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Biography of James L. Van Etten

Green algae, in surface layers of almost every lake or stream, are some of the most common aquatic creatures. However, unbeknownst to researchers until recently, viruses that infect algae are almost as widespread. Entire ecosystems of algal hosts and their corresponding viruses lay hidden until the 1980s, when James L. Van Etten, a professor of plant pathology at the University of Nebraska (Lincoln), and his colleague Russ Meints discovered and began to characterize the first member of what is now a rapidly expanding family of algal viruses. Van Etten and his colleagues have continued to study these intriguing viruses, focusing on those that infect *Chlorella* and other similar green algae. The chlorella viruses have many unusual properties, ranging from their large genome sizes to unique modifications in their DNA.

Van Etten's findings have earned him continuous grant support from the National Institutes of Health as well as election to fellow status in several professional societies. In 2003, he was elected to the National Academy of Sciences. His Inaugural Article, found on page 5318 (1), explores the electrophysiological properties of a unique potassium ion channel protein encoded by the chlorella viruses. The small size of this protein could make it a useful model for studying how more complex potassium ion channels work.

Stop and Smell the Yeast

Van Etten's father, a former United States Department of Agricultural (USDA) chemist at the Northern Regional Research Laboratory in Peoria, IL, had an enthusiasm about science that rubbed off on Van Etten and two of his three siblings. "When I started my undergraduate education, I thought I might be a chemist, but I was never really turned on by it," Van Etten said. He found his calling just prior to beginning his sophomore year at Carleton College in Northfield, MN. While home working in a steel mill for the summer, he accompanied his father to the laboratory one weekend to check on an experiment. There, the elder Van Etten introduced his son to a microbiologist, Lynferd Wickerham, who was conducting experiments with lyophilized yeast. Fascinated by the idea that viable yeast could be stored by dehydrating and freezing, Van Etten asked Wickerham, "How do you learn about this stuff?" "He replied, 'You should take a course in botany,' which was the furthest thing from my mind," Van Etten said.

James L. Van Etten

Upon returning to Carleton, Van Etten sought out the biology department and enrolled in a botany class taught by a new professor, Bill Muir. "Bill's infectious enthusiasm for scientific research had a tremendous influence on my subsequent decision to attend graduate school," Van Etten said. After completing his B.A. degree in 1960, Van Etten entered a Ph.D. program in plant pathology at the University of Illinois at Urbana–Champaign in Urbana. Originally, he was offered an assistantship to work on corn diseases. "I would have spent summers in the field collecting pollen. I didn't know it at the time, but I'm somewhat allergic to corn pollen," he said. Serendipitously, the plant pathology department chairman suggested that Van Etten meet with Dave Gottlieb, a University of Illinois microbiologist who studied antibiotics, fungal physiology, and biochemistry. "I went to his lab and saw microorganisms growing on shakers, and I thought, this is what I want to do," Van Etten said.

Gottlieb offered Van Etten an assistantship, which he immediately accepted. He spent the next five years studying aging in filamentous fungi, a project he was assigned to but admits he had little interest in. However, Van Etten managed to bring enthusiasm to his work, and he and his colleagues published several papers on respiratory enzymes that change with aging in fungi (2). "We generated a lot of data, but I was never totally convinced that we were very close to understanding the aging process," he said.

Nebraska or the Italian Riviera?

By the time Van Etten completed his doctoral degree in 1965, he had forged valuable connections with several leading scientists, including Orio Ciferri, a plant molecular biologist in the Department of Genetics at the University of Pavia in Italy. Yearning to spend time away from the Midwest, he accepted a postdoctoral fellowship from the National Science Foundation to work with Ciferri. However, a few months before he was to leave for Italy, Van Etten was invited for a job interview at the University of Nebraska. With his plans in Italy already set, he was hesitant to attend the interview. However, he decided to go after receiving encouragement from several professors at Illinois. "On the plane ride back, I was thinking that it's a good opportunity; but Lincoln, Nebraska, or an hour and a half by car from the Italian Riviera?" he said.

Luckily, he ended up with both. Deferring a job offer to study fungicidal mode of action at Nebraska, he spent 12 months in Ciferri's laboratory determining differences in protein synthesis between prokaryotic and eukaryotic organisms. The research established that ribosomes and translation elongation enzymes were functionally interchangeable between different bacteria (prokaryotes) or among yeast, higher plants, and animals (eukaryotes). However, the components were not interchangeable between prokaryotes and eukaryotes (3, 4). These findings were significant, because researchers were just beginning to appreciate the differences between prokaryotic and eukaryotic organisms.

