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An Analytical Approach to Modulating Effects of Heat Shock Proteins towards Immune Responses of Cancer in the Context of Protein Vibration

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Abstract A brief account on cancer – one of the devastating diseases of the world has been outlined here. Cancer being a genetic disease arises from accumulation of mutations in critical genes. There are no unilateral reasons for its development. However, some proteins have by this time been identified for the development of cancer in human body. On the other hand, some proteins namely Heat shock proteins (Hsp) are induced either in different cancer affected cells or induced due to external administration of therapeutic agents including Indian medicinal herbs like Bacopa Monnicri etc. These are now found to modulate immune system by stimulating both innate and adaptive responses. Hsp – based therapeutic in cancer trials are also now available. One Hsp – band Vaccine Vitespen by name, made of Hsp gp - 96 is now licensed for use. This paper focuses on the dynamism of the use Hsp – 70, Hsp gp - 96 in the context of protein vibration approach due to electrostatic potential of the cell in the range of (0.8 to 1.0 and 25) mv. The potential range has arbitrary been choosen for sake of the paper. The paper also focuses on the process of modulation of the immune system by Hsp – 70 and gp – 96 basing on the frequency generated by the respective Hsp.

Keywords Cargo Proteins, Oncogene, Protein Receptors, Heat Shock Proteins, Protein Vibration, Modulation, Immunogenicity

1. Introduction

Cancer is one of the most devastating diseases in the world. It is numerous in nature. The available number at present amounts to 200 approximately. The cause of the disease is not unilateral. The scholar's cannot still specify the particular causes for the disease. The actual reason of attacking with the disease is also unidentified. And also the age of attacked person is uncertain. An individual can be attacked at any age. In this crucial juncture, it is held that uncontrolled cell growth or cell division may be considered as development of cancer cells. The essential alterations as identified by the scholars (1) for malignant growth include the followings

(i) Self sufficiency in growth signals
(ii) Insensitivity to growth inhibitory signals
(iii) Evasion of programmed cell death
(iv) Limitless replicative potential
(v) Sustained angiogenesis
(vi) Tissue invasion and metastasis

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From all these parameters it is held that "cancer arises from accumulation of mutations in critical genes".

Since proteins constitute the major constituents of the living beings, proteins of different kinds may be held responsible for the cause and cure of cancers. Different types of proteins are responsible for different varieties of cancers. The study of the researchers in Felsher's Laboratory (2) focuses on the role of Myc protein. Myc protein is encoded by a gene known as oncogene. Oncogene being a vital cellular functionary becomes powerful cancer proteins when they are mutated or expressed incorrectly. The Myc oncogene is found to be mutated or misregulated in nearly half of human cancers. The researchers of the same Lab. also studied on a particular phenomenon known as "oncogene expression addiction" which showed that tumor cells are completely dependent on the expression of oncogene. Thus Myc causes an increase in the levels of proteins that promote cell division with the ability of outwitting the immune molecules. The dean (2) of Felsher Lab. described the causal connection between the mode of causing cancer cells to evade the immune system. Thus this constitutes the basic principal of oncogene expression and development of cancer in animals.

In case of human genome, Myc is located on chromosome 8 and it is believed to regulate expression of 15% of all genes through binding on enhancer box sequences (E – boxes). A

mutated version of Myc is found to be expressed in many cancers. Hence, it is held that Myc is a strong proto – oncogene and is very often seen to be unregulated in many types of cancers. Myc over expression stimulates gene simplification which causes several types of cancers like breast, colorectal, pancreatic, gastric, uterine etc. Similarly, other oncoproteins like mutated P_{53} - the most devastating one, may appear during carcinogenesis. The mutated and conformation ally altered proteins become expressed or over expressed in cancer / tumor cells. In addition heat shock proteins (Hsp) of different molecular weights are also found to be associated with proteins responsible for causing cancers. For example, Hsp -27 is found to be associated with Erά in female breast cancers and Hsp – 70 is found to be associated with Erά in breast cancers.

2. A Brief Note on the Role of Heat Shock Proteins

It is now an established fact that some proteins produced in respective cells are exposed to stressful conditions. These are known as Heat shock proteins (Hsp). These proteins are better used as (i) up regulation in stress and (ii) as chaperones. Recent development in Hsps as chaperones with respect to both immunity and therapeutic aspects attracts the scholars much.

