As the phone on Johannes Reisert’s desk rings, he leans his lanky frame across the desk to answer. On the other end is Robert Margolskee, wanting to discuss a recent seminar. As the two Monell scientists — one an olfactory cell physiologist, the other a taste biologist and both focused on a similar problem — chat, the phone converts sound waves into electrical signals that travel across the phone wires. On the other end, the electrical signals are transformed back again to sound. In the researchers’ inner ears, the sound waves bend tiny hair cells, eventually triggering their auditory nerves to send electrical signals to their brains. This signal is then translated by their brains as the complex pattern of voices.

Putting down the phone, Reisert turns back to his computer to analyze recordings that depict the activity of olfactory receptor neurons under different conditions. Light waves travel to his retina, stimulating the photoreceptors, where they are transformed into electrical signals and then into a visual representation in his brain.

He reaches for his coffee mug and takes a sip, enjoying the bitter taste and complex aroma. The hundreds of chemicals that comprise ‘coffee’ activate Reisert’s taste and smell receptors, located on cells that subsequently transform the chemical information into electrical signals. The electrical information travels to the brain, where it is integrated into the percept of ‘coffee.’

The process of converting one form of energy into another is known as transduction. In the case of taste and smell,
transduction involves converting the chemical energy of molecules into electrical signals that can communicate with the nervous system. While much is known about transduction in the visual and auditory systems, this process is still being actively studied for taste and smell. "Color vision was solved some time ago, in part because there are only three receptors that do most of the work," says olfactory neuroscientist Joel Mainland. "In taste, you have 40 receptor types, and in olfaction we have yet another order of magnitude. It’s quite overwhelming to try and figure out how all these receptor cells are initiating and sending messages."

Over the past decade, identifying and isolating those receptors has engaged much of the focus of molecular biologists in the chemical senses. "Receptors are sexy," says Margolskee. "They’re obvious, they’re important. Receptors make great targets for pharmaceutical companies looking to come up with a medication." In contrast, what goes on inside the receptor cell is more difficult and time-consuming to study.

**Transducing taste**

A great leap forward was made 20 years ago when Margolskee’s group discovered gustducin, a so-called G protein located inside taste cells that bears a striking resemblance to transducins, the G proteins that underlie signal transduction in visual cells. The gustducin G protein is made up of α, β, and δ subunits; when Margolskee’s team created a ‘knockout’ mouse missing the gene for α-gustducin, the mice’s ability to taste bitter and sweet substances was disrupted. However, the mice still had normal responses to salty and sour tasting compounds. This indicated that α-gustducin is involved specifically in the transduction of bitter and sweet tastes. Later studies revealed that gustducin also plays a role in umami taste transduction — in retrospect this is not surprising, as detection of all three taste qualities is mediated by closely related G protein-coupled receptors (GPCRs). Remarkably enough, rod transducin (one of the visual G proteins) is also expressed in taste cells, where it is involved in umami taste transduction.

Since then, Margolskee and his co-workers have focused on unraveling the intricate processes involved in taste transduction. He estimates that at least a dozen proteins are involved in the intracellular signaling cascade that extends from chemical activation of a receptor to nerve cell electrical transmission. How those proteins work together is a current area of exploration in Margolskee’s research program.

"The combinatorial complexity is probably important," he says. "For example, in a sweet cell, you may have different signal pathways to indicate whether it’s a metabolically active sweet or a noncaloric sweet." Such knowledge may someday be important in the development of drugs against metabolic disorders or in the identification of new sweeteners.
Other studies in Margolskee’s lab seek to identify the array of individual proteins within different taste cell types. This knowledge gives researchers the ability to compare cells, potentially leading to identification of new transduction elements and even new receptors, such as the sugar sensors SGLT1 (sodium-dependent glucose cotransporter 1) and K<sub>ATP</sub> (ATP-gated potassium channel) recently described by Margolskee’s group. Subsequent experiments address the physiological functions of transduction proteins by asking what happens when a specific protein is removed (‘knocked out’) or activated and how that then relates to the taste molecule’s sensory or metabolic properties.

