

"A drug could be a simple answer" to treating a vexing form of skin cancer, says Dr. Ervin Epstein.



Fruit flies, 'hedgehogs' take on skin cancer fight

It all began with a fruit fly and a hedgehog.

Now the work of Dr. Ervin Epstein, a host of other skin disease researchers and South San Francisco-based biotech powerhouse Genentech Inc. could be on the verge of producing a happy ending to the story.

Children's Hospital Oakland Research Institute, where Epstein studies the molecular bases of skin diseases, next month will be a national center for a late-stage, 41-patient trial of a treatment for a

ERVIN EPSTEIN

Title: Dermatologist.

Institution: Children's Hospital Oakland Research Institute.

Focus: Basal cell carcinoma.

rare genetic condition that leaves patients at a higher risk of developing disfiguring basal cell carcinoma and a rare childhood form of brain cancer. The goal is to see if the Genentech drug GDC-0449 will reduce the number of basal cell carcinomas on patients' bodies.

"A drug could be a simple answer," Epstein says.

But it almost didn't come to this point.

Collaborating labs — including Epstein's, then at the University of California, San Francisco, and another at Stanford University — in 1996 found the gene that causes the genetic condition, called Gorlin syndrome. It was a satisfying discovery for Epstein, whose National Institutes of Health-funded lab in the mid-1980s started looking at the inheritance of basal cell carcinoma.

But almost no pharmaceutical companies showed interest in developing a gene replacement therapy out of the research.

Why should they? Surgery offered a 90 percent-plus cure rate and less than 1 percent of the 1 million or so basal cell cases reported each year in the United States are related to Gorlin syndrome. What's more, the treatment would be costly, and it would be repeated every couple months as new tumors appeared.

Only Curis Inc. of Cambridge, Mass., was interested. The company jumped on basic science research that had used fruit flies to identify the so-called hedgehog signaling pathway. The hedgehog, a gene so named because of its prickly appearance, normally is involved in development but, when it goes awry, helps cancer cells proliferate.

Over the next eight years, hedgehog research largely went unnoticed until a couple of high-profile papers in the journal *Nature* said hedgehog signaling could be involved in as many as one of every four human cancers.

Genentech licensed Curis' program and eventually tried a compound, GDC-0449, in a 35-patient Phase I trial that focused on severely ill cancer patients. Of the nine patients with basal cell, eight showed a significant benefit from the drug, Epstein says.

Basal cell is easily studied, and gathering more information about hedgehog this way could give Genentech insight into other cancers. While cancers like those of the breast and colon require multiple switches to flip the wrong way, basal cell requires only abnormal signaling of the hedgehog. Plus, the skin is a readily accessible research canvas.

The Genentech study starts enrolling patients this month, Epstein says, focusing on Gorlin syndrome patients who face annoying but rarely fatal basal cell removal surgeries every couple of months.

"Our story started with those patients," Epstein says.



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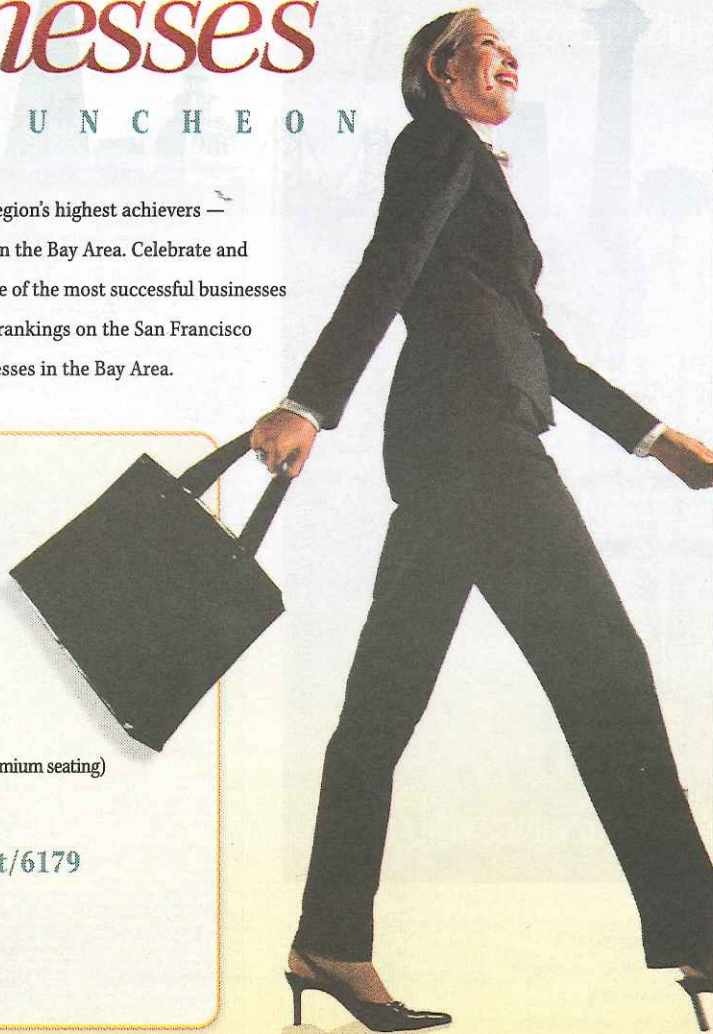
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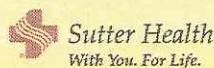
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