Heat shock proteins (Hsp) as the scholars held, are found to carry on antigenic profile or fingerprint of the cells from which they are derived, possess adjuvant activity and bind to receptors on DC to promote their respective functioning (3). At present a good number of Heat shock proteins have been identified. These are now grouped in several families. These are named in accordance with the molecular weights of family members (3) as

While Hsp – 90, Hsp – 70, Hsp – 60 / chaperone and Hsp – 40 families have been identified in man, gro EL (Hsp – 60), Dnak (Hsp – 70) constitute as members of main Hsp families in prokaryotes (4). Heat shock proteins are induced only under stress conditions in normal cells. Stress condition means protein are getting denatured by heat shock, oxidative stress and other protein damaging events. Under this condition, Hsps are expected to modify the structure and interactions of other proteins as molecular chaperones. It was held by a number of scholars that Hsp – 27, Hsp – 70, Hsp – 90 and Hsp – 110 are found to be dominantly expressed proteins after stress.

Studies conducted by the scholars have shown that Hsp – 10 and Hsp – 60 complexes are able to mediate protein folding while Hsp – 70 and Hsp – 90 are involved in both generic protein folding pathways and also in specific association with key regulatory proteins within the cell. On the other hand, Hsp – 90 plays a pivotal role in cell regulation, forming complexes with cellular kinesis, transcription factors and other molecules.

With respect to functioning as intracellular protein chaperones, Hsps modulate the immune system by stimulating both innate and adaptive responses. Usually Hsps are found to undertake the functioning as chaperones and as cytokine. Being released from a host or pathogen cell, Hsps bind to cellular receptors and trigger an innate immune response. It also includes pro- inflammatory cytokines and chemokines. This results in processing of cargo proteins to be carried by Hsp along with and acquired immune responses to pathogens leading to the functioning as vaccine adjutants with respect to infections and cancers. A number of receptors which play a vital role in Hsp binding are shown (3) in table 2.

It was held by C.A. Colaco (5) that priming of adaptive immunity leading to MHC presentation depends on the delivery of peptides as cargo to DC by Hsp. By using inhibitors, it has been observed by A.A. Tobin and others (6) that Hsp – 90 plays a pivotal role in chaperoning antigenic peptides in presentation. Particular Hsp may process differing capabilities to induce cross presentation. For example, an extract prepared from human melanoma lines contain (3) four chaperone proteins namely Hsp -70, Hsp – 90, gp – 94 and gp – 96 and culreticulin. All these are functioning with enhancing presentation of exogenous peptides. But of these four chaperone proteins, Hsp – 70 rich presentations is found to exhibit superior activity (7). Hence, Hsp – 70, gp – 90 and gp – 96 each bind distinct antigen precursors (8). These are found to deliver a brand range of antigen and antigen coverage and hence to maximize the immune protection.

Thus the potential roles of Hsp being complexes with antigenic peptides released from tumor cell in vivo during lysis (9) are taken by APC (antigen – presentation cells) and hence the use of Hsp in cancer immunotherapy is being demonstrated extensively.

On the other hand, Hsp based therapeutics in cancer trials are also available. Some of these trials are shown (3) in table -3

One Hsp vaccine, vitespen (3) made of Hsp gp 96, the master chaperone for Tall – like receptor is now a day's licensed and marketed. Vitespen was first approved in Russia as a patient – specific adjuvant treatment of kidney cancer. It has been studied extensively in clinical trials in phase I and phase II settings. Phase III studies have been completed with 1300 patients of renal cell carcinoma or malignant melanoma, who are being treated with vitespen. The study reflects neither toxicity nor autoimmunity induced by vitespen. Moreover, pre-clinical studies with vitespen comprising of gp 96 were found promising while clinical studies show limited efficacy.

It was held by H. Udono and P.K.Srivastava (10) that vaccination with Hsp 70 derived from the Meth A Sarcoma showed dose-dependent immunity to challenge with Meth A Sarcoma in mice. However, chaperones with high molecular weights like Hsp 110 or grp 170 tyrosinase related protein 2 peptide ($Trp2_{175-192}$) are considered as superior chaperones as a vaccine elements with respect to delivering tumor-related antigens (11).

