

# **Grand Challenges in Global Health**

## **Background on the Initiative and Research Projects**

The Grand Challenges in Global Health initiative was launched in 2003 by the Bill & Melinda Gates Foundation, in partnership with the National Institutes of Health, to harness the power of science and technology to dramatically improve health in the world's poorest countries. The initiative is supporting groundbreaking research projects to discover and develop scientific breakthroughs for preventing, treating, and curing diseases that kill millions of people each year in developing countries.

A total of 14 Grand Challenges were identified based on suggestions from more than 1,000 scientists from around the world. Solving these challenges could transform health in the world's poorest countries, and bring state-of-the-art solutions to people who need them most.

Some of the projects are focused on adapting existing health tools, like sophisticated laboratory tests, to novel technology platforms so that they are practical for developing countries. Other projects seek to fundamentally redefine our understanding of how to prevent and treat disease, potentially leading to entirely new vaccines and drugs for diseases of the developing world. Many of the projects are applying cutting-edge technology that has never before been used to advance global health.

After the 14 challenges were published in the journal *Science* in October 2003, scientists submitted more than 1,500 project ideas. From these, 43 projects, involving collaborators in 33 countries, were selected for funding, described in the following pages.

The Grand Challenges initiative is supported by \$450 million from the Gates Foundation, \$27.1 million from the Wellcome Trust, and \$4.5 million from the Canadian Institutes of Health Research (CIHR). The Gates Foundation funding includes a \$200 million commitment managed by the Foundation for the National Institutes of Health.

### **The Grand Challenges**

The 14 Grand Challenges are:

#### **GOAL: Improve childhood vaccines**

1. Create effective single-dose vaccines that can be used soon after birth
2. Prepare vaccines that do not require refrigeration
3. Develop needle-free delivery systems for vaccines

#### **GOAL: Create new vaccines**

4. Devise reliable tests in model systems to evaluate live-attenuated vaccines
5. Solve how to design antigens for effective, protective immunity
6. Learn which immunological responses provide protective immunity

#### **GOAL: Control insects that transmit agents of disease**

7. Develop a genetic strategy to deplete or incapacitate a disease-transmitting insect population
8. Develop a chemical strategy to deplete or incapacitate a disease-transmitting insect population

#### **GOAL: Improve nutrition to promote health**

9. Create a full range of optimal, bioavailable nutrients in a single staple plant species

GOAL: Improve drug treatment of infectious diseases

10. Discover drugs and delivery systems that minimize the likelihood of drug resistant microorganisms

GOAL: Cure latent and chronic infection

11. Create therapies that can cure latent infections
12. Create immunological methods that can cure latent infection

GOAL: Measure health status accurately and economically in developing countries

13. Develop technologies that permit quantitative assessment of population health
14. Develop technologies that allow assessment of individuals for multiple conditions or pathogens at point of care

## The Grand Challenges in Global Health Research Projects\*

### **GOAL: Improve childhood vaccines**

Each year, 27 million children in poor countries do not receive basic preventive vaccines. As a result, serious diseases that were eliminated in industrialized countries long ago remain widespread in the developing world, causing more than 1 million child deaths annually. Most vaccines must be given multiple times over weeks or months, and must be kept constantly refrigerated – these are serious obstacles for families who must travel long distances to the nearest health clinic, and for communities without electricity. For example, an estimated 151 million vaccine doses delivered to developing countries this year will spoil because they are not properly refrigerated. In addition, most vaccines are delivered by injection, which increases the risk that HIV, hepatitis, and other infections could be transmitted by unsterile or reused syringes and needles. An estimated 500,000 serious infections could be avoided this year by using needle-free vaccines.

Recent advances in chemical engineering and other scientific disciplines could lead to a new generation of childhood vaccines that are effective after a single dose, and do not require refrigeration or needles.

### **Grand Challenge #1: Create effective single-dose vaccines that can be used soon after birth**

Grants under this challenge:

- Linking Innate and Specific Immunity to Develop Single-Dose Vaccines for Neonates

*Lead investigator: Lorne A. Babiuk, University of Saskatchewan, Canada*

*Grant amount: \$5.6 million*

Very young children are the most vulnerable to infectious disease. Dr. Babiuk's team will develop novel vaccine formulations that could protect newborns and young children from whooping cough (pertussis) with a single dose. Whooping cough is one of the most serious respiratory diseases among young children worldwide, causing 200,000 to 400,000 deaths each year. The researchers will develop vaccines that could be delivered via the mucosal lining of the nose or mouth, stimulating immunity at the surfaces where most disease-causing agents enter the body. It is anticipated that these novel vaccine formulations could also be used in vaccines against other diseases affecting newborns and young children.

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\* Please note that for some Grand Challenges projects described in this document, the total grant amount listed is contingent upon the investigators meeting interim research and development milestones.

