Life Extension Magazine January 2015

Report

Activate Your Natural Killer Cells

By Stephen Posnick

Flu viruses are responsible for as many as 50,000 deaths every year in the US.[1]

Bacterial pneumonia[2] causes over 60,000 deaths annually.[3,4]

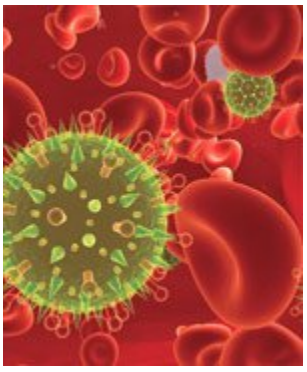
Annual flu and pneumonia vaccines are common, but they might not be sufficient to fight off wintertime infections in the presence of a weakened immune system known as ***immune senescence***. [5-8]

The first line of defense against new invaders is our **natural killer (NK) cells**. As we age, NK cells lose their *functionality*, thus leaving us far more vulnerable to viral diseases—and the formation of tumors.[9,10]

Aging humans don't have to succumb to this massive loss of **NK cell** function. Scientists have uncovered an **enzymatically modified rice bran** that has been shown to increase **NK cell activity** in circulating blood cells by up to **84%**![11]

By optimizing your NK cell function, you will be raising defenses against early death from viral illness—and against cancer as well. **Enzymatically modified rice bran** has been proven to help restore ***NK cell activity*** and may thereby shorten the duration and severity of winter illnesses.[12]

Powerful Immune Defense



Natural killer cells (NK cells) are one of your body's most powerful defenses against infections and cancer.[13-15] These tiny security guards seek and destroy cells that have been transformed by an infection with a virus or by one of many malignant changes that transform them into cancer cells.[9,16]

NK cells work by triggering apoptosis (programmed cell death) in cells that have been transformed by a virus or malignancy.[17,18] Without this critical defense mechanism, viruses can be spread throughout the body and cancer cells can form invading, metastasized tumors.[9,19]

The health of these cells is critical to a robust immune system. Unfortunately, your NK cell function rapidly declines as part of the natural decline in your immune system as you age.[20-22] This degeneration of immune function is medically termed **immune senescence**.

This explains, in part, why aging individuals become such a ready target of each year's new influenza outbreak despite being vaccinated against the flu.

Anywhere between **5** to **20%** of the US population gets the flu every year, in a seasonal wave that begins as early as October, often peaks in February, and can last until May.[23-25] Older adults are at especially high risk: **90%** of seasonal

flu-related deaths, and up to **60%** of flu-related hospitalizations, occur in people 65 and older,[26] which happens to be the age when NK cell function precipitously declines.[27,28] And the older we get, the higher the risk of a hospitalization or death from the flu.[29]

When you were younger, your NK cells, which are part of your ***innate*** immune system, could destroy the new strain of virus while your ***adaptive*** immune system "learned" its properties and then made antibodies to destroy any remaining virus.[30-33] But because your NK cell function declines with age, you can easily be rapidly overwhelmed by new viral strains before your slower ***adaptive*** immunity can develop.

Similarly, older adults are at an increased risk of cancer because falling NK function fails to destroy malignant cells early on, allowing them time to develop various tricks that evade adaptive immunity while they grow into life-threatening tumors. Younger people have more robust NK function, which helps explain why cancers are generally so rare before late middle age.

