The Role of the Rockefeller Foundation in Malaria Vaccine Research, 1970s-1980s

by Kirsten Moore-Sheeley
Cedars-Sinai Medical Center

© 2024 by Kirsten Moore-Sheeley
Abstract

Over the 1970s, scientists finally began to make significant headway in the creation of a malaria vaccine. New developments such as hybridoma technology, recombinant DNA, and the ability to cultivate continuous cultures of malaria parasites in vivo spurred enthusiasm among scientists that they could finally create the first vaccine against a parasitic disease. A new influx of funding into parasitic disease research during this decade accelerated scientific discoveries related to malaria vaccines. The Rockefeller Foundation’s Health Sciences Division, led by Dr. Kenneth Warren from 1977 to 1988, contributed significantly to this acceleration by sponsoring cutting edge research on malaria immunology and biology as part of a new “Great Neglected Diseases of Mankind” program. This report examines the role of the Rockefeller Foundation in stimulating research around malaria vaccines and related areas of malaria immunology and molecular biology, and the effects its funding had on scientists, scientific institutions, and populations in malaria endemic regions. While an effective malaria vaccine did not materialize as quickly as the scientific community had hoped, the Rockefeller Foundation nonetheless played a substantial role in raising the profile of malaria vaccines and vaccine research.
In July 1989, members of the Institute of Medicine, an American non-profit organization, crafted a proposal to study the state of malaria prevention and control. “Malaria is a complicated disease with an erratic history,” they claimed, and current efforts to manage the disease were too meagre and precarious to curb rising malaria rates.¹ This stood in stark contrast to previous eras, in which scientists were quite optimistic about the possibility of eradicating the disease. In fact, scientists were so optimistic about this prospect in the mid-twentieth century that the World Health Organization (WHO) had launched a campaign to eradicate malaria globally in 1955. While successful in some respects, this campaign failed to eradicate malaria from many countries due to, among other things, the emergence of mosquitoes’ resistance to the pesticide DDT and malaria parasites’ resistance to the antimalarial drug chloroquine. Malaria not only persisted in large swaths of the Global South, but it actually began to resurge in some places as people previously protected lost their immunity to this deadly, vector-borne disease as well as the best tools to mitigate it. The WHO’s cessation of its Malaria Eradication Programme in 1969 and the declining efficacy of malaria interventions led to sharp declines in donor funding for malaria projects over the remainder of the twentieth century, leading to the state of affairs that prompted the Institute of Medicine’s 1989 report.²

The end of the WHO’s Malaria Eradication Programme shed light on the fact that certain infectious diseases—especially parasitic diseases—continued to plague millions of people across the Global South and that there were few effective therapeutics or prevention measures to address these ailments. In response to this realization, some organizations decided it was time to invest in research related to infectious diseases predominantly affecting the “tropical” or “developing” world. The Rockefeller Foundation (RF) was one of those organizations. In 1977 Kenneth Warren, who joined the RF as director of its Health Sciences Division that same year, made the case to the RF’s Board of Trustees to launch a new initiative targeting these maladies: the Great Neglected Diseases of Mankind program. Parasitology and the study of diseases like malaria were becoming “neglected,” Warren argued, as the workforce for investigating, teaching, and practicing tropical medicine had declined since World War II.³ Misplaced faith that malaria would be eradicated, along with the end of imperial rule in countries where parasitic diseases remained rife, had contributed to this decline. Partly because
of the small scientific and medical workforce, as well as the more general lack of attention and resources given to so-called tropical diseases, parasitology had not benefited from recent advances in molecular biology, genetics, immunology, and biotechnology. The Great Neglected Diseases of Mankind program (hereafter, the GND program), Warren hoped, would help correct these imbalances by investing in medical and scientific investigators dedicated to studying a cluster of diseases with high morbidity and mortality rates in the Global South.4

