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The Impact of Sequencing Genomes on The Human Longevity Project

Hameed Khan, Ph.D*

Senior Scientist, NCMRR (National Center for Medical Rehabilitation Research), National Institutes of Health (NIH), Bethesda, Maryland.

***Correspondence:**
Dr. A. Hameed Khan, Ph.D. (London), Senior Scientist, NCMRR (National Center for Medical Rehabilitation Research), National Institutes of Health (NIH), Bethesda, Maryland, 11965 Old Columbia Pike, Silver Spring, MD 20904, USA.

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ABSTRACT

Treating old age diseases to achieve human longevity is the greatest challenge. This abstract describes how human longevity is shortened by three old aged deadly diseases namely Cancer, Cardiovascular Diseases and Alzheimer. To prolong human life beyond one hundred years, we focus on the rational drug design to treat one old age disease one at a time. Our work began on Cancers starting in England and completed in America. More research fund is available by both The Royal Cancer Hospital of the University of London, England, and The National Cancer Institute (NCI) of America to develop drugs to treat Cancer than any other diseases. We describe below how novel drugs, like Aziridine Dinitro-benzamide (CB1954) was developed in England to treat Cancer in animals, such as Walker Carcinoma 256, a solid aggressive tumor in Rats and how the animal work is translated in humans, by developing AZQ (US Patent 4,146,622) a rationally designed drug to treat Glioblastoma, a solid aggressive brain tumor in human at the NCI. For the discovery of AZQ, our work was honored with, "The 2004, NIH Scientific Achievement Award" one of America's highest awards in medicine." Using the same rational approach, this abstract also describes how novel drugs could be developed on rational basis to treat Breast and Prostate Cancer to achieve human Longevity. Ethical issues achieving longevity are also described.

A Note to My Readers

Part of this lecture will be delivered at the Global World Cancer Conference organized by "BIT's 14th Annual World Cancer Congress - to be held during March 10-12, 2022, in Barcelona, Spain and also, to the 2022 National Youth Leadership Forum (NYLF) scholars from around the country organized by the **"Leadership in Medicine Program"**. The NYLF scholars are the very best and brightest students selected from all over the USA and the world brought to Washington by Envision, an outstanding organization that provides future leaders of the world. I have been honored to be associated with the Envision as a speaker of the NYLF scholars for the past twenty years. All previous lectures are available on the following website: https://www.facebook.com/hameed.khan.7773/notes

Historical Background

Since the dawn of human civilization, achieving human longevity has been the dream of every King, every Queen, every Pharos and every Caesar. But they all died in their fifties by infectious diseases. Then came the Science and Technology revolution. In 1928, Alexander Flaming, [1] while working on influenza virus, observed that a mold had developed accidently on a staphylococcus culture plate and by killing the bacteria around itself had created a bacteria-free circle around itself. He was so inspired by the presence of the bacteria free zone, he conducted further experiment and he found that the mold culture prevented growth of staphylococci, even when diluted 800 times. He named the active substance penicillin. The discovery of Penicillin was followed by a host of new antibiotics such as Streptomycin, Kanamycin, Adriamycin which wipeout Gram-positive and Gram-negative bacteria. Even Viral infections are wipeout by antiviral drugs and vaccines.

The origin of a new virus is usually due to poor farmers in villages of Asian countries who share living quarters with animals. In my own country, India, farmers share quarters with cows, goats, chickens and ducks. The interactions of animal viruses with humans may result in the evolution of novel pathogenic viruses. The recently developed Coronavirus Flu was first identified in Wuhan, China.

The origin of Coronaviruses has potential of spillover of bat-born coronaviruses, as evidence by the recent spillover of swine acute diarrhea syndrome coronavirus to pigs. The only treatment would be a vaccine. Scientists at NIH have already developed a vaccine and they have launched a Phase I clinical trial to test mRNA-1273 as a vaccine for COVID-19 in February 2020 and the trial is expected to end in June 2021.

We conquered infectious diseases. We increase our life span from 50 to 60 years. Then came the Genetic Revolution. We broke the Genetic Code and unlocked the secrets of life. Now, we are ready to manipulate life not only to produce new food, new fuel and new medicine to treat every disease known to mankind, but also to increase human longevity beyond 60 to 75 years by launching Human Longevity Project by shutting off genes responsible for causing old age diseases such as Alzheimer, Cancers, and cardiovascular diseases.

Next, we read the entire book of Human life. We read the total genetic information that make the Human Life; we completed the Human Genome Project. Next, we sequenced the Human Genome that is we read the number of nucleotides and the order in which they are arranged. With advancement in Science and Technology, we sequenced the Human Genome cheaper and faster using the next generation sequencers such as Nanopore. Then, we completed the 1,000 Human Genome Project. We are able to compare the reference sequence of every gene with the 1,000 copies of the same gene from different individuals to identify differences. These differences are called Variants. If the good variant came from the Pancreas, it produces Insulin which is used to treat Diabetes. If the variant came from a mutated gene, it is responsible for causing diseases such as Cancers, Cardiovascular diseases or Alzheimer. Soon, we will prepare a variant map of the entire Genome to identify all six thousand diseases then we can design drugs to treat these diseases by shutting off their genes. The thousand Genome Project will help us single out the rare mutation responsible for causing rare genetic diseases with precision and accuracy. With advent of new technologies, we embark on the more ambitious project such as The Human Brain Project and The Human Longevity Project.

The Human Longevity Project is studied in three Eras: The Pre-antibiotic Era (before year 1950); the Post-antibiotic Era (the present treatment when people live up to 75 years) and the Genetic Era (the Era of Centenarian). During the Pre-antibiotic Era, most people died of infectious diseases around age 50. Most women died of infections during the Childbirth. We conquered infectious diseases. Now, we live up to 75 years and beyond in the Post-antibiotic Era in which infectious diseases are treated with a variety of antibiotics such as Penicillin, Tetracycline, Erythromycin, Neomycin, Kanamycin, and dozens of their derivatives are available to treat most sensitive to most resistant germs. As a result of the antibiotics, our age span has increased to 75 years. Now, we embark on Genetic Era. We are likely to live up to 100 years. As we achieve longevity, we are confronted with three major old age diseases, and they are Cancers, Cardiovascular Diseases and Alzheimer. To find cure for these diseases, we must look into the Human Genome.

