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Paradigm shift in Discovery & Secretion of Biosimilars via path breaking Innovation

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Abstract:

Radha108 nano peptides stimulate the Cytotoxic T-cells of the innate immune system to naturally produce bio similars like cytokines (interleukins and interferons). Radha108 is proven to increase the production of these cytokines by 5 folds. These nano peptides get absorbed in the blood through buccal mucosa and have potential of crossing the blood brain barrier (BBB).

Radha108 acts on pituitary gland that in turn promotes the differentiation of B cells, maturation of macrophages, monocytes and stimulates the production of cytokines IL-1 to IL-11, TNF-α, INF–γ. It also helps in the maturation of immature thymocytes either into helper or suppressor T cells that help in priming body's immune system against infections and immune disorders like asthma, allergy, upper respiratory tract infection (URTI), carcinomas and type 2 diabetes thereby saving huge amount of resources and money that are spent in treating such ailments with little or no efficacy.

Radha108 acts as a molecular signaling device which works through receptors on target cell surfaces. These nano-informational peptide proteins mitigate cell fusion by docking on the glycoprotein receptors present on the CD4+ and CD8+ T cells for Gp120, Gp180 and Gp160 thereby closing the entry of virus, foreign antigen and allergens.

Radha 108 nano peptides SEQ ID 1-8 was extracted from bovine colostrum and has been granted the US patent (U.S. Patent No. 9,249,188 & 8,518,454 B2). These nano peptides consist of ELVPGVPRGTQL (DNA- binding Protein Inhibitor ID -3), VAIIQHMIKKLR (Epstein – Barr virus induced gene-2), LPQEVLNENLLRF (Alpha S1- Casein), RLNARMAELR (S-adenosylm ethionine synthetase isoform type -1), SSLQVLNMSHN(Toll- like receptor -4), EYQELMNVK (Keratin type II cytoskeletal 59kDa component IV), VDTLNDEINFLR (Keratin type II cytoskeletal 7), DGIVNENLAER (Ribonucleoside – diphosphate reductase small chain).

Thus, Radha 108 nanopeptides stimulate the secretion of bio- similars (wide range of cytokines like interleukins and interferons) that are very effective in treating viral infections like HIV, cold, swine flu and immune disorders like allergy, asthma, arthritis, diarrhea, fatigue-malaise, anaemia, endometriosis by stimulating the cytotoxic T cells

Keywords: Radha 108, Infection, PRP, Interferon, Cytokines

Introduction:

Our health is directly influenced by our immune system. A balanced and healthy immune system is of utmost importance for our body's ability to defend against infections. It is our ability to create a healthy immune system that represents the greatest potential for gains in human well being. Therefore, creating a healthy immune system harnesses maximum benefit towards human health.

Today, however, many factors contribute to the general weakening of the body's defences. Antibiotics have begun to fail due to multidrug resistance being developed over the period of time by species of microorganisms to multiple antimicrobial drugs. Due to the failure of government control of health codes, deterioration of water quality, and lack of adequate quarantine measures following

frequent international travel, diseases now spread more easily than ever before. Fortunately, recent research has uncovered a natural agent, which can increase our ability to fight disease and improve the quality of life for many people.

Radha 108 nano peptides extracted from mammalian colostrum (first milk) stimulates our body's own immune system as a broad-spectrum anti-viral and a new generation immunomodulator to fight against several diseases and prevents all communicable infections. It is a natural product manufactured by nano-biotechnology patented proprietary ultra-nano filtration processes from bovine colostrum.

Radha 108 consists of low molecular weight active pharmaceutical ingredients (API) - Proline Rich Polypeptides (PRPs). Radha 108 is registered under Ayush license number GA/1647 (Validity, 2018). Radha-108 belongs to a class of nano informational peptides, consisting of an oligo ribonucleotide attached to a peptide molecule. It acts as a broad spectrum immuno-modulator and antiviral agent via increasing body's own immune system naturally.

The innovation of Radha 108 in the field of immunotherapy is quiet revolutionary in therapeutic and preventive medicine. It is a form of treatment that uses different aspects of the immune system, its cells and molecules, and its various stratagems to tip the balance in favour as our body battles to maintain a healthy state.

Almost all individuals, healthy or diseased, with a few exceptions have benefited from regular Radha 108 supplementation. The use of Radha 108 did not cause any side effects even when given in high doses, exceeding the normal doses for prolonged periods. It has been shown to be beneficial in people with specific ailments as well.

Numerous studies have shown the effectiveness of Radha 108 in eliminating or alleviating symptoms of herpes, chronic fatigue syndrome, and viral infections including Epstein Barr, hepatitis, secondary infections due to AIDS, Candida, cancer and many other diseases and infections. Studies have also shown that continued use provides the greatest benefit, with maximum immune activity occurring 24 to 48 hours after taking the first dose.

The need for Radha 108 for better health stems from the growing awareness that prevention is the best cure. With the increasing risks of antibiotic resistance and significant health threats, such as severe acute respiratory syndrome (SARS), the medical community increasingly turns to the inherent concept of immunization using vaccinations.

Radha 108 is a kin to a vaccine but rather than exposing the patient's immune system to the actual disease or a deactivated version of the same, Radha 108 exposes the patient's immune system to the memory of a health threat, whether foreign or native, and the knowledge of how to best respond to protect itself. In view of proven global safety and efficacy, the product is now ready for a global launch with the product having been patented in several countries like the United States, Africa, Canada and Asia (Singapore and India).

The background of the invention

• Colostrum is the pre-milk substance produced from the mother's breast of all mammals during the first 24 hours of lactation, typically the first 3 milks.

• Colostrum has been known as an immune booster since time immemorial. Colostrum triggers at least 50 processes in the newborn, including transferring all immune factors and the entire immune defense memory from the mother's own immune system.

• Bovine colostrum is up to 40 times richer than human colostrum in immune factors including nano informational peptides, PRPs, immunoglobulins, cytokines, interferons, lactoferrin, and transfer factor.

• They are produced by T-lymphocytes and can transfer the ability to recognize a pathogen to native cells. However, no one till date has been able to isolate active ingredients especially nano informational low molecular weight nano peptides and formulate a product that has the same effect as that of the mother's first three milks, after the birth of the child.

• It has been indicated that colostrum stimulates the lymphoid tissue providing benefits in aged or immune deficient people (Bocci, Bremen, Corradeschi, Luzzi and Paulesu in Journal Biology).

• In addition, researchers reported that colostrum stimulates maturation of B lymphocytes (type of white blood cell) and primes them for the production of antibodies, enhances growth and the differentiation of white blood cells. Similar activity in cow and human colostrum can also activate macrophages (Dr. M. Julius, McGill University, Montreal: Science News).

• Furthermore, it was indicated that bovine colostrum contains high levels of growth factors that promote normal cell growth and DNA synthesis (Oda, Shinnichi et. al).

• Besides, it has been suggested that an important role for growth factors is in promoting wound healing. Accelerated healing is important in treatment of trauma and surgical wounds (Bhora et. al).

• As such, colostrum contains hundreds of small peptides which serve numerous purposes. Studies have documented the presence of a number of bioactive peptides but no mention has been made of the use of these peptide fragments, their specific sequence or information regarding their isolation.

• Therefore, their segregation and isolation will facilitate gathering of further information with regard to their individual function and help formulate specific and targeted therapies for numerous diseases that are cured by colostrum.

