Biomedical science, world health and world peace

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Introduction

I would very much like to thank Uwe Morawetz and the International Peace Foundation for inviting me to participate in this important program. I am honored to be here and to have been included in the exceptional group of visitors who have been hosted by this program. I also am personally appreciative for the opportunity for my family and me to visit Malaysia and Thailand, two countries none of us had been to previously.

Biomedical science, world health and world peace

I have entitled my lecture "Biomedical science, world health and world peace." I believe that biomedical science, world health and world peace are vitally interconnected. World peace is threatened by inequalities around the world – inequalities in wealth, inequalities in education and, most fundamentally, inequalities in health. Without good health neither the education nor the wealth of a society can be improved in a meaningful way.

I am reminded of a conversation I had with Dan Vasella, who is the CEO of the international pharmaceutical giant Novartis. Dan was telling me that he had established a foundation to try to address some of the world's inequalities. The first project of this foundation was building a school in Mali, in West Africa, and Dan went to the dedication ceremony celebrating the opening of the school. What he found was disheartening: It was clear that the school was going to have very little impact, as the children were too ill to be able to take advantage of the existence of a new school. The lesson, Dan said, is that health must come first.

So what is needed to promote world health? In my view there should be one or more broad international consortia that focus on global health, and such efforts must involve the active participation of governments, foundations, pharmaceutical companies, hospitals and very, very dedicated individuals. There must be appropriate financial support, and there must be an appropriate infrastructure in each country to provide healthcare. In addition there must be advances in methods for diagnosing, treating and preventing disease. Many of today's diseases we simply do not know how to treat – consider dengue fever - or the treatments we have are themselves dangerous. Furthermore, resistance to existing treatments often arises, necessitating the development and sometimes the repeated development of new treatments – think about chloroquine-resistant malaria.

Novel advances in treatments are crucially dependent on discoveries driven by basic biomedical science. In this lecture I will demonstrate how basic research in biology can lead to discoveries that promise to provide new approaches to the treatment of disease. I also will advocate that governments and foundations allocate a significant portion of their research portfolios to basic research, despite the fact that it is often the need for specific applications of research that seems most pressing.

Genes and programmed cell death

I will focus on aspects of the research from my laboratory that resulted in my sharing the Nobel Prize in Physiology or Medicine in 2002. Many people know that the Nobel Prize comes with a gold medal and money. The Nobel Prize also comes with a diploma. At the end of my diploma is a citation that states that this prize was in part for "the understanding of … programmed cell death". What does this mean, and why did I receive the Nobel Prize in Physiology or Medicine for studies of a microscopic worm?

What is meant by the phrase "the genetic regulation of programmed cell death"? What is genetics? What is a cell? And, most importantly, what is programmed cell death, and why should anyone care about dying cells?

Genetics is the study of genes. Genes are responsible for all of the biological processes that occur in living organisms. Genes are the basis of heredity, and each of us has inherited half of our genes from our father and half from our mother. Variations in genes among individuals lead to variations in the biological processes they control, i.e. to variations in particular traits of those individuals. It is differences in genes that make humans different from monkeys, from insects and from seaweed. Other variations in genes have more subtle effects. Some such variations make us slightly different from one another: For example, eye color and blood type are defined by genes. Variations in other genes result in variations in other traits: For example, dwarfism, deafness and color blindness can be caused by variations in genes. Variations in still other genes result in variations in our traits that we label "disease": For example, Huntington's Disease is caused by one such gene. Variations in other genes cause or predispose us to cancer, cardiovascular disorders, asthma, cystic fibrosis, premature aging, Alzheimer's Disease, bone loss and many, many other diseases.

So, genes are important to us and crucial to our health. How can we learn about our genes, what they do and how they sometimes go wrong? One approach is to study our genes - human genes - directly. Many biologists do this. In fact, I do this, but only part time. There is a difficulty in studying human genes as such studies are in many ways very slow and inefficient. Furthermore, some types of studies are simply impossible to do with people. For example, a classic method of genetics is to cross individuals with different gene variants (called mutations) to get offspring derived from two genetically distinct parents; we cannot perform such informative crosses with people.

Fortunately, biology has provided us with an approach that is feasible: many genes are strikingly conserved among organisms, which means that we can study genes in experimental organisms and in this way learn what similar genes do in us. Many different experimental organisms are used in modern biology for studies of genes, including mice, zebrafish, fruit flies and single-celled yeasts that are also used to make bread or brew beer. Another organism used in genetic studies is a microscopic

roundworm or nematode called *Caenorhabditis elegans*, or *C. elegans* for short. *C. elegans* is the organism I have primarily studied, and I'll return to *C. elegans* in a few moments.