At the same time that the RF’s GND program began to take shape, around 1977 and 1978, research on malaria was heading in a new direction. For a variety of reasons, including the rising rates of malaria morbidity and mortality and recent discoveries related to malaria parasites, scientists began to turn their attention to the development of a malaria vaccine. Prior to the 1970s, most experts felt the malaria parasite—of which there are hundreds of species—and its life cycle were too complex to create a vaccine for the disease. However, advances in the biological sciences during this decade seemed to provide new opportunities for developing this technology, which could replace increasingly ineffective malaria interventions.5 The RF’s GND Program did not make malaria vaccine research a main priority at its outset; Warren sought to promote the development of tools and scientific insights for a variety of diseases with this initiative. Due to the program’s particular emphases and structure, however, it ultimately fostered and accelerated malaria vaccine research, so much so that malaria vaccine research stood out as one of the program’s major successes by its end in 1986. While this research did not lead immediately to an effective human vaccine—still decades in the making—the RF and its GND program played a substantial role in shaping malaria vaccine research globally by supporting new investigators and their work in this field.

The Beginnings of the RF’s GND Program

Ken Warren was the lead architect and organizer of the RF’s GND Program. He came to his position as director of the RF’s Heath Sciences Division as a physician and prolific schistosomiasis researcher with experience working in both clinical contexts and the laboratory, in the United States and in tropical regions of the Global South. Warren was not an unknown entity at the RF before his appointment. The RF had actually helped
fund a new division at Case Western Reserve University Department of Medicine—Warren’s institutional home since 1963—in “Geographic Medicine” for which Warren served as founding director. This was the first institution in American academic medicine devoted to “diseases in the developing world.” John Knowles, a fellow physician and president of the RF from 1972 to 1979, later invited Warren to join the organization, hoping to launch a new effort to promote the well-being of populations around the world. Knowles’s interest in this endeavor, along with Warren’s medical-scientific background and interests, laid the foundation for what would become the GND program.

For Warren, neglect served as a key theme in his arguments for the new program. “Many of the great diseases of the developing world (largely the so-called tropical diseases) appear to have been neglected,” he wrote in a draft statement to RF Board of Trustees in 1977. “In the great burgeoning of funding for biomedical research by the United States government over the last three decades this area was never supported adequately,” particularly in comparison to cancer, which affected many fewer people globally than did diseases such as malaria, schistosomiasis, and diarrheal diseases. Furthermore, although the WHO had recently launched a multilateral initiative to promote tropical disease research—the Special Programme on Research and Training in Tropical Diseases—Warren felt the WHO still had not had a significant impact on these problems. “Thirty years of disinterest has left us bereft of adequate tools to prevent or treat many of the major world diseases,” he decried. By bringing in “scientists in the outstanding medical schools and research institutes of the developed world and in a few fine institutions in developing countries” to the study of tropical disease, he hoped to use his proposed GND program to improve the quality of research on the subject and redress its neglect.

One of Warren’s major contentions in his creation of the GND Program was that parasitology had not benefited from new advances in molecular biology, genetics, and immunology as much as had, for example, virology. Typically separated off into schools of public health and tropical medicine, parasitology remained relatively untouched by these rapidly developing sciences as well as the biomedical research institutions and investigators now gravitating toward these sciences. “As a consequence,” Warren argued, “the current armamentarium for coping with many of the major health
problems of mankind [wa]s woefully inadequate.” Warren therefore planned to “turn to the heartland of the biomedical revolution” and invite people from some of the “best biomedical research establishments” to apply to be a part of the GND program. This included people with little prior experience in tropical medicine or parasitology research but who demonstrated the potential and interest in contributing to these subjects. Doing so would advance one of the GND main aims: “to create a network of high quality investigators who would constitute a critical mass in this field, attract the brightest students and conduct research of excellence.”

Another element of Warren’s plan for the GND program included encouraging, and even mandating, that research units sponsored by the program spend “a significant part of [their] efforts [...] in applied collaborative research in developing countries.” This aspect of the GND program built on Warren’s own experiences studying schistosomiasis. Before taking up his position at the RF, Warren had spent considerable time in places such as Brazil and St. Lucia conducting research among populations and testing out control measures in schistosomiasis-endemic areas. As Anthony Cerami, head of the Pharmacoparasitology Unit at the Rockefeller University and a beneficiary of the GND program, remembered, Warren stressed to him and other investigators the importance of seeing the diseases they were studying in the field, as Warren had done in his own scientific career. Sitting in laboratories in the United States or Europe would not be enough. The funding structure of the GND program, which provided each research unit with up to eight years of continuous and flexible funding, facilitated this kind of collaborative work. David Weatherall, head of the Oxford Tropical Medicine Research Unit and another beneficiary of the GND program, emphasized in his reflections that funding from the RF enabled his group to establish overseas links and send researchers to carry out field work, “which would have been completely impossible with any other form of support.” The British Medical Research Council, for example, funded his unit’s basic molecular biology work but would not support its field research. The GND program’s imperative for institutions in the Global North to work in field sites and with institutions based in the Global South complemented Warren’s plan to fund medical and scientific units in the Global South in their own right as part of the program.
Moving Into Malaria Vaccine Research (Late 1970s-1980s)