• The challenge with this task is that the peptides are extremely sensitive to temperature, pH, stress, and shear factors. This poses several difficulties in their isolation and in preserving their biological activity and in the method of collection of colostrum so as to be able to deliver it to the patient while retaining its full biological activity.

• The present invention addresses these shortcomings by providing isolated nano peptides from colostrum, establishing their method of isolation and the therapeutic uses of the isolated nano peptide fragments. With reference to this innovation, the US patent for this product, US 20070212367 is notable:

• US 20070212367- This patent application discloses an immunologically active PRP isolated from mammalian colostrum fluids for treatment of viral and non- viral diseases, a method and a system for processing mammalian colostrum fluids and a pharmaceutical formulation.

Mode of action:

• The informational proteins, Radha 108 are active in mitigating cell fusion.

• Radha 108 series docks on glycoprotein receptor on the cell surface and thus restricts viral entry into the immune cells.

• Radha 108 series get absorbed in the blood stream through buccal mucosa and crosses the BBB.

• The levels of interleukins and cytokines are increased substantially.

• It supports the regulation of the thymus by producing functionally active natural killer (NK) cells.

• Radha 108 augments cell-mediated immunity and activates T-cell precursors to produce helper and suppresser T-cells increasing CD4/8 counts.

• Radha 108 promotes growth and differentiation of stem cells in response to any disease.

Fusion of human immunodeficiency virus (HIV) particles with human white blood cells, particularly CD4 cells occurs with the aid of glycoprotein (Gp) epitopes on the viral wall. Radha108 docks on HIV Gp120 mimicking receptor on the cell surface and thus restricting virus/antigen entry into the immune cells.

Radha 108 proteins directly support the NK cells of the immune system. NK cells provide the front line of defense specially equipped to locate and kill disease cells. NK cells attach to the surfaces of foreign substances or their outer cell wall, and inject a chemical "grenade" (granule) into the interior. Once inside, the granules explode and destroy the foreign invader within five minutes.

The NK cell itself remains intact and moves on to destroy the next immune attacker. Many doctors and clinicians are finding Radha 108 helpful in promoting NK function and activity as well as supporting a healthy immune system for all patients.

The immune system plays a great role in the quality of our health. Strong, active and optimally functioning NK cells promote optimal health and deter foreign substances from affecting immune function.

• Radha108 (PRP) promotes differentiation of B cells, differentiation and maturation of macrophages and monocytes.

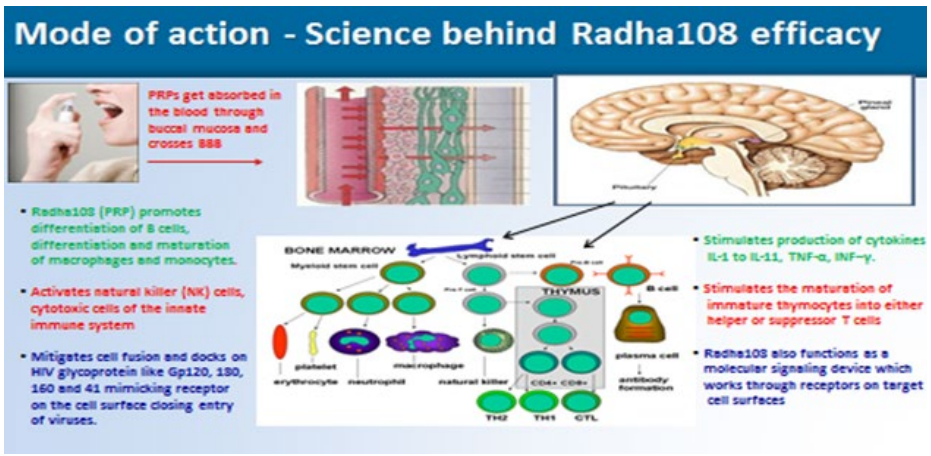
• Activates NK cells, cytotoxic cells of the innate immune system.

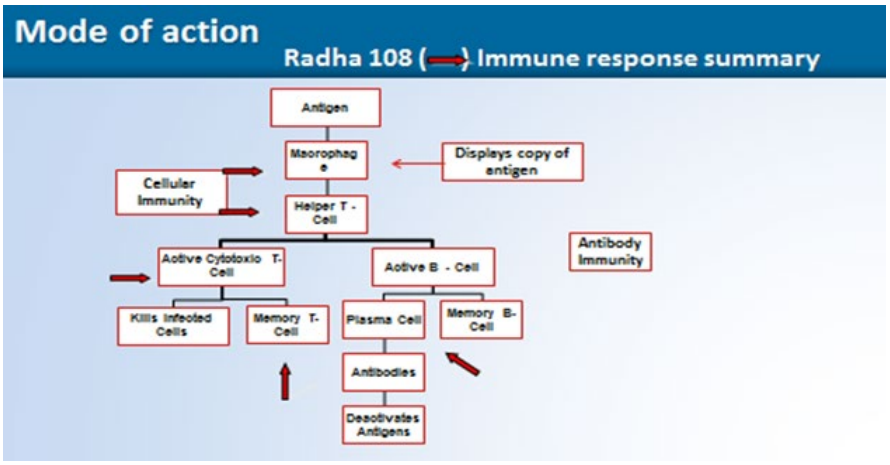
• Mitigates cell fusion and docks on HIV glycoprotein like Gp120, 180, 160 and 41 mimicking receptor on the cell surface closing entry of viruses.

• Stimulates production of cytokines interleukin (IL)-1 to IL-11, tumor necrosis factor (TNF)-α, Interferon (INF)–γ.

• Stimulates the maturation of immature thymocytes into either helper or suppressor T cells.

• Radha108 also functions as a molecular signaling device which works through receptors on target cell surfaces.





Radha 108 acts as cytokine modulator. Cytokines are a diverse group of soluble proteins and peptides which act as humoral regulators at nano to picomolar concentrations and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues.

These proteins also mediate interactions between cells directly and regulate processes taking place in the extracellular environment. The cytokines interleukin 1 and 6, interferon-gamma and lymphokines have been shown to stimulate the lymph glands and are thought to be highly effective antiviral immune substances.

Interleukins regulate the duration and intensity of the immune response and are responsible for cell to cell communication, boost T-cell activity and the production of immunoglobulins.

The cytokine IFN-beta is involved in the regulation of unspecific humoral immune responses and immune responses against viral infections.

Extensive preclinical studies have documented a direct cytostatic and cytotoxic effect of the cytokine TNF-alpha against subcutaneous human xenografts and lymph node metastases in mice as well as a variety of immunomodulatory effects on various immune effector cells, including neutrophils, macrophages, and T-cells.

Following is a description of some of the biological activities of the IFN-beta and TNF-alpha cytokines:

IFN-beta (beta-interferon)

It is a glycoprotein with 20,000MW consisting of 166 amino acids. It is also known as fibroblast interferon, Type-1 interferon, pH2-stable interferon, and R1-GI factor. IFN-beta is produced mainly by fibroblasts and some epithelial cell types.

IFN-beta is involved in the regulation of unspecific humoral immune responses and immune responses against viral infections. IFN-beta increases the expression of HLA class I antigens and blocks the expression of HLA class II antigens stimulated by IFN-gamma. IFN-beta stimulates the activity of NK-cells thereby activating antibody-dependent cytotoxicity.

The activity of T suppressor cells is also stimulated by IFN-beta. IFN-beta enhances the synthesis of the low affinity IgE receptor CD23. In activated monocytes, IFN-beta induces the synthesis of neopterin.

