

THE UNIVERSITY OF MEDICINE &amp; DENTISTRY OF NEW JERSEY



# UMDNJ RESEARCH

FOR THE RESEARCH COMMUNITY FROM THE STATE UNIVERSITY OF THE HEALTH SCIENCES

## Improving prostate cancer care – from byte to bedside

by **Grace Lu-Yao and collaborators**

GRACE LU-YAO, PHD, MPH, ASSOCIATE PROFESSOR, DEPARTMENT OF MEDICINE, UMDNJ-ROBERT WOOD JOHNSON MEDICAL SCHOOL

**T**he Cancer Institute of New Jersey (CINJ), located at 195 Little Albany Street, is the site where we have used a large national database on cancer, crunching hundreds of gigabytes of data in search of answers to unresolved clinical issues related to prostate cancer. This cancer is the most common non-skin cancer among men. However, unlike the majority of other cancers, it often progresses slowly, so has little impact on overall survival for the majority of patients. The slow progression of the disease, in most cases, presents special challenges to oncologists, who need to balance the risks and benefits of intervention in early stage prostate cancers. Our research team, led by Grace Lu-Yao, PhD, MPH, which is defining standards for modern patients diagnosed in the prostate specific antigen (PSA) era, has received international attention in recent years for this work.

### UMDNJ's Schools

Graduate School of Biomedical Sciences

New Jersey Dental School

New Jersey Medical School

Robert Wood Johnson Medical School

School of Health Related Professions

School of Nursing

School of Osteopathic Medicine

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The University of Medicine and Dentistry of New Jersey is a statewide network of eight schools on five campuses in Camden, New Brunswick/Piscataway, Newark, Scotch Plains and Stratford. The schools include New Jersey Medical School, Robert Wood Johnson Medical School, School of Osteopathic Medicine, New Jersey Dental School, Graduate School of Biomedical Sciences, School of Health Related Professions, School of Nursing and School of Public Health. The University has more than 5,600 students in more than 100 degree and certificate programs, more than 15,000 employees, including nearly 3,000 faculty members, more than 24,000 alumni and more than 200 education and healthcare affiliates throughout New Jersey. The University is dedicated to pursuing excellence in the education of health professionals and scientists, conducting research, delivering healthcare, and serving the community. UMDNJ is ranked among the 70 top research universities in the country.

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William F. Owen, Jr., MD  
President

Kathleen W. Scotto, PhD  
Vice President of Research

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## COLLABORATION AND THE FUTURE OF UMDNJ'S SCIENCE



**T**eamwork drives research. The notion of a scientist laboring long hours in relative isolation went by the wayside long ago. Laboratories are small communities, where a spectrum of investigators pools their talents and skills on shared projects that often continue for years.

Young researchers work side by side with, and learn from, more experienced ones; long-term scientists are re-energized with fresh ideas from those just entering the field.

But in the last 10 to 15 years, our notion of what constitutes a research community has changed dramatically. With the introduction and growing use of the Web, and the ever-increasing sophistication of telecommunications, scientists no longer have to be in the same geographical locale in order to team-up. While working side-by-side in the lab is still more customary — since researchers, like workers in other industries, enjoy exchanging personal insights at the bench or the “water cooler”— the virtual shared workplace is quickly gaining proponents.

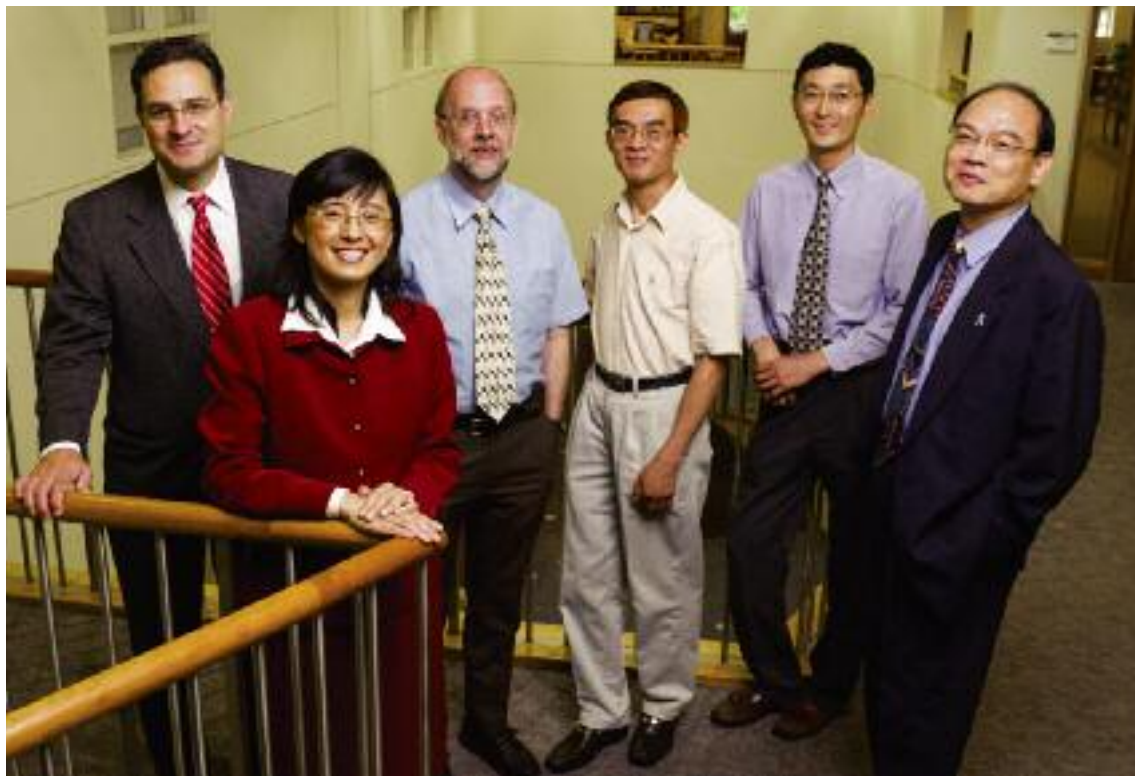
The obvious benefits of collaboration hardly need to be restated. But, certainly, one stands out: Researchers coming from distinctly different backgrounds, disciplines and places, together can approach problems that neither could tackle alone.

That is what this issue of *UMDNJ Research* is all about. We are a large research university with eight schools on five campuses. Our research runs the gamut from the most basic discoveries to the translation of those discoveries into better understanding, prevention and treatment of human disease, and we are dedicated to training and nurturing the researchers of the future. We have a long history of intra-school research and training partnerships, but have in the past been less likely to reach across campuses to establish collaborations. To foster more University-wide collaborations, the Office of the Vice President for Research has provided financial support to several research teams whose members come from two or more of the University's schools. These collaborators, and others, are featured in this publication.

Their partnerships are already yielding successful outcomes. Several articles have been accepted and/or published by major journals. In addition, a University spin-off company, involving UMDNJ-Dental School investigator Scott Kachlany, who is working with UMDNJ-Robert Wood Johnson Medical School oncologist Roger Strair, has attracted initial funding and is beginning FDA-required studies of a novel therapeutic agent.

I hope you will take the time to read about the work of these researchers who have reached beyond school and geographical boundaries to forge new professional networks and novel scientific investigations.

Kathleen W. Scotto, PhD  
VICE PRESIDENT OF RESEARCH



LEFT TO RIGHT: ROBERT DIPAOLO, MD; GRACE LU-YAO, PHD, MPH; DIRK MOORE, PHD; YONG LIN, PHD; SIU-LONG YAO, MD; JOE SHIH, MD

Since 2004, Dr. Lu-Yao has been working with the biostatistics team at CINJ. Our group of researchers has refined and applied instrumental variable analytic (IVA) methods to address clinical issues that are unlikely to be solved by clinical trials. IVA is a method of capturing the random component of patient treatment choice and using it to balance treatment groups, so that two different treatments can be compared with minimal bias.

The first major clinical problem that the team tackled was setting out to determine whether use of hormone therapy improves survival among men with prostate cancer that has not spread elsewhere in the body. Hormone therapy is a treatment that suppresses prostate cells and is commonly used for men whose prostate cancer has spread to other parts of the body. This type of therapy highlights a treatment dilemma. In order to treat this type of cancer early, many oncologists have been using hormone therapy in prostate cancer patients even before the disease has spread beyond the prostate. But this practice has generated controversy since its value in such early stage cancer has not been well-established, and this therapy has many undesirable side-effects. Furthermore, randomized clinical trials — the gold standard for evaluating risks and benefits of a therapy — are difficult to conduct in the largely elderly population for which the therapy might be given. The number of patients with localized disease who are treated with hormone therapy tripled between 1989 and 2001 even though there has not been any clinical proof that it works in these circumstances.

Through the use of instrumental variable analysis and a large national database, our team found that hormonal therapy was not clinically beneficial for most men with localized prostate cancer who did not undergo surgery or radiation therapy. However, the team also found that some men with very aggressive disease might benefit. Although many people think that when a patient is diagnosed with cancer, doing something is better than nothing, this may not be true. Because of the potential side effects of the treatment, men with localized, non-aggressive tumors should carefully consider whether hormone therapy is the best option, and they should discuss other options, such as localized radiation therapy, surgery, and active surveillance (watch and wait) with their physicians.

At the 2008 Genitourinary Cancers Symposium in San Francisco, our team gave a presentation that provided benchmarks for conservative management of prostate cancer. In July 2008, we published a study in *JAMA* comparing the 10-year outcomes of almost 20,000 men older than 66 who had early stage, localized prostate cancer. Approximately 40% of these men were treated with PADT (primary androgen deprivation therapy), which deprives the prostate of the male hormone androgen. At the end of 10 years, the group treated with PADT and the group that was not had similar survival rates. We concluded that hormone-blocking drugs do not improve survival in older men with early-stage prostate cancer. (A small subgroup of men suffering from a very aggressive form of the disease may have derived some benefit from the therapy). The study received wide international coverage and was awarded best faculty research endeavor at Robert Wood Johnson Medical School.

*Grace Lu-Yao is an associate professor in the Department of Medicine at Robert Wood Johnson Medical School (RWJMS). Her primary research interests are the study of the epidemiology of prostate cancer and outcomes assessment of prostate cancer therapies. She earned her MPH and PhD from Yale University School of Medicine and was an assistant professor at Dartmouth Medical School before joining CINJ. She has received research funding from the Department of Defense, the NCI, the NIH, and the New Jersey Commission on Cancer Research. Her work has been published in the Journal of the American Medical Association (JAMA), Lancet, the Journal of Urology and the Journal of the National Cancer Institute. She is an elected fellow of the American College of Epidemiology.*

*Robert DiPaola's primary research interest is prostate cancer. He is the director of CINJ and a professor in the Department of Medicine at RWJMS. He is chair of the Genitourinary Committee of the Eastern Cooperative Oncology Group (ECOG), an NCI supported cooperative group that develops national and international clinical trials. Dr. DiPaola is a recognized expert on prostate cancer and has authored numerous papers on this topic.*

Siu-Long Yao is an adjunct assistant professor of medicine at RWJMS and executive director of oncology clinical research at Schering-Plough Research Institute. In addition to his research interests in prostate cancer, he is responsible for clinical development of promising oncology drugs at Schering-Plough. After completing undergraduate studies at the University of Pennsylvania, he attended Yale University School of Medicine and completed postgraduate studies in internal medicine at Dartmouth-Hitchcock Medical Center and in hematology and oncology at Johns Hopkins Hospital.

