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The Impact of Sequencing Human Genome on Novel Drug Delivery Method to Treat Cancers

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Abstract: Sequencing Human Genome has identified 24,000 genes in our genome. Out of which six- thousand genes are mutated and are responsible for causing six thousand different diseases including old age diseases such as Alzheimer, Cardiovascular Disease and Cancers. Of all the cancers, brain cancer is most difficult to treat. The drug delivery methods require to transport active drugs components from the injection site to the target site. To treat all mental illnesses including brain cancer, the greatest challenge for most scientists is to deliver drug across the natural filter called, the Blood Brain Barrier (BBB). Besides addictive narcotics, most drugs are filtered out by BBB. Of all the cancers, developing drugs to treat brain cancer presents the greatest challenge. Glioblastoma is the solid, aggressive and the deadliest form of brain cancer. Once diagnosed, most patients die within fourteen months of their diagnosis. By making AZQ (US Patent 4,233,215), I have demonstrated, a novel drug delivery method by attaching Quinone, a non-addictive, non-toxic chemical as a carrier, I could deliver prodrug moieties like Aziridines and Carbamates across BBB to attack Glioblastoma, the brain tumor. Once it crosses the BBB, AZQ, a prodrug, remains inactive at natural pH, but it is activated by the growing brain tumor. To grow, the Glioblastoma uses glucose as a source of energy. Glucose is broken down to produce Lactic Acid. In the acidic media, the prodrug moieties Aziridines and Carbamates are activated producing the most powerful Carbonium ions which attack the tumor DNA shutting off the genes. Instead of growing, the Glioblastoma starts shrinking. By making AZQ and using Quinone as a drug delivery chemical across BBB, I opened the path to attack all other mental illnesses such as Epilepsy, Schizophrenia, Bipolar disorder, Depression, Anxiety disorders, Paranoia, Psychosis and Aggression. In future, male and female hormones could be used to deliver active drug components such as aziridines and carbamates to attack Breast and Prostate cancers.

Keywords: Glioblastoma, Aziridines, Carbamate, Quinone, Blood Brain Barrier, AZQ

1. Introduction

To understand the basis of all diseases, we must read and understand the total genetic information that makes us humans that is to read our genome which is our normal book of life. What makes our normal book of life abnormal? What changes make us sick and how can we treat them? That is how the story of our book of life begins: As we all know that we are the loving union of our parents. Our mother's egg receives our father's sperm, and we are conceived. The fertilized egg carries complete information to make us. More than seventy years ago, the Nobel Laureate, Irvin Schrödinger, examined for comparison, the fertilized egg of a human, mouse, and monkey under a microscope. He observed that all fertilized eggs look the same and yet first fertilized egg carries the instructions to make a man, the second carries the information to make a mouse and third carries the information to make a monkey. He postulated that there exists a secret code within those fertilized eggs; he called that secret code, the Script Code now known as the Genetic Code. To understand the secret code, we must examine the internal structure of the fertilized egg. He proposed that we examine three "C". The first C stands for the chromosome, the coloring bodies inside the cell. The traits to make man, mouse or monkey must be located on the Chromosomes. These traits must be held together tightly by the second C, the covalent bonds that hold them tightly together. As the living cells grow, they must have the ability

to copy the instructions accurately that copying is the third C. The Genetic Code to make man, mouse or Monkey must be written on the Chromosomes. He stated that if we break the Genetic Code, we would be able to unlock the secrets of life. If we unlock the secrets of life, we will understand how evolution puts the traits together over millennia to separate man, from mouse and mouse from monkey. If we unlock the secrets of life, we would be able to understand how the normal cells work and how the normal cells become abnormal leading to all diseases including cancerous.

On further examination of the Chromosomes, we learned that the chromosomes are made of four chemicals, and we also found that the essence of life is information and information is located on these four molecules called nucleotides bases which are the building blocks of all living creatures from a tiny blade of grass to mighty elephant including, man, mouse, monkey, mosquitos or microbes. These bases are made of Deoxy Ribonucleic Acid (DNA). DNA is made of a string of nucleotides. It is a store house of information and is made of the same four nucleotide bases and they are: Adenine (A), Thymine (T), Guanine (G), and Cytosine (C). According to Crick's Central Dogma, [1] the information flows from the DNA which is transcribed into RNA which is translated in Ribosome into proteins. RNA is converted into an active form and is transcribed into RNA (or messenger RNA) by converting Thymine to active form Uracil (U) and from a double stranded DNA to a single stranded RNA and where the sugar Deoxy Ribose is replaced by sugar Ribose. The RNA is translated by Ribosome into proteins.

Gene Expression begins in Ribosome when a 4-letter genetic text is converted to a three-letter Codon. By comparing Gene Profiles of normal genes with mutated genes, one can identify with precision and accuracy the exact location of mutated (altered or damage) nucleotide responsible for causing the diseases. Comparing Gene Profiles is an excellent diagnostic method which helps us design drugs to specifically shut off the mutated genes. Delivering drugs from injection site to the target site is the essential way of treating diseases.

More than seventy years ago, Schrödinger was using such a poor resolution microscope that we don't even use in our high school today. Instead, we have electron microscope. We can magnify the same fertilized egg to a million times of its original size, almost the size of a house. What we observe inside the fertilized egg is very analogous to the house. The house has a kitchen; the cell has a nucleus. Suppose your kitchen has a shelf which contains 46 volumes of cookbooks which contain 24,000 recipes which carry instructions to cook food for your breakfast, lunch, and dinner. The nucleus in the fertilized egg contains 46 chromosomes; (23 from our mother and 23 from our father), which carry 24,000 chapters called genes. Genes are units of inheritance which code for all 20 amino acids. Hundreds of amino acids join to form a protein and thousands of proteins interact to make a cell. Millions of cells interact to make an organ and several organs interact to make a man or a mouse or a monkey. The number and the order of the nucleotides determine the composition of a species.

