Scientists With Clout

Britain's Wellcome Trust is a funding agency run by researchers. It made a killing on the stock market and now nearly eclipses the U.K. government's own biomedical funding agency

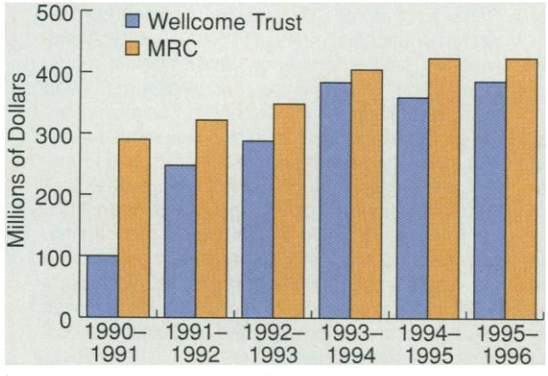
LONDON AND MANCHESTER, U.K.—University of Manchester biochemist Michael Grant has spent the past 30 years studying the extracellular matrix—the "glue" that holds cells together and allows them to organize into complex tissues. For much of this time, matrix research was regarded as a backwater by most scientists, but about 15 years ago researchers began to discover that the matrix was not just an inert adhesive but a dynamic system of large molecules that plays a vital role in both disease and normal growth and development. And Manchester's matrix research group, which had grown steadily over the years, was poised to become a world leader in what today is a very hot area of research. But there was one big obstacle: The group's laboratories, built on the cheap more than 25 years ago, were in desperate need of refurbishment, and the cash-strapped university did not have the funds to do it.

Enter the London-based Wellcome Trust, the world's richest biomedical charity. Trust officials came to the rescue with a $2.2 million renovation grant (the university kicked in $800,000), plus $1.6 million for new equipment. On 1 May this year, the Wellcome Trust Centre for Cell-Matrix Research—boasting a research staff of nearly 100—was officially inaugurated with Grant as its head. When additional salaries and project grants are included, the trust's total commitment to the new center comes to nearly $10 million over the next several years. "Without the Wellcome Trust, it isn't obvious where we would have gotten this money," Grant says. "The trust is a total godsend for biomedical research in the United Kingdom."

If this sounds like a testimonial, Grant is far from alone in singing the trust's praises. In addition to awarding about 2100 new grants each year, the trust currently funds the salaries of more than 3000 university-based research workers. And over the past decade, its annual spending on biomedical research has grown ninefold—largely as a result of the sale of the Wellcome pharmaceutical company, which the trust once wholly owned. Today the trust disperses about $380 million annually on research, which puts it nearly equal to the Medical Research Council (MRC), the major government funder of biomedical research, and just behind the U.S.-based Howard Hughes Medical Institute, which might be considered Wellcome's American counterpart.

"The increased wealth of the Wellcome Trust couldn't have come at a better time," says Dai Rees, who stepped down as MRC chief executive on 30 September after 4 years in the post. "The U.K. is just about holding its own in world research. If not for trust money, I'm not sure this could have been sustained." This bonanza for biomedical science is the legacy of Sir Henry Wellcome, an entrepreneur who founded the Wellcome Co. and left it in trust when he died in 1936. "The trust is Henry Wellcome on Earth," says Bridget Ogilvie, the charity's director. But given that seven of the trust's nine governors are leading U.K. researchers, perhaps another way to put it would be: The trust is scientists with money and power.

Funding with style. Wellcome Trust's London headquarters and director, Bridget Ogilvie.



Catching up. The Wellcome Trust is challenging the Medical Research Council as Britain's biggest biomedical spender.