It also enhances serum concentrations of beta-2-microglobulin. IFN-beta selectively inhibits the expression of some mitochondrial genes. IFN-beta shows anti proliferative activity against a number of cell lines established from solid tumors.

IFN-beta can be used for topic treatment of condylomata acuminata. It is also suitable for the prophylactic use following surgical removal of large condylomas. Some studies suggest that IFN-beta tends to prevent disease activity in patients with multiple sclerosis.

IFN-beta has been used in the treatment of chronic active hepatitis B and appears to be most promising if the disease has not lasted longer than 5 years. The antiviral activity of IFN-beta is demonstrated also in the treatment of severe childhood viral encephalitis.

IFN-beta is a lipophilic molecule that should be particularly useful for local tumor therapy due to its specific pharmacokinetics.

It is hardly removed from the tumor tissues after intraregional administration and hence also shows little systemic side effects. Head and neck squamous carcinomas, mammary and cervical carcinomas, and also malignant melanomas respond well to treatment with IFN-beta.

IFN-beta also appears to be very promising for the adjuvant therapy of malignant melanomas with a high potential for metastasis. Response rates have been reported to be improved by combining IFN-beta with antineoplastic agents or other cytokines.

In many instances a combination of the various interferons has been found to cause synergistic effects. The antiviral/anti proliferative/antitumor properties of IFN-beta are potentiated by febrile temperatures.

TNF-alpha (Tumor Necrosis Factor-Alpha)

TNF-alpha is a glycoprotein with a 17,000MW consisting of 157 amino acids. It has immuno-modulating effects on various immune effector cells. TNF-alpha shows a wide spectrum of biological activities.

It causes cytolysis and cytostasis of many tumor cell lines in vitro. Sensitive cells die within hours after exposure to picomolar concentrations of the factor and this involves, at least in part, mitochondria-derived second messenger molecules serving as common mediators of TNF cytotoxic and gene-regulatory signaling pathways.

The factor induces hemorrhagic necrosis of transplanted tumors. Within hours after injection TNF-alpha leads to the destruction of small blood vessels within malignant tumors. The factor also enhances phagocytosis and cytotoxicity in neutrophilic granulocytes and also modulates the expression of many other proteins. Radha 108 promotes the production of these cytokines (IFN beta and TNF-alpha).

Summary of Pre clinical & clinical trials

1. Pre clinical study (for acute and sub-chronic toxicity): Carried out as per the International Conference on Harmonization (ICH) guideline at Nation Institute of Nutrition, Hyderabad.

2. Phase I clinical trial: Ohio, USA.

The trial was conducted to evaluate the safety of Radha 108 Oral Spray on 12 HIV patients for a period of 30 days.

• No adverse effects were reported during the study.

• Improvement was observed in HIV associated clinical symptoms (Table 1).

• Week after week weight gain showed a positive response.

Table 1: Clinical improvement during Phase I - USA

Symptom	Number of patients with symptom N=12	Number of patients with elimination of symptoms N=12
Diarrhea	8	5
Fatigue	9	9
Nausea	8	5
Cough	4	2

3. Phase II study: Nairobi, Kenya.

A t-Trial was conducted on 30 patients with HIV/AIDS, who received a 90 day treatment with Radha 108 Oral Spray with an objective to demonstrate efficacy and safety under clinical conditions.

• Radha 108 Oral Spray appeared to be safe and well tolerated.

• Significant viral load reduction in minimizing the infection associated with HIV/AIDS.

• Week after week weight gain showed a positive response.

• Marked reduction in symptoms.

• Significant increase in CD4 count.

4. Phase III study: Rwanda, Africa

A t-Trial was conducted in 60 patients with HIV/AIDS, where patients received a 12 month treatment with Radha 108 Oral Spray with an objective to study the efficacy and safety under clinical conditions.

• Patients were unaware of positive potentials of drug so as to avoid any bias.

• After day 1 moderate level of relief of diarrhea and fever was observed.

• Week after week weight gain showed a positive response.

• After 14 days, relief from skin lesion, mouth thrush, fever, diarrhea, tuberculosis symptoms was seen.

• After 90 days relief of all symptoms with increase in absolute CD4 counts and reduction in viral load.

• No adverse effects observed over 12 months follow up even after 5 years of therapy, and an improvement in Quality of Life was noted.

5. Phase III revalidation trial in Indian ethnic population: At Mumbai

An Interventional / Prospective Phase III (Stand alone Mono Therapy)

The study was conducted in LTMMS Tertiary Care Sion Hospital, Mumbai on 50 patients who were HIV+. Absolute CD4 cell count and HIV Viral Load were tested at CAP, USA accredited Metropolis lab, Mumbai. Clinical and physical symptoms study was done at ART Center, Sion Hospital, Mumbai.

• The objective was to evaluate safety & efficacy of Radha 108. The symptoms studied were HIV, Diarrhea, Fatigue/Malaise,

Nausea, Cough.

• Inclusion criteria was absolute CD4 cell count greater than 100 cells/mm3 and exclusion criteria was no pre- exposure to ART.

• Statistically significant reduction in mean HIV log viral load ($p<0.001$) and significant increase in CD4 cell count ($p=0.06$) were observed. Clinical symptoms disappeared in 3 weeks of treatment in all patients ($p<0.05$). Statistically significant weekly weight gain in all patients ($p<0.001$) was seen.

Table 2: Summary of Study 1 data

Visit (Weeks)	No. of Subjects with Nausea	No. of Subjects with Vomiting	No. of Subjects with Fatigue/ Malaise	No. of Subjects with Diarrhea	No. of Subjects with Fever	No. of Subjects with Cough
1	8	7	44	9	12	14
2	3	2	32	5	3	10
3	2	2	26	1	6	6
4	1	1	17	1	1	3
6	0	1	1	0	0	1
8	0	0	1	0	0	2
10	0	0	1	0	0	0
12	0	0	0	0	0	0

18 % of the total study cases had diarrhoea at basal and after treatment from 5th week onwards all the patients had relief from diarrhea.(Figure 1)

Figure 1: Reduction in number of patients with diarrhoea during the 11 weeks trial treatment with Radha 108.

Fever was reported by 24 % of total study cases at basal and from 7th week onwards not a single patient had fever with significant fall started 4th week onwards. (Figure 2)

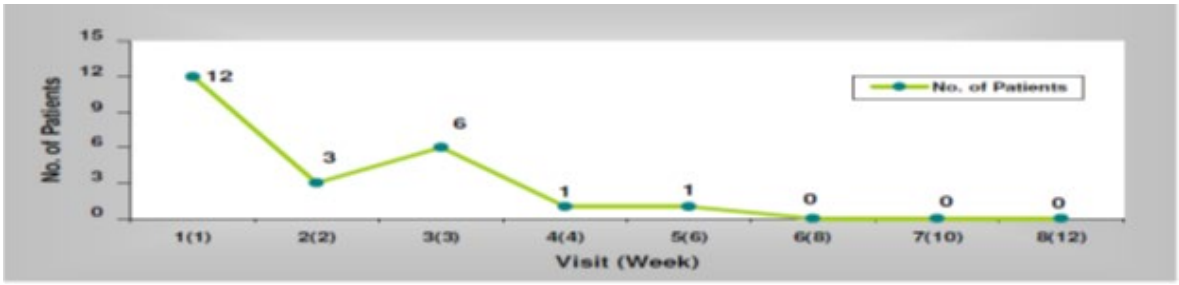


Figure 3: Reduction in number of patients with cough during 11 weeks trial treatment with Radha 108 88 % of the total study cases had symptoms of Fatigue/Malaise at baseline. After treatment of Radha 108 at the end of 2nd week proportion of symptoms of fatigue had a significant fall from baseline. After 6th week onwards only one or two patients had Fatigue/Malaise (Figure 4).