Why Mainstream Medicine's Solutions Don't Work

Mainstream medicine has little to offer to counteract declining NK cell function. Although new vaccines can help protect against specific viruses, a decline in immune function (as part of immune senescence) limits vaccine efficacy in older people.[34] More potent antiviral drugs can be developed—again to combat specific viruses—but the problem with these drugs is that they have substantial toxicity,[35] they are given only *after* a viral infection has established itself, and they are extremely costly.[36-39] Specific cytokine injections (such as low-dose interleukin-2) may help replace other components of waning immunity, but again, side effects and high costs[40] limit their widespread use.[41,42]

A better approach would be to change the way the body responds to threats like viruses and tumor cells by directly *boosting* **NK cell function** and restoring waning immunity caused by immune senescence.[5,43]

By enhancing NK cell function, you would potentially be improving resistance, not to one or a few related viruses, *but to virtually all viruses at once*.[44] In the process, you would also be potentially enhancing natural cancer resistance, not to specific cancer types, *but to virtually all malignancies at once*.[45]

Fortunately, as a result of years of research by immunologists, infectious disease experts, and oncologists, a natural compound has been discovered that can significantly improve declining NK cell function precisely when it is needed the most—during the vulnerable winter season when infectious flus are at their peak.

SEASONAL FLU DEFENSE

- Immune senescence is the age-related dysregulation and steady loss of function of various components of the immune system; it explains the rise in infections, cancers, and even autoimmune problems seen in elderly populations.
- The reduction of one particular component of immunity—activity of natural killer cells—leaves older adults uniquely vulnerable to viral infections, especially during the wintertime peak in influenza.
- Natural killer (NK) cells are the body's front-line security team, identifying and eliminating cells infected with viruses or transformed by cancer.
- A unique product, enzymatically modified rice bran (EMRB), has now been developed, EMRB boosts NK cell activity by nearly 84%.
- EMRB is also effective at reducing deaths from certain cancers, further testimony to its boost of NK function.
- The wintertime viral season is precisely the time that this product should be used for optimum protection.
- Support the rest of your immune system year-round with other supplements capable of fighting off immune

senescence in all branches of your defenses, and use EMRB as your wintertime immune enhancer.

Natural Compound Boosts NK Cell Function

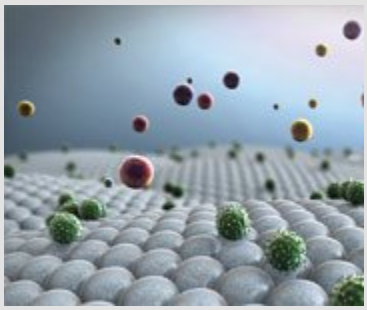
A derivative of rice bran called **enzymatically modified rice bran (EMRB)** has been shown to promote robust NK cell function in animal and human studies.[11,46]

By mechanisms that are still under investigation,[46,47] EMRB has been shown to increase NK cell activity in circulating blood cells by up to **84%**.[11]

Arabinoxylan is a type of indigestible fiber found in cell walls of the hard components of plants, such as in the husks, or bran, of cereal grains.[48,49] *Enzymatically modified rice bran* is produced by exposing crude fiber from rice bran to enzymes isolated from the Japanese culinary mushroom, shiitake (*Lentinula edodes*).[50,51]

Recently, there has been an explosion of interest in **EMRB** as an NK cell-boosting agent to overcome the reduction of NK cell activity due to immune senescence. Several basic laboratory and animal studies have helped to set the stage for EMRB's effects on NK cell function.

HOW YOUR LIFE DEPENDS ON NATURAL KILLERS



"**Natural killer cells**" are one of your body's leading defenses against dying. That's because these specialized immune cells are natural killers of cells that have become transformed, either by infection with a virus or by one of many malignant changes that mutate them into cancer cells.[9,16]

Natural killer (NK) cells are part of your ***innate immune system***, that part of the immune system that was ready to go the moment you were born (innate means "from birth").[64] Unlike cells belonging to your ***adaptive immune system***, NK cells don't require specific antibodies to do their work.[65]

Rather, NK cells come fully equipped to recognize any cells that don't belong in your body.[65] Such cells include those whose replicative machinery has been taken over by a virus, and also cells that have gone rogue to replicate without natural controls, such as cancer cells.[16]

