

# CytImmune Banks on Gold Nanoparticles

## Clinical-Stage Firm Delivers TNF- $\alpha$ to Tumors with Proprietary Colloidal Gold System

*Ilene Schneider*

**C**ytImmune Sciences ([www.cytimmune.com](http://www.cytimmune.com)), a clinical-stage biopharmaceutical company based in Rockville, MD, is attempting to use nanotechnology to change the way we treat cancer, according to cofounder, president, and CEO Lawrence Tamarkin, Ph.D. "Our technology is designed to treat cancer medically first and then surgically intervene, thus reducing hospital stays and costs and improving the quality of life of the cancer patient."

When Dr. Tamarkin founded the company in 1988 along with Giulio F. Paciotti, Ph.D., currently vp of research and development, they intended to set up a diagnostic assay company. In working with colloidal gold particles to develop antibodies, they discovered that the gold particles were safe to use in drug delivery.

Colloidal gold had been used since the 1930s to temporarily relieve joint inflammation associated with rheumatoid arthritis. CytImmune observed that animals injected with cytokines exhibited strong toxicological responses, whereas, animals receiving injections of cytokines bound to colloidal gold did not. This observation led to the conclusion that colloidal gold may be a universal, clinically safe, commercially sound drug/gene delivery system.

A 1999 grant from the National Institute of Standards and Technology enabled the company to begin its work. The idea of binding colloidal gold particles to tumor necrosis factor alpha (TNF- $\alpha$ ) to target tumors directly and limit the exposure of healthy tissues and organs to this cytokine came in the mid-1990s.

What evolved was a company with a core focus on the discovery, development, and commercialization of multifunctional, tumor-targeted therapies. Based on an R&D strategy that harnesses the unique properties of gold nanoparticles, CytImmune is developing a pipeline of proprietary drug candidates that bind potent anticancer agents—whose toxicity profiles currently prevent or severely limit their clinical use—to its patented colloidal gold tumor-targeting nanotechnology.

The company has more than 60 issued and pending patents for its colloidal gold nanotechnology and 11 issued and pending patents for its monoclonal antibody (mAb) technology in the U.S., EU, Japan, and Canada.

TNF- $\alpha$  was discovered in 1975, and Genentech made recombinant TNF- $\alpha$  in 1985. Clinical testing during the next decade showed that there was no efficacy for TNF- $\alpha$  at a safe dose. While regarded as an effective anticancer agent, when administered systemically, TNF- $\alpha$  attacks endothelial cells, causing hypotension

that may lead to organ failure, Dr. Tamarkin explains.

Between 1992 and 2004, isolated limb perfusion (ILP) studies in Europe demonstrated that TNF- $\alpha$  could be administered safely if the blood supply were isolated. Using mouse cancer models, CytImmune discovered that attaching TNF- $\alpha$  to gold nanoparticles is a safe and effective targeted drug delivery formulation, Dr. Tamarkin explains.

The mechanism underlying CytImmune's tumor-targeted delivery of TNF- $\alpha$  is attributable to the size and composition of the nanoparticles, regardless of the tumor type, Dr. Tamarkin notes. The therapeutic payload travels safely through the bloodstream, avoiding immediate immune detection and arriving at the targeted disease site.

### Lead Compound

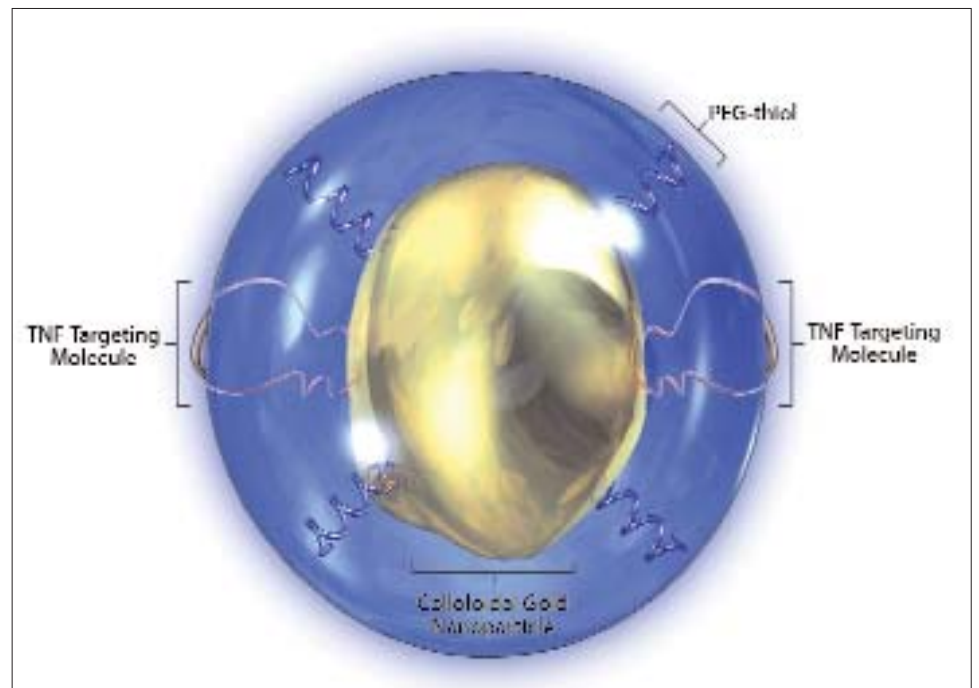
Aurimune™ (CYT-6091), the company's lead drug compound, simultaneously binds PEG-Thiol and recombinant TNF- $\alpha$  to colloidal gold nanoparticles. The result is an anticancer agent that is invisible to immediate immune detection, thereby avoiding uptake by the liver and spleen, and targeting delivery of TNF- $\alpha$  directly to tumor sites at acceptable toxicity levels, Dr. Tamarkin says.