- A Live Recombinant Attenuated Salmonella Anti-Pneumococcal Vaccine for Newborns

*Lead investigator: Roy Curtiss, Arizona State University, U.S.*

*Grant amount: \$14.8 million*

The current vaccine against bacterial pneumonia (pneumococcus) requires a complicated regimen of four injections given at specific intervals. Researchers in the U.S., Australia, and South Korea will attempt to improve the vaccine so it requires only a single dose. The project will formulate the vaccine with a safe, low-cost additive derived from weakened *Salmonella* bacteria, which early studies suggest can enhance a vaccine's ability to stimulate a potent immune response. The investigators will also work to design the vaccine so that it can be given orally. If effective, this technology has the potential to be used for a range of existing and new vaccines.

## **Grand Challenge #2: Prepare vaccines that do not require refrigeration**

Grants under this challenge:

- Bacterial Spores as Vaccine Delivery Systems

*Lead investigator: Abraham L. Sonenshein, Tufts University School of Medicine, U.S.*

*Grant amount: \$5 million*

Dr. Sonenshein and his team plan to create childhood vaccines that can withstand a wide range of temperatures without refrigeration by encapsulating them in harmless bacterial spores that are naturally heat-resistant. Early studies suggest that the spore-encased vaccines can be easily produced in large quantities at low cost. The investigators believe that vaccines prepared in this way could be distributed in ready-to-use packets for people to mix with water and drink, avoiding the need for an injection. The project will focus on vaccines for diphtheria, tetanus, and pertussis (the DTP combination vaccine), and rotavirus-related diarrhea. If effective, this way of preparing vaccines may be able to be used for a range of childhood vaccines.

- Increasing Vaccine Stability Through Novel Technology

*Lead investigator: Colin R. Gardner, TransForm Pharmaceuticals, Inc., U.S.*

*Grant amount: \$8.8 million*

TransForm Pharmaceuticals, Inc., has developed a technology for quickly screening different formulations of a medicine to identify those that are most likely to be stable, safe, and effective. Using this technology, TransForm will undertake studies to discover novel vaccine formulations with a reduced need for refrigeration. If successful, this project could significantly increase access to immunization in the developing world. The project will initially focus on the measles vaccine, although the technology may apply to a wide range of vaccines.

- Thermostable Vaccines With Improved Stability at Non-Refrigerated Temperatures

*Lead investigator: Marazban Sarkari, RxKinetix, Inc., U.S.*

*Grant amount: \$789,000*

Investigators at the pharmaceutical company RxKinetix, Inc., will explore ways to make vaccines temperature-stable using polymers already used in the formulation of many drugs. These inexpensive compounds are designed to protect vaccines from extreme heat and cold, and allow vaccines to be shipped in ready-to-use condition. Researchers will apply this method of vaccine temperature stabilization to the measles and hepatitis B vaccines, and the technology is potentially applicable to a wide variety of vaccines. The project involves a collaboration with public and private sector partners based in the developing world.

### **Grand Challenge #3: Develop needle-free delivery systems for vaccines**

Grants under this challenge:

- Development of a Targeted Mucosal Vaccine Delivery Technology

*Lead investigator: David D. Lo, Neurome, Inc., U.S.*

*Grant amount: \$3.9 million*

Dr. Lo and investigators at the biotechnology company Neurome, Inc., will develop needle-free vaccine delivery systems by coupling vaccines to specially designed molecules that target the respiratory or intestinal mucosal immune tissue. Many serious infections enter the body by inhalation or ingestion, and vaccines that stimulate immune defenses in the respiratory or intestinal tracts could be particularly effective against these infections. Using influenza as a model, the project will assemble the new molecules and conduct preclinical testing of several approaches to identify the most effective delivery methods.

- Nanoemulsions as Adjuvants for Nasal-Spray Vaccines

*Lead investigator: James R. Baker, University of Michigan, U.S.*

*Grant amount: \$6.3 million*

Dr. Baker's team will develop a new way of preparing vaccines so that they can be given as nasal drops rather than as injections. Early studies suggest that mixing vaccines with a microscopic emulsion of water and oil allows them to be absorbed through the nasal passage. This low-cost, easy-to-prepare emulsion also forms a protective coating against heat and contamination, so that the vaccines may not require refrigeration. Initially, Dr. Baker's team will demonstrate this technology with the hepatitis B vaccine. In the future, the technology could be applicable to vaccines against a number of other diseases.

- Needle-Free Delivery of Stable, Respirable Powder Vaccine

*Lead investigator: Robert E. Sievers, Aktiv-Dry, LLC, U.S.*

*Grant amount: \$19.5 million*

Investigators at Aktiv-Dry, LLC, will develop a dry-powder version of the measles vaccine that can be inhaled through a disposable plastic device. If it is proven to be effective, this needle-free vaccine technology could potentially be applied to other vaccines and also reduce the need for these vaccines to be refrigerated. The project involves a collaboration with a number of partners, including the Serum Institute of India, the U.S. Centers for Disease Control and Prevention, the University of Colorado, and private companies.