Thus, NK cells normally patrol throughout your body, acting almost like tiny but well-armed security guards. As they circulate in your bloodstream, NK cells constantly seek out cells that lack the proper "ID badge," in the form of molecular patterns indicating that they are authorized parts of your biological self.[66-69]

Once such unauthorized cells have been identified, NK cells shoot to kill, destroying virally or malignantly transformed cells, while leaving intact any normal, healthy cells that can prove their identity.[68] NK cells use as weapons chemical substances that punch holes in target cell membranes, allowing them to insert proteins that trigger the cell death program called apoptosis, which lies latent in every cell.[70]

Cells infected by viruses are detrimental to our body, both acutely and chronically. Destruction of virally infected cells by apoptosis prevents continued intracellular replication of viruses.[16,70]

Functional NK cells are needed to destroy virus-infected cells before viral replication gets out of control. Failure of NK cells to control an infection results in release of new viruses, followed by more rapid infection, viral replication, and

destruction of millions of additional cells, spreading the virus throughout the body.

In the case of malignant cells, NK cell-induced apoptosis can stop a developing cancer in its tracks, preventing further replication of cells before they can form an invading, metastasizing tumor.[71]

NK cells have recently been found to have other important functions vital to infection- and cancer-free survival:

- NK cells secrete cytokines, which are chemical signaling molecules that regulate the activity of other immune system cells;[5]
- NK cells are essential to stopping inflammatory responses once they've done their work, [72-74] for example, by deleting populations of senile immune cells. NK cells can shift the immune system's focus away from a target that has already been neutralized;[75]
- NK cells can enhance the immune response to ongoing threats by stimulating "B-lymphocytes" to produce antibodies that destroy specific antigens.[76]

Unfortunately, a decline in **NK cell function** with age can leave older adults uniquely vulnerable to viral infections, especially during the wintertime peak in influenza. But a unique formula of **enzymatically modified rice bran** (**EMRB**) has been developed that boosts NK cell activity by nearly **84%**, potentially reducing the severity and duration of viral illnesses—and death from certain cancers as well.

EMRB Boosts NK Cell Activity In Just Two Days!

An especially promising early animal study demonstrated the power of EMRB for boosting NK cell activity. When old mice with age-related reduction of NK function were injected with EMRB, they showed a greater than **five-fold** increase in NK cell activity within just **two days** of treatment.[46] The enhanced NK activity in this study also resulted in increased binding of NK cells to target tissues and boosted the amounts of cell-killing chemicals inside each cell.

As a number of lab studies have shown, this increase in NK cell activity could have important benefits, including enhancing the body's response to vaccines and chemotherapy. This magnitude of restoration of immune cells is usually accomplished only by very expensive injectable drugs, such as interleukin-2[52] and granulocyte colony-stimulating factor (GCSF).[53-55]

Another important benefit derived from EMRB's activation of NK cells is that it enhances the body's immune response to vaccines against both infections and cancers.[56] This is of special importance to older adults, whose vaccine responses are often weaker than desired. Finding effective ways to boost the vaccine's efficacy is a major priority in adult vaccine development.

In a landmark study of cultured human blood cells, EMRB inhibited the replication of one of humanity's most-feared viruses, HIV, by *boosting* multiple immune responses that are typically *suppressed* by the AIDS virus.[57]

A series of cell culture studies has also established that EMRB's ability to activate NK cells helps fight cancer. One such study showed that EMRB increased susceptibility of both human and mouse breast cancer cells to a common chemotherapy drug *by more than **100-fold** !*[58] This has tremendous implications for reducing the doses of toxic chemotherapy agents in current use.

And in cells from human T-cell leukemia, EMRB alone induced the death of malignant cells.[59]

Human Studies Prove EMRB's Benefits

Human studies on supplementation with EMRB are equally impressive.

