Biobran/MGN-3, Arabinoxylan Rice Bran, for the Treatment of Chronic Hepatitis C

Mamdooh Ghoneum, Ph.D.



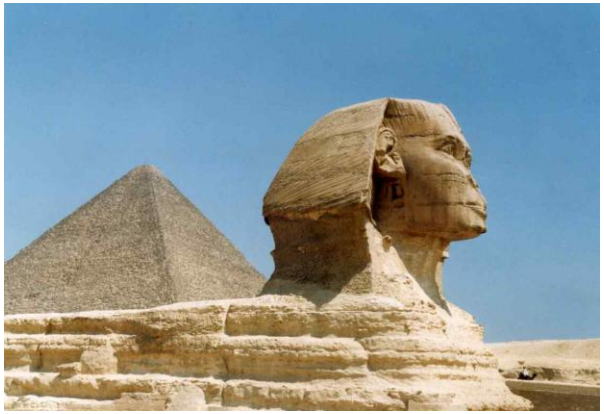
Charles R Drew University
of Medicine and Science
Los Angeles, CA, USA



Cairo University
Cairo, Egypt

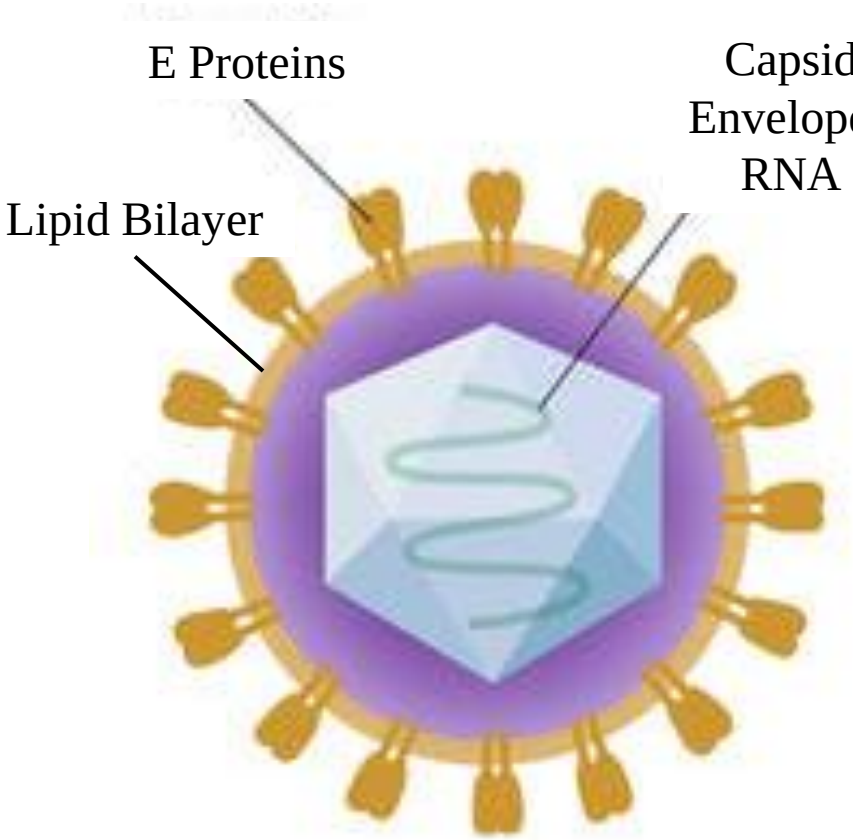
OUTLINE

1. HCV Background
   a. Types of HCV, HCV Prevalence, Cost, Toxicity
2. Biobran anti-HIV activity
3. Biobran anti-HCV activity
   a. Study Design
   b. Results
4. Possible Mechanisms
   a. NK, CD8+ T cells and Dendritic cell (DC) activation
   b. Interferon production
5. The Uniqueness of Biobran
6. Acknowledgements/Conclusion

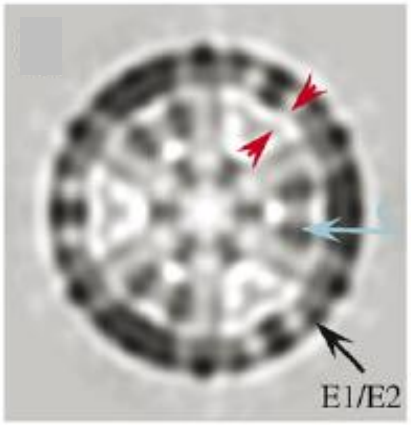


Hepatitis C virus (HCV)

Model of HCV



Cryo-EM Image*



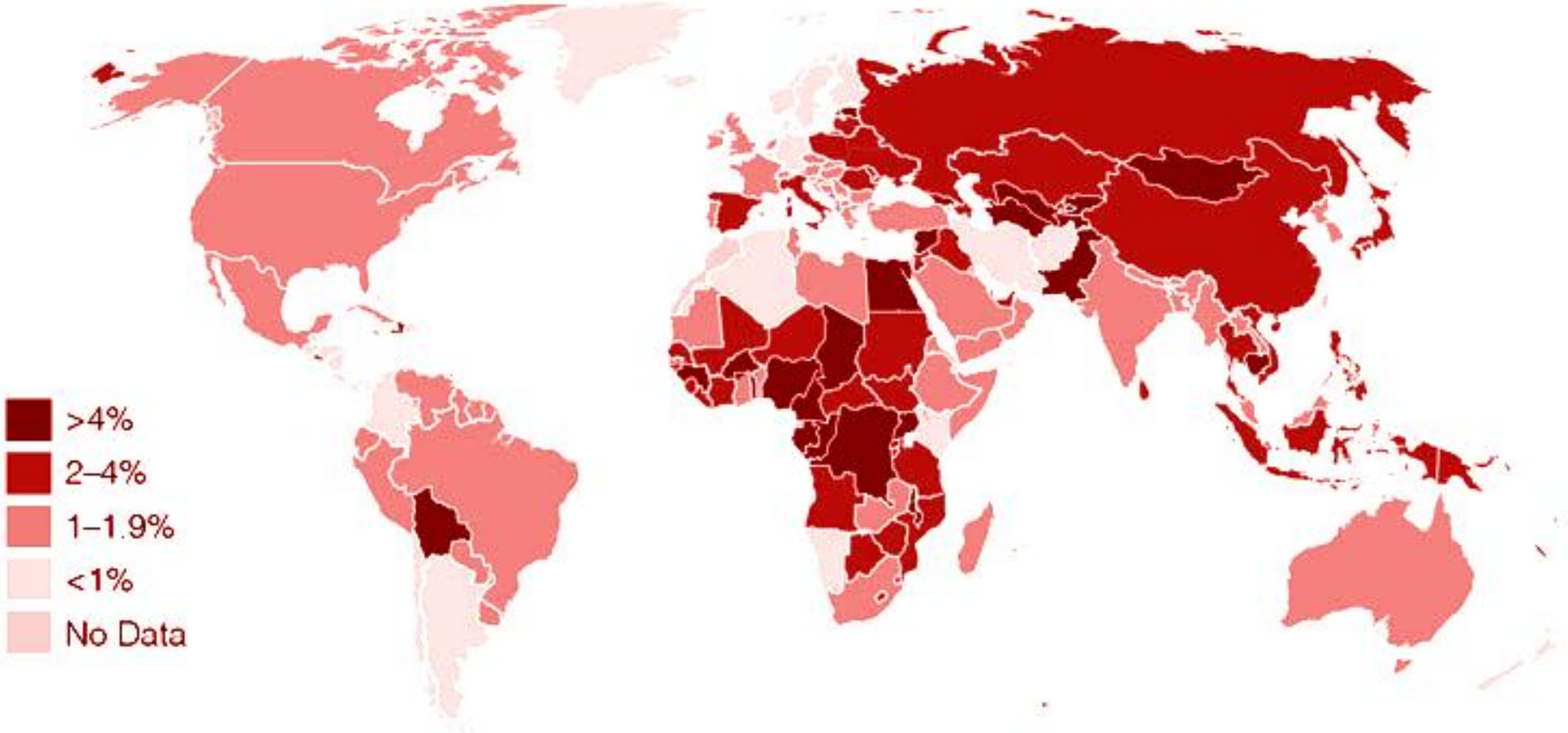
7 Å thick slice of HCV

- **Red Arrows**: Lipid Bilayer
- **Blue Arrow**: Capsid
- **Black Arrow**: E1/E2 Glyco-proteins

Cross-section model and electron microscope image of HCV

* Xuekui Yu et al. Cryo-electron microscopy and three-dimensional reconstructions of hepatitis C virus particles. Virology 367. 126–134. 2007.

Global Hepatitis C Prevalence



Source: Lavanchy, D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect. 2011; 17:107–115.

