NewalR&D

Ezrin Peptide Pharmaceuticals control Immunology & Inflammation

Products for Infection Protection, Treatment of Chronic Inflammation & Healthy Aging

Dr Rupert Holms, CEO, Inventor, Founder: rupertholms@newalrnd.com, www.newalrnd.com

NewalR&D Management

Dr Rupert Holms

- Founder & CEO of NewalR&D Ltd,
  (inventor of ezrin peptide pharmaceuticals)
- Dr Holms has already founded two successful biomedical businesses
- Nearmedic in Moscow, a ~ £120 million immune-pharmaceutical business
- hVIVO PLC in London, a ~£70 million drug screening and clinical trial business

(~£200 million LSE market cap)

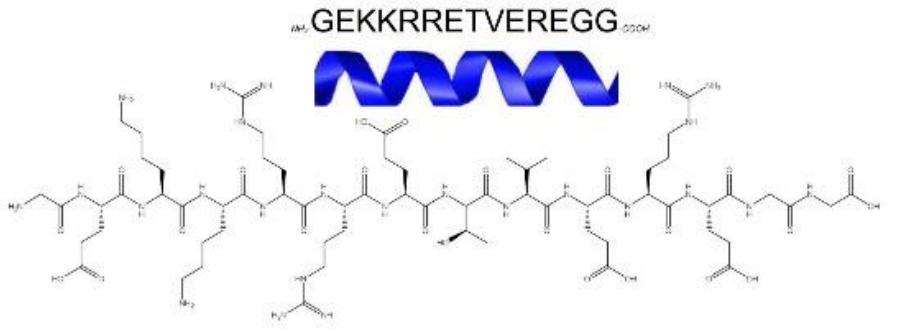
Dr John Abeles

- Chairman of NewalR&D Ltd
- Biotech founder and financier based in New York, responsible for multiple start-ups and successful exits via IPOs or corporate acquisitions
- Joined the board to assist with new capital and corporate connections in USA.

Immunology & Inflammation
Big Disease Problems, Big Markets

- The immunology & inflammation treatment market is surging, forecast to grow to $257 billion by 2032.
- https://www.fortunebusinessinsights.com/industry-reports/immunology-market-100657
- Sex infection is at an all-time high, respiratory infection is growing rapidly, acute & long COVID is still with us, there are risks of a new type of dangerous influenza, and super-bugs with anti-microbial-resistance (AMR) are evolving.
- Age related inflammatory disease is increasing as the population ages.
- There is a growing market for healthy aging and longevity products.

The Ezrin Peptide Solution



- Ezrin peptides are SAFE
- IMPROVE natural adaptive immune amplification
- SUPPRESS chronic expression of inflammatory cytokines
- STOP age-related inflammatory diseases
- Ezrin peptides can treat ANY infection
  (Viral, Bacterial, Fungal or Protozoan)
- STOP sex infections & respiratory infections
- Ezrin peptide products are protected by patents world-wide

Newal R&D
Chance of a BIG WIN

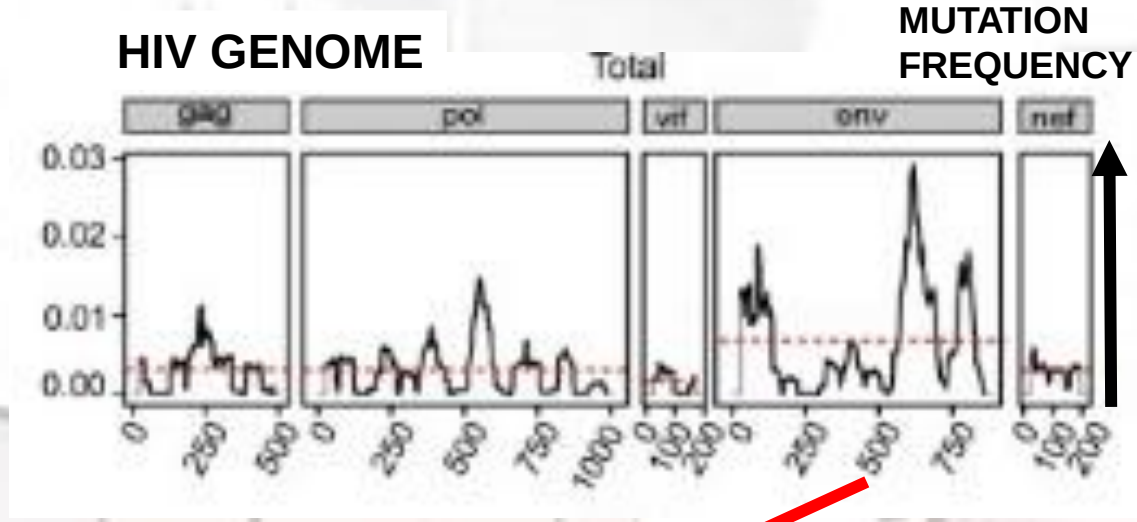
- Ezrin peptide efficacy in chronic inflammatory diseases:
- Inflammatory spine diseases (e.g. ankylosing spondylitis)
- Inflammatory bowel diseases (e.g. ulcerative colitis)
- Inflammatory heart diseases (e.g. myocarditis)
- Inflammatory brain diseases (e.g. Long COVID “brain fog”)
- Ankylosing spondylitis and ulcerative colitis are due to weak FOXO3 activity.
- Ezrin peptide activation of FOXO3 could also lead to healthy aging, health-span extension and longevity
- Investors in NewalR&D have a chance of a $ billion+ exit

NewalR&D
Technical Presentation

The origin of Ezrin Peptide Technology

Ezrin Peptide Technology

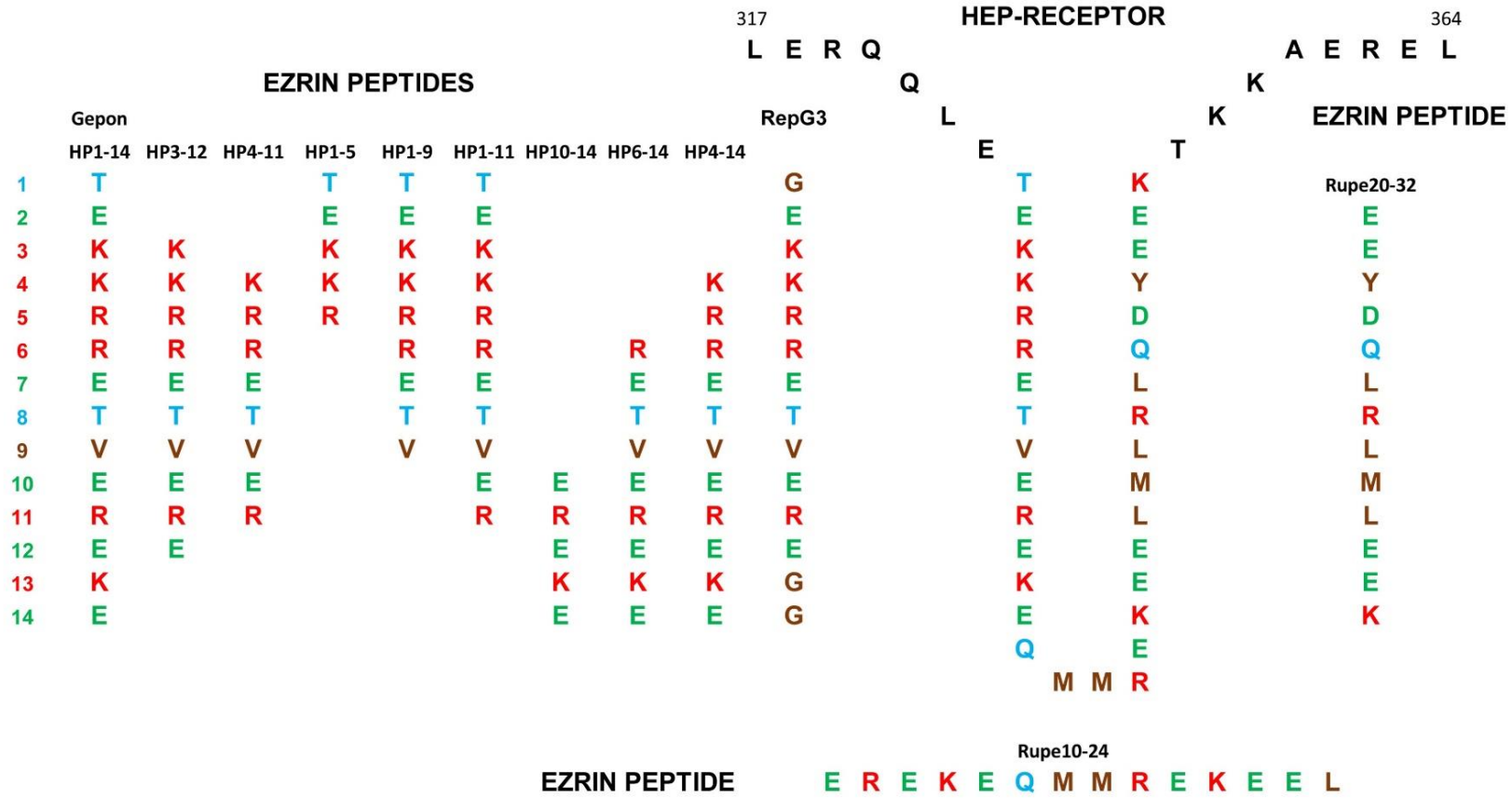
- In 1994 Dr Holms discovered that the mutation-stable C-terminus of HIV gp120, mimics the Alpha domain of human ezrin protein.
- Dr Holms invented synthetic peptides mimicking this region of ezrin.
- Ezrin peptides are safe and effective immune amplifiers of adaptive B cell and T cell immunity.
- Ezrin Peptides also inhibit pro-inflammatory cytokine expression.
- An ezrin peptide product is already sold in one national market.



