BY KIM RIBBINK

One Step AHEAD

Mitchell S. Steiner, M.D.

An apt descriptor for Mitchell S. Steiner, M.D., F.A.C.S., is a man ahead of his time. This character trait has helped him in his academic background, in helping patients, and in establishing a biopharmaceutical company focused on novel hormonal therapeutics for cancer, muscle wasting, osteoporosis, bone loss, as well as other serious conditions.

From his undergraduate days, the chosen path was molecular biology, which in 1978 was a field few had heard about. As a postdoctoral fellow, he conducted research in what was then a new area of medicine called gene therapy.

And thanks to the large level of knowledge and expertise he had gained during his years of study, in 1999 Dr. Steiner was appointed professor and chairman of the department of urology at the University of Tennessee Health Science Center.

An ability to think beyond current knowledge is what Dr. Steiner maintains makes great science and gives individuals an edge in their careers.

"It's important to have a prepared mind, to move forward in the direction where you think the future is going to go, and try to be 20 years ahead of everybody else," he says.

This progressive philosophy, which is vital to finding a unique path, is one that Dr. Steiner learned from his mentors Don Coffey, Ph.D., and Evelyn R. Barrack, Ph.D., while at Johns Hopkins, and it's something he carries with him today in all of his research.

"There's no point in doing research in an area that is already well-understood," he says. "It's important to find something new, because if you want to create your own universe the only way to do that is to delve into an area that no one understands anything about."

A researcher, practitioner, and now company leader, **Mitchell S. Steiner, M.D., F.A.C.S.**, has been committed to finding ways to tackle urologic diseases, such as prostate cancer, by thinking beyond the tried and tested and having the courage of his convictions.

The decision to forge ahead in what was a little-understood field — TGF beta in prostate — has put GTx Inc., the company Dr. Steiner founded in 1997 to discover, develop, and commercialize novel hormonal therapeutics for cancer and serious conditions related to men's health, in a strong position.

Thanks to Dr. Steiner's research efforts over the years, GTx has a drug, Acapodene (toremifene citrate), in late-stage clinical trials to treat the side effects associated with the standard prostate cancer treatment, Androgen Deprivation Therapy (ADT). (For more information, see box on page 74.)

And Dr. Steiner looks to keep GTx on the cutting edge by maintaining strong ties with academia through his ongoing work with the University of Tennessee.

"I think those connections are our strength," he says. "What makes our company a little different is how easily it can move in and out of academic circles; after all that's where new ideas are born."

INQUIRING MIND

Even while studying, the young Mitch Steiner took on far more intricate and studious roles than the average high school graduate.

Both as an undergraduate student at Vanderbilt and then while studying medicine at the University of Tennessee, the inquiring student was conducting independent research in his own lab.

"The lab always drew me," he says. "I was always eager to do more than just read the text books. I wanted to figure out answers to questions that no one else was addressing and so I was learning about all of the scientific tools to answer those questions."

He managed all this while coming in top of his class in medicine and enjoying the usual social hijinks of a college student.

That intense workload continued through his postdoctoral research. After earning his M.D., followed by an internship and preliminary residency in surgery and a full residency in urology at Johns Hopkins, Dr. Steiner decided more study was in order.

"I did an 18-month postdoctoral fellowship in cancer research and loved it and decided to do another fellowship at Vanderbilt," he says.

He was granted funding from a prestigious fellowship study called the American Foundation for Urologic Disease Fellow. It was an important journey, since the move to Vanderbilt took him to the lab of Harold Moses Jr., M.D., who was one of the researchers to discover TGF beta.

"This is what got me to Vanderbilt, and it was one way to cross pollinate from urology to cancer research," Dr. Steiner says. "This move led me down the path in multiple ways to some of the drugs we're working on at GTx, such as toremifene."

Dr. Steiner took on a huge workload at Vanderbilt.

"In addition to the research I was doing on prostate cancer and an area of medicine called gene therapy, I was made assistant professor of three different departments: urology, cell biology, and pathology," he says.

Most importantly, the research at both Johns Hopkins and at Vanderbilt gave Dr. Steiner the skills, insight, and authority to apply research from the lab into patient care.

