Profile of Barry Ganetzky

Maybe you *can* judge a book by its cover, or at least a fly by its phenotype.

For more than 30 years, Barry Ganetzky has scrutinized mutant fruit flies that shake, shimmy, and pass out if overheated, in his search for the genes that underlie this unusual appearance and behavior. Some may consider his use of phenotypic analysis old-fashioned, but it has served him well, leading him to discover numerous genes involved in development and neural function and earning him election to the National Academy of Sciences in 2006.

"I never met a mutant I didn't like," says Ganetzky, the Steenbock Professor of Biological Sciences and a professor of genetics, neuroscience, and medical genetics at the University of Wisconsin (Madison, WI). "My philosophy is that every mutant has the answer to a biological question if you know the right question to ask."

Most recently, this approach resulted in the discovery of *wasted away*, a fly mutant with features that may offer clues about neurodegenerative diseases like Alzheimer's and Parkinson's, which published as Ganetzky's Inaugural Article in PNAS (1).

Awakening

Ganetzky felt drawn to science from an early age. "I always had questions and was never quite satisfied with the answers I got," he says. "I appreciated, without being able to articulate it, that science was a way of getting more exact answers."

But growing up in a working-class neighborhood in Chicago with no scientists in the family as role models, he could not imagine making a career out of asking and answering scientific questions. He began college at the University of Illinois (Chicago, IL), intending to major in chemistry, because he figured a chemist could find a job. However, an honors biology project quickly derailed that decision when it opened Ganetzky's eyes to the life of academic science.

He was working in the laboratory of Michael Cummings, a young developmental geneticist studying *Drosophila* oogenesis. Not only was the work interesting and fun, but Cummings' mentorship provided the role model Ganetzky needed.

"It was a transforming experience from the start," says Ganetzky. "I finally knew what it was I wanted to do with my life."

He also realized that those unsatisfied feelings he had as boy were not flaws but highly valued strengths in the world of science. "All the things you got in trouble for in school: not trusting in authority, asking questions, wanting to figure out your own solutions, not relying on what's known, but focusing on what's unknown. . . I realized, this is what you're supposed to do [in science]," he says.

The honors project that was supposed to last for one quarter ended up lasting 2 years and introduced Ganetzky to what would become his life-long research companion: the fruit fly. The project also awakened his desire to learn as much as he could about genetics.

"Of all the biological sciences, genetics captivated me the most," he says. "Understanding for the first time this is how life works, this is what genes do. It was just so incredibly fascinating, and I knew I wouldn't be satisfied if I didn't know more. I just had to learn the details."

Cummings recommended that Ganetzky move to the University of Washington (Seattle, WA) for graduate school.

"I'd never heard of it," says Ganetzky. But after reading about the department, which was one of the only ones devoted entirely to genetics, he realized that Seattle might be the perfect place for delving deeper into the nuts and bolts of genetics at the molecular level.

In contemplating his career path, Ganetzky sensed that *Drosophila* would be too complicated for studying gene regulation. He decided to switch to yeast and planned to work with the large cadre of yeast geneticists in Seattle. But when he arrived in Seattle in the fall of 1971, the other graduate students in his class had already taken the available rotation spaces in the yeast labs.

After rotating through several other promising labs, Ganetzky decided to try out the *Drosophila* genetics lab led by Lawrence (Larry) Sandler, "just for fun."

"It was never my plan to go to Seattle to become a hardcore *Drosophila* geneticist," says Ganetzky. But from the moment he stepped into the lab, he knew it was a special place. Sandler's infectious enthusiasm for his research and the simple force of his personality led Ganetzky to an epiphany, he says. "I didn't care what I worked on," he says. "I just wanted to be in his lab."

Old-Time Genetics

In Sandler's lab, Ganetzky developed a love for the simple and elegant approach of phenotypic analysis.

Midway through graduate school, Ganetzky began working on a fly mutant, called *Segregation distorter*, a project that would become his thesis and a recurring research theme later in his career. This naturally occurring fly mutation appeared to violate the basic rules of Mendelian genetics. Normally, a mutant fly that carries one mutant chromosome and one normal chromosome will transmit the mutant chromosome half the time. Instead, heterozygous *Segregation distorter* males transmit the mutation 100% of the time.

