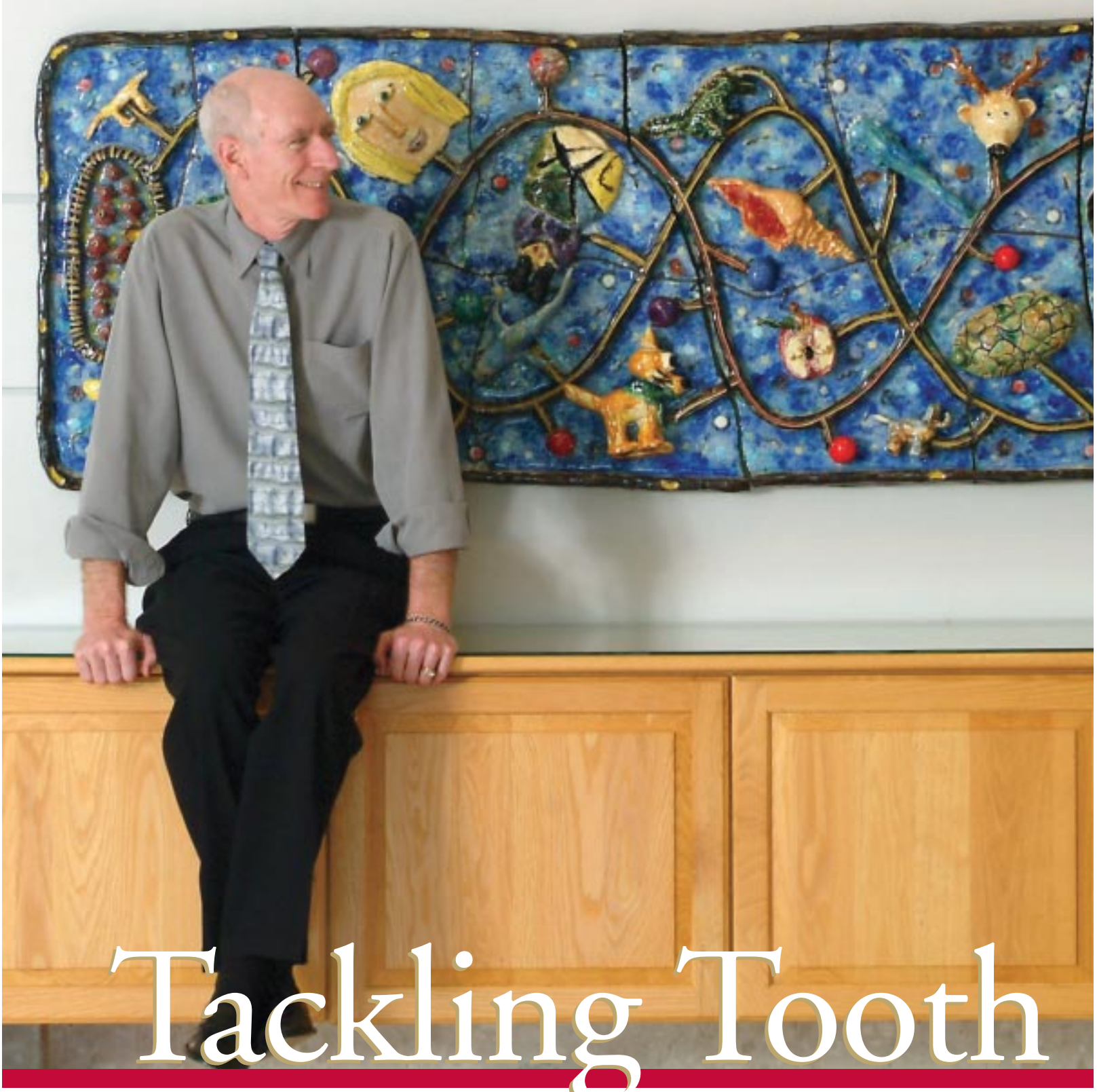
