

THE MONELL CONNECTION

THE NEWSLETTER OF THE MONELL CENTER

Tasting beyond the tongue

Monell's newest faculty member is uncovering new answers to old questions

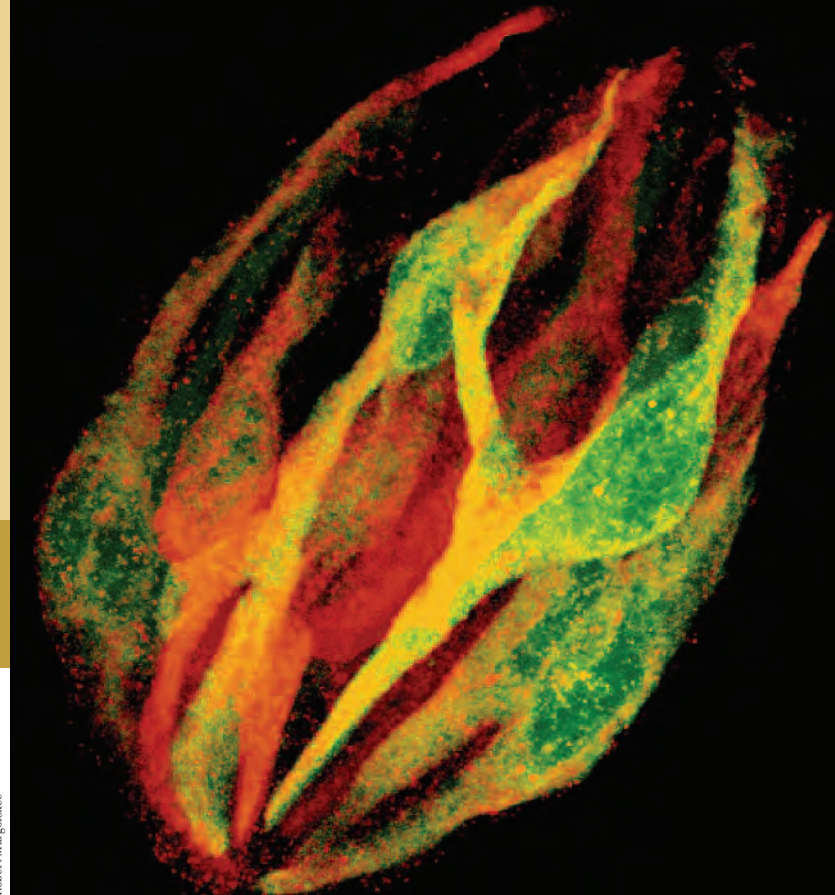
Imagine a fast-paced episode of Jeopardy. The category is "Tasty Tales" for \$400, prompting Alex Trebeck to smoothly recite, "Where much of taste takes place." When the quick-fingered contestant asks "What is the tongue?" the podium scoreboard jumps and the audience breaks into appreciative applause.

Robert Margolskee, however, might have a different answer. "What is the gut?" he would ask. Margolskee, a world-renowned expert on the molecular mechanisms of taste and Monell's newest faculty member, is extending his studies of taste to probe the mechanisms and functions of the sweet and bitter taste receptors recently discovered in cells lining the gastrointestinal tract.

This remarkable discovery is changing the concept of taste, with far-reaching implications that could include innovative therapeutic approaches to diet-related diseases such as obesity and diabetes.

A pioneer in the use of molecular biology and knockout mouse models to study the mechanisms of taste, Margolskee has been responsible for major advances in the field of taste biology. His seminal 1992 discovery of gustducin, a so-called "G-protein" expressed exclusively in taste cells, ultimately led to an enhanced understanding of taste cell biology. Activated when a

Liqun Huang, Copi Shanker,
Robert Margolskee



Immunofluorescent image of an individual taste bud from the tongue expressing green fluorescent protein and doubly stained for gustducin and G-gamma13



Robert Margolskee

Continued from cover page

sweet, bitter or umami taste molecule binds to its receptor on a taste cell, gustducin initiates the intracellular cascade that allows taste receptor cells to translate the chemical information from taste stimulus molecules into electrical information that can be processed by the brain. A decade later, Margolskee was among the researchers (who also included some at Monell) responsible for the discovery of the T1R3 sweet taste receptor subunit.