When a group of 20 healthy adult men and women were supplemented with EMRB for 60 days, with either a dose of **1,000 mg/day** or **3,000 mg/day**, NK cell activity in both groups jumped by approximately **35%** in the first week.[12]

A similar effect was shown in another study when a lower dose of **500 mg/day** of enzymatically modified rice bran was given to healthy subjects between 45 and 55 years old. With EMRB supplementation, all participants experienced a significant **three-fold** enhancement of NK activity in just three to four weeks—with no side effects.[60]

In a four-month study in individuals who were initially low in NK cell activity, supplementation with **1,000 mg/day** of EMRB led to a **four-fold** increase in NK cell activity at two months, compared to control responses. And at the end of four months, participants showed a **seven-fold** increase in NK cell activity![61]

EMRB has also been studied in human patients with malignancies with remarkable results. In 48 patients with multiple myeloma, a blood cancer, whose median age was 65 years, a dose of **2,000 mg/day** for three months produced a significant near **84%** increase in **NK cell activity** by the end of the second month of supplementation.[11]

This increase in NK cell activity could potentially result in longer life spans, as demonstrated by the next study on patients with a deadly form of liver cancer called ***hepatocellular carcinoma***. In a three year randomized, controlled trial of EMRB vs. placebo, supplemented patients had a reduced recurrence rate of the cancer (**31.6%** EMRB-group versus **46.7%** in controls).[47] Supplemented subjects also lived longer.

- At one year, **76%** of supplemented subjects were alive, but only **63%** of control patients survived;
- At two years, **35%** of supplemented patients were alive, but only **6.7%** of control subjects survived; and
- By two and a half years, **11%** of supplemented subjects survived, while no control patient remained alive.

An Optimum Regimen For A Potent Supplement

EMRB (enzymatically modified rice bran) provides a much-needed boost for aging immune systems, specifically by restoring NK cell activity. The only other way to accomplish this is with expensive pharmaceutical drugs that have to be closely monitored by an expert physician to protect against side effects.

However, EMRB may only need to be taken for a limited period of time each year. Some researchers are concerned that *overstimulation* of NK cells over long time spans may not be desirable.[62,63]

We recommend taking EMRB when your body is most vulnerable to viral infections: the roughly four-month period of the flu season's peak activity, from early December to the end of March. [23] That is when your NK cell activity is most vital for protection against influenza and its consequences. During this period of intensive immune stimulation, your body may also rid itself of incipient premalignant cells and "senile" cells that can contribute to chronic inflammation.

Once the flu season is over, you can stop the EMRB supplement until next year's season begins. All-year immune support can be obtained by supplementing with other immune enhancers such as *Cistanche* and *Reishi* that provide broad-spectrum immune support, including enhanced NK cell activity.

Summary

At the peak of the wintertime virus season, older adults are uniquely vulnerable to potentially life-threatening infections. This is part of the bigger picture of ***immune senescence***, the natural decline of our immune function with age.

NK cells normally provide your body's first, immediate response to previously unknown threats.

Since NK cell function declines with age, we should consider taking special steps during the winter season to fill in this critical component of immune function.

Studies show that **enzymatically modified rice bran** (EMRB) rapidly and significantly boosts aging **NK activity**, with real-world effects demonstrated on both viral infections and cases of malignancy.

Maturing individuals should take steps to maintain and strengthen immune function year-round with supplements (such as ***Cistanche*** and **Reishi**) aimed at the **innate** and **adaptive** immune responses.

During the high-risk winter months, however, it would appear to be quite beneficial to add the **NK cell** activity-boosting effects of **EMRB**. This can provide the added protection needed to conquer acute and chronic issues that can markedly shorten life spans.

During that four-month period, you may also be ridding your body of accumulated precancerous cells and inflammation-generating senescent cells that have outlived their usefulness.

If you have any questions on the scientific content of this article, please call a **Life Extension**® Health Advisor at 1-866-864-3027.