HIV-1 [HV1EL]	497	498	499	500	501	502	503		504	505	506	507	508	509	C term
gp120 C-term	T	K	A	K	R	R	V	_	V	E	R	E	K	R	13aa
Side Chain Charge		+		+	+	+				-	+	-	+	+	
Matches	x			x	x	x			x	x	x	x	x	9 of 13	69%
Side Chain Charge		-	+	+	+	+	-			-	+	-	+	-	
EZRIN Alpha	T	E	K	K	R	R	E	T	V	E	R	E	K	E	14aa
[HUMAN]	324	325	326	327	328	329	330	331	332	333	334	335	336	337	

Generation of Ezrin Peptides

SPECTRUM OF EZRIN HEP-RECEPTOR PEPTIDES INVESTIGATED



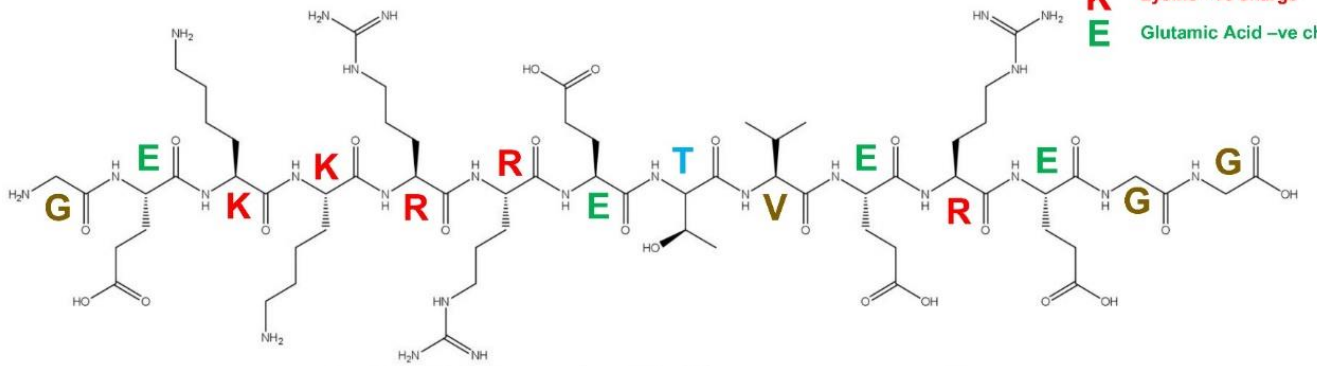
AMINO ACID PROPERTIES

Hydrophobic	A	C	F	G	I	L	M	P	V	W	Y
Polar uncharged	S	T	N	Q							
Polar charged+ve	R	K	H								
Polar charged-ve	D	E									

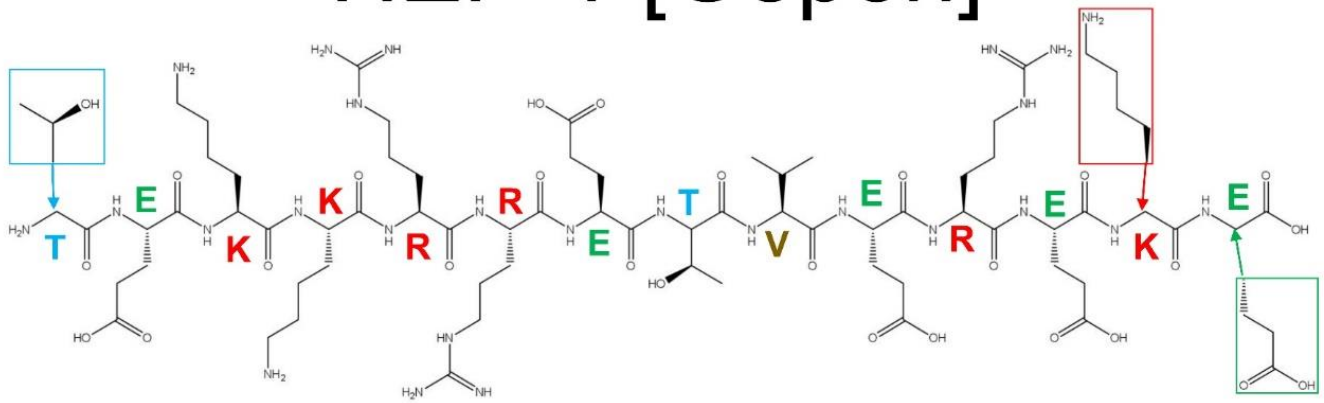
Regulatory Ezrin Peptide Glycine 3 (RepG3)
derived from Human Ezrin Peptide 1 (HEP1)

RepG3

G Glycine non polar no charge
V Valine non polar no charge
T Threonine polar no charge
R Arginine +ve charge
K Lysine +ve charge
E Glutamic Acid –ve charge



HEP-1 [Gepon]



Cell Signalling Induced by Ezrin Peptides

HEP1 [TEKKRRETVEREKE] activation of an NK cell line

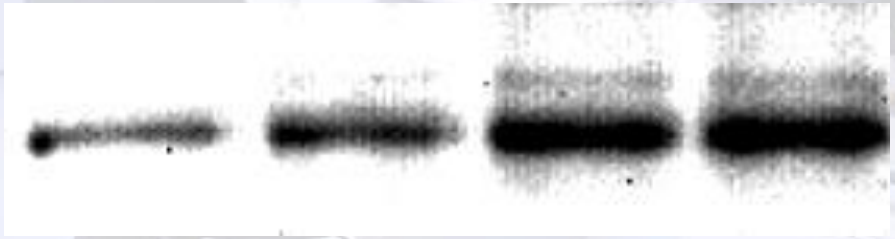
HEP1 activation of phosphorylated pERK in an NK cell line, shows an approximately linear dose dependence between 25 μg/ml to 500 μg/ml [micrograms per ml]

Phosphorylated pERK

HEP1 μg/ml 25 75 250 500 zero

The time course of HEP1 activation of phosphorylated pERK in an NK cell line, shows increasing pERK from zero to 30 minutes, at an HEP1 concentration of 75 μg/ml [micrograms per ml]
Activation peak at 30 minutes.

