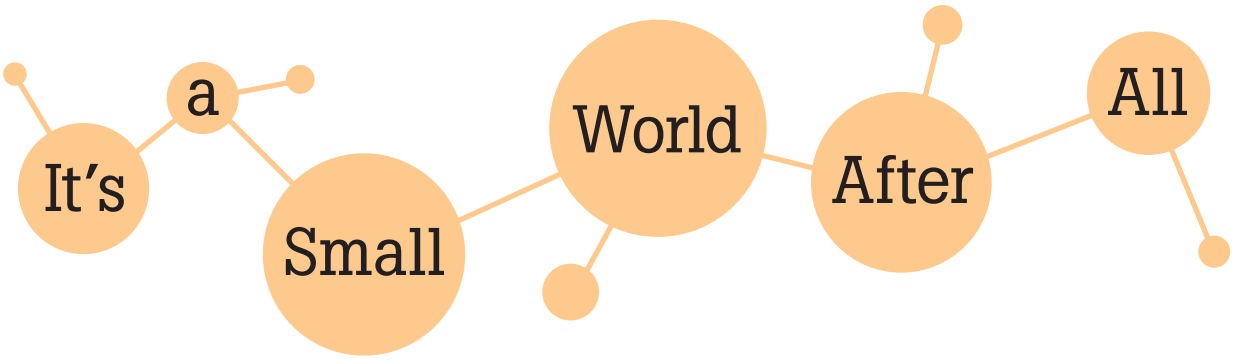

Nanotechnologies promise to revolutionize a swath of industries, including medicine.

In 2001 scientists discovered that a new class of molecules could turn off disease-causing genes in mammals, but one vexing problem remained: There was no way to send these advanced medications—which are fragile and require protection as they travel through the bloodstream—to human cells. For nearly a decade, many companies raced to develop a delivery system, but none succeeded.

That changed in March 2010, when results from a clinical trial conducted by Calando Pharmaceuticals, a subsidiary of Pasadena-based Arrowhead Research Corp., were published in the journal *Nature*. The report indicated that Calando had a method to shuttle this promising new type of drug into the cells of patients to silence a gene associated with cancer. Founded in 2004, publicly traded Arrowhead Research Corp. (NASDAQ: ARWR) is a holding company that forms, acquires, and operates portfolio companies to commercialize innovative nanotechnologies.

Calando's Phase I clinical trial used a drug candidate known as CALAA-01, which uses a cellular process called RNA interference, or RNAi, to block target genes by delivering a molecule known as short interfering RNA, or siRNA, into tumors. "It is a watershed event," says Dr. Mauro Ferrari, director of scientific strategy for Arrowhead Research, and professor of internal medicine and chairman of the Department of Nanomedicine and Biomedical Engineering at the University of Texas Health Science Center at Houston. "This is the first-ever clinical trial showing you can actually deliver these drugs. It completely changes what medicine is going to look like."

If its drug and delivery system were to get FDA approval, it could turn Arrowhead Research into a leading player in a potentially huge market. "We think we hold a very strong position here," says Christopher Anzalone, the company's CEO and president. "We're the only company to have silenced target genes in this way in humans."

But while the Phase I clinical trial for Calando Pharmaceuticals' drug delivery system has generated impressive early data, more patients are required to prove consistent effectiveness of the treatment. "We cannot yet claim we know it is going to be an acceptable therapy for humans," says Dr. Ferrari. "That is Phase II of the study." And even if that phase is a success, Calando must do a larger-scale Phase III trial with many patients to get FDA approval, he adds.

The New Molecular Order

Calando Pharmaceuticals is just one of Arrowhead's portfolio companies poised to capitalize on the promise of nanotechnology, a field that focuses on using tiny particles of matter to do

"We realized that high-quality science is critical but not sufficient to build a quality company."

ARROWHEAD'S COMPANIES

Calando: Enabling gene slicing in cancer patients

Unidym: Using carbon nanotubes for next-generation touch screens and LCDs

Nanotope: Developing therapies to reverse paralysis and regenerate cartilage

Leonardo Biosystems: Engineering multi-stage drug delivery systems

Artist's view of Calando's cancer-fighting nanoparticles traveling in the bloodstream.

everything from treating disease to making commercial electronic products. Arrowhead Research also owns Nanotope, which is moving toward clinical trials with a suite of product candidates that, if injected into human tissues, could potentially help the body regenerate itself from spinal cord injuries, Parkinson's disease, serious bone breaks, cartilage damage, and wounds. Another Arrowhead subsidiary, Unidym, is working with large partners such as Samsung to develop nanotechnology-enabled touch-panel electronics with stronger, more flexible screens. It expects to release its first commercial product later this year.

Arrowhead is something of an anomaly in nanotechnology, a field in which many startups concentrated on coming up with scientific developments first, then looked for ways to market them. The field took shape around the time that Nobel Prize winner Richard Smalley, a chemistry professor at Rice University in Houston, co-discovered a new form of carbon particle, C60, in 1985.

Smalley soon began investigating how carbon nanotubes—cylindrical carbon molecules with unusual strength, special electrical properties, and an extraordinary ability to conduct heat—were synthesized, igniting widespread interest in their potential uses in a wide range of industries. It is the intellectual property portfolio developed in the lab of Dr. Smalley, who died in 2005, that Arrowhead acquired to develop the technology that subsidiary Unidym is using in its electronics products.

"It is like building with Legos, using atoms and molecules."

Commercializing Breakthroughs

In the last decade, nanotechnology research has exploded because of an influx of federal funding from the Defense Advanced Research Projects Agency, the Department of Energy, and the National Institutes of Health. New discoveries powered a wave of startups that opened their doors in 2000 and 2001, after the dot-com bust. However, many of these new ventures couldn't find ways to market the technologies they developed. "A lot of those companies failed," says Anzalone.

When Arrowhead started six years ago, its founders were determined to create a new model. "We realized that high-quality science is critical but not sufficient to build a quality company," Anzalone says. Arrowhead looked for huge gaps in the marketplace and then acquired or built subsidiaries to address them, licensing intellectual property from a variety of universities and companies. To maintain tight control of operations, Arrowhead decided to stick with a small number of startups and to maintain a majority stake in Calando and Unidym. It also centralized key management responsibilities among the subsidiaries to keep costs down. Anzalone, for instance, is CEO of both Calando and Nanotope.

At the moment, interest in nanomedicine is high. According to Lux Research, an independent research and advisory firm focusing on emerging technologies, although overall venture capital investments in nanotechnology were down in 2009 because of declines in energy and environmental deals, venture capital investments in nanotechnology-driven health-care and life-sciences firms increased by 42%, attracting $404 million.

Arrowhead Research Corp. seems well positioned to capitalize on its technology. According to Douglas Jamison, CEO of Harris & Harris, a publicly traded venture fund in New York City that invests in nanotechnology companies, and co-editor-in-chief of *Nanotechnology Law & Business*, "They have the expertise to be successful on multiple fronts." ●