- **Genotype Type 1 is most common in US**
- **Genotype Type 4 is most common in Egypt**

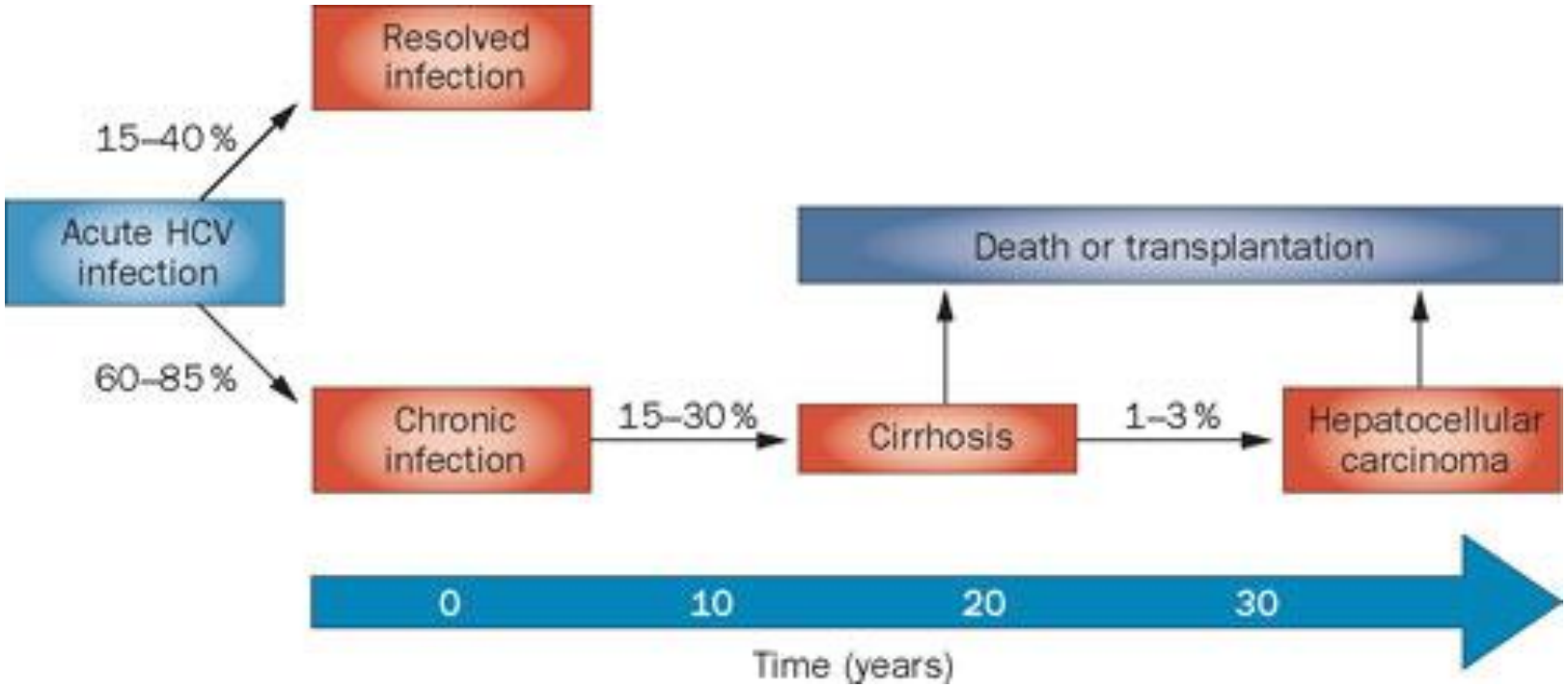
HCV Prevalence & Deaths per Year

HCV	Worldwide	USA*	Egypt**
Prevalence	**185 Million**	**3.9 Million**	**12 Million**
Deaths/Year	**> 350, 000**	**17,000 (2012)**	**40,000**

*University of Washington/Seattle STD/HIV Prevention Training Center. Hepatitis Web Study. 2013. http://www.cdc.gov/hepatitis/Resources/Professionals/PDFs/ABCTable.pdf

**A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. Sievert, William et al. Liver Int. 31. 61-80. 2011. http://www.dailynewsegypt.com/2015/01/05/lawsuit-targets-army-officials-claiming-hiv-hepatitis-c-cure/

The Natural Progress of HCV Infection



Treatment for Hepatitis C Virus Infections

- No protective vaccine available.
- Interferon (Pegylated IFN)
  - Pegylated IFN is used due to increased stability in vivo. Activates cellular antiviral responses. ~50% of responders will relapse upon withdrawal of treatment.
- Ribavirin
  - Mechanism unknown, but may be direct inhibition of RDRP or alteration of nucleotide pool needed for replication. *The combination of interferon and ribavirin* is more effective than interferon alone.
- Sovaldi
  - A nucleotide analog that is used with other drugs such as Riba for genotypes 2 and 3, and with pegylated IFN for genotypes 1 and 4. It inhibits RNA polymerase that the hepatitis virus uses to replicate its RNA.

Toxicity of Treatment for HCV Infections

Pegylated IFN
- Injection site inflammation
- Fatigue
- Headache
- Rigors
- Fever
- Nausea
- Myalgia
- Anxiety or emotional lability/irritability
- Hematologic toxicity: neutropenia/thrombocytopenia
- Ophthalmologic disorders

Ribavirin
- Hemolytic anemia
- Cardiac disease
- Myocardial infarction
- Birth defects

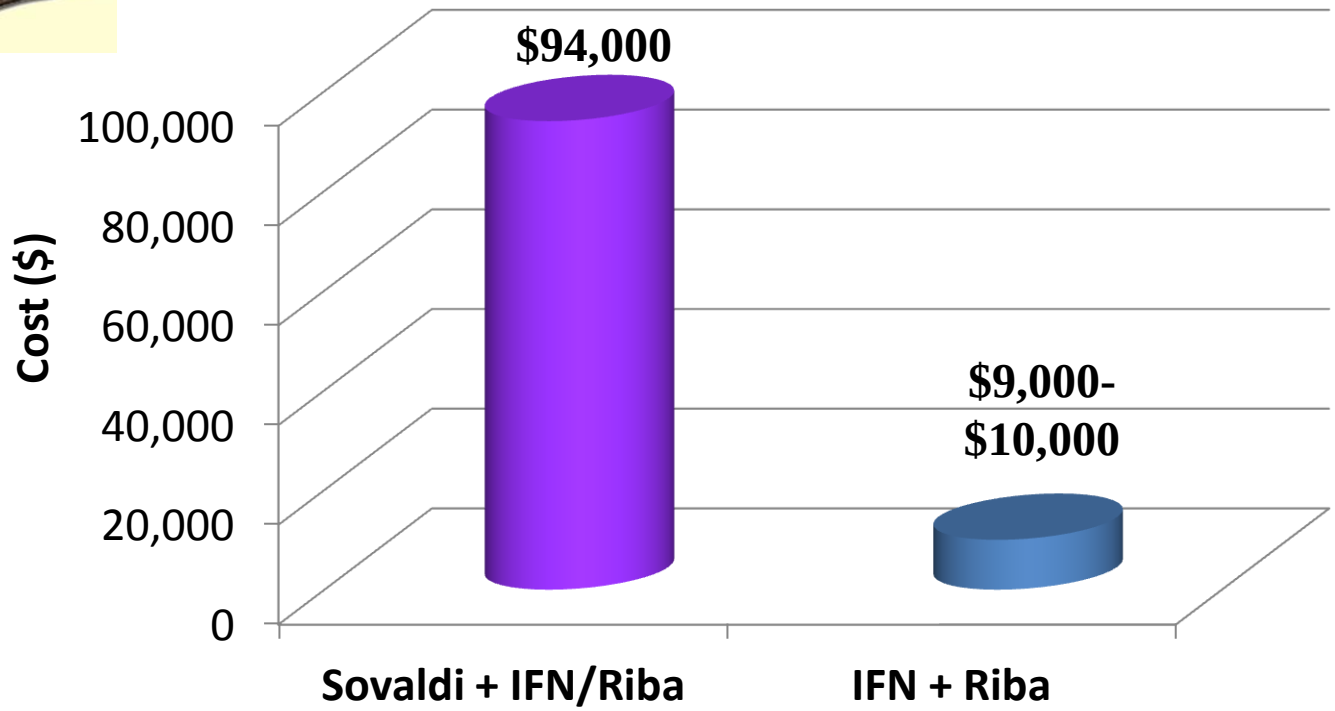
Sovaldi
- Fatigue
- Headache
- Birth defects



http://www.hepatitisc.uw.edu/page/treatment/drugs/peginterferon-alfa-drug
http://www.hepatitisc.uw.edu/page/treatment/drugs/ribavirin-drug
http://www.hepatitisc.uw.edu/page/treatment/drugs/sofosbuvir-drug



