancer center,

Completed in 2000, the McNamara Alumni Center is on University property, but is owned by the University of Minnesota Gateway Corporation, made up of the Alumni Association, University of Minnesota Foundation, and Minnesota Medical Foundation.

supported this arrangement. Speedie, however, stipulated that the new hire would be assigned as the course director for a newly established Pharm.D. seminar course. Medicinal chemistry agreed to the proposal, which led to the hiring of Natalia Tretyakova with a 50 percent appointment in medicinal chemistry and 50 percent position in the cancer center.

To this joint position Tretyakova brought a unique set of strengths in chemical carcinogenesis. She set out to establish a research program that focused on the chemical modifications of nucleic acids by drugs and carcinogens. The effectiveness of her research was enhanced by her skill in employing biological mass spectrometry, along with organic synthesis, computational chemistry, and molecular biology, to study the interactions of carcinogens with nucleic acids, elucidate the structures of the resulting nucleobase adducts, quantify their concentrations *in vivo*, and identify DNA repair pathways responsible for their removal in cells. Tretyakova's contributions to the field were recognized by the University with her appointment as a McKnight Land-Grant Professor.

Re-Departmentalization Redux

In terms of funding, re-departmentalization of medicinal chemistry came in just the nick of time. When royalties from Ziagen began coming in (averaging approximately $7.1 million a year to the department), the new College structure ensured that not only would a fair portion of that money come to medicinal chemistry but that the department would have a say in how it would be used. In turn, those funds helped underwrite several endowments and graduate fellowships and provided resources to pay for many other research and structural innovations.

In addition, during the past decade those royalties have played a critical role in the expansion and evolution of the Department of Medicinal Chemistry, eventually making possible the establishment of a new unit, the Institute for Therapeutics

NATALIA Y. TRETYAKOVA

B.Sc. 1988; M.Sc. 1990, Moscow State University

Ph.D. 1997, University of North Carolina-Chapel Hill

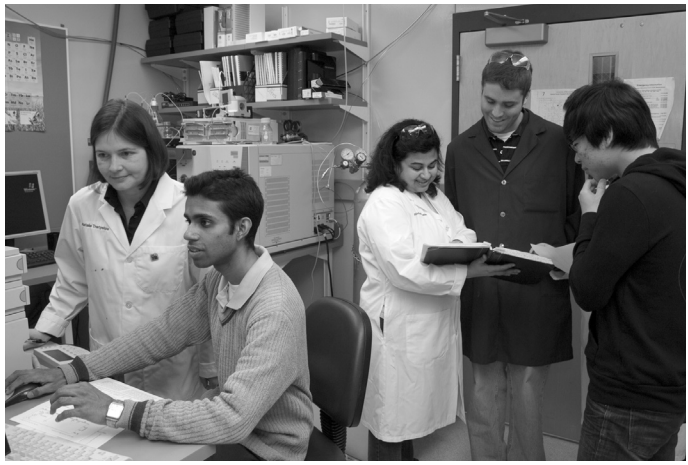
Assistant Professor 2000-05; Associate Professor 2005-11; Professor 2011-present, University of Minnesota

Born, Moscow, Russia, 1968.

Discovery and Development (ITDD) within the department and to create and to fund a new center within the Academic Health Center. But to reach the point where Ziagen could be created and marketed meant not just re-departmentalizing the College of Pharmacy. It also entailed persistence—and some luck—in navigating the vagaries of research funding and intellectual property rights. Failure to do so at any point could very well have resulted in failure for the whole project. That it didn't is testimony to the persistence of the lead researcher, Robert Vince, the foresight of the AHC, and even the willingness of then-President Mark Yudof, to undertake a multi-million dollar lawsuit for which the outcome was far from uncertain.

Ziagen is based on carbovir, an antiviral compound patented by Vince and his research associate, Mei Hua, in 1988. It inhibits HIV's ability to produce DNA and replicate itself. In turn that work was based upon Vince's previous research into compounds with potential antiviral and anticancer effects with the focus of his work influenced by the always evolving national research priorities.

Initially, Vince and Hua sent several related compounds to the NIH for study as potential anti-AIDS drugs, but were told that all of them fell outside the range of what the institute established as the parameters of potential effectiveness.



Natalia Tretyakova discusses with graduate students the results from an LCMS chart.

Soon the NIH contracted out the testing of several active compounds to research laboratories around the United States. One of them, the Southern Research Institute (SRI), happened to employ a researcher, William M. Shannon, who shared a close friendship with Robert Vince. At the friend's urging, Vince sent his compounds to the SRI. About two weeks later, Vince received a phone call informing him that five of the compounds were highly effective in combating HIV. Given that at the time there was only one medication available—AZT—that had much effect on HIV, SRI's findings pointed the way toward a tremendous potential for Vince's compounds.

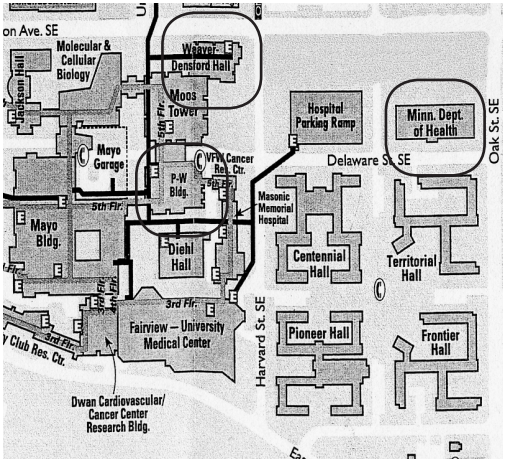
SRI sent the compounds to the NIH, and shortly thereafter, the institute contacted Vince and requested that he apply for patents on the compounds. The reason

was simple. NIH was willing to fund pre-clinical testing but no pharmaceutical company would be interested in pressing forward with the drugs unless they were patented.

