Philanthropy's Rising Tide Lifts Science

When Microsoft chair Bill Gates and his wife Melinda added $5 billion to the William H. Gates Foundation last June, the enormous donation took many by surprise—including the foundation's head, Bill Gates Sr. "My son doesn't confide in me what he's going to do the next quarter ... and I don't think he knows himself right at this moment," said Bill Sr., sitting in a conference room at his Seattle law firm a few weeks after the gift. True to form, 2 months later, the richest man on the planet and his wife donated another $6 billion. Recently renamed the Bill and Melinda Gates Foundation, the philanthropy now has a $17.1 billion endowment, making it the largest private grantmaker in the United States.

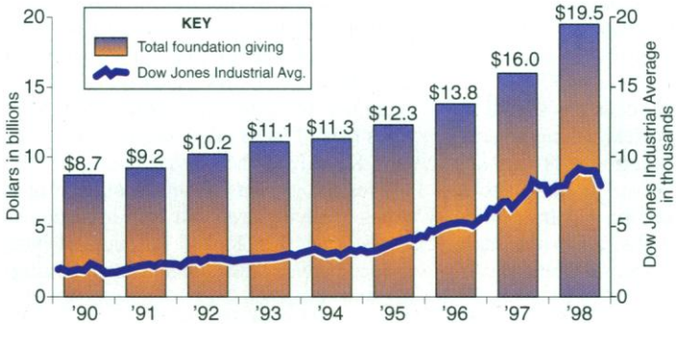
Philanthropy is booming. U.S. private foundations will spend more than $20 billion this year, the total going into science is growing fast, and several new players have joined the big spenders. The profiles that follow are just some of the organizations that are funding research

The sudden ascendancy of the Gates Foundation is part of a sea change taking place in the philanthropy world. Fueled by profits made in the stock market—especially the explosive growth of Internet stocks, which has created overnight billionaires—Gates and other neophilanthropists have begun to give away substantial portions of their fortunes, enjoying substantial tax breaks in return for their largess. Many, Gates included, are devoting impressive sums to scientific research. The bull market has also dramatically increased the endowments of more established foundations, leading several U.S. nonprofits—which must spend 5% of their assets each year or face tax penalties—to launch bold new science-oriented projects. And, in what appears to be a spillover effect, even foundations that have not realized tremendous gains in their endowments are getting in on the act with high-impact, big-bucks gifts to science. More surprises are surely in store. "It's a rapidly changing picture," says David Hamburg, former head of the venerable foundation known as the Carnegie Corp. and past president of the Institute of Medicine. "What would happen if there were to be a deflation? God only knows."

According to the latest figures compiled by the Foundation Center, a New York City–based group that tracks grantmaking nonprofits, endowment values in 1997 jumped 23% to $329.9 billion. Total giving, in turn, went from $15.98 billion in 1997 to $19.46 billion in 1998—the largest jump since the Foundation Center began keeping records nearly 25 years ago. (This does not include giving either by public charities, such as the American Cancer Society, which typically raise money from the public, or corporate foundations.) There's no evidence that science is receiving a larger share—the Foundation Center calculates it received 5.4% of the total in 1997, slightly down from 5.7% in 1991—but the rising financial tide is lifting all ships. "The surge of the stock market has had enormous implications for foundations," says Burton Weisbrod, an economist at Northwestern University who studies nonprofits. "It's had a profound impact."

Although biomedical-related research is the major scientific beneficiary of this philanthropic bonanza, the disciplines that nonprofits support are varied, as are the organizations' styles of giving, the processes they use to make funding decisions, and the amount of attention they seek. During the past year, the fast-changing Gates Foundation has sunk $100 million into groups researching and developing vaccines to combat AIDS, malaria, and tuberculosis, sometimes not even issuing a press release to announce a major donation. The higher profile W. M. Keck Foundation announced a $110 million gift to the University of Southern California, part of which will help establish a new neurogenetics institute. Keck, the offbeat James S. McDonnell Foundation (see p. 220), and the low-profile David and Lucile Packard Foundation (see page 222)—second only to Gates in its U.S. endowment—recently launched generous programs that award young investigators up to $1 million over several years. Somewhat smaller, but still plum, grants for young researchers now come from three highly specialized foundations—Whitaker (which funds biomedical engineering; see p. 220), the Ellison Medical Foundation (aging research; see p. 220), and the Doris Duke Charitable Trust (clinician-researchers who don't experiment with animals). And during the past 4 years the North Carolina–based Burroughs Wellcome Fund has nearly doubled the number of awards it makes to biomedical researchers in the early stages of their careers.

Following the model of the staid Howard Hughes Medical Institute (HHMI), which mainly hires researchers as employees instead of awarding grants—a distinction that puts it in a different tax category, so it only has to spend 3.5% of its assets annually—two new large medical research institutes now are under construction: the Van Andel Institute in Grand Rapids, Michigan, and the Stowers Institute for Medical Research in Kansas City, Missouri (p. 218). Both are named after their wealthy benefactors. Hughes itself—the largest private, nonprofit U.S. funder of biomedical research—increased its spending by $50 million last year to $557 million, an increase that went largely to renovating labs and upgrading equipment. The Wellcome Trust, the world's largest charity with an endowment topping $19 billion,



Bull market. Total spending by U.S. grantmaking nonprofits more than doubled in the 1990s, mirroring the rise in the Dow.

SOURCES: THE FOUNDATION CENTER; DOW JONES & COMPANY, INC.