If the cookbook in your kitchen is written in English language, it uses 26 letters, but the book of life of all living creatures is written in 4 letters and they are A, T, G and C. These are the initials of four chemicals called nucleotides found in the nucleus of all living creatures and they are Adenine (A), Thymine (T), Guanine (G) and Cytosine (C) found the nucleus of all living cells. Nucleotides are made of sugar Ribose (Deoxy Ribose in DNA and Ribose in RNA), a phosphate group and one of the four above Nitrogen bases, two Purines and two Pyrimidines and the Thymine is converted to Uracil in RNA. The total genetic information to make any living creature, called it genome, is based on the above four-letter text and out of these four letters, only three letter Codon which carries the Genetic Code for an amino acid (such as GUU is for amino acid Valine, GCU is for Alanine, GAA is for Glutamine etc.) the building blocks for all proteins. Sixty-four codons code for 20 amino acids and codons for all 20 amino acids have been decoded. All living creatures use the same genetic code from a tiny blade of grass to Mighty Elephant including man, mouse, and monkey. A string of these nucleotides is called the DNA (Deoxy Ribonucleic Acid). Reading the number and the order of nucleotides are called genome sequencing.

In 1990, United State Congress authorized three billion dollars to NIH to decipher the entire human genome within 15 years that is to read the total genetic information that makes us human called the Human Genome Project. Thousands of scientists from six industrialized nations and 20 biomedical centers joined our effort and within 13 years the entire human genome was deciphered and published in the Scientific Journal Nature and linked to website. If you have access to a computer keyboard, you have access to all that information.

On April 14, 2003, Dr. Francis Collins, the past Director of NIH announced that we read the book in which God created life. We read the book of life of a human being letter by letter, word by word, sentence by sentence and chapter by chapter. All 46 volumes (Chromosomes) containing 24,000 chapters (Genes) consisting of six billion four hundred million letters. In a few sentences, the described the Human Genome Project, the greatest biological experiment ever conceived by human mind. It will answer the most fundamental questions we have asked ourselves since the dawn of human civilization, what does it means to be human, what is a nature of our memory and our conscientiousness and our development from a single cell to a complete human being, the biochemical nature of our senses, the process of our aging. The scientific basis of our similarity and dis-similarity; similarities that all living creatures from a tiny blade of grass to the mighty elephant including man, mouse and monkey are all made of the same chemical building blocks and yet they are so diverse that no two individuals are alike even identical twin are not exactly identical, they grow up to become to separate individuals.

We deciphered all 46 chromosomes. What surprised us

most was that our genome contains six billion four hundred million nucleotide bases less than two percent of our Genome contains genes which code for proteins. The other 98 percent of our genome contains non-coding regions which carries switches, promoters, terminators etc.

Before sequencing (determining the number and the order of the four nucleotides), it is essential to know how many genes are present in our Genome. 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 nucleotides bases and it has only 2,610 genes. The chromosome (2) contains 255 million nucleotides bases and has only 1,748 genes. The chromosome (3) contains 214 million nucleotide bases and carries 1,381 genes. The chromosome (4) contains 203 million nucleotide bases and carries 1,024 genes. The chromosome (5) contains 194 million nucleotide bases and carries 1,190 genes. The chromosome (6) contains 183 million nucleotide bases and carries 1,394 genes. The chromosome (7) contains 171 million nucleotide bases and carries 1,378 genes. The chromosome (8) contains 155 million nucleotide bases and carries 927 genes. The chromosome (9) contains 145 million nucleotide bases and carries 1,076 genes. The chromosome (10) contains 144 million nucleotide bases and carries 983 genes. The chromosome (11) contains 144 million nucleotide bases and carries 1,692 genes. The chromosome (12) contains 143 million nucleotide bases and carries 1,268 genes. The chromosome (13) contains 114 million nucleotide bases and carries 496 genes. The chromosome (14) contains 109 million nucleotide bases and carries 1,173 genes. The chromosome (15) contains 106 million nucleotide bases and carries 906 genes. The chromosome (16) contains 98 million nucleotide bases and carries 1,032 genes. The chromosome (17) contains 92 million nucleotide bases and carries 1,394 genes. The chromosome (18) contains 85 million nucleotide bases and carries 400 genes. The chromosome (19) contains 67 million nucleotide bases and carries 1,592 genes. The chromosome (20) contains 72 million nucleotide bases and carries 710 genes. The chromosome (21) contains 50 million nucleotide bases and carries 337 genes. The Chromosome-22 contain 56 million nucleotide base pairs and carries 701 genes. Finally, the sex chromosome of all females called the (X) contains 164 million nucleotide bases and carries 1,141 genes. The male sperm chromosome (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 or less. The remaining genes are called the pseudo genes. Since these genes are not routinely used, they are broken and have lost their functions. For example, millions of years ago, humans and dog shared some of the same ancestral genes; we both carry the same olfactory genes. Since humans don't use these genes to smell for searching food, these genes are broken and lost their functions in humans, but we still carry them. We call them Pseudogenes. Recently, some Japanese scientists have activated the pseudogenes, this work may create ethical problem in future as more and more pseudogenes are activated. [2-6].

The above DNA nucleotide bases constitute the genetic map of the normal human being what makes it abnormal and makes us sick is the mutations in the coding regions of the genome. As I said above, less than two percent of the genome codes for amino acids. Slightest damage to the coding regions of the four nucleotides A, T, G and C either by exposure to ionizing radiations, or chemical environmental pollution, genetic inheritance, viral infection or by insertion, deletion, or inversion of the nucleotide bases code for wrong or abnormal amino acids resulting in diseases.

Out of 24,000 genes, 16,000 are good genes which produce good proteins that keep us healthy. These genes produce protein like Insulin for treating diabetics; thousands of scientists are working in about three thousand biotechnology firms producing good proteins. There are about six thousand bad genes which are mutated, and they are responsible for causing six thousand different diseases. About three thousand mutated genes are identified as responsible for causing diseases. Single genetic defect can be treated with the Gene Therapy by replacing the bad genes with the good genes. Most diseases are due to multiple genetic defects. They cannot be treated with Gene Therapy, but Drug Therapy will work. Treating multiple genetically defected diseases with novel drugs is a laborious and expensive process. It requires a series of safety and efficacy and drug delivery tests before it goes for clinical trials in humans.

In Gene Therapy, a single mutated gene could be replaced by a normal gene. The most successful example of Gene Therapy is the treatment of SCAD (Sever Combined Immuno-Deficiency Syndrome). French Anderson and Mike Blasé the fathers of Gene Therapy at NIH, cut, paste, and copy the normal gene in vitro, harvested normal SCAD genes in the WBC obtained from the patient and returned to the same patient the harvested normal cell to cure SCAD. More than three thousand single nucleotide mutated genetic diseases have been identified so far. Diseases like Cancer, Cardiac and Diabetic illnesses are due to the multi-nucleotide genetic mutations. These diseases cannot be treated by Gene Therapy, but Drug Therapy will work.

