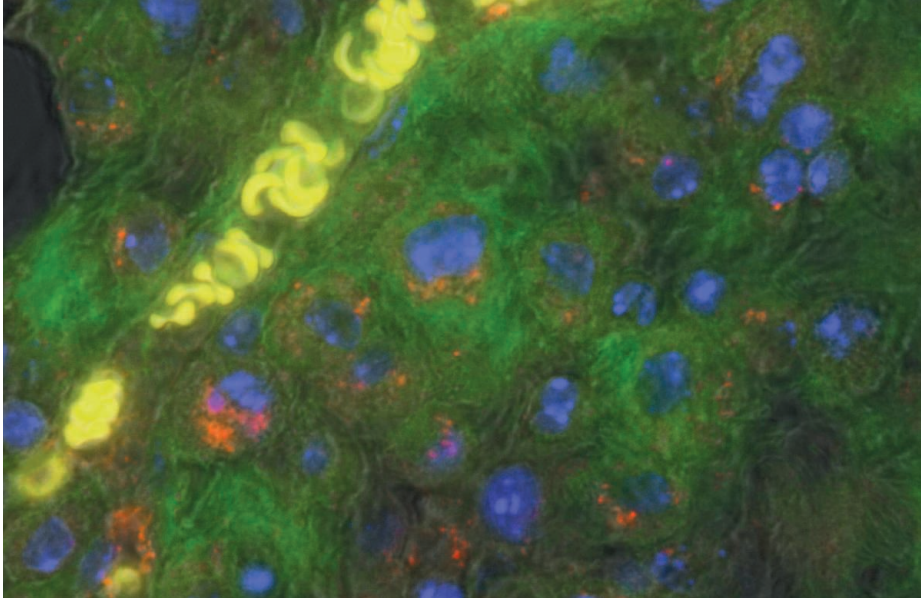

On target. Red blood cells (yellow) ferry nanoparticles (red) containing a chemotherapy drug to tumor tissue (green) in a mouse. Nanoparticles shield normal cells from chemotherapy toxins and deliver higher doses to tumors.

CREDIT: COURTESY OF CERULEAN PHARMA INC.

NANOTECHNOLOGY

Nanoparticle Trojan Horses Gallop From the Lab Into the Clinic

Experimental cancer treatments aim to deliver toxic medicines to cells inside packages that protect normal tissues and evade the body's immune system

In the early 1990s, Mark Davis's career was thriving. As a chemical engineer at the California Institute of Technology (Caltech) in Pasadena, Davis pioneered work on catalysts called zeolites. Then in 1995, his wife, Mary, was diagnosed with breast cancer and his research interests took a sharp turn.

After a mastectomy, Mary's oncologist recommended chemotherapy with a medicine nicknamed the Red Death because its toxic side effects are so debilitating. The surgery and medication worked: Mary's cancer is in remission. During a treatment, she made an offhand comment to Mark that there had to be a better way to design chemotherapy drugs so others wouldn't have to endure what she had to go through. He took the comment to heart and in 1996 turned part of his lab over to engineering nanoparticles to ferry toxins into tumor cells before they release their cargo. Now, 14 years later, one of Davis's compounds has been picked up by a Cambridge, Massachusetts–based company called Cerulean Pharma that is now in the middle of a midstage clinical trial to measure its safety and establish doses for combating various cancers.

Davis's novel nanoparticle-based medicine is not the only one under development. After many years of studies with cell cultures and animals, nearly a dozen nanoparticle-based drugs are in clinical trials, most of which aim at treating or diagnosing cancer. Many other compounds are progressing through preclinical studies and are nearing human trials. "There is a continuous pipeline" with numerous nanomedicine compounds at each stage of development, says Piotr Grodzinski, who directs the National Cancer Institute's Alliance for Nanotechnology in Cancer in Bethesda, Maryland. Grodzinski, Davis, and others underscore that it will require several more years of testing to determine whether the compounds are safe and effective. However, Davis says, "I'm very optimistic. I think the potential is very high to have some good results."

