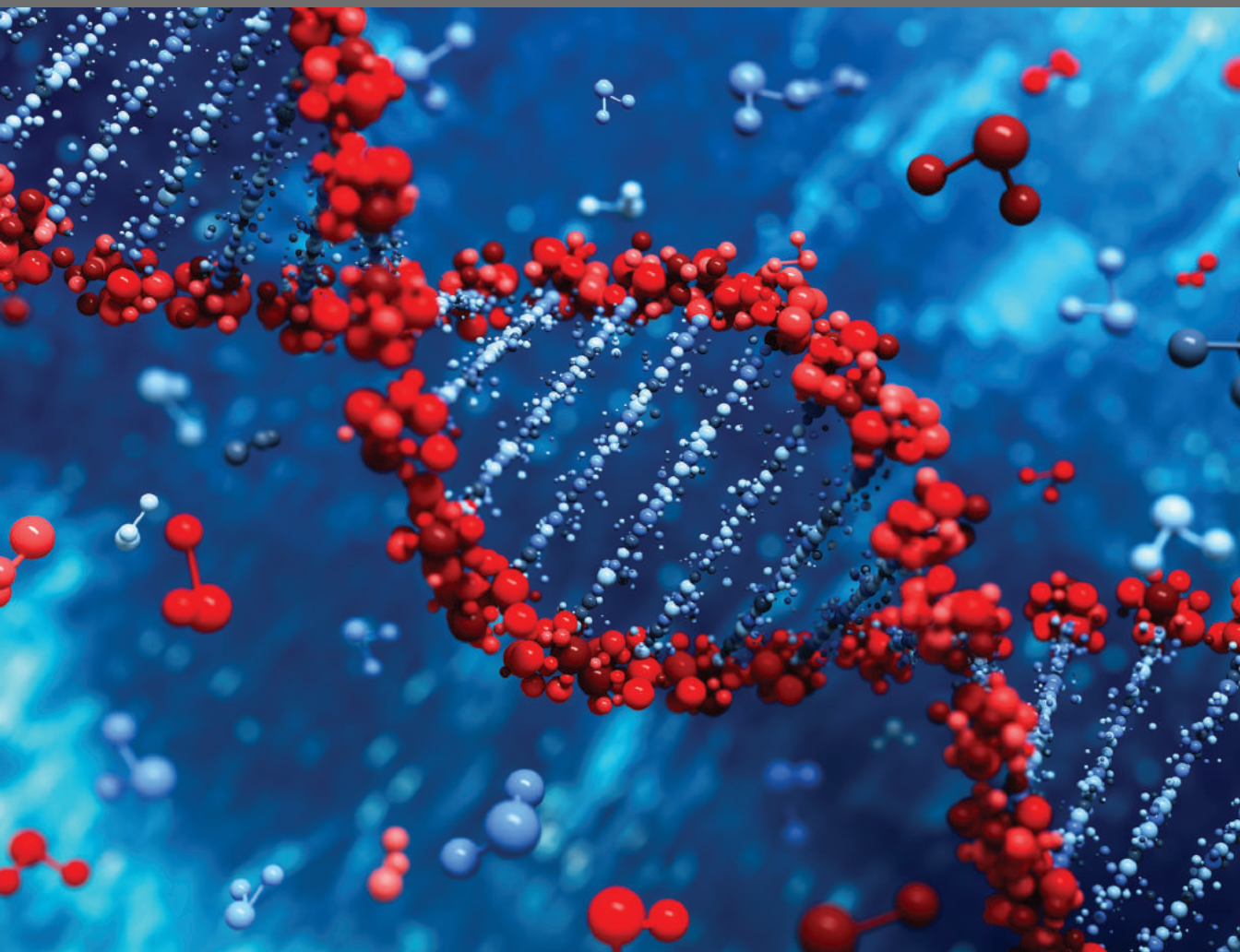


# THE XO FILES

**Extraordinary Opportunities to Support Basic Science Research**



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# THE XO FILES

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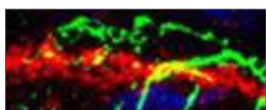
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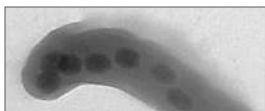
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# Introduction

Basic science research aims to increase our scientific knowledge base of the fundamental aspects of our natural world. It can lead, often in completely unexpected ways, to discoveries that improve our lives. Examples include the MRI, which came out of basic physics research, novel gene therapies, which built on basic research on bacteria, and many cell phone technologies which were made possible by basic research on the properties of materials. Basic research is also important because it satisfies the curiosity we all have about the world around us.

The Extraordinary Opportunities Files (XO Files) highlight some examples of cutting edge basic science research that, with support, could potentially improve lives or change our future. These case studies were selected by a distinguished editorial board for their extraordinary intellectual and social potential.

The Science Philanthropy Alliance aims to increase philanthropic support for basic scientific research. As advisors to philanthropists and foundations, we provide information and resources to assist in their support for basic science research.

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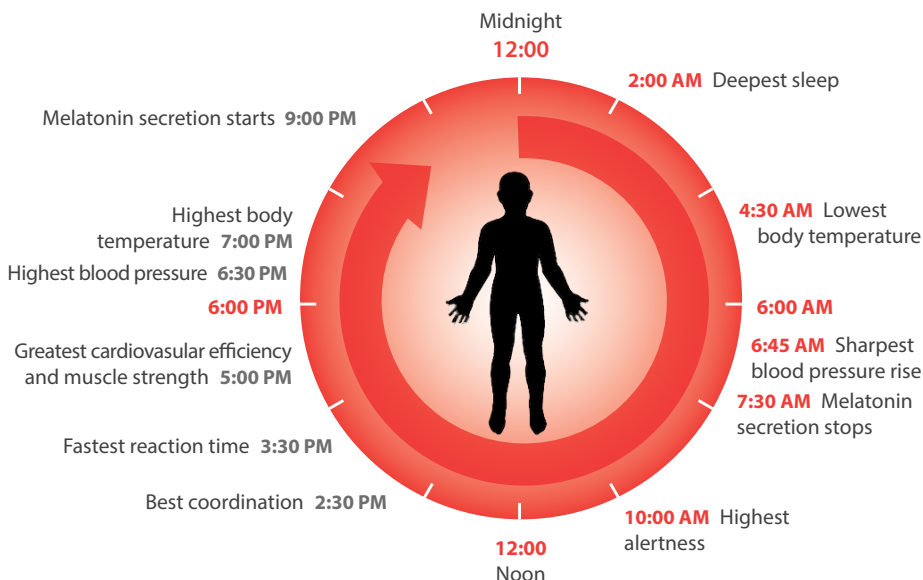
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*The circadian clock controls or influences the timing of a huge range of biochemical reactions and bodily processes, all tied to the 24-hour rhythm of the earth. That in turn has implications for how we sleep, how we function when awake, and when medical therapies are most effective.*



# Resetting the Clock of Life

We know that the circadian clock keeps time in every living cell, controlling biological processes such as metabolism, cell division, and DNA repair, but we don't understand how. Gaining such knowledge would not only offer fundamental insights into cellular biochemistry, but could also yield practical results in areas from agriculture to medicine to human aging.

*Ning Zheng and Michele Pagano*

**N**ight shifts. Jet lag. Disturbed sleep. Far from causing just drowsiness, these have a more profound effect. That's because they disrupt our circadian clock, so-called because it synchronizes biological processes to the earth's 24-hour rotation and, in turn, governs the basic chemical mechanisms of our body. The clock controls when thousands of genes turn on and off, and these in turn synthesize proteins that operate the machinery of a cell. Every cell has its own clock, and the clocks control different genes in different cell types. Life is, in effect, a marvelously intricate clockwork process—in

bacteria, in fungi, in plants, in insects, and in animals. In humans and likely in other animals, there is a central clock in the brain which is influenced by light and which synchronizes all the other clocks throughout the body. So when the clock is disrupted or when it doesn't work right, we feel the effects in every tissue and organ.

It may seem strange that such a fundamental biological process still lies outside our understanding, but that's the case. Research in bacteria, fruit flies, plants, and mice has shed some light on the clock. We know that in mammals it has four central components, four clock proteins and the genes

that synthesize them, which are interconnected in a feedback loop with a “positive” arm and a “negative” arm: the proteins turn on and off the genes, which in turn dictate the levels of the clock proteins, such that the levels of the clock proteins fluctuate in an intricate dance. Think of it as the biochemical equivalent of a two-pendulum grandfather clock. Only in this case, each swing of the pendulum influences a whole swath of other genes and sets in motion other essential processes, such as the process—which takes exactly 24 hours—by which mammalian cells divide and replicate themselves, or by which photosynthesis occurs in plants. The clock seems to be as old as life itself. Even ancient bacteria have a clock. The specific clock proteins found in people are also found in all animals—from bees to lizards to whales—showing how closely conserved the mechanism has been throughout hundreds of millions of years of evolution and thus how central it is to all living things.

In plants, flowering is controlled by the length of days. The molecular mechanisms are not understood, but it’s clear that plant sensors detect the quality of the available light, which in turn interacts with the plant clocks, which in turn control 5 or 10 percent of the genes in a plant. If we did understand, might it be possible to alter the clock mechanisms so we could get plants to speed up fruit and seed production, to produce harvests two or three times a year? Or would we be able to move plants from one region, for example the tropics, and get them to function properly in colder regions, where the available light is less?

There is also evidence that the clock plays a role in how bees and other insects, migratory birds, and perhaps other animals find their way home. In some way, the clock seems linked to the ability of such creatures to sense the earth’s magnetic field and use it to navigate or orient themselves spatially. The Monarch butterfly is one such species,

and one of its clock genes is quite similar to human clock genes. Might humans, too, have a dormant ability to sense the earth’s magnetic field?

Laboratory mice bred with no clock genes can still function, but they get cancer or have other abnormalities—their DNA repair mechanism doesn’t work. Is that why night shift workers and pilots or stewardesses who fly international routes have a higher incidence of some kinds of cancer? Experiments with mice prone to breast cancer have shown that continued disruption of normal sleep cycles accelerated the development of tumors. So there is at least some cause for concern in people with family histories of breast cancer.

Could we manipulate the clock as a way to improve cancer treatment? We don’t know. But we do know that DNA repair works differently at different times of day, which suggests that radiation or chemotherapies would be most effective if given when DNA repair is least active.

The clock also influences our basic metabolic processes—the way our bodies break down the organic matter and harvest energy from the food we eat and then use that energy to construct proteins and other components of cells. But it works the other way too—fasting for a period, then eating helps to reset the clock. Fasting, or very low calorie diets, are also known to slow down the aging process—which is controlled by the clock. Could we instead simply reprogram the clock—if we understood its mechanisms in greater detail—to slow aging directly? We don’t know, but the possibilities are more than intriguing.

Potential applications aside, research doesn’t get much more basic than this. The clock might well claim to be one of the fundamental secrets of life itself. At the very least, understanding the chemistry of living cells means understanding the clock that orchestrates when and often how that chemistry functions. *(continued next page)*

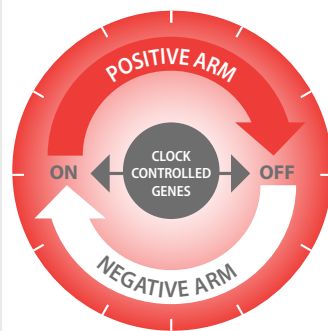
# How to Unlock the Clock Mechanism

To understand how the clock works and to answer a myriad of questions about practical applications will require systematically mapping the clock mechanisms in different human tissues and at different times of the day. Then scientists can begin to work out how clock proteins interact with clock genes and other proteins both chemically and structurally. Equally important is investigating the signaling mechanism by which the central clock synchronizes the individual cellular clocks, so that they all work together in rhythm with the earth's rotation. Another approach is likely to involve screening millions of small molecules to identify those that can alter the clock's periodic rhythm or increase/decrease the amplitude of clock oscillations. Such molecules could be used as tools to help study clock mechanisms as well as suggest potential candidates for future drug development.

To discover the precise molecular mechanisms by which proteins, metabolic compounds, and signaling chemicals sustain and regulate the clock will require a wide range of scientific talent—in genetics, in protein mapping and structure determination, and in protein biochemistry. It will require working first with model organisms such as fruit flies or mice, then seeing whether the same mechanisms are present in people. And then eventually, it will also require clinical investigations to use that knowledge to strengthen, correct, or fine tune the clock to devise new therapies in people or more productive crops or new ways to control harmful bacteria.

This is not a small project. It will require equipment, but even more it requires building up the needed scientific talent, sustaining research groups at multiple universities over at least a decade. Estimates are that \$100 million and 10 years of effort are needed to make significant progress—well beyond a normal research grant. A project such as this also does not fit well with funding mandates focused on specific diseases. In effect, the project requires doing for cellular biology what the genome project did for genetics—which is not surprising, given how central the clock is to life itself. By the same token, however, the fundamental knowledge gained is likely to have profound impacts on our ability to solve problems in human behavior and health, and indeed, in all other living organisms as well. And maybe in the end we will also understand why we are clockwork mechanisms, and why life keeps time to the earth's rhythm.

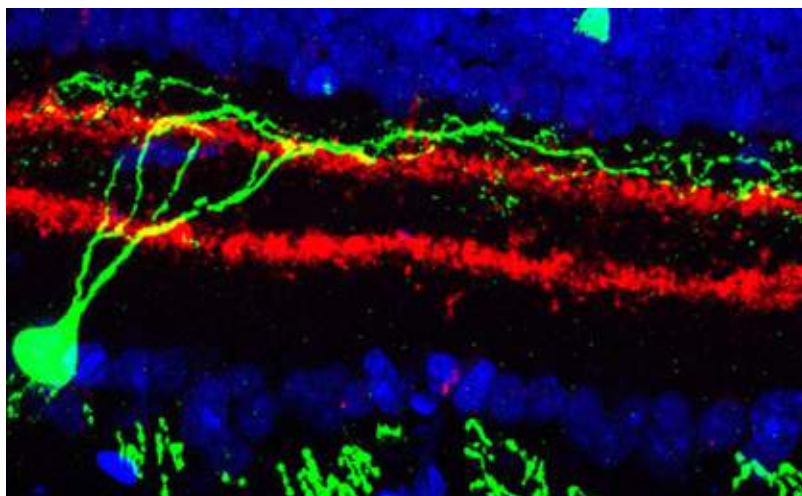
*Unlocking the clock means working out the detailed molecular mechanisms by which clock genes and proteins both influence and are influenced by a wide variety of biochemical processes, such as metabolism (diabetes), DNA repair (cancer), homeostasis (heart disease), nervous system (mood disorders, memory), and steroid hormones (cancer).*



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*Ning Zheng, Howard Hughes Medical Institute and Department of Pharmacology, University of Washington*

*Michele Pagano, Howard Hughes Medical Institute, Department of Pathology and NYU Cancer Institute, New York University School of Medicine*



*High-resolution images of retinal tissue from the human eye, showing ganglion cells (in green). The circular cell body is attached to thin dendrites on which nerve synapses form—in different tissue layers depending on the cell type and function. Credit: Lab of Joshua Sanes, Harvard*

# Creating a Census of Human Cells

For the first time, new techniques make possible a systematic description of the myriad types of cells in the human body that underlie both health and disease.

*Aviv Regev*

**I**magine you had a way to cure cancer that involved taking a molecule from a tumor and engineering the body's immune cells to recognize and kill any cell with that molecule. But before you could apply this approach, you would need to be sure that no healthy cell also expressed that molecule. Given the 20 trillion cells in a human body, how would you do that? More fundamentally, without a map of different cell types and where they are found within the body, how could you systematically study changes in the map associated with different diseases, or understand where genes associated with disease are active in our body or analyze the regulatory mechanisms that govern the production of

different cell types, or sort out how different cell types combine to form specific tissues?

We suggest the answer to these questions is to create a Human Cell Atlas that organizes cells by type and location in specific tissues. What makes this now possible is the recent development of three new tools:

- ***The ability to rapidly determine cell types by rapid capture, processing and RNA sequencing of single cells.*** The RNA sequence reveals the genetic profile of an individual cell—identifying which genes are turned on, actively making proteins. It is in effect the zip code for cell types. Newly-invented automated tools can now process thousands of cells for sequencing per second for a low cost.

■ ***The ability to map the location of specific cell types within living tissue at high resolution.*** One technique uses ion beams that scatter cell particles from specific locations in a tissue; the cell types are identified by the proteins they use and that information is synthesized with the location into an image that locates the cells of interest.

■ ***Sampling algorithms and Big Data computational techniques that enable creation of an overall cell census.*** These approaches are new to biology on the scale proposed here. With appropriate sampling, analyzing just 50 million cells—one for every 400,000 in the body—can give a detailed draft picture of human cell types. Big Data techniques can then be used to combine zip codes and physical locations into a unique and invaluable reference database.

Cells are the basic unit of life, yet they vary enormously. Huge quantities of new red blood cells are made every day, whereas nerve cells—especially the neurons that are the processors of the brain—are made early in life and new ones are rarely born thereafter. The types of cells also vary widely from one tissue to another. The lining of the gut contains cells that absorb nutrients, immune cells to fend off harmful microbes, and neurons—as well as cells of the beneficial bacteria that colonize us. The retina at the back of the eye functions as a kind of digital camera, capturing an image and shipping it off to the brain for analysis—and it contains more than 100 different types of neurons; one kind of neuron can be important to identify when the light is turned on, another for when the light is turned off, and so on. The T-cells of our immune systems come in different forms, depending on whether they are found in the blood, in the gut, in the mouth, or in nasal passages. Moreover, variations in specific genes that can lead to disease typically manifest themselves in specific cells, those cells where the genes would normally be active—muscular dystro-

phy in skeletal muscle cells, for example. Both this enormous variety from one type of cell to another, and the mix of cells from tissue to tissue are critical to the functioning of our body, but have not been fully studied or characterized.

Already, in preliminary studies of the type proposed here, our lab and collaborators have discovered a completely unknown type of dendritic cells—immune cells that constitute our first line of defense against pathogens—that make up only 4 of every 10,000 cells in the blood. Another study of a particular class of T-cells associated with autoimmune diseases found subtle differences in cells taken from the gut and from the brain, changes that appear to stem from fats in the diet and that may suggest new drug targets for treating these autoimmune diseases. Analyzing tens of thousands of retina cells led to discovery of two new cell types that have eluded decades of meticulous research.

