ISSN: 2755-0176

Journal of Cancer Research Reviews & Reports

SCIENTIFIC Research and Community

Review Article

Open Access

The Impact of Sequencing Human Genome on the Psychosomatic Illnesses

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

This abstract attempts to explore if psychosomatic illnesses are genetic in origin. The word *psychosomatic* comes from two roots: *psycho* meaning mind and *somatic* meaning body. The symptoms of psychosomatic illnesses are caused by emotional stress rather than an organic, physical source in the body. Our mind is outside of our brain and cannot be studied, but we can study its effect our body. To ensure if the psychosomatic illnesses have any association with our body and to identify the root cause of these illnesses in our body if any, we sequenced the human genome that is we read the entire book of our life. Our genome provides the total genetic information that make us humans. It carries the greatest catalog of human genes on planet Earth. Our genome consists of 46 volumes of encyclopedia called chromosomes which carry 24,000 chapters called genes. Of all genes in our genome, 16,000 are good genes, 6,000 bad (or mutated) genes responsible for causing six thousand different diseases and 2,000 pseudogenes which have lost their functions. Out of 6,000 variants, not a single mutated gene is linked to any symptom of psychosomatic disorders such as stress, hypertension, respiratory ailments, gastrointestinal disturbances, migraine, tension, headaches, pelvic pain, impotence, frigidity, dermatitis, ulcers. stress and anxiety. We examine the association of any of these psychosomatic symptoms with any of those six thousand mutated genes in our genome, we found no correlation with genetic diseases. We conclude that psychosomatic illnesses are not organic in nature and cannot be treated with organic molecules.

***Corresponding author**

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. E-mail: hameedkhan111@comcast.net

Received: July 21, 2022; **Accepted:** July 26, 2022; **Published:** July 30, 2022

Keywords: Psychosomatic, Genome, Mutations, Nucleotide, Chromosome, Gene AZQ

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, because 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 conducting 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.

Historical Background

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. 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, was the first person to propose that the hereditary molecule must contain a "code-script" that determined "the entire pattern of the individual's future development and of its functioning in the mature state". This was the first clear suggestion

that genes contained some kind of "code". Now, we know that the essence of life is information and genes are the bearers of that information, carrying it in a tiny, complex code inside every cell of our bodies. If we examine for comparison, the fertilized egg of a human, mouse, and monkey under a microscope. We 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. We are certain that there exists a secret code within those fertilized eggs; Schrodinger 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. We propose 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. 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. Based on this information Crick and Watson broke the Genetic Code and unlocked the secret of life. If we unlock the secret of life, we will understand how evolution puts the traits together over millennia to separate man, from mouse and mouse from monkey. By unlocking the secret of life, we can understand how the normal cells work and how the normal cells become abnormal leading to all diseases including cancerous.

On further examination, we found that the chromosomes are made of four chemicals and information is located on these four molecules called nucleotides bases. These bases are made of Deoxy Ribonucleic Acid (DNA). DNA is made of a string of nucleotides. It is a storehouse 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, 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 mRNA (or messenger RNA after splicing out noncoding DNA) and 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 mRNA is translated by Ribosome into proteins [1].

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 disease. Comparing Gene Profiles is an excellent diagnostic method which helps us design drugs to specifically shut off the mutated genes.

Seventy years ago, Schrödinger was using such a poor resolution microscope that we don't even use in our high school today. Instead, we use 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 [2,3].

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 (Adenine, Thymine, Guanine and Cytosine) 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 Nitrogen bases, two Purines and two Pyrimidines and the Thymine is converted to Uracil in RNA. These molecules are found in the nucleus of all living cells from a tiny blade of Grass to mighty elephant including man, mouse, and monkey. The total genetic information to make any living creature 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. A string of these nucleotides is called the DNA (Deoxy Ribonucleic Acid). Reading the number and the order of nucleotides are called genome sequencing [4,5].

Like all other mental illnesses, psychosomatic (mind/body) illnesses are also considered as a disorder of our brain. Our brain is the most complex organ in the Universe. To treat psychosomatic illnesses, we must first identify what part of our brain carries this illness. Where is our mind is in our brain and how it affects the body to cause illnesses?

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 number of visible stars at night sky. 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 processes the information. A small fraction of the information is retained in the hippo campus and the 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 of our brain. Neuronal circuits connect 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. 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.

Information is stored in the neuronal circuits of our brain. Neuronal circuits serve as the information superhighway through which information flows from brain to every part of our body. Millions of neuronal circuits interact to form the wiring diagram linking the entire brin which communicate with the outside world. Psychosomatic illnesses imply a link between mind and body. Illnesses are caused by mutated genes. If psychosomatic illnesses are originated in our brain. I was trained to design drugs to shut off genes. Before I design drugs to shut off the mutated genes, I would like to know which part of our brain carries those mutations. Our brain is made of multiple organs performing multiple functions.

Are there specific genes responsible for making our mind? If our mind is the site of the mutations, we must know which part of brain carries those mutations. Is it neuronal circuits, synapses, or a part of the wiring diagram? Our genome is the catalog of all genes good and bad both. Are there genes for psychosomatic illnesses? Genes code for proteins, it is the bad protein that is responsible for causing diseases.

Our mind is not made of cells. It is an abstract concept. Could we sequence those genes and find mutations responsible for coding for wrong proteins? If there is a family history of psychosomatic illness, could we sequence the egg and sperm of the adult children of the family members before fertilization to identify the mutation responsible for causing the psychosomatic illnesses. Among 86 billions neutrons of the patient's brain, if we could obtain a single neuron for sequencing, by using the latest Nanopore Sequencer which will sequence the entire genome cheaper and faster, we could identify the mutation responsible for causing the psychosomatic illness. If mind is an abstract concept, it cannot be sequenced.

Genes Code for Protein

Out of 86 billion neurons in our brain, a tiny number of genes collectively create human mind. The activity in our mind has a basis in our brain. We still don't understand how nerve cells interact and how they behave. Our thoughts are the product of our brain. The mind is what the brain does. Our mind has the origin in our brain and the brain is in our genes which shape our mental life. Genes don't control our destiny, but they do contribute to our personality and temperament and the quality that make each individual unique.