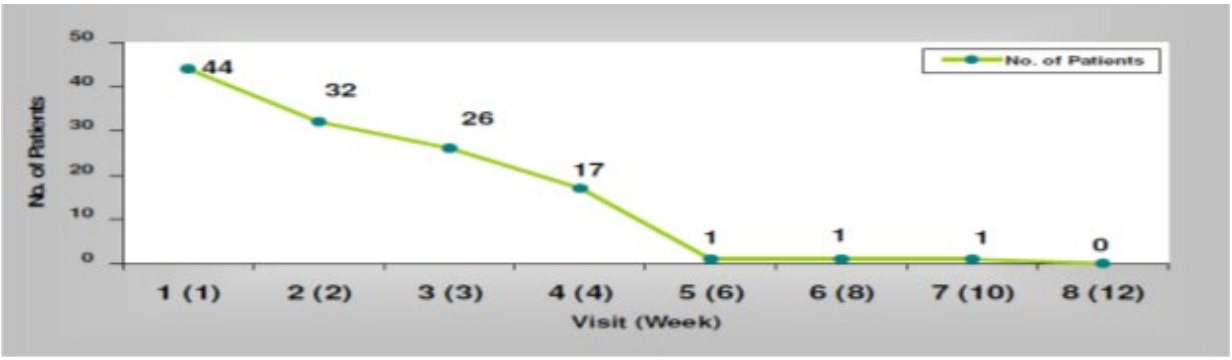


Figure 4: Reduction in number of patients with Fatigue/Malaise during 11 weeks trial treatment with Radha 108

Sr. No.	CD4 count N=48	Baseline	After 12 Weeks	p-value
1.	Median	312.5	363.5	0.06
2.	25th Percentile	275.5	294.2	
3.	75th Percentile	430	435	

Table 3: Summary CD4 count, baseline vs week 12

Sr. No.	Parameter	Baseline	After 12 Weeks	p-value
1.	Log of HIV-1, RNA (N=34)	5.11(0.090)	4.103(1.32)	< 0.001
2.	Median	206057	25280	< 0.001
3.	25th Percentile	62884	1665	
4.	75th Percentile	508038	87511	

Table 4: Summary CD4 count, baseline vs week 12

Absolute CD4 Count:

Absolute CD4 cell count was available for all 50 patients with pre and post treatment values. There was an increase in Absolute CD4 count in 26 (52%) patients. Absolute CD4 cell count range with number of patients at baseline and at the end of study is shown in Figure 5.

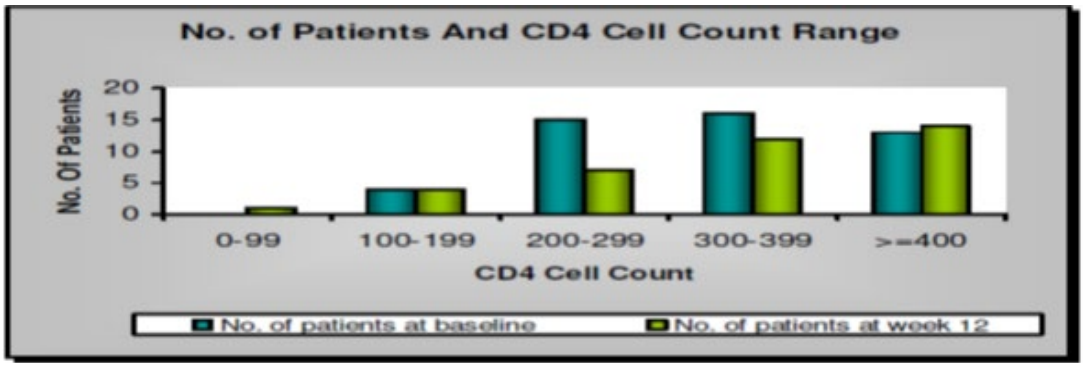


Figure 5: Number of patients and absolute CD4 cell count range

An Interventional / Prospective Phase III (A Stand-Alone Mono Therapy)

This study was conducted in Sion Hospital, Mumbai on 51 AIDS Patients. Absolute CD4 cell count and HIV viral load was tested at Institute of Immuno Hematology (IIH), Indian Council of Medical Research (ICMR), King Edward Memorial (KEM) Hospital, Mumbai.

The inclusion criteria was absolute CD4 cell count greater than 100 cells/mm3and 100% symptomatic patients at baseline and exclusion criteria was no pre-exposure to ART.

The drop in the mean HIV log viral load was statistically significantly ($p<0.009$). Statistically significant increase in the CD4 cell count ($p< 0.042$) was seen. Clinical symptoms disappeared in 3 weeks of treatment in all patients ($p<0.001$). Statistically significant weekly weight gain in all patients ($p<0.001$).

Clinical Symptoms	N	At Baseline	Responders At Week-2
Diarrhea	51	51(100%)	12 (23.53%)
Nausea	51	51(100%)	3 (5.9%)
Vomiting	51	51(100%)	17 (33.3%)
Fever	51	51(100%)	13 (25.5%)
Cough	51	51(100%)	13 (25.5%)
Paraesthesia	51	51(100%)	16 (31.4%)
Disturbed Sleep	51	51(100%)	0 (0%)
Skin Rash	51	51(100%)	7 (13.7%)
Fatigue/Malaise	51	51 (100%)	51 (100%)
Herpes Zoster	51	51 (100%)	18 (35.3%)
Hair Changes	51	51 (100%)	16 (31.4%)
Leukoplakia	51	51 (100%)	5 (9.8%)
Oral Thrush	51	51 (100%)	51 (100%)

Table 5: Indian re-validation phase III trials, Mumbai - Study II

51 patients (100%) had diarrhea at baseline and all patients had relief from diarrhoea from 3rd week onwards with the treatment of Radha 108. (Figure 6)

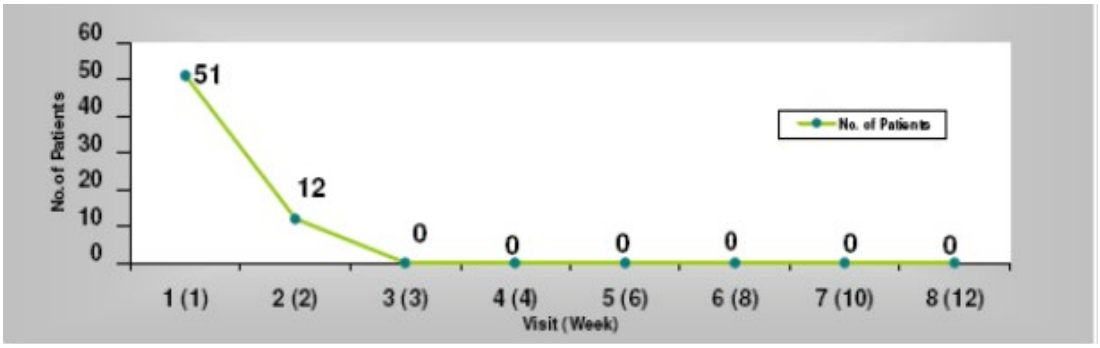


Figure 6: Reduction in number of patients with diarrhoea during the 12 weeks trial treatment with Radha 108

