Uncontrolled proliferation of cells: lung cancer

Exhibit the uncontrolled proliferation of cells and constant progress of malignant cells in the body.

1. 6. 2. 1. Lung Cancer:

The normal lungs tissues are composed by normal cells and they are intending to determine the right size, appropriate shape and the normal function of the lungs. In a cancerous cell, the genetic material DNA is altered by the encoding of the genes which are responsible for the transformation of normal cells into muted or cancerous cells.

The lung cancer is classified into two major categories, known as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The SCLC is exceptionally assertive, and it spreads all over the body very rapidly. A high percentage of the lung cancer patients, when diagnosed, are already in metastatic phase of the disease (48). NSCLC is the most common type oflung cancer. It usually grows and develops gradually, and progress at moderate rate as compared tosmall cell lung cancer. Therefore, it is treatable most of the times when NSCLC is diagnosed.

1. 6. 2. 1. 1. Risk Factors for Lung Cancer:

Research has proposed numerous risk factors that may contribute to enhance the chances of getting lung cancer. They may include air pollution, and exposure to inorganic compounds. Additionally, family history, use of tobacco, mineral oil exposure, and occupational contact may contribute to the development of lung cancer. Furthermore in certain cases it was also observed that the previous cancer and treatment, silica interaction,

inhalation of welding fumes, are also responsible for developing lung cancer in humans as well.

1. 6. 2. 2. Blood Cancer:

Blood is a unique type of body fluid. The main component of blood is plasma, which is a yellowish high viscous liquid and is more than 90% of the blood. The solid material present in the blood consist of platelets, red and white blood cells, whereas whole blood is a mixture of about 55 percent plasma and 45 percent blood cells. It has been observed that 7 to 8 percent of the total body weight is consist on blood whereas an average-sized man has about 12 pints of blood in his body, and an average-sized woman has about 9 pints of blood (49).

The blood looks like a red fluid due to the presence of a great numbers of red blood cells called erythrocytes, and more than 40 – 45 % of blood volume consist of erythrocytes. The leukocytes are white blood cells and they are part of our immune system. The task of immune system is to offer defense to the body of an organism against undesirable entities present inside the body as well as in the environment. Another specialized type of white blood cells is neutrophil, which get stimulated immediately after the invasion of any foreign particles and disease causing agent to the body.

Blood plasma is composed of 92% of water and 8% plasma proteins, mineral ions, glucose, clotting factors and carbon dioxide, serum albumin, lipoprotein particles, immunoglobulin electrolytes, etc.

Blood plays a vital role in keeping an organism alive. If for some reason blood is not healthy enough or it is not able to perform its functions properly, the situation could be life threatening. Blood performs many different functions inside the body that include, supplying oxygen and nutrients all over the body. It has specific proteins that help in forming blood clots to avoid excessive blood loss, which is a natural mechanism for the repair of cells. In addition, it manages waste products such as urea; lactic acid and carbon dioxide by collecting from our body take them to the kidneys and liver, which sieve out harmful species from blood. Furthermore, blood normalizes and maintains normal body temperature. It also keeps the normal pH inside the body. The homeostasis mechanism remains dependent on regular circulation of blood inside the body. Blood maintains pressure inside the body in order to coup the out side pressure i. e. atmospheric pressure exerted by air and this pressure is approximately 14lb/ sq inch (50).

There are various types of blood cancer that have been discovered in human beings. The most frequent diagnosed blood cancers areleukemia, lymphoma, andmyeloma.

All cellular blood components are derived fromhaematopoietic stem cells. The hematopoietic process is controlled through a series of chemical reactions, which are regulated with the support of immune system. A failure in any of these steps can lead to the uncontrolled division of immature blood cells. These types of malfunction can occur due to a variety of reasons, including spontaneous gene mutation and chromosomal aberrations and exposure to chemicals and radiations etc.

