medicine at MICHIGAN
Spring 1999

150 YEARS AND GOING STRONG:
THE U-M MEDICAL SCHOOL
CELEBRATES ITS SESQUICENTENNIAL

Bench-to-Bench GENIUS

Two **MacArthur awards** in biological chemistry honor the creativity of two **great** scientific **minds** at **Michigan**

Understanding the

If cells could be said to speak

Michael Marletta and

are two of the

language of cells:

their own language, **Kun-Liang Guan** best translators around

By Jane Myers

The laboratories on the fourth and fifth floors of the University of Michigan Medical School's Med Sci I building where Michael Marletta and Kun-Liang Guan do their work look a lot like biological laboratories everywhere. Their appearance suggests the organized chaos common to such spaces: shelves and bench-tops covered with an array of beakers and lidded jars, vials and pipettes, plastic tubs and tubing, centrifuges, the bulletin boards covered with bits of chemical shorthand on scraps of paper side-by-side with kiddie art.

But there is something else here: a certain esprit de corps, a palpable feeling of shared enthusiasm that may not be found in every such scientific enterprise. Part of it is sheer pride — how many other academic departments in America have not one, but two members of the faculty who have been selected to receive the coveted MacArthur "genius" awards three years apart? Part of it is the energy and great good cheer that emanates from the chair of the Biological Chemistry Department, Jack Dixon, who describes himself as a kind of "bus driver," a man whose job it is to keep everyone traveling happily down the road toward the next great discovery on an itinerary that hasn't been short of great discoveries yet.

And part of it is what might be termed "historical pride" — an awareness that this department in this medical school at this university has been truly outstanding for a very long time, going back to the 20s when it was known as the Department of Physiological Chemistry and gaining increased stature in the 70s and 80s under the legendary Minor J. "Jud" Coon, holder of the Victor C. Vaughan Distinguished University Professorship of Biological Chemistry, member of the National Academy of Sciences and a man so enamored of his work that now, at the age of 77, he is still frequently found at his bench in the lab. Professor Coon's highly regarded work on cytochrome P450 enzymology and his role in training many of the leaders in the field who did their graduate or postdoctoral training in his laboratory set a standard that has inspired everyone who has followed.

The generous collaborative instincts that have helped make Biological Chemistry such a productive place are shared by its two stars of the moment, Marletta and Guan. "There are occasionally people who are brilliant and difficult to get along with," Jack Dixon notes. "These two are brilliant and a joy to be with. I, personally, and the people here in the lab, benefit from their presence. They interact with each other and with me and others on a daily basis. You don't have to have all the great ideas yourself in this lab. We all bump into each other all the time, and we talk about what's going on."

"These two are **brilliant** and a **joy** to be with. I, personally, and the people here in the lab, benefit from their **presence**.

What's going on in Michael Marletta's labs is the outgrowth of work on nitrate synthesis he began almost 14 years ago as an assistant professor of toxicology at the Massachusetts Institute of Technology. So fundamental and revolutionary was his discovery that hundreds of scientists around the world are now engaged in research derived from his unlikely finding: that nitric oxide (NO), a ubiquitous, chemically reactive, toxic compound, plays a major role in the human body's immune system (from killing bacteria to killing tumors), in the nervous system, the cardiovascular system, and because of its action on smooth muscle, in activities as removed as digestion and sexual intercourse. (The wildly popular Pfizer product, Viagra, could not have been developed without initial discoveries about NO.)

The implications of his work have turned Marletta into a philosopher of sorts these days. "In the last year and a half I've been doing a lot of reading about evolution," he says quietly. The question that torments him in the way that only a scientist can be tormented is a very simple one: Why NO?

"Why did nature choose NO as a signaling device? Marletta muses. "People know that carbon monoxide is toxic. NO is even more toxic. It's chemically reactive. It inhibits electron transport. How is it possible that it could work?"

