ISSN: 2755-0176

Journal of Cancer Research Reviews & Reports

SCIENTIFIC Research and Community

Research Article

Open Access

Space: The Ultimate Frontier
The Impact of Sequencing Human Genome is not only to Treat all Genetic Diseases, But also to Extend Human Life to Travel into Deep Space in Search of Exo-Planets to Protect, Preserve and Spread Human Intelligence Across the Universe

A Hameed Khan

Department of Genetics & Robotics, Senior Scientist, NCMRR (National Center for Medical Rehabilitation Research), National Institutes of Health (NIH), Adjunct Professor NYLF, Bethesda, Maryland, USA

ABSTRACT

The purpose of this abstract is to show not only to design drugs to treat genetic diseases, but also to extend human life to travel in deep space in search of new homes for humanity and to spread human intelligence in every corner of the Universe. Most genetic diseases are often caused by either a single point mutations or multiple genetic defects in specific genes. Genes code for protein. The nucleotide mutated genes code for non-functional proteins resulting in different diseases such as blood disorders like ß-thalassemia, sickle cell disease, hereditary spherocytosis, Cystic fibrosis, Tay-Sachs disease. Second, additional diseases are identified due to Chromosomal abnormalities which occur when there is a frame shift mutation due to the deletion or insertion of an extra chromosomes such as Down Syndrome, Tay-Sachs disease. and Hemophilia A and B. More than thirty-five thousand such genetic disorders have been identified. The point mutation diseases are inherited.

Treating such diseases present the greatest challenges to the next generation of scientists. The first line of treatment is Gene Therapy and CRISPER-Case9 therapy in which mutated gene is replaced by a normal gene in one generation. In cases where replacement of the mutated gene is not possible, Drug therapy could be developed by designing drugs to shut off those mutated genes. By comparing with all 35,000-point mutations sequences with the Reference Sequence data from the 1000-genome project, we can easily identify with precision and accuracy, the specific mutated nucleotide responsible for causing the genetic diseases due to nucleotide or chromosomal mutations. Once the mutation on the nucleotide in a gene is identified, we can design drugs to shut off that gene. By making AZQ (US Patent 4,233,215), I have demonstrated how to design drugs to shut off frame-shift mutation in a gene responsible for causing Glioblastoma, the brain cancer.

Using the same rationale, it is the challenge for the next generation of scientists (my students) to design drugs to shut off genes to treat genetic diseases and to prolong life. Now, we have learned to convert the analog language of Biology into digital language of computer, by sending convertor and receiver in the spaceships, we can not only send the data across Universe with the speed of light, but also to protect, preserve and spread human intelligence across the Universe

***Corresponding author's**

A Hameed Khan, Department of Genetics & Robotics, Senior Scientist, NCMRR (National Center for Medical Rehabilitation Research), National Institutes of Health (NIH), Adjunct Professor NYLF, Bethesda, Maryland, USA.

Received: January 06, 2024; **Accepted:** January 09, 2024; **Published:** January 20, 2024

Keywords: Human Genome, Point Mutation, Gene Disorder, DNA Repair, Glioblastoma, BBB, Drug Design, Aziridine, Carbamate, AZQ

Note to My Readers

The Impact of Sequencing Human Genomes are 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.

Special Notes

I am describing below the use of highly toxic lethal chemical weapons (Nitrogen Mustard) which was used during WWI and its 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.

Ancient References That Can Be Googled on Your Cell Phone Are Removed

Historical Background

Humanity on Earth are trapped in the middle age dying star system. Our Sun has been burning for the past four and a half billion years. It has used up more than half of its energy. As it cools, the Sun begins to expand, swallowing the nearest two planets, Mercury and Venus. As it continues to cool, it continues to expand, its outer rim reaches Earth; the intense heat boils off our oceans. The approaching excessive heat burns and incinerate all life forms on Earth. Within the next four billion years, the Sun would have used up most of its energy. It will not expand any further. It will collapse on itself. The gravitational forces holding our solar system of nine planets and 140 moons will fall on itself and explode with Titanic force as Supernova resulting in the total destruction of our Solar System.

We have enough time to develop technology to escape Earth and find new home for humanity. More than five thousand exo-planets have been discovered within lightyear distance. It is time to prepare an army of future space travelers. We should move forward with the following important steps: First to increase human age beyond one hundred years, we have discovered TRT gene to extend human lifespan. Next, to find cure for all genetic diseases. Next, we could build fleets of city-sized spacecraft for vertical takeoff like Orian Spacecraft, with new material impenetrable to heat, cold and radiations. Next to develop fusion energy to provide unlimited source of energy to propel spaceships in the direction of the nearest exo-planet at least with half the speed of light. Next, we must develop vaccines against all microbial infections.

We must learn to recycle all life-saving elements, including air, and water in our spaceship for long distance travel. More than five thousand exo-planets have been discovered so far, the nearest is light years away. To reach one of those exo-planets, we need to increase human age. We don't want them to die on our way to settle on a new home for humanity.

One of the greatest challenges the scientists face today is to design drugs to shut off a gene responsible for causing a disease. A gene is a piece of DNA which codes for a protein. Any changes called mutations in the DNA of a gene disrupts the expression of a gene producing an abnormal protein responsible for causing the disease. A point mutation occurs when there is damage to DNA, when a single nucleotide is replaced by another nucleotide resulting in a wrong codon which codes for wrong amino acids in a protein Single base modification, called the monogenic disorders such as a single base substitution, insertion or deletion, when occurring in the coding region of the DNA, alter the expression of a gene. effecting the entire peptide chain.

Monogenic disorders are often the result of single point mutations in specific genes, leading to the production of non-functional proteins. Different blood disorders such as ß-thalassemia, sickle cell disease, hereditary spherocytosis, Fanconi anemia, and Hemophilia A and B are usually caused by point mutations.

Sequencing the entire human genome has identified about six thousand mutated genes responsible for causing six thousand different diseases. We can easily identify those mutations by taking a blood sample from six thousand patients suffering from six thousand different diseases. After extracting the DNA, we can sequence their six thousand different genomes and compare each genome with the Reference Sequence. Once the mutation is identified, we can design drugs to shut off the that specific mutation responsible for causing the disease. The mutation of a DNA nucleotide is caused by damage to DNA either by radiations, chemical/environmental pollutions, viral infection or genetic inheritance.

DNA is made of sugar, phosphate or and nucleotide bases. It is the attack to the nucleotide bases which poses the great damage to DNA. The N-7 Guanine is most basic and most sensitive to be attacked by a positively charged Carbonium ion. Designing drugs to generate a Carbonium ion is the best way to attack the N-7 Guanine to shut off that gene.

It was Professor Ross of London University who first identified the interaction between the Nucleotide, N-7 Guanine and a Carbonium ion to shut off a gene. Ross was studying the data from soldier who died in the tranches during WWII who were exposed to deadliest Nitrogen Mustard gases. Soldiers who died over a period of time showed a sharp decline in the WBC. He immediately realized that Children who suffered from Leukemia showed a sharp increase of WBC. He thought that he could use minimum amount of Nitrogen Mustard to control the WBC and control Leukemia. It is indeed found to be true. To understand the mechanism, He synthesized radiolabeled Nitrogen Mustard and reacted with Nucleotide bases. He discovered that Nitrogen Mustard generate a Carbonium ion which binds to the N-7 Guanine shutting off the gene responsible for causing Childhood Leukemia. His radiolabeled studies showed the Nitrogen Mustard cross-ling both stand of DNA shutting off that gene.

How to Design Drugs to Shut off Genes Carrying Mutations?

A mutation appears when the Genome is exposed to DNA damaging substances such as radiations, carcinogens (chemical/environmental pollution), viral infection or genetic inheritance. The following section describes how many different kinds of mutations appear in our genome leading to different kinds of genetic diseases. The best way to identify theses mutations is to sequence the patient's genome and compare with the Reference Sequence. By comparing with the Reference Sequence, we have identified the following mutations, our greatest challenge is to design drugs to attack that specific mutation and shut off that gene and treat the disease. We provide below the list of not all but most important mutations responsible for different diseases:

Single Nucleotide Mutations

Nucleotide Mutation

In nucleotide mutation, we have either Silence, or Missense. or non-sense nucleotide mutation and they are called point mutation. On the other hand, Insertion and Deletion of a piece of DNA are called frameshift mutation. For example, Sickle cell anemia is caused by substitution while Insertion of apiece of DNA is responsible for causing beta-thalassemia.

Non-Sense Mutation

The changes results in the stop codon (UAG. UAA, UAG) which causes no damage to the replicating cells. Mutation carries a stop codon for example UGG becomes UGA which is a stop codon. Nonsense mutations account for about 10–12% of all inherited human diseases including cystic fibrosis (CF), Duchenne muscular dystrophy (DMD), Usher syndrome (USH), Hurler syndrome (HS), and a variety of cancers. We could rationally design drugs to treat these diseases.