In this chapter, I will attempt to answer an important question about human longevity using the information available from the Human Genome Project. Is our longevity written on our DNA? Is the secret of our longevity hidden in the long string of four nucleotides text on a three-letter codon carrying 24,000 genes in 46 chromosomes in our Genome containing six billion four hundred-million nucleotides? Could we identify the genetic variants responsible for our longevity by comparing the Whole Genome Sequence of the Centenarians with the 1,000 Human Genomes Project completed by US and a Million Human Genomes Project to be completed by European and a three Million Human Genome Project announced by the Chinese to identify rare alleles responsible for causing rare diseases with accuracy and precision and identifying in the whole genome the specific genetic variations and the few nucleotides responsible for our longevity? As I said above, before the discovery of antibiotics, most people died in their fifties. Today, all infectious diseases are treated with antibiotics. Now, we must treat the old age diseases such as Cancers, Cardiac diseases and Alzheimer. To attain longevity, we have to design drugs to shut off genes responsible for causing these old age diseases.

Next, I will describe how I design drug to shut off genes which cause brain cancer, Glioblastomas. Similar rationale could be used to design drugs to shut off genes responsible for causing cardiovascular diseases and Alzheimer and achieve longevity.

Keywords

Genome, Cancer, Cardiovascular Diseases, Alzheimer, DNA.

Genotype - Phenotype Correlations

Our genes, a strip of DNA, carry instructions to make proteins and when the proteins fold, they become active and carry out a specific function. Hundreds of proteins interact to make a cell and millions of cells interact to make a tissue. Hundreds of tissues interact to make an organ and several organs interact to make a human being. We carry in our body 220 different tissues. The instructions to make tissues are written in our genes. A defected tissue could be identified by looking at the mutation in the genes. By sequencing a fertilized egg, the genotype, we could identify the mutations responsible for future diseases in tissues, the phenotype. If a patient has a family history of a specific disease, to prevent future generation from inheriting the disease, it is best to have *in-vitro* fertilization implanting the fertilized egg after sequencing its genome and making sure that it is free from the mutation causing the disease.

Our entire genome, the book of our life, is written in four nucleotides and they are A, (Adenine) T (Thiamine), G (Guanine) and C (Cytosine). The chain of these nucleotides forms a double stranded string called the DNA (Deoxy Ribonucleic Acid). According to Francis Crick's Central Dogma, [2] double stranded DNA is transcribed into a single stranded RNA which is translated in the Ribosome into proteins. The discovery of the double helical

structure of DNA explained how the information to create life is stored, replicate, evolved and passed on to the next generation. This discovery opened a New World Order of ideas and buried the old explanation of the magical mystical appearance of life on Earth.

The double stranded DNA explained that the essence of life is information, and the information is located on these four nucleotides. Every set of three nucleotide on the mRNA forms a Codon which codes for a specific amino acid. The four-letter text of nucleotides forms a three letter Codon which codes for an amino acid. There are 64 different combinations of Codons which codes for all 20 amino acids.

Sequencing human genome identifies the number and the order of nucleotides in which they are arranged. Less than two percent of our genome contains regulatory region, a piece of DNA, which controls the function of genes. More than 300 regulatory regions have been identified. More than ninety eight percent of our Genome contains non-coding region used to be called Junk DNA which makes up to sixty percent of our entire Genome. The non-coding regions contains repetitive piece of DNA which is tightly packed and mostly remain silent. The sequencing of this region showed that the non-coding region is the part of Viruses and Bacteria picked up by our Genome during the million years of our evolutionary process. During Bacterial or Viral infection, the non-coding DNA could unfold transcribing into RNA resulting into hazardous protein which could create havoc for our health.

Genes are the unit of inheritance. As I said above, out of four-letter text, that is A-T and G-C, and three letters code for an amino acid called the Codon. The starting Codon in a gene is the Codon AUG which codes for amino acid Methionine. Long chain of DNA synthesis begins. The starting Codon is followed by a series of hundreds of Codons which codes for different amino acids in different species. There are three Stop Codons, and they are AUG, UGG, and UGA. Once the stop codons appear, DNA synthesis stops. Bacteria and Viruses have short codon chain. The longest chain is in a gene of Ducharme Muscular Dystrophy, a neurological disease whose chain extends to two and a half million codons. Once a gene is identified, using Restriction Enzymes, like EcoR1, we can cut, paste and copy all genes individually making a Restriction Site map. Once a single gene is isolated and stored in cell libraries, we could compare the sequence of this gene with the Reference Sequence and the Thousand Genome Project to identify rare mutations. Sequencing genome is like extracting Gold from its Ore.

Let us examine the sequence of the Genome of human Egg and Sperm. An Egg contains a single strand of 164 million nucleotide bases carrying 1,144 genes while the Human Sperm contains a single strand of 59 million nucleotide bases carrying 214 genes. When comparing the sequence of an Egg or Sperm with sequence of the thousand Eggs and Sperms of difference people, we notice changes. These changes are called Variants. These variants are mutations caused by Radiations, Chemical and Environmental Pollution, Viral infection or Genetic Inheritance resulting in rare diseases. Once a bad gene is identified, we will demonstrate in the Cancer Section below that we could design drugs using Aziridines and Carbamate to shut off these genes and to prolong human life. We are allowed to shut off and remove bad genes. On the other hand, we are not allowed to introduce good genes in the Egg and Sperm to enhance the abilities of Egg and Sperm because modification introduced in the Egg and Sperm will pass on to the next thousand generations. Is it Ethical to determine the quality of life of individuals who will not even be born before the century is over?

The reading of the total genetic information that make us human is called the Human Genome. The reading of the entire book of our life is authorized by the US Congress under The Human Genome Project. It will answer the most fundamental question we have asked ourselves since the dawn of human civilization. What does it mean to be human? What is the nature of memory and our consciousness? Our development from a single cell to a complete human being? The Biochemical basis of our senses, the process of our aging. The scientific basis of our similarity and dissimilarity. Similarity that all living creatures from a tiny blade of grass to mighty Elephant including Man, Mouse, Monkey, Mosquitos and Microbes are all made of the same chemical building blocks and yet we are so diverse that no two individuals are alike even identical twins are not exactly identical, they grow up to become two separate individuals.

In 1990, US Congress authorized three billion dollars to NIH to decipher the entire Human Genome under the title, “The Human Genome Project.” We found that our genome contains six billion four hundred million nucleotides bases half comes from our father and another half comes from our mother. Less than two percent of our Genome contains genes which code for proteins. The other 98 percent of our genome contains switches, promoters, terminators etc. The 46 Chromosomes present in each cell of our body are the greatest library of the Human Book of Life on planet Earth. The Chromosomes carry genes which are written in nucleotides. Before sequencing (determining the number and the order of the four nucleotides on a Chromosomes), it is essential to know how many genes are present on each Chromosome in our Genome. The Human Genome Project has identified not only the number of nucleotides on each Chromosome, but also the number of genes on each chromosome [3-7].