At Monell, Margolskee will take advantage of the Center's interdisciplinary environment to expand his research, seeking new answers to old questions that ultimately will change the concept of taste. "Monell has the largest collection of chemosensory scientists in the world and is an incredible place for collaboration," he says. "I cannot think of a better place to do the kind of work I want to be doing, which focuses on how the taste system is relevant in other organ systems and the endocrine system. Also, identifying what role taste has in the hormonal regulation of how we digest and metabolize food, including any involvement in diabetes and obesity."

Intestinal sweet taste

The first evidence for taste beyond the mouth came from the surprising 1996 finding of gustducin in cells of the gastrointestinal tract. More support came a little less than a decade later, when taste receptors for sweet, bitter and umami were directly identified in the gut.

Although it made sense that the intestines would have nutrient-sensing receptors to

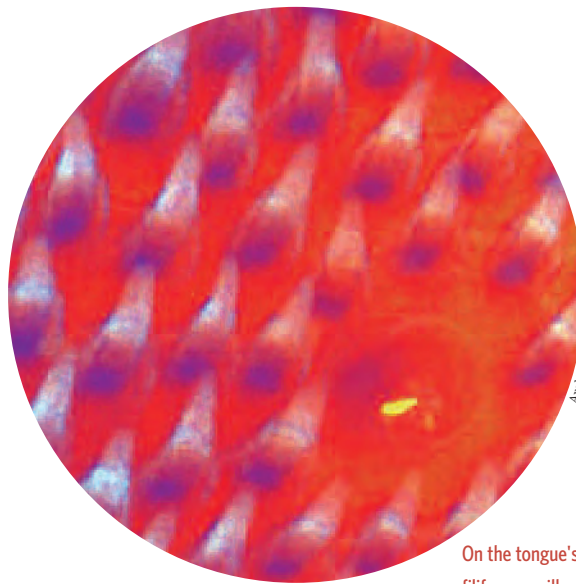
aid in digestion and metabolism, it was not clear exactly what these gut taste receptors were doing. Their function remained unknown until 2007, when Margolskee and colleagues discovered that gut sweet taste receptors help regulate sugar absorption from the intestines into the bloodstream.

Reporting in the *Proceedings of the National Academy of Sciences*, Margolskee and his collaborators localized sweet receptors on enteroendocrine cells in the intestinal wall. Using a series of sophisticated approaches, they further found that enteroendocrine cells also contain gustducin and other taste signaling proteins used by oral taste receptors; the findings suggest that the gut and the mouth utilize very similar mechanisms to taste sugars and sweeteners.

Additional studies by Margolskee's team revealed that enteroendocrine cells secrete multiple gut hormones: glucagon-like peptide-1 (GLP-1), GLP-2, and glucose-dependent insulintropic peptide (GIP). One or more of these hormones then acts on neighboring cells to regulate glucose transport through the intestinal wall. Thus, intestinal sweet taste receptors on enteroendocrine cells help regulate the absorption of sugar from the intestines. The receptors sense the amount of sugar in the gut, with more sugar leading to greater hormone secretion from the enteroendocrine cell. In turn, the hormones act on neighboring cells to increase the rate of sugar absorption from the intestine.

Yet another function of the gut hormone GLP-1 is to stimulate insulin release from the pancreas, which in turn promotes glucose uptake from the blood into the body's cells. This aspect strongly piques Margolskee's interest. With dual degrees in medicine and molecular biology, he is highly tuned to human health and the potential translational applications of basic research discoveries. He explains, "My interest has always been in medically relevant research. At Monell, I am collaborating with Karen Teff to take some of our basic science discoveries and see whether they carry over to translational applications in human populations. Karen is a fantastic resource; her human clinical work and expertise are going to be particularly important to me."