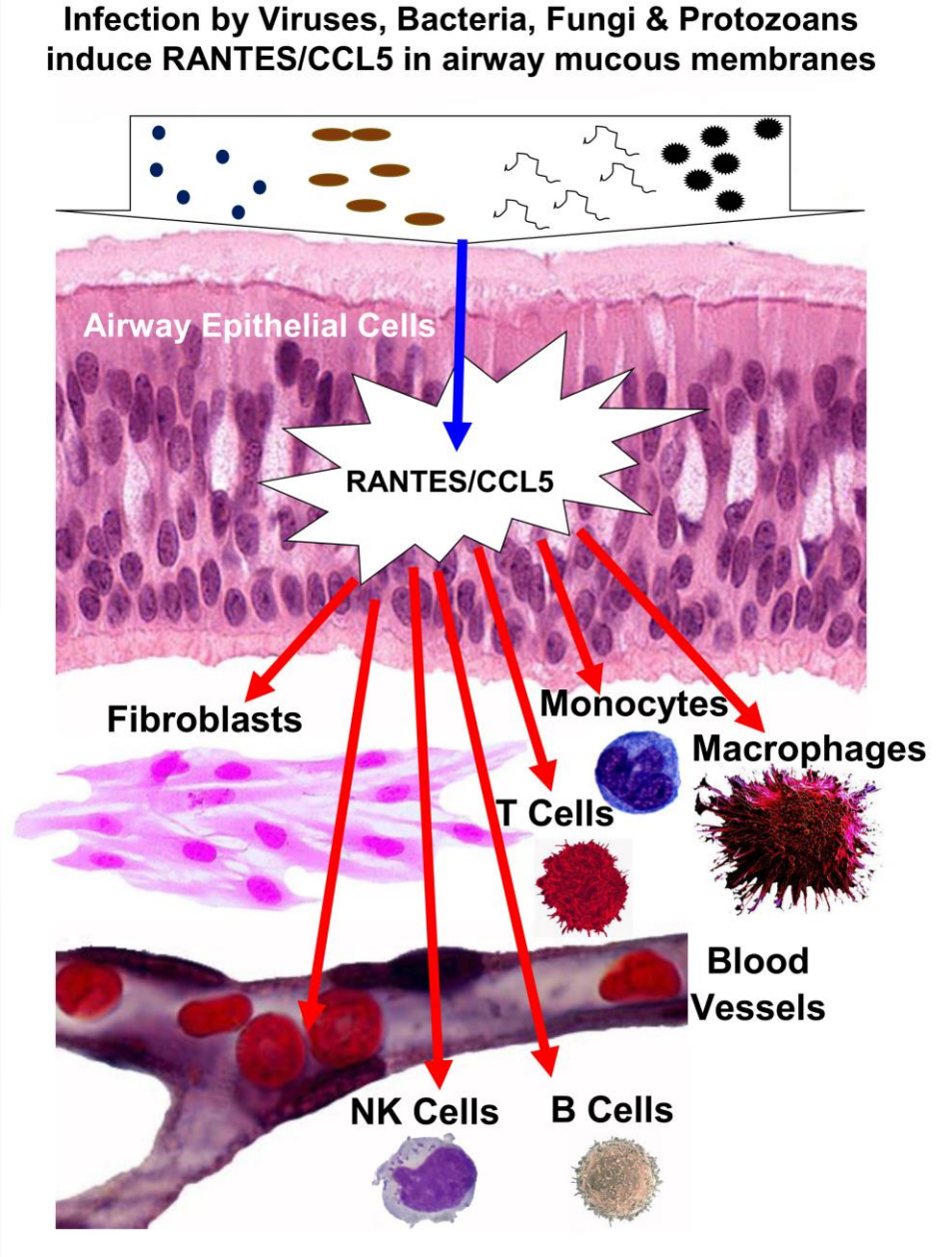
Phosphorylated pERK

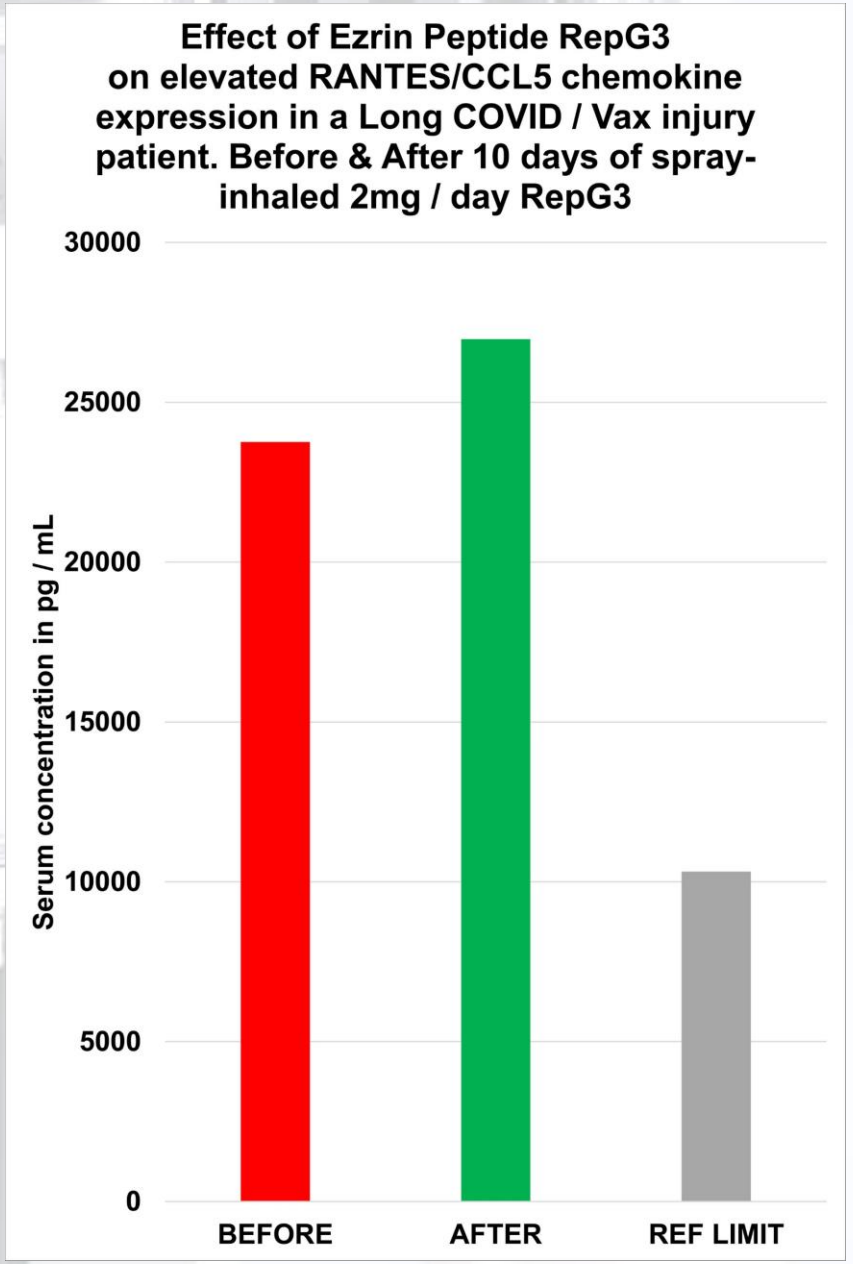


Minutes ZERO 5 15 30

HEP1 75 μg/ml

Ezrin Peptides induce RANTES / CCL5





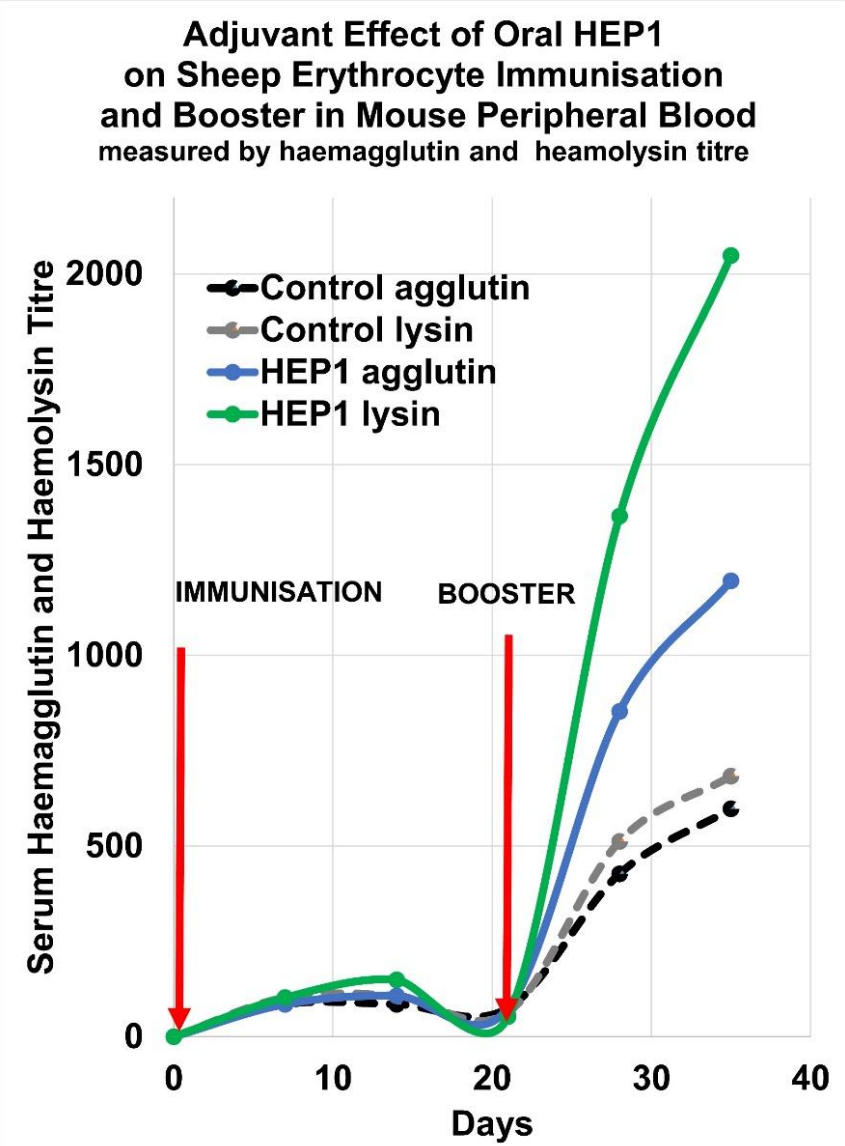
Human Ezrin Peptide One (Gepon)

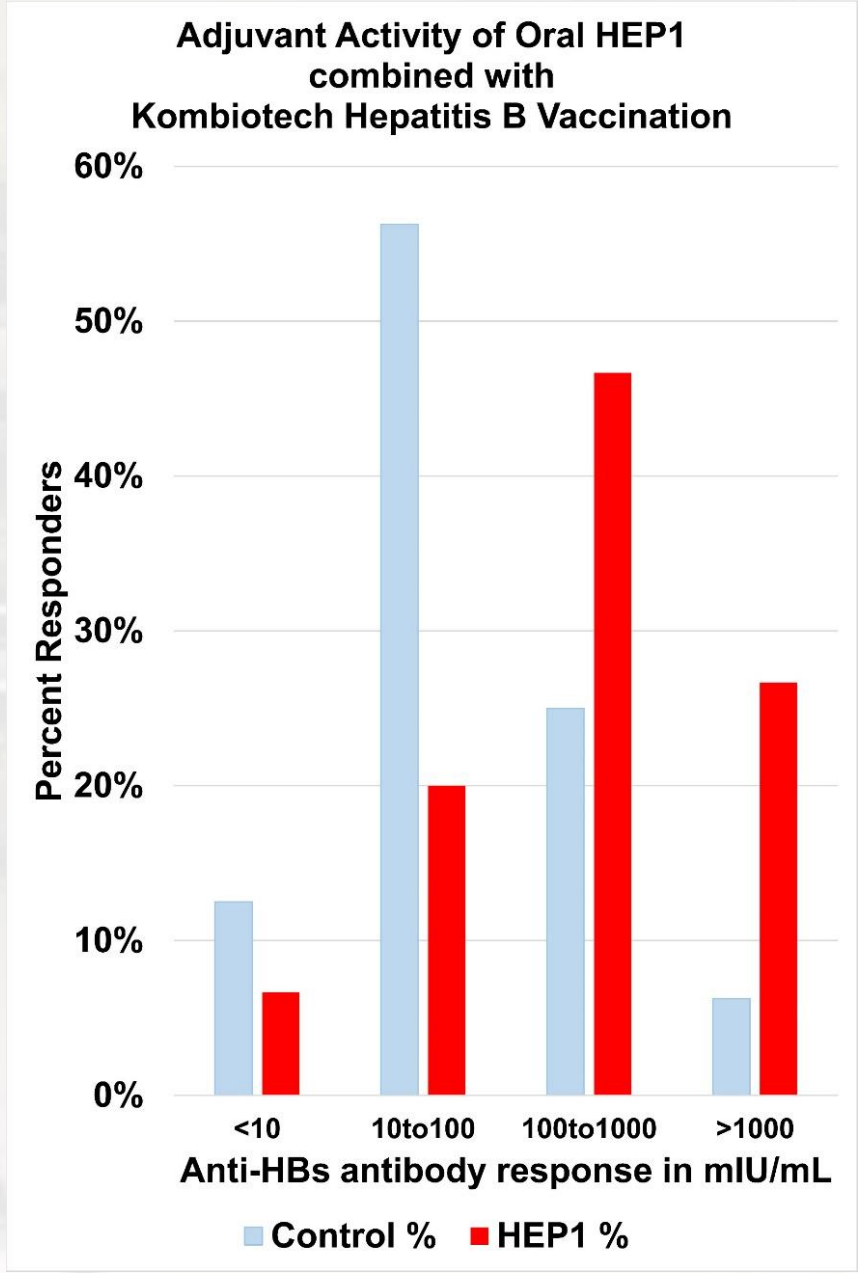
- Human Ezrin Peptide One, HEP-1 (Brand name “Gepon”).
- Treatment of STIs: Candida, Chlamydia, Herpes, HPV, Syphilis.
- Treatment of Hepatitis (HepA HepB and HCV).
- Treatment of Stomach & Duodenal Ulcers and Ulcerative Colitis.
- Treatment of Influenza and COVID.

Human Ezrin Peptide One (Gepon)

- **Medical Claims**
- Immuno-modulating and antiviral activity:
- Increases activity and number of CD4+ T cells and NK cells
- Mobilizes and activates Macrophages
- Increases activity of neutrophils and CD8+ T of cells
- Stimulates production of alpha- and beta- interferons
- Anti-Inflammatory: inhibits IL-1b, IL-6, IL-8 and TNFa cytokines
- Stimulates the production of antibodies against infections
- Induces protection from bacteria, viruses, fungi and protozoans

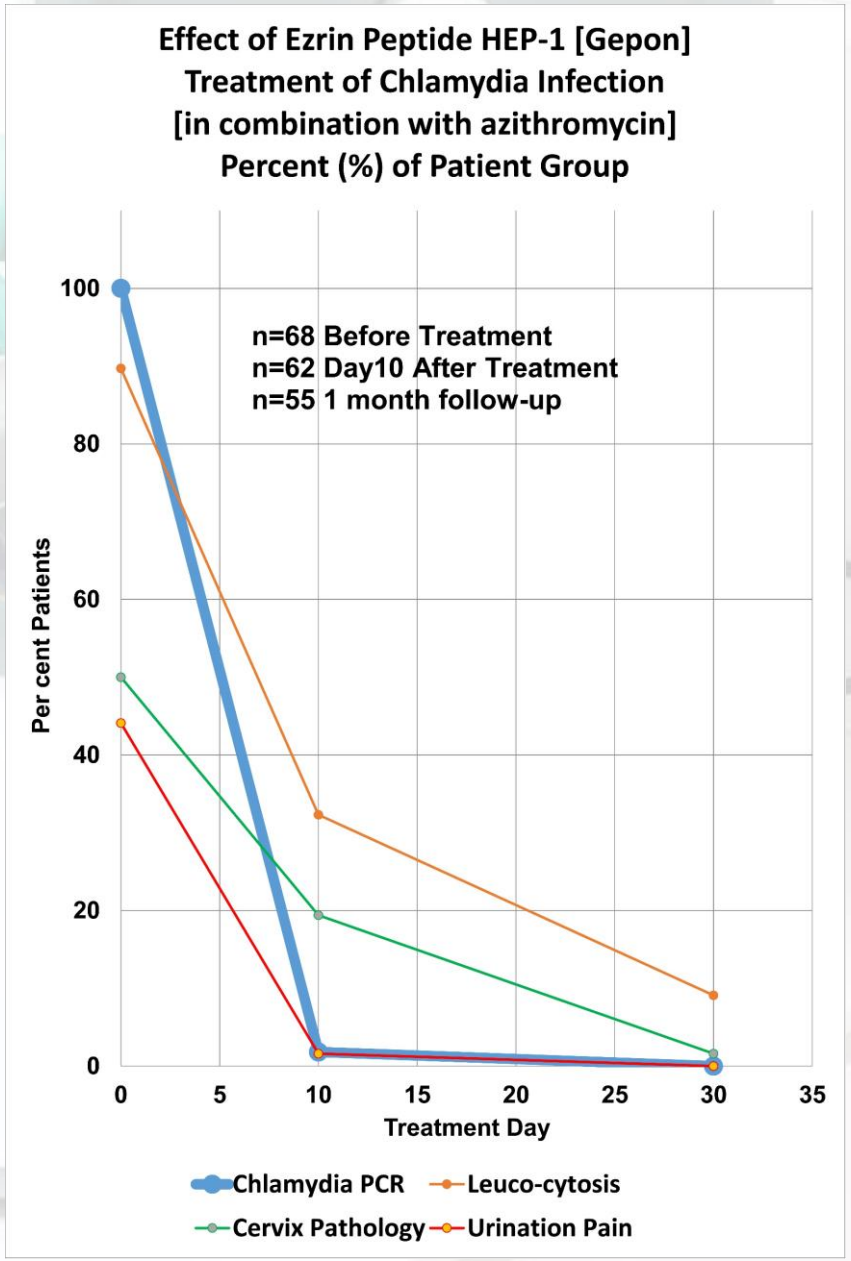
Amplification of T cell & B cell responses