After a presentation about his work at a conference, Vince was approached by researchers with the pharmaceutical company, Burroughs Wellcome, but ended up licensing the drug with another company, Glaxo. Two years later, Glaxo informed him that it was directing its attention to another anti-AIDS compound and was terminating its agreement with the University of Minnesota. In 1992, after further consultation, Burroughs Wellcome returned to the bargaining table and signed a licensing agreement with the University of Minnesota. Not long after, Glaxo bought out Burroughs Wellcome and, after a couple of more acquisitions, became GlaxoSmithKline.

After several more years of testing, the most promising of Vince's compounds, now called Abacavir, was approved by the FDA in late 1998 and then marketed by Glaxo under the brand name Ziagen. Over the next 12 years—the average life of a patent—Ziagen was expected to yield some $300 million in royalty payments. In actuality it yielded over $510 million in royalties by 2011.

The only problem was that Glaxo claimed that on technical grounds it was not required to make any royalty payments. If the University was going to get anything out of the marketing of the drug, it would have to use legal channels. In consultation with Vince—who'd envisioned using his portion of the royalties to create a center dedicated exclusively to the development of new drugs—AHC and College of Pharmacy officials, legal counsel, and President Yudof made what, in retrospect, was a gutsy but logical decision to sue Glaxo. Glaxo countersued, but in October 1999 the company conceded, agreeing to pay royalties under a modification of the originally envisioned payments and schedule (Vince, interview, 2011).



A map of the Minneapolis campus in 2002. Circled areas are the current sites for medicinal chemistry research.

According to a University of Minnesota Board of Regents policy, a third of the royalty funds would go to Vince and Mei Hua, a third to central University programs, 25 percent to the discoverer's department, and 8 percent to the discoverer's college.

Following the settlement there were questions in the minds of several administrators whether medicinal chemistry could make effective use of the new stream of funds. At an

New graduate students, 2003.

initial meeting, Frank Cerra, Vice President for Research Christine Mazier, Dean Speedie, Vince, and Abul-Hajj discussed the most effective ways of using the funds. This was followed by many meetings between Cerra and Abul-Hajj, and still other meetings involving Cerra, Abul-Hajj, and Vince and at times including Rodney Johnson.

For his part, Vince pressed forward with the establishment of a Center for Drug Design that reflected his own research experience. The University's Center for Drug Design, established on January 8, 2002, would differ from such centers located at other research universities in that it would not be completely dependent upon external funding—and thus driven by external research priorities—but would draw upon the bulk of Vince's royalties as unrestricted seed money for projects initiated by researchers appointed to faculty positions in the center (ibid., 2011).

Following the settlement with Glaxo, President Yudof strongly supported the idea of establishing a drug center but the question arose of where it should be located. Discussions between the department and Cerra led to a proposal to build a new facility to house the Center for Drug Design, the Department of Medicinal Chemistry, and the Virtual Genomic Center. It was further proposed that this new facility be built, in part, with some of the royalty funds and should be located on East River Road behind the Children's Rehabilitation Center. President Yudof, however, did not approve of this site and suggested a location next to the Translational Research facility by Bierman Field. For its part, the department faculty did not accept this site and after further discussions with Cerra, approximately 3,000 square feet were allocated to the Center for Drug Design in the Phillips-Wangensteen Building with Vince appointed as its first director. Soon after the allocation of space, Vince, along with Ramaiah Muthyala (who became associate director of the center) began renovating the facility to accommodate the research programs in the center. Muthyala

was granted a research associate professor appointment in the department and graduate faculty status in the graduate program.

With the official grand opening symposium of the center held in May 2005 the hiring of senior and junior scientists began. Krzysztof Pankiewicz was appointed as a senior associate director of the center as well as a research professor in medicinal chemistry.

Pankiewicz had experience at Memorial Sloan-Kettering Cancer Center and Codan Pharmaceuticals and had a reputation as a talented nucleoside chemist with a good appreciation for biology. His major strength lay in structure-based drug design of nucleosides.

Since the establishment of the Center for Drug Design, the research funding and hiring of junior and senior scientists has proceeded at a rapid clip. Currently the major research at the center focuses primarily on developing new anticancer, antimicrobial, and antiviral drugs and therapies. The center is well equipped with state-of-the-art instrumentation to carry out the most sophisticated chemical and biochemical research. Looking toward 2013 when the Ziagen patent runs out—and with it, royalty payments—Vince established an endowment fund made up of royalty payments not directly needed to operate the center, which receives no University funding. Today, the endowment fund stands at $60 million—enough to maintain operations long after Ziagen's patent ends (ibid., 2011).

In addition to the direct boon brought into the department, Ziagen royalties indirectly opened up additional resources when Vince requested that his teaching commitment be reduced in order to free up more of his time for research. By taking him off faculty salary, the department found itself with the funding to undertake the hiring of two new assistant professors, Robert Fecik and Chris Xing.

President George W. Bush meets with Robert Vince during a visit to Minnesota on July 11, 2002, and congratulates him for his success in the discovery of a new anti-AIDS drug.

The first faculty member who was hired using Vince's

former salary line was Fecik. Trained by Lester Mitscher at the University of Kansas and Dale Boger at the Scripps Research Institute, Fecik came to the department with a unique background in natural products and synthetic chemistry. His laboratory focuses on ways to combat antimicrobial and anticancer multi-drug resistance through the use of combinatorial biosynthesis and total synthesis of natural product.

