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The Rational Drug Design to Treat Cancers

Abdul Hameed Khan

Abstract

Professor Ross of London University, England, was using nitrogen mustard to treat cancers by attacking both strands of tumor DNA. As a part of my doctoral thesis, I am to design drugs using aziridine to attack only one strand of DNA. Over the years, I made over 100 dinitrophenyl aziridine derivatives. One of them is dinitrobenzamide (CB1954) which gives a CI of 70, highest toxicity to animal tumor ever recorded. CB1954 wipes out a solid aggressive tumor by attacking a single-strand DNA of Walker carcinoma 256, in rat. My greatest challenge at NCI in USA is to translate the animal work which I did in London University to humans. As radiolabeled methylated quinone crosses the blood-brain barrier in mice, I decided to use quinone moiety as a carrier for aziridine rings to attack glioblastomas, the brain tumor in humans. By attaching two aziridines and two carbamate moieties to quinone, I made AZQ (US Patent 4,146,622). By treating brain cancer with AZQ, we observed that glioblastoma tumor not only stops growing but also starts shrinking. Literature search showed that AZQ is extensively studied.

Keywords: drug design, tumor treatment, novel drugs for cancer treatment

1. Introduction

Rational drug design is absolutely essential for developing novel drugs for treating any disease, especially cancers. Our Institute, the NIH (National Institutes of Health is an agency of US Government) learned this fact by spending enormous amount of money over the years by testing known and unknown products obtained by synthesis or from plants and animals on a variety of testing tumor systems. The discovery of a handful of drugs by trial and errors at a cost of millions was considered a waste of time and money. In early days, we absorbed the losses because our Institute, located about 10 miles from Washington, DC, is the largest biomedical center in the world. Our annual budget is over 40 billion dollars per year. Over 26 institutes have about 3000 labs where about 21,000 scientists work in 50 buildings. My lab was in the National Cancer Institute (NCI), which is the largest among all institutes and it has a budget of over 5 billion dollars per year. Now, we became more cautious screening drugs. About 20% of our budget is spent in-house and the 80% of our budget is provided to research labs around the world by reviewing their research projects by expert panels called the study sections to approve funds to projects most rational and most likely to be accomplished.

2. Genomic medicine

This chapter describes the novel drug design based on the genetic makeup of a patient. My main focus is on two major areas, and they are diagnostic and novel drug design to treat these diseases. Today, we are treated with the same medicine for the same disease as if we all have the identical genomes. In fact, no two people look alike and no two genomes are alike. Our genome is made of six billion four hundred million nucleotides, and in almost every 1000 nucleotides, we find a variant and in the entire script, we find 3.4 million variants called the SNP (single-nucleotide polymorphism). Each of us has a unique genetic makeup and requires the development of a specific medicine to treat that disease. This concept is now known as the pharmacogenomic, and it provides a paradigm shift in drug design.

To design a genomic medicine, first we need to sequence the whole genome identifying specific region (genes) which codes for specific proteins. Second, we need to sequence as many genomes as possible (such efforts are undergoing as a Thousand Genome Project, a Million or a Three Million Genome Project) to compare their sequences to identify differences called variants. Then, we need to develop next generation of sequencers to sequence everyone's genome as cheaper and as faster as possible. Next, we need to identify the differences in the genetic scripts, and then, we need to separate bad or abnormal mutated variants responsible for causing diseases. Next, we need to identify rare variants as diagnostic tools responsible for causing rare diseases (young people diseases) such as Parkinson, Huntington, cystic fibrosis, muscular dystrophy, color blindness, sickle cell anemia, etc. called the monogenic or Mendelian diseases. Next, we need to identify the common genetic diseases (old people diseases) such as cancers, cardiovascular diseases, and Alzheimer. First, we generate sequence data and then by comparing we find a correlation between variants and diseases. We can construct a correlation map of all variants responsible for causing all genetic disorders. After diagnosing the diseases, the next most important step is to treat those diseases by novel drug design.

