Analytical Approach to Cancer Therapy by Inhibition of Blockade Regulation in the Context of Protein Vibration

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Abstract A brief account of discovery of cancer therapy by overcoming the negative immune regulation of cancerous antigens (proteins) with cloned antibodies (proteins) for which Nobel Prize was awarded in Physiology or Medicine in 2018 has been analytically discussed here. These antibodies are now regarded as checkpoint inhibitors. These discoveries have opened a new channel for better treatment of different types of cancer. In view of these successful endeavours, attempts have been made by the author to explain the functioning of both curative and immune role of certain antibodies (proteins) like MDX 010, Nivolum ab and pembrolizum ab against cancer causing antigens like CTLA 4, PD 1, PDL 1, PDL 2, etc., in the context of "Protein vibration". A short note on the role of protein vibration was also discussed.

Keywords Immune responses, Blockades, Cancerous antigens, Cloned antibodies, T cell receptors, Co-stimulation, Inhibitors

1. Introduction

It is held by Hanahan and Weinberg [1] that all cancers display certain hallmarks, though etiologic and pathogenesis of cancer are found complex. It is now established that each hallmark being influenced by multiple pathway is found to render dysfunction by alteration in the genes of the cancer cells. While some of these genetic changes are inherited via the germ line DNA, majority is found to be acquired as mutations in somatic cells due to intervention of a number of external factors.

It is reflected in the report of Global Cancer Observatory, 2018 [2] managed by WHO that millions of population (more than 18 million) are estimated to be affected with cancer in 2018. This constitutes the fact that one in three is developed with cancer in economically developed countries and it is also estimated that this will turn to one in two in next two decades. The scenario of the diseases though devastating, yet life of the patients can be prolonged by different treatments which are usually within the economic capability of the patients. But the reverse is found in countries with less developed economy which results in fewer cures and reduced amount of survival of the patients. Thus treatment of cancer patients is found critical from the view point of application of appropriate medicine. These are also costly enough. In spite of all these hurdles, scientists of the day are toiling their best to innovate multiple ways of treatment of the patients with cost effective approach too.

A number of discoveries have magnified the present knowledge about cause and remedies of cancer. Most of these were awarded Nobel Prizes in Physiology or Medicine. These include

(1) Identification of infection as an etiological factor by Rous in 1966.

(2) Discovery of human papilloma virus as a cause of cervical cancer by zur Hauzen in 2008.

(3) Establishing the relation between cellular and viral genes in pathogenesis like (a) integration of retroviral genetic information into DNA by Batimore, Dulbecco and Temin in 1975 and (b) the cellular origin of viral oncogenes in 1989. Moreover, a good number of novel therapies discovered by a good number of scientists were also awarded Nobel Prizes in Physiology or Medicine. Some of these include

(1) Hormone treatment for prostate cancer by Huggins (1966).

(2) Discovery of the mechanism of cytostatic drugs affecting the metabolism of nucleic acid by Elion and Hitchins (1988).

(3) Discovery of bone marrow transplantation for treating blood cancer by Thomas (1990).

These therapies are being used as complement to the traditional methods of surgery and radiotherapy since latter part of the 20th century.

In addition, U.S. Food and Drug Administration (FDA) has approved (2a) good number (more than a dozen) of monoclonal antibodies (mAbs) for treatment of cancer. These are being used for both purposes of cancer treatment as curative agent and also an immune therapy agent. But identification and uses of these antibodies are not so easy. The antibodies so far cloned are now classified as naked monoclonal antibody and conjugated monoclonal antibody.

Naked antibodies work by themselves. No drug or radioactive material is attached to these. These are the most common type of mAbs for treating cancer. Some of these boost antigens found in lymphocyte (included in leukemia) cells, attracts immune cells to destroy these cells. Other naked mAbs like trastuzum ab (Herceptin) works mainly by attaching and blocking antigen like HER2 protein responsible for breast and stomach cancer cells.

Monoclonal antibodies (mAbs) joined to chemotherapy drug or radioactive material are called conjugated antibodies. These can be classified as radiolabeled and chemolabeled antibodies. As for example, Ibritumomab tiuxetan (Zevalin) a radioactive antibody works against CD20 antigen which is found in lymphocytes generally known as B cells. On the other hand, chemolabaled antibodies or antibody-drug conjugates (ADCs) are attached to chemotherapy. These are of two types as Brentuximab vedotin (Adcetris) and Ado-trastuzumab emtansine (called TDM 1). While Brentuximab together targets CD 30 antigen by attaching with chemo drug (MMAE) used to treat Hodgkin lymphoma and anaplastic large cell lymphoma. Ado-trastuzumab entansine (Kadcyla) antibody targets the HER2 protein attached to chemo drug called DMI is used to treat breast cancer, etc.