The second of these appointments was Chengguo Xing. Trained as a synthetic medicinal chemist under Edward Skibo at Arizona State University and with postdoctoral training under the guidance of Andrew Myers at Harvard University, Xing has research skills in chemistry and biochemical and molecular biology to support

RAMAIAH MUTHYALA
B.Sc. 1964, Osmania University of India
Ph.D. 1969, University of Sagar, India
Ph.D. 1975, University of East Anglia
Research Associate Professor 2000-05, University of Minnesota
Born, Andhra Pradesh, India, 1946.

his research programs at Minnesota, which covers synthesis of natural and unnatural small-molecule based drug candidates and molecular probes, molecular/cellular biology to understand cancer development and the working mechanisms for cancer therapies, and various animal models for drug efficacy evaluation. During his initial

KRZYSZTOF PANKIEWICZ
Ph.D. 1979, Polish Academy of Sciences
1983-95, Memorial Sloan-Kettering Cancer Center
1995-98, Codon Pharmaceuticals
Pharmacy Assistant, 1998-2004; Research Professor, 2004-present, University of Minnesota

years he had a strong emphasis on development of Bcl2 inhibitors, aiming to develop therapeutic candidates to eradicate drug resistance in cancer therapies, which is a common and serious problem for all malignancies. More recently his research focuses have expanded to cancer prevention and early diagnosis.

As with the faculty members hired in the late 1980s and early 1990s, strategic decision-making was applied to each of these new appointments, with an eye especially toward enhancing medicinal chemistry's ability to work collaboratively with other departments and centers around the University and to enhance both synthetic capabilities as well as strengthen the ties with the cancer center.

CENTER FOR DRUG DESIGN
UNIVERSITY OF MINNESOTA

Center for Drug Design Logo

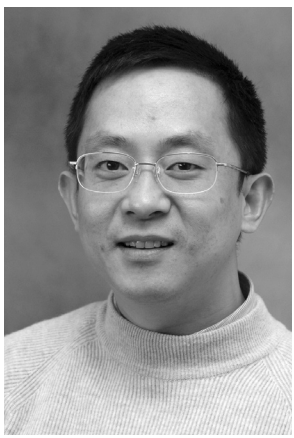
During the search process that led to the hire of Chengguo (Chris) Xing, one of the applicants was Shana Sturla. She was still early in her postdoctoral training with Hecht at the cancer center but was recognized as a promising faculty hire. While funds for a second position were not initially available, Speedie was willing to consider an additional faculty line and Abul-Hajj negotiated with the cancer center to create a joint appointment for Sturla. She was provided lab space in Weaver-Densford Hall by the department and salary by the cancer center to begin as an assistant professor one year later, at the conclusion of her postdoctoral work.

The Center for Drug Design held an opening celebration and mini-symposium on May 17, 2005. Speakers included (left to right): Sydney Pestka (Robert Wood Johnson Medical School); Robert Vince; Ronald Breslow (Columbia University); and Jack Secrist (Southern Research Institute).

By the time she began in that posi-

ROBERT A. FECIK
B.Sc., University of Iowa
Ph.D., University of Kansas-Lawrence
Assistant Professor 2001-07; Associate Professor 2007-present; Director of Graduate Studies in Medicinal Chemistry 2010, University of Minnesota
Born, Wilmington, Delaware, 1971.

tion in 2004, Sturla had been awarded a National Cancer Institute Career Development Award to initiate research aimed at understanding the process of cancer initiation by dietary and environmental chemicals. Combining research strategies in organic synthesis and toxicology with a medicinal chemistry focus, Sturla's research also evolved to encompass efforts to understand factors that control the toxicity of natural product-derived potential chemotherapeutic or chemopreventive agents. Sturla, who is from the Dominican Republic, was recognized as an American Association for Cancer Research Minority Scholar in Cancer Research and as



CHENGGUO (CHRIS) XING
B.Sc. 1996, Dalian University of Technology
Ph.D. 2001, Arizona State University
Assistant Professor 2003-09; Associate Professor 2009-present, University of Minnesota
Born, Dalian, China, 1971.

a McKnight Land-Grant Professor. By 2009, she was poised to be awarded tenure the following year and was an ever-enthusiastic member of the department. An unexpected opportunity for a chaired professorship to lead a new Toxicology Program at the Swiss Federal Institute of Technology (ETH) in Zurich, however, lured Sturla and her research program to Switzerland.

The combination of the new departmental structure and increased revenues

Robert Fecik checks Annie Ngyunís results on the anticancer activity of the tubulysin analogs.

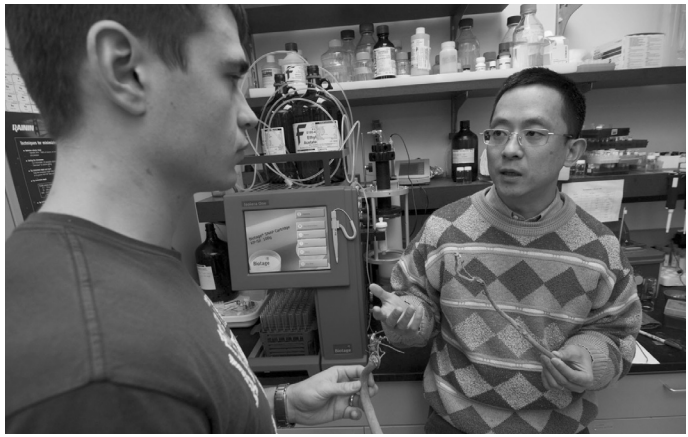
coming not only from royalties on Ziagen (which ultimately made possible perhaps the most significant hire in medicinal chemistry in several decades—the 2007 appointment of Gunda Georg as head of the Department of Medicinal Chemistry) but also from sponsored research boosted the department's fortunes. The beginning of the new decade was not free, however, of a share of looming issues.

As had occurred time and again over the department's history, medicinal chemistry's growing roster of faculty and graduate students were running up against the

SHANA J. STURLA
B.Sc. 1996, University of California-Berkeley
Ph.D. 2001, Massachusetts Institute of Technology
Assistant Professor 2004-09, University of Minnesota
Born, Brooklyn, New York, 1975.

