Double knockout lands a breast cancer gene

It takes a one-two punch to knock out many human genes. Since people inherit one set of chromosomes from their father and one from their mother, human cells hold two copies of most genes. If a mutation eliminates the action of one copy, the other alone can often serve the cell adequately.

Researchers have recently developed an experimental strategy that allows them to knock out the activity of both copies of randomly chosen genes. In the first test of this approach, the scientists have had the good fortune to identify a previously unknown gene involved in breast cancer. Nearly 50 percent of breast cancer patients tested so far have mutations in one or both copies of the gene, called *tsg101*.

"It looks like they've latched onto a pretty interesting tumor suppressor gene," says Lawrence C. Brody of the National Center for Human Genome Research in Bethesda, Md. Tumor suppressor genes produce proteins that regulate cell growth; mutations in both copies of such genes are usually required to turn a cell cancerous.

Using the new gene discovery method they had developed, Limin Li and Stanley N. Cohen of the Stanford University School of Medicine last year identified the mouse form of *tsg101*. Working with Stanford colleagues Xu Li and Uta Francke, they have now located the human version of *tsg101* on a region of chromosome 11 suspected of containing a tumor suppressor gene involved in breast and other cancers. The Stanford group reports in the Jan. 10 CELL that 7 out of 15 people with advanced breast cancer have mutations in one or both copies of *tsg101*.

The mutations appear in cancerous tissue but not in the surrounding, normal breast tissue. This observation implies that the mutations were not inherited, though *tsg101* may yet be defective in some families plagued by breast cancer. Mutations in *BRCA1* and *BRCA2*, the known inherited breast cancer genes, do not account for all such families. Researchers plan to examine these families immediately for *tsg101* mutations.

The DNA sequence of *tsg101* suggests that the gene encodes a protein that can bind to other genes. It may also interact with stathmim, a protein implicated in cell growth and differentiation.

Li and Cohen's gene discovery method, described in the May 3, 1996 CELL, relies on the ability of retroviruses, such as the AIDS virus, to insert their genetic material into a cell's DNA.

The two researchers add a payload of genetic material to a retrovirus that has been made harmless. In each cell it infects, the virus inserts that payload at a random location on the cell's chromosomes.

The inserted payload not only mutates the gene, a portion of it can also silence the cell's other copy of the gene. When the researchers trigger this portion, the cell reads the sequence of the mutated gene backwards. This creates antisense molecules, which interfere with the protein-coding instructions produced by the normal copy of the gene (SN: 2/16/91, p. 108).

To find *tsg101*, Li and Cohen used their strategy to create mutations in a population of mouse cells. They then isolated any mutant cells that would grow in a thick substance called agar. Since tumor cells grow easily in agar but noncancerous cells do not, they concluded that the selected cells were missing a tumor suppressor gene. In fact, some of the isolated mutant cells produced tumors when injected into mice.

The two scientists finally used another part of the viral payload, an easily detectable genetic tag, to identify and sequence the cells' mutated genes.

Li and Cohen's gene discovery strategy may have many uses beyond finding tumor suppressor genes. For example, by isolating mutant cells that resist infection by a specific virus, researchers might unearth cellular genes whose proteins are co-opted by the virus. Indeed, the method used to find *tsg101* may become as important as the gene itself, says Brody. —*J. Travis*

Brewing a quantum computer in a coffee cup

In Douglas Adams' *The Hitchhiker's Guide to the Galaxy*, a hungover physicist creates the "infinite improbability drive," which uses unlikely events to propel starships across the cosmos at impossible speeds. He accomplishes this marvel by linking a quantum computer to a "fresh cup of really hot tea." Now, in a case of life imitating art, scientists are proposing to build a quantum computer inside a mug of hot coffee.

"Quantum computing could solve problems faster than ever thought possible," says Isaac L. Chuang of the University of California, Santa Barbara. He explains that, instead of using semiconductor elements as logic switches, these computers of the future would employ single atoms.

Quantum computers will achieve their unparalleled speed by taking advantage of the bizarre behavior of elementary particles. According to the theory of quantum mechanics, the properties of any atom, such as spin, location, or momentum, exist in all possible states at once—as long as they remain unmeasured (SN: 5/14/94, p. 308). In a conventional computer, a bit stores information by assuming one of two possible states. Quantum bits, or qubits, store more information by using all the potential states of an atom.

Qubits would allow a quantum computer to perform myriad steps at once. In contrast, today's computers calculate only one step at a time.

Past attempts at creating qubits have run into a fundamental problem. "It requires heroic efforts to control a single atom," says Chuang.

As an easier alternative, he and Neil A. Gershenfeld of the Massachusetts Institute of Technology propose using nuclear magnetic resonance devices to corral millions of atoms within an evenly heated volume of material. By coordinating the nuclear spin of many particles, the physicists could make these blocks of atoms act collectively as qubits. A liquid with the right thermal properties could hold up to 10 qubits, Chuang and Gershenfeld argue in the Jan. 17 SCIENCE.

"We'd probably use a cup of coffee as the medium," quips Gershenfeld, noting the unusually even heating characteristic of java.

"The big challenge is isolating your quantum computer from the environment," notes Gilles Brassard of the University of Montreal. In the new method, the sheer number of atoms in each qubit buffers the computer against unwanted external interactions that disrupt the calculations.

Within a few years, Chuang expects to build such a device and use it to factor numbers, one of the few programs that scientists have already adapted for quantum computers. The hypothetical 10-qubit design, however, would only handle numbers up to 15. To surpass this unimpressive milestone, the scientists will have to cool and control their liquid to eliminate disturbances in the calculations. In theory, by smoothing the temperature variations, they can create a computer with more qubits.

David P. DiVincenzo of the IBM Research Division in Yorktown Heights, N.Y., calls the new approach valuable but adds that "it is not a cure-all." Significant technical problems accompany cooling a material evenly enough to control more qubits. A true quantum computer would need at least 40 qubits, in DiVincenzo's view.

"There's lots of physics between here and a working quantum computer," he says.

If the liquid computer design succeeds, Chuang believes that engineers may eventually cook up a useful quantum device out of "a really expensive cup of structured coffee." —*D. Vergano*