

Advancements in prostate cancer research provide hope for finding a cure and lead to the discovery of new treatments to minimize the impact of a man's prostate cancer and maximize his quality of life. This regular *Hot SHEET* supplement includes some of the latest research from the Prostate Cancer Foundation ([www.pcf.org](http://www.pcf.org)).

The PCF is the world's leading philanthropic organization funding and accelerating prostate cancer research. Founded in 1993, the PCF has raised more than \$745 million and provided funding to more than 2,000 research programs at nearly 200 cancer centers and universities.

### Aggressive Prostate Cancer and Our "Dark DNA"

Imagine you're a scientist studying human genes, looking for a way to cure prostate cancer. You could learn many things by studying the genes that make the code that becomes proteins: our building blocks – or, you might say, **our hardware**.

These protein-coding genes make up **just two percent** of our human genome. The **other 98 percent** are non-coding. "Not too long ago, says PCF-funded investigator Hui Li, Ph.D., of the University of California-San Francisco, "scientists thought these genes were just 'junk,' the genetic equivalent of background noise." But now, Li and an increasing number of scientists believe, "these non-coding genes *play a very important role in many cellular processes, including the development and progression of cancer.*"

These non-coding genes that *don't* make proteins make something else that is important: RNA. "They're like the **hidden software** of our bodies," says medical oncologist and molecular biologist Jonathan Simons, M.D., CEO of the PCF. It turns out that these genes – our very own "**dark matter**," or "**dark DNA**" – might not make the difference between getting cancer and *not* getting it, but they might make the difference between *getting cancer that's easy to cure and cancer that is much more likely to be lethal*. "There's a lot of genetic software running in the background," adds Simons. "If you have a single letter wrong, it can set you up for trouble. Some of those changes in code might mean you have higher cholesterol, and then a higher chance of having a heart attack or stroke. **But that one letter could also change the command for cancer to grow fast or grow slowly; if you have cancer, it could mean you have a much higher chance of having a bad one** – one that will go at 75 miles per hour, instead of maybe 25."

In research with his mentors, Felix Feng, M.D., and Peixuan Guo, Ph.D., Li has painstakingly looked at thousands of RNA-sequencing genes. "This kind of work wouldn't have been possible, even a few years ago," notes Li. "Because of the advancement of next-generation sequencing technology, we now have the bioinformatics and the ability to analyze these novel genes."

Many genetics studies are like a game of "spot the misspelled word" – on steroids, a task akin to speeding through the *Encyclopedia Britannica*, one letter at a time, looking for something that is wrong or out of place.

Li's work is more like a genetic game of, "Where's Waldo?" Except he didn't know what Waldo looked like. But he may have found Waldo, after all: a suspicious gene called SchLAP1-AS.

SchLAP1-AS is a long non-coding RNA gene that is "**highly expressed in prostate cancer, and is highly prognostic for metastasis**," explains Li. It is "only guilty by its presence. We have identified that SchLAP1-AS is more closely associated with the *progression* of prostate cancer than any other protein-coding or non-coding gene in our patient cohort."

His studies have found that inhibiting this gene in prostate cancer cells causes them to become less oncogenic (less proliferation of cancer). One aim is to see whether this gene can be employed as a novel therapeutic target – to turn back the disease, or halt its progression. Li also believes it could become a prognostic biomarker. The presence of SchLAP1-AS in prostate cancer when it is first diagnosed could tell doctors: *This cancer is going to be aggressive. Don't do active surveillance; treat it aggressively*. Maybe it could even be looked for earlier, to indicate: *This young man has a bad gene; he needs to start checking for prostate cancer at an earlier age, and he needs to be tested every year*.

Li believes this is just the beginning of looking at RNA-coding genes in personalized medicine. "We think studying this gene, and learning how to block it, will enhance our understanding of prostate cancer biology in a subset of patients with aggressive disease." And more: "**The non-coding genome was considered undruggable before**," says Li. "If we can make a real breakthrough in this area – hit a previously unknown target – it may also mean a breakthrough in how we treat patients with other forms of cancer, like pancreatic cancer and brain cancer, which share some common traits with prostate cancer."