100 % of the total study cases had Nausea at baseline and all patients had relief from Nausea from 3rd Week onwards. (Figure 7)

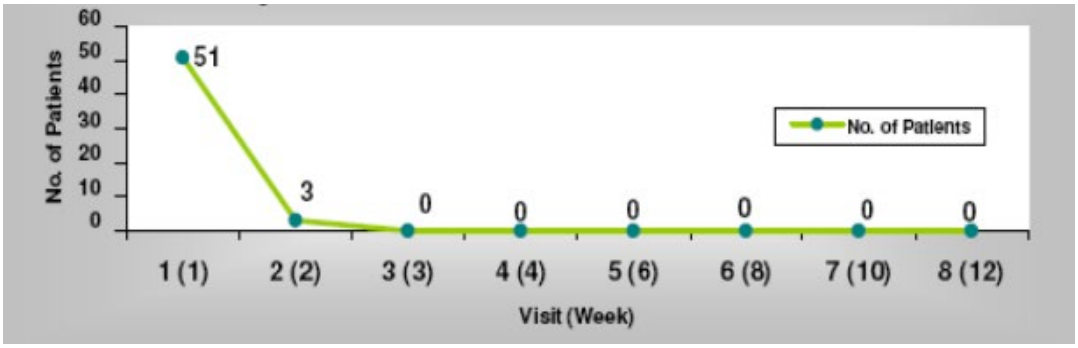


Figure 7: Reduction in number of patients with nausea during the 12 weeks trial treatment with Radha 108

100 % of the total study cases had vomiting at baseline and all the patients had relief from vomiting after treatment from 3rd Week onwards. (Figure 8)

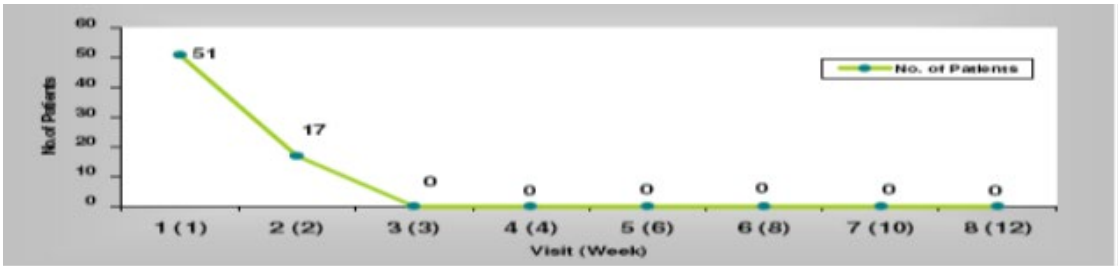


Figure 8: Reduction in number of patients with vomiting during the 12 weeks trial treatment with Radha 108

100 % of the total study cases had fever at baseline and all the patients had relief from fever from 3rd week onwards. (Figure 9)

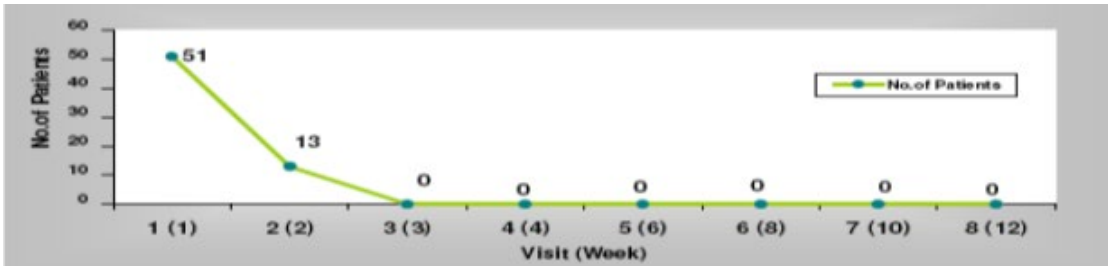


Figure 9: Reduction in number of patients with fever during the 12 weeks trial treatment with Radha 108

100 % of the total study cases had cough at baseline and all the patients had relief from cough from 3rd week onwards. (Figure 10)

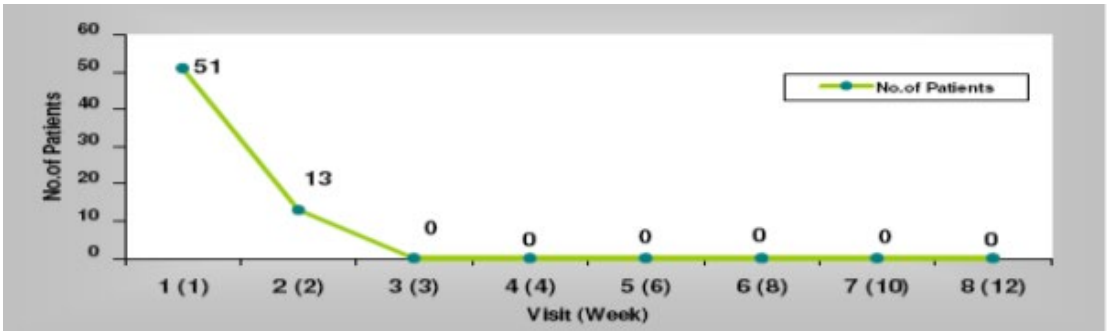


Figure 10: Reduction in number of patients with cough during the 12 weeks trial treatment with Radha 108

100 % of the total study cases had fatigue/malaise at baseline which reduced from 3rd week onwards and all the patients had relief from fatigue/malaise from week 5 of the treatment with Radha 108 (Figure 11)

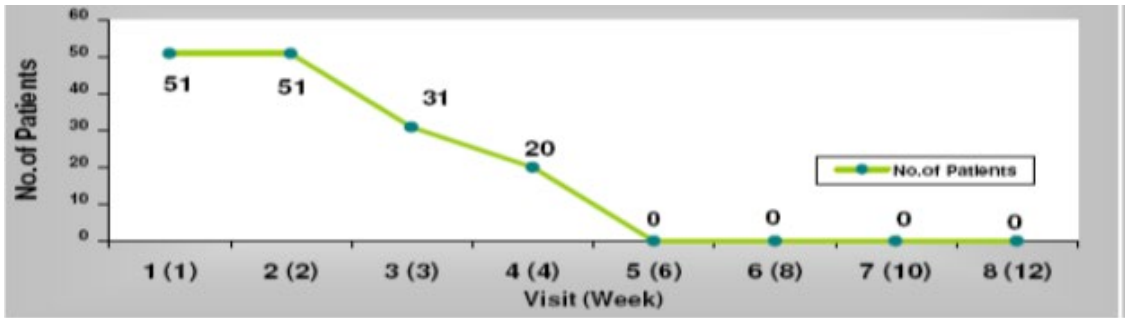


Figure 11: Reduction in number of patients with fatigue/malaise during the 12 weeks trial treatment with Radha 108

Table 6: CD4 Count, Baseline vs Week 12

Parameter	Baseline Mean ± SD	Week 12 Mean ± SD	Difference (Week 12-Baseline) Mean ± SD	P-value
CD4 Counts (cells/ mm)	317.16 ± 128.67	344.24 ± 165.79	+ 27.08 ± 92.47	0.042
CD8 Counts (cells / mm^3)	1037.06 ± 285.02	1139.75 ± 386.76	+102.69 ± 267.44	0.008

Absolute CD4 and CD8 cell count:

• CD4 cell counts were available for all 51 patients with pre and post treatment values. There was an absolute increase in CD4 counts for 67% patients and an average increase in CD4 count by 27 (The median CD4 cell counts increased from 276 to 305). This effect was found statistically significant ($p < 0.05$). CD4 cell counts range with number of patients at baseline and at the end of study is shown in figure 12a.