A lone furrow

The trust has clearly taken it upon itself to plug the gaps left by ever-increasing demands on the MRC's budget, which has only risen modestly in recent years. "Because the MRC has to cover all bases, they are inevitably paring down grants, trying to cut them to the bone," says University of Oxford neuroscientist Julian Jack, deputy chair of Wellcome's board of governors. Nevertheless, says Jack, the trust is always on the lookout for "opportunities to experiment with funding ... to select particular areas, if we see a way of improving what was a weakness." Trust staff have been known to exert their influence behind the scenes, encouraging researchers to submit proposals in areas they see as priorities, and grooming those proposals for peer review.

The trust is in a good position to experiment. As an endowed charity that is not dependent on public donations, Wellcome is answerable only to Britain's charity commissioners and the board of governors. "If we wanted, we could have total freedom to do what we like, to be as idiosyncratic as we like," says Jack. "But in practice, it's very far from that, because the governors recognize that they have responsibilities."

But although the trust has tried to encourage innovative research—in 1996 it awarded 19 special $80,000 grants for "high-risk" projects—most of its funding goes to mainstream and often high-profile science. For example, trust-funded scientists played an important role in creating the latest map of the human genome (*Science*, 25 October, p. 540), and Wellcome has funded key research on the relationship between bovine spongiform encephalopathy and human Creutzfeldt-Jakob Disease.

The charity's largesse has drawn grant-hungry researchers like bears to honey. "There are two kinds of biomedical researchers in Britain today," says one Wellcome-funded scientist, who asked to remain anonymous. "Those who have Wellcome Trust grants, and those who want them." Although this may be a slight exaggeration, the trust's policy of generously funding projects and researchers it deems worthy of support has made it the first port of

Generous Funding Wins a Seat at the Genome Top Table

HINXTON, U.K.—The Wellcome Trust may be pulling even with the Medical Research Council (MRC) as the chief benefactor of biomedical research in the United Kingdom (see main text), but in one area, it has already surged ahead: genome research. The evidence is here, in the Wellcome Trust Genome Campus, spread over 22 hectares of land at the edge of this peaceful village 13 kilometers south of Cambridge. In the past few years, this research complex has become the strategic hub for British participation in international genome research, and its influence is being felt in everything from new sequencing technologies to the adoption of policies for the rapid sharing of genetic information throughout the world.

The centerpiece of the campus is the Sanger Centre, the world's most productive gene-sequencing lab, with more than 50 million DNA base pairs already logged in its databases. As the effort to sequence the 3 billion base-pair human genome gears up, the Sanger Centre is planning to take on at least one-sixth of the job, thus assuring the United Kingdom a major role in this multinational project, which also includes the United States, France, Germany, and Japan.

The Wellcome Trust is "anxious to make the world a different place."

—John Sulston

The campus is also home to the European Bioinformatics Institute (an outstation of Heidelberg's European Molecular Biology Laboratory) and the MRC's Human Genome Mapping Project Resource Centre, both of which will provide key support for the sequencing effort. But while these other agencies have made significant investments at Hinxton, the campus is clearly the Wellcome Trust's show. In addition to a $160 million grant to the Sanger Centre for the period 1992 to 2002 (compared to about $48 million from the MRC), the trust is also pumping in $105 million for construction of additional laboratory and conference facilities at the site—a total commitment of $265 million.

"Our object is to provide the same sort of environment as at Cold Spring Harbor or Woods Hole [laboratories], where there's a long-term scientific activity and a very active meeting and conferences program," says Michael Morgan, the trust's head of science funding, major building projects, and genetics research. But perhaps more importantly, the charity's investment at Hinxton and other sites—including the Wellcome Trust Centre for Human Genetics at Oxford, which specializes in genetic diseases—has won it a seat at the world table of agencies responsible for genome research.

Moreover, the trust has increasingly emerged as a key coordinator of the human genome sequencing program, gradually supplanting the function that the Human Genome Organization (HUGO), set up in 1989 by scientists involved in the project, was intended to perform. The trust's new leadership role was very much in evidence in February of this year when it organized an international powwow of scientists and funding agency representatives in Bermuda to discuss sequencing strategy and principles (*Science*, 29 March, p. 1798). "The trust has stepped in to fill a need," says Elke Jordan, deputy director of the U.S. National Institutes of Health's (NIH's) National Center for Human Genome Research. "They're doing things you might say HUGO could have done, but HUGO has suffered from lack of funding."