Some 25 years ago, scientists first proposed the Human Genome Project to systematically discover all of the cellular components encoded by our genes. At the time it seemed an audacious goal, but one that proved achievable. We now propose a similar systematic effort to define the cells that underlie human health and disease.

Specifically, within five years we propose to generate a detailed first draft of a molecular atlas of cells in the human body. This Human Cell Atlas will:

1. Catalog all cell types and sub-types;
2. Distinguish cell states (e.g. a naive immune cell that has not yet encountered a pathogen compared to the same immune cell type after it is activated by encountering a bacterium);
3. Map cell types to their location within tissues and within the body;
4. Capture the key characteristics of cells during transitions, such as differentiation (from a stem cell) or activation; and

5. Trace the history of cells through a lineage—such as from a predecessor stem cell in bone marrow to a functioning red blood cell.

Just as with the Human Genome Project, the task is large but finite and can only be done successfully within the context of a unified project that engages a broad community of biologists, technologists, physicists, computational scientists, and mathematicians.

Some factors that point toward success of the project include:

**Manageable Scale.** The number of human cell types depends on the level of resolution at which they are defined. A few hundred types are often quoted, but just the blood and immune system alone may have over 300 molecularly and functionally distinct sub-types. While the number appears daunting at first, there are multiple cell “copies” of the same type, and thus this is a sampling problem. Statistical considerations and mathematical theory suggest that we can sample a manageable number of cells and still recover fine distinctions with confidence.

**Sample Collection.** Experience has shown how to acquire excellent collections of human tissue samples with a well-concerted effort, even by individual labs. And, unlike genetic studies, a large number of individuals is not required. We propose to complement human sampling with limited similar studies of model organisms—primates, mice, and others—to obtain otherwise inaccessible samples and to relate knowledge from human cells to that obtained from lab experiments, for which there is extensive legacy knowledge from decades of scientific research.

**Inclusive Organization.** We envision a community-wide effort that balances the need for domain-expertise in a biological system with

opportunities for new technologies (more so than in past genomics projects), and yet also enables data collection that is comparable across systems. Within such a consortium, to be defined through a community process, there will be working groups for human samples, model organisms, and technology development, in addition to centralized data acquisition and management. We would expect multiple analytics efforts.

**Appropriate Staging.** A Human Cell Atlas is an endeavor of new scale and type. A pilot phase that can be established quickly and serve to test alternative strategies and to evaluate the basic premises of the work would likely be particularly effective. We propose a pilot phase with a relatively sparse survey of 100,000 cells from each of 50 carefully chosen tissues from human and mouse, complemented by a much deeper survey in a few well-chosen complementary systems, such as peripheral blood and bone marrow, gut, and liver. A full-scale project, building on the pilot, would analyze more cells per tissue, additional tissues, expand work in model organisms, and deploy more measurement techniques; it could also extend analysis to disease tissues.

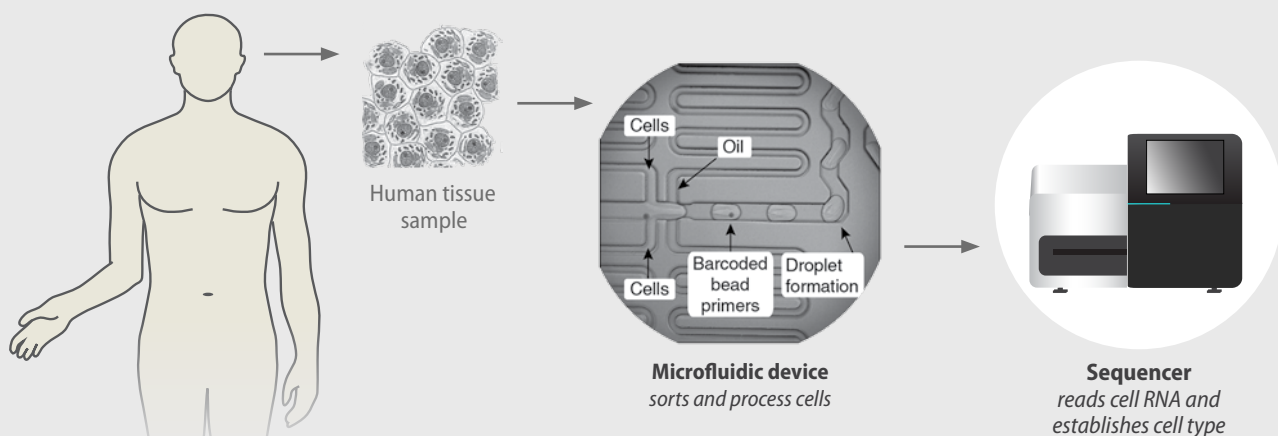
Having a complete Human Cell Atlas would be like having a unique zip code of each cell type combined with a three-dimensional map of how cell types weave together to form tissues, the knowledge of how the map connects all body systems, and insights as to how changes in the map underlie health and disease. This resource would not only facilitate existing biological research but also open new landscapes for investigation. A Human Cell Atlas will provide both foundational biological knowledge on the composition of multicellular organisms as well as enable the development of effective medical diagnostics and therapies.

# How to Create a Human Cell Atlas

The field of genomics has substantial experience in large-scale projects such as proposed here, but there are important differences. Genetic studies often focus on differences in the DNA between individuals, but cannot tell the critical differences between individual cells, including where the genetic differences manifest themselves. Indeed, within an individual, nearly every cell has the same DNA, but it uses (or “expresses”) only a portion of it. In contrast, a Human Cell Atlas focuses directly on the differences among cell types and is thus more diverse and complex—tracking several very different types of data—and requires more technological and computational innovation.

What make such a project possible are very recent advances in the ability to analyze the genomic profile of a single cell. That means determining which RNA molecules it expresses from its DNA, which proteins are expressed from the RNA, and related information such as how the cell’s DNA is decorated with additional molecules that control it. With recent breakthrough technologies this can be done for large numbers of cells very quickly and inexpensively. This data characterizes which genes are active in a given cell—in effect, which proteins it produces, and what the cell does.

These innovations—based on advances in molecular biology, microfluidics, droplet technology, and computation—now enable massively-parallel assays that can process hundreds of thousands of cells at very low cost; we estimate a cost of about \$0.17 per cell. A second emerging method of characterization involves imaging cells inside tissues at high resolution. Finally, new experimental and computational techniques couple molecular profiling (of RNA or proteins) with ion beams to high resolution spatial information about their location within a tissue or even within a



cell, providing a unique characterization of the structure of tissues. We estimate that overall cost for characterizing cells by these combined methods will be \$1.00 per cell (an estimate that assumes continuing reduction in sequencing and storage costs, and a focus on RNA measurements as the first line of characterization). We propose to analyze 50 million cells in a five year initial effort.

This initial phase of the Human Cell Atlas will also define markers for different cell types, for which antibodies and other probes can be developed to find specific cell types within a tissue. It will provide a direct view of living human tissue—removing distorting effects of cell culture on which much current knowledge is based. It will provide a way to integrate a large body of legacy data. Moreover, the Human Cell Atlas will help uncover the regulatory processes that control cell differentiation and cell interactions. Finally, and non-trivially, the project will generate standardized, tested, and broadly applicable experimental and computational methods that will be useful in many other contexts.

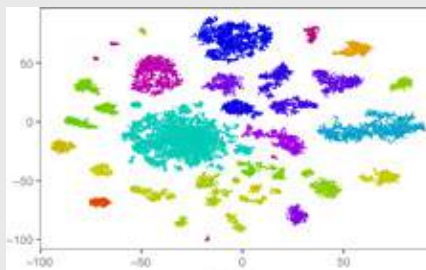
A level of support of \$100M over five years would support the initial organization and execution of this ambitious effort. Federal funding on this scale is unlikely, and multiple grants would not allow the integration of expertise across many groups of investigators and the complex coordination needed to ensure comparable and reproducible results. The Human Cell Atlas is thus an extraordinary opportunity for private philanthropy.

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*Aviv Regev, Professor of Biology, MIT; Core Member and Chair of the Faculty, Broad Institute; Investigator, Howard Hughes Medical Institute; Director, Klarman Cell Observatory, Broad Institute*



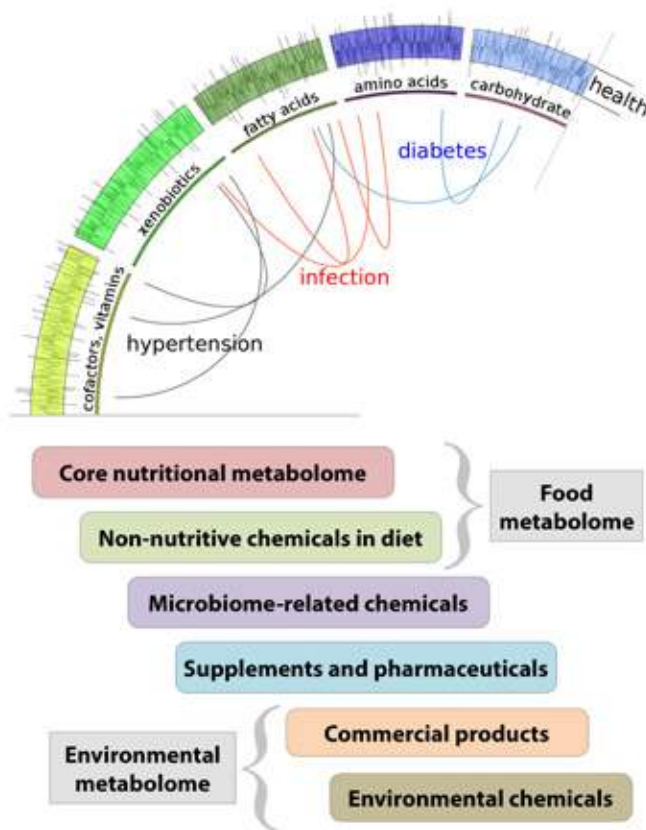
**Big Data Tools**  
synthesize and categorize  
information to create a map



**Map**  
shows cell types and abundances

*The process shown here, which can sort and categorize 5,000 cells per second at very low cost, illustrates the power of single cell genomics. The map illustrates the abundance and variety (by color) of an analysis of 44,000 human retinal cells, distinguishing 39 separate clusters of distinct cell types.*

*The exposome includes hundreds of thousands of biochemical markers from many different sources, including those shown here. Currently, only about 20,000 of those have been mapped and categorized.*



# Mapping the Human Exposome

Documenting the human genome catalyzed fundamental new approaches in medicine. But genes are only the “nature” half of the story. And it’s now possible to map and understand the biological markers that define “nurture”—the total of a person’s lifetime exposure to nutrition, bacteria, viruses, and environmental toxins—which also profoundly influence human health.

*Gary Miller and Dean Jones*

**O**ur genetic blueprint charts the course for our life, yet we rarely achieve our full genetic potential because of external forces that continually steer us off course. Many environmental influences are beneficial—good nutrition, education, and socialization—while others such as malnutrition, pollution, and poverty contribute to ill-health and the

woes of humankind. We can now measure and utilize over a billion features of the genome—the sequence of DNA, epigenetic changes that turn genes on and off, and how genes interact with the biochemical machinery of cells—and that knowledge is enabling powerful new insights and therapeutic approaches. But genetics can explain less than 25 percent of most major

disorders. And at present our ability to measure the complex environment in which we live and its impact on our bodies is very limited. No wonder we lack more useful models of disease and health.

One measure of the potential environmental impact on health is the registry of nearly 80,000 industrial chemicals that is maintained by the Environmental Protection Agency. The interaction of each of these chemicals with living organisms can generate multiple chemical markers, which if we knew what they were could be used to assess exposure and potential harm. One example that has generated widespread concern is the class of phthalate chemicals used as plasticizers in a wide range of products, from infant lotions and powders to credit card purchase receipts, markers from which are found in virtually every U.S. resident, and which have been implicated as hormone-like endocrine disrupters that can affect sexuality. Those aren't the only powerful chemicals in consumer products—think suntan lotions and beauty creams, preservative additives in food products to extend shelf life, pesticide residues on fresh produce. Food itself generates many different metabolic chemicals found in our bodies, both directly and as a result of processing of food by our microbiome—the colony of bacteria that inhabit our gut and our skin and that are very much part of who we are. Add in air pollution, workplace hazards, the markers left by allergens and disease agents and immune system reactions to them, the medicines we use—they all leave a biochemical marker. The number of such markers in our bodies is estimated to be as many as one million, but what they are and which ones indicate conditions or exposures harmful to health is still for the most part unknown.

As it turns out, there is no reason for knowledge of the environmental mediators of disease and health to lag so far behind that of the genome. When the concept of the

exposome—the totality of our exposures from conception onward—was first put forward in 2005, it seemed an impossible challenge: how to detect and measure a million different chemicals? But just as a single sample of blood contains the core of our genetic data (in the DNA within white blood cells), so that same blood sample contains hundreds of thousands of biochemical markers. And because of advances in high resolution mass spectrometry and high throughput screening, it is now possible to identify, catalogue, and understand each marker, each constituent of the exposome, and link it to the process or environmental factor that produced it. Mapping and annotating these biochemical markers, creating reference databases that define the human exposome and to which individual profiles can be compared, using big data techniques to correlate genetic and environmental factors—all of this portends a revolution in how we understand the complex chemistry of life. That knowledge in turn is likely to lead to more specific insights into how environmental factors affect human health and how we might intervene to protect and enhance it. Within a decade, potentially, a truly precise approach to personalized medicine could be possible.

Mapping the exposome is ultimately about understanding the divergence between our genetic predispositions and our biological reality. It requires not just studying environmental chemicals, it is about studying all of the chemicals, endogenous and exogenous alike, that influence human biology. Yet today, in a typical laboratory analysis of a blood sample, it is run through an instrument called a gas chromatograph that groups fractions of the blood by their volatility and then these fractions are subjected to more detailed analysis by a specific chemical test or by mass spectrometry. In virtually every such analysis, for whatever

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These preliminary results are the beginnings of knowledge of the chemistry of nurture, of life as it is really lived amidst a complex array of environmental exposures.

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purpose, there are hundreds of peaks (compounds) that are simply unknown. This is where increased efforts in fundamental research in mass spectrometry and bioinformatics could yield great returns.

What made rapid mapping of the human genome possible was sequencing of many small parts of the genetic code whose function was known—so-called shotgun sequencing—and then putting the pieces together. The equivalent for mapping the exposome is an approach that identifies the environmental mediators that have the greatest effect on human biology and looks for the markers associated with them. As it turns out, many different institutions—from the Centers for Disease Control to university laboratories working under grants from the National Institutes of Health—have collected and stored blood samples from specific individuals, whose subsequent medical histories are known at least in part. The Department of Defense, for example, has over 100 million blood samples from soldiers collected at enlistment and again post-deployment from a specific mission such as Iraq. And these archival blood samples turn out to be a treasure trove for linking specific impacts to biochemical markers and thus building up the map of the exposome.

One recent example of this process at work is a child health study conducted by the University of California at Berkeley with blood samples going back 50 years from families that lived in California's

Central Valley—where concern over pesticide exposure from the intensive farming activity has long been a concern. The Berkeley study looked at the blood from the mothers of daughters who subsequently (as adults) were diagnosed with breast cancer, and sure enough, found clear evidence of pesticide residues that would have exposed those daughters in utero. The study is now extending the analysis to the granddaughters. Another study at Emory University looked at glaucoma, a condition in the eye that leads to nerve damage and blindness and whose exact cause is not known. The study compared biomarkers in blood samples from people suffering from glaucoma with comparable individuals who did not have glaucoma, and turned up four specific markers in the glaucoma patients. When analyzed, the markers turned out to be related to steroids produced only by fungal infections. Further work to see if the fungal infections might be causal is underway. Another study found markers from two specific environmental chemicals associated with macular degeneration, a condition in older adults that damages the retina and is also a common cause of blindness. These results are likely only the forerunners of a flood of new findings. More fundamentally, these are the beginning of a more complete knowledge of the chemistry of nurture, of life as it is really lived amidst a complex and changing array of foods, industrial chemicals, environmental toxins, and infectious agents.

# How to Map the Exposome

While genomics serves as a blueprint of a human being, personal health is also a product of life history and interactions with the environment. Big data from high-throughput molecular technologies that detect the chemical markers in blood or other tissue samples—from metabolic processes, from immune system processes, from activated genes, from foreign proteins—thus provide critical information towards health monitoring, disease diagnosis and treatment. The key technology that enables detection of these molecular footprints of biological processes is ultra high-resolution mass spectrometry, which in effect sorts these chemicals by their unique mass. Such machines yield nearly 10 times the data quality of earlier versions, cost about \$1 million apiece, and must be supported by laboratories, trained technicians, and biometric specialists.

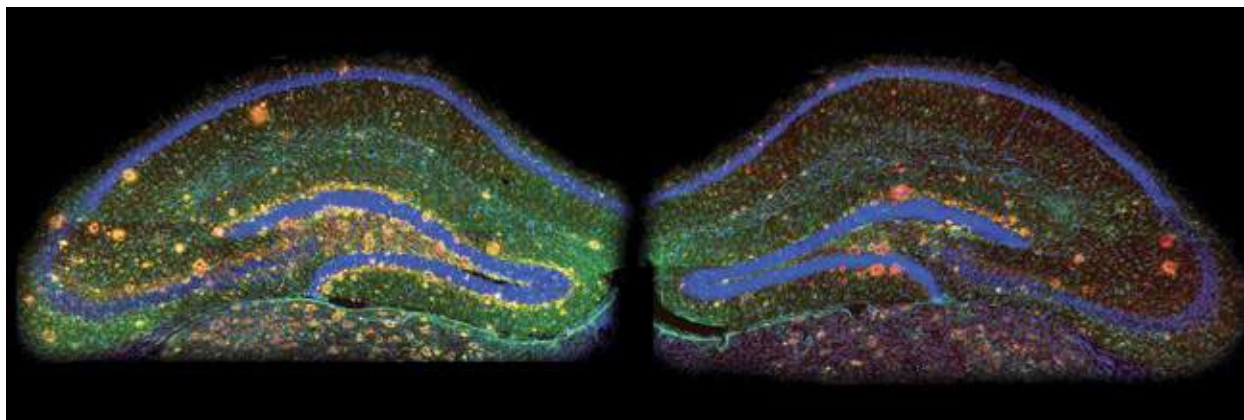
In a good lab, with a current model ultra high-resolution mass spectrometer, it is possible to separate and identify between 5,000 and 20,000 new biomarkers per year, including building the algorithms to automate future recognition of that marker. Thus with 10 instruments spread across several universities, mapping 100,000 biomarkers a year might be feasible. With sufficient research funding, a comprehensive, annotated database amenable to big data tools and to inter-comparison with rapidly expanding genomic databases might be feasible within 5–7 years. Unlike the billion-dollar human genome project, the likely price tag to map the exposome is more like \$100 million. Nonetheless, the scale and duration of such a project puts it outside the range of typical federal research grants, which in turn discourages many scientists from tackling it. Moreover, research on the environment has historically been within the domain of the National Science Foundation, while human health falls under National Institutes of Health: the exposome doesn't fit neatly into either funding structure. Hence there is an extraordinary opportunity for private philanthropy. Quite apart from the fundamental knowledge of how genes and environmental factors interact to influence human illness or capacity, the potential of identifying a person's lifetime exposure history from a sample of blood, quickly and cheaply—like the \$1100 tests for an individual gene map now available—is a tantalizing prospect. Moreover, the technology of mass spectrometry is advancing rapidly. And given the potential value of such services, once academic basic research has shown the feasibility and built the core knowledge, it seems likely that the biotech industry would invest additional capital to extend the database and the inferences that can be drawn from it to improve human health and well-being.