• While there was a significant improvement in CD8 count with 75% of patients showing an increase in CD8 counts and the average difference in CD8 count from baseline to the week-12 was found to be 102.69 ± 267.44. This effect was statistically significant ($p < 0.05$). (Figure 12b)

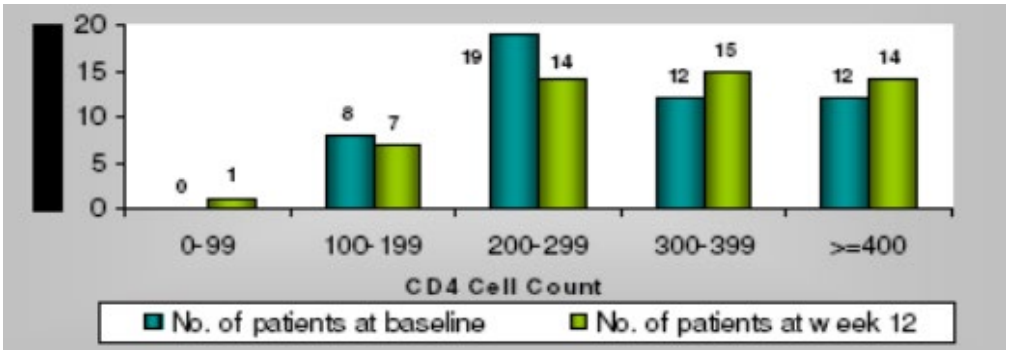


Figure 12a: Comparison of the number of patients in CD4 cell count ranges at baseline and end of treatment measurements.

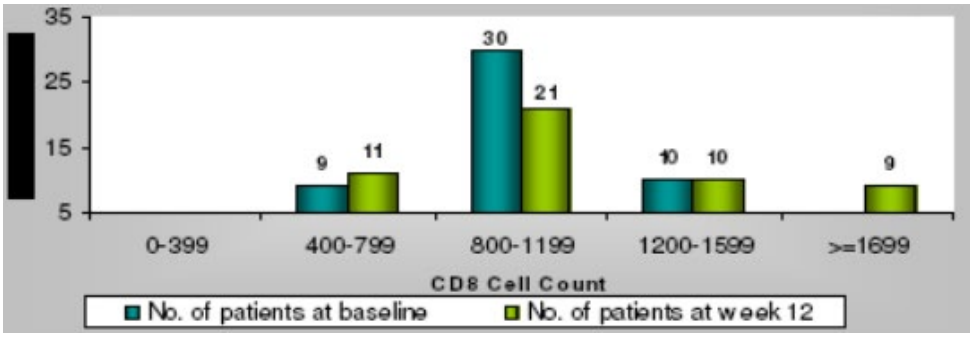
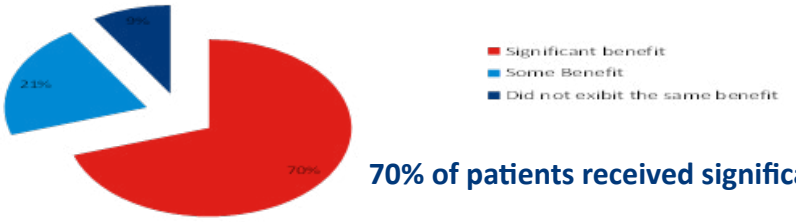


Figure 12b: Comparison of the number of patients in CD8 cell count ranges at baseline and end of treatment measurements.

Radha 108 in Non-communicable Diseases (NCDs): Rheumatoid Arthritis Study
Reporting Patients*: 63
Duration of Treatment: 6 months

56% of patients found the product to be highly effective!

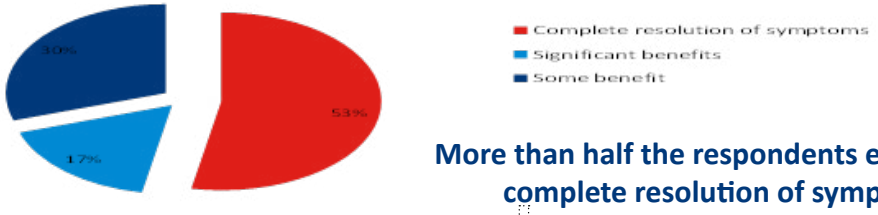
Radha 108 in NCDs: Fatigue Syndrome Study
Reporting Patients*: 108
Duration of Treatment: 6 months



70% of patients received significant benefits!

Radha 108 in NCDs: Allergy Study

Reporting Patients*: 24
Duration of Treatment: 6 months



More than half the respondents experienced complete resolution of symptoms!

Radha 108 in NCDs: Endometriosis Study

Reporting Patients*: 106
Duration of Treatment: 6 months

Similarly for Endometriosis, complete resolution in most cases!

Summary: Safety & Efficacy data as per global study on Radha 108

KEY DIMENSIONS	PHASE I, II & III INTERNATIONAL TRIALS	STUDY I	STUDY II
Phase	Phase I – HIV trial, US Phase II – HIV trial, Nairobi, Kenya Phase III – HIV trial, Rwanda	Phase III validation trial by GOI on HIV patients, Stand-alone monotherapy	Phase III validation trial by GOI on HIV patients, Standalone monotherapy
No. of patients	Phase I – 12 cohorts Phase II – 30 cohorts Phase III – 60 cohorts	50 HIV seropositive patients	51 HIV seropositive patients
Duration	365/ 30 days	3 months	3 months
Compliance	Very good	Very good	Very good
Side effect	None	None	None
Weight gain	6 lbs average gain	4.73 kg per patient, $p<0.05$	4.68 ± 1,9 kg per patient, $p<0.001$
Clinical symptoms	90 days relief from symptoms	Improved within 3 weeks from starting of therapy	Improved within 3 weeks from starting of therapy
CD4 cell count	Phase II: Average by 31	Average by 51, median CD4 cell count from 312 to 363 ($p = 0.06$)	On an average by 27 ($p = 0.042$)
HIV Viral load	Phase II: Mean HIV log viral load from 4.6 to 2.5	Mean HIV log viral load from 4.63 to 4.18 ($p = 0.001$)	Mean HIV log viral load from 4.41 to 4.02 ($p = 0.009$)

References:

1. Saharan P. Mammalian Colostrum derived Nanopeptides for broad spectrum viral and recurrent infection with a method of isolation thereof, US Granted product patent (#8518454 B2).

2. Saharan P. Mammalian colostrum derived Nanopeptide for broad spectrum viral 7 recurrent infections with method of isolation thereof, Singapore patent (Patent No. 172793)

3. Saharan P. Mammalian Colostrum Derived Nanopeptides For Broad spectrum Viral And Recurrent Infections With A Method Of Isolation Thereof, South Africa Patent (Patent No. # 2011/04687

4. Mammalian Colostrum Derived Nanopeptides For Broadspectrum Viral And Recurrent Infections With A Method Of Isolation Thereof, Europe (Application no. EP 09827010.1)

5. Saharan P. Mammalian Colostrum derived nanopeptides for broad spectrum viral and recurrent infection with a method of isolation thereof. Patent submitted to Indian Patent office, 2007.