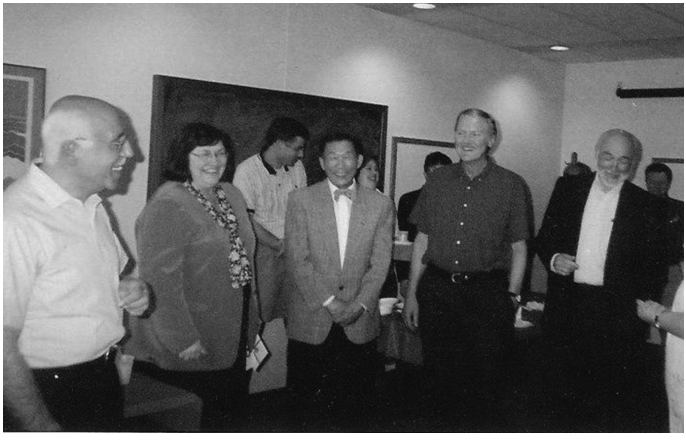
limits of space available at Weaver-Densford Hall. In addition, the department's emphasis on cross-disciplinary collaboration, sponsored research, and structure-based drug design—all requiring the most advanced instrumentation available—and the space to house that instrumentation. As the new millennium dawned there was also concern about the graying of medicinal chemistry's faculty, with seven of the department's 11 tenure track faculty having come to the University prior to 1980 (Department of Medicinal Chemistry, 2005). This led to a conscious attempt to recruit younger, top-notch faculty to the department.

With Ferguson's shift of research emphasis towards synthetic medicinal chemistry and developing therapeutic agents for viral diseases and cancer, and the department's increased emphasis on molecular modeling and computational chemistry for structure-based drug design, Elizabeth Amin was hired. Prior to joining the department she carried out investigations with Donald Truhlar in the University's Department of Chemistry and had been collaborating with faculty members in medicinal chemistry. Amin's research program involves the development of new computational techniques to model transition metals in unusual coordination states with a focus on designing countermeasures to biological warfare agents, specifically anthrax toxin and organophosphates nerve gases (Amin, interview, 2011).



Chris Xing asks Dave Hermanson what should be done with the Kava roots.

Other new faculty hires helped ease concern about an aging faculty base, while the University's 2005 acquisition of a 170,000 square foot building located two blocks from Weaver-Densford Hall opened up the possibility of answering the department's space needs—and then some. The building, which belonged to the Minnesota Department of Health, had been constructed to accommodate offices and laboratories. Not surprisingly the sudden availability of so much space set off an intra-University scramble, especially



Herb Nagasawa and Dennis Larson at their retirement party, 2005. L to R: Yusuf Abul-Hajj, Dean Marilyn Speedie, Herb Nagasawa, Dennis Larson, and Philip Portoghese.

within the Academic Health Center.


Shana Sturla is concerned about a small impurity in the acylfulvene sample.

The building at 717 Delaware Street Southeast was purchased from the state of Minnesota in 2005 to accommodate the expanding research needs by AHC units. Frank Cerra approved the allocation of approximately 20,000 square feet to house the expansions in medicinal chemistry and the establishment of the Institute for Therapeutics Discovery and Development. The facilities were renovated to house state-of-the-art instruments and to accommodate the large number of research personnel brought by Gunda Georg.

In the end, medicinal chemistry acquired the space it needed. But to do that entailed breaking with tradition and going outside the department to seek new leadership as well as the establishment of an innovative new research institute that would help advance the work of several other schools, departments, and research centers around the University.

Changes Continue

By 2002, Yusuf Abul-Hajj was ready to step down as department head. After a series of discussions, Dean Marilyn Speedie agreed to his proposal that the College look

ELIZABETH AMIN
B.Sc. 1996; M.Sc. 1998; Ph.D. 2002, University of Missouri-St. Louis
Assistant Professor 2006-present, University of Minnesota
Born, St. Louis, Missouri, 1966.

Awards
- ACS Hewlett-Packard Outstanding Junior Faculty Award, 2011

Elizabeth Amin explains the interaction between an anthrax inhibitor and the molecular structure of anthrax toxin.

outside for a candidate to replace him. After a year-long search failed to turn up a suitable candidate, the position was reposted and a new search committee formed.

This time, however, the committee also actively solicited candidates. One potential candidate Abul-Hajj brought to notice was a distinguished faculty member at the University of Kansas: Gunda Georg.

Abul-Hajj knew Georg from her research in medicinal chemistry of small molecule anticancer drug agents, in particular her focus on the development of both synthetic and natural products using the most advanced techniques. Although not an administrator per se, Georg had demonstrated strong leadership skills as principal investigator of a state-wide project funded as part of a larger NIH grant focusing on the research of junior faculty at schools around Kansas. In allocating the money, the NIH gave recipients broad latitude in exactly how they would structure their programs. The research infrastructure whose implementation she spearheaded was not only deemed the most effective of all the models adopted around the country, it also became the model for perhaps the most significant development in the recent history of the Department of Medicinal Chemistry—the Institute for Therapeutics Discovery and Development (ITDD) (Georg, interview, 2011).

The building at 717 Delaware Street Southeast, Minneapolis.

Initially, Georg was not interested in being considered for head of the Department of Medicinal Chemistry in Minnesota. But Abul-Hajj persisted. Knowing her inter-

est in cancer therapeutics, he approached the University's cancer center to see if there might be researchers there interested in expanding collaborations between the center and the department. With Masonic Cancer Center Director John Kersey and AHC Vice President Frank Cerra both interested in strengthening the Cancer Experimental Therapeutics Program at the University, it was thought that someone like Georg might be a good fit. Informed that the department was working on such a development, she agreed to submit her curriculum vitae. Around the same time, she visited the University to lecture about her work and to meet with faculty and administrators, including Cerra and Kersey. In 2005, two years after the initial search for a replacement for Abul-Hajj, she called and informed him that she was indeed interested in coming to Minnesota.

This led to a period of negotiations between Georg and the University. In August 2005, in response to a request from the provost's office, she wrote a 16-page proposal outlining both what she would personally accomplish if she took over the department but also the conditions the University would have to meet if she were to take the job. These conditions went beyond the conventional issues of personal compensation and moving expenses. The heart of her memo was a detailed proposal for the faculty, staffing, instrumentation, space, and—most importantly—the operating philosophy of what would become the Institute for Therapeutics Discovery and Development (ITDD).