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*Alzheimer's symptoms in mice brains include amyloid plaques (yellow-orange) and brain inflammation (yellow-green) in the left image; both symptoms recede when levels of a certain protein are reduced, as seen in the image on the right. Credit: Jinsoo Seo, laboratory of Professor Tsai, Picower Institute for Learning and Memory, MIT*

# Alzheimer's Disease

We Are Seeing Breakthroughs in Treating Cancer—Why Not Alzheimer's?

*Andrew W. Lo*

In the past two years the FDA approved 19 new cancer drugs, and more are in the pipeline—including a powerful new class of immunotherapies that have the potential to transform many deadly cancers into manageable chronic conditions. In contrast, during the past decade not a single new drug for Alzheimer's disease has been approved. Yet over 5 million Americans currently suffer from Alzheimer's—more than for most forms of cancer—and AD prevalence is projected to double in coming decades.

The disparity is shocking, but the reason for it is quite simple: cancer is much better understood than AD. And that in turn stems from more than four decades of sustained investment in basic research into the biology of cancer, beginning in 1971 when President Nixon launched the “War

on Cancer.” Within a decade, the budget of the National Cancer Institute had tripled. And by the end of the century, enough was known about the mechanisms of cancer and potential targets and pathways for drug therapies that pharma and biotech companies could begin to invest large sums of private capital in drug development with a reasonable chance of success. Today's bounty of oncology drugs is the result, but it would not have happened without the foundational knowledge from which to begin.

Alzheimer's disease has its own unique challenges. AD drugs will be more costly to develop because of the need to follow patients over longer periods, the expense of current neuroimaging techniques, and the difficulty of brain biopsies. Even more challenging is that

the blood/brain barrier blocks most drugs—and all large molecule drugs—from even reaching affected cells. But even before drug development can begin, many basic questions remain unanswered: very little is known about what causes AD, how and when it begins, how it progresses, and whether it can be slowed, arrested, or reversed. The foundational knowledge is simply missing. Yet Medicare spending for Alzheimer's treatment is now \$150 billion per year and growing rapidly. Private burdens are high too—last year caregivers provided 17 billion hours of unpaid care for AD family members. Total public and private costs in the U.S. are expected to reach \$1.2 trillion by 2050.

There are, however, real opportunities for progress. One might be simply to slow the aging process itself, by altering what appears to be an internal “clock” that drives the process. There are strong but imperfectly understood links between nutrition and human development beginning in utero and continuing throughout life, and it is well established that sharply restricted, low-calorie diets can slow the aging clock. If we understood the links better, could drugs or sophisticated nutritional interventions be found that have the same effect? In fact, drugs that activate a particular group of genes known as sirtuins are showing promise in extending lifetimes and mitigating age-related diseases in animal models, but they need further investigation and exploration of their impact on Alzheimer's.

Another opportunity might come from exploring in detail how brain cells communicate with each other—in effect mapping and understanding the brain's neural circuitry and compa-

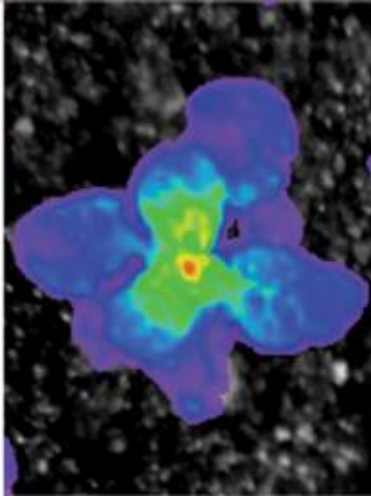
ring the circuit diagrams of healthy versus AD patients. For some other brain diseases—severe depression, Parkinson's disease—electrical stimulation of the brain has proved helpful. If we understood how the neural circuitry was affected by Alzheimer's, might a similar non-invasive electrical stimulation approach be of use?

Finally, it is becoming clear that there are likely many causes of Alzheimer's—many different genes that increase the risk. Yet virtually all of the clinical trials of potential AD drugs so far have focused only on a couple of genes—those that appear to trigger early onset forms of the disease. Classifying AD patients by their genetic variations, identifying the relevant genes, and understanding the mechanisms that they control or influence might lead both to a deeper understanding of the disease and to potential targets for drug development.

So it is a good thing that the “War on Alzheimer's” is beginning, with the passage of the National Alzheimer's Project Act (NAPA) in January 2011 and the creation of the Brain Initiative in 2013 which coordinates brain disease research efforts at NIH, NSF, and DARPA. Just as with cancer, it will likely take decades of sustained and rising investments in basic research to understand Alzheimer's, other dementias, and the fundamental biology of the brain well enough that drug development has a reasonable chance of success. Yet under current funding constraints, the National Institute of Aging can fund only 6 percent of the research ideas it receives. If we are serious about mitigating the human tragedy of AD and reducing the huge financial burden of caring for millions of affected seniors, then the time to start these investments is now.

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*Andrew W. Lo, Director of the Laboratory for Financial Engineering, and Charles E. and Susan T. Harris Professor of Finance at the Sloan School of Management, Massachusetts Institute of Technology*



*A image of the Arabidopsis plant (left). The rainbow colors (right) are generated by a chemical reaction—chemiluminescence--and show the expression of a gene artificially added to the plant. Warmer colors indicate higher gene expression.*

*Credit: Ben Williams*

# Plant Sciences

Growing more food, and more nutritious food, for a hungry world is again an urgent challenge. Productivity needs to increase by at least 50 percent.

*Mary Gehring*

**F**ifty years ago, rapid population growth in developing countries was outracing global food production, creating the prospect of mass famine in many countries. What forestalled such a tragedy were the agricultural innovations known as the Green Revolution, including the creation of higher yielding varieties of wheat and rice. While world population grew from 3 billion to 5 billion, cereal production in developing countries more than doubled; crop yields grew steadily for several decades. By some estimates, as many as 1 billion people were saved from starvation.

Now the world faces similar but more complex food challenges. Population is expected to grow from 7 billion to 9 billion by 2040, but little arable land remains to be put into production.

So productivity needs to increase still further, by at least 50 percent. Moreover, the Green Revolution did not specifically address the nutritional content of the food produced—and today that is critical, because of widespread malnutrition from deficiencies of iron, vitamin A, and other micronutrients. Traditional breeding approaches, and even the kind of genetic engineering that has produced more pest-resistant commercial crops, will not be enough to meet these challenges; more fundamental innovations in plant science—integrating knowledge of genetic, molecular, cellular, biochemical, and physiological factors in plant growth—will be required.

One example of the opportunities for such fundamental innovation comes from research

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Creating golden rice involved adding two new genes to the plant, which increased yield and also enriched the crop in vitamin A. Such self-fortifying crops could address malnutrition far more effectively than traditional methods.

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on a non-food plant, *Arabidopsis thaliana*, which is the “lab mouse” of plant molecular biology research. Recently scientists were seeking to better understand the process by which a plant’s chromosomes—normally, one set each from the male and the female parent—are distributed when a cell divides. They inserted into the plant cells a modified version of the protein that controls chromosome distribution. The resulting plants, when “crossed” or bred to unmodified plants and then treated chemically, had eliminated one set of chromosomes and had instead two copies of a single chromosome set. Such inbred plants usually don’t produce well, but when two different inbred lines are crossed together, the resulting variety is usually very high yield. This phenomena, called hybrid vigor, has been created in a few crops—such as corn—via conventional breeding techniques and is responsible for huge increases in yields, stress tolerance, and other improvements in recent decades. The new “genome elimination” method could make these same improvements possible for crops such as potatoes, cassava, and bananas that have more heterogeneous chromosomes.

Another research frontier is new methods to protect crops from devastating disease, such as the papaya ringspot virus that almost comple-

tely wiped out the Hawaiian papaya crop in the 1990s. What researchers did was develop a crop variety that includes a small portion of genetic material from the virus—in effect, inoculating the crop to make it immune from the disease, much like a flu vaccination protects people. Virtually all Hawaiian and Chinese farmers now grow this resistant papaya. The technique, known as RNA silencing, was initially discovered and understood through basic research into the molecular biology of tobacco and tomato plants, but seems likely to be useful against viral diseases in many crops.

Similarly, Chinese researchers doing basic research on wheat—a grain that provides 20 percent of the calories consumed by humans—developed a strain that is resistant to a widespread fungal disease, powdery mildew. The researchers identified wheat genes that encoded proteins that in turn made the plant more vulnerable to the mildew, then used advanced gene editing tools to delete those genes, creating a more resistant strain of wheat. The task was complicated by the fact that wheat has three similar copies of most of its genes—and so the deletion had to be done in each copy. The result is also an example of using genetic engineering to remove, rather than to add, genes. Since

mildew is normally controlled with heavy doses of fungicides, the innovation may eventually both reduce use of such toxic agents and increase yields.

Modifications in a single gene, however, are not enough to increase the efficiency of photosynthesis, improve food nutritional content, or modify plants for biofuel production—these more complex challenges require putting together multiple traits, often from different sources, in a single plant. This will require more basic understanding of plant biology, as well as developing and utilizing new technologies like synthetic chromosomes and advanced genome editing tools that are still in their infancy, and thus will require sustained research. One example of the potential here is golden rice—the creation of which involved adding two new genes to the plant—which is not only high yielding but also produces a crop rich in vitamin A. Such “self-fortifying” crops, because they incorporate micronutrients in a “bioavailable” form that is accessible to our bodies, could address malnutrition far more effectively than traditional methods of fortifying food or typical over-the-counter supplements. Another possibility may come from efforts to convert C3 plants such as rice into C4 plants that are more efficient at capturing and utilizing the sun’s energy in photosynthesis and perform better under drought

and high temperatures—a modification which may require, among other things, changing the architecture of the leaf.

Capturing these opportunities and training necessary scientific talent cannot be done with existing resources, as has been amply documented. Not only is federal investment in plant-related R&D declining, it is already far below the level of investment (as a percentage of U.S. agricultural GNP) of many other fields of science. Yet the agriculture sector is responsible for more than two million U.S. jobs and is a major source of export earnings. Moreover, the USDA research effort effectively ignores fundamental research; the research breakthrough on genome elimination described above could not have been supported by USDA funds, which are narrowly restricted to research on food crops.

In contrast other countries, particularly in Asia, are increasing investments in plant research. The impact of these investment are exemplified by the surge in publication in fundamental plant molecular biology research; 70% of the research published in the leading journal in this field now comes from outside the United States, and the entire field has seen a sharp increase in publications from Chinese labs. The U.S. is at clear risk of no longer being a global leader in plant sciences.

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*Mary Gehring, Assistant Professor of Biology, and Member of the Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology*



*Bacterium, collected from the Southern Ocean, infected with viruses (dark dots) that are replicating within it.*

*Credit: Jennifer Brum, Sullivan Lab at The Ohio State University*

# Unveiling the Viral Ecology of Earth

Viral infections modify and transform the functioning of individual cells. They do this not just for humans, animals, and plants, but also for the microbes that drive the Earth's carbon cycle. Could this tiniest form of life impact the balance of nature on a global scale?

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*Joshua Weitz, Steven Wilhelm, and Matthew Sullivan*

**E**bola, HIV, influenza—even the common cold. Each of these maladies reinforces the commonly-held belief that viruses are harmful parasites that are potentially deadly to their host. The virus's ability to disrupt human health belies its relatively simple form—it's no more than a microscopic package of genes wrapped in a molecular shell. But when a virus infects a living cell, it can commandeer the genetic machinery of the host to replicate itself.

What is not widely understood, however, is that not all viruses are bad for their host, or for the world around them.

Viruses infect all types of living cells, including those of animals, plants, and microbes. Indeed, the targets of most viruses are microbes—including the ubiquitous bacteria living in soil, lakes, and throughout the oceans. Viruses play a critical role in altering the fate of

*continued next page*

## VIRUSES, MICROBES, AND HUMANS

*Compared to either microbes or people, viruses are very small in physical size, in the number of genes, and overall genome size. But they reproduce more rapidly and in sheer numbers overwhelm all other forms of life.*

	Virus	Microbe	Person
Size	.02 – .1 micrometer	0.5 – 5 micrometer	1.5 – 2 meters
Number of Genes	10 – 100	500 – 5,000	~20,000
Genome Length (base pairs)	10,000 – 100,000	500,000 – 5 million	3 billion
Reproduction Time	hour(s)	hour(s) – day(s)	9 months
Population Density (18 million occupy)	0.1 ml of seawater	1 ml of seawater	New York City

individual organisms, and potentially that of the earth's ecosystems. In effect, viruses modulate the function and evolution of all living things, but to what extent remains a mystery.

This uncertainty has many causes. For one, viruses are tiny, which makes them more difficult to isolate, study, and understand. A virus is usually one- to ten-thousand times smaller in volume than a typical bacterium, and therefore, like bacteria, are invisible to the naked eye. Viruses seem simple, usually including just a handful of genes. But actually they are wildly diverse and not easy to identify and characterize. There is not a single gene common to all viruses, nor is there consensus about classes of viral genes. And this diversity is itself evolving. Some viruses multiply rapidly, creating a new generation as often as every 20 minutes. Other viruses need only a handful of genes (and a host) to make new copies of themselves, while still others carry hundreds of genes, blurring the lines of delineation from living cells.

The scope of our uncertainty of how viruses shape the planet is compounded by the fact that virus-host interactions operate on a huge scale. A liter of water in the Earth's surface

oceans typically contains hundreds of millions of cyanobacteria (see photo next page). These bacteria and other oceanic microbes take in carbon dioxide and convert it to organic matter (i.e., new cells and cellular life), and in the process "fix" as much carbon in a day as all of the land plants on Earth. The cyanobacteria, in turn, become the bottom of the marine food chain—food for zooplankton, which feed the krill, which feed the fish and whales. But viruses also infect, transform, and destroy uncoun- ted billions of cyanobacteria every day—they are part of the ecosystem too.

When a virus infects a living cell there are several potential outcomes: it can kill the cell, it can go dormant until activated later, or it can co-exist with that cell for generations. Further, as mentioned above, not all viral infections are bad. They can create immunity to other infections, mediate the interaction of human gut bacteria and the immune system, or preferentially increase the food supply for some types of microbes by killing other microbes, releasing cell debris that is valuable feed material. Thus viruses shape ecosystem-level microbial diversity and metabolic processes. These same features make

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## Viruses play potentially critical roles in ecosystems — so it's important to understand the ecological role of viruses in the earth's carbon cycle.

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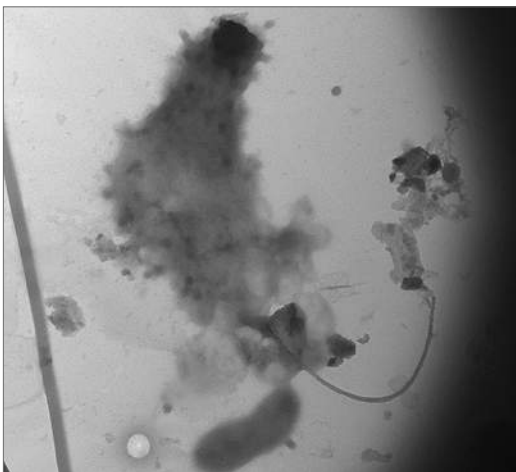
viruses increasingly attractive to biotechnology researchers who find them useful to deliver drugs and genetic therapies into living cells.

Viruses play potentially critical roles in ecosystems. However, a more detailed quantitative picture is needed to predictively model their impact. Of special note is the urgent need to understand the ecological role of viruses in the earth's carbon cycle—how viruses modulate the microbial processes that dominate the fixation and respiration of carbon that in turn modulates earth's climate. Microbial populations are now routinely mapped in soils, lakes, oceans, and even within humans, but the corresponding viral communities remain relatively unexplored. In the past, technological barriers impeded our

ability to observe these nanoscale partners and investigate their actions. But emerging instrumentation and processing techniques, along with new methods we are proposing, now enable a quantitative understanding and the resulting predictive models for how viruses impact a changing Earth system.

We propose here a systematic study of environmental viruses, especially those that infect microbes, with the overall goal of linking virus-host biology to ecosystems ecology. An in-depth knowledge of viral ecology would lead to insights on the structure and function of living systems on a variety of scales, ranging from genes to ecosystems to the global carbon cycle.

*continued next page*



***A marine bacterium infected with viruses that have burst the cell, freeing up organic matter that can be consumed by other microbes, thus potentially affecting microbial diversity and metabolic processes across entire ecosystems.***

*Credit: Jennifer Brum, Sullivan Lab at The Ohio State University*

# How to Probe Earth's Viral Ecology

The goal proposed here is to study and understand the viral interactions that govern natural ecosystems—in essence, to link virus-host biology with ecosystems ecology so as to develop a quantitative and predictive viral ecology. This will require the development of an inter-connected network of virus-focused investigators, including virologists, microbiologists, molecular biologists, ecologists, engineers, ecosystem modelers, and theoreticians. This network will collaborate with and build on the results of existing research groups and centers that have revolutionized the study of microbes and their ecology.