With respect to GLP-1, Margolskee wants to determine the relative significance of intestinal cells containing taste receptors and signalling proteins compared to other cells that stimulate GLP-1 release. "If we can use the taste cells to identify stimulators of GLP-1 that could in turn promote insulin release, it could have beneficial effects for the treatment of type 2 diabetes. This is why the collaboration with Karen is so important."



Axel Preuss, Robert Margolskee

On the tongue's surface, filiform papillae involved in tactile sensing surround a single fungiform papilla containing a gustducin-expressing taste receptor cell (yellow)

The Flip Side: Tongue Hormones

Recent findings from Margolskee's group further highlight the intricate connections between the taste and endocrine systems — and the advantage of conducting taste research in the interdisciplinary environment at Monell. He explains, "Not only are taste receptors found in endocrine cells, but we also have observed that taste cells on the tongue secrete metabolically-active hormones, including GLP-1." He suspects that the tongue hormones contribute to *cephalic phase reflexes*, a link between food's sensory components and its subsequent digestion and metabolism. At Monell, the cephalic reflexes have been an ongoing area of study since the Center's founding, with pivotal work by Karen Teff during the 1990s helping to elucidate how the sensory qualities of food influence insulin release and blood glucose regulation. Noting that GLP-1 is a potent stimulator of insulin release, Margolskee says, "One set of important studies will ask whether GLP-1 release from the tongue contributes to the cephalic phase endocrine pathway."

In turn, Teff, who also serves as Director of Translational Research at Penn's Institute for Diabetes, Obesity and Metabolism, notes that Margolskee's expertise will complement her own established research program on hormonal systems associated with obesity and diabetes. She comments, "Bob's influential work is increasing awareness of the important role of the chemical senses in nutrition, metabolism and hormonal regulation."

Tasteful interactions

Margolskee, who comes to Monell from the Mount Sinai School of Medicine in New York City, observes that his research on taste started at Monell over 17 years ago. Trained as a molecular biologist and neuroscientist, he was seeking to apply his expertise to an emerging area where he could have an impact. Noting that colleagues had successfully used molecular approaches to increase knowledge of the olfactory and visual systems, he decided to turn to taste. "Being able to identify components of the sensory systems enabled insight to the function of those systems," he recalls. "I decided that I wanted to do the same for taste and then immediately

turned to Monell for advice. So my interest in and collaborations with Monell are deeply-rooted, which helped to make the decision to join the Center an easy one."

Already taking advantage of Monell's style of collegial interaction, he remarks, "Just by wandering down the hallways, I have had the opportunity to discuss many potential projects." Sensory scientist Paul Breslin looks forward to extending his own research interests through mutually-beneficial collaborations, "The physiological impact of sweet, bitter, and savory tasting stimuli that occurs along with the sensory signaling is an area that looks highly relevant for medicine. My work is growing more in the functional side of taste, so our combined interests should allow for some wonderful interactions."

Another potentially fruitful collaboration centers on Michael Tordoff's extensive work on calcium taste. Tordoff and Margolskee already have published one paper together, using strains of knockout mice to identify the T1R3 component of the sweet taste receptor as also being involved in calcium taste responses. Yet another calcium receptor may have a dual role to function in both taste and other organs of the body, such as bone.

Taste geneticist Danielle Reed also plans to gain from Margolskee's expertise, noting that the benefit will extend to both sides of the partnership. "Discussions with Bob and his laboratory should give us a fresh perspective on some of my research questions. In turn, I think he may benefit from being at Monell because of the direct access to experts in human taste psychophysics and taste genetics."

