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Changing of the guard

GlaxoSmithKline, an instrumental force in North Carolina's textiles-to-test tube transformation, slims down as cancer expert Stephen Frye and other researchers bulk up.

BY EDWARD MARTIN

Frye, right, is among ex-Glaxo employees with an entrepreneurial bent and limitless opportunities.



PHOTO BY STEVE EXUM

No heavy machinery rumbles here. At a plant east of Raleigh, down shrubbery-lined Apothecary Drive in Zebulon, stunningly fast production lines fill purple inhalers with talc-like powder that has the remarkable ability to shrink swollen airways that leave asthmatics and others with lung disorders gasping. In near-sterile surroundings, scores of workers, some in white lab coats, primarily monitor quality.

GlaxoSmithKline PLC, the world's eighth-largest pharmaceutical company, touts this plant as one of its most advanced. More than 850 employees work here, and another 130 or more are being hired. A new production line is part of \$90 million in upgrades. "In Zebulon," says GSK's Research Triangle Park-based spokeswoman Marti Skold Jordan, "we handle over 30 brands which are sold in over 500 different selling presentations." The company's best-known product, Advair, is both produced and prepared here.

GSK's showplace is 40 miles east of its vast, 500-acre U.S. headquarters in Research Triangle Park. Momentum alone would seem to make it indomitable: Last year, Jordan adds, the Zebulon plant produced more than 200 million capsules and tablets, filled more than 65 million inhalers and put together more than 112 million drug packs.

Instead, this plant is on the front lines of global pharmaceutical warfare. GSK has seen profits plunge and has shed tens of thousands of workers worldwide. Its North Carolina employment has declined to about 4,000 — more than 20% lower than peak levels — and it is leasing empty space in its 35-building headquarters complex amid scars inflicted by competitors, a tumultuous health care environment and scandals of its own making. The scars are vivid reminders that in North Carolina, more than the future of a charter member of the global big-pharma club is in play.

For more than four decades, Research Triangle Park has ridden the coattails of GSK and legacy companies such as Burroughs Wellcome & Co. that it has absorbed as the state grew from life-sciences obscurity to global prominence. As economic transitions go, it's a remarkable one, from smokestacks, tobacco and textiles to clean-room manufacturing and labs, such as Burlington's Laboratory Corporation of

America, that test blood for diseases, and giant contract-research organizations, like Durham's Quintiles Transnational Inc., that enlist people to test new drugs that might cure them.

Life sciences, a sweeping term encompassing pharmaceuticals and other processes dealing with living organisms, has more than 228,000 employees and an annual economic impact of \$73 billion in North Carolina, second only to the \$77 billion of agriculture, the N.C. Commerce Department says. The Raleigh-Durham market ranked second to the Boston metropolitan area as a life-sciences hub, according to a recent ranking by Jones Lang LaSalle Inc., a Chicago-based company that analyzes commercial real estate. "We don't want this industry to go the way of textiles, furniture and tobacco," says Doug Edgeton, CEO of the North Carolina Biotechnology Center based in the Research Triangle Park.

SOME LIFE-SCIENCES EXPERTS say the state has reached the critical mass necessary to maintain its commanding role in the industry regardless of GSK. The corporation's vulnerabilities, though, underscore that in the rowdy arena of big pharma in 2015, any cloud over GSK casts a shadow over life sciences in North Carolina as well. Surprisingly, many observers say the state isn't helping its own cause.

The biotechnology center, created in 1984, has been instrumental in attracting the industry to North Carolina and nurturing it. Now, while GSK struggles to find its footing, the center faces an existential threat from lawmakers as the N.C. General Assembly considers cutting its funding, about \$13 million of its \$18 million budget in 2014. Without state money, "We would probably have to go into a wind-down mode," Edgeton says. The center has 62 employees in six statewide offices, and has offered grants, funding assistance, technical and business advice and other aid to hundreds of existing and startup life-sciences companies.

In addition to global competitors, other proposals threaten to chill the life-sciences climate in North Carolina. The legislature also has declined to extend tax incentives for pharmaceutical research and development activities that amounted to more than \$40 million in 2014, along with tax breaks for purchasing laboratory equipment. Many business incentives are being cut and now,

life-sciences supporters fear parallels with the state's once-thriving, 30-year-old, \$250 million-a-year movie industry. Loss of tax breaks and other incentives has prompted some film and television productions to choose other states.

