very now and then, as dusk fell on the San Diego coast, Stewart Sell swam out to sea, children in tow. As the shore dwindled in the distance, Sell would stop, bobbing in the water to wait for the perfect wave. He had a special talent for spotting the good ones, and wouldn’t give up until he found one that would take them all back to shore. As it crested behind him and his children, he would yell for them to swim hard, arch their bodies, and ride the wave as far as they could. After a good ride, they would pull themselves onto shore and head home, where Sell then climbed into bed, spread out his papers, and dove into some of the most pivotal research in stem cell history. It was the 1970s and 1980s, and Sell (MD ’60) was riding the biggest wave of his life: the oval cell, a tiny liver cell that may provide researchers with a key for treating cancer, cirrhosis, diabetes, and any number of other disorders. But people said he was wasting his time.

In the 1970s, Stewart Sell suggested certain stem cells cause liver cancer. Now some people are thinking he was right.
Sell first caught the oval cell wave in a small conference room in Scaife Hall. After a residency at Massachusetts General Hospital and a postdoc at the University of Birmingham Medical School in England—where he and his advisor described what would later become known as B-cells—Sell came back to Pittsburgh in 1965. He was born and raised here, and when he’s excited, he still drags his vowels in true Pittsburghese fashion. During his years away from Pittsburgh, Sell published a paper now considered a “citation classic” (Journal of Experimental Medicine, August 1, 1965), which helped him become one of the thousand most quoted scientists of the 1980s, and launched what looked like a promising immunology career. He would soon write a widely used immunology textbook—now in its sixth edition. Sell joined the Pitt pathology department planning to continue his earlier research, which had nothing to do with stem cells. But his plans changed after several lab meetings, where 20 or 30 researchers gathered to discuss their work over libations—sometimes coffee, Sell recalls with a chuckle. “But back in those days, we often had something stronger than coffee . . . something to stimulate conversation.”

The meetings were run by Emanuel Farber, then chair of pathology, who had a keen interest in liver cancer. Specifically, he wanted to know what cellular changes precipitated malignancy. Farber’s group found that in the earliest stages of liver cancer, the primary liver cells—called hepatocytes—develop small foci. The foci then grow to become actual nodules on the liver, which grow into cancer.

Sell followed these developments with each meeting, until Garri Abeler, a young researcher in Moscow, found something called alpha-fetoprotein (AFP), a protein required for fetal development that disappears later in life, then reappears mysteriously in animals with liver cancer. That news hit Sell like a wave, and he knew he had to ride it.

“I just had to find out how the production of this protein related to those early changes that Dr. Farber was studying,” he says.

Sell figured that AFP was produced by the hepatocytes in Farber’s model, and he had a hunch they started producing it before they developed foci. Since AFP circulates in the blood, Sell figured the best place to start was by developing a test for its presence. So he turned to his notes from sophomore microbiology at Pitt. His former instructor, Richard Farr, had developed what’s known as the Farr Assay, which utilizes antigen and antibody binding as a way to measure proteins, even in miniscule amounts. Using Farr’s technique, Sell developed a test for AFP and discovered that animals exposed to cancer-causing agents had elevated AFP levels long before they actually developed liver cancer. (Incidentally, Sell’s test for AFP is now used to screen for some birth defects, in which AFP leaks from the fetus into the mother’s system.) To truly understand his findings, Sell needed to know exactly where the AFP came from. So he began looking in liver foci and nodules for cells that produced AFP. But he couldn’t find them.

I magine the liver is a house made of bricks. Tucked within the layers, within the mortar that holds them together, are a few scattered stones: The bricks are hepatocytes; the stones are oval cells. Oval cells are a fraction of the size of hepatocytes, and if you’re not looking for them, chances are you’ll never see them. They were actually discovered by Emanuel Farber, but since he was sure cancer arose from hepatocytes, he didn’t give oval cells much thought. Initially, neither did Sell.

After taking a faculty position at the University of California, San Diego in 1970, Sell would spend his Saturday mornings in a darkroom, scanning countless liver samples for AFP traces. He stained samples with a marker that fluoresced green in the presence of the protein, and he was stumped when
they didn’t seem to fluoresce, even when the sample had already tested positive for AFP.

But one day, a tiny speck of green light caught his eye and he yelled, “Oh boy, there it is!”

To his amazement, the light came from oval cells, not hepatocytes. The more he looked, the more his amazement grew: Oval cells were tiny, completely undifferentiated cells with no organelles (the organized structures within cells), all of which are characteristics of stem cells.

In 1976, Sell announced that oval cells were the source of AFP, and therefore liver cancer. People smirked. The field of stem cell research had yet to take hold. When he said oval cells were stem cells, people told him he was ridiculous. But he kept at it, developing markers to trace their development, showing that they proliferated wildly as cancers grew, and publishing papers saying stem cells were the root of liver cancer. Finally, a few researchers caught on and began replicating his findings.

“This opened a new view of liver carcinogenesis as potentially being a problem of stem cell development as opposed to the mutation of hepatocytes,” says Hyam Leffert, professor of pharmacology at the University of California, San Diego, and a long-time collaborator. “That really shifted thinking around and got a lot of people focused on understanding oval cells.”

A few years ago, decades after researchers told Sell he was crazy for thinking liver stem cells existed, Bryon Petersen, then a Pitt faculty member, made headlines around the world when he took stem cells from bone marrow and created liver cells. Before becoming full-fledged liver cells, they became oval cells. Now Petersen, an assistant professor of pathology at the University of Florida, has shown that liver stem cells can become various cell types.

So what does Sell—who started out looking for the root of liver cancer—think of the way science has embraced the therapeutic promise of stem cells? “I think it’s fantastic,” he says. And he has helped set the pace with researchers like Petersen by developing his own lines of oval cells he will attempt to grow into liver, lung, and a multitude of other tissues. “Hopefully we’ll use them to replace damaged organs someday,” he says, “or we’ll insert genes and use them for gene therapy. . . it all depends. But right now, these cells are hot.”

George Michalopoulos, chair of pathology at Pitt, speaks of oval cells as a phenotypic bridge: “Hepatocytes and cells of the bile ducts can change into each other, and they do so by going through the oval cell route. Cancer can come from all three types [of liver cells], but when it does, it looks very often like oval cells.”

Though the scientific community still awaits formal proof, many now suspect those little cells lie at the root of liver cancer. But back when Sell first said this was so, few believed his findings.

“It was a violation of the dogma at that time,” says Leffert. “But he really showed that the dogmatic models of liver cancer may well be wrong.

“That iconoclasm, that persistence, was so important to the field.”

“Stewart was one of the pioneers in this field,” says Petersen, “by making antibodies to help identify oval cells, he made it possible to find them and pull them out to work on them.”

“He’s tenacious; he doesn’t give up,” notes Leffert.

Sell always told his kids that holding out for the best wave will take you far. At the age of 66, he’s been riding oval cells for more than three decades: He has yet to hit the coast, and he’s not heading home just yet.