Blood cancer is the result of abnormal development of bone marrow or the collapse of lymphatic system. Malignancies caused by blood cancer have shown distinct rate of augmentation that are directly associated with the type of blood cancer, and patient’s capacity of tolerance. However, rate of survival with blood cancer has dramatically increased in late 20th century due to the improvement of invasive treatment and the development of new strategies with the compliance of revolutionary medicines. Despite this fact, the timely diagnosis of blood cancer is highly manageable in these days.

Like every cancer, blood cancer also starts from a single cell that has abnormal or mutant DNA in its nucleus. That muted cell divides rapidly and forms a bulk of abnormal cells. This bulk of cells, rather than maturing and completing its life cycle and following a pattern of natural death, it starts accumulating in the body of an organism until the individual is diagnosed with blood cancer. Nevertheless the causes of blood cancer remain unidentified. However, it is imperative to know the rationale explanation for the initiation of these irregularities in the bone marrow, which is the main cause of transformation of a healthy cell to cancerous cell.

1. 6. 2. 2. 1. Risk Factors for Blood Cancer:

The immune system has an assigned and a prominent role endowed by nature, which is to provide protection to a body against internal and external factors that may initiate a chain of disorders and in turn can cause serious consequences for the body in the form of disease. The defective or damaged immune system cannot perform in adequate manners and therefore, in this situation, the risk of having cancer increases at the magnitude of many folds.

Certain factors that can influence the immune system are exposure to viruses and chemicals. Furthermore, contaminated environment and infections have also been associated with poor defense system and, consequently, have been linked to a cause of blood cancer as well. It is also reported that there are many other cancer triggering agents such as tobacco, radiation exposure, growing older, and family history, which may also contribute to the etiology of blood cancer. Blood cancer may also be inherited but cancer usually skips generations and can be transmitted to more than one member of a family. There are two types of blood cancer; chronic type of blood cancer develops slowly over a period of years while acute cancer develops rapidly and when it diagnosed it could be too late to be cured (51).

1. 6. 2. 3. Breast Cancer:

Although it has been observed that the occurrences of cancer have considerably decreased in United States in last three decades. The breast cancer is still at the top among the other types of cancers in European nations such as Spain, Portugal, Greece, Hungary, Poland, and Italy (52).

It has been observed that for a long period of time breast cancer was the foremost cause of death in North America and Northern Europe (53) while least number of breast cancer cases were registered in Asia and Africa. In addition, other countries such as Southern Europe and Latin America show that the number of breast cancer patients remains the same and not very distinct among the other types of cancer (54). Therefore, it is a distinguished feature that could be monitored and enable the scientist to a point where

they can speculate the reasons for the existence of this type of trend. Moreover, they were being able to establish some guidelines that were helpful in determining the order of severity of the disease in these regions.

Breast cancer is known to have a long latency period; there may be several decades between the initiation of the carcinogenic process and clinical detection (55). Environmental factors during embryogenesis, childhood, and adolescence may affect breast cancer occurrence in adulthood by enhancing or deterring carcinogenic processes (56). The embryo develops rapidly and toxic agents that do cross the placental barrier can have specific effects on organ development depending on the time at which the exposure occurs (57). Even though breast tissue begins to differentiate by the fourth week of development, the breast has distinct features among body parts in contrast to other body parts in that it remains relatively unchanged until puberty or later.

Environment in which we live and breathe is already contaminated with various types of chemicals. These chemicals present in the environment can behave as an impersonator of certain hormones and they can impact the other chemical reactions inside the body of an organism, as well as the cell division. Some breast tumors depend on estrogen for their occurrence and progression. The chemicals and trace elements that can influence the metabolism of estrogen, prop the development of breast tumor. For example, preliminary research suggests that the exposure to an environment that is contaminated with estrogen 4-octylphenol is highly linked with the risk of breast cancer (58). In another study it was found that the metal ions in the environment are capable of promotion of DNA double-

strand breaks and the process of strand-breakage is complicated however it has the ability to replicate the altered DNA. This is probably the consequence of conversion of a DNA single-strand break into double-strand breaks (59).