These observations may constitute the back ground of the

present paper which is concerned with modulation process of Hsp 70 and Hsp 96 with respect to immune system of cancer/tumor cells. However, studies concerning the mechanism of functioning Hsps as immune and therapeutic agents are not clear till the date.

Table 1

Heat-shock protein (hsp) families		
Family	**Family members**	**Intrace llular location**
Small hsp	**hsp 10,** GroES, **hsp 16, ά crystallin hsp 20, hsp 25,** hsp 26, **hsp 27**	Cytosol
hsp 40	**hsp 40, DnaJ,** SIS_1	Cytosol
hsp 47	**hsp 47**	Endoplasmicreticulun
calreticulin **Calreticulin, calnerxin**		Endoplasmicreticulun
hsp 60	**hsp 60,** hsp 65, GroEL	Cytosol and mitochor
		Cytosol
	hsp 72, Hsc 70 (hsp 73), hsp110 / SSE, Dnak	
hsp 70	**SSC** $_1$ SSQ $_1$, ECM $_{10}$	Mitochondria
	Grp 78 (BiP), Grp 170	Endoplasmic reticulun
	hsp 86, HTPG	Cytosol
hsp 90	**gp 96 (Grp 94, hsp 108, endoplasmin)**	Endoplasmic reticulum
	hsp 104, **hsp 110**	Cytosol

Table 2

Heat-shock protein (hsp) receptors on cells of the immune system		
Ligand(s)	**Receptor**	**Receptor cellular**
gp 96, hsp90, hsp70, Calreticulin	CD91	Dendritic cell (DC), macro
hsp70	LOX-1	DC, macrophage, monocy
gp96, hsp60, hsp70, hspBS, Crystallin	άToll-like receptor 2/4	DC, macrophage, mast cell microglia, neutrophil
hsp70	CD 14	DC, macrophage, monocy
hsp70	CD 40	DC, macrophage, monocy
gp96, Calreticulin	Scavenger Receptor type A	DC, macrophage, microglia
mycobacterial hsp70	CCR5	DC, macrophage, T-cell, n
Calreticulin, gp96, hsp 110, Grp170, hsp70	Scavenger Receptor expressed by Endothelial Cells (SREC) -I	DC, macrophage

Table 3

Examples of heat-shock protein (hsp) –based cancer therapeutics in clinical trials		
Therapeutic	**Disease targeted**	
Vitespen Gp96 based vaccine derived from patient tumor	Various cancers including but not limited to, kidney, liver, ovarian, colorectal, glioma and melanoma	Marl Dise II an
hspE_7 fusion protein consisting of BCG hsp 65linked to HPV 16 E_7	diseases caused by human papillomavirus (HPV)	Phas
hspPC-$_{96}$, Gp $_{96}$ based vaccine, administered with GM-CSF and interferon ά derived from patient tumor	Melanoma	Phas
hsp70, PC-F hsp70 based vaccine, derived from patient tumor	Breast cancer	Phas
Chaperone-rich cell lysates from patient tumor	Breast cancer	Phas

3. Methodology

In view of the above discussions, an attempt has been taken here to examine the functioning of Hsps with respect to immune system and therapeutic aspects of cancer / tumor cells in the context of protein vibrations. It is an established fact that protein vibrate due to either electrostatic force (potential) or due to external stimuli. In a paper (12) the authors 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 (12) that more the molecular weights of protein is, the less is the number of vibration frequency. On the other hand, less the value of molecular weight of protein is, the more is the number of frequency. Thus the vibration pattern of proteins may be described as

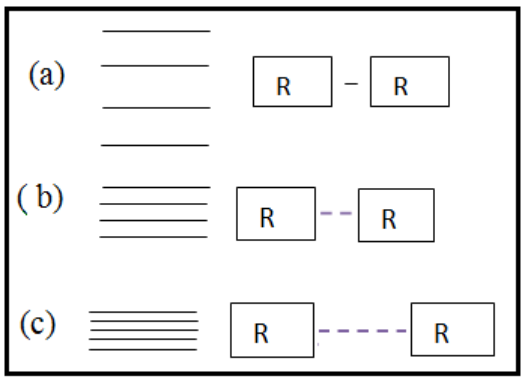

Figure 1. Vibration energy spacing of protein molecules

The vibration frequency and vibration energy of the concerned protein can be evaluated by using one dimensional Schroclinger'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 (13) 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.

