ISSN: 3069-132X

Katalyst Publishers

Open Access

Journal of Current Trends in Clinical and Biomedical Research

Research Article

The Impact of sequencing Human Genome on the development of Precision Medicine like AZQ

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Received Date: 10 Dec, 2025
Accepted Date: 24 Dec, 2025
Published Date: 31 Dec, 2025

Abstract

We broke the genetic Code [1] and unlocked the secrets of life. Now, we are ready to manipulate life not only to clean up our environmental pollution, but also to provide new food, new fuel and new medicine to treat every disease known to mankind. This lecture attempts to explain how to design precision medicine to attack a single specific mutated gene in the presence of several mutated genes. For example, in our brain every nucleated neuron carries complete human genome. Some cells carry deleterious mutations causing diseases such as Epilepsy, Alzheimer, Tay sack, Huntington, Schizophrenia, Parkinson etc. It also carries mutated genes for Glioblastoma, brain cancer, it is a solid aggressive tumor of all the cancers, Gliobasatoma is the deadliest. Most patients die within 14 months of their diagnosis. One of the greatest challenges is to design drugs to shut off Glioblastoma gene in the presence of several mutated genes. Professor Ross of London University has demonstrated that War chemicals such as Nitrogen Mustard (which cross-link both strands of DNA) or its intermediate Aziridine, generate a single powerful Carbonium ion which attacks DNA shutting off a gene. Aziridine and Carbamates act as a substitute pro-drug. Both decompose in the presence of acid generating Carbonium ions which attack the N-7 Guanine of DNA. Once I learnt that Quinone crosses the blood-brain-barrier, I decided to attach both prodrug substituents Aziridine and Carbamate to the Quinone molecule, which gives 45 different combinations (all Patented US Patent 4,233,215) giving the AZQ. the most active drug against Glioblastoma. Only the Glioblastoma tumor grows. It uses Glucose as a source of energy. Glucose in the absence of Oxygen breaks down to produce Lactic Acid. It is the acid which activates the prog-drug moieties generating the most powerful primary Carbonium ions which attack tumor DNA shutting off the gene. No other mutated genes are attacked. AZQ is the best example of precision medicine.

Keywords: Genes, altered genes, Nucleotides, DNA, Genome, Mutations, Genetic Diversity, Genomic diseases, Inbreeding, Glioblastoma, AZQ

Introduction

I I.A Note to my readers:

The Impact of Sequencing Human Genomes is a series of lectures to be delivered to the scholars of the National Youth League Forum (NYLF) and the International Science Conferences. 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 am

reproducing here part of the lecture which was delivered at the International Science Conference that was PCS 6the Annual Global Cancer Conference held on November 15-16, 2019, in Athens, Greece.

II. Special Notes:

Below I describe the use of highly toxic lethal chemical weapons (Nitrogen Mustard) which were used during WWI and their more toxic analogs developed as more toxic weapons during WWII. I described the use of Nitrogen Mustard as anti-cancer agents in a semi-autographical way to accept the responsibility of its use. When we publish research papers, we share the glory with colleagues and use the pronoun "We" but only when we share the glory not the misery. In this article by adding the names of my coworkers, the animal handers, I will share only misery. The Safety Committee is interested to know who generated the highly lethal Chemical Waste, How much was it generated and how was it disposed. I accept the responsibility. The article below sounds semi-autobiographical, it is, because I am alone responsible for making these compounds of Nitrogen Mustard, Aziridines and Carbamate. To get a five-gram sample for animal screening, I must start with 80 grams of initial chemicals for a four-step synthesis. To avoid generating too much toxic chemical waste, instead of using one experiment with 80 grams, I conducted 80 experiments with one gram sample, isolating one crystal of the final product at a time. The tiny amount of waste generated at each experiment was burned and buried at a safe place according to safety committee rules.

III. Ancient References that can be Googled on your cell phone are removed.

Our next challenge is to read the entire book of life that is the human genome, the greatest human encyclopedia of humans on planet Earth. By 2003, we completed the human genome project. We found that the human genome is made of 46 chromosomes half from each parent. The 46 chromosomes carry 24, 000 genes which carry instructions to make different proteins. About 3,000 genes are mutated and responsible for causing 3,000 different diseases. Our next challenge is to sequence the circular piece of DNA the Mitochondrial DNA resides outside the nuclear DNA. Mitochondrial DNA is made of 16,600 nucleotide base pairs in length and carry 37 genes. Several hundred mitochondrial DNA exist in each cells which provides all the energy a living cell needs by breaking down the phosphate bonds. The mitochondrial DNA carries Adenosine triphosphate (ATP) which releases energy by breaking down the Phosphate bonds to give Adenosine di phosphate which is further broken down to Adenosine monophosphate. The enzyme phosphor kinase attaches the inorganic phosphate to reproduce ATP. Mutations of Mitochondrial DNA are responsible for causing mitochondrial diseases. Mutations are caused either by exposure to Radiations, chemical/ environmental pollution, viral infection or genetic inheritance. Because of rapid replications, mutations are also caused by DNA deletion, insertion or DNA rearrangement.

Precision medicine, sometimes known as "personalized medicine" is an innovative approach to tailoring disease prevention and treatment that considers differences in people's genes, environments, and lifestyles.

Although the term "precision medicine" is relatively new, the concept has been a part of healthcare for many years. For example, a person who needs a blood transfusion is not given blood from a randomly selected donor; instead, the donor's blood type is matched to the recipient to reduce the risk of complications.

The human book of life, the human genome, is written with four genetic letter called nucleotides and they are A (Adenine), T (Thiamine), G (Guanine) and C (Cytosine). During replication the less water-soluble T loses a methyl group with Hydroxyl group and more water-soluble U (Uridine). Our genome is made of two genome. our father genome and our mother genome. Our genome is made of six billion two hundred million nucleotide. We inherit Three billion and two million from our mother and another three billion two hundred nucleotides from our father. Sequencing means that we read our entire genome, that is we read all nucleotides letter by letter and the order in which they are arranged. Out of four nucleotides, three code for an amino acid called Codon and the four nucleotides give 64 different codons which code for all 20 amino acids. Hundreds of codon code for a protein. Hundreds of protein code for a polypeptide which join to make a tissue. Two hundred-twenty-two tissues make an organ and several organ makes a human being. Precision medicine, which tailors' healthcare to individual differences.

The following additional mental disorders are caused by genetic mutations: To design drugs to treat these horrendous diseases, first, we must isolate and identify the genes responsible for causing these diseases. This enormous task lies in front of future scientists (my students). Sequence the patient's genome and compare it with the Reference Sequence and you should be able to identify the deleterious gene.

Bipolar disorder

One of the most highly genetically inherited psychiatric disorders is bipolar disorder which may affect as much as 1-4% of the population: One of the most highly genetically inherited psychiatric disorders is bipolar disorder, which may affect as much as 1-4% of the population. Bipolar disorder is characterized by periods of depression followed by periods of abnormally elevated mood

Schizophrenia

Schizophrenia is thought to have up to 70-80% genetic heritability. Like bipolar disorder, having a first-degree relative with the disorder drastically increases the risk of developing schizophrenia later in life – though environmental factors are also incredibly important. However, separating whether this is due to genetic causes or shared environmental conditions is difficult. The cumulative effect of multiple inherited or de novo mutations/polymorphisms in combination with environmental triggers can increase the risk of developing

In summary, mental (psychiatric) disorders such as bipolar disorder, schizophrenia and ASD have strong genetic bases (mutations, polymorphisms and epigenetic changes) that can be directly inherited from an affected parent, or for de novo during development.

Whilst there are several key genes implicated in specific disorders, there are numerous pleiotropic genes that are implicated in all of these disorders rooted in deficits in single genes (e.g., DCC), and calcium channel genes (e.g., CACNA1C).

Thus, many of these disorders arise due to abnormal neurodevelopment which can either cause disorder from birth (ASD) or strongly predispose individuals to developing psychiatric conditions later in life especially in combination with additional environmental factors such as stress.

sSMI includes major depression, schizophrenia, bipolar disorder, obsessive compulsive disorder (OCD), panic disorder, post-traumatic stress (PTSD) and borderline personality disorder (VA). schizophrenia. Schizophrenia is a chronic mental health condition that affects a person's thoughts, feelings, and behaviors. It is characterized by a combination of symptoms that typically include:

Delusions: False beliefs that are not based on reality.

Hallucinations: Sensory experiences (e.g., hearing voices, seeing things) that are not real. Disorganized thinking and speech:

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that affects movement, balance, and other bodily functions.

Key Features:

Motor symptoms: Tremors, rigidity, bradykinesia (slowed movements), postural instability

Non-motor symptoms: Cognitive decline, sleep disturbances, depression, anxiety, gastrointestinal issues

Progression: Symptoms gradually worsen over time

Huntington's disease (HD)

HD is a progressive, inherited neurodegenerative disorder that affects the brain and causes a wide range of symptoms, including involuntary movements, cognitive decline, and behavioral changes.

Epilepsy is a neurological disorder characterized by recurrent, unprovoked seizures. Seizures are brief episodes of abnormal brain activity that can cause a variety of symptoms, including: Loss of consciousness, Convulsions, Staring spells, Confusion, and Sudden changes in mood or behavior. Epilepsy is typically diagnosed when a person experiences two or more seizures without an identifiable cause.

Schizophrenia is a chronic mental health condition that affects a person's thoughts, feelings, and behaviors. It is characterized by a combination of symptoms that typically include:

Disorganized thinking and speech: Difficulty organizing thoughts and communications:

The future of precision medicine will enable health care providers to tailor treatment and prevention strategies to people's unique characteristics, including their genome sequence,

Mental disorders (or mental illnesses) are conditions that affect your thinking, feeling, mood, and behavior. They may happen over a short period of time or come and go. Some can be chronic (long-lasting). They can affect your ability to relate to others and function each day.

While no single gene is solely responsible for a specific mental disorder, several genes and genetic variations have been identified as contributing to the risk of developing various mental illnesses. These genes often play a role in brain development, neurotransmitter function, and the body's response to stress. Environmental factors also interact with these genetic predispositions to influence the onset and severity of mental disorders.

Mental disorders are the result of both genetic and environmental factors. There is no single genetic switch that when flipping causes a mental disorder. Consequently, it is difficult for doctors to determine a person's risk of inheriting a mental disorder or passing on the disorder to their children.

Certain genes may increase your risk of developing a mental illness, and your life situation may trigger it. Environmental exposures before birth. Exposure to environmental stressors, inflammatory conditions, toxins, alcohol or drugs while in the womb can sometimes be linked to mental illness. Brain chemistry

Schizophrenia is not directly inherited from one parent (mother or father) in a simple Mendelian pattern. It's a complex condition influenced by a combination of genetic and environmental factors. While having a parent with schizophrenia increases the risk, it's not inevitable, and many individuals with schizophrenia have no family history of the

In a study conducted with a large sample, the prevalence of disease was found to be higher in children of fathers with bipolar disorder than in the children of mothers with bipolar disorder. These results lead us to think that bipolar disorder may be a paternal disease.

Which mental illness is the most genetic?

Schizophrenia. Schizophrenia is thought to have up to 70-80% genetic heritability. Like bipolar disorder, having a first-degree relative with the disorder drastically increases the risk of developing schizophrenia later in life – though environmental factors are also incredibly important.