Silence Mutation

Has no effect on the protein synthesis because two different codons codes for the same amino acid for example TTA and TTG codes for the same amino acid Leucine. There is more than one codon that codes for the same amino acid. When designing drugs if you fail to attack A in the first codon, you could design drugs to attack G of the second codon. Silent mutations that cause such skipping of exon excision have been identified in genes thought to play roles in genetic disorders such as Laron dwarfism, Crouzon syndrome, β+-thalassemia, and phenylalanine hydroxylase deficiency (phenylketonuria (PKU)) syndrome. We could rationally design drugs to treat these diseases.

Missense Mutation

Substitution of one amino acid by another amino acid. for example, GLU (glutamine) is replaced by VAL (Valine) causing sickle cell anemia. The red blood cells become sickle instead of circular. Malaria cannot survive on sickle cells. While protected against malaria. Sickle cell clog the blood arteries causing pain and suffering. Missense mutations can render the resulting protein nonfunctional, and such mutations are responsible for human diseases such as Epidermolysis bullosa, sickle-cell disease, SOD1 mediated ALS, and a substantial number of cancers. There is no rational drug design to treat these diseases.

How to Design Drugs to Shut off Single Nucleotide Mutations

For the next generation of scientists, my students, I present below the example of my own doctoral and postdoctoral work of the synthesis of Aziridine, Dinitrophenyl Benzamide (CB1954). Over the years, I synthesized more than one hundred Aziridine analogs to shut off a single nucleotide mutation. Among all of them, CB1954 gives the highest toxicity against Walker Carcinoma 256 in Rats. The detail rationale of their synthesis is described below.

Insertion and Deletion are Frame Shift Mutation

Insertion

During replication if a nucleotide base is lost, the changed codon borrows a nucleotide from the nearest codon to make triplicate codon. The new codon changes the frame to a new codon coding for a different amino acid. Insertion changes all subsequent codons. For example, ATG (codes for methionine), TTA (codes for Leucine) followed by CCT (codes for Proline). Suppose from the sequence ATGTTACCT, the nucleotide A from the codon TTA, is lost. By shifting the frame, the new arrangement gives a new codon which codes for a new amino acid.

The new arrangement will be ATG (codes for methionine, TAC codes for Tyrosine and CTA codes for leucine resulting in a new protein with disastrous consequence to the entire cell. It would be the real challenge for the new generation of scientists to design drugs to prevent the frame shift mutation by Insertion of the previous nucleotide A. Examples of genetic diseases that can be caused by frameshift mutations include Tay-Sachs Disease, Cystic Fibrosis, Crohn's, Charcot-Marie-Tooth Disease (Hereditary Polyneuropathy), and Hypertrophic Cardiomyopathy. A specific frameshift mutation in the CCR5 gene has also been linked to HIV resistance. Additional example includes Crohn's disease, cystic fibrosis, and certain types of cancer are due to frameshift mutations. We could rationally design drugs to treat these diseases.

Chromosomal Mutations

Diseases caused by frame-shift mutation includes certain types of Cancers, Crohn's Cystic fibrosis. HIV, Tay–Sachs disease, and Hypertrophic cardiomyopathy.

Deletion

Example of the frameshift mutations include Crohn's disease, cystic fibrosis, and certain types of cancer.

Glioblastoma & Retinoblastoma

I present below two examples of two deadly diseases caused by Insertion/Deletion of Chromosomal DNA. Over a period of quarter of a century, I developed a sound rational to treat Glioblastoma, the brain tumor. Unfortunately, no such effort is made to develop treatment for Retinoblastoma.

Glioblastoma

In designing AZQ to treat Glioblastoma, I faced the following great challenges: First, our brain is covered by a fatty layer which present a barrier to crossing most drugs. This barrier is called the Blood Brain Barrier (BBB). The BBB filters out most toxic chemicals, but it allows narcotics to cross, I am not allowed to use narcotics to treat Glioblastoma. So I must find a non-toxic, nonaddictive carriers that cross BBB. Once cross the BBB, we must find DNA binding agents to attack Glioblastoma without harming the normal cells. As I said above, Glioblastomas, the brain cancers, is a solid and aggressive tumor and is caused by mutations by deletions on several Chromosomal DNA. Mutations in Glioblastoma DNA is also the result of damage to DNA nucleotides by exposure to radiations, chemical and environmental pollution, viral infections or genetic inheritance.

All known Glioblastomas causing genes are located on five different Chromosomes and carries 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 data, 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. (see detail rationale for the synthesis of AZQ in the following section) 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. A chemical called benzoquinone (a nontoxic, non-addictive substance) has the ability to cross the BBB. With the Quinone ring, I could introduce different combinations of DNA binding Aziridine rings and Carbamate moieties act as prodrug activated in the presence of acid produced cancer cells.) and could create havoc for Glioblastomas. My major concern was how toxic this compound would be to the normal human brain cells. Fortunately, normal brain cells (neurons) do not divide, only cancer cells divide. As I said above, our Rational Drug Design using Aziridine/Carbamate work began in the University of London, England, and completed in the Laboratory of the National Cancer Institute (NCI), of the National Institutes of Health (NIH), in Bethesda, Maryland, USA.

Over a period ten years from UK to USA, we conducted over 500 experiments which resulted in 200 novel drugs. They were all tested against the experimental animal tumors. Forty-five of them were considered valuable enough to be patented by the US Government (US Patent 4,146,622). One of them is AZQ. Radiolabeled studies showed that AZQ has the ability to cross organ after organ, cross the Blood Brain Barrier, cross the nuclear membrane and attack the nuclear DNA shutting off the gene. X-ray studies showed that the radioactivity is concentrated in the tumor region. Glioblastoma stop growing and start shrinking.

A literature search shows that the International Scientific Community recognizes the significance of Dr. Khan's work. Using AZQ, they published more than 300 research papers in scientific literature. NIH considers his work is so valuable and innovative that he was honored with the "2004 NIH Scientific Achievement Award" one of the America's highest awards in Medicine.

Retinoblastoma

Retinoblastoma is an eye tumor and Glioblastoma is a brain cancer Although they both are caused by Chromosomal insertion/deletion mutation. Because I had some success in reducing the size of Glioblastoma, by designing drugs like AZQ, my colleagues mistakenly thought that I would succeed in treating Retinoblastoma.as well. They are wrong. These two tumors develop by two different mechanisms.

Retinoblastoma is rare eye tumor, occurred one in 20,000 kids, cell that makes rods and cones forming the retina, are affected, The gene is 190 kilobase long. If you sequence the Retinoblastoma gene, you find portion of gene is deleted at several places; pieces of DNA are cut out. Such deletion is not enhancing the performance of retinoblastoma, they wipe out important function of the gene we can begin to imagine. Cancer cells develop due to elimination of theses chunk of DNA, rather than their hyper action of their DNA. In spite of these deletions the cell continues to function because the other normal allele takes over. The other allele which is still active and still able to adequately function. Several deletions occur in the chromosome either during replication or chromosol cross-over. The condition appears to get better and then get worst. The mutated Retinoblastoma gene is inherited. By sequencing the egg and sperm of the couple before conception, Retinoblastoma could be stopped by sequencing egg and sperm. Millions of sperms are produced each time. Defected sperm is discarded and a healthy sperm is selected for fertilization. A sperm, (the Y chromosome), is made of 59 million nucleotide base pairs carrying 231 genes. On the other hand, an egg, (the X chromosome) is much larger than the sperm and is made of 164 million Nucleotide base pairs carrying 1,144 genes). Only one mature egg is produced each month. If it is not used, it is washed down. Sequencing is cheaper and faster. Even ABI computer can sequences a thousand nucleotide per second. Nanopore sequencer is much faster. If there is a family history of Retinoblastoma, the couple must go through in vitro fertilization to achieve conception. After conception, any changes to alter the embryo is against the law.

Duplication

Pieces of DNA is copied many times resulting in Duplication. The type IA form of Charcot-Marie-Tooth disease is an example of an inherited human genetic disease that's caused by a gene duplication. Individuals with Charcot-Marie-Tooth disease have damage to their peripheral nerves, resulting in muscle weakness.

Inversion

Research of Chromosome Inversion has been linked to Cytogenetic Abnormality, Leukemia, Myelocytic, Acute, Myeloid Leukemia, Chromosomal Translocation. (DNA sequence is reversed).

Insertion

For example, some diseases caused by insertional mutations include: Fragile X Syndrome., Huntington's Disease., Myotonic dystrophy., Cystic fibrosis.

My own work on the synthesis of AZQ (US Patent 4,233.215) described below to treat Glioblastoma, the brain cancer presents an example of for treating insertion/deletion disease.

Translocation

(DNA sequence is exchanged or swapped) Down syndrome, Translocations occur when two chromosome breaks share time and space. An incorrect pair of ends must then join in trans – generating a translocation – before either of the two correct end-pairs have a chance to join in cis (Translocation Down syndrome. We could rationally design drugs to treat these diseases.

As I said above, different diseases are associated with different mutations, Nucleotide as well as Chromosomal mutations. To understand diseases associated with various organism, scientists started sequencing the genomes of different organism.