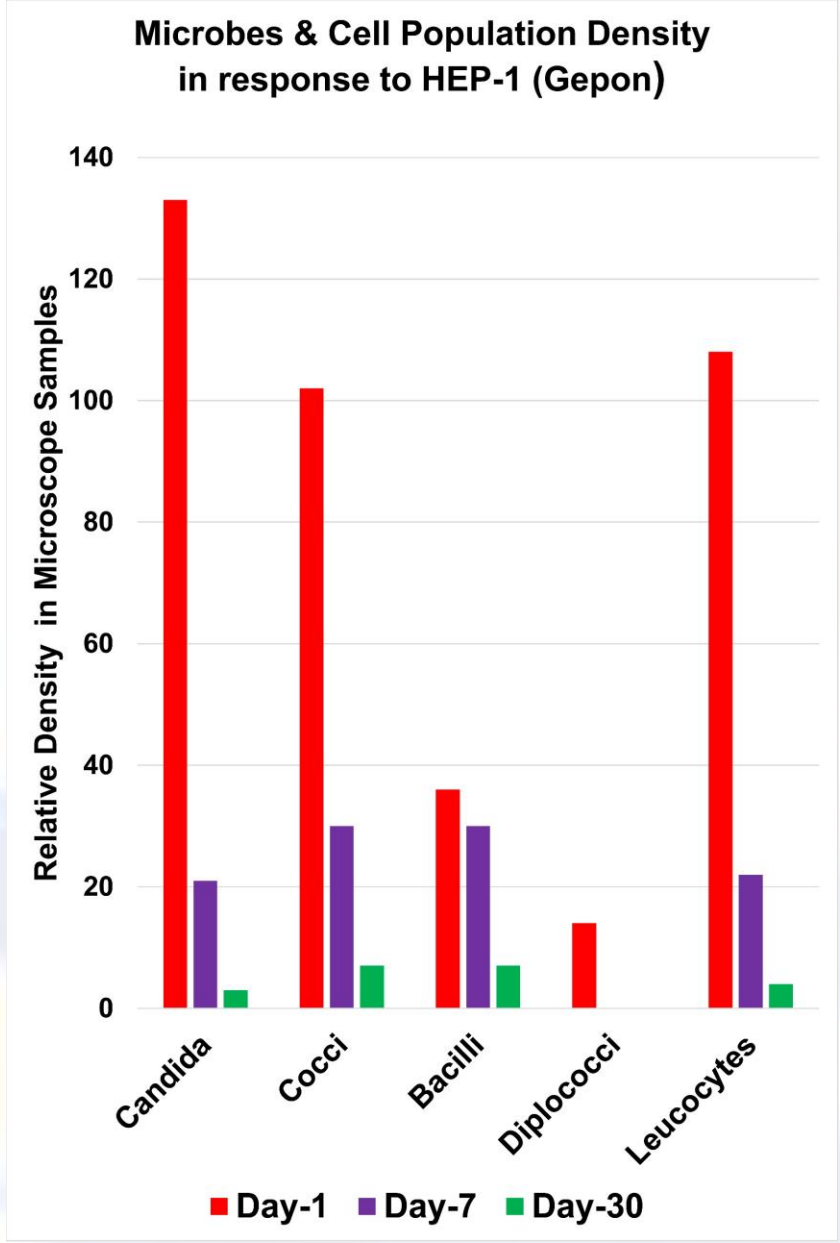
Ezrin Peptide Treatment of Chlamydia

- 68 Women: antibiotic treatment failures
- In One Day: Pain Stopped
- In One Week: Chlamydia infection gone in 98% of patients
- Itch and discharge gone in 97% of patients
- Leuco-cytosis gone in 73% of patients
- No Side Effects



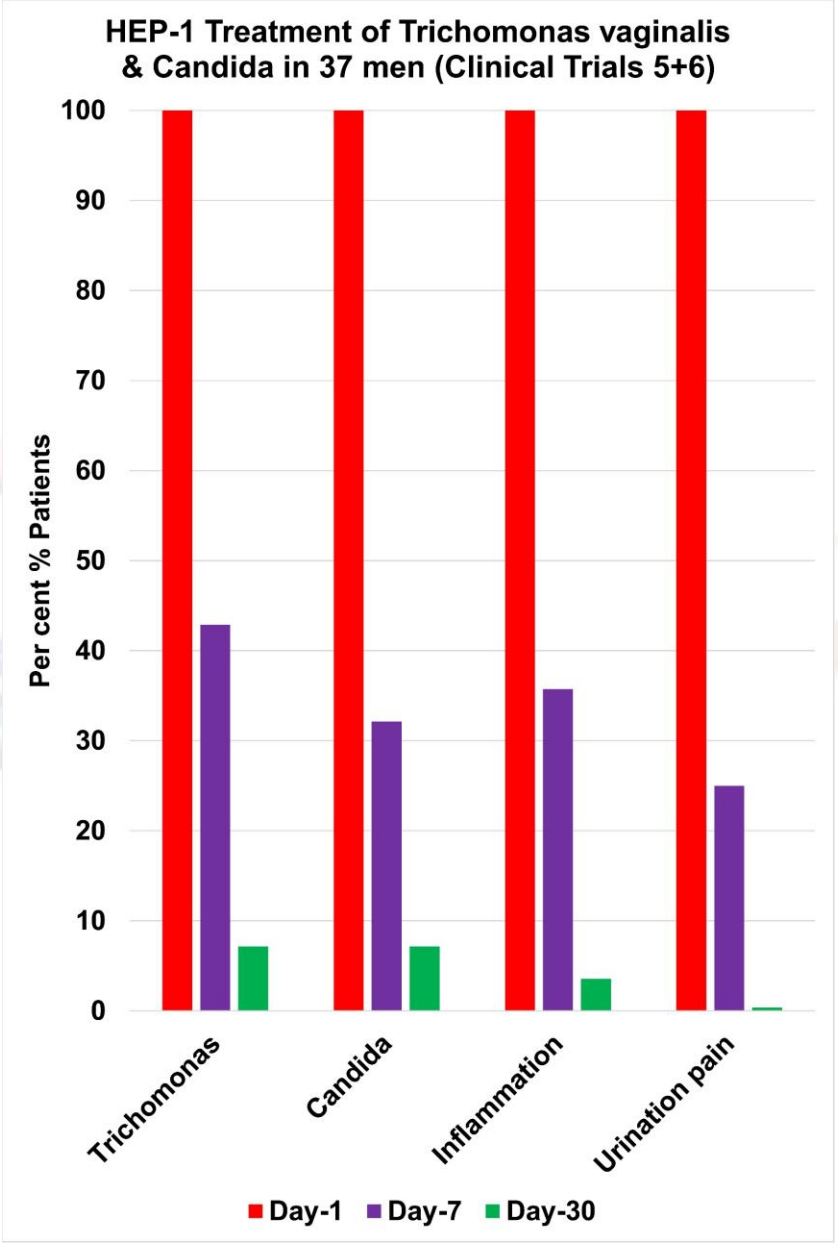
Treatment of Fungi & Bacteria

- 25 women with chronic candida and bacterial infection who were non-responsive to anti-fungal treatment
- In One Day of ezrin peptide therapy NO Inflammation
- In One Week, NO fungal infection in 92% of patients
- Cocci & Baccilli substantially reduced
- NO side effects
- NO relapse in the following months