"This area of study gave me the credibility as a urologist to be able to work with the basic scientists, talk their language, and go to the clinics, having being trained at Johns Hopkins in surgery, and put into practice the latest techniques in what was then the most pioneering area, which was to remove the prostate and to allow the patient to maintain continence and potency at the same time," he says.

Since those early days at Johns Hopkins and Vanderbilt, Dr. Steiner has made a name for himself in the field of urology. He conducted research into how epithelial cells — the cells that cover and line the body and organs — and stromal cells — the connective tissue cells of an organ — talk to each other.

"Cancer cells grow because they stop talking to the cells around them," he says. "I realized if I could understand that language better then maybe this communication would be a potential target as a way to stop the cancer cells from growing."

He began by looking into a small molecule called transforming growth factor (TGF) beta, a powerful, naturally occurring substance in the body that enables cancer cells to evade surveillance by the body's immune system. He postulated that one possible way to tackle cancer would be to work out how to initiate the command to tell cancer cells to stop replicating.

"I was able to get to a gene that makes TGF beta, which I then put it into prostate cancer cells to understand why the prostate cells were making this cell in the first place," he says. "Two very interesting things came out of this research. One, it turned out that these ugly prostate cancer cells, which were growing like wildfire, were producing lots of inhibitor growth factors. Two, perhaps the answer was that this protein was not acting like an inhibitor. So I put this gene back into prostate cancer cells and overexpressed it, and sure enough it turns out cancer cells do not see this

type of cell. It's not an inhibitor; if anything it's stimulating cancer to grow.

"This work led me to gene therapy and to understanding how cells talk in the micro environment and how cells become cancerous," he says.

VENTURING FORTH

Always eager to push the research envelope, Dr. Steiner established a urology laboratory at the University of Tennessee while also seeing patients. It was here, he says, the discovery for prostate cancer prevention emerged, and it was at this point and through a chance meeting with a wealthy and influential patient that his career path took an exciting and important departure.

"A very prominent patient who had developed prostate cancer came to see me after being referred by Johns Hopkins; I was able to help him and he gave my lab $1 million," Dr. Steiner says.

The money was put into research that led to the identification of a new drug with a novel mechanism of action to prevent prostate cancer.

Realizing the potential, Dr. Steiner turned to the University of Tennessee for advice on commercializing the drug and ultimately was advised to start his own company. With no knowledge about business, he sought out individuals with experience in business and met Marc Hanover, now president of GTx, who had started up three companies and had the business expertise to move the project forward.

"About this time I got a phone call from Pitt Hyde, the patient who had given my lab $1 million, asking how the research was going," Dr. Steiner says. "I told him about the drug we had discovered and he asked if I had considered starting a company. I told him

A TRUE VOLUNTEER

IN AN EXCLUSIVE INTERVIEW WITH PHARMAVOICE, MITCHELL S. STEINER, M.D., F.A.C.S., TALKS ABOUT THE IMPORTANCE OF A BALANCED LIFE AND THE JOY HE DERIVES FROM BEING ABLE TO GIVE BACK TO THE COMMUNITY.

For a scientist who has committed himself to cancer care and research, the desire to help is omnipresent. Mitch Steiner, M.D., works with nonprofit organizations and spends time helping poorer patients as part of his commitment to those battling cancer.

He and his wife help raise money for the American Cancer Society and the Prostate Cancer Foundation, as well as for St. Judes Children's Research Hospital in Memphis, Tenn.

"The second thing I do on a personal level is I give a lot of my free time to help indigent patients in Memphis who have tumors and don't have a way to pay for treatment," Dr. Steiner says. "I'm more than happy to help take care of these patients by donating my time and spending a day operating."

Through his close association with nonprofit organizations, such as the American Cancer Society, Dr. Steiner also helps to ensure that GTx is well-versed in issues affecting patients and practitioners.

"We want to stay close to patients because so much of what we are doing will affect how they are treated and how ultimately some of the medicines we're developing are going to fit in their treatment algorithms," he says.

Additionally, Dr. Steiner supports the goals of organizations such as Us TOO International Prostate Cancer Education and Support Network and other prostate cancer advocacy groups formed by cancer survivors and their families that bring information to patients and create public awareness around the disease state.

"Such organizations and their work are critical because developing public networks fuels the enthusiasm for more not-for-profit and for-profit research funds and also helps patients navigate through the possible options, and in some cases no options, for treatment," Dr. Steiner notes.