In the future, other studies will look across different populations of taste cells, for example comparing sweet taste cells of lean versus overweight individuals. “These will be potentially important studies with medical relevance,” says Margolskee, who holds a medical degree along with his doctorate. “Looking ahead, we’re really just beginning to see the tip of the iceberg regarding what we will be able to learn.”

**Inside the smell cell**

Opportunities abound in the field of olfaction as well. Much progress has been made in understanding olfactory receptors, although this body of knowledge lags behind what is known about taste receptors, a disparity that exists despite the fact that the olfactory receptors were identified a decade before taste receptors. Similarly, there have been significant advances in understanding how and where olfactory nerves interact with the brain. “What’s currently not so well understood is the part in the middle — which is transduction,” says Reisert.

The 300 or so human olfactory receptors also are GPCRs, but not closely related to the GPCR taste receptor family. As such, while some principles of transduction are the same for the taste and olfactory GPCRs, the proteins involved are quite different.

Reisert speculates that one of the reasons that olfactory transduction is less well-understood than its gustatory cousin is the relative scarcity of researchers currently working in the field. This contrasts to the early 1990s, when it was “quite a hot bed.” At Monell, physiologist Geoff Gold used principles involved in his earlier work on phototransduction to identify a critical link in olfactory transduction. At the same time Monell neuroscientist Diego Restrepo, now at the University of Colorado, was working on the same problem with a differing perspective, leading to memorable animated discussions during in-house seminars.

To aid in understanding chemosensory transduction, Reisert suggests splitting the process into two parts: activation and termination. Activation begins when an odor molecule interacts with a receptor, initiating an intracellular cascade of molecular events that results in a neural signal. With regard to olfaction, that part is fairly well understood. But what shuts the cell off?
“How do we use a molecule’s structure to predict what it smells like?” asks Joel Mainland. Rather than go all the way from molecule to percept, Mainland breaks the problem down and focuses his research on linking molecular structure with activation of different receptor types. Some models look promising, but they don’t work for every receptor. “There seems to be some component we’re missing, and they likely could involve proteins within the cell,” he says.

A molecular biologist, Huang identifies proteins involved in the taste transduction cascade. He then utilizes a specialized ‘subtraction’ approach to look at how these components differ across taste cells. “Let’s say this is a sweet taste receptor cell and there’s what appears to be an identical sweet taste receptor cell right next to it. For some reason they may respond to different sweets. Are the cells different inside?”

Trained in immunology, Wang’s research explores how inflammation may contribute to taste disorders. Utilizing a mouse model of autoimmune disease, she found a disruption of taste function in these animals. Using fluorescent-tagged gustducin antibodies to identify taste receptor cells, subsequent studies revealed a decreased number of Type 2 taste cells, which are thought to transduce sweet, bitter and umami taste. Wang suspects the mice have overactive immune systems that interfere with the typical 2-week taste bud life span and turnover. She also thinks that there’s more to the story. “There likely is an interaction between the immune pathway and the taste signaling pathway. but we don’t yet know where the two converge.”

“Olfaction is a rhythmic sense, meaning that your receptors are stimulated every time you breathe. If you don’t have a way to terminate the first response, the second one might not get noticed. That’s important because olfaction, like all sensory systems, is all about noticing changes in the environment,” Reisert says.

Trained as a cellular physiologist, Reisert entered the field of olfaction on an undergraduate advisor’s advice. He wryly notes, “My English wasn’t very good at the time, so I didn’t even know what olfaction was.” He found the field interesting and his research since has traveled from describing how olfactory receptor neurons code for odorant stimulation and adaptation to identifying the intracellular neurons critical to response termination and molecular identification of the proteins involved. Another study, conducted with colleagues from Johns Hopkins University, pinpointed the molecular identity of ANO2, a calcium-activated chloride channel that may amplify signals in the olfactory receptor cell.

Discovery notwithstanding, Reisert estimates that it will be 10 years before scientists achieve a thorough understanding of the cellular mechanisms that control the sensitivity of olfactory receptor cells. “If the receptor’s not sensitive to an odor, you will never get a response,” he notes, adding that this will be a crucial link in connecting olfaction with behavior.