A SELECTION OF SCIENCE-FUNDING PHILANTHROPIES

Name	Founded	1995 Assets	1999* Assets	1999* Science expenses	Research focus
Wellcome Trust	1936	$9.6 billion	$19.2 billion	$640 million	Biomedical, no cancer
Bill and Melinda Gates Foundation	1994	$2.8 million	$17.1 billion	$230 million	Vaccines, reproductive medicine, public health
David and Lucile Packard Foundation	1964	$2.4 billion	$13.5 billion	$84.7 million	Ocean sciences, computer science, math, natural science, engineering, interdisciplinary
Howard Hughes Medical Research Inst.	1953	$8.2 billion	$12 billion	$427.7 million	Biomedical
Pew Charitable Trusts	1948–79	$3.7 billion	$4.7 billion	$6.95 million	Biomedical, neuroscience
Rockefeller Foundation	1913	$2.4 billion	$3.5 billion	$20 million†	Reproductive health, agriculture, vaccines, epidemiology, malaria
Andrew W. Mellon Foundation	1940–69	$2.5 billion	$3.5 billion	$3.1 million	Contraception, reproductive biology, ecology
Kresge Foundation	1924	$1.72 billion	$2.1 billion‡	$4.6 million†	Scientific equipment
Carnegie Corporation	1911	$1.2 billion	$1.7 billion	$1 million	Russian science
W. M. Keck Foundation	1954	$1 billion	$1.7 billion	$38.1 million†	Science & engineering, medical, astronomy
Donald W. Reynolds Foundation	1954	$955 million	$1.4 billion	$35.2 million over 5 years	Cardiovascular clinical research, geriatrics
Doris Duke Charitable Trust	1997	N/A	$1.4 billion	$13.8 million	Physician-scientists, no animal research
Alfred P. Sloan Foundation	1934	$935 million	$1.2 billion†	$5.6 million	Astronomy, molecular evolution, neurobiology, marine biology, computational biology
Burroughs Wellcome Fund	1955	$318 million	$669 million	$35 million	Biomedical
Edna McConnell Clark Foundation	1969	$525 million	$640 million	$898,000	Trachoma, onchocerciasis vaccine
Welch Foundation	1954	$374.8 million	$632 million	$23 million	Chemistry, primarily in Texas
Carnegie Institution of Washington	1902	$444.6 million	$527.1 million†	$31.4 million	Astronomy, geophysics, plant biology, embryology
M. J. Murdock Charitable Trust	1975	$308 million	$525 million†	$4 million	Natural sciences, primarily in Pacific Northwest
James S. McDonnell Foundation	1950	$318 million	$480 million‡	$19 million‡	Neuroscience, genetics, astronomy, complex systems
Arnold and Mabel Beckman Found.	1977	$254 million	$450 million	N/A	Chemistry, biochemistry, medicine
Whitaker Foundation	1975	$420 million	$390 million	$65.7 million	Biomedical engineering
Stowers Inst. for Medical Research	1994	$67 million	$340 million	$5 million	Systems biology, genomics, proteomics
Whitehead Inst. for Biomedical Research	1982	$168 million	$312 million	$6.2 million (from endowment)	Genomics, cancer, infectious diseases, developmental and structural biology
Charles A. Dana Foundation	1950	$250 million	$311 million	$10 million	Neuroscience
Van Andel Institute	1996	N/A	$200 million	N/A	Cancer
Research Corporation	1912	$100.1 million	$152.3 million	$6.4 million	Chemistry, physics, astronomy
Camille and Henry Dreyfus Found.	1946	$86.6 million	$125 million	$3.4 million	Chemistry
Buck Center for Research in Aging	1999	N/A	$106 million†	$5.5 million	Aging
Ellison Medical Foundation	1998	N/A	N/A	$100 million over 5 years	Aging

* Many of these are estimates † 1998 Figures ‡ 1997 Figures.

SOURCES: THE FOUNDATION CENTER AND INDIVIDUAL FOUNDATIONS

added nearly $20 million to the U.K.'s Sanger Centre in March to speed the decoding of the human genome and the next month ponied up $25 million for a new consortium with the pharmaceutical industry that aims to create a public database of genetic markers.

Still, it's important to remember that philanthropic spending on science is dwarfed by the amount the U.S. government invests, says W. Maxwell Cowan, chief scientific director of HHMI. Cowan estimates that, worldwide, philanthropies last year spent no more than $2 billion on science. By comparison, the U.S. National Institutes of Health (NIH) last year alone had a $13.6 billion budget, which was complemented by more than $3 billion each at the U.S. National Science Foundation (NSF) and NASA, and another $2.2 billion at the Department of Energy.

The trick for foundations, then—especially ones that fund biomedical research—is figuring out ways to distinguish themselves without becoming so idiosyncratic that they limit their impact. "Private foundations are in the rifle business whereas the federal government is in the shotgun business," says John Schaefer, head of Research Corp., an Arizona-based foundation devoted to research in the physical sciences. "We have to define very specific targets."

Bridging gaps

Before World War II, philanthropies like The Rockefeller Foundation and Carnegie played a leading role in funding—and shaping—American science. With strong scientific leaders, the most celebrated of whom was Rockefeller's Warren Weaver, this form of patronage birthed new fields such as molecular biology, encouraged interdisciplinary research, and strongly supported the careers of chosen individuals. But with the rise of NIH, and to a lesser degree NSF, the big foundations began to invest their money more in social action, such as feeding the world and controlling population growth, than in basic research. "They couldn't begin to compete with NIH and they backed out," says Joshua Lederberg, a Nobel Prize–winning researcher at The Rockefeller University in New York City who sits on the board of the Ellison foundation.

The support that philanthropies did give to scientific research began to focus on filling gaps, which often meant funding research that was either too high-risk or too controversial for the government. "Foundations have many more degrees of freedom

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PROFILE

Biomedical Heavyweights

The Howard Hughes Medical Institute (HHMI) and the U.K.'s Wellcome Trust are the undisputed heavyweights of private biomedical funding. They spend more on research than do most governments, and their influence is soaring along with their endowments. Their differences are as striking as their similarities, however

Hughes

Aviator and industrial mogul Howard Hughes, a famously unusual man, in 1953 made a most unusual business move: He gave all the stock of his Hughes Aircraft Co. to the newly formed Howard Hughes Medical Institute, which would support itself with company profits. Instead of building a central institution like the Carnegie Institution of Washington, Hughes and his scientific advisers decided to "hire" leading academics around the country, paying their salaries but allowing them to stay at their universities. The goal was to free some of the best biomedical scientists to pursue whatever research avenues they desired.

HHMI continued to follow that model as it became a biomedical powerhouse, starting in 1985, when the Hughes Aircraft Co. was sold for $5 billion. That nest egg has since grown to $12 billion, and the institute is now spending almost $600 million a year. In addition to supporting 313 researchers in cell biology, immunology, neuroscience, structural biology, and genetics, it has expanded its grants programs, providing almost $100 million a year for activities ranging from improving science education to creating museum exhibits to helping medical schools shore up their research infrastructure.

The $428 million Hughes spent last year on its far-flung investigators gives them the kind of freedom Hughes envisioned. HHMI investigators, who are nominated to Hughes by their institutions and then compete for slots, receive an average of $600,000 a year to cover salaries and research expenses. (Tax laws stipulate that they cannot use the money to hire graduate students, however.) HHMI does not tell them what to research, and they are encouraged to take risks, such as venturing into new fields. The institute does not make investigators write grant applications, but it evaluates them for refunding every 5 years.

They are the biomedical world's elite, publishing a disproportionately high number of the papers in the best journals and working at the country's leading biomedical universities. More than 60 are members of the U.S. National Academy of Sciences (NAS). "Obviously, they're supporting some of the best scientists in the States," says Wellcome Trust director Michael Dexter. "They have such a high level of quality, it's hard to criticize them," says David Hamburg, now a president emeritus at the New York–based Carnegie Corp.

Yet Hamburg and others have raised questions about Hughes's philanthropic funding model. "Fundamentally, it was a very useful augmentation of the NIH's [National Institutes of Health's] work, and it certainly put some outstanding senior scientists in a position of freedom," says Hamburg. "But it's very hard to make the case that those people wouldn't have been well supported otherwise." Bruce Alberts, head of the NAS, also has high praise for HHMI, especially in feeding nascent biomedical fields, liberally supporting transgenic mouse research, and funding creative educational programs.

But Alberts says he has worried from the outset that generously funding accomplished researchers would have a downside. "You take a lab of 20 and tell them to double the size of the group," he says. "I think that's not an effective way to spend money."