6. Saharan P. Rajadhyaksha G., An Interventional Phase III Accelerated Study to Determine The Efficacy and Safety of Radha 108 Oral Spray (Radha108 nanopeptides derived from Bovine Colostrum) Used to Delay the ART Treatment in HIV Positive Patients With Multiple Symptoms as a Stand-Alone Mono Therapy with comparative data of HIV patients on ART (could be an Answer to Swine flu, Ebola?), publishing in BMJ open

7. Saharan P. Rajadhyaksha G., A study on Novel Broad Spectrum Antiviral & new generation Immunomodulator (Radha108) Nanopeptides from Bovine Colostrum for the Treatment of recurrent infection in HIV, Publishing in Journal of AIDS.

8. Saharan P., Singh T., Safety and efficacy Clinical Trial of Radha 108: New Nano biotechnology based immunomodulator in HIV therapy. Unpublished Patented data (2005-2006).

9. World Health Organization. Progress on global access to HIV antiretroviral therapy: a report on "3 by 5" and beyond. 2006.

10. Brahmbhatt H, Kigozi G, Wabwire-Mangen F, Serwadda D, Lutalo T, Nalugoda F, Sewankambo N, Kiduggavu M, Wawer M, Gray R. Mortality in HIV-infected and 11 uninfected children of HIV-infected and uninfected mothers in rural Uganda. J Acquire Immune Defic Snyder 2006;41(4):504-8.

11. Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet 2004; 364(9441):1236-43.

12. Taha TE, Dallabetta GA, Canner JK, Chiphangwi JD, Liomba G, Hoover DR, Miotti PG. The effect of human immunodeficiency virus infection on birth weight and infant and child mortality in urban Malawi. Int J Epidemiol 1995; 24(5):102

13. Wieczorec Z., Zimecki M., Spiegel K., Lisowski J., Janusz M., Differentiation of T-Cells from immature precursors: identification

of a target cell for a proline-rich polypeptide (PRP) Archivum immunological therapies experimentalists (Warszawa) 37(3-4):313-322(1989).

14. Kubis A., Marcinkowska E., Janusz M., Lisowski J. Studies on mechanism of action of a proline-rich polypeptide complex (PRP): Effect on stage of cell differentiation peptides 26(11) : 2188-2192 (2005).

15. Modulation of 4HNE-mediated 20(2):125-134 (2003).

16. Zibiocka A., Janusz M., Rybka K., Wirkus – Romanowska I. Kupryszewski G., Lisowski J. Cytoline inducing activity of a proline-rich polypeptide (PRP) from ovine colostrum and its active nanopeptide fragment analogs. European Cytokine Network 12(3) :462-467 (2001).

17. Fernadez- ortega C. Dubed M. Ruibal O. Vilarruba OL. Menendez de San Pedro JC. Navea L. Ojeda M. Arana MJ. Inhibition of in vitro HIV infection by dialyzable leucocyte extracts, Biotherapy 9(1-3)33-40 (1996).

18. Zimecki M,Staroscik K, Janusz M, Lisowski J, Wieczorek Z. The inhibitory activity of proline-rich polypeptide on the immune response to polyvinyl pyrolidone (PVP). Arch Immunol Ther Exp (Warsz)1983;31(6):895-903.

19. Julius MH, Janusz M, Lisowski J. A colostral protein that induces the growth and differentiation of resting B lymphocytes. J Immunol, 1988; 140(5):1366-371.

20. Boldogh I, Liebenthal D, Hughes TK, Juelich TL, Georgiades JA, Kruzel ML, Stanton GJ. Modulation of 4HNE-mediated signaling by a proline-rich polypeptides from ovine colostrum. J Mol Neurosci. 2003;20(2):125-134.

21. Pizza G, Chiodo F, Colangeli V, Gritti F, Raise E, Fudenberg HH. Preliminary observations using HIV-specific transfer factor in AIDS. Biotherapy. 1996;9(1-3):4-47.

22. Eggena MP, Barugahare B, Jones N, Okello M, Mutalya S, Kityo C, Mugyenyi P, Cao H. Depletion of regulatory T cells in HIV infection is associated with immune activation. J Immunol. 2005; 174(7):4407-4414.

23. Shi M, Hao S, Chan T, Xiang J. CD4+ T cells stimulate memory CD8+ T cell expansion via acquired pMHC I complexes and costimulatory molecules, and IL-2 secretion. J Leuco Biol, 2006; 80(6):1354-1363.

24. Granitov, VM et al. Usage of RECEPTOL in treatment of HIV – Infected patients. Russian Journal of HIV AIDS and Related Problems 2002, 1, 79-80.

25. Lawrence HS, Borkowsky W:Transfer factor:Current status and future prospects,Biotherapy9:1:5,1996.

26. Brenneman, D. and others. Neuronal cell killing by the envelope protein of HIV and its prevention by vocative intestinal peptide. Nature, 335(6191), pages 639-642,October13,1988.

27. Brenneman, D. and others. Peptide T prevents gp120 induced neuronal cell death in vitro: relevance to AIDS dementia. Drug Development Research, volume15,pages361-369,1988.

28. Immunology, Immunopathology and Immunity, Sell S, Appleton and Lange: Stamford CT 1996.

29. Bishop GA., Haxhinasto SA., Slunz LL., Hostager BS. Antigen specific B-lymphocyte activation. Critical reviews in immunology 23(3): 159-197 (2003).

30. Claes – Henrik Floren S., Chinenye L., Elfstrand C., Hagman L. Thse. Coloplus a new product based on bovine colostrum alleviates HIV- associated diarrhoea. Scandinavian journal of Gastroenterology 2006: 41-68 2-686.

31. Effects of oral dietary supplementation with Ai/E10® upon Natural Killer (NK) cell activity in a healthy human population. Quantum Research, Inc., Scottsdate, Arizona, 2001.

32. An examination of Immune Response Modulation in Humans by Ai/E10® utilizing a double blind study. Immune Consultants, Inc., Tucson, Arizona, 2001.

33. Macroft A, Youle M, Moore A, et al. Reaseons for modification and discontinuation of antiretroviral: results from a single center. AIDS, 2001; 15:185-94.

34. Fatenkeheur G, Romer K, Cramer P, et al. High rates of changes of first antiretroviral combination regimen in an unselected cohort of HIV 1 infected patients. 8th ECCAT Greece, 2001; abstract no. 50.

35. Raise E, Guerra L, Viza D, Pizza G, De Vinci C, Schiattone ML, Rocaccio L, Cicognani M, Gritti F. Preliminary results in HIV I infected patients with transfer factor (TF) and zidovudine (ZDV). Biotherapy. 1996;9(1-3):49-54.

36. Shi M, Hao S, Chan T, Xiang J. CD4+ T cells stimulate memory CD8+ T cell expansion via acquired pMHC I complexes and costimulatory molecules, and IL-2 secretion. J Leuco Biol, 2006; 80(6):1354-1363.

37. Razonable, Raymund, R., et.al. Division of Infectious Diseases and Internal Medicine, Mayo Clinic and Foundation, Selective Reactivation of Human Herpes virus 6 variant A Occurs in Critically Ill Immunocompetent Hosts, The Journal of Infectious Diseases, January , 2002.

38. Dwyer JM. The use of antigen-specific RECEPTOL® in the management of infections with herpes viruses. In: Kirkpatrick CH, Burger DR and Lawrence HS eds. Immunobiology of RECEPTOL®. New York Academic Press 1983:233-243.

