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REVIEW ARTICLE

The clinical applications of Hematopoietic growth factor - GCSF

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ABSTRACT

Enormous number of Hematopoietic growth factors like CSF, GCSF, and GMCSF have been cloned, purified and produced in *E.coli.* Recombinant human GCSF is a Hematopoietic growth factor, extensively used in Cancer therapy to treat Neutropenia and to combat infections, immune suppression, anti-inflammatory responses, immunomodulation, stem cell transplantation, myocardial infarctions etc. This review discusses about G-CSF signaling, mechanisms of G-CSF-induced stem cell mobilization, and influence of G-CSF on T-cell function and dendritic cell activation. An attempt has been made to link the current issues about the biology of G-CSF with its clinical uses, both present and future.

It also depicts various applications of GCSF in Chemotherapy, radiation therapy and the use of GCSF in repair, regeneration of neuronal tissues etc. by Stem cells and progenitor cells.

Keywords: Hematopoietic growth factor, Granulocyte Colony Stimulating Factor (GCSF), neutropenia. Colony stimulating Factors (CSF3), Granulocyte Colony Stimulating factor Receptor(GCSFR), therapy, myeloablative therapy, chemotherapy, cancer, neutrophils, stem cells, bone marrow.

1. INTRODUCTION

GCSF is a Hematopoietic growth factor, produced by a number of tissues that stimulate bone marrow to produce granulocytes and stem cells [3] and release them into the blood. It also stimulates the survival, proliferation, differentiation, and neutrophil precursors and maturation functions [4-6]. GCSF is also involved in the regulation of various signal transduction pathways like JAK, STAT, MAPK, P13K, and Akt [1-2, 7].

During past 10 years a major change has been observed in understanding the role of biological molecules in production and activation of blood cells [8-10]. It is evident that some of the molecules like granulocyte colony stimulating factors play vital role in granulopoiesis stimulate bone marrow to produce more WBC and enhance circulating neutrophils. GCSF has found its use for new therapies for cancer patients [11], for combating life threatening infections, healing and regeneration of tissues. With the recent advances in science and enthusiasm for the use of biological molecules like Colony stimulating factors, cytokines, biological response modifiers are used in cancer therapy .The recovery and enhancement of circulating blood cells is a new paradigm for molecular medicine.

The mature human glycoprotein-GCSF exists in two forms with 174 and 180 amino acid –long protein which differs by the presence or absence of 3 amino acids, but the active form is 174 amino acids long protein with a free cysteine at 17th position, two intra molecular disulfide bonds between Cys36 - Cys42 and Cys64 – Cys74 [12-13] which are necessary for biological activity of GCSF [14-15].

GCSF is a Hematopoietic growth factor of myeloid lineage [16] that affects proliferation and differentiation of

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progenitors of neutrophil [17-19] and granulocyte lineages. It is produced mainly by monocytes, macrophages, endothelial cells [6, 20-21], fibroblasts, astrocytes and a number of immune cells. In addition various carcinoma cells and myeloblastic leukemia cells constitutively express GCSF.

Mechanism of action:

GCSF produced in the bone marrow in response to cell stimuli, it binds to specific receptors called cytokine receptors with one trans membrane domain, intracellular signal transduction domain and homo-oligomerizes upon ligand binding. GCSF receptors are present on hematopoietic progenitors, monocytes, platelets, neurons, endothelial cells [20, 22-24] and small-cell lung cancer cells [25-26].

Activation of these receptors, upon binding of GCSF, followed by induction of signaling cascade like Janus kinase (JAK) / signal transducer and transcription activator pathways (STAT), Ras/ Mitogen activated protein (MAP) kinase and Phosphotidyl inositol 3-kinase (P13K) / Protein kinase B (pkb) / (Akt) pathways. These pathways have shown to induce cellular proliferation [27], anti-inflammatory processes and anti-apoptic processes [28-33] these signaling pathways play a role in mobilizing stem cells and targeted to injured site especially to heart and brain. These investigations lead to the potential use of GCSF in bone marrow transplantations, treating myocardial infarctions [34-38] and cerebral ischemia [1, 39].

GCSF-R involved in a range of malignancies due to the mutations in this receptor has been seen in several clinical implications like severe congenital neutropenia [40], myelodysplastic syndrome and acute myeloid leukemia [41].

Applications of GCSF

1.GCSF used in therapy since it stimulates the production of white blood cells (WBC),a recombinant form of GCSF used in oncology and hematology to treat certain cancer patients[11] to accelerate- recovery from neutropenia after chemotherapy[42].