These features of the GND program brought the RF into the world of malaria vaccine research just as this line of investigation was beginning to take off. Ken Warren courted a number of investigators and their laboratories to be part of the program, who would end up focusing their research on various aspects of malaria immunology, genetics, and biochemistry. This is not entirely surprising considering that the GND program’s eight-year duration coincided with a time of great optimism about the prospect of creating a malaria vaccine. In 1976, two researchers at the Rockefeller University, parasitologist William Trager and microbiologist James Jensen, facilitated the investigation of malaria parasites by developing the first-ever method for cultivating these organisms in a continuous culture.18 This scientific development, along with new tools and techniques in biotechnology pioneered during the 1970s, fostered new hope in the ability of scientists to understand and exploit the vulnerabilities of malaria parasites. It also opened the door for scientists from outside the fields of malariology and parasitology to apply their laboratory skills to the problem of malaria vaccine development.

The GND units that pursued research related to malaria vaccines did so following different trajectories. Scientists at the Walter and Eliza Hall Institute for Medical Research in Melbourne, Australia, for example, focused on malaria vaccination from the beginning of their GND grant funding. Graham Mitchell, head of the Institute’s Laboratory of Immunoparasitology, led the Australian GND unit. Mitchell came to his position as an immunologist who had shifted his focus from pure cellular immunology to parasitology in the early 1970s.19 Coming in with this expertise, Mitchell’s laboratory engaged in research that would facilitate the development of vaccines for parasitic diseases, including schistosomiasis and leishmaniasis as well as malaria. They used some of the latest techniques from molecular biology and genetic engineering, such as screening complementary DNA strands synthesized from RNA strands of malaria parasite proteins, to isolate and identify antigens with protective potential. Members of the Walter and Eliza Hall Institute also successfully expressed blood-stage antigens of *Plasmodium falciparum*—the most deadly form of malaria parasite and the main target of vaccine research—in *E. coli*, marking “a breakthrough in molecular parasitology.”20 By using this method to clone parasite antigens, they hoped to
accelerate the study of the human immune response to blood-stage parasites and identify potential candidates for a malaria vaccine.\textsuperscript{21} New insights and techniques in biotechnology alone did not make their work possible; the group also relied heavily on blood samples collected from populations in malaria endemic areas of Papua New Guinea to access malaria parasites. As Warren envisioned, the Walter and Eliza Hall Institute’s GND unit made productive use of both laboratory and field resources in their efforts to understand and control parasitic disease.

Like the Walter and Eliza Hall Institute, the University of Oxford’s Department of Medicine also established a GND unit in 1978, though not initially with a main focus on malaria. Rather, the unit, led by hematologist David Weatherall, aimed to continue and expand its existing work on thalassemia and other genetic disorders of the red blood cell. Around that same time, the Wellcome Trust had set up a unit in Thailand for clinical tropical medicine research linked to Oxford’s Department of Medicine. As a result, the Oxford GND unit also expanded its work on “medicine in the Third World,” including its malaria research, investigating the process by which malaria parasites invaded red blood cells.\textsuperscript{22} Around 1984, in fact, the unit’s leaders decided to repurpose the expertise of its hemoglobin researchers in recombinant DNA technology to advance work on human and animal malarias.\textsuperscript{23} Doing so, these researchers were able to produce new knowledge about the genome of \textit{Plasmodium falciparum} and particular DNA sequences coding for functionally or immunologically important malarial proteins.\textsuperscript{24} While this work did not deal with the development or testing of malaria vaccines specifically, it contributed to malaria vaccine researchers’ understanding of how malaria parasites interacted with red blood cells and might potentially be inhibited from invading these cells through a vaccine or drug. It also paved the way for future work at the University of Oxford’s new Institute for Molecular Medicine, launched in 1989, which specialized in molecular parasitology and the application of recombinant DNA to clinical research.\textsuperscript{25} The foundations laid through RF funding, in other words, persisted beyond the GND program.