"This chromosome had figured out a way to gain this completely unfair advantage, to transmit itself 100% of the time," says Ganetzky. "It did so in the most diabolical and Shakespearean manner: by fratricide." The sperm that carried this strange chromosome called SD killed their "normal" brethren.

Under Sandler's guidance, Ganetzky spent his graduate career scrutinizing these mutant flies to identify the genes responsible for the phenomenon (2). This genetic puzzle proved so fascinating that Ganetzky continued to work on it for more than 20 years (3, 4).

He practiced old-fashioned genetics: setting up crosses, delicately sorting flies, counting offspring, and making inferences based on their phenotypes.

"I didn't need test tubes, fancy equipment, and sophisticated machinery. I had a dissecting microscope, an etherizer, and a paintbrush," says Ganetzky. "But Larry could make the most arcane aspect of chromosome mechanics seem so intellectually exciting. I really learned to appreciate and love the approach."

Soon Ganetzky stopped thinking of *Drosophila* genetics as an adjunct to what he wanted to learn. "It became the only thing I really cared about. I loved the art of it."

Although many of his classmates thought he was crazy for focusing on the "passé" field of *Drosophila* genetics, Ganetzky stuck with what he loved.

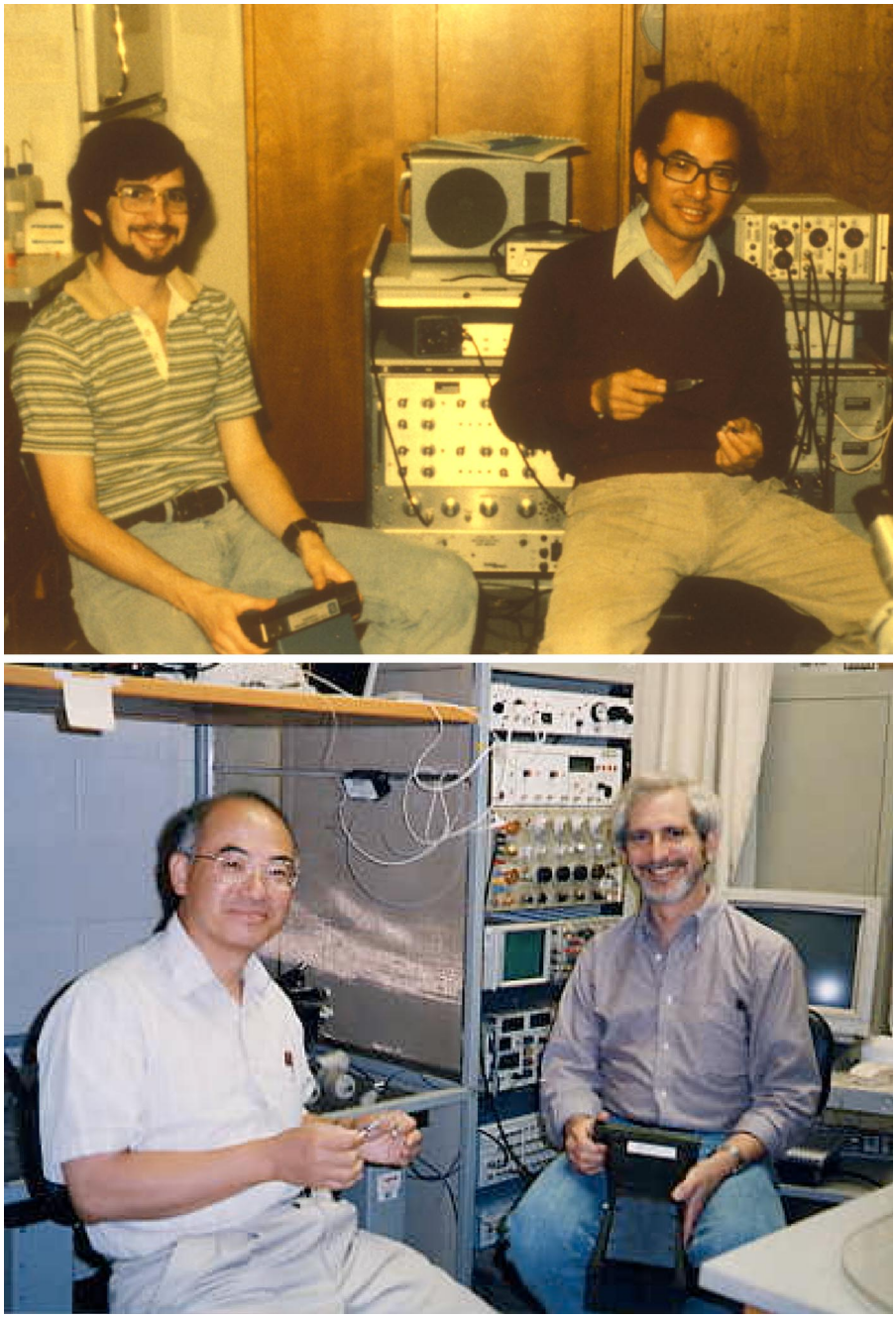
A few years later, the resurgence of *Drosophila* as a research organism redeemed Ganetzky, and his training put him ahead of the game. "I was extremely lucky again that I was trained as a *Drosophila* geneticist at a time when there were very few," he says.