That would be welcome news in the fight against cancer. Despite a decades-long "war" on the disease, the number of people diagnosed remains stubbornly high. In the United States alone, more than 1.3 million people this year will be diagnosed with cancer, and more than 550,000 will die from it. Overall, the rate of death among those who contract cancer has barely changed since 1950. There has been progress, Grodzinski acknowledges. Researchers know far more about the myriad different tumor types and about molecular hallmarks of some forms of the disease, and few novel treatments have earned widespread attention. Still, today most cancers are treated with the same blunt instruments of surgery, radiation, and harsh chemotherapy that oncologists have wielded for decades. And of the chemotherapies available to patients, many are as toxic to normal cells as they are to cancer cells.

Nanomedicines have the potential to change that, Grodzinski says, because unlike traditional medicines they can be engineered to optimize several different functions. To treat cancer, a medicine must not only kill tumor cells but also be soluble in water in order to travel through the bloodstream; it must evade immune cell sentries and avoid being cleared out by the liver or kidneys; and it must find its targets. Traditional medicines have to build all these functions into single molecules. Nanomedicines, by contrast, can divide them among different components. Particle surfaces can be tailored for solubility, friendliness to immune cells, and target-seeking ability, while the particles' cargoes can be tailored to kill tumor cells.

That was the hope, anyway, more than a decade ago when Davis and other researchers first looked into nanoparticle-based medicines. The field received widespread hype early on, and a handful of compounds made it all the way to market. In 2005, for example, the U.S. Food and Drug Administration approved Abraxane for treating metastatic breast cancer. The compound is simply a conventional anticancer compound called paclitaxel—better known by its trademarked name, Taxol—linked to a common blood protein called albumin. The albumin shields the paclitaxel, increasing its solubility and circulation time and giving it a greater chance of winding up in tumor cells. In addition to proving effective in fighting metastatic breast cancer, Abraxane is now in a phase III clinical trial for treating advanced lung cancer and in phase II trials against pancreatic cancer and melanoma. A handful of other compounds, packaged in lipid vessels called liposomes or combined with biofriendly polymers, have also made it to market. Those successes have the field booming. Grodzinski says more than 50 companies are developing nanoparticle-based medicines as diagnostics and treatments for cancer alone; 34 of them formed in the past 4 years.

Most early successes have been very simple drug carriers; many next-generation nanoparticles are more complex. In December, for example, Bind Biosciences in Cambridge, Massachusetts, expects to launch a phase I clinical trial of nanoparticle carriers made from a trio of biodegradable polymers abbreviated PLA, PLGA, and PEG. PLA and PLGA are the polymers currently

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Some Nano-Oncology Drugs in Clinical Trials

COMPANY	AGENT	INDICATION	STATUS
Cerulean Pharma	Cyclodextrin NPs/Camptothecin	Various cancers	Phase 2
Calando Pharmaceuticals	Cyclodextrin NPs/siRNA	Solid tumors	Phase 1
Alnylam Pharmaceuticals	Lipid NP/siRNA	Liver cancer	Phase 1
BIND Biosciences	PLGA/PLA NPs/Docetaxel	Prostate cancer and others	Phase 1, Dec. 2010
Memgen	Adenovirus NPs/Tumor necrosis Factor (TNF)	Chronic lymphocytic leukemia	Phase 1
CytImmune Sciences	Gold NP/TNF	Solid tumors	Phase 1
Nanospectra Biosciences	Gold-coated silica NPs	Head and neck cancer	Phase 1

On trial. Several first-generation nanomedicines have already made it to market. Now, more than 50 companies are working to bring second-generation nanomedicines to market. A dozen such nanoparticles (NPs) are in clinical trials, most for treating, imaging, and diagnosing cancer.

used to make biodegradable sutures; PEG helps shield the particles from being recognized and cleared by immune cells. The combination was originally developed by Robert Langer, a chemical and biomedical engineer at the Massachusetts Institute of Technology, and colleagues. In recent work, Langer's team incorporated the anticancer compound docetaxel into the PLGA polymer matrix and added a targeting molecule that seeks out prostate-specific membrane antigen, a protein expressed on the surface of prostate cancer cells and other types of solid tumor cells. According to Bind's CEO Scott Minick, animal trials showed that the combination of the targeting compound and slow release of the docetaxel by degrading nanoparticles increases the tumor cell concentration of the anticancer drug 20-fold over docetaxel packaged in conventional liposomes. Moreover, Langer notes that the byproducts of the polymer are lactic acid and glycolic acid, naturally occurring substances safe to the body.