The following list provide the details composition of all Chromosome:

We found that the chromosome-1 is the largest chromosome carrying 263 million A, T, G and C nucleotides bases and it has only 2,610 genes. The chromosome-2 contains 255 million nucleotides bases and has only 1,748 genes. The chromosome-3 contains 214 million nucleotide bases and carries 1,381 genes. The chromosome-4 contains 203 million nucleotide bases and carries 1,024 genes. The chromosome-5 contains 194 million nucleotide bases and carries 1,190 genes. The chromosome-6 contains 183 million nucleotide bases and carries 1,394 genes.

The chromosome-7 contains 171 million nucleotide bases and carries 1,378 genes. The chromosome-8 contains 155 million nucleotide bases and carries 927 genes. The chromosome-9 contains 145 million nucleotide bases and carries 1,076 genes. The chromosome-10 contains 144 million nucleotide bases and carries 983 genes. The chromosome-11 contains 144 million nucleotide bases and carries 1,692 genes. The chromosome-12 contains 143 million nucleotide bases and carries 1,268 genes. The chromosome-13 contains 114 million nucleotide bases and carries 496 genes. The chromosome-14 contains 109 million nucleotide bases and carries 1,173 genes. The chromosome-15 contains 106 million nucleotide bases and carries 906 genes. The chromosome-16 contains 98 million nucleotide bases and carries 1,032 genes. The chromosome-17 contains 92 million nucleotide bases and carries 1,394 genes. The chromosome-18 contains 85 million nucleotide bases and carries 400 genes. The chromosome-19 contains 67 million nucleotide bases and carries 1,592 genes. The chromosome-20 contains 72 million nucleotide bases and carries 710 genes. The chromosome-21 contains 50 million nucleotide bases and carries 337 genes. Finally, the sex chromosome of all females called the (X) contains 164 million nucleotide bases and carries 1,141 genes. The male sperm chromosome contains 59 million nucleotide bases and carries 255 genes.

If you add up all genes in the 23 pairs of Chromosomes, they come up to 26,808 genes and yet we keep on mentioning 24,000 genes needed to keep us function normally. A gene codes for a protein, not all 24,000 genes code for proteins. It is estimated that less than 19,000 genes code for protein. Because of the alternative splicing, each gene codes for more than one protein. All the genes in our body make less than 50,000 protein which interact in millions of different ways to give a single cell. Millions of cells interact to give a tissue, hundreds of tissues interact to give an organ and several organs interact to make a human.

Not all genes act simultaneously to make us function normally. Current studies show that a minimum of 2,000 genes are enough to keep human function normally; the remaining genes are backup support system and they are used when needed. The non-functional genes are called the Pseudo genes. For example, millions of years ago, humans and dogs shared some of the same ancestral genes; we both carry the same olfactory genes needed, only in dogs they still function to search for food. Since humans don't use these genes to smell for searching food, these genes are broken and lost their functions, but we still carry them. We call them Pseudo genes. Recently, some Japanese scientists have activated the Pseudo genes, this work may create ethical problem in future as more and more Pseudo genes are activated. Nature has good reasons to shut off those Pseudo genes.

Next, we converted the analog language Biology to the Digital language of Computer that is from A-T, G-C nucleotides to Zero and One. Now, we can write a program and design a computer to read the book of life faster and faster. Today, we can read our entire Genome in one day at a cost of a thousand dollars. We can also upload our digitized Genome on the Computer. Once uploaded on the website, our Genome could travel with the speed of light to anywhere in the World or in the Universe.

Once the good and bad genes are identified, we learned that the good genes codes for good proteins which keep us healthy, and the bad genes produce bad protein that make us sick. Using good genes, we make good protein to treat diseases such as Insulin is used to treat Diabetes. On the other hand, we could identify bad gene and design drugs to shut off bad genes to prevent diseases. This starts a new era of Genomic Medicine. It is the medicine designed based on the genetic make-up of the disease.

The double stranded DNA in the normal cell, the Autosome, is retained with the individual. When the person dies, the Genome dies with him. On the other hand, the DNA in a Germ-line cells lives on for generations. Through egg and sperm cells, the DNA is passed on to the future generations that is the information is passed on from parents to the fetus in different combinations.

A sperm, the Y-chromosome, is made of a single string of 59 million nucleotides bases and carry 231 genes while an egg, the X-chromosome, is made of a single string of 164 million nucleotides bases and carry 1,144 genes. No two sperms nor any two eggs are alike. Once the egg is fertilized, the nucleotides and genes are exchanged (recombination occurs) among nucleotides forming a double stranded DNA. Now, each string is a complete genome. During replication, each string separates and picks up the complimentary nucleotide bases (such as nucleotide A picks up T and G picks up C) from the nucleotide pool and forms two double stranded DNA forming two daughter cells. The two strands of each chain run in opposite direction.

Reactive and Predictive Medicine

Reactive medicine is the treatment of a disease after its symptoms are revealed and the full- blown disease appears. During your annual health check-up, your Physicians order a number of tests. For example, if you are a 40-year-old male and go to the doctor, he prescribed a PSA (Prostate Specific Antigen) test for the early signs of prostate cancer and if you are 40-year-old woman, your doctor prescribes the Mammography for the early signs of breast cancer and if you are 50-year-old, he prescribes the Coloscopy for Colon cancer. Once the symptoms are revealed, the standard treatment is prescribed for a disease such as Surgery, Radiations Treatment or Chemotherapy. The treatment after the appearance of its symptoms is considered as the Reactive Medicine.

A specific example is as follows: supposed your Physician finds that you are sick with high temperature and high blood pressure, he prescribes Plavix a medicine of standard treatment for lowing your blood pressure and temperature. It is a Reactive Medicine. You received treatment after your illness is diagnosed. Plavix is a useful drug for treating High Blood Pressure, but it does not respond in fifteen percent of the patients. In treating Reactive Medicine, we do not really know what is going on in our body.

On the other hand, Predictive medicine is the treatment of a disease

long before its onset by examining your normal genomic script of the effected organ from your book of life and comparing its entire script with the genome of a sick patient. Identifying what, spelling errors, mutations (genotype) are exactly responsible for causing the disease (phenotype). The difference between the Reactive Medicine and the Predictive Medicine is whether you have the disease or weather you will come down with the disease because you are carrying a mutation which could become activated and make you sick. Genomic medicine will have predictive quality. When comparing Genome sequences, we find differences called variations. Good variants are responsible for our evolution and bad variants are responsible for causing diseases. Using Restrictions enzymes like EcoR1, we can prepare a chart (called Restriction Site Map) of all 6000 variants responsible for causing all 6000 diseases. By comparing the sequence of a genes from the chart, we can predict which specific gene variant is expected to cause which disease.

