



Biomedical philanthropy, Silicon Valley style

Entrepreneurs who made their fortunes in high technology are now giving money away to fund biomedical research. These new philanthropists are sending a breath of fresh air through the labs they support, says Trisha Gura.

In the early 1990s, Ben Barres wanted to explore a wild idea: could a long-ignored type of cell play a major role in building the brain's neural circuitry? At the time, most neurobiologists thought these glial cells provided little more than physical support for the brain's neurons.

At his lab at Stanford University in California, Barres painstakingly filled in three consecutive grant applications to the National Institutes of Health (NIH). After each was summarily rejected, Barres was on the point of giving up. But in late 1999, he received word of three reports due to be published in *Nature*. They revealed the identity of a protein — produced by a subset of glial cells — that stunts the regeneration of nerve cells.

The findings were of obvious medical significance, as blocking the protein's function might help treat patients suffering from brain injuries or stroke; they also fitted with Barres's broader thesis that glial cells were doing much more than providing scaffolding within the brain. Barres spent his Christmas holiday co-writing a News and Views article¹ that appeared alongside the three papers²⁻⁴, explaining and celebrating the findings.

Then Barres received a telephone call that changed his working life. The caller was the chief executive of a Californian company that makes microscopes used to check the fabrication of integrated circuits. He had

been fascinated by Barres's article. "He said he'd like to talk to me about the possibility of supporting our work," Barres recalls. "I'd never had a call like that before in my life."

A meeting was swiftly arranged, and Barres is now the recipient of funds generated by a \$3 million endowment. His entrepreneurial benefactor, who wishes to remain anonymous, is an engineer and chemist who holds 17 patents related to nanotechnology.

"I've always been fascinated with the chemical side of the brain," says the donor. He had also seen his mother succumb to dementia.

Barres's story is part of an emerging trend. Having made fortunes in high-tech companies or Internet ventures, many of Silicon Valley's entrepreneurs want to give something back. Some have followed the traditional route of endowing their Alma Mater to set up an institute bearing their



Beneficiaries: Ben Barres (left) and Stephen Strittmatter are funded by the same wealthy individual.



name, or launching a foundation that follows established modes of funding. But others, having grown up in a system where there is no system, are writing their own rules.

Risk takers

These philanthropists have cast aside lengthy grant applications and cumbersome peer-review panels. Instead, funding decisions are placed in the hands of individuals who are told to get to know the scientists working in a field and judge their projects to seek promising and innovative ideas. Sometimes, the benefactors take a hands-on role in deciding where the money should go. The approach has been dubbed 'venture philanthropy', and is the antithesis of the careful but conservative peer review operated by the NIH. By providing seed money to risky projects such as Barres's, the idea is that the winners will eventually amass funding from more traditional sources.

"The money should be viewed as the risk capital in the system," says Queta Bond, president of the Burroughs Wellcome Fund in Research Triangle Park, North Carolina, one of the more traditional biomedical philanthropies. "The new entrepreneurs are good at doing strategic analyses and finding where philanthropy dollars can make a difference. And they do make a difference." Indeed, although the hundreds of millions of dollars being awarded by such philanthropists is easily dwarfed by the \$16.9 billion devoted to extramural research programmes by the NIH for 2001, the speed, flexibility and careful targeting of the new philanthropists' dollars magnifies their actual amount.

In Barres's case, the investment is already bearing fruit. In January, he published a paper³ showing that neurons in culture dishes will not form functional synapses, the connections through which they communicate, unless glial cells are also present. Not surpris-

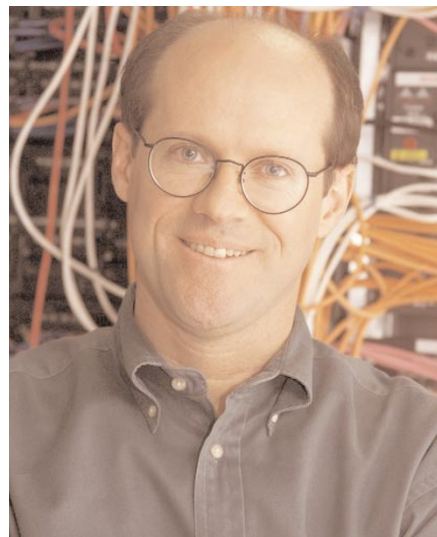
ingly, Barres is wildly enthusiastic about the contribution being made by the new breed of philanthropists. And other beneficiaries are similarly delighted at being freed from the treadmill of writing grant applications. "It lessens the pressures of raising grant dollars from other sources," says Stephen Strittmatter of Yale University in Connecticut, lead author of one of the papers about which Barres wrote his News and Views, and the recipient of funds from the same benefactor.