References

1. Centers for Disease Control and Prevention (CDC). Estimated influenza illnesses and hospitalizations averted by influenza vaccination - United States, 2012-13 influenza season. *MMWR Morb Mortal Wkly Rep*. 2013 Dec 13;62(49):997-1000.
2. Available at: http://www.mayoclinic.org/diseases-conditions/flu/basics/complications/con-20035101. Accessed October 14, 2014.
3. File TM Jr, Marrie TJ. Burden of community-acquired pneumonia in North American adults. *Postgrad Med*. 2010 Mar;122(2):130-41.
4. Available at: http://www.cdc.gov/pneumococcal/about/facts.html. Accessed October 14, 2014.
5. Hazeldine J, Lord JM. The impact of ageing on natural killer cell function and potential consequences for health in older adults. *Ageing Res Rev.* 2013 Sep;12(4):1069-78.
6. Haq K, McElhaney JE. Immunosenescence: Influenza vaccination and the elderly. *Curr Opin Immunol*. 2014 Aug;29:38-42.
7. Dorrington MG, Bowdish DM. Immunosenescence and novel vaccination strategies for the elderly. *Front Immunol*. 2013 Jun 28;4:171.
8. Weinberger B, Herndler-Brandstetter D, Schwanninger A, Weiskopf D, Grubeck-Loebenstein B. Biology of immune responses to vaccines in elderly persons. *Clin Infect Dis*. 2008 Apr 1;46(7):1078-84.
9. Wu J, Lanier LL. Natural killer cells and cancer. *Adv Cancer Res*. 2003;90:127-56.
10. Fulop T, Larbi A, Kotb R, Pawelec G. Immunology of aging and cancer development. *Interdiscip Top Gerontol*. 2013;38:38-48.
11. Cholujova D, Jakubikova J, Czako B, et al. MGN-3 arabinoxylan rice bran modulates innate immunity in multiple myeloma patients. *Cancer Immunol Immunother.* 2013 Mar;62(3):437-45.
12. Ali KH, Melillo AB, Leonard SM, et al. An open-label, randomized clinical trial to assess the immunomodulatory activity of a novel oligosaccharide compound in healthy adults. *Functional Foods in Health and Disease.* 2012;2(7):265-79.