Under the tip of the iceberg

Over the next decade, emerging knowledge of the complex processes that govern the structure and function of chemosensory receptor cells will provide great insight into individual differences in sensory perception and health-related behaviors. ”We are at a remarkable point where we soon will be able to ask and answer significant questions once we have the general blueprint of what goes on inside these cells,” says Margolskee, commenting on the opportunities ahead. “It’s going to last a long time.”
New Board Members

Jane E. Henney, MD
Commissioner of the US Food and Drug Administration during the Clinton administration, Jane E. Henney recently joined Monell’s Board of Directors. During her distinguished career, Henney has served as Deputy Director of the National Cancer Institute and as Senior Vice President and Provost for Health Affairs at the University of Cincinnati.

Henney and Monell Director Gary Beauchamp first met in 2009 when Beauchamp was invited to serve on the Committee to Make Recommendations on Strategies to Reduce Sodium Intake in the United States, convened by the Institute of Medicine and chaired by Henney. At Beauchamp’s invitation, Henney later toured the Center, where she learned firsthand about the “key contributions Monell scientists are making in the complex fields of taste and smell.”

Combining leadership roles at large complex organizations in both academia and the federal sector with service on boards spanning a range of missions, Henney’s broad experience enables her to analyze and understand issues through many different lenses. She looks forward to using her skills to help guide Monell over the upcoming years.

“The Monell Center, through its longstanding relationship with other academic organizations and industry, has been able to translate many of its basic findings into practical realities. Supporting an organization that produces science with the capability of impacting people’s lives is very exciting – and satisfying,” she comments.

Henney has received numerous honors and awards, including election to the National Academies of Science Institute of Medicine, the Society of Medical Administrators and honorary membership in the American College of Health Care Executives. She is a recipient of the Excellence in Women’s Health Award from the Jacobs Institute, the Public Health Leadership Award from the National Organization of Rare Disorders, the DHHS Secretary’s Recognition Award and, on two separate occasions, the PHS Commendation Medal.

Steven J. Fluharty, PhD
A highly respected scientist with extensive administrative and leadership experience, Steven J. Fluharty recently joined Monell’s Board of Directors. As Senior Vice Provost for Research at the University of Pennsylvania, Fluharty possesses a blend of scientific knowledge and strategic planning experience, a valuable perspective that sits at the crux of Monell’s mission, vision, and future. “I have always been impressed with the mission of Monell, its unique interface between traditional academe and industry collaborations, and its history of strong leadership,” he comments.

At Penn, Fluharty plays a major role in advocating for federal funding for basic research and development of new research facilities. His track record ranges from directing a 10-year university-wide program project and institutional training grant on behavioral neuroscience to thirty continuous years of personal grant funding from the National Institutes of Health. He also is the recipient of numerous honors and awards, including the Louis Flexner Prize in Neuroscience and the Beecham Award for Research Excellence.

Fluharty brings an in-depth understanding of the synergy between academia and industry to his role on Monell’s Board, with an eye towards the transfer of technologies from the lab into the public sector. Such a viewpoint enriches Monell’s continued study of the chemical senses and how they function in disease prevention, work that he emphasizes is “very important for public health initiatives.”

As a bench scientist, Fluharty utilizes a multidisciplinary approach to investigate hormone action in the brain as it relates to food and fluid ingestion and related disorders. During his graduate studies at Penn, Fluharty’s mentors forged strong ties with Monell, and Fluharty followed suit. “I vividly recall participating in a symposium at Monell that resulted in a publication of our work on the hormonal controls of salt appetite,” he says.

Fluharty received his undergraduate degree from Manchester College, her medical degree from Indiana University, and completed subspecialty training in medical oncology at the M.D. Anderson Hospital and Tumor Institute and the National Cancer Institute.
Monell can be thought of as a non-profit manufacturer that makes two products — knowledge and scientists. The Center’s training programs for students in high school, college and graduate school, and for postdoctoral fellows, produce scientists for the future, although we cannot claim to have made them ourselves. Scientists are created with the help of families, teachers, governments and industry, to say nothing of the motivated individuals themselves.

The scientific knowledge Monell produces is most clearly visible in the papers our researchers publish in scientific journals. Most of Monell’s research is “basic research,” meaning that it addresses fundamental questions about how the chemical senses work. Our clinically-oriented research also focuses on fundamental issues, in this case about the causes and consequences of taste and smell disorders as well as the role of the chemical senses in diseases such as diabetes, obesity, hypertension and cancer.