Branching Out

Ganetzky received his doctorate in genetics in 1976 and left Seattle for a postdoctoral fellowship at the California Institute of Technology (Caltech; Pasadena, CA) at the insistence of his mentor, Sandler. As the heyday of classical genetics was drawing to a close, Sandler knew that his students would have to branch out and apply their genetics to particular biological problems to be successful. He suggested that

---

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 14987 in issue 41 of volume 103.



Now and then: Barry Ganetzky (left in *Upper* and right in *Lower*) and longtime collaborator Chun-Fang Wu as postdocs at Caltech (*Upper*) and in the more recent past at Cold Spring Harbor Laboratory (*Lower*).

Ganetzky go to Caltech to work with Seymour Benzer, the "father of *Drosophila* behavioral genetics."

"I took that not as a suggestion but as an order," Ganetzky says, laughing.

Benzer's mentoring style was different, more hands-off, than Sandler's. "We were expected to find our own way," recalls Ganetzky. "It was frightening, but good. I was on my own, forced to mature as a scientist."

Ganetzky found a comrade in fellow postdoc Chun-Fang Wu, who was trained as a physiologist. The two quickly became allies and remain best friends. "We were both in the same position of not knowing what we were going to do," Ganetzky says. "I knew *Drosophila* genetics. He knew everything else. We were perfectly complementary."

Although Benzer was famous for his work in behavioral genetics, Ganetzky had reservations about the field. "Behavior seemed so remote and complex," says Ganetzky. "How can you hope to understand how the brain works if you don't understand how individual neurons develop and function?"

Ganetzky reasoned that he could identify genes involved in neuron function by first finding the right kind of mutations: ones with highly visible and relevant neurological phenotypes. These mutants would lead to genes and, eventually, to encoded proteins.

So, with Wu's encouragement and participation, Ganetzky embarked on his lifelong journey into the emerging field of "neurogenetics," a term that had not yet been coined.

"We were definitely thinking that what we were doing was not behavioral genetics," says Ganetzky. "This was different. We had to not only figure out how to play the game, we had to make up the game."

The first major hurdle was selecting the most promising phenotypes. He and Wu decided to focus on a class of mutants called "temperature-sensitive paralytic mutants," which consisted of flies that became paralyzed when exposed to high temperatures.

One of the first mutations Ganetzky identified was *nap* (*no action potential*) (5). With Wu's expertise in electrophysiology, they found that axonal conduction failed at high temperatures. And with Ganetzky's knowledge of chromosomal analysis, they located the mutant gene on the second chromosome.