How do you stop the growth of the multi-nucleotide mutated genetic diseases producing solid tumor like Glioblastoma, the most aggressive brain tumor? We need equally powerful weapon to destroy this solid aggressive tumor. The pioneering work to attack solid tumor was done by Professor WCJ Ross of London University, England. He developed a series of biological alkylating agents like Nitrogen mustards which cross-linked the double stranded DNA shutting off genes. Nitrogen mustards are extremely toxic substances and were developed and used during World War I (WWI) and it more toxic analogs were developed during World War II (WWII) as chemical weapons. I was a graduate student of Professor Ross at the London University then I was his Post-Doctoral Fellow and then was his Special

Assistant. I worked for him for almost ten years at the University of London making analogs of Nitrogen Mustard as anti-cancer drugs.

Most drugs are fat soluble and stay at the injection site. One of the greatest challenges of treating diseases is to deliver drugs from the injection site to the target site. The purpose of structure-activity relationship is to design drugs which is equally soluble in fat and water so that the drug moves across fat layer to water layer with equal ease to reach the target site. A drug which has a partition coefficient (ratio between fat and water) of one is equally soluble in water and fat, they are highly active. To move drug from injection site to the target site, the partition coefficient should be as close to one as possible because the drug must move layers of fat and water.

The National Institutes of Health, NIH, if the greatest biomedical center in the world, the microcosmos of America? It is in Bethesda, Maryland, USA. Only America, the leader of the free world, could provide NIH $50B annually supporting 27 institutes in thousands of Labs hiring more than 20,000 scientists from around the world. Of all the 27 institutes, National Cancer Institute (NCI) has the largest budget, it is over $5B. My Lab was in NCI. I was educated in England and graduated from the University of London. After receiving my doctorate and post doctorate from the University of London and working at the Royal Cancer Hospital, I came to NCI as the Fogarty International Fellowship awardee. My assignment is to design drugs to treat cancers. While working at the Royal Cancer Hospital, I had already sent 120 novel drugs for the NCI screening program. Of all the drugs I made, one of them CB1954 showed the highest toxicity ever recorded when tested against the Walker Carcinoma 256 in Rats, I was invited to translate my work from animals to humans.

Cancers

At NCI (National Cancer Institute), we received thousands of old and new drugs from the around the world for the cancer screening program. Cancer is the leading cause of death and has surpassed the death of cardiovascular diseases. Over 636,000 people died of cancer; 1.9 million new cases will be diagnosed this year including 78,000 Prostate Cancer, 40,000 Breast cancer, 16000 Lung and Bronchus Cancer and 15,000 Colon and Rectal Cancer. Once diagnosed by Gene Sequencing, the next step is to design drug to shut off those genes.

2. The Rational Drug Design to Deliver Drugs for Treating Cancers

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

The supreme intellect for Drug Design is Ross, an Englishman, who is a Professor of Chemistry at the London University. Ross was the first person who designed analogs of Nitrogen Mustards drugs for treating Cancers. Nitrogen Mustard cross-link both strands of DNA that we inherit one strand from each parent. Cross-linking agents such as Nitrogen mustard are extremely toxic and were used as chemical weapon during the First World War (WWI). More toxic derivatives were developed during the Second World War (WWII). Using the Data for the toxic effect of Nitrogen Mustard used during the First World War (WWI), Ross observed that Soldiers exposed to Nitrogen Mustard showed a sharp decline of White Blood Cells (WBC) that is from 5,000 cell/CC to 500 cells/CC. Children suffering from Childhood Leukemia have a very high WBC count over 90,000 cells/CC. In sick children, most of the WBCs are premature, defected, and unable to defend the body from microbial infections. Ross used analogs of mustard to treat cancers and his rationale was that cancer cells divide faster than the normal cell, by using Nitrogen Mustard to cross linking both strands of DNA, one can control and stop the abnormal WBC cell division in Leukemia patients. It was indeed found to be true. More powerful analogs of Nitrogen Mustard were developed during the Second World War (WWII).

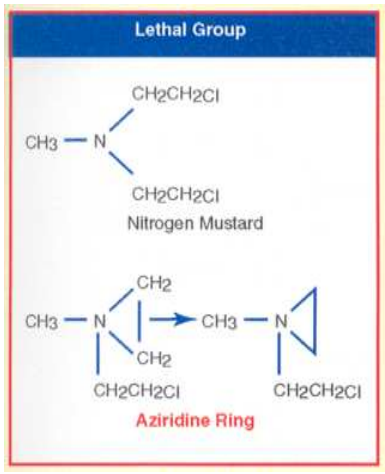

Figure 1. *DNA Binding Lethal Groups.*

Professor Ross was the first person to synthesize many derivatives of Nitrogen Mustard to be tested an anti-cancer

agents. By using an analog of Nitrogen Mustard, called Chlorambucil, he was successful in treating Childhood Leukemia. In America, two Physicians named Goodman and Gilman from the Yale University were the first to use Nitrogen Mustard to treat cancer in humans. Nitrogen Mustards and its analogs are highly toxic. Ross was a Chemist, over the years, he synthesized several hundred derivatives of Nitrogen Mustard molecules to modify toxicity of Nitrogen Mustard. [7-10]

Although analogs of Nitrogen Mustard are highly toxic, they are more toxic to cancer cells and more cancer cells are destroyed than the normal cells. Toxicity is measured as the Chemotherapeutic Index (CI) which is a ratio between toxicity to Cancer cells versus the toxicity to Normal cells. Higher CI means that the drugs are more toxic to cancer cell. Most cross-linking Nitrogen Mustard have a CI of 10 that is they are ten times more toxic to cancer cells. Some of the Nitrogen Mustard analogs Ross made over the years, are useful for treating cancers such as Chlorambucil for treating childhood leukemia (which brought down the WBC level down to 5,000/CC). Professor Ross Chlorambucil showed no sign of Leukemia even after 20 to 25 years. Chlorambucil made Ross one of the leaders of the scientific world. He also made Melphalan and Myrophine for treating Pharyngeal Carcinomas. [11-13]

As I said above, at the London University, I was trained as an Organic Chemist in the Laboratory of Professor WCJ Ross of the Royal Cancer Hospital, a post-graduate medical center of the London University. After working for about ten years at the London University, I moved to America when I was honored by the Fogarty International Fellowship Award by the National Institutes of Health, NIH, and the National Cancer Institute, NCI, of the USA. NIH has been my home for over a quarter of a century, I designed drugs to shut off mutated genes.