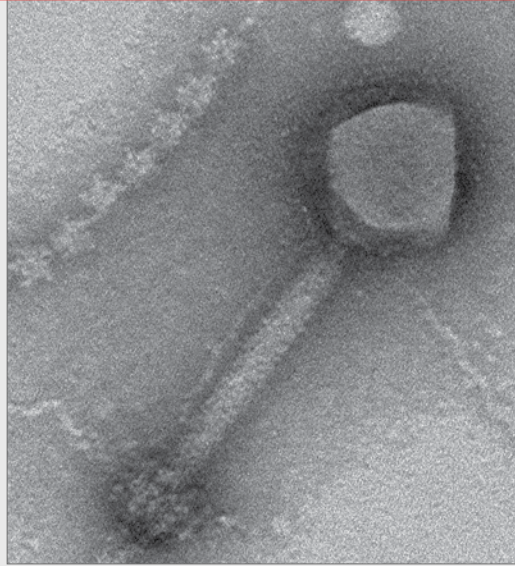
We propose establishing six core investigator teams and an additional dozen collaborating solo investigators. In addition, we propose repeated field surveys at specific coastal and offshore sites, and two trans-ocean transect surveys, to measure seasonal and geographic variations in viral ecosystem effects. We estimate that \$150 million over 10 years will be needed to support both the research groups and expeditionary field surveys.

Specifically, we expect this project to provide answers to questions such as:

- How do viral infections change the way cells interact with their environment?
- How do viruses alter carbon cycling in the oceans? Do they reduce the fixing of carbon or stimulate the regeneration of carbon dioxide? What is the effect at the level of the ecosystem? Do viruses change the relative ratio of microbes to krill or fish in the surface oceans or the amount of organic carbon exported to the deep ocean?
- How do we scale-up quantitative measurements of virus effects? And how do we integrate such measurements from the cellular to the ecosystem scale?
- Starting with ocean virus ecology, how do we evaluate the risks, possibilities, and consequences of virus-mediated feedbacks to the Earth's carbon cycle? How do we extend discoveries in the ocean to virus-induced effects in soils, lakes, and even the health of animal- or human-associated microbiomes?

The funding we seek will also enable critically-needed technological innovations that don't fit the requirements for standard funding mechanisms. These include advanced microfluidic devices for sample processing, advanced sequencing approaches for assessing single-viral genes and genomes, nanoprobe sensing devices, and integrated *in situ* sampling devices.

One notable recent conceptual advance in viral ecology has to do with cell debris. Scientists have discovered that the process of virus-induced rupture of host microbial cells releases cell debris, which in turn can be used by other local microbes to boost their growth, maintaining the local microbial loop and enhancing ecosystem-level productivity. The rapid turnover of viruses and their microbial hosts suggests that ecosystem responses to changes in climate have the potential to be strongly influenced by virus-microbe dynamics, particularly on the time-scales most relevant to human activities. That we know so little about such an important component of a changing Earth system is daunting, but also exciting—given the right scope of investment.



*Myovirus, collected from the Mediterranean Sea, a type of virus that infect marine cyanobacteria.*

*Credit: Jennifer Brum, Sullivan Lab at The Ohio State University*

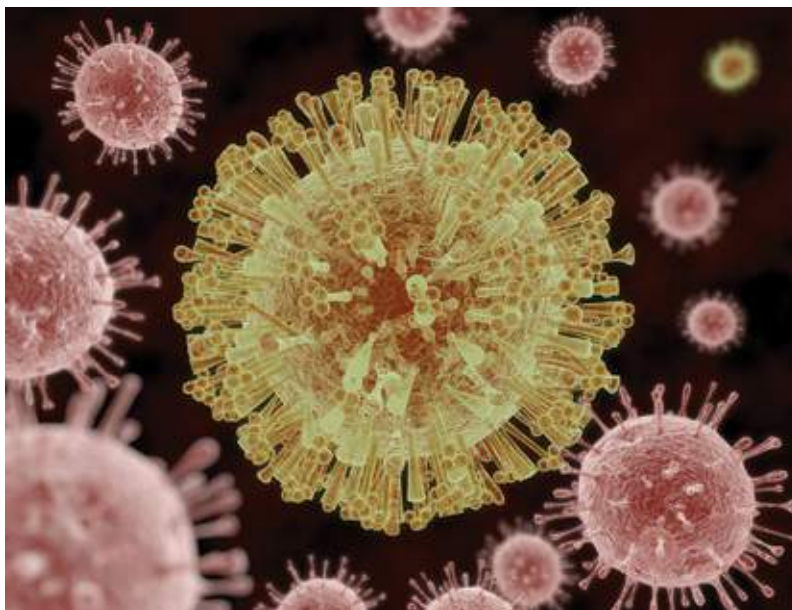
Prior support from national funding agencies has enabled transformative advances in microbial systems science. However, the majority of such projects have since been retired or scaled back. Indeed, virus-microbe dynamics are not a core priority for any agency, and the emphasis of funding continues to be in areas of human-disease associated virology. There is an extraordinary opportunity for private philanthropy to broaden this focus, influence the entire discipline of viral ecology, and greatly advance our understanding of the dynamics of Earth's carbon cycle.

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*Matthew B. Sullivan, Assistant Professor, Department of Microbiology, The Ohio State University*



*An illustration of the Zika virus, which typically causes mild headache, rash, and fever, but is also suspected in pregnant women to cause microcephaly in their babies. There is no vaccine against Zika infection.  
Image: Shutterstock*

# Infectious Disease

The ability to understand and manipulate the basic molecular constituents of living things has created an extraordinary opportunity to improve human health.

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*Chris A. Kaiser*

**T**he ongoing revolution in molecular biology has shown that all forms of life contain the same basic set of molecular parts and operate by the same biochemical rules, which scientists increasingly understand and can manipulate. That has created an extraordinary opportunity to improve human health, both by preparing for and thus preventing epidemics of emerging infectious disease such as Ebola and by finding solutions to the even more deadly threat from drug resistant bacteria.

Ebola outbreaks have occurred periodically in rural Africa for many decades, and the cause of this highly transmissible and deadly disease—the Ebola virus—has been known since 1976. As

the world struggles to contain the current epidemic in Western Africa, it is clear that there have been many missed opportunities to prepare the tools we now desperately need to detect, treat, and immunize against this still poorly understood disease. How did we come to be so little prepared to confront a disease that posed such an obvious risk to global health?

The answer, in part, may have been over-confidence in the established alliance between publicly funded university and hospital based research and privately funded research in pharmaceutical and biotechnology companies that has been so successful in developing drugs, tests, and procedures needed to combat the

diseases of the developed world. It now seems clear that existing priorities and incentives are not sufficient to prepare for diseases that emerge by jumping from animals to humans in impoverished parts of the developing world—of which Ebola is only one of at least half a dozen equally dangerous threats.

How viruses invade and multiply within human cells is generally understood. But basic research is needed to delineate the exact molecular mechanism for each virus, because development of drugs to combat infections depend on these specifics. Likewise, the development of effective vaccines also requires extended basic research into the structure of the virus, and specifically into how it evolves by changing proteins on its surface to evade the body's immune system: then it is possible to identify surface proteins that do not change, and which become the targets for vaccines. If we are to be prepared for the next viral epidemic, we need to invest in the basic research to characterize and understand all known viruses with the potential to be highly infectious. It is not that long a list; this is a task well within the capacity of the U.S. biomedical research system; and, since these diseases threaten all countries, it would be easy to make common cause with partners in Europe and Asia.

As dramatic as exotic emerging viral diseases seem, they are not the only or even the most serious infectious disease threat that the world faces. Potentially more deadly to most Americans is the spread of antibiotic resistance that undercuts our ability to treat bacterial infections we have long considered to be under control, from tuberculosis to staphylococcus and streptococcus. In fact, drug-resistant bacteria infect at least two million people in the U.S. every year, a growing number of them fatally.

The development of antibiotics—drugs that kill specifically bacterial cells by targeting differences between bacteria and the cells in our body—is one of the great achievements of modern medicine and we now take it for granted that if a child has strep throat we can cure it within days with the right antibiotic. But it is now clear that the more widely an antibiotic is used, the more rapidly that bacteria will evolve to acquire a resistance to it—and the bacteria are increasingly winning this war. Especially alarming is the spread of drug-resistant forms of staph and strep bacteria, especially in hospitals; the emergence of resistance to two “last resort” antibiotics, Methicillin and Vancomycin, used to treat infections resistant to other drugs; and the spread of a multi-drug-resistant form of tuberculosis, for which no other treatment options now exist.

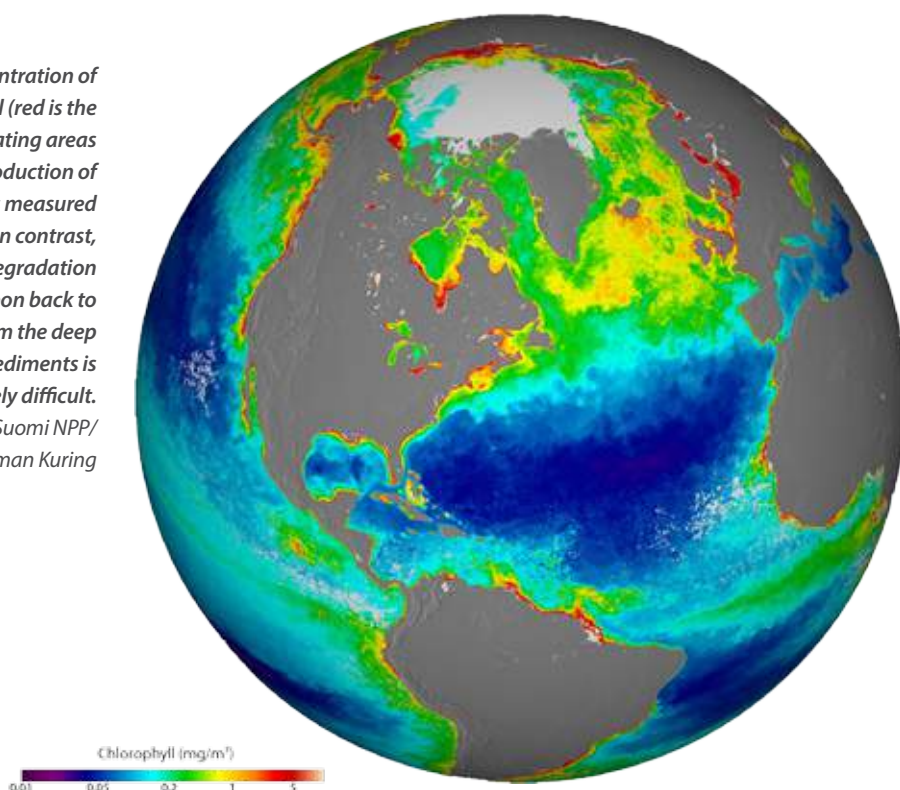
Development of entirely new antibiotics is at present the only way to keep ahead of the threat of incurable bacterial infectious disease. But the pharma industry has developed very few new antibiotic drugs in the past two decades—economic incentives are clearly insufficient. The alternative strategy is basic research into new bacterial processes, so that it would be possible to attack multiple targets within a bacteria, making it much harder for resistance to evolve. For that we need an infusion of fresh ideas and incentives for independent investigators—in effect, investments in a major basic research effort in the physiology and genetics of pathogenic bacteria that will attract new talent to this area. If we don't begin this effort now, the threat to U.S. public health a decade from now may well look very challenging.

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*Composite concentration of ocean chlorophyll (red is the highest), indicating areas with the highest production of organic carbon, as measured by satellite. In contrast, measuring the degradation and release of carbon back to the atmosphere from the deep ocean or oceanic sediments is extremely difficult.*

*Credit: NASA/Suomi NPP/  
Norman Kuring*



# Are We Headed for a Sixth Extinction?

The stability of life on Earth depends on the biogeochemical cycles of carbon and other essential elements, which in turn depend on microbial ecosystems that are, at present, poorly understood. New approaches could help gauge the potential for another mass extinction.

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*Dan Rothman*

**F**ive times in the last 500 million years, more than three-fourths of living species have vanished in mass extinctions. Each of these events (see Table 1 next page) is associated with a significant change in Earth's carbon cycle. Some scientists think that human-induced

environmental change—including our massive discharges of carbon into the atmosphere—may soon cause a sixth major extinction. Is such a catastrophe really possible?

The key to answering this question lies in the recognition that the Earth's physical environment

TABLE 1 | MAJOR EVENTS IN THE HISTORY OF LIFE

Event	Date (Ma)	Description
Great Oxygenation Event	2,450	earliest oxygenation of atmosphere
Cambrian Explosion	542	rapid diversification of animal life
End-Ordovician extinction	446	86% of species lost
Late Devonian extinction	372	75% of species lost
End-Permian extinction	252	95% of species lost
End-Triassic extinction	201	80% of species lost
End-Cretaceous extinction	65	76% of species lost
Sixth extinction?	??	

Ma: Millions of years ago

and the life it supports continuously interact as a closely coupled system. The core of this interaction is the carbon cycle. Plants and microorganisms, both on land and in the surface layers of the ocean, take carbon dioxide from the atmosphere and “fix” the carbon in organic matter through the process of photosynthesis. Other organisms—most importantly microbes, but also including animals and people—metabolize organic matter, releasing carbon back to the atmosphere, a process known as respiration. But while photosynthesis is visible in the greening of leaves and the spectacular algal blooms on the ocean surface (see photo), respiration is neither visible nor well understood. That’s because respiration occurs in different places and at very different timescales. In the ocean’s surface layers, for example, respiration happens fairly quickly—minutes to months. A small percentage of organic matter escapes degradation and drops slowly to the bottom of the ocean, becoming buried in the sediments, where respiration can take thousands of years. So over time, lots of organic carbon accumulates at the bottom of the ocean. And some of that gets embedded in sedimentary rocks, where the effective time-scale for respiration can be many millions of years. Virtually all of the fossil fuels we

burn—oil, coal, natural gas—come from that latter reservoir of organic carbon.

Over the last billion years, including through multiple ice ages, the Earth’s carbon cycle has remained mostly stable. That means that the process of fixing carbon through photosynthesis and the process of respiration have remained approximately in balance. But because the ocean sediments contain much more carbon than the atmosphere—at least 10 times as much—even small changes in respiration rates could have a huge, de-stabilizing impact. A disruption in the carbon cycle that rapidly released large amounts of carbon dioxide, for example, could potentially cause mass extinctions—by triggering a rapid shift to warmer climates, or by acidifying the oceans, or by other mechanisms.

The conventional explanation for what killed off the dinosaurs and caused the most recent, end-Cretaceous mass extinction was a huge asteroid impact on Earth—which certainly caused a massive debris shower and likely darkened the sky, perhaps for years. This and some other extinctions are also associated with massive and widespread volcanism. Are these sufficient

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The global carbon cycle is inextricably linked to the stability and continuity of life itself. That linkage plays out most significantly in the microbial ecosystems found in the oceans and sediments, which control the release of carbon back to the atmosphere.

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to trigger mass extinctions, even in the deep oceans? In at least one case, our calculations strongly suggest that these physical events, by themselves, were not enough to explain the observed changes—that whatever triggering role impacts or volcanism may have played, other factors contributed to and amplified changes in the carbon cycle. We believe that acceleration of the microbial respiration rate must have been involved, thus releasing carbon from the deep ocean and sediment reservoirs. In any event, the evidence is clear that significant disruptions or instabilities have punctuated an otherwise stable carbon cycle throughout Earth's history, with changes so rapid or so large that they triggered a shift to a new and different equilibrium, with profound impact on all living things.

One example is the microbial invention, about two-and-a-half billion years ago, of photosynthesis—resulting in a transition from an atmosphere without oxygen to a stable oxygenated state. That in turn enabled the evolution of macroscopic, multi-cellular life, including us. Another example is the end-Permian extinction, the most severe in Earth history, which was immediately preceded by an explosive increase of carbon in the atmosphere and the oceans. A recent research paper attributes the surge of carbon to the rapid evolution of a new

microbial mechanism for the conversion of organic matter to methane, which accelerated respiration. In both cases, the disruption of the carbon cycle was driven or at least accelerated by life itself—microbial life. Other mass extinctions are also associated with severe disruption of the carbon cycle, although the specific triggering mechanisms are not known. But what seems clear is that small changes in the ways microbes respire organic matter can have considerable global impact. Might the current human releases of carbon trigger such a change as well, enabling microorganisms to accelerate their conversion of the huge reservoir of marine sedimentary carbon into carbon dioxide? Understanding the mechanisms of respiration in detail—including in the deep ocean and the sediment reservoirs of organic carbon—is thus critical to understanding the potential for another mass extinction. That is what we propose to do.

The needed research must focus on three key objectives:

- 1) identifying the principal mechanisms controlling slow respiration in the modern carbon cycle;
- 2) determining the mechanisms underlying past mass extinctions; and
- 3) clarifying the conditions or triggering forces leading to instability and a new equilibrium.

For the modern carbon cycle, the principal problem concerns the fate of marine organic carbon that resists degradation for decades or longer. Two reservoirs are critical: dissolved organic carbon, which can persist for thousands of years, and sedimentary organic carbon, which can persist for millions of years. Imbalances in the carbon cycle are determined by shifts of these time scales or respiration rates. These rates are especially hard to determine when organic compounds are complex and/or the organic matter is tightly embedded in sedimentary rocks. We will use new tools that enable us to measure how specific enzymes bind to specific organic molecules found in seawater. And we will do controlled experiments to measure how microbes, organic matter, and minerals interact in sediments, developing new methods such as high-resolution calorimeters to measure the rates of degradation in the lab and in the field.

Unlike the major extinction events already mentioned, many past disturbances of the carbon cycle had no large-scale impact on life. What sets them apart? Sedimentary rocks deposited at different times (see picture of end-Permian sediments) record indications of environmental change, but the interpretation of these signals is an evolving science. The project will reconstruct, for as many events as possible, the sequence of environmental changes, focusing on fluxes of carbon. By employing mathematical techniques similar to those used to establish the modern theory of chaos, we expect to discover distinct classes of behavior that separate true instabilities from more gradual environmental change.

