



## Radiotherapeutics: New Hope for Treating Metastatic Disease

Along with key academic and pharmaceutical partners, Siemens is leading the charge to improve and expand the effectiveness of radiation to treat rare neuroendocrine tumors with a revolutionary new type of targeted radiotherapy used in conjunction with SPECT imaging technology.

By Tim Friend

The treatment of cancers of the neuroendocrine system in children and adults is being revolutionized by Molecular Insight Pharmaceuticals, Inc. in collaboration with doctors at Duke University, Durham, NC, USA.

The focus is on a new, ultrapure form of a proven radiopharmaceutical developed by Molecular Insight Pharmaceuticals of Cambridge, MA, USA. The company has developed an elegantly simple, yet pioneering, technology for producing a highly-concentrated, targeted radiotherapeutic with iodine-131 T 1 (I-131). Cancer treatment with radioactive iodine has been conducted for decades for thyroid carcinoma, and iodine-131-labelled molecules, and has been used to target other types of tumors for decades. Radioactive iodine combined with a targeted molecule called meta-iodobenzylguanidine (MIBG) has become the standard approved therapy for neuroendocrine tumors in Europe. MIBG is a compound originally developed by the University of Michigan in the USA. MIBG therapy is easily monitored using single photon emission computed tomography (SPECT). Because SPECT imaging technology is already widely available in

hospitals, adopting the new ultrapure radiotherapy to clinical practice, if proven effective, will be simple and easy. Standard Siemens SPECT technology clearly images tumors that take up the standard and ultrapure forms of MIBG. Patients with tumors treated by I-131 MIBG could be imaged at any medical facility with a SPECT scanner.

Molecular Insight's proprietary technology, called Ultratrace™, is being used to radiolabel this same MIBG molecule with iodine-131, but in a way that produces a much purer, higher specific activity product, which means that it can target and deliver a greater amount of therapeutic radiation to a greater percentage of tumor cells. The name of the new radiotherapeutic under development is Azedra™, and John Babich, PhD, President and Chief Scientific Officer of Molecular Insight Pharmaceuticals, is excited about its potential.

"One of the major benefits of Azedra really has to do with the fact that aside from surgery, radiation is the most effective way to treat a cancer," says Babich. "So we asked ourselves, 'How can we optimize radiotherapy for cancer patients?'"

With the conventional way of delivering radiotherapy – external beam radiation – you cannot eradicate tumors that have spread through the body. However, a systemically administered, highly targeted radiotherapeutic has the ability to reach these tumors. The promise is that you can use these products to go after metastatic disease."

### An Improved Ratio of 'Hot' to 'Cold' Molecules

MIBG is a synthetic version of the body's natural hormone norepinephrine (also known as noradrenaline). Its nerve cells produce and release from the adrenal gland in response to stress and low blood pressure. MIBG molecules mimic natural norepinephrine and accumulate in tumors selectively because they are drawn in by the same receptor or transporter on the tumor's cell surface that controls epinephrine (or adrenaline) and norepinephrine reuptake. Tumor dosimetry is calculated from the SPECT data which show the tumor uptake patterns. This selective uptake of MIBG makes it a prime candidate for delivering therapeutic radiation to



Norman LaFrance (left) and John Babich (right) believe in radiation as one of the most effective ways to treat cancer.

neuroendocrine cancers. However, tumor cells can only absorb a certain amount of MIBG molecules before becoming saturated. That the maximum number of MIBG molecules are radiolabeled is critical to efficient and successful delivery of therapeutic radiation to a tumor. Until now, this limit on the amount of radiation that can be delivered through MIBG uptake has been the major barrier to more effective therapy.

For years, patients in Europe with neuroendocrine tumors have been treated with MIBG radiolabeled with iodine-131. The standard method of manufacturing this radiotherapy results in a high percentage of MIBG molecules that essentially contain no radioactive potency and compete with radiolabeled molecules for scarce space on the tumor receptor sites. Ultratrace technology represents a radical improvement because it reduces the number of nonradioactive molecules by 1,000-fold, says Norman LaFrance, MD, Chief Medical Officer of Molecular Insight Pharmaceuticals.