In 1966, Van Etten moved to Nebraska and set up his laboratory. However, his time in Italy had shifted his interests away from fungicides and toward fungal development. Using his newly acquired molecular biology skills, Van Etten and his colleagues investigated several metabolic processes associated with fungal spore germination. One of the most significant features of germination is initiation of and rapid increases in the synthesis of proteins and RNA. Van Etten's laboratory assayed the biological activity of many components involved in these macromolecular processes in ungerminated and germinated spores with the goal of trying to explain how protein and RNA synthesis are suppressed in spores and rapidly activated during germination. Although

This is a Biography of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 5318.

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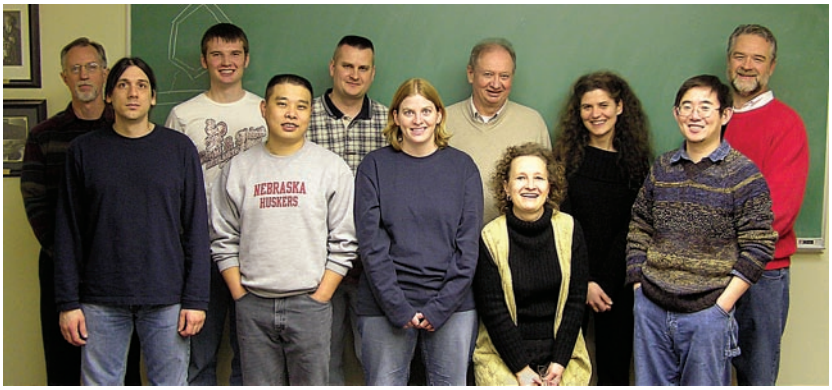

James Van Etten's laboratory members, from left to right: Gary Duncan, Bernard Kronschabel, Tony Fehr, Yuanzheng Zhang, James Gurnon, Lisa Fitzgerald, James Van Etten, Irina Agarkova, Paola Valbuzzi, Ming Kang, and David Dunigan.

the question has not yet been answered, "we learned many things that germination isn't due to," Van Etten said. For example, in 1970, Van Etten's first graduate student, Bob Brambl, established that fungal spores contain preformed mRNA (5). The finding suggested that transcription is not a triggering event for spore germination, as some researchers had previously thought.

While performing his fungal spore research, Van Etten shared a laboratory with Anne Vidaver, a microbiologist who began working at Nebraska just prior to his arrival. Vidaver's primary interest was using bacterial viruses to control plant pathogenic bacteria, a field just starting to receive recognition at the time. Using a gas chromatograph originally purchased for Van Etten's fungicide research, he and Vidaver found that one of her viruses, ϕ6, had a lipid component, a unique property among known bacterial viruses at that time. "The ϕ6 virus was worthless as a biological control agent, but scientifically, it turned out to be a very unusual virus," he said. Following advice from Myron Brakke, a now retired University of Nebraska plant virologist, Vidaver's and Van Etten's research on ϕ6 produced a number of "firsts": the virus was the first bacterial virus with an external lipid membrane, the first bacterial virus with a segmented genome, the first bacterial virus with a double-stranded RNA genome, and the first virus that had both a lipid envelope and a double-stranded RNA genome (6, 7). The virus was assigned to its own family, and until recently it was the only member. "The virus was so unusual and interesting that a couple of scientists have spent most of their careers studying ϕ6 since our initial discoveries," Van Etten said.

Beer and Algae

The ϕ6 virus changed the course of Van Etten's career as well. "I had no experience in virology at this point, and I had never taken a course in virology. This was my introduction," he said. Fascinated with his new interest, he took every opportunity to share his enthusiasm with colleagues. One night while drinking beer at Van Etten's house, biology department chair Russ Meints mentioned that he thought an alga from his own research might be infected with a virus. Meints, now retired, studied the symbiotic relationship between *Chlorella* algae and the aquatic organism hydra. Meints had taken hundreds of electron micrographs of *Chlorella* that were isolated from their hydra hosts, and one cell in one photograph contained what appeared to be a virus-like particle. Furthermore, researchers had been unable to culture *Chlorella* from hydra; thus, Van Etten and Meints suspected that there might be a connection between the viruses and the inability to grow these *Chlorella* outside hydra. Working together, the researchers did a simple experiment. After isolating algae from hydras, the researchers let the algae sit for various periods of time, then examined them by electron microscopy. "It was clear that once the algae were released from the hydra, they filled up with virus particles and lysed," Van Etten said (8).