Students on the walkway to Coffman Memorial Union, which was originally built in 1940 and renovated in 2003 for more square footage to accommodate the rising number of students from 22,000 to more than 50,000.

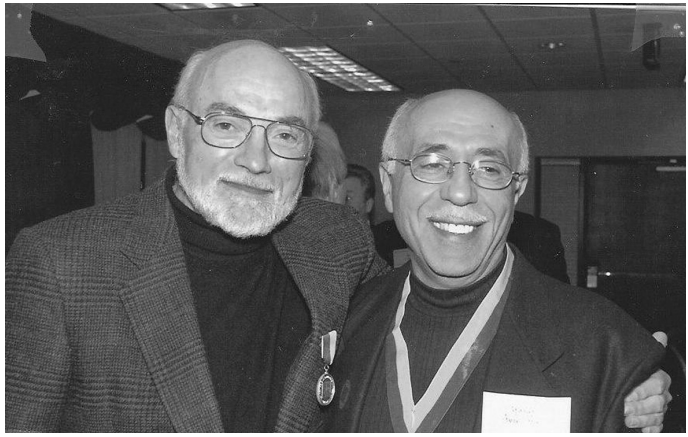
The key to the proposal—and to the institute that would come out of it—was to create a collaborative, translational research organization that would have an industrial approach to research taking place alongside a traditional academic approach. This meant focusing on application and commercialization of research projects from the outset. In turn, this meant that at least this portion of the ITDD's work would have to be carried out by researchers whose primary objective was creating procedures and products that might be eligible for patents rather than on publication in scholarly journals or the training of graduate students, although both of those out-

Coffman Memorial Union viewed from the rear, showing the top of the ìgrand staircaseî that gives access to East River Parkway and the Mississippi River.

comes would also be included in the institute's operations (Georg, 2005).

In consultation with the dean and faculty, Cerra offered Georg the position as head of the department and director of the new research institute. Given the space and personnel such an organization would need, Georg made it known that she planned to bring 25 people with her from Kansas as well as to recruit more staff and faculty when she arrived. Cerra also allocated some 20,000 square feet of space in the Delaware Street building just acquired as home to the ITDD. Georg, too, was offered the first Robert Vince Endowed Professorship in Medicinal Chemistry. To strengthen the offer President Robert Bruininks offered her a five-year McKnight Land Grant Professorship. Georg accepted the offer and began building on the already strong medicinal chemistry department.

Georg is best known in the medicinal chemistry community for her work with paclitaxel, a clinically important agent for the treatment of ovarian, breast, and other cancers. The work with paclitaxel eventually led her to investigate the hypothesis that tubulin-stabilizing agents could be used in the treatment of Alzheimer's disease. Her work on non-hormonal male contraceptive agents has resulted in the discovery of several new lead compounds. One of the lead compounds, named Gamendazole, has advanced to studies



Philip Portoghese, who was recipient of the 2001 Weaver Medal, congratulates colleague Yusuf Abul-Hajj for his selection as recipient of the 2005 Weaver Medal.

in primates in preparation for clinical trials. Her recent investigations, initiated at the University of Minnesota in collaborations with Ashok Saluja and others from the Academic Health Center, concerns a water-soluble prodrug of triptolide, named Minnelide, which showed potent cytotoxic activity across several cancers *in vivo*, displays potent antiangiogenic properties, and has been shown to be highly efficacious in animal models of several cancers, including an orthotopic animal model of pancreatic cancer. Other projects in the Georg group are centered on the development of novel synthetic methods in organic chemistry.

Architects met with Georg and Vadim Gurvich during the transition period between her accepting the position and her departure for Minnesota—the newly acquired facility had an insufficient amount of lab space, among other things. Two search committees were formed to look for ITDD core directors as soon as she arrived at the University, which included faculty from both within and beyond the Department of Medicinal Chemistry (Georg, interview, 2011).

Vadim Gurvich, who was working with Georg at Kansas, moved to Minnesota in 2006 to assume oversight of the construction of the research facilities in 717 Delaware Street Southeast to accommodate the needed space expansion in medicinal chemistry and for the creation of the ITDD. Since 2007, Gurvich has been the associ-

GUNDA I. GEORG

B.Sc. 1975; Ph.D. 1980, Philipps University of Marburg, Germany

Assistant Professor 1983-84, University of Rhode Island

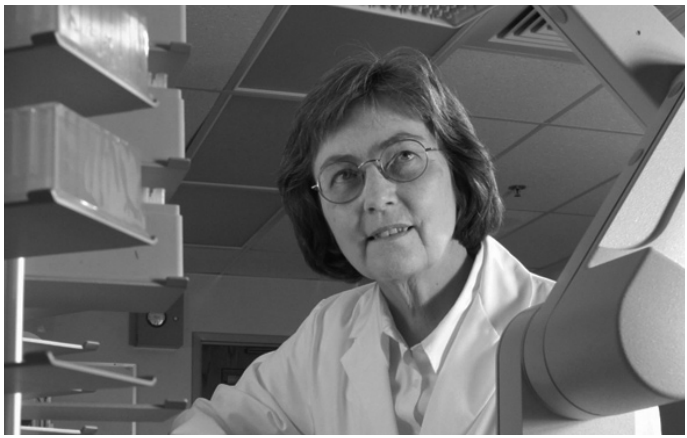
Assistant Professor 1984-89; Associate Professor 1989-94; Professor 1994-2005, University of Kansas

Vince Professor, McKnight Presidential Chair and Head of the Department of Medicinal Chemistry, 2006-present; Director of Institute for Drug Discovery and Development, 2006-present, University of Minnesota

Born, Herborn, Germany.