Lu Gift Endows New Professorship in Department of Biological Chemistry

Anthony Y.H. Lu, Ph.D., (second from left) came to Michigan as a postdoctoral fellow in biological chemistry in 1966 to work under the direction of Professor Minor J. Coon. He and his wife, Lillian Lu, last year established a charitable remainder unitrust of more than $1 million to endow the Anthony and Lillian Lu Professorship in Biological Chemistry. Their gift was matched by $750,000 from a fund set up by former Interim Dean A. Lorris Betz. Dr. Lu retired last year as executive director of drug metabolism at the Dupont Merck Pharmaceutical Company. He is also an adjunct professor in the Department of Chemical Biology in the School of Pharmacy at Rutgers University. The Lus are pictured here at a dinner in their honor in Ann Arbor last fall with their daughter, Deborah Lu, who received her doctorate in biological chemistry from the department in 1996 and now works in the structural biology program at the Skirball Institute of Biomedical Medicine at New York University, and with Jack E. Dixon (left), chair of the department, and Minor J. Coon (right), Dr. Lu's mentor at Michigan.

Similar questions were asked by Marletta's incredulous senior colleagues at MIT when they denied him tenure in 1987 and propelled his move to Michigan, where he has joint appointments in the Medical School and the College of Pharmacy. Marletta is the John Gideon Searle Professor of Medicinal Chemistry and Pharmacology in the College of Pharmacy and became a Howard Hughes Medical Institute investigator in the Medical School in 1997. Nobody along the Charles River believed the brash 36-year-old when he said then that nitrates and the immune system had something to do with one another. But MIT's loss, and Marletta's gutsy gamble to trust his intuitive hunches, were Michigan's gain.

Marletta started out trying to figure out how and why the body makes its own nitrates, chemicals which in the late 70s had been identified as undesirable in such preserved meats as bacon and salami because of their potential cancer-causing properties. Marletta left MIT having made a couple of important discoveries: 1) that macrophages, those immune-system cells that attack invading organisms, manufacture nitrates, and 2) that nitrates are derived from the amino acid arginine.

Soon after arriving at Michigan, he made the discovery that would define his professional life and that of hundreds of other scientists for decades to come: the biochemical pathway from arginine to nitrates goes arginine-NO-nitrates – and it is the nitric oxide that through a process of cell-to-cell diffusion causes so many other things to happen in the human body.

Exactly how arginine makes nitric oxide is still unknown today. But the biochemical pathway discovered by Marletta has led to many other discoveries, and resulted in the Nobel Prize in Medicine last year for three American scientists studying physiological aspects of NO. Marletta contemplates with pleasure the tidy closed circle geometry suggested by the fact that Nobel's fortune was based on nitroglycerine and its macro- applications (i.e., blowing things up) and that that same fortune has now rewarded scientists who have advanced our micro-understandings of one of the things that nitroglycerine becomes in the human body: NO.

Jack Dixon, chair of the Department of Biological Chemistry.

Michael Marletta with graduate student Jon Winger of Madison, Wisconsin.

...the **discovery** that would define his **professional** life...

National Recognition for Faculty Members in the Department of Biological Chemistry

In addition to the MacArthur Fellowships received by Michael Marletta and Kun-Liang Guan, many other members of the Department of Biological Chemistry have also received national honors. They include the following:

NATIONAL ACADEMY OF SCIENCE
Minor J. Coon
Vince Massey

INSTITUTE OF MEDICINE
Bernard W. Agranoff
Minor J. Coon
Jack E. Dixon
Gary J. Nabel