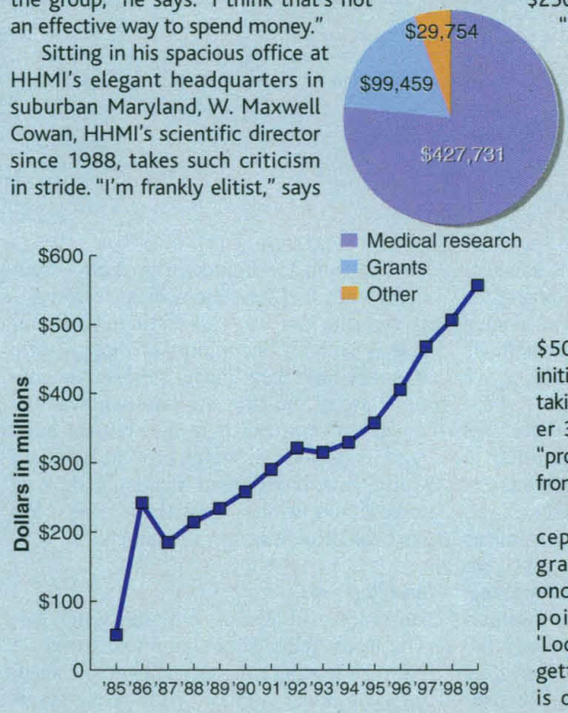
Sitting in his spacious office at HHMI's elegant headquarters in suburban Maryland, W. Maxwell Cowan, HHMI's scientific director since 1988, takes such criticism in stride. "I'm frankly elitist," says Cowan, a native of South Africa who formerly was vice president of the Salk Institute for Biological Studies and provost of Washington University. "We're in the business of supporting, if we can, the best science, and if the best science is in places where there are already substantial resources, that's fine." He adds: "The institution has supported a large number of very good scientists and enabled them to do things they might otherwise not have done."

Hughes investigators agree. "It makes a huge difference," says Carla Shatz, a neurologist at the University of California, Berkeley, who became an HHMI investigator in 1994. Shatz says that since being funded by HHMI, she moved from researching the physiology of the brain to molecular studies that focus on the genetics of neural activity: "The degree of risk and creativity I can exercise with Hughes funding allowed me to embark on a completely new set of experiments." Shatz adds that before becoming a Hughes investigator, she had research grants from five different organizations, which was drowning her in administrative work: "It was an extremely inefficient use of my time."

Tyler Jacks of the Massachusetts Institute of Technology, who studies mouse cancer genetics, echoes these sentiments. His Hughes funding, he says, has been especially important for his work. "I run a fairly large mouse colony," says Jacks, noting that he spends $250,000 a year on the animals alone. "Hughes allows me to do bigger scale science."

One particularly sensitive point among biomedical researchers is the amount of money Hughes investigators draw from other sources, particularly NIH. An analysis by *Science* indicates that although roughly 20% of the 332 HHMI investigators in 1998 did not receive any NIH grants the preceding year, 45 received $500,000 or more in investigator-initiated NIH grants, with five of those taking in more than $1 million. Another 30 HHMI investigators had NIH "program project" grants that ranged from $750,000 to $7.6 million.

Cowan himself says he takes exception to those who draw large grants from NIH, noting that he once confronted a researcher on this point. "I wrote to him and said, 'Look, the amount of money you're getting from the federal government is obscene given how much we're providing you.' " But Cowan, who is retiring in March, says he believes HHMI investigators are wise to seek



Looking up. HHMI's spending has soared since the sale of Hughes Aircraft. The bulk of its 1999 funding (*inset*) supports elite Hughes investigators.

SOURCE: THE HOWARD HUGHES MEDICAL INSTITUTE

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some NIH funding, as it "helps them remain in the real world." Some, he notes, use NIH money solely to support grad students. "This notion that Hughes investigators are awash in money is just not true," he says.

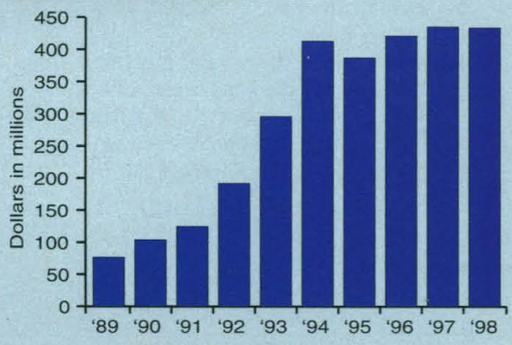
As for Hughes's future, it plans to branch into computational biology and hire possibly a dozen new investigators. And its relatively low-key image will likely begin to change in January when Purnell Chopin, president since 1987, hands the reins to Nobelist Thomas Cech. "Purnell is by nature not someone who takes public stands on issues," says Cowan. "He's a much quieter individual. I think Tom Cech may be quite different in this regard. He'll be a much more outspoken, and perhaps a better, spokesman."

Wellcome

At roughly the same time that HHMI rose to prominence, the London-based Wellcome Trust emerged as the world's largest charity—and leading private funder of scientific research. Established in 1936 upon the death of pharmaceutical company founder Sir Henry Wellcome, the Wellcome charity (which has had several names over the years) used profits from Sir Henry's pharmaceutical company to fund "scientific research which may conduce to the improvement of the physical conditions of mankind." The annual amount spent by the charity jumped dramatically following the 1986 decision to take the pharmaceutical company public, and then again when it sold a heft of shares in 1992. Last year, the Wellcome Trust spent more than $600 million on its various projects, which range from supporting individual biomedical researchers to bankrolling entire institutions.

Just as HHMI devotes most of its budget to scientists in the United States, Wellcome Trust devotes most of its resources to scientists in the United Kingdom. But whereas HHMI is a small player in biomedical funding compared to the U.S. government, Wellcome outspends the combined budgets of the U.K.'s main government funders of biological research, the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council. "We're doing our bit to pull England up to standards," says trust director Dexter. Andrew McMichael, a leading immunologist at Oxford University, notes that Wellcome's surge in spending on science has made an enormous difference. "This happened at a time when government funding, particularly from the MRC, was declining," explains McMichael. "For people in medical science, we felt we were saved by the Wellcome Trust."

Wellcome's ability to alter the funding landscape in the United Kingdom is but one of several important distinctions between the trust and HHMI. Wellcome, for example, targets specific diseases (such as malaria) and altogether avoids others (namely, cancer) if they're relatively well funded. Where HHMI shies away from taking political stands on issues, Wellcome has mixed it up with the U.K. government over its attempt to force charities to pay overhead costs on grants (*Science*, 22 November 1996, p. 1292) and fought to keep genomics data public (*Science*, 16 April, p. 406). Wellcome also helped found an entire institution, the Sanger Centre, a premier genomics institute.



Welcome funding. The Wellcome Trust now outspends the U.K. research councils on biomedical research. Trust director Mike Dexter (*above*).

Wellcome has its own biotechnology company, Catalyst BioMedica, that hopes to translate trust-funded basic research into products. And Wellcome's career development program devoted $60 million last year to up-and-coming researchers, three times as much as HHMI spent on various research grants for younger investigators. As Dexter sees it, HHMI mainly helps established researchers, while "we're looking for stars before they emerge in the sky."