2. Background of Immune Therapy to Cancer

In addition to successful chemotherapy endeavours, scholars have been trying their best to involve them to the principle of immune therapy. The basic understanding of the immune system revealed in the beginning of the 20th Century when Leo Loeb discussed the possible role of immunity for the growth of experimentally transplanted tumours [3] with establishing inbred mouse strains. Using this possibility, it was observed by Snell and Higgins in 1951 that "alleles within the histocompatibility-2 (H-2) locus in the mouse were the key determinants for tumours transplantation". George D. Snell was awarded Nobel Prize for his discovery in 1980. These discoveries paved the way for further understanding; the phenomenon of discriminating self from 'non-self' with respect to using lymphocyte molecules of the Major Histo Compatibility Complex (MHC). Based on this Peter C. Doherty and Rolf M. Zinkernagel discovered "the specificity of the cell mediated immune defence" for which they were awarded Nobel Prize in 1996. Above these scientists, Paul Ehrlich shared the prize

with llya llyich Mechnikov in 1908 for reorganization of his in-depth study in the potential effects of natural and acquired immunity for cancer [4]. Sir Frank Macfariane Burnet shared Nobel Prize in 1960 for his discovery of acquired immunological tolerance which proposed that "immune system serves as a surveillance system for cancer" [5].

Moreover, a number of fundamental discoveries in tumour immunology like demonstration of tumour-specific antigens by Klein and Klein in 1962 and their molecular nature by Lurquin et al. in 1989, cytotoxic Tcell killing of tumour cells by Brunet et al. in 1968, tumour-infiltrating lymphocytes by Klein et al. in 1977 [6,7,8,9] and their role in immunotherapy by Rosenberg et al. in 1986 [10], immune selection and immune editing during tumour progression [11], etc., observed profound and beneficial effects on tumour growth with respect to animal.

3. T Cell Activition

Development of monoclonal antibody technology in 1980 by George J. F. Kohler and Cesar Milstein for which they were awarded Novel Prize in 1984 opened the door for identification of novel cell surface makers though prior to this, antigen-specific receptor on B cell had already been characterized. Thus, it may be held that understanding of cellular adaptive immune responses was started to take place from 1980. During this decade, T cell receptor (TCR) was identified and its interaction with MHC-associated peptides on antigen presenting cells was revealed. This paved the way for cloning a gene, namely, interleukin-2, an important regulator of T cells. This results in understanding the principle of signaling of TCR. As a result, CD 28 was identified as the first cell surface molecule in TCR co-stimulation. This was recognized as a monoclonal antibody protein/protein receptor on T cells and thymocytes [12]. Since then rapid development in this field occurred with identification of B7 molecule as legend for CD 28. B 7 is now known as CD 80 and is found to be expressed on antigen-presenting cells by Lindsten et al. in 1993 [13].

It was also observed that like CD 28, CTLA 4 binds to B 7. Prior to 1993, the function of CTLA 4 was unknown but both CD 28 and CTLA 4 belong to the immunoglobulin super family. It is now established that CTLA 4 resides intracellularly in resting T cells but translocates rapidly to the membrane after activation [14,15]. In 2000, it was also observed by the scholar [16] that CTLA 4 is expressed as a membrane protein in regulatory T cells [17] and acted in similar co-stimulatory way as that of CD 28. However, different group of scholars by Krummel and Allison in 1995 [18] and the group of Allison with Hurwitz and others [19] came to the conclusion that CTLA 4 serves as a negative regulator of T cell activation, which means CTLA 4 induces negative signaling against positive signals elicited by TCR and co-stimulatory receptors.

4. Role of Immune Checkpoint Inhibitors

The aforementioned findings opened the door to the scientists to develop treatments for autoimmunity. Among these scientists, James P. Allison attempted to find a cure for cancer by blocking the negative effects that are induced by CTLA 4. By the end of 1994, Allison set up the first experiment in his laboratory at the University of California, Berkley to treat tumour transplanted mice with monoclonal antibodies against CTLA 4. The Allison laboratory carried this experiment with number of cancer affected animals other than mice. These include tumour models including prostate cancer [20], mammary tumours [21] and melanoma [22]. Some of these experiments were carried with combined therapies of anti-CTLA 4 and immune stimulatory cytokine like GM-CSF (granulocyte-macrophage colony stimulating factor). Thus, it is observed that monoclonal antibodies are capable to unleash responses against tumours and this is referred to as Immune Checkpoint Inhibitors (ICIs).

Allison had to face trouble for translating his research into clinical program, since no pharmaceutical company showed least interest in this respect. At last a small biotech namely Medarex came forward and ultimately an anti-CTLA 4 igG1, monoclonal antibody named MDX010 and popularly known as ipilimumab was developed. Nine melanoma patients [23] were administered MDX010 in phase-1 clinical trial with a single dose of 3 mg/kg and the response was recorded. Complete regression was reported in another trial in some treated melanoma patients. A special feature like increase in tumour volume, namely "pseudoprogression" owing to infiltration of immune cells rather than reducing it was also observed. Major breakthrough was observed in phase III trial when metastatic melanoma showed significant increase in survival [24]. Based on this trial, FDA and EMA approved the treatment of anti CTLA-4.