"With little additional information, we concluded that the mutation was affecting sodium channels," Ganetzky says. Many were skeptical of Ganetzky's conclusions. After all, any number of things could impair action potentials. But his geneticist "gut" told him that sodium channels were the culprit (6).

"For me," he says, "phenotype was all-important. And blocking action potentials was sufficient justification to go after the gene. It was central to the kinds of problems we were interested in studying."

Double, Double, Toil, and Trouble

Ganetzky continued to pursue the genes underlying neuronal signal transduction by creating double mutants. He believed that he could create fruit flies with two mutations and use the resulting phenotype to determine whether the mutations were likely to be affecting similar cellular components or affecting components with opposing functions.

"Chun-Fang Wu was the only other person in the world that agreed that [double mutants] were interesting," Ganetzky says. "Left to myself, I never would have had sufficient courage to do this."

Ganetzky's first double mutant combined *nap* with a famous mutation called *Shaker* (*Sh*), which causes flies' legs to shake when they are under ether anesthesia.

But the double-mutant flies looked fairly normal, even at temperatures where

nap mutants would typically be paralyzed. Because *Sh* was known to have enhanced membrane excitability due to a potassium channel disruption, Ganetzky concluded that *nap* must be having the opposite effect: reducing excitability as expected if it were a sodium channel mutation. (7)

Ganetzky then crossed *nap* with another previously identified mutation called *para* and found that that double mutant was lethal. He concluded that *nap* and *para* must be affecting the same protein: the sodium channel (8).

Using this strategy, Ganetzky created a double mutant with *Sh* and "*ether a go-go*" (*eag*), another shaky-legged mutant discovered in the 1960s. By looking at their phenotype and conducting pharmacological manipulations, he reasoned that *Sh* and *eag* disrupted different potassium channels (9).

"It was almost too good to be true," says Ganetzky. The double mutants lived up to his expectations. His persistence paid off just as it had for another of his informal mentors at Caltech, Nobel Laureate Ed Lewis.

"[Lewis] always did things his way," says Ganetzky. "He didn't change his approach despite many doubters. He just kept doing what he did best. He made his work so important that the rest of the field came to him."

From Lewis, Ganetzky says he learned not to chase the current fashion but to persistently pursue the observations that he felt were interesting and important until they paid off.

Opening Doors

Ganetzky accepted a faculty position at the University of Wisconsin in Madison in 1979 and began to investigate the mutants he had worked on at Caltech in more detail.

One of the first major projects his new laboratory tackled was cloning the gene responsible for the *para* phenotype. With the dogged determination of postdoc Kate Loughney, Ganetzky cloned the enormous *para* gene, a gargantuan 26 exons distributed over >60 kb of genomic DNA with thousands of alternatively spliced isoforms (10).

"*para* turned out to be one of the most complicated genes in the *Drosophila* genome," Ganetzky says. "The very first gene we cloned turned out to be a monster."

The sequence definitively showed that *para* was a sodium channel, just as Ganetzky had inferred years earlier.

The results motivated him to sequence some of the other genes he had studied in Benzer's laboratory, including *eag* and another gene affecting potassium channels, called *slowpoke*. Fortunately, these genes were much easier to clone and sequence (11–15).

Based on *eag*'s sequence, Ganetzky suspected that it was a prototype for a family of related potassium channels. He was right. His laboratory later identified the mouse, rat, and human *eag* counterparts (16, 17). Other researchers subsequently found that one of the human counterparts, called HERG (human *eag*-related gene), is involved in both heritable and drug-induced cardiac arrhythmias called long QT syndrome. Researchers now routinely screen new pharmaceuticals for their ability to block HERG.

Although Ganetzky is happy to see his work applied to help others, he has never been interested in single-mindedly pursuing one particular gene, protein, or biological problem. Instead, what brings the most satisfaction, he says, is the ability to be at the "leading edge" of a field: to identify problems and "discover the doors that need to be opened."

"Each time these fields became too developed, I moved in a slightly different direction," he says. Having had success identifying and characterizing ion channels from the temperature-sensitive paralytics, he reasoned that his collection, which had grown to approximately 150 mutants, likely held the key to unlocking many more such doors.

