Bacterial cell division is an intricate process involving the highly coordinated interplay of many different proteins. Joe Lutkenhaus, a microbiology professor at Kansas University Medical Center, was elected to the National Academy of Sciences in 2014 for his key contributions to unraveling the complexities of this process. Among other findings, Lutkenhaus discovered a protein, FtsZ, which is essential for cell division in *Escherichia coli*, and showed that the protein assembles into a ring, called the Z-ring, at the future site of cell division in the middle of the cell. Investigating the mechanisms of the spatial regulation of FtsZ led Lutkenhaus to the Min system of proteins—MinC, MinD, and MinE—that inhibit FtsZ everywhere except in the middle of the cell. In his Inaugural Article (1), Lutkenhaus and colleagues reveal how MinE switches between membrane-bound and cytoplasmic forms, thus elucidating a key step in the spatial regulation of bacterial cell division. He recently spoke to PNAS about his findings.

**PNAS:** How did you become interested in studying bacterial cell division?

**Lutkenhaus:** When I was a graduate student at UCLA [University of California, Los Angeles], I came across an article by William Donachie that sparked my interest in studying bacterial cell division, and I went to do a postdoc with him at Edinburgh. My goal became to try to find the genes that were essential for division and how they functioned. I started by trying to complement some of the division mutants, and that led to the isolation of what turned out to be critical genes involved in cell division, one of which we designated ftsZ. After we identified FtsZ as a critical component of cell division, and then demonstrated that it forms a Z ring in the middle of the cell, the question became how the Z ring is spatially regulated.

**PNAS:** What led you to study the role of the Min system in regulating FtsZ spatial regulation?

**Lutkenhaus:** The Min system has been around for a long time, and if you mutate or delete the Min system you make “minicells,” due to Z rings forming at the poles of the cell. One of the things we discovered early on is that when you overproduce FtsZ, it causes the cells to make minicells. The prevailing theory was that the Min system was blocking division at the poles, and since overproduction of FtsZ causes division at the poles, it suggested there was an antagonism between FtsZ and the Min system. We showed that the components of the Min system actually target FtsZ, and we gradually became interested in how the Min system’s spatial regulation occurs.

**PNAS:** What was previously known about the regulation of the Min system?

**Lutkenhaus:** The Min system turns out to be a very interesting system, because it undergoes this dynamic oscillation from one end of the cell to the other. There are three components that make up the Min system—called MinC, MinD, and MinE—and they interact to produce this oscillation with a period of about 10 seconds. We followed up on the biochemistry of it, trying to figure out how these proteins interact and what they interact with to produce this oscillation. The oscillation only depends on two of those proteins, MinD and MinE. We showed that MinD can bind reversibly to the membrane in one end of the cell, and that MinE stimulates MinD’s ATPase activity and causes MinD to fall back off the membrane. What we also discovered is that MinE goes through a drastic conformational change. But we were not sure how it occurred, and whether it was spontaneous or if it was somehow induced by its interaction with MinD.

**PNAS:** What does your Inaugural Article (1) reveal about MinE’s conformational change?

**Lutkenhaus:** The main point of this paper is answering how MinE undergoes this conformational change (1). What we show is that the MinE conformational change depends upon the interaction of MinE with MinD. The
idea is that when MinE is in the cytoplasm it has its membrane targeting sequences, or amphipathic helices, kind of sequestered, but the structure is somewhat dynamic and these amphipathic helices can become available to bind the membrane, so it's a very reversible situation. It's kind of like MinE is scanning the membrane, looking for MinD. If it encounters MinD, then it undergoes a complete conformational change where it can now bind MinD and stimulate MinD's ATPase activity, causing it [to] come back off the membrane. I think MinE has to do this conformational change because, on the one hand it has to be able to diffuse in the cytoplasm, and on the other hand it has to interact with MinD to stimulate its ATPase activity and cause it to fall off the membrane. When it hits the MinD it’s kind of trapped because it has to induce the ATPase, and that's kind of a very slow step compared with diffusion.

PNAS: Why are these findings remarkable?

Lutkenhaus: The remarkable thing is that MinE is such a small protein, only 88 amino acids long, and yet it's got all this conformational complexity built into it. It's just amazing to me to have seen this conformational change, and then the fact that this change has to be triggered by MinD. That makes for a very nice story.

PNAS: What are some of the broader takeaways from your research on bacterial cell division?

Lutkenhaus: I think one of [the] things that we’ve learned is that the spatial regulation of division in bacteria is very complex. I was just rereading a 1974 article that said that, when it came to bacterial cell division, one has to recognize that “the structural simplicity of bacteria is deceptive.” Over the last 25 years, with all these discoveries—that FtsZ is like tubulin, MreB is like actin, and bacteria have these cytoskeletal elements—that’s proven to be the case. As one looks in different bacteria, people are finding that the mechanisms of spatial regulation vary. The Min system is quite conserved, present in a large number of bacteria and even chloroplasts. Bacteria are morphologically simple and yet have to put proteins at particular locations. The Min system has evolved to inform the cell where its center is. Nobody would have predicted how any of this works, so that's been kind of fun.