Thirty-eight other states offer companies such as GSK tax breaks for R&D expenditures, including states covetous of North Carolina's thriving life-sciences sector. Mirroring nationwide cutbacks in federal drug-research funds, North Carolina has also cut the budget of its University Cancer Research Fund, a catalyst for new drugs and startups, and other programs.

"It's a competitive country and world," Edgeton says. "We can't turn around without seeing Texas pouring hundreds of millions of dollars into trying to attract life-sciences jobs. Florida, Georgia, Massachusetts, California, Maryland, Virginia, all are doing the same. We hope to keep these folks in our state, rather than having them recruited away."

For now, in what once was the quiet bedroom community of Zebulon, production lines roll out the iconic purple disks of Advair at a frenetic pace. (Except for a week in August, when a large part of the plant closed because the bacteria that causes Legionnaires' disease was discovered in cooling towers. No illnesses were reported.) GSK, Jordan says, "treasures our heritage in North Carolina." For the state, that's a past inexorably linked with its life-sciences future.

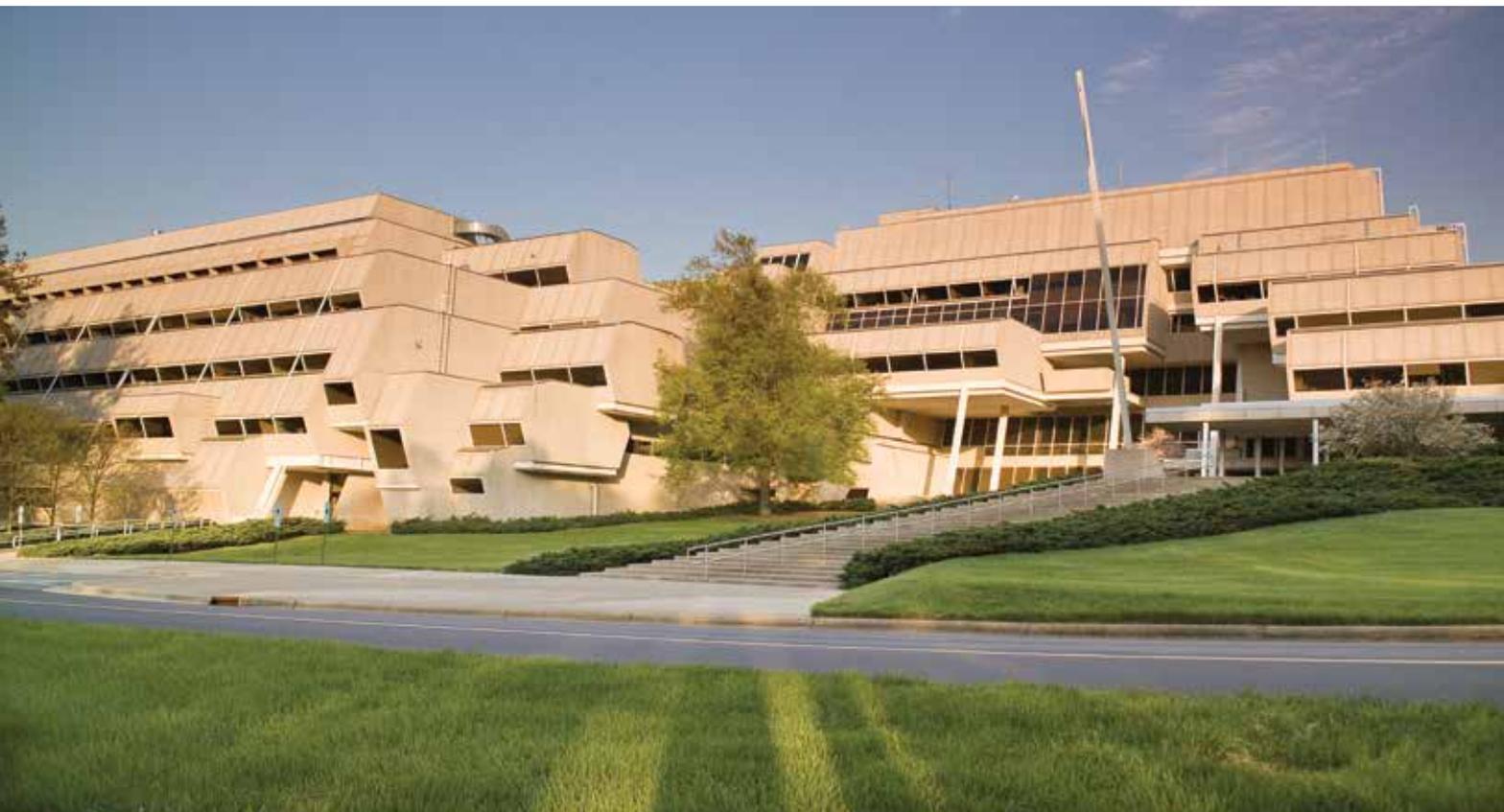
MEMOS WENT OUT LAST DECEMBER to 900 employees of GSK in the Research Triangle. They were being fired, part of a three-year campaign by the Brentford, England-based drugmaker to slash \$1.6 billion in worldwide expenses. Not clerks and technicians, most were research and development scientists, the glamour corps of pharmaceuticals. GSK won't reveal salary information, but many likely earned far above the state average for life-sciences workers of about \$81,000 a year.