Beyond his work and volunteer activities, Dr. Steiner throws himself into a completely different life.

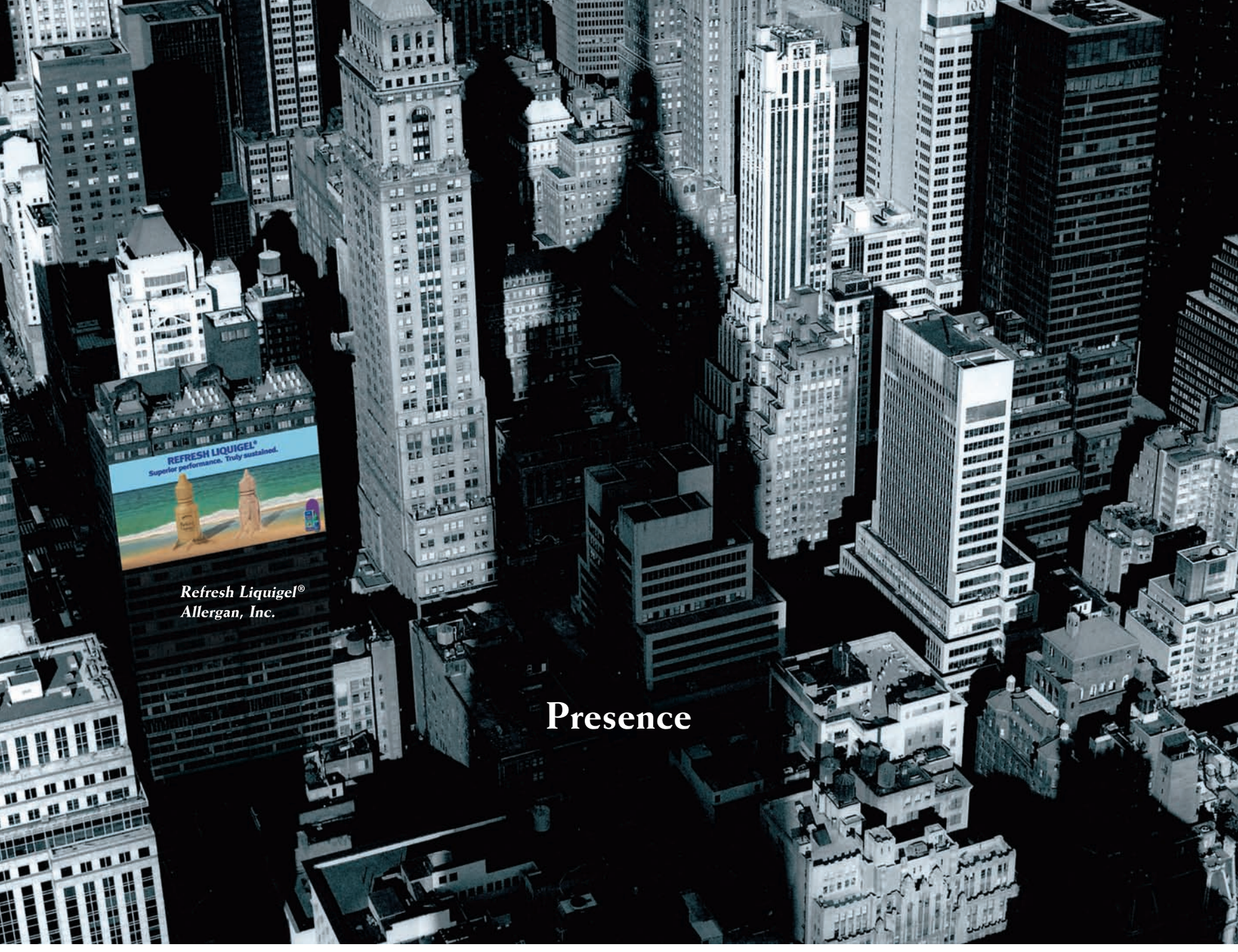
"One of the things that's interesting about physicians is our ability to compartmentalize life," he says. "It's not that doctors don't care; we care very much but it's important to find a way to turn that switch off so it's possible to go from dealing with a patient who is dying to celebrating at a birthday party for your child."