Investigators at the Walter and Eliza Hall Institute and University of Oxford started in the GND program by expanding on topics in which they already had expertise. Others, however, came into the program to do research that was new to them. Peter Perlmann, an immunologist at the University of Stockholm in Sweden, had been working for many
years on mechanisms of autoimmunity and tumor immunology when he decided—“maybe just because almost everybody around us worked in these fields”—to shift his focus. It happened that around that same time, Warren created the GND program. “Once the thought had come up,” Perlmann later recalled, “it was not difficult to grasp that “the Great Neglected Diseases of Mankind” should be the real targets for such efforts [in immunology], not only because of their enormous importance, but also because of the amount of immunological research going into the field was so obviously out of proportion to its global significance.” He teamed up with Hans Wigzell, and immunologist at Uppsala University (and later the Karolinska Institute) who had worked a bit on rodent malaria, to establish a GND unit looking at the different factors relating the immune system’s response to falciparum malaria. “An experiment in Ken Warren’s efforts to bring people into an old field,” the Swedish team of immunologists took a few years to get their research up and running, but by 1986 was considered by Warren at “the very forefront of research leading to a malaria vaccine.” Like members of the Walter and Eliza Hall Institute, they had used new techniques, such as the development of monoclonal antibodies against specific blood-stage antigens, to find potential vaccine candidates. They also pushed the boundaries of work on malaria vaccines by, for instance, examining the capacity of antigens to stimulate cellular immunity (i.e., by activating killer T-cells) rather than just humoral immunity (i.e., antibody production), which most teams had focused on but seemed to yield less-than-promising results. The combination of Perlmann’s and Wigzell’s previous immunology experience, combined with new breakthroughs from the “biotechnology revolution” and support from the RF—including support for field research and collaborations in malaria endemic countries, such as Liberia and Colombia—made possible their major contributions to malaria vaccine research during the 1980s.

Although not as focused initially on malaria vaccine research, the Rockefeller University also received money from the RF to initiate investigations in this area. The Rockefeller University’s pharmacoparasitology unit had been a core GND unit from the program’s early years, but its malaria work—led by Anthony Cerami—focused primarily on parasite biochemistry and research toward the development of new antimalarial drugs. In 1986 head of the Rockefeller University’s Laboratory for Molecular Parasitology, George Cross, received a separate grant from the GND program to study malaria parasite surface antigens potentially responsible for the parasite’s ability to
evade the human body’s immune response. His proposed study grew from the observation that while scientists had characterized multiple surface antigens of *Plasmodium falciparum*, and had even begun testing them for their potential use in a malaria vaccine, no antigen yet provided complete protection.30 Again, using some of the latest techniques from molecular biology and genetic engineering, Cross hoped to draw on funding from the RF to push the search for a viable malaria vaccine forward.

The RF’s Health Sciences Division contributed to malaria vaccine research beyond its support of the core GND units. It also provided grants to institutions for specific projects related to malaria vaccines. For example, the Division provided funds to a collaborative group based out of New York and Rome to examine malaria transmission in Burkina Faso in preparation for field trials of a malaria vaccine.31 In 1986, it provided $4,000 to a team from New York University’s Medical Center to capture Brazilian *Aotus* monkeys for use in malaria vaccine research.32 As malaria vaccine trials progressed over the mid-1980s and it became clear that current vaccine candidates did not offer effective, prolonged protection in humans, the Health Sciences Division awarded $75,000 to the University of Hawaii for research on synthetic adjuvants (substances which enhance the body’s immune response) for blood-stage malaria vaccines.33 The RF also did not stop at institutional support. The GND program funded specific investigators, particularly young, up-and-coming scientists, who proposed to study parasites and parasitic diseases. In 1984 Altaf Lal, an Indian biochemist and senior research officer at the National Institute of Immunology in New Delhi, received a grant to train in molecular biology and parasitology at the US National Institutes of Health, where he cloned and sequenced genes from an important sporozoite-stage antigen and set up a system for testing anti-sporozoite malaria vaccines in mice.34 Beyond its main activities in funding and cultivating a core group of scientists and scientific units, the GND program did much to bring new researchers into the field of parasitology and support small steps in the larger endeavor to create a human malaria vaccine.
Vaccines and the Legacies of the GND Program