Our work below describes over a quarter of a century's effort by first designing drugs to shut off genes responsible for causing cancers in animals and then we further describe how we translated the animal work in humans. The following pages describe the development of genomic medicine based on the drug design and on the genetic makeup of a patient. I will cover three areas. First, I will provide historical background which describes the early development of medicines to treat diseases. Second, I will describe the rational drug design to treat abnormal mutated genes and the specific nucleotide identified by the human genome sequencing to develop new drugs to treat old diseases, and finally, I will discuss the ethical problems in an attempt to answer the consequences of prolonging human life on planetary resources and environment.

3. 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 50s by infectious diseases. Then came the science and technology revolution. In 1928, Alexander Fleming, while working on influenza virus, observed that a mold had developed accidentally on a staphylococcus culture plate. By killing the bacteria, the mold had created a bacteria-free circle around itself. He was so inspired by the presence of the bacterial free zone that he conducted further experiment and found that the mold culture produced a substance which prevented growth of staphylococci, even when diluted 800 times. He named the

active substance penicillin. The discovery of penicillin [1] was followed by a host of new antibiotics such as streptomycin, neomycin, kanamycin, paromomycin, apramycin, tobramycin, amikacin, netilmicin, and gentamicin and dozens of their derivatives which wipeout Gram-positive and Gram-negative bacteria. Misuse and overuse of antibiotics in agriculture resulted in the bacterial resistance. For example, farmers overuse the antibiotics in food-producing animals not only to kill the bacteria in cows, goat, and chicken farms but also use to promote growth in these animals exposing excessive amount of antibiotics residues to humans in their food. We developed a spectroscopic method [2] to detect their residue in PPT (parts per trillion) to provide safe food for consumption.

We conquered infectious diseases. We increased 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 clean up our environmental pollution but also to produce new food, new fuel, and new medicine to treat every disease known to mankind. We also succeeded in increasing human lifespan beyond 60 to 70 years.

Next, we read the entire book of human life. We read the total genetic information that makes 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 1000 Human Genome Project. We are able to compare the reference sequence of every gene with the 1000 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 an abnormal mutated gene, it is responsible for causing common diseases such as cancers, cardiovascular diseases, or Alzheimer. Soon, we will prepare a variant map of the entire genome to identify all 6000 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 such as Parkinson 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.

Next, I will attempt to answer an important question about how to design drugs to treat diseases to save human life by using the information available from the Human Genome Project. How many diseases we inherit from our parents? We identified good and bad genes in our genome. We wonder if bad mutations are written on our DNA. Is the secret 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 diseases by comparing the whole-genome sequence of the centenarians with the 1000 Human Genome Project completed by US and a Million Human Genome 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. We want to identify in the whole genome the specific genetic variations and the few nucleotides responsible for our health. As I said above, before the discovery of antibiotics, most people died in their 50s. Today, all infectious diseases are treated with antibiotics. Now, we must treat the old age common diseases such as cancers, cardiac diseases, and Alzheimer. To save human life from these dreadful diseases, we have to design drugs to shut off genes responsible for causing these old age diseases. Next, I will describe how I design drugs 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.

4. Genotype-phenotype correlations

Our genes are units of inheritance and carry instructions to make proteins, and when the proteins fold, they become reactive 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. We can prevent diseases at a very early stage of our lives. 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 advice for such families to have conception by in vitro fertilization after making sure that the fertilized egg is free from all abnormal mutations responsible for 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 of nucleotides, one strand is inherited from our mother and another from our father, running in opposite directions called the DNA (deoxyribonucleotide). According to Francis Crick's Central Dogma [3], 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 nucleotides 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 of nucleotides and the order in which they are arranged. Less than 2% 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 98% of our genome contains non-coding region used to be called the junk DNA which makes up to 60% 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 millions of 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 (instead of T nucleotide, we use U nucleotide because thiamin is converted to more water-soluble uracil), 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 Duchenne 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, we could compare the sequence of this gene with the Thousand Genome Project to identify abnormal mutation responsible for the disease and design drugs to shut off that gene. Sequencing 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 1144 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 1000 eggs and sperms of different 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, sequencing will identify the abnormal nucleotide. Now, we can design drug to bind to this nucleotide and shut off its function. We present in the “Cancers” section below a novel drug design. Using aziridines and carbamate how we design drugs to shut off these genes to restore health.