2. Recombinant human GCSF used for the treatment of severe chronic neutropenia patients receiving myelosuppressive therapy [43], bone marrow transplants [15]. GCSF is also used in Stem cell or bone marrow transplantation in order to increase the number of hematopoietic stem cells.

3. GCSF is an important cytokine in regulating Immune defense against pathogenic bacterial infections. Recently GCSF is widely used in Cancer patients with Chemotherapy induced neutropenia and in the preparation of hematopoietic stem cells mobilization for transplantation before the initiation of myeloablative chemotherapy. In addition to this HSC donors receive GCSF for 5 days, their T cells produce more IL-4 and less IFN-g associated with a lower risk of acute GVHD.

4. Besides the function of Hematopoietic effect, it can also act as Neurotrophic factor, induce neuorogenesis and to counteract apoptosis. These properties Plays a major role in the development of treatments of neurological diseases such as cerebral ischemia [33, 44].

5. GCSF decreases the cytotoxicity of NK cell activity by cytokine receptors and other signaling regulated pathways of P13K/Akt and ERK/MAPK and decrease the cytotoxicity related gene expression [45]. GCSF impairs NK cell cytotoxicity usually seen in Autoimmunity and transplant rejections [46]. After the GCSF administration for 5 consecutive days the number of WBCs, CD34+, and neutrophils are markedly increased might regulate the immunological network, activation of CD34+ cells, lymphocytes and granulocytes [45].

6. GCSF also plays a potent role in inducing the mobilization of hematopoietic stem cells (HSCs) from the bone marrow into the blood stream [47-48].

7. GCSF has an important role in defense against infection, inflammation and repair processes and also in maintenance of steady state hematopoiesis [49-51].Recent studies reported that GCSF has regenerating and repairing function in the skeletal muscle regeneration therapy [52] and to reduce the hepatic damage [53].

8. Apart from this GCSF have special properties like tumorocidal activity, blast cell growth factor activity and in controlling the neuropathic pain [54].

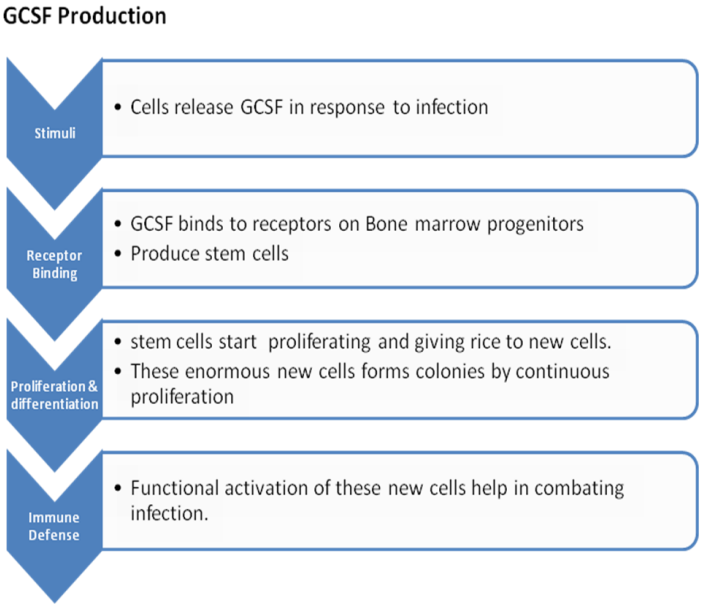

Fig 1: Depicts the GCSF production in response to infection and contributes to Immune defense.

Mechanism of Action of GCSF

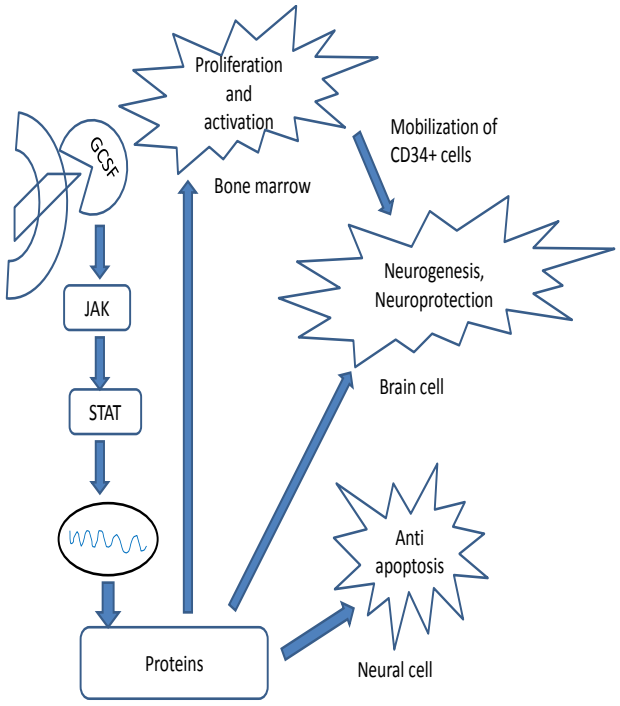

Fig 2: GCSF binds to GCSF receptors, activates signaling pathways (JAK / STAT) and has specific functions in different cells.