Genome is a set of genes within a particular organism. A single mutation leads to a variety of diseases. Identical genomes do not yield identical nervous system. The identical twins neither have identical brain nor identical mind. About five thousand genes contribute to human intelligence and only a few hundred genes in a variety of ways contribute to differences between one person and the next. Traits can be attributed to genes. We are born to learn acquiring new knowledge. Nature creates the first draft of our genome, as we grow, we gain experience and revise and update our genome. Most learning thoughts depend on electrical communication across synapses which join neurons. All our body cells are renewed except neurons. You carry the same neurons that you are born with. We found no defect in any of our neuron that correlates to psychosomatic illnesses.

Mind/Body Interaction?

The human brain is primarily composed of neurons, glial cells, neural stem cells, and blood vessels. Various types of neurons which include interneurons, pyramidal cells, Betz cells, and motor neurons. The brain is divided into 7 main functional sections, called lobes. These sections are called the Frontal Lobe, Temporal Lobe, Parietal Lobe, Occipital Lobe, the Cerebellum, and the Brain Stem. Each carries a specific function. There is something very special about our brain, it creates mind. Brain is a physical system and the change in the brain leads to changes in the mind. Mind is not physical and is outside of our brain. Mind altering drugs like Prozac can influence mood by altering the flow of information through neurotransmitters. Brain is made of special nerve cells called neurons and there are 100,000 different kinds of neurons each contributing to a different aspect of mental life. Genes guide neural development. We cannot deliberately alter genome to alter behavior. Ethically we can alter genome to study the effect of genes on human mind. Genes play the same role in the development of human mind. Mind like the body significantly influence by genes. It is highly unlikely that any single gene would ever be solely responsible for the entire complex behavior.

As I said above, the building blocks of brain like our body is made of the same four organic molecules called nucleotides. They are A-T and G-C. Our brain is made of three-pound flesh. It is interconnected by 86 billion neurons and each neuron is linked to another neuron by 10,000 to 100,000 connections called synapses. A lesion in the connections interrupt the flow of information causing various mental illnesses. Treating mental illnesses present the greatest challenge because our brain is covered by a fatty layer called the Blood Brain Barrier (BBB). Very few chemicals except addictive narcotic crosses BBB. Most mental diseases are caused by the damage to one of the four nucleotides in our brain. Damage (mutations) to nucleotides is caused by either ionizing radiations, chemical/environmental pollutants, viral infections, or genetic inheritance. Nucleotides are information molecules. When damaged, the mutated codons code for wrong amino acid and whose gene codes for wrong protein resulting in a variety of mental diseases including cancers.

Our mind is the product of our brain. Our brain communicates through electrical/chemical signals from one place to other. It takes information from our senses, analyze that information, and translate it into commands that send back to muscles. Transforming signals carrying information from outside world to the inside world from cells to molecules to the events inside the cells. Human brain is the best information processor on the planet Earth and some of the basic signals it uses to process information are almost as old as life itself. What changes in our brain are responsible for causing psychosomatic illnesses? Since we cannot exactly locate the site of our mind in our brain, how can we sequence the mind and identify the mutation responsible for causing psychosomatic illnesses? Our mind is not made of organic molecules. Our mind is outside of our brain. Psychosomatic illnesses are not organic in nature and cannot be treated by organic chemicals. We cannot design novel drugs unless we find the abnormal mutations responsible for causing psychosomatic illnesses. The total genetic information that makes our book of life is called Human Genome. The reading of Human Genome.is considered essential if we were to identify mutations and to design novel drugs to treat all six thousand diseases in our Genome.

The sequencing of the Human Genome is authorized by the US Congress under The Human Genome Project. Sequencing Genome will answer some of the most fundamental questions we have asked ourselves since the dawn of human civilization. What does it mean to be human? What is the nature of our memory and our consciousness? 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 dissimilarity, Similarity that all living creatures from a tiny blade of grass to the mighty elephant including man, mouse, monkey, mosquitos and microbes are all made of the same chemical building blocks and yet we are so diverse that no two individuals are alike even identical twins are not exactly identical, they grow up to become two separate individuals.

Sequencing Human Genome

The entire book of life is written in four genetic letters called nucleotides. They are Adenine (A), Thiamine (T), Guanine (G), and Cytosine (C). A string of AT/GC base pairs is called the

Deoxyribose nucleic acid (DNA). Out of four nucleotides, three nucleotides code for an amino acid called Codon. Different combination of four nucleotides gives sixty-four Codons which code for all twenty amino acids. The entire genome is written using six billion four hundred million nucleotides. Less than two percent of our genome carries genes which code for protein. Thousands of proteins interact to give a single cell; millions of cells interact to give a tissue; 220 different tissues interact to give an organ and several organs interact to make a human.

In 1990, US Congress authorized three billion dollars to our Institute NIH to decipher the entire Human Genome under the title, "The Human Genome Project". We found that our genome contains six billion four hundred million nucleotides base pairs and 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, enhancers etc. The 46 chromosomes present in each cell of our body are the greatest library of the Human Book of Life on planet Earth. The chromosomes carry genes which are written in nucleotides. Before sequencing (determining the number and the order of the four nucleotides on a Chromosomes), it is essential to know how many genes are present on each chromosome in our Genome. The Human Genome Project has identified not only the number of nucleotides on each chromosome, but also the number of genes on each chromosome.

The following list provide the details composition of each chromosome including the number of nucleotides and the number of 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. Chromosome-22 contains 56 million nucleotides 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 contains 59 million nucleotide bases and carries 255 genes.

If you add up all genes in the 23 pairs of chromosomes, they come up to 26,808 genes and yet we keep on mentioning 24,000 genes needed to keep us function normally. As I said above, a gene codes for a protein, not all 24,000 genes code for proteins. It is estimated that less than 19,000 genes code for protein. Because of the alternative splicing, each gene codes for more than one protein. All functional genes in our body make less than 50,000 protein which interact in millions of different ways to give a single cell. Millions of cells interact to give a tissue; hundreds of tissues interact to give an organ and several organs interact to make a human. Slightest damage to a single nucleotide in the coding region caused by either ionizing radiations, chemical/ environmental pollutants, viral infections, genetic inheritance or by deletion, insertion, or inversion of DNA result in mutations. Mutated genes code for wrong proteins resulting in diseases [6-8].