"Each element serves a unique purpose," he adds. The colloidal gold limits the distribution of the TNF- $\alpha$ , so that every nanoparticle exerts its bioactivity in the right place. PEGylation—treatment with polyethylene glycol masks the colloidal gold particles from immediate immune recognition and primarily prevents uptake in areas of the body other than tumors.

The PEG-Thiol hydrates each nanoparticle of gold. At 27 nanometers, the gold particles are small enough to traffic safely through the body, but too big to exit through the circulation system. Thus, Aurimune "primarily and preferentially exits the circulation through leaky, newly formed vasculature at tumor sites, selectively passing through gaps in blood vessel walls called fenestrations," according to Dr. Tamarkin.

"The ideal cancer nanomedicine is built like a three-legged stool," he says. "By design, it avoids uptake by the liver and the spleen. By design, it targets tumors in two ways—passively through leaky blood vessels and actively by binding to tumor-associated receptors like those on endothelial cells. Finally, nanomedicines must be manufactured to defined specifications by a process that is simple, robust, characterizable, and cost-effective.

Because Aurimune attacks blood vessels that support solid tumor growth, it may be used in combination with chemotherapies and improve overall efficiency, explains Dr. Tamarkin. "By pretreating a patient with Aurimune, clinicians may destroy intra-



**Design of CytImmune Sciences' colloidal gold-based cancer nanomedicine Aurimune™ (CYT-6091): Both TNF- $\alpha$  and thiolated polyethylene glycol (PEG-Thiol) are independently bound to the surface of 27 nm colloidal gold particles. PEG-Thiol serves to hydrate each particle (the blue circle), preventing immediate immune recognition, while TNF- $\alpha$  serves as a tumor-targeting ligand and as the therapeutic payload.**

tumor pressure gradients, causing a leak in the tumor vasculature and allowing subsequent chemotherapies to work more effectively. We believe we can systemically deliver Aurimune and follow it with chemotherapy, potentially offering better results than either treatment alone."

Recently completed Phase I trials of Aurimune, conducted at and by the NCI, showed that the drug was well tolerated, with no drug-related serious adverse events, despite treatment with doses far exceeding the previously established maximally tolerated dose for TNF- $\alpha$  alone, while showing gold nanoparticles at tumor sites. Data demonstrated that Aurimune safely and systematically delivered TNF- $\alpha$  in humans far beyond concentrations attained in previous studies—and in an amount equal to that used in ILP where 60–85% cancer response rates have been observed, Dr. Tamarkin reports.

Slated to begin in 2009, the Aurimune Phase II clinical protocol is designed to mimic the ILP protocol. Combining Aurimune with chemotherapy, these studies will treat pancreatic cancer, melanoma, soft tissue sarcoma, ovarian, breast, and non-small-cell lung cancer patients.

AuriTol, another nanomedicine under development by CytImmune, is currently in preclinical development. It is based on a formulation of an analog of paclitaxel and TNF- $\alpha$  bound to CytImmune's nanoparticle. This formulation has the potential to offer improved efficacy and a reduction of side effects relative to current forms of paclitaxel, according to Dr. Tamarkin. AuriTol Phase I trials may begin in early 2010.

In addition, CytImmune has developed a method to generate fully human monoclonal antibodies using lymphocytes from normal donors. The technology uses the properties of gold nanoparticles to create an antigen presentation system that loosely mimics

the natural presentation of antigens by cells. CytImmune has begun proof-of-principle studies with antibodies against multiple components of the interleukin-2 receptor to block the production of T-cells for the treatment of leukemia and lymphoma.

"Our goal is to suppress the growth of cancer cells by disrupting the blood vessels that support cancer growth, and thus keep cancer at bay with a less invasive, less traumatic procedure," Dr. Tamarkin concludes. "Cancer should be a chronic illness, not a death sentence." **GEN**

## At-a-Glance

### CytImmune Sciences

#### Location

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#### Phone

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#### Website

[www.cytimmune.com](http://www.cytimmune.com)

#### Principals

**Lawrence Tamarkin, Ph.D.**  
founder, president & CEO

**Giulio Paciotti**  
founder and vp, R&D

#### No. of Employees

16

#### Focus

The company uses nanotechnology to target tumors with PEGylated colloidal gold.