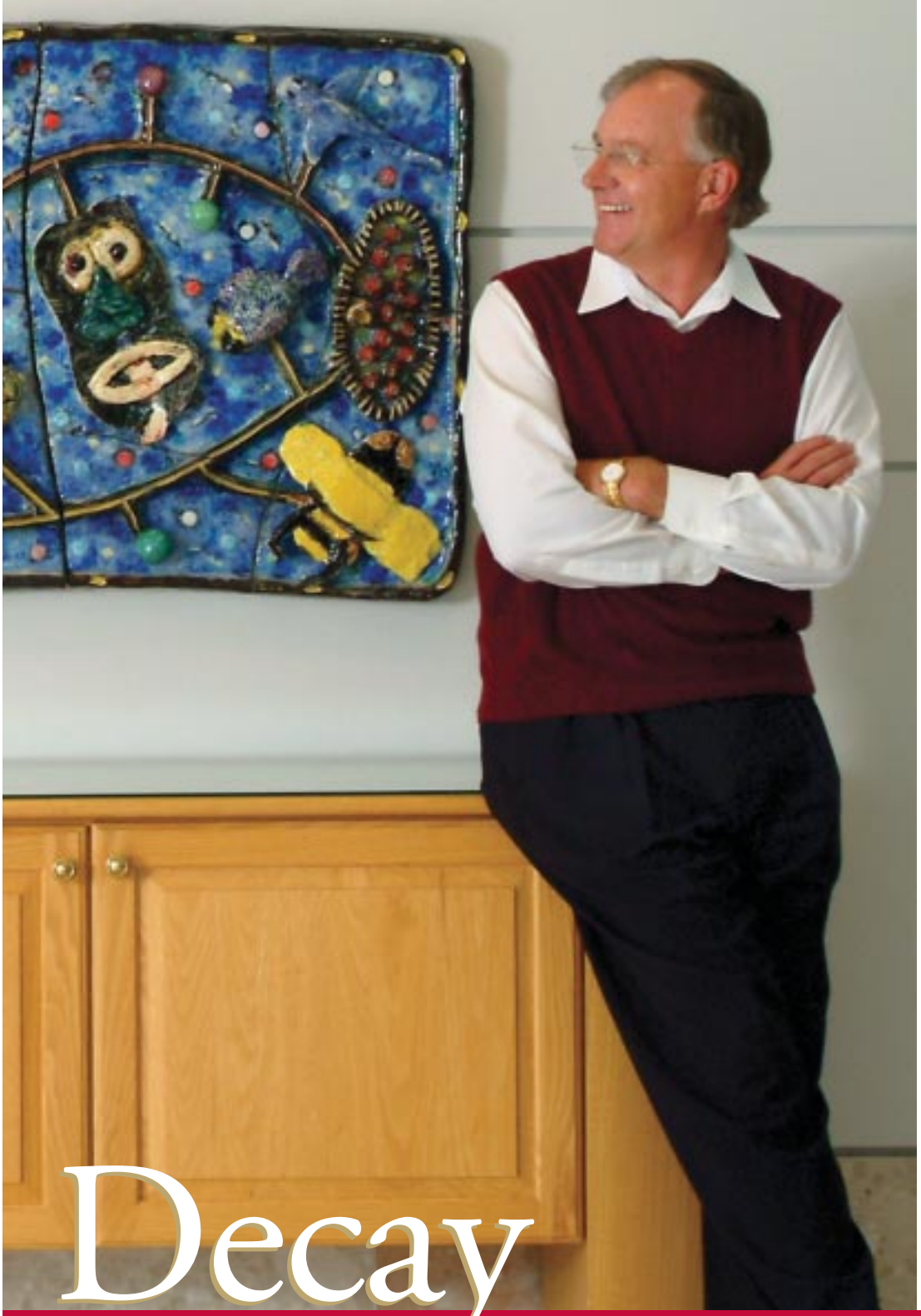