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

The Post Genomic Era

More than 20 years have passed since we completed the Human Genome Project. By using Nanopore sequencer which sequence the genome cheaper and faster, we are sequencing the genome of many other species from microbes to mosquitoes, to monkeys and to men to study evolutionary changes occurred over eons. We have also sequenced the genomes of thousands of people. By comparing the genomes of healthy person, we are identifying variations called polymorphism. We found the answer to the question why no two people look alike. When we compare the genomes of two persons, we found that between 1,000 to 1,300 nucleotide base pairs, a single nucleotide base pair is located at a different place. This variation is called the Single Nucleotide Polymorphism (SNP). Our genome is made of three billion two hundred million nucleotide base pairs and carries three million two hundred million variants (SNP). These variants make us different from each other except the identical twins. Comparing genomes of healthy person with a sick patient will help us identify the mutation responsible for causing the disease. For example, when we compare the nucleotides sequence of Chromosome-17 of two persons, if we find a mutation in the coding region, we detect the presence of a new amino acid. The peptide carrying the amino acid is responsible for causing mental retardation called the Fragile-X Syndrome.

Once the diagnostic test confirms, the first step is the prevention. If there is a family history of mental illnesses in the couple's family, they can sequence the fertilized ovum before conception. If the ovum carries the mutation, it could be discarded, and they could use a new ovum for in vitro fertilization. The alternative treatments would be to remove the mutation either by CRISPER, or by Gene Therapy for single mutation or Drug Therapy for multiple mutations. The use of CRISPER in treating mental illnesses present great risk. If an error is introduced in the treating mental disease, it

cannot be repaired. The other two options are either Gene Therapy or the Drug Therapy. Gene Therapy would be successful for a single gene mutation. For multiple genetic defects, Gene Therapy will not work, but Drug Therapy will work. In Drug Therapy, we design drugs to shut off mutated genes. Highly toxic Nitrogen mustard will cross-link double stranded DNA and shut off the mutated genes. Aziridines, a prodrug, shut off a gene by binding to a single strand of DNA.

Next, we converted the Analog language Biology to the Digital language of Computer that is from A-T, G-C nucleotides to number Zero and One. Now, we can write a program and design a Computer to read the book of life faster and faster. Today, we can read our entire Genome in one day at a cost of a thousand dollars per genome. We can also upload our digitized Genome on the Computer. Once uploaded on the website, our Genome could travel with the speed of light to anywhere in the World or in the Universe. As we plan to colonize the planet Mars before this decade is over, we must sequence as many species on Earth as possible. We must be ready to send any sequence to the future Martian humans may need.

No Genes are Identified for Causing Psychosomatic Illnesses

In future if a gene is identified for causing psychosomatic illness, I would dearly love to be the first chemist to design drugs to shut off that gene and treat psychosomatic illness. This is how I would design the drug once the site of mutation is known. By using Profess Ross method, I could shut off a gene by designing cross-linking double stranded DNA by using highly toxic Nitrogen Mustard, or by using less toxic prodrug Aziridine, I could bind to a single strand of DNA shutting off the genes.

For over a quarter of a century, I have been designing drugs to shut of mutated genes. I was trained in the Laboratory of Professor WCJ Ross of London University, England. I graduated from the University of London. After receiving my doctorate and post doctorate, I worked for Professor Ross for almost ten years designing anticancer drugs at the Royal Cancer Hospital, a post-graduate medical center of the University of London, England, before I came to America as a Fogarty International Postdoctoral Fellow to work in the Laboratory of the National Cancer Institute (NCI) of the National Institutes of Health (NIH), Bethesda, Maryland.

How to Design Drugs to Shut off Bad Gene Variants?

We design drugs to shut off genes responsible for causing cancers because largest amount of funds is available to the National Cancer Institute (NCI) about $5B per year. 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. As I said above, if a gene variant is identified responsible for causing psychosomatic illness, I would show you how to design drugs to shut off that gene variant. I describe below how I designed drugs to shut off cancer causing genes in animals and then translate the work in humans.

The Rational Drug Design to Treat Cancers

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

Cross-linking Double Stranded DNA (By Nitrogen Mustard)

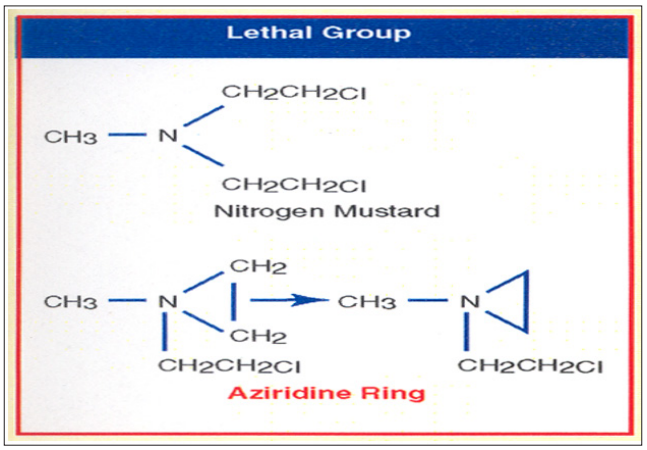
As I said above, the supreme intellect for drug design is Ross, an Englishman, who is a Professor of Chemistry at the London University, England. Professor WCJ Ross is also the Head of Chemistry Department at the Royal Cancer Hospital, a post-graduate medical center of the London University. Ross was the first person who designed drugs for treating Cancers. He designed drugs to cross-link both strands of DNA that we inherit one strand from each parent. Cross-linking agents such as Nitrogen mustard are extremely toxic and were used as chemical weapon during the First World War (WWI). More toxic derivatives were developed during the Second World War (WWII). Using data for the toxic effect of Nitrogen Mustard on soldiers during the First World War, Ross observed that Soldiers exposed to Nitrogen Mustard showed a sharp decline of White Blood Cells (WBC) that is from 5,000 cell/CC to 500 cells/CC. He immediately realized that children suffering from Childhood Leukemia have a very high WBC count that is over 90,000 cells/CC. In sick children, most of the WBCs are premature, defected, and unable to defend the body from microbial infections. Ross rationale was that cancer cells divide faster than the normal cell, by using Nitrogen Mustard to cross linking both strands of DNA, one can control and stop the abnormal WBC cell division in Leukemia patients. It was indeed found to be true. Professor Ross was the first person to synthesize many derivatives of Nitrogen Mustard. 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 derivatives to modify toxicity of Nitrogen Mustard [9].