Weichung (Joe) Shih is professor and chair of the Department of Biostatistics at UMDNJ-School of Public Health (SPH) and director of the Biometrics Division of CINJ. He received his PhD degree in statistics from the University of Minnesota. His research focuses on statistical methodologies for laboratory and clinical studies. He is an associate editor for several journals, including *Statistics in Medicine*, *Clinical Cancer Research* and *Statistics in Biopharmaceutical Research*.

Dirk Moore has been an associate professor of biometrics at CINJ and at SPH since 2003. He received his PhD in biostatistics from the University of Washington. Before joining CINJ, he was associate professor of statistics at Temple University, where he also collaborated with researchers at the Fox-Chase Cancer Center.

Yong Lin is an associate professor of biometrics at CINJ and at SPH. He received his PhD in statistics from Pennsylvania State University in 1997 and joined UMDNJ in 1999. His research focuses on statistical methodologies; and he does a lot of collaborative work with laboratory and clinical scientists.

Calpurnyia Roberts recently received her doctorate from the University of North Carolina at Chapel Hill. She has a Master's degree in epidemiology from Harvard School of Public Health and a BS in anthropology and human biology from Emory University. She is a post doctoral fellow whose research interests include understanding, reporting, and reducing health disparities in treatment practices by integrating epidemiology with health policy.

Yu-Hsuan (Joni) Shao is an epidemiologist who recently received her doctorate from SPH. She has a Master's degree in environmental sciences from Johns Hopkins School of Public Health. She is a post doctoral fellow whose interests include creating clinical algorithms to improve the management of prostate cancer.

The team members above also work closely with Hui Li, analyst and PhD student in biostatistics, and research coordinator Thanusha Puvananayagan, as well as Michael Barry from Harvard Medical School, a past president of the Society of General Internal Medicine, and renowned urologist Peter Albertsen from the University of Connecticut.

## “Chance favors only the the prepared mind”

— Louis Pasteur

by **Melissa Rogers and John Langenfeld**

**T**his is a story of how a lab problem led directly to a new biological discovery relevant to lung cancer, a disease that kills about 185,000 people each year in the United States. For many years, my lab has studied the molecular mechanisms that control the synthesis of an essential cell signal, bone morphogenetic protein 2 (BMP2). Precisely regulated BMP2 synthesis is indispensable for normal embryogenesis and adult physiology. Indeed, BMP2 is often synthesized at abnormal levels in adult pathologies, including cancers. Consequently, our overall objective is to understand the factors that control the level of BMP2, because these are putative drug targets for diseases that involve abnormal BMP2 synthesis.

These studies require comparable tissue culture cell lines that either do or do not synthesize BMP2. Several years ago, Shan Jiang, a recently graduated PhD student, began a survey of matched transformed and non-transformed cell lines. We chose these cell lines because BMP2 was induced in human tumors of the same type relative to adjacent normal cells. Shan contacted several local labs to obtain feeder stocks and set about measuring BMP2 RNA and protein in these cells. She also simultaneously tested

these lines for a common tissue culture contaminant, *Mycoplasma*, the smallest known self-replicating bacteria.

We were not too surprised to find that many of the lines were contaminated. Others have estimated that 15% to 80% of cell cultures may be *Mycoplasma*-contaminated. We were astounded, however, to realize that the contaminated cells synthesized huge amounts of BMP2 RNA and protein relative to non-contaminated cells. Relative to previously studied chemical compounds — such as the vitamin A derivative retinoic acid — *Mycoplasma* was the best inducer of BMP2 expression that I had seen. By intentionally infecting cells, we then found that *Mycoplasma* induced BMP2 in cell types from many lineages, suggesting that *Mycoplasma* is a nearly universal BMP2 inducer.

Because BMP2 is a potent cell signal that can regulate cell differentiation, growth, and death, we had discovered one more good reason to be paranoid about cleanliness in the tissue culture room. Undetected *Mycoplasma* contamination would confound the interpretation of how BMP2 functions in any lab model of growth, differentiation and apoptosis.

However, our findings also had potential clinical ramifications. John Langenfeld, a colleague at UMDNJ-Robert Wood Johnson Medical School, had found that most non-small cell lung carcinomas (NSCLC) synthesize far more BMP2 than normal lung tissue or benign lung tumors. Experimentally increased BMP2 levels increase tumor growth of the A549 lung cancer cell line in nude mice, while anti-BMP2 antibodies or Noggin, a BMP2 antagonist, reduce both primary and metastatic tumor growth. BMP2 increases lung cancer cell line invasiveness, promotes signaling pathways known to stimulate proliferation (e.g., Erk 1/2; PI 3-kinase/mTOR), and increases blood vessel formation in tumor models. Not surprisingly, given these data, high expression of BMP2 mRNA in non-small cell lung carcinomas (NSCLC) has been found to be negatively associated with patient survival. Following John's suggestion, we tested the effect of *Mycoplasma* on BMP2 expression in non-transformed, BEAS-2B immortalized bronchial epithelial lung cells.

Shan, a highly observant student, noticed that *Mycoplasma*-infected, but non-transformed, BEAS-2B began to look different from the clean cells. Instead of growing in nice, contact-inhibited monolayers, infected BEAS-2B cells changed morphology and piled up in clumps. Infected cells also grew significantly faster than the uninfected cells. This antisocial behavior typical of malignant, transformed cells was *never* observed in uninfected cells grown in parallel.

Because anchorage-independent growth in soft agar is a hallmark of oncogenic transformation, we examined the ability of *Mycoplasma*-infected cells to form colonies in soft agar. After 10 days, the infected BEAS-2B cells

seeded in the plate formed large colonies. In contrast, the uninfected BEAS 2B cells *never* formed colonies. Loss of contact inhibition and the ability of the infected BEAS-2B cells to grow robustly when suspended in soft agar indicate that *Mycoplasma* infection transformed the BEAS-2B cells. We also treated

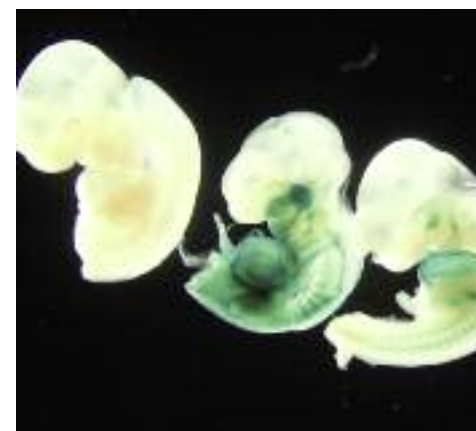
the cells with a BMP2 inhibitor, both on plates and in soft agar, and showed that blocking the BMP2 signal reversed the growth promoting effects of *Mycoplasma* infection. *These results showed for the first time that Mycoplasma transforms human lung cells and that BMP2 promotes the proliferation rate of Mycoplasma-transformed human lung cells.*

John compared the abilities of non-infected and *Mycoplasma*-infected BEAS-2B cells to form tumors *in vivo*. Although BEAS-2B cells are immortalized, they are not transformed, and do not form tumors readily *in vivo*. John injected 10 million infected or non-infected cells subcutaneously into female NCJ athymic nude mice. Two weeks later, palpable tumors were observed exclusively in the mice injected with *Mycoplasma*-infected cells. In contrast, animals injected with the uninfected BEAS-2B cells were tumor free 14 weeks after injection. Histological analysis of the tumors indicated that the tumors were poorly differentiated, highly malignant, and invasive. *These results demonstrated that Mycoplasma infection stimulated the progression of these human lung cells through both transformation and tumorigenicity.*

*Mycoplasma* is associated with various human diseases including pneumonia, asthma, and cancer. At least 10 species can colonize the human respiratory tract and lungs. Improved detection methods have shown that healthy individuals are often colonized without obvious clinical effects.



LEFT TO RIGHT: SHANCHITA GHOSH, STUDENT IN THE ORSP SUMMER PROGRAM AND THE COMBINED TCNJ/UMDNJ – NJMS BS/MD PROGRAM; MELISSA ROGERS, PHD; DAVID FRITZ, MS, RESEARCH ASSOCIATE II, BIOCHEMISTRY & MOLECULAR BIOLOGY



Images from Rogers Lab: Mouse embryos expressing a BMP2 lacZ reporter gene.

Because Mycoplasma are mutagenic and induce BMP2 and other cell signals, sub-clinical infections may exert a long-term, pro-cancer effect. In fact, Mycoplasma has been found in a variety of carcinomas including small cell lung cancer. We demonstrated for the first time that Mycoplasma infection also is highly transforming in human lung cells. Because antibiotic intervention is feasible, an association between Mycoplasma infection and even a subset of lung cancers could have a major impact on human health.

Lung cancer is an intractable disease. More people die from lung cancer than breast, colon, and prostate cancer combined. Despite advances in research, 85 percent of patients diagnosed with lung cancer will die from their disease. Our serendipitous finding that a common microbe induces BMP2 has revealed novel therapeutic approaches based on modulating BMP2 signaling and/or anti-Mycoplasma therapy.

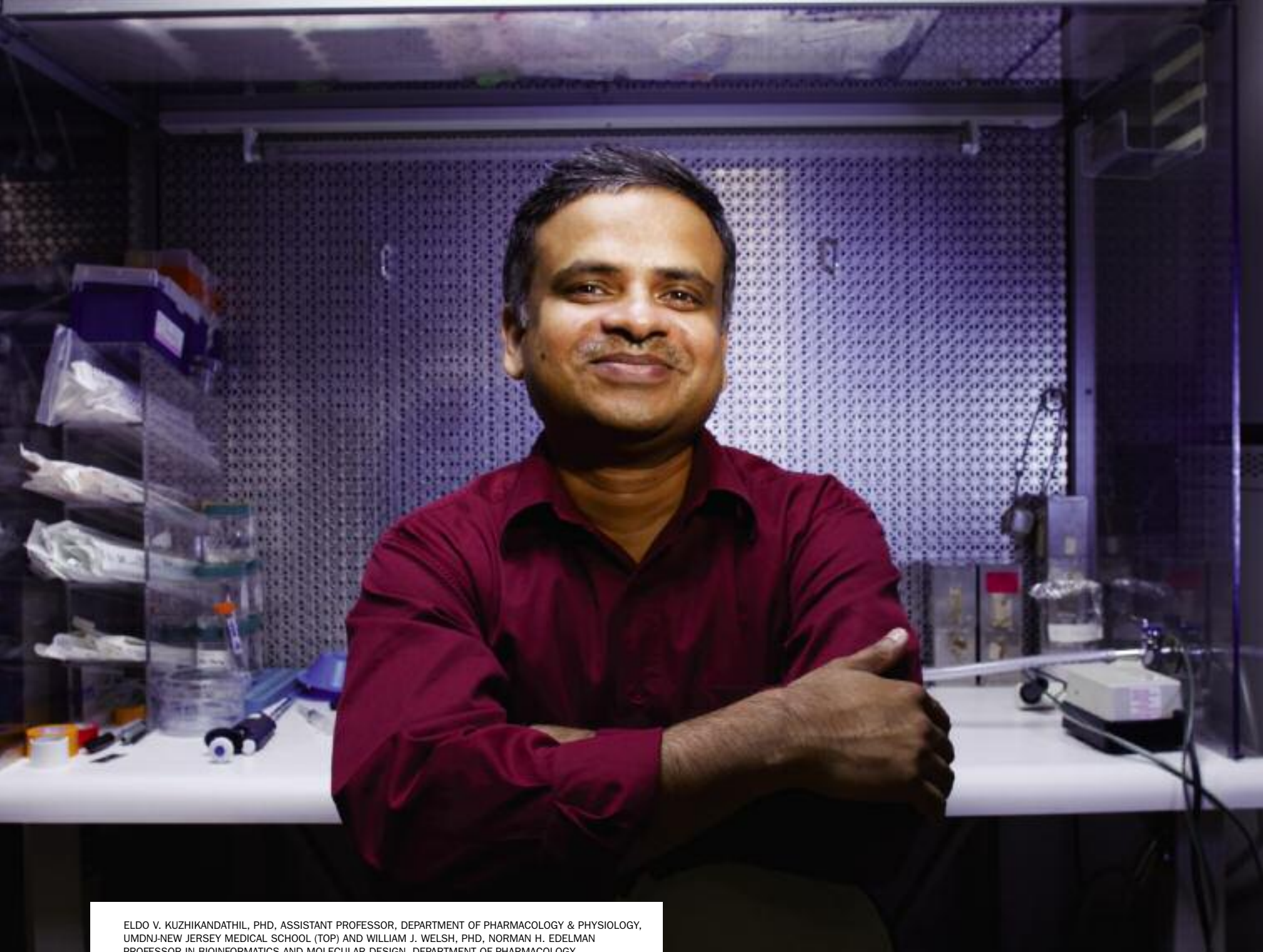
*Melissa Rogers earned her BS from Rensselaer Polytechnic Institute in Troy, NY, and her PhD from Brandeis University in Waltham, MA. She received postdoctoral training at the Dana Farber Cancer Institute and was a Hughes Fellow in the Department of Genetics, Harvard Medical School. She was assistant, then associate, professor in the Department of Biology at the University of South Florida (USF) in Tampa. In 2001, Dr. Rogers moved to her present position as associate professor of biochemistry and molecular biology at UMDNJ-New Jersey Medical School.*