All three Common old age diseases that is Alzheimer, Cardiovascular and Cancers diseases have genetic origin. The rationale I used to synthesize anti-cancer drugs could also be used to treat the other two old age diseases like Alzheimer or cardiovascular diseases. In the following sections, I will describe in detail how anti-cancer drug like AZQ was designed to shut off Glioblastoma genes which cause Brain Cancer in humans. Using the same rational, we will consider how each of the other two diseases namely cardiovascular disease and Alzheimer could also be treated by shutting off their genes to save human life: The order of these diseases is arranged based on the level of funding provided by NIH specifically by the NCI (National Cancer Institute).

As I said above, Professor Ross was designing drugs to attack both strands of DNA simultaneously by cross-linking using Nitrogen Mustard analogs, which are extremely toxic. Nitrogen Mustard neither have selectivity or specificity. They attacked all dividing cells including normal cells. During the study of the mechanism of action of radiolabeled Nitrogen Mustard on DNA, it was discovered that the two arms of Nitrogen Mustard do not bind to the double stranded DNA simultaneously. It binds to one strand of DNA at a time. The Carbonium ion of the other arm of Nitrogen mustard attacks its own Nitrogen atom forming a stable three-member aziridinium ion. We were unable to isolate the aziridinium ion as growing tumor which produces acid which break down aziridinium ion to produce a second carbonium ion which attacks the second strand of DNA. We were able to isolate cross-linking DNA product. This study showed that to attack a single strand of DNA, we could make aziridine analogs which will give two advantages: first, instead of cross-linking, aziridine binds to one strand of DNA, reducing its toxicity of double strand Nitrogen Mustard by half. Second, it gives selectivity, the aziridine 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.

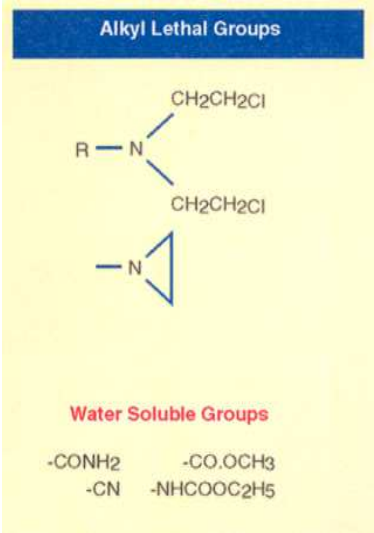

Figure 2. *The above structures are Nitrogen Mustard (2-bischloroethyl methyl amine) and Aziridine.*

The Above Structures Are Nitrogen Mustard (2-bischloroethyl Methyl Amine) and Aziridine

As a part of my doctoral thesis, I was assigned a different path. Instead of cross-linking DNA by Nitrogen Mustard, I am to design drugs to attack only one strand of DNA by making Aziridine analogues.

2.1. Drug Delivery Method Is Key to Success in Treating Diseases

We decided to use Aziridine moiety 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 DNA, we decided to use Dinitrophenyl moiety as a delivery agent because its analog Dinitrophenol disrupt 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 back on the AMP giving back

the ATP. This cyclic process of Oxidative Phosphorylation is prevented by Dinitrophenol. I decided to use Dinitrophenol as drug delivery method for the active ingredient aziridine. Dinitrophenol also serves as a dye which stains a tumor called the Walker Carcinoma 256, a solid and most aggressive tumor in Rat. The first molecule I made by attaching the C-14 radiolabeled aziridine to the dinitrophenol 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 was tested against the implanted experimental animal tumor, the Walker Carcinoma 256 in Rats, it showed a TI (Therapeutic Index) of ten. The TI was like most of the analogs of Nitrogen Mustard. Since this Aziridine analog was not superior to Nitrogen Mustard, it was dismissed as unimportant.

Reexamination of the X-ray photographs showed 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 to move the drug from the injection site to the tumor site. Because of the lack of an effective drug delivery method, Dinitrophenyl Aziridine stays at the injection site. A very small amount of radioactivity was found on the tumor site.

Figure 3. *1st Eureka Moment: Dinitrophenyl Benzamide a Novel Drug Delivery Molecule for Aziridine.*

I immediately realized that by making water and fat-soluble analogs of dinitrophenyl aziridine, 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 least soluble group such as Cyano- group or to introduce an intermediate fat/water siuble Amido group.

An additional substituent could give three isomers, Ortho, Meta, and Para substituent. Here confirmational chemistry plays an important role in drug delivery. 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. 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.

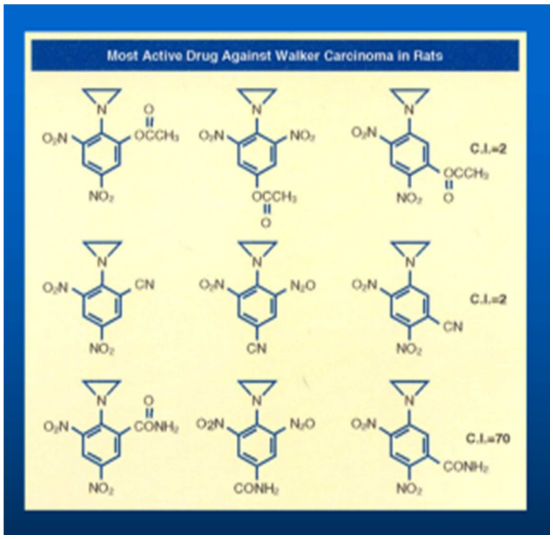

Figure 4. *Derivatization of Dinitro phenyl Benzamide based on Partition Coefficient.*

The Most Water-Soluble Substituent

The first three compounds on top line of the above chart carry all three isomer of most water-soluble ethyl ester group attached to 2,4-dinitropehny aziridine. The compound in vivo is hydrolyzed ester to produce most water-soluble carboxylic group. Within 24 hours of injection, the entire radioactive compound was extracted from the Rat's urine washed down from the cages. 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 activity.

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 activity.

The Moderately Soluble Substituent, The Perfect Drug Delivery Method

The last line of the above chart showed that the first two amido analogs 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 biological 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.