In technical terms, MIBG molecules that contain therapeutic radiation are considered 'hot.' Nonradiolabeled MIBG mole-

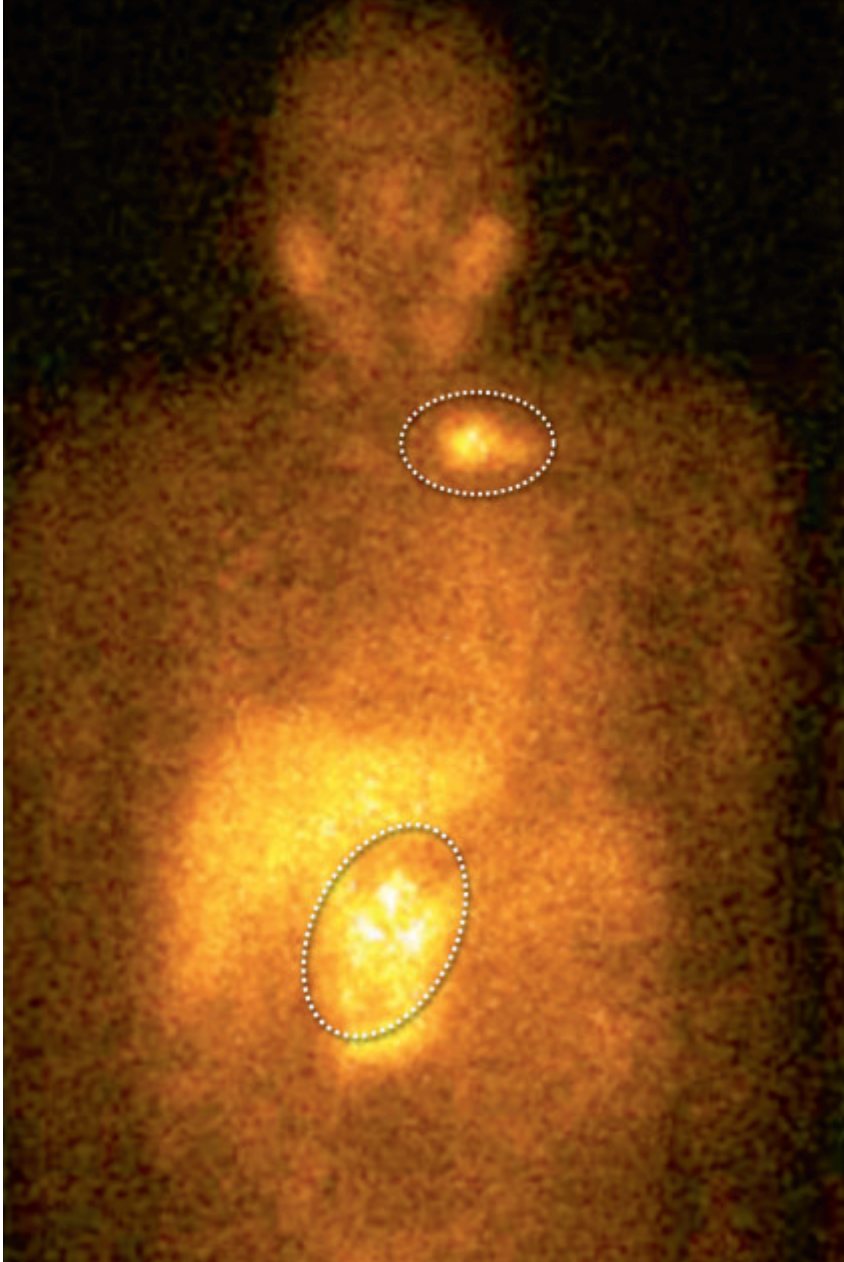
cules in the currently available product are considered 'cold' molecules, which essentially are contaminants. These 'cold contaminants' reduce the effectiveness of therapy and may produce unwanted side effects. Babich says Ultratrace technology delivers therapeutic radioactivity into a higher number of MIBG molecules in any given dose by eliminating these cold contaminants. Animal studies conducted in Europe have clearly demonstrated that tumors absorb Azedra with greater efficiency. The results were so promising that Phase I clinical trials in patients with neuroendocrine tumors have begun at Duke University.

R. Edward Coleman, MD, of Duke University is leading the new human clinical trials. Coleman is one of the leading nuclear medicine specialists in the United States for treating patients with neuroendocrine tumors. Until Azedra became available to him in April for use in a Molecular Insight-sponsored clinical trial, he had been using the previous form of MIBG and iodine-131.