Basic research can be contrasted to “applied research,” which focuses on a practical outcome such as a way to build a better mousetrap or a product that can block unpleasant odors. While basic research can inform applied research, its greatest practical value lies in the new discoveries, ideas, know-how and inventions it generates. Such intellectual property, or IP, is the other significant product that Monell produces. Of the various forms of IP, patents are most valuable because they can provide a competitive commercial advantage by preventing others from using the IP to form the basis for an invention or product.

I have given innumerable tours of the Center during my 30 year tenure here. One of the most consistent reactions of visitors to Monell is their surprise at the wide range of research that goes on at the Center. Monell’s patent portfolio reflects this broad range of interests. For example, we have patents related to the use of non-toxic chemicals as repellents for animal pests, which were developed in conjunction with scientists stationed at the USDA Monell field station. The use of the domestic cat’s unique taste receptors for screening novel palatable compounds for inclusion in cat food is also covered by Monell patents. Monell scientists were the first to successfully culture human taste cells and several patents protect these methods and the use of such cultures in screening for new taste molecules in humans. More recently, patents have been filed on an alternative pathway for sweet taste and, extending Monell’s IP reach, on the use of taste receptors in sperm and in the cells that produce sperm as targets for male contraception. And we have just begun marketing a new series of flexible, highly sensitive and inexpensive olfactometers based in part on a patent pending design for such an instrument that can be used in brain imaging studies of olfaction.

Monell’s Corporate Sponsors program is in essence a technology transfer program. One of the benefits of Monell corporate sponsorship is early access to our intellectual property. Corporate sponsors have the right of first refusal to license Monell IP derived from general funds or government grants. Further, sponsors that fund a specific basic research project have the opportunity to negotiate a right of first refusal on inventions resulting from that project. In cases where the project is collaborative, corporate scientists may be joint inventors of IP stemming from the research. Other sponsor benefits that support technology transfer include an annual review for sponsors during which we give participating companies an early look at the most recent Monell research; consultative meetings focused on more detailed discussions about Monell research and commercial problem solving; sharing of proprietary chemicals and animal models; and short- and long-term visits to the Center by sponsor scientists to learn new techniques and research approaches.

The challenges of technology transfer at Monell are familiar ones to universities and other non-profit scientific research organizations. The gap between inventions stemming from basic research and the development of commercial products is one that has not been adequately addressed. The “and” between research and the development is a wide one bridged only through large investments of money and time.

The costs of patent prosecution and technology transfer are substantial, which is why tech transfer programs at most universities and research organizations are not profitable. Close evaluation of Monell IP at the initial disclosure stage for its commercial value thus becomes a critical component. This diligence plus other tight controls over patenting and licenses processes has allowed Monell to minimize the costs of its technology transfer. Along with our success in the commercialization and licensing of Monell IP, we have moved forward from breaking even to now realizing a profit on our technology transfer efforts. Ultimately, however, this success, just like the success of Monell as a whole, depends on our scientists, their outstanding work and their exceptional ideas.
New Old Gifts

Monell’s Morley Kare Library, one of many intellectual gems housed at the Center, recently received valuable contributions from two distinguished scientists. Bruce Halpern, PhD, and Harry Lawless, PhD, each donated their professional book collections to the Center. Both chemosensory researchers have roots that run deep at Monell.

“My connection started before Monell existed,” says Halpern, Susan Linn Sage Professor of Psychology, Emeritus and Professor Emeritus of Neurobiology & Behavior at Cornell University. “Morley Kare (Monell’s first director) was my sponsor when I was a NIH–Postdoctoral Fellow, and I was a Visiting Scientist for a year at Monell during the mid 1990’s. I also served for some years on the Advisory Board of the Chemosensory Clinical Research Center.”

Also at Cornell, where he is Professor of Food Science, Lawless was on the Monell faculty from 1980 to 1983. He credits Monell’s support of young scientists as a critical factor in driving the Center’s success, and says his wish to find the books a home “where they would be useful and appreciated” guided his inspiration to give to Monell. Halpern notes, “as a unique institution devoted to research in the chemical senses, Monell seemed to be an ideal repository” for the scholarly works.