In 2018, Nobel Prize was shared by Tasuku Honjo of Kyoto University in Japan for almost similar discovery of James P. Allison. PD-1 (CD 279) was first identified and cloned by Tasuku Honjo's group at Kyoto University in 1990 [25] prior to Allison's discovery of CTLA 4 inhibition for treating cancer. Two studies, one from Chen's laboratory [26] and the other from the Kyoto groups of Minato and Honjo [27] focused on PDL 1 molecules are found to be expressed on tumour cells and it was held after demonstration that these expressions would "protect transformed cells from immune attack in vivo and this could be reversed by suitable antibodies to PDL 1". Hence, it becomes necessary to devise the path of using appropriate antibody which may be involved in immune response to tumour.

The 1st experiment with antibody to the receptor PD 1 responsible for cancer conducted with mice was published in 2005 by Honjo's groups. The paper presented several pathways with respect to anti PD-1 treatment like '(i) induction of immune responses also to tumours which do not express detectable PD 1 or PDL 2; (ii) it is at least as efficient as CTLA 4 therapy to tumours; (iii) it shows less severe auto immune side effects than CTLA 4' [28]. The name of the antibody as synthesized is nivolumab and it was also observed that the drug was well tolerated in its 1st phase trial during 2006 [29]. Two years later it was reported [30] that the antibody used in 296 patients in phase 1 trial indicated remarkable efficacy in treatment of different types of tumours which were found in advanced stage. After a good number of trials during the last 15 years with anti-CTLA 4 antibodies and 12 years of the same with anti-PD 1 antibodies for treatment of different types of cancer, it was held that anti-PD 1 antibodies treatment yields better response as compared to that of anti-CTLA 4 antibody. However, combined therapy with respect to ICIs against PD 1 or its legend PDL 1 and CTLA 4 is found to respond "stronger anti-tumour effects" in melanoma [31] and renal cell carcinoma [32].

Now the question arises, what would be the functioning mechanism of primary as well as acquired resistance of tumour cells to anti-CTLA 4 and anti-PD 1 therapy. Though there are number of interesting observations regarding up-streaming of T cell activation like (i) mutational load in the tumour expressed with antigens, (ii) previous infections or vaccination, (iii) micro environment and microbiome in niches [33,34], the actual mechanism where antibodies interfere with negative responses are full of complexes. Allison's group provided four possible evidences for four different mechanisms like (i) "blockade of a direct inhibitory signaling pathway in effectors T cells, (ii) sequestration of activating legends on antigen presenting cells, (iii) interference with the function of regulatory T cells, and (iv) elimination of regulatory T cells".

All these findings follow biochemical processes. The characteristics of these biochemical processes require to be analysed from the view point of physical phenomenon too. In a recent paper, the author [35] explained analytically the modulating effects of Heat Shock Proteins (HSPs) towards immune responses of cancer in the context of protein vibration. Heat Shock proteins are found to be either auto induced or to be induced due to external administration of therapeutic agents including some kinds of Indian Medicinal Herbs like Becopa Monnieri (BM), Ashwagandha [36,37] etc. These proteins are found to modulate the immune system by stimulating both inmate and adaptive responses. The paper [35] focuses on the dynamism of modulating effects of HSPs towards immune responses of cancerous proteins based on the vibration frequencies of both cancer causing proteins or protein receptors and cancer curing proteins (Say HSPs).

5. Proposed Analytical Approach

In view of the aforementioned discussion, the author attempts to explain the functioning of antibody (cancer curing protein) with respect to cancerous antigens from the

view point of protein vibration. It is to be noted that protein vibrations enable proteins to change their shape quickly so that they can readily bind to other proteins and also now held responsible for conformational changes with respect to protein misfolding which is being considered as causes of a number of disorders in human bodies. This constitutes the basis of the present study. The author has been working analytically on the utility of protein vibration in learning and memory losses along with therapeutic aspects of old age diseases like Parkinson, Alzheimer, Huntington, [38] etc. The analytical results evaluated on the basis of protein vibration hypothesis are found to be compatible with those derived from experimental results of disaggregation of aggregated protein responsible for old age diseases *in vitro* phase which thus established the rule of protein vibration in mammalian body.

