Photo by Douglas Levere

Allen Barnett, PhD '65, outside UB's New York State Center of Excellence in Bioinformatics and Life Sciences, where Kinex Pharmaceuticals is headquartered.

By S. A. Unger

A Course in Obstacles

Allen Barnett, PhD '65, has never taken "no way" for an answer

Growing up in Newark, New Jersey, Allen Barnett, PhD '65, knew by the time he was in high school that he wanted to be a pharmacologist, even though he admits today that he "didn't have the faintest idea about what was involved."

What he did know, however, was that his father, a house painter and wallpaper hanger, suffered from poor health and took a slew of drugs that provided him with marginal relief, at best.

The youngest of four sons, with ten years separating him from his next oldest brother, Barnett spent a lot of time with his father and would ask him about the drugs he was taking, what he was taking them for and how they were supposed to work.

"I was pretty good at math and science, so I had some interest in those areas," Barnett says, "but, for some reason, at a relatively early age, drug development fascinated me. I think it was because my father had a lot of health problems. He had a couple of severe heart attacks and had ulcers before the new drugs came along, so he was always fighting that battle; in fact, he used to tell me that a new drug for ulcers was the first thing I should work on."

Little did father and son know then that Barnett's interest in drug discovery would culminate several decades later in his being recognized as one of the top pharmacologists of his day, responsible not only for a key basic-science discovery in the field of dopamine receptors, but also for the lead role he played in developing the allergy medication Claritin, which today is the fifth most successful drug in the world, based on sales.

In 1999,

at the height of his career, Barnett stepped down from his position as vice president of technology acquisition at Schering-Plough Pharmaceuticals, where he had worked for 33 years and had achieved his greatest successes.

Four years later, at age 66, he set aside his consulting business (and fledgling golf game) to re-enter the workforce as chief executive officer of a new Buffalo-based biotechnology company called Kinex Pharmaceuticals, which had licensed technology from the UB Department of Chemistry to develop a line of cancer drugs that had shown the ability to bind to the kinase Src (pronounced "sarc") and inhibit tumor growth.

The chemical compounds that target Src were developed by David Hangauer, PhD '80, UB associate professor of chemistry, whose talents had been noticed by Barnett years earlier when he was at Schering-Plough and heard Hangauer present a seminar on his work.

Kinex, which today focuses its efforts on the development of drugs to treat autoimmune diseases, as well as cancer, is a company that has attracted significant interest from venture capitalists, private investors and several major pharmaceutical companies. It is currently moving its lead cancer drug, called KX2-391, through Phase I testing at Roswell Park Cancer Institute and M. D. Anderson Comprehensive Cancer Center in Houston, Texas, in an effort to win approval from the Food and Drug Administration (FDA).

Working alongside Barnett and Hangauer are Lyn Dyster, PhD '91, the successful founder of her own biotech firm, GenCyte, who took the initial steps to recruit Barnett to Kinex and who now serves as the company's vice president for operations; and Johnson Y. N. Lau, MD, FRCP, former chairman and CEO of California-based Ribapharm, who serves as chairman of the board for Kinex, a role he was recruited into by his longtime friend Barnett.

Lau, who resides in Orange County, California, launched the second largest biotech initial public offering in history ($300 million) while with Ribapharm. Although his official title is chairman of the board for Kinex, Lau does much more for the company than his title reflects, says Barnett, who notes that "he has used all his contacts" to help generate interest in and support for the company.

When Barnett talks about KX2-391 and the long road it has traveled to get to where it is today, he methodically explains the basis for his optimism regarding the drug's potential. "We've shown that with one target you could deliver a molecule that has all the properties that we wanted: orally effective, orally bioavailable, acceptable duration of action (so it could be given twice a day), and selective for one target versus other targets. So, we've proven that the technology does work."

What he doesn't talk about as easily is the fact that his granddaughter, Carly, died of cancer at age 11, several months after he began his formal association with Kinex.

Carly was adopted by Barnett's daughter and son-in-law, CarolAnn and Chuck Collard, of East Amherst, New York, after both of the girl's parents died of cancer before age 40. After being diagnosed with a brain tumor at eight, Carly became an inspiration at Roswell Park Cancer Institute for the bravery with which she endured the illness and treatment, and today she is memorialized by the institute's Carly's Club, which supports research in pediatric cancers, as well as many patient and family support programs.

When asked about his granddaughter and how her life and death have affected his work, Barnett's response is brief and halting. "That's a tough one," he says, " . . . but at the time I decided to get involved with Kinex, I knew she was dying. That was early in the summer, and she died in August."

Lyn Dyster, PhD '91, left, is vice president of research operations for Kinex, and David Hangauer, PhD '80, associate professor of chemistry, is the company's senior vice president of research and development.

