THE START-UP ENGINE

Third Rock Ventures made its name by placing big bets on the biotechnology companies it launched. Now, everyone is waiting for the pay-off.

BY HEIDI LEDFORD

Bioengineer Mikhail Shapiro got a rude shock one day when he arrived for work at Third Rock Ventures, then a brand-new venture-capital firm headed by a handful of biotech elites. Only three weeks into his internship, Shapiro found a notice on the door: "Closed for business." Inside, 'For sale' signs hung on desks, equipment, everything — even the office's giant gumball machine. The company had folded, a note explained, because it could not raise enough money.

Kevin Starr, a partner at Third Rock, still beams with pride over that 2007 prank, which he and his confederates had filmed to capture Shapiro's reaction. "You could tell Mikhail was thinking, 'I knew that was going to happen to these guys!'" he recalls.

Few would fault Shapiro, now a professor at the California Institute of Technology in Pasadena, for his credulity. By 2007, the technology bubble of the early 2000s had burst, and investors were baulking at the long timelines and high failure rates involved in getting biotechnology products to the market. People laughed, says Starr, when he and Third Rock's other founders told them that the company wanted to raise US$378 million to create an investment fund to build biotech companies from scratch. "They advised us to aim for about a tenth of that."

But Third Rock, based in Boston, Massachusetts, did raise its initial fund, and it has not slowed down since. The company has brought in $1.3 billion and invested in more than 30 young companies, many based on cutting-edge research in fields such as cancer epigenetics, gene therapy and medical diagnostics (see 'Due diligence').

Products are only just starting to trickle out into clinical testing, but this year brought several signs that the firm has bet well. In January, Third Rock sold off Lotus Tissue Repair — a tissue-engineering company with an experimental therapy for a devastating rare disease that weakens skin. The deal could garner a 20-fold return for Third Rock if Lotus meets certain milestones. In March, Third Rock's third round of funding — $516 million to launch up to 16 more companies — had so many aspiring investors that the firm had to turn some away. And this summer, two of Third Rock's companies went public, their share prices soaring the moment they hit the market. As *Nature* went to press, a third firm — cancer diagnostics company Foundation Medicine in Cambridge, Massachusetts — was preparing to follow suit.

"For a long time, people said investing in these early-stage companies was not a great idea," says Robert Langer, a bioengineer at the Massachusetts Institute of Technology (MIT) in Cambridge who has spun off dozens of companies from his research (see *Nature* **458,** 22–24; 2009). "Third Rock has taken that risk and I think it's paying off."

LAID-BACK BIOTECH

Since 2007, Third Rock has expanded its offices on Boston's trendy Newbury Street — a neighbourhood filled with high-end boutiques and cafes. On a flaming day this summer, Starr sits in his office arrayed in silver jewellery, camouflage shorts and a green T-shirt that reads "Beach Punk 1982". A standard business shirt bides its time on a hanger behind the door.

Starr's laid-back style has found lots of attention in the business press, and it serves as a reminder that he does not have to be here. In 2003, he left a post as chief operating officer of Millennium Pharmaceuticals, a Cambridge-based biotech powerhouse that had just launched the blockbuster cancer drug Velcade (bortezomib). Millennium founder Mark Levin retired some time after Starr, and the two did the usual things that young retirees with plenty of money do — travelling the world and producing independent films and Broadway shows. In 2006, Starr says, during an annual pilgrimage to the golf courses and blackjack tables of Las Vegas, Nevada, Levin turned to him and said, "Hey Kev, why don't we just go do something again?"

Venture capital has a pivotal role in transforming science into medical advances, supporting companies during the long, lean, research-intensive years before they have any hope of turning a profit. In the United States, biotech soaks up billions of dollars in venture capital each year, second only to the software industry. In the mid-2000s, infusions into fledgling companies made up just a tiny fraction of that investment. Most of the money was going to established companies, often with products already in clinical testing. But the pharmaceutical industry was tightening internal research budgets and looking to small biotechnology firms for new medicines.

Amid that changing landscape, Starr and Levin saw an opportunity. There would be demand for innovative biotechnology companies, yet few venture capitalists were in a position to fill it. Through a series of meetings at Starbucks, Levin and Starr assembled a skeleton crew of biotech nobility and mapped out their ideal venture-capital firm.