Now it is an established fact that proteins vibrate *in vivo* either due to inherent electrostatic force (potential) of the order of 0.8 to 30 mv with respect to variable Ph by Sivasankar et al. in1998 [39] or due to external stimuli. In a paper [40], the author suggested that the vibration characteristics of protein depend on the magnitudes of molecular weights of the concerned protein. It was also held by the authors that the more the molecular weight of protein, the less is the number of vibration frequency. On the other hand, the less value of molecular weight of protein is, the more the number of frequency. Thus the vibration pattern of protein may be described as shown in Figure 1.
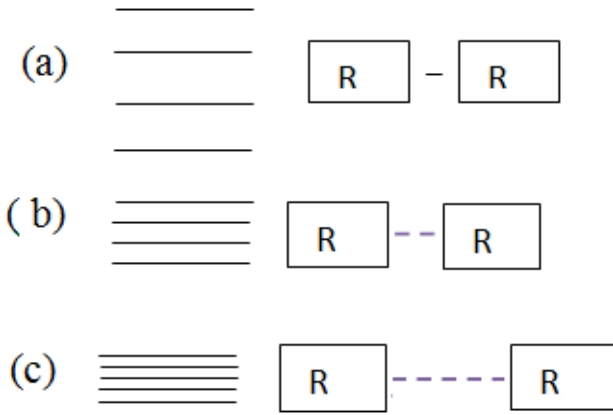

Figure 1.   Vibration energy spacing of protein molecules

The vibration frequency and vibration energy of the concerned protein can be evaluated by using one dimensional Schrodinger's Equation. The reason of considering one dimensional Schrodinger's Equation lies in the fact that an electrostatic force can control atomic motion in a protein. For a protein this can be divided into two components, a large and a small.

Conformational substrates for the protein in its native state may correspond to the same position 'r' of the particle at time 't.

Thus r (t) can be split into two independent components

$$r(t) = r_v(t) + r_t(t)$$

where rv (t) stands for the vibration component about the equilibrium position with the host molecule and rt (t) stands for transient component about the equilibrium position at time t. The electrostatic force required for this purpose may be deduced from the relation:

$$f = -dv/dr$$

Which means force is nothing but rate of change of potential:

$$V(r) = Vr_v r_t = \frac{1}{2}[k_v\ (r_1)\ r_v{}^2] + U\ (r_1) \qquad (1)$$

where $k_v\ r_1$ is the vibration component of the force and U (r) stands for the translational component of the same. Since the translational component of the force is very small with respect to the vibration component of the same, the second term of Equation 1 may be neglected. So Equation 1 may be rewritten as:

$$V(r) = V(r_v r_t) = \ 1/2[k_v\ (r_v)\ r_v{}^2] \qquad (2)$$

The magnitude of this transformed energy may be evaluated by following quantum mechanical treatment of harmonic oscillator. By inserting vibration potential energy function, we may write f = -dv / dr, which stands for the rate of change of potential energy with change of co-ordinate. Let us now state with f = - kr which on integration leads to potential energy v = ½ kr². This potential energy rises parabolic on either side of the equilibrium as illustrated in Figure 2.
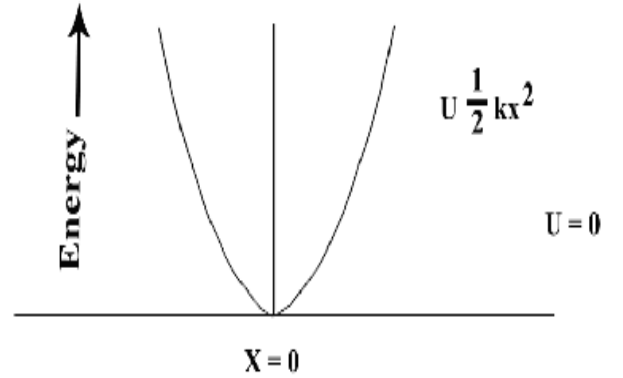

Figure 2.   Oscillation of vibrating particle

The vibration energy and vibration frequency of concerned proteins may be evaluated by using the solution of one dimensional Schrodinger's Equation:

$$\frac{-h^2}{8\pi^2 m}\frac{d^2\psi}{dr^2} + v\ (r)\psi = \varepsilon\ \psi \qquad (3)$$

which turns to

$$\frac{-h^2}{8\pi^2 m}\frac{d^2\psi}{dr^2} + \frac{1}{2}\ kr^2\psi = \varepsilon\psi \qquad (4)$$

with potential energy

$$V = \frac{1}{2}\ kr^2,$$

while other symbols stand for usual meaning.

The energy of the allowed vibration states derived from the solutions of the Schrodinger's Equation is

$$\varepsilon_{vib} = (\nu + \tfrac{1}{2})\, \frac{h}{2\pi} \sqrt{\frac{k}{m}}\ ,\ \nu = 0,1,2 \qquad (5)$$

while the expression for vibration frequency stands as

$$\nu_{vib} = \frac{1}{2\pi} \sqrt{\frac{k}{m}} \qquad (6)$$

6. Results and Discussion

Physical characteristics of the concerned cancer causing antigens (proteins / receptor proteins) with respective cancer curing antibiotics (proteins) are shown in Table 1.