*John Langenfeld earned his medical degree from Rush Medical School in Chicago. He completed a general surgery residency at UMDNJ, and thoracic surgery training at West Virginia University and Memorial Sloan Kettering Cancer Institute, followed by a research fellowship at UMDNJ and Memorial Sloan Kettering. He has been on the faculty of UMDNJ-Robert Wood Johnson Medical School since 1999, specializing in thoracic oncology surgery. His research focuses on lung cancer.*



JOHN LANGENFELD, MD, ASSOCIATE PROFESSOR, DEPARTMENT OF SURGERY, UMDNJ-ROBERT WOOD JOHNSON MEDICAL SCHOOL

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ELDO V. KUZHIKANDATHIL, PHD, ASSISTANT PROFESSOR, DEPARTMENT OF PHARMACOLOGY & PHYSIOLOGY, UMDNJ-NEW JERSEY MEDICAL SCHOOL (TOP) AND WILLIAM J. WELSH, PHD, NORMAN H. EDELMAN PROFESSOR IN BIOINFORMATICS AND MOLECULAR DESIGN, DEPARTMENT OF PHARMACOLOGY, UMDNJ- ROBERT WOOD JOHNSON MEDICAL SCHOOL (RWJMS)

## Developing a novel class of drugs for treating levodopa-induced dyskinesias in parkinson's disease

by Eldo V. Kuzhikandathil, William Welsh, and Sandhya Kortagere

**P**arkinson's disease is the second most common neurodegenerative disease. It is a neurological disorder whose prevalence increases with age. With the average age of the population rising in many countries of the world, including the U.S., there is an urgent need to develop safe and effective treatments. While the cause of Parkinson's disease remains unknown, the symptoms associated with the disease are due to a loss of a specific subset of neurons in the brain that synthesize and secrete a neurotransmitter called dopamine. The most effective therapy for treating Parkinson's disease involves administration of dopamine to make up for the loss of the cells that normally make dopamine in the brain. Unfortunately, about 60-80% of the patients treated with exogenous dopamine eventually develop severe movement disorders that are collectively called dyskinesias. The biological reason for the development of dyskinesias remains unclear. Currently, there are no pharmacotherapeutic means to effectively treat drug-induced dyskinesias in Parkinson's disease.

The molecular mechanisms underlying the development of levodopa-induced dyskinesia (LID) in Parkinson's disease (PD) are not well

understood. Studies have shown that expression of a number of genes are altered in dyskinetic animals. In particular, in both rodents and primates, studies have reported a specific increase in the D3 dopamine receptor expression in the basal ganglia of

dyskinetic animals. The functional consequence of the increased D3 receptor expression, in areas that normally express the D2 dopamine receptor, is unknown. We have shown that the D3 dopamine receptor, but not the D2 dopamine receptor, exhibits tolerance and slow response termination (SRT) properties. The tolerance property of the D3 receptor describes the progressive decrease in receptor signaling function upon repeated stimulation by classical agonists, including dopamine. The SRT property describes the prolongation of time taken to terminate the signaling function of the D3 receptor, after removal of the agonist. Differences in the properties of D2 and D3 receptors give rise to a differential modulation of neuronal firing.

Based on these results, we have proposed a hypothesis that in LID the alterations of D2/D3 receptor expression ratio leads to aberrant expression of D3 receptor tolerance and SRT properties, which could result in aberrant modulation of neuronal firing in the basal ganglia of the dyskinetic animals and contribute to the development of dyskinesia symptoms. Thus, if D3 receptor tolerance and SRT properties could be abolished, then the modulation of neuronal firing by the over-expressed D3 receptor in the basal ganglia of dyskinetic animals would be similar to the natively expressed D2 receptors and potentially prevent the expression of dyskinesia. The hypothesis predicts



that if the D3 dopamine receptor properties associated with dyskinesia could be selectively abolished using synthetic drugs, one could potentially cure dyskinesia associated with Parkinson's disease treatment.

To test the hypothesis, we first screened a library of D3 receptor agonists and identified a compound that was a full agonist at D3 receptor but lacked the tolerance and SRT properties. Using electrophysiological and biochemical functional assays in a heterologous expression model, we demonstrated that the newly identified D3 agonist showed no evidence of tolerance and SRT. The new D3 receptor agonist essentially converted the D3 receptor to a functional equivalent of the D2 dopamine receptor. With the help of Dr. Steven Zalcman in the Department of Psychiatry at UMDNJ-New Jersey Medical School, we next compared the effect of this novel D3 receptor agonist to classical D3 receptor agonists (which elicit tolerance and SRT) in mice locomotor behavior assays. These experiments showed that the novel D3 agonist induced different locomotor behavior compared to traditional tolerance and SRT-inducing D3 receptor agonists. Finally, to directly test our hypothesis, we evaluated the effect of the novel D3 receptor agonist in a rodent PD model that can be induced to exhibit dyskinesia following chronic levodopa treatment. The preliminary results supported our hypothesis that the novel D3 receptor agonist significantly attenuated dyskinesia in the rodent PD model.

To discover novel D3 agonists as potential clinical treatments for dyskinesia, we employed computational tools to screen extensive chemical databases to identify additional lead compounds that are structurally analogous to the original D3 agonist. The goal is to identify and characterize several lead candidates that can be tested for function, safety and efficacy. The long-term goal of this collaborative effort is to validate these novel drug candidates in the clinical setting to treat the negative symptoms associated with dopamine replacement therapy in Parkinson's disease. If the attractive

side-effects profile of this new D3 agonist is validated, we anticipate pursuing further preclinical and clinical studies aimed at FDA approval and eventual marketing of this novel prospective drug candidate.

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*Eldo Kuzhikandathil earned his PhD from the University of Delaware in molecular biology and received postdoctoral training in neurobiology at the University of North Carolina at Chapel Hill. He joined the Department of Pharmacology & Physiology at UMDNJ-New Jersey Medical School in 2000, and is currently an assistant professor there.*

*William J. Welsh holds the appointment of Norman H. Edelman Chair in Bioinformatics & Molecular Design, and professor in the Department of Pharmacology, UMDNJ-Robert Wood Johnson Medical School (RWJMS). Dr. Welsh serves as director of the Informatics Institute of UMDNJ. Concurrently, he serves as director of the EPA-supported Environmental Bioinformatics & Computational Toxicology Center (ebCTC). Dr. Welsh received his PhD from the University of Pennsylvania and postdoctoral training at the University of Cincinnati (OH) and the National Institutes of Health in Bethesda, MD. He joined the RWJMS faculty in 2001.*

*Sandhya Kortagere earned her PhD from the National Institute of Mental Health & Neurosciences in India and did her postdoctoral training at Mount Sinai School of Medicine and Weill Cornell Medical College. She was a research teaching specialist at RWJMS from 2005 to 2008 and is currently an assistant professor at Drexel University College of Medicine.*

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SCOTT KACHLANY, PHD, ASSOCIATE PROFESSOR, DEPARTMENT OF ORAL BIOLOGY, UMDNJ-NEW JERSEY DENTAL SCHOOL, AND DEPARTMENT OF MICROBIOLOGY AND MOLECULAR GENETICS, UMDNJ-NEW JERSEY MEDICAL SCHOOL

## A bacterial toxin to attack **cancer cells**

by **Scott Kachlany and Roger Strair**

**L**eukemia is a serious white blood cell cancer that more than 44,000 Americans develop every year. Currently there are approximately 218,000 people in the U.S. living with the disease, and each year 21,000 people die from leukemia. While advancements have been made in the diagnosis and treatment of leukemia, the 5-year survival rates for many forms of the disease remain relatively low and have changed little over the last 20 years. Thus, there is a great need to identify newer therapeutics with greater activity and fewer side effects. Bacterial toxins have been used as anti-cancer agents and represent a new class of targeted therapeutics. The bacterium *A. actinomycetemcomitans* produces a leukotoxin that has specificity for certain white blood cells. *In vitro* and *in vivo* studies with leukotoxin indicate that it could be an effective anti-leukemia therapeutic with high specificity. To further develop leukotoxin as a novel therapeutic agent, Actinobac Biomed Inc. was recently founded. FDA-required studies are currently underway.

It all started as a protein band on a gel. I was a graduate student at Columbia University, in the Department of Microbiology, studying an oral bacterium, *Aggregatibacter* (that was formerly *Actinobacillus*) *actinomycetemcomitans* that causes a juvenile form of periodontal disease. I was examining proteins that are released by the bacterium and found a secreted protein that was not supposed to be there. The protein is known as leukotoxin. Up until this time, it was believed that leukotoxin was not a secreted protein, and so this discovery was both novel and surprising. (I have learned that in science the most powerful tool is observation.) This result could have been ignored, but instead I chose to let the experiment dictate how to proceed. We subsequently worked out techniques to isolate large amounts of purified leukotoxin and began studies to understand how the toxin is expressed and secreted by the bacterium.

Leukotoxin is a protein that kills only white blood cells, and only those from humans and primates. Why would a bacterium want to produce such an agent? For any pathogen to cause disease, it must be able to evade the host immune response, which is composed predominantly of white blood cells. Thus, leukotoxin allows *A. actinomycetemcomitans* to avoid being killed by our white blood cells. Indeed, bacteria are exquisitely adapted to survive within their hosts as they provoke disease.