As a self-described gentleman farmer, Dr. Steiner finds enormous pleasure and relaxation by doing a variety of projects with his four children.

"I build horse stalls, drive the tractor around hauling rocks, stock the pond with fish one by one, plant a garden, help deliver a piglet, or ride horses," he says. "When I'm doing these things I don't think about anything other than getting those projects done and enjoying the outdoors."

It's also a way for him to use his hands, something he misses now that he spends less time doing surgery.

"In business, it's all go, and there isn't the opportunity to spend two or three hours focused on a single project," he says. "The farm serves to provide me with those opportunities."



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AGENCY OF THE YEAR

AN ACADEMIC PATH

MITCHELL S. STEINER, M.D., F.A.C.S. – RESUME

APPOINTMENTS

1999 — PRESENT. Professor of Urology, College of Medicine, University of Tennessee, Memphis, Tenn.

1999 — 2003. Chairman of the Department of Urology, College of Medicine, University of Tennessee, Memphis, Tenn.

1997 — PRESENT. CEO, Vice Chairman, and Cofounder, GTx Inc., Memphis, Tenn.

1995 — PRESENT. Endowed Chair of Excellence in Urology, College of Medicine, University of Tennessee, Memphis, Tenn.

1995 — 1999. Associate Professor of Urology and Pharmacology, College of Medicine, University of Tennessee, Memphis, Tenn

1995 — 1999. Director of Urologic Oncology, College of Medicine, University of Tennessee, Memphis, Tenn.

1992 — 1995. Assistant Professor of Urology, Cell Biology, and Pathology, Vanderbilt University School of Medicine, Nashville, Tennessee

1992 — 1994. Postdoctoral Research, Department of Cell Biology, American Foundation for Urologic Research Scholar (Mentor: Harold L. Moses, M.D.)

1992. Instructor of Urology, Assistant Chief of Service, James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Baltimore

1991 — 1992. Chief Resident in Urology, The Johns Hopkins Hospital, Baltimore

1989 — 1990. Postdoctoral Research, James Buchanan Brady Urological Institute, The Johns Hopkins Hospital, Baltimore (Mentors: Evelyn R. Barrack, Ph.D., Donald Coffey, Ph.D.)

1988 — 1991. Resident in Urology, The Johns Hopkins Hospital, Baltimore

1987 — 1988. Assistant Resident in General Surgery, The Johns Hopkins Hospital, Baltimore

1986 — 1987. Halsted Surgical Intern, The Johns Hopkins Hospital, Baltimore

EDUCATION

1986. Doctor of Medicine; Highest Honors, University of Tennessee, College of Medicine

1982. Bachelor of Arts; Magna Cum Laude. Major: Molecular Biology/Minor: Chemistry, Vanderbilt University

BOARD MEMBERSHIPS, GRANTS, AUTHORSHIP, PATENTS

Dr. Steiner is a Diplomate of the American Board of Urology and a Fellow of the American College of Surgeons. He is a member of the Endocrine Society, American Society of Clinical Oncologists, American Association for Cancer Research, American Urological Society, Society for Basic Urology Research, Society for Urologic Oncology, and other prestigious societies.

Dr. Steiner serves as a member of the editorial board of *Gene Therapy* and *Molecular Biology Journal*, past Editor-in-Chief of the *World Journal of Urology*, Section Editor of Prostate Cancer section of *Current Opinions in Urology* and was a member of the NIH, NCI, American Foundation for Urologic Disease, and American Cancer Society study sections. Dr. Steiner is a member of the Urological Research Association, American Association for Cancer Research, and the American Society of Gene Therapy. He also serves as the Research Editor for the *World Journal of Urology* and is a Reviewer of *Urology, Journal of Urology, Human Pathology, International Journal of Cancer,* and *Urologic Oncology*.

He has authored more than 300 abstracts and publications and has almost 300 patents issued and/or pending.

rather shyly that I had started a company and he was so excited. He told me he wanted to help finance this."

In late 1997, when GTx was a newly incorporated company of about five months, Mr. Hyde stepped in as an angel investor, putting about $30 million or $40 million of his own money into the company before it went public.

"We had an agreement: he would teach me business and I would teach him science," Dr. Steiner says. "Pitt picked up the science so well; I wish some of my residents would pick up the science as well as he did. We developed this wonderful relationship and grew this company from nothing to where it is now — a publicly traded biotech company with exciting products to move forward."