Many people also experience stigma, discrimination and violations of human rights due to:

Anxiety Disorders; Depression; Bipolar Disorder.

Post-Traumatic Stress Disorder (PTSD) Schizophrenia. Eating Disorders. ...

Disruptive behavior and dissocial disorders. Neurodevelopmental disorders.

Several major mental disorders have a significant genetic component and are known to run in families. These include autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, major depressive disorder, and schizophrenia. Research indicates that these disorders share some common genetic risk factors, suggesting a degree of shared biology.

As I said above, Glioblastomas, brain cancer, is a solid and aggressive tumor and is caused by mutations on several Chromosomal DNA. Mutations in Glioblastoma DNA are also the result of damaging DNA nucleotides by exposure to radiation, chemical and environmental pollution, viral infections or genetic inheritance.

All known Glioblastomas causing genes are located on five different Chromosomes and carry a total of 9,579 genes. It appears impossible to design drugs to attack all mutated genes 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 Reference Sequence, the exact variants or mutations responsible for causing the disease could be identified. Our next challenge is to identify in Glioblastoma which mutated nucleotides on which gene of which chromosome is attacked by AZQ. Radiolabeled AZQ provided the answer. 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 responsible 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. Once the diagnosis is confirmed, the next step is how to treat the disease

The Human Genome: The greatest Catalog of Human Genes on planet Earth

Reference Sequence:

We deciphered all 46 chromosomes, 23 from each parent. The 46 chromosomes present in each cell of our body are the greatest library of the Human Book of Life on planet Earth. The Human Genome Project has identified the following genes on each chromosome:

We found that the chromosome-1 is the largest chromosome carrying 263 million A, T, G and C nucleotide 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. The chromosome-22 contains 56 million nucleotide bases and carries 701 genes. Finally, the sex chromosome of all females called the chromosome-X contains 164 million nucleotide bases and carries 1,141 genes. The male sperm called chromosome-Y contains 59 million nucleotide bases and carries 255 genes.

Our genome is made of 46 books of life called Chromosomes. Chromosomes are written in millions of nucleotides base pairs. They always come in pairs such as A-T and G-C. Chromose-1 is the largest chromosome. It is made of 263 million bases. If you stretch Chromosomes-1, it is made of A-T and G-C. bases. It does not make sense. If you carefully examine, you find that some three letters code appears such as AUG which codes for an amino acid called Codon (AUG is a start codon which codes for amino acid Methionine). AUG is the start codon of a gene, which is a unit of inheritance, after several codons, the stop codon appears. The stop codons are UAG, UGG, UGA. The codons trapped between start and stop codons are a series of codons which code for Proteins. It is called a gene, it is like. A book chapter, which is a unit of inheritance. Chromosome-1 carries 2610 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. There are 16,000 good genes, 6,000 defected or mutated genes and 2,000 Pseudogenes. A gene codes for a protein, not all 24,000 genes code for proteins. It is estimated that less than 19,000 genes are 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, and hundreds of tissues interact to giving an organ, and several organs interact to make a human. [2.,3., 4., 5., 6.,]

Our next step is to isolate proteins from the good genes and design drugs to shut off bad genes. We can isolate and manipulate a single gene from human genome. We can insert a single gene in the fertilized egg of an experimental animal in such a way that the new gene is turned on in the host cell producing a new protein. Using the restriction enzyme, (like EcoR1 which acts like molecular scissors), we cut down the chromosomes to pieces at specific sites. We separate and isolate genes by gel electrophoresis. We are preparing a restriction site map. Each gene is confirmed by comparing it with the Reference Sequence. A Molecular Vehicle, Vector (such as disabled Viruses, Bacteria, or Plasmids), is created that will carry the gene into the nucleus of the cell where it permanently integrates into the genome of the host cell creating a trans-gene. As the cell begins to grow and divide, it makes copies of the trans-gene.

For example, Insulin isolated from a gene located in Pancreas was harvested in large scale bacteria. It is now used to treat 300 million diabetics around the world. Similar method could be used to make proteins from all 16,000 good genes of our genome.

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

Our Genome provides the genetic road map of all our genes, past, present and future. For example, it can tell us how many good or bad genes we inherit from our parents and how many of those gene we are going to pass on to our children. If a family has too many bad genes, and have a family history of serious illnesses, they can break off the information flow either by stop having children or stop donating mutated eggs and sperms.

We can scan the whole genome (Reference Sequence) for its response to a given situation. When we look at a normal cell and compare it with an abnormal cell, we see the differences. Or when we compare their gene expression looking for specific proteins, from specific genes and for a specific nucleotide sequence, we can identify a specific mutation responsible for the disease.

In the olden days, before sequencing human genome, when a patient visits a physician for some unknown ailment, the Physician would order several tests and would say to his patient, I do not know what is wrong with you, but I will see if any of these tests show if my guess is right and if he is wrong, he will recommend few more tests to see if he could identify the illness. The guesswork and the trial-and-error days are over.

Now, after sequencing the human genome, the physician would say to his patient, "I do not know what is wrong with you, but I know where to find it. It is written in your Genome." Let us sequence your genome and compare it with the Reference Sequence. He would order the sequence of patient's genome. It would be easy for a Physician to scan the patient entire genome and compare against the Reference Sequence to identify the mutations responsible for causing the disease. He will refer the patient to a biotechnology Lab. The Lab Technician will take a small blood sample from the patient, separate his WBC, extract DNA, sequence his Genome and compare with the Reference Sequence letter by letter, word by word by word and sentence by sentence and send the result to the Physician who can easily identify the mutations responsible for causing the disease. The result will provide the best diagnostic method to identify a disease.

Our Genome is not just a diagnostic road map of our genes; it tells us to clone the good genes and shut off the bad genes. Using good genes, it also tells us to make its large-scale protein for worldwide use such as Insulin and Human growth hormone. On the other hand, identifying the bad genes and tells us to design novel drugs to shut off bad genes responsible for causing serious diseases. We have already demonstrated that using genetic engineering techniques, we can cut, paste, copy, and sequence a good gene for industrial scale preparation as I said above such as Insulin to treat 300 million diabetic around the world.

Genome sequencing of bad genes starts a new era of Genomic Medicine which is based on the development of new drugs for treating a disease based on the genetic make-up of the individuals.

The next step would be to design drugs to shut off the mutated genes. Gene Therapy will work if the disease is caused by a single gene mutation. Drug Therapy will work if multiple genes are responsible for causing diseases such as Cancers, Cardiovascular diseases, and Alzheimer.

The advantages of Sequencing Human Genome:

The knowledge gained by sequencing human genome has summarized the past 150 years of genetic science. We have taken away the power from Mother Nature to alter billions of years of our evolutionary past. We now have all the tools we need to alter the genetic make-up of our species. Genetic Revolution has taught us that Darwinian evolution can be hastened by the rules of genetic engineering. By using genetic tool kits, we can cut, past, copy and sequence a gene in days not in eons. The development of new tools like CRISPER-Cas 9 is making it possible to edit the genes of all species including our own with far greater precision, accuracy, speed, flexibility, and affordability than ever before. Now, we control our own destiny. We ignore the scientific facts at our own peril.

One of the advantages of sequencing the personal genome is that after seeing our own sequence most of us will conceive of our offspring in the Lab rather than in our bed. What they see in their personal genome is the three and a half billion years of random mutations whose ancestors have continuously outcompeted their competitor in a never-ending cage match of survival. From this point onward, no one will take an unnecessary risk. Our offspring will not carry random mutations. It will be designed. From this point onward, our selection will not be natural. It will be self-directed. The current version of our Homo Sapiens species will never be evolutionary endpoint but always be a stop along the way in our continuous evolutionary journey. During the last few hundred years, we moved from Agricultural Age to Industrial Age and then from Atomic Age to the present Information Age. Now we are entering the Space Age trying to find out how to survive on exo-planets.

The best advice for those couples who have a family history of long-term illnesses to compare their personal sequence with the Reference Sequence. In the entire human genome, we find five thousand mutations responsible for causing five thousand diseases. Each of us carries a single copy of at least five to six deleterious mutations; we are carriers, but if we marry someone who is also carrying the other copy, we are most likely to have a sick child. In the lab, before conception,

we could sequence and discard a defected embryo to prevent the high cost of raising a sick child. The defective embryo can always be replaced by an embryo free from all mutations.

Some parents may consider the possibility of not just selecting the best embryo for in vitro fertilization but also to introduce superior traits to genetically alter the future of their children Although in vitro fertilization is encouraged to prevent the introduction of mutated genes in the gene pool, but introduction of gene enhancing traits is not permitted at this time. The following studies are forbidden: For example, a combination of genes which impart long life, high athletic or singing ability, or to make them smarter and superior to the other children, or to the introduction of new genes which make them resistant to many infectious diseases, or to introduce genetic traits associated with genius, or animal like extra-sensory perception, or to synthesize new traits, not yet known in humans, but made from the same nucleotide sequence which give rise to great diversity of life,

Prolonging human life: (Such studies are not funded currently). We need to sequence the Genomes of Centenarian who live beyond hundred years. By comparing it with the Reference Sequence, we should be able to identify the rare allele which prolong their lifespan. 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.

The Human Genome Project showed that our Aging is a combustion process. The tail end of each chromosome carries a set of a six-letter code called Telomer. Aging is related to the loss of Telomeres, the six-letter code (TTAGGG) that shorten the length our DNA also shorten our lifespan. During replication, each Chromosome loses about 30 Telomeres each year. If we slow down the loss of Telomeres by using the enzyme Telomerase Reverse Transcriptase (TRT), we could slow down the aging process. We have already demonstrated in worm C. Elegance that by using TRT genes, we have increased its lifespan by several folds. Now, we could translate this work first in mice then in human embryo; we could try by making a Vector, a virus, carrying TRT gene when infected the embryo and harvested to eight-cell and sequence to confirm the presence of the trans gene. The TRT gene would have been inserted in the entire genome of every cell of the growing embryo. By sequencing a single cell to confirm that the TRT transgene is spliced, we could implant TRT gene carrying embryo in the mice womb. If this transgenic experiment in mice is reproducible and verifiable, we could try in human embryo. Suppose this experiment conducted in humans is successful and suppose the sequence shows that at each replication only 15 Telomeres are lost instead of 30 Telomeres. Since the longevity treatment with the TRT transgenic virus is safe, inexpensive and would be easily available to humans. Should we provide the treatment to every man, woman, and child on the face of the Earth or make it available to long distance space travelers only?

To control early symptoms of a disease, frequent genome sequencing will help us identify a single gene mutation that will begin to grasp more complex genetic patterns that could lead to polygenic or multigenic conditions such as coronary heart diseases, cancers, and Alzheimer. Early detection will help us control their expansion.

Some genes are activated at the later part of our life causing serious illnesses. If there is a family history of such diseases, frequent sequencing becomes more important for early detection.

With development of the genetic toolkit, we can perform genetic engineering. We can separate good and bad genes. We can cut a good gene (using restriction enzyme such as EcoR1), paste a gene (using enzyme DNA ligase) and copy a gene or move the gene from species to species. As I said above, we can harvest good genes to produce large scale protein such as Insulins to treat diabetics or design drugs to shut of bad genes to treat diseases cancers.