2.2. Prodrug Delivery Method

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 Acidic media. Aziridine attacks DNA in acidic medium, particularly the N-7 Guanine. The dye Dinitro benzamide has great affinity for Walker Tumor. The Aziridine dinitro benzamide (CB1954) stain the tumor. As the tumor grows, it uses Glucose as a source of energy. Glucose is broken down to 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 shutting off the Walker Carcinoma gene in Rat.

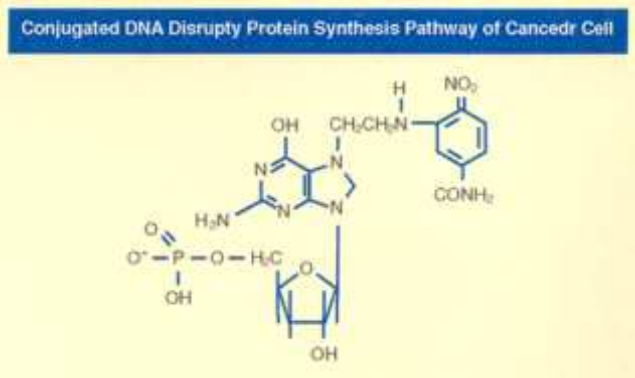

Figure 5. *Conjugated DNA Disrupting Protein Synthesis Pathway of Cancer Cell.*

For the discovery of CB1954, The University of London, honored with the Institute of Cancer Research (ICR) post-doctoral 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 aziridine, one of them is aziridine dinitrophenyl Carbamate was so toxic that its Therapeutic Index could not be measured. Further work in London University was discontinued for safety reason. [14-16]

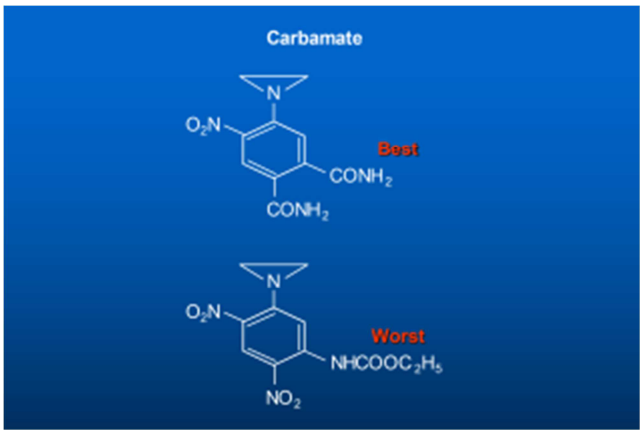

Figure 6. *The Best and the Worst Dinitro phenyl Aziridine Analogs.*

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

2.3. Quinone a Novel Drug Delivery Molecule Across BBB

One day, I heard an afternoon lecture at the NIH in which the speaker described that radio labeled Methylated Quinone cross 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 deliver method for Aziridine rings to attack Glioblastomas. By introducing an additional Carbamate moiety, I could increase its toxicity several folds. I planned to use this rationale to translate animal work to human by introducing multiple Aziridine and Carbamate moieties to the Quinone to test against Glioblastomas in humans.

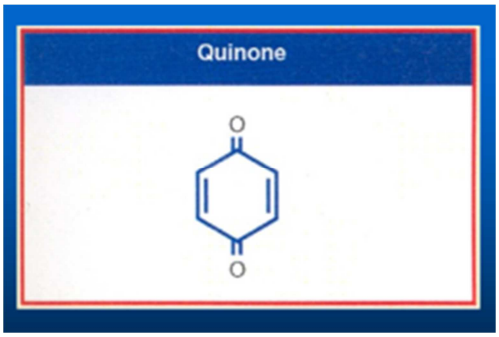

Figure 7. *The Structure of a non-toxic and non-addictive Quinone used for crossing the Blood Brain Barrier (BBB).*

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 adults. We have identified over 120 different types of brain tumors and the most common is Gliomas from which one third of all primary brain tumors originate in the glial (supportive) tissues.

A single spelling error in the coding region of the brain cell could result in the mutation of a single cell. It is accumulation of mutated cells which result in the tumor formation. There are several reasons for the mutation. It could be the exposure to ionizing radiations, or chemical environmental pollution, or viral infection or genetic inheritance. A healthy cell grows rapidly. The doubling time is about 20 minute. The entire genome doubles so rapidly that it is most likely to make mistakes such as deletion of

nucleotide base pairs or insertion of DNA, or translocation of base pairs or inversion or miss pairing of DNA, or triplet repeat or frame shift mutation etc.

Normal brain cells do not divide. Because of its inability to grow, the damaged to brain cells cannot be healed. It is a permanent damage. If any cell is mutated, it grows and accumulated mutated cells become cancerous forming the Glioblastoma multiforme (GBM). It is a primary tumor, and it is a solid tumor; it is aggressive tumor. It grows so rapidly within months it becomes so large that its sheer size crushes the wiring diagram, crush the neuronal circuits, and crush the synopsis and most patients internally bleed to death within fourteen months.

3. Result

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

When an additional piece of nucleotide is attached to a DNA string, it is called Insertion, or a piece of DNA is removed from the DNA string; it is called Deletion or structural Inversion of DNA is responsible for mutations. Since the gene in a DNA codes for Proteins, Insertion and Deletion on DNA have catastrophic effects on protein synthesis. Glioblastomas represent such an example. In Glioblastomas, three major changes occur on Chromosomes (C-7, C-9 & C-10) and two minor changes occur on Chromosomes (C-1 & C-19). These mutations are 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.

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 don't know which nucleotide on which gene and on which Chromosome is responsible for causing the disease. One of the advantages of using Prodrug is that we can easily identify the site of mutation by using radiolabeled studies. For example, AZQ is a prodrug, it remains inactive in non-acidic medium. By using C-14 radiolabeled AZQ, we can easily identify the site of mutations. The growing tumor produces acid and activates AZQ which attacks only five tumor sites located on Chromosome-7, 9 and 10 and Chromosome 1 & 19.

With the completion of 1,000 Human Genome Project, it becomes easier and we can identify the site of mutations on the chromosomes. By simply comparing the patient's Chromosomes with the one thousand genomes, letter by letter, word by word and sentence by sentence, we could identify the difference called the variants with precision and accuracy, the exact variants, or mutations responsible for causing the disease. Once the diagnosis is confirmed, the next step is how to treat the disease.