About one-third of Wellcome's money supports unsolicited proposals sent in by researchers. Wellcome explicitly excludes researchers who want to "top off" support from other sources and will not fund anyone who receives a salary from a U.K. research council. Still, like HHMI, Wellcome often supports work that otherwise might be funded by the government, making it difficult to distinguish between the two. "That's a problem for both of us," says MRC executive director George Radda, who meets regularly with Wellcome's Dexter. "The distinction is the way we support science but not necessarily what we support." Wellcome has also joined forces with the government on a large scale. It launched a new program last year, the Joint Infrastructure Fund, with the Chancellor of the Exchequer. In all, Wellcome committed $650 million to the massive project, which plans to revamp universities and construct a new-generation synchrotron (an x-ray–emitting particle accelerator used for crystallography and other applications).

A few weeks ago, says Radda, he and Dexter talked about Wellcome's future. "He said, 'We have to decide what we are, now that we're so large,' " recounts Radda. "I think it's fair to say that they are searching for what their role really is." Once Wellcome comes up with a long-range plan, says Radda, "we can start planning together."

than the federal agencies do," says Schaefer. "They don't have to answer to Congress. And they can take gambles that governmental entities are not permitted to take."

Many foundations that support scientific research attempt to fill voids and make a name for themselves by concentrating their resources on narrow areas of research. Many focus on one disease and even specific populations, such as the Edna McConnell Clark's program, which supports research to prevent blindness caused by trachoma and onchocerciasis in poor countries. Others make their name by promoting a scientific discipline—the Camille and Henry Dreyfus Foundation funds only chemistry; some take this a step further, like the Welch Foundation, which aims to boost the resources of chemists working at universities in Texas.

Some science-friendly foundations make a mark by purchasing expensive equipment, like the $140 million that Keck spent on the world's two largest optical and infrared telescopes at Hawaii's W. M. Keck Observatory, which is run by NASA, the University of California, and the California Institute of Technology. The Arnold and Mabel Beckman Foundation rose to prominence by building five institutes and centers, which conduct research in a vast range of science and engineering disciplines, at topflight universities and medical centers. Wealthier foundations also can afford to distinguish themselves by awarding large gifts to individuals, as HHMI does. The 2-year-old Doris Duke Charitable Trust now is introducing a

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CREDIT: (TOP) SUSIE BARKER & HARLEY EVANS PHOTOGRAPHIC DESIGN; (BOTTOM) SOURCE: THE WELLCOME TRUST

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variation on the HHMI theme: Last week, the trust decided to award $3 million over the next 5 years to four preeminent clinician-researchers (Kenneth Anderson, Dana-Farber Cancer Institute; David Scheinberg, Memorial Sloan-Kettering Cancer Center; Bruce Walker, Massachusetts General Hospital; and Alan Gewirtz, University of Pennsylvania). "Very few Howard Hughes investigators do clinical research," explains Duke's Elaine Gallin, who heads their medical research. "We're trying to fill that gap."

Another strategy is to back only terrifically imaginative projects. Take the 65-year-old Sloan Foundation: In recent years, its scientific research grants have funded theoretical neurobiology, studies of the limits of knowledge, and a sky survey that promises to map millions of galaxies and 100,000 quasars.

This emphasis on carving out a niche can have a downside, however. As Lederberg puts it, "Foundations have been very jealous of their own identities." As a result, they rarely work together or with the federal government, fearing that they will dilute their own impact. The result, says Schaefer, can be missed opportunities and duplication of effort. He points out, for example, that many foundations feature grant programs for young researchers. "It's silly for everyone to try to develop the exact same kind of stuff," he says. Schaefer has attempted to attack the coordination problem head on, organizing two meetings during the past year with the leaders of different philanthropies that support science. "I've been a foundation president for 18 years, and it always frustrated me that there wasn't good communication between foundations," he says.

Maxine Singer, head of the Carnegie Insti-

PROFILE

Making a Name For Themselves

The Stowers Institute for Medical Research and the Van Andel Institute are about to join a distinguished list of research institutes named after their wealthy benefactors

Kansas City, Missouri, and Grand Rapids, Michigan, aren't exactly hotbeds of biomedical research. Neither boasts a heavyweight biology department at a major university. Neither is home to a world-class medical center. Neither features a thriving biotechnology or pharmaceutical industry. But both have wealthy native sons—mutual fund billionaire Jim Stowers in Kansas City and Amway co-founder Jay Van Andel in Grand Rapids—who have decided to share their fortunes with their hometowns by building multimillion-dollar medical research institutes. Their budding research centers have healthy endowments, prestigious scientific advisers, and the promise of more money to come.

In 1994, Stowers, founder of American Century Companies, and his wife, Virginia, started the Stowers Institute for Medical Research in Kansas City with a $50 million gift of company stock. The institute immediately began funding a consortium of outside researchers studying gene expression. A second consortium began mapping the DNA of the sea urchin in 1997.

Ellen Rothenberg of the California Institute of Technology in Pasadena, a member of the first consortium, has used the money to develop an in vitro assay system that aids in the hunt for mouse lymphocyte genes. "Unquestionably, the most important research my lab has been doing for the last 5 years has been entirely because of this funding," says Rothenberg. Because developing assays often is not perceived as cutting-edge research, the National Institutes of Health "in a million years wouldn't have funded us to move in this direction," she says.

Since the institute's founding, further stock donations and the booming market have pumped up its endowment to $340 million today. But the Stowerses have bigger plans than simply funding networks of researchers around the country: They're building a new 56,000-square-meter building, set on 4 hectares in Kansas City, that will open in mid-2000 and eventually will house as many as 60 principal investigators.

Embracing science. The Stowerses at the site of their new institute.

Molecular biologist Leroy Hood of the University of Washington, Seattle, who heads the nascent institute's scientific advisory board and is part of the consortium with Rothenberg, says the Stowerses initially "had a pretty ill-defined idea" of what they wanted their institute to do. "I said what I'm looking to do is talk about systems biology with the tools of genomics and proteomics [studying all the proteins in an organism]," says Hood. The Stowerses liked that idea, and their institute will try to make its mark in those burgeoning fields, focusing largely on developmental biology.

In Grand Rapids, Van Andel and his wife Betty have taken a chunk of the fortune they've made from Amway, the famous door-to-door retailer of home products, and created the Van Andel Institute, which now has an endowment of about $200 million. In January, the Van Andels plan to open a stunning, 15,000-square-meter research facility that will accommodate 25 principal investigators. Designed by noted New York architect Rafael Viñoly, the building is just the first phase of a facility that will eventually be more than twice that size. Van Andel also plans to "hire" researchers offsite, in the way that the Howard Hughes Medical Institute employs its investigators. (Like Hughes, both the Van Andel and the Stowers must spend an average of 3.5% of their assets each year.)

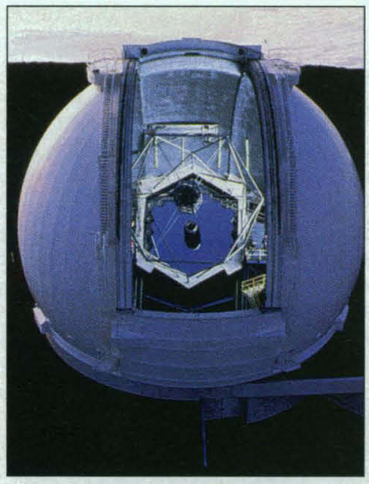
A scientific advisory board that includes four Nobel laureates encouraged the Van Andels to specialize in cancer research and recruit George Vande Woude, a longtime official and researcher at the National Cancer Institute, as director of their institute. "I have no doubt that in 50 years it will be one of the major research institutes," says Vande Woude, who will take the helm in November. Louis Tomatis, a retired cardiac surgeon in Grand Rapids who is president of the new institute, says he expects the Van Andel to stand out by taking on research projects that others avoid. "Government cannot take risks," says Tomatis. "Here, if four Nobel researchers tell us to research something that everyone thinks is a dog, we'll do it."

