

Infectious diseases kill 15 million people a year, and are the leading cause of death in developing nations. But until recently, U.S. pharmaceutical companies found little profit in vaccines, antibiotics and related drugs.

Vaccines are costly to produce but have low profit margins. Sometimes the actual number of doses used is small, while the potential for pandemic is large. Often the afflicted live in countries too poor to buy drugs, or in spots too remote to store refrigerated products.

Small Companies Fighting Small Bugs

These market forces are changing. The National Institutes of Health and private foundations are investing hundreds of millions of dollars into vaccine research and commercialization, as part of an effort to wipe out global scourges as well as defend against biological agents that could be used as bioterrorism weapons. Further, an affluent middle class that can afford medications has emerged in some developing nations, widening the market. As a result, the biotechnology industry is taking a closer look at treating communicable illnesses, and Colorado's schools and companies stand at the forefront of this infectious disease revolution.

Colorado State University in Fort Collins has a long history of infectious disease research; it is home to a Level-3 biocontainment lab and neighbor to the Division of Vector-Borne Infectious Diseases of the Centers for Disease Control. The university's microbiologists specialize in studying zoonotic infectious diseases, those transmitted to humans by animals or insects.

In 2005, the school was awarded a four-year, \$40 million federal grant to develop treatments and vaccines for bioterrorism agents and infectious diseases, such as plague and hantavirus. The award designates CSU as a "regional center of excellence," linking it with other universities, hospitals and companies in the Rocky Mountain region, and providing funding to test new ideas.

The grant, part of a federal effort to speed product development by fostering partnerships between universities and industry, was the single largest research award in the school's history.

At the same time, the school broke ground on a \$33 million regional biocontainment lab. The new building will more than double CSU's Level-3 lab space to 50,000 square feet, and provide FDA-certified "good laboratory practice" and "good manufacturing practice" facilities. These certifications must be met for companies to submit their products to the FDA, and their existence is the gateway to new product development.

"Fundamentally we're going to have the infrastructure and human resources to take basic discoveries into preclinical FDA testing situations," says CSU microbiologist Dr. Barry Beaty, who heads the center.

Companies across the country have already contacted Beaty to book time in the lab, even though it won't be finished until mid-2007. But the national interest, he says, will fuel significant economic development in Colorado.

"Our belief is that companies will eventually co-locate to Northern Colorado," he says. "This is a world center for research on these types of pathogens."

Other Colorado companies researching or manufacturing products to aid the fight against infectious diseases include Roche Colorado, Mycologies, RxKinetix and Windom Peak Pharmaceuticals.

One of the first companies to take advantage of the CSU center is **InViragen**, a two-year-old Fort Collins startup. The firm has licensed technologies from the Fort Collins-based division of the Centers for Disease Control and is working to commercialize vaccines for plague, West Nile virus and dengue fever.

Dengue has no cure, and leads to 10 million cases of dengue fever a year and as many as a half a million hospitalizations – mainly for children. The disease is transmitted by mosquitoes and can be caused by four different strains of an RNA virus. For a vaccine to be safe, it must neutralize all four strains, a challenge no manufacturer has met.

InViragen's most advanced vaccine is based on an attenuated strain of the dengue-2 virus, much as the

Near the end of 2005, privately held **Replidyne** filed its first new drug application with the FDA for Orapem. The Louisville company hopes Orapem will be approved to treat bacterial infections such as pneumonia, sinusitis and bronchitis, an \$8.5 billion market. The firm expects the FDA to respond by the end of 2006.

Orapem is a unique antimicrobial that, according to the company, in lab tests has shown promise against types of antibiotic-resistant bacteria. Further clinical studies are planned. Drugs similar to Orapem are delivered intravenously, but there has been no oral antibiotic of its type in the U.S.

"We feel Orapem has certain features that make it very attractive for the antibiotic marketplace," says Jill Clark, Replidyne's senior director of finance and administration.

