



Steve Campbell / Houston Chronicle

Dr. Wallace McKeehan is among a growing group of scientists who think that flawed cell division causes much of cancer, not genetic mutations. McKeehan works at the Institute of Biosciences and Technology at Texas A&M University in the Houston Medical Center.

Cancer: Looking beyond mutations

Newest field of research sees more complex reasons behind a genetic puzzle

By **ERIC BERGER**

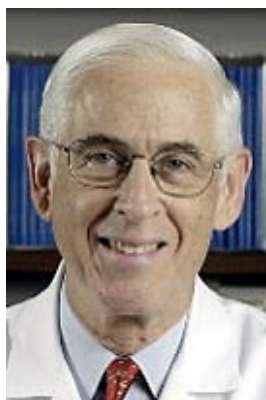
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For a long time, Wallace McKeehan counted himself among the believers.

The cure for cancer, McKeehan and much of the cancer research community believed, lay in our DNA, the genetic blueprint that controls human development. Just a critical few of the 30,000 human genes watched over the biological machinery of cells to ensure they didn't stray from normal and become cancerous, scientists thought.

All that need be done, then, is find these kingpin genes on the Human Genome Map and devise drugs to correct the genetic mutations causing the body to go awry. In fact, scientists have been gloriously successful at finding genes associated with cancer.

Too successful for their own good, actually. They've found hundreds. So tangled is the cancer-genetics puzzle that a growing number of scientists, including McKeehan, believe solving it may be hopeless. He's stopped trying. With so many genes, McKeehan says, studying simple genetic



Chronicle file
Dr. John Mendelsohn

eventual treatment of it.

"There are just a mind-boggling number of mutations associated with cancer," said McKeehan, a professor of biochemistry at Texas A&M University Health Science Center's Institute of Biosciences and Technology.

"We need some new ideas."

And they have some. Promising ideas that may explain why current science has not found the silver-bullet genes.

Among them is a growing field in cancer research called epigenetics, in which DNA letters of genes are not changed or mutated, but rather some other external force, like a hydrocarbon, bonds with a healthy gene and stops it from working. What is causing this to happen remains anyone's guess.

"It's becoming quite obvious that cancer is a complex process," said Dr. Guillermo Garcia-Manero, a University of Texas M.D. Anderson Cancer Center scientist who studies the epigenetics of leukemia.

"On one hand, this is bad news because we're unlikely to have one single drug to cure a particular type of cancer. But on the other hand, it will provide a lot more targets for new drugs."

A pricey misstep

The problem, say McKeehan and a number of cancer researchers, is that scientists who control research funding in the United States remain wedded to the idea that gene mutations, even perhaps just a few of them, largely control the development of cancer.

This view has been reaffirmed in recent months by a proposal to determine the DNA sequence of at least 12,500 tumors taken from the 50 major types of cancer. The goal is to determine whether a handful of genes are common to all human tumors.

The cost of the proposed Human Cancer Genome Project at current prices is about \$12 billion. Considering the tightness of funding for medical and cancer research — only about one of every six grant applications receives funding from the National Institutes of Health — some scientists view the new genome project as a misstep in the war on cancer.

Uncertainty remains

One is George Gabor Miklos, a respected Australian geneticist. In a commentary published last month by the journal *Nature Biotechnology*, Miklos noted that since 1976, when the first gene associated with cancer was found, survival rates for many of the main killers, including breast, lung and prostate cancers that have spread, remain largely unchanged.

"The simple truth is that the money would be much better spent if research priorities were re-evaluated," he wrote.

Nobody is pretending that curing cancer will come down to finding a few

Medicine's Human Genome Sequencing Center. But much uncertainty remains in how much control genes have over tumor development, Gibbs said, and the question needs to be answered for cancer research to move forward.

In the last 30 years, genetics has made significant contributions to cancer research and treatment. A decade ago researchers identified the BRCA1 gene as a significant predictor of cancer: Its presence in women conferred about an 80 percent chance of developing breast cancer. The problem, as later became apparent, is that less than 10 percent of women — even among those who have a family history of breast cancer — carry the gene, so its early detection value was limited.

More recently, drugs that target specific gene mutations associated with cancer have begun entering the market.

One new drug, ImClone's Erbitux, works in combination with chemotherapy to shrink colon tumors by 50 percent or more in almost one-fourth of the patients. Another drug, Avastatin, extended the lives of colon cancer patients by five months in a recent trial.

Advocates of this approach, such as Dr. John Mendelsohn, president of M.D. Anderson and the lead developer of Erbitux, say other genetic drugs are coming. It's a slow process, he said, because bringing a new drug to market takes about a decade.

Other scientists argue that these drugs in development are likely to fit the pattern of gene mutation-based medicines already on the market: affecting only a minority of patients, or only modestly extending lives.

"If it could have happened, it would have already happened with genetic mutations," said William Brinkley, a senior vice president at Baylor who says other research should take precedence over the cancer genome project.

That's coming from an administrator whose institution would almost certainly benefit financially by acquiring research contracts. Baylor's DNA sequencing center and M.D. Anderson's cancer research expertise make the pair a virtual shoo-in to be a lead participant in the proposed project, local officials say.

The National Cancer Institute will hold a meeting next month to consider the proposal, but even if supported, it will begin as a smaller-scale pilot project, said Dr. Anna Barker, a deputy director at the institute.

Mendelsohn agrees with the cautious approach.

"Any claims that this is going to be the key to curing cancer are not appropriate," he said. "If I were designing it, I'd probably take a holistic approach. For example, let's look at DNA methylation."

Environmental factors

As scientists have improved their ability to poke around human genes and their interplay with cancer, they have discovered that mechanisms like DNA methylation, in which a hydrocarbon molecule gets attached to a particular gene and blocks its function, are involved with development

At appropriate times, genes signal the cell's protein-making factory to churn out proteins for essential cell functions, such as cell division.

The central question in cancer research is understanding why cell division goes awry — which can allow cancer cells to form — and to do that, scientists need to know why the genes aren't working. The main theory, until the rise of epigenetics, is that the genes were mutated.

In addition to DNA methylation, scientists have recently found other epigenetic methods. One is histone codes, in which the proteins that DNA wraps around somehow muffle genes. Another is RNA interference, the strangulation of the messenger carrying the signal from a gene to the cell's protein-making machinery.

Despite these advances, most cancer researchers still believe that other, upstream genetic mutations in a person's DNA are triggering the epigenetic mechanisms to silence critical cancer genes.

But a minority of researchers, including McKeehan, contend that flawed cell division — a catastrophic phenomenon called aneuploidy — causes cancer. When cell division goes bad, the new cells are freer to mutate, which explains their genetic diversity and ability to proliferate through the body as cancerous cells. Under this line of thinking, epigenetic changes, likely influenced by environmental factors, cause cancer, not gene mutations.

McKeehan says this model for cancer would explain why agents like asbestos and arsenic, which do not mutate genes, so effectively cause cancer.

The bottom line: No one knows for sure, and if funding is tight, newer ideas could get squeezed out.

"When the competition is so fierce for NIH grants, inevitably the old-boy system creeps in, at least to some extent," said Melanie Ehrlich, a molecular biologist at Tulane University who founded the DNA Methylation Society.

Barker, of the National Cancer Institute, said nearly all epigenetics research in the United States is already supported by the cancer institute. "We support a lot of epigenomic research, and we think it's very important," she said. "But everyone is entitled to their opinion."