For both institutes, the key to their success will be the quality of researchers they hire. Yet cancer researcher Robert Weinberg of the Whitehead Institute for Biomedical Re-

CREDIT: STOWERS INSTITUTE FOR MEDICAL RESEARCH

tution of Washington in Washington, D.C.—which is independent from the Carnegie Corp.—also worries that some modern philanthropists are myopic. "The big problem I see with the current fashion in philanthropy is that the donors are quite specific in what they want for their money, and therefore they don't have the kind of impact that they could have," says Singer. "Very often they limit their goals because they're in touch with a specific group of scientists." She says she's particularly struck by how much of new philanthropic money for scientific research is limited to biomedicine.

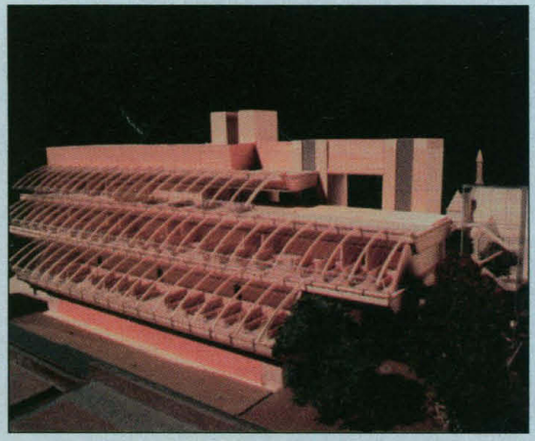
Singer, who is researching a book about the history of philanthropy and science, notes that Andrew Carnegie set a broad agenda in 1902 when he established the institution she now runs. He stated only that it should "encourage, in the broadest and most liberal manner, investigation, research, and discovery, and the application of knowledge to the improvement of mankind." As a result, researchers at the Carnegie Institution of Washington—who, incidentally, have enjoyed raises recently because that endowment has flourished—to this day specialize in an array of disciplines ranging from planetary sciences to embryology to plant biology. "Philanthropists don't think enough about what's going to happen to their philanthropy when they're gone. Will it be doing great things in 50 years? Those with more specific instructions will be time-bound," says Singer.



Eponymous scope. One of two Keck Telescopes, courtesy of the Keck Foundation.

search—a Cambridge, Massachusetts, powerhouse that the leaders of both new institutes cite as an example of what they hope to become—notes that "attracting high-quality researchers to Grand Rapids or Kansas City can be quite an undertaking." Indeed, both institutes are wrestling with this now.

Hood says recruiting high-quality junior researchers should be no problem: "It's hard as hell for young people to get started. For very, very ambitious, good [people], these research institutions could be very attractive." But top-notch, accomplished investigators are another story. "Really good senior people are generally happy where they are," says Hood. Tomatis and Vande Woude acknowledge the challenge, too. "One of the biggest drawbacks is not having a university here," Tomatis says. But he anticipates that the Van Andel will catalyze the growth of a biotech industry: "It will take five or 10 years." Vande Woude jokes that he's also banking on the weather patterns changing. "I keep on telling everyone I'm waiting for global warming."



CREDIT: (TOP) ROGER RESSMEYER/W. M. KECK OBSERVATORY; (BOTTOM) RAFAEL VIÑOLY ARCHITECTS PC

Home base. A model of the Van Andel Institute's stunning new building, now going up in Grand Rapids.

Another potential recruiting hurdle for both institutions has to do with a different kind of climate: political and religious. As an article in *Business Week* last year bluntly put it, the Van Andels and their co-partner in Amway, the DeVos family, are well known for being "fervently conservative, fervently Christian, and hugely influential in the Republican Party." Vande Woude acknowledges that he had some concerns about his independence because of this. "It was discussed," he says, and he was assured that the family's political and religious beliefs would not influence the running of the institute. "I don't think so, I know so," says Vande Woude.

For the Stowers Institute, the recent decision by the Kansas school board to remove the teaching of evolution from public schools could be a drawback because many people who work in Kansas City, Missouri, prefer the housing across the river in Kansas City, Kansas. "Having a state with that kind of attitude could well have an impact on recruiting," says Hood.

Whatever recruiting difficulties these two institutions face, money won't be a problem. When the Stowerses die, they plan to give the institute their remaining stock in American Century, which is now worth nearly $900 million. The Van Andels similarly have pledged to donate all of their taxable assets, which Tomatis says may now be worth as much as $2 billion, to their institute.

Anything goes

One of the great virtues of foundations is that they can be far more freewheeling than government funding agencies. Except for government regulations regarding financial disclosure, they can largely ignore the public, with some multibillion-dollar foundations, such as the Indiana-centric Lilly Endowment (which has roughly $13 billion but stays away from scientific research to avoid competing with the Eli Lilly pharmaceutical company), not even bothering to offer home pages on the Web. They can throw themselves into the middle of sensitive societal issues, just as Rockefeller has supported contraceptive research, without suffering any obvious repercussions. Many pay little attention to how their grantees spend the money. And when it comes to science, much to the chagrin of some observers, they can completely ignore the system of peer review to determine who gets their largess.

Bill Gates Sr., for example, says he doesn't want the Gates Foundation to become hidebound by bureaucracy, so he runs a lean and mean staff and doesn't use formalized peer review. Although he did consult medical and scientific experts before awarding a total of $100 million to the three vaccine R&D efforts, "I wouldn't want you to overestimate the amount of research we do on this stuff," says Gates. "Responsible people represent to us that there is a need, and there are all sorts of ways money can be spent to enhance the probability of coming up with something, and we take their word for it." Gates's decision-making process, though, may soon become more conventional, as the foundation is undergoing significant changes (see p. 222).

The Los Angeles–based Keck Foundation similarly relies on informal contacts with experts before presenting ideas to its board, which independently decides whether to give a project a yea or nay. "We do send all requests to two or three outside experts," explains Roxanne Ford, head of Keck's medical research grants program. "But these opinions don't make or break our directors' opinions."

Foundations that turn to more traditional

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PROFILE

Niche Players

Whitaker

Like athletes who hang up their uniforms while they are still at the top of their game, the Whitaker Foundation declared in 1992 that it would spend itself out of business by 2006. One reason was to prevent future boards of directors from shifting the foundation away from the vision of its founder, engineer U. A. Whitaker, who started AMP Inc., the world's largest maker of electrical connectors, and died in 1975. Another was that the Rosslyn, Virginia–based foundation had achieved one of its goals: Whitaker specializes in biomedical engineering, and partly thanks to its efforts, the field was beginning to receive strong support from other funders. "We'll get more return on our investment at this period of time than if we continue forever," explains Miles Gibbons Jr., the foundation's director.