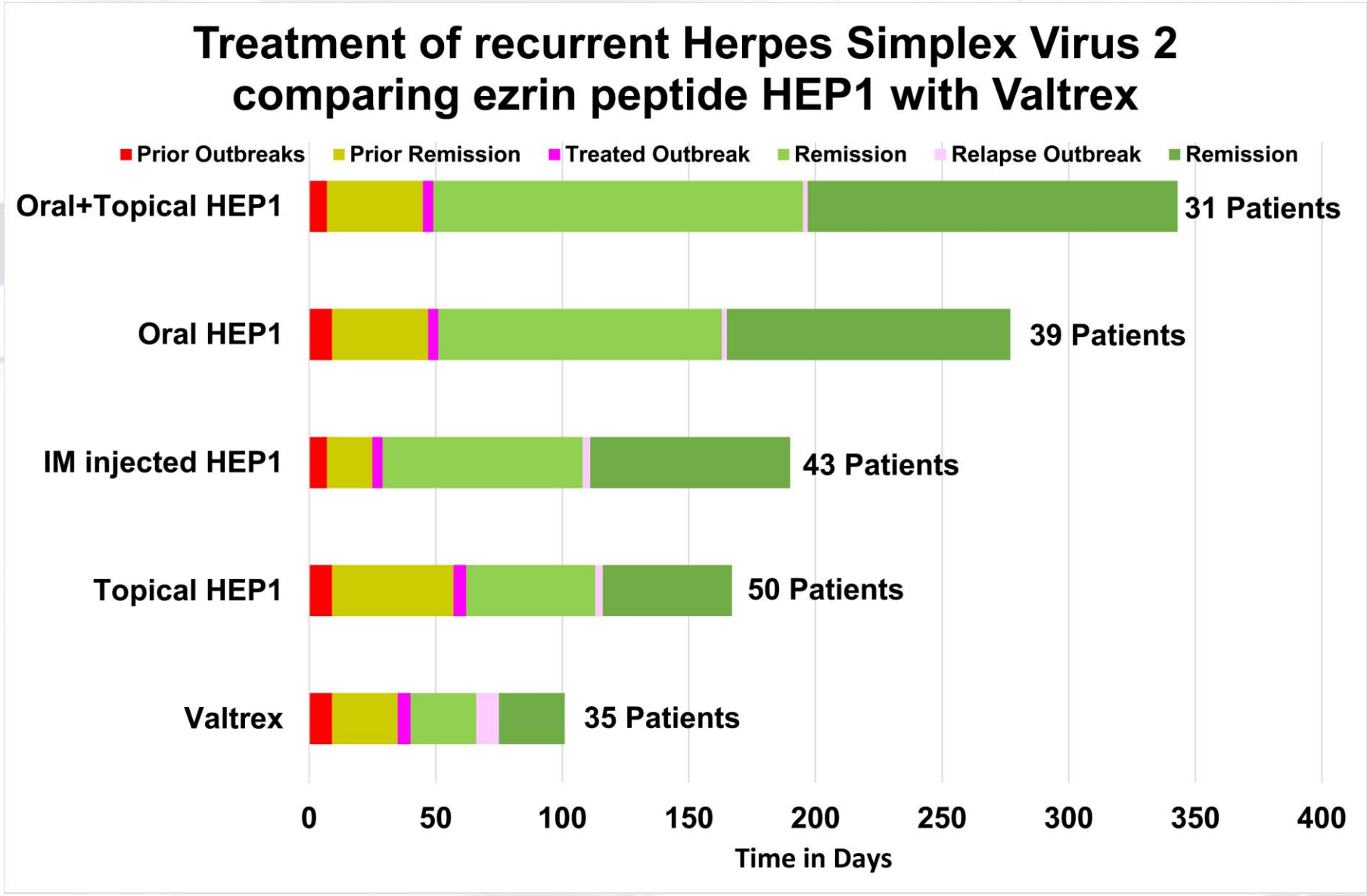


Treatment of Protozoan Trichomonas

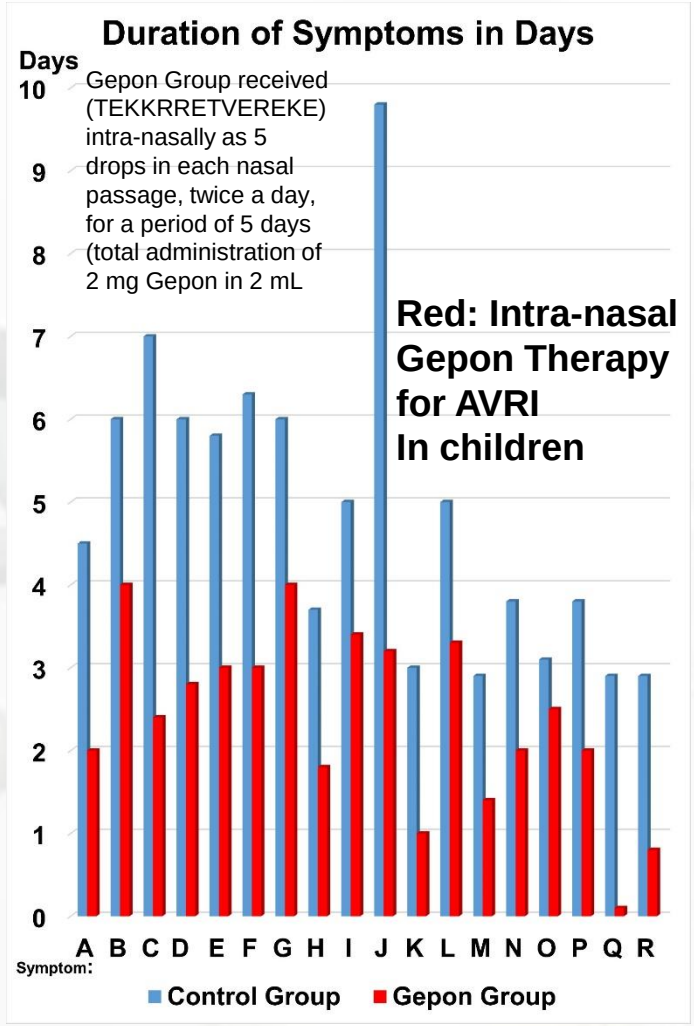
- Trichomonas vaginalis is a protozoan parasite
- >11% of STIs world-wide
- Big problem with drug resistance
- Ezrin peptide therapy induces massive lysis and death of trichomonas
- Trichomonas and Candida co-infection eliminated in 35 men
  (2 non-responders)



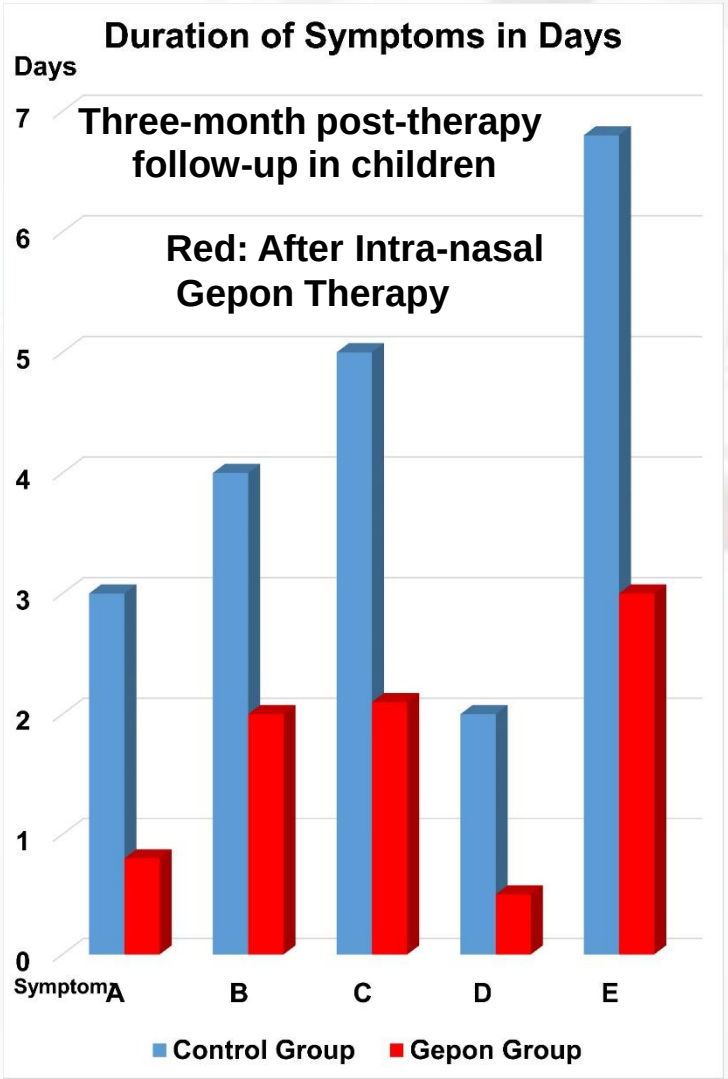
Treatment of Sexually Transmitted Herpes



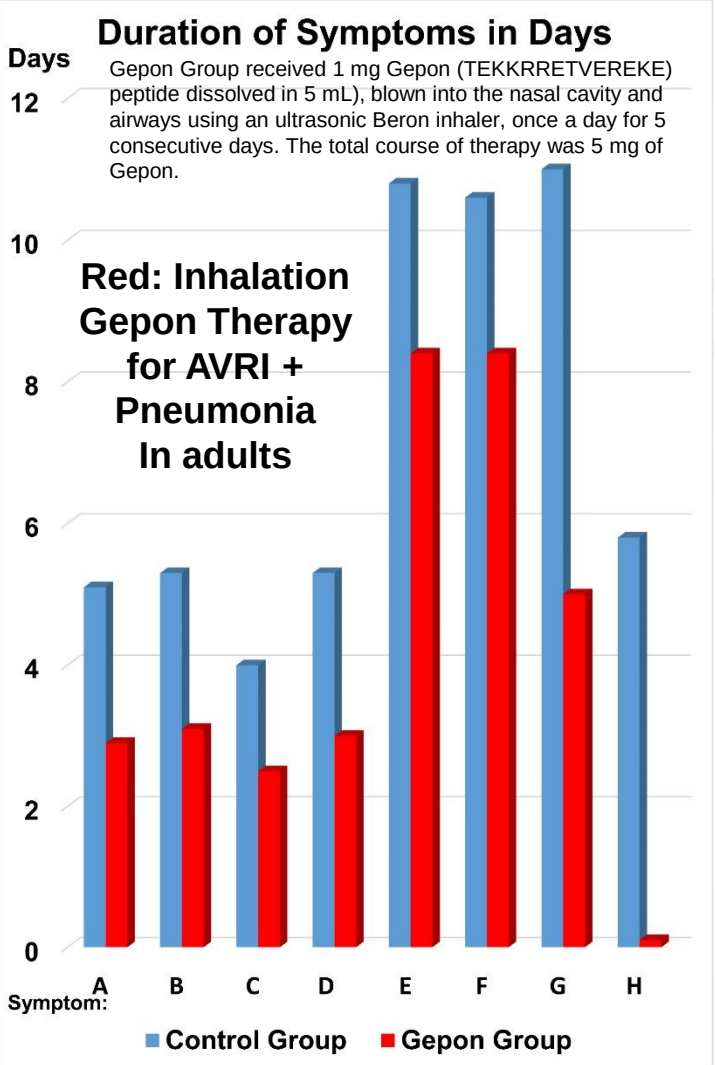
HEP1 vs Acute Viral Respiratory Disease



Control Group *n* = 50 (blue) Gepon group *n* = 50 (red). Horizontal divisions in days. Symptoms: A—Fever, B—difficulty in breathing, C—serous rhinitis, D—swelling of nasal mucous membrane, E—hyperaemia of tissues, F—pharyngitis, G—swollen palatine glands, H—hoarseness of voice, I—dry cough, J—moist cough, K—stenosis of larynx, L—swollen neck lymph nodes, M—reduction in the appetite, N—weakness, O—sleepiness, P—reduction in physical activity, Q—conjunctivitis, R—complications.