Cost of 12-Week Treatments for HCV Infections

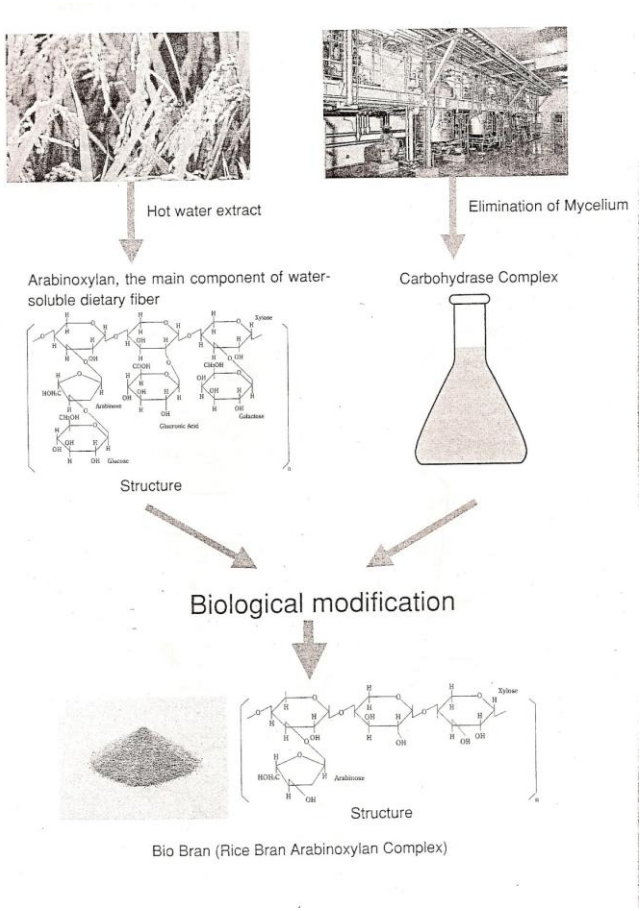


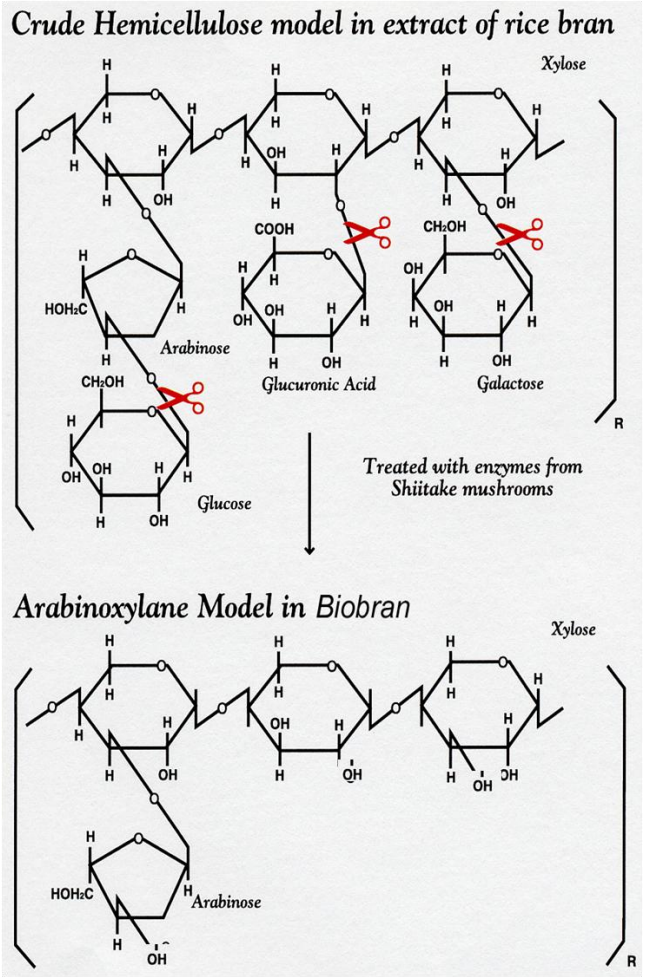
Due to the high-cost and severe side effects of current HCV treatments, we are in great need of finding new agents that are less expensive and less/non-toxic AND highly effective in combating the Hepatitis C Virus


Biobran/MGN-3
Arabinoxylan rice bran

What is arabinoxylan (Biobran/MGN-3)?

- **Biobran is a denatured hemicellulose, which is obtained by reacting rice bran hemicellulose with multiple carbohydrate hydrolyzing enzymes from the Shiitake mushrooms.**
- **The main chemical structure of Biobran is an arabinoxylan with a xylose in its main chain and an arabinose polymer in its side chain.**

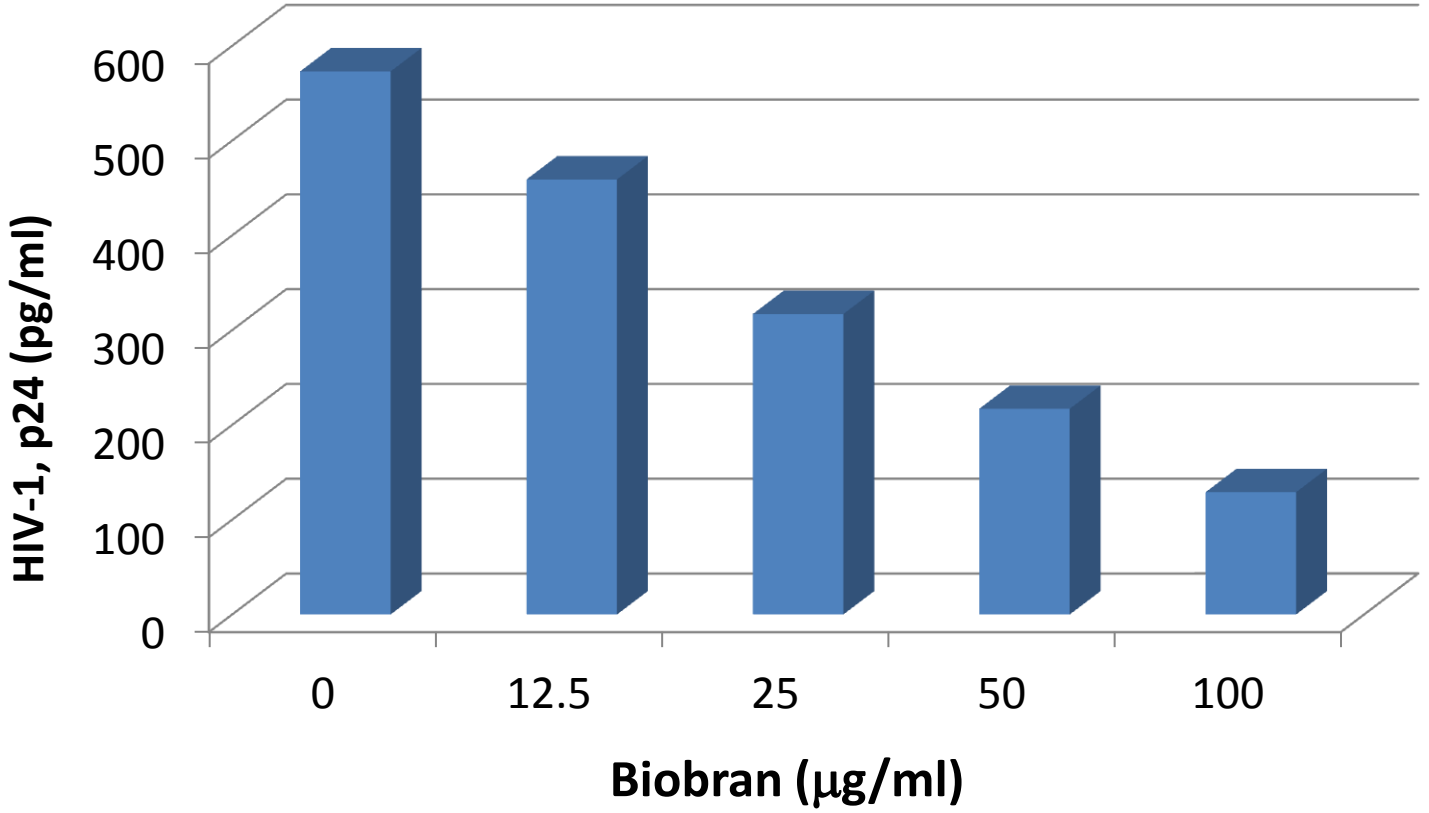




Ghoneum M.. *Biochem. Bioph. Res. Comm.* 243, 25-29 (1998).

Biobran Exerts Anti-Viral Activity

1- Biobran/MGN-3 Inhibits HIV-1 Replication (PBMC from healthy subjects infected with HIV)*



*HIV-1 SF strain, HIV-1 p24 of 3000 pg/million cells.
Data represents the mean +/- standard deviation from three subjects.

Ghoneum, M. Biochemical and Biophysical Research Communication 243, 25-29 (1998)

2-Biobran/MGN-3 Inhibits Syncytia Formation

MGN-3 dosage (μg/ml)	Healthy Subjects*		AIDS Subjects		
	No. of SF	% Inhibition	Small	Medium	Large
0	42 ± 8	0	+	+	+
12.5	25.8 ± 7	38.5	+	+	+
25	21.5 ± 5	50	+	+	±
50	15.8 ± 4	62.5	+	±	-
100	10.5 ± 3	75	+	-	-

Syncytia Formation (SF): During infection with HIV, viral fusion proteins used by the virus to enter the cell are transported to the cell surface, where they can cause the host cell membrane to fuse with neighboring cells.

* HIV-1 SF strain, HIV-1 p24 of 3000 pg/million cells. Data represents mean +/- s.d. from 5 subjects.

*Ghoneum, M. Biochemical and Biophysical Research Communication 243, 25-29 (1998).
Ghoneum M. Anti-HIV Activity by MGN-3 *In vitro*. XI International Conference on AIDS. Vancouver July 7-12, 1996.