Now, back to the phrase "the genetics of programmed cell death". What is a cell? In short, a cell is the fundamental unit of life. Our bodies are made up of cells, and these cells are of many different types: skin cells, nerve cells, muscle cells, blood cells and so on.

Given that a cell is the unit of life, what do we mean by "programmed cell death"? Programmed cell death is synonymous with "naturally-occurring cell death", i.e. cell death that is a part of the normal genetic "program" of an organism. Let me explain how it is that cell death can be naturally occurring. During the development of an animal from a single cell, the fertilized egg, many things happen. The fertilized egg divides, and then its daughter cells divide over and over again, generating large numbers of cells, as many as 10^{13} - ten million million - in humans. Then each of these cells must take on specific characteristics such as becoming a nerve cell or a muscle cell or a skin cell. Furthermore, all of these cells must interact so as to form groups of cells with the proper structures - say an arm or a nose or a heart - and proper interconnections - as in the highly complex brain.

These processes of cell division, cell differentiation and morphogenesis constitute the basic events of animal development and define the basic problems of the field of developmental biology. In addition to these processes, there is another process that appears to be universal among developing animals - the process of cell death. Quite remarkably, many of the cells that are generated as animals develop do not survive, but instead die. It is this naturally-occurring cell death that is often referred to as programmed cell death.

It has been known for some years that cell death occurs during the normal course of animal development. For example, the regression of a tadpole's tail as it undergoes

metamorphosis to become a frog involves the programmed deaths of the cells in the tail. Similarly, the formation of digits such as our fingers and toes occurs by the removal of inter-digital webbed regions by programmed cell death. Chicken feet are formed by this inter-digital programmed cell death, whereas, by contrast, the webbed feet of a duck are generated because this process of programmed cell death does not occur.

Programmed cell death can be a major event. For example in areas of the developing mammalian brain as many as 85% of the nerve cells generated die. Similarly, approximately 95% of the thymocytes, blood cells of our immune system, that are generated die by programmed cell death. Despite its widespread occurrence this process of programmed cell death was, to a great extent, overlooked for many years. One reason, I think, is that biologists simply couldn't think of cell death as being something that organisms would want to do. Cells, they thought, died only if they could not be kept alive. Biologists know all too well how easy it is to make cells die, and for a long time biologists tended to think about cell death - if they thought about it at all - as simply what happens when cells are unhappy.

It was in part our discovery that this view is wrong that led to the Nobel Prize. In short, what we found is that there is a biology of cell death and that programmed cell death is an active process on the part of cells that die. Specifically, as I will discuss in a few minutes, studies in my laboratory revealed that specific genes must function for programmed cell death to occur and that these genes must act within those cells that are to die. Thus, there appears to be a biology of cell death every bit as much as there is a biology of other basic cellular processes such as cell division, cell migration and cell differentiation.

So far I have been discussing the role of cell death in normal biological processes such as development. Any basic biological process, if it goes wrong in us, can lead to disease. Programmed cell death is no exception to this rule, and abnormalities in the control of programmed cell death have proved to be involved in a wide variety of human diseases. For example, the major clinical features of many neurological disorders - such

as the neurodegenerative diseases (Alzheimer's, Huntington's, Parkinson's and amyotrophic lateral sclerosis as well as about two dozen other diseases which are neurodegenerative diseases), stroke and traumatic brain injury - are consequences of too much cell death. In each of these diseases specific nerve cell types die, leading to particular neurological features. What causes these nerve cells to die? One current hypothesis is that at least some of the cell deaths in these disorders are ectopic programmed cell deaths, i.e. cell deaths that are mechanistically similar to those that occur in normal development, but that for some reason are expressed by the wrong cells or at the wrong time. There are numerous other human disorders associated with too much cell death including AIDS, heart attacks and heart failure, a variety of liver diseases, aplastic anemia, sepsis, and kidney failure.

Conversely, some human disorders involve too little cell death like cancer. Cancerous growth is often a consequence of too much cell division. However, the increase in cell number that is associated with cancerous growth can also be caused by too little cell death: The cell number is defined by an equilibrium between rates of cell addition and cell removal so that increasing cell division rates and decreasing cell death rates can have comparable effects. As an analogy, think about a bathtub. If you have a bathtub that is half full of water and water is flowing in from the spout and out from the drain at equal rates, the level of water will remain constant. If you turn up the water flow from the spout, the bathtub will overflow. That is cancer from too much cell division. By contrast, if you keep the flow into the tub constant but slightly block the drain, the bathtub also will overflow. That is cancer from too little cell death. Thus, certain human cancers result from a decreased rate of programmed cell death.

