Peer Review Notes May 2014

Power of Peer Review: Basic Research in Yeast May Yield New Approach to Treating Cancer

Since the 1930s, scientists knew that calorie restriction could extend lifespans. But it is only in recent years that the tools were available to discover how this happens.

In 2002, a new investigator at the University of Southern California—Davis School of Gerontology, Dr. Valter Longo, submitted an R01 application to study the mechanisms of longevity regulation in yeast. He proposed to elucidate the molecular pathways that "promote reproduction in response to glucose/nutrients, activate multiple stress resistance systems and extend the life span of non-dividing yeast" in low-nutrient states.

Armed with this information, one could then modulate one of the pathways to "increase resistance to damage and extend longevity in organisms ranging from yeast to mammals by shifting the investment of energy from growth and reproduction to multiple stress resistance systems."

It was an ambitious application that impressed CSR reviewers. "[It] breaks significant new ground by developing a new model system for studying chronological aging," said one reviewer who was quoted in the summary statement. "The proposal is strongly hypothesis driven, and closely argued throughout. A wealth of preliminary data is presented."

The National Institute on Aging (NIA) was also impressed and funded the grant. "This was exciting research," said Dr. Felipe Sierra recently, speaking on behalf of NIA as its Director of the Division of Aging Biology. "It wasn't translational research at all," he noted. "But by understanding these mechanisms in depth, there was the chance of getting something useful." No one, however, probably imagined how much would come from this research.

Dr. Longo achieved his aims and then some. He identified the Tor-S6K and Ras-PKA pathways as central promoters of aging, and showed how restricted diets lengthened lifespans by decreasing their activity. The role of these pathways in aging was later confirmed in multiple organisms, including mice. He was able to get his yeast cells to live 10 times longer. His research then opened up a whole new approach to fighting cancer.

The Leap into Cancer Research

Dr. Longo knew the genes that mutate and give rise to cancer were the same genes that block protection and promote aging. The genes are always on in cancer cells to help maximize growth. Thinking about how normal and cancer cells evolved, he hypothesized that cancer cells might respond differently if “starved.” “Normal cells know what to do because they have seen it throughout evolution,” he said. “But cancer cells have gained mutations that make them very good in normal, high nutrition environments but unresponsive to the starvation signal to go into a protected anti-aging mode, and unable to survive well in a starvation environment in which glucose and many other nutrients are scarce.”

Dr. Longo and his colleagues conducted a series of studies in yeast, mouse and human cells and found that starved normal cells could survive otherwise lethal doses of chemotherapy and starved cancer cells could not thrive and were more susceptible to chemotherapy. They called these effects Differential Stress Resistance and Differential Stress Sensitization.

The next step was to try it in humans, but this wasn’t an easy one. “He had a lot of opposition from physicians,” said Dr. Sierra. “Putting cancer patients on a fasting diet was counter-intuitive because, when you’re on chemo, you lose your appetite, you don’t eat and of course that weakens you.”

Dr. Longo went back into the lab with his mice, which also suffer weight loss on chemotherapy. The calorie restricted mice on chemo lost weight like the control group, but they recovered much faster than the controls.

Clinicians at USC Norris Cancer Center, the Mayo Clinic and in Europe are now collaborating with Dr. Longo. After a small clinical trial produced promising results, a larger one was initiated and is ongoing. In addition, the National Cancer Institute is funding small business research to develop a nutritional regimen and products for cancer patients on chemo that would be as good as fasting.

“The results are very exciting,” said Dr. Sierra. “I don’t know if they will pan out in the larger trial. But if they do, it will be a major breakthrough.” In any event, countless avenues for aging and cancer research are now open for exploration. It should be no surprise that Dr. Longo is now a professor at the USC Davis School of Gerontology and the Director of the USC Longevity Institute.

The Power of Peer Review

“All of that came from the NIH-funded yeast research,” said a grateful Dr. Longo. Of course, there are others to thank. The CSR reviewers who reviewed his application deserve credit for recognizing the potential in it. But this isn’t something Dr. Longo seems to have forgotten. Despite all it has taken to keep up with the

robust flow of his research and academic responsibilities, he has made time to review NIH grant applications four times over the last five years.

Why Tell This Story?

CSR launched this series of stories in January 2014 to highlight how NIH peer reviewed science powers science and health. “Scientific and health breakthroughs are heralded in the press almost every day,” said CSR Director Dr. Richard Nakamura. “And you often can trace them back—directly or indirectly—to one or more NIH peer review groups that found great promise in an application. There are powerful stories that need to be told. They illustrate why support for peer-reviewed science is so important to our future.”

Let us know if you have a story you would like us to share about how peer reviewers identified research that had a big impact.