AMERICAN ACADEMY OF ARTS AND SCIENCE
Minor J. Coon
Jack E. Dixon

BURROUGHS WELLCOME TOXICOLOGY SCHOLAR AWARD
Dennis Thiele

BURROUGHS WELLCOME NEW INVESTIGATOR AWARD IN THE PHARMACOLOGICAL SCIENCES
Ronald Taussig

PEW SCHOLAR IN THE BIOMEDICAL SCIENCES
Mark Saper

SEARLE SCHOLAR
Lawrence Matthews

AMGEN AWARD FOR BIOMEDICAL RESEARCH
Gary Nabel

SCHERING-PLOUGH YOUNG INVESTIGATOR AWARD
Kun-Liang Guan

LUCILLE P. MARKEY SCHOLAR
Robert Fuller

"Research always goes interesting results

A British physician, Lauder Brunton, discovered in 1867 that organic nitrates were effective in relieving pain in angina pectoris, and Nobel himself was prescribed nitroglycerine (which he declined to take) for his own chest pain in 1890. Why nitroglycerine relieves chest pain was not understood for more than a century, even though it did become known eventually that nitroglycerine breaks down into several compounds, including nitric oxide, in the human body. It wasn't until scientists learned that NO is produced by the body itself and plays an important role in the dilation of blood vessels that the connection between nitroglycerine and the relief of chest pain became clear.

Post-doctoral students working with Kun-Liang Guan: Thomas Lanigan (above) of Waterloo, Iowa, and Weiquan Li (right) of Shanghai, China.

where the most lead you..."

Marletta would be even more pleased, needless to say, if the Nobel Prize had not been given for physiological discoveries related to NO but for the fundamental molecular discoveries that came first.

The initial skepticism surrounding the discoveries showing that nitric oxide is endogenously synthesized and plays a central role in cell-to-cell signaling as well as in response to infection has largely disappeared, although central questions in all aspects of the biological function of NO still remain. As the facts have unfolded over the past decade, it has become clear, however, that NO functions very effectively as a cell-to-cell signaling agent. The chemical properties of NO, namely a fast diffusion rate from the site of generation, the ability to cross cellular membranes and a chemical reactivity that allows it to function without the apparent need for a complicated system to terminate the signal are well suited to its cellular tasks. NO also plays a crucial role in response to infection. It appears that the immune system has harnessed the toxic properties of NO to induce cytostasis in invading microorganisms as well as tumor cells.

Michigan's leadership in NO research in recent years has been in figuring out how, when NO diffuses from one cell to an adjacent cell, say, from an endothelial cell to a smooth muscle cell, it "turns on" an enzyme known as soluble guanylate cyclase (sGC) which then catalyzes the conversion of guanosine 5'-triphosphate (GTP) to cyclic guanosine 3',5'-monophosphate (cGMP). It is this cGMP that acts in the cardiovascular system (in the regulation of vascular tone and platelet function) and in the nervous system (in neurotransmission and, possibly, long-term potentiation and depression). Marletta and his team have been leaders in clarifying on a molecular level how this chain of events occurs (from sGC to GTP to cGMP) and how the further downstream elements of the sGMP-induced protein-targeting work.

How these so-called "second messenger" enzymes get turned off again is another big question. Discoveries in recent years have shown that a category of enzymes known as phosphodiesterases are crucial to the signal termination. New understandings of how phosphodiesterases work are what led to the development of Viagra.

The basic question that drives Kun-Liang Guan's work at Michigan involves another kind of signaling, the understanding of which will allow us to one day know some of the answers to a deceptively simple question: How does a cell control its growth? The answers of course will be fundamental contributors to our understanding of many diseases, including cancer. What Kun-Liang and the many other people engaged in similar research around the world know is that cells have a complex communication system that's almost, he says, "like the communication system for a company. There is information flow from outside the cell, which the cell has to convert to its own language."

Kun-Liang's specific interest is "Ras," a cancer-causing gene in that class of genes known as "oncogenes." "It has an essential role to tell the cell to grow or not to grow," Kun-Liang says.

But how?

"We try to interfere with the signal to figure this out," he explains as simply as possible. "We try to understand what's happening." About five or six years ago, Kun-Liang says, he thought it would be interesting to look "downstream" from the Ras gene and he began studying some of the other chemicals that seem to be part of the Ras signaling system, specifically the proteins tyrosine phosphatase and MAP kinase. Kun-Liang doesn't know where this work will ultimately lead: "Research always goes where the most interesting results lead you," he says cheerfully, but he is hoping that great progress will be made in the years to come. "Many people are working on similar areas," he says. "There is lots of competition and lots of helping, almost at every campus."