During periods of unstable growth, important changes in the molecular composition of organic matter are likely, and by analyzing these changes we expect to discover mechanisms associated with or leading to instabilities of the Earth's carbon cycle. Especially pertinent is the potential for rapid evolution in microbial ecosystems. Rapid evolution modifies the structure of populations and thus can alter the respiration rates—with impact on all components of ecosystems and potentially leading to instability, disruption, and the emergence of new stable states.

The central challenge will be to use these new findings to develop a theory of instability for the Earth's carbon cycle system. Linking the specific mechanisms discovered in our studies of the past and present carbon cycles to such a theory is a key objective. It requires learning how to translate molecular, genomic, and microbial metabolic information into an understanding of evolutionary feedbacks that can drive instability and mass extinctions. Collectively, this work amounts to the design and execution of a stress test of the carbon cycle system. Our studies of the modern carbon cycle will provide a base case. Theoretical models of carbon cycle dynamics will yield specific hypotheses for the conditions that determine its unstable evolution. These hypotheses will then be tested using geochemical signals derived from past extreme environmental events. That should provide an explicit understanding of the range of stability of the carbon cycle system and the potential for a sixth extinction.

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# How to Stress Test the Earth's Carbon Cycle

The project's ambitious scope requires multiple activities and skills, empirical and theoretical. The empirical work will include laboratory experiments to identify the microbial pathways and molecular mechanisms of slow respiration, along with the development of new methods to measure respiration rates in the lab and in the field; field studies of the modern carbon cycle to collect natural samples and test hypotheses; and field studies to collect rock samples containing the record of past events. These will then be followed by geochemical analyses of collected samples. The research will result in the development of a new theory of carbon cycle dynamics that will enable quantitative prediction of the risks of instability.

To perform these tasks, the project expects to need significant resources. Specifically, studies of the modern carbon cycle will require about 15 teams devoted to laboratory and field investigations. Analyses of past events will require about another 15 teams for sample acquisition and geochemical analyses. New theory and related modeling to motivate and support the entire effort will require an additional 10 teams. An average of \$2.5M/year for each team would result in a \$1B, ten-year project. The outcome would be a fundamental understanding of carbon cycle dynamics, revolutionizing earth and environmental science and resulting in a comprehensive, objective evaluation of the long-term risks of modern environmental change. This is necessarily an extraordinary opportunity for enlightened philanthropy, since a project of this scope could not be funded from public resources.

A five-year project, in which half as many teams work with a budget of \$1M/year, would cost a total of \$100M. Such an effort would likely result in important new ideas, but the shorter time period and relatively limited budget would make difficult the definitive testing of their significance.

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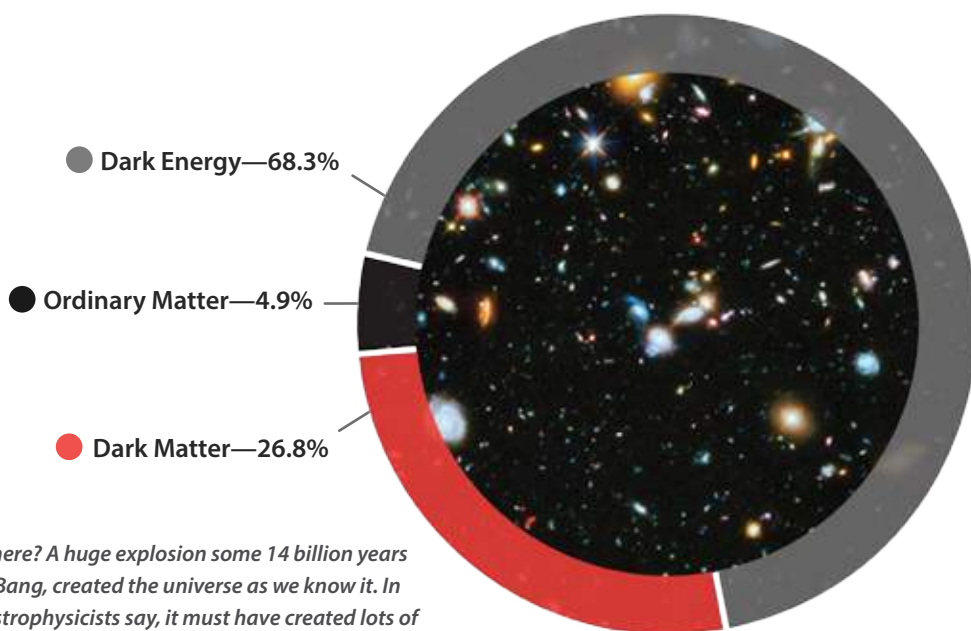
*Daniel H. Rothman, Professor of Geophysics and Co-Director, Lorenz Center, Massachusetts Institute of Technology*

## **Sedimentary Section in Meishan, China**

*The geochemical information contained in these rocks that span the Permian-Triassic boundary record a catastrophic disruption of Earth's carbon cycle coincident with the greatest extinction of life (about 95 percent of all species) in Earth history.*

*Credit: Shuzhong Shen*





*What's out there? A huge explosion some 14 billion years ago, the Big Bang, created the universe as we know it. In particular, astrophysicists say, it must have created lots of dark energy and dark matter, and a relatively small amount of ordinary matter.*

# The Mystery of Dark Matter

What's out there in the vastness of the universe? Stars, of course, made of "normal" matter like our sun. But mostly what's out there is dark matter and dark energy, which we can't see and don't yet understand.

*Harry N. Nelson*

**C**an this mysterious substance, a new form of matter whose existence is inferred from the behavior of the universe, be detected in an earth-bound laboratory?

The presence of a clump of matter deforms space-time, so that light passing near matter appears to bend. When it's a very big clump—whole galaxies—light bends enough that astronomers can measure the bending and deduce how much

matter is there. But when astronomers compare the result to the amount of matter they can see (the starlight from the ordinary matter in stars), there's a problem—not enough matter. In fact, about 85 percent of the matter in the universe is invisible, and although it exerts a gravitational force, it doesn't form stars that emit light. Scientists call it "dark matter," and just what it is constitutes one of the most fascinating mysteries in physics today.

It might seem a bit uncomfortable that the familiar electrons, protons, and neutrons that make up the atoms and molecules that constitute the earth, our homes, all of our tools, and our bodies and brains add up to only 15 percent of the matter in the universe. In fact the true picture is even more extreme: when scientists account for the presence of “dark energy,” an equally mysterious concept, ordinary matter accounts for less than 5 percent of the stuff of the universe. It’s almost as if ordinary matter and the universe that we can see in the night sky is just a sideshow, an afterthought of creation. Indeed, it’s clear that in the early eons of the universe, it was the dark matter that clumped together first, and then its gravitational pull caused ordinary matter to fall into those clumps and ignite to form the stars and galaxies that we can observe.

Even more unsettling, dark matter can flow right through ordinary matter—our bodies—with less interaction than any known particle, even the ghostly neutrino. The electromagnetic force doesn’t seem to affect dark matter in conventional ways, so dark matter and normal matter don’t interact chemically. And the strong nuclear force doesn’t seem to affect dark matter either, or if it does, only very weakly. So what kind of physical laws—other than gravity—govern its behavior, and how can scientists study it if they can’t measure it in the laboratory?

Theoretical physicists have proposed two main types of models—two types of hypothetical particles—that could constitute the dark matter. One is called Weakly Interacting Massive Particles (WIMPs); the other is called axions. And based on those particles and their hypothetical properties, physicists have devised ingenious ways to detect them, if they exist.

Take axions, for example. Under certain circumstances, and in the presence of a strong magnetic field, axions are thought capable of transforming into radio waves, which could be measured with very sensitive antennas. Conveniently, thanks to new superconducting quantum devices known as SQUIDs that work as a form of quantum amplifier, that sensitivity has recently increased dramatically, so detection is potentially feasible.

WIMPs, on the other hand, are thought to be capable (very infrequently) of colliding with normal atoms, and when they do, because they are massive, they would scatter those atoms like billiard balls. And subsequent collisions of the billiard balls could be observed. It turns out that atoms of xenon, a noble gas, constitute the best billiard balls for this purpose, because when two of them collide they emit a faint burst of light that can be detected by very sensitive phototubes—vacuum tubes with a light sensitive coating that converts the light into an electrical signal and that are commonly used in high energy physics. So detecting WIMPs, too, is potentially feasible.

Direct detection in the lab is one very promising approach to discovering the nature of dark matter. Producing dark matter at the Large Hadron Collider in Europe is a second approach. Using cosmic ray detectors to observe annihilating dark matter in space is a third. Whichever approach sees first evidence of dark matter, that will likely be just the first step to sorting out its properties. Ultimately, there may need to be a whole new set of physical laws that govern its behavior and that of dark energy—in effect, a whole new physics for this new, invisible, and fundamentally different kind of universe that we have discovered around us.

# Detecting Dark Matter in the Lab

The race to find evidence of dark matter is underway, and underground searches for weakly interacting massive particles (WIMPs) are among the most promising approaches. One of these is the Large Underground Xenon (LUX) experiment. LUX is located about a mile underground (to screen out false signals from cosmic rays) in the Homestake Mine near Lead, South Dakota, in a laboratory previously used for a Nobel Prize-winning experiment to detect neutrinos. The LUX experiment consists of a large tank that will be filled with 10 tons of purified xenon and lined with very sensitive phototube detectors. When a WIMP collides with a xenon atom, it sets off a kind of cosmic billiards game: the WIMP is so massive that it accelerates the xenon atom to nearly 700 times the speed of sound until it collides with another xenon atom. The xenon-xenon collisions give off a flash of light that can be detected.

The LUX experiment is supported by both public and private funds, but does yet have enough to pay for the xenon and run the experiment for 3 years—likely long enough to see if WIMPS exist. Thus an opportunity exists for \$10–\$12 million in private philanthropy to complete this search for dark matter.

The Axion Dark Matter Experiment (ADMX) is located at the University of Washington in Seattle. It is designed to detect axions by searching for their conversion to microwave photons, a conversion believed to occur in the presence of a strong magnetic field. What is unique about ADMX is the exquisite sensitivity of the experiment, which can reduce false signals and other noise to the limit allowed by quantum mechanics. The experiment consists of a powerful magnet and a superconducting resonant microwave cavity that acts as a kind of antennae when tuned to the mass of an axion particle. When an axion article passing through the magnet field transforms to a microwave photon, it deposits a tiny amount of energy in the cavity. That energy is then amplified by a superconducting radio amplifier known as a SQUID and converted to a measureable electric current. The SQUID is itself a quantum device—it detects the microwave energy produced by the axion in a way not possible for conventional detectors, which accounts for its extreme sensitivity. By systematically tuning the experiment to explore a wide range of possible axion masses, ADMX should be able to find axions if they exist in two of three likely mass ranges. ADMX, which is an international collaboration, has multiple sources of funding, but it too still needs funds—and estimated \$10 to \$15 million—to complete its search for dark matter.

Together these experiments have the potential to discover a new form of matter and initiate a whole new area of basic physics, and to shed some light on the dark nature of the universe.



Axion Dark Matter Experiment (ADMX)



*The current South Pole telescope measuring small variations in the cosmic microwave background radiation that permeates the universe. Multiple telescopes with upgraded detectors could unlock additional secrets about the origins of the universe. Credit: Jason Gallicchio*

# The Origin of the Universe

Measuring tiny variations in the cosmic microwave background will enable major discoveries about the origin of the universe, including details of its early expansion and of physical phenomena at energies a trillion times greater than those of the largest earthbound accelerators.

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*John Carlstrom*

**H**ow is it possible to know in detail about things that happened nearly 14 billion years ago? The answer, remarkably, could come from new measurements of the cosmic microwave radiation that today permeates all space, but which was emitted shortly after the universe was formed.

Previous measurements of the microwave background showed that the early universe was

remarkably uniform, but not perfectly so: there were small variations in the intensity (or temperature) and polarization of the background radiation. These faint patterns show close agreement with predictions from what is now the standard theoretical model of how the universe began. That model describes an extremely energetic event—the Big Bang—followed within a tiny fraction of a second by a period of very accele-

rated expansion of the universe called cosmic inflation. During this expansion, small quantum fluctuations were stretched to astrophysical scales, becoming the seeds that gave rise to the galaxies and other large-scale structures of the universe visible today.

After the cosmic inflation ended, the expansion began to slow and the primordial plasma of radiation and high-energy sub-atomic particles began to cool. Within a few hundred thousand years, the plasma had cooled sufficiently for atoms to form, for the universe to become transparent to light, and for the first light to be released. That first light has since been shifted—its wavelengths stretched 1,000-fold into the microwave spectrum by the continuing expansion of the universe—and is what we now measure as the microwave background.

Recently the development of new superconducting detectors and more powerful telescopes are providing the tools to conduct an even more detailed study of the microwave background. And the payoff could be immense, including additional confirmation that cosmic inflation actually occurred, when it occurred, and how energetic it was, in addition to providing new insights into the quantum nature of gravity. Specifically the new research we propose can address a wide range of fundamental questions:

- The accelerated expansion of the universe in the first fraction of a second of its existence, as described by the inflation model, would have created a sea of gravitational waves. These distortions in space-time would in turn would have left a distinct pattern in the polarization

of the microwave background. Detecting that pattern would thus provide a key test of the inflation model, because the level of the polarization links directly to the time of inflation and its energy scale.

- Investigating the cosmic gravitational wave background would build on the stunning recent discovery of gravity waves, apparently from colliding black holes, helping to further the new field of gravitational wave astronomy.
- These investigations would provide a valuable window on physics at unimaginably high energy scales, a trillion times more energetic than the reach of the most powerful Earth-based accelerators.
- The cosmic microwave background provides a backlight on all structure in the universe. Its precise measurement will illuminate the evolution of the universe to the present day, allowing unprecedented insights and constraints on its still mysterious contents and the laws that govern them.

The origin of the universe was a fantastic event. To gain an understanding of that beginning as an inconceivably small speck of space-time and its subsequent evolution is central to unraveling continuing mysteries such as dark matter and dark energy. It can shed light on how the two great theories of general relativity and quantum mechanics relate to each other. And it can help us gain a clearer perspective on our human place within the universe. That is the opportunity that a new generation of telescopes and detectors can unlock.

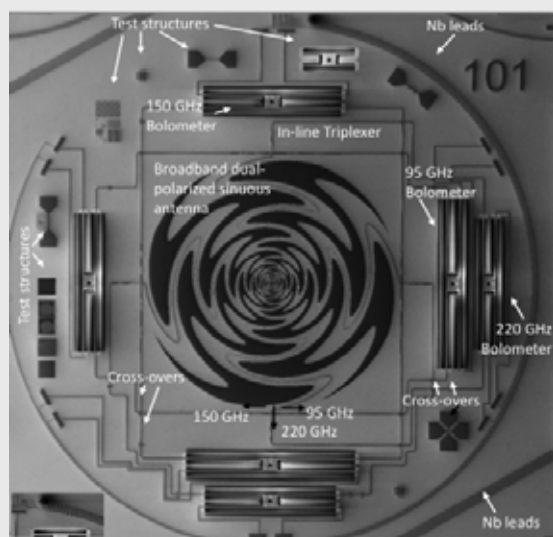
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# How to Measure Variations in the Microwave

The time for the next generation cosmic microwave background experiment is now. Transformational improvements have been made in both the sensitivity of microwave detectors and the ability to manufacture them in large numbers at low cost. The advance stems from the development of ultra-sensitive superconducting detectors called bolometers. These devices (Fig. 1) essentially eliminate thermal noise by operating at a temperature close to absolute zero, but also are designed to make sophisticated use of electrothermal feedback—adjusting the current to the detectors when incoming radiation deposits energy, so as to keep the detector at its critical superconducting transition temperature under all operating conditions. The sensitivity of these detectors is limited only by the noise of the incoming signal—they generate an insignificant amount of noise of their own.

Equally important are the production advances. These new ultra-sensitive detectors are manufactured with thin film techniques adapted from Silicon Valley—although using exotic superconducting materials—so that they can be rapidly and uniformly produced at greatly reduced cost. That’s important, because the proposed project needs to deploy about 500,000 detectors in all—something that would not be possible with hand-assembled devices as in the past. Moreover, the manufacturing techniques allow these sophisticated detectors to automatically filter the incoming signals for the desired wavelength sensitivity.

To deploy the detectors, new telescopes are needed that have a wide enough focal plane to accommodate a large number of detectors—about 10,000 per telescope to capture enough incoming photons and see a wide enough area of the sky (Fig. 2). They need to be placed at high altitude, exceedingly dry locations, so as to minimize the water vapor in the atmosphere that interferes with the incoming photons. The plan is to build on the two sites already established for ongoing background observations, the high Antarctic plateau at the geographic South Pole, and the high Atacama plateau in Chile. Discussions are underway with the Chinese about developing a site in Tibet; Greenland is also under consideration. In all, about 10 specialized telescopes will be needed, and will need to operate for roughly 5 years



*Figure 1. Ultra-sensitive superconducting bolometer detectors manufactured with thin-film techniques. The project proposes to deploy 500,000 such detectors.  
Credit: Chrystian Posada Arbelaez*

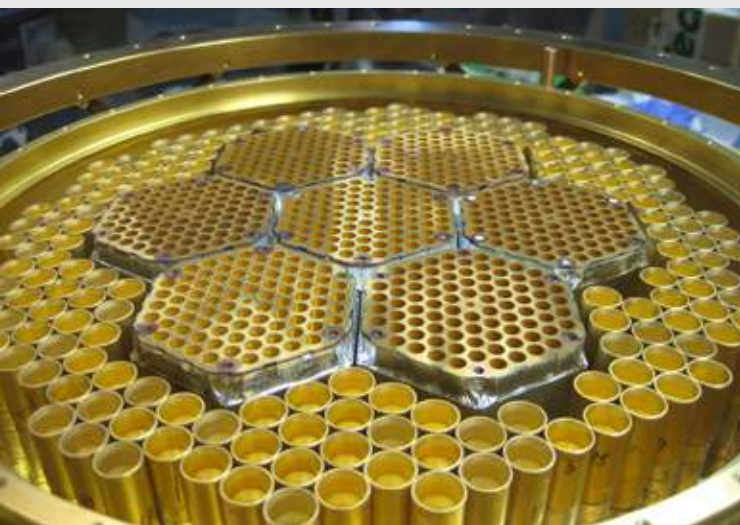
# Background with Unparalleled Precision

to accomplish the scientific goals described above. Equally important, the science teams that have come together to do this project will need significant upgrades to their fabrication and testing capabilities.