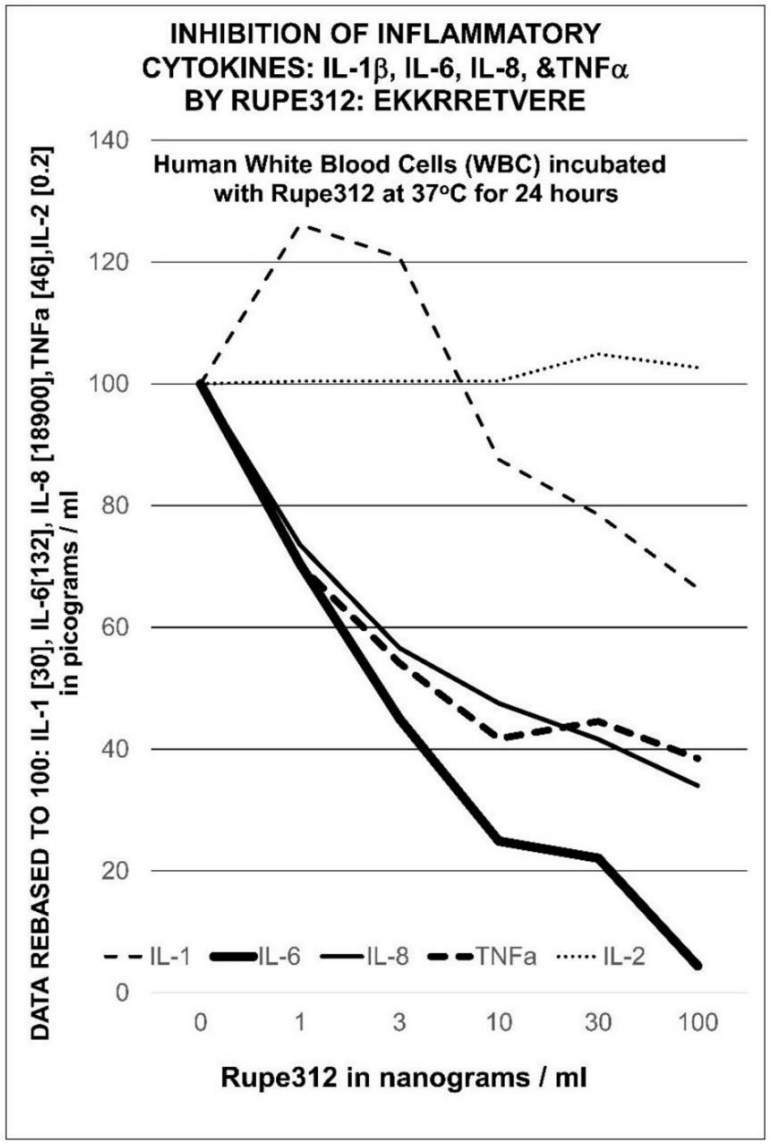


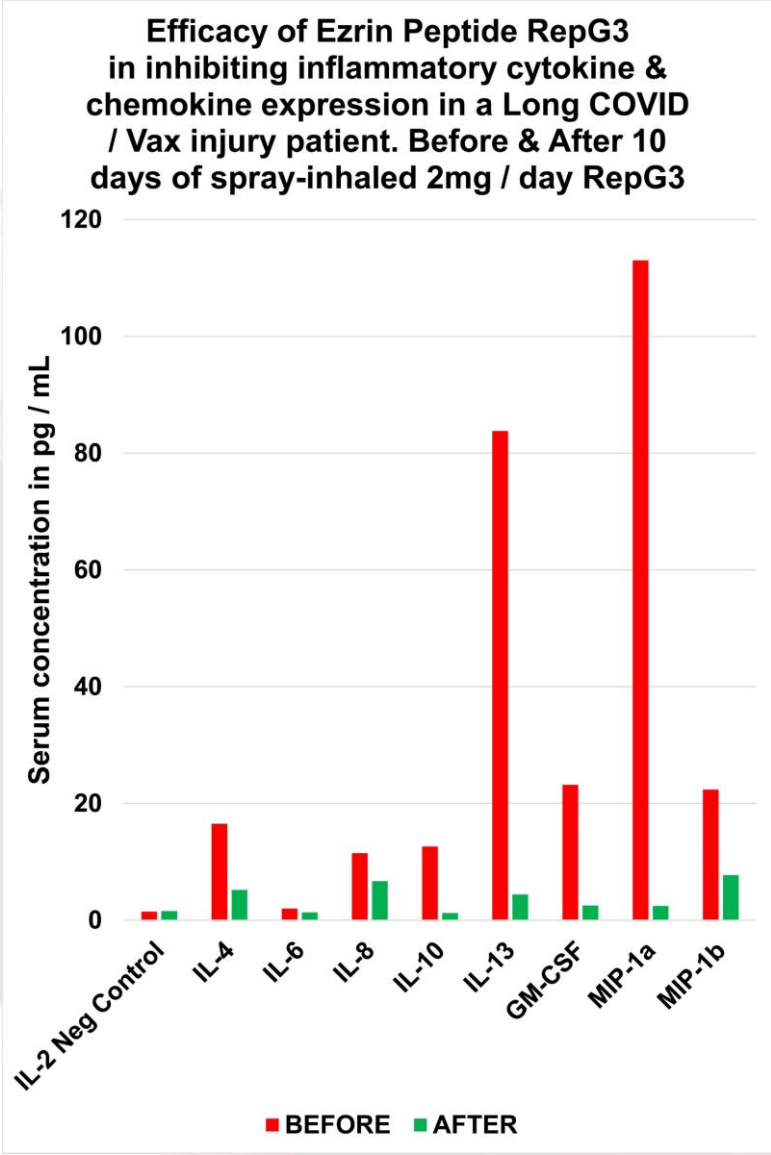
Control Group *n* = 50 (blue). Gepon group *n* = 50 (red). Duration of clinical symptoms in days (horizontal divisions). Symptom: A—Fever, B—Rhinitis, C—Wet-Cough, D—Antibiotics, E—AVRI



Patients with acute viral respiratory infection and pneumonia. Symptoms: A—fever, B—intoxication, C—headache, D—weakness, E—inflamed tonsils, F—mucosal hyperaemia, G—swollen lymphnode and H—purulent stomatitis