Tackling Tooth

Oragenics hopes people worldwide will embrace its genetically modified bacteria to prevent a lifetime of tooth decay



Decay

Jeff Hillman and Mento "Chuck" Soponis bring UF genetic research to market

Photos by John Jernigan

By Nancy Walsh

Tooth decay. The Surgeon General has called it a "silent epidemic." It's the most common childhood disease, five times more common than asthma. By first grade, half of American schoolchildren already have a cavity. By age 17, it's 78 percent. More than 51 million school hours are lost each year to dental-related illness.

We've always been told that sugar causes cavities, but it's really lactic acid that does the damage. A bacterium in our mouths called *Streptococcus mutans* converts sugar to lactic acid, which eats tooth enamel.

"Most studies suggest that of the 500 or so bacterial species in the mouth, *Streptococcus mutans* causes the majority of decay," says University of Florida oral biology Professor Jeffrey Hillman.

After more than two decades researching *S. mutans*, Hillman found a way to genetically tweak a strain of the bacterium so it doesn't convert sugar to lactic acid. No lactic acid, no cavities. The strain he chose is naturally dominant, ensuring that the modified bacterium will successfully colonize the tooth surface.

Hillman calls the approach "replacement therapy," and he is staking his future on it by taking a hiatus from academia to found a company called Oragenics to commercialize the discoveries.

Hillman says humans and *S. mutans* lived in harmony for eons until relatively recently, when our diets began to include more and more refined sugar. That upset the balance, causing the bacterium to make the excessive acid that causes tooth decay. In another 100,000 years or so, he says, evolution would restore that balance, producing a bacterium very similar to the one he has engineered.

"What we're trying to do with replacement therapy is speed up this natural process," says Hillman, whose research on the problem has garnered some $16 million over the years, primarily from the National Institute of Dental and Craniofacial Research.

"The mechanisms by which bacteria adhere to and grow on the teeth as biofilm communities, and then convert sugar to acids that damage the enamel, are extremely complicated," says Dennis Mangan, chief of the Infectious Diseases and Immunity Branch at the NIDCR. "Dr. Hillman's work exploits this knowledge in a clever, yet scientifically feasible, manner and takes us one step closer to the day when everyone will be free from dental caries throughout their lifetime."

While Hillman knows the science, he admits that he's no businessman. So he has teamed up with Mento "Chuck" Soponis, Oragenics' president and CEO. Soponis has more than 20 years of experience as a biotech executive, most recently with USBiomaterials Corporation, a firm that develops health-care products for bone regeneration and dental care.

"How often does a scientist have the opportunity to eliminate a disease?" Soponis says. "With replacement therapy, Oragenics can make an enormous impact on world health; that's the part I find exciting."

Oragenics is also developing a "probiotic" that inhibits the growth of disease-causing bacteria that cause periodontal, or gum, disease.

Hillman says that of all the bacteria normally residing in a person's mouth about a half dozen are the primary cause of periodontal disease. By studying samples from people without periodontal disease, Hillman was able to identify two types of bacteria that prevent the growth of these disease-causing bacteria.

"At the very least, this probiotic will allow people to maintain periodontal health," Soponis says of the product, which would likely take the form of a daily mouth rinse.

Hillman and Soponis don't expect Oragenics' technologies to eliminate the need for visits to the dentist. They just think those visits will be for different procedures.

"There's a lot more to dentistry than just filling cavities," Soponis says. "And if we can help people keep their natural teeth longer, we will really be helping dentists to achieve their goal of better oral health for their patients."

Soponis envisions replacement therapy being administered through a simple procedure in dentists' office. Patients would swish an application of the modified bacterium around their mouths for a few minutes, then chew some sugary gum to activate it, and they could be cavity-free for life.

"The ideal application would be to treat infants when their first teeth appear, although it can be used with people of all ages," Hillman says. And although the company hasn't determined pricing for the treatment yet, he adds that "if this turns out to be a once-in-a-lifetime treatment, then you're talking about a really good investment."

Hillman has even engineered the *S. mutans* bacterium so that it cannot be transmitted from one person to another through kissing or sharing eating utensils, ensuring controlled administration of the product in dentists' offices.