Translating taste

In addition to the tongue and gut, Margolskee has identified taste receptor components in the pancreas, which secretes insulin and glucagon. Recent studies suggest that the pancreatic taste cells may help to regulate the release of these metabolically important hormones. As such, these taste cells may be particularly important to diabetes and other

Taste Team Players



Three members of Margolskee's research team also made the move to Monell. "I am delighted that these extraordinary scientists are joining me at Monell," he said. "They will be bringing much expertise and continuity to our research." With extensive expertise in animal modeling and transgenic knockout mouse strains, physician and geneticist **Bedrich Mosinger** is developing conditional knockout models. By selectively eliminating signal proteins or receptors from the tongue, gut or pancreas, the group will be able to evaluate the specific contributions of those elements. Physiologist **Zaza Kokrashvili** is an instrumental contributor to the team's work on taste cells in the gut and pancreas. Approaching the group's questions from another angle, molecular biologist **Peihua Jiang** works with cell cultures to characterize the impact of various sweeteners on hormonal response of endocrine cells. Margolskee states, "We intend to hit the ground running."

endocrine disorders related to glucose regulation.

"Each of the areas we are looking at – the tongue endocrine cells, the gut endocrine taste cells and the pancreatic endocrine taste cells – each has important implications for human health. Although I decided that a clinical practice would be too distracting, I always am looking for the potential translational relevance of basic science discoveries. That's why I am at Monell." ■■

Of Note at Monell

Recent Grants

Foundation Awards

Monell Member **Paul A. S. Breslin** recently was awarded a Grand Challenges Explorations grant from the Bill & Melinda Gates Foundation to support an innovative global health research project "Taste-Guided Behavior on Mosquitoes Helps Eradicate Malaria." Breslin proposes that a deeper understanding of mosquito taste will reveal novel approaches to the design of strategies to reduce mosquito-mediated transmission of malaria and other diseases. As a first step, studies funded by the Grand Challenges Explorations grant will assess taste responses of mosquitoes to a range of human skin compounds. Member **George Preti** also is an investigator on the grant. An analytical organic chemist, Preti's expertise on human skin compounds is integral to the effort.

National Institutes of Health

Johan Lundström, "Odor Processing, Differences Determined by Origin of Odorants"; 3-year grant from the National Institute on Deafness and Other Communication Disorders

Robert Margolskee, "Functional Characterization of Endocrine Taste Cells"; 5-year grant from the National Institute on Deafness and Other Communication Disorders

Danielle Reed, "Mapping Adiposity in Mice"; 5-year grant from the National Institute of Diabetes and Digestive and Kidney Diseases

Danielle Reed, "Labmaster: Food and Water Intake, Activity and Metabolic Rate"; Shared Instrumentation Grant from the National Center for Research Resources

Karen Teff, "Olanzapine and Muscarinic Blockade of Early Determinants of T2DM in Humans"; 4-year grant from the National Institute of Diabetes and Digestive and Kidney Diseases

Michael Tordoff, "Physiology of Calcium Appetite"; 5-year grant from the National Institute of Diabetes and Digestive and Kidney Diseases

Paul Breslin, Gary Beauchamp, Beverly Cowart, Pamela Dalton, and Johan Lundström, "Research Supplements to Promote Diversity in Health-

Related Research Program"; funding from the National Institute on Deafness and Other Communication Disorders to support five summer student apprentices

Other Government Sources

Gary Beauchamp, Julie Mennella, and Danielle Reed; 1 year of funding from the Pennsylvania Tobacco Settlement Funds Formula Grant.