When I started as an assistant professor at UMDNJ in 2003, I began



LEFT TO RIGHT: JACKIE MANAGO, RN, AND ROGER STRAIR, MD, PHD, DIRECTOR OF HEMATOLOGICAL MALIGNANCIES AT THE CANCER INSTITUTE OF NEW JERSEY AND PROFESSOR OF MEDICINE, UMDNJ-ROBERT WOOD JOHNSON MEDICAL SCHOOL

to ponder the idea of using leukotoxin as a therapeutic agent. The use of a bacterial toxin as therapy is not completely new. BOTOX is the neurotoxin from *Clostridium botulinum* used to treat neuromuscular disorders, and the drug ONTAK, used for the treatment of T-cell lymphoma, is composed of diphtheria toxin from *Corynebacterium diphtheriae*. As a microbiologist, I knew that bacteria were smarter and more efficient (evolutionarily-speaking) than we are. If *A. actinomycetemcomitans* figured out how to target only white blood cells, perhaps it would also kill preferentially the cancerous white blood cells (such as in leukemia and lymphoma) in the body, in contrast to conventional chemotherapy, which affects many different types of cells, hence causing a multitude of side-effects. But while leukotoxin has been shown to kill cancerous white blood cells under laboratory conditions, there was nothing known about how it might work in a living animal, such as mice or primates.

I acknowledged early on that in order to continue our efforts with animals and leukemia models, it would be necessary to work with a hematologist/oncologist who studies blood cancers. My search brought me to Roger Strair, MD/ PhD, director of hematological malignancies at The Cancer Institute of New Jersey (CINJ) and professor of medicine at UMDNJ-Robert Wood Johnson Medical School (RWJMS). He was very enthusiastic about our initial proposal and indicated that there is a great need to identify novel therapies for the treatment of hematological malignancies. And so, we began meeting to discuss projects. An important question we had to answer was whether leukotoxin is an effective anti-cancer agent in an animal. However, because it is specific for human and primate cells, we had to use a human xenograft model. As Dr. Strair described to me, in this model human leukemia cells are injected into immunodeficient mice. After several weeks, these mice develop disease and get sick.

In collaboration with Dr. Strair, we were fortunate to receive a grant from the Foundation of UMDNJ and the Office of Patents and Licensing/NJCST to perform these pilot studies with leukotoxin and mice. The results we obtained were striking (see Figure 1). The mice that received the leukemia cells, but no other treatment, got sick and died after several weeks. However, almost all of the mice that were treated with leukotoxin remained healthy and never developed disease. The leukotoxin-treated mice lived to be at least a year old, which is about the normal life-span for these mice. To further understand the effects of the toxin *in*

*in vivo*, we administered leukotoxin intravenously to nonhuman primates. We found that leukotoxin was specific for only white blood cells, was very well-tolerated by the animals at effective doses, and no toxicity was observed. While these studies will be followed up, the results thus far look positive.

Encouraged by our data, Dr. Strair asked very important questions that we still had to address. For example, does leukotoxin target cancer cells better than normal cells? One drawback to many current chemotherapeutic agents is the lack of specificity for the cancerous cells. We proceeded by testing leukotoxin against normal human white blood cells and leukemia cells, and noted a significant difference. The normal white blood cells were relatively unaffected by leukotoxin while leukemic white blood cells were very effectively killed. We discovered that the reason for this difference is due to the levels and type of receptor that leukotoxin uses to recognize cells.

Given these very exciting results, I was encouraged to start a biopharmaceutical company to further develop leukotoxin as a therapeutic agent. With an initial investment commitment of \$500,000 from the Foundation Venture Capital Group, I founded Actinobac Biomed, Inc. in January of 2009. Actinobac Biomed has licensed the patents for the clinical use of leukotoxin from UMDNJ. To date, I act as an advisor to the company and chair the Scientific Advisory Board. The goal of the company is to bring leukotoxin and derived agents into clinical trials for testing. The types of studies required by the FDA for approval of a drug are often quite different from the experiments we carry out in an academic laboratory.

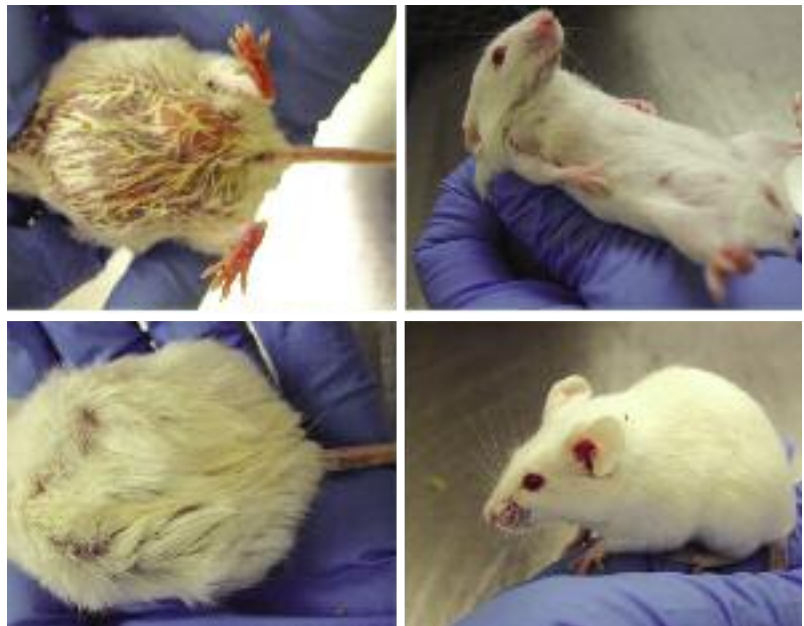


Figure 1: Mouse model for human leukemia. Mice were injected with human leukemia cells and remained untreated (left) or treated with leukotoxin (right)

Learning about the drug approval process and necessary studies has been a very satisfying challenge for me. It is not often that a basic scientist in academia has the chance to see his work in a truly translational setting and I feel very fortunate to have been given this opportunity. I look forward to the day when a patient may actually be treated with that obscure protein band that was not supposed to be there.

*Scott Kachlany received his BS degree in microbiology from Cornell University in 1997 and PhD in 2001 from the Department of Microbiology at Columbia University. In 2003, he joined the faculty of UMDNJ-New Jersey Dental School as an assistant professor in the Department of Oral Biology and jointly in the Department of Microbiology and Molecular Genetics at UMDNJ-New Medical School. In 2008, he was promoted to associate professor.*

*Roger Strair received his BS in biology from SUNY Stony Brook and his MD and PhD degrees from Albert Einstein College of Medicine. He completed a residency and fellowship at Harvard Medical School — Brigham Women's Hospital. Dr. Strair is director of hematologic malignancies at The Cancer Institute of New Jersey and professor of medicine at UMDNJ-Robert Wood Johnson Medical School.*

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LEFT TO RIGHT: SHAHID R. AZIZ, DMD, MD; ROBERT N. FEMMINELLA, MS, MS; SUSAN GOULD FOGERITE, PHD; AND NATHAN WUEBBLES, DMD, MD

# Mind/body medicine meets jaw surgery

by Susan Gould Fogerite and Shahid R. Aziz

**O**rthognathic surgery, which is usually done for people between the ages of 15 and 35, is surgery to correct dentofacial deformities of the maxilla and mandible (upper and lower jaw). These deformities can consist of skeletal malocclusions such as “open bites,” “underbites,” or “overbites,” which are not correctable by conventional orthodontics (such as braces) alone, but rather require surgical intervention to correct. Orthognathic surgery requires planning and prepara-

tion on the part of the patient, patient’s family, orthodontist, and surgeon. Most patients have a natural anxiety in the days prior to surgery. This anxiety is generally addressed in the form of reassurance and education by the surgeon, or having the patient speak to former patients who have undergone similar procedures. Immediately after the surgery, these patients often require maxillomandibular fixation (wiring the teeth together) for 3-4 weeks to stabi-

lize the jaw while it heals. They need to deal with seeing their face significantly changed and swollen after surgery, concerns about post-operative pain management, and fears about breathing adequately and the inability to eat solids or speak properly while the teeth are wired.

## Guided imagery, breathing and relaxation

We believe that conventional medical/surgical techniques may not address these pre- and post-surgical issues in an optimal way. We would like to find out whether certain complementary and alternative medicine (CAM) techniques within mind/body medicine can be used to help the mind act as a positive force in decreasing anxiety and pain, and facilitating postoperative healing in orthognathic surgery. Guided imagery helps the listener get into a relaxed state and suggestions are made relating to desired outcomes.

In the case of preparing for surgery, these could include staying calm and having positive expectations about the surgery and about the postoperative healing. Physically, imagery has the ability to directly influence the autonomic nervous system, and the power of imagination can be recruited to promote specific physiological changes as an aid to healing. Studies indicate that certain imagery techniques may stimulate immune and endocrine

**PHYSICALLY, IMAGERY HAS THE ABILITY TO DIRECTLY INFLUENCE THE AUTONOMIC NERVOUS SYSTEM, AND THE POWER OF IMAGINATION CAN BE RECRUITED TO PROMOTE SPECIFIC PHYSIOLOGICAL CHANGES AS AN AID TO HEALING. STUDIES INDICATE THAT CERTAIN IMAGERY TECHNIQUES MAY STIMULATE IMMUNE AND ENDOCRINE (HORMONAL) RESPONSES, WHICH CAN ACCELERATE THE HEALING PROCESS.**



**Figure 1.**  
3-Dimensional CT scan of orthognathic surgery patient immediately following maxillary and mandibular advancement surgery

(hormonal) responses, which can accelerate the healing process. In addition to guided imagery, yoga also has breathing and relaxation techniques that can help a person calm down and be less affected by stressful situations.

### The clinical trial

One of the best ways to investigate the effects of a change in medical practice is to do a randomized clinical trial. Patients who are eligible and interested in participating are randomly assigned to one of two or more groups being studied. Comparisons can be made within a group over time and between groups. This pilot randomized clinical trial, which is currently recruiting subjects, is supported partially by a seed grant from the UMDNJ Foundation through the UMDNJ-New Jersey Dental School (NJDS). The goal of this study is to compare the use of guided imagery (GI) and relaxation techniques to listening to music in helping to prepare patients for orthognathic surgery and improving post surgery recovery. Twenty six orthognathic surgery patients, ages 15 to 35, treated at the dental school, will be randomized into either a “guided imagery” or a “music” group. Both groups will be given education and reassurances about the surgery, a portable MP3 player, earphones and a journal. The guided imagery subjects will be given an MP3 download of a guided imagery program called “Successful Surgery,” written and recorded by Belleruth Naparstek, LISW, which has been shown to be safe and effective in improving outcomes in other clinical trials. It contains specially designed background music, guided relaxation, auto-suggestions and reassurances about the surgical experience and recovery. In addition, GI subjects will be personally taught diaphragmatic breathing and progressive relaxation techniques prior to surgery. The music group subjects will be asked to listen to music of their choosing for the same amount of time pre- and post-surgery as the GI program will be listened to by the other group. All subjects will record their listening time and either their music choices or their practice time in their journal.

Recovery will be evaluated, including weight loss, swelling, and nerve function. Mouth opening will be measured and chewing function assessed at baseline and all time points after wires restricting jaw movement are removed. Pain and anxiety will be quantified using the most commonly used and well validated visual scales and questionnaires. All subjects will be given questionnaires to determine how well they felt they were prepared for surgery, to what degree they felt that the guided imagery, relaxation and breathing techniques, or the music, made the pre-surgical and post-surgical phases less stressful, and whether they would recommend this program be made available to future patients. Biochemical markers of stress, inflammation and tissue damage will be measured in the ICAM research lab on subjects’ blood samples to help characterize emotional stress and the rate and extent of healing post surgery.