$$\mathbf{r(t) = rv\ (t) + r\ t\ (t)}$$

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

$$\mathbf{f = -dv/dr}$$

Which means force is nothing but rate of change of potential

$$\mathbf{V(r) = V(rv9rt)1/2\ [kv\ (r1)\ rv^{\,2}\ ] + U\ (r1)} \qquad (1)$$

Where Kvr1 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

$$\mathbf{V(r) = V(rv) = 1/2[kv\ (rv)\ rv^{\,2}\ ]} \qquad (2)$$

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 (14) in Fig. 2.

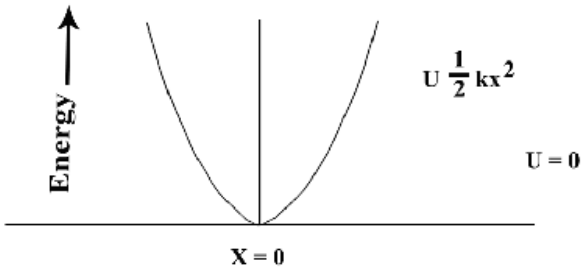

Figure 2. Oscillation of vibrating particle

Inserting potential energy as

$$\mathbf{V = ½kr^2}$$

The one dimensional Schrodinger's Equation

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

which turns to

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

The energies of the allowed vibration states derived from the solutions of the Schrodinger's Equation are

$$\vartheta_{\mathbf{vib}} = \left(\nu + \frac{1}{2}\right)\frac{h}{2\pi}\sqrt{\frac{k}{m}} \qquad \nu = 0, 1, 2 \qquad (5)$$

While the expression for vibration frequency stands as

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

The vibrations occurring in protein depends on molecular weight of the concerning proteins available in particular portions of the brain. Thus, frequent vibrations, as the authors held, are created in light proteins of small molecular weight while slow vibrations are created in proteins of middle range molecular weight.

The expression for vibration energy is

$$\mathbf{E}_{\mathbf{vib}} = \frac{h}{2\pi}\sqrt{k/m} \qquad (7)$$

Basing on the approaches the author evaluated the vibration frequencies and energies of a number of proteins with different molecular weights responsible for learning and memory traces (15) and for a number of degenerative and TSE diseases (16) from the view point of this hypothetical approach of protein vibration.

4. Results and Discussions

Since a good number of proteins are responsible for the cause and cure of cancers, let us identify some of the proteins causing cancer as well as functioning as immune and therapeutic agents like

Table 4

Name of the cancer Causing (cargo) proteins	Molecular weights (KD)	Name of the receptor proteins	Molecular weights (KD)
Myc P_{53}	49 KD 53 KD	CD 47 PDL – 1 Mdm - 2	50 (predicted) 40 KD 55 KD (predicted)

In addition some Heat shock proteins with their molecular weights have been identified here as immune and therapeutic agents like

Table 5

Name of the Heat shock proteins	Molecular weights in KD
Hsp – 70 gp - 96	70 96

The vibration frequency and vibration energy of the above listed proteins are evaluated on the basis of the Equations (6) and (7). There vibrations are expected to be generated due to electrostatic potential, the magnitude of which is < 30 mv with respect to variable pH (17). However, for the interest of the paper, the magnitude of electrostatic potential has been considered arbitrary in between (0·8 to 1.0 and 25) mv with respect to variable pH. The numerical values of vibration frequencies and vibration energies of the above listed proteins are tabled in Table – 6(A) and 6(B), 7(A) and 7(B).