- Needle-Free Vaccination Via Nanoparticle Aerosols

*Lead investigator: David Edwards, Harvard University, Division of Engineering and Applied Sciences, U.S.*

*Grant amount: \$7.6 million*

Researchers will attempt to improve the currently available tuberculosis and diphtheria vaccines by reformulating them into aerosol sprays that can be inhaled. In addition to being simpler and safer to administer than the current vaccines, which are injected, this new platform for aerosolized vaccination may be especially effective for respiratory diseases like TB, because the vaccine is delivered directly to the lungs. The aerosol sprays will be created by binding the vaccines' active ingredient to safe and biocompatible nanoparticles, which are tiny particles one-ten-millionth the size of a fingernail.

- Surface Modified Nanostructures as Delivery Vehicles for Transmucosal Vaccination

*Lead Investigator: Maria J. Alonso, University of Santiago de Compostela, Spain*

*Grant amount: \$662,000*

Dr. Alonso's team will attempt to develop a version of the hepatitis B vaccine that can be delivered nasally. The project will explore a number of potentially low-cost methods for encapsulating the vaccine in chemical structures that can pass through the mucosal lining of the nose. These chemical structures could also protect the vaccine so that it can be dried into a powder and stored for long periods without refrigeration. If effective, this method for preparing vaccines could potentially be applied to other vaccines.

## **GOAL: Create new vaccines**

While scientists have developed vaccines for many of the most common diseases in wealthy countries, the world still lacks vaccines for the biggest infectious killers – including malaria, tuberculosis, and malaria, which together kill more than 5 million people every year. To create effective vaccines for these diseases, Grand Challenges projects are focused on solving three key challenges: identifying the specific types of immune responses that effective vaccines must elicit, identifying effective new antigens for eliciting these immune responses, and improving the reliability of the animal tests that are used to evaluate potential vaccines prior to human trials.

Recent advances in scientific understanding of the causes of disease, the biology of the immune system, and genetics have significant potential for the development of effective

vaccines for HIV, TB, and malaria, as well as many other diseases prevalent in the developing world.

#### **Grand Challenge #4: Devise reliable tests in model systems to evaluate live-attenuated vaccines**

Grants under this challenge:

- [A Mouse Model to Evaluate Live-Attenuated Vaccine Candidates](#)

*Lead investigator: Richard A. Flavell, Yale University and Howard Hughes Medical Institute, U.S.*

*Grant amount: \$17 million*

The investigators propose a novel solution to a significant problem facing many vaccine researchers: for HIV and a range of other diseases, some of the most promising potential vaccines are made from weakened live versions of the infectious agent, but they cannot be studied in human trials unless researchers can be confident that the weakened vaccines will be safe. This project will attempt to genetically engineer laboratory mice so that their immune systems are similar enough to humans to permit reliable assessments of weakened live vaccines prior to human trials. The project involves a collaboration with the Institute for Research in Biomedicine in Switzerland and partners in the private sector.

- [Novel Mouse Models for Testing HIV and HCV Vaccines](#)

*Lead investigator: Rudi Balling, German Research Center for Biotechnology, Germany*

*Grant amount: \$9 million*

Dr. Balling's team, partnering with researchers at the Institut Pasteur in France, will try to genetically engineer mice with livers and immune systems that are similar to those of humans, so that the animals can be used to test potential HIV and hepatitis C vaccines prior to human trials. It is not possible to test these vaccines in current mouse models because mice are not naturally susceptible to the diseases. This project involves a collaboration with researchers at Hanover Medical School in Germany, the Rockefeller University in the U.S., the Academic Medical Center of the University of Amsterdam in the Netherlands, and INSERM and the Necker Hospital in France.

- [Development of Novel Mouse Models for HIV and HCV Infection](#)

*Lead investigator: Hongkui Deng, Peking University, China*

*Grant amount: \$1.9 million*

Dr. Deng and colleagues at Peking University in China will attempt to develop improved techniques for creating mouse models for testing potential vaccines for HIV and hepatitis C. The work will focus on using stem cells to aid in the creation of mouse models with immune systems and livers that more closely resemble those of humans. Current mouse models are inadequate for testing live-attenuated vaccines, and this project focuses on solving this critical bottleneck in vaccine development.

## **Grand Challenge #5: Solve how to design antigens for effective, protective immunity**

Grants under this challenge:

- Enhancing the Immunogenicity and Efficacy of Vectored Vaccines

*Lead investigator: Adrian Vivian Hill, University of Oxford, U.K.*

*Grant amount: \$10 million*

Dr. Hill and colleagues will explore ways to improve two vaccine technologies that are being widely used in the design of potential vaccines for HIV, tuberculosis, and malaria. These technologies, called “naked DNA” and “recombinant viral vector,” have previously been shown to stimulate important immune responses. This project plans to improve upon these vaccine approaches by adding recently discovered molecular signals that could either increase the potency of the initial immune stimulus, or overcome regulatory mechanisms in the body that can limit protective immunity. These improvements have the potential to result in a new generation of vaccine candidates that are both easily delivered and highly effective.