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STARTING FROM SCRATCH

Although Barnett's career has culminated in his being a highly respected and acknowledged expert in his field, his lifelong work to discover and develop new drugs is as much a chronicle of setbacks and obstacles as it is a story of success and acclaim. In fact, one could say that his ability to persistently maneuver around barriers, over pitfalls and under the radar are the traits that have gotten him to where he is today as much as his obvious talents as a scientist.

And one of the first places to test his dexterity (albeit accidentally) was his postgraduate alma mater, the UB School of Medicine and Biomedical Sciences.

After high school and with the encouragement of one of his older brothers who took an interest in his career-planning efforts, Barnett entered Rutgers University on a scholarship and completed pharmacy school, after which he began a one-year internship.

While the internship was professionally rewarding, Barnett soon realized that if he were ever to have his own pharmacy, he would need something that had been in very short supply all his life—money. Beset by frustrations and doubts about where all of his hard work had taken him, he was forced to revisit the motives that had led him to pursue a pharmacy degree in the first place. This, in turn, rekindled his desire to be a pharmacologist and spurred him to apply to graduate schools with the goal being to earn his doctorate in the field and turn his attention to drug discovery.

He sent off applications to three graduate programs around the country, one of them being at UB, and then sought out a professor in Rutgers' Department of Pharmacology who had been his designated advisor during his undergraduate years, although Barnett had never met with him.

"I was seeking out somebody who was in the field I wanted to be in, although he didn't know me from a hole in the ground," recalls Barnett. "So, he looked at my record and said, 'You didn't really stand out as a student; therefore, I advise you to go back to retail pharmacy and continue on.'"

When Barnett probed further, the professor was even more unsparing in his advice.

"He told me, 'First of all, it's very competitive getting into graduate school, and they only take the best. And you're not the best.'"

Recounting the conversation, Barnett nods his head, smiles widely and says, "Yeah, diplomacy was not his strong suit."

Although deeply discouraged, Barnett still held out hope that one of the graduate applications he had sent out would result in an invitation to come for an interview. He had received preliminary communication from two of the schools, but nothing came from UB, not even an acknowledgment that the university had received his application.

In the meantime, he had a commitment with the Army Reserves to fulfill and had to focus on readying himself to go on active duty for six months.

While making these preparations, Barnett decided to travel to Buffalo to visit his aunt and uncle and cousins, whom he had remained close to over the years.

After he arrived in Buffalo, thinking he had nothing to lose, he picked up the phone and called UB, inquiring about his application and the response he got was, "What application?"

PHOTO BY TIM LONG

Johnson Y. N. Lau, MD, FRCP, former chairman and CEO of Ribapharm, serves as chairman of the board for Kinex Pharmaceuticals.

"To make a long story short," says Barnett, "my application had been misplaced, but once they located it, they called me right back and asked if I could come in for an interview, and that's how I got accepted to UB.

"It was a life-changing experience," he adds. "The UB program turned out to be much, much better than the other one I had been considering. For me, it was the perfect program. It prepared me for moving on."

THE POLITICS OF BUSINESS

With his doctorate in hand, Barnett took a position with Roche Pharmaceuticals and a year later he moved to Schering-Plough, where he was hired to start a program that focused exclusively on centrally acting muscle relaxants.

After planning his lab and ordering equipment, he had some time to spare until everything arrived, so he was handed a file and told, "While you're waiting, you might want to take a look at this."

The file he was given was on a series of compounds that had been shown to have a variety of pharmacological effects on the central nervous system (CNS), but the mechanisms for the effects were unknown.

"It was a total curiosity at the time," explains Barnett. "The chemist was interested in the molecule and making more molecules, and the biologists were trying to decide what to do with it, so it was not the usual program you have now, where you pick the target first and then look for a molecule to hit that target. In those days, some of the scientists could take this other approach—they had the time and the latitude to make a new molecule."

That "innocent, temporary project," as Barnett refers to it, lasted for 30 years (a record in the industry, he thinks) and resulted in his making two pivotal discoveries: (1) the elucidation of the world's first D1-specific dopamine receptor antagonist, and (2) the understanding of how to get things done in a large organization when leadership turns over fairly often and a project you believe in is (once again) on the new management team's short list of projects to close down.

In reference to the first discovery, Barnett explains that, at that time, all of the drugs for schizophrenia were dopamine blockers in the CNS and they blocked the D2 receptor subtype. "No one knew there was a D1 and a D3 and a D4 receptor; that was before the technology was available to make those determinations," he notes.

Barnett's team began to see from the profile of the drug they had developed that it could, in theory, work on schizophrenia, but when it went into clinical trials, it did not work because it hit only one target, as opposed to the five or six targets that today's drugs hit.