Nevertheless, the authors have reached the consensus that the metals ions have the ability to initiate many trails that can make a cell vulnerable and expose it to toxic elements, which could increase the risk of breast cancer. Antioxidants that have selenium as an essential part of their structure can provide protection by pursuing free radicals in the upper lining of epithelial cells in the breast.

1. 6. 2. 3. 1. Risk Factors for Breast Cancer:

The involvements of certain factors, which are consistently found in the history of cancer patients, are known to be as “ established risk factors”. For instance, getting older and having regular menstrual periods earlier or going through menopause later in life are considered as established risk factors. Moreover, having a first baby late in life or not having any pregnancy in their life time is well known established risk factor. It was also observed that the risk was significantly elevated among those who have family history of having breast cancer in their blood relatives such as mother or sisters and the siblings of parents as well. It is also important that the breast cancer victim have the radiation exposure in their record (64). A study shows that trace elements exposure increases the risk of breast cancer occurrence as well.

1. 7. Cancer and Trace Elements:

The physiochemical properties of a metal greatly contribute to the determination of the toxicity of their compounds such as oxidation state, charge and ionic radii, the coordination number, ionization potential, etc. The similar physiochemical properties of a toxic metal, such as charge and size as those of essential ions, may compete for the biological binding sites of the latter and cause structural perturbations resulting in peculiar function of biochemical macromolecules.

1. 7. 1. Cancer and Chromium:

Chromium is a human carcinogen primarily through inhalation exposure in occupational settings. Although lung cancer has been established as a consequence of hexavalent chromium exposure in smokers and nonsmokers, some cancers of other tissues of the gastrointestinal and central nervous systems have also been noticed (65). Several studies of the chrome-plating industry have demonstrated a positive relationship between cancer and exposure to chromium compounds (66).

The chromium (VI) compounds are toxic and carcinogenic. These compounds have a wide range of capabilities and can contribute to the development of cancer. The bronchial tree is the major target organ for carcinogenic effects of chromium (VI) compounds. Chromium (VI) is a powerful epithelial irritant and a confirmed human carcinogen. Cancer primarily occurs following inhalation exposure and uptake in the respiratory organs. This is of great significance with respect to the subsequent risk of lung cancer in humans. IARC has stated that chromium and certain chromium compounds have shown sufficient evidences for considering the chromium as a carcinogen for

humans. Moreover, the most recent carcinogenic risk of chromium and its compounds was evaluated in another study and an increased incidence of lung cancer has been observed among workers in the chromate producing industry. In addition, it was observed that the chromium alloy workers were diagnosed with lung cancer (67-69). The findings were consistent with the hypothesis that soluble hexavalent chromium compounds are potent human lung carcinogens (70). Subsequently, the same was reported by a prospective cohort study of the same cohort of 1, 193 workers at small Japanese plating facilities, while a trend toward statistical significance for risk of lung cancer was seen in the chromium plating subgroup (71).

Several studies have shown that chromium (VI) occupational exposure was identified as an important risk factor of lung cancer. Higher percentage of SCLC was found in chromium exposed individuals (72).

1. 7. 2. Cancer and Selenium:

The epidemiological survey and the data collected by several scientists have irrefutably reported that selenium is an antioxidant and can be used as an inhibitor of cancer. The flux in genetic material generated by carcinogens or endogenous means has been believed to be crucial for the development of cancer. The role of selenium in a biological system as an anti-carcinogen and the extent of its protective behavior are not implausible. It has been widely recognized, and recommended that the combination of vitamin E, selenium and methionine must be taken as an essential nutrient, however the dose has the ultimate edge over the recommended theory (37).

The role of selenium as an essential trace mineral in human health and disease is currently a subject of keen interest. The essential role of selenium for animals was discovered in the 1950s (73) and for humans in the 1970s (74). Selenium has shown to benefit in reducing the risk of cancer incidence and mortality in all cancers, and specifically in liver, prostate, colon-rectal and lung cancers (75).