Although we are allowed to shut off and remove bad genes, 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 1000 generations. For this reason, germ line gene therapy is forbidden in all countries. At this time, we cannot answer a simple question. Are we to determine the quality of life of individuals who will not even be born before the century is over?

We cannot design novel drugs unless we find the abnormal mutations responsible for causing that disease. The reading of the total genetic information that makes 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 nature of our senses and the process of our aging? The scientific basis of our similarity and dissimilarity: similarity is that all living creatures from a tiny blade of grass to the mighty elephant including man, mouse, monkey, mosquitos, and microbes are all made of the same chemical building blocks, 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 3 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 nucleotide bases, half comes from our father and another half comes from our mother. Less than 2% of our genome contains genes which code for proteins. The other 98% 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 chromosome), 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 [4–8].

The following list provides the details composition of each chromosome including the number of nucleotides and the number of genes on each chromosome.

We found that chromosome-1 is the largest chromosome carrying 263 million A, T, G, and C nucleotide bases and has only 2610 genes. Chromosome-2 contains 255 million nucleotide bases and has only 1748 genes. Chromosome-3 contains 214 million nucleotide bases and carries 1381 genes. Chromosome-4 contains 203 million nucleotide bases and carries 1024 genes. Chromosome-5 contains 194 million nucleotide bases and carries 1190 genes. Chromosome-6 contains 183 million nucleotide bases and carries 1394 genes. Chromosome-7 contains 171 million nucleotide bases and carries 1378 genes. Chromosome-8 contains 155 million nucleotide bases and carries 927 genes. Chromosome-9 contains 145 million nucleotide bases and carries 1076 genes. Chromosome-10 contains 144 million nucleotide bases and carries 983 genes. Chromosome-11 contains 144 million nucleotide bases and carries 1692 genes. Chromosome-12 contains 143 million nucleotide bases and carries 1268 genes. Chromosome-13 contains 114 million nucleotide bases and carries 496 genes. Chromosome-14 contains 109 million nucleotide bases and carries 1173 genes. Chromosome-15 contains 106 million nucleotide bases and carries 906 genes. Chromosome-16 contains 98 million nucleotide bases and carries 1032 genes. Chromosome-17 contains 92 million nucleotide bases and carries 1394 genes. Chromosome-18 contains 85 million nucleotide bases and carries 400 genes. Chromosome-19 contains 67 million nucleotide bases and carries 1592 genes. Chromosome-20 contains 72 million nucleotide bases and carries 710 genes. Chromosome-21 contains 50 million nucleotide bases and carries 337 genes. Chromosome-22 contains 56 million nucleotides and carries 701 genes. Finally, the sex chromosome of all female called the (X) contains 164 million nucleotide bases and carries 1141 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. As I said above, 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 functional genes in our body make less than 50,000 proteins 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 2000 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, only in dogs, they still function to search for food. Since humans do not 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 and G-C nucleotides to numbers 0 and 1. 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 1 day at a cost of 1000 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 code for good proteins which keep us healthy and the bad genes produce bad proteins 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 based on differences of the genetic make of each individual.

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 cell 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 for generation after generation.

A sperm, the Y-chromosome, is made of a single string of 59 million nucleotide bases and carry 231 genes, while an egg, the X-chromosome, is made of a single string of 164 million nucleotide bases and carry 1144 genes. Neither 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 directions.

5. 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 checkup, 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, if you are a 40-year-old woman, your doctor prescribes the mammograms for the early signs of breast cancer, and if you are 50 years old, he prescribes the colonoscopy 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: suppose your physician finds that you are sick with high temperature and high blood pressure, he prescribes Plavix a medicine of standard treatment for lowering your blood pressure and temperature. It is a reactive medicine. You receive treatment after your illness is diagnosed. Plavix is a useful drug for treating high blood pressure, but it does not respond in 15% of the patients. In treating reactive medicine, we do not really know what is going on in the body of those patients until after sequencing their genome, and identifying the abnormal mutation in their genetic makeup and then designing drugs to treat those patients is the true genomic medicine.