"I have treated neuroendocrine tumor patients with MIBG here at Duke for 15 years – more than 350 of them – so we

have a lot of experience with it," Coleman says. "I'm very optimistic that this radiotherapeutic will help a significant number of patients, and will be more effective than the previous product that we were using." Neuroendocrine tumors develop in the body's endocrine and nervous systems. These cancers exploit natural hormones involved in the body's flight-or-fight syndrome. No currently approved therapies exist in the United States for treating these types of cancers, which include pheochromocytoma, carcinoid tumors, and neuroblastoma.

"We recently began the first stage of a planned Phase I/II safety, dose ranging and efficacy clinical trial with Azedra in adults at Duke University, in which an estimated 12 to 18 patients at four to six centers in North America will participate," LaFrance says. "This trial will allow us to define the therapeutic dose during Phase I and the efficacy of Azedra during Phase II in patients with pheochromocytoma and paraganglioma. The anticipated endpoints will include tumor response measures as well as safety. If results of these ongoing and anticipated trials are positive, we believe that the resulting data, together



Azedra transforms the known MIBG molecule into a highly targeted radiotherapeutic for neuroendocrine tumors that is free of unnecessary cold contaminants which may produce unwanted side effects and impede efficacy.

with data from our previous clinical trials, will provide a basis for us to file for regulatory approval in the United States." Those involved in the studies believe that delivering the highly concentrated dose of hot, radioactive therapeutic 'tumor killers' should be more effective than the currently available MIBG treatment. LaFrance and Babich believe that patients should experience fewer side effects, as well as greater tumor specificity than what is delivered with the currently available product. In laymen's terms, Azedra may deliver more bang for the buck. Siemens Venture Capital became involved and invested in Molecular Insight Pharmaceuticals at an early stage for a variety of reasons. "As the leading innovator in the

field, it makes sense for the company to help bring new agents to market that are compatible with our SPECT imaging equipment," said Dr. Andrew Jay, manager of the group's healthcare investing activities. "Additionally, Molecular Insight Pharmaceuticals has a unique combination of attributes that make it highly attractive. There is great innovative technology, a well-balanced management team with great experience, and a gigantic opportunity to improve care for patients around the world using an imaging technology that is extremely accessible. Those three factors usually make for exciting investments." MIBG scans are a very sensitive and accurate way to look for the spread of neuroblastomas and other neuroendo-

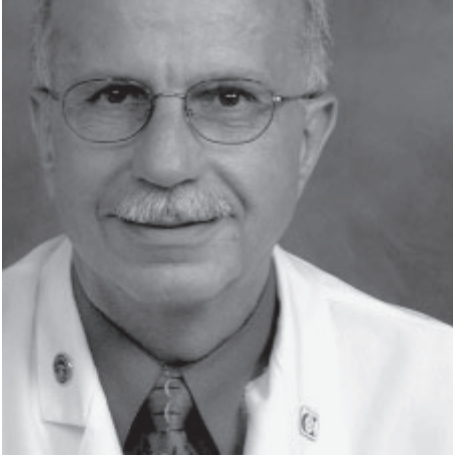
crine tumors. The idea of increasing the concentration of radioactive iodine in MIBG molecules for therapy is very exciting.

## The Trojan Horse for Tumors

"When you treat a patient with a radiotherapeutic, the concept is to maximize the delivery of radioactive molecules to the tumor," says Babich. "When designing a drug to hone in on a tumor, you have to select a target – hopefully one that is selective to the tumor, as is the case with Azedra. What we are targeting with Azedra is a norepinephrine transporter, which is a protein that recognizes adrenaline, or noradrenaline, and actually grabs it as it floats by, pulling it into the cell. Essentially, we send a Trojan horse version of adrenaline in the guise of radiolabeled MIBG, which gets pulled into the tumor as though it were adrenaline. This concept was pioneered by Professor Donald Wieland at the University of Michigan twenty years ago, and Molecular Insight now has a robust technology to optimize this therapeutic approach for a variety of neuroendocrine tumors."