The impact was almost as jolting as 19 years earlier, when news broke that Glaxo had bought Burroughs Wellcome, which established its Research Triangle Park headquarters in 1970 and was Glaxo's neighbor there. "I was driving to work on Interstate 40 that morning," says Bill Shore, a retired senior executive at both companies. "Three-thousand sets of brake lights came on."

Some laid off in December would be offered jobs at other GSK sites, and more than 400 were steered to Parexel International LLC, a Waltham, Mass.-based contract-research organization with about 1,100 Triangle workers. In July, Parexel began slashing Triangle jobs too. The company will cut 125 jobs starting Sept.30, according to a state filing.

"RTP will not be an R&D hub moving forward," Jordan says, though she adds that the park is still GSK's U.S. headquarters. "A substantial group of our commercial, manufac-

Architect Paul Rudolph devised Burroughs Wellcome's RTP site in the late '60s, when many global giants prized provocative design.



North Carolina's Anglo-American triumph

Few companies have made a larger economic and philanthropic mark on the state than GlaxoSmithKline and its predecessors. Entrepreneurial success stories keep spinning out of GSK, even as it consolidates its own research efforts.

■ **1830** John K. Smith opens a drugstore in Philadelphia.

■ **1842** Thomas Beecham launches Beecham's Pills in England.

■ **1880** Burroughs Wellcome & Co. is established in London by American druggists Henry Wellcome and Silas Burroughs.

■ **1906** The Glaxo name is trademarked. It is derived from Lacto, a food for infants.

■ **1969** Glaxo begins making Ventolin, an asthma treatment.

■ **1970** Burroughs Wellcome moves its U.S. headquarters from Tuckahoe, N.Y., to Research Triangle Park.

■ **1972** Beecham scientists discover amoxicillin, a revolutionary antibiotic.

■ **1981** Wellcome unveils Zovirax, for herpes infections.

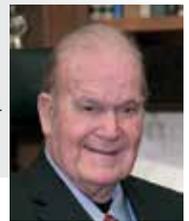
■ **1981** Brainstorm, a science-fiction movie starring Natalie Wood, is filmed at the Burroughs Wellcome building. Wood drowns in an accident unrelated to the filming.

■ **1985** Fred Eshelman leaves Glaxo to found Wilmington-based contract-research organization Pharmaceutical Product Development. It sells for \$3.9 billion in 2011. In 2014, he founded Eshelman Ventures, which mostly invests in private health care companies.



■ **1989** SmithKline and the Beecham Group merge to form SmithKline Beecham.

■ **1989** Charles Sanders is named CEO of Glaxo's U.S. subsidiary. He left the company in 1995 and has served on many corporate boards.



GlaxoSmithKline, or GSK, and its legacy components date to the 18th century. It is based near London, has market capitalization of about \$101 billion, and makes both drugs and consumer products such as Aquafresh toothpaste and Breathe Right nasal strips. British and U.S. executives have comprised its leadership, including many living in North Carolina.

■ **1995** Glaxo and Wellcome merge, forming Glaxo Wellcome.

■ **1995** Christy Shaffer leaves Glaxo to co-found Inspire Pharmaceuticals. She is a partner at Hatteras Venture Partners in Durham and serves on the boards of RTP-based GI Therapeutics and Alpharetta, Ga.-based Clearside Biomedical.



■ **1997** Robert Ingram is named CEO of Glaxo Wellcome and becomes chairman in 1999. He is a partner at Hatteras Venture Partners and serves on the boards of Valeant Pharmaceuticals and Durham-based Cree.



■ **2001** Glaxo Wellcome and SmithKline Beecham merge, forming GSK, with dual headquarters in RTP and Philadelphia.