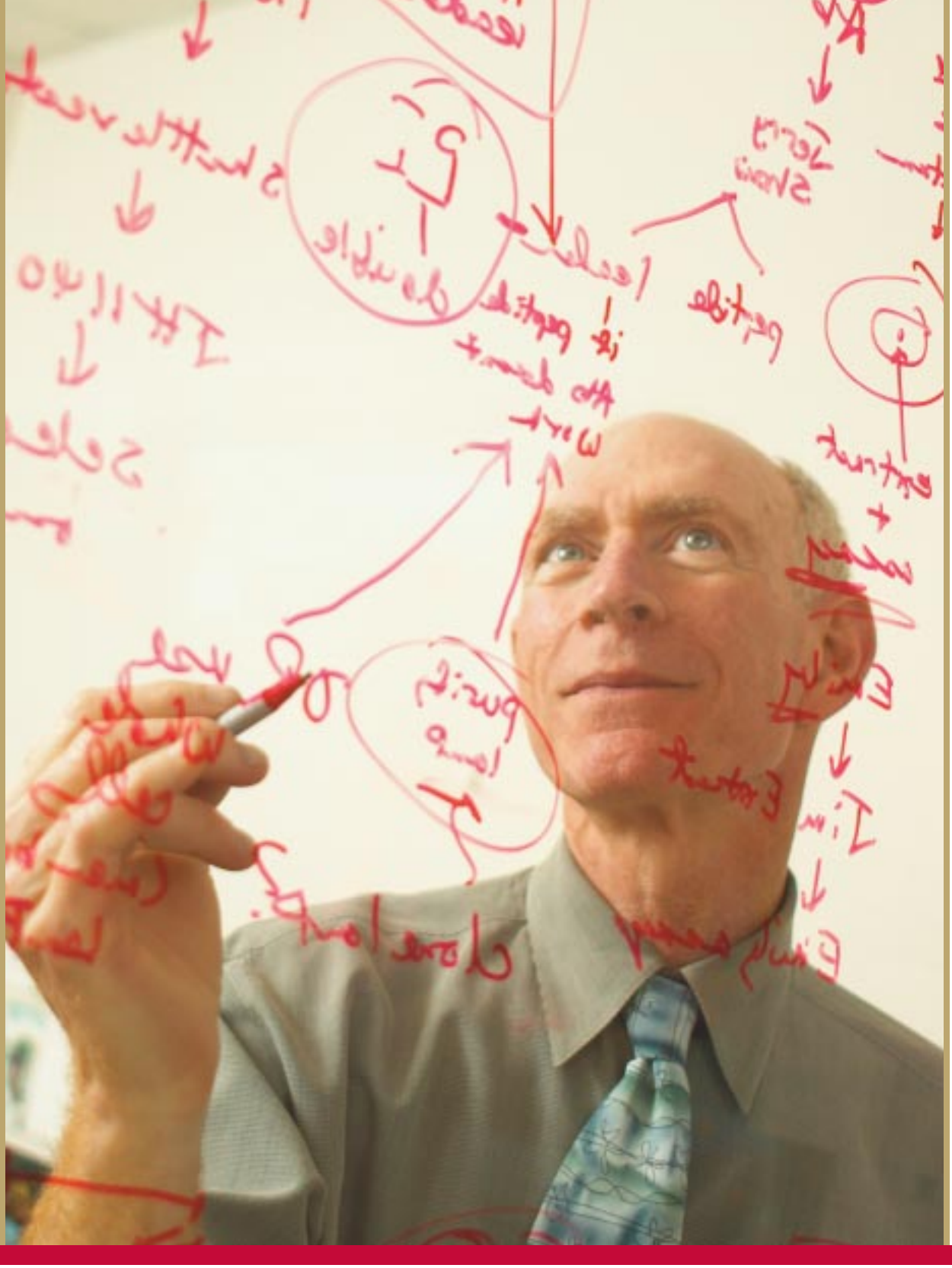
Replacement Therapy has already undergone laboratory and animal studies and Soponis says he expects the company to receive approval of its Investigational New Drug, or IND, application from the Food and Drug Administration by the end of 2004. Once the IND is approved, human clinical trials can begin. Oragenics hopes to have the product on the market by 2009.

Soponis says he is in "continuing conversations" with companies worldwide that would market and distribute Oragenics' product. The estimated market size for replacement therapy is 200 million people in the United States, 275 million in Europe and 275 million in Asia.

While much of its resources are focused on oral hygiene treatments, Oragenics has several other products in the pipeline.

One is a new type of antibiotic, called mutacin 1140, that could protect against a wide range of disease-causing bacteria, including staph. In preliminary laboratory studies, mutacin 1140 shows no evidence of pathogen resistance, which has become a major problem with the six leading classes of antibiotics in use today.