Cancer and Neutropenia

Since 1990 the role of GCSF in clinical treatment has gone from strength to strength in raising white cell counts and protect from potentially lethal infections following high dose chemotherapy, radiation therapy and bone marrow transplantation.

The American Society of Clinical Oncology (ASCO) and recently several other organizations have renovated the clinical guidelines [55] for cancer therapy by using Colony stimulating factors/hematopoietic growth factor like GCSF. Since GCSF influence the proliferation, differentiation and maturation of neutrophils and increase the rate of neutrophil recovery following chemotherapy [56-57].

As per the European Society of Medical Oncology (ESMO) and the Infectious Diseases Society of America (IDSA) recommended broad spectrum antibiotics [58-59] for immediate treatment of neutropenia. Neutropenia is a hematological disorder characterized by an abnormal decrease in neutrophil count that is less than 500cells/mm3 (0.5 X 10 9/L) [60] which reflects a higher infection risk, usually seen in malignancies, bone marrow transplantation, suppression, chemotherapy, leukemia, lymphoma, multiple myeloma and extensive myelosuppressive therapy [61].

GCSF has been used in clinics to treat congenital, acquired and febrile neutropenia before or during the cytoreductive therapy [62]. GCSF is used to decrease the incidence of infection [63-64], as manifested by febrile neutropenia, patients with non-myeloid malignancies receiving myelosuppressive anti cancer drugs associated with incidence of severe neutropenia and the duration of fever. It can be managed by reducing the chemotherapy doses in order to reduce the myelosuppression but these also reduce the clinical effectiveness of chemo. GCSF effects mainly on reducing the time of neutrophil recovery in oncology patients receiving chemotherapy [65]. The mean time of neutrophil recovery is 5 days.

In Clinical studies GCSF currently given to shorten the duration of neutropenia following chemotherapy [66] induction in older adults of AML, for BMT failure to mobilize the stem cells for transplantation and for myeloid reconstitution in BMT (bone marrow transplantation).

GCSF has been used in combination therapy to treat advanced endometrial cancer, breast cancer patients [67-70], transitional cell carcinoma of the urothelium [71-72], and small cell lung carcinoma [73]

Recombinant human GCSF is used as primary prophylaxis in reducing the incidence of Febrile neutropenia [74] and chemotherapy induced neutropenia [75] in patients with myelosuppressive chemotherapy for various cancers(Breast cancer, colorectal cancer) lymphoma and solid tumors(lung, ovarian, breast). It is also given to prevent premature labor in severe neutropenia patients [76].

Bone marrow suppression

The bone marrow is the thick liquid present in the inner part of some bones and it produces white blood cells (WBCs), red blood cells (RBCs) and platelets.

Bone marrow suppression or myelosuppression is a common side effect of chemotherapy, characterized by reduced number of blood cell production [77]. The majority of chemotherapy drugs associated with myelosuppression, affecting the immune system is Azathioprine, Flurouracil, Oxalipatin, Irinotecan and Capecitabine. The patients will develop moderate to life threatening infections as well as bleeding.

Growth factor injections (GCSF) ,a natural chemical that boost the bone marrow performance is widely used to mobilize the bone marrow stem cells in leukemia patients [78] treated with bone marrow transplantation and chemotherapy induced neutropenia [79-80].

The blood cell count falling below the lowest count is called nadir, usually WBCs and platelets will reach nadir in 7-14 days of chemotherapy treatment because of their little life span. Whereas RBCs take few weeks (3-4 weeks) after chemotherapy to reach their nadir.

Doctors prescribe hematopoietic factors/colony stimulating factors to keep the WBC from falling too low so that chemotherapy can be given as scheduled. Normal human body produces hematopoietic or growth factors to prompt the bone marrow to make various blood cells.

Aplastic Anemia

Aplastic Anemia patients have impaired proliferation and differentiation of hematopoietic stem cells. Recombinant GCSF has been extensively evaluated clinically for transient increase of neutrophil count and is used in treatment and prophylaxis of infections in majority of Aplastic Anemia (AA) patients**.** It also used to alleviate anemia in aplastic anemia, CSF3 is essential for an emergency granulopoiesis [81-83], in response to invading bacterial pathogens and infections by enhancing multiple neutrophil functions [84].