As cells grow, the mutations accumulate and defects in Genotype manifests in Phenotype. By using MRI (Magnetic Resonance Imaging which provides three-dimensional image) method, one could see the progressive microscopic abnormal changes in the nucleotide bases and predict the on-set of a disease. The three-dimensional MR Imaging could serve as a diagnostic technique. There are 220 different tissues in our body. We take the MRI of all 220 tissues of a healthy person and during his annual medical check-up compare the present MRI and with the previous years' MRI to see any unusual microscopic changes predicting diseases.

Genomic Medicine

As I said above, genomic medicine is a predictive medicine. It predicts the onset of a disease long before it appears. It involves examining genetic damage of a patient specifically his Genome by comparing the entire sequence of DNA looking for the mutations responsible for predicting the disease. A genetic disorder is a disease caused in whole or in part by a change in the DNA sequence away from the normal sequence. Genetic disorders can be caused by a mutation in one gene (monogenic disorder), by mutations in multiple genes (multifactorial inheritance disorder), by a combination of gene mutations and environmental factors, or by damage to chromosomes (changes in the number of copies or structure of entire Chromosomes, or part of the Chromosome that carries genes). What specific nucleotide damage forming the codon is responsible for causing catastrophic diseases? By comparing the mutations in a DNA sequence (Genotype), we can predict the onset of a disease in human (Phenotype). The microscopic changes not detected by observations, can be confirmed by three-dimensional MRI (Magnetic Resonance Imaging) technique which will diagnose diseases long before the symptoms appear.

Historical Background

Diseases of Young Age

Before the development of antibiotics, most people died of infectious diseases around age 50. First, antibiotics, Penicillin, (discovered by Alexander Fleming) was used for treating wounds before the WWII. Enormous funds were made available by the Army to develop large scale antibiotics to treat wounded soldiers returning from the battle ground during WWII. During the following decades, novel class of aminoglycoside antibiotics were discovered which are valuable therapeutic agents. Some of them are Streptomycin, Neomycin, Kanamycin, Paromomycin, Apramycin, Tobramycin, Amikacin, Netilmicin, Gentamicin. etc. Hundreds of their water/fat soluble derivatives were synthesized. They are considered broad spectrum antibiotics because they inhibit the growth of both Gram-negative and Gram-positive bacteria causing deadly diseases and prolong human life. All aminoglycoside antibiotics are relatively small, basic and water-soluble molecules that form stable salts. Most aminoglycoside antibiotics are products of fermentation of filamentous actinomycetes of the genus Streptomyces.

Diseases of Old Age

Now a day, people rarely died of infectious diseases. Because of the availability of a variety of antibiotics, today, most people live beyond age 70 years and some of them go on living beyond 80 years of age. Those who live beyond 70 are faced with three major old age diseases which are responsible for causing the death of most patients during their lifetime and they are **(1) Cancers, (2) Cardiac Diseases and (3) Alzheimer**. In the following section, I will discuss all three major diseases one by one and the progress we have made in each of them. My entire carrier spent on developing ani-cancer drugs. I will begin with Cancer:

These are genetic diseases and could be treated either by Gene Therapy or by Drug Therapy. There are about three thousand monogenic diseases and could be treated by replacing the defected gene with good gene that is by Gene Therapy or designing drugs to shut off the bad genes that is Drug Therapy. Gene Therapy cannot be applied to treat multiple genetic defects such as Alzheimer, Cancers or cardiovascular diseases. Drug Therapy could be used to develop novel treatments. Recently completed 1,000 Human Genome Project identify with precision and accuracy the genes responsible for causing these diseases, it is now possible to design drugs to shut off these genes and increase Human Longevity. Genes code for Proteins and a mutated gene codes for abnormal proteins resulting in these diseases.

At the London University, I was trained as an Organic Chemist in the Laboratory of Professor WCJ Ross of the Royal Cancer Hospital, a post-graduate medical center of the London University. After working for about ten years at the London University, I moved to America when I was honored by the Fogarty International Fellowship award by the National Institutes of Health, NIH, and the National Cancer Institute, NCI, of the USA. NIH has been my home for over a quarter of a century, I designed drugs to shut off mutated genes. All three longevity diseases have genetic origin. The rationale I used to synthesize anti-cancer drugs could be used to treat the other two longevity diseases like Alzheimer or cardiovascular diseases. In the following sections, I will describe in detail how anti-cancer drug like AZQ was designed to shut off Glioblastoma genes which cause brain cancer and using the same rational we will consider how each of the other two diseases

namely Cardiovascular Disease and Alzheimer could be treated by shutting off their genes to prolong human life: The order of the importance of these diseases are arranged based on the level of funding provided by NIH specifically by the NCI (National Cancer Institute).

Cancers

Cancer is the leading cause of death and has surpassed the death by cardiovascular diseases. Over 636,000 people died of cancer; 1.9 million new cases will be diagnosed this year including 78,000 Prostate Cancer, 40,000 Breast cancer, 16000 Lung and Bronchus Cancer and 15,000 Colon and Rectal Cancer.

The Rational for Designing Drugs to Treat Cancers

All three old age diseases that is Cancer, Cardiovascular Diseases and Alzheimer carry multiple mutated genes responsible for causing these diseases. In each of the above three diseases, it is the mutated genes that produce wrong protein which causes these diseases. If we design drugs to shut off mutated genes in one disease, we should be able to shut off bad genes in all three old age diseases to prolong human life. Although Coronary artery disease is a complex disease, researchers have found about 60 genomic variants that are present more frequently in people with coronary artery disease. Most of these variants are dispersed across the genome and do not cluster on one specific Chromosome. Drugs are designed to seek out the specific malignant gene which replicate faster producing acids. Aziridines and Carbamate moieties are sensitive to acid. Drugs carrying the Aziridines, and Carbamates are broken in acidic media generating Carbonium ions which attack DNA shutting off genes. Only the acid producing genes will be attacked no matter where they are located. It does not matter whether they are clustered or dispersed.