Purpose of the Current Study

- The ability of Biobran to exert anti-HIV activity encouraged us to pursue the current study.

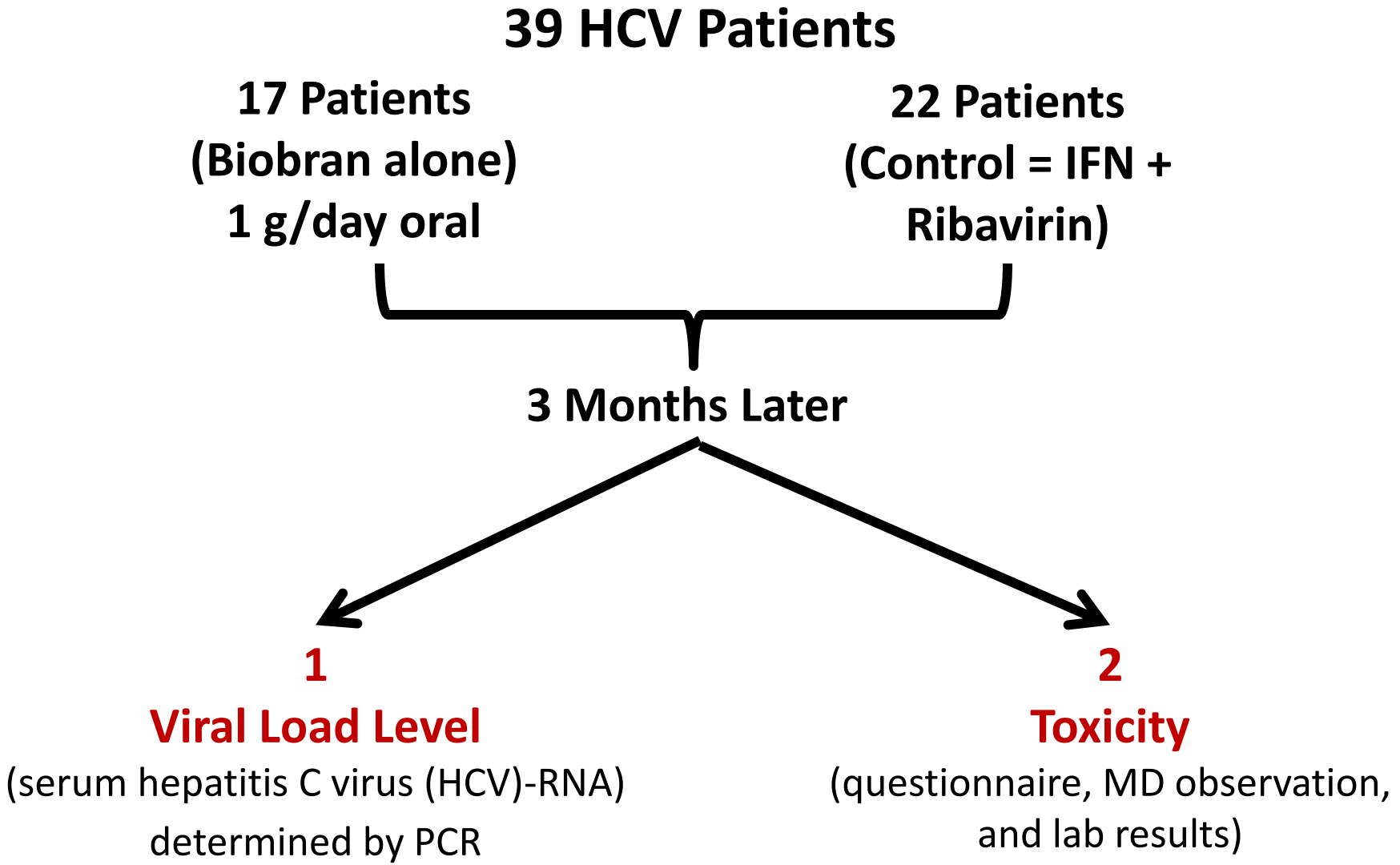
- The purpose of the current study is to examine the anti-HCV effect of Biobran on viremia in clinical trials of patients with positive chronic HCV.

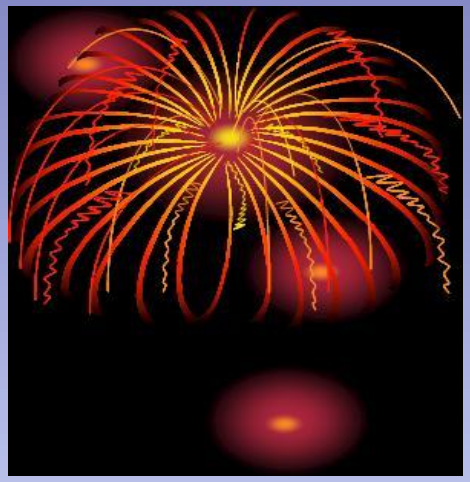
The study was approved by the Institutional Review Board (IRB) at:

- **Cairo University, Egypt**
  [IRB#: A-13-3012]

- **Charles R Drew University (CDU), Los Angeles CA, USA**
  [IRB #: 14-07-2431-01]

Study Design
[Randomized Control Trial]





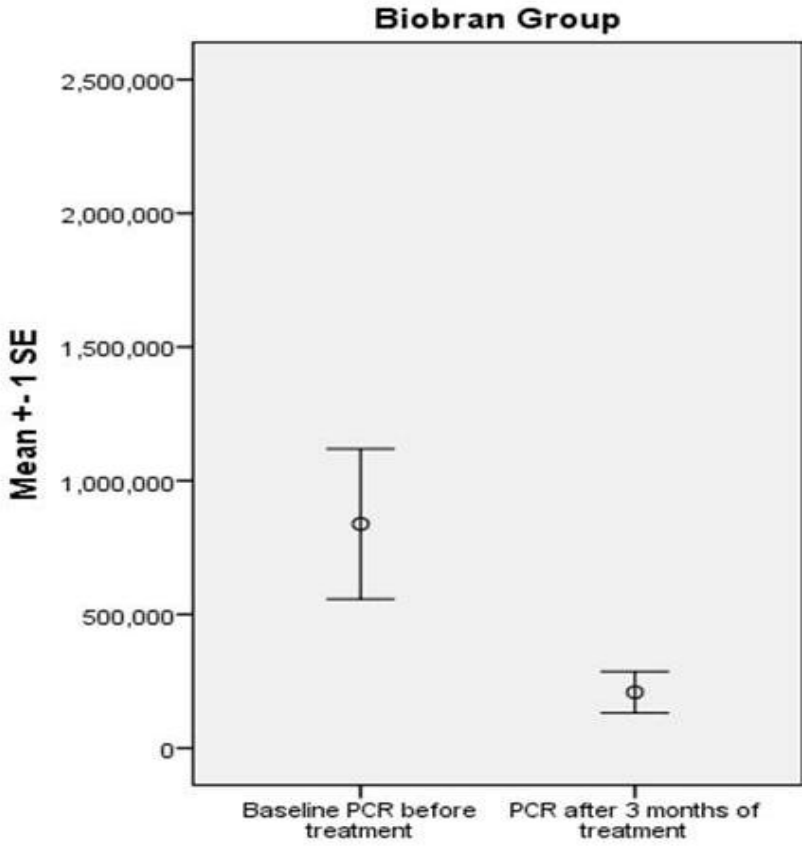
RESULTS

1-Viral Load
2-Toxicity
3-Cost

1- Viral Load

Biobran effect on the level of the viral load

- **PCR levels before and 3 months after treatment showed that:**
  - **patients given Biobran demonstrated significant reduction in the viral load relative to the baseline value (p=0.023).**



Hypothesis Test Summary

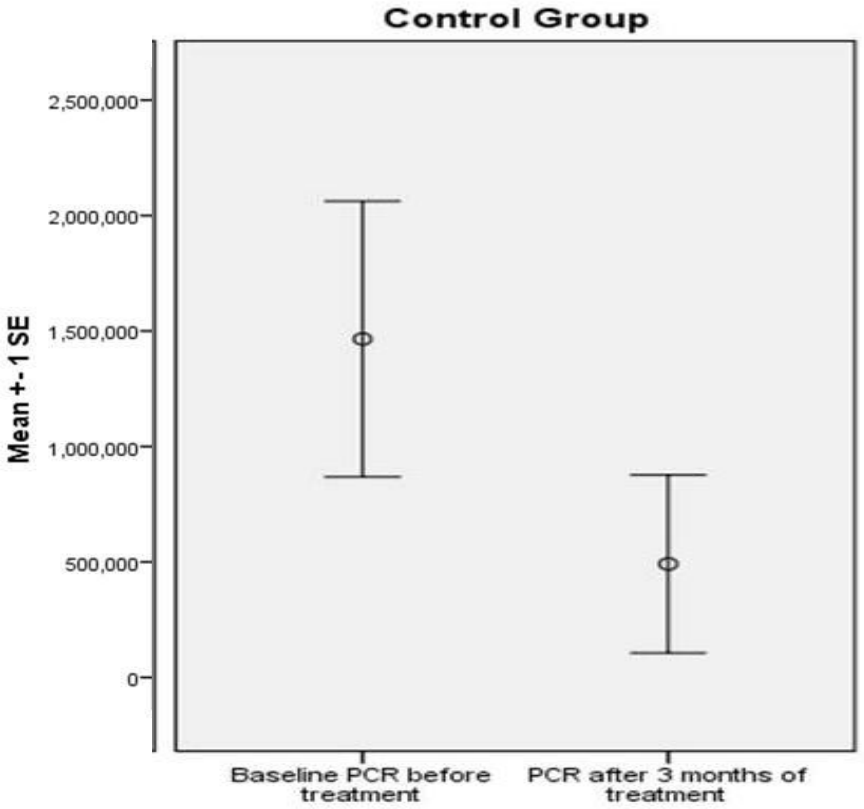
	Null Hypothesis	Test	Sig.	Decision
1	The median of differences between Baseline PCR and PCR 2 equals 0.	Related-Samples Wilcoxon Signed Rank Test	.023	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