1. 7. 3. Lung Cancer and Chromium:

Industrial uses of hexavalent chromium compounds include inks, chromate pigments in dyes, anticorrosive agents to paints, and plastics. The use of chromates is tremendously increased due to the development of high technology, such as chromic acid is utilized for electroplating and ornamental purposes as well. Hexavalent chromium can also be formed when performing jobs at elevated temperature such as welding metallic objects. The high temperature favors the conversion of chromium, from one oxidation state to another oxidation state and most likely during the process of welding or coating, the chromium transforms into chromium (VI) (76). Therefore, the excess risk can be contemplated to be the result of exposure to hexavalent chromium. It is important to measure hexavalent chromium exposure and lung cancer risk along with cigarette smoking as a risk factor as well. As a whole, the chromium exposure was associated with an increased risk of lung cancer (77). Hexavalent chromium is not only a carcinogenic form of chromium, its adverse health effects have long been known as a risk factor as is reported by Mancuso (78-79). The International Agency for Research on Cancer concluded that chromium and certain chromium compounds were known as human carcinogens (80). The

Recommended Exposure Limit (REL) for hexavalent chromium is 1 g Cr/m3 (approximately 2 g CrO3/m3) (81). An elevated risk of lung cancer among workers in chromate production facilities has previously been reported. This excess risk is accepted to be the result of exposure to hexavalent chromium. However, the results of other studies indicate that moderate or heavy exposure to zinc chromate may give rise to a severe risk of developing lung cancer, but that exposure is relatively mild or lasts less than a year and may not constitute an effective risk (82).

1. 7. 4. Blood Cancer and Trace Elements:

Bone marrow is the soft tissue located in the cavities of bones and is the source of generating all types of blood cells. It has been observed that the malfunction, nutrient deficiency and the trace elements alteration leads to a condition where the risk of cancer escalates considerably. The various types of blood cancers have been discovered, and it would be very difficult to explain all of them individually. Therefore, it is appropriate to use the general term ‘ cancer’ where it permits for all types of blood cancers to be characterized without mentioning their names separately.

There are multiple reasons as to why the normal bone marrow starts developing malignant cells. It has been observed that there is a depletion of bone-marrow cells due to deficiencies of trace elements (83). A study revealed remarkable alteration in thetrace elemental concentration of zinc and selenium in both pre-cancer and cancer patients as compared to the control group. In this study it was concluded that there is a critical relationship between alternation in the level oftrace elements, oxidative

stress and leukoplakia (84). Another study has suggested that the trace element concentration in the blood of cancerous and controls subjects present a significant difference and it can be related distinctively to the carcinogenesis (85). For instance, copper deficiency affects various physiological characteristics that may be important in immunological defense to pathogenic challenge (86), while certain trace elements level in leukemia patients are considerably higher as compared to the normal individuals (87).

Trace elements play an important role in biological processes through their action as activators or inhibitors of enzymatic reaction, or by influencing the permeability of cell membrane or by their essential role as direct anti-oxidant enzymes (88-89). Several researchers have found that the depressed antibody response is the result of deficiency of certain trace elements (90-92). Therefore, malfunctioning of the immune system which in turn creates a suitable environment for the development of leukemia and it has especially demonstrated a high negative correlation between the selenium content of soil and the mortality ofleukemia (93).

1. 7. 5. Breast Cancer and Trace Elements:

Breast tissue is unique due to its complex hormonal influences and dramatic changes during various life events. Individual hormonal levels and metabolism are affected by environmental factors as well and some frequently used chemical and metals that have the ability to disrupt endocrine function and thus mimic the effects of estrogen (94). On a daily basis we interact with various chemicals and some of them are naturally

present in our environment and others are the by-products of several industrial process. The breast is a sensitive organ and it responds to even a minor event that occurs in the form of chemical changes inside the body. However, the exposure of certain elements brings changes in the concentration levels present in our body even though these elements are indispensable for the life and also have significant importance for our livelihood. These elements play a very critical role in the body and in certain amount they are advantageous. However, their concentration variation may impact the gene activation and is an example of gene-environment interaction as well. For example, in a study it was mentioned that if a woman is already exposed to an organic complex known as polychlorinated biphenyls (PCBs) she still does not have an extraordinary risk of developing breast cancer. While in another research work it has been reported that if a woman shows the combination of both factors, such as if she already has been exposed to PCBs and exhibits the alteration in their CYP1A1 gene, she has immense chances to develop breast cancer in her life time (95).