■ **2008** GSK makes Research Triangle Park its sole U.S. headquarters.

■ **2015** GSK acquires some of Novartis' vaccine lines.

■ **2014** GSK announces thousands of job cuts worldwide, including about 900 in RTP.

■ **2012** GSK sells the 550,000-square-foot, former Burroughs Wellcome headquarters building and other properties to United Therapeutics Corp. for \$17.5 million.



turing and support function teams are located at the RTP campus," including the office of Jack Bailey, president of GSK's U.S. pharmaceuticals. He succeeded Deirdre Connelly, who abruptly retired in February. GSK did not make senior executives available for this story. In a recent conference call with analysts, Bailey cited "unprecedented change" in pharmaceuticals as necessitating cost cuts. "We have sharpened our focus," he said.

GSK earned \$4.3 billion in 2014, slumping from \$7.3 billion two years earlier. Sales declined 16% to \$36 billion in that period. Its stock traded in mid-August at about \$44, well below its historic high of \$70 in 1999. With its shares mired in a long-term slump, GSK has considered breaking itself into separate consumer products, pharmaceutical and vaccines units. Company officials have rebuffed suggestions of a merger with another giant such as New York-based Pfizer Inc. Antitrust regulators would probably block such a move, some analysts say.

One reason for the stock's slide is that the patent for Advair expires in 2016, opening the door to generics that sap profitability. In recent years, Advair has generated about 20% of GSK sales, while revenue is likely to slip from \$8.3 billion in 2013 to less than \$2 billion in 2020. GSK is optimistic about Breo, a well-regarded new respiratory drug, and advanced Ellipta inhalers, which will be made in Zebulon.

But it's a tough environment as generic drug giants such as Israel's Teva Pharmaceutical Industries Ltd. are pushing down prices for off-patent drugs. Bailey concedes GSK has had too many eggs in the Advair basket, calling the loss of patent protection "traumatic."

"The chickens are coming home to roost, in the sense that we've been talking about changes in big pharma for many years, and now we're seeing a lot of these things happening simultaneously," says Atul Nerkar, an associate dean at UNC Chapel Hill's Kenan-Flagler Business School who focuses on pharmaceutical research and development. "It will get worse before it gets better. The shakeout is not complete yet, and you're going to see a lot more volatility." He and others say a core reason for the shakeout is a fundamental shift in the kinds of drugs coming online, not only at GSK but scores of other Tar Heel drugmakers and research companies.

"The days of all drugs being 80% to 90% small-molecule formulations are gone," says

Christy Shaffer, who left Burroughs Wellcome in 1995 to help found Inspire Pharmaceuticals Inc. in Raleigh, which developed ophthalmic and other drugs. It went public in 2000, and was acquired by Merck & Co. for \$430 million in 2011. Small-molecule drugs — the simplest example is aspirin — are inorganic compounds, relatively cheap to produce and dispense. "Everyone now is more interested in what are called precision or targeted drugs," Shaffer says. "That's what you hear even from President Obama." The president in January announced what he called a \$215 million precision-medicine initiative to discover drugs to fight genetic diseases such as cystic fibrosis.

Called biologics, they derive from natural organisms and include gene therapies and cancer treatments, highly focused but expensive and difficult to perfect, manufacture and administer. "We see this changing even more," says Shaffer, now a partner who analyzes drug startups for the Durham investment firm Hatteras Venture Partners. "We're going to have even more personalized medicine, more customized."

GSK is scrambling to increase its stake in biologics, which includes vaccines. It has launched more than a half dozen drugs in two years and has about 40 in late-stage development. Its most dramatic move came last fall when it sold its oncology lines to Swiss giant Novartis AG for \$14.5 billion, while in turn paying Novartis \$7.1 billion for its vaccine business, excluding influenza.

Novartis, which had a 550-employee, \$1 billion plant in Holly Springs in Wake County that makes primarily Flucelvax flu vaccine, recently sold that plant to an Australian pharmaceutical company, but GSK's acquisition of its other vaccine lines ensures North Carolina's status as a global vaccine epicenter. Four of the five largest vaccine makers — GSK, Merck & Co., Pfizer and Novartis — have operations in the state, Edgeton says.