- Improved Vaccine Efficacy via Dendritic Cells and Flavivirus Vectors

*Lead investigator: Ralph Marvin Steinman, Rockefeller University, U.S.*

*Grant amount: \$14 million*

Dr. Steinman’s team plans to develop vaccines that stimulate the immune system’s dendritic cells, which are known to play an important role in stimulating protection against infectious diseases. The project will focus on creating experimental vaccines for a range of diseases, including HIV and malaria. If successful, this technology could identify a better way to create vaccines that stimulate multiple components of the body’s immune response, including those that have been difficult to target with existing vaccine approaches.

- Novel Antigen Design and Delivery for Mucosal Protection Against HIV-1 Infection

*Lead investigator: Robin John Shattock, St. George’s, University of London, U.K.*

*Grant amount: \$19.7 million*

Dr. Shattock and collaborators in the U.K. and South Africa will attempt to develop an HIV vaccine that stimulates immunity to the virus in the lining of the vagina. The investigators hypothesize that an HIV vaccine will be most effective at the site where the virus enters the body. Innovative combinations of vaccine antigen formulas and delivery technologies will be used to develop a potentially potent and effective vaccine. The vaccine will be designed to be delivered via low-cost vaginal gels or via silicone rings that fit inside the vagina and can be self-administered. The gel and ring will be formulated with a mechanism to release the vaccine in small amounts over time.

- A Protective Genetically Attenuated P. Falciparum Sporozoite Vaccine

*Lead investigator: Stefan Hans Irmfried Kappe, Seattle Biomedical Research Institute, U.S.*

*Grant amount: \$13.5 million*

Dr. Kappe's team will explore the use of a weakened malaria sporozoite as a potential vaccine against the disease. A sporozoite is the form of the malaria parasite that is transmitted from mosquito to human; after entering the bloodstream, the sporozoite moves to the liver, where it grows and divides into thousands of parasites that invade and destroy red blood cells, causing malaria disease. The vaccine would be designed to deliver weakened malaria sporozoites to the liver, where they will stimulate immune responses that could recognize and destroy incoming mosquito-transmitted sporozoites.

### **Grand Challenge #6: Learn which immunological responses provide protective immunity**

Grants under this challenge:

- Biomarkers of Protective Immunity Against TB in the Context of HIV/AIDS in Africa

*Lead investigator: Stefan H.E. Kaufmann, Max Planck Institute for Infection Biology, Germany*

*Grant amount: \$13.1 million*

Dr. Kaufmann will lead an international consortium of 15 institutions in Europe, Africa, and the U.S. They will attempt to identify immune system differences between people who are exposed to tuberculosis and never become sick, and those who develop serious disease. The researchers will focus particular attention on people infected with both TB and HIV. The study results could help guide the design and testing of new TB vaccines, drugs, and diagnostics, especially in areas with high HIV infection rates.

- Comprehensive Studies of Mechanisms of HIV Resistance in Highly Exposed Uninfected Women

*Lead investigator: Francis Allen Plummer, University of Manitoba, Canada*

*Grant amount: \$8.3 million*

Dr. Plummer and colleagues will expand on past research that has identified groups of commercial sex workers in Kenya who do not become infected with HIV despite repeated sex without condoms. While the phenomenon is well documented, it is not well understood. The project will undertake a comprehensive analysis of these women's immune systems and genetics. Understanding what makes them apparently immune to the virus could guide HIV vaccine and drug development.

- Immunity to Prevent Pneumococcal Transmission: Correlates of Protection and Herd Immunity

*Lead investigator: Helena Käyhty, National Public Health Institute, Finland*

*Grant amount: \$8.5 million*

Dr. Käyhty and colleagues will try to reduce the time and cost required for trials of vaccines against bacterial pneumonia. Currently, researchers determine whether a potential pneumonia vaccine is effective by studying whether it prevents vaccinated individuals from developing pneumonia disease. This requires studying a large number of people over a long period of time, as only a subset of people who become infected with pneumonia bacteria develop pneumonia disease. Dr. Käyhty's team believes that researchers may be able to study a surrogate measure that can be observed much more quickly and inexpensively: whether the vaccine reduces the amount of pneumonia bacteria that are able to infect the body.