Alan Gelperin, "RealNose Program"; 15 month grant from the Defense Advanced Research Projects Agency

Subcontracts Funded Through Other Organizations

Karen Teff, "Endophenotypes of Sleep Apnea and Role of Obesity"; 5-year grant from the National Heart, Lung, and Blood Institute through the University of Pennsylvania

Meritorious Monellians

In April, Member **Alan Gelperin** delivered plenary talks at the IBEC Symposium on Bioengineering and Nanomedicine in Barcelona, Spain and the International Society for Olfaction and Electronic Noses in Brescia, Italy

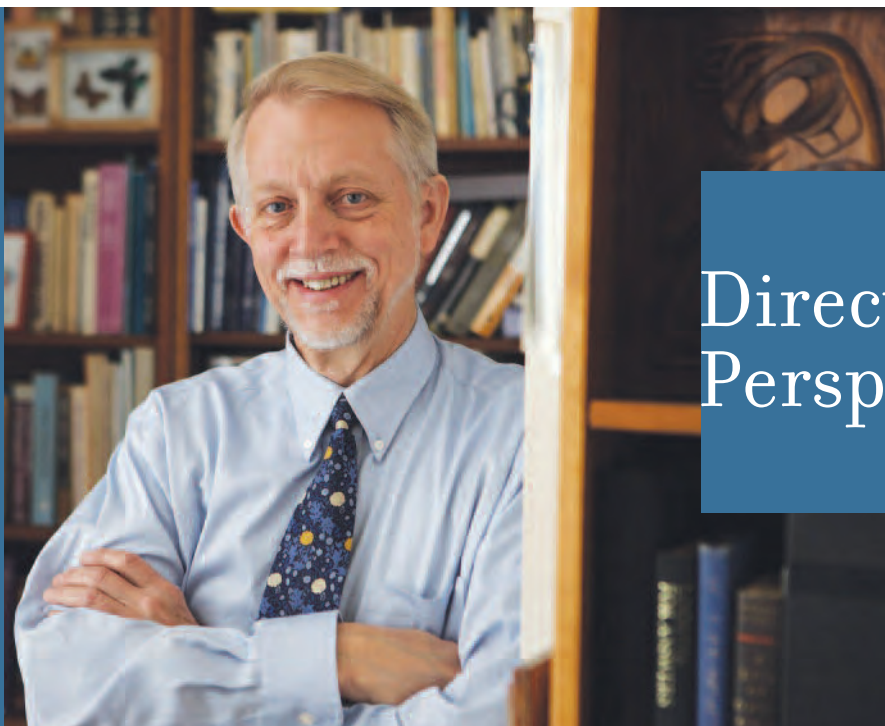
Postdoctoral fellow **Antti Knaapila** was honored by the Finnish Society of Food Science and Technology for his outstanding doctoral thesis.

Research Associate **Xia Li** received first place for her poster, "Towards understanding the significance of duplications detected by genome-wide array analysis" at Children's Hospital of Philadelphia's 2009 Research Poster Day.

Monell Assistant Member **Johan Lundström** is the 2009 recipient of the *Moskowitz Jacobs Award for Research Excellence in the Psychophysics of Taste and Smell*. Lundström was honored in April at the AChemS meeting in Sarasota.

Koichi Matsumura, a postdoctoral fellow, received both a 2009 Keystone Symposia Scholarship and an AChemS Polak Young Investigator Award.

Member **Amos Smith, III**, received an honorary Doctorate of Science for distinction in organic chemistry on July 8 from Queen's University, Belfast, Northern Ireland. ■■



Director's Perspective

Peter Olson

Gary K. Beauchamp

An Expanded View

I recently helped edit a volume on the chemical senses for a massive project by Academic Press to fully survey the senses (*The Senses*, 6 volumes, 2008). As is typically the case, vision and hearing commanded the majority of space (2093 pages). However, I was delighted that 932 pages — almost half as much material — were devoted to the senses of taste and smell. How different from an earlier compilation published a little over 25 years ago (Barlow & Mollon: *The Senses*), in which articles on hearing and vision comprised 300 pages, almost ten times more than the mere 35 pages on taste and smell.

This deserving increase in the relative amount of space devoted to the chemical senses reflects both the remarkable progress in wonderful science as well as the growing realization, pioneered by Monell, of their relevance to human health and well-being.