Awards

- Sato Memorial International Award of the Pharmaceutical Society of Japan, 2000
- Fellow, American Association for the Advancement of Science, 1996



Georg suggests screening an additional 50,000 compounds from the special library in the ITDD.

ate director of ITDD, director of its chemical and API process development facility, and research assistant professor of medicinal chemistry. Gurvich mainly directs applied research in the areas of organic chemistry of drug candidates, their intermediates and metabolites, chemical process development and scale up, manufacturing of small-molecule and protein-based active pharmaceutical ingredients to support clinical and translational research. He is also the associate director and one of the founding members of the National Institute for Pharmaceutical Technology and Education (NIPTE), a nonprofit national organization consisting of schools and colleges of pharmacy and chemical engineering engaged in pharmaceutical research (Institute, 2010).

Walters comes to Minnesota with both academic and industrial experience. After spending a few years as a professor of chemistry at Dartmouth College, he joined Warner-Lambert, which later merged with Pfizer, at its Ann Arbor laboratories. He worked in the area of second-generation atypical antipsychotics and subtype selective GABA positive allosteric modulators as novel anxiolytics. Additionally, he served as a leader in the Lead Discovery Group, a discovery team charged with hit-

Medicinal chemistry faculty and staff, 2008. The arrival of Gunda Georg to head the department led to doubling the space, as well as a significant increase in faculty and staff.

to-lead operations. He joined the University of Minnesota as a research associate professor in medicinal chemistry and as director of the Lead Discovery and Probe core group of the ITDD, where he is involved with multiple projects in the institute in the early process of drug discovery, especially in the stages involving active compound-to-lead optimization. He is currently working in the areas of the design and synthesis of new anti-fungals, the development of neuroprotective agents for the treatment of Alzheimer's, agents to treat ataxia, and anticancer therapeutics. Additionally, he is collaborating on computer methods to design compound libraries aimed at novel targets and fast algorithms to determine the synthetic accessibility of new compound scaffolds.

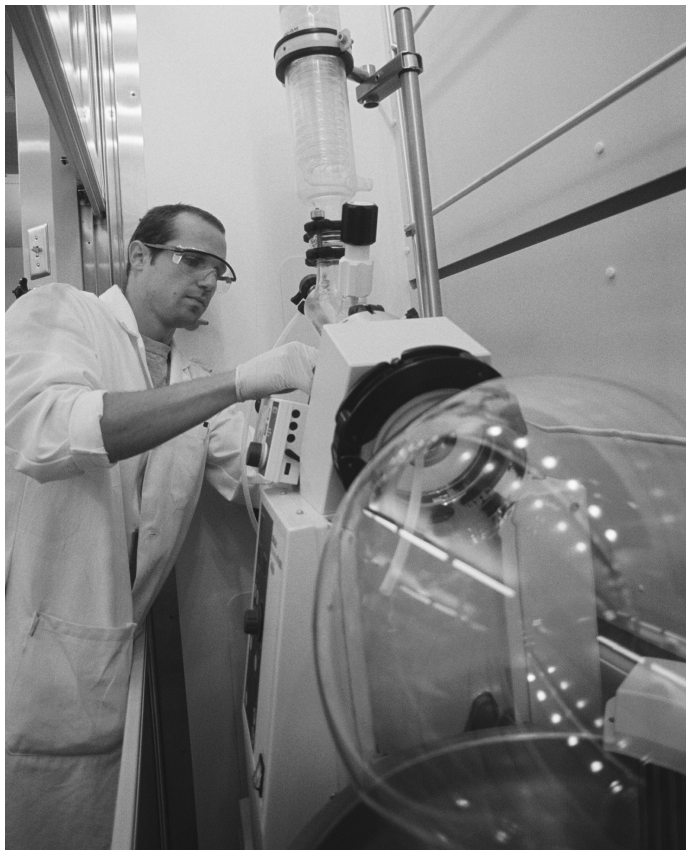
Derek Hook has spent almost all his scientific career working for pharmaceutical companies before joining Minnesota as research professor in medicinal chemistry and as director of the High Throughput Screening Core Facility at ITDD. His state-of-the-art laboratory is set up not only to provide a service function to the

VADIM J. GURVICH
M. Sc. 1987, Mendeleev University of Chemical Technology
Ph.D. 1996, Hebrew University
Research Assistant Professor 2007-present, University of Minnesota
Born, Moscow, Russian Federation, 1964.

University of Minnesota but also to work collaboratively with other institutions and to provide an educational environment in which students, postdoctoral research associates, and faculty gain experience in modern industrial drug discovery technologies and philosophy.

As part of the agreement by which Georg was appointed head of the department, the College appropriated funds to hire a new assistant professor in cancer experimental therapeutics. A national search led to hiring Daniel Harki, who spent several years as a postdoctoral research associate at Caltech working with Peter Dervan before joining the Department of Medicinal Chemistry. Harki's research focuses on the synthesis and biochemical evaluation of small molecules for applications as chemical probes of biological processes and for development as potential anticancer agents. The Harki laboratory is particularly interested in tumor cell hierarchy, espe-

cially as it relates to cancer stem cells. One project in the laboratory aims to better understand the unique biology of cancer stem cells utilizing small molecule probes. Concurrently, the Harki laboratory is developing small molecule inhibitors of this population of tumor cells. A second area of research interest resides in the field of transcription factor-DNA binding and the development of small molecules that can be utilized to manipulate such processes.



Industrial scale evaporator at the new labs in 717 Delaware Street Southeast.

MICHAEL WALTERS
B.Sc. 1981, Hope College
Ph.D. 1986, University of Michigan
Assistant Professor 1989-97, Dartmouth College
1997-2007, Pfizer Research
Associate Professor 2007-present, University of Minnesota
Born, Dearborn, Michigan, 1958.

400 MHz NMR Spectrometer in the ITDD.

Dynamic Developments

The four years that followed Georg's appointment as chair of the department would prove to be among the most dynamic in the department's long history.