13. Harizi H. Reciprocal crosstalk between dendritic cells and natural killer cells under the effects of PGE2 in immunity and immunopathology. *Cell Mol Immunol*. 2013 May;10(3):213-21.
14. Biron CA, Nguyen KB, Pien GC, Cousens LP, Salazar-Mather TP. Natural killer cells in antiviral defense: function and regulation by innate cytokines. *Annu Rev Immunol*. 1999;17:189-220.
15. Paananen A, Mikkola R, Sareneva T, et al. Inhibition of human natural killer cell activity by cereulide, an emetic toxin from Bacillus cereus. *Clin Exp Immunol*. 2002 Sep;129(3):420-8.
16. Bernardini G, Santoni A. The pathophysiological role of chemokines in the regulation of NK cell tissue homing. *Crit Rev Oncog*. 2014;19(1-2):77-90.
17. Cheng M, Chen Y, Xiao W, Sun R, Tian Z. NK cell-based immunotherapy for malignant diseases. *Cell Mol Immunol*. 2013 May;10(3):230-52.
18. Aicheler RJ, Stanton RJ. Functional NK cell cytotoxicity assays against virus infected cells. *Methods Mol Biol*. 2013;1064:275-87.
19. Tai LH, de Souza CT, Bélanger S, et al. Preventing postoperative metastatic disease by inhibiting surgery-induced dysfunction in natural killer cells. *Cancer Res*. 2013 Jan 1;73(1):97-107.
20. Akatsu H, Iwabuchi N, Xiao JZ, et al. Clinical effects of probiotic Bifidobacterium longum BB536 on immune function and intestinal microbiota in elderly patients receiving enteral tube feeding. *JPEN J Parenter Enteral Nutr.* 2013 Sep;37(5):631-40.
21. McFarlin BK, Flynn MG, Phillips MD, Stewart LK, Timmerman KL. Chronic resistance exercise training improves natural killer cell activity in older women. *J Gerontol A Biol Sci Med Sci.* 2005 Oct;60(10):1315-8.
22. Campos C, Pera A, Sanchez-Correa B, et al. Effect of age and CMV on NK cell subpopulations. *Exp Gerontol.* 2014 Jun;54:130-7.
23. Available at: http://www.cdc.gov/flu/about/season/flu-season.htm. Accessed October 14, 2014.
24. Available at: http://www.cdc.gov/flu/about/qa/disease.htm. Accessed October 14, 2014.
25. Available at: http://www.flu.gov/about_the_flu/seasonal/. Accessed October 14, 2014.
26. Available at: http://www.cdc.gov/flu/about/disease/65over.htm.Accessed October 14, 2014.
27. Santos MS, Meydani SN, Leka L, Wu D, Fotouhi N, Meydani M, et al. Natural killer cell activity in elderly men is enhanced by beta-carotene supplementation. *Am J Clin Nutr*. 1996 Nov;64(5):772-7.
28. Mocchegiani E, Malavolta M. NK and NKT cell functions in immunosenescence. *Aging Cell*. 2004 Aug;3(4):177-84.
29. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA*. 2004 Sep 15;292(11):1333-40.
30. Si-Tahar M, Touqui L, Chignard M. Innate immunity and inflammation--two facets of the same anti-infectious reaction. *Clin Exp Immunol*. 2009 May;156(2):194-8.
31. Woods JA, Davis JM, Smith JA, Nieman DC. Exercise and cellular innate immune function. *Med Sci Sports Exerc*. 1999 Jan;31(1):57-66.
32. Priest SO, Baumgarth N. The role of innate signals in B cell immunity to influenza virus. *Front Biosci (Schol Ed).* 2013;5:105-17.
33. Alberts B, Johnson A, Lewis J, et al. *Molecular Biology of the Cell*. 4th edition. New York: Garland Science; 2002. Chapter 24, The Adaptive Immune System.
34. Antrobus RD, Lillie PJ, Berthoud TK, et al. A T cell-inducing influenza vaccine for the elderly: safety and immunogenicity of MVA-NP+M1 in adults aged over 50 years. *PLoS One*. 2012;7(10):e48322.
35. Lewis W, Day BJ, Copeland WC. Mitochondrial toxicity of NRTI antiviral drugs: an integrated cellular perspective. *Nat Rev Drug Discov*. 2003 Oct;2(10):812-22.
36. Available at: http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/282/monthly-suggested-wholesale-price-of-antiretroviral-drugs. Accessed October 2014, 2014.
37. Stiver G. The treatment of influenza with antiviral drugs. *CMAJ*. 2003 Jan 7;168(1):49-56.
38. Allen U. The battle against influenza: The role of neuraminidase inhibitors in children. *Paediatr Child Health*. 2000 Nov;5(8):457-60.
39. McGeer A, Sitar DS, Tamblyn SE, Faron K, Orr P, Aoki FY. Use of antiviral prophylaxis in influenza outbreaks in long-term care facilities. *Can J Infect Dis*. 2000 Jul;11(4):187-92.

