ORAL CANCER: AFTER THE COMPLETION OF THE HUMAN GENOME PROJECT

Note: "Gene Profile" is one of the book chapters written for the upcoming book entitled: "Human Oral Cancer: Risk Factors & Prevention Strategies", to be published by "Springer".

Dr. A. HAMEED KHAN, Ph.D. (London)

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GRAPHICAL ABSTRACT

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This article describes the rationale for Gene profiling leading to gene expression leading to diagnosis (identification of mutated genes) and leading to treatment (development of novel drugs to shut off mutated genes). Gene expression profiling measures the amount of mRNA which is produced by normal as well as abnormal or cancer cell.

INTRODUCTION

Gene Profiling: (A Personal Journey):

This article describes the rationale for Gene profiling leading to gene expression leading to diagnosis (identification of mutated genes) and leading to treatment (development of novel drugs to shut off mutated genes). Gene expression profiling measures the amount of mRNA which is produced by normal as well as abnormal or cancer cell. The amount of mRNA measures the progress of a disease. Several hundred genes are expressed simultaneously. We have expression of good as well as bad gene profiles. Gene profiling identify which gene is functioning normally to produce healthy cells. For developing treatment or cure, we are also interested in indentifying mutated genes whose expression produces bad proteins causing abnormal growth resulting in cancers.

Oral and Lung cancers are usually caused by chewing and smoking Tobacco products. (see my lectures on **Smoking and Cancer** - https://www.facebook.com/hameed.khan.7773/ notes). Tobacco contains dozens of carcinogenic chemicals and the major culprit is Nicotine which is considered as one of the most addictive chemicals. Some studies showed that it is more addictive than many known narcotics such as Marijuana, Opiates and Heroin. Oral Cancer (OC) is caused by chemicals released by chewing tobacco. Most Football players chew Tobacco. Smoking burns Tobacco generating more aromatic amines which are known carcinogens. Nitorso-amines bind to DNA producing mutations. Mutated DNAs, code for wrong amino acids which causes abnormal growth. In addition to chemicals from Tobacco products, mutations are also caused by

radiations, chemical pollutions (heavy metal particles), genetic inheritance or viral infections. As mutation begins in a single biological molecule, it is called a point mutation. To study changes in genetic profile of a single cell, we examine the entire Genome of a single cell. As cells grow rapidly, mistakes in DNA replications are most likely to occur such as deletion, insertion or inversions of nucleotides sequence. Such mutations are responsible for major diseases. Mutations in oral cavity are responsible for causing oral cancer. More than 90% of cancers of the oral cavity and oropharynx are squamous cell carcinomas and Verrucous carcinoma is a type of squamous cell carcinoma that makes up to less than 5% of all oral cancers. In addition, there are several types of salivary gland cancers including adenoid cyctic carcinoma, mucoepidermoid carcinoma and polymorpous low grade adenocarcinoma. Tonsils and base of the tongue tissues also develop lymphomas.

To understand the causes and progression of diseases, it is absolutely essential to get Gene Profiles (gene expression) for comparison. One hundred and fifty years ago, Darwin stated that life evolves and nature selects which is now known as the Darwin's Theory of Natural Selection. As living things grow their gene profile changes; drugs develop for children may not be as effective for adults. Drug resistance is due to changes in the genetic profiles. In the following chapter, I will discuss the causes and diagnosis of oral cancers and their treatment by designing novel drugs for treating cancers in general and oral cancer in particular.

Sequencing the genomes of these cancers and comparing their genomes with the normal cells genomes (by GWAS; Genome Wide Association Studies) will identify the responsible mutations with great accuracy and precision. Once the mutations sites on as specific chromosome are identified, the next logical step is to develop treatment by designing drugs to shut off those genes. In addition, our oral cavity is home to hundreds of known microbial life forms. Almost 400 microorganisms have been identified in our mouth so far (1) and only few are responsible for causing infections. Infectious micro flora of the oral cavity could be treated with either antibiotics or vaccines.