Space available for use by the department more than doubled—from 18,000 square feet in Weaver-Densford Hall to some 35,000 square feet shared between Weaver-Densford Hall and the building at 717 Delaware Street Southeast. The ITDD quickly evolved into a major organization that carries out interdisciplinary research

DEREK HOOK
B.A. 1968, Hull University
Ph.D. 1972, Dalhouse University
1974-77, Rayola Chemicals
1978-97, Bristol-Meyers Squibb;
1997-99, NPS Pharmaceuticals
2000-03, Psychiatric Genomics
2003-07, 3M Pharmaceuticals Research
Professor 2007-present, University of Minnesota.

and offers scientific services to research and business communities in drug discovery and development and currently employs more than 30 scientists across a range of disciplines. It has acquired an array of instrumentation that gives it state-of-the-art capabilities in screening, synthesizing, and analysis of compounds.

Initially focused on small molecule research, it has evolved to include protein-based research. It has four scientific cores—medicinal chemistry, directed by Gunda Georg; lead and probe discovery, directed by Michael Walters; high throughput screening, directed by Derek Hook; and chemical process development, directed by Vadim Gurvich. In addition, the institute hired three experienced industrial scientists: Chris

High throughput screening at the ITDD.

Integrated laboratory HTS automation system for conducting assays in microplates at the ITDD.

Medicinal chemistry faculty sing Christmas carols at the annual holiday party in 2008.

DANIEL A. HARKI
B.A. 1999, West Virginia University
Ph.D. 2005, The Pennsylvania State University
Assistant Professor 2009-present, University of Minnesota
Born, Morgantown, West Virginia, 1976.

Stenland, a protein chemist; Peter Dosa, a synthetic medicinal chemist; and Henry Wong, a pharmacologist.

Peter Dosa came to the University of Minnesota in June 2009 from Arena Pharmaceuticals. While at Arena, Dosa worked on several programs that reached the clinic, including an antithrombotic agent. Now part of the ITDD, Dosa is pursuing the development of water-soluble prodrugs of ursodeoxycholic acid, an antiapoptotic bile acid that has been shown in animal models to significantly reduce the damage caused by a heart attack or stroke. He has also been working on designing safer analogs of the dopamine agonist cabergoline, which could potentially be used to treat Parkinson Disease, Cushing's Disease, or sexual dysfunction.

Today, the ITDD is home to almost 60 projects, the majority of them interdisciplinary and involving partners within the University, like the Masonic Cancer Center, as well as partners outside the University, like the Mayo Clinic and University of Kansas, and sponsored by a wide array of institutions, including NIH, the Gates Foundation, the

Medicinal chemistry faculty at a 2009 picnic. Left row (front to back): Philip Portoghese, Barry Finzel, Chris Xing, Derek Hook, Dan Harki, Mrs. Harki. Right row (front to back): Yusuf Abul-Hajj, Gunda Georg, Rick Wagner, Pat Hanna, Natalia Tretyakova, Gregg Janis. Standing: Tom Shier. In the background: Mrs. Abul-Hajj, Mrs. Hanna, Peg Houck, and Peter Dosa. It is interesting to compare faculty attire with the 1936 faculty picnic (see page 34).

Mayo Clinic, the Minnesota Partnership, the University of Chicago, and the Northern California Institute for Research and Education (Institute, 2010).

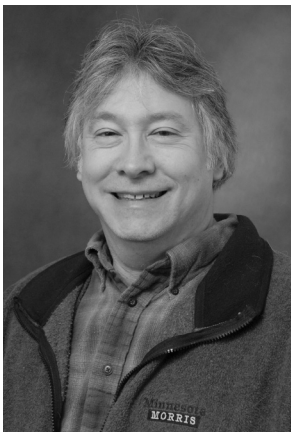
In the fall of 2006, the Minnesota Partnership for Biotechnology and Medical Genomics, which had previously invested in research projects, research infrastructure, and new research facilities, launched a new initiative involving paired faculty hires between the University of Minnesota and the Mayo Clinic. The partnership planned to make available in 2006-07 approximately $6 million for start-up packages for new faculty recruits to the two institutions.

New graduate students enjoy the 2009 medicinal chemistry departmental picnic at Como Park in St. Paul.

Through the partnership, the department sought to capitalize on this opportunity to accomplish one of the strongly endorsed initiatives in its strategic plan. Rodney Johnson, interim chair, submitted a joint proposal for the paired hires between the Division of Oncology at the Mayo Clinic and the Department of Medicinal Chemistry. The Division of Oncology Research proposed to search for an established investigator of DNA damage-induced signaling, cell cycle regulation/checkpoint activation, and/or DNA repair while the Department of Medicinal Chemistry proposed to search for an established investigator with expertise in the

PETER I. DOSA

B.A. 1995, Princeton University
M.S. 1998, Massachusetts Institute of Technology
Ph.D. 2002, University of California, Berkeley
2002-09, Arena Pharmaceuticals
Research Assistant Professor 2009-present, University of Minnesota
Born, Manchester, England, 1973.



BARRY C. FINZEL
B.S. 1979, Eastern Michigan University
Ph.D. 1983, University of California at San Diego
1983-86, Genex Corporation
1986-87, Dupont Company
1988-92, Upjohn
1992-2003, Pharmacia
2003-07, Pfizer
Professor 2008-present, University of Minnesota
Born, Monroe, Michigan, 1956.