Table 6(A)

Vibration frequencies (m^{-1}) of different proteins and receptor proteins

Electrostatic potential	Molecular weights (KD) of Cancerous proteins & Receptor protein				
	Myc (49)	P_{53} = (53)	Mdm – 2 = (55)	CD 47 (50)	PDL1 (40)
0.8 mv	2.66	2.56	2.48	2.63	2.73
1.0 mv	2.96	2.87	2.82	2.93	3.03
25 mv	14.98	14.40	14.10	15.10	16.65

Table 6(B)

Electrostatic potential	Molecular weights (KD) of Cancer curing protein		
	Hsp - 70	Hsp - 90	gp – 96
0.8 mv	2.19	1.97	1.89
1.0 mv	2.46	2.21	2.13
25 mv	12.50	10.90	10.60

Table 7(A)

Vibration energies of the above listed proteins in 10^{-22} Joules unit

Initial energy in mv	Vibration energies of Cancer causing proteins in 10^{-22} Joules unit			
	Myc (49)	P_{53} = (53)	Mdm – 2 = (55)	CD 47 (50)
0.8 mv	0.18	0.17	0.16	0.17
1.0 mv	0.20	0.19	0.19	.20

Table 7(B)

Initial energy in mv	Vibration energies of Cancer curing proteins in 10^{-22} Joules unit		
	Hsp - 70	Hsp - 90	gp – 96
0.8 mv	0.15	0.13	0.13
1.0 mv	0.16	0.15	0.14

It reveals from Table No.6 (A) & 6 (B) that the numerical values of vibration frequencies of Myc, CD47, PDL-1 and P_{53} etc as some of cancer causing proteins and protein receptors are almost of same magnitudes. This is in quite support of the findings of Felsher (2) with respect to the levels of Myc expressions which are correlated strongly with the expression of CD47 and PDL-1 genes in different types of cancers like liver, kidney, colorectal tumors etc as found from tumor samples of hundred of patients.

Since the frequency levels of Myc protein as well as CD47 and PDL-1 receptors are almost in resonance levels, it can also be held analytically from resonance point of view that Myc protein is directly related to both CD47 and PDL-1 receptor proteins. These are almost compatible with the experimental findings of the researchers of Stanford laboratory of the Stanford University where it was observed that this type of binding (relation) increases the expression of CD47 and PDL-1 receptor proteins in mouse leukemia and also in human bone cancer cells.

On the other hand, P_{53} better known as TP_{53} or tumor protein is a gene which codes for a protein that able to regulate the cell cycle for a protein to act as tumor suppresser. Now it is held by the researchers that more than 50% of human tumors contain a mutation of P_{53} gene. P_{53} is a transcriptional activator and it regulates the expression of Mdm 2 protein. The predicted molecular weight of Mdm 2 is 55KD. Since from the view point of molecular weight, P_{53} and Mdm 2 are almost in the same range, the vibration frequencies of bothP_{53} and Mdm 2 are also in resonance range. This supports the degradation of P_{53} resulting in high level suppression of tumors associated with Mdm 2 binding. These are some of the physical characteristics of some primary proteins and protein receptors responsible for causing cancers and tumors as considered in the context of protein vibration.

Let us now concentrate our attention to the role of some heat shock proteins in immune and therapeutic aspects of cancers in the context of "protein vibration" approaches. In a recent paper (18) the author examined the functioning of induced Hsp-70 when the subject was administered mother tincture extract of Bacopa Monnieri. It was held that induced Hsp-70 is able to disaggregate aggregated alpha synuclein protein responsible for Parkinson's diseases segment wise.

It is held by the scholars that Hsps functioning as intra-cellular protein chaperones is able to modulate the immune system by stimulating both innate and adaptive responses. It was also pointed out by the scholars that Hsps being released from a host or pathogen cell bind to cellular receptors and trigger an immune response. This may be occurred chemically. But the phenomenon of modulating the immune system by stimulating adaptive responses desires further explanation. This constitutes the reason for examining the phenomenon of modulation from the view point of vibration frequency and vibration energy generated due to protein vibration by electrostatic force in cells.

In this context let us examine the findings analytically from the view point of "protein vibration". From table 6(A) it reveals that the molecular weights of proteins like Myc, CD47, PDL -1 P_{53} along with Mdm 2 etc are almost of same magnitudes and hence their frequencies are also in the same range of resonances. These frequencies can be modulated by the application of heat shock proteins with molecular weights larger than the proteins responsible for causing cancers.