More generally, an understanding of the process of programmed cell death is important for the understanding and treatment of diseases as diverse as neurodegenerative disorders, AIDS, cancer and autoimmune disease. It was our contributions to this understanding that was recognized by the Nobel Prize.

The genetics of programmed cell death

We analyzed the process of programmed cell death not in humans or even in another mammal but rather in a very simple animal, the microscopic roundworm *C. elegans*. *C. elegans* played the central role in this Nobel Prize, as my two co-recipients, Sydney Brenner and John Sulston, also were honored because of their landmark studies involving *C. elegans*.

What did the three of us do? Sydney, working at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England, introduced *C. elegans* to biology and developed the basic methods for its study. Sydney was drawn to *C. elegans* in part because it is very simple - we now know that there are only 959 cells in the *C. elegans* adult, as contrasted with approximately 10 million million in a mammal and 100,000s to millions in insects. Sydney also was drawn to *C. elegans* because of features that make it exceptionally well-suited for genetic studies: Geneticists are concerned with rare individuals, e.g. mutants that occur one in a million, and with experiments that involve many generations. 10,000 *C. elegans* can be grown in a single small plastic dish, and this animal grows from an egg to an adult in only three days. This cellular simplicity and appropriateness for genetic studies led Sydney to conclude that *C. elegans* would be superb for genetic analyses of developmental biology and neurobiology, and he initiated such analyses.

John Sulston was a staff member in Sydney's laboratory. John studied the developmental biology of *C. elegans* and in particular identified the precise pattern of cell divisions that leads from the single-cell fertilized egg to the adult. During the development of any organism one cell divides to make two, and then two divide to make four and so on, until all of the cells of the organism are generated. John defined this "cell lineage" of *C. elegans*. This cell lineage describes the developmental origin of every cell in the animal. *C. elegans* is the only organism for which a complete cell lineage is known. The simplicity and knowledge of this cell lineage have allowed the analysis of problems of developmental biology at single-cell resolution. Consider what the cell lineage of a person would look like with 10 million million cells instead of only 959!

John discovered that in addition to the 959 cells found in the *C. elegans* adult, there are 131 additional cells that are generated, but not found in the adult. These cells are not present, because they die, because they undergo programmed cell death. That cells undergo programmed cell death during *C. elegans* development made it possible to use genetics to analyze the mechanisms of programmed cell death.

That is what my laboratory did. In short, we identified genes responsible for controlling the process of programmed cell death. We did this by seeking mutants – genetic variants – of *C. elegans* in which the process of programmed cell death was abnormal. For example, we identified a mutant worm in which programmed cell death does not occur. This mutant defined a gene necessary for programmed cell death, i.e. a killer gene. We called this gene "*ced-3*," for cell death abnormal. Since a specific gene is needed for cells to die by programmed cell death, we concluded that programmed cell death is an active biological process, analogous to other fundamental biological processes, such as cell division, cell migration and cell differentiation.

We found a second killer gene ("*ced-4*) and then demonstrated that both of these killer genes act within the dying cells themselves. This observation indicated that programmed cell death is a process of cellular suicide. We then discovered a gene that acts to antagonize these two killer genes. This gene, called *ced-9*, protects cells against programmed cell death. With our identification of a third killer gene, which was named *egl-1*, and our genetic analyses of how these genes interact, we defined a core genetic pathway for programmed cell death in *C. elegans*. We showed that CED-3 kills, CED-4 kills by promoting the activity of CED-3, CED-9 protects by preventing CED-4 from promoting the activity of CED-3, and EGL-1 kills by preventing CED-9 from preventing CED-4 from promoting the activity of CED-3.

Our molecular studies of these genes revealed their molecular natures. *ced-9* looks like a human cancer gene, Bcl-2, and this cancer gene is known to cause cancer by preventing programmed cell death, just like *ced-9* prevents programmed cell death. We

showed that we could put the human gene into a worm, and it would substitute for *ced-9*. This discovery established that not only are these genes similar between *C. elegans* and humans, but also that they must interface with similar molecular genetic pathways. In other words, the pathways for programmed cell death must be similar between worms and humans.

Our molecular studies of the other three genes in the *C. elegans* core pathway for programmed cell death revealed that they, too, have human counterparts and led to the discovery that some of these counterparts function in programmed cell death in humans. CED-3 looks like an enzyme called ICE, which had been identified by two pharmaceutical companies – Merck and Immunex - based on its role in human inflammatory disease, but not suspected at the time to have anything to do with programmed cell death. CED-3 can cause mammalian cells to undergo programmed cell death. Subsequent studies have revealed that humans have many CED-3/ICE-like enzymes that act in programmed cell death. These enzymes are now called caspases. CED-4 was novel when we characterized it, but some years later a human counterpart, also involved in programmed cell death, was found. Finally, EGL-1 also looked like members of a family of human proteins involved in programmed cell death. The upshot is that we defined a core molecular genetic pathway for programmed cell death that is conserved between *C. elegans* and humans.