Human body carries two genomes besides Human Genome; there is also a microbial genome captured millions of years ago called the Mitochondrial genome. Mitochondria live in human cytoplasm in a symbiotic relationship. It provides energy to host cells by breaking down phosphate bond of ATP (Adenosine Triphosphate) to ADP (Adenosine Diphosphate) to AMP (Adenosine Monophosphate). In the presence of enzyme Phosphokinase and Phosphate ions, AMP is converted back to ATP. For providing energy, in return, Mitochondria get free food, shelter and protection from the host. During conception, when mother's egg is fertilized by father's sperm, the tail of the sperm is dropped off, and father's Mitochondria are lost. We inherit only mother's Mitochondria. Any mutations in the Mitochondrial genome could cause sever diseases in infants. During vitro fertilization, if mutation is discovered in Mitochondria, it can either be discarded or could use a healthy Mitochondria carrying embryo to prevent the transmission of the disease.

Genomic Medicine:

Once we sequenced the genome, we thought that we could compare the entire genome of a healthy person with the genome of a sick person and easily identify mutated nucleotides responsible for causing diseases. We called GWAS: Genome Wide Association Studies. It is not as simple as we thought. We found that while some people having the mutated nucleotide come down with the disease, others with the same mutation do not show any signs and symptoms. We have no idea if other genes are protecting them. In some cases, we found the presence of a single copy of the mutated gene responsible for causing the disease called dominant gene while in other cases both copies of the mutated genes, called the recessive genes, do not cause any disease. The only way to solve this problem is to have as many genomes sequenced as possible and compare them using computers to identify the mutated nucleotides responsible for causing the disease with precision and accuracy. To pinpoint a specific gene responsible for causing a disease, we need to compare the genome of a healthy person with the genomes of hundreds and thousands of genomes of sick persons. The cost of sequencing is high, but the next generation of sequencers (Nanopore sequencer) could bring the cost of sequencing down to $100 per genome, it would be less expensive to sequence the egg and sperm to identify specific inheritable diseases in the family. To develop the next generation of DNA sequencers, my institute, NIH, provided enormous funds to Dr. Leroy Hood and his group. They accomplished miracle. The next generation of DNA sequencers use Nanopore technology that electrically pushes DNA fragments through tiny pores of proteins to read their content at the fastest speed. The faster we read the genome, the cheaper sequencing becomes. Presently, we could sequence

the entire genome in one day at a cost of $700. Further improvement could bring the cost down to $100 per genome.

Many nations are providing large sums of money to sequence as many genomes of their population as possible. For example, United Kingdom launched a 1000-Genome Project. My own institute, NIH, in America launched a ten-years project at a cost of one and a half billion dollars to sequence a million genomes. The Chinese government is launching the most ambitious project; they committed $9 billion to sequence millions of genomes. Eventually, we will have to sequence the genome of every man, woman and child on Earth and use this data as a part of the medical record.

Now, we have digitized the entire Human Genome, that is we converted the analog language of biology that is from A-T to G-C nucleotides bases to digital language of computer that is Zero and One. Once the genome is digitized, it could be uploaded on the internet and could be moved around the world with the speed of light. Once the genomes move to the distant part of the world with the speed of light, the recipient countries will have converters to convert back from the digital language of computers to analog language of biology. The great advantage of this conversions is that if a new deadly virus appears in one part of the world, its genome would be sequenced and sent to distant labs with the speed of light. For example, the recently identified Black Fungus in India could be sequenced and send it to Labs around the world. Identifying lethal genes on its chromosome, we could prepare its vaccine which would be readily prepared on large scale and within days it could be made available to everyone around the world.

Replication is a rapid process. It also occurs in germ cells. Mistakes also occur in genetic cells like eggs and sperms during replication. In his lifetime, a man produces enough sperms to populate the entire world. Most sperms are damaged and broken and unacceptable for breeding purposes. A sperm carries a single string of 59 million AT-GC nucleotides base pairs which carry 355 genes. On the other hand, a woman produces a single mature egg each month. The egg carries 164 million AT-GC nucleotides and 1,144 genes. Of course, T (Thiamine: the more fat-soluble methyl group in DNA is replaced by a water-soluble Hydroxyl group in RNA) in DNA, T is replaced by U (Uracil) in RNA. Because a Woman produces one matured egg per month, she has a right to make her own reproductive decision. The choice to reproduce or not to reproduce; with whom to reproduce; and how many times to reproduce. In a pregnant mother so, many genes are turned on to provide growth hormones and nourishment to the fetus. Once the baby is born, those genes are not turned off immediately. Her body faces havoc produced by hormones. Soon after the baby is born, she is euphoric due to the production of a high level of Oxytocin, a kind of opioid. Once Oxytocin is depleted, she undergoes severe depression. She sees herself as fat, ugly, sick and no good. This is the worst time of her life. Some women suffer quietly; others behave violently.

By examining and comparing the sequences of thousands of abnormal and normal genomes of egg and sperms, we can identify all mutated genes in a genome. Each of us carries a single copy of half a dozen mutated genes. We are a carrier of one copy of the bad gene, if we marry closely related person who is bringing the other copy of the same mutated gene; the fetus is affected. Related couples in which both parents are the carriers of the same mutated gene; they are most likely to have children who inherit both recessive copies of the same genes. Such couples are most likely to have a baby which comes down with horrendous genetic diseases, and they are most likely to terminate the pregnancy. Although it is a painful decision, it is better than watching their children suffer and die of a terrible disease.

If the fetus carries both bad copies, it will be severely sick. Let me explain with an example how this work will help parents to decide to have a baby even before conception or during pregnancy. A newlywed couple could either conceive a baby either in the bedroom or in the test tubes. If there is a family history of a disease, it is advisable to have vitro fertilization. The couple give a sample of eggs and sperms for genetic analysis before conception. Detection kits for several hundred genes are already being developed. The test result may show that the sperm is carrying a genetic defect on Y-chromosome that will make the baby a blind color or give him MS (muscular dystrophy). Doctors will inform the parents whether the child will be incurably blind, or carry a gene for defected heart, kidney, or liver. During ancient times when Eugenic was at its peak, the authority made the decision about the fate of the fetus. These days, Parents make the decision whether to bring this child into this world. How many parents would love to have a blind or permanently sick child in their families? Not many. We must run the census among our people to get the results. It seems reasonable to assume that most parents will not be able to care for that fetus. We may not be able to correct that defects tomorrow, but day after tomorrow may be or in some distant future. We will be able to correct that defect at an enormous cost. Is there any reason for poor parents to keep that fetus alive and grow to full term at an enormous medical expanse? I am sure some rich parents will love to have children at all costs. Such children in rich families will not be burdened on society or on our health care system. Since completing the Human Genome Project, out of six thousand mutated genes, we have already developed over 1,500 tests to identify mutated genes, we can provide in vitro fertilization (IVF) of fertilized egg free from all genetic defects. Instead of having children in the bedroom, couples will be able to select out the very healthy eggs and sperms and fertilized them in the test tube and implant them in the mothers. This way we can have the quality control of the babies that we choose to bring into this world. The quality control of the population could be accomplished by in vitro fertilization. About 25,000 Mendelian diseases (single gene defects) have been identified and approximately ten thousand diseases are confirmed to specific genes. Developing novel drugs to treat those diseases is expensive and time consuming.

Different overpopulated countries are practicing different methods to stabilize the world population. Let us see if we want to adapt to any of those methods. I doubt it if you would accept them, but I will explain to you anyway. On one extreme, we have China where government controls population (now they permit three children per couple) and on the other extreme is India where nobody does anything to stabilize the over population. You can have as many children in India as you want whether you could afford them or not.

Most of the people live in thousands of cities across the nation. How do many villagers understand the difference between "Family Planning" and "Population Control?" China practices population control. Now, they have relaxed by the rules. For almost a decade and a half, the Chinese government has mandated the insertion of Intra-Uterine Devices (IUD) for

all those mothers who have one child. Mothers are forced to undergo sterilization after two children. The third child is aborted without the consent of mothers. (now they permit a third child). China has the largest population in the world. India is number two and most likely to be number one soon. China does not have a democratic system of government. A handful of strong men rules the country. They have adapted an undemocratic system to control over population. In Western countries China's policy on newborn is considered Eugenic and repugnant and for that reason most Western countries refused to send their delegates to attend a conference on population control in China over the years.

In South America, Mexico follows Chinese policy. Mexican women will receive an IUD without their consent or knowledge after the third child. In Peru, a mother gets a fifty-pound free food if she agrees to Tubal Ligation which could be removed later if a mother decides to have children. The government is also putting heat on doctors. If they want to practice medicine in Peru, each doctor must provide Tubal Ligation to six women per month or loose privilege to practice medicine. If sequencing confirms an abnormal fetus, RU486, is one of the cheapest and safest agents to terminate a pregnancy. Once the diagnostic tests confirm the location of mutated genes for either monogenic or poly genic diseases such as cancers, cardiac diseases, or Alzheimer; we could design drugs to shut off those genes. The greatest challenge is either to replace a mutated gene by gene therapy or to shut off genes by drug therapy.

On April 3, 2003, several groups simultaneously sequenced the entire Human Genome and confirmed that less than two percent of the Genome codes for proteins the rest is the non-coding regions which contain switches to turn the genes on or off, pieces of DNA which act as promoters and enhancers of the genes. Using restriction enzymes, we can cut, paste, and copy genetic letters in the non-coding region which could serve as markers, but a slight change in the coding region of the genome called mutations could make a normal cell abnormal or cancerous. By sequencing human genome, and comparing it with genomes of illnesses, we conclude that:

Our search for unknown diseases has come to a closure:

There are two most powerful implications of the human Genome Sequencing. One of them is that we have come to closure. What it means is that we have the catalog of all genes in the Human Genome, we can search the entire genome and locate the desired gene. we will not wonder in the wilderness anymore. Everything there is to know about human health and traits are written on these genes in nucleotide sequences. Our Genomes provides the catalog of all genes.

The second implication is that we can scan the entire genome against the suspect region of the genome to identify the mutation responsible for causing the disease. Using the recently completed 1000-genome project, we can scan the suspect region a thousand time to identify the disease-causing nucleotide with precision and accuracy. Once the nucleotide is identified, it will point to the codon which codes for the wrong amino acid. The mutated codon will point to the gene which codes for wrong protein responsible for causing the disease. The next step is to shut off that gene either by gene therapy or drug therapy.