The trajectories of these various GND units and grantees reflect a broader phenomenon that unfolded over the course of the GND program. Malaria vaccine research did not begin as a main focus; however, as investigators began to bring new technologies and techniques to bear on the study of parasites, they found fruitful avenues for advancing the study and development of malaria vaccines. Indeed, as Warren admitted, by 1986 “the research network [wa]s very different than when it began. As the scientists were equipped to work at the frontiers of modern biomedical science they rapidly took advantage off the powerful new techniques made available by the “biotechnology revolution.” By the nature of the technologies, this led to an emphasis on vaccines rather than drugs and environmental control measures such as pesticides.”

Indeed, the RF and its GND program had recently phased out support for the pharmacoparasitology unit at Case Western Reserve University because, among other things, “the unit’s work did not fit into the developing major programmatic interest in vaccines.” The GND program added two new units in 1984 and 1985 which were involved in research related to vaccine development. Due to the nature of the development of the biological sciences in general, including the advent of hybridoma technology and genetic engineering during the late 1970s, vaccines became seen as a promising avenue through which to apply basic scientific research to the management of parasitic diseases and the health problems of the developing world.

Thus, while members of the GND program investigated a variety of topics and diseases, by the end of the program, progress toward the development of a malaria vaccine stood out as one of the GND program’s most notable successes. According to one review of the GND program, the units in Sweden and Australia had made “the most important contribution to the development of a vaccine against the crucial blood stages of the malaria parasite.” Using different techniques, both units had identified and isolated a parasite antigen from merozoites (the parasite’s blood stage form), which seemed to prevent the malaria parasite from entering red blood cells and causing clinical malaria disease. Scientists at the University of Stockholm and Karolinska Institute went on to develop protective antibodies against a portion of this antigen, “opening the way to [...] a synthetic vaccine.” Meanwhile, scientists at the Walter and Eliza Hall Institute had begun to add genetic material from this antigen to a vaccinia virus (the basis of the
smallpox vaccine), which might potentially help immunize someone against malaria. The latter unit even began to explore linkages to the Australian biotech industry to expand research and development efforts directed at a blood-stage malaria vaccine. These efforts did not lead immediately to the production of an effective blood-stage vaccine—for which the world is still waiting—but it significantly enhanced researchers’ understanding of the possibilities and challenges of bringing this technology to fruition.

Even as optimism in developing a malaria vaccine began to give way to disappointment during the late 1980s, the RF’s Health Sciences Division continued to invest in work on this technology. In 1988 it awarded the Rockefeller University $300,000 over two years to fund a Malaria Consortium, a group of scientists which would help formulate fundamental research on malaria biochemistry aimed at identifying targets for pharmacological or immunological intervention against “the single most important parasitic infection of mankind.” This initiative built from the GND program in spirit and in infrastructure, fostered at the Rockefeller University during its time as a core GND unit. “Mobilization of the finest scientific minds globally to work on the relatively neglected diseases of the developing world – a goal of the [Health Sciences] division through 1987 – was accomplished by providing long-term funding and allowing freedom to investigate any aspect of any of the major diseases of the South,” the Consortium’s proposal stated. “Scientists who have become committed to finding practical solutions to these diseases are now thinking in terms of consortia that concentrate on specific problems of maximal importance for developing-world health.”

Acknowledging the persistent lack of a malaria vaccine or effective antimalarial drugs, the proposal went on to note that, “it must be realized that the outcome [of this new scientific collaboration] is basically unpredictable and that [...] the development of effective new prophylactic and therapeutic agents will take a considerable period of time. Nevertheless, the knowledge gained about the biochemistry of the parasite will enable many other investigators to become involved in this effort.”