39. Viza D, Vich JM, Phillips J et al. Orally administered specific RECEPTOL® for the treatment of herpes virus infections. Lymphok Res 1985;4:27-30.

40. Jones JF, Jeter WS, Fulginiti VA et al. Treatment of childhood combined Epstein-Barr virus/cytomegalovirus infection with oral bovine RECEPTOL®. Lancet 1981;2:122-124.

41. Ablashi DV, Levine PH, DeVinci C et al. Use of anti HHV-6 RECEPTOL® for the treatment of two patients with chronic fatigue syndrome (CFS). Two case reports. Biotherapy 1996;9:81-

86.

42. Steele RW, Myers MG and Monroe VM. RECEPTOL® for the prevention of varicella-zoster infection in childhood. N Engl J Med 1980;303:355-359.

43. Lang I, Nekam H, Gergely P et al. Effect of in vivo and in vitro treatment with dialyzable leukocyte extracts on human natural killer cell activity. Clin Immunol and Immunopathol 1982;25:139-144.

44. Boucheix C, Phillips J, Pizza G et al. Activity of animal RECEPTOL® in man. Lancet 1977;1:198-199.

45. Fudenberg H and Pizza G. RECEPTOL® 1993: New frontiers. Progress in Drug Res 1994;42:309-400.

46. Arala-Chaves M, Ramos MTF and Rosado RMF. Evidence for prompt and intense constitution of cell-mediated immunity by means of RECEPTOL® in a case of complex immune deficiency. Cell. Immunol. 1974;12:160.

47. Ballow M and Good RA. Report of a patient with T-cell deficiency and normal B-cell function: a new immunodeficiency disease with response to RECEPTOL®. Cell. Immunol. 1975;19:219.

48. Jones JF, Pizza G, DeVinci C. Infectious mononucleosis: immunotherapy with EBV-specific RECEPTOL®. J Exp Pathol 1987;3:399-406.

49. Khan A, Hansen B, Hill NO et al. RECEPTOL® in the treatment of herpes simplex types 1 and 2. Dermatologica 1981;163:177-185.

50. Winkelman RK, DeRemee RA, Ritts RE Jr. Treatment of varicella-zoster pneumonia with RECEPTOL®. Cutis 1984;34:278-281.

51. Rozzo SJ and Kirkpatrick CH. Purification of RECEPTOLs. Mol Immunol 1992;29:167-182.

52. Pizza G, Viza D, Roda A et al. RECEPTOL® for the treatment of chronic active hepatitis. N Engl J Med 1979;300:1332.

53. Nkrumah F, Pizza G, Viza D et al. Regression of progressive lymphadenopathy in a young child with acute cytomegalovirus (CMV) infection following the administration with specific anti-CMV activity. Lymphok Res 1985;4:237-241.

54. Neequaye J, Viza D, Levine PH et al. Specific RECEPTOL® with activity against Epstein-Barr virus reduces late relapse in endemic Burkittâs lymphoma. Anticancer Res 1990;10:1183-1187.

55. Viza D, Vich JM, Phillips J et al. Specific RECEPTOL® protects mice against lethal challenge with herpes simplex virus. Cell Immun 1986;100:555-562.

56. Wilson GB, Poindexter C, Fort JD et al. De novo initiation of specific cell-mediated immune responsiveness in chickens by RECEPTOL® (specific immunity inducer) obtained from bovine colostrum and milk. ACTA Virol 1988;32:6-18.

57. Kirkpatrick CH, Hamad AR, and Morton LC. Murine RECEPTOLs: dose-response relationships and routes of administration. Cell Immunol 1995:164:203-206.

58. Viza D, Lefesvre A, Patrasco M et al. A preliminary report on three AIDS patients treated with anti-HIV specific RECEPTOL®. J Exp Path 1987;3:653-659.

59. Pizza G, DeVinci C, Palareti A et al. 25 years of clinical experience with RECEPTOLs. XI International Symposium on RECEPTOL®. March 1-4, 1999. Monterey, Mexico.

60. Barnes, D. Debate over potential AIDS drug. Science, 237(4811), pages 128-130,July10,1987.

61. Brenneman, D. and others. Neuronal cell killing by the envelope protein of HIV and its prevention by vasoactive intestinal peptide. Nature, 335(6191), pages639-642, October13, 1988.

62. Brenneman, D. and others. Peptide T prevents gp120 induced neuronal cell death in vitro: relevance to AIDS dementia. Drug Development Research, volume15, pages361-369,1988.

63. Bridge, P. and others. Peptide T: Improvements in phase I trial of AIDS patients. Draft of letter submitted to Lancet, July 1989.

64. Kowalski, M. and others. Functional regions of the envelope glycoprotein of human immunodeficiency virus type 1. Science, 237 (4820), pages 1351-1355,1987.

65. Lasky and others. Delineation of a region of the human immunodeficiency virus type 1 gp120 glycoprotein critical for interaction with the CD4 receptor. Cell, volume 50 number 6, pages 975-985, 1987.

66. Nygren and others. 95- and 25-kDa fragments of the human immunodeficiency virus envelope glycoprotein gp120 bind to the CD4 receptor. Proceedings of the National Academy of Sciences U. S. A., volume 5number17,pages 6543-6546,1988.

67. Pert, C., and others. Octapeptides deduced from the neuropeptide receptor-like pattern of antigen T4 in brain potently inhibit human immunodeficiency virus receptor binding and T-cell infectivity. Proceedings of the National Academy of Sciences U. S. A., volume 83, pages 9254-9258, December 1986.

68. Pert interview, Science Impact, pp. 6-7, June 1987.Ruff, M., and others. Peptide T[4-8] is core HIV envelope sequence required for CD4 receptor attachment.Lancet,2(8561),page751,Sept.26,1987.

69. Sodroski, J., and others. HIV envelope-CD4 interaction not inhibited by synthetic octapeptides. Lancet, 1(8547), pages 1428-1429, June 20, 1987.

70. Wetterberg, L., and others. Treatment with peptide T in seven immunodepressed HIV infected patients. Draft of paper submitted to AIDS, Gower Academy Journal, London, June, 1988.

71. Wetterberg, L., and others. Peptide T in treatment of AIDS. The Lancet, 1(8525), page 159, Jan. 17, 1987.

72. Granitov, VM et al…Usage of RECEPTOL® in treatment of HIV – Infected patients. Russian Journal of HIV AIDS and Related Problems 2002, 1, 79-80.

73. World Health Organization. Progress on global access to HIV antiretroviral therapy: a report on "3 by 5" and beyond. 2006.

74. Lawrence HS, Borkowsky W: TRANSFER FACTOR: current status and future prospects. Biotherapy 9:1-5, 1996

75. Dr. Olle Hernell, At the University of Ulmea, Sweden; Science, www.nextdimension.org, 4 Aug 1999

76. Dr. Bocci, Bremen, Corradeschi, Luzzi and Paulesu; Journal Biology

77. Boesman – Finkelstein M, Finkelstein R, Lancet, 1989, 2:1336

78. Dicchtemuller W, Lissner R, J. Clin. Bio. Chem., 1990, 28:19-23

79. Ogra SS, Ogra P.L., J. Pediatr, 1978, 92:546-549

80. Szaniszlo, P; German, P; Hajas, G; Saenz, D; Woodberry, M; Kruzel, M; Boldogh, I, International Immunopharmacology , 2009, 9 (2): 181–93.

81. Bacsi, A; Woodberry, M; Kruzel, M; Boldogh, I, Neuropeptides, 2007, 41 (2): 93–101