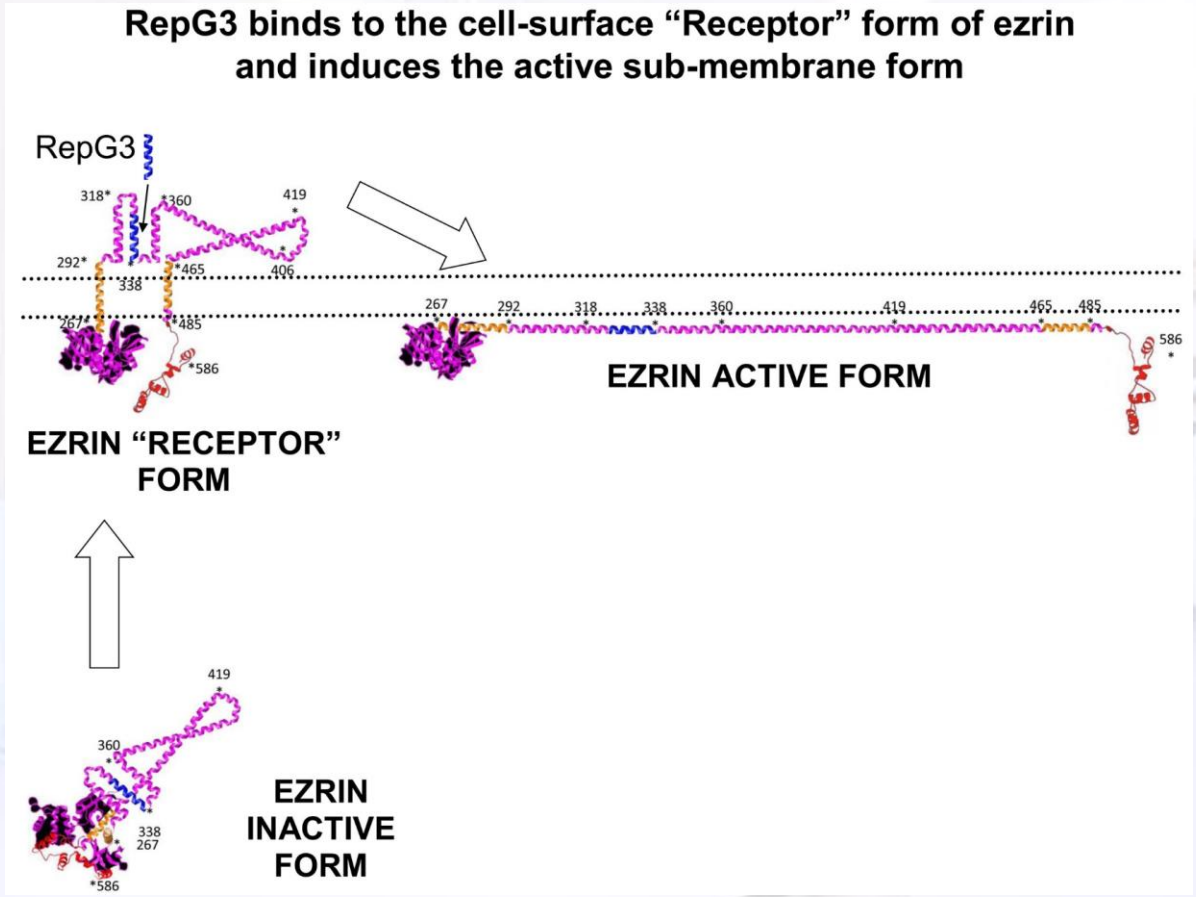
Ezrin Peptides are Anti-inflammatory

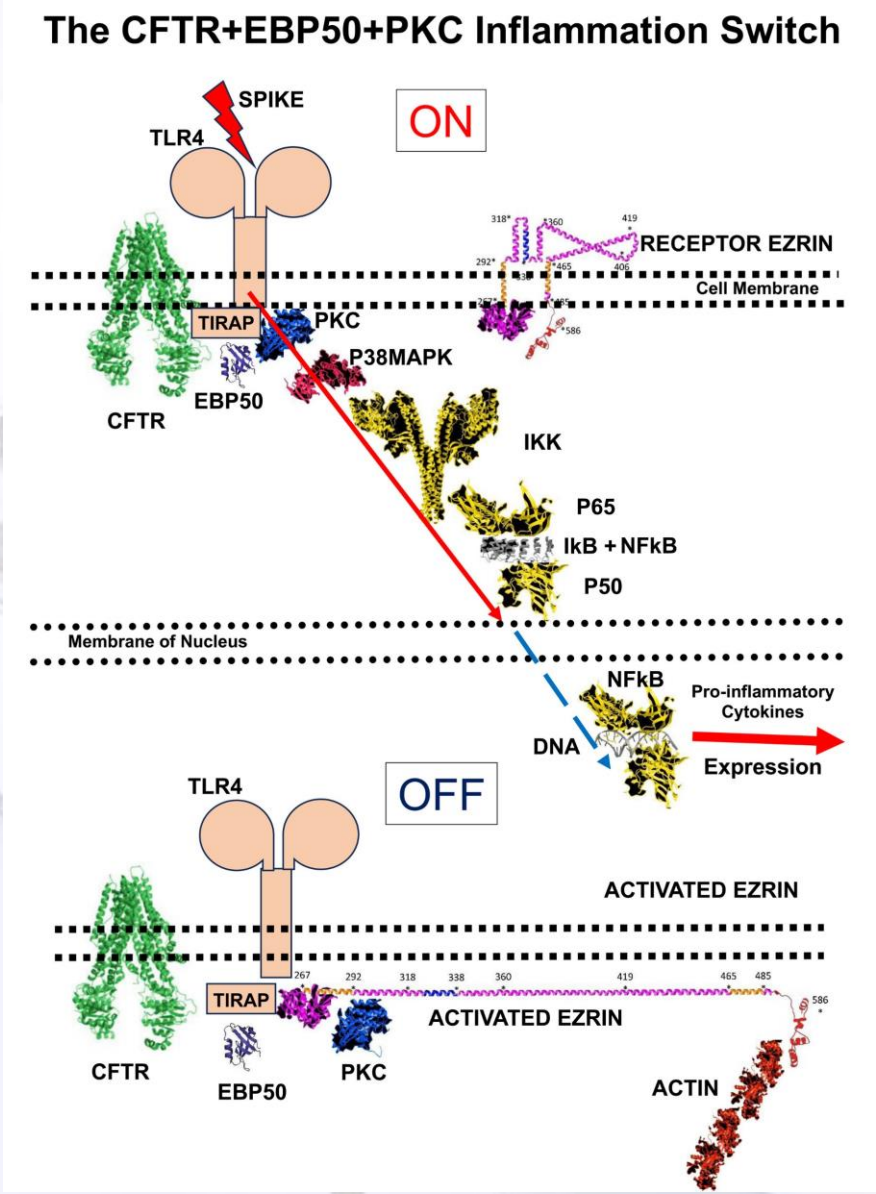




Anti-inflammatory Mechanism

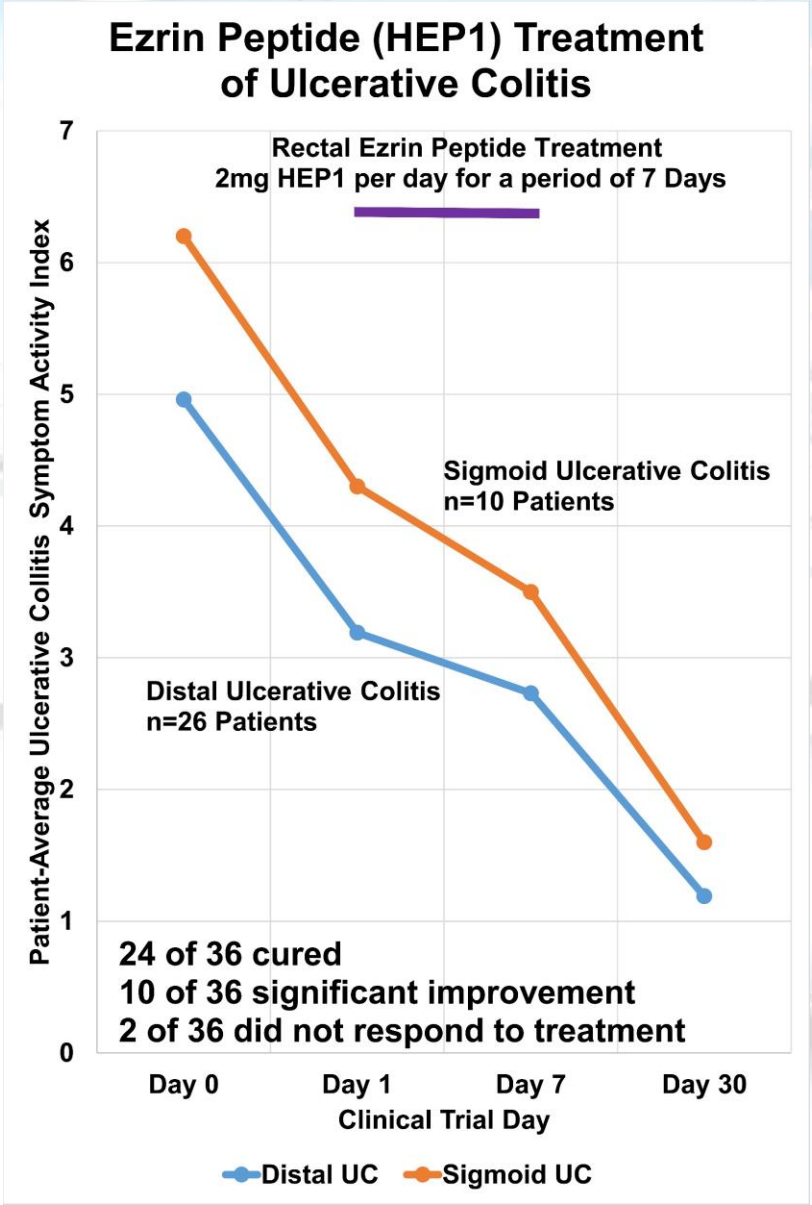
RegG3 targets cell-surface "Receptor" conformation of ezrin





Ezrin Peptides cure Ulcerative Colitis

- Ulcerative Colitis treatment using once-a-day 2mg ezrin peptide HEP1 solution delivered intra-rectally for 7 days, was performed in 36 patients who had failed to respond to all other forms of treatment.
- HEP1 cured 24 of 36 patients suffering Ulcerative Colitis (UC) in less than 30 days. In addition, another 10 of these patients enjoyed significant improvement.
- In total, a 94% treatment success rate.
- Similar IBD results have been obtained in Long COVID patient / vaccine injury patients with co-morbidities, using 2mg ezrin peptide RepG3 solution spray-inhaled daily.



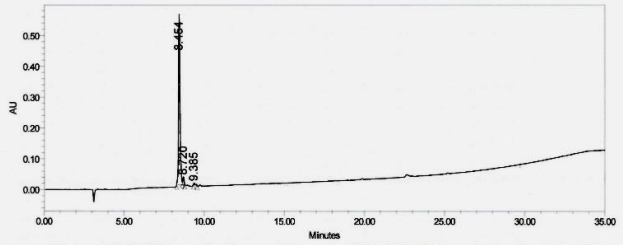
High Quality RepG3 Peptide Manufactured in the UK [GMP]

PEPCEUTICALS

Reported by User: Kamal Badiani (KB01)

SAMPLE INFORMATION

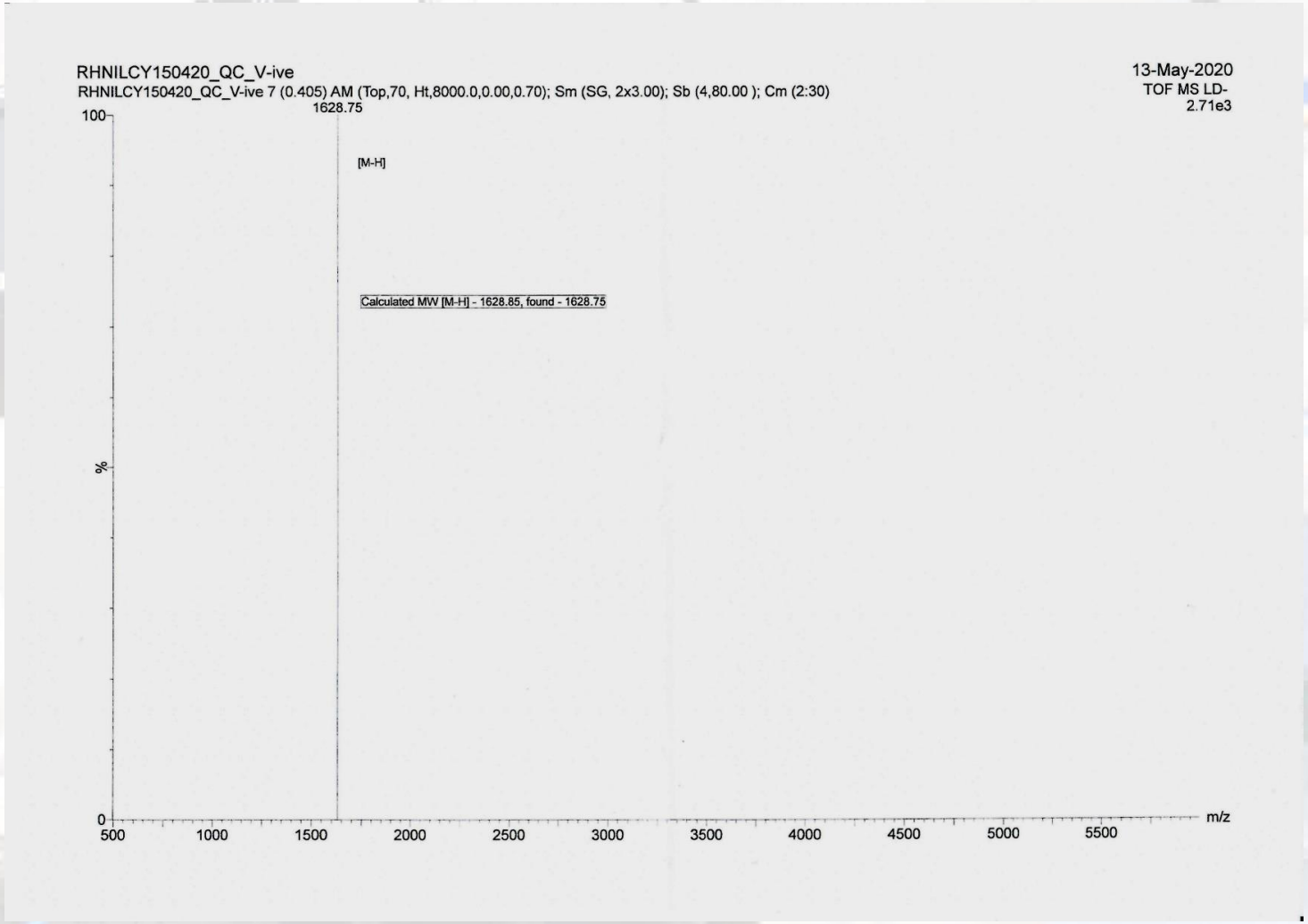
Sample Name:	RHNIL-CY150420_QC	Acquired By:	KB01
Sample Type:	Unknown	Date Acquired:	Wednesday, May 13, 2020
Vial:	2	Acq. Method Set:	SOPAN004_1 no temperature
Injection #:	1	Date Processed:	Thursday, May 14, 2020 9:44:17
Injection Volume:	15.00 ul	Processing Method	Pepceuticals CofA
Run Time:	35.0 Minutes	Channel Name:	W2996 220.0nm-1.2
Sample Set Name	13MAY20	Proc. Chnl. Descr.:	W2996 PDA 220.0 nm at 1.2



Channel W2996 220.0nm-1.2; Processed Channel: W2996 PDA 220.0 nm at 1.2; Result Id: 1605; Processing Method: Pepceuticals CofA

	RT	Area	% Area	Height
1	8.454	3475781	95.35	549112
2	8.720	128985	3.54	24853
3	9.385	40505	1.11	6353

Report Method: PEPCEUTICALS Printed 9:44:37 AM Thursday, May 14, 2020 Page: 1 of 1



PATENTS

"Ezrin-Derived Peptides and Pharmaceutical Compositions Thereof"

Granted Patents [Expire 01/06/2036]

AMERICAS

United States of America, Canada, Mexico, Brazil

EUROPE

Albania, Austria, Belgium, Bosnia & Herzegovina, Bulgaria, Croatia, Cyprus, Czech, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Moldova, Monaco, Montenegro Netherlands, San Marino, Serbia North Macedonia, Norway, Poland, Portugal, Romania, Sweden, Switzerland, Turkey, Slovenia, Spain, Slovakia and United Kingdom.