Academia and the practice of medicine have brought enormous satisfaction to Dr. Steiner, in part because of the opportunity to come up with new ideas and to constantly inquire about better ways to conduct research or patient care and improve people's lives.

"I always ask the question why," he says. "I have never been afraid to take the next step to answer the next question. The fascinating thing about academics is having the time, space, and positive reinforcement to understand something new and different, write about it, present it, and build upon it to create something no one knew before."

But there are also incredible frustrations that plague the academic world. In particular, Dr. Steiner battled with the shortage of resources — both in terms of money and talented people — necessary to conduct research and take it forward.

"In academia, you have to write numerous grants to get financial support from the government and it's never enough to get the work done," he says. "The beauty of being an entrepreneur is it's possible to raise the money to bring the right people together with the right equipment and the right space, instead of having to beg to get these resources."

It's the pressure of acquiring resources for research — whether in the profit or nonprofit realm — that Dr. Steiner maintains is the biggest threat to innovation. This has only been exacerbated by the downward pressure on drug prices, blockbusters coming off patent, and the push to import cheaper drugs from Canada, where, as he says, the healthcare system is quite different from the American system.

"In the United States, we are going to lose the resources for innovation," he says. "Without innovation we'll be back to the days when patient care involved comfort or surgery."

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SCIENCE IN TRANSITION

Despite those concerns, Dr. Steiner and his colleagues continue to forge ahead with innovative ideas. One of the great thrills of the field of urology for Dr. Steiner is how quickly it has evolved in the years since he began his training and the opportunity to be on the cutting edge in both surgical practice and drug development.

Dr. Steiner explains that in the early days, urology was predominantly a surgical practice since there were few treatments around for patients.

"To treat prostate cancer, the patient was surgically castrated; treating BPH (benign prostate hypertrophy) meant scraping out the prostate tissue so the patient could void; and erectile dysfunction was either deemed to be psychological or the patient was given a prosthesis to enable him to have sexual intercourse," he says. "The only medicines we had were antibiotics for bladder infection."

During his residency, the urology field began to change: Lupron and Zoladex for the treatment of prostate cancer were discovered; BPH drugs such as Proscar and alpha-blockers emerged to shrink the prostate; and drugs such as Viagra, Cialis, and Levitra became available for the treatment of erectile dysfunction.

"All of a sudden urology transitioned from a surgical specialty to a medical specialty," Dr. Steiner says. "In other specialties there's always a medical component to the surgical component; neurologists help neurosurgeons, cardiologists help cardiovascular surgeons, and so on. There's no medical component to the prostate and to the bladder."

As a scientist and doctor, straddling the worlds of surgery and medicine is a thrill. Moreover, it has meant his company GTx is

A PROGRESSION FOR MEN'S HEALTH

Formed in 1997 with a goal of finding cures for serious men's health issues such as prostate cancer, GTx Inc. is on the brink of witnessing some big breakthroughs.

GTx has developed four distinct clinical programs using Selective Estrogen Receptor Modulators (SERMS) and Selective Androgen Receptor Modulators (SARMS.)

A SERM is a small molecule that binds to and selectively modulates estrogen receptors. These molecules have the ability to either stimulate or block estrogen's activity in different types of tissue. For example, it can stimulate estrogen's beneficial action in bone, block estrogen's harmful activity in the breast or prostate, and potentially block hot flushes in men.

A SARM is a small molecule that binds to and selectively modulates androgen receptors depending on tissue type. In men, SARMs may be able to: stimulate testosterone's beneficial action in bone, muscle, and brain; and block testosterone's harmful action in the prostate and skin.

GTx has a product on the market, Fareston, for treating advanced breast cancer, and has several other compounds in advanced clinical trials, one of which is Acapodene (toremifene citrate), which blocks the estrogen receptor in the prostate.

Acapodene is a SERM being developed for two separate large indications in men's health — the prevention of prostate cancer in high-risk men and the treatment of serious side effects of androgen deprivation therapy in men who have advanced prostate cancer.

According to Mitchell Steiner, M.D., F.A.C.S., CEO of GTx, the most common treatment for prostate cancer, Androgen Deprivation Therapy (ADT), has meant patients are living 10 years to 15 years longer than in the past.