THE JOHN D. AND CATHERINE T.
MACARTHUR FOUNDATION

MacArthur Fellows Program

"Creativity appears to be something that gets lost in the definition, like humor. This is not because creativity cannot be described, but because it can be interpreted in so many ways. In this program we have found it useful to regard creativity as an expression of human endeavor in actively making or finding something new, or in connecting the seemingly unconnected in ways that are significant.

"We believe that creativity is a universal human attribute, present to some extent in everyone, and that it may be manifest in virtually any activity. As we see it, this quality deserves recognition and careful handling in each individual, not simply in certain individuals. This may seem at odds with our program in which we select only a small number of individuals each year for recognition and reward. We identify individuals whose creativity has been especially pronounced, those with promise of benefiting from the award, and of then benefiting society. These individuals also exemplify human possibility."

. . . the MacArthur Fellows Program

In Marletta's and Guan's labs there is also an element of what might be described as the magical, a perhaps unlikely concept to introduce when talking about two scientists rigorously probing the boundaries of our knowledge about extremely important biological processes.

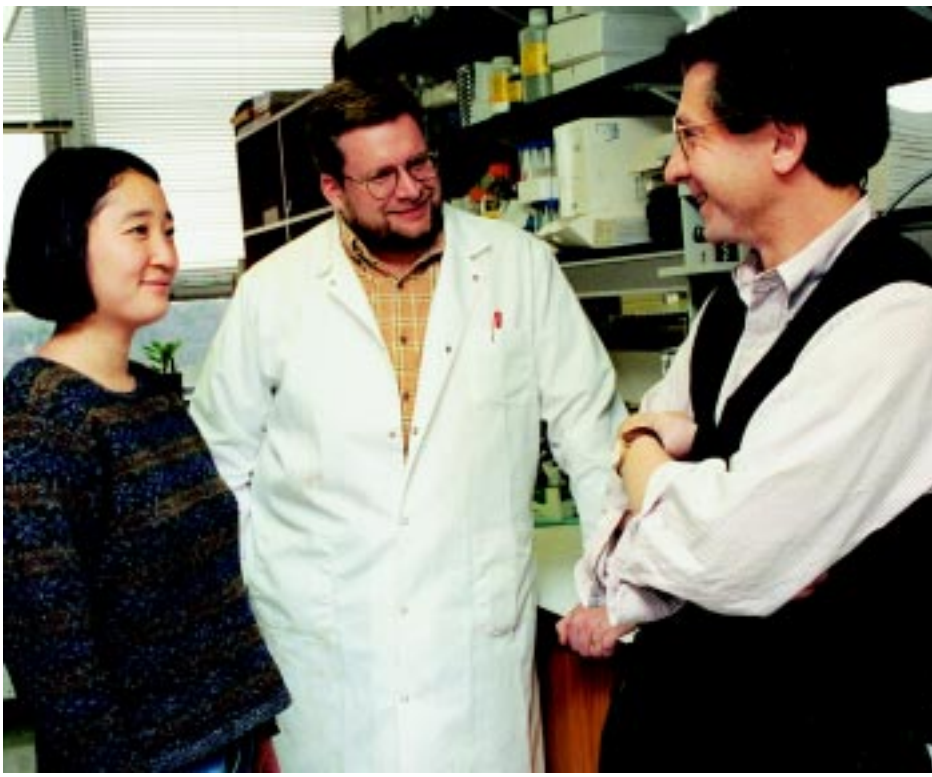
But how else to explain that the son of a poor rice-farming peasant in the tiny village of Tong-xian in southern China, a child surely destined to plant rice himself, and a young man from a blue-collar community in upstate New York whose father earned his living manufacturing mustard in a French's plant, would end up in the same department as two of the great scientific minds of their generation?