4. Discussion

With the Quinone ring, I could introduce different combinations of Aziridine rings and Carbamate moieties and could create havoc for Glioblastomas. My major concern was how toxic this compound would be to the human brain cells. Fortunately, brain cells do not divide, only cancer cells divide.

Our brain receives information through our five senses. It not only encodes information, but also store information in our memory bank, the Hippocampus. Our brain connects our memory from past to the present and to the future. When needed, it retrieves a piece of information from the entire memory bank; it processes that information to perform a function and return information when not needed. The information flows flawlessly through the wiring diagram hundred times thinner than our hair and hundred times faster than any computer known to exist.

Quinone presents the best drug deliver system across the BBB to treat all mental diseases including Glioblastomas. I decided to use Aziridine and Carbamate analogs to develop a series of anti-tumor agents to attack Glioblastoma. Over the years, I synthesized several dozen analogs of Quinones. One of them is highly active against Glioblastoma. By attaching two Aziridines and two Carbamate moieties to Quinone, I made Diaziridine Dicarbamate Quinone, I named this novel compound AZQ. By treating brain cancer with AZQ, we observed that Glioblastoma tumor not only stop growing, but also start shrinking. I could take care of at least one form of deadliest old age cancers that is Glioblastomas. Literature search showed that AZQ is extensively studied.

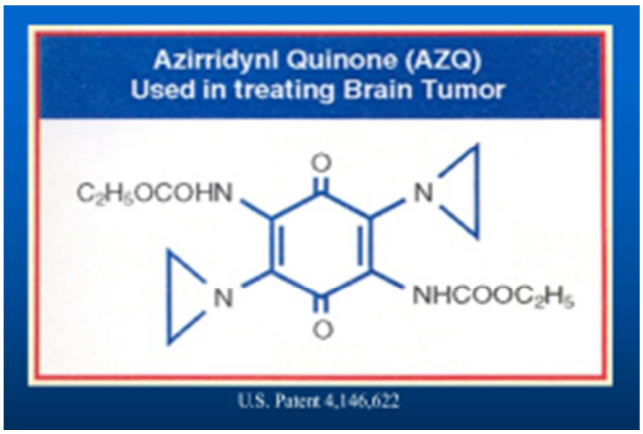

Figure 8. *Structure of the most active AZQ against Glioblastoma.*

Our Rational Drug Design work began in the University of London, England, and completed in the Laboratory of the National Cancer Institute (NCI), of the National Institutes of Health (NIH), in Bethesda, Maryland, USA. Over this period, we conducted over 500 experiments which resulted in 200 novel drugs. They were all tested against the experimental animal tumors. Forty-five of them were considered valuable enough to be patented by the US Government (US Patent 4,146,622 & 4,233,215). One of them is AZQ. Radiolabeled studies showed that AZQ can cross organ after organ, cross the Blood Brain Barrier, cross the nuclear membrane, and attack the nuclear DNA shutting off the gene. X-ray studies showed that the radioactivity is concentrated in the tumor region. Glioblastoma stop growing and start shrinking. [17-19].

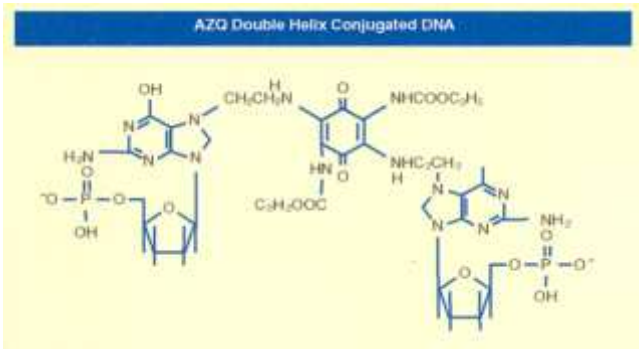

Figure 9. *The structure of DNA bound AZQ.*

I was responsible for synthesizing additional 45-analogs of AZQ for treating brain cancer. As I said above, more than 120 different kinds of tumors have been identified in brain cancers. Hundreds of different genes are responsible for causing various kinds of brain cancers. We thought that protecting brain is the most important. For example, the mutations on BRCA1 gene located on Chromosome-17 are responsible for causing breast cancer. By the time, the cancer is diagnosed and confirmed in the Breast, the cancer has spread and accumulated over three thousand mutations and it has probably spread to liver, lung and it is on its way to brain. We could transplant Breast, Liver or Lung, but we cannot transplant Brain. Therefore, protecting the Brain is essential.

Other neurological cancers

Aside from tumors in the brain, cancer can begin in, or spread to, other areas of the central nervous system, such as the spinal cord or column, or the peripheral nerves. Cancer that develops in the spinal cord or its surrounding structures is called spinal cancer. Most tumors of the spine are metastatic tumors, which could spread to the spine from another location in the body.

Quinone molecule can deliver across BBB to attack the damaged neurons attached to Aziridine and Carbamate moieties which are activated in acid medium generating Carbonium ions and could attack rapidly dividing cancer cells. Suppose a patch of brain cells contain multiple mutated genes causing a variety of brain illnesses such as Tay-Sac Disease, Parkinson Disease, Huntington disease, Triplet Repeat Disease. Bipolar Disorder, Muscular Dystrophy. Color Blindness, Schizophrenia, Glioblastomas etc. Also suppose that they are growing rapidly and competing for the same source of food. How could you design drugs to treat all of them at the same time or treat one of them at a time? Molecules which show affinity for these tumors could be attacked by attaching Aziridine and Carbamate moieties.

The drug now in use to treat Brain Cancer is BCNU (Bis-2-chloroethly Nitroso Urea) is a DNA cross-linking alkylating agent which is extremely toxic. It binds to both strands of DNA simultaneously. There is no selectivity. While synthesizing Aziridines, Carbamate Quinone derivatives, we achieved selectivity. Aziridine and Carbamate moieties are activated by the presence of acid. Only those cells that produce acid will be attacked.

If the source of food for all brain cancers is Glucose. If Glucose is broken down to Lactic Acid, we propose a Grand Unification Theory to attack all growing brain tumors with one AZQ molecule. Aziridine ring and Carbamate moiety of Quinone (the derivative is called AZQ) are stable in alkaline media but are very sensitive to Acid.