Professor WCJ Ross of London University was the first person who designed drugs for treating Cancers. He designed drugs to cross-link both strands of DNA that we inherit one strand from each parent. Cross-linking agents such as Nitrogen mustard are extremely toxic and were used as chemical weapon during the First World War. More toxic derivatives were developed during the Second World War. Using the Data for the toxic effect of Nitrogen Mustard generated during the First World War, Ross observed that Soldiers exposed to Nitrogen Mustard showed a sharp decline of White Blood Cells (WBC) from 5000 cell/CC to 500 cells/CC. Children suffering from Childhood Leukemia have a very high WBC count over 90,000 cells/CC. In sick children, most of the WBCs are premature, defected and unable to defend the body from microbial infections. Ross rationale was that cancer cells divide faster than the normal cell, by using Nitrogen Mustard to cross linking both strands of DNA, one can control and stop the abnormal WBC cell division in Leukemia patients. It was indeed found to be true. Professor Ross was the first person to synthesize a large number of derivatives of Nitrogen Mustard. By using an analog of Nitrogen Mustard, called Chlorambucil, he was successful in treating Childhood Leukemia. [8-11]. In America, two Physicians named Goodman and Gilman from the Yale University were the first to use Nitrogen Mustard to treat cancer in humans. Nitrogen Mustards and its analogs are highly toxic. Ross was a chemist, over the years, he synthesized several hundred derivatives of Nitrogen Mustard molecules to modify toxicity of Nitrogen Mustard.

Although analogs of Nitrogen Mustard are highly toxic, they are more toxic to cancer cells and more cancer cells are destroyed than the normal cells. Toxicity is measured as the Chemotherapeutic Index (CI) which is a ratio between toxicity to Cancer cells versus the toxicity to Normal cells. Higher CI means that the drugs are more toxic to cancer cell. Most cross-linking Nitrogen Mustard have a CI of 10 that is they are ten times more toxic to cancer cells. Some of the Nitrogen Mustard analogs Ross made over the years are useful for treating cancers such as Chlorambucil for treating childhood leukemia (which brought down the WBC level down to 5,000/CC). Children with Childhood Leukemia treated with Professor Ross Chlorambucil showed no sign of Leukemia even after 20 to 25 years later. Chlorambucil made Ross one of the leaders of the scientific world. He also made Melphalan and Myrophine for treating Pharyngeal Carcinomas. [12-14].

The Discovery of AZQ (US Patent 4,146,622) for Treating Brain Cancer

As I said above, at the London University, I worked for Professor Ross for about a decade. First, I was his graduate student then as his Postdoctoral Fellow and then as his Special Assistant. For almost ten years, I worked with Professor Ross making biological alkylating agents. Professor Ross was designing drugs to attack both strands of DNA simultaneously by cross-linking using Nitrogen Mustard analogs, which are extremely toxic. As a part of my doctoral thesis, I was assigned a different path. Instead of cross-linking DNA, I am to design drugs to attack only one strand of DNA. This class of drugs is called Aziridines. Over the years, I made over 100 Dinitrophenyl Aziridines derivatives. One of them is Dinitro benzamide (CB1954) which gives a CI of 70 highest ever recorded. CB1965 wipes out a solid tumor by attacking the DNA of Walker Carcinoma 256, a solid aggressive tumor in Rat. [15-17].

Nitrogen Mustards are highly toxic because they have neither specificity nor selectivity. They attack all dividing cells whether they are normal or abnormal. On the other hand, the analogs of Aziridines and Carbamates remain inactive in the basic and neutral media. They become activated only in the presence of Acidic media.

I used a simple rationale, the Aziridine attacks DNA in acidic medium, particularly the N-7 Guanine. The dye Dinitro benzamide has great affinity for Walker Tumor. The Aziridine dinitro benzamide (CB1954) stain the tumor. As the tumor grows, it uses Glucose as a source of energy. Glucose is broken down to Pyruvic Acid. It is the acid which attacks the Aziridine ring. The ring opens to generate a Carbonium ion which attacks the most negatively charged N-7 Guanine of DNA shutting off the Walker Carcinoma 256 gene in Rat. To continue my work, I was honored with the Institute of Cancer Research post-doctoral fellowship

award of the Royal Cancer Hospital of London University. To increase the toxicity of CB1954 to Walker Carcinoma, I made additional 20 analogs as a postdoctoral fellow. When I attached one more Carbonium generating moiety, the Carbamate moiety to the Aziridine Dinitrobenzene, the compound Aziridine Dinitro benzamide Carbamate was so toxic that its Therapeutic Index could not be measured. We stop the work at the London University for the safety concern.

To translate animal work to humans, I continued my work on the highly toxic Aziridine/Carbamate combination in America when I was offered the Fogarty International Fellowship Award to continue my work at the National Cancer Institute (NCI) of the National Institutes of Health (NIH). I brought the idea from London University of attacking one strand of DNA using not only Aziridine, but also Carbamate without using the same dye Dinitro benzamide.

My greatest challenge at NCI is to translate the animal work which I did in London University to humans. One day, I came across a paper which described that radio labeled Methylated Quinone cross the Blood Brain Barrier in mice. The X-ray photograph showed that the entire radioactivity was concentrated in the Mice's Brain. I immediately realized that Glioblastoma multiforme, the brain tumor in humans, is a solid aggressive tumor like Walker Carcinoma in Rats. I decided to use Quinone moiety as a carrier for Aziridine rings to attack Glioblastomas. By introducing an additional Carbamate moiety, I could increase its toxicity several folds. I planned to use this rational to translate animal work to human by introducing multiple Aziridine and Carbamate moieties to the Quinone to test against Glioblastomas in humans. Over the three-year period, I made 45 analogs of Quinone dicarbamate diaziridine. One of the analogs would not only stop tumor growth, but also it starts to shrink the tumor. (I named it AZQ). To increase human longevity, I could take care of at least one form of deadliest old age cancer that is Glioblastomas. Literature search showed that AZQ is extensively studied. [18-20].

As I said above, Glioblastomas, the brain cancers, is a solid and aggressive tumor and is caused by mutations on several chromosomal DNA. Mutations on DNA is the result of damaging DNA nucleotides by exposure to radiations, chemical and environmental pollution, viral infections or genetic inheritance. The other factors responsible for causing DNA mutations are due to the fast rate of replication of DNA. For example, the bacteria E-coli grows so rapidly that within 24 hours, a single cell on a petri dish forms an entire colony of millions when incubated on the Agar Gel overnight. Mistakes occur in DNA during rapidly replication such as Insertion of a piece of DNA, Deletion, Inversion, Multiple Copying, Homologous Recombination etc.