Oxford University neuroscientist Julian Jack, deputy chair of the trust's board of governors, says the Wellcome Trust's involvement in the genome center began as an effort to keep one of Britain's top genome researchers, John Sulston, from accepting an offer from an American entrepreneur to set up a private sequencing center in the United States (*Science*, 7 February 1992, p. 677). Says Jack, "The whole initiative came when [former MRC chief executive] Dai Rees came over to see [Wellcome Trust director] Bridget Ogilvie and said, look, this chap Sulston is about to go off to America; can't we strike some arrangement to keep him in Britain and in the public sector?" Hence the trust and the MRC launched the Sanger Centre, with Sulston as its director.

The two organizations started off as roughly equal partners in the center, and the MRC heavily funded a nematode sequencing project that laid the groundwork for the human sequencing effort. But the balance soon changed as the scope of the project grew logarithmically. "We were not in a position to do anything like that ourselves," Rees told *Science*.

In taking on Sulston as head of the Sanger Centre, the trust also adopted a set of ethical principles for genome research that Sulston strongly espouses. He insists that sequencing data should be in the public domain and released as soon as possible, and it is now Sanger Centre policy to immediately upload new sequences onto its site on the World Wide Web. Although this general guideline was adopted by the participants at the Bermuda meeting, there remain continuing debates about just how soon is soon, as well as over rights to patent genome sequences (*Science*, 25 October, p. 534).

The trust's assertive stance has displeased some genome researchers. "Data generation is not science," says Craig Venter, head of The Institute for Genomic Research in Rockville, Maryland, a nonprofit lab associated with the biotech company Human Genome Sciences. According to Venter, who favors peer-reviewing raw DNA data before release, "What the Wellcome Trust and the Sanger Centre are advocating would be like asking Charles Darwin to immediately put all his collections into a museum."

But the trust's influence over the genome scene is becoming harder and harder to ignore. As evidence, in recent months Morgan has been traveling the world knitting together a consortium of funding agencies and pharmaceutical companies to carry out a major new project: sequencing the genomes of some 50 pathogenic organisms, including those that cause tuberculosis, meningitis, and cholera, with the aim of developing new drugs, particularly against antibiotic-resistant strains. The plan has already drawn interest from several drug giants including Merck, Bayer, Abbott, SmithKline Beecham, and Glaxo Wellcome, as well as the MRC and the NIH.

Says Sulston: "The Wellcome Trust is able to act catalytically, because they have enough money so that if they apply it wisely, they can have enormous leverage. They are anxious to make the world a different place." **–M.B.**

call for an increasing number of scientists.

But Wellcome's relatively recent transformation into a behemoth of British research funding—and the accompanying clout in debates over research policy—has occasionally caused tensions with government and university officials. Indeed, the trust's growth spurt initially led to strained relations with the MRC: For the first time, it faced serious competition for the loyalties of British biomedical researchers from a charity with very similar funding interests.

More recently, however, Wellcome and MRC officials have sought to play down these frictions, and have pulled together to lobby for adequate funding for British research. "Way back in the distant past, there might have been some personality conflicts," says Rees. "But the trust and the MRC have recognized that there are some challenges that are bigger than either of us." Thus Rees says that he met often with Ogilvie during his tenure as MRC chief and, while not coordinating funding strategies, MRC and trust officials do come together frequently to discuss issues of common interest. "A plurality of funding [sources] doesn't do any harm," Rees says.

Nevertheless, trust officials are keenly aware of the balancing act required by their new role, particularly as the charity has expanded its funding beyond the borders of the United Kingdom, as well as become heavily involved in international coordination of genome research (see box). "We walk a political tightrope," says Jack. "The government looks at us and hopes we will remain national, a second MRC. They hope that if they take a little bit away from the MRC, the trust will just fill in the cracks."