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When the new management announced plans to close out the Claritin program, Barnett protested the decision and placed his own job on the line by stating his opposition in open meetings.

The discovery made by Barnett, however, moved the basic science forward, and the methodology he developed is still used as an experimental tool. "Anybody who ever studies dopamine receptors and wants to see if it's D1, D2, D3 or D4 uses this [method] as a tool," he explains.

When the initial clinical trial failed, the company dropped the project, a move Barnett resisted because he believed strongly that the drug had other potential properties and that if it didn't work on schizophrenia, it could have been effective in other diseases.

It was at this juncture in his career that Barnett's second discovery began to take shape and led him to formulate his own pipeline strategy that later made it possible for him to develop the drug Claritin against all odds.

Around the time Schering-Plough made the decision to drop Barnett's D1 project, the company reorganized and a new management team was brought in, a process Barnett was learning to appreciate for its hidden opportunities.

"When there was a changing of the guard, the first thing they would do is ask us if there was anything near term that we'd put aside that might be of interest," he recalls with a broad smile. "*That's* the question I would wait for, and I'd say, 'Funny you should mention that,' and I'd trot out the D1 project—that's how it lasted 30 years.

"But," he adds, "that's also how I learned to get things done in a large organization, to know when it's time to let a program fall back—lie underneath the radar, keep working on it in my spare time—and when it's time to bring a program forward."

With this second discovery under his belt, Barnett had all the tools and experience he needed to make the discovery of his lifetime, and, in retrospect, that's about how long it seemed to take.

THE CLARITIN MARATHON

By the time Barnett began working on the Claritin project in the 1980s, he already had achieved other successes at Schering-Plough, including the discovery and development of Doral, a sedative hypnotic that the company eventually licensed out.

The goal of the team working on the new project headed by Barnett was straightforward: to discover an antihistamine that didn't cause drowsiness.

This was something many pharmaceutical companies had tried to do at one time or another, but had only met with failure.

It was against this "backdrop of failure" that Barnett and a group of six chemists set to work on an approach he devised that involved the central nervous system.

They soon found a compound that met all of the initial criteria they were looking for except that it was not very long acting, a crucial hurdle to overcome if the drug were to be commercially successful.

Just as the team began to work on lengthening the compound's duration of action, Schering-Plough reorganized yet again and a new management team came in whose goal was "to elevate the quality of science being done," recalls Barnett. "What that meant was the people who were already there had already failed—that was the prevailing view."

When the new management announced plans to close out the Claritin program, Barnett protested the decision and placed his own job on the line by stating his opposition in open meetings.

"Fortunately," he explains, "the new management also brought with them the concept that although you are going to end a project, you give the scientists a chance to wind it down, to file patents and publish papers and so on."

This gave Barnett the leeway he needed to negotiate a threadbare compromise with his boss, a chemist, who agreed to let the team make 25 derivatives of the compound in a last-ditch effort to see if one would increase duration.

After 24 of the compounds failed to achieve this outcome, the lead chemist on the team was ready to terminate the project. Barnett intervened, reminding him that the deal was for 25 compounds and pointing out that all 24 of the molecules made up to that point had been substitutions on one site. With nothing left to lose, Barnett brought up an idea he had earlier put forth that represented a radically new approach.

"That was the only time in my whole career that I had ever suggested a molecule," he says. "I'm not a chemist. I don't have a feel for structure activity, but based on what had been done around the structure, I suggested they put a chloro group on a particular position in the ring."

The chemist responded by delineating all the reasons why such a compound would be difficult, if not impossible, to make and concluded "there's no way it will work."

"At the time, it was a 15-step process, so naturally he left it for last," recalls Barnett. "And I have to give him credit, the chemistry was tough, but he did it, he finally made the compound, and that was Claritin—the 25th compound."

Convinced they had a winner, Barnett and his team were elated, but management remained skeptical.

"Even after we had the new compound and it did everything that we predicted, and it didn't do anything else—it was like a dream compound—management still didn't believe that it was for real. They said, 'You've got to do something to prove it,'" says Barnett.

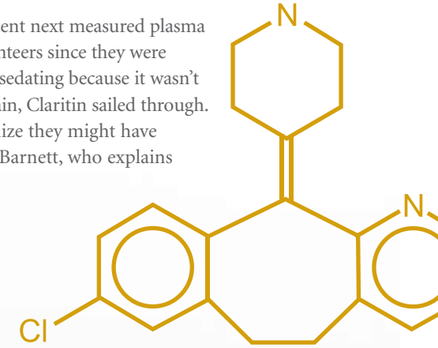
"I saved the minutes from the meeting in which they agreed to do one very limited safety study in humans—just one."