1- Viral Load

Interferon plus Ribavirin effect on the level of the viral load (Control group)

- **PCR levels before and 3 months after treatment showed that:**
  - **patients given Interferon plus Ribavirin (Control group) demonstrated significant reduction in the viral load Relative to the baseline value (p=0.001).**



Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The median of differences between Baseline PCR and PCR 2 equals 0.	Related-Samples Wilcoxon Signed Rank Test	.001	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

1- Viral Load

COMPARISON BETWEEN THE TWO GROUPS

Patients in both groups showed significant reduction in the viral load relative to the baseline value.

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The medians of Baseline PCR are the same across categories of GROUP_NUMBER.	Independent-Samples Median Test	.851	Retain the null hypothesis.
2	The medians of PCR 2 are the same across categories of GROUP_NUMBER.	Independent-Samples Median Test	.836	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

- There is no statistical difference between the median of two groups in the baseline (p=0.851)
- There is no statistical difference between the median of two groups in the PCR after 3 months of treatment (p=0.836).

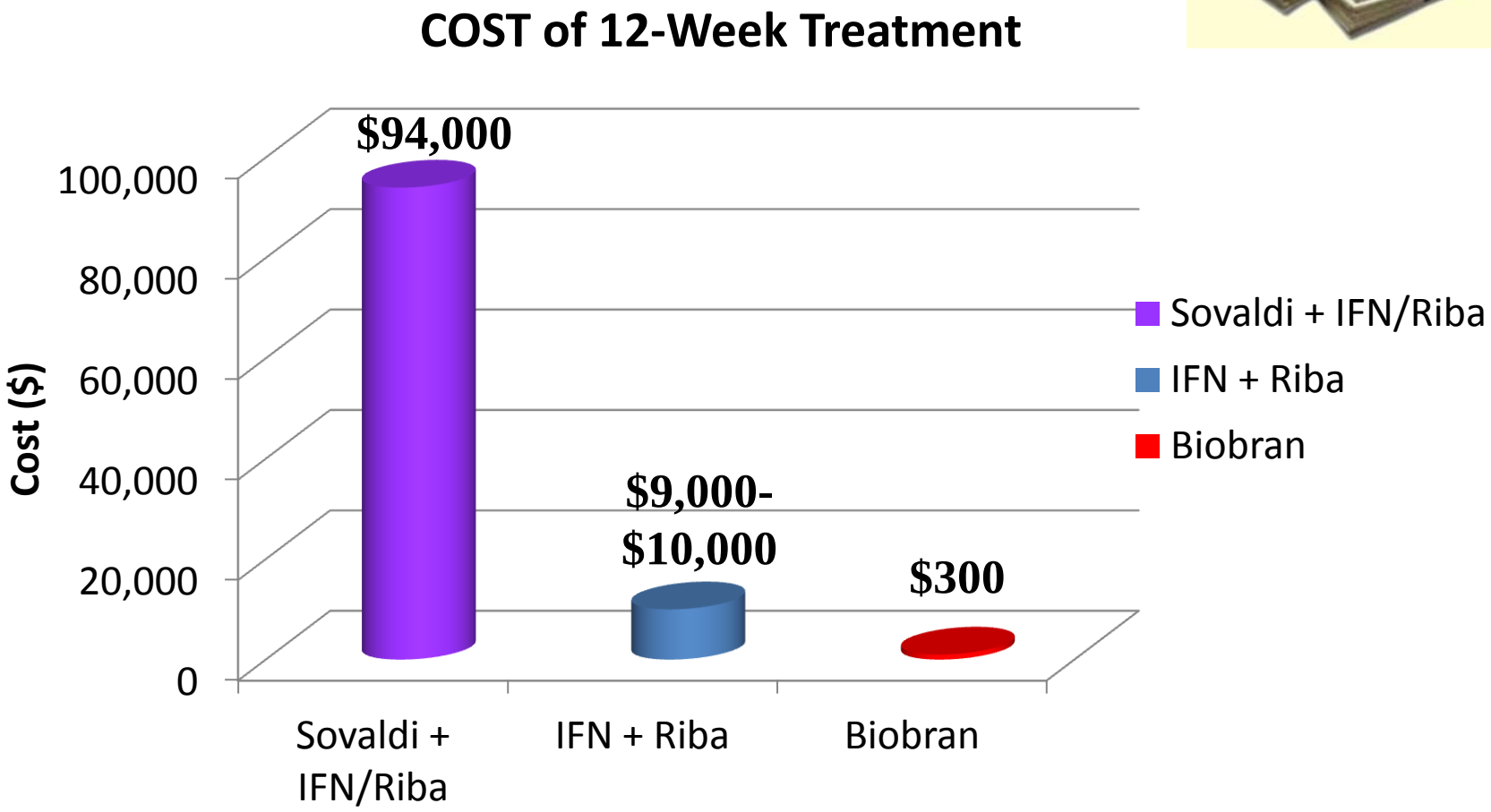
2- Toxicity

Evaluated by: Questionnaire, MD observation, and lab results

Biobran group	Control group (IFN-γ + Ribavirin)
• No side effects • Patients reported good health	• Fever • Anemia • Thrombocytopenia • Dry cough • Headache • Body ache • Patients reported easily fatigued

3- Cost of 12- Week Treatments for HCV Infections





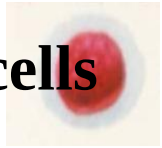
Mechanisms Underlying the Anti-HCV Activity of Biobran