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

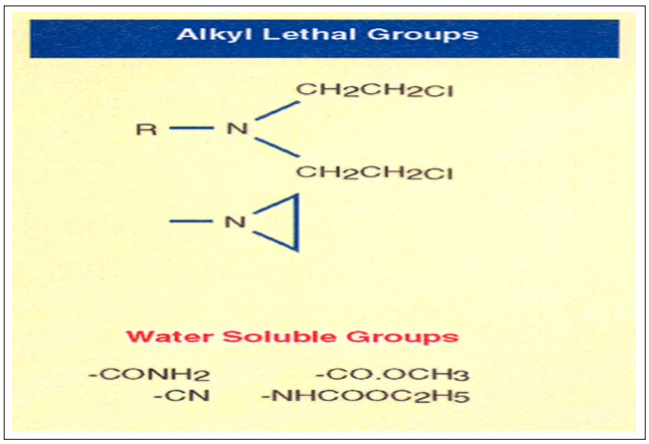
As I said above, at the London University, I was trained as an Organic Chemist in the Laboratory of Professor WCJ Ross of the Royal Cancer Hospital, a post-graduate medical center of the London University. After working for about ten years at the London University, I moved to America when I was honored 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 Allele diseases have genetic origin. The rationale I used to synthesize anti-cancer drugs could be used to treat all other mental diseases which include, Anxiety disorders, Aggression, Mood disorders, Psychotic disorders, Eating disorders, Personality disorders, Post-traumatic stress disorder (PTSD), Impulse control and addiction disorders, Factitious disorders, schizophrenia, Epilepsy, including psychosomatic illnesses if genes are identified.

In the following sections, I will describe in detail how I translated animal work to humans to transport toxic chemicals across BBB to treat mental illnesses particularly anti-cancer drug like AZQ which was designed to shut off Glioblastoma genes which cause Brain Cancer in humans. Using the same rational, we will consider how the other mental disorders could 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 double stranded DNA using Nitrogen Mustard analogs, which are extremely toxic. As a part of my doctoral thesis, I was assigned a different path. Instead of cross-linking DNA, I am to design drugs to attack only one strand of DNA. This class of drugs is called Aziridines.



Nitrogen Mustard neither have selectivity nor 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 must synthesize Aziridine in the Lab. 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 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.



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

DNA Binding Lethal Groups

Designing Drugs to Bind to a Single Stranded DNA to Treat Animal Cancers

As a part of my doctoral thesis, I was assigned a different path. Instead of cross-linking 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 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 group 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 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 was like most of the analogs of Nitrogen Mustard. Since this Aziridine analog was not superior to Nitrogen Mustard, it was dismissed as unimportant.

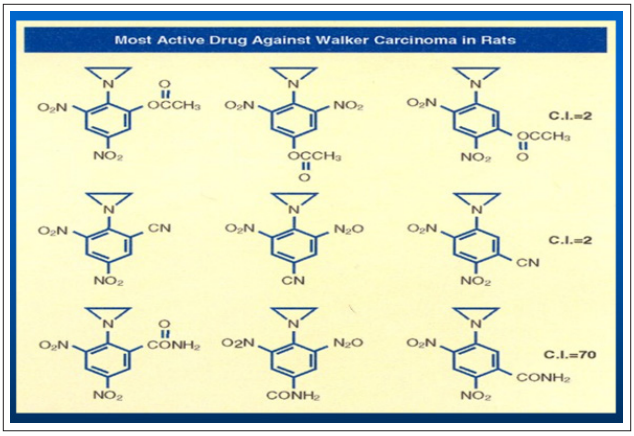
Reexamination of the X-ray photographs showed that most of the radioactivity was concentrated at the injection site. Very little radioactivity was observed at the tumor site. It was obvious that we need to make derivatives Dinitrophenyl Aziridine to move the drug from the injection site to the tumor 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.

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 water-soluble group such as Cyano- group or to introduce an intermediate fat/water double 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. 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.



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.

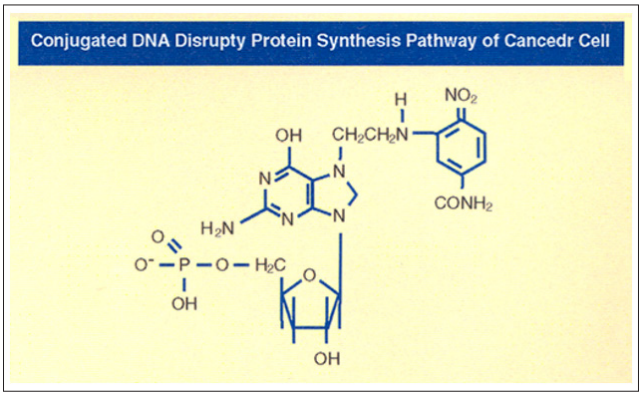
The Least Water-soluble Substituent

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 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 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 [14-16].

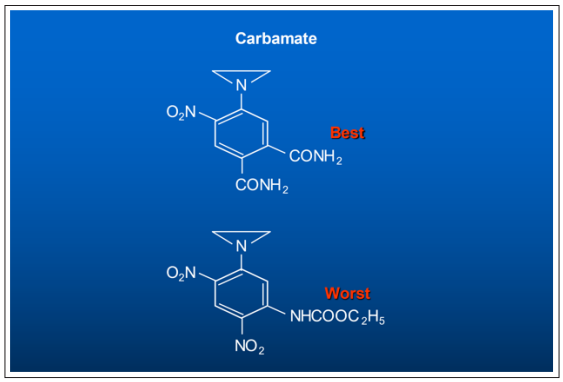
Nitrogen Mustards are highly toxic because they have neither specificity nor selectivity. They attack all dividing cells whether they are normal or abnormal. On the other hand, the analogs of Aziridines and Carbamates serve as prodrug and remain inactive in the basic and neutral media. They become activated only in the presence of acid producing 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) 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 (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 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 which was so toxic that its Therapeutic Index could

not be measured. To continue my work, I was honored with the Institute of Cancer Research Post-Doctoral Fellowship Award of the Royal Cancer Hospital of London University. To increase the toxicity of CB1954 to Walker Carcinoma, I made additional 20 analogs as a postdoctoral fellow. When I attached one more Carbonium 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 [17,18].