Upward mobility in America is not an unknown concept, but there is a powerful element of luck in Kun-Liang Guan's story. Born in 1963, he was a child of the Cultural Revolution, an ultimately disastrous period of great suffering for many Chinese people but one that saw great advances in literacy across the Chinese countryside. "In a farmer's family in our village, a child would go to school no more than a few years," Guan explains. "But because of the Cultural Revolution, they built a school in my village." When Guan was 15, the Cultural Revolution ended and Chinese universities, which had been closed, reopened. Through standardized national exams, Guan's academic abilities were identified and he was sent off to Hang-zhou University, only 30 miles but two hours by bus from his village. The fellow student he bunked with in the dorm was 30 years old, as were many of his classmates. Because no one in China had attended college for an entire decade, teens and 30-somethings whose educational careers had been rudely interrupted found themselves sitting side by side in the newly opened institutions.

Guan thought he wanted to be a physicist, but his scores in physics were not good enough and he was assigned to study biology. Shortly thereafter a molecular biologist at Cornell University, Ray Wu, started an exchange program for American and Chinese biology students, and Kun-Liang's scores on the exams given to qualify students for the program put him at the top of a new list. "I never thought about coming to the U.S.," he says. "But whenever I was supposed to take an exam, I took it!"

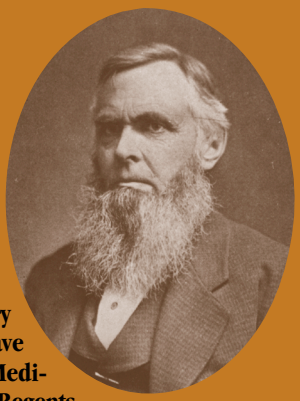
That he is now the holder of a MacArthur Fellowship and richer by a no-strings-attached $230,000 because of it, does not seem to have affected Guan's sense of himself in any way. "I basically took a ride – I was not in the driver's seat," Guan, now 35, says about his career. The new happy surprises that continue to come his way are, it seems, as welcome as they have ever been, but not to be crowed about. "Luck is the most important thing in getting it," he says modestly of his MacArthur award. "Many people are doing fantastic work."

Well, has he taken any message from it? "Maybe what you're doing is worthy of the effort," he says simply.



Michael Marletta with M.D.-Ph.D. student Clara Choi of Los Angeles, and post-doctoral student Robert Busby of Philadelphia.

The Evolution of the Department of Biological Chemistry at Michigan



One of the first members of the Medical School faculty, Silas Douglas, was appointed to teach chemistry. In fact, the first chemistry courses taught at Michigan were taught as part of the Medical School curriculum. Dr. Douglas had a small laboratory in the medical building, and he gave chemical demonstrations before the Medical School classes. He persuaded the Regents in 1855 to build the first building at any American university solely devoted to chemistry. Douglas was in charge of the University's building program and he placed the Chemical Laboratory immediately behind the Medical Department. The two buildings were connected by a wooden walkway spanning the mud.

Dr. Douglas and his staff taught chemistry to the rest of the University, and the Chemical Laboratory was repeatedly enlarged. At first, Preston Rose taught toxicology and the elements of urine analysis to medical students, but the latter subject was soon included in a course in physiological chemistry taught by Victor Vaughan, who later became dean of the Medical School.

Albert Benjamin Prescott taught the practical aspects of materia medica and the elements of pharmacy to medical students who often had to be their own pharmacists when in practice in the countryside. His program grew into a full-fledged College of Pharmacy housed in the Chemical Laboratory. Engineering students studied inorganic analysis and metallurgical chemistry and Literary College students learned organic and inorganic chemistry from Medical School faculty.

In 1883, Victor Vaughan was appointed professor of physiological and pathological chemistry. He was the first man to hold a professorship in physiological chemistry in a medical faculty in this country. Under the able leadership of Dr. Vaughan and his pupil, Frederick Novy, the subject was developed as part of the offerings of the combined Department of Bacteriology, Physiological Chemistry, and Hygiene.