Biobran induces various immune cells to attack viral infected cells

NK cells

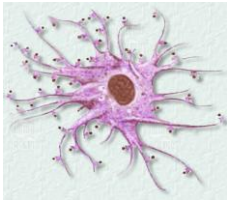


CD4+T cells



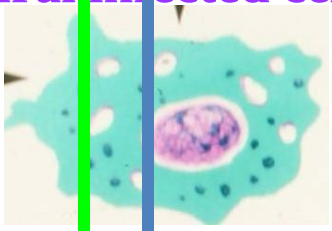
4. IFN-γ

3. DCs



IFN-α
IFN- λ

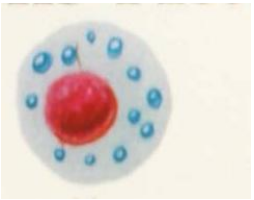
Viral infected cell



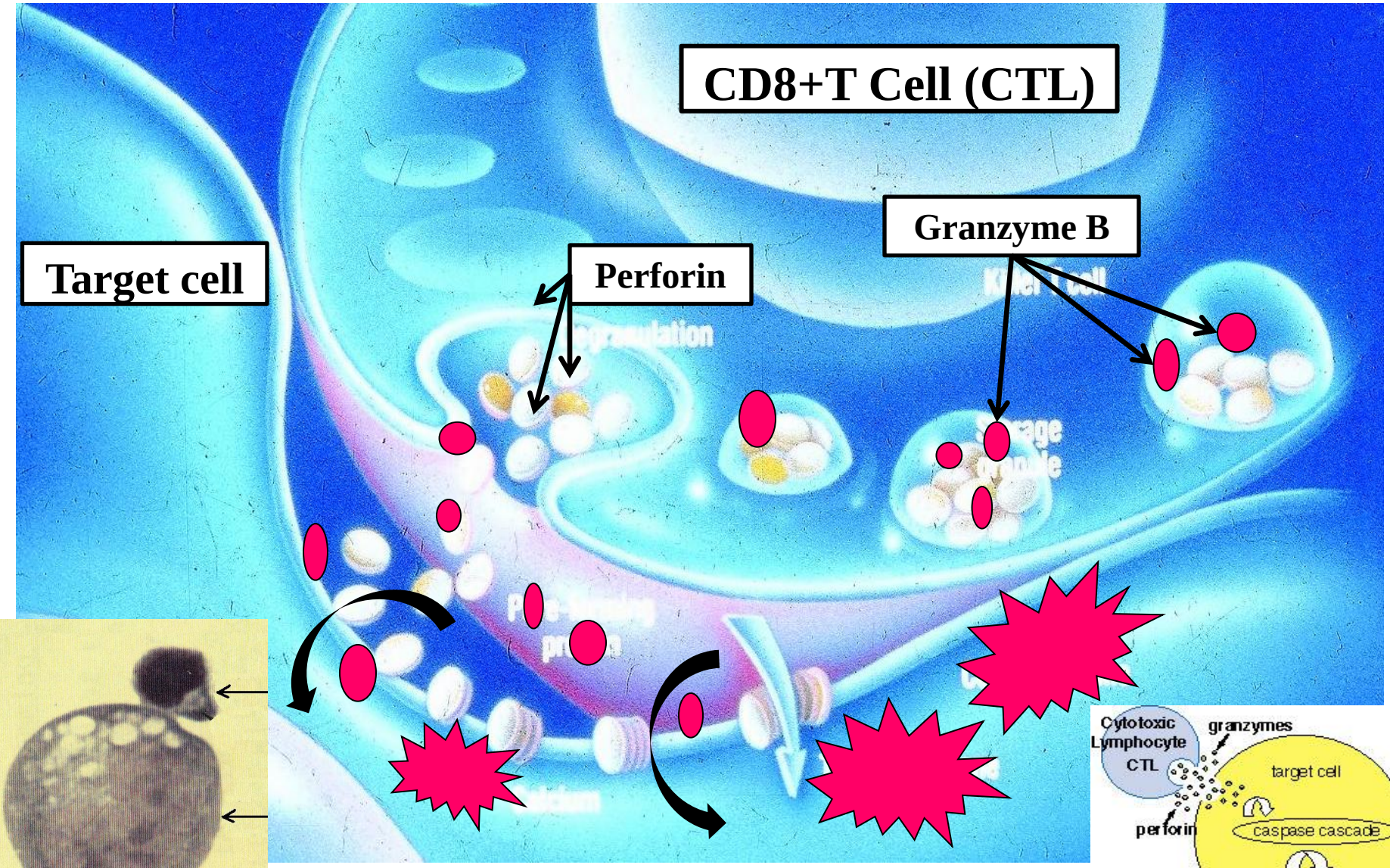
1. NK cells



2. CD8+T cells

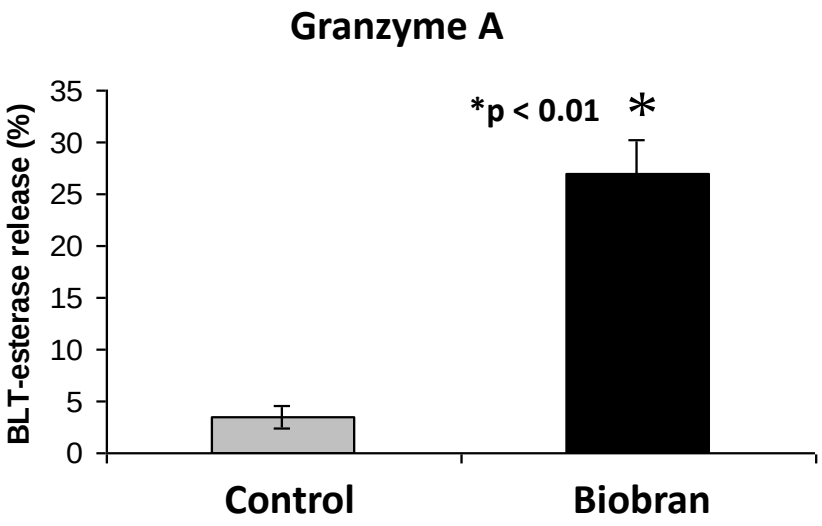


NK/CD8+T cell activity against target cells



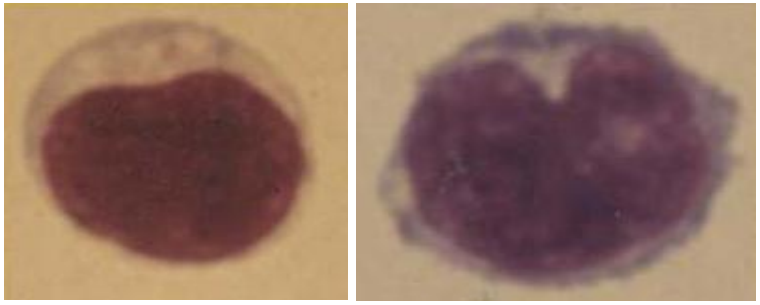
Biobran increases granular content of NK & CD8+ T cells

1. NK Cells

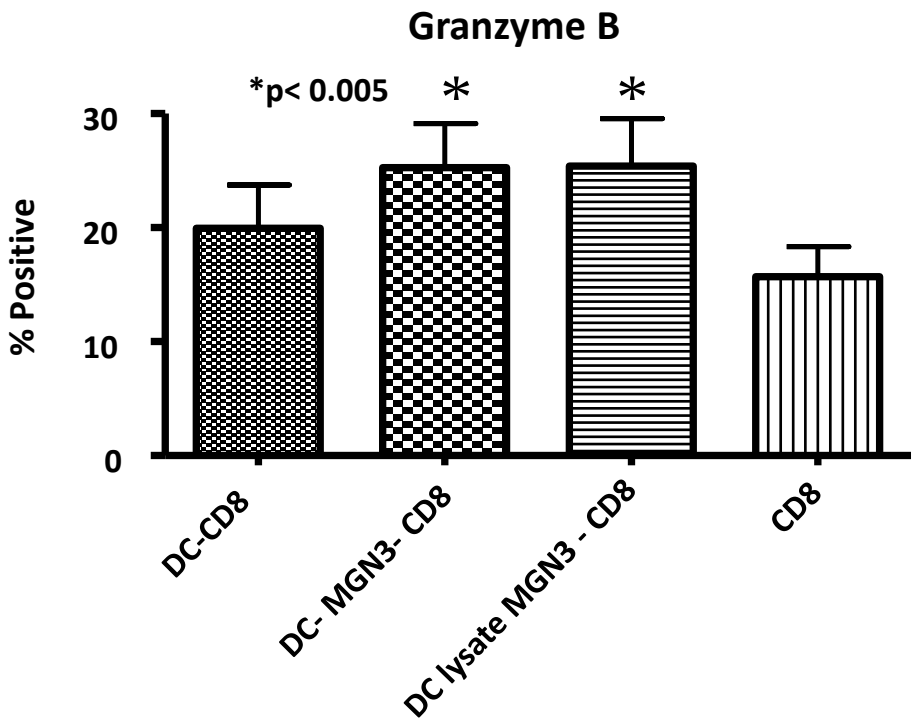


Degranulated NK/CD8+ T Cell

Biobran Regranulated NK/CD8+ T Cell



2. CD8+T Cells

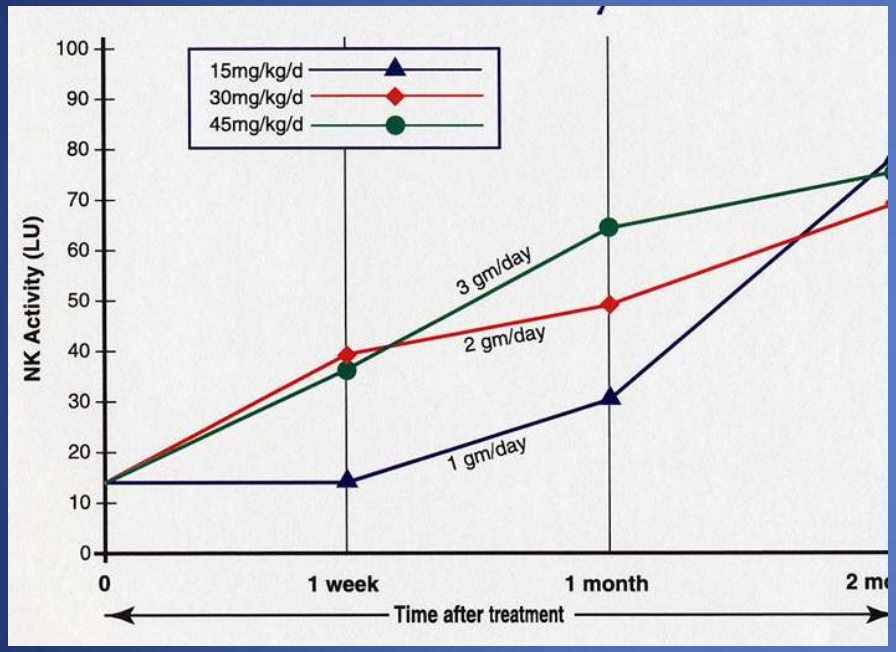


Bar graphs depict the percentage of CD8+ T cells expressing granzyme B. Data represent the mean ± S.E. of 5 experiments.