As co-principal investigators, Dr. Aziz will be performing all the

orthognathic surgeries and Dr. Gould Fogerite will be teaching the relaxation and breathing practices to the guided imagery subjects in this trial. Co-investigators include Nathan Wuebbles, DMD, MD, chief resident, NJDS Department of Oral/Maxillofacial Surgery, who will be assisting with surgeries, doing many of the assessments, and serving as study coordinator; Malvin Janal, PhD, senior research associate, UMDNJ-New Jersey Medical School (NJMS) Department of Psychiatry, will serve as chief statistician; and Robert Femminella, MS, MS, will be assisting with the laboratory analysis, relaxation training and literature research in partial fulfillment of the requirements for his PhD in Health Sciences at UMDNJ-School of Health Related Professions (SHRP). NJMS student Charles Tyshkov also helped with some of the preparation for the study.

*Shahid R. Aziz, DMD, MD, is an associate professor in the Department of Oral & Maxillofacial Surgery at UMDNJ-New Jersey Dental School and the Division of Plastic and Reconstructive Surgery in the Department of Surgery at UMDNJ-New Jersey Medical School. Dr. Aziz received his DMD from Harvard University School of Dental Medicine, his MD from Columbia University College of Physicians and Surgeons, and completed surgical training at Columbia Presbyterian Medical Center. He practices the full scope of oral and maxillofacial surgery, including orthognathic, facial trauma, and cleft lip and palate surgery.*

*Susan Gould Fogerite, PhD, is Director of Research for the Institute for Complementary and Alternative Medicine and associate professor in the Departments of Primary Care and Clinical Laboratory Sciences at UMDNJ-School of Health Related Professions.*

*She earned her PhD in microbiology and immunology from Albany Medical School of BioMedical Sciences, and her BS from Albany Medical School of Medical Technology and SUNY at Albany. She teaches mind/body practices, and microbiology and immunology, and leads research on the biochemistry and immunology of stress and relaxation.*

You can access additional information about the surgery, the clinical trial or complementary and alternative medicine at ICAM on these Websites:  
<http://dentalschool.umdj.edu/depts/oral-surgery/faculty-practice.htm> or  
<http://umdj.edu/icam>.

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## Improving management strategies for alzheimer’s disease

by Anita Chopra and William Puentes

# A

lzheimer’s disease is one of the most devastating illnesses an individual can experience. This devastation is, in large part, based on the possibility of existing for years without what most people consider to be the essence of humanity, our memories. Bender and Cheston (1997) presented a model of the subjective experience of individuals diagnosed with dementia. This model describes 3 discrete stages. The first stage focuses on the feelings experienced as a result of being diagnosed with dementia: anxiety, depression, grief, and despair/terror. In a study conducted by Dr. Puentes during his post-doctoral work with funding from the John A. Hartford Foundation and the Rand/Hartford Initiative, he found evidence to support Bender and Cheston’s model. Study participants and their caregivers described feelings of apprehension and anxiety prior to and following the diagnosis of Alzheimer’s disease that had a negative impact on their quality of life. For 12 to 18 months following the diagnosis, these individuals devoted most of their energies to trying to assimilate their diagnosis and plan for the future. The uncertainty associated with the disease process contributed to feelings of clinical and sub-clinical anxiety. Study



ANITA CHOPRA, MD, DIRECTOR, NEW JERSEY INSTITUTE FOR SUCCESSFUL AGING, AND PROFESSOR, UMDNJ-SCHOOL OF OSTEOPATHIC MEDICINE, AND WILLIAM PUENTES, PHD, RN, ASSOCIATE PROFESSOR, UMDNJ-SCHOOL OF NURSING

participants also described the negative impact that even sub-clinical symptoms of anxiety had on their functional status. Sometimes, healthcare providers and patients explored and attempted to manage these feelings. But more often, they were looked at as expected sequelae of the disease process and not specifically addressed in the disease management plan. The management of co-morbid anxiety associated with Alzheimer's disease presents a significant challenge to healthcare providers. The idiosyncratic response to anti-anxiety medications in this population and lack of empirically validated anxiety self-management strategies challenge healthcare providers to offer interventions that respond to patients' needs for control and positive quality of life.

moderate Alzheimer's disease. The current study is being conducted with the financial support of the UMDNJ Foundation. Using a phenomenological qualitative research approach, individuals who utilize the services of the NJISA are invited to participate in interviews regarding their experiences with Alzheimer's disease. Particular emphasis is placed on the stressors they experience and the techniques they use to self-manage these stressors. The goal of this study is to begin developing a model of the subjective experience of anxiety for these patients. Identification of precipitating factors and stressors as well as patient and caregiver responses will provide the data needed to model the unique dynamics associated with anxiety as experienced by this

**THE GOAL OF THIS STUDY IS TO BEGIN DEVELOPING A MODEL OF THE SUBJECTIVE EXPERIENCE OF ANXIETY FOR THESE PATIENTS. IDENTIFICATION OF PRECIPITATING FACTORS AND STRESSORS AS WELL AS PATIENT AND CAREGIVER RESPONSES WILL PROVIDE THE DATA NEEDED TO MODEL THE UNIQUE DYNAMICS ASSOCIATED WITH ANXIETY AS EXPERIENCED BY THIS PATIENT POPULATION.**

A growing body of literature supports the proposition that healthcare providers need to shift paradigms that drive dementia care. The predominant paradigm is deficit and loss-based and emphasizes the patient's dependent role in the disease management process. Bender and Cheston (1997), Sabat (2001) and others suggest that the emerging paradigm needs to be strengths-based and to engage the patient as an active partner in the disease management process.

Our current collaboration builds on Dr. Puentes' earlier work exploring the subjective experience of anxiety for individuals diagnosed with mild to

patient population. This is the first step in the development of empirically validated anxiety management strategies that will contribute to successfully recognizing and controlling symptoms, extending the period of effective functional status and enhancing quality of life for this patient population and their caregivers.

Our future collaborations will focus on the development of empirically validated self-management strategies that can be incorporated into patients' treatment plans. Consistent with the mission of NJISA, we are planning to explore ways to empower patients and their families to be active partners in

managing their illness. Dr. Puentes is particularly interested in exploring the anxiety management functions of reminiscence.

*William J. Puentes, PhD, RN, PMHCNS-BC, an associate professor at the UMDNJ- School of Nursing, teaches gerontological and mental health nursing. He is a former John A. Hartford Foundation/AACN Building Academic Geriatric Nursing Capacity Postdoctoral Claire Fagin Fellow. His research focuses on geropsychiatric nursing issues. He is the author of 30 peer-reviewed journal articles and abstracts in the area of gerontological mental health nursing and has presented his work in national and international forums.*

*Anita Chopra, MD, a geriatric physician and educator, has been an advocate for older adults for more than 25 years. She is director of the New Jersey Institute for Successful Aging at the UMDNJ-School of Osteopathic Medicine. She is also a professor of medicine, board certified internist/geriatrician, certified medical director for long-term care, and fellow of both the American College of Physicians and the American Geriatrics Society.*

*Since 1981, Dr. Chopra has been integral in the development of geriatrics at UMDNJ; and the Institute is recognized as one of the premier sources of geriatric care in New Jersey. The Institute provides interdisciplinary training in geriatrics and gerontology to physicians-in-training, undergraduate and graduate students in the biomedical sciences and health related professions, physicians in the community, other health related professionals, and the lay public. Three of its educational initiatives have achieved national reputations. The Institute's research programs include behavioral science, basic science, and clinical research. For the past 9 years, the Institute has been consistently ranked by US News and World Report among the top 20 graduate schools in geriatric medicine in the nation. In 2009, it ranked 13th.*

*Dr. Chopra has a special interest in Alzheimer's disease and related disorders, osteoporosis, pain management, end of life care, and long-term care and has published in these areas. She has also served as either the principal investigator or co-investigator for 19 clinical trials related to dementia, depression, and osteoarthritis and numerous grants funded by both the public and private sectors.*

*References: Bender, M.P., & Cheston, R. (1997). Inhabitants of a lost kingdom: A model of the subjective experiences of dementia. Ageing and Society, 17, 513-532.*

*Sabat, S.R. (2001). The experience of Alzheimer's Disease: Life through a tangled veil. Malden, MA: Blackwell Publishers.*

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## Patient targeted informatics to improve healthcare and clinical trials

by **Barbara H. Gladson, Andrew N. de la Torre, Stanley H. Weiss, Daniel M. Rosenblum and Christopher P. Tuohy**

**T**he proportion of individuals developing chronic diseases is growing, particularly among the urban poor, unemployed, and immigrants. These populations experience disparities in healthcare access and treatment. Since healthcare facilities that care for these patients are often understaffed, Andrew N. de la Torre, MD, a liver transplant surgeon at UMDNJ-University Hospital, has developed a "Patient-Targeted Informatics" kiosk that uses a computer to elicit medical history and identify individuals in need of specific medical testing. The kiosk will now be expanded to elicit risk factors and screening history for other chronic diseases and to survey attitudes toward participation in clinical trials. Collaborators for this project are Stanley H. Weiss, MD, and Barbara H. Gladson, PhD.

Patients are interviewed on a touch-screen computer work-station where questions appear on the screen and are read through headphones in Spanish, English or Creole. Patients are educated about risk factors for hepatitis — including certain sexual histories and drug and alcohol use — and are then asked whether they have any of those risk factors (without having to specify which ones). Patients are more likely to divulge personal health information to a computer screen than to a healthcare practitioner. Risk based on ethnicity and country of birth is also assessed using an interactive world map. If a patient answers "yes" to risky behaviors or touches a location on the map where hepatitis is endemic, their de-identified information is electronically transmitted to Dr. de la Torre and to the health clinic. The patient is then notified to return for testing.

The kiosk is now functioning in a federally funded health clinic in East Orange and in UMDNJ-University Hospital. Between March 2008 and April 2009, 1,016 patients began, and 980 completed, the survey. The patients were ethnically and racially diverse with about 40% non-Hispanic black and about a third Hispanic of any race, and came from a broad mix of countries, with about one third from North America, 29% from the Caribbean, 23% from South and Central America, and others from Africa, Asia, the Pacific islands, Europe, and the Middle East. There were 246 patients identified as needing blood tests for chronic viral hepatitis; 150 of these had a complete chronic hepatitis screen (HCV antibody, HBV surface antigen, HBV core antibody, and HBV surface antibody). Twenty patients were found to test positive for chronic viral hepatitis (14 HCV, 6 HBV) and 96 patients were hepatitis-B naïve (i.e., all three HBV tests were negative). More than 70 patients are in the process of HBV vaccination. As an internal control, patients were asked if they had a history of viral hepatitis. Of the 66 patients noting a history of viral hepatitis, 37 (56%) acknowledged any risk factor.

Since the CDC predicts that steatohepatitis-related cirrhosis, resulting from non-alcoholic fatty liver (NAFL), will be the leading cause of liver failure by 2025, the kiosk was also programmed to calculate body mass index (BMI) to identify patients with a BMI greater than 35, or greater than 30 with concurrent diabetes. We found 27% of patients met these criteria for NAFL risk.

In addition to the two clinic locations, the kiosk was featured at the Essex County Cancer Coalition's third annual health/cancer fair, held in the UMDNJ-New Jersey Dental School pavilion in April, in conjunction with several types of cancer screening. The response from the public was very positive and 13 individuals completed the survey.