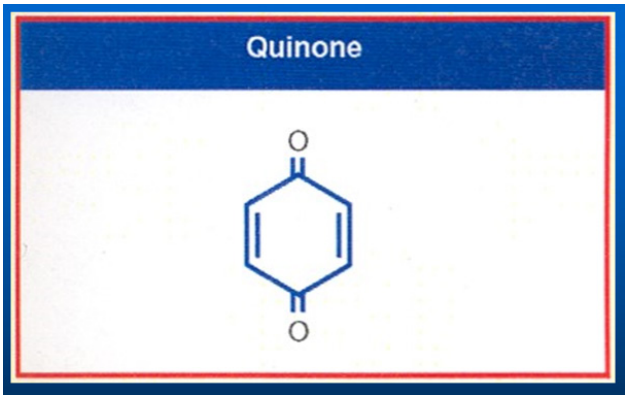


The Best and the Worst Dinitro phenyl Aziridine Analogs

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.

Designing Drugs to Treat Glioblastoma the Human Brain Cancers

One day, I heard an afternoon lecture at the NIH in which the speaker described that radio labeled Methylated Quinone crosses the Blood Brain Barrier (BBB) in mice. When injected in mice, the X-ray photograph showed that the entire radioactivity was concentrated in the Mice's brain within 24 hours. I immediately realized that Glioblastoma multiforme, the brain tumor in humans, is a solid aggressive tumor like Walker Carcinoma in Rats. I decided to use Quinone moiety as a novel drug delivery molecule to cross BBB 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 to test against Glioblastomas in humans.



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. Attaching Nitrogen Mustard group to Quinone 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 remain inactive in the basic and neutral media. They become activated only in the presence of acid producing cancer cells.

DNA Binding Aziridines

I continued my work on the highly toxic Aziridine/Carbamate combination in America. 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.

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. By attaching two Aziridines and two Carbamate moieties to Quinone, the most useful Diaziridine Dicarbamate Quinone, I named this novel compound AZQ. Over the years, 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 [19].

As I said above, Glioblastomas, the brain cancers, is a solid and aggressive tumor and is caused by mutations on several chromosomal DNA. Deleterious mutations of 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 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, 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 in a DNA codes for Proteins, Insertion and Deletion on DNA have catastrophic effects on protein synthesis.

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

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. Besides identify the site of binding of DNA with C-14 radiolabeled studies, we can also confirm by comparing with the mega sequencing project.

With the completion of 1,000 Human Genome Project, it becomes easier. By simply comparing the patient's genome with the sequencing of 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.

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 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 stop the growth of Glioblastoma, but also the tumor start 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).

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

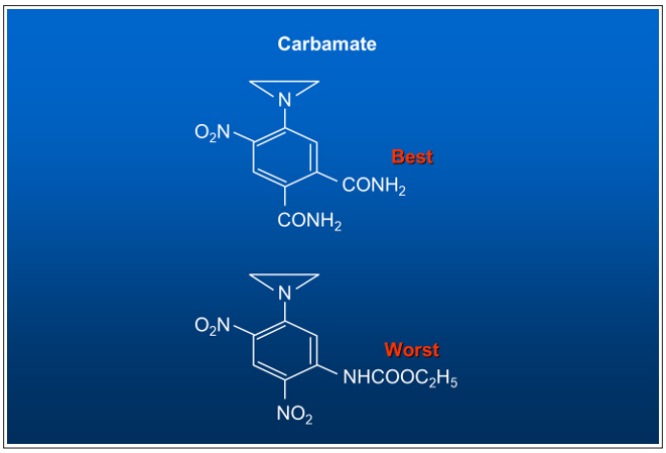
Dr. Khan is the Discoverer of AZQ (US Patent 4,146,622), a Novel Experimental Drug Specifically Designed to shut off a Gene that causes Brain Cancer for which he receives a 17-year Royalty for his invention (License Number L-0I9-0I/0). To this date, more than 300 research papers have been published on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

2004 NIH Scientific Achievement Award

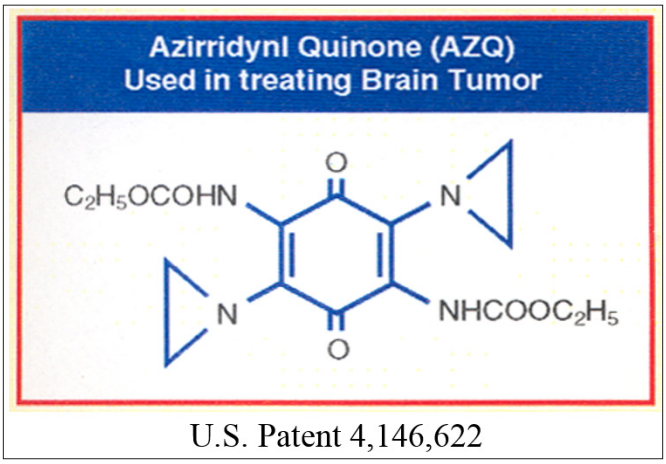
His Excellency, Dr. A.P.J. Abdul Kalam,
The President of India
Greeting
Dr. A. Hameed Khan,

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.
India's National Medal of Honor

Single Strand DNA Binding Aziridine and Carbamate



DNA Single Strand Binding Agents



Structure of AZQ for treating Glioblastoma

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.

For Discovering AZQ Dr. Khan was Awarded a Gold Medal

The Royal Family of Travancore honored Dr. Khan

Is Research Grant available from NIH to develop treatment for the psychosomatic illnesses? Remember Best ideas are always funded

Our 27th Institutes is called the National Center for complementary and Integrative Health (NCCIH). The aim of the program is to support synergistic, multidisciplinary, multi-project research programs that have strong potential to significantly advance the mission of NCCIH. Under the objective two of this program if an Investigator propose to develop and improve complementary health approaches and integrative treatment strategies for managing symptoms such as pain, anxiety, and depression. He is qualified to submit the research proposal for committee's consideration. The main aim of this program is to update and improve Alternative medicine to bring its treatment into mainstream medicines by modern techniques.

For up-to-date information go to NIH Website Home page.