GSK is also recovering from self-inflicted wounds. In 2012, it was hit with \$3 billion in fines and penalties by U.S. regulators for marketing drugs such as Flovent, an asthma drug made in Zebulon, for unapproved uses and for disregarding safety data and cheating Medicaid, the national health insurance program for the poor, out of \$300 million. Two years later, China slammed the company with \$500 million

in fines and sentenced its top in-country executive to prison for bribing doctors to prescribe GSK drugs. China said it let GSK off lightly because the defendants admitted guilt. While besmirching GSK's brand, an adverse impact on its future is doubtful. "With today's 24/7 news cycle, these things blow over when the cycle goes on," Nerkar says.

Of more concern to GSK and the pharmaceutical industry, Nerkar and others say, is upheaval in U.S. health care as it revamps under the Affordable Care Act. Supreme Court challenges and attempts to repeal the law create uncertainty for drugmakers. "It's rare that you have an industry in which you don't know who your customers are," Nerkar says. "Big pharma produces the drugs, patients use them, the insurance company pays for them, but it is employers and employees who bear the cost."

The December layoffs, though, hit ground zero in another of the challenges facing GSK and its rivals. "Once, big pharma would spend eight or 10 years in R&D to come out with one big drug," Nerkar says. "That model is not there anymore." Now, instead of spending billions on developing new drugs that might not pan out, industry titans are shedding R&D and pushing risk out to highly focused startups.

In that regard, ironically, even GSK's malaise is again fostering a new generation of pharmaceutical swashbucklers. Shaffer calls it "the circle of life."

IN MID-FEBRUARY, with an ice storm bearing down outside, Andrew Young sat in an auditorium on GSK's Research Triangle Park campus. A medical doctor and native of New Zealand, until the month before he'd been a researcher in GSK's enteroendocrine discovery unit searching for drugs for such metabolic diseases as diabetes. "It was clear near the end of 2014 there would be layoffs," he says, "but it was a surprise that they cut all of the research and development in North Carolina." He and more than a hundred others listened as Shaffer and other panelists addressed a question aimed at potential entrepreneurs: Is there life after GSK?

Eight months later, Young has a new job. As chief scientific officer, he is one of six former GSK research teammates, all terminated, who founded Research Triangle Park-based Phoundry Pharmaceuticals Inc. to continue

their search for drugs based on peptide hormones such as insulin. It's fueled by a \$50,000 biotechnology center loan and venture capital from Durham-based Pappas Ventures and underscores why the future of a global pharmaceutical giant is of interest to more than shareholders: GSK and its ancestral companies have long served as spawning grounds for new life-sciences companies.

Cutbacks, layoffs, expansions and mergers and acquisitions have characterized pharmaceuticals since 1970, when Burroughs Wellcome set up headquarters in what was then a fledgling office park with big ambitions. Its iconic office, with spaceship-like cubes seemingly stacked at random on each other and designed by Paul Rudolph, was one of the state's first examples of postmodern architecture.

Then the college-age son of a Durham pharmacist, Bill Shore visited the building with his father. "We were both blown away not only by the architecture, but by the fact Burroughs Wellcome had chosen Research Triangle Park as its home," says Shore, who retired as GSK's community relations director in 2012. The building is now owned by Silver Springs, Md.-based United Therapeutics Corp., which researches such treatments as transplanting porcine lung tissue into humans. It bought the property from GSK for \$17.5 million in 2012.

A study last year led by Maryann Feldman, a UNC Chapel Hill public-policy professor, traced 144 firms whose founders and principals cut their teeth at GSK and antecedents Glaxo Wellcome, Glaxo and Burroughs Wellcome. "The vast majority of these new firms were established in the wake of acquisitions, mergers and major corporate restructurings," she says. Separately, biotechnology center records show a bump in startups in 1995 and 1996 after Glaxo acquired Burroughs Wellcome. Jim Shamp, an ex-Glaxo employee and now public relations director at the center, asked its librarian to trace former GSK workers.

"Of 239 people identified by GSK in the Research Triangle Park and Zebulon, 52 have president or vice president in their current job titles and 34 have C-level titles," such as chief executive officer, chief operating officer and chief scientific officer. The list includes life-sciences legends in North Carolina, such as Fred Eshelman, who left Glaxo Wellcome

in 1985 to create what is now Wilmington-based Pharmaceutical Product Development LLC, which has about 14,000 employees in 46 countries. PPD sold to an investment group in 2011 for \$3.9 billion. In December, as GSK was announcing layoffs, Eshelman said he would donate \$100 million to UNC Chapel Hill's pharmacy school.

GSK is giving many like Young and his colleagues at Phoundry a shove. "Probably at some stage we would have done something like this, but it was made easier by GSK forcing the decision on us," he says. Others left on their own, convinced that smaller, innovative entrepreneurial ventures can respond to the vagaries of big pharma better than GSK-scale behemoths. "You've got talent," Young says, "thinking they can do a better job on their own."