Development of the kiosk has been facilitated by partnerships with the Health Care Foundation of New Jersey, NJMS Department of Family Medicine (Mark Johnson, MD), NJMS Department of Internal Medicine (Iris Herrera, MD), NJMS Division of Hepatology (Carroll B. Leevy, MD), and the Newark Community Health Center (Nancy Tham). Recently

Dr. de la Torre and his research assistant, Ismael Castaneda, MD, partnered with Dr. Weiss and his team — including Daniel M. Rosenblum, PhD, and Christopher P. Tuohy, MPH — to expand the kiosk to include screening for cancer, cardiovascular disease, and depression. Patients will be surveyed to determine whether they are up to date with recommended screenings for breast, colon and cervical cancers and whether they have been screened for

prostate cancer. The kiosk will be programmed to identify patients needing further medical testing based on their demographics, medical history, and lifestyle. For example, women younger than 26 will receive education on the human papillomavirus (HPV) and woman over 40 will receive information on mammography. Patients over 60 with a history of cigarette smoking will be informed of their risk of lung cancer and advised to discuss the need for cancer screening with their physician. Questions evaluating risk factors for cardiovascular diseases ask about the presence of hypertension, high cholesterol, and diabetes, and smoking history.

On completion of the survey, the kiosk will print summary pages of prioritized health risks for the patient and for the physician. The patient's printout will be in his/her chosen language, at a level easily understood.



LEFT TO RIGHT: BARBARA GLADSON, PT, PHD; DANIEL ROSENBLUM, PHD; CHRISTOPHER TUOHY, MPH; ANDREW DE LA TORRE, MD; AND STANLEY H. WEISS, MD

Dr. Gladson has led the development of a module to educate patients on, and measure attitudes toward, participating in a clinical trial. Clinical trials are used to identify the efficacy and safety of new drugs, but poor enrollment leads to significant delays in bringing new drugs to market. Despite governmental intervention and high rates of disease burden, minority recruitment has remained low. Barriers to enrollment may be sponsor-centered (reflecting the inclusion/exclusion criteria of a study), investigator-centered (lack of cultural competence, too few minority investigators, time constraints, and lack of funding), and subject-centered (mistrust, low health literacy, lack of access, fear of side effects, and lack of awareness). Attitudes about clinical trials among different ages, genders, and ethnicities will be identified. These results will be used to inform the development of culturally appropriate vignettes addressing some of the most significant factors influencing willingness to participate in a trial. The kiosk will then be programmed to show the appropriate vignette to future subjects based on their demographics. Ultimately, we will determine if these matched vignettes improve trial participation.

Audio-computer assisted surveys can be used to help clinicians acquire critical patient data to help assess and treat diseases while ensuring that routine health screening is up to date. Based on pilot data, our kiosk is predicted to reach more than 4,000 patients a year, improving their health and providing critical education. Preventing illness and delaying the progression of disease with our kiosk is an exciting prospect that will reach many more patients as our project expands.

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*Andrew N. de la Torre, MD, a graduate of Johns Hopkins Medical School, is currently associate professor of surgery at UMDNJ-New Jersey Medical School (NJMS) and director of laparoscopic and minimally invasive liver surgery and clinical director of UMDNJ-University Hospital's (UH) hepatobiliary immunotherapy research team (HIRT). He completed his surgery residency and liver surgery training at NJMS/UH and a kidney/pancreas transplant fellowship at the University of Maryland. Among his major interests are public health*

*education, early diagnosis of chronic viral hepatitis and prevention of hepatocellular cancer.*

*Stanley H. Weiss, MD, a graduate of Harvard Medical School, is professor of preventive medicine & community health at NJMS and professor of quantitative methods at UMDNJ-School of Public Health (SPH), and is board certified in medical oncology. He is a well-known researcher in the epidemiology of cancer, asthma, and infectious diseases, including HIV/AIDS. Dr. Weiss is a fellow of the American College of Epidemiology, the Cancer Liaison Physician for UH/NJMS to the American College of Surgeons' Commission on Cancer, and the founder and director of the Essex County Cancer Coalition and the northern NJ Prostate Cancer Initiative.*

*Barbara H. Gladson, PhD, earned her doctorate in pharmacology from UMDNJ's Graduate School of Biomedical Sciences (GSBS), and is currently professor of rehabilitation & movement sciences at UMDNJ-School of Health Related Professions, and associate professor of pharmacology & physiology at GSBS in Newark. She is also the Director of the UMDNJ Biopharma Educational Initiative and the MS in Clinical Trial Sciences in SHRP.*

*Daniel M. Rosenblum, PhD, earned his degree in public policy analysis from Carnegie Mellon University and is currently assistant professor of preventive medicine & community health at NJMS and assistant professor of quantitative methods at SPH. He analyzes epidemiologic, survey and clinical data, mostly in collaboration with Dr. Weiss. He is also co-coordinator of the Essex County Cancer Coalition.*

*Christopher P. Tuohy, MPH, is a graduate of UMDNJ's School of Public Health. He is coordinator of the Essex County Cancer Coalition, and a research assistant with a lead role on many of Dr. Weiss's projects.*

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# Developing the medical home in primary care: using a **patient navigator** to coordinate care

by **Jeanne M. Ferrante, Deborah Cohen, and Jesse C. Crosson**

**T**he patient-centered medical home (PCMH) is widely advocated as a way to help reform the U.S. healthcare system into one that is more accessible, effective, safer and economical. Central to the PCMH concept is care that is “coordinated or integrated across all elements of the complex healthcare system and the patient’s community.” This is crucial since fragmented care leads to unnecessary services, duplication of information gathering and testing, and poorer health outcomes. Currently, time, personnel, and reimbursement constraints limit efforts by primary care practice organizations to provide coordinated care. Recognizing that New Jersey has one of the most fragmented healthcare environments in the country, Overlook Hospital Foundation funded a pilot project aimed at demonstrating how a patient navigator — someone who provides education and emotional support to patients and helps guide them through the healthcare system — can help improve care coordination for patients of primary care practices. The funding supported a patient navigator, shared by 4 community-based primary care physicians, to coordinate care for patients, help them obtain needed resources, and facilitate communication between the patient, primary care office, and specialist offices. With support from the Overlook Foundation and the UMDNJ Team Science Initiative grant, we evaluated this project by documenting the types of services the navigator provided, determining the barriers and facilitators to patient navigation in primary care practices, and understanding patients’, physicians’ and the navigator’s perspectives and experiences with this service.

The concept of the PCMH is supported by all the primary care specialty organizations and includes these principles: 1) an ongoing relationship with a personal physician for first contact, continuous and comprehensive care; 2) a physician-directed team that collectively cares for the patient; 3) whole-person orientation including acute, chronic,

preventive and end-of-life care; 4) coordinated care across all elements of the healthcare system and the patient’s community; 5) quality and safety achieved through evidence-based medicine, clinical decision-support tools, information technology, registries and

continuous quality improvement; 6) enhanced access through systems such as open scheduling, expanded hours and new options for communication between patients, their physician and practice staff; and 7) payment reform to reflect the added value that a PCMH provides to patients.

Most PCMH demonstration and pilot projects focus on information technology capabilities, yet much of what is needed to foster a medical home for patients involves highly personal and individualized interaction with physicians to assist patients in obtaining the needed resources and care at the right time. While physicians have the capacity to provide ongoing patient-centered care, helping patients gain access to needed services can be complicated in the current primary care business environment. Robert Eidus, MD, MBA, a solo physician at Cranford Family Practice, received a grant from Overlook Hospital Foundation for a 12-month pilot project using a patient navigator (PN) to provide care coordination as well as education and emotional support to patients while guiding them through the healthcare system.

## Intervention

A social worker was hired to act as the PN and her services were shared by 4 physicians in 4 different primary care (internal medicine and family medicine) practices. Although 3 of the 4 physicians were in group practices, the pilot was limited to one physician per practice so that the navigator could develop a good working relationship with each physician. Physicians referred patients whom they felt needed extra coordinating services to the navigator. Patient selection was purposefully not restricted by a disease process to be consistent with how patients with multiple chronic conditions are cared for in primary care practices.

## Evaluation

Building on our research team’s expertise in patient navigation, organizational

CENTER: JEANNE M. FERRANTE, MD, MPH, ASSOCIATE PROFESSOR, DEPARTMENT OF FAMILY MEDICINE, UMDNJ-ROBERT WOOD JOHNSON MEDICAL SCHOOL (RWJMS); RIGHT: DEBORAH J. COHEN, PHD, ASSISTANT PROFESSOR, DEPARTMENT OF FAMILY MEDICINE, RWJMS; JESSE C. CROSSON, PHD, ASSISTANT PROFESSOR, DEPARTMENT OF FAMILY MEDICINE, UMDNJ- NEW JERSEY MEDICAL SCHOOL AND RWJMS (SINCE MARCH 2009)



change, and practice improvement, we conducted a mixed methods evaluation of this pilot project. Data analyzed included patient surveys, navigator tracking tools and biweekly debriefings, email communications from Dr. Eidus, project meeting notes, and in-depth interviews of 15 patients or family members and the 4 physicians (at the beginning and end of the project).

### Key Findings

*Navigator activities:* The PN provided services to 75 mostly elderly patients with varied health conditions. The bulk of the PN's activities focused on arranging social services and locating ancillary resources. Other activities included assessing patients' needs, providing emotional support to patients and family members, coordinating complex referrals, and enhancing communication between physicians and patients. Most activities were conducted by telephone, although the PN met in person with 7 patients.

*Integration with practices:* The PN communicated directly with physicians and often had no communications with other practice members. Aspects of the research design (patient selection from patient list rather than at point of care, collection of survey data from patients before PN contact) affected flow of referrals. Lack of dedicated office space hindered integration of the PN within practices. However, both the PN and physicians, in the context of this study, did not report a need for greater integration to meet patient needs.

*Patients' and physicians' perspectives:* Many patients reported the PN relieved their own or their family members' burdens. Most physicians saw the PN as providing a new service for patients rather than helping meet existing practice demands. Although patients and physicians found this service helpful, neither group expressed a willingness to pay for it.

### Conclusion

Patient navigation services are useful for patients who need emotional support and coordination of social services and complex referrals. These services are typically not provided in community-based primary care practices. Payment reform, one of the key principles of the PCMH, will be needed to make the PN financially feasible in primary care. This pilot project laid the foundation for the submission of an application (PI: Ferrante) to the Agency for Healthcare Research and Quality entitled "Increasing Preventive Services in Medical Homes Using Patient Navigation," that is currently pending review. In this project we will demonstrate the cost-effectiveness of patient navigation for delivering the patient-centered, team-based, coordinated care principles of the PCMH in community primary care practices, and provide validation for third party payment and dissemination of the patient navigator role into primary care sites.

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*Jeanne Ferrante, MD, MPH, is associate professor of family medicine at UMDNJ-Robert Wood Johnson Medical School (RWJMS). She is a family physician and health services researcher with expertise in primary care research and patient navigation. She is a recipient of an NCI career development award focusing on obesity and cancer screening.*

*Deborah Cohen, PhD, is assistant professor of family medicine at RWJMS and associate editor for the Annals of Family Medicine. She examines the role of clinician-patient communication and practice organization in healthcare quality. She has developed methods for evaluating translation research in primary care.*

*Jesse C. Crosson, PhD, is assistant professor in family medicine at RWJMS and director of the New Jersey Family Medicine Research Network. His research is focused on the use of health information technologies and improving the quality of chronic illness care in primary care settings.*

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ARKADY MUSTAEV, PHD, ASSISTANT PROFESSOR, DEPARTMENT OF MICROBIOLOGY AND MOLECULAR GENETICS, UMDNJ-NEW JERSEY MEDICAL SCHOOL, AND THE PUBLIC HEALTH RESEARCH INSTITUTE, AND DMITRY TEMIAKOV, PHD, ASSISTANT PROFESSOR, DEPARTMENT OF MOLECULAR BIOLOGY, UMDNJ-SCHOOL OF OSTEOPATHIC MEDICINE (RIGHT)

## Mitochondrial RNA polymerase as a novel target for anti-malarial drugs

by **Arkady MustaeV and Dmitry Temiakov**

**M**alaria is one of the most ancient and grievous human diseases and results in more than 1,000,000 deaths each year. The World Health Organization estimates that 300-500 million cases of malaria take place around the world. Most deaths occur in young children and pregnant women. Because malaria causes so many illnesses and death, it also has a devastating effect on many national economies. Since many countries with malaria are already among the poorer nations, the disease maintains a vicious cycle of sickness and poverty. Until recently, treatment of malaria with chloroquine was inexpensive and effective; however, resistance of *Plasmodium falciparum* (the causative agent) to this drug has spread from Asia to Africa making this drug ineffective. Chloroquine-resistance is also associated with reduced sensitivity to other antimalarial drugs such as quinine and amodiaquine. Successful treatment of this disease will therefore require development of new approaches. A collaborative project between our laboratories aims to develop new therapies by searching for drugs using a simple high throughput assay that employs derivatives of substrate NTPs and mitochondrial RNA polymerase, a key enzyme



involved in mitochondrial gene expression of the malaria parasite. Development of this assay would allow efficient screening of hundreds of thousands of chemical compounds to find potential antimalarial drugs.