For example, the result of a recent study suggests that cigarette smoke exerts a dual action on the breast, with different effects in premenopausal and postmenopausal women. It is relevant because investigators found an association between environmental carcinogens and putativeendocrinedisruption and risk ofbreast cancer(96).

Selenium is an important cofactor in the production of antioxidant enzymes that may influence cancer progression. However, the findings suggest that selenium intake before breast cancer diagnosis may improve breast cancer-specific survival and overall survival (97). On the other hand, the association

between selenium and breast cancer has been studied and it was concluded that selenium levels were significantly lower among patients suffering from breast cancer. However contrary reports were also submitted by other researchers and they concluded that they did not find any direct relationship between selenium levels in the blood of patients and breast cancer (98).

A study was conducted on Dutch women aged 55–69 years. In this study they tried to find out the association between selenium and breast cancer. The analysis was based on the diagnosis of breast cancer in various patients between one and more than three years. It was found that selenium concentration was considerably lower in the blood of individuals diagnosed earlier during follow-up process. The authors provided no evidence for an inverse association between selenium status and breast cancer (98).

1. 8. Analytical Techniques:

Analytical techniques are the basic tool for the analysis of chemical elements from major to smaller trace levels in variety of matrices. These tools provide complete information about the composition of a simple to complex substrate and these techniques are usually applied for the qualitative and quantitative analysis of samples of interest. There are many types of analytical techniques available for the analysis of elements in biological matrices in terms of their sensitivity and accuracy. The choice of an analytical technique is contingent to many factors, such as the nature of the problem, type of the sample, elements of interest, and moreover the attention of the analyst that dictates the end use of analytical results (99).

However, there are some other traits that may also influence the use of a particular technique for the elemental analysis, for instance the principle, and instrumental limitations. Therefore, every analytical technique may not be considered appropriate for the analysis of certain elements. Moreover, the interference due to the presence of other elements and due to the instrumental technology is another important contributing factor in selection of an analytical technique, as well as the intentions of the scientist which inadvertently dictates the results the analyst would like to obtain from the experiment.

A few analytical instrumental techniques are concisely discussed with their limitations and preferences over one another because of their sensitivity and accuracy for the analysis of certain trace elements in human whole blood.

1. 8. 1. Inductively Coupled Plasma Spectrometry (ICP):

The Inductively Coupled Plasma (ICP) is a multi-elemental technique that has ensured its place with established techniques such as atomic absorption spectroscopy and x-ray fluorescence spectroscopy. It has detection limits that are usually attainable at the parts per billion (ppb) levels, while most of the samples are introduced in liquid form as aqueous solutions. The technique has widespread applications in the fields of metallurgy, geology, environment, agriculture, industries, and biology.

The excitation source for ICP is argon plasma that operates at atmospheric pressure and sustained by inductive coupling to a radio frequency electromagnetic field. The plasma furnishes a chemically inert, high temperature environment that is very effective for vaporization, atomization,

ionization and excitation of the sample material that is injected into it. Two types of ICPs are discussed here:

1. 8. 1. 1. Inductively Coupled Plasma – Atomic Emission Spectrometry:

The Inductive Coupled Plasma – Atomic Emission Spectrometry (ICP-AES) is inherently a multi-element technique with two types of spectrometer configurations that are used to detect the atomic emission radiations of elements of interest. Simultaneously, Poly-chromators are used for multielement analysis and mono-chromators for sequential multi-element analysis (100). The ICP-AES consists of an excitation sources for atomic emission and a spectrometer that helps in order to detect the emission spectra.