When an additional piece of nucleotide is attached to a DNA string, it is called Insertion, or a piece of DNA is removed from the DNA string; it is called Deletion or structural Inversion of DNA is responsible for mutations. Since the gene in a DNA codes for Proteins, Insertion and Deletion on DNA have catastrophic effects on protein synthesis. Glioblastomas represent such an example. In Glioblastomas, three major changes occur on Chromosomes (C-7, C-9 & C-10) and two minor changes occur on Chromosomes (C-1 & C-19). These mutations are involved for causing brain cancers in humans. In a normal human cell, Chromosome-7 which is made of 171 million nucleotide base pairs and it carries 1,378 genes. When Insertion occurs on Chromosome-7. Ninety-seven percent of Glioblastoma patients are affected by this mutation. On the other hand, a different mutation occurs on Chromosome-9 which is made of 145 million nucleotide base pairs and it carries 1,076 genes. A major Deletion of a piece of DNA occurs on Chromosome-9 which results in eighty- three percent patients who are affected by this mutation. A minor Deletion of DNA also occurs on Chromosome-10 which is made of 144 million base pairs and it carries 923 genes. Although it is a minor deletion of a piece of DNA and yet it contributes to ninety-one percent patients with Glioblastoma. To a lesser extent, small mutation occurs on Chromosome-1 (the largest Chromosome in our Genome). It is made of 263 million nucleotide base pairs and carries 2,610 genes) and Chromosome-19 (it is made of 67 million base pairs and carries 1,592 genes) is also implicated in some forms of Glioblastomas.

All known Glioblastomas causing genes are located on five different Chromosomes and carries a total of 9,579 genes. It appears impossible to treat Glioblastomas since we don't know which nucleotide on which gene and on which Chromosome is responsible for causing the disease. With the completion of 1,000 Human Genome Project, it becomes easier. By simply comparing the patient's Chromosomes with the one thousand genomes, letter by letter, word by word and sentence by sentence, we could identify the differences called the variants with precision and accuracy, the exact variants or mutations responsible for causing the disease. Once the diagnosis is confirmed, the next step is how to treat the disease.

With the Quinone ring, I could introduce different combinations of Aziridine rings and Carbamate moieties and could create havoc for Glioblastomas. My major concern was how toxic this compound would be to the human brain cells. Fortunately, brain cells do not divide, only cancer cells divide. To grow, cancer cells use Glucose as a source of energy. Glucose is broken down to produce Pyruvic Acid. It is the acid which activates the aziridine and carbamate moieties generating Carbonium ions attacking the mutated genes on Glioblastomas. Radiolabeled C-14 Aziridine will identify which genes on which Chromosomes is attacked by AZQ.

At the NCI Lab, I continued the work on developing anti-tumor agents which I left off at the London University. As I said above, Quinone has the ability to cross the Blood Brain Barrier. Using Quinone, I started attaching different combination of Aziridine and Carbamate moieties as a possible CNS active anti-tumor agent. NCI's Fogarty International Award lasts only three years. I did not have much time. I worked with utmost ferocity making AZQ and its 45 analogs (US Patent 4,146,622 & 4,233,215) for treating Glioblastomas and for which I was honored with the "2004 NIH Scientific Achievement Award" one of America's highest award in

medicine and I was also honored with the India's National Medal of Honor, "Vidya Ratna" a Gold Medal.

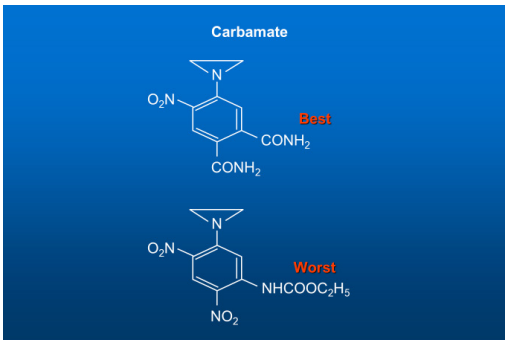
Exhibit # 1
2004 NIH Scientific Achievement Award
Presented to
Dr. Hameed Khan
By
Dr. Elias Zerhouni,
The Director of NIH
During the NIH/APAO Award Ceremony held on December 3, 2004.

Dr. Khan is the Discoverer of AZQ (US Patent 4,146,622), a Novel Experimental Drug Specifically Designed to shut off a Gene that causes Brain Cancer for which he receives a 17-year Royalty for his invention (License Number L-0I9-0I/0). To this date, more than 300 research papers have been published on AZQ. The award ceremony was broadcast live worldwide by the Voice of America (VOA). Dr. Khan is the first Indian to receive one of America's highest awards in Medicine.

Exhibit # 2
His Excellency, Dr. A.P.J. Abdul Kalam,
The President of India
Greeting
Dr. A. Hameed Khan,

Discoverer of anti-cancer AZQ, after receiving 2004, Vaidya Ratna,
The Gold Medal, One of India's Highest Awards in Medicine At The Rashtrapathi Bhavan (Presidential Palace), in Delhi, India, during a Reception held on April 2, 2004.

Exhibit # 3
Single Strand DNA Binding Aziridine and Carbamate



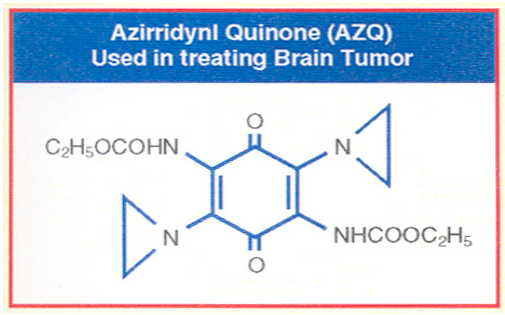


Exhibit # 4
Gold Medal for Dr. Khan

Dr. A. Hameed Khan, a Scientist at the National Institutes of Health (NIH) USA, an American Scientist of Indian Origin was awarded on April 2, 2004. Vaidya Ratna; The gold Medal,

one of India's Highest Awards in Medicine for his Discovery of AZQ (US Patent 4,146,622) which is now undergoing Clinical Trials for Treating Bran Cancer.

Cardiovascular Diseases

Coronary artery disease is a complex involving about 60 genomic variants. All variants are not clustered on any specific Chromosome. These variants are dispersed across the entire genome. Although all variants have not been sequenced, we can shut off only the mutated gene without knowing the sequence of all other genes. As I mentioned above in the Cancer Section, the mutated gene grows rapidly forming the tumor. As it grows, it uses Glucose as a source of energy which is broken down to produce Pyruvic Acid. In the presence of Acid, the analogs of Aziridine and Carbamate are activated to generate Carbonium ion which attack the tumor DNA shutting off their genes. While we may someday be able to sequence all 60 variants associated with the coronary artery disease, presently, we can single out and identify the mutated gene bound complex using radiolabeled Aziridine and Carbamate. The following example explain how some Arrhythmias causing genes could be identified and how drug could be designed to shut off these genes.