Big bucks

So who are the new philanthropists, and what are they funding? The most prominent is Microsoft founder Bill Gates, whose Bill and Melinda Gates Foundation, founded in 1994, holds assets worth \$21 billion, and is ploughing hundreds of millions of dollars into targeted health-related programmes — in particular efforts to find vaccines against developing-world killers such as AIDS, malaria and tuberculosis. In January, for instance, the Gates foundation gave \$100 million to the International AIDS Vaccine Initiative (IAVI), providing a major boost to its effort to raise \$550 million to move at least six vaccine candidates into clinical trials by 2007. "I think you have to give Gates enormous credit," says Kenneth Shine, president of the Institute of Medicine in Washington. "By investing as he has in vaccines and infectious disease, he has galvanized others to participate." Indeed, the Internet company Yahoo! announced in January that it was donating \$5 million to IAVI.

But many of the high-tech philanthropists are more interested in supporting research into ageing and neuroscience. "They are interested in how we as humans perceive, use and store information," says molecular biologist Phillip Sharp of the Massachusetts Institute of Technology (MIT), who has been selected to direct the McGovern Institute for Brain Research — for which MIT is receiving \$350 million over the next 20 years from computer publishing mogul Patrick McGovern and his wife Lore Harp McGovern, a high-tech entrepreneur.

Placing cash figures on the rise in biomedical philanthropy by such entrepreneurs is difficult. The Foundation Center in New York, which monitors overall US philanthropic spending, does not break its figures down according to the business background of the donating individuals. But observers



New breed: Steve Kirsch (left) and Sarah Caddick want scientists to have a 'business plan'.

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MARY MERRICK

such as the Institute of Medicine's Shine say that the rise in donations from high-tech entrepreneurs has been eye-catching.

In 1998, the Community Foundation Silicon Valley published a survey that provided a portrait of Silicon Valley's new philanthropists. The community foundation is an umbrella body that distributes money on behalf of donors who do not wish to set up their own foundations, but nevertheless want to dictate where the money should go. Its survey showed that the typical donor fell in the 35–44 years age bracket, was newly wealthy, and had an affinity for science.

Peter deCourcy Hero, president of the Community Foundation Silicon Valley, provided a tongue-in-cheek description of these philanthropists in a discussion paper for the Indiana University Center on Philanthropy's 13th Annual Symposium last August: "These are the 40-year-old engineers whose mid-Western school-teacher parents saw Sputnik go up ... [They] said: 'Johnny you become an engineer and you will never starve.' Well, now young Johnny is worth about \$20 million and neither Mom nor Dad left any instructions as to what to do with such a mind-boggling sum."

Gifts for the gifted

Steve Kirsch is one of the new breed. The founder of four successful start-ups — Infoseek, Mouse Systems, Frame Technology and most recently, Propel Software — Kirsch was asked in the early 1990s to serve on a fundraising committee by Leonard Ely, an old-school philanthropist in Silicon Valley. Kirsch was initially perplexed by the request, asking Ely why people donated to such committees. Ely recalls his response: "Steve, believe it or not, some people like giving their money away." He took Kirsch under his wing and taught him about philanthropy.

To begin with, Kirsch deposited his funds with the Community Foundation Silicon Valley, his donations totalling more than \$12 million by 1998. Kirsch's donor-advised fund began supporting individual researchers with interests consistent with his desire to cure or prevent diseases.