Predictive medicine, on the other hand, 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. Spelling errors in our genome are the mutations responsible for causing diseases. The difference between the reactive medicine and the predictive medicine is whether you have the disease or 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 variants. Good variants are responsible for our evolution, and abnormal variants are responsible for causing diseases. Using restriction enzymes (molecular scissors) like EcoR1, we can cut, paste, and copy a gene (conduct genetic engineering) and 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 onset of a disease. The three-dimensional MR imaging could serve as a diagnostic technique. Once the diagnosis is confirmed, drug design must begin to treat the disease. 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 checkup compare the present MRI with the previous years' MRI to see any unusual microscopic changes predicting diseases. Once identified, the next logical step is to design drugs to shut off mutated genes to prevent diseases.

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 technique, which will diagnose diseases long before the symptoms appear.

To some degree, we have achieved the quantity control of the population by genome sequencing. Western countries are far ahead of the Eastern nations. The sequencing of the human genome provides rational approach to the quality control of the population. We have good news for those families who are suffering from severe heritable diseases generations after generations. Some of those rare allele diseases are mental diseases such as Parkinson, Huntington, schizophrenia, bipolar disorder, etc. often known as the Mendelian diseases. Those family members can still have children, but we recommend that they have conception by in vitro fertilization, that is, they conceived children outside their bodies, that is, in the test tube. The fertilized egg is harvested in the incubators for 3 days until it grows from a single cell to eight number cells. Without any ill effect, one cell could be removed and its genome is sequenced. Suppose the sequenced cell identify abnormal mutations when implanted will produce an incurably blind child or mentally retarded child. Is there a reason to bring this child into this intensely competitive world? Education is a very long process. To complete his education from age 5 to 25 years, when he completes his education and receives his Doctorate Degree, a child has to take several tests. If he fails one test, he is thrown out of the success train. No matter how painful it is on either religious or moral ground, we must ask ourselves a simple question. Does this fertilized ovum produce an acceptable member of the human society? If the answer is no, then we must throw out the defected ovum and use a new ovum. Out of eight, we have screened only a single cell. Should we sequence and select a cell for implantation which is free from all harmful mutations? Will society approve this reasonable request?

5.1 Drug design for rare allele diseases

These are the diseases of people of all ages. 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. As I said above, 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. Dozens 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 save 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*.

5.2 Drug design for common allele diseases

These are the diseases of old age people. Nowadays, people rarely die 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 cancers, cardiac diseases, and Alzheimer. These are genetic diseases and could be treated either by gene therapy (using CRISPER technology by replacing bad gene with the good gene using CRISPER-Cas9) or by drug therapy. There are about 3000 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, cancer, and cardiovascular diseases. Drug therapy could be used to develop novel treatments. Recently completed 1000 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 save human life. Genes code for proteins and a mutated gene codes for abnormal proteins resulting in these diseases.

6. Cancers

Cancer is the leading cause of death and has surpassed the death of 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, 16,000 lung and bronchus cancer, and 15,000 colon and rectal cancer. Once diagnosed by gene sequencing, the next step is to design drug to shut off those genes.

6.1 The rational drug design 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 code for wrong protein which

causes these diseases. If we design drugs to shut off mutated genes in one disease, using the same rationale, we should be able to shut off bad genes in all three old age diseases. 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 replicates faster producing acids. Aziridines and carbamate moieties are sensitive to acid. Drugs carrying the aziridines and carbamate moieties are broken down 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 across genome.

The supreme intellect for drug design is Ross, an Englishman, who is a Professor of Chemistry at the London University. Professor WCJ Ross is also the Head of Chemistry Department at the Royal Cancer Hospital, a postgraduate medical center of the London University. Ross 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 used during the First World War, Ross observed that soldiers exposed to nitrogen mustard showed a sharp decline of white blood cells (WBC) that is 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-link 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 [9], he was successful in treating childhood leukemia. 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 [10–14].