Role of GCSF in central nervous system

In response to stimuli like hematopoietic growth factors, myeloablative therapy and infection, there is an increase in the number of hematopoietic stem and progenitor cell (HSPCs) in the circulation [85].GCSF has a potential role in protecting the myocardium. Stem cell mobilization with GCSF has a potential regenerative strategy for treating acute myocardial infarction [86-87]. The potential beneficial action GCSF cytokine attributed by inhibiting the apoptosis on injured myocardium [88] rather than the stem cell mobilization and differentiation from bone marrow into myocytes.

GCSF has a prominent role in central nervous system and of potential relevance to a number of neurological conditions [33]. Neurons have expressed GCSF and its receptor [89] in many regions of brain and are up regulated in experimental stroke. GCSF activates several neuroprotective pathways like mobilization of hematopoietic stem cells [90-91] neuronal differentiation, angiogenesis and anti inflammation [92-93] and act anti-apoptotically [94-95]. An optimal dose of GCSF will increase the CD-34+ cells [96-97] in peripheral blood it decreases infarct volumes [98] in vivo acute stroke models [99].

First indication of protective effect on cultured neurons against glutamate induced cell death. [1-2].GCSF stimulates the brain neuronal stem cell differentiation and improves the long term recovery in more chronic stroke models. Thus GCSF is considered as a novel neurotrophic factor and is considered as attractive model for the treatment of neurodegenerative conditions. GCSF plays an important role in neuroprotection [100-101] and neurogenesis relevant to ischemia [33,102].

GCSF has been shown to promote structural and functional regeneration of the central nervous system in strokes patient. Neural growth factor like GCSF has been used to counteract neutropenia and mobilize hematopoietic stem cells from bone marrow in stem cell transplantation [33]. Animal strokes data showed that GCSF passes the intact blood brain barrier, acts on neurons for recovery. GCSF not only counteracts cell death but also has the potential to enhance neuroplasticity which leads to functional recovery at long intervals of stroke [1,33,103-105].Recent study showed that GCSF treatment in elderly chronic stroke patients with concomitant vascular disease is safe and is reasonably well tolerated [106].

Apart from the hematopoietic recovery, neuronal death inhibition GCSF also induces the repair and regeneration of new neuronal tissues like spinal cord and brain by the mobilization of stem cells from bone marrow to the injured tissues [99].

Regulation of Immune system by GCSF

Immunosuppression

Immunosuppression means that reduces the activation or efficacy of immune system. Suppressing the excessive immune activation usually seen in the bowel walls of Crohn's disease. Crohn's disease (CD) is characterized as an immune deficiency disorder, also known as chronic inflammatory, granulomatous bowl disease. A variety of defects in Apoptosis [107] and T-cell regulation, which results in the modification in immune tolerance and predisposes the intestinal inflammation. Intestinal homeostasis can be maintained by special cells like T-regulatory cells have tolerance to microbial and dietary antigens. Treg cell defect [108-109] is observed in chronic intestinal inflammation. In this case GCSF plays a very important role, acts as an anti-inflammatory agent which could enhance the intestinal innate immune system by modulating the cellular proliferation, differentiation, angiogenesis, inflammation and serves as messengers between various systems including intestine, enteric nerves and immunity.

Clinically GCSF has been used in treating fistula in a CD patient which could act by enhancing the activity of subpopulations of T- regulatory cells [110] and reduces the T-cell activation [111] and gastro intestinal symptoms have been improved in CD [112-114].

Indirectly GCSF also acts on CD patients with neutropenia and septic complications [111] occurred due to intake of drugs like azathioprine / immunosuppressant drugs.

GCSF also has a profound role in immuno regulatory effects in adoptive immunity by mediating anti inflammatory reactions accompanied by TH2 cell differentiation and promoting T cell tolerance [91].These findings have highlighted the impact of GCSF even on Autoimmunity [115].

Several reports demonstrated that GCSF exerts immuno regulatory properties by expanding monocytes and macrophages and promote anti inflammatory processes.

These hypotheses help in therapeutic potential in autoimmune diseases like experimental auto immune encephalomyelitis (EAE) [116], human demyelinating

disease-multiple sclerosis. It is mediated by the activation of inflammatory Th1 cells [117].Immune prevention of EAE with GCSF have been achieved by eliciting the regulatory T cells which release anti inflammatory cytokines [118-119]. GCSF not only prevents the development of EAE but it also protects from the onset of disease by exerting its remarkable, long lived protective effects on the clinical course of EAE and the progression of the disease is inhibited in the central nervous system (CNS) [116].