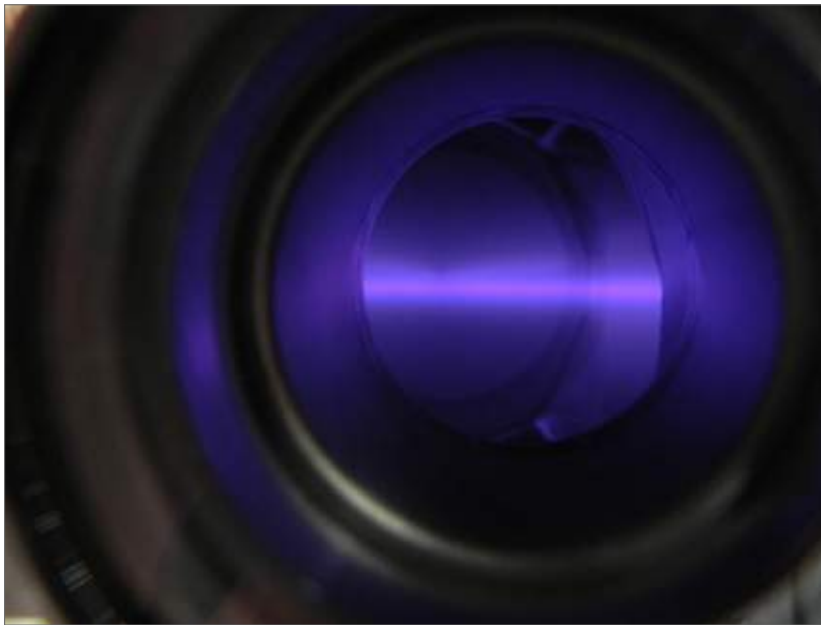
The resources needed to accomplish this project are estimated at \$100 million over 10 years, in addition to continuation of current federal funding. The technology is already proven and the upgrade path understood. Equally important, a cadre of young, enthusiastic, and well-trained scientists are eager to move forward. Unfortunately, constraints on federal funding situation are already putting enormous stress on the ability of existing teams just to continue, and the expanded resources to accomplish the objectives described above are not available. This is thus an extraordinary opportunity for private philanthropy—an opportunity to “see” back in time to the very beginning of the universe and to understand the phenomena that shaped our world.

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*John E. Carlstrom, Subhramanyan Chandrasekhar Distinguished Service Professor at the University of Chicago*



*Figure 2. The current focal plane on the South Pole Telescope with seven wafers of detectors plus hand-assembled individual detectors. A single detector wafer of the advanced design proposed here would provide more sensitivity and frequency coverage than this entire focal plane; the project would deploy several hundred such wafers across ten or more telescopes.*  
*Credit: Jason Henning*



*A beam of  $H_2^+$  particles (two protons and an electron) in a vacuum chamber at an MIT test facility. The beam excites a small amount of air bled into the chamber, producing a glow that shows the presence of the particle beam. Deep underground in Japan, this beam will be used to generate an intense source of neutrinos, whose behavior can then be measured precisely. Credit: Daniel Winklehner.*

# The Hunt for a New Neutrino

Physicists are hot on the trail of a new fundamental particle, whose discovery would not only revolutionize particle physics and require major revisions to current theories, but might also help resolve astrophysical mysteries.

**Janet Conrad**

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**N**eutrinos are perhaps the most exotic particles known to science. They are everywhere—an estimated billion of them fill every cubic meter of space, and trillions more are emitted by our sun every second—but you can't see them. Neutrinos are a form of matter, but they interact with normal matter so rarely and so weakly that it's hard to detect them. Scientists have known how to produce neutrinos in reactors and accelerators for more than 50 years. And yet, even after multiple discoveries and three Nobel Prizes, scientists still know very little about them. But these elusive little wisps of matter may hold the key to the next major

advance in our understanding of basic physics and the nature of the universe.

Neutrinos come in three types or flavors. And over the past two decades, scientists have discovered an effect called neutrino oscillations, where neutrinos morph from one flavor to another. This is a quantum mechanical effect that can only occur if neutrinos have mass, in contradiction to the current theories that describe fundamental particles and their properties, known as the Standard Model. Maybe the model can still be patched up—this is yet to be seen. But the discovery was a clear hint that understanding neutrinos may require new physics.

The surprises in neutrino physics have not stopped with neutrino mass. More recent experiments have detected additional anomalies in neutrino oscillations. The hints of unexplained neutrino behavior come from several directions, and are reasonably consistent. The first are accelerator-based experiments that search for oscillations from one flavor of neutrino to another. The second are reactor-based experiments that search for one flavor of neutrinos to oscillate away—so-called “disappearance” experiments. The last are beta-decay sources that also show neutrino disappearance. Over the last decade, as oscillations have gone from speculation to established fact, evidence has accumulated that cannot be explained by simple extensions of current theory.

One solution that might explain these anomalies would be the existence of neutrinos that simply don’t interact with normal matter at all—so-called “sterile” neutrinos—with the suggestion that neutrinos can oscillate both between different types and between regular and sterile forms. That would be startling enough.

But even more recent experiments suggest still additional anomalies: they seem to show that neutrinos are changing flavor with a completely different (higher) frequency than has been observed before. If this result is confirmed, it would mean that an additional fundamental particle, in the form of a new and more massive neutrino or set of neutrinos, is causing these oscillations.

It’s important to note that the newly observed anomalies or unexpected oscillations of neutrinos, although they have been observed in several ways with several types of experiments, are not yet definitive. That’s not surprising, because it requires either a much more intense source of neutrinos, or a very long observing period (many years), as well as an ideal physical setup of the neutrino source and a detector,

gauged to match the character or frequency of the expected oscillations.

Just such a definitive experiment is what we propose to do. Our experiment has several unique elements:

- A re-designed, very compact accelerator utilizing state-of-the-art technology that will be a very strong source of neutrinos, thus shortening observing time;
- Placement of the neutrino source immediately next to a massive 1,000 ton detector, with the precise geometry—a travel distance from neutrino source to target of about 16 meters—to observe the anomalous oscillations that would signal a new neutrino particle;
- An international collaboration of scientists from Europe, the U.S. and Japan that will enable use of an existing neutrino detector, called KamLAND, in a deep underground laboratory in Japan, thus saving the time and expense of constructing such a facility from scratch.

The discovery of a new fundamental particle—just when, with the recent discovery of the Higgs particle, physicists thought they had finished cataloging such things—would completely revolutionize particle physics and require significant revisions to current theories. A new neutrino might also help solve astrophysical mysteries, providing a possible candidate for the dark matter that comprises most of the universe: we can’t see dark matter, but can observe its gravitational effects on clusters of galaxies. Some theorists think that a new neutrino could also help to explain other fundamental mysteries, such as why there is such an imbalance in the presence of matter and anti-matter particles (anti-matter particles are relatively rare). In short, a new neutrino, if it exists, would create all sorts of excitement and open new research directions in basic physics and astrophysics.

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# How to Search for a New Neutrino

The research we propose, the IsoDAR (Isotope-Decay-At-Rest) project, is at the forefront of neutrino research. It involves building an advanced cyclotron accelerator capable of ten times the beam current of current commercial cyclotrons. This advance is due in large part to accelerating  $\text{H}_2^+$  ion particles consisting of two protons and a single electron instead of single protons, but also includes advances in the efficiency of ion injection into the accelerator and beam extraction from it.

The ions are injected at the center of the circular accelerator (see illustration). The magnetic field of the cyclotron causes these slow moving particles to bend and begin to orbit. Energy is added through radiofrequency (RF) waves, generated by RF cavities, pushing the particles to higher and higher velocities as they spiral around the accelerator following larger and larger loops in the magnetic field. When the beam leaves the accelerator, the electron is stripped off and the resulting energetic proton beam is directed to a beryllium target, generating a cascade of neutrons and a lot of heat—so much that the target has to be continuously water cooled. The neutrons in turn are captured by a blanket of an isotope of lithium, forming the unstable  $\text{Li}^8$  isotope, which decays by emitting an anti-neutrino. The accelerator can run continuously, and the process is relatively efficient, generating about 16 neutrinos per 1,000 protons, far more than produced at any conventional accelerator.

The anti-neutrinos will stream through the shielding and the underground tunnel walls into the existing KamLAND neutrino detector in Japan, which is a 1,000 ton tank of scintillator oil that contains hydrogen (protons). The walls of the detector are lined with phototubes that detect the flash of light given off when an anti-neutrino hits one of the protons; the interaction also releases a neutron, whose detection provides a co-incident confirmation. The close proximity of the detector to an intense neutrino source—just 16 meters will separate the source from the center of the detector tank—will allow detection of an oscillation in the neutrinos, characterized by the disappearance and reappearance of the produced neutrinos as some change flavor to become “sterile” or non-interacting. Such an oscillation, hinted at in previous experiments, would confirm the existence of one or more new neutrinos.

The cost to build this advanced cyclotron accelerator and the neutrino source in the underground cavern at KamLAND is estimated to be \$50M. Construction is expected to take three years. With just six months of operation, the experiment can definitively determine whether the existing anomalies are due to a new neutrino. With five years of running, the oscillation wave can be precisely mapped so as to establish the actual number of new neutrinos contributing to the oscillations. After the technology is fully developed, a number of these small-sized, low-cost, and portable accelerators are envisioned to be installed next to several large neutrino detectors throughout the world, leading to a number of opportunities within the larger neutrino program. This is an extraordinary opportunity for philanthropy.

Quite apart from their central importance in particle physics, astrophysics, and cosmology, these accelerators are also likely to have commercial importance. In particular, they are of interest for the world-wide production of medical isotopes and accelerator-driven, sub-critical reactors.

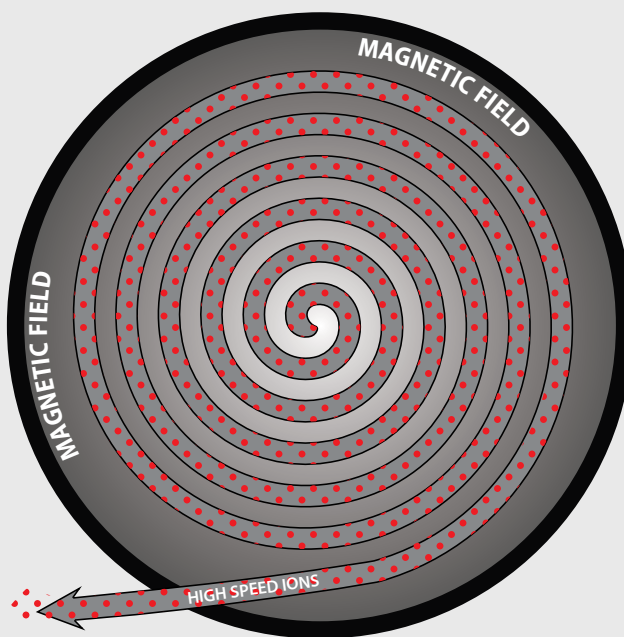
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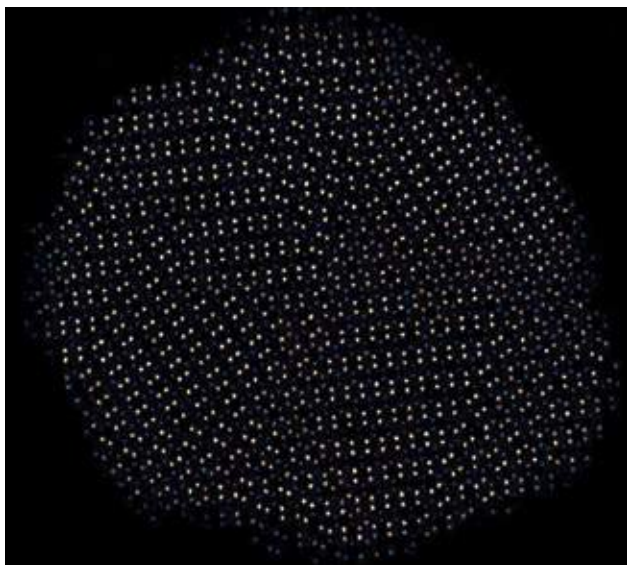
*Janet Conrad, Professor of Physics, Massachusetts Institute of Technology*

### Cyclotron Particle Accelerator

*Ion particles are injected at the center of the accelerator. A powerful magnetic field keeps the particles confined to a spiral path as they are accelerated by radio waves. The IsoDAR cyclotron is similar in design to the very first cyclotron built by E.O. Lawrence in 1934, but larger and much more powerful—10 times more so than any commercially available device.*

*Credit: Maggie Powell*





*A scanning transmission electron microscope image showing an interlaced crystalline structure in a copper-indium-sulfide nanoparticle. The structure has both crystalline and polycrystalline properties, which make it ideal for applications that turn heat into electricity, which could lead to more efficient power generation and air conditioning.*

*Credit: Wu Zhou, Oak Ridge National*

# Materials Discovery and Processing

If the U.S. is to be a competitive player in the next generation of advanced materials, it will need to invest significantly more in materials research, in crystal growth and similar facilities, and in training the next generation of material scientists.

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*Michael F. Rubner and Joseph Checkelsky*

**S**ince the times of early civilization, the advancement of the human race has been closely connected with the development of new materials and the means to process them into tools and other useful forms. We even keep track of history in terms of important materials—the Bronze Age, the Iron Age. This process has accelerated in the last half-century, in what is sometimes referred to as the Information Age, resulting in a wide variety of advances:

- integrated circuits and batteries small enough to enable tablets, laptop computers, and cell phones, as well as massive data storage facilities that comprise the internet “cloud”;

- solid state lasers and optical fibers used in surgery, manufacturing, and long distance communications;
- low-cost solar cells and ultra-high efficiency, long-lived LED lightbulbs;
- sophisticated new medical diagnostic tools such as CAT and MRI scans;
- more efficient, safer, and more reliable automobiles.

In all of these cases and many more, advancements made in the development of new materials and materials processing techniques have enabled the implementation of structural

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U.S. industry has essentially eliminated corporate sponsored basic research. Without adequate investment at universities, this country will simply not generate the fundamental knowledge for the next generation of materials and processing techniques.

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materials and electronic and optical devices with remarkable performance characteristics. These developments, in turn, have resulted in significant improvements in the quality of life and the strength of our economy.

A key factor in these remarkable developments was heavy investment by industry, especially in the United States, in basic science and engineering. Particularly in the first half of this period, in what might be called the Bell Labs era, industry took a relatively long-term view of the process of new technology development. Coupled with the fundamental knowledge generated at universities, this led to the explosive growth of many materials dependent industries. In addition to most of the examples mentioned above, these included superconducting wires and magnets, silicon-based semiconductor materials for electronics, and a variety of high performance polymers, metals and ceramics. But over the past few decades, international competitive pressures and the short term focus of the financial sector have caused U.S. industry to move away from long-term investments in R&D and to essentially eliminate corporate sponsored basic research, instead relying heavily on academic-based dis-

covery. Thus, without adequate investment in the funding of basic science and engineering at universities, this country will simply not be generating the fundamental knowledge required to enable the next generation of new materials and materials processes.

One example is the facilities for growing crystals, an area in which the U.S. was the undisputed leader 25 years ago, but is no longer. Growing crystals is an important method of discovering new materials and improving existing ones. High purity silicon crystals served as the canvas for modern electronics; single crystals of inter-metallic alloys made possible modern jet engine turbines; and still other crystals gave rise to high temperature superconductors. New computational techniques may soon allow the design of even more complex materials. Yet the U.S. does not support an open access crystal growing facility nor a facility which couples dedicated supercomputer-based materials design to synthesis and characterization as done at, for example, Japan's leading materials laboratory at the University of Tokyo.

That means that the U.S. is not training a new generation of experts in crystal growth and related materials specialties. The innovation defi-

cit can be measured in the scientific literature, where U.S. contributions now account for less than 12 percent of publications in the leading crystal growth journals, including a steadily declining proportion of the most-cited (e.g. most important) articles.

At the same time, investment in crystal growth research and facilities has expanded significantly in other countries, most notably Japan, China, South Korea, and Germany. China has become a major and at times dominant contributor to the crystal growth literature, with innovations in both synthesis of new materials and measurements of their properties. Industrial investment in materials R & D has also been stronger abroad, especially in Japan and Korea, resulting in such important developments by Samsung of commercially important organic light-emitting diodes (OLEDs)—in which a thin film of an organic compound emits light in response to an electric current—that now provide some of the dramatic displays in TVs and many other digital devices. In this later case, the materials and device technology was actually invented in the U.S. at Eastman Kodak more than 40 years ago, but it took the intensive R&D efforts of companies like Samsung and LG to finally capitalize on this new technology. Samsung's commitment to R&D is illustrated by its practice of sending some of its best employees to work for a time in the laboratories of leading U.S. universities.

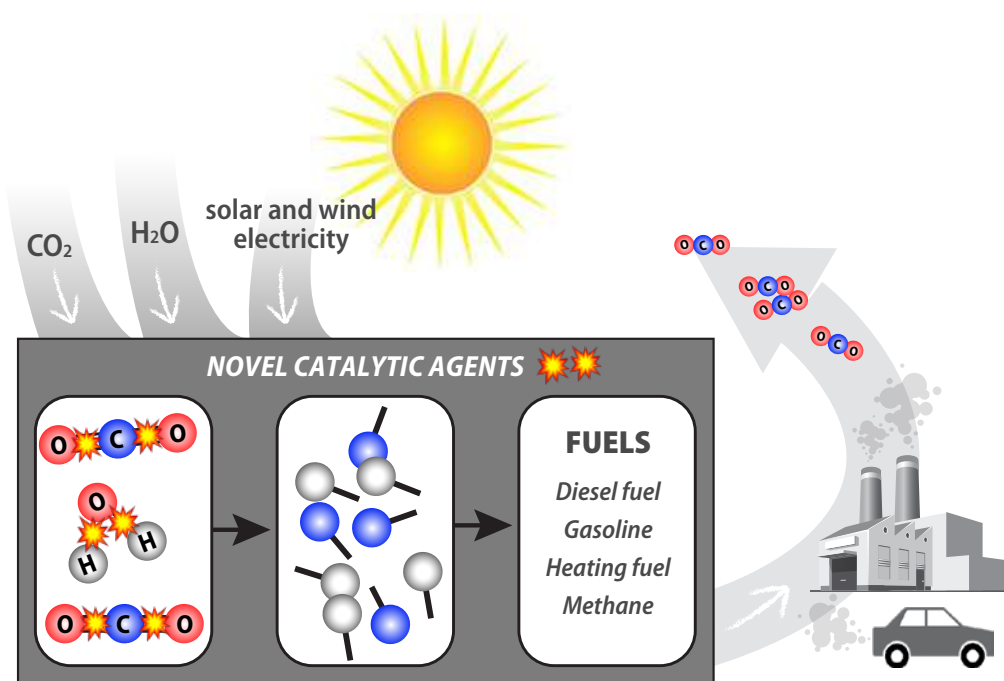
The opportunities in advanced materials are many, including the growing area of nano-materials, in which the composition is controlled almost atom by atom. Another example is computational efforts to identify all possible types of new materials and calculate their structural properties, as proposed by the Administration's Materials Genome initiative.