40. Góra-Sochacka A, Redkiewicz P, Napiórkowska B, Sirko A. Plant-based production of recombinant cytokines. *Postepy Biochem*. 2009;55(1):85-94.
41. Sportes C, Babb RR, Krumlauf MC, et al. Phase I study of recombinant human interleukin-7 administration in subjects with refractory malignancy. *Clin Cancer Res.* 2010 Jan 15;16(2):727-35.
42. Krawczenko A, Kieda C, Du D. The biological role and potential therapeutic application of interleukin 7. *Arch Immunol Ther Exp (Warsz). 2005 Nov-Dec;53(6):518-25.*
43. *Tarazona R, Gayoso I, Alonso C, et al. NK cells in human ageing. Handbook on Immunosenescence.* Netherlands: Springer;2009:531-44.
44. Zucchini N, Crozat K, Baranek T, Robbins SH, Altfeld M, Dalod M. Natural killer cells in immunodefense against infective agents. *Expert Rev Anti Infect Ther*. 2008 Dec;6(6):867-85.
45. Terunuma H, Deng X, Nishino N, Watanabe K. NK cell-based autologous immune enhancement therapy (AIET) for cancer. *J Stem Cells Regen Med*. 2013 Apr 30;9(1):9-13.
46. Ghoneum M, Abedi S. Enhancement of natural killer cell activity of aged mice by modified arabinoxylan rice bran (MGN-3/Biobran). *J Pharm Pharmacol.* 2004 Dec;56(12):1581-8.
47. Bang MH, Van Riep T, Thinh NT, et al. Arabinoxylan rice bran (MGN-3) enhances the effects of interventional therapies for the treatment of hepatocellular carcinoma: a three-year randomized clinical trial. *Anticancer Res.* 2010 Dec;30(12):5145-51.
48. McCartney L, Marcus SE, Knox JP. Monoclonal antibodies to plant cell wall xylans and arabinoxylans. *J Histochem Cytochem.* 2005 Apr;53(4):543-6.
49. Hopkins MJ, Englyst HN, Macfarlane S, Furrie E, Macfarlane GT, McBain AJ. Degradation of cross-linked and non-cross-linked arabinoxylans by the intestinal microbiota in children. *Appl Environ Microbiol.* 2003 Nov;69(11):6354-60.
50. Kim HY, Kim JH, Yang SB, et al. A polysaccharide extracted from rice bran fermented with Lentinus edodes enhances natural killer cell activity and exhibits anticancer effects. *J Med Food.* 2007 Mar;10(1):25-31.
51. Choi JY, Paik DJ, Kwon DY, Park Y. Dietary supplementation with rice bran fermented with Lentinus edodes increases interferon-gamma activity without causing adverse effects: a randomized, double-blind, placebo-controlled, parallel-group study. *Nutr J.* 2014;13:35.
52. Riccardi C, Giampietri A, Migliorati G, Cannarile L, D'Adamio L, Herberman RB. Generation of mouse natural killer (NK) cell activity: effect of interleukin-2 (IL-2) and interferon (IFN) on the in vivo development of natural killer cells from bone marrow (BM) progenitor cells. *Int J Cancer*. 1986 Oct 15;38(4):553-62.
53. Hollingshead LM, Goa KL. Recombinant granulocyte colony-stimulating factor (rG-CSF). A review of its pharmacological properties and prospective role in neutropenic conditions. *Drugs*. 1991 Aug;42(2):300-30.
54. Rubinstein MP, Salem ML, Doedens AL, et al. G-CSF/anti-G-CSF antibody complexes drive the potent recovery and expansion of CD11b+Gr-1+ myeloid cells without compromising CD8+ T cell immune responses. *J Hematol Oncol.* 2013 Oct 1;6:75.
55. Goa KL, Bryson HM. Recombinant granulocyte-macrophage colony-stimulating factor (rGM-CSF): an appraisal of its pharmacoeconomic status in neutropenia associated with chemotherapy and autologous bone marrow transplant. *Pharmacoeconomics*. 1994 Jan;5(1):56-77.
56. Ghoneum M, Agrawal S. Activation of human monocyte-derived dendritic cells in vitro by the biological response modifier arabinoxylan rice bran (MGN-3/Biobran). *Int J Immunopathol Pharmacol.* 2011 Oct-Dec;24(4):941-8.
57. Ghoneum M. Anti-HIV activity in vitro of MGN-3, an activated arabinoxylane from rice bran. *Biochem Biophys Res Commun.* 1998 Feb 4;243(1):25-9.
58. Ghoneum M, Badr El-Din NK, Ali DA, El-Dein MA. Modified arabinoxylan from rice bran, MGN-3/biobran, sensitizes metastatic breast cancer cells to paclitaxel in vitro. *Anticancer Res.* 2014 Jan;34(1):81-7.
59. Revilla E, Santa-Maria C, Miramontes E, et al. Antiproliferative and immunoactivatory ability of an enzymatic extract from rice bran. *Food Chem.* 2013 Jan 15;136(2):526-31.
60. Daiwa Pharmaceutical Co., Ltd. NK Cell Immunomodulatory Function by Modified Arabinoxylan Rice bran (MGN-3/Biobran) at Low Concentration (500 mg/day = 7 mg/kg/day). Unpublished Study 2012.
61. Ghoneum, M. Immunostimulation and Cancer Prevention. *The Study Abstract of the 7th International Congress on*