SE ASIA & AUSTRALIA

Malaysia, Singapore

Indonesia, Australia, New Zealand

RUSSIA, CHINA, JAPAN, KOREA

Russian Federation, China, Hong Kong, Japan, Korea

AFRICA

Morocco, South Africa

PATENTABLE Generation-4 Ezrin Peptides new IP to 2043 and beyond

Some Ezrin Peptide Publications

International Journal of Molecular Sciences

MDPI

Review

Ezrin Peptide Therapy from HIV to COVID: Inhibition of Inflammation and Amplification of Adaptive Anti-Viral Immunity

Rupert D. Holms [1,*] and Ravshan I. Ataullakhanov [2]

[1] Newal R&D Ltd., London NW1 7SX, UK
[2] Institute of Immunology, Ministry of Health of the Russian Federation, 115478 Moscow, Russia; ravshan.ataullakhanov@gmail.com
* Correspondence: drrupertholms@googlemail.com; Tel.: +44-780-304-2576

Abstract: Human Ezrin Peptides (HEPs) are inhibitors of expression of IL-6 and other inflammatory cytokines, amplifiers of adaptive B cell and T cell immunity and enhancers of tissue repair. The mutation stable C-terminus of HIV gp120, mimics 69% of the "Hep-receptor", a zipped α-helical structure in the middle of the α domain of human ezrin protein. Synthetic peptides homologous to the Hep-receptor of ezrin of five to fourteen amino acids, activate anti-viral immunity against a wide range of viruses (HIV, HCV, herpes, HPV, influenza and other human respiratory viruses). Human Ezrin Peptide One (HEP1) TEKKRRETVERKE (brand name Gepon, registered for human use in Russia from 2001) is a successful treatment for opportunistic infections in HIV-infected patients. That treats HEP1and prevents mucosal candidiasis, herpes zoster outbreaks and infection-induced chronic diarrhea. There are clinical publications in Russian on the successful treatments of chronic recurrent vaginal candidiasis, acute and chronic enterocolitis and dysbacteriosis, which are accompanied by normalization of the mucosal microbiome, and the decline or disappearance of inflammation. HEP1 is also an effective treatment and prevention for recurrent inflammation and ulceration in the stomach, duodenum and colon. HEP1 and RepG3 GEKKRRETVERKGG (a derivative of HEP1) have been used successfully as an inhaled spray peptide solution to treat a small number of human volunteers with mild-to-moderate COVID, resulting from SARS-CoV-2 infection, based on earlier successes in treating acute viral respiratory disease with inflammatory complications. Ezrin peptides seem to correct a dysregulation of innate immune responses to SARS-CoV-2. They are also adjuvants of B cell adaptive immunity and increase antibody titres, resulting in protection from lethal virus infection of mice. In a clinical study in Moscow, orally administered HEP1 was shown to enhance antibody-titres produced in response to hepatitis B vaccination. These very preliminary but promising results with ezrin peptide treatment of COVID must be replicated in large-scale randomised placebo controlled clinical studies, to be verified.

Keywords: COVID; ezrin peptides; therapy

Citation: Holms, R.D.; Ataullakhanov, R.I. Ezrin Peptide Therapy from HIV to COVID: Inhibition of Inflammation and Amplification of Adaptive Anti-Viral Immunity. *Int. J. Mol. Sci.* **2021**, *22*, 11688. https://doi.org/10.3390/ijms222111688

Academic Editors: Cristina Martínez-Vilalvarez and Blanca Hernández-Ledesma

Received: 30 August 2021
Accepted: 25 October 2021
Published: 28 October 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

1.1. Treatment of COVID and Prevention of SARS-CoV-2 Reinfection

There is a great need for a safe, effective, cheap and reliable therapy for acute and chronic COVID disease induced by SARS-CoV-2 infection. It is well established that high levels of inflammation and IL-6 expression in response to SARS-CoV-2 infection predicts severe COVID-19 and death [1–3]. It has also been demonstrated that 2019 SARS-CoV-2 spike protein subunit 1 (CoV2-S1) induces high levels of NF-κB activation, production of pro-inflammatory cytokines and epithelial damage in human bronchial epithelial cells [BCi-NS1.1 cell line] [2]. SARS-CoV-2 infection or spike protein expression in human epithelial cells [Huh7.5 and A549 cell lines] inhibits ACE2 expression leading to the induction of AT1

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Review

Long COVID (PASC) Is Maintained by a Self-Sustaining Pro-Inflammatory TLR4/RAGE-Loop of S100A8/A9 > TLR4/RAGE Signalling, Inducing Chronic Expression of IL-1b, IL-6 and TNFa: Anti-Inflammatory Ezrin Peptides as Potential Therapy

Rupert Donald Holms

Newal R&D Ltd., London NW1 7SX, UK; drrupertholms@googlemail.com; Tel.: +44-780-304-2576

Abstract: Long COVID, also referred to as Post-Acute Sequelae of COVID (PASC), is probably triggered during SARS-CoV-2 infection and acute COVID-19 by SARS-CoV-2 Spike-protein binding and hyper-activating the cell-membrane expressed Receptor for Advance Glycation End-products (mRAGE) and Toll-Like Receptor 4 (TLR4). SARS-CoV-2 infects lung monocytes by Spike binding to mRAGE (not ACE2). During acute COVID-19, high levels of IL-6 hyper-stimulate S100A8/A9 expression and secretion. Although no viral protein nor mRNA can be detected in half of long COVID (PASC) patients, there is a significant elevation of serum levels of IL-1b, IL-6, TNFa, and S100A8/A9. It appears that a pathological pro-inflammatory feedback loop (the TLR4/RAGE-loop) is established during acute COVID-19, which is maintained by S100A8/A9 > RAGE/TLR4 chronic inflammatory signalling, even after SARS-CoV-2 has been cleared from the body. During long COVID/PASC, Ca^{2+}-binding protein S100A8/A9 chronically stimulates TLR4/RAGE signalling to induce chronic expression of IL-1b, IL-6 and TNFa. Secreted IL-6 binds to its IL-6R receptor on the surface of other cells and signals via STAT3 and C/EBPb for more S100A8/A9 expression. Secreted IL-1b binds to its receptor IL-1R on other cells, and signals via NFkB for more mRAGE and TLR4 expression. New S100A8/A9 can bind and activate cell-surface mRAGE and TLR4 to stimulate expression of more IL-1b, IL-6 and TNFa. This process establishes a pathogenic pro-inflammatory TLR4/RAGE-loop: IL-1b ↑ IL-6 > IL-1R ↑ IL-6R > TLR4/mRAGE ↑ S100A8/A9 > IL-1b ↑ IL-6, which generates multi-organ inflammation that persists in the blood vessels, the brain, the liver, the heart, the kidneys, the gut and the musculo-skeletal system, and is responsible for all the complex pathologies associated with long COVID/PASC. Chronic expression of IL-1, IL-6 and TNFa is critical for the maintenance of the TLR4/RAGE-loop and persistence of long COVID/PASC. Ezrin peptides are inhibitors of IL-1, IL-6, IL-8 and TNFa expression, so are now being investigated as potential therapy for long COVID/PASC. There is preliminary anecdotal evidence of symptomatic relief (not confirmed yet by formal clinical trials) from a few long COVID/PASC patient volunteers, after treatment with ezrin peptide therapy.

Keywords: long COVID; PASC; RAGE; TLR4; p38MAPK; IL-1b; IL-6; IL-8; TNFa; S100; S100A8/A9; AGE; HMGB1; ezrin peptide therapy; HEP-1; RepG3

Citation: Holms, R.D. Long COVID (PASC) Is Maintained by a Self-Sustaining Pro-Inflammatory TLR4/RAGE-Loop of S100A8/A9 > TLR4/RAGE Signalling, Inducing Chronic Expression of IL-1b, IL-6 and TNFa: Anti-Inflammatory Ezrin Peptides as Potential Therapy. *Immuno* **2022**, *2*, 512–533. https://doi.org/10.3390/immuno2030033

Academic Editor: Stefano Aquaro

Received: 1 August 2022
Accepted: 5 September 2022
Published: 8 September 2022

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1. Introduction

This review focuses on the possibility of an underlying chronic self-stimulated inflammatory mechanism that causes long COVID and Post-Acute Sequelae of COVID-19 (PASC). Observations in long COVID/PASC patients show significant chronic elevations of serum concentrations of the pro-inflammatory cytokines: Interleukin-1 beta (IL-1b); Interleukin-6 (IL-6); Tumour Necrosis Factor alpha (TNFa); together with Ca^{2+}-binding protein S100A8/A9 and High Mobility Group Box-1 protein (HMGB1). In contrast, viral mRNA and protein is undetectable in half of long COVID/PASC patients. The hypothesis

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Microbes & Immunity

REVIEW ARTICLE

The therapeutic potential of RANTES/CCL5 across diverse infections and its synergistic enhancement by ezrin peptide RepG3 for long COVID

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Abstract

The amplification of anti-infective immunity against a wide spectrum of acute and chronic infections caused by various pathogens is mediated by RANTES/CCL5. This chemokine controls infections caused by viruses, bacteria, fungi, and protozoans. In addition, RANTES/CCL5 exhibits anti-cancer effects by increasing NK-cell activity and targeting tumors. RANTES/CCL5 acts by amplifying antigen-specific immunity on mucosal surfaces, programmed T-cell responses, cytotoxic T lymphocytes (CTL), B-cell activation, and antibody production. RANTES/CCL5 exerts its effects by binding to C-C receptors, thereby triggering JAK/STAT signaling and inducing the migration of lymphocytes, NK cells, and monocytes. In the brain, RANTES/CCL5 activates astrocytes and upregulates anti-inflammatory interleukin (IL)-10 expression. Inflammatory cytokines rapidly induce RANTES/CCL5 expression in fibroblasts, epithelial cells, and monocytes/macrophages. In T-cells, RANTES/CCL5 expression is mediated by translational control of the transcription factor RFLAT-1/KLF13, which is responsible for a 3-day delay in RANTES/CCL5 secretion after T-cell activation. A cell membrane multi-protein complex containing CFTR, EBP50, ezrin, and PKC is a dominant regulator of both RANTES/CCL5 and inflammatory cytokine expression. Treatment of a volunteer patient suffering from long COVID/vaccine injury with the ezrin peptide RepG3 alleviated symptoms, substantially reduced serum proinflammatory cytokines to normal levels, and enhanced the expression of RANTES/CCL5. The immune amplification activities of RANTES/CCL5 and the ezrin peptide RepG3 exhibit striking similarities. In contrast, the ezrin peptide RepG3 differs from RANTES/CCL5 in its ability to significantly inhibit the expression of proinflammatory cytokines IL-1β, IL-6, IL-8, IL-13, TNF-α, and proinflammatory chemokines MIP-1α and MIP-1β. The mechanism through which the ezrin peptide RepG3 enhances adaptive immunity likely involves its induction of systemic elevation of RANTES/CCL5 expression and the simultaneous inhibition of proinflammatory cytokine expression.

Keywords: RANTES; CCL5; CCR5; Ezrin peptide; Immune amplification; Anti-inflammatory; SARS-CoV-2; Long COVID

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Citation: Holms R. The therapeutic potential of RANTES/CCL5 across diverse infections and its synergistic enhancement by ezrin peptide RepG3 for long COVID. *Microbes & Immunity.* 2024;1(1):2474. https://doi.org/10.36922/mi.2474

Received: December 19, 2023

Accepted: February 4, 2024

Published Online: March 6, 2024

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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