It has taken me almost ten years to find a class of chemicals called Quinones which could selectively deliver Aziridine and Carbamate moieties to the brain cancer cell which selectively attacked the cancer cell without attacking any other brain cell. Once AZQ molecule reaches in the vicinity of the brain, it is stable in the basic and neutral SF (Spinal Fluid) environment, and it hangs around waiting for the tumor cells to divide. As the tumor grows, as I mentioned above, it uses glucose as the source of energy. In absence of oxygen, glucose breaks down to produce lactic acid. AZQ is unstable in the acidic environment, the AZQ ring opens, and it attacks the tumor cells shutting of its gene.

My drug AZQ is successful in treating experimental brain tumor because I rationally designed to attacks dividing DNA. Radio labeled studies showed that AZQ binds to the cancer cells DNA and destroys brain tumor and normal brain cells are not affected at all. AZQ is a new generation of drugs. Not so long ago, brain cancer means 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.

By making AZQ and using Quinone as a drug delivery chemical across BBB, I opened the path to attack all other mental illnesses such as Epilepsy, Schizophrenia, Bipolar disorder, Depression, Anxiety disorders, Paranoia, Psychosis and Aggression. In future, male and female hormones could be used to deliver active drug components such as aziridines and carbamates to attack Breast and Prostate cancers.

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 [17-19].

As I said above, I rationally design drugs to treat Brain cancer. I am the discoverer of AZQ (US Patent No. 4,146,622 & 4,233,215). I shared a 17-year royalty with two of my colleagues. The discovery of AZQ has been a quarter century long effort starting from the Royal Cancer Hospital, University of London, England and ending in the National Cancer Institute, Washington, America. Some may think that we are very lucky. The fact is that luck has nothing to do with it. It is a shear hard work. Before I came to America to join NCI (National Cancer Institute, I had already made over one hundred derivatives of Aziridine drugs which tested against experimental animal tumors and published with Professor Ross. Let me share with you how we sweated for making AZQ. To introduce one successful drug for treating one kind of cancer, over the last 25-year period, I had conducted over 500 experiments, out of which 200 drugs were tested in thousands of animals and only 45 drugs were considered valuable enough to be patented by US government and only one drug, AZQ, has recently undergoing extensive several Phase-III clinical trials which showed that tumor is shrinking not growing. Patients receiving AZQ live 20 to 24 months longer than the untreated patients. This period gives physicians enough time to develop alternative treatment to eliminate the remaining resistant cancer cells by Immunotherapy. For the discovery of AZQ, I was honored with the "2004 NIH Scientific Achievement Award", one of America's highest awards in medicine.

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.

Figure 10. *2004 NIH Scientific Achievement Award.*

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.

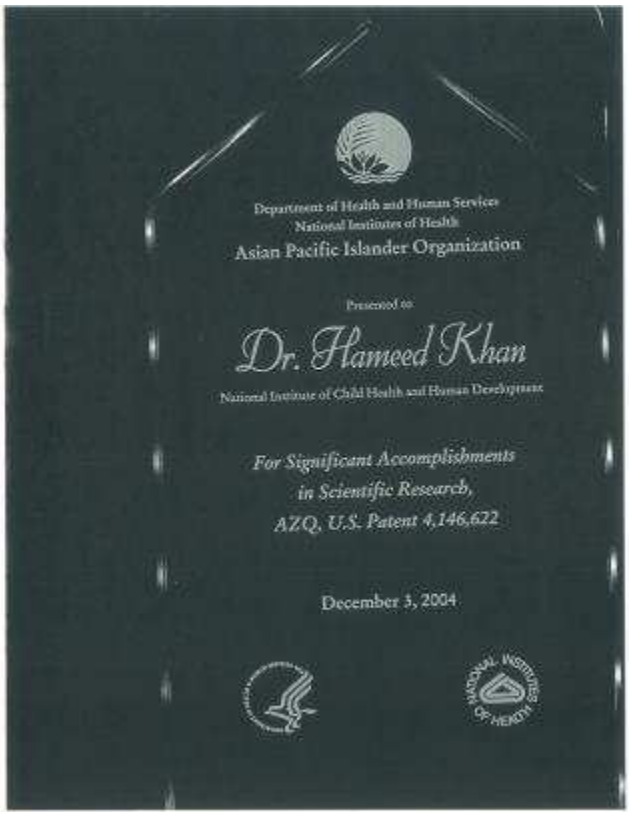

Figure 11. *2004 NIH Scientific Achievement Award.*

Exhibit # 2

His Excellency, Dr. A. P. J. Abdul Kalam,

The President of India

Greeting

Dr. A. Hameed Khan,

Figure 12. *India's National Award.*

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

Exhibit # 3
Single Strand DNA Binding Aziridine and Carbamate

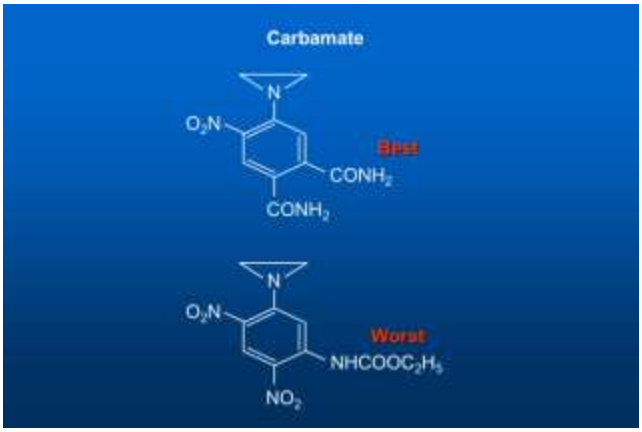

Figure 13. *Single Strand DNA Binding Aziridine and Carbamate.*

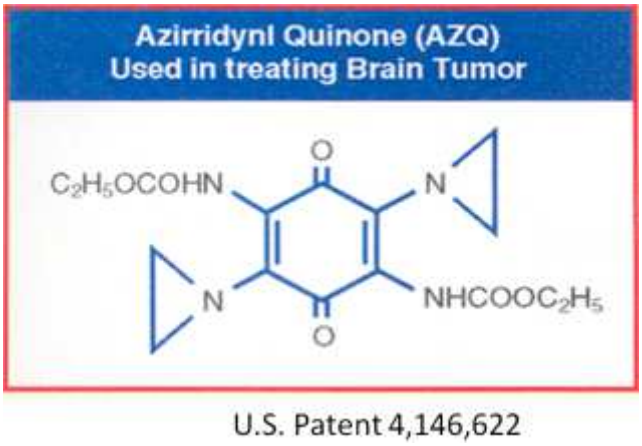

Figure 14. *Aziridine Quinone (AZQ) used for treating Glioblastoma.*

Exhibit # 4
Gold Medal for Dr. Khan

Figure 15. *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.