Gene Therapy:

The first step is to cut the human genome with specific enzymes (prepare a Restriction Site Map) at the specific sites using restriction enzymes (molecular scissors such as EcoR1) first accomplished by El Salvador Luria, Max Delbruck, and Hamilton Smith. The fragment of human DNA (a single gene) if not protected will be destroyed by antibody. A naked gene is a piece of DNA (which has a start codon AUG and after a few thousand nucleotide (codons) end at one of the three stop codons UAG, UGA or UGG if not protected by recombinant technology (making a hybrid) that is by recombining with the DNA of Virus, or Plasmids, or Chloroplasts (for plants) which serves as Vectors. If not protected it will be destroyed by enzymes. One can store the fragments or genes in the Vectors once the human DNA fragment is stabilized in Vectors by recombinant technology; we can not only purify this fragment (genes), but also, we can make millions of copies (clone) of this fragment of DNA by transferring into the host cells such as Bacteria, mammalian cells or Yeast cell which autonomously replicates to produce library of genes. Each Library contains millions of copies of identical genes that produce the same protein. Before the genetic revolution, Insulin is extracted from pancreas of the slaughtered animals which is used to treat old diseases such as diabetes; a tiny fragment of impurity could set anaphylactic shock and kill the patients. Now, large scale highly pure human Insulin produced by Genetic Engineering firm named Genentech is used to treat 300 million diabetic patients worldwide without the loss of a single life. Other products of Genomic Medicine such as Growth hormones and hormone proteins to treat Hemophilia by factor VIII protein are being developed as genomic medicines by recombinant technology. Attempts are being made to design drugs to attack cancer cells on all three levels that is DNA, RNA and Protein. Herceptin, a novel class of drug, has been successful in attacking protein. Craig Milo has designed double stranded RNA to shut off gene and prevent its translation into protein. One of the greatest challenges in designing drugs is to attack the DNA to shut off a gene. It was successfully carried out by Ross using highly toxic Nitrogen Mustard.

Drug Therapy:

Gene Therapy cannot be applied to treat diseases with multiple genetic defects such as cancers or heart diseases. Drug Therapy could be used to develop novel treatments.

Historical Background for Using Nitrogen Mustard for Treating Cancer

Fitz Haber, a German Army officer, worked on the development of Chemicals as a Weapon of War. He was responsible for making deadly Nerve gases and Nitrogen Mustards. Before WWI, he was honored with a Nobel Prize for capturing Nitrogen directly from the atmosphere for making Nitrate fertilizers by burning the element Magnesium in the air forming its Nitride. Upon hydrolysis, Nitride is converted to its Nitrate. Using this method, we could make unlimited amount fertilizer. Nitrate is also used for making explosives. Soon after the WWI, Haber was charged with a crime against humanity for releasing hundreds of cylinders of Chlorine gas on the Western front killing thousands of soldiers in the trenches. When Germany lost the war and Allied forces were looking for Haber. When they reached his residence, his son shot himself and his wife committed suicide. Haber went in hiding in Swiss Alps. After the War, German Government got

his release as a part of the peace negotiations. Haber returned home to welcome the hero. Although he promised never to work on the chemical weapons again, secretly he continued to develop more lethal analogs of highly toxic chemicals like Nitrogen Mustards. It was Haber who first made the notorious Bis-dichloro-ethyl Methyl Amine. Because it smells like Mustard seeds, it is called Nitrogen Mustard. During the next 20 years, before the beginning of WWII, hundreds of more toxic analogs of Nitrogen Mustard were developed. The bad news is that they are highly toxic, and the good news is that they shut off genes.

Ross' Rationale for using War chemicals to treat Cancers:

Professor WCJ Ross of London University was the first person who used Nitrogen Mustard, a chemical weapon, to attack DNA for Cancer Treatment. Radiolabeled study showed that Nitrogen Mustard shut off a gene by cross-linking both strands of DNA that we inherit one strand from each parent. It was the same Cross-linking agents such as Nitrogen mustard made by Haber. Solders exposed to Nitrogen Mustard showed a sharp decline of White Blood Cells (WBC) from 5000 cell/CC to 500/CC. Children suffering from Childhood Leukemia have a very WBC count (over 90,000/CC). Most of the WBCs are premature, defective, 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 he could use cross linking DNA and prevent cell division. Once he demonstrated that he could shut off a gene by cross-linking DNA; he could shut off any mutated gene including the genes of all 220 tissues present in a human by finding a dye that could specifically color that tissue. He could attach the Nitrogen Mustard group to the dye and attack the cancer genes in any one those 220 tissues.

Ross was the first person to use war chemicals successfully to treat cancer. Although such drugs are highly toxic, more cancer cell will be destroyed than the normal cells. Over decades, Ross made several hundred derivatives of Nitrogen Mustard as cross-linking agents. Some of the Nitrogen Mustards are useful for treating cancers such as Chlorambucil for treating childhood leukemia (which brought the WBC level down to 5,000/CC) and Melphalan and Myrophine for treating Pharyngeal Carcinomas. Because of the high toxicity of Nitrogen Mustard, new drugs could not be developed to treat other types of Oral or Lung Cancers. [7., 8., 9., 10., 11., 12.]

When we sequenced our entire genome, we read our book of life, letter by letter word by word, sentence by sentence, chapter by chapter all forty-six volumes (chromosomes) written in six billion four hundred million genetic letters (nucleotide) of a healthy human being under the Human Genome Project. We can use our healthy Genome as a Reference Sequence for comparison. Using Nano Capillary Sequencing method, it took us 13 years to sequence the entire human genome at a cost of $3 billion. Now, we have developed next generation sequencers like Nanopore technology which will sequence the entire genome cheaper and faster. Using biopsy sample, we can take a single cell from the Lung or Oral tumor of smoker, sequence its genome, and compare it with the Reference sequence to identify the number and location of all mutations or damage genes caused by smoking. Recently, we also completed the 1000-genome project which will provide thousand copies of the same gene sequence for comparison. We also learned to convert Analog language of Biology into the Digital language of computer. Now, we can write a program and design a computer to read and compare and send the data to any country in the world at the speed of light. When comparing with the Reference Sequence with the smoker's gene sequence, it will identify all the mutations with precision and accuracy. Once the mutations responsible for causing any cancer including Lung, or Oral Carcinoma are identified, we can design drugs to shut off those genes.

Nitrogen Mustard was mercilessly used as a weapon during the WWI by both German and Italian Armies against Allied forces. Most soldiers exposed to Nitrogen Mustard were freeze to death. Their blood analysis showed a sharp decline in White Blood Cell (WBC). Since patients with the cancer of the blood called Leukemia showed a sharp increase in WBC, Professor Ross and his group at London University, England, wondered if minimum amount of Nitrogen Mustard could be used to control Leukemia in cancer patients. It was indeed found to be true. During the following 30 years, Ross developed hundreds of derivatives of Nitrogen Mustard to treat a variety of cancers. His most successful drugs are Chlorambucil, Melphalan and Myrophine [13]. As his graduate student, during the following ten-year period, I made for Professor Ross dozens of analogs of Nitrogen Mustards. The deadliest among them was the Phenylenediamine Mustard. We use these compounds to check the sensitivity of the Experimental Tumors in the Tumor Bank. If tumors in the Tumor Bank become resistant, we must replace resistant tumor cells with fresh more sensitive tumors for testing other compounds.

Synthesis of Nitrogen Mustard as Anti-Cancer Drugs

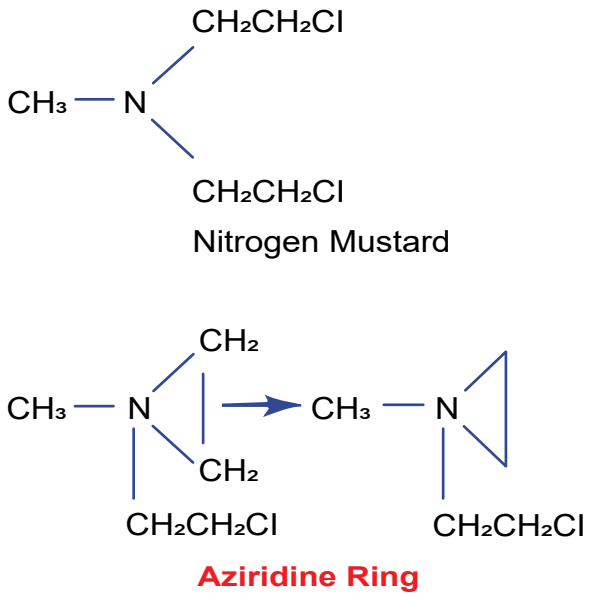
As I said above, I had made several dozens of analogs of Nitrogen Mustards for Professor Ross. I will describe how to make the Nitrogen Mustard by using Haber's crudest method. Haber reacted to Methylamine with Ethylene oxide to make 2-bis dihydroxy ethyl methyl amine. It was chlorinated by heating Phosphorus Penta Chloride in Phosphoric Acid. If you noticed a faint smell of Mustard Seed, Congratulations, you got Nitrogen Mustard; you cooled the solution and diluted with ice cold water, the oil floating in the aqueous solution was extracted with Chloroform. The solution is dried, and Hydrogen chloride gas is passed through to make its solid Hydrogen-Chloride salt. Nitrogen Mustard Hydrogen Chloride salt is separated. No matter how much precautions you take, after the completion of the experiment, if you take an alcohol swab of working bench or walls, doors, knobs and run a mass spectra of the alcohol extract, you find a spectral line corresponding to Nitrogen Mustard. If you are exposed to Nitrogen Mustard and cross the threshold level, your WBC drops sharply and the energy providing Mitochondria die and you are most likely to freeze to death even during summer. Someone in the Defense department may make it, now-a-day. Safety committee will not approve this study in the University Research Lab. Your IRB (Institutional Review Board) and the safety committee will reject your proposal; and who will provide the funds for such an expensive study. The drug sensitivity between normal cell to cancer cell gives a ratio of toxicity called the Chemotherapeutic Index (CI). The higher the ratio the more toxic chemicals are to cancer cells. When tested against Walker Carcinoma 256 in Rats, most Nitrogen Mustards cross-link both strands of DNA and give a CI of ten. [13.,]

Aziridine Analogs as Anti-Cancer Pro-Drugs

A radiolabel study to understand the mechanism of action of Nitrogen Mustard showed that cross-linking of DNA occurred in two steps. The first step is involved in the formation of a three-member aziridine intermediate which remains stable and inactive in the neutral media (acts as a pro-drug). The second arm of the Nitrogen Mustard generates a highly reactive carbonium ion by enzyme which attacks the first arm of the double stranded DNA. The second arm is attacked, as the cancer cells grow; they use Glucose as a source of energy. Glucose is broken down Lactic Acid. In the presence of acid, the Aziridine ring become activated by generating the carbonium ion which attacks the second arm of the DNA resulting in the cross-linking.

This study result showed that cross-linking both strands of DNA is not necessary to shut off a gene, only binding to a single strand of DNA by aziridine could also shut off a gene with half the toxicity. To attack a single strand of DNA, aziridine analogs are separately synthesized. As a part of my doctoral thesis, I was assigned a different path. Instead of cross-linking DNA strands, I am to design drugs to attack only one strand of DNA. The following chart describes the formation of Aziridine ring intermediate.

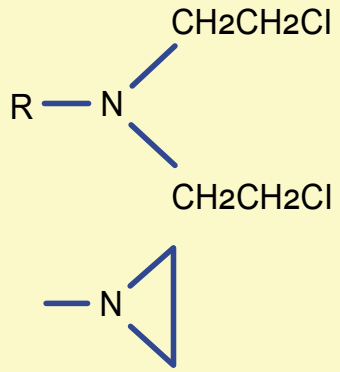
Lethal Group



DNA Binding Aziridine Group

This study showed that to attack a single strand of DNA, we must synthesize Aziridine in the Lab by using ethyl amino methyl sulphonate in sodium hydroxide. Pure Aziridine was distilled off. Synthesis of Aziridine analogs will give two advantages over Nitrogen Mustard: first, instead of cross-linking, Aziridine binds to one strand of DNA, reducing its toxicity of the double stranded Nitrogen Mustard by half. Second, it gives selectivity, the Aziridine ring serves as a prodrug. Its ring opens only in the acidic medium. Once the active ingredient Aziridine was determined to attack DNA, the next question was what drug delivery method should be used to deliver Aziridine at the tumor site.