The challenge is not only in the materials, but also the means to process them efficiently. Thin film solar cells, for example, is an area in which the U.S. still leads, for now, and which holds the potential for both far more efficient cells and processing techniques far less costly than the Chinese-dominated market for single-crystal silicon cells. Equally important are multi-functional materials, such as glass that is both anti-reflective, anti-static and super-hydrophobic, which would make possible dust resistant, self-cleaning windows and solar cell covers. Another important, high-growth area is nano-manufacturing, such as in 3-D printers, in which the required functionality has to be embedded in the tiny particles sprayed into position by a device equivalent to an inkjet printer. But if the U.S. is to be a competitive player in the next generation of advanced materials, it will need to invest significantly more in materials research, in crystal growth and similar facilities, and in training the next generation of both academic and industrial materials scientists.

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*Michael F. Rubner, Director of the Center for Materials Science and Engineering, TDK Professor of Polymer Materials Science and Engineering, and Margaret MacVicar Fellow, Massachusetts Institute of Technology*

*Joseph Checkelsky, Assistant Professor of Physics, Massachusetts Institute of Technology*



*The novel catalysts proposed here would facilitate chemical reactions that would otherwise not occur. In effect, they would help break existing chemical bonds (e.g., between the atoms of carbon dioxide and water) or selectively favor the creation of new bonds to form a desired fuel product. Burning the fuels reverses the process and returns carbon dioxide to the atmosphere. Credit: Maggie Powell*

# The Ultimate Clean Energy Strategy

Could nanoscale catalysts bring us inexpensive fuels and fertilizers—made from air and sunlight—that do not contribute to climate change?

*Arun Majumdar and Jens Norskov*

**E**lements that are critical to life—carbon, hydrogen, nitrogen, and oxygen—are also the principle components of the fuels and fertilizers that our civilization depends on. These elements are all found in abundant quantities in the earth's atmosphere. In principle, we could

make all the fuels we need from air. Indeed, that's exactly how nitrogen-based fertilizer is made, thanks to the invention of catalysts. A century ago, scientists Fritz Haber and Carl Bosch devised catalysts that enabled a chemical process to "fix" atmospheric nitrogen into a form

usable by plants—and ultimately by people via the food we eat. The invention was arguably one of the most important of the 20<sup>th</sup> century, and won Nobel Prizes for both scientists. It transformed agriculture, which in turn enabled expansion of the earth's human population from 2 to 7 billion. If we could apply the same “fix” for fuels, then the result of burning them would simply return carbon taken from the air back to the atmosphere—a sustainable cycle with negligible impact on climate.

The challenge of creating such a fuel “fix” comes from the fact that the small molecules of these elements found in the atmosphere are extremely stable. In water (H<sub>2</sub>O), the atoms are connected by strong chemical bonds, needing temperatures above 2000 °C to split them into hydrogen and oxygen. Carbon dioxide (CO<sub>2</sub>) is equally difficult to pry apart into carbon and oxygen. Nitrogen (N<sub>2</sub>) is even harder to break apart. So it's not surprising that synthesis of nitrogen fertilizers with the Haber-Bosch chemical process requires high temperatures, and consumes 2 percent of all global energy use, mostly from natural gas.

Long ago, nature found ways to solve this problem. In plants and algae, photosynthesis uses sophisticated biochemical catalysts (enzymes) to split CO<sub>2</sub> and H<sub>2</sub>O and use the freed elements to create larger complex molecules that form the ingredients of food (proteins, carbohydrates, fats, etc.) and fuels (hydrocarbons). That's where the fossil fuels we burn today ultimately come from. But the present scale of our energy and fertilizer use is such that we are putting far more CO<sub>2</sub> back into the atmosphere—35 billion tons a year—than is being removed from it. As a result, current and future generations face serious environmental consequences.

But what if we could harness scientific creativity to replicate what Haber and Bosch did—

only better? Could we split water to liberate hydrogen, carbon dioxide to liberate carbon, and “fix” nitrogen—all without using any fossil carbon-based forms of energy? Can we chemically transform CO<sub>2</sub>—affordably and at scale—into the source of the carbon that we use as fuels, chemicals, concrete, fiber composites, and so much else? If so, then sustainable carbon and nitrogen cycles for the earth would be in reach.

Meeting this challenge requires three things:

- 1) a source of inexpensive non-carbon energy that can help split the molecular bonds (in fact, electricity from wind energy is almost cheap enough and solar photovoltaic electricity costs are nearly so and trending lower).
- 2) an inexpensive source of carbon-free hydrogen to combine with the liberated carbon or nitrogen (this can potentially come from splitting water, but existing catalysts to activate the chemical transformation are simply not good enough).
- 3) new catalysts that can activate CO<sub>2</sub> or N<sub>2</sub> and the transfer of hydrogen to form C-H and N-H bonds far more efficiently than any currently available.

The catalysts are the core of the challenge, and trial and error experimentation has not yielded many promising candidates to date. Most conventional catalysts don't have the ability to distinguish among different intermediate chemical species, or to suppress undesired products during the course of the chemical reaction. The most promising way forward is to mimic nature's catalysts—enzymes—whose three dimensional nature makes them more selective and able to overcome these problems. Furthermore, the growing ability to control the composition of materials at nanometer scale—essentially atom by atom—makes it possible to fabricate such advanced catalysts. It's also now

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We are attempting to restore the balance in the Earth's carbon cycle that has been lost through the exponential increase in the demand for fossil fuels — perhaps the most important challenge of the 21<sup>st</sup> century.

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becoming feasible to predict the properties of potential new catalysts from theory, using large-scale computations on the basic equations of quantum mechanics—which should enable scientists to focus on the most likely catalyst designs. So combining theory, nanoscale synthesis techniques, and advanced characterization and testing makes possible a new paradigm for materials design, one that is potentially able to address the challenge of novel and extremely powerful catalysts.

This is an extremely ambitious scientific challenge—to invent artificial cycles for carbon

and nitrogen that are efficient and affordable enough to operate on an unprecedented industrial scale. Essentially we are attempting to restore the balance in the earth's carbon and nitrogen cycles that has been lost through the exponential increase in the demand for food and fossil fuels—perhaps the most important challenge of the 21<sup>st</sup> century. We are in the best position ever to undertake this effort, scientifically and technologically. But to do so requires major resources, an unprecedented approach, and urgency: the time to act is now.

*continued next page*

# How to Create Novel Catalysts of Unprec

The research needed to address this challenge involves creation and integration of knowledge from multiple disciplines, including materials science, electrochemistry, photochemistry, computational science, and chemical engineering, among others. The fundamental research should be sufficiently open and unconstrained to explore new materials and energy-matter interactions. But scientific solutions are not enough. We need catalysts that can become part of large scale, affordable industrial technologies—ultimately capable of processing more than 10 billion tons of carbon per year. So the overall effort needs to be guided by a strong sense of engineering practicality. Moreover, since we can't predict the outcomes of basic research in advance and the challenge is urgent, it makes sense to focus research on several parallel catalytic paths at the same time—thermochemical, electrochemical, biochemical and photochemical—by investing in a portfolio of approaches. It may even be possible to combine two or more of these catalytic pathways.

Under these constraints, the pace and efficacy of research will likely be highest if teams of 3–5 researchers collaborate and combine their expertise with very little administrative overhead. Thus we suggest investing in multiple investigative scientific teams, not just in individual investigators. Think of these as the scientific equivalent of a Silicon Valley startup, capable of failing fast, adapting quickly, and innovating rapidly. Moreover, funding multiple teams for each catalytic pathway—also a portfolio strategy—is analogous to the way venture capitalists deploy money, and is likely to increase the chances of success.

The challenge we face is to make ordinary materials do things they don't normally do. So the investigative teams will need access to unprecedented computational power to do quantum calculations. They will need the ability to synthesize materials with unprecedented nanoscale control—which means ultraclean rooms, high vacuum systems, new kinds of microscopes. They will need to probe the properties of prototype catalysts with ultrafast light beams, x-rays, and other advanced spectroscopy techniques. They will need to test materials and to characterize reaction products precisely with advanced mass spectrometers and other tools.



*A circular sample that is heated in ultra-high vacuum to measure desorption of carbon dioxide molecules that are recorded by a mass spectrometer, as part of studying chemical bonding at surfaces.  
Photo by Anders Nilsson*

# edented Power

And they will need to design and build first-of-a-kind experimental reactors to show that the catalysts function as expected, and to demonstrate their potential to produce—cost-effectively—large volumes of C-H and N-H chemicals—the building blocks for fuels and fertilizer.

We believe that this effort will cost about \$100 million a year for period of 10 years. This level of funding would support between 25 to 50 teams across research universities and laboratories in the U.S. and elsewhere. Federal funding for this research is necessary but certainly not sufficient to create the scale of the portfolio approach proposed here. We need to augment it with private-sector funding. Thus there is an extraordinary opportunity for private philanthropy—for an objective that could be, quite literally, life-sustaining for the Earth.



An X-Ray photoelectron spectrometer at Stanford Synchrotron Radiation Lightsource that does not require ultra-high vacuum and hence allows the study of materials in more realistic conditions.  
Photo by Anders Nilsson SLAC

While the focus of the proposed research is to invent energy-efficient artificial cycles for carbon and nitrogen, it is worth noting that these efforts will likely have broader impacts. Catalysts are widely used in the production of chemicals, pharmaceuticals, plastics, and many other materials. The ability to discover and synthesize novel catalytic materials with properties that are controlled at nanoscale will be useful in many aspects of the economy, and will likely enable many novel and useful products. In effect, this research would lay the foundations for an industrial renaissance that is cleaner, more efficient, and enormously valuable.

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*Arun Majumdar, Jay Precourt Professor, Department of Mechanical Engineering, and Director, Precourt Institute for Energy, Stanford University*

*Jens Norskov, Leland T. Edwards Professor, Department of Chemical Engineering, and Senior Fellow, Precourt Institute for Energy, Stanford University*



*The Arctic Ocean in summer, with the sea ice melting more every year. Photo by Chris Linder, WHOI*

# An Arctic Early Warning System?

The Arctic Ocean could become a critical laboratory for understanding the process of climate change, an early warning system for alterations that will affect the entire Earth.

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*Carin J. Ashjian and James G. Bellingham*

**U**nderstanding the impacts of climate change on the Arctic Ocean is one of the great challenges of the 21<sup>st</sup> century. The Arctic has remained a truly hidden ocean, veiled by its ice sheet nearly year-round. Its harsh conditions and remote location have left it largely unexplored—the last ocean region to give up its secrets to science. Indeed, it's been 20 years since

the last major effort to measure biological activity along a transect of the Arctic Ocean.

This ignorance could be costly, however, as the Arctic is changing rapidly. For one thing, atmospheric warming from climate change at polar latitudes is double that of lower latitudes. As a result, more and more of the Arctic sea ice now melts off during the summer, and when it

refreezes in winter, the ice is thinner. By some estimates, the summer Arctic could be effectively ice-free in two or three decades. That in turn will bring a host of changes, some of which are already starting—more human activity from shipping, commercial fishing, tourism, and oil and mineral exploration, increased coastal erosion, stormier weather, and potentially large changes to the marine ecosystem. The end of the summer sea ice will also likely mean the end for polar bears and other species that depend on it for access to fishing.

At a less visible level, the end of the sea ice will eliminate the algae that grow on its lower surface and may also diminish native plankton, altering the ocean's biological productivity and disrupting the marine food chain. The Arctic is also more sensitive than other oceans to increasing acidification from higher levels of dissolved carbon dioxide.

These changes make the Arctic a critical laboratory in which to study climate change—in effect, a place where we can understand and document the linkages between global warming and the physical and chemical changes that in turn drive ecosystem change. However, understanding of the Arctic is sparse because it has been difficult and expensive to mount expeditions in the summer; during the winter, the region has been effectively inaccessible. We don't even have a baseline for the Arctic against which to measure change, let alone the kind of continuous monitoring and observing tools that are needed to understand processes and measure rates of change.

The basic research challenge is thus to identify the present state of the Arctic marine system, explore system responses to climate change, and identify and predict ongoing and future changes.

That's important, because as climate change accelerates, many of those changes and impacts will happen in latitudes where people live too. Moreover, changes in the Arctic have impact elsewhere. Melting polar ice sheets, such as the Greenland Ice Sheet, accelerate rising sea levels. Warming temperatures in the Arctic modify atmospheric patterns, particularly the high altitude jet stream that flows from west to east around the earth, with direct impacts on weather across the Northern Hemisphere. One theory is that the jet stream will exhibit greater meanders, driving greater extremes in temperature and drought for the United States and Europe. The unseasonably warm weather in Alaska and Boston's record snow falls this past winter might be examples of such meandering. A warmer Arctic will also mean thawing permafrost, which not only increases local coastal erosion and run-off of organic materials into the ocean, but also releases methane—a very potent greenhouse gas—to the atmosphere. In effect, thawing permafrost creates a positive feedback loop: the warmer it gets in the Arctic, the more atmospheric warming accelerates.

That makes the Arctic an invaluable laboratory, as well as an early warning system for climate change—if we make the effort to pay attention and understand.

*continued next page*

# How to Monitor the Arctic

Arctic research has been limited by the high logistics costs of operating in a demanding and remote environment. A 6-week summer expedition on an icebreaker costs about \$2 million for the ship time alone. Winter expeditions are so challenging they are seldom carried out, leaving the Arctic largely unobserved for most of the year.

Fortunately new ways to monitor the Arctic Ocean and measure its properties are emerging. Autonomous platforms such as gliders, ice-tethered profilers, and long-range unmanned, self-guided vehicles—underwater drones—can complement ship-based methods, making possible more efficient and year-round observations. More capable sensors are under development that are smaller, more energy-efficient, and capable of measuring additional chemical and biological properties. The data these new platforms and sensors could collect, together with ship-based expeditionary research, would help scientists sort out how physical and chemical changes affect the Arctic ecosystem—in effect, what climate change means for living things.

As the Arctic region fast approaches a potential tipping point, philanthropy can make a pivotal difference, providing a unifying force for otherwise fragmented efforts. An investment of \$100 million over 5 years would accelerate technology development, expand collaborative international observing and expeditionary efforts, and enable scientists to create the first

*A novel robotic drone, the Nereid Under Ice vehicle, being launched in the Arctic Ocean. The vehicle is designed to conduct surveys and collect samples, operating under the remote control of a scientist on the support vessel. It can be equipped with a range of acoustic, physical, chemical, and biological sensors in addition to high definition still and video cameras and specialized sampling devices. Thus it can collect data more efficiently than an icebreaker ship and operate under the ice where ships cannot go.*

*Photo by Chris German (WHOI)*



comprehensive assessment of the state of the physical, chemical, and biological Arctic Ocean.

An investment of \$1 billion over 10 years would enable the creation of a comprehensive Arctic observation system. Investments would extend existing technology and accelerate new technology to create an efficient basin-scale observation system capable of year-round data collection. Expeditions would be used to develop a phenomenological foundation for improved models coupled to the observation system and to look more closely at interactions and processes that cannot be completely described using sensors. Such an effort would transform our understanding of the Arctic and create a monitoring system capable of both tracking the evolving state of the Arctic and improving our capabilities to predict changes, mitigate impacts, and minimize the risks to human activities, both in the region and globally.

Given that we only have one Earth, that we continue to use carbon-based fuels that cause warming, and we're uncertain about how climate change will unfold, the Arctic provides a window to the future that philanthropy can open.

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*Carin J. Ashjian, Senior Scientist, Woods Hole Oceanographic Institution*

*James G. Bellingham, Director, Center For Marine Robotics, Woods Hole Oceanographic Institution*



*A ship-based rosette instrument, here being retrieved from the Bering Sea. It is equipped with bottles (gray tubes) that can be opened and closed at specific depths to collect seawater, as well as other sensors to measure temperature, salinity, fluorescence, and dissolved oxygen levels. The water collected is analyzed for concentrations of nutrients and other compounds such as plant chlorophyll, and for the amount of microscopic bacterial, plant, and animal plankton in the water.*

*Photo by Chris Linder (WHOI)*



*This Hubble Space Telescope image combines visible and near-infrared to illustrate the central Westerlund 2 star cluster, with visible light observations in the surrounding region. Credit: NASA/ESA, the Hubble Heritage Team (STScI/AURA), A. Nota (ESA/STScI), and the Westerlund 2 Science Team*

# Space Exploration

Is there life on other earth-like planets? What exactly are “dark matter” and “dark energy” and how have they shaped the universe? Only research in space can answer such questions.

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*Timothy Grove*

**T**he U.S. role in space has been significantly reduced in recent years. What captured the public’s imagination in this past year was the dramatic rendezvous with a comet—somewhere out past the orbit of Mars—by a European spacecraft. The mission was not only daring—it took a decade for the spacecraft to reach and match

orbits with the comet—but also yielded important science: water on the comet is isotopically different from that on Earth, making it unlikely that comets were the source of Earth’s abundant water resources. This past year, too, India has placed a spacecraft in orbit around Mars with instruments that are as sophisticated as those used by NASA,

and China has successfully launched a spacecraft that orbited the moon and returned safely to Earth.