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—Dr. Barry Beaty, Head of the Regional Center of Excellence



measles-mumps-rubella and yellow fever vaccines are based on safe modifications of virulent viruses. But here's the twist: scientists genetically engineered the safe dengue-2 backbone to contain antigens for the other three viral strains. The result is a vaccine shown to be safe and effective against dengue fever in mice and monkeys.

"We're excited for two reasons," says InViragen Chief Executive Officer Dan Stinchcomb. "First and foremost is the opportunity to save children's lives worldwide, and secondly, there is a significant commercial opportunity as well."

Stinchcomb founded InViragen after working in nearby Loveland at publicly traded Heska Corp. **Heska**, originally founded on research done at CSU, now holds more than 200 patents on animal diagnostics, therapies and vaccines. The 300-person company had product sales of \$65.7 million in 2004, and anticipates a growing market for its companion animal products such as its diagnostic instruments, feline respiratory disease vaccine and one-step diagnostic tests for canine heartworm and other diseases.

Forty miles south of CSU, three Boulder area firms have infectious disease programs in various stages of development.

"If Orapem were to be approved, it would be positioned as a unique, first-in-class drug."

The focus on antibacterial drugs was strategic, Clark says. While big pharmaceutical companies have largely ignored the anti-infectives market, it could provide attractive returns for a lean firm such as 57-person Replidyne. Investors agree: the company has raised \$121.5 million to date.

Much smaller **MicroPhage** has taken a different approach to antibiotic-resistant bacteria. The Longmont firm is developing a way to more rapidly identify these pathogens, helping doctors prescribe the correct drugs.

MicroPhage's name tells its story. The three-year-old company has found phages, or inert viruses, that infect particular bacteria. The virus then replicates within the bacteria, making it easy to identify their presence.

Researchers at the **Colorado School of Mines** first applied phages to bacteria in biological warfare research. MicroPhage spun out of the university in 2002, and turned its attention to *E. coli* and *Staphylococcus aureus*, bacteria prevalent in wound and blood-borne infections.

The company has raised \$3.55 million largely from Colorado-based angel investment groups such as CTEK Angels and Vail's Alpine Angels. With the money, it plans to run clinical trials of its E. coli and Staphylococcus aureus diagnostics this summer. If the results are good, MicroPhage will submit to the FDA in the fall.

"It's been exciting," says Marketing Manager Scott Conlin. "When I started it was just a few of us, and now we are 13 people. And we're on the cusp of having a product, and see that the technology works very well."

Many biotech entrepreneurs are motivated by a passion to save lives and the chance to strike it rich. Aktiv-Dry is an exception.

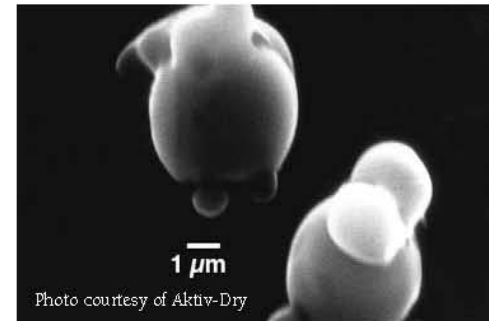
"We're not doing it for the money," says the company's co-founder Dr. Brian Quinn. "This is purely a humanitarian project for us."

Boulder-based **Aktiv-Dry's** technology and products are based on biochemistry work at the University of Colorado

in Boulder on how to make very fine, dry powders. The six-person company was founded in 2005 with a \$19.5 million grant from the Foundation for the National Institutes of Health. Through a worldwide collaboration of industry and research partners, Aktiv-Dry aims to develop a dry, inhalable measles vaccine that needs no refrigeration at a cost of about 25 cents a dose.

"Key to the success of this project is that we make very, very inexpensive inhalation technologies," Quinn says. He and his partners are experimenting with a delivery system that could be as simple a drinking straw through which the vaccine could be inhaled in one puff.

Measles remains a huge burden to the developing world, killing 2,000 people a day. Victims are mainly poor children who live in hot climates who cannot access the refrigerated-serum measles vaccine.



Infectious Diseases

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