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 10 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 5000/CC). Childhood leukemia is the name of a disease occurs in children only. Chlorambucil made Ross one of the leaders of the scientific world. He also made melphalan and myrophine for treating pharyngeal carcinomas [15].

6.2 The discovery of AZQ (US Patent 4,146,622) for treating brain cancer

At the London University, I was trained as an organic chemist in the Laboratory of Professor WCJ Ross of the Royal Cancer Hospital, a postgraduate medical center of the London University. After working for about 10 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 common allele diseases have genetic origin. The rationale I used to synthesize anticancer drugs could be used to treat the other two old age diseases like Alzheimer and cardiovascular diseases. In the following sections, I will describe in detail how anticancer drug like AZQ was designed to shut off glioblastoma genes which cause brain cancer in humans. Using the same rationale, we will consider how each of the other two diseases, namely, cardiovascular disease and Alzheimer could be treated by shutting off their genes to save human life: The order of these diseases are arranged based on the level of funding provided by NIH specifically by the NCI (National Cancer Institute).

As I said above, 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 aziridine derivatives. One of them is dinitrobenzamide (CB1954) which gives a CI of 70, highest ever recorded. CB1954 wipes out a solid tumor by attacking the DNA of Walker carcinoma 256, a solid aggressive tumor in rat.

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 dinitrobenzamide has great affinity for Walker tumor [16–18]. The aziridine dinitrobenzamide (CB1954) stains 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 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 dinitrobenzamide carbamate was so toxic that its therapeutic index could not be measured. We stopped the work at the London University for the safety concern.

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 dinitrobenzamide [19–21].

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 radiolabeled methylated quinone cross the blood-brain barrier in mice. When injected in mice, the X-ray photograph showed that the entire radioactivity was concentrated in the mice's brain within 24 hours. 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 rationale to translate

animal work to human by introducing multiple aziridine and carbamate moieties to the quinone to test against glioblastomas in humans. Attaching two aziridines and two carbamate moieties to quinone, I made AZQ. By treating brain cancer with AZQ, we observed that glioblastoma tumor not only stop growing but also start shrinking. I could take care of at least one form of deadliest old age cancers, that is, glioblastomas. Literature search showed that AZQ is extensively studied.

As I said above, glioblastoma, the brain cancers, is a solid and aggressive tumor and is caused by mutations on several chromosomal DNA. Mutations on DNA are 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. Rapid replication is responsible for introducing genetic defects causing diseases.

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, and C-10) and two minor changes occur on chromosomes (C-1 and C-19). These mutations are responsible for causing brain cancers in humans. In a normal human cell, chromosome-7 which is made of 171 million nucleotide base pairs and carries 1378 genes. When insertion occurs on chromosome-7, 97% 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 1076 genes. A major deletion of a piece of DNA occurs on chromosome-9, which results in 83% 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, it contributes to 91% 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 2610 genes), and chromosome-19 (it is made of 67 million base pairs and carries 1592 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 9579 genes. It appears impossible to design drugs to treat glioblastomas since we do not know which nucleotide on which gene and on which chromosome is responsible for causing the disease. With the completion of 1000 Human Genome Project, it becomes easier. By simply comparing the patient's chromosomes with the 1000 genomes, letter by letter, word by word, and sentence by sentence, we could identify the difference 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.