In late eighty, scientists at the University of Wisconsin, Madison, announced that they have unravel the genome of the bacterium E. coli which contains four million six hundred thirty-eight thousand eight hundred and fifty-eight base pairs and carries four thousand and three hundred genes. Fifteen percent of the human gene sequence contains part of the E. coli genome. Presently, scientists working on many fronts performing DNA sequencing of a variety of organisms simultaneously. We expect to see scientists in the next few years announcing the DNA sequencing of increasingly complex organism. In summary, using Sanger's method, other groups started sequence the genome of more complex living species and found that a common virus genome is made of 0.1

million base pairs; Yeast is made of 12 million base pairs, Fly Drosophila is made of 180 million base pairs, Tomato is made of 700 million base pairs, mouse is made of 3 billion base pairs. The greatest challenge was to sequence the entire human genome made of 3.2 billion base pairs from mother and 3.2 billion base pairs from father. A total of 6.4 billion base pairs spread over 46 chromosomes.

The Human Genome Project
"Know Thyself'

This phrase was spoken by Socrates more than 2,300 years ago. It was carved into stone at the entrance to Apollo's temple at Delphi in Greece. Socrates believed that the first step to true wisdom is to "know thyself" because only then can one appreciate what one understands and what it remains to be learned. Aristotle agreed that "Knowing yourself is the beginning of all wisdom." For millennia, we had been constantly striving to achieve self-knowledge. Now, we found the answer to the phrase by sequencing human genome. Everything we want to know about ourselves is written in our genome.

As I said above, the entire book of life of all living creatures on Earth is written in four genetic letters called nucleotides. These nucleotides are found in the nucleus of all living cells including humans, plants, and animals. Instruction in a single gene is written in thousands of AT/GC base pairs that are linked together in a straight line and we call them DNA (Deoxyribose Nucleic Acid) - Nobel prize was awarded to Crick, Watson & Morris Wilkins for discovering the double helical nature of the DNA structure which is transcribed into a single stranded of RNA (in mRNA the less water soluble methyl group, Thiamine, (T), is converted to more water soluble Uracil, (U), by replacing Methyl group with a Hydroxyl group) which leaves the nucleus and moves into Cytoplasm where it is translated in Ribosomes into Amino Acids leading to proteins) [1].

When thousands to millions of AT/GC base pairs contain information to make a single protein, we call that portion of AT/GC base pairs a gene (Nobel Prize was awarded to Khorana & Nauenberg for making a functional gene). If we count all the AT/GC base pairs in a single cell of our body, we will find that there are 3.2 billion pairs of bases present in the nucleus of every cell. The entire AT/GC sequence of 3.2 billion base-pair is called the Human Genome or the book of our life which carries total genetic information to make us. The reading of the total genetic information that make us human is called the Human Genome.

In 1990, US Congress authorized three billion dollars to NIH (my institute) to decipher the entire Human Genome under the title, "The Human Genome Project." We found that our genome contains six billion four hundred million nucleotides bases half comes from our father and another half comes from our mother. Less than two percent of our Genome contains genes which code for proteins. The other 98 percent of our genome contains switches, promoters, terminators etc.

The 46 Chromosomes present in each cell of our body are the greatest library of the Human Book of Life on planet Earth. The Chromosomes carry genes which are written in nucleotides. Before sequencing (determining the number and the order of the four nucleotides arranged on a Chromosomes), it is essential to know how many genes are present on each Chromosome in our Genome. The Human Genome Project has identified not only the number of nucleotides on each Chromosome, but also the number of genes on each chromosome. This is how we began our work on sequencing human genome.

As you know, you and I are the loving union of our parents. Our mother's egg receives our father's sperm, and we are conceived. The fertilized egg attaches itself to our mother's womb. It draws nourishment; it grows, divides and multiplies and in nine months, we are born as a complete human being. By the time we are matured that single cell has replicated over one hundred trillion times. Each cell carries the same information as the first cell. We study a single cell.

A single cell is so small that we cannot even see with our naked eyes. We must use a powerful microscope to enlarge its internal structure. Under an electron microscope, we can enlarge that one cell up to nearly a million times of its original size. Under the electron microscope, a single cell looks as big as our house. There is a good metaphor with our house. For example, our house has a kitchen, the cell has a nucleus. Imagine for a moment, that our kitchen has 23 volumes of cookbooks which contain 24,000 recipes to make different dishes for our breakfast, lunch, and dinner.

The nucleus has 23 pairs of chromosomes which contain 24,000 genes which carry instructions to make proteins. Proteins interact to make cells; cells interact to make tissues; tissues interact to make an organ and several organs interact to make a man, a mouse, or a monkey. In every cell of our body, we carry sixteen thousand good genes, six thousand mutated (bad) genes responsible for six thousand diseases and two thousand Pseudo-genes that have lost their functions, during evolutionary time.

The Human Genome: The Greatest Catalog of Human Genes on Planet Earth

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.

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 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 give an organ and several organs interact to make a human [2-6].

More than 20 years have passed since we sequenced the entire Human Genome that is we read the entire book of life of a human being, letter by letter, word by word and sentence by sentence and chapter by chapter (genes) all 46 volumes (Chromosomes) consisting of six billion four hundred million letters (nucleotides), the greatest book of life of a human on planet Earth.

Sequencing exome of a specific organ shows that out of 24,000 genes in our genome, our Brain requires 3,195 genes (to express) to function normally. This is the highest proportion of genes expressed in any part of the body. This study was conducted in identical and fraternal twins; around one-third to one-half of the individual variation in brain measures is due to genetic variations among us, and much of the rest is shaped by environmental factors ranging from education and diet to trauma and stress. While our brain requires 3,195 genes, our heart requires 1,195 genes and eye requires 545 genes. Using the second generation Nanopore sequencers and by comparing with the Reference Sequence, it would be easier, cheaper, and faster to identify mutations responsible for identifying any disorder in those organs.

With the completion of the thousand genome project, we can compare the patient's mutated gene with the thousand Reference Sequence to identify the mutation with precision and accuracy. By sequencing the patient's genome and comparing it with the Reference Sequence, presents an additional advantage that can identify the mutations if it is autosomal, that it is occurred in the first 22 chromosomes (Every child born to an affected parent has a 50% chance of inheriting the genetic variant that causes the disease) or in germ-line cells that is if it is occurred in X and Y chromosomes. Mutations in the X and Y chromosomes are of great concerns because they could be passed on to the future generations.

When Our Perfect Genome Becomes Imperfect?

When our genome is exposed to radiations, chemical/environmental (carcinogenic) pollution, viral infections or genetic inheritance. Undesirable DNA changes called mutations occur in the sequence of the human genome resulting in different diseases. A mutation is a change in DNA sequence. During replication, change could occur either in a single nucleotide or in the entire chromosome. The nucleotide mutation could either the Point mutation or the Frameshift mutation. Point mutation is made of Silence mutation, Missense mutation or non-sense mutation. A point mutation occurs when a codon is substituted by another For example Sickle Cell Anemia occur when a codon for replaced by Valine causing the circular Red Blood Cell to become Sickle.

Diagnosis, Prevention and the Treatment

Is the ultimate goal of sequencing human genome. After diagnosing the mutations in the patient's genome, the next step is the prevention. If there is family history of mental illnesses, to avoid a disease in the next generation a couple can achieve conception by in vitro fertilization that is conception in the test-tube. By sequencing the embryo and selecting and implanting the very best embryo free from all mutations, and finally the treatment either by gene therapy or by drug therapy. Finally, even after successful diagnosis and prevention, treating mental disorders present the greatest challenge. Our brain is the most complex organ in the Universe, and it is protected by a fatty layer called the Blood Brain Barrier (BBB). Prevention is the responsibility of a pregnant mothers.

Diagnosis and treatment of the mental disorders is our responsibility. A smoking pregnant mother should know that her growing fetus is exposed to hundreds of toxic chemicals and many of them are identified as cancer causing. Taking any drug legal or illegal would interfere with the growth and the development of the fetus. About one third of all genetic disorders show some neurological involvement, and many of these represent neurodegenerative diseases of infancy. Genetic or genetically influenced conditions rank among the leading causes of organically based mental retardations. Our challenge is to examine the molecular genetic mechanisms (genomic imprinting, triplet repeats, mitochondrial inheritance (gene mapping, enzymatic function, behavioral genetics, prenatal diagnosis, genetic counselling, epidemiologic studies, animal models, gene therapy and 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 contains 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.

After Sequencing the Human Genome, 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 by drug therapy. Gene editing tools including

TALENs, ZFNs, or CRISPR/Cas-9 platforms have been developed to correct mutations responsible for different diseases.

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 prevents 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.

How To Design Drugs To Shut Off A Gene?

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 the 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 explosive. 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 hero's welcome. 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 as Nitrogen Mustard. During the next 20 years, before the beginning of the 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, defected, and unable to defend the body from microbial infections. Ross rationale was that cancer cells divide faster than the normal cell, by using Nitrogen Mustard 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 [7-12].