NIH annual budget is about $50B. Research grants are available to new investigators. About 12% budget is spend on in-house research (which supports about 20,000 scientists in three thousand labs.) and remaining 88% are distributed to extramural scientists by three different mechanisms such as Grants, Contracts and Co-operative Agreement. Grants are gift given to you to translate theories into practice, and concepts into results, Research Contracts are granted to independent contractors to scale up or modify the results or to provide services to NIH.

Will Alternative Medicine Institute of NIH may support the development of novel drugs to treat psychosomatic illnesses? The answer seems to be not currently. It may change later as more information becomes available.

To request funds to develop Alternative medicine, the Principal Investigator (PI), must submit a Concept Study Proposal if approved, it provides $ 100,000 per year grant for 2 years. The PI will have to provide answer to the following questions: (1) Is this study doable? (2) Is PI qualified to conduct such studies? (3) has he received the Institutional support to conduct such a study which provide research facilities? I knew this process well since

I served as the Scientific Review Administrator (SRA). A dear friend and colleague of mine was appointed as the Director of the Division of Scientific Review (DSR) in the NIH. His branch received thousands of research proposals request funding. Since we had worked together for years in FDA, he thought that I would be able to help him. Since I Was also teaching the NYLF scholars, the general formation collected would be useful for preparing my lectures. While Genome Center was supporting sequencing and mapping of the Genomes, my Institute NICHD was supporting research on Gene Markers associated with diseases. Over a quarter of the century of work, I was able to accomplish all the goals of NIH that is to conduct research, to support research and to report research. I describe below all three missions of NIH.

NIH Mission 1

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

NIH Mission 2

NIH Speaker Bureau informed me that when you teach the students, you touch the future. It is the responsibility of the scientists to train a new generation of scientists. I was told that of all teaching organizations, one organization, Envision, stands out. Envision is an outstanding organization that trains and provides future leaders of the world. Envision performs a Herculean task by selecting thousands of best and brightest students from around the country and from all over the world and bring them to Washington DC to train them to become the future leaders of the world. They are called the scholars of the National Youth League Forum (NYLF). I am to start teaching them first. I am honored to be associated with the Envision as a speaker of the NYLF scholars for more than two decades. More than 30 previous lectures are available for the future scholars and scientists on the following website: https://www.facebook.com/hameed. khan.7773/notes.

At the conclusion of the lectures, the NYLF scholars evaluated my teaching performance. They send the following evaluation to the NIH Speaker Bureau:

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

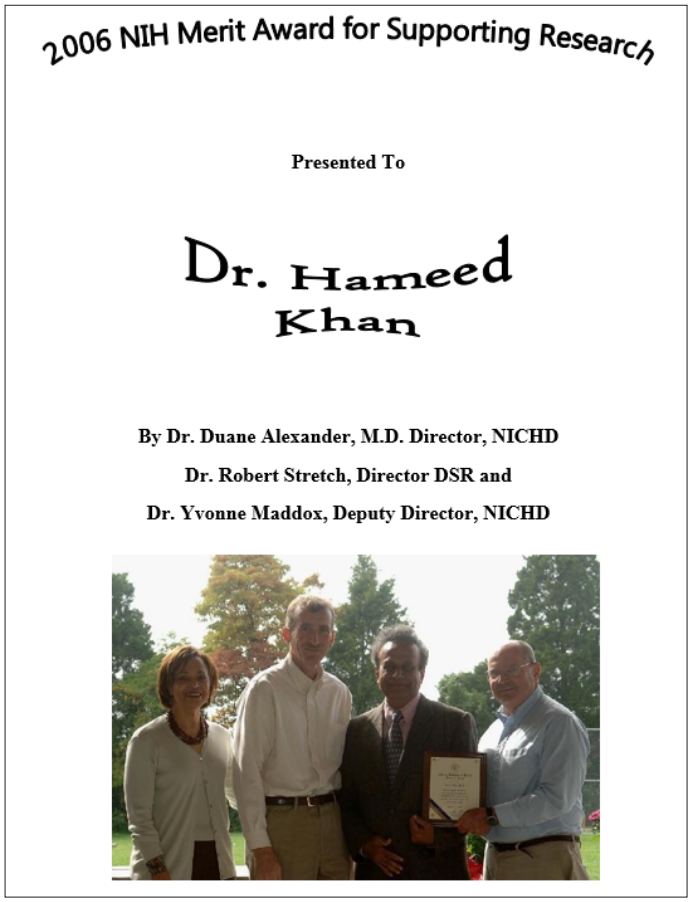
NIH Speaker Bureau Honored Dr. Khan with An Award

NIH Mission 3

Of all the challenges of NIH Missions, supporting research presents the greatest challenge. I was accidentally involved in supporting research. I was invited to speak at an International Science Conference in Europe. I was shocked when I saw the program. Someone is presenting a paper for treating Breast Cancer with my drug AZQ. My rationale for designing AZQ was that Quinone cross the Blood Brain Barrier and take the Aziridine in the vicinity of Glioblastoma.

I was curious to know the rationale for using AZQ to treat Breast Cancer. The speaker informed the audience that AZQ has no effect against Breast tumor. At the end of the presentation, I asked the speaker for the rationale for using AZQ. The shocking answer was that AZQ is extensively studied on different cancers, so her group tried to study the Breast Cancer because funds were available. Upon my return to NIH, I told my colleagues what a waste of precious resources. One of my colleagues was the Director of the Division of Scientific Review. He asked me to join him in controlling the Research Funds and help the new investigators by reviewing their Research Proposals. NIH annual budget is $50 billion. About twelve percent of the budget is spent in-house (called the Intramural Program). The remaining eighty-eight percent money is given out to extramural Research Program both nationally and internationally as Research grants, Research contracts and Research co-operative Agreements. He gave me a couple of research proposal to review. As I read the research proposal, I immediately pulled out strengths, weakness in the proposal. I checked the Principal Investigator (PI) qualifications, experience, his publications, his support staff, research environment availability of instruments. I contact the PI for missing information. I was given incredible freedom to set up committees to invite the best and the brightest scientists from any part of the country to serve as the reviewers of the expert panels. NIH treat these experts with utmost courtesy, utmost respect and accommodate them in the best hotels, paid all their expenses with honorarium. Reviewing Research Proposals was in the beginning was a passion for me, then it became obsession.