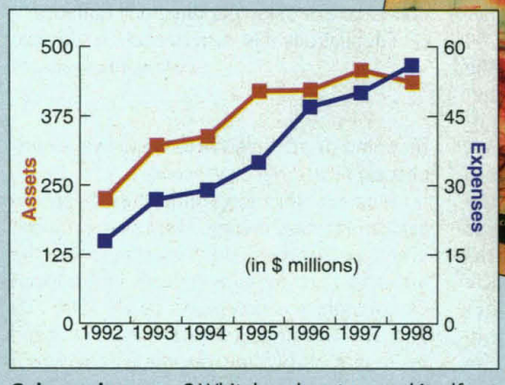
Whitaker has been thrown a curve by the stock market boom, however. Despite spending more and more money, it saw its 1992 assets of $227 million nearly double by the end of 1995; last year assets still totaled $436 million. "The endowment has grown a lot more than we projected and a lot more than anyone had projected," says Gibbons. But Whitaker, with help from a select group of scientific advisers, is stepping up its rate of spending, most of which goes to individuals, and Gibbons is confident that it will go broke on schedule. "We're not having any problem identifying new programs or expanding existing programs," he says. "We basically look upon it as a wonderful opportunity." Last year, in fact, Whitaker gave two awards that were three times the size of any they had given previously: The Johns Hopkins University received $17 million to create the Institute of Biomedical Engineering, and another $18 million went to the University of California, San Diego, to construct a new building and add new faculty to the existing bioengineering department.

Clinton Rubin, a scientific adviser to Whitaker who does orthopedics research at the State University of New York, Stony Brook, says the impact the foundation has had on his field is plainly visible. "By focusing on biomedical engineering, the Whitaker Foundation has given this discipline tremendous credibility in the eyes of universities, and a tremendous surge in interest in biomedical engineering has resulted," says Rubin. "They are a great foundation. I only wish they would stay forever!"

The Whitaker Foundation, the Ellison Medical Foundation, and the James S. McDonnell Foundation are among many foundations trying to make a difference in areas dominated by government funding

Ellison

High risk. Ahead of the curve. Innovative. Interdisciplinary. Those are the buzzwords that foundations invoke when they describe the type of scientific research they're looking to fund. But given the substantial budget of the National Institutes of Health (NIH), philanthropies that fund biomedical research have a hard time identifying high-quality projects that meet those criteria and yet would not qualify for NIH funding. So the Ellison Medical Foundation, which specializes in aging research, hired as its director somebody who should be able to spot promising research that's not part of NIH's traditional fare: a top official from the National Institute on Aging, Richard Sprott. "I headed the biology of aging program at NIH for close to 20 years," says Sprott. "I know what NIH can and cannot fund."



Going, going, gone? Whitaker plans to spend itself out of business, but its assets keep rising.

Larry Ellison, CEO of the software behemoth called Oracle, started the foundation in 1998 at the suggestion of his friend Joshua Lederberg, the Rockefeller University Nobel laureate. "Josh convinced Larry that putting money into aging could make a real difference," says Sprott. Indeed, Ellison even spent a few weeks in 1995 working in Lederberg's lab to see what basic research really looks like.

Lederberg now serves on the foundation's scientific advisory board, which ultimately serves as a peer-review group that makes funding decisions (see main text). "At Ellison, we've spent a lot of effort making sure that we coordinate with NIH," says Lederberg. "And we're very pleased to get tips from the inside." Sprott is quick to praise his old employer, but he clearly sees its limits, too. "NIH does what it does really well, but taking risks is not on the list," says Sprott. "Our interest really is to complement what NIH does and not to compete with it." One critical difference: Ellison has a penchant for pilot and feasibility studies, which means applicants need not provide much (if any) preliminary data. Applicants also are encouraged to explain why their work likely would not be funded by NIH.

In contrast to many foundations with a similar bent, Ellison does not have an endowment. Instead, Larry Ellison has committed to giving the foundation $100 million over 5 years. "This model probably makes some people nervous because they'd rather have the money in the bank," says Sprott. "But if you do that, you tie up a whole lot of money."

Although the National Institute on Aging spent about $350 million on research this year, the Ellison money will provide a substantial boost to the field. The foundation aims to attract established investigators working in other fields to aging research as well as provide support to promising young investigators. Ellison is particularly proud of its decision to fund Seymour Benzer, the renowned *Drosophila* researcher at the California Institute of Technology in Pasadena. Benzer already had NIH funds to do aging-related research, but he says the $1 million he'll receive over the next 4 years from Ellison will allow him to branch out. "Those funds are more flexible, so they provide an opportunity to explore adventurous new avenues," says Benzer.

Sprott, who largely runs the foundation by himself, says he does not know how long it will be in existence but expects it to thrive as long as "we do our job properly." Says Sprott: "Probably the only way I could disappoint Larry Ellison is to turn conservative."

McDonnell

Most science-oriented philanthropies cultivate an above-the-fray, aristocratic image, favoring subtlety and understatement, a discreet public profile, and a controversy-free atmosphere. Log on to the home page of the James S. McDonnell Foundation (www.jsmf.org), and it's immediately apparent that this philanthropy is different. One click takes you to revolving photos of the McDonnell Centennial Fellows, 10 "early career" researchers from diverse fields, each of whom recently won a whopping $1 million worth of sup-

CREDITS: THE WHITAKER FOUNDATION

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port. Another click takes you to presentations and publications by philosopher John Bauer, the foundation's president, that assail links between brain research and education policy. Then there's a spicy attack on the media (including *Science*) by neurologist Susan Fitzpatrick, McDonnell's program director, who lists "the worst examples of journalism about the brain."

"The history of American philanthropy certainly has been let's be very quiet about what we do, we don't want to call attention to ourselves," Fitzpatrick laughs when told that McDonnell appears to have a healthy dose of attitude. "I don't want every foundation to work the way the James S. McDonnell works. This is what works for us."

Started by the founder of the McDonnell Aircraft Corp. in 1950 with $500,000 worth of company stock, which he kept adding to over the years, this St. Louis–based philanthropy last year had assets of $480 million. From an office with mismatched furniture and a lean staff, McDonnell runs like an academic department and relies heavily on outside peer reviewers. The foundation largely supports neurosciences and has made a name for itself by fostering the subdiscipline of cognitive neuroscience. "They're terrific because they're very creative in looking for new ways to do things," says neuroscientist Fred Gage of the Salk Institute for Biological Studies in La Jolla, California, adding that Fitzpatrick is "gutsy."

Spotlight on aging. Oracle founder Larry Ellison is donating $100 million over 5 years to aging research.

Whereas philanthropies commonly avoid collaborating with each other because they fear it will dilute their own identity, not so McDonnell. In the past few years, it has formed high-profile brain-related research programs with both the Pew Charitable Trusts and the MacArthur Foundation.

The McDonnell-Pew awards for young investigators are one result of this collaboration. A recipient, neuroscientist Rick Cai of the University of California, Los Angeles, says his award has made a world of difference to him. Cai notes that postdocs who work in good labs don't have to get grants. But having one, he says, establishes a track record that can boost one's career. It also buys freedom. "When you have your own money, you completely design your project," says Cai, who for 3 years will receive $50,000 annually, about twice what the National Institutes of Health awards to postdocs.

