Kool Insights

Overcoming the Failure Factor

By Xin Gao

Features

"Stanford Physicist Wins Nobel Prize." "Twenty-three Projects Win Research Incentive Grants." "Professor Wins Kyoto Prize." Such are the headlines usually found atop news articles documenting scientific research at Stanford. From these headlines, one would think that all Stanford research projects are completed flawlessly. But, are Stanford research projects always so perfect? Are Stanford researchers blessed with a magical insight that repeatedly rewards them with experimental success? While the multimillion dollar startup company or the Nobel Prize winning research discovery may outshine the scientific ventures that go awry, it is precisely the ability to learn from and adjust to the "mistakes" that lead Stanford researchers to their ground-breaking discoveries.

Chemistry Professor Eric Kool

Everyone knows that no large-scale projects, including Stanford research projects, run smoothly from the beginning to the end. Beneath the glossy surface of successful scientific research lie the trials and tribulations that all researchers must face. Chemistry Professor Eric Kool, whose research interests dwell in the realms of organic and biophysical chemistry, was generous enough to reveal the difficulties he initially encountered with one of his most successful research ventures.

As a post-doctoral fellow searching for a job in 1988, Eric Kool sent research proposals to the institutions in which he was interested. One such proposal planned the construction of molecules that mimic DNA bases and form hydrogen bonds in a helical structure. The idea, however, was soon overtaken by other research interests when Kool joined the Chemistry department at the University of Rochester in 1990. "As a younger faculty member, I felt it was safer not to attempt something so risky," explained Kool. By 1995, he had established himself well enough and decided to experiment with a riskier research idea – his synthetic DNA mimics. Using a DNA synthesizer and unnatural nuclei, the Kool group created synthetic molecules that mimic DNA base structures of adenosine, thymine, cytosine, and guanine. When the group tested the molecules' ability to form a double helix, however, they discovered that the structures lacked hydrogen bonds and, therefore, were unable to form the characteristic helix of DNA.

The group was ready to conclude the project was a failure when they decided to perform one additional experiment on the DNA mimics. "We had already constructed the molecules, so it didn't hurt to try one last experiment," commented Kool. The molecules were fed into DNA polymerase, and surprisingly, the enzyme was able to replicate the DNA bases. This ability indicated that DNA polymerase treated the synthetic mimics as if they were normal DNA bases. The group later concluded that the shapes of the synthetic DNA molecules, which were identical to that of normal DNA, were able to fool the DNA polymerase. However, their inability to form hydrogen bonds prevented formation of double helices. This unexpected discovery, which was reported in 1997, triggered controversy among researchers. DNA shape was established as the sole factor in DNA replication. The results of the Kool experiment were soon verified by others and eventually led to Kool's professorship here at Stanford.

The project became a tool by which Kool and other researchers could study the internal mechanisms of DNA and the proteins that interact with DNA. Because these structures partially retain the functions of normal DNA, researchers can learn basic information about these complex systems. Kool also remarked, "Way in the future, we may even design new DNA base pairs."

Beyond the success of the experiment, Kool's brush with failure in his research venture conveys a more important lesson. Ready to terminate the experiment as a total loss, he made a final, determined attempt that led to an extraordinary discovery. While Kool admits that there was an "element of luck" involved with his project, he also added that "*persistence* is the key." Had Kool decided to terminate the project before performing that last experiment, no amount of luck could have changed the results. "Whenever science tells you no, try something else," says Kool. Indeed, trying something a little different may turn a flawed research project into a marvelous success. Kool ended, "Although risky, it's fun to try for bigger, harder things."

Many other Stanford faculty members have undoubtedly been through similar research endeavors. Such experiences constantly reinforce our faith that persistence does pay off and stress the value of innovative thinking outside the conventional mold. Students can apply Eric Kool's lessons and insights in scientific research and many other endeavors. Everyday life can be improved with a Kool mindset.