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



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

Dr. Khan was honored with the NIH Merit Award

While Genome Center sequence and map the Genomes, my Institute NICHD (National Institute of Child Health and Human Development), provides funds to new investigators to identify Gene Markers that is to identify deleterious mutations responsible for causing various genetic diseases. Identification of the genetic make-up for causing diseases will help us design drugs to shut off those genes. How could we help new investigators to design novel drugs to treat old diseases? The following example will illustrate rational approach to treat Breast Cancer. Future genomic medicine

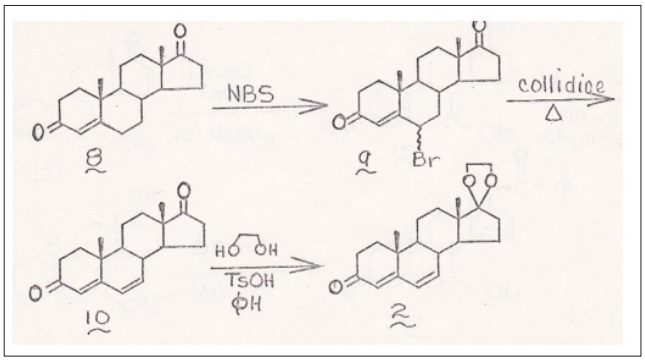
Based on the Genetic Make-Up
What other Cancers Should be Explored Next?

Of all cancers, the largest killer of women is the Breast Cancer. Despite the use of highly advanced treatment methods such as Chemotherapy, Radiation therapy and Surgery, within three years, the tumor returns as metastatic cancer and kill the patient. On the rational basis, I propose the following approach to develop novel drug to treat Breast Cancer.

Although mutations on BRCA1 gene responsible for causing Breast Cancer located on Chromosome-17 has been identified years ago, so few drugs were designed on rational grounds. Now, we have sequenced Chromosome-17. We found that it is made of 92 million nucleotide bases pairs carrying 1,394 genes. By comparing with the Reference Sequence, we can easily identify which nucleotide on which gene of the Chromosome-17 is responsible for causing Breast Cancer. As I said above, Genomic medicine is a predictive medicine. By MRI (Magnetic Resonance Imaging which takes three-dimensional images) and gene sequencing, we should be able to predict if the abnormal changes in the cellular DNA will lead to Breast Cancer. Without this knowledge, it has been so difficult to design drugs on rational basis to treat Breast Cancer. By the time the Breast Cancer diagnosis is confirmed in a patient, the BRCA1 gene has accumulated more than three thousand mutations. Genotyping of the blood sample would also show the existence of many cells carrying mutated cells responsible for creating secondary deposits. It is also found in some cases when not detected earlier, by the time Breast Cancer is confirmed, metastatic cancer cells have already been spread from Liver Lung on their way to Brain.

As a Fogarty International Postdoctoral Fellow at the NCI, I was given the chance to work on any cancer, I was pleased. Since all other organs including Breast and Liver could be removed and replaced by organ transplant except Brain, I thought that protecting Brain is utmost important to save life. For years, I work on the development of AZQ. Once the AZQ was developed to protect the Brain Cancer, I could focus on the Breast and Prostate Cancers. Recent, Radiolabeled studies in mice showed that male hormone Testosterone has great affinity for female organs like Breast, Ovary, and Fallopian tube cells. On the other hand, Estrogen, the female hormone, has great affinity for male Prostate gland. By attaching multiple Aziridine rings and Carbamate ions to both Hormones, I could design novel drugs to attack both the Breast and the Prostate cancers. Now, I found that I could increase its toxicity several folds to abnormal cells by attaching more than four Aziridine and Carbamate moieties to both Male and Female Hormones.

In a Breast tumor, within the start and stop codon, BRCA1 gene has captured over two hundred thousand nucleotide bases. The BRCA1 gene carries about three thousand mutations. These mutations are caused by exposure to radiations, chemical or environmental pollutants, viral infection or genetic inheritance. To attack the mutated nucleotides among the three thousand mutations in BRCA1 gene, we could use male hormone, Testosterone, and bind multiple radio labeled Aziridine and Carbamate ions to attack BRCA1 mutations. By using three dimensional MRI, we could show how many radio-labeled nucleotides were bound to which mutations. Out of seventeen positions available for substitutions on Testosterone ring system. There are only three positions that is 1,3 and 17 are available for substitution on Testosterone ring system.



Carl Djerassi [C. Djerassi et al. J. Amer. Chem. Soc. 72. 4534 (1950)] 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 be further brominated 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 as a carrier and by attaching multiple Aziridine and Carbamate ions to attack Prostate tumor in Men. Since seventeen positions also available are 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.

Conclusion

All mental disorders including psychosomatic illnesses originate in our brain. To treat mental illness, like Glioblastoma, the brain cancer, we must transport novel drugs across BBB. Those chemicals like AZQ are specifically designed to shut off that gene carrying the mutations using non-addictive non-narcotic compounds like Quinone analogs.

Our mind is outside of our body, but psychosomatic disorders are inside of our body and are real which results from extreme stress, and which include hypertension, respiratory ailments, gastrointestinal disturbances, migraine and tension headaches, pelvic pain, impotence, frigidity, dermatitis, and ulcers. stress and anxiety. Are these symptoms real or psychological? Are these illnesses inside our genome or outside of our genome? Since our genome is the catalog of all genes in our genome, is there any gene responsible for any of the above psychosomatic illnesses? Highly stressed people produce high level of hormones which may interfere with gene regulation. It is well known that Genes are turned on and off in different patterns during development to make one cell look and act differently from another cell, for example. Gene regulation also allows in cells to react slowly over years to changes in response to their environments. Gene expression is the

process by which the cell uses to produce the molecule it needs by reading the genetic code written in the DNA. All diseases are genetic in origin.

One of the outside sources affecting our genomes is sunlight. Sunlight travels 93 million miles to reach Earth, its UV radiations penetrate our skin and interfere with our DNA replication causing mutation resulting in skin cancer called the Melanoma of the skin. Due to high stress in the psychosomatic patients, is the gene expression altered by the high level of hormone? The hormone is Cortisol which is produced by the high level of stress. High level of Cortisol tends to destroy Telomers which are linked to our early aging. At the tip of each chromosome, there is a six-letter nucleotide code called Telomere which is made of TTAGGG. We are all born with thousands of Telomeres. Soon after conception, human embryo begins its development with about twenty thousand Telomeres. As the earliest cells divide so rapidly, by the time the baby is born almost half of its Telomeres are gone. The remaining Telomeres lasts the lifetime losing thousands at each replication of cells dividing for cell growth and development. People of shorter Telomeres have a much higher risk of dying with infections and heart attack than the people of the same age who have longer Telomers. The correlation between loss of Telomere with Aging was discovered by Carol Grider and Elizabeth Blackburn (for their discovery, they were honored with the Nobel Prize).