Alkyl Lethal Groups



Water Soluble Groups

$-CONH_2$ $-CO.OCH_3$

$-CN$ $-NHCOOC_2H_5$

The above structures are Nitrogen Mustard (2-bischloroethyl methyl amine) and Aziridine, DNA Binding Lethal Groups

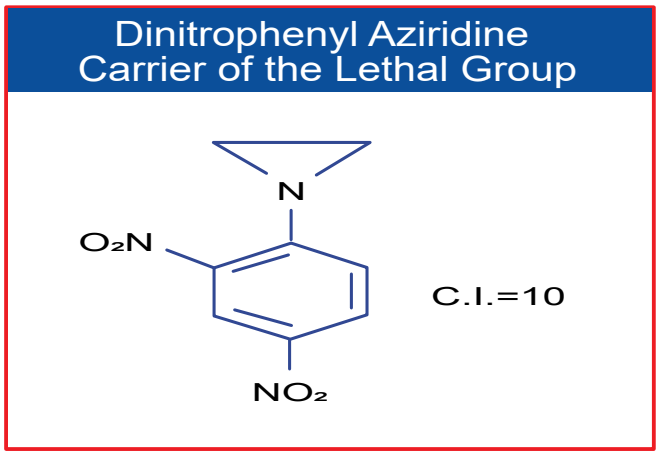
Designing drugs to bind to a Single Stranded DNA to Treat Animal Cancers:

As a part of my doctoral thesis, I was assigned a different path. Instead of cross-linking both strands of DNA by Nitrogen Mustard, I am to design drugs to attack only one strand of DNA by making Aziridine analogues. We decided to use Aziridine moiety (as an intermediate of Nitrogen Mustard) that would be an excellent active component to shut off a gene by binding to a single strand of DNA. To deliver Aziridine to the target site which is the N-7 Guanine of DNA, we decided to use Dinitrophenyl (DNP) moiety as a drug delivery agent. DNP is a dye which colors the tissues of the experimental animal tumor such as Walker Carcinoma 256 in Rats.

It is well known that analogs of DNP such as Dinitrophenol disrupts the Oxidative Phosphorylation of the ATP (Adenosine Triphosphate) which provides energy to perform all our body functions. To provide energy to our body function, the high energy phosphate bond in ATP is broken down to ADP (Adenosine Diphosphate) which is further broken down to AMP (Adenosine Mono Phosphate), the enzyme Phosphokinase put the inorganic phosphate group back on the AMP giving back the ATP. This cyclic process of Oxidative Phosphorylation is prevented by Dinitrophenol. As a part of my doctoral thesis, I decided to use Dinitrophenol as drug delivery method for the active ingredient aziridine. The analog of DNP such as Aziridine Dinitrophenol could also serves as a dye which stains Walker Carcinoma 256, a solid and most aggressive tumor in Rat. The first compound I made by attaching the C-14 radiolabeled Aziridine to the DNP dye. The Dinitrophenyl Aziridine was synthesized using Dinitrochlorobenzene with C-14 radiolabeled Aziridine in the

presence of Triethyl amine which removes the Hydrochloric Acid produced during the reaction. When the compound Dinitrophenyl Aziridine was tested against the implanted experimental animal tumor, the Walker Carcinoma 256 in Rats, it showed a TI (Therapeutic Index) of ten. The TI of ten was like most of the analogs of Nitrogen Mustard. Since this Aziridine analog was not superior to Nitrogen Mustard, it was dismissed as unimportant.

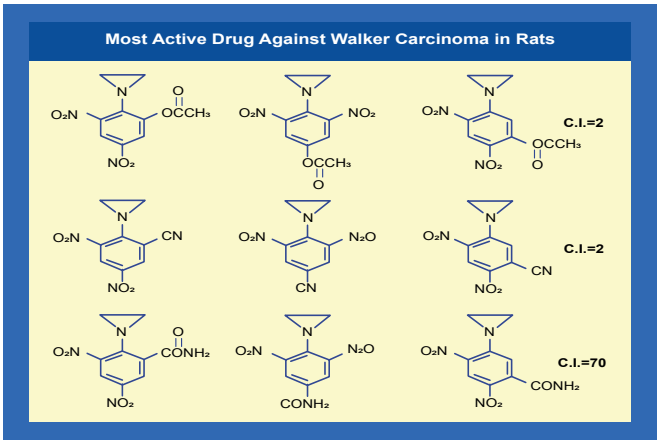
On further reexamination of the X-ray photographs of Dinitrophenyl Aziridine, it appeared that most of the radioactivity was concentrated at the injection site. Very little radioactivity was observed at the tumor site. It was obvious that we need to make derivatives of Dinitrophenyl Aziridine to move the drug from the injection site to the tumor site. Because of the lack of fat/water solubility to be effective drug delivery method, Dinitrophenyl Aziridine stays at the injection site, a very small amount of radioactivity was found on the tumor site.



Structure Activity Relationship:

I immediately realized that by altering structure, I could enhance biological activity by making water and fat-soluble analogs of Dinitrophenyl Aziridine. By attaching water soluble groups, I should be able to move the drug from the injection site to the tumor site. To deliver 2,4-Dinitrophenylaziridine form the injection site to tumor site, I could alter the structure of 2,4-Dinitrophenylaziridine by introducing the most water-soluble group such as ethyl ester to the least water-soluble group such as Cyano- group or to introduce an intermediate fat/water soluble such as Amido group.

An additional substituent in the Dinitrophenyl Aziridine could give three isomers, Ortho, Meta, and Para substituent. Here confirmational chemistry plays an important role in drug delivery methods. Ortho substituent always give inactive drug. Model building showed that because of the steric hinderance, Aziridine could not bind to DNA shutting off the genes. On the other hand, Meta and Para substituents offer no steric hindrance and drug could be delivered to DNA. When injected in Rat, because of the high solubility, most of the drugs was pass down through urine and extracted the drug from Rat urine by chloroform, The following chart showed that I synthesized all nine C-14 radiolabeled analogs of 2,4-Dinitrophenyl aziridines and tested them against implanted Walker Carcinoma 256 in Rats.



Derivatization of Dinitro phenyl Benzamide based on Partition Coefficient

The most water-soluble substituent:

The first three compounds on top line of the above chart carry all three isomer of the most water-soluble **Ethyl Ester group** attached to 2,4-Dinitropehny aziridine. The compound in vivo is hydrolyzed Ethyl Ester to produce most water-soluble carboxylic group. Since it is the most water-soluble substituent, within 24 hours of injection in Rats, the entire radioactive compound was passed down from in the Rat urine and it can be extracted by Chloroform. Since the Ortho position was not available for DNA binding, it showed no biological activity, but the third compound in which Ortho position was free to bind to DNA showed some anti-tumor activity in Rats.

The least water-soluble substituent:

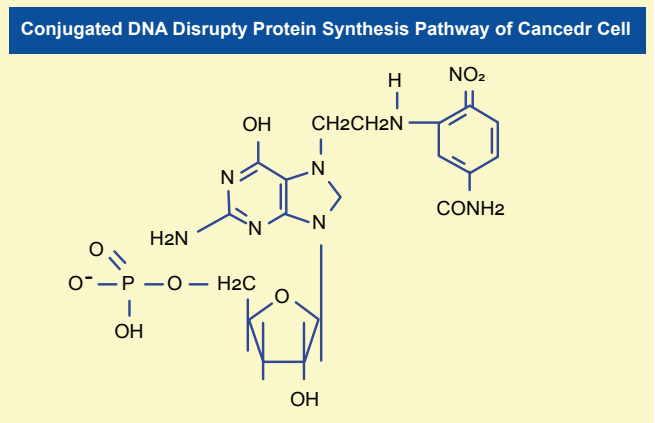
On the other hand, when the least water-soluble **Cyano-group** was attached to all three isomers of the 2,4-Dinitrophenyl aziridine compound as shown in the second line of the above chart, most of the compound stayed at the injection site. Only the last Cyano-derivative attached to DNA showed some anti-tumor activity.

The moderately soluble Amido-substituent:

The last line of the above chart showed that the first two **Amido groups** were sterically hindered and did not bind to DNA and showed no biological activity, but the last compound presents the perfect drug delivery method. The entire drug was delivered from the injection site to the tumor site. The drug 1-Aziridine, 2,4-dinitro, 5-benzamide (CB1954) showed the highest anti-tumor activity. It has a CI of seventy; it is seventy times more toxic to cancer cells; highest toxicity ever recorded against Walker Carcinoma 256 in Rats.

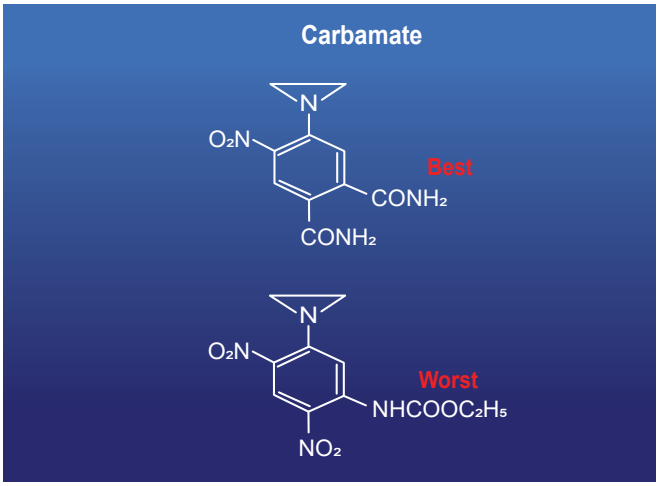
As I said above, Nitrogen Mustards are highly toxic because they have neither specificity nor selectivity. They attack all dividing cells whether they are normal or abnormal. On the other hand, the analogs of Aziridines and Carbamates serve as prodrugs and remain inactive in the basic and neutral media. They become activated only in the presence of acid produced by growing cancer cells. 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) has the highest toxicity to Walker Tumor cells ever recorded. As the tumor grows, it uses Glucose as a source of energy. Glucose is broken down to

Lactic Acid. It is the acid which activates the Aziridine ring. The ring opens to generate a carbonium ion which attacks the most negatively charged N-7 Guanine of DNA (as shown below) shutting off the Walker Carcinoma gene in Rat. The following conjugate structure show how CB1954 binds to a single strand of DNA shutting off the gene.



Conjugated DNA Disrupting Protein Synthesis Pathway of Cancer Cell

For the discovery of CB1954, The University of London, honored with the Institute of Cancer Research (ICR) post-doctoral fellowship award to synthesize more analogs of CB1954. Over the years, I made over a hundred additional analogs of Dinitro phenyl aziridines. To increase the toxicity of CB1954 to Walker Carcinoma, I made additional 20 analogs as a postdoctoral fellow. When I attached one more Carbonium ion 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 stopped working. Further work at London University was discontinued for safety reasons.