Fitzpatrick acknowledges that the foundation does worry about distinguishing itself from federal funding sources. "This is very hard and something we really struggle with," she says. "We have to constantly look for ideas that are a little risky."

The foundation's new program of million-dollar grants to young researchers fills that bill, funding a richly varied assortment of projects that range from astrophysics and mathematical modeling of ecological systems to genetics, scientific philosophy, and, yes, human cognition. "We really hoped this would start a debate in philanthropy" about the merits of such generous support for young investigators, says Fitzpatrick. "It fell like the biggest lead balloon. We couldn't get anyone interested. It was a nonstory."

McDonnell scientific director Susan Fitzpatrick.

As for the foundation's decision to regularly take the media to task, Fitzpatrick says she and her colleagues simply cannot understand why journalists often tie the smallest finding in brain research to the most complex human behaviors. "We really felt we had to make a statement about this," she says. "We think we're the last true ivory tower. Academia is now so beholden to find money that they can't be honest. We can be honest."

Sprott, notes that this prominent group does not function like a "study section" of peers that evaluates NIH grants. "They don't have to give endless reports about each grant," says Sprott. "We can do in half a day what would take 3 days at the NIH."

Robert Lichter, executive director at Dreyfus, which takes its directions from a standing group of eminent scientific advisers, worries about foundations that don't use peer review. "There are a lot of wealthy individuals who have recognized there's an opportunity there," says Lichter. "The challenge is, are they going to do this wisely? They may do it intelligently. But if they make their decision only in their own house, I think they run the risk of not doing it wisely."

Susan Fitzpatrick, scientific director at McDonnell, says this is especially important for large philanthropies. "It's one thing when you're giving away a million or so a year and another when you're Bill Gates or Wellcome Trust," says Fitzpatrick. "They could very much influence the kind of research that gets done." And that's not always a positive thing. She cites the Rockefeller Foundation's support of eugenics, which took place in the 1920s. "It's a tremendous responsibility that they have to do this well," says Fitzpatrick of philanthropists.

In this vein, Bruce Alberts says the National Academy of Sciences, which he heads, plans to publish a guide to help new and would-be philanthropists understand the best way to help scientific research. "We want to guide them to models that have been particularly effective," says Alberts. The academy, he suggests, might even offer its members to philanthropists. "Could we and others generate a service where a wealthy person who wants to help science could come to us to set up a peer-review panel?" he asks.

Advice about specific projects isn't the only kind of guidance that foundations are seeking these days. As their coffers fill up with new money, many are searching for broader visions of where they can do the most good. Keck held two meetings in May with esteemed scientists to pick their brains about future directions the foundation should explore. "We asked these people to think outside the box, to tell us where they would like science to go," says Ford. "We're still digesting the information."

Jacqueline Dorrance, executive director of the Beckman Foundation, says she is wrestling with similar issues as its endowment has jumped from $356 million to $450 million during the past year. "As we move forward, we're going to have to come up with more and more programs and think more carefully about how we project our spending," says Dorrance. "Good lord, there's a lot of money. It's going to take an

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CREDITS: (TOP TO BOTTOM) ASSOCIATED PRESS; THE JAMES S. MCDONNELL FOUNDATION

PROFILE

The New Behemoths

Five years ago, the David and Lucile Packard Foundation had assets of $1.5 billion: a healthy sum, but not enough to put it in the top 10 foundations in the United States. Much farther down the list was a new foundation started by Microsoft CEO Bill Gates, with a mere $2.8 million in assets. Today, Gates has assets of $17.1 billion and Packard is up to $13.5 billion, making them number one and two on the U.S. foundation totem pole. And because both support scientific research, these suddenly wealthy funders are attracting attention from the scientific community.

Packard became a major player in 1996, when David Packard (co-founder of Hewlett-Packard) died, leaving stocks, bonds, and real estate that more than doubled the foundation's total assets to $7.3 billion that year. Since then it's ballooned thanks to the bull market. The Gates Foundation entered the big leagues just this year, when Gates and his wife Melinda made donations equivalent to the gross national product of many countries (see main text).

The Bill and Melinda Gates Foundation

and the David and Lucille Packard Foundation

are now the largest private philanthropies in the United States. Both are mapping out their scientific agendas

Each of these new heavyweights is in the enviable position of figuring out where to spend more than half a billion dollars a year. Both are putting a substantial portion of their largess into science, but with a marked difference in focus. Gates, at least in its early days, is largely backing health-related projects, while Packard's science spending tends to be spread more broadly. "Packard is more like the National Science Foundation: We fund across the board," says Jaleh Daie, Packard's director of scientific programs.

Gates and his wife set the overall direction of the Gates Foundation, which, because it technically is classified as a trust, has no need for a board of directors. The foundation is run by Bill Gates Sr., a prominent Seattle attorney, and former Microsoft executive (and friend of Bill Jr. and Melinda) Patty Stonesifer. Gates Sr. says he wants to keep the bureaucracy to a minimum. "That may not turn out to be true, but it is a deliberate, current strategy," he says. To that end, the foundation has no formal peer review, and Gates Sr. himself sometimes personally checks out potential grantees. In February, for example, he attended a 2-day meeting of board members from the International AIDS Vaccine Initiative (IAVI) and 3 months later gave them a grant of $25 million.

Broad focus. Packard's Jaleh Daie is planning a varied scientific agenda.

In the past year, the foundation has donated $230 million to science-related projects—about 10 times the amount it spent during the previous 12 months. The bulk of the money has gone to vaccine-related work. In addition to the IAVI grant, Gates gave $50 million to the Seattle-based Program for Appropriate Technology in Health (PATH) to support a malaria vaccine initiative; $25 million to Rockville, Maryland's Sequella Global Tuberculosis Foundation to develop a TB vaccine; and another $100 million to PATH for a children's vaccine program that will do the epidemiologic studies needed to design vaccination programs in poor countries. These donations have "very effectively re-energized the whole global immunization movement," says PATH president Gordon Perkin. Another focus has been reproductive health research, with a $20 million award to The Johns Hopkins University for a new institute and $10 million to a collaborative United Nations program run by the World Health Organization.

Health focus. Bill Gates Sr., keeping bureaucracy to a minimum, scouts out ventures himself.

A strong focus on health is likely to continue: On 24 September, the Gates Foundation announced that Perkin will leave PATH in November to head the foundation's global health program. Epidemiologist William Foege, former head of the Centers for Disease Control and Prevention and then the Carter Center, has been hired as Perkin's senior adviser.

Packard's spending has tilted further toward basic research. The board of directors, which includes five Packard family members, sets the scientific agenda, and until recently, board member Franklin Orr Jr., dean of earth sciences at Stanford University and husband of a Packard daughter, was the main voice for science. In March, however, the foundation hired a new president, former *Los Angeles Times* publisher and CEO Richard Schlosberg III, and in July, it brought on Daie, then a plant researcher at the University of Wisconsin, as its first formal scientific director.