One of the psychometric illnesses is Stress. People under stress tend to lose more Telomeres. The stress hormone is the Cortisol. The higher the level of Cortisol, the more Telomeres are lost. Under stress some people see life as threat and others as challenge. Those who take life as a challenge have much higher level of Telomeres. By sequencing more and more genomes if we identify the variant gene responsible for producing more Cortisol, we can design drugs to control the level of Cortisol. Although the enzyme Telomerase Reverse Transcript has been identified as the Anti-aging agent, Meditation has been implicated in reducing Stress, the main thrust of this paper is to show the next generation of scientists (my students) how to design drugs to shut off those genes. Until we identify a single mutated nucleotide in a single codon which codes for a wrong amino acid and which is a part of a gene which codes for a wrong protein to cause these illnesses, we have no evidence to say that psychosomatic illnesses are genetic in origin and no rational drug could be designed to treat these diseases. As I said above, if you would identify the variant of a gene responsible for causing psychosomatic illness, I would show you how to design drugs to shut off that gene variant [19-33].

More men and women in uniform suffer from psychosomatic illnesses than civilians. NIH annual budget is $50B (for saving life) while our Defense budget is $750B (for taking life). Maybe we should transfer some of the Psychosomatic Research Program to the Defense Department in Pentagon. I have a simple message for the future generation of scientists that is our world has achieved brilliance without wisdom, power without conscience. We are nuclear giant and ethical dwarf. We know more about war than we know about peace. We know more about killing than about living. We need debate and discussion and come up with guidelines for our society. One person cannot provide answers to all your questions. All I want to do is to raise these questions in your mind. My aim will be fulfilled if I have made you think along these lines.

Opinion expressed in this lecture is mine and does not represents NIH policy.

References

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

1. Watson JD, Crick FHC (1953) A structure for deoxyribose nucleic acid. Nature 171: 737-738.
2. A Hameed Khan (2021) The Impact of Sequencing Human Genome on Genomic Food & Medicine. International Journal of Genetics and Genomics 9: 6-19.
3. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, et al. (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 RxList. Chlorambucil - Journal of the American Chemical Society 136: 5860-5863.
8. Ross WCJ (1953) The Chemistry of Cytotoxic Alkylating Agents. In Advances in Cancer Research by Greenstein JP, Haddow A, Academic Press Inc, New York, 397-449.
9. Ross WCJ (1962) Biological Alkylating Agents. Butterworth London.
10. Ross WCJ (1949) Aryl-2-halogenoalkylamines. Part. Journal of Chemical Society 183.
11. Ross WCJ (1950) The Chemistry of Cytotoxic Alkylating Agents. J Chem Soc 2257.
12. Ross WCJ, Mitchley BCV (1964) Empire Cancer Campn. Ann Rep Brit 42: 70.
13. Facon T, Mary JY, Hulin C, Benboubker L, Attal M, et al. (2007) Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial 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 18: 1519-1527.
15. Khan AH, Ross WCJ (1969) Tumor-Growth Inhibitory Nitrophenyl aziridines and related compounds: Structure-Activity Relationships PART I. Chem Biol Interactions 1: 27-47.
16. Khan AH, Ross WCJ (1971) Tumor-Growth Inhibitory Nitrophenyl aziridines and related compounds: Structure-Activity Relationships. PART II. Chem Biol Interactions 4: 11-22.
17. Hameed Khan A, John Driscoll (1976) Potential Central Nervous System Antitumor Agents: Aziridine benzoquinones. PART I. Journal of Medicinal Chemistry 19: 313-317.
18. Ed Chou, Hameed Khan A, John Driscoll (1976) Potential Central Nervous System Antitumor Agents: Aziridine Benzoquinones. 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 (2020) The Impact of Sequencing Human Genome on Drug Design to Treat Oral Cancer: Published in the Intech Open.
21. Ala-Eddin Al Moustafa (2018) Development of Oral Cancer – Risk Factors and Prevention Strategies Springer.
22. Leon V Berhardt (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.
23. Abdul Hameed Khan (2021) The Rational Drug Design to Treat Cancers: Drug Design - Novel Advances in the Omics Field and Applications: Edited by Arli Aditya Parikesit. A book published in London 117.
24. Khan HA (2021) The Impact of Sequencing Genomes on The Human Longevity Project. J Med - Clin Res & Rev 5: 1-12.
25. Arli Aditya Parikesit (2021) Chapter 5 Drug Design - Novel Advances in the Omics Field. and Applications. The Rational Drug Design to Treat Cancers 95-115.
26. EAS Journal of Biotechnology and Genetics Abbreviated Key Title: EAS J Biotechnol Genet ISSN: 2663-189X (Print) & ISSN: 2663-7286 (Online) Published By East African Scholars Publisher, Kenya.
27. 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, Crimson Publishers AZQ was Designed to Treat Glioblastoma, the Brain Tumor. Nov Appro in Can Study. 6: NACS.000634.
28. A Hameed Khan (2021) The Impact of Sequencing Human Genome on Cancer Chemotherapy. Journal of Cancer Research Reviews & Reports SRC/JCRR-153.
29. A Hameed Khan (2021) The Impact of Sequencing Genomes on the Understanding of the Origin of Life on Earth. Biomed J Sci & Tech Res 40: 006416.
30. A Hameed Khan (2022) The Impact of Sequencing Human Genome on the Genetically Engineered Life. J Cancer Research and Cellular Therapeutics 6: 102.
31. A Hameed Khan (2022) Sequencing the Human Genome to Study the correlation between Genes and Violence, Horizon publishers.
32. A Hameed Khan (2022) The Impact of Sequencing Human Genome on the 2nd Genesis on Earth, Journal of Current Trends in Agriculture, Environment and Sustainability, Katalyst publisher.
33. A Hameed Khan (2022) Assessment of Human Genome Sequencing on the New-World Order. Research Aspects in Biological Science 4: 16232D.