Changes in the concentration of coexistent elements may generate gradual changes in the background. These background shifts are assumed to have great importance for the determinations and are made at declining concentration levels. However the stray light may be responsible for this effect (101). The disadvantage of this technique is that some elements readily form non-emitting and refractory oxides that result in an underestimation of their concentration.

1. 8. 1. 2 Inductively Coupled Plasma – Mass Spectrometry:

In this set up, the ICP source is mounted horizontally and the sample is introduced into the plasma by standard ICP nebulization process. The mass spectrum can be recorded in a short period of time i. e. approximately one minute, and can enable the instrument to analyze the sample at a faster rate

than the conventional mass spectrometric technique. The advancement in technology has made the ICP-MS more efficient, and improved its performance due to altering its design of the interface between the atmospheric plasma and the vacuum spectrometer.

ICP-MS is incredibly sensitive, with its detection limits of parts per billion (ppb) for most of the elements and exhibit comparatively less spectral interferences. This technique is particularly useful in the analysis of rare earth elements, and appropriate for the analysis of the actinides. These are characterized to produce complex optical spectra. The natural applications of the ICP-MS technique include isotope ratio measurements and isotope dilution analysis as well (101). The emission techniques always presented an incomplete resolution of radiations emitted by the analyte and the back ground interferences. The high temperature supports transitions to various excited states of the atom thus the wavelength of the emission line selected for an analyte may coincide with a line emitted by another component of the sample i. e. direct spectral overlap or the two lines may be so close that they partially overlap i. e. partial or wing overlap with each other. If these lines are not distinctively separated, the spectral interference may occur, and hence demonstrates a counterfeit level that is higher than the true concentration of the respective element.

The ICP-MS is not a pertinent analyzing technique for noble gases. Similarly, halogens and some non-metals are difficult to be analyzed by setting standard parameters of this technique. In addition to that, poor sensitivity of ICP may also be observed for alkali metals. Another disadvantage of this technique is the spectral overlapping generated by the interferences of

polybaric, polyatomic and doubly charged ions. As a result, elements like manganese, vanadium, and arsenic are sometimes difficult to determine with good precision at low concentration with ICP-MS.

The technique imparts accuracy for solutions; therefore, sample dissolution procedures are recommended, however dissolution may involve additional steps for sample preparation and consequently add up contamination in analyte and introduce more problems to the method of analysis. Therefore, it is not recommended for high purity materials and for those samples that have low levels of elements concentration. In this technique, varieties of interference are met, such as nebulization interferences, transfer and desolvation interferences, chemical interferences, ionization interferences, and atomization and volatilization interferences (102). All interferences introduce the transformation or rotation of the calibration curve. However, ICP-MS is a technique that offers reduced spectral and isotopic interferences.

1. 8. 2 Anodic Stripping Voltammetry (ASV):

The most sensitive analytical technique is anodic stripping technique (ASV) that is convenient and cost effective analytical method for the detection and quantization of metals in drinking water as well as in biological materials (103). The advantage of this technique is that the various metals such as Pb, Cd and Cu can be analyzed simultaneously. The ASV can be considered as a small scale electroplating experiment. The metals are present as an ion form in the solution, and are plated on an electrode by applying a negative potential that initiate deposition on it for a specific period of time. The deposition serves to concentrate the metal ion from the solution on the

electrode as metal (0). For example, if the electrode is mercury, the metals often develop a form of amalgam on it. After deposition the potential is switched towards positive potential. The peaks of the current appear at a point where potential corresponds to the oxidation of metal as they are oxidized and back stripped from the electrode into the solution. The peak height/ area can be correlated with the concentration of the metal ions in the solution. It is necessary to calibrate the procedure with the standard solutions of known quantities of respective metal ions. Along with advantages of ASV, some disadvantages are also associated with this technique as well. For instance, only mixture of metals can be analyzed, however the analysis time is longer than usually taken by spectroscopic method. In addition, the technique is extraordinary sensitive for interferences as well. It is also important to start the analysis by a profe