But Kirsch, a quintessential Silicon Valley entrepreneur, wanted to do something bigger. "Steve would like to cure all diseases, if he could," says the Kirsch Foundation's Sarah Caddick, who formerly administered the cancer research grant programme of the Damon Runyon–Walter Winchell Foundation in New York. His chance came with a windfall of cash from the sale of a portion of Infoseek to Disney in 1999. The deal gave Kirsch and his wife Michele \$50 million to plough into a new San José-based foundation. By creating the Kirsch Foundation, Kirsch freed himself from the restrictions imposed on donor-advised funds. Foundations, for instance, can engage in political lobbying. "Steve comes from the point of view that you have to use the most

effective moral and legal means to accomplish your goals," says Kathleen Gwynn, the foundation's president.

For Kirsch, 'effective' also meant eschewing the bureaucracy associated with traditional modes of biomedical research funding. Instead of asking for grant applications and putting their review in the hands of committees, Kirsch hired Caddick as director of medical and scientific programmes. Caddick's background in neuroscience fitted with one of Kirsch's priorities, and she is now in charge of figuring out who and what to fund.

Thought experiments

Caddick uses her scientific connections to seek out individuals with promising projects. In addition to reading the literature, she calls people she knows and asks for introductions to people she does not. In short, she networks. "I talk to leaders in the field — Nobel prizewinners, presidents of major institutions, deans and directors of departments," says Caddick. "Often these people don't need money, but they can be most objective about who does."

Instead of a detailed grant proposal, Caddick asks for a 'concept' — an outline of the proposed research in less than two pages. "Assuming that you are a top-notch scientist, I know that you can write a grant proposal," she says. "We don't ask for reams and reams of data. We ask: 'Are you thinking along the same lines that we are thinking of? If you are, then we can craft a business plan together.'"

With such talk of business plans, it is clear that the Kirsch Foundation operates more like a Silicon Valley start-up than a traditional foundation. What it wants is creativity with a sound scientific basis: risky, innovative ideas that are likely to draw further funding down the road. Having picked potential winners, the foundation carefully scrutinizes ongoing projects to check that they are delivering the goods. "A researcher may not be able to accomplish in a year what they set out to do," says Caddick. "We just ask that you make some headway in getting there or be able to explain why you cannot." But those that fail this test will find that the plug is pulled. "If you are a scientist not focused on curing diseases, then we are not the right funder for you," says Gwynn.

But for researchers with the appropriate

mindset, the Kirsch Foundation can represent, as Ronald DePinho of Harvard Medical School and the Dana-Farber Cancer Institute puts it, "a match made in heaven". DePinho is interested in the role of telomeres — the 'caps' on the ends of chromosomes — in cellular ageing. Telomeres grow shorter with successive cell divisions, and DePinho wondered if this might explain why diseases involving constant turnover of liver cells, such as hepatitis or alcoholism, often lead to the eventual failure of the organ.

DePinho had gained NIH funding to create mice lacking telomerase, the enzyme that rebuilds telomeres, and last year he published a paper showing that these mice struggle to repair their livers if the organs are damaged, but can be treated by replacing the enzyme⁶. As he prepared this paper for publication, he wanted to push the research forward and realized that getting further NIH funding would entail inevitable delays. So he went to Harvard's development office, leafed through a book of funders, and came up with the Kirsch Foundation. Harvard backed his application for an investigator's award that would pay out \$150,000 annually to DePinho and an additional \$30,000 to the university, for indirect costs. The foundation liked the idea, and started funding DePinho's lab. "They allowed me to seize the moment," says DePinho.

Kirsch anticipates that his foundation will be influential. "I hope that others will adopt the techniques we use to fund medical research," he says. "As we achieve success, this will be much more likely."

The new philanthropies are also cutting through a deceit at the heart of the traditional funding system — the fact that researchers often make their grant applications look convincing by applying for money to conduct research that they have, in fact, already done. They then use the funding to do the research that forms the basis of the next grant application, and so on. The problem lies in producing a competitive grant proposal if you genuinely want to move into a new area. "You can find any number of investigators who will tell you that if you haven't already done the first two years of work, you are in trouble," says Richard Sprott, executive director of the Ellison Medical Foundation in Bethesda, Maryland.

The Ellison foundation, launched in 1998

These are the 40-year-olds whose parents saw Sputnik go up. They said: 'Johnny you become an engineer and you will never starve.' Well, now Johnny is worth about \$20 million and neither Mom nor Dad left any instructions as to what to do with such a mind-boggling sum.