The Best and the Worst Dinitro phenyl Aziridine Analogs

Although Aziridine Carbamate is extremely toxic, it is also very useful in testing the sensitivity of tumors in Tumor Bank. Over the years, some tumors in the tumor bank could become resistant. If a tumor culture survives in a petri dish by adding a solution of Aziridine Dinitrobenzene Carbamate, it means that this tumor has become resistant over the years and must be replaced by new sensitive tumor cells.

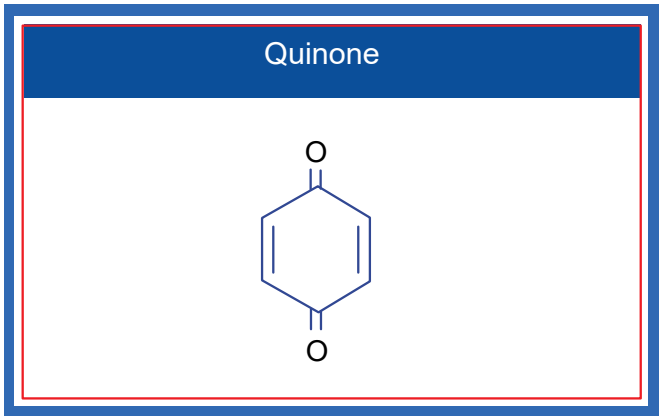
As a part of the inter-government agreement between UK and USA, all novel drugs developed in England were sent to the National Cancer Institute (NCI) in America for further screening. To translate animal work to human, I was invited to continue my work on the highly toxic Aziridine/Carbamate combination 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), USA. For making more Aziridine/Carbamates, 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 animal work to humans.

In developing drugs for treatments, we poison bad DNA selectively. All poisons are a class of chemicals that attack all DNA good and bad alike. Chemicals that cause cancer, at a safe level, can also cure cancer. Science teaches us to selectively attack bad sets of DNAs without harming the good sets of DNAs. Poisons are injurious to living creatures. There is a small class of chemicals, when exposed to humans, disrupt the function of DNAs, and make normal cells abnormal and they are called cancer causing chemicals or carcinogens. I must confess, we still use surgery to cut off cancerous breasts; we still burn cancer cells by radiation; and we still poison cancer cells by chemicals. The largest killer of women is breast cancer. After all the treatment, the remaining cancer cells return as metastatic cells and kill breast cancer patients in three years. A decade from now, these methods could be considered brutal and savage, but today that is all we have. We hope to develop new treatment for Breast Cancer. Hope means never ever to give up.

Glioblastoma (GBM) is a primary type of brain cancer which originates in the brain, rather than traveling to the brain from other parts of the body, such as the lungs or breasts. GBM is also called glioblastoma multiforme which is the most common type of primary brain cancer in adult humans. Attaching Nitrogen Mustard group to a carrier dye will produce highly toxic compound which will have neither specificity nor selectivity. Such a compound will attack all dividing cells whether they are normal or abnormal. On the other hand, the analogs of Aziridines and Carbamates serve as prodrugs that is they remain inactive in the basic and neutral media. They become activated only in the presence of acid produced by cancer cells.

Designing drugs to treat Glioblastoma, the human brain cancers:

One day, I heard an afternoon lecture at the NIH in which the speaker described that radio labeled Methylated Quinone crosses the Blood Brain Barrier (BBB) 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 novel drug delivery molecule to cross BBB (Blood Brain Barrier) delivering 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 molecule to test against Glioblastomas in humans.



The Structure of a non-toxic and non-addictive Quinone used for crossing the Blood Brain Barrier (BBB)

With the Quinone ring, I could introduce two Aziridine rings and two Carbamate moieties and could create havoc for Glioblastoma. Within three years, I made 45 analogs of Quinone. One of the Quinone carries two aziridines and two carbamate moieties which was highly toxic to Glioblastoma. The tumor stopped growing and started shrinking. I named the Di-aziridine Dicarbamate Quinone, AZQ. My major concern was how toxic this compound would be to normal brain cells. Fortunately, brain cells do not divide, only cancer cells divide. AZQ acts as a Prodrug. A Prodrug is compound carrying a chemical by masking group that renders it inactive and nontoxic. Once the prodrug reaches a treatment site in the body, removing the mask frees the active drug to go only where it is needed, which helps avoid systemic side effects. Aziridine and Carbamate show selectivity. As I said above, to grow rapidly, cancer cells use Glucose as a source of energy. Glucose is broken down to produce Lactic acid. It is the acid which activates the prodrug aziridine and carbamate moieties generating Carbonium ions attacking Glioblastoma which stops growing and start shrinking.

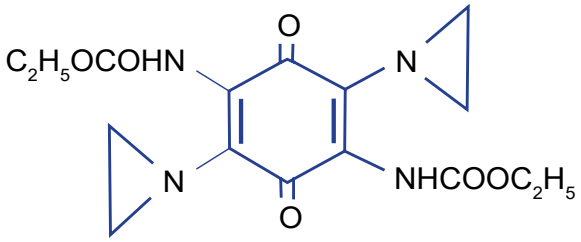
My drug AZQ is successful in treating experimental brain tumor because I rationally designed to attacks dividing DNA. Radio labeled studies showed that AZQ bind to the cancer cells DNA and destroy brain tumor and normal brain cells are not affected at all. AZQ is a new generation of drugs. Not so long ago, brain cancers mean death. Now, we have changed it from certain death to certain survival. The immunologists in our laboratories are developing new treatment techniques by making radio labeled antigens to attack remaining cancer cells without harming normal cells.

We have cured many forms of cancer. We have eliminated childhood leukemia, Hodgkin disease, testicular cancer and now AZQ type compounds which are being developed rationally. While most anti-cancer drugs such as Adriamycin, Mitomycin C, Bleomycin etc., in the market are selected after a random trial of thousands of chemicals by NCI, AZQ is rationally designed for attacking the DNA of cancer cells in the brain without harming the normal cells. We are testing combinations of these drugs to treat a variety of experimental cancers in animals.

DNA Binding Aziridines:

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 years, I made dozens of analogs of Aziridine Quinone. By attaching two Aziridines and two Carbamate moieties to Quinone, I synthesized the most useful compound, Diaziridine Dicarbamate Quinone, I named this novel compound AZQ. Over three-year period, I made 45 analogs of AZQ. They were all considered valuable enough to be patented by the US Government (US Patent 4,233,215). By treating brain cancer with AZQ, we observed that Glioblastoma tumor not only stops growing, but it also starts shrinking. I could take care of at least one form of deadliest old age cancer, Glioblastomas. Literature search showed that AZQ is extensively studied as a pure drug and in combination with other anti-cancer drugs.

Azirridynl Quinone (AZQ)
Used in treating Brain Tumor



U.S. Patent 4,146,622

Single Strand DNA Binding Aziridine and Carbamate

As I said above, Glioblastomas, brain cancer, is a solid and aggressive tumor and is caused by mutations on several sites in chromosomal DNA. Deleterious genetic mutations are the result of damaging DNA nucleotides by exposure to radiation, 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 containing nutrients forms an entire colony of millions when incubated on the Agar Gel. Mistakes occur in DNA during rapidly replication such as Insertion of a piece of DNA, Deletion, Inversion, Trans location, 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 also responsible for mutations. Since the genes in DNA codes for Proteins, Insertion and Deletion on DNA have catastrophic effects on protein synthesis. With the Quinone ring as a carrier across BBB, I could introduce different combinations of Aziridine rings and Carbamate moieties to Quinine 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.

Attempting to find the site of mutations on Glioblastomas represents the greatest challenge. 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 responsible for causing brain cancers in humans. Let us examine the effect on each chromosome.

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 carry a total of 9,579 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. It becomes possible by using C-14 radiolabeled Aziridines, we can confirm the binding site of a nucleotide on a specific gene and on a specific chromosome. By comparing with the mega sequencing genome project, we can further confirm the sites of mutations.

With the completion of 1,000 Human Genome Project, it becomes easier. By simply comparing the patient's genome with the sequencing of 1000-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. As I explained above, by making CB 1954 to treat solid Walker Carcinoma in Rats, I established the structure activity relationship, and by making AZQ to treat human Glioblastoma, we have demonstrated that all bad genes can be shut off using Aziridine or Carbamate or both as attacking agents to shut off a gene. If you plan to develop drugs to treat other cancers, all we need to do is to identify carriers such as coloring dyes which stains a specific tumor. By attaching Aziridines and Carbamate moiety to carriers to the dyes, we could attack other tumors.

One of the greatest challenges of nanotechnology is to seek out the very first abnormal cell in the presence of billions of normal cells of our brain and shut off the genes before it spread. I worked on this assignment for about a quarter of a century; conducted over 500 experiments which resulted in 200 novel drugs. They were all tested against experimental animal tumors. Forty-five of them were considered valuable enough to be patented by the US Government (US Patent 4, 146, 622 & 4,233,215). One of them is AZQ which not only stops the growth of Glioblastoma, but also the tumor starts shrinking. For the discovery of AZQ, I was honored with, "The 2004 NIH Scientific Achievement Award." One of America's highest Award in Medicine. I was also honored with the India's National Medal of Honor, "Vidya Ratna" a Gold Medal. (see Exhibits 1,2,3,4)

NIH Mission # 1 Conducting the research

In the Lab, using Quinone ring to transport across BBB, I introduced different combinations of highly toxic Aziridine rings and Carbamate moieties and created havoc for Glioblastomas. My major concern was how toxic this compounds would be to normal brain cells. Fortunately, brain cells do not divide and do not grow only cancer cells divide and grow. AS I said above, Radiolabeled studies showed that AZQ can cross organ after organ, cross the Blood Brain Barrier, cross the nuclear membrane and attack the nuclear DNA shutting off the cancerous gene. X-ray studies showed that radioactivity is concentrated in the tumor region. Glioblastoma stopped growing and started shrinking for this discovery, I was honored with the above scientific achievement award. [18., 19]

While Genome Center was supporting sequencing and mapping of the Genomes, my Institute NICHD was supporting research on Gene Markers associated with diseases. Over a quarter of the century of work, I was able to accomplish all the goals of NIH, that is to conduct research, support research and report research. I describe below all three missions of NIH.

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-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.