This justification for the Malaria Consortium captures much of what the Rockefeller Foundation ended up contributing to the search for malaria vaccines during the late 1970s and 1980s. While the research it sponsored did not immediately generate an effective human malaria vaccine, it drew more people into the investigation of this
technology than would have otherwise been the case. This includes researchers who would not have studied malaria immunology or biology were it not for support from the GND program, such as those at the University of Stockholm, Karolinska Institute, or the University of Oxford. It also includes populations from places like Colombia, Liberia, Papua New Guinea, and Thailand, whose serum was used in GND-sponsored research on malaria parasites and parasite antigens. The work to which these various participants contributed to—whether through their scientific investigations or their blood “donations”—advanced knowledge about the development and operation of malaria vaccines, helping pave the way for future research. The RF and its Health Sciences Division made this work possible.

I would like to thank the Rockefeller Archive Center’s Research Stipend Program for the financial support to conduct research for my book project. I appreciate all of the help of the RAC archivists who facilitated my research in these collections, particularly Bethany J. Antos.

2 For more on the history of malaria and malaria eradication, see Randall Packard, The Making of a Tropical Disease: A Short History of Malaria (Baltimore: Johns Hopkins University Press, 2007).
3 Excerpt from Draft Program Statements prepared for Trustees, “Health Program,” Sept 14, 1977, PH-27, RF records, Projects, Box R2757, RG 1.20, RAC.
5 For some discussion of this reasoning, see National Academy of Sciences Institute of Medicine, Proposal No. 90-003, “Malaria Prevention and Control,” 3.
6 Keating, Kenneth Warren, 19.
8 Ibid., PH-24.
9 Ibid., PH-29.
10 Ibid., PH-26.
11 Ibid., PH-28-29.
12 Sir Christopher Booth and Dr. Fakhry Assad, “Review of the Program on the Great Neglected Diseases of Mankind of the Rockefeller Foundation,” undated, 2, RF records, Projects, Box R2757, RG 1.20, RAC.
Their method was specifically for the cultivation of blood stage *Plasmodium falciparum* parasites.


“The Walter and Eliza Hall Institute of Medical Research Eighth Annual Report – 1984-85,” 1985, 2, RF records, Projects, Box R2758, RG 1.20, RAC.


Letter of grant award to the University of Oxford, 1984, RF records, Projects, Box 25, Folder 153, RG 1.19, RAC.

“Report for the Tropical Medicine Research Unit, Nuffield Department of Clinical Medicine, University of Oxford, 1985-86,” undated, RF records, Projects, Box 26, Folder 154, RG 1.19, RAC.

Peter Perlmann, “How It All Began,” undated, 1, RF records, Projects, Box 25, Folder 150, RG 1.19, RAC.

Ibid.

Ibid., 2; Letter from Ken Warren to Dr. Peter Condliffe, Dec 24, 1986, RF records, Projects, Box 25, Folder 150, RG 1.19, RAC.

Draft, “Rockefeller University Plan for Parasitic Research,” September 14, 1981, RF records, Projects, Box 80, Folder 493, RG 1.18, RAC.

Grant to The Rockefeller University, February 3, 1986, RF records, Projects, Box 7, Folder 40, RG 1.18, RAC.


Grant to New York University Medical Center, December 2, 1986, RF records, Projects, Box 11, Folder 69, RG 1.18, RAC.

Pre-grant approval to the University of Hawaii at Manoa, May 1, 1989, RF records, Projects, Box R2842, RG 1.20, RAC.

Altaf Lal, Progress Report for Year March 1986-February 1987 and Proposed Plan of Work for March 1987-February 1988, RF records, Projects, Box 7, Folder 41, RG 1.18, RAC.

Letter from Ken Warren to Kenneth Dayton, July 8, 1986, RF records, Projects, Box R2757, RG 1.20, RAC.


Ibid., 5.

Ibid., 6.
39 Letter from Graham Mitchell to Ken Warren, July 5, 1983, RF records, Projects, Box 28, Folder 167, RG 1.19, RAC.
40 Grant to the Rockefeller University, “Malaria Consortium,” 1988, 3-4, RF records, Projects, Box 126, Folder 775, RG 1.19, RAC.
41 Ibid., 3.
42 Ibid., 5.