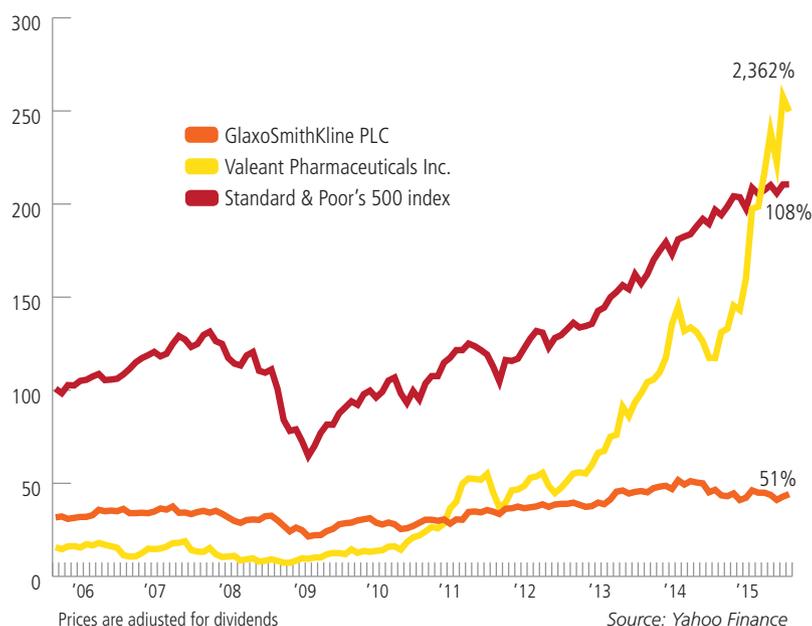
Stephen Frye underscores the point. He joined Glaxo immediately after receiving a doctorate in organic chemistry from UNC Chapel Hill in 1987. He achieved pharmaceutical rock-star status as project leader of the company's blockbuster Avodart, which became a \$1 billion-a-year drug for prostate disease. His last seven years there, he was world vice president for medicinal chemistry. He quit in 2007, and now heads the Center for Integrative Chemical Biology and Drug Discovery at UNC. "Over the years, GSK had a number of changes in direction, and I just wanted to try something different," he says. Two years ago, Frye, oncologist Doug Graham and Shelton Earp, former director of UNC's Lineberger Comprehensive Cancer Center, formed Meryx Inc. to seek treatments for leukemia and other cancers. The seven-employee company — some others came from GSK — has received funding from Eshelman, who is a director.

Still, GSK's challenges in 2015 differ in one respect from earlier ones. This time, a giant corporation is minimizing its risk, encouraging staffers to strike out on their own. "We were a functioning team at GSK," Young says of Phoundry's creators. "GSK was generous with us. We were able to keep the fruits of our work and some clinical information — they licensed it to us for a royalty — and they gave us a lot of the equipment we needed. They helped us get started."

Startup Meryx has discussed its projects with several large companies, Frye says. "The

GSK lags the market

GSK shares gained 51% in the last decade, half the increase of the S&P 500 index. Canada's Valeant, whose board includes ex-Glaxo CEO Bob Ingram, has soared.



most likely route for small companies like this is, if you're successful, somebody buys the product and completes the clinical development." Somebody like GSK? "Yes, if everything worked out, that's certainly a possibility."

Time will tell how much further the long coattails of GSK carry the life-sciences industry in North Carolina. Some insiders fear the chilly regard by some lawmakers sends shivers through the industry, which once enjoyed unquestioned political esteem. Former Gov. Jim Hunt made three trips to London to help recruit Glaxo in 1983, Shore says.

Regardless of GSK, the state has the necessary ecosystem, says Nerkar. "You have a bunch of talented people, you have the universities, the specialized knowledge, the hospitals, everything in place, for the equivalent of a Silicon Valley for life sciences." And often, motivation. Christy Shaffer relates how Martine Rothblatt founded United Therapeutics in 1996 to license and perfect a compound Glaxo had shelved because its worldwide market, about 200,000 patients, was too small to be profitable. It would treat pulmonary arterial hypertension, lethal high blood pressure in the lungs.

Since, Remodulin has saved thousands of lives worldwide. Rothblatt, the chairman and CEO, had become interested after her dying young daughter, today healthy and in her early 30s, asked, "Mom, isn't there a pill for this?" ■