- Learning from the Human Genome How Protective Immunity Against Malaria Works

*Lead investigator: Dominic Kwiatkowski, Oxford University, U.K.*

*Grant amount: \$16.4 million*

Dr. Kwiatkowski's team will integrate and build on the work of malaria research groups around the world through the formation of the Malaria Genomic Epidemiology Network, MalariaGEN. Across 14 malaria-endemic countries, MalariaGEN partners are studying individuals with malaria – those who survived, others who died of the disease, and some who were infected without becoming ill. By using new technologies to discover natural variations in the human genome that determine an individual's ability to resist infection, MalariaGEN aims to identify the many different molecular building blocks that the human body uses to defend itself against the malaria parasite. This information will be shared with other malaria researchers to guide the design of vaccines and more effective ways of treating severe malaria.

- Molecular Analysis and Modeling of HIV-1 Transmission, Containment, and Escape

*Lead investigator: George M. Shaw, Howard Hughes Medical Institute at the University of Alabama at Birmingham, U.S.*

*Grant amount: \$16.3 million*

Investigators from clinical and laboratory research sites in the U.S., Europe, and Africa will study people who have recently become infected with HIV, to analyze the changes that occur over time in their immune systems and in the virus itself. Upon exposure to HIV, most individuals develop an early immune response that limits but does not stop the virus from spreading throughout the body and destroying host immune defenses. The project's goal is to guide the development of an HIV vaccine by better understanding the initial strengths and ultimate weaknesses of the natural immune response to the virus.

- Protective Immunity Against Severe Malaria in Young Children

*Lead investigator: Patrick Emmet Duffy, Seattle Biomedical Research Institute, U.S.*

*Grant amount: \$19 million*

Dr. Duffy's team will attempt to identify the forms of the malaria parasite that are responsible for the most severe disease in young children. This project builds on previous research that has found that different parasite forms cause different disease syndromes, and will determine whether an individual's immune system can respond to these parasite forms and prevent severe illness and death. The results of these studies could help guide efforts to develop a malaria vaccine that can protect children from the disease.

### **GOAL: Control insects that transmit agents of disease**

Many serious diseases are spread by insects. These include malaria, which infects 350-500 million people and causes more than 1 million deaths annually, primarily among young children in sub-Saharan Africa, and dengue fever, which infects up to 100 million people each year and can cause severe fever, hemorrhaging, and death. The main strategy for fighting these diseases has been to use insecticides to kill disease-transmitting insects. This approach has met with mixed success, and is increasingly ineffective as mosquitoes grow resistant to available insecticides, and the insecticides that are effective tend to be too toxic or expensive for developing countries to use on a large scale.

Grand Challenges projects will pursue a number of promising approaches to controlling disease-transmitting insects that are safer, more effective, and more affordable than current insecticides. These include genetic strategies to cause mosquitoes to die before they can transmit disease, and using cutting-edge chemistry to make insecticides that are inexpensive and safe to handle.

### **Grand Challenge #7: Develop a genetic strategy to deplete or incapacitate a disease-transmitting insect population**

Grants under this challenge:

- Developing Novel Transgenic Strategies for Introducing Dengue Virus Refractivity in Mosquito Cells and Tissues

*Lead investigator: Malcolm James Fraser, University of Notre Dame, U.S.*

*Grant amount: \$2.5 million*

Researchers will develop a new approach to suppress the replication of dengue virus within mosquitoes, using genetic strategies to introduce a molecular mechanism that harnesses the dengue virus' own genetic make-up to activate a cell death pathway that kills infected cells. This "death upon infection" strategy would make the mosquitoes immune to dengue, effectively limiting their ability to transmit disease.

- Genetic Strategies for Control of Dengue Virus Transmission

*Lead investigator: Anthony Amade James, University of California at Irvine, U.S.*

*Grant amount: \$19.7 million*

This multinational team will employ a combination of molecular, field, and social science research to advance a genetic-based strategy for preventing mosquitoes from transmitting the dengue virus. The project will examine genetic approaches to controlling dengue virus transmission, including those that could inhibit viral development within the mosquito, reduce the ability of infected mosquitoes to successfully transmit the virus, and reduce or eliminate mosquito populations.

- Homing Endonuclease Genes: New Tools for Mosquito Population Engineering and Control

*Lead investigator: Austin Burt, Imperial College London, U.K.*

*Grant amount: \$8.8 million*

The inability to ensure that newly introduced genes will become established within the regional mosquito population has been a major roadblock to the advancement of genetic strategies for vector control. In this project, Dr. Burt and colleagues will test a class of artificially engineered genes known to spread rapidly from parent to offspring to move newly introduced traits, such as sterility or inability to transmit disease, through a mosquito population. Laboratory experiments will predict whether such a strategy could eradicate mosquito populations or render them unable to transmit malaria.

- Modifying Mosquito Population Age Structure to Eliminate Dengue Transmission

*Lead investigator: Scott Leslie O'Neill, University of Queensland, Australia*

*Grant amount: \$6.7 million*

Dr. O'Neill and a multinational team plan to interfere with the mosquito's ability to transmit the dengue virus by altering its lifespan. Scientists will introduce a bacterial parasite that occurs naturally in other insects into mosquitoes so that it causes them to die before they are old enough to transmit the virus. Mosquitoes would "inherit" the parasite and pass it from generation to generation. The approach will be tested on controlled mosquito populations in the laboratory. Dengue virus currently infects up to 100 million people each year.