Figure 16. *The Royals of Travancore.*

Rationale For Designing Future Drug Delivery Method

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

In the absence of any rational drug, I must confess, we still use surgery to cut off 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 current treatments, 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. Based on rational design, we hope to develop new treatment for Breast Cancer. Hopes means never ever to give up.

To design drug rationally to treat Breast Cancer, and to shut off a gene of a specific cancer by using Aziridine or Carbamate, we need a carrier for these groups. For example, to treat Breast and Prostate cancers in humans, may I suggest that we try using hormones which could serve as carriers for Aziridine and Carbamate moiety. Could I use the same rationale for treating Breast tumor? 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 gene 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 (US Patent 4,233,215) is developed to protect the brain, I could focus on the Breast and Prostate Cancers.

Radiolabeled studies showed that male hormone Testosterone has great affinity for female Breast, Ovary, and Fallopian tube cells. On the other hand, Estrogen, the female hormone, has great affinity for male prostate gland. By using male and female hormones, I could attach multiple Aziridine rings and Carbamate ions to both Hormones to attack the Breast and the Prostate cancer.

In a Breast tumor, within the start and stop codon, BRCA1 gene has captured over two hundred thousand nucleotide base pairs. The BRCA1 genes 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. 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.

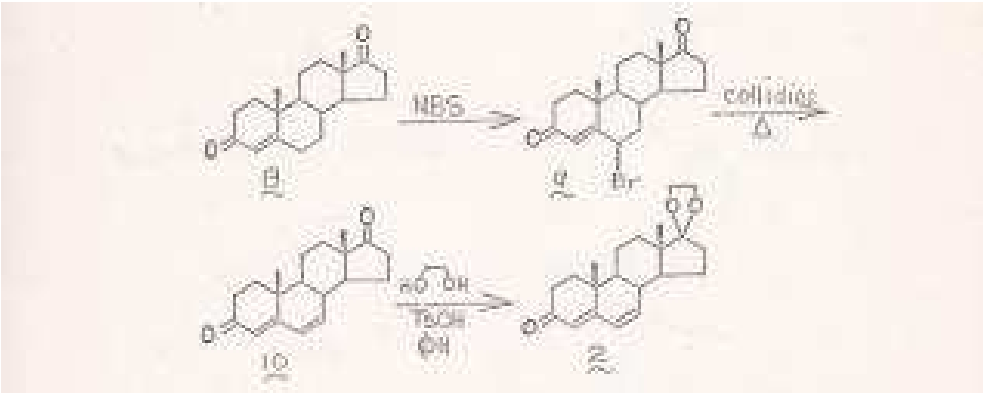

Figure 17. *Bromination of Hormones by Bromo-acetamide (Carl Djerassi.*

Carl Djerassi (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. The next generation scientists, my students, have heard my lectures. [20-38].

5. Conclusion

The sequencing of the Human Genome is not just the discovery of the century, it is the greatest discovery of all times. Every nuclear cell in our body carries our complete genome consisting of 24,000 genes which code for proteins. Our genome is made of 16,000 good genes, 6,000 bad genes and 2,000 mutated genes. Even good genes could become mutated or bad genes if exposed to ionizing radiations, chemical pollution, viral infection of genetic inheritance. From one good gene taken from pancreas which produces Insulin, we could produce enough Insulin to treat 300 million diabetics around the world. Imagine how many good genes could we use to produce good proteins to keep us healthy and give us long life. On the other hand, designing drugs to shut off bad genes responsible for causing diseases presents the greatest challenge. Even greater challenge is to deliver the drug from the injection site to the target site. As I have shown above, dinitrophenyl aziridine has all essential components to shut off a bad gene such as aziridine to bind to DNA and dinitrophenyl group which prevent the Oxidative Phosphorylation of energy producing mitochondria and yet it is inactive because most of the drug stays at the injection site. What is missing is a sound drug delivery method. By adding amide group, I made Aziridine Dinitro benzamide (CB1954), a perfect drug delivery molecule. X-ray photograph of C-14 radiolabeled CB1954 showed most of the drug moved from the inject site to the target site. When tested against an implanted solid aggressive tumor like Walker Carcinoma 256 in Rats, the tumor was wiped out. It shows the highest toxicity to tumor ever recorded.

At the National Cancer Institute, NIH, I translated the animal work on humans. By using Quinone as a drug delivery molecule, I attached two Aziridines and two Carbamate moieties, and made AZQ (US Patent 4,233,215). AZQ crosses the Blood Brain Barrier and attack the solid aggressive tumor like Glioblastoma, the brain tumor. Instead of growing, the Glioblastoma starts shrinking. The derivatives of AZQ were considered so valuable, all 45 analogs of AZQ were patented by the US Government. I am eternally grateful to NIH for honoring me for the discovery of AZQ with the "2004, NIH Scientific Achievement Award" one of America's highest award in medicine. By making AZQ and using Quinone as a drug delivery chemical to cross BBB, I opened the path to attack all other mental illnesses such as Epilepsy, Schizophrenia, Bipolar disorder, Depression, Anxiety disorders, Paranoia, Psychosis and Aggression.

My students, the next generation of NIH scientists will pursue this line of research on mental illnesses with unlimited zeal and unlimited enthusiasms. To succeed in this endeavor, we need outstanding men and women. Who among you will be the vanguard of research and technology in NIH the greatest biomedical center in the world, the microcosmos of America? Only America, the leader of the free world, could provide NIH $50B annually supporting 27 institutes in thousands of Labs hiring more than 20,000 scientists. We bequeath the future of NIH and America in your hands. We know that you will do your best to keep America, the greatest county in the world, the soul remaining superpower of the western World, a jewel in the crown, a beacon of light and a shinning city on the hill.

A Note to My Students

All previous lectures are available on your cell phone; go to facebook.com/hameed.khan.7773/notes.

A 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 developed more toxic weapons during WWII. I describe 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 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, 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.

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