Based on Equations 6, let us evaluate the vibration frequencies of the aforementioned noted proteins shown in Table 2.

It is revealed from Table 2 that the numerical values of vibration frequencies of CTLA 4, PD 1, and PDL 1 as some

of cancer causing proteins (antigens) are almost of the same magnitudes. Since the molecular weights of CTLA 4, PD 1, and PDL 1 are almost in the same magnitudes, the vibration frequencies of all these proteins are also in same range. These are some of the physical characteristics of proteins and protein receptors responsible for causing cancers and tumors as considered from the view of protein vibration.

Now let us pay attention to the role of antibodies like MDX-010, targeting CTLA 1, Nivolumab targeting PD 1 and pembrolizumab targeting PD 1 and PDL 1, the molecular weights of which are almost in the same range. From Tables 1 and 2, it is also found that the vibration frequencies of these antibodies (Proteins) are also in same range.

Thus, it is suggested by the author that the aforementioned antibodies are not only to bind with cancer causing antigens (proteins) but also to modulate the immune system by stimulating both innate and adaptive responses.

Table 1. Characteristics of cancer causing antigen and cancer curing antibodies

Cancer causing proteins (antigens)		Respective cancer curing proteins (antibodies)		
Name of cancer causing proteins/Receptor proteins	Magnitude of molecular weights	Name of cancer curing/immunity growing proteins	Magnitudes of molecular weights	Principal characteristics
CTLA 4	30/34 KD in membrane form 41/43 KD in glycosylated form 15 KD as recombinant human	MDX 010 (Ipilimum ab)	148.63 ≈ 149 KD	Used to treat melanoma/immune therapy drug
PD 1	32 KD	Nivolum ab	146 KD	Immuno therapy drug targeting PD1
PDL 1	33 KD	Pembrolizumab	149 KD	Blocks the activity of PD 1, PDL 1, and PDL 2. This protein protects T-cell

Table 2. Frequencies (m⁻¹) generated by different proteins in the presence of ES potential (0.8 to 30 mv)

Magnitudes of frequency	Magnitude of E.S. Potential													
	0.8 mv	1 mv	2 mv	3 mv	4 mv	5 mv	6 mv	7 mv	9 mv	10 mv	15 mv	20 mv	25 mv	30 mv
Mass of CTLA 4, 30 KD	**1.332**	**1.519**	**2.149**	**2.693**	**3.039**	**3.398**	3.723	4.020	4.559	4.806	5.886	6.797	6.937	8.325
34 KD in membrane form	**1.276**	1.427	2.019	2.472	2.855	3.192	**3.497**	**3.771**	4.283	4.514	5.529	6.384	7.138	7.819
41/43 KD in glycosylated form	**1.162**	**1.300**	**1.836**	2.251	**2.600**	2.907	3.180	3.439	3.900	4.111	5.035	5.814	6.500	7.121
15 KD recombinant human	1.922	**2.149**	3.039	3.723	4.299	4.806	5.265	5.687	6.443	6.797	8.325	9.612	10.747	11.773
32 KD for PD 1	1.316	1.471	**2.081**	2.549	2.943	3.290	3.604	3.893	4.414	4.653	5.699	6.581	7.350	8.060
33 KD for PDL 1	1.296	1.448	**2.047**	2.510	2.898	3.240	3.549	3.834	4.347	4.582	5.612	6.481	7.245	7.937
Mass of curing/immunity growing anti-bodices (Proteins)														
Ipilimum ab (MDX-010) 148.632 ≈ 149 KD (Target CTLA – 4)	0.610	0.682	0.964	**1.181**	**1.364**	**1.525**	1.670	**1.804**	**2.046**	**2.156**	**2.641**	**3.050**	**3.410**	**3.735**
Nivolum ab 146 KD (Target PD 1)	0.616	0.688	0.974	**1.193**	**1.377**	**1.540**	1.681	1.822	**2.046**	2.178	**2.668**	**3.081**	**3.410**	**3.773**
Pembrolizum ab 149 KD (Target PD 1, PDL 1, PDL 2)	0.610	0.682	0.964	**1.181**	**1.364**	**1.525**	1.670	**1.804**	**2.046**	**2.156**	**2.641**	**3.050**	**3.410**	**3.735**

These are expected to occur due to biochemical system of the body. At this stage, this paper focuses on the different process of activation of cancer curing antibodies from the view point of vibration frequency and vibration energy generated due to protein vibration in the presence of electrostatic force in cells. It is now an established fact that protein vibration has paved the way for (i) conformational change in protein which means change in signaling pathway of misfolded proteins; (ii) explaining protein-protein binding and (iii) modulating the proteins (antibodies) of higher molecular weights with respect to proteins (antigens) of lower molecular weights. Protein-protein bindings mean binding of hydrogen molecules. The stronger the hydrogen bonds, the faster apart and deeper their energy levels. This happens when the atoms near the ends of amino acid residues are bound. This type of bound condition shows stiff oscillation with widely separated energy levels so that only one value of E_r, the energy value in r level may contribute to $\Sigma_r e$ - E_r / KT. The term $\Sigma_r e$ - E_r / KT [41] is known as partition function. But when loose binding of the molecules or separation of chains occurs naturally or by any means, the levels will be closer and several terms may remain present making the partition function greater and F the Gibb's free energy per mol smaller (Majumder, 1997). The diagrammatical representation of these two cases is similar to those described in Figure 1.