The term "QT" refers to the segment of an electrocardiogram which measures the duration of time for the heart to relax after a heartbeat. In long QT syndrome, the duration of time is abnormally prolonged and creates a vulnerability to dangerous arrhythmias. Ever since the syndrome was described in 1957, researchers have engaged in a genetic race to identify the genes associated with long QT syndrome, which currently includes 17 genes. Three genes, *KCNQ1*, *KCNH2* and *SCN5A,* had sufficient evidence to be implicated as "definitive" genetic causes for typical long QT syndrome. Four other genes had strong or definitive evidence supporting their role in causing atypical forms of long QT syndrome, presenting in the newborn symptoms associated with heart block, seizures, or delays in development. Once the mutated genes are identified, we could design drugs to shut off these genes as described in the Cancer Section.

Alzheimer

In 1906, the German Physician Scientist Dr. Alois Alzheimer identified the microscopic changes in the brain of a patient with the memory loss. He was the first Physician to identify the disease in a fifty-year old woman who suffered from Psychosis and who died within 4 years. Using special dyes, he stained the brain tissues which carried abnormal protein deposit around her brain which controlled brain function. He identified two kinds of legions of amyloid patches which he mistakenly thought was fatty patches and now turned out to be proteins. He observed a Patch of fatty deposit on the top of the brain cells called Plaques and the legions inside the nerve cells called Tangles. He accurately correlated the abnormal protein deposits around brain cells with the controlled of brain function. Recently, we discovered that the accumulation of beta Amyloid reduces the ability to communicate between neurons causing the slow decline in cognition.

Today, we know that the Age is the single most risk factor for developing Alzheimer. More than six million people suffer from Alzheimer and by the age 65 or older, the risk for developing Alzheimer is about 10 percent and by age 85 or older the risk factor is as high as 40 or 50 percent. As people grow old, they become senile. When he performed the autopsy of many senile persons, Dr. Alzheimer found the same Plaques and Tangles in many other samples. Early onset or late onset of Alzheimer resulted in the epidemic of Alzheimer. When comparing a normal brain with the Alzheimer brain, we find that the Alzheimer brain has shrunken and there is a concentration of Plaques and Tangles in neurons. In healthy brain cells, we see occasional Plaques and Tangles. It defines the disease; the Plaque and Tangles start building up as we grow old and over years and decades, the symptoms begin to develop. Symptoms include Memory loss and decrease ability of learning and recall. Early onset affects cognition which encompasses memory and other mental functions such as erosion of attention, thinking, reasoning, visual functions, spatial function, and Dementia with Memory loss and other cognitive functions resulting in mental impairment which affects to the degree interfering with the daily life.

Recent studies confirm that Alzheimer is an irreversible brain disorder which slowly destroys memory and thinking skills. The damage to the brain is not particularly associated to any specific gene, but the presence of the one form of the Apolipoprotein E (APOE) is a suspect gene whose presence does increase a patient's risk for developing Alzheimer. The early onset of Alzheimer is associated with three single gene mutations: First, the presence of an Amyloid Precursor Protein (APP) located on Chromosome-21; the presence of Presenilin 1 (PSEN1) on Chromosome-14 and the presence of Presenilin 2 (PSEN2) located on Chromosome-1. All three Chromosomes are very large and carry hundreds of genes. For example, Chromosome-1 is the largest Chromosome in the Genome. It is made of 163 million nucleotide bases carrying 2,610 genes. Chromosome-21 is made of 50 million nucleotide bases carrying 337 genes while Chromosome-14 is made of 109 million nucleotides bases carrying 1,173 genes.

A recent 7-million Utah population study identified two additional genes RAB10 located on Chromosome-2 (which is made of 155 million nucleotides bases and carry 1,798 genes) and SAR1A gene located on Chromosome-10 (which is made of 144 million nucleotide bases and carry 983 genes) associated with the formation of Plaques and Tangles. Mutations on these genes may be associated with the onset of Alzheimer.

Of all the genes on these Chromosomes, only five single-gene mutations are associated with the early onset of the Alzheimer, it is the greatest challenge to design drugs to attack only the mutated genes. As I said above in the Cancer Section, the good news is that the only mutated genes grow rapidly using Glucose as a source of energy. Glucose is broken down to produce Pyruvic Acid. It is the acid which activate the Aziridine and Carbamate moieties producing powerful Carbonium ion which attack N-7 Guanine of DNA and shut off only the mutated genes. Other genes are not

affected. Using C-14 radiolabeled Aziridines, we can identify the mutated gene which form the Aziridine/Protein Complex as described in the Cancer Section.

Rationale for Designing Drugs to treat Alzheimer

It is well known that using the TFT dye, which is (3,6-dimethyl-2-(4-dimethlaminophenyl)-benzothiazoline, could be used to stain the Plaques and Tangles of Alzheimer tissues. As I described above that there are two established ways to shut off a mutated gene. Either using Ross 'method by cross-linking the double stranded DNA using highly toxic Nitrogen Mustard which offers neither specificity nor selectivity. On the other hand, our method of shutting off a mutated gene by attacking a single stranded DNA using Aziridine. As we demonstrated in the Cancer section, Aziridine is activated in the presence of acidic media created by the rapidly growing abnormal cells. Using TFT dye as a carrier for the Aziridine and Carbamate moieties, we could design drugs to attack the mutated DNA to shut off genes which form Plaques and Tangles to prevent the progress of Alzheimer.

In the above Cancer section, I have described in detail how I had used Quinone as a carrier for Aziridine and Carbamate ions in designing AZQ to attack the brain tumor DNA to shut off genes for treating Brain Cancer. Similarly, the analogs of Benzothiazoline dyes could be used to carry Aziridine and Carbamate moieties to attack the Plaque and Tangle DNA and shut off genes responsible for causing Alzheimer.

What other cancers should we explore next?

Could I use the same rationale for treating Breast tumor?

Although BRCA1 gene located on Chromosome-17 (which is made of 92 million nucleotide bases carrying 1,394 genes) has been identified years ago, we wonder why it has been so difficult to design drugs on rational basis to treat Breast Cancer. By the time the Breast Cancer diagnosis is confirmed in a patient, the BRCA1 gene has accumulated more than three thousand mutations. Genotyping of the blood cells would also show the existence of many cells carrying mutated cells responsible for creating secondary deposits. It is also believed that by the time Breast Cancer is confirmed, metastatic cancer cells have already been spread from liver lung on its way to brain. Since all other organs including breast and liver could be removed and replaced by implant except brain, I thought that protecting brain is utmost important to save life. Once AZQ is developed to protect the brain, I could focus on the Breast and Prostate Cancers.