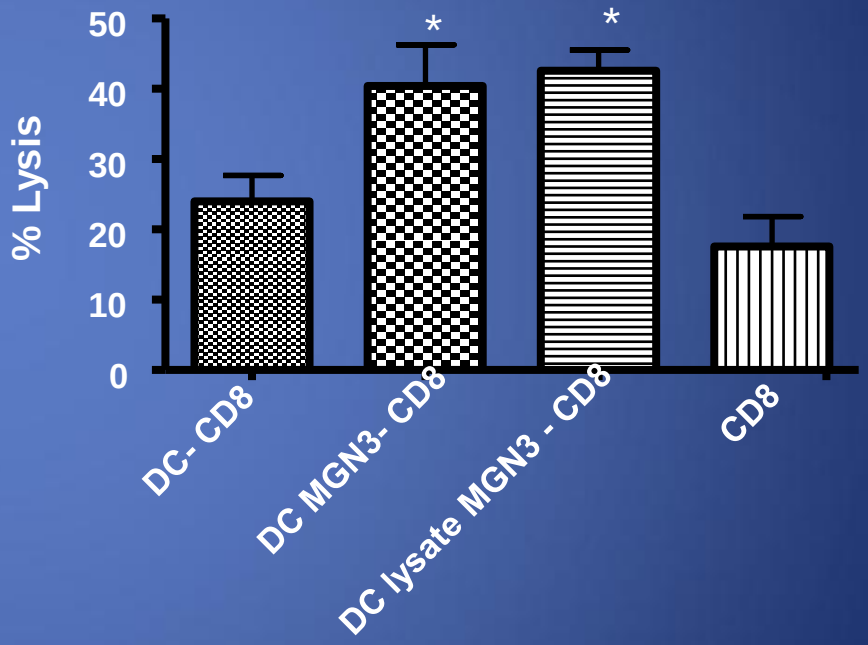
NK Study: Ghoneum, M. & Abedi, S. JPP 56: 1581-1588 (2004).
CD8+ Study: Ghoneum M and Agrawal S. *Int J Immunopathol Pharmacol* 27 (4): 523-530 (2014).

Biobran enhances human NK & CD8+ T cell activity

1- NK cell activity

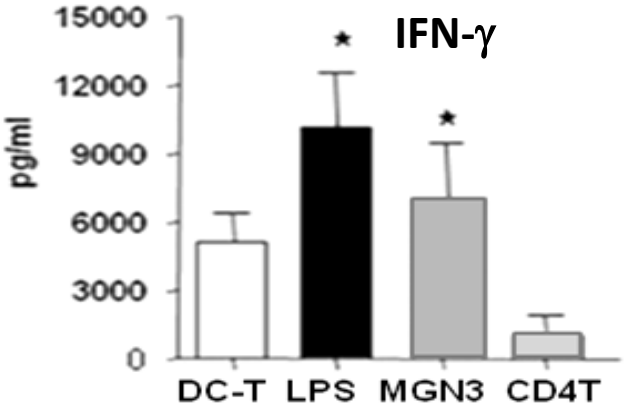


2- CD8 + T Cell activity



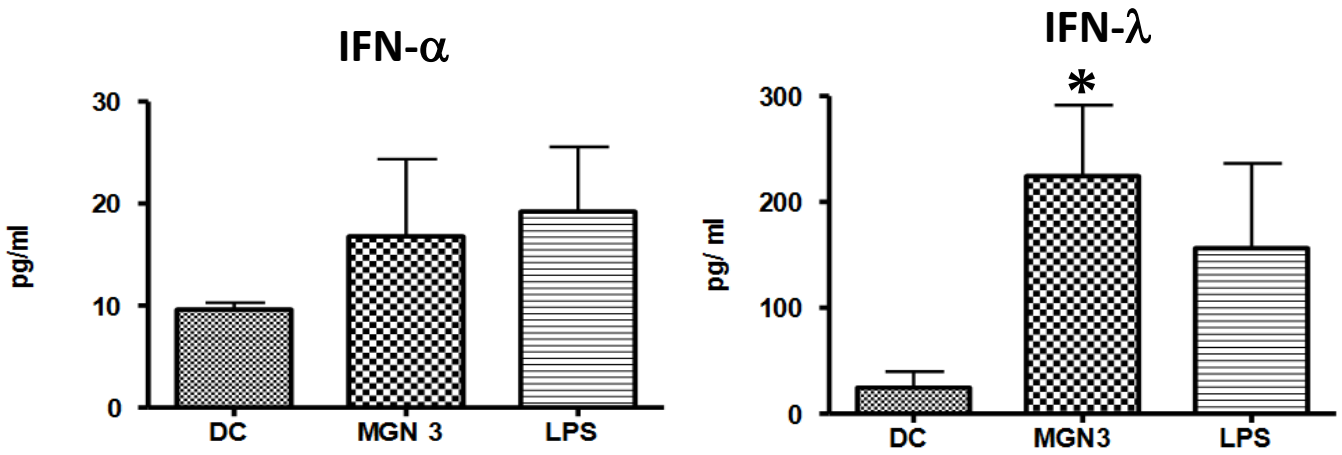
NK Study: Ghoneum M, International Journal of Immunotherapy XIV(2) 89-99 (1998).
CD8+ T Cell Study: Ghoneum M and Agrawal S. *Int J Immunopathol Pharmacol* 27 (4): 523-530 (2014).

1. Biobran primed DC-induced IFN-γ secretion by CD4+ cells



The secretion of IFN-γ in the supernatants was assessed using specific ELISA kits. The data are the mean ± SD from 4 individual experiments; *p<0.05, as compared to control DCs.

2. Biobran activated DCs secrete Type I IFN (IFN-α) and Type III IFN (IL-29/IFN-λ)



Biobran activates dendritic cells to induce a distinct profile of Type I and III IFNs cytokine secretion. Data represent the mean ± S.E. of 6 experiments. *(p<0.05) as compared to DCs alone.

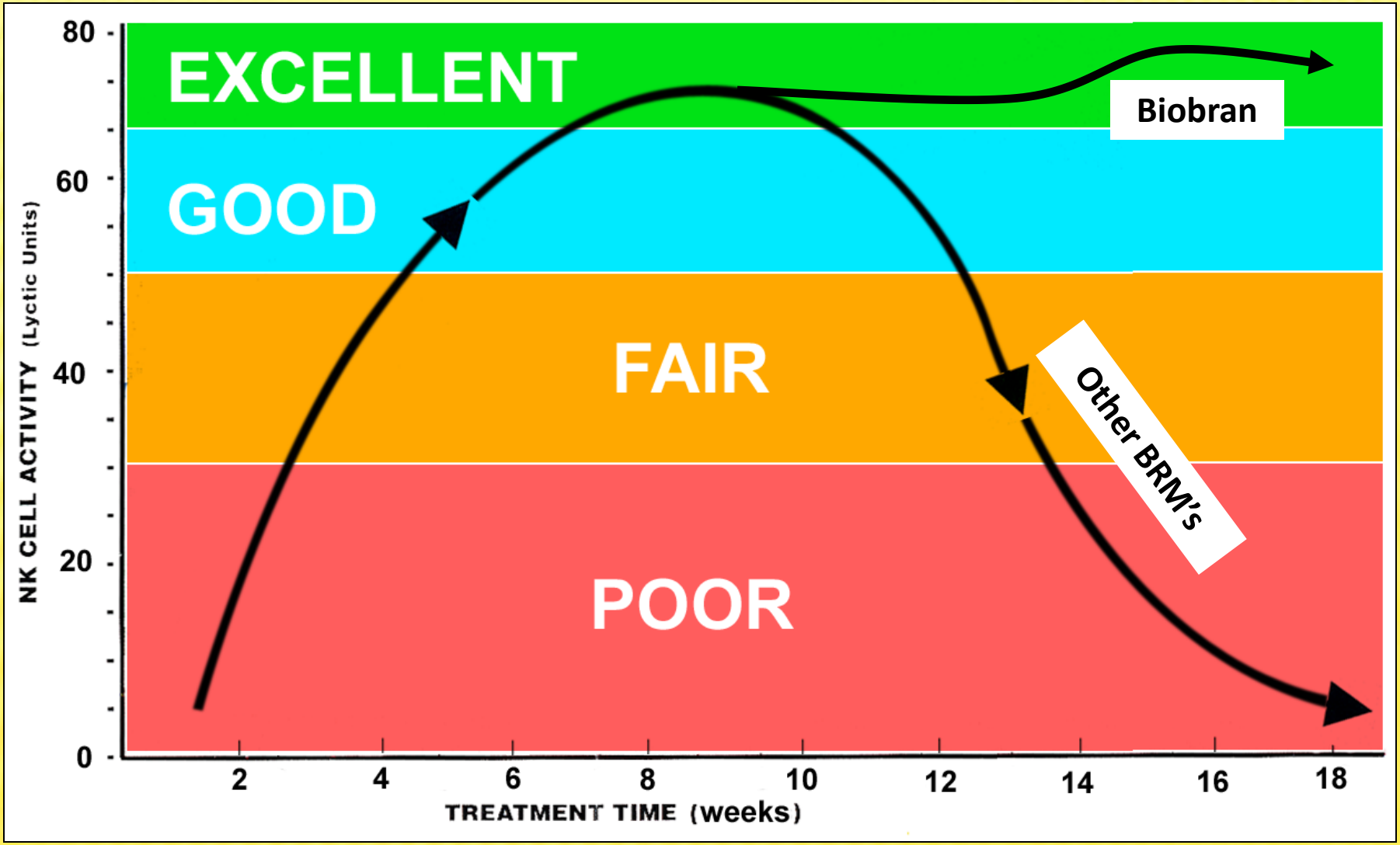
Ghoneum M and Agrawal S. *Int J Immunopathol Pharmacol* 27 (4): 523-530 (2014).