STANDING OUT

Levin, Starr and Bob Tepper, former head of research and development at Millennium, wanted to do things differently from typical venture capitalists, who sift through ideas and business proposals from external researchers, help to set up a company and then hand over control to a newly recruited executive team. Starr says that he and his co-founders wanted to recreate some of the magic they had felt at Millennium, carrying over its 'anything is possible' mantra. They would hire only the best people, even if that meant interviewing candidates for months. And, rather than relying on proposals from the outside, they would focus on the hottest science, mostly investing in companies conceived by Third Rock's team. "Last year we saw 982 outside plans," says Starr. "We invested in zero."

All venture capitalists need to understand the science behind their investments, but Shapiro, who has since worked with other venture-capital firms, says that Third Rock is unique in how far its members personally immerse themselves in the details. "It's a bunch of nerds," he says. "You're in a commercial setting, but the rigour of the science was as high as it was at MIT or Caltech." Of the more than 40 employees now at Third Rock, only Levin, a chemical engineer by training, had worked in venture capital before. The rest had trained in the trenches as scientists, physicians and biotech business leaders. "They have decades of real, hands-on experience," says Michelle Dipp, a venture capitalist at the Longwood Fund in Boston. "It's an incredibly talented team."

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Third Rock also takes its time handing over the reins of its companies to outside executives; it often waits 18 months or longer. That is important for luring top talent, says Langer. "A lot of good chief executives are not willing to take the risk with a new company," he says. "With Third Rock, rather than getting the company when it's a newborn baby, a new executive is getting a pretty active 2-year-old."

Finding newborns to raise means exploring promising ideas, something that Third Rock spends about one-third of its time doing. Those that pass muster get up to $2 million and must go through a rigorous and lengthy screening process that employees refer to as the 'Third Rock Ultra Killer Kriteria' (TRUKK). Independent labs must be able to replicate key findings and find no warning signs of toxicity for drug candidates.

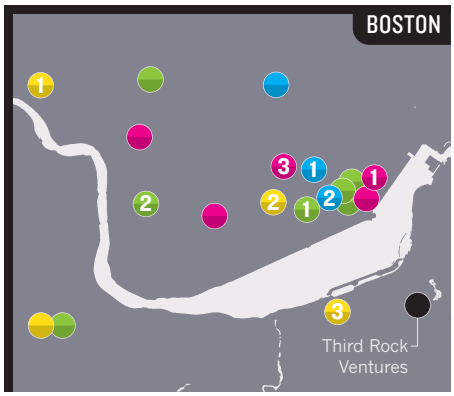
Third Rock also circulates the project idea to contacts at large pharmaceutical firms. If those companies have internal scientists working on the same project, Third Rock generally will not try to compete. Or if pharmaceutical insiders say that they like the idea but would not invest in it without seeing data from late-stage clinical trials, the project is scrapped. For all the talk of how anything is possible, Third Rock is ruthlessly practical.

To meet the TRUKK, a project must be no more than about three years away from clinical testing — a brutal necessity of the ten-year

Kevin Starr (right) and Mark Levin founded one of the hottest venture-capital firms in biotechnology.

DANA SMITH

DUE DILIGENCE *Third Rock Ventures has a portfolio of more than 30 companies that are developing drugs and therapies in several fields.*

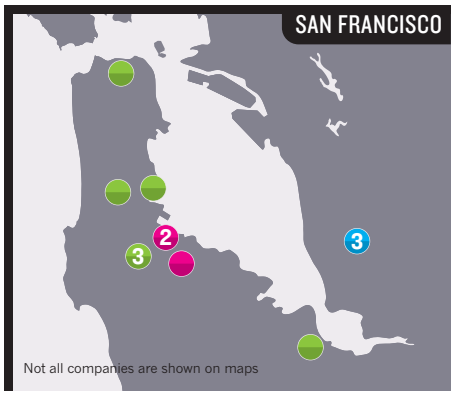


CANCER

1. **Constellation Pharmaceuticals**
   Targets proteins that regulate the genome epigenetically, such as the methyltransferase EZH2.
2. **Igenica**
   Aims to identify effective antibody treatments for cancer.
3. **Foundation Medicine**
   Develops tools to profile cancers genetically and better match patients to therapies.