After the retirement of Dr. Vaughan in 1921, it was felt that physiological chemistry, in view of its rising importance, could hardly be kept in the position of an adjunct to other subjects. A separate Department of Physiological Chemistry was established in 1922. In 1935, with the approval of the executive committee of the Medical School, the department's name was changed to Biological Chemistry. It was felt that the broader term "biological" was more in keeping with the recent developments in this branch of chemistry.

Horace W. Davenport, Not Just Any Medical School: The Science,Practice, and Teaching of Medicine at the University of Michigan,1850-1941 (Ann Arbor: University of Michigan Press, in press).

Howard B. Lewis, "The Department of Biological Chemistry," in The University of Michigan, an Encyclopedic Survey, ed. Wilfred B. Shaw (Ann Arbor: University of Michigan Press, 1951).

For Marletta, who received more than $275,000 from the MacArthur Foundation (the amount awarded increases with the age of the awardee), the money has meant the freedom of not having to worry about money and, equally importantly in his view, increased credibility. Because of the award, he was able to take a six-month sabbatical and spent a month at Brandeis University. He liked the freedom of being able to afford an apartment large enough so that his wife, Margaret, and their four-year-old son, Matthew, could come and visit him during his time there. He has also enjoyed the increased visibility. "People do pay more attention to you," he says. "They think you know more, even if you don't. It gives you an audience, and that's important to me. It gives me an opportunity to talk to people about science, and in the process hopefully raise people's awareness of how real science is done."

Marletta has had offers from other institutions, but he's firmly planted in the Midwest, at least for the time being. "They've treated me better than they even should," he says about the Biological Chemistry Department and his recent move into new lab space there. "It's an exciting time to be working at the interface of chemistry and biology, and an exciting time to be at Michigan," he says. "The leadership in this department from Jack Dixon and the leadership from both the president and the provost have been great. They're committed to taking science to the next level and to supporting the cross-disciplinary efforts that are one of this institution's strengths."

"Their intelligence, enthusiasm and willingness to freely share ideas with others are characteristics which I hope will be replicated many times over as we marshall our efforts to participate fully and at the highest levels in this area of human knowledge."

What's next for Marletta? Is it NO forever? "Between 1.5 and 2 million people die every year of malaria, and 70 percent of those who die are under the age of ten," he says carefully, as though he's thought about this question before. "I'd like to do something about that. I'll always be doing chemistry, but chemistry of the kind that can have an impact on human health is what interests me."

Guan, who is a member of the Biological Chemistry Department as well as holding a position in the Institute of Gerontology, was recruited to Michigan by Jack Dixon when he moved to Michigan from Purdue. Guan doesn't have any trouble thinking of reasons why he loves Michigan either. "I'm so glad Michael is here," he says. "And I want to emphasize that it's the people in the lab, most of whom are outstanding graduate students, who are so important. The research environment here is very good," he says. "I have outstanding colleagues and the department is very supportive. There is the collegial interaction. And another thing – I like Ann Arbor. It's a small town, good for raising children. I have two kids, a daughter, nine, and a son, six. My wife, Yuli Wang, who is also a biochemist, likes her work at Parke-Davis. I think that I am very, very happy."

University President Lee C. Bollinger, who in May, 1998, appointed a 19-member Life Sciences Commission to undertake a study of the potential for new directions and new collaborations in the life sciences at Michigan, and who invited Dixon and Marletta to be members of the Commission, applauds the success of their department and Marletta's and Guan's achievements. "In the University's quest to become one of the leading academic centers for the study and application of the life sciences, Michael Marletta and Kun-Liang Guan and the Department of Biological Chemistry stand as inspiring models for our future efforts," he says. "Their intelligence, enthusiasm and willingness to freely share ideas with others are characteristics which I hope will be replicated many times over as we marshall our efforts to participate fully and at the highest levels in this area of human knowledge." m

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