Since the molecular weights of cancer causing proteins and their receptors are small, these proteins vibrate frequently but their energy spacing's are small. On the other hand, the molecular weights of Hsps like Hsp-70 and gp-96 are higher than those of the cancer causing proteins. These proteins vibrate slowly (as shown in Fig: 1) in comparison with proteins of small molecular weights. But their energy spacing's are large in comparison with those of small proteins. Thus it is held that the process of modulation of Hsps to immune responses of cancerous proteins is hypothesized as frequency modulation of vibrating protein. Frequency of individual protein increases due to increase in electrostatic potential. This variation may be affective with respect to small frequencies of Hsps protein. From the standard relation wavelength is inversely proportional to frequency when velocity of the concerned particle remains constant. As a result, the wavelength of vibration of Hsp 70, gp 96 will be higher than those of cancer causing proteins and receptor proteins. Hence, absorption of lower wavelength by higher ones will occur. This phenomenon also supports the modulating effects of Hsp 70 and gp 96. However, this absorption phenomenon usually constitutes vibration spectra. But large molecules like protein may have complicated spectra which are seldom indentified and hence understood (14) in terms of vibration frequency. Moreover, no report on the complicated vibration spectra due to protein molecule is available at present for which the author is unable to compare the results of "protein vibration" phenomenon with any sort of practical data. So, it is held that the vibration frequencies and energy spacing's of Hsps can modulate (change in signaling pathway) those vibrations executed by the cancer causing proteins and receptor proteins. Let us examine this from the principle of frequency modulation.

As the vibration frequencies of Myc, CD47, PDL-1, P_{53} etc are frequent in comparison with those of Hsp-70, gp-96 etc. their wavelengths will be smaller than the wavelength of vibration frequencies of Hsps with molecular weights as mentioned. As a result, these short wavelength of the cancer causing proteins and receptor proteins (high frequency) will henceforth be modulated by those of Heat shock proteins to long wavelength (small frequency).

However, this is an alternative approach to immunization carried out with tumor / cancer derived Hsps (gp 96, ssp 70 and others) when injected as therapeutic vaccines interact with particular receptors on the professional antigen presenting DC.

Thus it is predicted that Hsp-70, gp-96 induced from particular cancer / tumor cell can modulate (change in signaling pathway) the functioning of cancer causing and

receptor proteins and hence these will be able to act towards immune and therapeutic responses. These are found to be compatible with the observations of Shaun Mc Nulty and others (3) which are stated as "expression or over expression of Hsp-70 increases significantly the immunogenicity of cancer cell extracts; with the mechanism of cell death and thus modulating positively the immune response against tumors and therefore provide an additional approach for therapeutic interpretation". This is a brief account of immune and therapeutic role of cancer / tumor induced Hsps examined from the view point of "protein vibration". This can be tested by measuring vibration frequency of cancer causing protein and receptor proteins and Hsp by a suitable experimental arrangement which is right now beyond the scope of the author.

5. Conclusions

Our analytical approach is found to be in parity with the experimental studies of the scholars with respect to the role of Hsps in many aspects of cancer / tumor immunity and therapeutic responses. Our studies may be essential in interpreting the information on how Hsp regulation is subverted in cancer and how Hsp intervenes the molecular events which take part in tumor growth, invasiveness and metastasis etc though at present it is hard to set-up adequate experimental arrangement at Tripura. Scholars are of the opinion that Hsps possessing significant properties may open the door for their inclusion in the next generation of vaccines to target DC. In this anticipation the scholars have categorized three important properties of Hsp which include (3) as

(i) Hsps are natural adjuvant.
(ii) Hsps are able to deliver multiple antigens which are capable to induce adaptive immune responses against pathogens and effective cancer.
(iii) Data concerning different studies show that Hsps are safe constituents of existing vaccines.

Similarly, Hsp 70 derived particularly from Bacopa Monnieri (B.M) and producing recombinant antigens may be utilized to develop multi epitomic vaccines. This means B.M induced Hsp 70 is also able to modulate the immune responses of cancer causing protein and protein receptors.

In conclusion, it is our expectation that our studies many also stand in good stead in explaining immune response as well as therapeutic aspects of cancer / tumor – a devastating disease of the day.

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