From Table 2, it reveals that vibration frequencies generated due to antigen proteins of masses 30, 32, 33, 34, and 41 KDs are found to be in parity levels of antibody proteins of masses m=146 and 149 KDs at certain levels of electrostatic potentials in between 0.8 and 6 mv. This means there would be strong binding of cancer curing antibodies to cancer causing antigens. These are shown in Table 2 by colour circles. In case of other values of electrostatic potential, the frequencies generated due to the same antigens and antibodies are not found to be in good unison. Rather they are found to be distributed in scatter forms. However, numerical values of frequencies generated due to antibody proteins for electrostatic potential of magnitudes 7 to 30 mv as found shown in Table 2 are lower than those of antigens for the same order of electrostatic potential. But the wavelength of the frequencies generated due to antibody proteins are higher than those generated by antigen proteins.

These higher values of wavelength will be able to modulate the lower values of wavelength as it is found in frequency modulation of electromagnetic waves. Similarly, modulation of antibody protein will stand as change in signaling pathway of frequencies generated by cancer causing proteins.

Practically speaking, vibration of proteins is nothing but vibration of electrons in hydrogen molecules which take part in binding of proteins. Hence, frequency generated due to protein vibration obviously takes part in binding process of proteins. In this context, both binding and modulation can be thought to be synonymous with frequency modulation in electromagnetic propagation process which is nothing but change in signaling pathway.

Recently, the author (Majumder, 2017) explained analytically the modulating effects of Heat Shock Proteins (HSP) towards immune responses of cancer from the view point of protein vibration. But most of the interventions of the therapeutic uses of HSP are still in experimental/trial stage with mice, along with demonstration on vaccination with HSP 70 derived from Math A sarcoma in mice. On the other hand, therapeutic uses in the form of injection of antibodies (proteins like MDX010, Nivolumam, pembrolizumab) against cancerous antigen (proteins) like CTLA 4, PD 1, PDL 1, PDL 2, etc., are significantly increasing. And hence the possibility of getting cure from cancerous antigens with injection of antibodies as mentioned is now found stable particularly with comparison to modulating effects of Heat Shock Proteins towards immune responses of cancer since induction of positive Heat Shock Proteins in body system of mammalian bodies is uncertain. Thus treating cancerous antigens like CTLA 4, PD 1, PDL 1, andPDL 2 with injection of antibodies like MDX010 and others for which Noble Prizes in Physiology or Medicine has been awarded for 2018, will stand certainly in good stead for mankind.

7. Conclusions

The antibodies approved by US Food and Drug Administration are being used for long now. But the implications of cloned MDX-010 targeting CTLA 4 and other antibiotics like Nivolumab and Pembrolizumab targeting PD 1 and PDL 1, respectively or combination of both has nowadays been found to be more successful than those of other antibodies noted so far. Thus, the therapeutic uses of antibodies (proteins like MDX010, Nivolumab, Pembrolizumab etc.) against cancerous antigens like CTLA 4, PD 1, PDL 1, PDL 2, etc., are significantly increasing. This results in possibility of getting cure as well as modulating effects of immune responses on the part of the patients. These are found to be more effective in comparison with other endeavours undertaken by different group of scientists with other proteins like HSPs, etc. Recent interventions of therapeutic use of HSPs along with demonstration on vaccination with HSP 70 derived from Math A sarcoma in mice are still in trail stage. Hence, successful therapeutic use of cancer curing antibodies against respective antigen as discussed for which Nobel Prize was awarded in Medicine or Physiology in 2018 conferred great benefit on mankind by opening a new channel to almost stable cancer treatment.

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REFERENCES

[1] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation, Cell, 144: 646-74 (2011).

[2] Global Cancer Observatory, 2018. http://gco.iarc.fr/.

(a) American Cancer Society Monoclonal antibodies to treat cancer. (2015/2016)

[3] Loeb L. Further Investigations in Transplantation of tumors. J Med Res. 8(1): 44-73. (1902).

[4] Ehrlich P. Über den jetzigen Stand Karzinomforschung. Nederiandsch Tijdschrift voor Geneeshunde 5:273-90. (1909)

[5] Burnett FM. The concept of immunological surveillance. Prog Exp Tumor Res. 13:1-27. (1970)

[6] Klein G, Klein E. Antigenic properties of other experimental tumors. Cold Spring Harb Symp Quant Biol 27: 463-70. (1962).