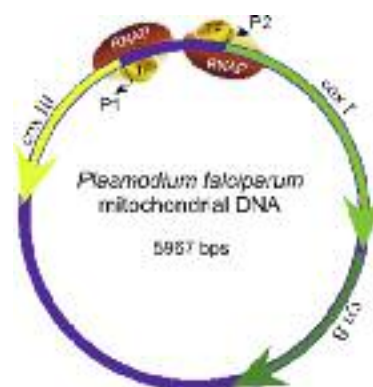
shares very limited homology with human mitoRNA polymerase, and likely operates using a quite distinct set of transcription factors and promoters. We propose that there should be compounds that specifically inhibit *Plasmodium*

**UNTIL RECENTLY, TREATMENT OF MALARIA WITH CHLOROQUINE WAS INEXPENSIVE AND EFFECTIVE; HOWEVER, RESISTANCE OF PLASMODIUM FALCIPARUM (THE CAUSATIVE AGENT) TO THIS DRUG HAS SPREAD FROM ASIA TO AFRICA MAKING THIS DRUG INEFFECTIVE. CHLOROQUINE-RESISTANCE IS ALSO ASSOCIATED WITH REDUCED SENSITIVITY TO OTHER ANTIMALARIAL DRUGS SUCH AS QUININE AND AMODIAQUINE.**

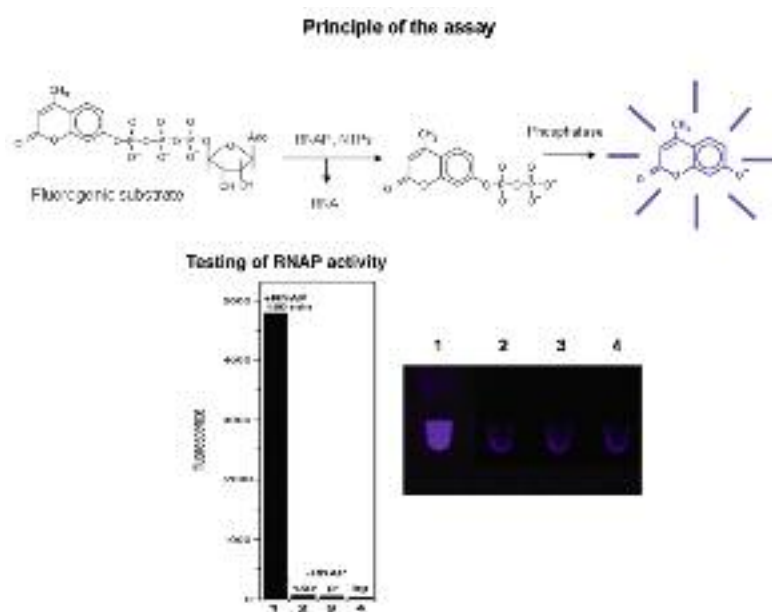
The first step in gene expression, transcription of the information in the DNA genome into messenger RNA, is carried out by RNA polymerases (RNAPs). These enzymes therefore play a key role in all organisms, and have become attractive targets in the development of antibiotics. For example, the front-line anti-tuberculosis drugs rifampin and rifampicin effectively inhibit bacterial RNAPs. A number of other potent inhibitors that affect different stages of transcription or target different regions of the bacterial RNAP have been reported, such as streptolydigin, microcin, and myxopyronin. These proteins are thus attractive therapeutic targets in the search for new antibiotics.

In addition to the large multi-subunit nuclear RNAPs, eukaryotic cells also have a smaller mitochondrial RNAP (mitoRNAP) that is responsible for transcription of the genome of the organelle. While differences between human nuclear RNAPs and nuclear RNAPs of single cell eukaryotic parasites can, in principle, be exploited to find specific inhibitors, the high structural and relatively high sequence homology between these enzymes will likely make this task difficult. In contrast, mitoRNAP of single cell eukaryotes

mitoRNAP (or other components of mitochondrial transcription) but have little or no effect on transcription by human mitoRNAP. Because the viability



**Figure 1. Mitochondria of malaria parasite contain the smallest known genome that encodes just three proteins involved in electron transfer and energy production. Transcription of these genes is carried out by mitoRNAP assisted by at least one transcription factor (TF) and involves two promoters (P1 and P2) located in the opposing DNA strands.**



**Figure 2.** Fluorescent high throughput assay is one of the most sensitive and cost-effective assays to detect RNAP activity. Top panel: Principle of the fluorescent assay. Bottom: RNAP activity as measured by fluorescence emission.

of the parasite depends on mitochondria function, it is reasonable to expect that specific prevention of mitochondrial gene expression and replication will result in death of the parasite.

All mitoRNAPs appear to have arisen from an ancient bacterial endosymbiont, and are related to a well characterized RNAP encoded by a bacterial virus (phage T7) that is structurally distinct

and shares no sequence homology with large multi-subunit nuclear RNAPs. It is therefore expected that such compounds will have minimal toxicity associated with their effects on nuclear transcription.

The genome of *Plasmodium* mitochondria is one of the smallest genomes and encodes mRNAs for only three proteins (Figure 1). Transcription of this genome is carried out by nuclear-encoded mitoRNAP which is assisted by at least one transcription factor. A strategy to develop a fluorescent high throughput screening assay to examine large libraries of chemical compounds for specific inhibitory activity will be based on the ability of recombinant *Plasmodium* mitoRNAP, obtained in Dr. Temiakov's laboratory to carry out promoter-independent RNA synthesis and utilize fluorogenic substrate analogs. All known RNAPs can synthesize RNA on templates containing runs of poly (A)-poly(dT) sequences eliminating the need for specific transcription factors and regulatory DNA regions (promoters).

A fluorescence-based assay for RNAPs previously developed in Dr. Mustaev's laboratory utilizes nucleoside triphosphate substrates with substitutions at the  $\alpha$ -phosphate position that introduce a fluorescent 4-methylumbelliferone moiety (Figure 2). Incorporation of the nucleoside monophosphate residue of these compounds into RNA is accompanied by the release of the pyrophosphate derivative of 4-methylumbelliferone. Subsequent treatment with alkaline phosphatase releases the umbelliferoyl anion, which is highly fluorescent and can be easily detected. The unincorporated portion of the umbelliferone NTP derivative is resistant to phosphatase. It is not fluorescent, and therefore does not contribute to the signal. It is expected that the intensity of the final fluorescent signal would reflect RNAP activity. We have chosen 4-methylumbelliferone because it has been commonly used in enzymatic assays due to high fluorescence and because of its relatively small size, which would allow the NTP derivative to be utilized as an RNAP substrate. Originally this assay was developed for bacterial RNA polymerases. In the present work we demonstrated applicability of the assay for mitochondrial RNA polymerase. This opens the possibility to use the assay for a search of the inhibitors of mitoRNAP using high throughput screening. Identification of inhibitors of this key enzyme would enable targeted drug design and provide new drugs for efficient disease treatment.

Dmitry Temiakov is an assistant professor in the Department of Molecular Biology at UMDNJ-School of Osteopathic Medicine. He received his MS degree in biotechnology in 1993 from Mendeleev University, Moscow, Russia, and his PhD in molecular biology in 1996 from the Institute of Genetics, Moscow, Russia. He pursued his post-doctoral training at the Downstate Medical Center in Brooklyn, NY. Dr. Temiakov is currently involved in studies of molecular mechanisms of transcription regulation in human mitochondria.

Arkady Mustaev is an assistant professor in the Department of Microbiology and Molecular Genetics at UMDNJ- New Jersey Medical School. He received his PhD in 1987 from Novosibirsk Institute of Bioorganic Chemistry, Siberian Branch of the Russian Academy of Sciences. His post-doctoral training was done at the Limnological Institute, Irkutsk, Russia, as well as at Columbia University and the Public Health Research Institute, NY. Currently Dr. Mustaev is involved in drug discovery projects, development of highly sensitive fluorescent probes for biological applications and in studies of the molecular mechanisms of prokaryotic transcription.

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## Changes in air quality during the Beijing Olympics: individual differences in health effects

by Scott R. Diehl and Junfeng (Jim) Zhang

**T**he adverse effects of air pollution on health are well-established. However, the actual biological mechanisms that underlie our bodies' responses to different types of gases and particles in the air are only partially understood. Very recently, scientists have begun to recognize that all people are not the same in terms of how air pollution affects their health. A new focus is beginning to emerge on individual differences in responses to these toxic substances. This strategy is based on studying inherited variation in genes that metabolize the toxic substances or are involved in cardiovascular or pulmonary pathways that are most severely affected by air pollution exposure.

With the great expansion of industrial activity in recent years, much of China has seen decreases in air quality. In Beijing, air pollution levels are usually much higher than even in the most severely polluted places in the U.S. During last summer's (2008) Olympics, unprecedented measures were implemented by the government with the goal of reducing air pollution during the Games so that athletes' performances would not be adversely affected. A collaborative team of UMDNJ and Chinese scientists and clinicians worked together to take advantage of this unique opportunity to learn more about the "how and why" of air pollution's effects on human health.

Great improvements have been made in the air quality in this country and in much of the developed world during the past 50 years. Nevertheless, even the reduced levels of pollution in the air here still cause serious health problems, especially for those who are at increased risk due to other health conditions such as asthma, emphysema, COPD and cardiovascular diseases. Unfortunately, the air quality in much of the developing world has declined dramatically, coincident with the rapid economic growth accompanied with increased industrial activities and motor vehicles. China has been one of the primary locations where this rapid industrialization has taken place, and a major increase in levels of air pollution has occurred throughout much of the country. In Beijing, air pollution levels are usually much higher than even in the most severely polluted places in the U.S. Efforts by the government are beginning to



SCOTT R. DIEHL, PHD, PROFESSOR, DEPARTMENT OF ORAL BIOLOGY, AND DIRECTOR, CENTER FOR PHARMACOGENOMICS AND COMPLEX DISEASE RESEARCH, UMDNJ-NEW JERSEY DENTAL SCHOOL

address this very serious problem, and these were given a major jump start and test run last August when the Olympic Games were held in Beijing. As a condition of being awarded the opportunity to host the Games, the Chinese authorities committed to taking truly unprecedented measures to improve the air quality in Beijing. Although some of these measures could only be implemented for a few weeks around the games themselves, others were designed to improve air quality over the longer term. These measures were mostly successful, and the Games were generally considered a great success.