## **Grand Challenge #8: Develop a chemical strategy to deplete or incapacitate a disease-transmitting insect population**

Grants under this challenge:

- Disruption of Malaria Transmission by Chemical Manipulation of Anopheline Olfactory Responses

*Lead investigator: Laurence J. Zwiebel, Vanderbilt University, U.S.*

*Grant amount: \$8.5 million*

### Molecular Approaches to Alter Olfactory-Driven Behaviors of Insect Disease Vectors

*Lead investigator: Richard Axel, Howard Hughes Medical Institute at Columbia University, U.S.*

*Grant amount: \$5 million*

The mosquitoes that transmit the malaria parasites to humans use their sense of smell to guide them to their human targets. These two projects will complement each other to build on state-of-the-art knowledge of insects' sense of smell in order to develop safe, effective, and low-cost mosquito repellants that will reduce malaria transmission in endemic areas. Molecular technology will be used to identify compounds that interfere with the host-seeking behavior of malaria-transmitting mosquitoes by stimulating or blocking the responses of specific odor receptors.

- Molecular Design of Selective Anticholinesterases for Mosquito Control

*Lead investigator: Jeffrey R. Bloomquist, Virginia Polytechnic Institute and State University, U.S.*

*Grant amount: \$2.7 million*

Insecticide-treated bed nets have been proven to have a community-wide effect on malaria control by reducing the number of infected mosquitoes. However, nets must be periodically re-treated to maintain their effect, and most insecticides are too toxic for untrained people to use safely. This project will use a novel chemical synthesis method called "click chemistry" to produce an insecticide that is inactive and nontoxic until its components reach the mosquito central nervous system. This approach could develop a safe, lasting, and highly potent insecticide that is targeted specifically to the mosquito species that transmits malaria, and is nontoxic to humans and other animals.

## **GOAL: Improve nutrition to promote health**

Poor nutrition is a major global health problem, contributing to more than half of the nearly 11 million deaths that occur each year in children under 5. It is estimated that half of the population of sub-Saharan Africa suffers from iron deficiency and a third from zinc deficiency, and 90% of children in the region receive inadequate amounts of vitamin A. Inadequate intake of these and other essential micronutrients can cause impaired immune systems, blindness, low birth weight, impaired neuropsychological development, and stunting. Arid climates with poor soil cannot support the fruits, vegetables, and grains needed to naturally supply essential vitamins, minerals, and other nutrients. As a result, billions of people rely primarily on less healthy food like rice, which grows easily in a variety of climates but is one of the poorest sources of

essential nutrients. A promising long-term solution to this problem is to genetically modify crops that grow well in harsh climates so that they contain high levels of essential nutrients.

**Grand Challenge #9: Create a full range of optimal, bioavailable nutrients in a single staple plant species**

Grants under this challenge:

- Development of Bananas With Optimized Bioavailable Micronutrients

*Lead investigator: James Langham Dale, Queensland University of Technology, Australia*

*Grant amount: \$1.1 million*

In Uganda, more than 38% of children under the age of 5 years are stunted due to malnutrition. Vitamin A deficiency and iron deficiency anemia are major public health problems in Uganda. Researchers in Australia, Uganda, and the United States will attempt to genetically modify Ugandan bananas – a staple food in that country – so that they contain increased levels of pro-vitamin A, vitamin E, and iron. These essential nutrients are lacking in the diets of more than a third of Ugandan children. The country is the second largest producer of bananas in the world, and Ugandans eat an average of one kilogram of bananas each day.

- Improving Cassava for Nutrition, Health, and Sustainable Development

*Lead investigator: Richard T. Sayre, Ohio State University, U.S.*

*Grant amount: \$7.5 million*

Dr. Sayre's team will attempt to genetically modify cassava, a starchy root crop that is the staple food for more than 250 million people in Africa, yet provides less than 30% of the amount of protein needed for a healthy diet, and just 10-20% of the required amounts of vitamins A and E, iron, and zinc. Cassava can also be toxic if not prepared properly, due to low levels of naturally occurring cyanide. In addition to increasing the levels of key micronutrients in cassava, researchers will modify the plant to eliminate naturally occurring cyanide and to allow it to be stored for longer periods of time.

- Improving Rice for High Beta-Carotene, Vitamin E, and Enhanced Iron and Zinc Bioavailability

*Lead investigator: Peter Beyer, Albert-Ludwigs University, Germany*

*Grant amount: \$11.3 million*

Although rice is the primary source of food for more than half of the world's population, it is a poor source of many essential micronutrients, and widespread reliance on rice is the primary cause of micronutrient malnutrition throughout much of the developing world. Dr. Beyer and colleagues will work to develop new varieties of Golden Rice that will contain more complete nutrition, including increased levels or bioavailability of pro-vitamin A, vitamin E, iron, and zinc, and improved protein quality. Golden Rice, containing high levels of beta-carotene, is already being introduced in Asia.