More generally, we defined a longer and detailed molecular genetic pathway for the entire process of programmed cell death. I won't go into specifics today but rather will summarize our findings by saying that we identified and characterized four key steps in this pathway. First, every cell in the animal must decide whether to live or to die by programmed cell death. The next three steps involve the killing process, the engulfment of the dying cell by neighboring cell and the degradation of the debris of the cell corpse. In other words, these four steps can be described as: Identify the victim, kill, get rid of the body and destroy the evidence. For each of these steps the genes we identified in *C. elegans* have counterparts in humans. Many of these counterparts have been

characterized and found, when their functions are disrupted, to lead to disease, such as the cancer caused by misexpression of the *ced-9*-like anti-death gene Bcl-2.

That most and possibly all of these genes have human counterparts that function in the process of programmed cell death means that these human counterparts define potential therapeutic targets. For example, consider retinal degenerations or heart attacks in which cells die by programmed cell death. If we could inhibit a killer gene – e.g., a CED-3-like caspase gene, we could prevent programmed cell death and save eye cells or heart cells. In fact, a caspase inhibitor developed by a biotech company I founded has been in late-stage clinical trials for a variety of liver diseases that involve too much liver cell programmed cell death, diseases such as those caused by the Hepatitis C virus. Conversely, in a disease like cancer in which there is too little programmed cell death, if we could inhibit a protector gene and unleash programmed cell death, we could kill cancer cells. Such an anti-Bcl-2 compound co-developed by the company I founded is in clinical trials for cancer. Many other drugs are being developed by many other companies for diseases of programmed cell death. Thus, our identification of the genes and proteins that function in the process of programmed cell death in *C. elegans* has provided new targets for possible intervention in a wide variety of human diseases.

Basic science, translational research and global health

At this point, I'd like to put the discoveries I have discussed into a somewhat broader context. The work I have described involved absolutely basic research. When I began, neither the generality nor the application of our efforts was at all clear. The roundworm *C. elegans* was an obscure organism, even to biologists. Genetic studies are often highly abstract. I did not target any disease, and I did not know if what we found would be relevant to any organism other than *C. elegans*. Nonetheless, our studies established mechanisms that appear to be universal among animals, and our findings might well help provide the basis for new treatments for a broad variety of human diseases.

I think there is a very important message here: Basic research, research that is discovery-based, will in my view very often lead not only to intellectually stimulating findings – an important aim in and of itself - but also to insights of major practical import. Basic research is the driver of scientific knowledge.

How and where should basic research be supported? True basic research cannot be supported by the private sector, as no company can confidently know ahead of time that discovery-based research will lead to a finding of relevance to its business plan. For this reason I strongly advocate that governments and foundations allocate a significant portion of their research portfolios to basic research, as it is basic research that most often results in the truly unexpected discoveries that drive science and technology forward. Furthermore, I believe that even countries with relatively small research budgets should provide significant support for pure basic research, as the knowledge and expertise that are necessary for basic research are crucial in ensuring that all research – including applied research directed toward pressing problems of high immediate need – will be critical, creative and of the highest quality. Only with support for basic research can biomedical scientists make the discoveries that will lead to the novel pharmaceuticals that will improve world health and help us on the road toward world peace.

There is another aspect of the relationship between science and government that I believe is important: Government policies should be informed by good science. All too often scientific data are ignored, distorted or even fabricated to serve a political agenda. Instead, public policies should be based on the soundest science available. Only in this way can the best decisions be made for a country and for the world. Unfortunately many countries have at times ignored this principle, even the U.S.

Last week I had the enormous privilege and honor to be present at the White House when U.S. President Barack Obama signed an Executive Order that, first, rescinded a political agenda-based rule that prohibited aspects of stem cell research in the U.S. and, more fundamentally, directed White House staff to develop a strategy to restore

scientific integrity to government decision-making. I think this Order is an enormously important step for the U.S. and the world, and I hope that other world governments will take note and, like the U.S. today, use scientific knowledge in making the best decisions for policies concerning energy, security and health. In this way we should progress toward a world with the best prospects for world health, world prosperity and world peace.

Acknowledgments

Finally, I would like thank the many members of my laboratory, both those who were responsible for the work I have just discussed and others who contributed to other projects over the years. To the scientists who have worked with me, and to you, I say thank you.