To understand the basis of all diseases, we must read and understand our genome that is our normal book of life, the total genetic information that makes us that is our Personal Genome and what changes make it abnormal which is responsible for causing disease including cancers especially OC. Our Genome carries the total genetic information that makes us. 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 exactly 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 Genetic Code. He stated that if we break the Genetic Code, we would be able to unlock the secret of life. If we unlock the secret of life, we would be able to create new life forms carrying instructions to create new food, new fuel and new medicine to treat every disease known to mankind.

DNA is a store house of information and is made of the 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 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 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 in the above experiment, Schrödinger was using such a poor resolution microscope that we don't even use in our high school today. Instead, we have electron microscope today. 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 together 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.

If the cookbooks 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.

In 1990, United State Congress authorized three billion dollars to NIH to decipher the entire human genome within 15 years that is 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 an access to a computer key-board, you have access to all that information.

We deciphered all 46 chromosomes. What surprise us most was that our genome contains six billion four hundred million nucleotide base pairs less than two percent of our Genome contains genes which code for proteins. The other 98 percent of our genome contains switches, promoters, terminators etc.

Before sequencing (determining the number and the order of the four nucleotide), 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. Finally, the sex chromosome of all female 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 chromosomes, they come up to 26,808 genes and yet we keep on mentioning 24,000 genes. The remaining genes are called the pseudo genes. 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 Pseudo genes. Recently, some Japanese scientists have activated the pseudo genes, this work may create ethical problem in future as more and more pseudo genes are activated.

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 radiations, or chemical pollution or genetic inheritance or viral infection or by insertion, deletion or inversion of the nucleotide bases code for wrong or abnormal amino acids resulting in diseases.

The basis of OC is that people who are chewing tobacco or inhaling burning tobacco by smoking (as in India) or chewing betel quid, betel nut etc. (as in Taiwan) causing major mutations in their genomes producing a host of chemicals which damage the normal function of the cell causing them to become abnormal or cancerous. To understand the molecular basis of cancers, we have to sequence the normal as well as cancer cell genomes for comparison.

The sequencing of first human genome cost us about three billion dollars. The advent of third generation sequencing machine has made sequence based expression analysis an increasingly popular. In addition techniques of DNA microarray technology which measures the relative activity of previously identified target genes and sequence based techniques, like serial analysis of gene expression is also used for gene expression profiling has lower the cost of sequencing significantly. As the third generation sequencers are becoming available, it is expected to sequence genome cheaper and faster and the cost of sequencing will come down from 3 billion dollars to a thousand dollars per genome, and then it would be possible to sequence the genome of every man, woman and child on Earth and place the data on a central data genome center for future use. Your personal genome can be placed on a microchip of the size of a penny which you could carry on person at all times. In case of medical emergency, the hospital emergency staff can help you instantly.

There are over two hundred twenty different types of tissues in our body. We will be able to sequence every tissue for the data center. From the central data base, it would be possible to examine a single cell which is responsible for causing oral tumor (squamous cell) and sequence its genome. Using GWAS (Genome Wide Associate Studies), we align the sequence of normal cell genome with the oral tumor cell genome. The computer will compare the two genomes letter by letter, word by word, sentence by sentence, gene by gene and chromosome by chromosome. With great precision and accuracy, the computer will identify the exact location of the mutations.

In future, we might be able to perform the Gene Therapy if the cancer is caused by a single

mutation, removing the bad gene using the restriction enzymes (scissors to cut DNA) and replacing the bad gene with the good gene using the enzyme ligase. If the oral cancer is caused by multiple mutations, Gene Therapy will not work, but Drug Therapy will work. We design drugs to shut off genes responsible for oral cancer mutations.

After the completion of the Human Genome Project, the next logical step is determining the Gene expression profile of good as well as bad gene. Gene profiling identify which gene is functioning normally to produce healthy cells. The next step is to separate normal genes from the mutated genes. This step will identify the good genes which produces normal proteins that keep us healthy. The work of large scale production of such proteins is best done by Biotechnology firms. The next logical step is to isolate the good gene whose product protein could be used to treat diseases. One of the greatest intellectual achievements of the 21st Century is the Genetic Engineering that is using biochemical scissors called restriction enzymes (more than three thousand restrictions enzymes have been discovered. In our chemical store at NIH, there are at least 300 restriction enzymes sitting on the shelves to be used) for cutting out a single normal gene from the entire human genome, pasting (Ligase) into a carrying vector (besides versus, other vectors include Plasmid, Cosmid, Phagemid, BAC, Bacterial Artificial Chromosome and YAC, Yeast Artificial Chromosome to carry the largest gene called Duchamp Muscular Dystrophy which is 2.5 million base pair long) and transferring into a replicating host (Yeast or mammalian cells) cell to make billions of copies of the good proteins used to treat diseases. For example, Genetic Engineers cut, paste and ligase a copy of a gene that codes for a specific protein. Scientists at Genentech, a biotechnology firm in California, were the first to produce Insulin to treat over 300 million diabetic around the world. They are also producing clotting factor VIII to treat Hemophilia.