Our rational drug design work began in the University of London, England, and completed in the Laboratory of the National Cancer Institute (NCI), of the National Institutes of Health (NIH), in Bethesda, Maryland, USA. Over this period, we conducted over 500 experiments which resulted in 200 novel drugs. They were all tested against the experimental animal tumors. Forty-five of them were considered

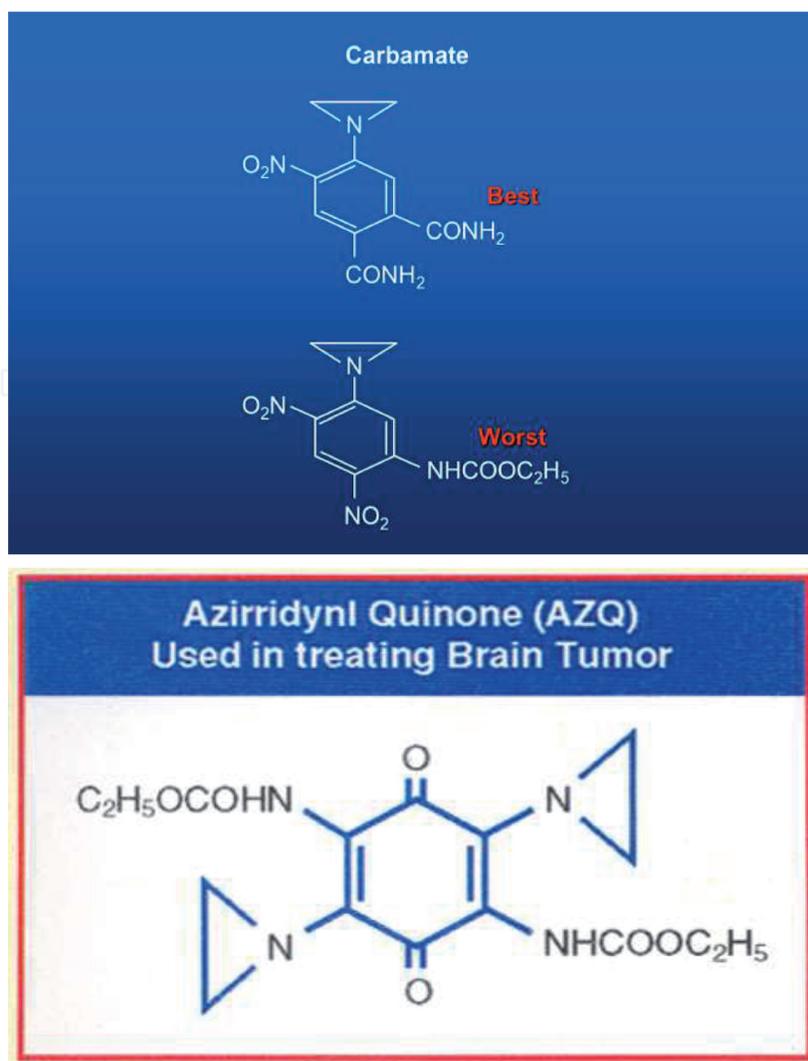
valuable enough to be patented by the US Government (US Patent 4,146,622). One of them is AZQ. Radiolabeled studies showed that AZQ has the ability to cross organ after organ, cross the blood-brain barrier, cross the nuclear membrane, and attack the nuclear DNA shutting off the gene. X-ray studies showed that the radioactivity is concentrated in the tumor region. Glioblastoma stop growing and start shrinking. For the discovery of AZQ, I was honored with the “2004 NIH Scientific Achievement Award,” one of America’s highest awards in Medicine and I was also honored with the India’s National Medal of Honor, “Vaidya Ratna,” a gold medal (see **Figures 1–4**).



Figure 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-019-01/0). 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.



Figure 2. His excellency, Dr. A.P.J. Abdul Kalam, the President of India greeting Dr. A. Hameed Khan, discoverer of anticancer AZQ, after receiving 2004, Vaidya Ratna, the gold medal, one of India’s highest awards in Medicine at the Rashtrapati Bhavan (Presidential Palace), in Delhi, India, during a reception held on 02 April 2004.



U.S. Patent 4,146,622

Figure 3. Single-strand DNA binding aziridine and carbamate.



Figure 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 brain cancer.

7. Cardiovascular diseases

Coronary artery disease is complex involving about 60 genomic variants (genes). 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 “Cancers” 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 genes 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 explains 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 [22]. 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 “Cancers” section.

8. 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 50-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 [23–26].