Silicon money: Larry Ellison's (left) foundation is spending \$45 million a year on biomedical research paid for from the fortune he made through his computer company Oracle, based in Santa Clara (above).

by Larry Ellison, chief executive of the computer giant Oracle, shares the Kirsch Foundation's ethos. Its main focus is ageing research — although Ellison recently decided to expand into tropical diseases. Sprott, formerly head of biology programmes at the National Institute of Aging (NIA) in Bethesda, was hired to work out how best to distribute the foundation's budget to complement the NIA's federal dollars. With the addition of its programme on tropical diseases, the foundation is now spending \$45 million a year.

"Our strategy is to pick cutting-edge people and turn them loose," says Sprott. To help find candidates, the foundation has assembled an impressive board, chaired by Nobel laureate Joshua Lederberg of Rockefeller University in New York, and including such luminaries as neuroscientist Eric Kandel of Columbia University, also in New York, who last year shared the medicine Nobel. "There are complaints that people of this calibre don't sit on NIH study sections any more," Sprott says. The reason, he suspects, is that NIH panels "get bogged down in trivia".

Again, paperwork is kept to a minimum. Lederberg's board reviews applications running to no more than four pages, supported by recommendations from colleagues and institutions. Sprott contrasts the Ellison foundation's procedures with the 25-page applications submitted to the NIH.

Wendy Baldwin, deputy director of extramural research at the NIH, defends the agency's peer-review procedures as necessary for quality control — and most scientists would agree that adopting the new philanthropists' techniques across the board would be a recipe for chaos. But even Baldwin admits that the NIH system moves slowly and shies away from more risky proposals. "We are never able to fund all the projects that

ought to get money," she says. Sprott agrees that the NIH and the new foundations are playing different, complementary roles: "We don't need to compete with the NIH," he says.

But for established biomedical foundations, the new philanthropies have brought a little competition. And some are now looking at the overall scene to work out whether they need to refocus their activities. David Seemungal, senior policy adviser at Britain's Wellcome Trust, notes that the new philanthropies tend to operate by "parachute funding — making large investments in specific research areas with little or no forewarning".

Federal bypass

Recognizing the need for better coordination, philanthropies new and old have recently started getting together to coordinate their activities. In a trend-setting initiative, representatives from the Howard Hughes Medical Institute, the American Cancer Society, the Pew Charitable Trust and the Burroughs Wellcome Fund have over the past 18 months organized two meetings for philanthropists, including the new players from Silicon Valley, to share their experiences. One topic of discussion has been how philanthropies can support research that is denied federal funding as a result of political sensitivities or legal restrictions. Private foundations could, for instance, become an important lifeline for scientists wanting to work with human embryonic stem cells, if the administration of George W. Bush, as expected, denies them NIH funding.

But researchers hoping to gain from the largesse of the new philanthropies have one big worry. Silicon Valley's entrepreneurs owe their immense wealth to the economic boom of the 1990s. With high-tech stocks already having faltered, and with talk of a recession

in the air, there is no guarantee that Kirsch, Ellison and their kind will carry on giving quite so generously. Indeed, neither Kirsch's nor Ellison's foundations have the security of an endowment — both are funded directly with cash from their founders' pockets. And Lori Arthur, who heads Stanford's development office, says that she is planning for a decline in income for the coming year.

But for now, those who have already benefited from Silicon Valley philanthropy urge researchers with an innovative proposal to get straight down to their university's development office, and ask for advice in selecting the donor best suited to fund their particular project. The result, say scientists such as Barres and DePinho, can be liberation from the continual and energy-sapping chase for federal research dollars. "We are buying back the researchers' time," says Caddick. ■

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Web links

Foundation Center

► <http://www.fdncenter.org>

Bill and Melinda Gates Foundation

► <http://www.gatesfoundation.org>

Community Foundation Silicon Valley

► <http://www.siliconvalleygives.org>

Survey of Silicon Valley philanthropists

► http://www.cfsv.org/giving_back_svway.html

Kirsch Foundation

► <http://www.kirschfoundation.org>

Ellison Medical Foundation

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