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 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 the 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
Nitrogen Mustard Shut Off a Gene by Cross-Linking Both Strands of DNA

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 Methylamine with Ethylene oxide to make 2-bis dihydroxy ethyl methyl amine. It was chlorinated by heating with Phosphorus Penta Chloride in the Phosphoric Acid. If you noticed a faint smell of Mustard Seed, Congratulations, you got Nitrogen Mustard; you cool 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 the solution to make its solid Hydrogen-Chloride salt.

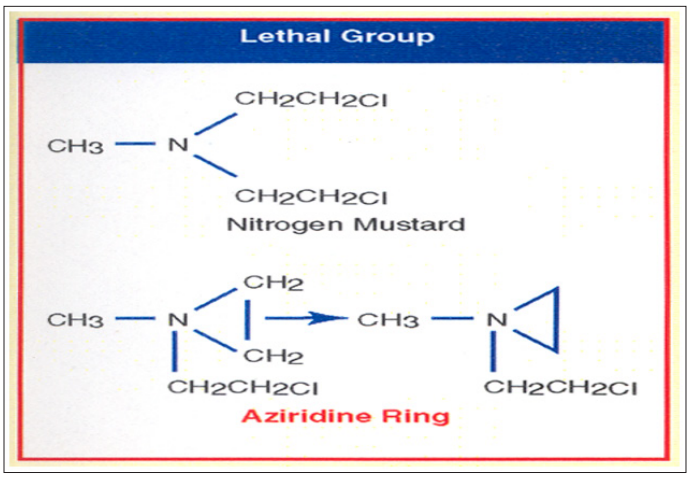
Nitrogen Mustard Hydrogen Chloride salt is separated. No matter how much precautions you take, after the completion of the experiment, if you would take an alcohol swab of working bench or walls, doors, knobs and run a mass spectrum of the alcohol extract, you find a spectral line corresponding to Nitrogen 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 the chemicals are to cancer cells. When tested against Walker Carcinoma 256 in Rats, most Nitrogen Mustards analogs cross-link both strands of DNA and give a CI of ten.

Shutting off a gene by binding to a single strand of DNA
Aziridine Analogs as Anti-Cancer Agents serving as Pro-Drugs

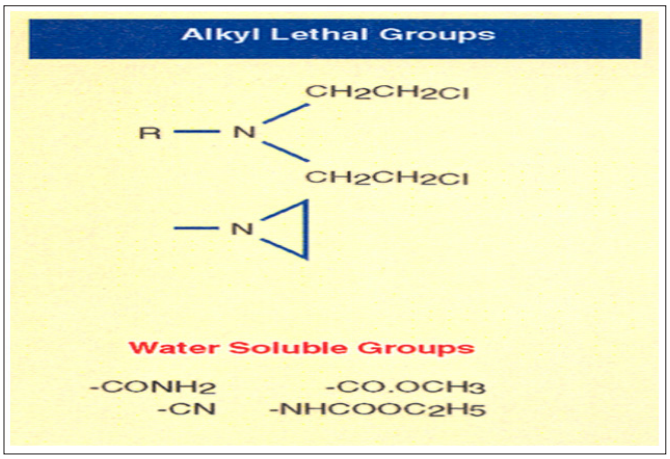
A radiolabel study to understand the mechanism of action of Nitrogen Mustard showed that cross-linking of DNA occurred in two steps. The first step is involved in the formation of a three-member aziridine intermediate which remains stable and inactive in the neutral media (acts as a pro-drug). The second 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 the 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 analog 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.



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.



The above structures are nitrogen mustard (2-bischloroethyl methyl amine) and Aziridine.
DNA binding lethal groups
Designing Drugs Like CB1954 For Treating Point Mutation of Nucleotide Bases To Treat Solid Aggressive Tumor Like Walker Carcinoma 256 In Rats
Synthesis of Point Mutation Drugs

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.

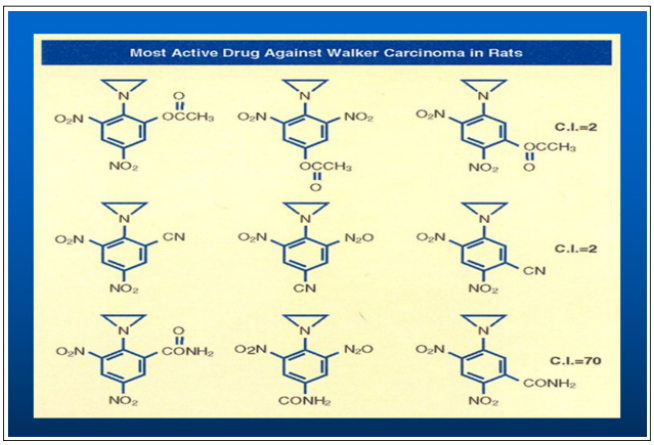
As a part of my doctoral thesis, I decided to use Dinitrophenol as drug delivery method for the active ingredient aziridine. The analog of DNP such as Aziridine Dinitrophenol could also serves as a dye which stains Walker Carcinoma 256, a solid and most aggressive tumor in Rat. The first compound I made 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 method. 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.

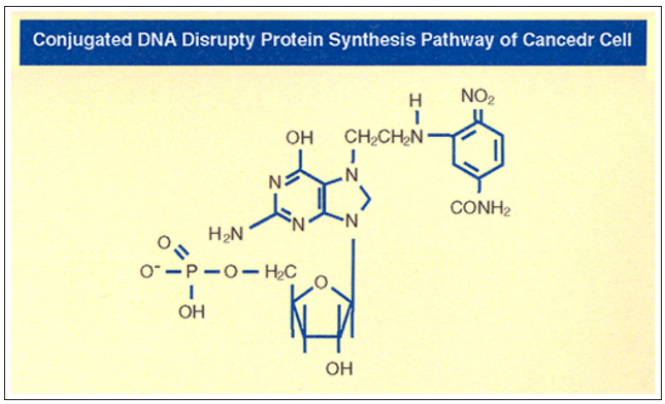
The Least Water-Soluble Substituent

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

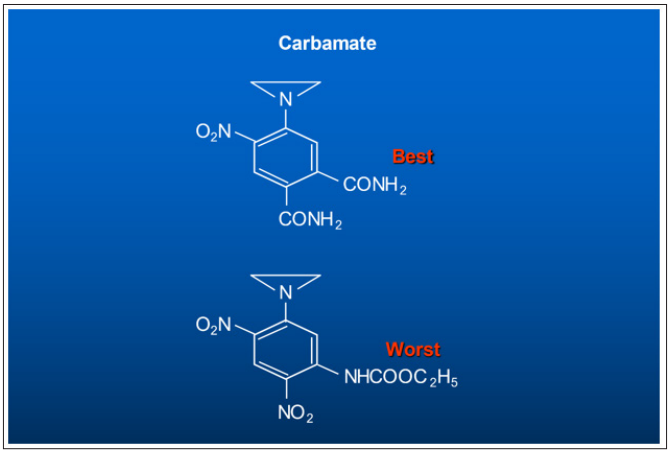
The last line of the above chart showed that the first two Amido groups were sterically hindered and did not bind to DNA and showed no biological activity, but the last compound presents the perfect drug delivery method. The entire drug was delivered from the injection site to the tumor site. The drug 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 [14-16].

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 prodrug 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 stranded 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. To improve drug delivery method, 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 stop the work. Further work in London University was discontinued for safety reason.



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 the animal work to humans.

In developing drugs for treatments, we poison bad DNA selectively. All poisons are a class of chemicals that attacks 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 chemical, 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 a cancerous breast; we still burn cancer cells by radiations; 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 as brutal and savage, but today that is all we have. We hope to develop new treatment for Breast Cancer. Hopes means never ever to give up.

The Human Brain Project

The Human Brain Project in which Swiss are trying to create a computer program that can simulate all of the brain basic features using transistors instead of neurons. So far, they have been able to stimulate the thinking process. of a mouse and a rabbit for several minutes. The goal of this project is to create a computer that can talk rationally like a human being. If build correctly, it should speak and have intelligent enough to behave very much like a human being. This approach is electronic. It attests to duplicate intelligence of brain and to combine a vast array of transistors with tremendous computing power, but a parallel approach is being pursued at NIH in US that is biological instead trying to map out the neural pathway of the brain. This approach is called the human brain initiative. Brain research is advancing though neuro technology. The goal is to unravel the human brain structure itself cell by cell ultimately to map pathway of every neuron of the brain.

Our Brain is a three-pound flesh. It is made of 86 billion neurons. Each neuron is linked to other neuron by 10,000 to 100,000 connections called Synapses. Total number of Synapses, their combination and their permutations exceed the more than 100 trillion connections with other neurons at junctions. Millions of Synapses join to form Neuronal Circuit. That is where our memory is stored. Our memory connects our past present to our future. Through our five senses, we receive a billion bits of data each day. When we sleep, our Brain process the information. A small fraction of the information is retained in Hippo campus and Cerebral Cortex of our Brain, which is the library of our language and our Consciousness.