Today, we know that the age is the single most risk factor for developing Alzheimer. By age 65 or older, the risk for developing Alzheimer is about 10%, and by age 85 or older, the risk factor is as high as 40 or 50%. 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 in 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 2610 genes. Chromosome-21 is made of 50 million nucleotide bases carrying 337 genes, while chromosome-14 is made of 109 million nucleotide bases carrying 1173 genes.

A recent 7 million Utah population study identified two additional genes RAB10 located on chromosome-2 (which is made of 155 million nucleotide bases and carry 1798 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 "Cancers" 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 activates 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 "Cancers" section.

9. Rationale for designing drugs to treat Alzheimer

It is well known that using the TFT dye, which is 3,6-dimethyl-2-(4-dimethylaminophenyl)-benzothiazoline, could be used to stain the plaques and tangles of Alzheimer tissues. 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 "Cancers" 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.

10. What other cancers should we explore next?

Could I use the same rational drug design and introduce a novel method for treating breast tumor?

Although mutations on BRCA1 gene located on chromosome-17 (which is made of 92 million nucleotide bases carrying 1394 genes) have been identified years ago responsible for causing breast cancer, 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 has accumulated more than 3000 mutations. Genotyping of the blood 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 organ transplant 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.

Recent, radiolabeled studies showed that male hormone testosterone has great affinity for female organs like 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. Now, I found that I could go even further by attaching more than four aziridine and carbamate moieties to both male and female hormones.

In a breast tumor, within the start and stop codons, BRCA1 gene has captured over 200,000 nucleotide bases. The BRCA1 genes carry about 3000 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 3000 cells in BRCA1 gene, I could use male hormone, testosterone, and bind multiple radiolabeled aziridine and carbamate ions to attack BRCA1 mutations. By using three-dimensional MRI, I could show how many radiolabeled nucleotides were bound to which mutations. Out of 17 positions available for substitutions on testosterone ring system, there are only three positions, that is, 1, 3, and 17 available for substitution on testosterone ring system. Carl Djerassi [27] had demonstrated that we could activate positions 9 and 10 by reacting with bromoacetamide which introduces a bromo ion on position 10 which could be de-brominated by collidine to introduce a 9,10 double bond which we could further brominate to produce 9,10 dibromo compound. This bromo ion could be replaced by additional aziridine or carbamate ions. I could increase or decrease the number of aziridine and carbamate ions to get the maximum benefit by further brominating positions 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 17 positions also available on estrogen ring as well; again, I could increase or decrease the number of aziridine and carbamate ions to get the maximum benefit.

11. Ethical issues (the impact of science on society)

By 2050, novel drug design would have produced new class of medicine to treat all known 6000 genes. We would not only produce new treatment but also we would have new food, new fuel, and new medicine to treat every disease known to mankind to protect, preserve, and prolong human life beyond 100 years. This section discusses the impact of prolonging human life beyond 100 years.

Our attempt to prolong human life by shutting off the genes of the old age diseases raises several ethical and moral questions. We face the same population problem 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. It raises several questions. What happens after we achieve that goal of reaching 100 years? What would be the quality of our life? By exercises and good nutrition, if the 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 of about 100 years of about a billion people, we need another billion caretakers. Will the society be happy with this achievement? I doubt it. The society is hardly likely to accept such a proposal.

To cure diseases to prolong human life, several present and future attempts are described below.

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 approach is to design drugs to shut off genes of old age to prolong life.

Next attempt to increase human life 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 could increase 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 inserted in the entire genome of every cell in his body (we can confirm the insertion by sequencing). 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?

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, they argue that 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 9 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, we will have serious problems such as lawlessness, riots, and chaos in the streets. The current population of Earth has polluted the water, the air, and 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 that we release in the atmosphere each year, how much pollutants we would accumulate in the atmosphere in 10 years or in 100 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 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 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 treatment to prolong human life.

What if we succeed tomorrow in developing treatment of all three old age diseases to double or triple our lifespan? If we do not 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. Who decide that person A will receive the longevity treatment and will live and person B will not receive the same treatment 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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