2004 NIH Scientific Achievement Award

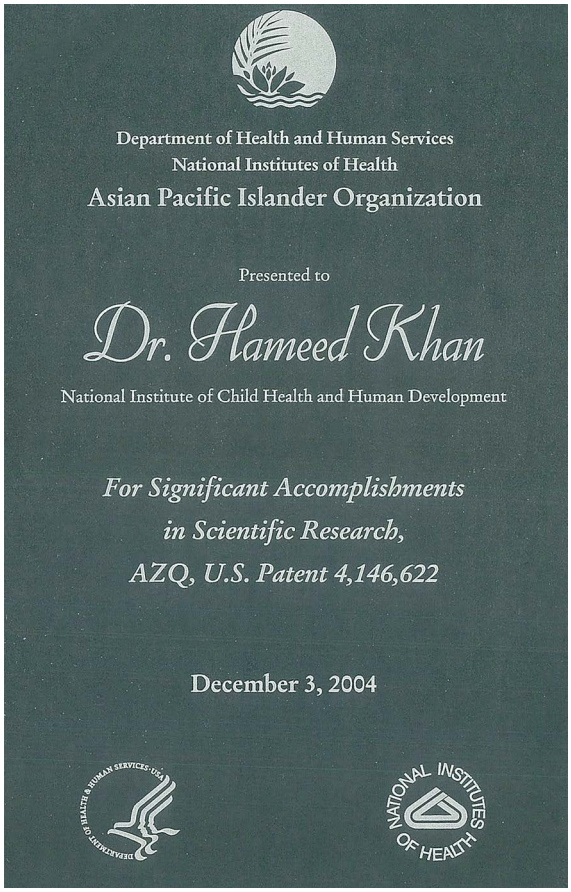


Exhibit # 2

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

Royals of Travancore

Dr. Hameed Khan, of NIH was invited to give the "Maharaja Thrumal Memorial Award lecture" "On the Impact of Genetic Revolution on our lives during 21st Century and Beyond" at the University of Trevandrum. After the Lecture, His Royal Highness Sree Padmanabha Dasa Marthanda Varma (the brother-in-law) of her Royal Higness Maharani Travancore (on his left) invited Dr. Hameed Khan and Mrs. Vijayalakshmi Khan for the Tea at the Pattom Palace at Thiruvanthapuram on May 12, 1999. Standing on Dr. Khan's right is the Son-in-law of Her Royal Highness, The Maharani.

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.

NIH Mission # 2

NIH Speaker Bureau informed me that when you teach the students, you will touch the future. It is the responsibility of scientists to train a new generation of scientists. I was told that of all teaching organizations, one organization, Envision, stands out. Envision is an outstanding organization that trains and provides future leaders of the world. Envision performs a Herculean task by selecting thousands of best and brightest students from around the country and from all over the world and bring them to Washington DC to train them to become the future leaders of the world. They evaluate my performance as a teacher which resulted in the Speaker' Bureau Award:

From: NYLF/Med Washington
[MedWashingtonCA@envisionemi.com]
Sent: Monday, July 09, 2007 7:29 PM
To: Khan, Hameed (NIH/NICHD) [E]
Subject: NYLF - Feedback
Dr. Khan,

You were the most popular speaker at our seminars! Congratulations! The students absolutely loved you, and your average score was a 5 out of 5. Here are some of their comments:

□ I loved his discussion, he was so knowledgeable about his field and I found it very interesting.□

□ It was so interesting and really well presented. Definitely bring him back!□

□ This speaker provided great insight into the behind the scenes work on the Human Genome Project.□

Thank you so much! I look forward to seeing you next forum!

Zaree Gliddon
Conference Assistant
National Youth Leadership Forum on Medicine
Washington, D.C.
Phone/Fax 703-584-9238
MedWashington@nylf.org

Over the years, Dr. Khan has given over one hundred speeches nationally and internationally. He is a discoverer of AZQ (US Patent 4,146,622), a Novel Drug specifically designed to silence a Gene that Causes Brain Cancer. The Main Topic of his Speech is, "The Impact of the Human Genome Project on Our Lives During The 21st Century and Beyonnd His Aim is to encourage Young Scientists and Investigators to use the same rationale as was developed for AZQ to design drugs to silence all other Oncogenes that cause cancers. He is a Fellow of the American Institute of Chemistry and was elected to the American Science Advisory Board.

NIH Mission # 3

Of all the challenges of NIH Missions, supporting research presents the greatest challenge. I was accidentally involved in supporting research. I was invited to speak at an International Conference in Europe. I was shocked when I saw the program. Someone is presenting a paper for treating Breast Cancer with my drug AZQ. My rationale for designing AZQ was that Quinone cross the Blood Brain Barrier and take the Aziridine in the vicinity of Glioblastoma. As the tumor grows, it uses Glucose as a source of energy. The Glucose is broken down to produce Pyruvic Acid. The acid activates the Aziridine which is broken down to generate a Carbonium which attacks Glioblastoma stopping the tumor growth. I was curious to know the rationale for using AZQ to treat Breast Cancer. The speaker informed the audience that AZQ has no effect against Breast tumor. At the end of the presentation, I asked the speaker for the rationale for using AZQ. The shocking answer was that AZQ is extensively- studied on different cancers so this group tried to study Breast Cancer because funds were available. Upon my return to NIH, I told my colleagues what a waste of precious resources.

One of my colleagues. Lawrence Johnson was promoted to become the Director of the Division of Scientific Review. He asked me to join him in controlling the Research Funds and helping the new investigators by reviewing their Research Proposals. NIH annual budget is $50 billion. About twelve percent of the budget is spent on the house (called the Intramural Program). The remaining eighty-eight percent money is given out as extramural Program nationally and internationally as Research grants, Research contracts and Research co-operative Agreements. He gave me a couple of research proposals to review. As I read the research proposal, I immediately pulled out strengths, the weakness in the proposal I checked the Principal Investigator (PI) qualifications, his publications, his support staff, research environment availability of instruments, the budget. I liked to help the PI and accepted the challenge and joined his group. I was given incredible freedom to set up committees to invite the best and the brightest scientists from any part of the country to serve as the reviewers to serve as the expert on panels. NIH treat these experts with utmost courtesy, utmost respect and accommodate them in the best hotels, paid all their expenses with honorarium. Reviewing Research Proposals in the beginning was a passion for me, then it became obsession.

During the following twenty years, I had set up more than 250 Expert Panels Committees called the Study Sections, reviewing thousands of research proposals, inviting hundreds of scientists. Anyone interested in finding these committees can either find in the Federal Registered Notices appear in Google or the entire list of all committees in my above Facebook website. The Director of NICHD honored me with the NIH Supporting Research Award.

2006 NIH Merit Award for Supporting Research Presented To

Dr. Hameed Khan By Dr. Duane Alexander, MD Director, NICHD Dr. Robert Stretch, Director DSR and Dr. Yvonne Maddox, Deputy Director, NICHD. In recognition of his superior commitment, dedication and accomplishment in the planning and executing of over 250 Peer Review Meetings for both Grants and Contracts. Dr. Khan was honored during the Director's Award Ceremony held on October 11, 2006.

In recognition of his superior commitment, dedication and accomplishment in the planning and executing of over 250 Peer Review Meetings for both Grants and Contracts. Dr. Khan was honored during the Director's Award Ceremony held on October 11, 2006.

What Should we explore next?

The next generation of scientists, my students, will face the great challenge to design novel drugs to treat breast cancer the largest killer of women.

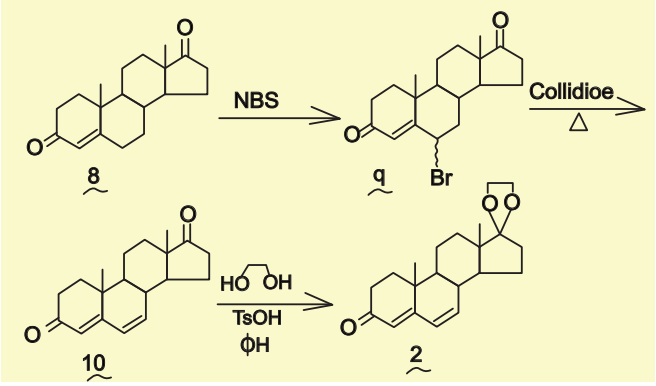
In the early history for developing drugs for treatments of cancers, we poison bad DNA selectively. All poisons are a class of chemicals that attack DNA molecules good and bad alike. Chemicals that cause cancer, at a safe level, can also cure cancer. Science teaches us to selectively attack bad sets of DNAs without harming the good sets of DNAs. Poisons are injurious to living creatures. There is a small class of chemicals, when exposed to humans, disrupt the function of DNAs, and make normal cells abnormal and they are called cancer causing chemicals or carcinogens.

In the absence of any rational drug, I must confess, we still use surgery to cut off cancerous breasts; we still burn cancer cells by radiation; and we still poison cancer cells with chemicals. After all the current treatments, the remaining cancer cells return within three years as metastatic cells and kill breast cancer patients. A decade from now, these methods could be considered brutal and savage, but today that is all we have. Based on rational design, we hope to develop new treatment for Breast Cancer. Hope means never ever giving up.

To design drug rationally to treat Breast Cancer, and to shut off a gene of a specific cancer by using Aziridine or Carbamate, we need a carrier for these groups. For example, to treat Breast and Prostate cancers in humans, may I suggest that we try using hormones which could serve as carriers for Aziridine and Carbamate moiety. Could I use the same rationale for treating Breast tumor as I used for making AZQ for treating Brain cancer? Although BRCA1 gene located on Chromosome-17 (which is made of 92 million nucleotide base pairs carrying 1,394 genes) was identified years ago, we wonder why it has been so difficult 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 would also show that composition of many cells carrying mutated cells 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 lungs on its way to brain. Since all other organs including breasts could be removed and replaced by breast implants except brain, I thought that protecting brain is utmost important treatment. Once AZQ (US Patent 4,233,215) is developed to protect the brain, I could focus on Breast and Prostate Cancers.

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 using male and female hormones as carriers, I could attach multiple Aziridine rings and Carbamate ions to both Hormones 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 base pairs. The BRCA1 genes carry about three thousand mutations. These mutations are caused by radiation, 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 [17], I could show how many radio-labeled nucleotides were bound to which mutations. Out of seventeen positions on Testosterone, only three positions are 1,3 and 17 are available for substitution on Testosterone ring system.



Carl Djerassi (C. Djerassi et al. J. Amer. Chem. Soc. 72. 4534 (1950) demonstrated that we could activate additional positions for substitutions on hormone ring system such as the 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 we could further brominate to produce 9,10 dibromo compound. These bromo ion could be replaced by additional Aziridines or Carbamate ions. We could increase or decrease the number of Aziridine and Carbamate ions to get maximum benefit by further brominating position such as 15 and 16 to introduce additional Aziridine and Carbamate moieties.

Similarly, we could use the female hormone Estrogen and by attaching multiple Aziridine and Carbamate ions to attack Prostate tumor in Men. Since out of seventeen positions, only three positions are available on Estrogen ring as well; again,

we could increase or decrease the number of Aziridine and Carbamate ions to get the maximum benefit by using Djerassi' method as we did with Testosterone. The above methods are novel approach to designing drugs to treat Breast and Prostate cancers using genetic make-up of a patient to treat metastatic cancers. The next generation scientists, my students, [20 to 44] will have the opportunity to translate this dream into reality. As I said above, the biggest killer of women is the breast cancer. Although I suggest my students to take the risk to using Nitrogen Mustard, Aziridine and Carbamate attach to male and female hormones to control breast cancer and test to see if it works.

To succeed, we need outstanding men and women like you. Who among you would be the vanguard of research and technology in the greatest country in the world. We bequeath the future of this greatest nation in your hands. We know that you will do your best to keep America the sole remaining superpower of the scientific world, a jewel in the crown, a beacon of light and shinning city on the Hill.

Had Darwin lived today; he would have been truly proud of our accomplishments to prove his theory. Within 150 years of his theory of evolution by natural selection, we proved this theory (guesswork) to be a scientific fact. We proved by sequencing hundreds of species from the simplest to the most complex including humans.

On April 3, 2003, Dr. Francis Collins, the Director of my Institutes, The National Institutes of Health (NIH) announced that we have re-read the book in which God created life.