Next, Barnett began to painstakingly negotiate with his supervisors about what the dosage would be for the test. At this juncture, the president of research intervened. Thinking he would put the matter to rest once and for all, he stipulated that the drug be tested at a whopping 160 mgs, about 16 times higher than Barnett had estimated the effective dose to be.

"And so, the first human test of Claritin was at a single dose of 160 milligrams," says Barnett, "and by some miracle, nobody nodded off."

Still not convinced, management next measured plasma levels of the drug in human volunteers since they were concerned that the drug was nonsedating because it wasn't getting into the plasma. Once again, Claritin sailed through.

"Suddenly, they began to realize they might have something on their hands," says Barnett, who explains



that one final test stood between success and skepticism. Called "the wheel and flare," the test involved provoking allergic reactions in individuals and then testing them to see if the drug blocked the reaction.

It did.

"And that's when everyone flipped out," says Barnett. "That's when they knew.

"They could have gotten all of that out of one study if they had been willing to assume that the drug was active, but instead it was a killer experiment."

In all, the drug took some 12 years to develop, including the six years it took the FDA to approve it.

Allen Barnett's granddaughter **Carly Collard,** who died of cancer at age 11.

By then, Barnett had moved on to leadership positions in Schering-Plough, eventually concluding his career with the company as vice president of technology acquisitions. In this position, which he held for five years, Barnett was responsible for evaluating new systems that had the potential to cross all areas of drug development, such as combinatorial chemistry and human genomic databases.

This experience made him acutely aware of the fact that a new era of drug development was dawning. The "good, basic, blood-and-guts pharmacology we used to develop Claritin involved solid drug design and testing," he says. "But it wasn't a very high-tech or exciting mechanism."

His work with Kinex Pharmaceuticals, in contrast, is all those things, and more.

BUFFALO BIOTECHNOLOGY

While Barnett and his wife still have their primary residence in New Jersey, they maintain a second home near Fort Erie, Ontario, only an eight-mile drive to UB's New York State Center of Excellence in Bioinformatics and Life Sciences in downtown Buffalo, where Kinex is headquartered.

Over the years, Barnett has remained connected to Buffalo through his wife's family and his association with UB. The tie to UB has been renewed and invigorated in recent years by his association with Wayne K. Anderson, PhD, dean of the School of Pharmacy and Pharmaceutical Sciences.

Anderson had reached out to Barnett while he was still at Schering-Plough and had invited him to sit on the school's National Industrial Advisory Council.

After he retired from Schering-Plough, Barnett let Anderson and other UB administrators know that he was available to assist them if they wanted to avail themselves of his expertise.

"I was rolling along in retirement," he says. "Life was good. But one of the things I believe in is giving back, so I got an appointment at UB [as a research professor of pharmacology and toxicology in the School of Medicine and Biomedical Sciences] and made it known to different people at the university that I was willing to consult and that there would be no fee attached. I just wanted to help out."

The university took him up on his offer and one of the things Barnett was asked to do was serve as a panelist at a Career Day event for students interested in the pharmaceutical sciences. One of his fellow panelists was Lyn Dyster, who, after becoming further acquainted with Barnett, began seeking him out for his advice on the company she and Hangauer were thinking about launching.

Seeing great potential in what the two scientists were exploring, Barnett eventually accepted their offer to serve as CEO of the start-up.

Having worked in this capacity for the last several years, Barnett says he's impressed with the ongoing efforts to attract biotechnology industries to the Buffalo Niagara Medical Campus downtown. He commends the planning and foresight involved in building the Center of Excellence in conjunction with the adjoining facilities built by Roswell Park Cancer Institute and Hauptman-Woodward Medical Research Institute.

"This is a state-of-the-art facility," he says, referring to the Center of Excellence. "It is very, very well built and it leaves room for having university people, as well as people like myself and smaller companies, all in close proximity to Roswell Park and Hauptman-Woodward people. We've gotten a lot of things done just within the complex. It's the way to go."

Barnett says he also is impressed with the influx of companies moving to the Buffalo Niagara Medical Campus, such as Cleveland BioLabs, as well as with the university's efforts to buy and refurbish buildings on the downtown campus.

He contends that more work still needs to be done, however, if a thriving biotechnology industry is to take root in Buffalo. In particular, he emphasizes that additional seed money needs to become available at the local and regional levels to support the establishment of new ventures, although he is hopeful that these resources will surface over time as companies, such as Kinex, gain momentum and serve as examples of what can be achieved.

For now, Barnett remains intensely focused on developing drugs that can mitigate or defeat the ravages of cancer and autoimmune diseases.

To this end, a large framed picture of his granddaughter, Carly, hangs on the wall of his office, the best of reminders for the important work that still lies ahead. BP

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