[7] Lurquin C, Van Pel A, Mariame B, De Plaen E, Szikora JP, Janssens C, Reddehase MJ, Lejeune J, Boon T. Structure of the gene of tum transplantation antigen P91A : the mutated exon encodes a peptide recognized with Ld by cytolytic T cells. Cell 58:293-303. (1989).

[8] Brunet KT, Mauel J, Cerottini JC. Chapus B. Quantitative assay of the lytic action of immune lymphoid cells on 5 "Cr-labelled allogeneic target cells in vitro; inhibition by isoantibody and by drugs Immunology. 14: 181-96. (1968)

[9] Klein E, Svedmyr E, Jondal M, Vanky F.Functional studies on tumour-infiltrating lymphocytes in man. Isr J Med Sci. 13: 747-52. (1977).

[10] Rosenberg SA, Spiess P, Lafreniere R 0. A new approach to the adoptive immunotherapy of cancer with tumor –infiltrating lymphocytes. Science. 233: 1318-21. (1986).

[11] Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 3:991-8. (2002).

[12] Linsley PS, Clark EA, Ledbetter JA. T-cell antigen CD28 mediates adhesion with B cells by interacting with activation antigen B7/BB-1. Proc Natl Acad Sci U S A. 87(13): 5031-5. (1990).

[13] Lindsten T, Lee KP, Harris ES, Petryniak B, Craighead N, Reynolds PJ, Lombard DB, Freeman GJ, Nadler LM, Gray GS, Thompson CB, June CH. Characterization of CTLA-4 structure and expression on human T cells. J immunol. 151(7): 3489-99. (1993).

[14] Linsley PS, Bradshaw J, Greene J, Peach R, Bennett KL, Mittler RS. Intracellular trafficking of CTLA-4 and focal localization towards sites of TCR engagement. Immunity. 4(6): 535-43. (1996)

[15] Takahashi T, Tagami T, Yamazaki S, Uede T, Shimizu J, Sakaguchi N, Mak TW, Sakaguchi S. Immunologic self-tolerance maintained by CD25(+)CD4(+) regulatory T cells constitutively expressing cytotoxic T lymphocyte-assoc iated antigen 4. J Exp Med. 192(2): 303-10. (2000).

[16] Walunas TL, Lenschow DJ, Bakker CY, Linsley PS, Freeman GJ, Green JM, Thompson CB, Bluestone JA, CTLA-4 can function as a negative regulator of T cell activation. Immunity.

1(5): 405-13. (1994).

[17] Linsley PS, Brady W, Urnes M, Grosmaire LS, Damie NK, Ledbetter JA.. CTLA-4 is a second receptor for the B cell activation antigen B7, J Exp Med. 174(3): 561-5. (1991).

[18] Krummel MF, Allison JP,. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med. 182(2): 459-65. (1995)

[19] Hurwitz AA, Yu TF, Leach DR, Allison JP. CTLA-4 blockade synergizes with tumour-derived granulocyte-macrophage colony-stimulating factor for treatment of an experimental mammary carcinoma. Proc Natl Acad Sci U S A. 95(17): 10067-71. (1998).

[20] Van Elsas A, Hurwitz AA. Allison JP. Combination immunotherapy of B16 melanoma using anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and granulocyte/macrophage colony-stimulating factor (GM-CSF)-producing vaccines induces rejection of subcutaneous and metastatic tumors accompanied by autoimmune depigmentation. J Exp Med. 190(3): 355-66. (1999).

[21] Wolchok JD, Hodi FS, Weber JS, Allison JP, Urda WJ, Robert C, O'Day SJ, Hoos A, Humphrey R, Berman DM, Londerg N, Korman AJ. Development of ipilimumab: a novel immunotherapeutic approach for the treatment of advanced melanoma. Ann NY Acad Sci, 1291:1-13. (2013).

[22] Hodi FS, Mihm MC, Soiffer RJ, Haluska FG, Butler M, Seiden MV, Davis T, Henry-Spires R, MacRae S, Wilman A, Padera R, Jaklitsch MT, Shankar S, Chen TC, Korman A, Allison JP, Dranoff G. Biologic activity of cytotoxic T lymphocyte-associated antigen 4 antibody blockade in previously vaccinated metastic melanoma and ovarian carcinoma patients. Proc Natl Acad Sci U S A. 100(8): 4712-7. (2003).

[23] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbe C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM. Hoos A, Urba WJ. Improved survival with ipilimumab in patients with metatatic melanoma. N Engl J Med. 363(8): 711-23. Erratum in: N Engl J Med. 2010, 363(13): 1290. (2010).

[24] Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J. 11(11): 3887-95. (1992).