After spending $3 billion on the Human Genome Project, if you would ask me what the single most important discovery is we made. My answer would be that sequencing the entire book of our life itself is one of the greatest achievements of our time. We are the only species who have not only read his own book of life, but also, we read the book of life hundreds of other species on Earth. Sequencing confirms the evolution of life from the simplest to the more complex life forms. Comparative sequencing of many species will keep our scientists busy for another century trying to find out what piece of human genome came from what species over three and a half billion years of biological evolution. Of dozens of discoveries, we made since the completion of the Human Genome, one stands out. We made an astonishing discovery about our own origin. Now, we can answer the questions, we, both science and religions, have been asking ourselves since the dawn of human civilization. Who are we? Where do we all come from? What was it that made us this way? Now, we can answer these questions with certainty that we are the result of three and a half billion years of Darwinian Evolution. We are the extension of the same single DNA molecule that was formed on Earth about four billion years ago.

Darwin's extraordinary prediction was confirmed by sequencing genomes or reading the book of lives of over a thousand species evolved on Earth. Of all the experiments in Biology, the Sequencing of Human Genome was the greatest accomplishment of all times.

Sequencing human genome identifies the number and the order of nucleotides which are arranged in our book of life. We found that 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 contain repetitive pieces of DNA which are 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. Once the mutated genes are identified, we can design drugs to shut off those genes,

Over thousands of years, we traveled a long distance from the Stone Age to Information Age. The ancient idea that reading and writing the book of life or sequencing human genome is in the domain of God that belongs to God alone is simply unacceptable. God loves scientists, He revealed the secrets of life to us not revealed to anyone before us. The Sequencing of Human Genome has enlightened us in ways; we have never been enlightened before. Now we know the answers to questions like who are we? Where do we all come from? What was it that made us this way.

It was Darwin's theory of evolution and natural selection that gave our ancestors human intelligence and human conscientiousness. They had little knowledge and understanding of survival when they came out of Africa about three million years ago, and within seven thousand generations, they walked around the world and settled down on all seven continents. They not only circumnavigated the world; they climbed the tallest mountain and went to the bottom of the deepest ocean; they split the heart of atom and walked on the surface of the Moon and came home safely. We are ready to take Darwinian evolution across the Universe. Our next step in the search for life in the cosmos is our dream to create settlements on the surface of Mars and send unmanned spacecrafts in search of habitable planets in distant star systems.

Darwin's evolutionary ideas taught us that the future can be greater than the past. Fifty-five years ago, we touched greatness when we walked on the surface of the Moon and came home safely and that was a turning point in history. There was a time when we soar to the Moon now, we must dream again to soar to Mars.

If we do not destroy ourselves by going to Nuclear War, as threatened by one superpower, within a million year, we will have human settlements on distant star systems, and we could spread human intelligence in every corner of the Universe. This is the message for the future generation of humans. For the present generation, the most important lesson is that we are the extension of the same DNA molecule that was formed three and a half billion years ago. Life must have started in some little worm pond as suggested by Darwin. Through the same DNA molecule, all living creatures relate to each other including humans. Recent mitochondrial DNA sequencing pointed to our origin to a single chimp/woman who was born in Hader Valley in Ethiopia about three million years ago called Lucy. Over the years, the dark, uninformed, and ignorant minds have divided us based on race, religions, or the place of origin. The enlightened mind must unite us all as single people. Science presents the undeniable truth that you and I are brothers and sisters, children of the same mother

Lucy, a Black woman who was born in Africa about three and a half million years ago. Today, our number has increased to eight billion. We are adding a hundred million new mouths to feed each year. Are we the last generation to survive on Earth?

America is one of the most democratic countries in the world. Also, being the richest country in the world, America provides the best information to her people to decide when and if parents would like to have children. Only 3 to 4 percent work force is unemployed in America, the lowest in the world. Both parents go to work. They hire babysitters to take care of their children. None of the parents has time to take care of their children. Some parents delay having babies until their careers are well-established. When women have children at later age, they tend to accumulate genetic defects. They want to make sure before conception if it would be a healthy baby. Nowadays, young couples are saving their fertilized eggs in frozen state in Cryo-Preservation Banks at an early age to be used when they become well-established. If parents ignore the sequence of egg and sperm, they must make that awful decision when to abort a defective fetus. Parents in the Western world are wondering if we should have an acceptability test for all newborn children. To see if their children are born healthy and that they are acceptable members of human society. Most people in the West believe that we have a moral obligation to take care of all those children who are already here whether they are healthy or not. They have right to be taken care of. But we are talking about children who are not here yet. What rights do they have?

The completion of the Human Genome Project helps us follow the selective genetic breeding by in vitro fertilization by discarding defected eggs and sperms. Some conservative members of our society will not accept the new discoveries. The question they must ask is should we add physically handicapped or mentally retarded children to our future gene pool? Or should we develop a series of medical tests on the fetus to eliminate unacceptable members to our society? How could we accomplish this goal? There are various biomarker tests (very expensive), we could conduct on the unborn fetus, such as examining the functioning of brain, nervous system, lungs damage, incurable blindness, kidney defect and malfunction of liver. Shouldn't we check before birth if the heart and blood pressure is functioning properly? All those children who fail these tests will place severe burden on our medical and financial resources. Should we allow nature to take its course and let them die or should we bring them into this world by providing medical intervention and prolonging their life, even though they will not live a quality life? Do you know that some handicapped children in America are suing their parents for bringing them into this world where they become burdened on society? Simple economy works here. The cost of medical treatment is unaffordable. May be some handicapped children will have to sue their parents in our country that will teach their parents a lesson,

Forbidden Areas:

Although gene therapy of the somatic cells is permitted, the gene therapy of the sex cells like the X and Y cells are not permitted at this time since a single cell cut, paste and insert a single cell much easier than the multiple cells. Insertion of carcinogenic or toxic genes in human cells. Our genetic toolkits contain all the essential tools to clone any species including humans. Human Cloning is forbidden by all the governments of world. Copying humans deprives genetic diversity. Other forbidden areas include manipulating Oncogenes, Toxic genes isolated from snake venom or rare bacteria. Darwinian Evolution can be hastened by the methods of genetic engineering by cutting, pasting, copying, and sequencing a gene or by moving genes from species to species with precision and accuracy. Although such studies are not permitted at this time, but with time, the restriction could be relaxed. Future studies will show that Proteins obtained from the toxic genes could be used to develop antibodies for treating various diseases.

Ethical Issues:

Do you want children by Chance or by Choice?

Professor Julian Savulescu, a prominent Australian philosopher and bioethicist known for his work in practical ethics, who was the Uehiro Chair in Practical Ethics at Oxford University, England, stated that after sequencing human Genome, it is immoral to have children by Chance, but not by Choice. Pregnant mother taking great risks, He stated that it is immoral to have children in the old fashion way. A woman who has a family history of serious illnesses should go to in vitro fertilization clinic to sequence the fertilized ovum before implanting. To decrease the population of prisons, mental institutions, and Asylums. We need to encourage pregnant mothers to have sequenced their fertilized ovum and compare it with the Reference Sequence. In three days, the fertilized ovum becomes an 8-cell ovum. Each cell carries a complete set of genomes. It is made of four chemicals, and they are Adenine (A) Thiamine (T), Guanine (G) and Cytosine (C). You can buy these powder chemicals from the pharmaceutical firm. They are merely chemicals; they are neither dead nor alive. Each cell carries complete set of DNA to code for a human being. These set of chemicals are not alive; they can be kept in liquid Nitrogen below 70 degree for years. When they thaw, they can be implanted in a surrogate mother and they become alive. As the cost of sequencing comes down to $100 dollars per genome, we can sequence and compare each cell with the Reference Sequence and select the very best cell free from all deleterious mutation for development. This way you can control the quality of the population, which is safer, cheaper, and faster. Having children by Chance, you are giving bad genes to your unborn children. Fertility Clinics could serve as a genetic selector when parents select traits. Knowing well, if a mother brings a mutated child to this world, the consequences is horrendous. Recently, on a local train, a Ukrainian woman was stabbed to death. While train video camera was recording, the man sitting behind her open his knife and stabbed the women several times until she was dead. Asked why he did it, his answer was that she was reading his mind. The genetic trash will be sent to psychiatric institutions for further evaluation on taxpayers' expenses. That is where he will live for the rest of his life. On the other hand, if you are rich enough to buy the best traits for your children. You can pay to the fertility clinic to cut, paste, and insert genes which gives your baby blue eyes, blond hair, high IQ, white skin, extra height and muscle, a child more likely to be straight rather than gay. The Clinic can also advice parents a choice of Sex Selection of the baby. What do you want, a boy or a girl? Society will have two classes of children, a gene rich child and a gene poor child. The gene rich will have every comfort of life while gene rich have none. We need new ethical principles based on moder science. The old principle also came from people's heads, but they were based on the pre-genomic era mostly guess work or prayers. Now, we have sequenced the human genome, every nucleotide should be carefully selected before implanting the fetus into the mother.

THE AUTHOR

Dr. A. Hameed Khan was born in Hyderabad, Deccan, India and was educated in England. After receiving Doctorate and post-doctorate from the University of London, he used to work at the Royal Cancer Hospital, London. America's National Institutes of Health (NIH) offered him the Fogarty International Award to come to America to work in the National Cancer Institute (NCI) where he discovered AZQ for treating brain cancer. For the discovery of AZQ, he was honored with numerous national and international awards. The Government of India presented him with Vaidya Ratna, national Medal of honor with a Gold Medal. Dr. Khan is a Fellow of the American Institute of Chemistry, and he serves as a member of American Science Advisory Board. He lives in Silver Spring, Marland USA.

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Conclusion:

Darwin's Evolution by Natural Selection taches us that individuals who are fit to survive in the existing environment will thrive and those who are not fit will die. Modern science could bring those unfit children to this world at a very high cost financially and emotionally. We have moral responsibility to take care of all those children who are already here. They have a right to be taken care of. What about those children who are not here? Do they have the same rights? Genetic sequencing of egg and sperm by Nanopore Sequencer will identify the genetic defects in an embryo, cheaper, faster with high precision and accuracy. In future, conception by in vivo fertilization will be the order of the day. The important point I want to convey to my students and readers is that We need new ethical principles based on modern science. This is the main thrust of my arguments. The old ethical principles also came from people's head, but they were based on the information available to our elders hundreds of years ago. Most ethical principles we used today were developed by Socrates about 2,500 years ago and everything that is written in philosophy since then is a footnote to his work. Although we have made little progress in philosophy, we have made tremendous progress in Darwinian Evolution and in understanding genomic science. We have been developing genomic medicine to keep people alive for the past one hundred years. Based on the genetic make-up, we are developing novel drugs to treat old age diseases such as Alzheimer, Cardiovascular diseases, and Cancers. What should we do, for example, to Mongolian babies (Down Syndrome who carries an additional chromosome-21) who do not survive past thirty years? Should we set up committees to draw guidelines for medical professionals so that they will make a rational judgment to determine if child A will receive the precious treatment and will live and child B will not receive the treatment and therefore will die. One person cannot provide answers to these ethical questions. What 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.

The ideas expressed in this article are mine and do not represent NIH Policy.

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