The most common malignant brain tumor, glioblastoma multiforme (GBM), is also the most intractable and lethal. Even the most aggressive therapies barely slow its devastating progress — 96 percent of patients die within five years of diagnosis. Since more than 15,000 new cases of GBM are diagnosed in the United States every year, researchers and doctors are eager to find better ways of treating the disease.

One of the most promising new approaches has been developed in the Yale lab of W. Mark Saltzman, PhD, the Goizueta Foundation Professor of Biomedical Engineering, Chemical & Environmental Engineering & Physiology. In a breathtaking feat of biomedical engineering, Dr. Saltzman and colleagues, Dr. Toral Patel and Dr. Jiangbing Zhou, have devised a way to load anti-cancer agents onto nanoparticles and deliver them in high concentrations, via catheter, directly to the parts of the brain where the chemotherapy is needed, and also to regions of the brain that current therapies do not reach. The particles measure about 70 nanometers — smaller than the spaces between cells.

This brand-new method of transporting drugs into the brain will soon move from Dr. Saltzman's lab to the Brain Tumor Program at Smilow Cancer Hospital at Yale-New Haven, co-led by Dr. Saltzman's clinical partner, Joseph Massa Piepmeier, MD, the Nixdorff-German Professor of Neurosurgery. Drs. Saltzman and Piepmeier are now applying for FDA approval, and they expect clinical trials to begin within a year.

Dr. Saltzman's innovation is a sharp departure from current therapies for glioblastomas, including his own earlier designs. Before coming to Yale he worked on a drug delivery system now marketed as Gliadel®, a biodegradable polymer wafer packed with drugs that surgeons implant in the brain. The wafer slowly releases the drug. The method was an advance in treatment and remains in common use, but like every other therapy for GBM, its effect on survival rates has been slight.

"The problem with it," said Dr. Saltzman, "is that because of the dynamics of how drugs migrate in the brain, the drug can't penetrate very far from the site of the implant and get to everywhere it's needed."

To build a better way of delivering drugs, Dr. Saltzman decided he needed to radically shrink the drug-carrying wafer (about the size of a dime) to a size that could penetrate the brain. The literature suggested that the required measurement would be somewhere between 100 and 120 nanometers. In fact, after many experiments, Dr. Saltzman and his research team discovered that even this infinitesimal size was too large by 40 percent. They needed to create particles no bigger than 60 to 70 nanometers, including their cargo of drugs. They succeeded. The resulting degradable nanoparticles are the size of a virus — small enough to slip between brain cells.

"They can be pumped into the brain through catheters placed wherever the surgeon selects," Dr. Saltzman explained. "A technique called convection-enhanced delivery allows you to create fluid flow, which sweeps the nanoparticles deeper into the brain. When the infusion stops, the nanoparticles are still there, and they keep releasing their agents."

"Instead of giving someone a pill or injecting something in a vein and having it circulate," said Dr. Piepmeier, "you can put the drug in the highest concentration precisely where the tumor is invading the brain. This also minimizes toxicity and side effects."

Dr. Saltzman also wanted to design a delivery system that neurosurgeons could control and manipulate to do the most good for patients. That meant giving the surgeons a way to see what was happening in the brain during the infusion. "So we created particles that they can image by MRI to see if the particles are going where they should, at the right dose and volume," said Dr. Saltzman. At Smilow Cancer Hospital, he pointed out, the neurosurgical operating rooms are equipped with MRIs, which allows this imaging to be done during surgery.

This new system offers many other advantages as well. No incision is required, which also decreases the chance of complications such as infection. The infusion time is shorter — 30 minutes instead of two to six days — and the duration of drug release is much longer (more than 50 days).

If the initial trials confirm that the particles can be controlled, distributed, and imaged, and that they release their cargo of drugs slowly over time, then patients with GBM will certainly benefit: their therapy will become less invasive and onerous, and their prognosis likely will improve.

"But the long term benefits could be even bigger," said Dr. Saltzman. If the clinical trial proves that nanoparticles carrying conventional chemotherapy can be deployed to fight brain tumors, he said, the broader applications could benefit patients with many other cancers. Dr. Piepmeier noted that it could be used to deliver local therapy to any solid tumor in the liver, breast, prostate, lung, or pancreas. "With other liquid agents," he said, "once you stop infusing, it's gone. But these particles reside at the site and persist for several weeks, so you get a much more robust and sustained release." The technique also opens possibilities for loading the particles with biological agents or therapies focused specifically on a tumor's genotype.

"Theoretically we could deliver whatever agent we want," said Dr. Saltzman. "We just have to figure out how to put that agent into the polymer."

In a breathtaking feat of biomedical engineering,

Dr. Saltzman and his colleagues have devised a way to load anti-cancer agents onto nanoparticles and deliver them in high concentrations, via catheter, directly to the parts of the brain where the chemotherapy is needed, and also to regions of the brain that current therapies do not reach.