The rest of the information is discarded. The retained information is restored, retrieved, cut and paste and process faster than any computer. All the information is stored in Neuronal circuits and Cerebral Cortex of our Brain. Neuronal Circuits connects every neuron with every other neuron forming a Wiring Diagram linking the entire Brain. Millions of Neuronal Circuits interact to generate our thoughts and our ideas and our visions. Neuronal circuits serves as an information superhighway through which information flows from Brain through neurons to every part of our body. The complexity of our Brain is the result of three and a half billion years of Biological Evolution. It is a perfect organ in the Universe. It is a seat of our consciousness.

One day something terrible happens to our Brain. A single molecule of a single nucleus of a single neuron is damaged by radiations, chemical/environmental pollution or Viral infection, or genetic inheritance, the whole Brain collapse like a house of card, it becomes non-functional. A single normal cell becomes abnormal leading to cancer forming a tumor called Glioblastoma, one of the deadliest forms of Brain cancer. Brain Cancer is very different from Liver or Lung cancer. For example, if a Liver cell is similarly damaged by radiations or chemical/environmental pollutants. The damaged Liver cell will mutate, divide, multiply, replicate, differentiate, metastasize, invade, and spread, shutting genes after genes and organ after organ killing the patient. It takes years, but not Brain tumor. Glioblastoma is a solid and aggressive tumor. It grows so rapidly within months it becomes so large. Its sheer size will crush the synapses, crush the neuronal circuits and crush the wiring diagram and most patients will internally bleed to death within fourteen months.

Scientists are now working on an ambitious effort to develop technologies to map these connections across the brain, from mice to humans. These detailed wiring diagrams can help uncover the logic of the brain's neural code, leading to a better understanding of how this circuitry makes us who we are and how it could be re-wired to treat brain diseases.

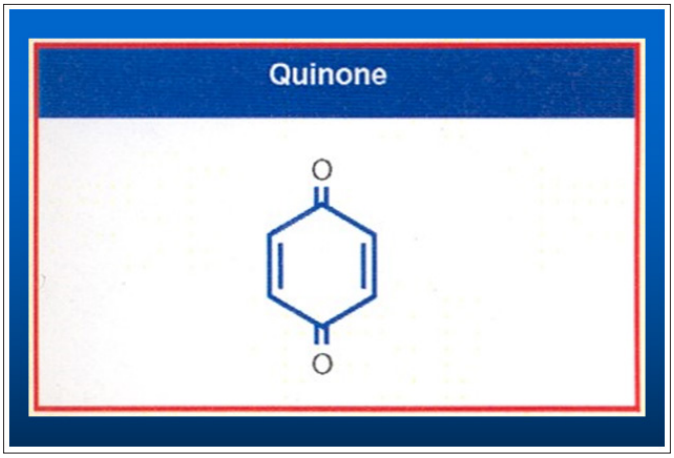
The goal of NIH's contribution is called the Human Brain Imitative whose purpose is to produce insights into brain disorders that will lead to better diagnosis, prevention, and treatment. Building a foundation of understanding of the emergent properties of the brain will provide an opportunity for deeper insights into diseases like Alzheimer, Parkinson, schizophrenia, bipolar illness, autism, epilepsy, attention deficit hyperactivity disorder, traumatic brain injury, and a long list of other brain disorders. Their clinical benefits will be the ultimate payoff of this initiative for human health—but we must be careful not to over-promise the immediacy of such outcomes.

As I said above, the European Human Brain Project plans to convert all 86 billion neurons to electronic circuit. using transistors instead of neurons. The ultimate goal of their project is to identify and treat mental diseases such as Cystic fibrosis: Tay-sacks Disease (TSD), Hemophilia, Parkinson Disease, Huntingdon Chorea, Schizophrenia, Duchenne Muscular dystrophy, Epilepsy, Alzheimer, Klinefelter syndrome, Fragile X syndrome, Down Syndrome and the worst Glioblastoma, the human brain cancer. Most patients die within fourteen months of the diagnosis.

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 serves 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 Like AZQ's to Treat Glioblastoma

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)

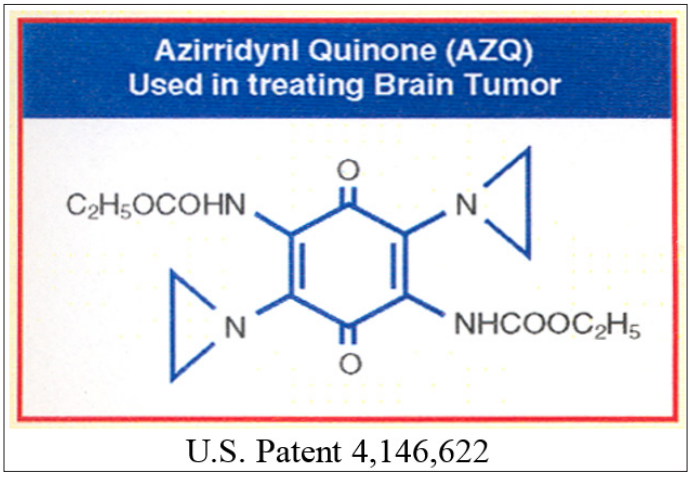
With the Quinone ring, I could introduce two Aziridine rings and two Carbamate moieties and could create havoc for Glioblastoma. Within three years, I made 45 analogs of Quinone. One of the Quinone carries two aziridines and two carbamate moieties which was highly toxic to Glioblastoma. The tumor stops growing and started shrinking. I named the Di-aziridine Dicarbamate Quinone, AZQ. My major concern was how toxic this compound would be to the 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 stop 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 technique 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 [17, 18].

Single Strand 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 cancers, Glioblastomas. Literature search showed that AZQ is extensively studied as a pure drug and in combination with other anti-cancer drugs.



Single Strand DNA Binding Aziridine and Carbamate
As I said above, Glioblastomas, the brain cancers, 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 to DNA nucleotides by exposure to radiations, chemical and environmental pollution, viral infections, or genetic inheritance. The other factors responsible for causing DNA mutations are due to the fast rate of replication of DNA. For example, the bacteria E-coli grows so rapidly that within 24 hours, a single cell on a petri dish 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 gene 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 represent 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 carries 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.

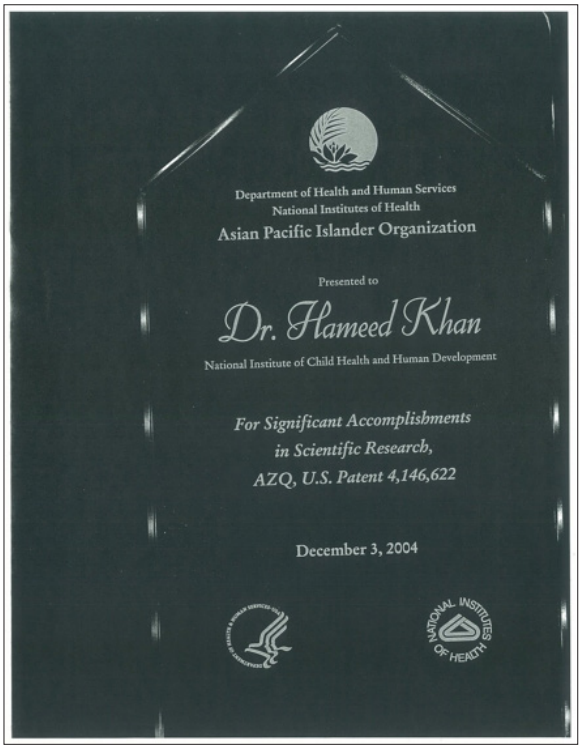
With the completion of 1,000 Human Genome Project, it becomes easier. By simply comparing the patient's genome with the sequencing of 1000-genomes, letter by letter, word by word and sentence by sentence, we could identify the differences called the variants with precision and accuracy, the exact variants, 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).

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 & 4,233,215), a Novel Experimental Drug Specifically Designed to shut off a Gene that causes Brain Cancer for which he receives a 17-year Royalty for his invention (License Number L-0I9-0I/0). To this date, more than 300 research papers have been published on AZQ. The award ceremony was broadcast live worldwide by the Voice of America (VOA). Dr. Khan is the first Indian to receive one of America's highest awards in Medicine.



NIH Scientific Achievement Award

Citation: A Hameed Khan (2024) The Impact of Sequencing Human Genome is not only to Treat all Genetic Diseases, But also to Extend Human Life to Travel into Deep Space in Search of Exo-Planets to Protect, Preserve and Spread Human Intelligence Across the Universe. Journal of Cancer Research Reviews & Reports. SRC/JCRR-196. DOI: doi.org/10.47363/JCRR/2024(6)186

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

Dr. Hameed Khan of NIH was invited to give the "Maharaja Thirumal Memorial Award Lecture" "on the Impact of Genetic Revolution on our lives during 21st Century and Beyond" at the university of Trivandrum. After the lecture, His Royal Highness Sree Padmanabha Dasa Marthanda Varma (the rother-in-law) of Her Royal Highness Maharani Travancore (on his left) invited Dr. Hameed Khan and Mrs. Vijayalakshmi Khan for the Tea at the pattom palace at Thiruvananthapuram on May 12, 1999. Standing on 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.