In the past, the importance that humans ascribe to each of the senses was equated, at least in part, to the discernible consequences of their loss: from this perspective, blindness and deafness are thought much more significant than

anosmia and agusia (even these terms are relatively obscure).

But recently, I and many of my colleagues have been rethinking this evaluation and in particular, moving away from equating the importance of the senses primarily with the impact of losing them. In this expanded view, research on the chemical senses is fundamental to improving human health.

Indeed, I argue that for human health, at least in the developed and developing world, the chemical senses are perhaps the most important of the classical five senses. Problems such as obesity, diabetes, hypertension and even some cancers are directly tied to what we eat and breathe. Sugar, salt, fat, pollutants — all these are detected by our chemical senses, which to some degree also regulate our exposure and intake.

Based on this belief, Monell is launching a new fundraising initiative, *The Monell Health Initiative: Innovative Research at the Interface of Appetite, Taste and Nutrition*. Our idea is that by highlighting the central role the senses of taste, smell

and chemesthesis play in human health, we can leverage this newly-recognized relevance to identify new approaches and potential solutions that benefit a broad spectrum of health-related concerns.

The overall goal is to provide support to faculty — both current and newly-recruited — who work directly on this critical intersection of sensation and human disease. Our scientists' discoveries will provide a better understanding of flavor preferences and aversions and the mechanisms underlying hunger, satiety, and cravings; I am convinced that this knowledge can focus efforts and resources on a global level to more effectively encourage healthy eating habits and improve nutrition.

This new initiative is particularly important to Monell right now in light of the many fiscal difficulties we currently face as a consequence of the changed economy. Government funding remains tight and support from our corporate partners and from individual donors is even tighter. Monell does not have an endowment or even a large reserve fund to carry us over during these hard times, so we must find ways to increase our income from grants and gifts; this initiative is one such effort. It also offers an important way to connect to people who are just learning about Monell, and help them understand why the research here is so important.

Monell remains strong, but in these very challenging times we are redoubling our efforts to inform all our constituencies of the importance, relevance and excitement of Monell's research enterprise. There is still much to learn about these remarkable senses that shape our lives in so many ways. ■■

Growing Scientific Leaders

Lessons learned at Monell

The nutritional scientist heads a research center devoted to studying healthy and disordered human feeding behavior at a major university.

The chemical ecologist directs the federal institution that develops methods to safely resolve conflicts between humans and wildlife.

What do these two influential leaders have in common? Each is a Monell alumnus who credits his time at the Center as central to his success.

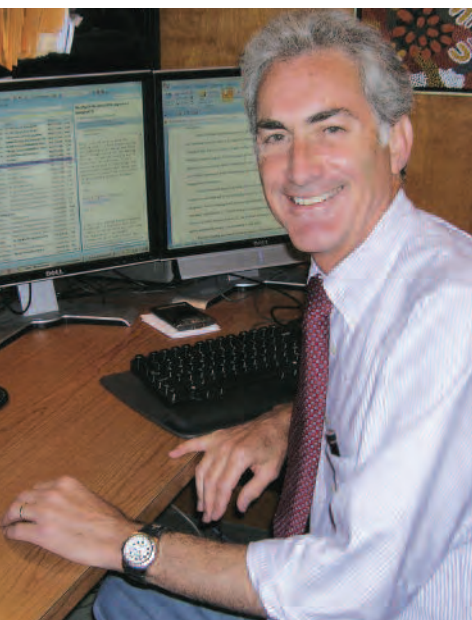
Larry Clark



“The integrative and synthetic approaches toward problem solving that I learned at Monell aided not only the scientific end of my career but also the development of my organizational and leadership philosophies,” remarks Larry Clark, Director of the National Wildlife Research Center (NWRC). Part of the US Department of Agriculture, the NWRC conducts research and provides information to resolve human-wildlife conflicts related to agriculture, human health and safety, property, invasive species, and threatened and endangered species.