Pheochromocytoma is a tumor of the adrenal gland in which too much epinephrine and norepinephrine are produced and released into the bloodstream, causing severe long-term effects by dramatically increasing heart rate and blood pressure. Pheochromocytomas occur as a single tumor or as multiple growths and usually arise in early- to mid-adulthood. Standard treatment is surgery to remove the tumor. However, surgery is not an option for patients who have tumors at multiple sites or who have tumors that have metastasized to other parts of the body. For these patients, only 50 percent survive beyond five years.

Neuroblastoma is a tragic childhood tumor of the developing peripheral nervous system. It is the most frequently diagnosed tumor in infants with the median age at diagnosis being two years. More than 90 percent of these cancers occur in children younger than five years of age. As many as 2,000 children are diagnosed with neuroblastoma each year in the United States and Europe. For advanced stages of the disease, the five-year survival rate is less than 60 percent. Patients with advanced stage four neuro-



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blastoma who are over one year of age have only a 25 percent probability of disease-free survival. Because the prognosis for patients older than one year of age with advanced tumors remains poor, a significant medical need for better therapy continues to exist for these children. In the United States, no approved therapies exist for patients with advanced neuroblastoma. These children must often undergo multiple experimental treatments, which include the standard MIBG therapy approved in Europe.

The primary reason that no approved therapies exist in the United States is that neuroendocrine tumors are relatively rare, and thus, are of little interest to large pharmaceutical companies. However, Molecular Insight Pharmaceuticals recognized that more than 90 percent of adults and children with neuroblastoma and pheochromocytoma tumors – including those with metastatic tumors – are prime candidates for treatment with Azedra. Molecular Insight believes that this niche market is worth the expense and effort of developing the therapy.

### Ultratrace Technology: Keeping Radiotherapeutics on Target

Radiation therapy has a long history of effectively treating numerous cancers, especially solid tumors that cannot be removed with surgery. Between 50 and 60 percent of cancer patients undergo some form of radiation therapy in the course of their treatment. The field of molecular medicine, in which Siemens is a leading developer and supporter, is improving radiation therapy through the

use of targeted radioactive compounds that hone in on tumor cells. The challenge is developing the right molecule for the right target, such as MIBG for neuroendocrine tumors. Injectable targeted radiotherapeutics emit beta particles that travel only a very short distance within the body, delivering radiation primarily to tumor cells while sparing surrounding normal tissues. The more selective the delivery, the better physicians can kill tumors with very few side effects to the patient.

“We believe there is an opportunity to further improve many targeted radiotherapeutics through the application of our proprietary Ultratrace technology. Ultratrace is designed to refine the targeting capabilities of radiotherapeutics by providing ultrapure compounds that enhance delivery of therapeutic radiation to a tumor while reducing the potential risk of side effects from unnecessary, nonradioactive cold contaminants that are present in many current products and technologies,” LaFrance says. Ultratrace technology applied to the known MIBG molecule thus makes for purer concentrations of the targeted therapeutic product. The initial target market for Azedra is for the treatment of metastatic neuroendocrine tumors, such as the already mentioned pheochromocytoma, carcinoid tumors, and neuroblastoma. Azedra is designated as a Fast Track drug by the US Food and Drug Administration (FDA). The agency has also designated it as an Orphan Drug, a status designed by the FDA to facilitate the development of new therapies for rare diseases or conditions that affect fewer than 200,000 individuals in the United States. Additional criteria for

Orphan Drug status include the ability of a product to address a medical need where there are no other treatment options or to provide a significant benefit over other therapies. Currently, MIBG therapy is available in Europe. It is provided to patients in the USA on a compassionate-use basis. A number of studies conducted by various academic centers show that patients who were administered MIBG therapy in the end-stage of their disease, after they have relapsed from surgery or stopped responding to other experimental treatment, had a 40 percent response rate. Babich advises oncologists and others to whom these developments will be of interest to stay tuned to the Ultratrace platform technology. The company is already developing a new, concentrated, ultrapure product to target prostate tumors. If site-specific molecules similar to MIBG can be found that are specific to these and other solid tumors, the company has a chance to truly revolutionize the diagnosis, treatment, and monitoring of metastatic disease – an area in which little progress has been made in more than 40 years.

*Tim Friend, a USA Today reporter for 17 years, is now a freelance science and medical writer based in Alexandria, VA, USA. He is the author of Animal Talk: Breaking the Codes of Animal Language, and has just finished a second book on the discovery of a new life form on earth, titled The Third Domain: The Untold Story of the Archaea and the Future of Biotechnology.*