[25] Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Files DB, Roche PC, Lu J, Zhu G, Tamada K, Lennon VA, Ceils E, Chen L. Tumor-associated B7-H1 prometes T-cell apoptosis : a potential mechanism of immune evasion. Nat Med. 8(8): 793-800. (2002).

[26] Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. . Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S.A. 99(19):12293-7. (2002).

[27] Iwai Y, Terawaki S, Honjo T. PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. Int Immunol. 17(2): 133-44. (2005).

[28] Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, Stankevich E, Pons A, Salay TM, McMiller TL, Gilson MM, Wang C, Selby M, Taube JM, Anders R, Chen L, Korman AJ, Pardoll DM, Lowy I, Topalian SL. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity. Pharmacodynamics, and immunologic correlates. J Clin Oncol. 28(19): 3167-75. (2010).

[29] Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, Mcdermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Horn L, Drake CG, Pardoll DM, Chen L, Sharfman WH, Anders RA, Taube JM, McMiller TL, Xu H, Korman AJ, Jure-Kunkel M, Agrawal S, McDonald D, Kollia GD, Gupta A, Wigginton JM, Sznol M. Safety, Activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 366(26): 2443-54. (2012).

[30] Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, Segal NH, Ariyan CE, Gordon RA, Reed K, Burke MM, Caldwell A, Kronenberg SA, Agunwamba BU, Zhang X, Lowy I, Inzunza HD, Feely W, Horak CE, Hong Q, Korman AJ, Wigginton JM, Gupta A, Sznol M. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 369(2): 122-33. (2013).

[31] Wolchok JD, Chiarion-Silent V, Gonzalez R, Ruthkowski P, Grob JJ, Cowey CL, Lao CD, Wagstaff J, Schadendorf D, Ferrucci PF, Smylie M, Dummer R, Hill A, Hogg D, Haanen J, Carlino MS, Bechter O, Maio M, Marquez-Rodas I, Guidoboni M, McArthur G, Lebbé C, Ascierto PA, Long GV, Cebon J, Sosman J, Postow MA, Callahan MK, Walker D, Rollin L, Bhore R, Hodi FS, Larkin J.. Overall Survival with Combined Nivolumab and ipilimumab in Advanced Melanoma. N Engl J Med. 377(14): 1345-56. (2017)

[32] Snyder A, Makarov V, Merghoub T, Zaretsky JM, Desrichard A, Walsh LA, Postow MA, Wong P, Ho TS, Hollmann TJ, Bruggeman C, Kannan K, Li Y, Elipenahil C, Liu C, Harbison CT, Wang L, Ribas A, Wolchook JD, Chan TA . Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med. 371(23): 2189-2199. (2014).

[33] Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, Miller ML, Rekhtman N, Moreira Al, Ibrahim F, Bruggeman C, Gasmi B, Zappasodi R, Maeda Y, Sander C, Garon EB, Merghoub T, Wolchock JD, Schumaccher TN, Chan TA.. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 348(6230): 124-8. (2015).

[34] Van Allen EM, Miao D, Schilling B, Shukla SA, Blank C, Zimmer L, Sucker A, Hillen U, Foppen MHG, Goldinger SM, Utikal J, Hassel JC, Weide B, Kaehler KC, Loquai C, Mohr P, Gutzmer R, Dummer R, Gabriel S, Wu CJ, Schadendorf D, Garraway LA.. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science. 350(6257): 207-211. (2015)

[35] Majumder. BG: An Analytical Approach to Modulating Effects of Heat Shock Proteins towards Immune Responses of Cancer in the Context of Protein Vibration, International Journal of Biophysics, 7(1), 8-15. (2017)

[36] Majumder. BG: An Analytical Approach to Anti – Parkinsonian Effect of Bacopa Monnieri in the Context of Protein Vibration, International Journal of Biophysics, 6(2), 21-25. (2016)

[37] Majumder. BG: Role of Protein Vibration in Anti – Alzheimer's Effect of Ashwagandha (Withania Symnifera) – An Analytical Approach, International Journal of Biophysics, 7(3), 41-47. (2017)

[38] Majumder. BG: Activation of Heat Shock Protein Induced by Curcumin to Prevent Huntington Disease- an Analytical Approach in the Context of Protein Vibration, International Journal of Biophysics. 8 (1), 1-8. (2018)

[39] Sivasankar S.S, Subramaniam S, and Lackband D.. Direct molecular Level measurements of the to Miss. Joysree Sutradhar for under taking the computer work Electrostatic properties of a Protein surface, Proc, Natn, Acad. Of science U.S.A, 95, 1261-1296. (1998)

[40] Majumder, BG and De, UC: Role of Protein Vibration In Learning and Memory – A mathematical Approach International Journal of Biophysics. 3(1), 33 -37. (2013)

[41] Majumder. BG: Electro-Chemical Correlates of learning and Memory Mapping, Indian Educational Review. 32 (1), 18-97. (1997)