Richard Mattes agrees. Professor of Foods and Nutrition at Purdue University, Mattes is Director of Purdue’s Ingestive Behavior Research Center (IBRC). “I learned to think critically and in an integrative fashion at Monell,” he says. “That transfers to any job setting.”

Richard Mattes



Both Clark and Mattes came to Monell in the early 1980’s as postdoctoral fellows and stayed on as faculty members to develop innovative research programs. Each praises the Center’s supportive and collaborative culture as being fundamental to his success. Clark, whose appointment to head the NWRC was announced earlier this year, says “One of my current challenges is to capture the critical elements, philosophies and management styles that embodied Monell and adapt them to my current organization. I already am beginning to see the fruits of those efforts.”

At the NWRC, Clark sets the research direction and oversees more than 160 scientists, technicians, and support personnel at the Center’s headquarters in Fort Collins, CO and several field stations across the country. Monell and the USDA have a long history of collaboration dating back to the Center’s founding. Clark joined the USDA in 1991 while still on the faculty at Monell; NWRC scientist Bruce Kimball currently is stationed at Monell.

Noting that the confidence he gained at Monell while tackling challenges across a diverse range of fields was critical to his success in developing new programs within the NWRC, Clark adds “These achievements in turn led to the opportunity to lead my organization.”

Mattes, whose research is at the interface of sensory and nutritional sciences, also credits the Center’s interdisciplinary approach that, combined with an “unprecedented intellectual freedom,” enabled him to develop an independent research program spanning both fields. A similar approach is evident at the IBRC, which includes 40 faculty members from five colleges and 13 departments across Purdue. Research and training at the IBRC integrates physiological, nutritional, developmental, genetic, sensory, socio-economic, and experiential studies of ingestive behavior to benefit public health.

Mattes and Clark left Monell in the same year, 1995. Both scientists remain closely associated with Monell as members of the affiliated faculty. “It’s a link that results in instant credibility and opportunity,” says Mattes. He notes, “My decision to leave Monell was based on enthusiasm to move in a new direction, rather than escape the old. With this orientation it is difficult to go wrong.” Clark agrees, “How we leverage our experiences will influence the potential for our success.” ■

Hands - on Success



The recap from the 2009 Summer Science Apprenticeship Program showcases the benefits of both teaching by example and learning through example.

This year, 24 students (19 from area high schools and five from local and national universities) worked for seven weeks as part of Monell's Science Apprenticeship Program. This was the 28th year for the program, which has provided direct, hands-on mentored experience in Monell's laboratories to more than 375 young scientists. Funded through the generous support of the PepsiCo Foundation, the Connelly Foundation, and the National Institutes of Health, the 2009 program received the highest number of applications to date, with over 150 students from across the United States and abroad competing to participate.

As part of the popular lecture series established by former director Julie Mennella, students listened to presentations from Monell faculty, covering a range of topics that included chemical ecology, nutrition science, and environmental and occupational health. New this year was the addition of an autobiographical component to the talks. "It is important for the students to appreciate the sense of joy that a scientific career can bring," says current program director Paul Breslin, a sensory scientist who himself has a long history of mentoring students. "The passion of Monell's faculty is inspiring and encouraging."

Equally inspiring were the presentations of two recent program alumni from Breslin's lab. Nelsa Estrella and Osama Ahmed both enter science doctoral programs in fall 2009. Estrella, who apprenticed in Breslin's lab for seven years, graduated Magna Cum Laude from University of the Sciences in Philadelphia, where she majored in Biology. She heads to Boston University with a full five year scholarship to study molecular biology.

Ahmed, who joined the Breslin Lab when he was only 13 years old, will cross the country to study neuroscience at the University of California, San Francisco. A graduate of the University of Pennsylvania, where he majored in bioengineering, Ahmed applied for a National Science Foundation Graduate Fellowship and received an Honorable Mention, a prestigious honor for an aspiring young scientist.

"I am tremendously proud of both Osama and Nelsa," says Breslin.