"But the problem with getting rid of testosterone is that it leads to estrogen depletion; men who are being treated for advanced prostate cancer with these drugs have similar symptoms to post-menopausal women: accelerated bone loss, hot flushes, breast enlargement, and lipid changes that lead to higher cardiovascular deaths," Dr. Steiner says.

Clinical trials of an 80-mg dose of Acapodene show an ability to increase bone density, block the breast from growing, deliver feedback to the brain to stop hot flushes and, potentially, lower lipids.

GTx has completed Phase II clinical studies and is now conducting a 1,400-patient Phase III program in 150 sites across the United States and Mexico. GTx expects to complete its study in the fourth quarter of 2007 and, if all goes well, file a new drug application (NDA) for Acapodene in 2008.

"We are also testing a 20-mg dose version as a prevention for prostate cancer in men who have a premalignant lesion of the prostate called PIN," Dr. Steiner says. "This study has almost 1,600 patients fully enrolled and is being done in about 150 centers in Canada and the United States."

Men with PIN have a 50% chance of developing prostate cancer in two or three years and an 80% chance if untreated in five years and beyond.

"In our Phase IIb study we were able to show that the drug can reduce prostate cancer by almost 50%," he says.

If further trials are successful, Dr. Steiner says the company hopes to file an NDA for that drug in 2008 as well.

Also in the pipeline is a drug called Ostarine, which is a SARM being developed to treat a variety of medical conditions related to muscle wasting and/or bone loss in acute and chronic diseases. GTx plans to initiate two Phase IIb trials this year. In addition, the company has a drug in preclinical studies to treat BPH.

Dr. Steiner says there is potential for GTx to soon have two drugs available for two important markets.

"For example, for the ADT market in the United States alone there are 1 million men with the disease and 100,000 new cases are diagnosed each year," he says. "And for prostate cancer prevention there are roughly 230,000 men diagnosed with PIN each year and about 1 million men who know they have it and about 15 million men who don't know they have it. We also are working with five diagnostic companies to come up with a urine test to identify these men, which will allow us to treat these patients much sooner."

> The lab always drew me in. I was always eager to do something more than just read text books. **I wanted to figure out answers to questions that no one else was addressing** and so I was learning all the scientific tools to answer those questions."

able to play a number of roles — discovering new drugs for urologists to use in men's health, continuing to investigate progressive surgical ways to handle cancers involved in men's health, and uncovering alternative approaches to issues related to aging as opposed to testosterone replacement.

And while the shift from academia to business has provided those opportunities, there were adjustments to be made. Dr. Steiner had to become accustomed to an environment where he was no longer dealing with patients one on one. He says he adapted by reminding himself that he is now in a position to effect change for hundreds of thousands of patients worldwide.

Today, GTx employs around 100 people, and it's the bringing together of those individuals that Dr. Steiner counts among his greatest achievements.

"GTx is an entity made up of scientists, medicinal chemists, smart clinicians, business people, and the sales and marketing people," he says. "The goal of the company is to maintain the intense focus needed to bring drugs to the patients who need them, and the way to achieve this goal is to bring all of the right people together and get them to talk and work together and share ideas."

With a deliberate management style aimed at fostering innovation, Dr. Steiner encourages discussion and chaos.

"Through chaos comes order and by letting people speak their mind and challenge decisions, emerges a very good discussion that eventually crystallizes into an obvious decision, then everybody feels that there's a little bit of them in that decision," he says.

Once the decision is reached, however, Dr. Steiner ensures that the company remains focused and doesn't deviate from the end goal.

GTx has come a long way since its beginnings, and Dr. Steiner is optimistic about the company's future and its goals.

"We run our own clinical trials, we have marketing and sales capabilities, we oversee manufacturing; we've become a full-service pharmaceutical company," he says.

With its headquarters in Memphis, Tennessee, rather than in the pharmaceutical hotspots of the Northeast and California, GTx is something of a maverick. But it's a position Dr. Steiner enjoys.

"In the coming years, our goals are to grow the pipeline, build our own specialty salesforce, and continue to enter into partnerships with other pharmaceutical companies so we can develop into a large company based in Memphis," he says. "By sticking to our plans, one day we will be able to look back and say: wow, we did all of this right here in Memphis." ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.