The next step is to separate diseases caused by a single gene mutation verses the multiple gene mutations such as cardiac diseases and Cancers. Almost three thousand diseases are caused by a single mutated gene called the MandelianDiseases. The next logical step is to conduct the Gene Therapy that is replaced the bad gene with the good gene. For example, French Anderson and Mike Blaze who are considered the Fathers of Gene Therapy, while working at NIH were responsible for using virus as a vector (carrier) to replace the bad gene responsible for causing Severe Combined Immuno-Deficiency (SCID) Syndrome with the good gene and cured the SCID. Today, more than 5,000 previously SCID children are free from the disease and living a normal life. At this time dozens of clinical trials on Gene Therapy to treat various diseases are in progress.

While Gene Therapy is successful for Mandelian Diseases to replace a single bad gene with the good gene, multiple genetically defected diseases such as cardiac diseases and cancers cannot be treated with Gene Therapy. The next step for multiple genetic defects is to develop Drug Therapy to treat such diseases. Two approaches were made: First to synthesize the Analogs of metabolites of the four nucleotide bases to interfere the normal function of the cancer cell to prevent its replication. The most successful examples of anti metabolite drugs to treat cancer are the synthesis of 5-Foloro-Uracil and 6-Mercapto Purine for treating childhood leukemia.

For shutting off multiple genetic defects, the most logical step is to shut off the gene replication by cross linking both strands of DNA carrying multiple mutated genes. All living creatures are the union of both parents. Each parent donating one strand of DNA making double stranded DNA in all living creatures except a few viruses which are single stranded.

Drug Design to Shut off Bad Genes:

Professor WCJ Ross, the Director of the Chemistry Division of the Chester Beatty Cancer Research Institute of the Royal Cancer Hospital, a postgraduate medical center of the University of London was the first person to develop a series of chemical compounds called Nitrogen Mustards developed by Fritz Haber as a chemical weapons used during WWI and WWII, to cross link the double stranded DNA to prevent its replication of multiple mutated genes along the double stranded DNA. Ross made highly successful cross linking drugs such as Chlorambucil (2) (for treating chronic

lymphocytic leukemia) and Melphalan (3) (used for treating multiple myeloma and ovarian cancer). Although they are highly useful drugs, they are also highly toxic. Ross has done the pioneering work in developing drug like Melphalan to treat Pharyngeal carcinoma.

Over decades, Ross made hundreds of derivatives of Nitrogen Mustard as cross-linking agents. All of his students were searching for dyes for all 220 tissues as coloring agents which could be used as carrier for Nitrogen Mustard to attack the tumor of that specific tissue. The rationale is that if a dye colors Pharyngeal tissues, by attaching Nitrogen Mustard, we could attack the tumor of the Pharynx. This rationale does work. Before the Human Genome Project, all drugs were developed by trial and error method. Finding a useful drug by trial and error is time consuming and expensive. In rare cases, this approach turned out to be successful. We were developing derivatives of mustard to attack the tumors. Large number of Nitrogen Mustards was tested against a variety of investigational tumors in Rats. One of the toughest tumors was the solid tumor called the Walker Carcinoma 256 in Rats. If a compound reduces the tumor growth of the Walker Carcinoma 256, it is most likely candidate to go for Clinical Trials.