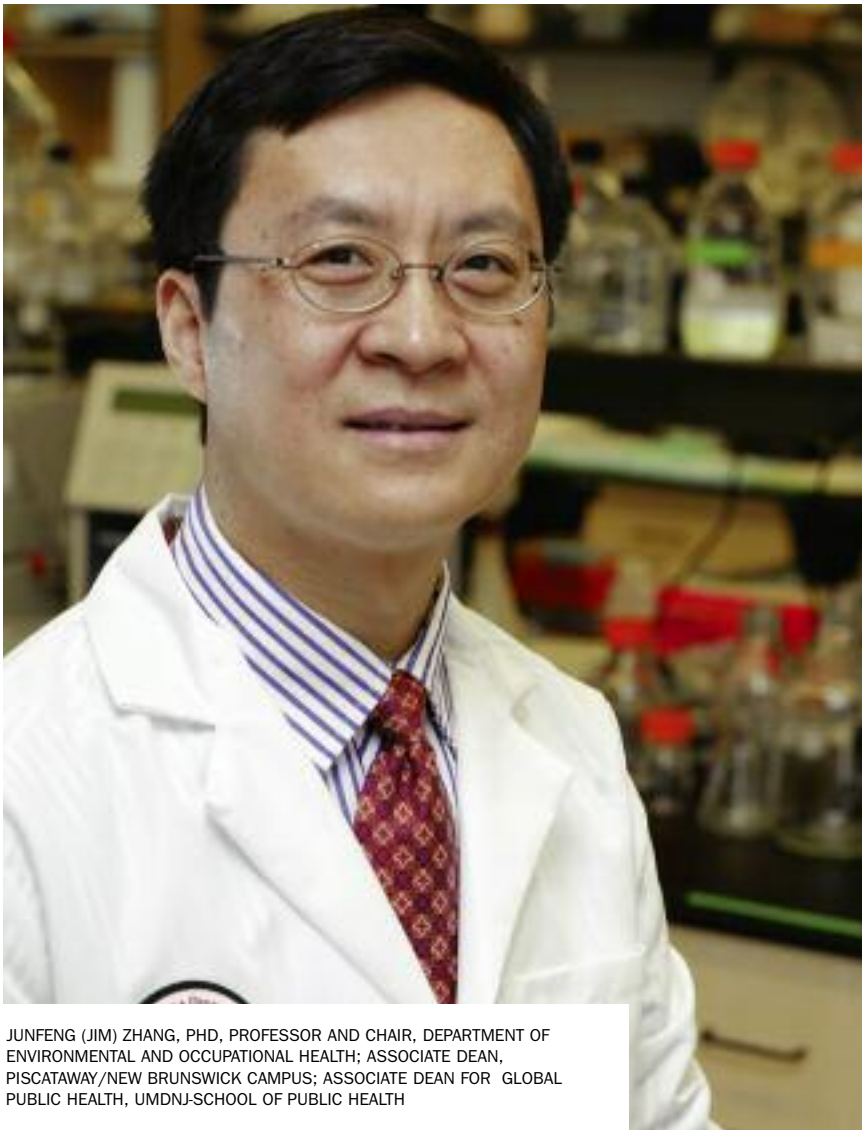
leads to substantially increased rates of sickness and death due to heart attacks and pulmonary crises. However, few studies have been conducted to examine health effects of air pollution reduction. The problem was that it is difficult if not impossible under normal circumstances to predict when a prolonged reduction in pollution across a large area would occur. The situation scheduled to take place in Beijing during the Olympics thus presented us with a unique opportunity to study the effects of air pollution reduction on human health. Our research team capitalized on this by developing a study plan and obtaining grants from both the Health Effects

**PERFORMING RESEARCH ON HEALTH EFFECTS OF EXPOSURE TO TOXIC SUBSTANCES REQUIRES US TO ADDRESS IMPORTANT ETHICAL AND LOGISTIC CHALLENGES AND LIMITATIONS. WE OBVIOUSLY CANNOT EXPOSE SUBJECTS TO VERY HIGH LEVELS OF POLLUTANTS FOR LONG PERIODS OF TIME IN THE LABORATORY, THEN TAKE AWAY THE POLLUTANTS AND SEE HOW THIS CHANGE AFFECTS MEASURES OF HEALTH.**

Performing research on health effects of exposure to toxic substances requires us to address important ethical and logistical challenges and limitations. We obviously cannot expose subjects to very high levels of pollutants for long periods of time in the laboratory, then take away the pollutants and see how this change affects measures of health. Research conducted in cities under naturally-occurring circumstances has shown that very large increases in air pollution for a period of days or weeks

Institute and the NIH to support the research. We recruited experts from the broad array of disciplines needed for this research including our colleagues Drs. Howard Kipen, Pamela Ohman-Strickland, David Rich and Shou-En Lu from UMDNJ and Drs. Tong Zhu, Wei Huang, Min Hu, GuangFa Wang, Ping Zhu and Yuedan Wang in Beijing.

Subjects participating in our study were evaluated for “biomarkers” of inflammation, body burden of oxidative stress, autonomic tone, and



JUNFENG (JIM) ZHANG, PHD, PROFESSOR AND CHAIR, DEPARTMENT OF ENVIRONMENTAL AND OCCUPATIONAL HEALTH; ASSOCIATE DEAN, PISCATAWAY/NEW BRUNSWICK CAMPUS; ASSOCIATE DEAN FOR GLOBAL PUBLIC HEALTH, UMDNJ-SCHOOL OF PUBLIC HEALTH

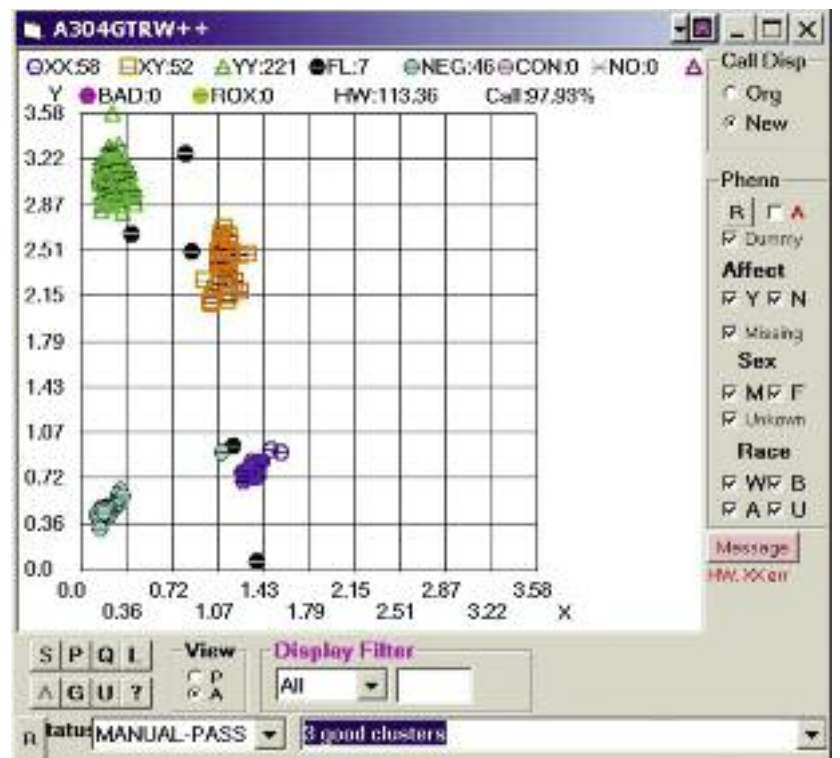
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cardiovascular function (thought to be responsible for many of the negative health effects) in their blood, urine and exhaled breath. In addition, subjects provided saliva samples that we used to extract DNA. Each participant was assessed six times, twice before the Olympics began and before the air pollution reduction measures were put in place, twice during the Olympics when air quality was supposed to be improved, and two more times after the Games were over when some of the air pollution control measures were relaxed and air pollution was expected to increase. We are currently analyzing these data by running assays in our labs here in the U.S. and in China and have already seen dramatic changes in some of the inflammatory and oxidative stress biomarkers that correlate nicely with these different time points.

Although the very negative effects of air pollution on health are well-established, the actual biological mechanisms that underlie our bodies' responses to different types of gases and particles in the air are only partially understood. A new focus is beginning to emerge on individual differences in response to these toxic substances. We are employing this strategy of "individualized medicine" in our study of the health effects of air pollution in Beijing. We are measuring inherited variation in genes that metabolize the toxic substances in the air or genes that are involved in the cardiovascular or pulmonary pathways most severely affected by air pollution exposure. Most of the DNA variants that we will study are Single Nucleotide Polymorphisms (abbreviated as "SNPs" and pronounced "snips"). These are places in the genome where a single DNA base has been changed, for example, from a "C" nucleotide to a "T" base. When these changes occur in the portion of a gene that codes for a protein's amino acids, a different amino acid may be inserted into the protein, changing the protein's function in a subtle or a dramatic way. Other SNPs may cause the protein's synthesis to be terminated prematurely and be totally non-functional. Still other inherited variants may affect the level of expression of mRNA and protein and thereby influence the

person's response to toxic substances in the air. Our laboratory uses several different assay methods to determine the DNA sequence at positions of interest in the genome. One of these methods is called the TaqMan assay and this is illustrated in Figure 1.

In the coming months, it will be exciting to see whether any of the candidate gene polymorphisms we are testing have a major impact as to how different people respond to changes in air pollution exposure. In the future, we hope to build on this experience to recruit a much larger number of subjects so that we're able to perform studies looking at the entire genome. If successful, our strategy of focusing on individuals' inherited differences offers great potential for advancing our understanding of the "how and why" of the biological mechanisms that underlie air pollution's effects on human health.



**Figure 1.** Molecular assay of a polymorphism in the vitamin K epoxide reductase complex gene. Each dot represents the genotype of individual subjects. Green is the common A/A genotype, orange A/G and blue G/G. Light blue dots are negative controls and black dots represent occasional failures of the assay. Vitamin K is essential for blood clotting but must be enzymatically activated for the carboxylation of glutamic acid residues in some blood-clotting proteins. This gene encodes the enzyme responsible for reducing vitamin K 2,3-epoxide to the enzymatically activated form. Fatal bleeding can be caused by vitamin K deficiency and mutations are associated with deficiencies in vitamin-K-dependent clotting factors and resistance to the drug warfarin. Air pollution exposure is thought to disturb the normal balance of clotting factors and this may be one mechanism by which it increases risk of heart attacks and stroke.

*Scott Diehl is the director of the Center for Pharmacogenomics and Complex Disease and a professor in the Department of Oral Biology at UMDNJ- New Jersey Dental School. He earned his PhD from the University of Texas at Austin and conducted research at the University of Michigan, the Medical College of Virginia and the National Institutes of Health before moving to UMDNJ in 2002. His other research involves genetic studies of susceptibility to pain and side effects of pain medications, periodontal disease, dental caries, dental fluorosis, head and neck cancer, and the birth defect, cleft lip and palate.*

*Junfeng (Jim) Zhang is a professor of Environmental and Occupational Health at UMDNJ-School of Public Health (SPH) and a member of the Environmental and Occupational Health Sciences Institute (EOHSI), jointly sponsored by UMDNJ-Robert Wood Johnson Medical School and Rutgers University. He received a PhD degree in Environmental Sciences and Public Health jointly from UMDNJ and Rutgers University and an MS degree in Atmospheric Chemistry from Peking University. His research interests include assessing human exposures to environmental contaminants and resulting health effects, both on a global scale and within a local context. Dr. Zhang's laboratories at SPH and EOHSI develop novel methods for biomarkers of human exposure and health effects.*