He was right. In recent years, Ganetzky and his laboratory have identified a mutation that leads to aberrant synaptic development, called *nervous wreck* (18), as well as several mutants that exhibit neurodegeneration (1, 19, 20).

His Inaugural Article (1), published in PNAS in 2006, illustrates how he once again applied old-fashioned phenotypic analysis to track down a gene involved in neurodegeneration (1). Called *wasted away*, this mutant shows neurodegeneration, progressive motor impairment, and severely reduced lifespan. The responsible gene encodes what some might have considered an uninteresting glycolytic enzyme, triosephosphate isomerase. However, the same enzyme turns out to be linked to a progressive neurodegenerative disease in humans as well. The mechanism by which disruption of this enzyme apparently leads to neurodegeneration and its potential links to other neurodegenerative disorders have proven to be more interesting and complex than anyone might have anticipated.

The parallels between several of the temperature-sensitive mutants and human diseases give Ganetzky plenty of incentive to continue probing his collection for mutations with biological and medical relevance. Importantly, he feels it validates the approach that he grew to love in Sandler's laboratory.

"Over the years, the problems I have worked on have changed, but this outlook on how to tackle them has never changed," he says. "This faith in phenotypic analysis, using genetics and dissecting problems beginning with mutational analysis, has been part of the work I've done ever since. I'm as proud of how we did things as much as anything we discovered."

He is even more proud that his mentorship has helped former students and postdocs become successful in their independent academic careers. That is another value that Sandler instilled in him. "I remember sitting at Larry's knee and him saying 'Success in academics means excellence in teaching as well as excellence in research.' So, I took that to heart."

Watching his apprentices mature and follow their own paths and continue the legacy with their own students "is, by far, my most important contribution," Ganetzky says.

Melissa Marino, *Freelance Science Writer*

1. Gnerer JP, Kreber RA, Ganetzky B (2006) *Proc Natl Acad Sci USA* 103:14987–14994.
2. Ganetzky B (1977) *Genetics* 86:321–355.
3. Kusano A, Staber C, Ganetzky B (2001) *Dev Cell* 1:351–361.
4. Kusano A, Staber C, Ganetzky B (2002) *Proc Natl Acad Sci USA* 99:6866–6870.
5. Wu C-F, Ganetzky B, Jan LY, Jan YN (1978) *Proc Natl Acad Sci USA* 75:4047–4051.
6. Wu C-F, Ganetzky B (1980) *Nature* 286:814–816.
7. Ganetzky B, Wu C-F (1982) *J Neurophysiol* 47:501–514.
8. Ganetzky B (1984) *Genetics* 108:897–911.
9. Ganetzky B, Wu C-F (1983) *J Neurogenet* 1:17–28.
10. Loughney K, Kreber R, Ganetzky B (1989) *Cell* 58:1143–1154.
11. Drysdale R, Warmke J, Kreber R, Ganetzky B (1991) *Genetics* 127:497–505.
12. Warmke J, Drysdale R, Ganetzky B (1991) *Science* 252:1560–1562.
13. Elkins T, Ganetzky B, Wu C-F (1986) *Proc Natl Acad Sci USA* 83:8415–8419.
14. Atkinson NS, Robertson GA, Ganetzky B (1991) *Science* 253:551–555.
15. Pallanck L, Ganetzky B (1994) *Hum Mol Genet* 3:1239–1243.
16. Warmke JW, Ganetzky B (1994) *Proc Natl Acad Sci USA* 91:3438–3442.
17. Trudeau MC, Warmke JW, Ganetzky B, Robertson GA (1995) *Science* 269:92–95.
18. Coyle IP, Koh YH, Lee WC, Slind J, Fergestad T, Littleton JT, Ganetzky B (2004) *Neuron* 41:521–534.
19. Palladino MJ, Hadley TJ, Ganetzky B (2002) *Genetics* 161:1197–1208.
20. Palladino MJ, Bower JE, Kreber R, Ganetzky B (2003) *J Neurosci* 23:1276–1286.