Moving forward, the Science Apprenticeship Program continues to diversify and expand. What started as a minority and female focused program has grown to become more encompassing. Last year, Yaritza Davila and Ron Schwoyer, two students with autism from Philadelphia's Kensington High School for International Business, Financing, and Entrepreneurship, participated in the program. Returning for a second summer, they were joined by Kensington peers William Dunbar and Shane McTamney.

"This is a huge accomplishment for any student, and even more so for a student with autism, which has a communication disorder component," comments Kristen Deppenschmidt, the autistic support teacher who works with the students both at Kensington and on-site at Monell. "I look forward to seeing my students grow." ■■

— Jennifer Marks

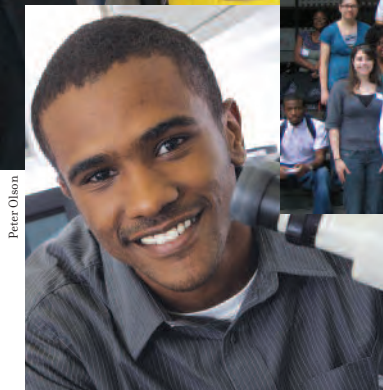
A Step Forward

A partnership between Monell and the Philadelphia School District's Community-based Vocational Training Program provides valuable work experience to students with autism, preparing them to be successful, independent adults.

Over the past two years, Kensington High School autistic support teacher Kristen Deppenschmidt and Monell Director of Facilities Management Donna Kupniewski have designed a vocational training program tailored to the needs of Deppenschmidt's students. To date, eight students with autism have received hands-on training in Monell's Animal Facility. The students clean bottles and cages, provide fresh food and water, and perform other essential duties for the animals at Monell.

Kupniewski reports that training at Monell has increased the students' levels of independence and capacity for learning new skills. "They are tremendously helpful, eager, and thirsty for knowledge. The students come to Monell enthusiastic to find their way in the adult world," comments Kupniewski. "I am honored to know and work with each of them."

Paul Breslin and Nelsa Estrella



Osama Ahmed



The 2009 student apprentices

Beijing International Meeting on Research in Taste and Smell

November 15 - 17, 2009
Beijing, China



The Monell Center invites the chemosensory scientific community to attend the first international meeting on the chemical senses to be held in China. Organized by Monell in collaboration with the Chinese Academy of Sciences, this historic meeting will take place in Beijing, China on November 15-17, 2009. Dr. Gary Beauchamp, Director of the Monell Center, and Dr. Le Kang, President of the Beijing Life Science Institutes of the Chinese Academy of Sciences, are Meeting Co-Chairs.

Dr. Alan Leshner, CEO of the American Association for the Advancement of Science (AAAS) and Executive Publisher of Science magazine, will open the meeting as Plenary Speaker. Dr. Leshner, who also sits on Monell's Board of Directors, has been leading efforts to create greater scientific exchange and collaboration between Chinese and US scientists and policymakers.

For Monell sponsor companies, particularly those with current or planned research operations in China, the meeting offers an opportunity to meet Chinese chemosensory researchers living abroad and in

China and also to learn about the range of chemosensory research being conducted in China. We encourage our sponsors to attend and offer

attendees from Monell sponsor companies a special reduced registration fee of \$200. For more information on this special registration rate, please contact Monell at chinaconference@monell.org.

Meeting sponsorship provides organizations with the exclusive opportunities to meet Chinese scientists at a private reception and to promote their companies at the meeting through posters and table set-ups. Sponsorship support levels are available at \$2,500, \$5,000 and \$10,000; please contact Dr. Carol Christensen at cchristensen@monell.org for details.

This international meeting has been made possible through the strong encouragement and financial support of Mr. Liu Riuji, Chairman of Heng Yuan Xiang (恒源祥), Monell's first sponsor company from China.

Please visit the meeting website at www.chinachemosensory.org for more information on this historic meeting.

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