*Anti-Aging & Biomedical Technologies Proceedings Manual.*1999.
62. Joncker NT, Raulet DH. Regulation of NK cell responsiveness to achieve self-tolerance and maximal responses to diseased target cells. *Immunol Rev*. 2008 Aug;224:85-97.
63. Baschuk N, Wang N, Watt SV, et al. NK cell intrinsic regulation of MIP-1 by granzyme M. *Cell Death Dis*. 2014 Mar 13;5:e1115.
64. Sta Maria NS, Barnes SR, Jacobs RE. In vivo monitoring of natural killer cell trafficking during tumor immunotherapy. *Magn Reson Insights.* 2014;7:15-21.
65. Fischer U, Koppang EO, Nakanishi T. Teleost T and NK cell immunity. *Fish Shellfish Immunol.* 2013 Aug;35(2):197-206.
66. Ivarsson MA, Michaelsson J, Fauriat C. Activating killer cell Ig-like receptors in health and disease. *Front Immunol.* 2014;5:184.
67. Poggi A, Prevosto C, Zancolli M, Canevali P, Musso A, Zocchi MR. NKG2D and natural cytotoxicity receptors are involved in natural killer cell interaction with self-antigen presenting cells and stromal cells. *Ann N Y Acad Sci.* 2007 Aug;1109:47-57.
68. Bonavida B. NK Cell phenotypic and functional heterogeneities and molecular mechanisms of cytotoxicity. *Crit Rev Oncog.* 2014;19(1-2):21-45.
69. Davies JO, Stringaris K, Barrett JA, Rezvani K. Opportunities and limitations of natural killer cells as adoptive therapy for malignant disease. *Cytotherapy.* 2014 May 20.
70. Warren HS, Smyth MJ. NK cells and apoptosis. *Immunol Cell Biol*. 1999 Feb;77(1):64-75.
71. Lapteva N, Szmania SM, van Rhee F, Rooney CM. Clinical grade purification and expansion of natural killer cells. *Crit Rev Oncog.* 2014;19(1-2):121-32.
72. Duthie MS, Kahn M, White M, Kapur RP, Kahn SJ. Critical proinflammatory and anti-inflammatory functions of different subsets of CD1d-restricted natural killer T cells during Trypanosoma cruzi infection. *Infect Immun*. 2005 Jan;73(1):181-92.
73. Hall LJ, Murphy CT, Quinlan A, et al. Natural killer cells protect mice from DSS-induced colitis by regulating neutrophil function via the NKG2A receptor. *Mucosal Immunol.* 2013 Sep;6(5):1016-26.
74. Gao Y, Li Z, Hassan N, et al. NK cells are necessary for recovery of corneal CD11c+ dendritic cells after epithelial abrasion injury. *J Leukoc Biol*. 2013 Aug;94(2):343-51.
75. Schuch A, Hoh A, Thimme R. The role of natural killer cells and CD8 T cells in hepatitis B virus infection. *Front Immunol.* 2014;5:258.
76. Lang ML. How do natural killer T cells help B cells? *Expert Rev Vaccines.* 2009 Aug;8(8):1109-21.