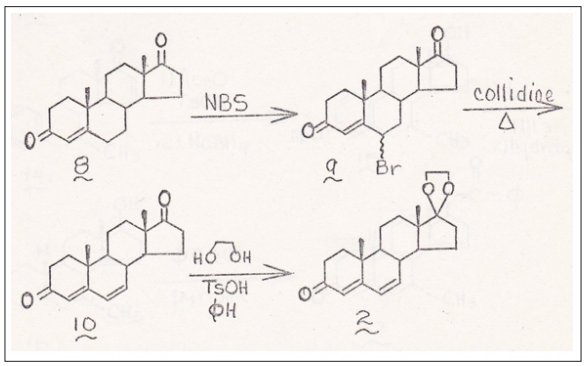
What Other Cancers Should We Explore Next?
Could I use the same rationale for treating Breast tumor?

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

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

In a Breast tumor, within the start and stop codon, BRCA1 gene has captured over two hundred thousand nucleotide bases. The BRCA1 genes carries about three thousand mutations. These mutations are caused by radiations, chemical or environmental pollutants, viral infection or genetic inheritance. To attack the mutated nucleotides among the three thousand cells in BRCA1 gene, I could use male hormone, Testosterone, and bind multiple radio-labeled Aziridine and Carbamate ions to attack BRCA1 mutations. By using MRI, I could show how many radio-labeled nucleotides were bound to which mutations [19, 20]. Out of seventeen positions available

for substitutions on Testosterone. There are only three positions that is 1,3 and 17 positions are available on Testosterone ring system. I could activate position 9 and 10 by reacting with Bromo-acetamide which introduce a Bromo ion on position 10 which could be dibrominated by Collidine to introduce a 9,10 double bond which I could further brominate to produce 9,10 dibromo compound. These bromo ion could be replaced by additional Aziridines or Carbamate ions. I could increase or decrease the number of Aziridine and Carbamate ions to get the maximum benefit by further brominating position 15 and 16 to introduce additional Aziridine and Carbamate moieties.



Carl Djerassi [20] [C. Djerassi et al. J. Amer. Chem. Soc. 72. 4534 (1950)] had 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 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 there are seventeen positions also 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.

Similarly, I could use the female hormone Estrogen and attach multiple Aziridine and Carbamate ions to attack Prostate tumor. Since there are seventeen positions available on Estrogen ring as well; again, I could increase or decrease the number of Aziridine and Carbamate ions to get the maximum benefit. Future generation of scientists (my students) will use this method to develop drugs to treat all cancers [21-44].

Future of Humanity

A Personal Journey

NIH main campus is located about ten miles from Washington DC in the heart of Bethesda. It is made of 50 buildings containing more than three thousand Labs where more than 21,000 scientists work. After completing my Doctorate and Post-doctorate from London University, England, I came to NIH on a Fogarty International fellowship to work in the Laboratory of the National Cancer Institute (NCI). NCI is located in Bldg. 37, I used to work on the 6th floor in the Drug Development Branch. International visiting fellows are provided first rate housing in Bldg. 21. The largest building in the compass is Bldg. 10, called the Clinical Center. Its basement is like a shopping mall. Cafeteria provides the best food; it also has Bank; credit union stores provide all the goods at discount rate. It was a heaven for my wife. She does not have to cook or clean. We used to walk from Building to building. She used to take Advanced English classes in Bldg. 31. NIH was like home to us for years.

Working environment is the best at NIH. Unlimited chemicals and equipment are available. I walked to get all supplies from different buildings. I want. Working hours are flexible. Scientists at NIH are highly productive because there is nothing else to do except to work. I work all the time. Lights are on in all the buildings at all the times. When hungry, I go to Bldg. 10 and when sleepy, I go to Bldg. 21.

A Message to My Students

For our immediate future, sequencing human genome gives us the total information about our book of life. This knowledge also gives us the ability to sequence the book of life of all living creatures on Earth from a tiny blade of grass to mighty Elephant including man, mouse, monkey and microbe. The most important genome is our own genome. Sequencing the personal genome gives us data to analyze our own genome. With the development of the next generation DNA sequencers such as Nanopore Sequencer, we should be able to sequence the genome of every man, woman and child on the face of the Earth cheaper, faster and with precision and accuracy. By the end of this decade, each of us will carry our personal genome data squeezed on a computer chip the size of a penny.

We carry this computer chip on us all the time either at the back of our wrest watch or inserted within our jewelry wearing all the time. In case of medical emergency, the hospital staff could sequence your genome and compare with reference sequence data on your computer chip and diagnose the problem and provide instant medical help. By the end of this decade, we will also be able to provide each of us a genetic card enlisting risk of developing a variety of genetic diseases. We should be able to prepare ourselves for any upcoming diseases and to live a long, healthy and happy life. Our concerns are who will have accesses to this information besides us. How will it affect our life, our family, and our community?

On the other hand, for our distant future, we must do everything to protect, preserve and spread human intelligence in every corner of the Universe. Humans on Earth are trapped in the middle age dying star system. Our Sun has been burning for the past four and a half billion years. It has used up more than half of its energy. As it cools, the Sun begins to expand, swallowing the nearest two planets, Mercury and Venus. As it continues to expand, its outer rim reaches Earth, the intense heat boils off our oceans. The approaching excessive heat burns and incinerate all life forms on Earth. Within four billion years, the Sun would have used up most of its energy. It will not expand any further. It will collapse on itself exploding as Supernova. The gravitational forces holding our solar system of nine planets and 140 moons will fall on itself and explode with Titanic force resulting in the destruction of our Solar System.

Humanity has come on a cross-road. One path leads to total annihilation and destruction of life on Earth, the other provides a

chance to escape. We have to make a choice. One group believes that God has created Heaven and Earth and He alone has the power to save or destroy His creation including us. We live as God wishes. The other group thinks that God has given us enough knowledge, intelligence and wisdom to build the spaceships to escape Earth and travel into deep space to explore His creation and to spread human intelligence in every corner of the Universe. The first path requires nothing from you except prayers. You are on a conveyor belt to Heaven. The other path requires enormous effort from the second group. Preliminary effort has been very successful. First to increase human age beyond one hundred years, we have discovered TRT (Telomerase Reverse Transcriptase) gene to extend human lifespan. Next, we could build fleets of city-sized spacecraft for vertical takeoff like Orian Spacecraft, with new material impenetrable to heat, cold and radiations. Next to develop fusion energy to provide unlimited source of energy to propel spaceships in the direction of the nearest exo-planet at least with half the speed of light.

Next, we must develop vaccines against all microbial infections. We must learn to recycle all life-saving elements, including air, and water in our spaceship for long distance travel. More than five thousand exo-planets have been discovered so far, the nearest is light years away. To reach one of those exo-planets, we need to increase human age. We don't want them to die on our way to settle on a new home for humanity.

The genomic knowledge also gives us the power to affect human evolution not by the slow Darwinian evolution taking tens of thousands of years and hundreds of generations over eon, but by rapid genetic evolution using CRISPER-Cas9 completing changes in next generation. Using the techniques developed by Biotechnology, we can not only cut paste and copy a gene in the next generation, but also to move around the genes from species to species from man to mouse to monkey to mosquito to microbes. We can also control the human evolution by inserting novel genes in early embryos. (Germ-line gene therapy is not permitted at this time- Governments will not provide the funds for such studies, but some modern-day investors could). We can create a Neo-human by selecting the best genes from animal kingdom. Could we cut, paste and copy their genes to make a Neo-human with superior quality.

For example, Cheeta runs faster than human, Birds can fly, Eagles can focus a pray on the ground flying five mile above, Dog smell better, and Turtle carries a protective shell. Humans don't. As we plan to land man on Mars by the end of the next decade, we need all those super genes to travel in deep space. If we plan to settle on Mars, using protective shell genes from Turtle, for example, we can make space suit for the future residents of Mars to protect them from exposure to UV radiations on the surface of Mars. By creating Neo-humans, we face new ethical problems, but as Harold Varmus, one of the former directors of NIH had said. New knowledge could create new problems, but knowledge is always superior to ignorance.

We must face the ethical problems in fast moving technology, advance civilization in the genetically and technologically advanced future. We can provide guide-lines for the residents of Earth only. The residents of exo-planets draw guide-lines for themselves based on their environmental conditions.

CRISPER-Cas9 technology may lead Somatic cell gene therapy where non-sex mutation do not spread to the next generation. But Germ-line gene therapy where sex cells are altered, the decedents carry alterations in the next generations. The next generations Inherit the modified genes.in Germ-line gene therapy could if unchecked would alter the genetic heritage of human race. It means if the modified humans crossbreed with the residents of exo-planets, the new genetic branches of human race might emerge. We have no control on them.