Other groups are working on variations on the strategy. Davis's and Cerulean's particles, for example, are engineered to degrade over time while leaving their building blocks intact. The shell of the particles, Davis explains, is made from sugars called cyclodextrins coated with PEG. These sugars contain hydroxyl groups that bind readily with water, making them—and the particles—highly soluble. But once they are inside tumor cells, the acidic environment there breaks the cyclodextrin particles and PEG apart, releasing an anticancer compound called camptothecin. The remaining fragments of the cyclodextrin are small enough to be cleared by the cells and the kidney. In August, at the American Chemical Society meeting in Boston, Cerulean researchers reported that initial results from a phase I trial showed that patients tolerated the compound well, and in several patients with advanced, progressive cancer, the disease stabilized for more than 6 months. Those results are encouraging, says Cerulean's senior vice president for research and business operations, Alexandra Glucksmann, because previous trials showed that giving patients camptothecin alone was too toxic. "This gives us the opportunity to rescue drugs that have failed before," Glucksmann says.

Nanoparticles are also being harnessed for less-traditional therapies. Numerous teams are using them to package tiny snippets of specific RNA molecules, in the hope that they can enter tumor cells and kill them by binding to the cells' own RNA molecules required for building essential proteins. This strategy, known as antisense, became a white-hot field in the early 2000s, when numerous teams developed antisense RNAs to block proteins critical to a variety of diseases. Numerous clinical trials using this strategy to kill cancer cells failed, however, primarily because researchers injected antisense RNA directly into patients' bloodstreams, where it was quickly chopped up by enzymes and cleared. "For RNA, nanoparticles are enabling, because delivery is such a key issue," Langer says.

An early clinical trial underscores this hope. In the 15 April issue of *Nature*, Davis and researchers at Calando Pharmaceuticals in Pasadena, California, and several other institutions reported the first results from an initial human clinical trial with nanoparticles packed with RNA designed to target melanoma tumor cells and interfere with critical protein production. The RNA-packed nanoparticles readily penetrated tumor cells, where they blocked the RNA target for a gene called *RRM2* that cancer cells need to multiply. The trial wasn't intended to gauge the particles' efficacy, but Davis says the early results look promising.

A very different approach to making nanoparticles may also soon revolutionize the way common vaccines are made and delivered. The work builds on progress by Joseph DeSimone and colleagues at the University of North Carolina, Chapel Hill, in using computer chip manufacturing techniques to make nanoparticle medicines. DeSimone's group came up with a sort of nano–cookie cutter approach to mold virtually any organic compound into nanoparticles of whatever size, shape, and stiffness they want. Along the way they found that making such changes yielded big results. Stiff nanoparticles injected into animals, for example, are cleared within as little as 2 hours. But soft, flexible ones circulate for 93 hours. Similarly, cylindrical particles have a knack for getting inside cells far more readily than spheres do. In animal studies, DeSimone says, as many as 15% of the particles they inject can find their way inside tumor cells, compared with about 5% for conventional spherical liposomes.

DeSimone recently launched a company called Liquidia to commercialize the technology. Liquidia is working to deliver particles packed with anticancer drugs and RNA. But in an initial clinical trial, likely to begin later this year, the company intends to deliver particles shaped like pathogenic bacteria to carry influenza proteins already used in vaccines. Animals injected with pathogen-shaped particles produce antibody titers as much as 10 times as high as animals dosed with conventional vaccines, DeSimone says. Working with flu proteins that are already part of conventional vaccines could also help Liquidia get its initial vaccines to market more quickly. "We think it's just a beachhead" and that many other products will soon follow, DeSimone says. **–ROBERT F. SERVICE**

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sciencemag.org
Podcast interview with author Robert Service.

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