Now, I found that I could go even further by attaching more than four Aziridine and Carbamate moieties to both Male and Female Hormones. Radiolabeled studies showed that male hormone Testosterone has great affinity for female Breast, Ovary, and Fallopian tube cells. On the other hand, Estrogen, the female hormone, has great affinity for male prostate gland. By attaching multiple Aziridine rings and Carbamate ions to both Hormones, I could design novel drugs to attack the Breast and the Prostate cancer.

In a Breast tumor, within the start and stop codon, BRCA1 gene has captured over two hundred thousand nucleotide bases. The BRCA1 genes carries about three thousand mutations. These mutations are caused by exposure to radiations, chemical or environmental pollutants, viral infection or genetic inheritance. To attack the mutated nucleotides among the three thousand cells in BRCA1 gene, I could use male hormone, Testosterone, and bind multiple radio labeled Aziridine and Carbamate ions to attack BRCA1 mutations. By using MRI, I could show how many radio-labeled nucleotides were bound to which mutations. Out of seventeen positions available for substitutions on Testosterone. There are only three positions that is 1,3 and 17 positions are available for Aziridine and Carbamate ions on Testosterone ring system. Using Djerassi's method [20], I could activate position 9 and 10 by reacting with Bromo-acetamide which introduce a Bromo ion on position 10 which could be de-brominated by Collidine to introduce a 9,10 double bond which I could further brominate to produce 9,10 dibromo compound. These bromo ion could be substituted by Aziridines or Carbamate ions. I could increase or decrease the number of Aziridine and Carbamate ions to get the maximum benefit by further brominating position 15 and 16 to introduce additional Aziridine and Carbamate moieties.

Similarly, I could use the female hormone Estrogen and by attaching multiple Aziridine and Carbamate ions to attack Prostate tumor. Since there are seventeen positions available on Estrogen ring as well; again, I could increase or decrease the number of Aziridine and Carbamate ions to get the maximum benefit.

Ethical Issues

To succeed the Human Longevity Project, several attempts are described below to prolong human life. We need to make two rationale approaches: First, to identify rare allele in the Genome of Centenarians responsible for prolonging their lives. Once identified the allele, we need to conduct genetic engineering that is to cut, paste, copy and splice the allele into the Genome of volunteers to study its function. Second, to design drugs to shut off genes of old age diseases (as I described above) such as Cancers, Alzheimer and Cardiovascular Diseases to prolong life.

Next attempt would be to prevent the loss of Telomeres, the six-letter code (TTAGGG) that shorten our DNA and shorten our lifespan. During replication, each Chromosome loses about 30 Telomeres each year. If we prevent the loss of Telomeres by using the enzyme Telomerase Reverse Transcriptase (TRT), we could slow down the aging process. We have already demonstrated in the worm C. Elegance that we increased its lifespan several fold. Now, we could translate this work in human being; we could try by making a less virulent Flu Virus carrying TRT gene when injected to a volunteer who comes down with a mild Flu. When he recovers from the Flu, the TRT gene would have been inserted in the entire genome of every cell in his body. Suppose at each replication only 15 Telomeres are deleted instead of 30 Telomeres. This person is likely to live twice as long. Also suppose the sequencing of his genome would confirm that every cell of his body carries the TRT gene. Since the longevity treatment with the Flu virus is safe,

inexpensive and would be easily available to everyone, should we provide the treatment to every man, woman and child on the face of the Earth?

Our attempt to prolong life is related to the second approach that is to shut off the genes of the old age diseases raises several additional ethical and moral questions. When we succeed in shutting off genes of all three old age diseases that is Cancer, Cardiovascular disease and Alzheimer, most people will live longer and happier life; we are likely to increase human age span to about 100 years and beyond. What happens after we achieve that goal. If body mass is not retained, the Centenarians are most likely to be fragile and weak. They need the help of caretakers to perform the daily routine. By 2050, if we increase the age for about a hundred year of about a billion people, we need another billion caretakers. Will the society be happy with this achievement? The society is hardly likely to accept such a proposal. Such studies are likely to raise two serious ethical questions. First, we have to ask ourselves, do people have a right to live and second do we have a right to live as long as we wish, no matter how old, how weak or how sick we are? The answer to first question is, according to the UN charter, we all have the right to life, liberty and pursuit of happiness. It is the second question which is troublesome. Do people have a right to extent their lives as long as they wish? Most people are reluctant to answer this question either no or yes. Both answers have some support.

Those who said no, have a good reason. First, there are seven and a half billion people live on planet Earth and we are adding 90 million additional people each year. According to UN estimate, by 2050, the population of the world is likely to reach nine billion. Does our planet Earth have all resources to support such a population explosion? Can we provide food, fuel and medicine to all the people of the world? In poor countries millions are starving now. By extending life span, we will have serious problems such as lawlessness, riots and chaos in the over-crowded streets. The current population of Earth have polluted the water, polluted the air and polluted the land. Today, they wonder if the water they drink is safe, the food they eat is safe and the air they breathe is safe. If we continue to pollute the Planet with the current rate which is 110 million ton of pollutant, we release in the atmosphere each year; how much pollutants we would have accumulated in the atmosphere in ten years or in hundred years.

On the other hand, those who say yes; we should extend life have good reasons as well. We have no Plan B to save human life on some other Planet. We must look up to Heaven to find another home for humanity. To search for a suitable Planet for human life to survive, we need to train an army of Astronauts to travel into deep space with extended life span. They may have to travel for centuries to find a habitable exo-planet for humans. We do not want them to die on their way to find a new home for humanity. We must continue to search for the longevity gene.

As I said above, the British have completed the ten thousand Genome Project. The Europeans are working to complete a million Genome project and the Chinese are completing the three million Genome Project. Sooner or later, by comparing the genomes of Centenarians with the ordinary human genome, we could detect unusual and rare alleles responsible for longevity. The longevity gene could be spliced in an altered flu virus with reduced virulence. What if we succeed tomorrow in developing treatment of all three old age diseases to double or triple our lifespan? If we don't succeed tomorrow may be day after tomorrow. Say the treatment is safe, inexpensive and easily available to every man, woman and child on the face of the Earth. Should we splice the longevity gene in all the people of the world? Some of you could say that only Astronauts have a right to live longer because they have to travel into deep space for centuries and other do not have the same right to live longer. Who decide that person A will receive the longevity gene and will live and person B will not receive the gene and therefore will die? We need debate and discussion and come up with guidelines for our society. One person cannot provide answer to all these questions. All I want to do is to raise these questions in your mind. My aim will be fulfilled if I have made you think along these lines.

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