METABOLIC DISEASES

1. **Ember Therapeutics**
   Develops diabetes and obesity drugs based on activating brown-fat stores in the body, among other mechanisms.
2. **Zafgen**
   Targets the enzyme methionine aminopeptidase 2, which regulates how the body metabolizes fat.
3. **Rhythm**
   Develops peptides to tackle obesity by regulating appetite-stimulating hormones.



DEVICES

1. **NinePoint Medical**
   Develops systems to perform real-time pathology on patient tissues without the need for biopsy.
2. **Seventh Sense Biosystems**
   Works on devices to track patient health by monitoring changes in the skin.
3. **Cibiem**
   Is testing a catheter-based approach to control symptoms of cardiovascular diseases, diabetes and renal failure by modulating the sympathetic nervous system.

OTHER

1. **Edimer**
   Works on X-linked hypohidrotic ectodermal dysplasia, which is associated with respiratory problems and a lack of sweat glands.
2. **bluebird bio**
   Develops gene-therapy approaches to treat conditions such as sickle-cell anaemia and childhood adrenoleukodystrophy.
3. **Afferent Pharmaceuticals**
   Targets a nerve receptor called P2X3 to treat chronic pain conditions associated with inflammation and injury.

funding cycles of venture capital, says Starr. This can mean painful decisions. A few years ago, the team evaluated the therapeutic promise of a class of gene regulators called long non-coding RNAs. The field is hot and the team loved its potential, but it was not close enough to the clinic to serve as the basis for a Third Rock company.

Although draconian on paper, Third Rock has bent its rules for some early investments. Agios Pharmaceuticals in Cambridge develops drugs to target metabolic changes that fuel tumours. It was among the first companies Third Rock backed, in 2007, but it was August 2013 before the firm began clinical trials on its lead compound — a drug to combat tumours that contain mutations in the metabolic gene *IDH2*.

Agios's chief executive, David Schenkein, says that the company's early drug leads did not work, forcing scientists to develop new candidates from scratch, but he has felt no pressure from Third Rock about the revised timeline. Starr says that Third Rock factors a few setbacks like this into its calculations. And when Agios went public in July, investors showed that the delay did not concern them either: Agios made $106 million and its stock rose 56% on the first day of trading.

DANGEROUS PRECEDENT

Some will watch companies such as Agios carefully, mindful of the history of Millennium Pharmaceuticals. Millennium was founded in 1993, intended — like many of Third Rock's companies — to be a 'product engine': a company based on a single scientific premise or technology that could generate multiple therapies. In Millennium's case, that premise was personalized medicine grounded on emerging human genomics data. That mission failed and, as with other firms of the era, Millennium's internal research programme foundered, burning up cash in the process. But the company did use its expertise to identify promising drug candidates from outside firms, bringing them into Millennium for the final stages of development and marketing.

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Long-term investors benefited: in 2008, the Japanese pharmaceutical company Takeda, based in Osaka, bought Millennium for $8.8 billion.

There may be debate about whether Millennium was a scientific success, but there is no doubt that the company had a tremendous impact on the booming Boston–Cambridge biotechnology industry. Former employees sit at or close to the helms of biotech companies across the region. They are often quick to credit Levin and the culture he created at Millennium. "We came in as scientists," says Rosana Kapeller, once director of molecular and cellular biology at Millennium and now chief scientific officer of Nimbus Discovery, a pharmaceutical company in Cambridge. "We left as entrepreneurs."

BRIGHT PROMISE

That environment allowed Millennium to succeed even after its initial mission failed, says Starr. "We built a company with the right formula and culture to be a successful long-term company," he says, "as opposed to a company that just stuck with one model and ran right into the wall."

Agios may be echoing Millennium in that respect. In addition to developing new compounds, it last year broadened its mission to include genetic diseases of metabolism. The firm has developed a compound that will enter clinical testing next year in patients with pyruvate kinase deficiency, a rare metabolic condition that causes severe anaemia.

Years will pass before Third Rock's success — whether measured in medical breakthroughs or in cash returns to investors — can be assessed. But people familiar with the team are certain of one thing: the pranks will continue. Asked to confirm the details of the joke that Starr played on him in 2007, Shapiro was confused. "Which one?" he asked.

"It's a really high-powered group of people with an incredible track record of achievement," he says. "But it's also a group of people who don't take themselves too seriously." ■

Heidi Ledford *reports for* Nature *from Cambridge, Massachusetts.*