Robert May, the British government's chief scientific advisor, agrees that the rise of the trust has brought "greater complexity" to Britain's biomedical funding scene, and "greater complexity makes greater problems." But, he says, "they are problems one should welcome."

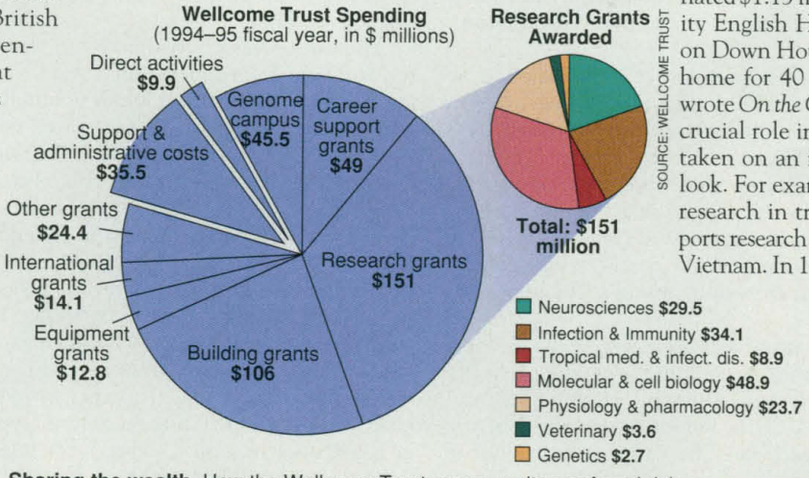
"The trust is a total godsend for biomedical research in the United Kingdom." —Michael Grant

Got rich quick

New money began flooding into the Wellcome Trust's coffers in 1986, when the charity sold 21% of the Wellcome Co. and began diversifying its investments. A second sell-off took place in 1992, and in spring 1995, the remaining shares in the company were sold to British rival Glaxo for $4 billion in cash and a small stake in the new Glaxo Wellcome company that was created out of the deal. In essence, the trust struck it rich on the stock market—and so did British biomedical science.

"Glaxo made an offer that made the governors realize where their duty lay," says Ogilvie. In discussions with *Science*, trust officials admit to a certain degree of giddiness when the money began rolling in. "It was a staggering opportunity," says Jack. And the charity wasted little time in exploiting it. A modest increase in the number and size of short-term project grants was accompanied by a dramatic growth in long-term funding of programs and individuals, which has become a trust specialty. And the trust embarked on an ambitious building and renovation program that is helping to give a fresh face to British biomedical science. In addition to Manchester's cell-matrix unit, for example, the trust has recently awarded $18.4 million for the construction of a new Institute for Cellular and Genetic Medicine at Cambridge University.

Although as a matter of policy the great majority of the trust's funding is funneled through the universities, its biggest and most ambitious project stands outside the university system: The Wellcome Trust Genome Campus at Hinxton, near Cambridge, which includes the Sanger Centre—home of the U.K.'s major gene-sequencing operation—and a variety of other research and conference facilities. The trust's long-term commitment to the campus currently stands at $265 million.



Sharing the wealth. How the Wellcome Trust carves up its newfound riches.

Such sums are not disbursed on a whim, however. All of the trust's research grants are peer-reviewed and, according to Ogilvie, more than 4000 referees were asked to review proposals in 1995. (Those called upon more than six times received a Christmas hamper, Ogilvie says.) But in discussions with *Science*, some researchers suggested privately that the governors' own institutions sop up a disproportionate share of the money. "It's a bit of an old-boys' club," says one researcher. Indeed, of the seven scientific governors—the other two are from business—five come from Cambridge or Oxford. And in 1995, out of 50 institutions receiving Wellcome grants, Cambridge and Oxford came in first and second, with $43.9 million and $43.2 million, respectively. Trailing in third place was University College London, with $26.6 million.