This year, Packard is spending about half of the $67 million it designated as science money on California's Monterey Bay Aquarium Research Institute, a reflection of the marine biology backgrounds of two Packard children, both of whom are board members. (One, Julie Packard, runs the Monterey Bay Aquarium, which, like the Aquarium Research Institute, was started with Packard funds.) Most of the rest is going to a new $10 million program for interdisciplinary science that's supporting such varied projects as culturing "unculturable" microbes from soil and developing "entangled-photon fluorescence microscopy" to study the brain. Additionally, Packard has a $15 million fellowship program for young faculty members studying engineering, computer science, natural science, and mathematics. A consortium of marine scientists receives another $18 million, but this does not come from the science budget.

Next year, Daie says Packard's science budget may run as high as $100 million. The board has yet to decide how to spend that sum, but several ambitious ideas are on the table. One is to nurture "centers of excellence" in developing countries. Known as Millennium Science Institutes, they would be built around a scientific discipline that already has a track record in that locale. Another proposal that has internal momentum is to beef up the existing conservation program with an environmental science initiative that would spend at least $10 million. Says Daie: "My every expectation is that the science is going to prosper under the leadership of our new president and trustees as long as the assets go up."

CREDITS: (TOP TO BOTTOM) THE PACKARD FOUNDATION; ROBBIE MCCLARAN/SABA

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effort so that we spend it wisely."

Foundation directors are not sitting behind their desks anxiously waiting for advice from researchers about how to reduce their philanthropy's assets, however. "Boy, am I not soliciting proposals," said Gates Sr. last June, echoing a sentiment voiced by several foundation heads. "If somebody heard that the director of the William H. Gates Foundation was trying to figure out a way to spend money, my life would be really rendered almost inoperative. I'd be overwhelmed with people." Then again, Gates does have to figure out how to spend what now amounts to $2.3 million a day. So it may pay, literally, for researchers to watch closely as Gates and other foundations that have more money than anyone would have imagined a few years ago articulate visions for their futures. –JON COHEN

DISCLOSURE

By way of full disclosure, it should be noted that various activities of the AAAS (*Science*'s publisher) are supported by grants from several organizations mentioned in the preceding articles, including the Howard Hughes Medical Institute, the Pew Charitable Trusts, the Burroughs Wellcome Fund, and the Wellcome Trust. In addition, the Sloan Foundation provided funding last year for a book by author Jon Cohen.

CELL BIOLOGY

A New Finger on the Protein Destruction Button

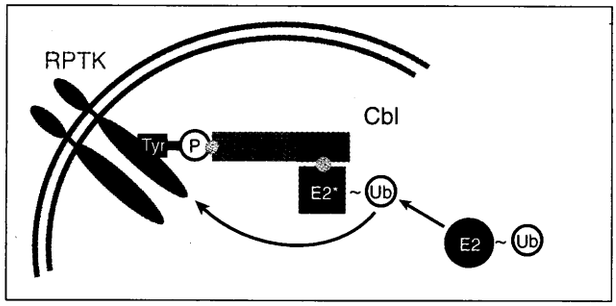
A protein motif called the RING finger helps add ubiquitin to proteins, thereby marking them for the cellular trash heap

To make an omelet you have to break a few eggs, and to keep a cell healthy you have to destroy some proteins. Recent evidence has shown that the timely eradication of proteins that drive cell division is vital to keeping normal growth from turning into runaway malignancy. In the biological equivalent of putting trash bags by the curb, cells tag proteins for elimination by attaching a small protein called ubiquitin. The tagging occurs in steps, with one kind of enzyme binding to the condemned molecule and another ferrying the ubiquitin label to the target. In the past few months, researchers have identified a molecular motif that marries these two kinds of proteins so that the tagging can take place.

Fittingly, it's called the RING finger, an evolutionarily conserved structure found in more than 200 proteins, in which two loops of amino acids are pulled together at their base by eight cysteine or histidine residues that bind two zinc ions. A new crop of results, including those reported on page 309 by Tony Hunter's team at The Salk Institute in La Jolla, California, show that several RING finger proteins participate in ubiquitination. Among these are two proteins that play roles in cell growth control: Cbl, which can cause cancer when it is mutated, and BRCA1, the breast cancer susceptibility gene.

But given the large number of proteins that contain RING fingers, these discoveries may be just the tip of the iceberg. "Many [of these proteins] have been implicated by genetics as participating in some process or other, but without any clear mechanistic insight as to how they are acting," says cell biologist Ray Deshaies of the California Institute of Technology (Caltech) in Pasadena. The new results are likely to touch off a wave of research on how these proteins might regulate cell activities and also exploration of how the chain of protein destruction might be restored in some cases to halt the growth of cancer cells.

Hunter and his colleagues, postdoc Claudio Joazeiro, and cell biologist Yun-Cai Liu at the La Jolla Institute for Allergy and Immunology in San Diego, made their observations while following up on recent work on the protein Cbl. A genetic analysis done in Paul Sternberg's lab at Caltech had revealed that the version of Cbl found in the roundworm *Caenorhabditis elegans* is necessary for turning down the activity of a growth-promoting protein, the receptor for epidermal growth factor (EGFR). And last year, groups led by Hamid Band at Harvard, Yosef Yarden at the Weizmann Institute of Science in Rehovot, Israel, and Richard Stanley at Albert Einstein College of Medicine in the Bronx reported evidence that Cbl down-regulates growth factor receptors by helping to ubiquitinate them, marking them for destruction.



Missing link. Cbl helps tag a membrane-bound receptor for destruction by bringing it together with a ubiquitin-loaded E2.

To pinpoint the parts of the protein required for ubiquitination, Yarden's group took a cue from two known Cbl mutants that cause lymphoma cancers in mice. Both are missing chunks of the protein's RING finger, suggesting that it is vital to the protein's normal function. They report in the 6 August issue of the *Journal of Biological Chemistry* that one of these natural mutations, as well as a lab-made mutation, both prevent Cbl from ubiquitinating the EGFR in cells.

Hunter's team went further to parse out Cbl's exact role in ubiquitination, which requires three different kinds of proteins. One called E1 activates ubiquitin, an E2 protein temporarily holds the activated ubiquitin, and the E3 enzymes bind the target and guide the transfer of the ubiquitin to it. Because Cbl binds ubiquitination targets such as the growth factor receptors, Hunter and others in the field wondered whether it might be an E3.

To investigate that hunch, and to test the RING finger's specific role, Joazeiro isolated Cbl's RING finger and tested its ability to trigger ubiquitination in a test tube. He engineered bacteria to manufacture just the RING portion of Cbl, linked for production purposes to a bacterial protein. He then mixed the hybrid protein with ubiquitin, E1, and E2 to see if it would function as an E3.

It worked. The researchers detected ubiquitination of proteins in the reaction, and mutations of key amino acids in the RING finger abolished the effect, pegging the RING finger as essential. What's more, Liu found that the RING finger directly binds to the E2 enzyme. That proves "that the RING finger domain of this protein is capable of recruiting the E2 component," says Band, "which is critical, because that begins to provide a basis for how Cbl might enhance ubiquitination."

But getting ubiquitination of one of Cbl's known targets, the platelet-derived growth factor receptor (PDGFR), required a bigger piece of Cbl, containing the RING finger

CREDIT: C. JOAZEIRO, MOLECULAR BIOLOGY AND VIROLOGY LABORATORY/THE SALK INSTITUTE FOR BIOLOGICAL STUDIES