While studying the mechanism of action of Nitrogen Mustard, Ross discovered that radio labeled Nitrogen Mustard does not bind to both strands of DNA at the same time. First, one arm of Nitrogen Mustard binds to one strand of DNA and then followed by the second arm of the Nitrogen Mustard binds to the second strand of the DNA. He proposed that it goes through an intermediate mechanism. The two Carbonium ions produced by Nitrogen mustard are extremely reactive while one attack the N-7 nitrogen atom of the Guanine, the second arm attack the Nitrogen atom of the mustard itself forming a three member Aziridine ring which open by acid produced by tumor and attack the second strand of the DNA cross-linking both strands. The intermediate Aziridine was unstable in acidic biological fluid and could not be isolated.

You might wonder what have I accomplished and how my work is different from my colleagues. Under Professor Ross' supervision, I received my Ph.D. degree in Organic Chemistry from London University. I worked for almost ten years in Ross' Lab as a student, as a post doctoral fellow and as his special assistant at the Chester Beatty Cancer Research Institute of the Royal Cancer Hospital, a post-graduate medical center of the University of London,

From Ross' study, I picked up the idea of binding to one strand of DNA by using the intermediate Aziridine ring. Using Dinitrophenyl as a dye which colors Walker Carcinoma 256 solid tumor cells, I made over 100 Aziridine analogs while working in the laboratory of Professor Ross for over a ten year period. Aziridine derivatives are completely harmless to touch, but highly toxic to animal tissues in acidic medium. As I said above, Toxicity is measured as the ratio (Chemotherapeutic Index as C/I) of it effect on normal to abnormal cells. All cross-linking compounds have a Therapeutic Index C/I of 10 when tested against Walker Carcinoma 256 in Rats. All my Dinitrophenyl Aziridine compounds were tested against Walker Carcinoma. One of my drugs, Dinitrophenyl AziridineBenzamide (CB 1954) showed the highest toxicity ever recorded to Walker Carcinoma 256 cells. It has a C/I of 70, it is seventy times more toxic to cancer cell compare to normal cell ever made. Ross and I published a series of three classical papers describing the synthesis of over one hundred Dinitrophenyl Aziridines compounds. (4,5,6).

I translated the animal work to human when I moved from England to America when I was honored with a Fogarty International Fellowship Award to come to America to continue my work on Azirdines at the National Cancer Institute (NCI) of the National Institutes of Health (NIH). NIH has been my home for over quarter of a century. The mission of NIH is to conduct research, support research and report research. Over the years, I participated in all its missions. At NCI, I worked in the Drug Development Branch where a major part of my work involved designing anti-cancer drugs.

We at NIH are working on the expression profiling of bad genes or the mutated genes whose proteins are responsible for causing all six thousands diseases including cardiac disease and cancers. Our Institute, NIH, is established to diagnose prevent and treat all diseases

known to mankind. We are interested in developing drugs to treat Cancers. Gene profiling of solid tumors is most important. For designing drugs to stop gene expression of solid tumors offers the greatest challenge.

Our group designed drugs which bind to DNA to shut off the gene expression of bad genes. By trial and errors, we find a coloring dye which colors a specific tissue. Using these dyes as carriers, we attach DNA binding Aziridines, Nitrogen Mustards, or Carbamates to attack the tumors of those tissues. These compounds have the ability to generate Carbonium Ions which preferentially attack the nucleotides Guanine of the abnormal cell DNA shutting off the gene.

If normal cell is attacked, we call the effect toxicity, but when the abnormal cells are attacked a cured is observed. The ratio of toxicity to normal versus abnormal cell is measured as the Chemotherapeutic or Toxicity Index or C/I. The higher the C/I Index mean that the drug is more toxic to abnormal cells compared to normal cells. Most Nitrogen Mustards shut off genes by binding to both strands of DNA and they are known as the Cross-Linking Agents. They generally have a toxicity Index C/I of 10.

At NCI, I abandoned the Dinitrophenyl dye as a carrier for Aziridine instead I used Quinone as a new carrier for Aziridine moiety because Quinone has the ability to cross the Blood Brain Barrier (BBB). I thought that if I could deliver the Aziridine ring across the BBB, I should be able to attack brain tumor. I had already demonstrated that CB 1954 could inhibit the growth of solid tumor in Rats. Using Quinone as a carrier, I thought that I should be able to attack solid brain tumor like Giloblastom in humans. Over the years, I made 45 Quinone Aziridines for screening against CNS (Central Nervous System) tumors system (7,8,9,). All 45 Aziridines are considered so valuable that they are patented by US government. One of them (10) is AZQ (US Patent 4,146,622) which is undergoing extensive screening as CNS active drug for treating brain cancer for which I was honored with the "2004 NIH Scientific Achievement Award." one of America's highest awards in medicine.