Monell Director Gary Beauchamp says, “These gifts from Bruce and Harry are very much appreciated. Special topic libraries are especially important because they contain material not otherwise available through internet resources. These donations also help to preserve the legacy connecting these eminent researchers, scholars, and friends with Monell. And, since I have a very personal interest in old and unusual books (they not only provide intellectual fodder, but also provide evocative odor stimulation), it particularly pleases me to have these volumes here in our library.”

The Halpern/Lawless books are a form of donation known as a gift-in-kind, a non-cash gift of goods or services. Such gifts are not as common as cash but can be equally meaningful when they enhance a unique resource like the Kare Library. To learn more, contact Development Director Katherine Fritz at 267-519-4715 or kfritz@monell.org.

Corporate Sponsor News

Monell is proud to welcome four new Corporate Sponsors: Ingredion Incorporated, Megmilk Snow Brand Company, Ltd., Nu-Tek Food Science, and Tate & Lyle. It is not surprising that this group of new sponsors includes three ingredient suppliers. Food and consumer products companies increasingly are asking suppliers to provide greater R&D innovation and in turn, the suppliers are turning to institutions like Monell for basic research discoveries that can fuel their development successes.

Of the four new corporate sponsors, only Tate & Lyle has a prior history of supporting Monell (and that was more than 20 years ago). Megmilk joins the ranks of Monell’s sponsors headquartered in Japan. A Megmilk scientist will spend two years at Monell contributing to basic sensory research and studying sensory psychophysics. In total there currently are four visiting corporate scientists participating in basic research studies at Monell.

Monell scientists currently are engaged in more than 15 sponsored basic research projects on taste, olfaction, and chemesthesis. The long-running Salt Consortium will end this October, offering opportunities for many more companies to collaborate with Monell on salt research. A new consortium is forming to investigate the temporal properties of sweet taste—the onset and duration of sweetness among common carbohydrate sugars and high intensity synthetic and natural sweeteners.

For more information on these or other sponsor benefits, please contact Carol Christensen, Director of Institutional Advancement, at 267-519-4712 or cchristensen@monell.org.
PHILADELPHIA SCIENCE FESTIVAL

Monell once again was a major presence at the eight-day Philadelphia Science Festival this past April, with a focus on educating the public about the chemical senses and health. Events such as Dangerous Foods — Facts, Fears, and Foibles; Orphan Diseases: Why Should We Care?; and Forgotten Sense: A World Without Smell drew interested and responsive audiences. The family-oriented Science Carnival attracted over 10,000 visitors, including many who were surprised to learn from Monell that chemicals are the building blocks of food - even natural foods!

TASTE OF CHEMISTRY

The third annual “Taste of Chemistry” (ToC) teacher education program capitalized on some of the most sensitive and accessible chemical detectors available — taste receptors on the human tongue. Under the auspices of Monell taste geneticist Danielle Reed and award-winning science teacher Scott Stein, ToC enables teachers to incorporate cutting-edge chemosensory knowledge and techniques into their classrooms. A week-long workshop for 33 high school science teachers from across the country, ToC is funded by the Henry and Camille Dreyfus Foundation.

MONELL STUDENT APPRENTICESHIP PROGRAM

Arguably one of the most valuable and wide-reaching methods of giving back is through outreach aimed at young people. Monell’s annual Summer Apprenticeship Program (MSAP) exposes minority and under-privileged high school and undergraduate students to careers in science. This year, 21 motivated students worked closely with Monell faculty to plan and carry out original research. At the crowded Final Symposium, the students presented their scientific discoveries to family, friends, and Monell’s community of scientists. Indya Brown, mentored by Johannes Reisert and Michele DiBattista, received the “Sense-sational Science” award — including a plaque and $100 stipend — for her poster on the role of olfactory marker protein (already known to play an important role in olfactory transduction) on directing nerves from olfactory receptor cells to their targets in the brain.
“Greater even than the greatest discovery is to keep open the way to future discovery.”
—John Jacob Abel

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One of our ongoing pleasures is being able to say THANK YOU to the friends, alumni, employees, foundations and corporations who enable Monell’s research mission through philanthropic support. We are grateful for your generosity.

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