"The ϕ6 virus was worthless as a biological control agent, but scientifically, it turned out to be a very unusual virus."

Invigorated by their initial findings, the researchers began to explore the virus's numerous unusual characteristics, such as its extraordinarily large genome (9). However, because algal hosts for these viruses did not grow in culture, procedures to study the viruses were limited. Fortunately, one of Meints's undergraduate students suggested that symbiotic algae living inside the protozoan *Paramecium bursaria* also might harbor viruses. Subsequent studies showed that *Chlorella* from this paramecium could be grown independently in the laboratory and were also readily infected with the virus. These findings allowed Van Etten and his colleagues to develop the first plaque assay for algal viruses, a valuable technique for studying individual virus particles (10).

Using the plaque assay, Van Etten and Meints discovered that chlorella viruses are present in fresh water from around the world. Furthermore, the titers from some samples were as high as 40,000–100,000 infectious particles per milliliter of native water (11). Thus, the researchers had discovered a previously unknown ecosystem in streams and ponds.

Nature as a Guide

After developing the plaque assay, Van Etten dropped his fungal spore and ϕ6 research programs to focus on chlorella viruses full-time. "At the time, I wasn't worried about changing my research focus, but I found out later that some of my colleagues were worried for me," he said. His research has since dispelled any doubts. Among his early discoveries, Van Etten found that chlorella virus genomes have various levels of methylated bases (12). This led to the finding that the viruses encode DNA methyltransferases and DNA restriction endonucleases, some of which cleave DNA at unique sites (13, 14). "We now know that the DNA restriction endonucleases are packaged in the intact virus particles, and we believe their function is to help degrade host DNA early in infection," Van Etten said (unpublished results).

Beginning in 1994, Van Etten's team collaborated with Dan Rock's laboratory at Plum Island, MA, a USDA research facility, to sequence the prototype chlorella virus PBCV-1 genome (15). The sequence revealed that PBCV-1 has ≈375 protein-encoding genes and 11 tRNA genes. "Until recently, this was the biggest virus genome ever sequenced," he said. The genome is approximately twice as large as the virus that causes smallpox and ≈30 times as large as the virus that causes AIDS.

Van Etten's laboratory has subsequently found that predicted gene products of ≈50% of the PBCV-1 genes resemble proteins of known function, including many that have never been found in a virus, e.g., the enzyme homospermidine synthase (16), three enzymes involved in the synthesis of the extracellular matrix polysaccharide hyaluronan (17), and two enzymes involved in nucleotide sugar metabolism (18). Some of the virus genes encode enzymes that are the smallest in their class and that may represent the minimal catalytic unit. In collaboration with electrophysiologists Gerhard Thiel (Darmstadt University of Technology, Darmstadt, Germany) and Anna Moroni (Institute of Thermal-Fluid Dynamics, Milan, Italy), Van Etten's group has also discovered that the chlorella viruses code for the smallest functional potassium ion channel protein (22). Because potassium ion channels are essential for all living organisms, the simple chlorella virus channel is an excellent model for studying how ion channels work. "It has all the basic functions of a potassium channel without all the extra bells and whistles, so it can be studied more easily," he said.

Van Etten's team has also shown that genes shared by independent chlorella virus isolates can encode functionally different proteins that vary in amino acid sequence by as much as 35%. Thus, comparative gene sequence analyses could identify amino acids responsible for the differences and consequently suggest site-directed mutations. In Van Etten's Inaugural Article (1), he and his colleagues describe some of their recent findings on the electrophysiological properties of various chlorella virus ion channels. The researchers compare how small variations in the protein between different virus isolates change the potassium ion channel's electrophysiological properties. "We've let nature serve as our guide in determining how amino acid substitutions affect individual channel properties," he said.

Van Etten is unsure which direction his research will go next. "My whole career has pretty much been pure luck, and I've never been a long-range planner," he said. However, Van Etten is certain that the constant stream of chlorella virus discoveries will keep his work exciting for years to come. "It might only happen once a year or so that you get a totally unexpected result that leads you in a different direction, but that's where I get my thrills. With almost 400 genes in this virus, I don't think we'll run out of things to do," he said.

Christen Brownlee, *Science Writer*

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