But the secrets of our solar system are not the only mystery out there in space. Are we alone in the universe? A definitive finding of life elsewhere would galvanize public attention around the world. Space telescopes including the U.S. Kepler mission have identified over 1000 confirmed planets circling other stars in our galaxy. Of these, a dozen are close enough and of a size—up to about 1.6 times the mass of Earth—that they appear to be rocky planets like Earth and with densities and apparent compositions to match. Some of them appear to be at the right distance from their stars to have liquid water, and thus could in theory support life. A new U.S. space observatory focused on such planets, the Transiting Exoplanet Survey Satellite, is to be launched in 2017, if budget cuts do not delay it.

A still more profound mystery concerns the basic “stuff” the universe is made of, how stars and galaxies evolved, and how the universe is still evolving. We know the broad outlines: our universe is almost 14 billion years old; about 5 percent of it is composed of normal matter—atoms and molecules; a much larger portion, about 27 percent, is made up of the still mysterious “dark matter” which helps to shape galaxies and the universe itself through its gravitational pull; and the rest is the even more mysterious “dark energy” that is pushing the universe to continue to expand outward, enlarging in size. The physics of both dark matter and dark energy—the dominant features of our

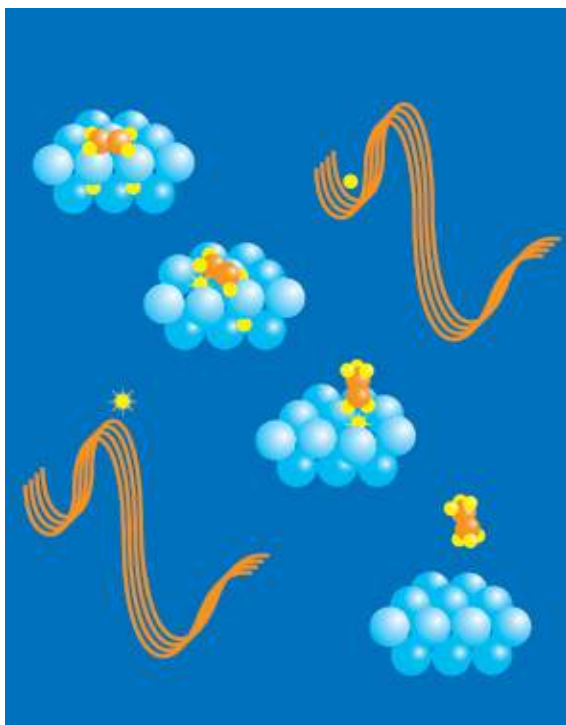
universe—are still completely unknown, as are the details of how the push and pull of these forces controlled the evolution of the universe in the first few billion years after the Big Bang. Breakthrough discoveries here would not only transform astrophysics, but physics itself.

The centerpiece of the U.S. program of space science in the coming years is the launch of the James Webb space telescope, which will focus on star formation, the evolution of galaxies, and the earliest moments of the universe itself. Scientists hope that it will help shed light on both dark matter and dark energy as well as related astrophysical phenomena. The Webb telescope is far larger than the 20-year-old Hubble space telescope, for which it is the successor: the main mirror is 6.5 meters across (the Hubble main mirror was 2.5 meters). More importantly, the Webb telescope is designed to see deeper into the universe and further back in time, and for that reason will observe mostly in infrared wavelengths (faraway objects are “red-shifted”), as compared to the optical and UV observing design for the Hubble. For the same reason, the new telescope will not be in Earth orbit, but instead will orbit the sun in tandem with the Earth but at a distance from us of 1.5 million kilometers, where there is less “noise” in the infrared spectrum.

This new capability will again give the U.S. a leadership role in astrophysics, but the cost of the telescope and recent budget cuts for space science will likely delay or prevent other high opportunity missions as well as related theoretical and computation research. Meanwhile, other nations are pressing ahead.

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*Timothy Grove, Associate Department Head of Earth Atmospheric and Planetary Sciences, and Cecil & Ida Green Professor of Geology, Massachusetts Institute of Technology*



*Graphic of molecular mechanism uncovered for catalytic hydrogenation, a fundamental process in design of clean fuel production.*

*Graphic credit : S.T. Ceyer*

# Catalysis

Today's industrial catalysts are relatively crude and imprecise. Nature's catalysts are far better, but how they work is not well understood. Solving that puzzle would have profound impact on energy and environmental challenges.

*Sylvia T. Ceyer*

**T**he production of catalysts is a \$500 billion industry in the United States alone.

But the economic shadow of catalysis is far larger, since catalysts play a critical role in the manufacture of virtually every fuel, all types of plastics, and many pharmaceuticals by speeding up chemical reactions or even enabling them to occur at all. Many of the industrial catalysts in use today involve precious metals, such as the platinum in your car's catalytic converter that changes pollutants such as carbon monoxide or oxides of nitrogen to more innocuous molecules.

But catalysis is also an area of scientific inquiry that is critical to energy and environ-

mental challenges that loom large in coming decades. In fact, many of today's industrial catalysts require very high temperatures and are relatively crude and imprecise compared to nature's catalysts, such as the enzymes in our body that enable and guide virtually all the biochemical reactions that sustain life. Enzymes work at room temperature, they are very selective (they enable only one reaction), and they don't involve scarce, expensive metals. Just how they do that is not really understood. So the challenge for basic research is first to figure out the mechanisms of catalytic reactions by studying them literally step by step and atom by

atom, and then to develop methods of synthesizing new catalysts that are well-defined (like enzymes) on sub-nanometer scales. And to do that will require development of more powerful research tools than now exist—such as synchrotron-powered spectrometers, electron microscopes so advanced that they could see the dance of the molecules in a reaction of interest, and research facilities capable of viewing the dance under the temperatures and pressures of existing commercial catalytic processes. It will also require the development of new catalytic materials—we don't want our transport systems to be dependent on platinum, which comes largely from Russia and South Africa—and advanced computational chemistry resources.

Why should we care about this area of science? Consider just three examples where the right catalyst could have a profound impact:

- Artificial photosynthesis. Plants use carbon dioxide from the air and sunlight to synthesize carbohydrates; if we could duplicate that reaction, then feeding the world would be a lot easier.
- Converting water and sunlight into hydrogen. An efficient way to catalyze this reaction could fuel a hydrogen economy.
- Converting carbon dioxide into fuels. This would not only mean an inexhaustible source of conventional carbon-based fuels, but by recycling carbon dioxide would ensure that we don't worsen global warming.

These and a large number of less dramatic but economically and environmentally important advances in catalysis won't happen anytime soon. They require not only investments in new fundamental science and the research toolset described above, as well as a many-years-long effort beyond the ability of commercial entities to sustain. But the potential payoff—not just for energy and environmental concerns, but for all of chemistry—is such that governments will finance this research. Indeed, some—especially Germany and China—already are. And those that do will gain a critical economic edge.

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*Sylvia T. Ceyer, Head of the Department of Chemistry, and John C. Sheehan Professor of Chemistry, Massachusetts Institute of Technology*



*Infrared images of the heart of our Milky Way, where a supermassive black hole hides, obtained from telescopes with adaptive optics to correct the blurring effects of the Earth's atmosphere (right) and without adaptive optics (left).*

*Credit: A. Ghez & UCLA/Keck Galactic Center Group.*

# Opening a New Window into the Universe

A new generation of adaptive optics technology could transform infra-red and optical astronomy and bring fundamental new insights into the nature of massive black holes, dark matter, and extrasolar planets.

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**Andrea Ghez**

**E**arthbound telescopes see stars and other astronomical objects through a haze. The light waves they gather have traveled unimpeded through space for billions of years, only to be distorted in the last millisecond by the Earth's turbulent atmosphere. That distortion is now even more important, because scientists are preparing to build the three largest telescopes on Earth, each with light-gathering surfaces of 20 to 40 meters across. In principle, the larger the telescope, the higher the resolution of astronomical images. In practice, the distorting veil of the atmosphere has always limited

what can be achieved. Now, a rapidly evolving technology known as adaptive optics can strip away the veil and enable astronomers to take full advantage of current and future large telescopes (see photos). Indeed, adaptive optics is already making possible important discoveries and observations, including: the discovery of the supermassive black hole at the center of our galaxy, proving that such exotic objects exist; the first images and spectra of planetary systems around other stars; and high-resolution observations of galaxies forming in the early universe.

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The next generation of adaptive optics could effectively take even the largest earth-bound telescopes “above the atmosphere” and make them truly amazing new windows on the universe.

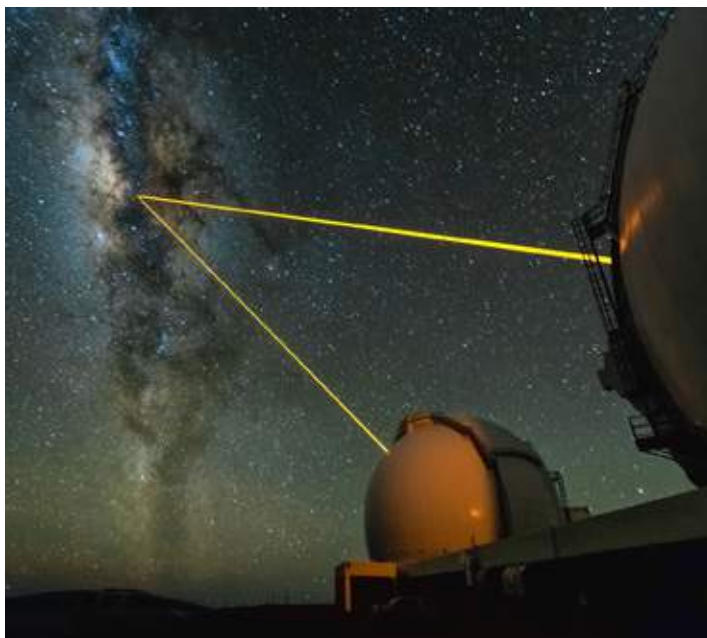
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But adaptive optics has still not delivered its full scientific potential. Existing technology can only partially correct the atmospheric blurring and cannot provide any correction for large portions of the sky or for the majority of the objects astronomers want to study.

The project we propose here to fully exploit the potential of adaptive optics by taking the technology to the next level would boost research on a number of critical astrophysical questions, including:

- What are supermassive black holes and how do they work? Adaptive Optics has opened a new approach to studying supermassive black holes—through stellar orbits—but only the brightest stars, the tip of the iceberg, have been measured. With next generation adaptive optics we will be able to take the next leap forward in our studies of these poorly understood objects that are believed to play a central role in our universe. The space near the massive black hole at the center of our galaxy, for example, is a place where gravitational forces reach extreme levels. Does Einstein’s general theory of relativity still apply, or do exotic new physical phenomena emerge? How do these massive black holes shape their host galaxies? Early adaptive optics observations at the galactic center have revealed a completely unexpected environment, challenging our notions on the relationship between black holes and
- galaxies, which are a fundamental ingredient to cosmological models. One way to answer both of these questions is to find and measure the orbits of faint stars that are closer to the black hole than any known so far—which advanced adaptive optics would make possible.
- The first direct images of an extrasolar planet—obtained with adaptive optics—has raised fundamental questions about star and planet formation. How exactly do new stars form and then spawn planets from the gaseous disks around them? New, higher resolution images of this process—with undistorted data from larger telescopes—can help answer this question, and may also reveal how our solar system was formed. In addition, although only a handful of new-born planets has been found to date, advanced adaptive optics will enable astronomers to find many more and help determine their composition and life-bearing potential.
- Dark matter and dark energy are still completely mysterious, even though they constitute most of the universe. But detailed observations using adaptive optics of how light from distant galaxies is refracted around a closer galaxy to form multiple images—so-called gravitational lensing— can help scientists understand how dark matter and dark energy change space itself.

*continued next page*



*The laser system used to make artificial guide stars that sense the blurring effects of the Earth's atmosphere being used on both Keck I and Keck II during adaptive optics observations of the center of our Galaxy. Next Generation Adaptive Optics would have multiple laser beams for each telescope.*

*Photo credit: Ethan Tweedie*

In addition, it is clear that telescopes endowed with advanced adaptive optics technology will inspire a whole generation of astronomers to design and carry out a multitude of innovative research projects that were previously not possible.

The technology of adaptive optics is quite simple, in principle. First, astronomers measure the instantaneous turbulence in the atmosphere by looking at the light from a bright, known object—a “guide star”—or by using a laser tuned to make sodium atoms in a thin layer of the upper atmosphere fluoresce and glow as an artificial guide star. The turbulence measurements are used to compute (also instantaneously) the distortions that turbulence creates in the incoming light waves. Those distortions are then counteracted by rapidly morphing the surface of a deformable mirror in the telescope. Measurements and corrections are done hundreds of times per second—which is only possible with powerful computing capa-

bility, sophisticated opto-mechanical linkages, and a real-time control system. We know how to build these tools.

Of course, telescopes that operate above the atmosphere, such as the Hubble Space Telescope, don't need adaptive optics. But both the Hubble and the coming next generation of space telescopes are small compared to the enormous earth-based telescopes now being planned. And for the kinds of research that require very high resolution, such as the topics mentioned above and many others, there is really no substitute for the light-gathering power of telescopes too huge to be put into space.

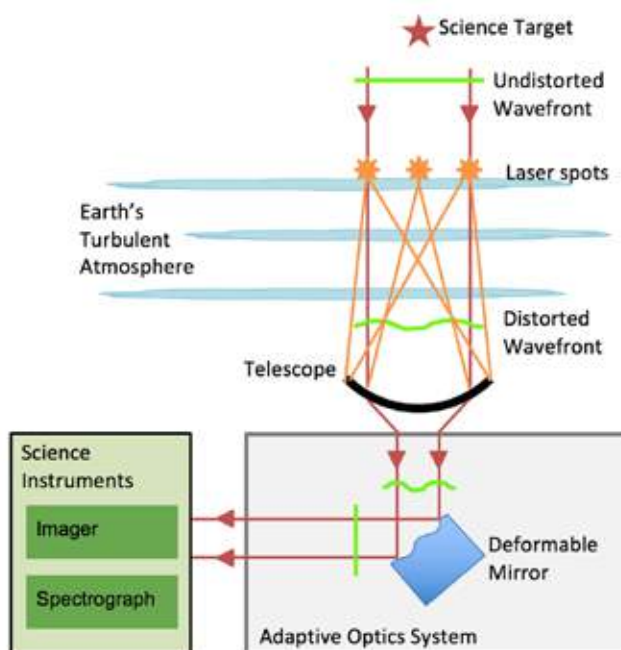
The next generation of adaptive optics could effectively take even the largest earth-bound telescopes “above the atmosphere” and make them truly amazing new windows on the universe. We know how to create this capability—the technology is in hand and the teams are assembled. It is time to put advanced adaptive optics to work.

# Creating Next Generation Adaptive Optics

Adaptive optics (AO) imaging technology is used to improve the performance of optical systems by correcting distortions on light waves that have traveled through a turbulent medium. The technology has revolutionized fields from ophthalmology and vision science to laser communications. In astronomy, AO uses sophisticated, deformable mirrors controlled by fast computers to correct, in real-time, the distortion caused by the turbulence of the Earth's atmosphere. Telescopes equipped with AO are already producing sharper, clearer views of distant astronomical objects than had ever before been possible, even from space. But current AO systems only partially correct for the effects of atmospheric blurring, and only when telescopes are pointed in certain directions. The aim of Next Generation Adaptive Optics is to overcome these limitations and provide precise correction for atmospheric blurring anywhere in the sky.

One current limitation is the laser guide star that energizes sodium atoms in the upper atmosphere and causes them to glow as an artificial star used to measure the atmospheric distortions. This guide "star" is relatively close, only about 90 kilometers above the Earth's surface, so the technique only probes a conical volume of the atmosphere above the telescope, and not the full cylinder of air through which genuine star light must pass to reach the telescope. Consequently, much of the distorting atmospheric structure is not measured. The next generation AO we propose will employ *seven* laser guide stars, providing full coverage of the entire cylindrical path travelled by light from the astronomical object being studied (see illustration).

This technique can map the 3D structure of the atmosphere, similar to how MRI medical imaging maps the human body. Simulations demonstrate that the resulting corrections



*The next generation of adaptive optics will have several laser-created artificial guide stars, better optics, higher performance computers, and more advanced science instruments. Such a system will deliver the highest-definition images and spectra over nearly the entire sky and will enable unique new means of measuring the properties of stars, planets, galaxies, and black holes.*

*Illustration credit: J.Lu (U of Hawaii) & T. Do (UCLA)*

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# Creating Next Generation Adaptive Optics

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will be excellent and stable, yielding revolutionary improvements in imaging. For example, the light from a star will be concentrated into a tiny area of the focal plane camera, and be far less spread out than it is with current systems, giving sharp, crisp images that show the finest detail possible.

This will be particularly important for existing large telescopes such as the W. M. Keck Observatory (WMKO)—currently the world’s leading AO platform in astronomy. Both our team—the UCLA Galactic Center Group (GCG)—and the WMKO staff have been deeply involved in the development of next generation AO systems.

The quantum leap in the quality of both imaging and spectroscopy that next generation AO can bring to the Keck telescopes will likely pave the way for advanced AO systems on telescopes around the globe. For the next generation of extremely large telescopes, however, these AO advances will be critical. This is because the cylindrical volume of atmosphere through which light must pass to reach the mirrors in such large telescopes is so broad that present AO techniques will not be able to provide satisfactory corrections. For that reason, next generation AO techniques are critical to the future of infrared astronomy, and eventually of optical astronomy as well.

The total proposed budget is \$80 million over five years. The three major components necessary to take the leap in science capability include the laser guide star system, the adaptive optics system, and a powerful new science instrument, consisting of an infrared imager and an infrared spectrograph, that provides the observing capability to take advantage of the new adaptive optics system. This investment in adaptive optics will also help develop a strong workforce for other critical science and technology industries, as many students are actively recruited into industry positions in laser communications, bio-medical optics, big-data analytics for finance and business, image sensing and optics for government and defense applications, and the space industry. This investment will also help keep the U.S. in the scientific and technological lead. Well-funded European groups have recognized the power of AO and are developing competitive systems, though the next generation AO project described here will set an altogether new standard.

Federal funding agencies find the science case for this work compelling, but they have made clear that it is beyond present budgetary means. Therefore, this is an extraordinary opportunity for private philanthropy—for visionaries outside the government to help bring this ambitious breakthrough project to reality and open a new window into the universe.

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