Usually changes by Darwinian Evolution will take tens of thousands of years to modify a trait, but CRISPER-Cas9 technology might reduce that evolutionary change in a single generation, if germ-line gene therapy becomes a reality. In summary, the dream of science fiction writers who speculated about modifying the human race to colonize distant planets. Once considered to be too unrealistic or fanciful. However, with the coming of the CRISPER-Cas9 technology that has become a reality.

NIH Extramural Program

NIH has a budget of $50 billion per year, less than 12% money is spent in-house on the intramural program, bulk of money is spent on the extra-mural program given to universities, research organization and research hospitals as grants, contracts and cooperative agreements. To control the flow of money in the right directions, I volunteered to conduct study sections. Over decades, I conducted dozens of study sections, listened to hundreds of discussions and wrote thousands of summary statements. I believe that most study sections do an outstanding job by supporting research Faily. they move science forward. Many Study Section Chairs believed that NIH must cautiously support Germ-line gene therapy. By providing little funds, NIH will have full control on the data that is being generated. By denying any funds, NIH have no control what private research Labs are doing behind close doors.

NIH Educational Program

The knowledge, we created in over 3,000 Labs in the 26 Institutes of NIH, must be passed on to the next generations of scientists. We must get out of our Labs and passed the new discoveries to students and scholars. I volunteered to teach at nights and over the weekends. The National Youth League Forum Scholar Program provides a unique opportunity to teach the best and the brightest scholars. The Impact of Sequencing Human Genomes are 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 lectures which I delivered at the International Science Conferences. These lectures were evaluated and sent to the NIH Speaker's Bureau. The following evaluation of my lectures were sent to the NIH Speaker's Bureau. All speakers are evaluated in the following three areas:

Citation: A Hameed Khan (2024) The Impact of Sequencing Human Genome is not only to Treat all Genetic Diseases, But also to Extend Human Life to Travel into Deep Space in Search of Exo-Planets to Protect, Preserve and Spread Human Intelligence Across the Universe. Journal of Cancer Research Reviews & Reports. SRC/JCRR-196. DOI: doi.org/10.47363/JCRR/2024(6)186

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

2000 NIH Speaker Bureau Award
Presented to
Dr. Hameed Khan
Dr. Ruth Kirschstein, Acting Director of NIH
&
Dr. Vivian Pinn, Associate Director of NIH
During the NIH/Speaker Bureau's Award Ceremony held on June 12, 2000.

Over the year Dr. Khan has given hundred speeches nationally and internationally. He is discoverer of AZQ (US Patent 4,146,622), a Novel Drug Specially designed to silence a Gene that Causes Brain Cancer. The Main Topic of the Speech is, "The Impact of the Human Genome Project on our Lives During the 21st Century and Beyond." His Aimis 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.

Published the Following Book Chapters
The following Lectures of my students appeared as book chapters and are available to my students on their cell phone at the following website: Facebook.com/hameed.khan.7773

Dr. Khan was Invited as a Speaker at the International Science Conferences by the following countries: Japan, Greece, Saudi Arabia, Marrakesh, Abu Dhabi, Omen, Turkey, India, Sri Lanka, Indonesia, Singapore, Malaysia, Pakistan, Portugal, USA (Philadelphia, and San Diego).

For his decades of his services, Dr. Khan was honored with all three NIH scientific achievement Awards.

"Keep Eyes on the Prize, Professor Walter Ross"

The Future of Humanity
Sequencing human genome gives us the total information about our book of life. This knowledge also gives us the ability to sequence the book of life of all living creatures on Earth. The most important genome is our own genome. Sequencing the personal genome gives us data to analyze our own genome. With the development of the next generation DNA sequencers such as Nanopore Sequencer, we should be able to sequence the genome of every man, woman and child on the face of the Earth cheaper, faster and with precision and accuracy. By the end of this decade, each of us will carry our personal genome data squeezed on a computer chip the size of a penny. We carry this computer chip on us all the time either at the back of our wrest watch or inserted within our jewelry wearing all the time. In case of medical emergency, the hospital staff could sequence your genome and compare with reference sequence data on your computer chip and diagnose the problem and provide instant medical help.

By the end of this decade, we will also be able to provide each of us a genetic card enlisting risk of developing a variety of genetic diseases. We should be able to prepare ourselves for any upcoming diseases and to live a long and healthy and happy life. Our concerns are who will have accesses to this information besides us. How will it affect our life, our family, and our community? On the other hand, we must do everything to protect, preserve and spread human intelligence in every corner of the Universe. Humans on Earth are trapped in the middle age dying star system. Our Sun has been burning for the past four and a half billion years. It has used up more than half of its energy. As it cools, the Sun begins to expand, swallowing the nearest two planets, Mercury and Venus as it continues to expand, its outer rim reaches Earth, the intense heat boils off our oceans.

The excessive heat burns and incinerate all life on Earth. Within four billion years, the Sun would have used up most of its energy. It will not expand any further. It will collapse on itself exploding as Supernova. The gravitational forces holding our solar system of nine planets and 140 moons will fall on itself and explode with Titanic force resulting in the destruction of our Solar System. Humanity has come on a cross-road. One path leads to total annihilation and destruction of life on Earth, the other provides a chance to escape. We have to make a choice. One group believes that God has created Heaven and Earth and He alone has the power to save or destroy His creation including us. We live as God wishes. The other group thinks that God has given us enough knowledge, intelligence and wisdom to build the spaceships to escape Earth and travel into deep space to explore His creation and to spread human intelligence in every corner of the Universe. The first path requires nothing from you except prayers. You are on a conveyor belt to Heaven. The other path requires enormous effort from the second group. Preliminary effort has been very successful. First to increase human age beyond one hundred years, we have discovered TRT gene to extend human lifespan. Next, we could build fleets of city-sized spacecraft for vertical takeoff like Orian Spacecraft, with new material impenetrable to heat, cold and radiations. Next to develop fusion energy to provide unlimited source of energy to propel spaceships in the direction of the nearest exo-planet at least with half the speed of light. Next, we must develop vaccines against all microbial infections. We must learn to recycle all life-saving elements, including air, and water in our spaceship for long distance travel. More than five thousand exo-planets have been discovered so far, the nearest is light years away. To reach one of those exo-planets, we need to increase human age. We don't want them to die on our way to settle on a new home for humanity.

The genomic knowledge also gives us the power to affect human evolution not by the slow Darwinian evolution, but by rapid genetic evolution. Using the techniques developed by Biotechnology, we can not only cut paste and copy a gene, but also to move around the genes from species to species from man to mouse to monkey to mosquito to microbes. We can also control the human evolution not by slow Darwinian evolution but by rapid genetic engineering. (Such studies are not permitted at this time- Governments will not provide the funds for such studies, but some modern-day investors could). We can create a Neo-human by selecting the best genes from animal kingdom. Could we cut, paste and copy their genes to make a Neo-human. For example, Cheeta runs faster than human, Birds can fly, Eagles can focus a pray on the ground flying five mile above, Dog smell better, and Turtle carries a protective shell.

Humans don't. As we plan to land man on Mars by the end of the next decade, we need all those super genes to travel in deep space. If we plan to settle on Mars, using protective shell genes from Turtle for example, we can make space suit for the future residents of Mars to protect them from exposure to UV radiations on the surface of Mars. By creating Neo-humans, we face new ethical problems. New knowledge could create new problems, but knowledge is always superior to ignorance.

Conclusion

NIH is a microsome of America and America is a nation of immigrants. The Irish came; the Polish came and the Swedish came. People of the Asian origin is last to arrive at the shores of this great county. Two important reasons brought them to this great country. First, America is a land of opportunity. From its very beginning, it opens its gates to all the people regarded less of race, religions or place of origin. Today, the doors remain open; they still come bringing their knowledge, their skills, their hopes, their dreams and their willingness and determination to work hard and succeed and if they fail, their more ambitious children will climb the ladder of success and get to the promised land. While President John Kennedy, a child of Irish immigrant who captured the number one spot by becoming the President of United States, our Vice President, Kalama Herris, is another supremely successful example of An Asian immigrant woman who captured the second highest spot in this country.

This has created the greatest ethnic diversity nowhere to be found in the world and has made Americans the most generous and tolerant people in the world to welcome a million immigrants into this great country. Second reason, America's love of freedom. It gives them the freedom of speech, freedom to practice their own religions, freedom to read and write any part of the literature, freedom to conceive novel scientific and business ideas and freedom to translate theories into practice concepts into results. In this climate new ideas, new capabilities could flourish and Flourish they have. This has resulted in technological achievements in this country unmatched by any other nations on Earth. This made America the greatest country in the world. The best schools are here; the best colleges are here. The best medical centers are here. Americans today live in the most prosperous society mankind has ever created. And the best medical center of them all is (National Institutes of Health).