"Many common pathogens that once succumbed to the six leading classes of antibiotics used today are now developing



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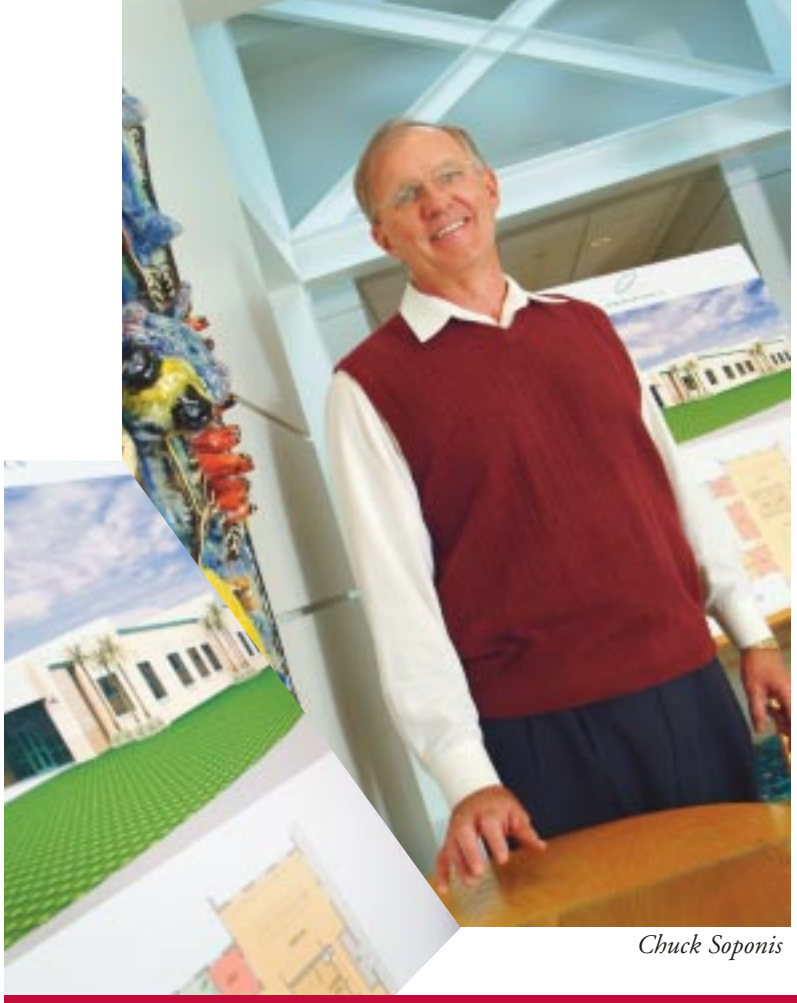
— Jeff Hillman



Chuck Soponis

In fall 2004, Oragenics plans to open a new laboratory facility in Alachua, Florida.

resistant strains at an alarming rate," Hillman says. "In fact, the single greatest problem in the use of antibiotics today is the growing resistance being developed by target pathogens."

Mutacin 1140 is still in research and development, with preclinical animal studies expected to begin later this year. Oragenics hopes to begin marketing the product by 2008.

Another Oragenics technology, called "change mediated antigen technology," or CMAT, identifies genes and the proteins expressed from them when a living cell changes from one condition to another, such as when a healthy cell transforms into a cancerous cell.

CMAT allows researchers to more easily identify "targets" for new vaccines and diagnostics — an instrumental step in the study of cancers, autoimmune diseases, coronary and vascular diseases and plant diseases.

Oragenics' evolution from a one-man shop to a thriving start-up company that is constructing its own building is, in many ways, a textbook example of how a university transfers its research to the market.

Hillman spent years documenting his research and working with the university's Office of Technology Licensing to patent several of his technologies. At one point, two of Hillman's technologies were on UF's list of the most likely to succeed.

Once he decided to start his own company rather than have the university license the technologies to an established firm, Hillman applied for and was accepted to UF's Sid Martin Biotechnology Development Incubator, or BDI, where promising young companies share scientific and business support at reduced cost so they can focus scarce resources on developing their product.

"The BDI is a terrific facility from the standpoint of development and getting technologies commercialized," Hillman says of the incubator, located in Progress Park in Alachua, Fla. "Allowing the university to work on that side of things enables us to work on the science. In the end we all benefit — the company and the university."

Oragenics is the first "graduate" of the BDI to build its own facility on the Progress Park campus, a 5,300-square-foot building expected to open in August.

With four technologies showing promise and a new facility in which to develop them, Soponis says, "Obviously there have been many challenges — like finding the right people, securing funding and working through the regulatory pathways. But there is tremendous potential here. It is rewarding building something from nothing. The future is exciting for Oragenics."

Related Web site:
www.oragenics.com