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Innovations

Genta Incorporated

Gallium Therapeutics: Take Two

About 20 years ago, researchers at Memorial Sloan-Kettering Cancer Center began publishing a series of papers describing the therapeutic benefits of gallium nitrate in the treatment of lymphoma and cancer-related hypercalcemia. What followed was a circuitous path from FDA approval, a brief stint on the market in the early 1990s for hypercalcemia, then a demise into therapeutic oblivion. Enter Raymond P. Warrell, Jr., MD, one of the original MSKCC gallium nitrate researchers, and now Chairman and CEO of Berkeley Heights, New Jersey-based Genta Incorporated. Warrell and colleagues are breathing new life into the old IV gallium formulation—known as Ganite—as well as developing a new oral product, all for treatment of cancer and cancer-related bone disorders.

Genta was founded in 1988 as a spin-off from the diagnostics company Gen-Probe. It was founded on the antisense technology behind its lead agent, Genasense, an anti-Bcl-2 drug now in several phase III clinical trials. Currently, about 90 employees work on four main technology programs, "but our unifying program is not technology," says Warrell. "Instead it's market based, focusing on oncology."

Long Walk in the Desert

The gallium nitrate story dates back to the 1970s, when NCI researchers discovered anticancer activity in several elements in group 111A from the periodic table of elements, which includes gallium. Gallium was found to be the most active, least toxic, and the only element with efficacy when given at a site remote from the tumor.

In the early 1980s, Warrell and colleagues demonstrated good activity with gallium nitrate against non-Hodgkin's lymphoma (NHL). "But we noticed an interesting side effect in our anticancer studies with gallium," Warrell recalls. Calcium levels in blood and urine began dropping in gallium-treated patients. "We interpreted that to mean it was probably having a direct effect on bone." This was proved and became the basis for several patents. The development focus then branched to include study of bone-sparing therapy in cancer patients.

IV gallium nitrate (Ganite) did make it to market in 1991 for hypercalcemia therapy but was quickly displaced by the big boys of bone metabolism therapy, the bisphosphonates, including Didronel (etidronate) and Aredia (pamidronate). Eventually, Ganite was removed from the market, with rights reverting back to MSKCC.

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Gallium Inhibits Bone Resorption

Under normal metabolic circumstances, bone generally forms and breaks down in equilibrium, a process called bone remodeling. But in cancer and certain other metabolic bone disorders, bone loss is accelerated. For example, in hypercalcemia, a life-threatening disorder affecting about 10%–20% of people with cancer, bone loss is so severe that the kidney becomes overwhelmed in its effort to remove excess calcium.

Gallium is reversibly absorbed in low levels into bone. It inhibits bone loss by interfering with the action of normal bone cells called osteoclasts that degrade bone by secreting acid onto bone surface. As the osteoclast secretes acid, small amounts of bone-bound gallium are liberated from the dissolved bone. The gallium then paralyzes the acid-producing proton pump of the osteoclasts. "The osteoclast doesn't die," says Warrell, "it simply can't dissolve bone due to the presence of gallium inhibiting that acid-producing pump."

IV Ganite for Hypercalcemia and NHL

Genta licensed the Ganite NDA and IND in 2000. "We intend to follow a two-track path with Ganite," says Warrell. They hope to relaunch the drug for its currently approved indication, hypercalcemia, but Warrell admits that market for first-line therapy is already well served by Novartis' Aredia (generic since December 2001) and now Zometa (zoledronic acid), approved in 2002.

Clearly the larger opportunity for Ganite is to track back into the anticancer indications. Toward that end, Genta is conducting a multicenter phase IIB trial now for NHL. The trial was recently launched at the Medical College of Wisconsin under the direction of Christopher R. Chitambar, MD. The drug is targeted for treatment in approximately 40 myelosuppressed patients who have relapsed on conventional therapy.

Nonmyelosuppressive

"The big advantage of gallium in cancer treatment is that it does not suppress bone marrow or cause a drop in white blood or platelet counts," says Chitambar, who has been studying gallium therapeutics for more than 20 years. "As a result, we're able to treat patients with lymphoma who may have low blood counts and cannot receive conventional therapy."