- Nutritionally-Enhanced Sorghum for the Arid and Semi-Arid Tropical Areas of Africa

*Lead investigator: A Harvest, Kenya, in collaboration with Dr. Paul Anderson of DuPont Crop Genetics Research, U.S.*

*Grant amount: \$16.9 million*

The African-based food organization A Harvest is partnering with scientific teams from agricultural company Pioneer Hi-Bred International, a subsidiary of DuPont, and the Council for Scientific and Industrial Research in South Africa. A Harvest will attempt to genetically engineer a new variety of sorghum for the more than 300 million people in arid regions of Africa who rely on this grain as their primary source of food. Sorghum is one of the few crops that grows well in arid climates, but it is deficient in most essential nutrients, and is difficult to digest when cooked. This project seeks to develop a more nutritious and easily digestible sorghum that contains increased levels of pro-vitamin A, vitamin E, iron, zinc, amino acids, and protein. A prototype, containing increased levels of the amino acid lysine, has already been successfully developed.

### **GOAL: Improve drug treatment of infectious diseases**

Disease-causing microbes often mutate and develop drug resistance. For example, the malaria parasite, which kills more than 1 million people each year, has mutated so that it is no longer affected by the drug chloroquine, which for years was an effective and inexpensive anti-malaria treatment. As a result, countries are turning to alternative malaria treatments, which can be more than 20 times as expensive. Recent advances in evolutionary biology have suggested new approaches to developing medicines that would be harder for microbes to resist.

### **Grand Challenge #10: Discover drugs and delivery systems that minimize the likelihood of drug resistant microorganisms**

Grants under this challenge:

- Natural Products Inhibit Intracellular Microorganisms Via Cellular Mechanisms

*Lead investigator: Jian-Dong Jiang, Chinese Academy of Medical Sciences, China*

*Grant amount: \$2 million*

Dr. Jiang's team plans to identify components of human cells that are used by microbes to establish an infection and replicate, but that are not essential to the human host. It is envisioned that once these host factors are identified, drugs can be developed to target them and prevent the microbes from causing infection or disease. By targeting components of human cells and not the microbes themselves, the researchers believe that it would be much more difficult for the microbes to develop resistance to drugs. The project will focus on potential treatments for HIV, tuberculosis, and hepatitis B.

- Novel Therapeutics That Boost Innate Immunity to Treat Infectious Diseases

*Lead investigator: Barton Brett Finlay, University of British Columbia, Canada*

*Grant amount: \$8.7 million*

Dr. Finlay's team will explore new ways to combat drug resistance by developing medicines that, rather than targeting specific disease-causing organisms, seek to boost the body's general defenses against infectious agents. Because the medicines would act on the human body and not the microbes themselves, the researchers expect that it will be more difficult for the microbes to develop resistance to this approach. The concept has already been demonstrated in animal studies.

### **GOAL: Cure latent and chronic infection**

Some of the most serious diseases, like tuberculosis and hepatitis C, can infect people for years or even a lifetime. While the initial infection may be in an inactive or "latent" state, it can activate without warning to cause serious illness or death and be passed to other people. Treating people with latent infections before the onset of active disease could significantly reduce illness and death and reduce disease transmission. For example, nearly two billion people – one-third of the world's population – are believed to be latently infected with TB, and up to 10% will develop active disease at some point in their lives. The biology of latent and chronic infections is not well understood, which has slowed the development of effective drugs to treat and cure these diseases.

Grand Challenges projects will pursue a number of promising avenues for developing drugs to cure latent and chronic infections. These include both drugs that would directly kill or slow an infection, as well as immunotherapies that would stimulate the immune system to eliminate the infection.

### **Grand Challenge #11: Create therapies that can cure latent infections**

Grant under this challenge:

- Drugs for Treatment of Latent Tuberculosis Infection

*Lead investigator: Douglas Young, Imperial College London, U.K.*

*Grant amount: \$20 million*

Dr. Young will lead an international collaboration involving researchers in the U.K., U.S., Singapore, Korea, and Mexico. They will attempt to fill a critical gap in currently available tuberculosis treatments: there are effective treatments for active disease, but none that can cure latent infection. Dr. Young's team will attempt to understand the fundamental biology of latency and use this to develop drugs that are effective against latent TB. Their work could also lead to improved treatments for active TB disease.