For the past hundred years, NIH has become the citadel of research and learning and it is home to some of the greatest minds in the world. More Nobel Laureates walk through the streets of NIH than anywhere on the face of the world. The discovery they make here benefit more than eight billion peoples around the world. The immigrants' children who are born and raised in this country have a unique opportunity to go to best schools, best colleges and the best universities to climb the ladder of success and capture the number one spot, the greatest office, the Presidency in this country, who among you would be the next president John Kennedy, and who among you would be the next Kamala Herris the next vice president of this country. Who among you would be the vanguard of research and technology to send human intelligence across Universe from the greatest county in the world. We bequeath the future of this country in your hands; we know you will do your best to keep America the sole remaining super power of the world, a jewel in the crown, a beacon of light and a shinning city on the hill.

The Ideas Expressed in this Article Are Mine and Do Not Represent NIH Policy.

References

1. Watson JD, Crick FHC (1953) A structure for deoxyribose nucleic acid. Nature 171: 737-738.
2. Lander ES, Linton LM (2001) The Impact of Sequencing Human Genome on Genomic Food Nature 409: 934-941.
3. Lander ES, Linton LM (2001) Initial sequencing and analysis of the human genome. Nature 409: 660-921.
4. International Human Genome Sequencing Consortium (2004) Finishing the euchromatic sequence of the human genome. Nature 431: 931-945.
5. Lindblad-Toh K, Wade CM, Mikkelsen TS, Karlsson EK, Jaffe DB, et al. (2005) Genome sequence, comparative analysis and haplotype structure of the domestic dog. Nature 438: 803-810.
6. Shendure J, Balasubramanian S, Church GM, Gilbert W, Rogers J, et al. (2017) DNA sequencing at 40: past, present and future. Nature 550: 345-353.
7. Ross WCJ (2015) Drug Information: Description, User Reviews, Drug Side Effects, Interactions – Prescribing Information at RxLis Chlorambucil. Journal of the American

Chemical Society 136: 5860-5863.
8. Ross WCJ (1953) The Chemistry of Cytotoxic Alkylating Agents In Advances in Cancer Academic Press 397-449.
9. Ross WCJ (1962) Biological Alkylating Agents. Butterworth, London https://journals.sagepub.com/doi/10.1177/146642406208200223.
10. Ross WCJ (1949) Journal of Chemical Society. 183.
11. Ross WCJ (1950) J. Chem. Soc. 2257.
12. Ross WCJ, Mitchley BCV (1964) Ann. Rep. Brit. Empire Cancer Campn 42: 70.
13. Ross WCJ (2007) Melphalan and prednisone plus thalidomide versus. Melphalan Lancet 370: 1209-1218.
14. Cobb LM, Connors TA, Elson LA, Khan AH, Mitchley BCV, et al. (1969) 2,4-Dinitro-5-Ethyleneiminobenzamide (CB 1954): A Potent and Selective Inhibitor of the Growth of the Walker Carcinoma 256. BIOCHEMICAL PHARMACOLOGY col 18: 1519-1527.
15. Khan AH, Ross WCJ (1969/70) Tumour-Growth Inhibitory Nitrophenylaziridines and related compounds: Structure-Activity Relationships PART I. CHEM.-BIOL INTERACTIONS 1: 27-47.
16. Khan AH, Ross WCJ (1971/72) Tumour-Growth Inhibitory Nitrophenylaziridines and related compounds: Structure-Activity Relationships. CHEM.-BIOL INTERACTIONS 4: 11-22.
17. Hameed Khan A, John Driscoll (1976) Potential Central Nervous System Antitumor Agents: Aziridinylbenzoquinones. PART I. JOURNAL OF MEDICINAL CHEMISTRY 19: 313-317.
18. Chou Ed, Hameed Khan A, John Driscoll (1976) Potential Central Nervous System Antitumor Agents: Aziridinylbenzoquinones. PART II. JOURNAL OF MEDICINAL CHEMISTRY 19: 1302.
19. Hameed Khan A (2021) The Impact of Diagnostic MRI on the Early Detection of Lethal Genes in Human Genome and to Develop Genomic Medicine to Treat Brain Cancers. J Med - Clin Res & Rev 5: 1-9.
20. Hameed AK (2021) The Impact of Diagnostic MRI on the Early Detection of Lethal Genes in Human Genome and to Develop Genomic Medicine to Treat Brain Cancers. J Med - Clin Res & Rev 5: 1-9.
21. Hameed Khan (2018) The Impact of Sequencing Human Genome on Drug Design to Treat Oral Cancer. IntechOpen https://www.intechopen.com/chapters/63395
22. Ala-Eddin Al Moustafa (2017) Development of Oral Cancer – Risk Factors and Prevention Strategies. Springer https://link.springer.com/book/10.1007/978-3-319-48054-1
23. Hameed AK (2021) The Impact of Diagnostic MRI on the Early Detection of Lethal Genes in Human Genome and to Develop Genomic Medicine to Treat Brain Cancers. Clin Res & 5: 1-9.
24. Berhardt LV (2021) e-Book, The Impact of Sequencing Human Genome on Genomic Medicine and the Discovery of AZQ (US Patent 4,146,622) Specifically Designed to shut off genes that cause Brain Cancer Chapter I. NOVA Medicine and Health 180 1- 63.
25. Abdul Hameed Khan (2021) The Rational Drug Design to Treat Cancers: Drug Design - Novel Advances in the Omics Field and Applications. London 117.
26. Hameed Khan (2021) The Impact of Sequencing Human Genome on Genomic Food & Medicine International Journal of Genetics and Genomics 9: 6-19.
27. Hameed Khan (2021) The Impact of Sequencing Genomes on The Human Longevity Project. J Med - Clin Res & Rev 5: 1-12.
28. Hameed AK (2021) The Impact of Diagnostic MRI on the Early Detection of Lethal Genes in Human Genome and to Develop Genomic Medicine to Treat Brain Cancers. J Med - Clin Res & Rev 5: 1-9.
29. Hameed AK (2021) The Impact of Sequencing Genomes on The Human Longevity Project. J Med - Clin Res & Rev 5: 1-12.
30. Hameed Khan (2021) The Impact of Sequencing Human Genome on Genomic Food & Medicine. International Journal of Genetics and Genomics 9: 6-19.
31. Hameed Khan (2021) ADVANCES IN MEDICINE AND BIOLOGY, VOLUME 180, The Impact of Sequencing Human Genome on Genomic Medicine and the Discovery of AZQ https://novapublishers.com/shop/advances-in-medicine-and-biology-volume-180/
32. Hameed Khan A (2021) The Rational Drug Design to Treat Cancers Chapter 5 Drug Design - Novel Advances in the Omics Field and Applications Page 95-115.
33. Abbreviated Key Title: EAS J Biotechnol Genet (Online) Published by East African Scholars Publisher, Kenya https://www.ipindexing.com/journal-details/EAS-Journal-of-Biotechnology-and-Genetics/1236
34. Hameed Khan (2021) Genomic Medicine: Using Genetic Make-up of the Human Genome, Genomic Medicine: Using Genetic Make-up of the Human Genome, AZQ was Designed to Treat Glioblastoma, the Brain Tumor. Nov Appro in Can Study https://crimsonpublishers.com/nacs/fulltext/NACS.000634.php
35. Hameed Khan A (2021) The Impact of Sequencing Human Genome on Cancer Chemotherapy. J Can Res Rev Rep 3: 1-10.
36. Hameed Khan A (2021) The Impact of Sequencing Genomes on the Under¬standing of the Origin of Life on Earth. Bi¬omed J Sci & Tech Res 40: 32008-32022.
37. Hameed Khan A (2022) The Impact of Sequencing Human Genome on the Genetically Engineered Life. J. Cancer Research and Cellular Therapeutics. 6(1); DOI:10.31579/2640-1053/102.
38. Hameed Khan A (2022) Sequencing the Human Genome to Study the correlation between Genes and Violence. Horizon publishers
39. Hameed Khan A (2022) The Impact of Sequencing Human Genome on the 2nd Genesis on Earth, Journal of Current Trends in Agriculture, Environment and Sustainability. Katalyst publisher https://www.youtube.com/watch?v=z4BGzLNSgpY
40. Hameed Khan A (2022) Assessment of Human Genome Sequencing on the New-World Order. Research Aspects in Biological Science 4: 978-993.
41. Hameed Khan A (2022) The Impact of Sequencing Human Genome on Novel Drug Delivery Method to Treat Cancers. International Journal of Genetics and Genomics 10: 64-78.
42. Hameed Khan A (2022) The Impact of Sequencing Human Genome on New Eugenic., The Impact of Sequencing Human Genome on the 2nd Genesis on Earth. J Cur Tre Agri Envi Sust 5: 1-21.
43. Hameed Khan A (2023) The Impact of Sequencing Human Genome on Idiopathic Diseases. Biomedical Sciences 5: 2421-2437.
44. Hameed Khan A (2023) The Impact of Sequencing Human Genome on Darwinian Evolution. Khan H. J Can Ther Res 3: 1-50.