At the same time Warrell was publishing papers at MSKCC showing IV gallium was active in lymphoma,

then bladder cancer, Chitambar began studying gallium's transport mechanism and how it inhibits cancer-cell growth. He found that gallium binds to transferrin (a protein that transports iron) fairly strongly when it enters the circulation. The gallium-transferrin complexes attach themselves to the transferrin receptor, found in high levels on lymphoma cells. "This is a real benefit because you're getting the metal directly to the target," he says. Bladder cancer cells also have transferrin receptors. "We showed gallium targets cellular iron metabolism and inhibits ribonucleotide reductase, an iron-dependent enzyme responsible for synthesis of deoxynucleotide precursors, dNTPs, prior to DNA synthesis," says Chitambar. "Iron is critical for that enzyme activity, and gallium either displaces the iron or it blocks the utilization of iron by this enzyme."

"Ganite is fairly well tolerated, though hydration is a must," he says. In a previous NHL study with gallium nitrate, he found that about half of 14 heavily pretreated patients had a good response; 4 of whom had "impressive" responses. "I also found that when patients respond, they tend to respond rapidly," says Chitambar. "Sometimes even during treatment the masses will start shrinking."

Oral Formulation for Bone Metastases

Genta is also developing an oral gallium agent for prevention of bone loss in patients whose disease has metastacized to bone. The presence of cancer, either directly in the bone or remotely by the release of certain stimulating factors, induces osteoclast overactivity. "This accelerated activity breaks down bone very quickly," according to Warrell.

"We think we have a drug that is superior in efficacy to any of the bisphosphonates that currently exist," says Warrell. "It is essentially a new chemical entity, but ionic gallium is the active species," he says. Genta will clearly target comparative studies against the Novartis drugs for the bone metastases indication.

Genta may also target oral gallium for treatment of myeloma, a malignancy of the bone marrow. "If you can make the bone environment more hostile to the expansion of myeloma cells, you may prevent the dissolution of bone," suggests Warrell. This is the general idea applied to other cancers, like breast and lung cancers, where bone metastases are a common, complicating problem. "These people usually don't die from their bone metastases, but their fractures give them lots of pain and reduced mobility," says Warrell of the quality of life benefit he hopes oral gallium can deliver. IV Aredia, the most popular therapy used for bone metastases treatment with more than $750 million in annual sales, has already validated this idea over the last 10 years.

A Titan to Compete With

Genta shares the gallium therapeutics stage with South San Francisco, California-based Titan Pharmaceuticals. "Both groups, Genta and Titan, are working on oral gallium formulations, and it is a very exciting development," says Chitambar. "It will be a major stride."

Titan, formed in 1992, is developing its own oral gallium compound, gallium maltolate, discovered by Lawrence Bernstein at Stanford University, who then formed GeoMed, Inc. to develop it. "We licensed it after it had proven good oral bioavailability and safety," says Frank H. Valone, MD, Executive Vice President, Clinical Development and Regulatory Affairs at Titan. Similar to Genta, Titan's focus is to develop an oral gallium therapy for cancer and bone damage produced by cancer. The company is now doing an expanded 30-patient phase I trial in prostate and bladder cancers, myeloma, and lymphoma. "We've found a dose where we can achieve sustained blood levels for therapeutic efficacy," says Valone, "and we have no known safety issues so far."

"We think gallium will probably be effective for prevention of bone pain and fractures, much the way bisphosphonates are," says Valone. And like Warrell, Valone believes the oral formulation will be the key for competing with the bisphosphonates in the bone metastases market. "We aren't limited in our ability to deliver gallium therapeutically now," he says. "In our case, the availability of the maltol complex gives us a chance to readdress the utility of gallium."

Whether it's on the East Coast or the West—and Chitambar is familiar with both gallium ventures—researchers are eager to investigate an oral formulation. "The pharmacokinetics and side effects are probably going to be different with an oral drug," says Chitambar, "It will first need to be absorbed from the gut, transferred to the circulation to bind to transferrin, and then home in on transferrin receptor-bearing cells." He hopes that in this way an oral formulation may get to its target in a more physiologic way, "similar to other metals such as iron." Chitambar guesses that to be effective any oral gallium will require daily or near-daily administration for several weeks. Whether in IV form or oral, or complexed as a salt or sugar, gallium appears to be a welcome therapy with a ready and patiently waiting market in the cancer-treatment arena.

***Chemistry & Biology* invites your comments on this topic. Please write to the editors at chembiol@cell.com.**

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