THE UNIQUENESS OF BIOBRAN

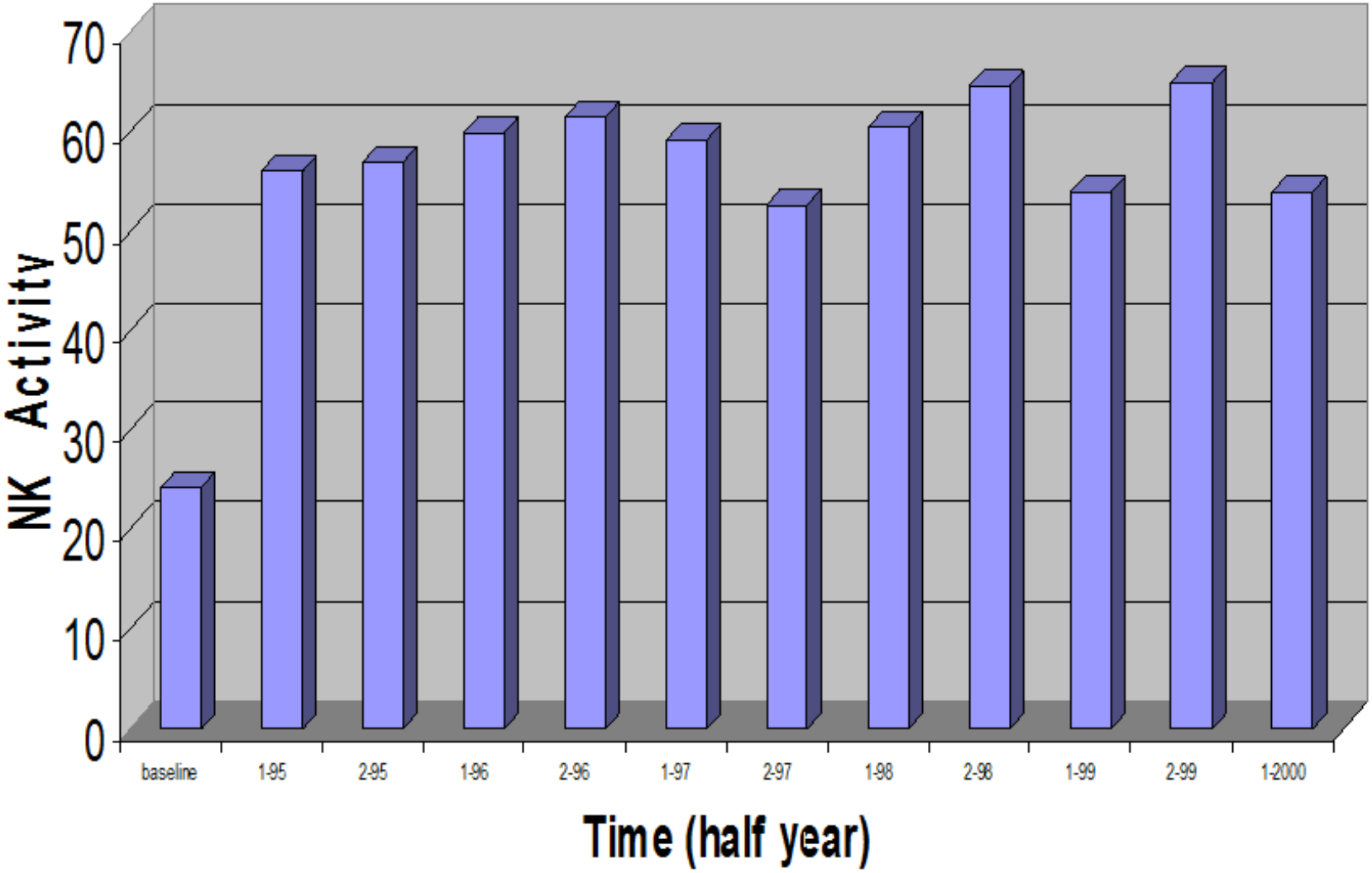
While several studies have shown that a single administration of BRMs can significantly enhance NK cell activity, repeated administration of the same BRM has resulted in depression of NK cell activity, an effect known as hyporesponsiveness. The hyporesponsiveness of NK activity is a serious problem and is an associated phenomenon with many BRMs. It is interesting to note that MGN-3 was evaluated for 5 years and NK activity was maintained at a high level throughout the continuation of treatment. This suggests that Biobran does not have hyporesponsiveness.

Ghoneum, M. 6th Int. Cong. Anti-aging and Biomed. Technologies. Las Vegas, NV. 1998.

Action of Many BRMs on NK Activity Over Time



Long Term (5 years) follow up of NK activity (Data of 8 Breast Cancer Patients)




CONCLUSION

CONCLUSION

1. **Biobran is a novel therapeutic regimen that is safe and effective in the treatment of chronic HCV**

2. **The mechanisms by which Biobran exerts its effect may involve activation of human immune cells that are known to exhibit antiviral activity.**

3. **Ongoing studies are designed to confirm the conclusions in larger samples and to examine the long-term effect of Biobran on the treatment and the recurrence of HCV.**

Contributors









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Acknowledgement

Biobran was provided by Daiwa Pharmaceutical Co., Ltd., Tokyo, Japan.



Published articles in peer-review journals on MGN-3/Biobran

1. Ghoneum M. Anti-HIV activity in vitro of MGN-3, an activated arabinoxylane from rice bran. Biochem Biophys Res Commun. 1998;243(1):25-9. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9473473&dopt=Abstract
2. Ghoneum, M. Enhancement of human natural killer cell activity by modified arabinoxylan from rice bran (MGN-3). Int. J. Immunotherapy. XIV. 89-00 (1998).
3. Ghoneum, M. and Brown, J. NK immunorestoration of cancer patients by MGN-3, a modified arabinoxylan rice bran (study of 32 patients followed for up to 4 years). Anti-aging medical therapeutics Vol. III (Klatz, R. and Goldman, R. ed.) 217-226 (1999). Proceeding of 6th Int. Cong. Anti-aging and Biomed. Technologies. Las Vegas, NV. Dec. 11-13, 1999.
4. Ohara, I, Agr, D, Tabuchi, R. et. al. Effects of modified rice bran on serum lipids and taste preference in streptozotocin-induced diabetic rats. Nutrition Research. 20(1), 59-68, 2000.
5. Tazawa, K, Namikawa, H, Oida, N. et. al. Scavenging activity of MGN-3 (arabinoxylan from rice bran) with natural killer cell activity on free radicals. Biotherapy. 14, 493-95, 2000.
6. Ghoneum M, Jewett A. Production of tumor necrosis factor-alpha and interferon-gamma from human peripheral blood lymphocytes by MGN-3, a modified arabinoxylan from rice bran, and its synergy with interleukin-2 in vitro. Cancer Detect Prev. 2000;24 (4):314-24. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11059563&dopt=Abstract
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8. Sudo, N, Totoe, K, Koyama, N. et. al. The basic study of arabinoxlan compound (MGN-3) on the activation of vital defense. Clinical Research, 78, 193-196, 2001.
9. Endo, Y, Kanbayashi, H. Modified rice bran beneficial for weight loss of mice as a major and acute adverse effect of cisplatin. Pharmacol & Toxicol. 92: 300-303 (2003). http://www.ncbi.nlm.nih.gov/pubmed/12787263?dopt=Abstract
10. Ghoneum M, Gollapudi S. Modified arabinoxylan rice bran (MGN-3/Biobran) sensitizes human T cell leukemia cells to death receptor (CD95)-induced apoptosis. Cancer Lett. 2003;201(1):41-9. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14580685&dopt=Abstract
11. Ghoneum M, Abedi S. Enhancement of natural killer cell activity of aged mice by modified arabinoxylan rice bran (MGN-3/Biobran). J Pharmacy Pharmacol. 56 (12): 1581-1588 (2004). http://www.ncbi.nlm.nih.gov/pubmed/15563765?dopt=Abstract

Published articles (Continued)

12. Takahara, K. and Sano, K. The Life Prolongation and QOL Improvement Effect of Rice Bran Arabinoxylan Derivative (MGN-3, Bio-Bran) for Progressive Cancer. Clinical Pharmacology and Therapy.14; 2004. http://sciencelinks.jp/j-east/article/200415/000020041504A0459788.php

13. Tomonori, Kawai. One Case of a Patient with Umbilical Metastasis of Recurrent Cancer (Sister Mary Joseph's Nodule SMJN) who has Survived a Long Time Under Immunomodulatory Supplement Therapy. Clinical Pharmacology and Therapy. 14(3). 2004.

14. Kaketani, K. A Case where an Immunomodulatory Food was Effective in Conservative Therapy for Progressive Terminal Pancreatic Cancer. Clinical Pharmacology and Therapy. 14, 273-279, 2004.

14. Tsunekawa, H. Effect of Long-Term Administration of Immunomodulatory Food on Cancer Patients Completing Conventional Treatments. Clinical Pharmacology and Therapy. 14(3). 2004.

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