Although trust officials insist that grants are awarded solely on scientific merit, Jack says the governors are "well aware" that to outsiders "it all looks rather incestuous," a perception reinforced by the fact that the board of governors is a self-perpetuating body—its members appoint their own successors. Jack defends this arrangement by pointing out that the governors seek input from the trust's own staff as well as the scientific community before making new appointments.

Funding with attitude

Wellcome's independent streak sometimes allows it to play the role of a whimsical do-gooder. Last May, for example, the trust donated $1.13 million to the preservation charity English Heritage to secure the freehold on Down House in Kent—Charles Darwin's home for 40 years and the place where he wrote *On the Origin of Species*. And despite its crucial role in British research, the trust has taken on an increasingly international outlook. For example, the trust has long funded research in tropical medicine and now supports research centers in Kenya, Thailand, and Vietnam. In 1993, the charity gave a big boost to the U.S.-based Burroughs Wellcome Fund with a one-time grant of $411 million, and it has recently launched a new program to fund biomedical research in Australia, Southeast Asia, and the Pacific.

Nor has the trust hesitated to use its influential position to take issue with government policies it disagrees with, particularly when it comes to cuts in funding. For example, the trust has helped lead a united stand by most of the U.K.'s biomedical charities against government requests that they include overhead costs in the grants they award to universi-

ties—which the MRC has recently been required to do. It has long been the tradition in Britain for the government to staff, equip, and maintain university laboratories and for funders to simply cover the cost of research. But in an effort to streamline its subsidy to the universities, the government is trying to shift to a system in which a portion for overhead is included in each grant. "We can't afford to just give [block grants] to all the universities," May says.

But Diana Garnham, general secretary of the Association of Medical Research Charities—which includes the British Heart Foundation and the Imperial Cancer Research Fund—says that its members have "a very strong position" against paying overhead costs. "What we spend is in addition to what the government spends," Garnham says, "not a substitution for it." Garnham adds that the charities "have been very generous on costs ... the average cost of a project grant has gone up by about 240% since 1987."

The charities have hardened their position since last November, when the government announced a 30% slash in capital and equipment funds for the universities. Ken Edwards, vice chancellor of the University of Leicester—which received $7.3 million in Wellcome Trust grants in 1995—says that "the universities have fallen into the crack in the middle" of this tussle between the government and the charities. With government grants shrinking, "it is extremely difficult for us to provide a sufficient level of [infrastructure] support without overhead," Edwards says, adding that "if we accept funds from the medical charities, we have to divert funds from other parts of our budget" to meet these costs.

Nevertheless, Edwards does not expect the charities to change their position. "Only government funding to support the national research base will solve this problem," he says, a position with which trust officials heartily agree. "It's crazy, this whole business of government pressure on everybody to get their money from somewhere else," says Ogilvie. "Why don't they fund things properly?"

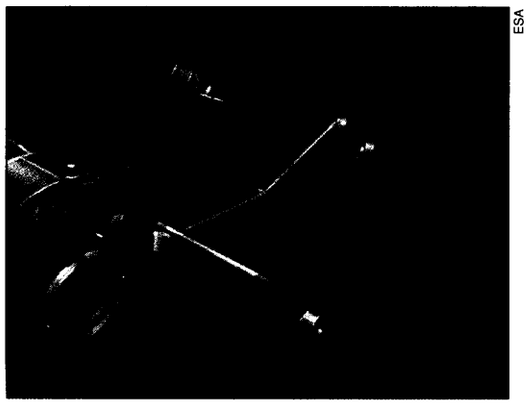
Few charitable bodies could take such a firm line against the government and be taken seriously. But for many who have benefited from the trust's generosity, the charity has taken on heroic proportions. "The Wellcome Trust has been the savior of British research," says Bryan Morgan, an immunologist at the University of Wales College of Medicine in Cardiff who has held a Wellcome senior fellowship for the past 9 years. But if the Wellcome Trust is out to save British science, it seems determined to take the British government kicking and screaming along with it.