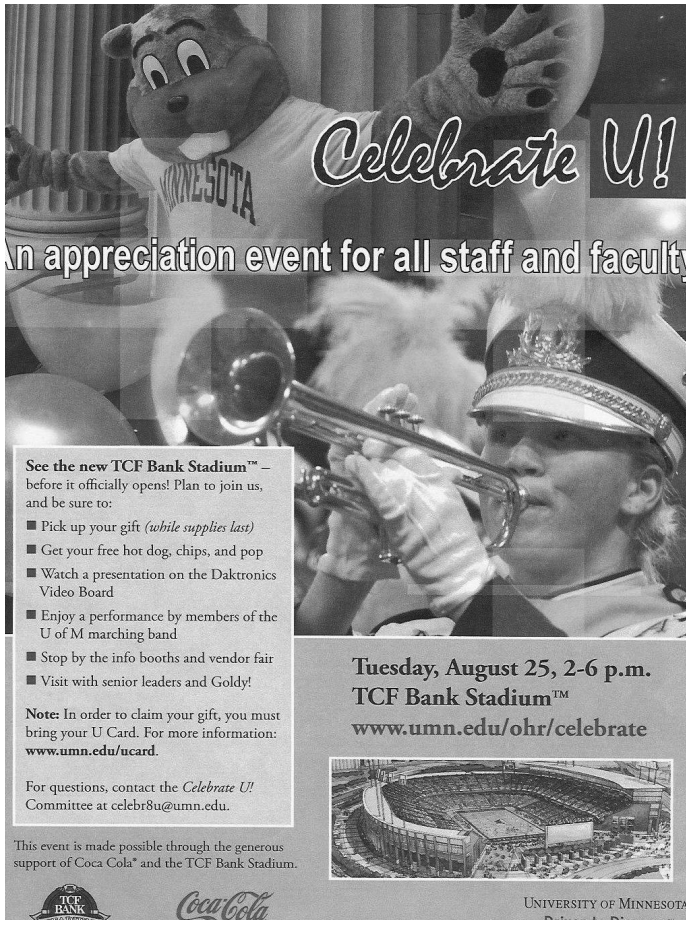
X-ray crystallography of drug-protein interactions that are identified as potential new targets for treating cancer. After a national search, Barry Finzel, a well-established X-ray crystallographer working for Pfizer for several years, was appointed as professor of medicinal chemistry.

Barry Finzel brings a strong industrial background and practical experience in the drug discovery process to the department. While working for nearly 20 years in large industry concerns, his research focused on providing timely, detailed experimental structural data to support medicinal chemistry, analog synthesis, and drug design. By applying X-ray crystallography to characterize targeted protein-ligand complexes, the molecular environment of drug action can be detailed and exploited

The Medicinal Chemistry Department, October 2010, showing faculty, staff, graduate students and research personnel. The department has doubled in size since 2006 as a result of the new faculty hires and the establishment of ITDD.

to help direct compound optimization and drug development. Since joining the department he has built upon the legacy of rapid structure delivery developed in industry to provide insightful experimental structural data to aid collaborators in the design of chemical probes with unique biochemical and pharmacological properties. Working in close collaboration with synthetic chemists and modelers, he is currently working to identify agents with antibacterial activity targeting anthrax, multi-drug resistant tuberculosis, vancomycin-resistant infections, and cancer and inflammation targets by utilizing structure-based drug design. He is also working to develop computational tools to mine existing databases for structural data and to simplify the way

Faculty and graduate students attend a luncheon for recruitment of graduate students for the 2010 academic year.



The University community celebrates the opening of TCF Bank Stadium, August 2009.

CARRIE HASKELL-LUEVANO
B.S. 1990, California State University-Fresno
Ph.D. 1995, University of Arizona.
Assistant Professor 1998-2004; Associate Professor 2004-08; Professor 2008-11, University of Florida
Portoghese Endowed Professor, 2011-present, University of Minnesota
Born, California, 1968.

collaborators who may not be experts in structural biology.

In recognition of Philip Portoghese's 50 years of teaching, research, and service (as the longest serving faculty member since the establishment of the College), the department held a symposium in his honor followed by dinner at the campus club. Faculty, Portoghese's family members, alumni, and friends were in attendance at the celebration.

Other additions to the faculty include Carrie Haskell-Luevano, who was selected by a search committee specifically to be the first faculty appointed to the newly formed Philip S. Portoghese Endowed Chair in Medicinal Chemistry.

Portoghese established the chairship as a way of marking his 50 years in the Department of Medicinal Chemistry and to express gratitude for the opportunity the College has provided him to conduct his groundbreaking research. The $2 million endowment, half of it donated by Portoghese and half by the Permanent University Fund, ensures ongoing support for research in chemical neuroscience—Portoghese's principal area of work—at a time when the majority of faculty in medicinal chemistry are engaged in research focused on cancer.

In keeping with that goal, Haskell-Luevano was hired on the basis of her research focusing on the understanding of the melanocortin hormone endocrine systems in the brain, and their involvement in feeding behavior, obesity, exercise, diabetes, and energy homeostasis. Multidisciplinary approaches to study this pathway include medicinal chemistry, chemical biology, biochemistry, molecular biology, pharmacology, physiology, and neuroscience. Through the use of rational design approaches and combinatorial chemistry library screening, Haskell-Leuvano works on developing pharmacologically distinct and receptor selective ligands (peptide and small molecule) to probe the physiological role or roles of the melanocortin pathway in mice. These ligand data will also be complimented by the generation and use of receptor mutations to probe putative ligand-receptor interactions and the molecular mechanisms of melanocortin receptor signaling in the brain.

Speakers celebrating Portoghese 50 years of service (left to right): Lawrence Marnett (Vanderbilt University); Ivy Carroll (Research Triangle Park); Chris McCurdy (University of Mississippi); Dean Marilyn Speedie; Philip Portoghese; Gunda Georg; Yusuf Abul-Hajj; Alex Makriyannis (Northeastern University).

Along with other interdisciplinary collaborations taking place involving department faculty outside ITDD's structure, the institute marks a step forward for medicinal chemistry. Many challenges, of course, still lie ahead. Many outstanding faculty are at or nearing retirement age and the establishment of the multidisciplinary, multi-institutional ITDD, although it is part of medicinal chemistry, may foreshadow a long-term transformation of traditional departmental organization and structure. Nevertheless, at its centennial celebration in 2012, the Department of Medicinal Chemistry—whether measured by faculty achievements, research funding, innovation, or long-range prospects—is perhaps stronger today than at any time since the beginning of its evolution when Frederick Wulling arrived in Minnesota in 1892 to found the University's College of Pharmacy. §