## **Grand Challenge #12: Create immunological methods that can cure latent infection**

Grants under this challenge:

- Engineering Immunity Against HIV and Other Dangerous Pathogens

*Lead investigator: David Baltimore, California Institute of Technology, U.S.*

*Grant amount: \$13.9 million*

Dr. Baltimore's team will explore a fundamentally new way of stimulating the immune system to fight off infectious diseases, focusing on HIV as a test of the concept. The premise of this project is that for some infections, including HIV, the immune system's natural responses are inherently inadequate, and therefore the traditional approach of using vaccines to stimulate and boost these responses is likely to be ineffective. As an alternative, Dr. Baltimore and his colleagues propose to genetically engineer immune cells that can produce adequate responses. Their work is intended to eventually lead to immunotherapy for people who are infected with HIV. It could also lead to new ways to prevent HIV infection.

- Immunological Strategies for Curing Chronic Hepatitis Virus Infections

*Lead investigator: Rafi Ahmed, Emory University, U.S.*

*Grant amount: \$12.5 million*

Dr. Ahmed and colleagues plan to develop a new therapy for hepatitis C that is more effective and affordable than the current treatment for the liver disease. The hepatitis C virus infects more than 3 million people every year and can cause severe liver damage. Scientists have recently discovered that viruses that cause chronic infections similar to hepatitis C are able to turn off the body's natural immune defenses against the disease, and then spread throughout the body virtually unchecked. This project will focus on developing a therapy that switches back on the immune system's natural defenses against hepatitis C. If successful, this approach could be applied to the treatment of several other chronic viral infections and possibly to certain parasitic diseases.

- Novel Therapeutic Vaccines for Acute and Persistent Papillomavirus Infections

*Lead investigator: Robert L. Garcea, University of Colorado, U.S.*

*Grant amount: \$3.5 million*

Researchers will attempt to develop an inexpensive therapeutic vaccine for human papillomavirus (HPV), the virus that causes nearly 500,000 cases of cervical cancer in women every year, the vast majority of which occur in developing countries. Building on research into vaccines to prevent HPV infection, this project will focus on developing a therapeutic vaccine that could cure someone who is already infected. A therapeutic vaccine may work by training the immune system to recognize the proteins that HPV produces when it infects cells.

- Preclinical and Clinical Evaluation of a Post-Exposure TB Vaccine

*Lead investigator: Peter Andersen, Statens Serum Institute, Denmark*

*Grant amount: \$11.3 million*

Dr. Andersen's team will study the tuberculosis bacteria to try to identify the mechanisms that allow it to escape the natural immune responses that help some people keep the disease under control for a lifetime, while other people succumb to serious illness, particularly if they also have HIV. The project hopes to use this information to design and test a potential therapeutic vaccine that can stimulate the immune systems of people with latent TB to eliminate the infection. The project team involves researchers in Europe, the U.S., and South Africa.

### **GOAL: Measure health status accurately and economically in developing countries**

Many developing countries lack reliable information about the health status of their people. While it may be apparent that significant numbers of people are becoming sick or dying, there is often little data on the major causes of disease. This impedes efforts to accurately target resources and disease control efforts. There are two major challenges to collecting better information on health problems: inadequate or expensive diagnostic tests that can identify the causes of illness, and inadequate or incomplete medical records, such as death certificates.

New advances across a number of scientific disciplines could greatly improve developing countries' ability to track health status and disease trends. These include using innovative statistical methods to accurately estimate an entire population's health status from limited information, and using new "miniaturizing" technology to reconfigure sophisticated diagnostic tests so they can be easily used in resource-poor settings.

### **Grand Challenge #13: Develop technologies that permit quantitative assessment of population health**

Grant under this challenge:

- Population Health Metrics Research Consortium Project

*Lead investigator: Christopher J.L. Murray, Harvard University, U.S.*

*Grant amount: \$18.8 million*

Dr. Murray's team will attempt to develop new methods and technologies for assessing the health status of populations in the developing world. The project pursues a creative approach that weds epidemiology, biomedical research, and population health assessment. Researchers will produce new measurement tools that are science-based, standardized, and widely applicable across different resource-poor settings. For example, the project will explore ways to extrapolate a country's leading causes of death, both in adults and children, from incomplete health records using mathematical models. These tools will be of use to policymakers and researchers to address persistent inequities in health outcomes. The international project team includes investigators from the U.S., Australia, the Philippines, Bangladesh, and Tanzania.

**Grand Challenge #14: Develop technologies that allow assessment of individuals for multiple conditions or pathogens at point of care**

Grant under this challenge:

- A Point-of-Care Diagnostic System for the Developing World

*Lead investigator: Paul Yager, University of Washington, U.S.*

*Grant amount: \$15.4 million*

Dr. Yager's team will attempt to develop a simple-to-use device that will help bring sophisticated medical tests to remote areas of the developing world. The device will be appropriate to test blood for a range of diseases prevalent in developing countries, such as bacterial infections, nutritional status, and HIV-related illnesses. The investigators envision that health care workers would load a small blood sample onto a disposable test card about the size of a credit card, which would contain all of the necessary test reagents. The test card would be inserted into the device, which itself would be about the size of a hand-held computer, and results would be available in about 10 minutes.

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