–Michael Balter

SPACE SCIENCE

Cluster Mission to Rise From the Ashes

It is turning out to be a bad year for space science, with Russia's Mars '96 probe tumbling back into the atmosphere last weekend (see p. 1297) and Europe's Cluster mission blown up by a faulty launcher in June. But Cluster scientists, at least, have something to look forward to: Earlier this month, the European Space Agency's (ESA's) Space Science Advisory Committee recommended that the mission be reconstructed and reflown. Cluster scientists will be keeping the champagne on ice until ESA's Science Program Committee gives it the seal of approval at the end of the month, but the mission's principal investigators met in Paris last week to hammer out the details of what the reconfigured mission would look like. "ESA has come out with a very good, very firm proposal, and we the scientists are 100% behind it," says André Balogh of London's Imperial College.



ESA

Flight delays. Artist's vision of the original Cluster spacecraft sweeping through the magnetosphere.

Cluster consisted of four identical satellites designed to fly in formation around the Earth, studying its magnetosphere in unprecedented detail (*Science*, 24 May, p. 1095). All four spacecraft were destroyed on 4 June when the inaugural flight of Europe's Ariane 5 launcher veered off course (*Science*, 14 June, p. 1579), but a fifth spare spacecraft was in storage, and this, now dubbed Phoenix, will form the nucleus of the Cluster-2 mission.

The 11 research groups involved in Cluster will now refurbish spare instruments from the development phase of the mission, and these will be installed on Phoenix. ESA hopes to have Phoenix ready to fly by next year at a cost of $37.5 million, but it will then have to wait for the three new spacecraft, which will be completed at half-yearly intervals, starting in late 1998. ESA has stipulated that the total cost of the project, including launches but excluding the cost of instruments, must remain under $262 million.

The spacecraft will be launched in two pairs, or "in the worst case, individually," says Rudolf Schmidt, Cluster's project scientist at the European Space Research and Technology Centre (ESTEC) in Noordwijk, the Netherlands. ESA will negotiate with Arianespace for slots on launches, and Schmidt is hoping for two not too far apart, one late in 1999 and one early in 2000.

Even if the Science Program Committee approves the plan next week, as expected, it will not be the end of Cluster's travails, however. Instruments are paid for not by ESA but by the government of the research group that provides them; so each team will have to persuade its funding agency to cough up for instruments it has already paid for. Balogh, at least, is upbeat: Following last week's investigators' meeting, "there are very positive signs that all countries will be able to support the rebuilding of the instruments," he says. Schmidt says that meetings with NASA have also secured its commitment to fund the sole U.S.-built instrument, a radio interferometer from Donald Gurnett of the University of Iowa, for Phoenix, but funds for the three new spacecraft are still under discussion.

Although this is good news for Europe's space plasma physics community, other groups whose missions may have been delayed or cut back to pay for Cluster-2 are not so delighted. ESA plans to delay for 6 months the microwave mapping mission COBRAS-SAMBA and make cuts to others, such as reduction in mirror size from 8 to 3.5 meters in its Far Infrared Space Telescope. George Miley of Leiden University in the Netherlands says he does "not believe that the rest of the ESA science program should be penalized for something that was not at all the responsibility of the science program."

Miley fears that ESA's decision is based on "political choices," and he is also concerned that budget constraints may affect ESA's ability to take part in NASA's planned Next Generation Space Telescope, the successor to Hubble. "If Europe does not get involved with projects such as the Next Generation Space Telescope, we are relegating European astronomy to a second place in the world," he says. The Space Science Advisory Committee will meet in January to come to grips with these problems.

–Alexander Hellemans

Alexander Hellemans is a science writer in Paris.