Conclusion:

Ethical Issues: Scientists in our group are working on different kinds of cancers. As I stated above, there are more than 220 different types of tissues and they could all become cancerous. We are all working to cure those cancers. Unfortunately, there was no great enthusiasm for working on either OC or Lung Cancer. Such diseases are considered self inflicting wounds. The users of tobacco products are addicted and frequently developed these types of cancers. Many scientists believe that all of us have Free Will. We have a right to live and we have a right to die. If you shoot in your foot, it will hurt you. Do we protect you from shooting yourselves? If you don't smoke or chew tobacco, you will not expose yourself to a host of carcinogens. Some of us believe that you are addictive to nicotine if we cure your OC, you will go back and chew tobacco again. How can we protect you from yourself? On the other hand, if you are one of those unfortunate persons who inherit a mutated gene, or exposed to radiations or heavy metal particles, you deserve all our help and many of us have been designing drugs for treating oral and lung cancer for them.

Let me summarize what I have written so far. It is expected that the Third generation sequencing would bring the cost down to a $1000/genome. Sequencing of cancer genome is of utmost important because at lower cost, we can sequence the genomes of all OCs including oropharynx which are squamous cell carcinomas or Verrucous carcinoma responsible for causing oral cavity cancer.

Sequencing could also include salivary gland cancers including adenoid cyctic carcinoma, mucoepidermoid carcinoma and polymorpous low grade adenocarcinoma or lymphomas of the Tonsils and base of the tongue tissues for GWAS comparison. We can not only identify the chromosome number on which mutations are located, but also the number of mutations responsible for causing cancer.

Once the mutation sites and chromosome number are identified, we can diagnose, prevent and treat the OCs either by Gene Therapy if a single gene mutation is responsible for causing any of the above cancers or by Drug Therapy if multiple mutations are involved. As I stated above, French Anderson and his

colleagues have successfully developed Gene Therapy for treating SCID (Severe Combined Immouno Deficiency Syndrome), we could use the same method to cut and paste and replaced bad gene with the good gene to treat those cancers. On the other hand if cancer is caused by multiple mutations, we could use the method developed by Ross for cross-linking both strands of DNA. Using dyes specific to OC cells as carriers for Nitrogen Mustard, we could develop new class of drugs which acts as cross-linking alkylating agents and which binds to both strands of DNA. On the other hand, you could also design drugs by using our method by attaching Aziridines to oral cancer specific dyes to shut off mutated genes by binding to a single strand of DNA. What would happen if we succeed, when next generation sequencers produce inexpensive and fast sequencing genomes becomes available to researchers? On that moment the dawn of a new day at last long will shine on all the members of medical staff for developing treatment for C.

THE AUTHOR:

Dr. A. Hameed Khan was born in India, educated in England and received his doctorate degree in Organic Chemistry from the University of London. He is a recipient of the Institute of the Cancer Research postdoctoral award of the Royal Cancer Hospital, University of London and a recipient of the Fogarty International postdoctoral award of the National Institutes of Health (NIH), and the National Cancer Institute of USA. He is a discoverer of AZQ (US Patent 4,146,622) for which he was honored with the "2004 NIH Scientific Achievement Award" one of Americas' highest awards in medicine. He was also honored with a Gold Medal by the Government of India. For the past nine years, Dr. Khan has been speaking to the exceptional scholars selected by the NYLF (National Youth League Forum) from around the country organized by the **"Leadership in Medicine Program"**, at either the Johns Hopkins University or the Georgetown University. All these lectures are available at the following website:
https://www.facebook.com/hameed.khan.7773/notes. Dr. Khan is a Fellow of the American Institute of Chemistry and was elected to the American Science Advisory Board. He works at NIH, an agency of the U.S. Government. The ideas expressed in this book chapter are his own and do not represent government policies.

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