The BRCA1 gene and its association with breast cancer were discovered in 1990. We have learned much about it since. We know that mutations in the gene can be inherited. We know that BRCA1 has been linked to additional cancers, including ovarian, prostate, and pancreatic. We also know that the BRCA1 gene produces a tumor suppressor protein that plays an important role in DNA repair. But the dark mystery at the gene’s core—the molecular mechanism that triggers mutations and leads to cancer—has stumped researchers for a quarter of a century, until now.

In 2017, Yale scientists revealed the elusive mechanism after purifying the BRCA1 protein in conjunction with an associated factor called BARD1. This breakthrough opens new possibilities for attacking cancers linked to mutations of BRCA1. The findings appeared in the October 2017 issue of the journal *Nature*.

"A lot of very good people have tried to purify the protein," said the paper’s senior author, Patrick Sung, DPhil, Professor of Molecular Biophysics and Biochemistry. "I am proud to say that we are the first to succeed."

They had to overcome considerable obstacles. The protein is fragile and prone to quick degradation, so the researchers had to work for many hours in a room being kept at four degrees Celsius. The protein is hard to express and tends to fold incorrectly, and it is unusually large, which makes it extremely challenging to purify. A misstep at any point in this painstaking process renders the protein inactive and useless for research. "You need a lot of training and experience to know what measures to take to preserve activity," said Dr. Sung. "We have to be incredibly tenacious," added Ryan B. Jensen, PhD, Associate Professor of Therapeutic Radiology, a supporting author on the paper. Dr. Jensen would know—in 2010 he was the first to purify the BRCA2 protein. Only a few laboratories in the world can successfully purify BRCA proteins, and two of them are at Yale—Dr. Sung and Dr. Jensen.

Dr. Sung has been tracking proteins related to DNA repair for more than 20 years, which is what led him to BRCA1. The gene’s precise role in the repair process was unknown. Purified BRCA1 protein allowed Dr. Sung and his colleagues to study its properties and run experiments that pinpointed its function in DNA repair.

They have found that the complex of BRCA1 and BARD1 binds and stimulates an enzyme called RAD51, known to be important in repairing double-strand breaks in DNA. (Dr. Sung first described the function of RAD51 in 1994.) Dr. Sung’s team found that when mutations occur in the BRCA1-BARD1 complex, RAD51 is not activated and DNA repair falters, which can lead to mutations and cancer. "Now that we know that BRCA1 and BARD1 interact with RAD51, we can target that interface," said Dr. Sung. "Before, we didn’t know what to target. That’s why basic science is so important. The next step would be to develop compounds that regulate the activity of the target, to enhance it or inactivate it."

"Many drugs are designed to kill cancer cells by damaging their DNA. Yet some cancer cells manage to repair their DNA and become resistant to chemotherapy and radiotherapy. Deciphering the mechanisms of DNA repair pathways is crucial," explained Dr. Jensen, because each knowledge point the way to therapies that target those pathways and kill resistant cells.

Understanding the mechanisms within BRCA1 and BRCA2 also has predictive value. Right now, if a young woman is worried about her family’s history of breast or ovarian cancer, she can get a diagnostic test to see if she carries a BRCA mutation. Sometimes the result clearly indicates either low risk or high risk, but often the test reports “variants of uncertain significance,” which leaves the woman in fear and limbo. Should she proactively remove her ovaries and breasts? Does she have time to have children first? These are challenging decisions. These new discoveries about BRCA1 and BRCA2 will make it possible to tell whether her mutation affects DNA repair severely or only slightly, and hence what her risk is for cancer with regards to age.

"And it all comes from understanding how the proteins work," said Dr. Jensen. "That’s why what Patrick and I do, biochemistry, is really important—it leads to work of purifying proteins one at a time and figuring out mechanistically what they do."

Dr. Sung agrees. "I understand why the general public wants to see cures, but unless you understand the basic biology, you will never have a cure."