Emerging evidence provided by experimental data for treating autoimmune type1 diabetes is a significant achievement which is a T cell-mediated disease in NOD mouse [120].

Recombinant human GCSF has been used to treat Felty's syndrome (FS) [121], chronic T-cell lymphocytosis (CTL) [122], rheumatic disease (RD) [123], severe chronic neutropenia [124] and Auto immune neutropenia, is a rare condition mostly associated with auto immune diseases, clonal lympho proliferative disorders and seen in young women. Auto immune neutropenia [125-126] may be a cell or antibody mediated destruction of granulocytes and their precursors due to the inhibitory CD8+ T-cells present in the marrow spaces.

GCSF role in Liver damage and Antiviral therapy

Mobilization of CD34+ cells improves the survival rate in Acute –on-Chronic Liver Failure (ACLF), Alcoholic hepatitis and liver cirrhosis patients using GCSF [127]. This condition is seen in chronic liver disease and is manifested by Jaundice, coagulopathy and results in multi organ failure [128].

There is no proper treatment other than the Liver transplantation, which is the only definitive therapy for patients with ACLF, but there is lack awareness in the management of patient, availability of donors, limited experience and expensive. So there an exciting opportunity for GCSF for hepatic tissue repair and regeneration [129] by mobilization and differentiation of blood derived stem cells into multiple lineages [130]. Hepatocytes, intra hepatic stem cells, bone marrow derived stem cells [131] play a major role in regeneration of damaged liver tissue [132] by its proliferative action.

GCSF therapy can reduce the development of sepsis and multi organ failure and improves the patient survival in ALCF patients [127]. Which has showed schematically (Fig: 3).

GCSF ROLE IN LIVER DAMAGE

Antiviral Therapy:

Hepatitis C is one of the leading chronic liver diseases seen globally; Hepatitis C Virus (HCV) infection can progress to liver cirrhosis and hepato cellular carcinoma and is the leading cause for liver transplants in US. Popular treatments now days for HCV are Peg interferon and Ribavirin [133-134]. In HCV treatment major goal is viral clearance, thereby reducing the risk for liver cirrhosis and hepato cellular carcinoma and improves the patient quality of life. Viral eradication is characterized by the absence of HCV RNA from the serum, is termed as a Sustained Virological Response (SVR) [135].

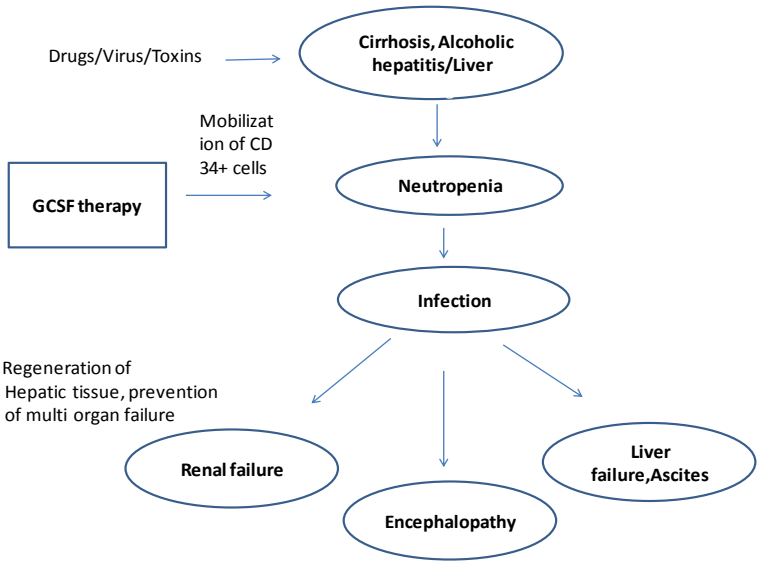

Fig 3: GCSF prevents sepsis and multi organ failure in liver damage by restoring the neutrophil function and mobilization of CD34+ cells.

Enormous improvements for Hepatitis C treatments have been seen from past two decades. A combination of antiviral drugs came into picture in spite of these advancements hematological side effects also seen like anemia, neutropenia and thrombocytopenia. These were commonly seen in combination of antiviral therapy with pegylated (PEG)-interferon alfa [136] and ribavirin.

Recent advancement in science and attempts has maximized the adherence towards the HCV treatment using Hematopoietic growth factors (GCSF) without altering the dose adjustments to treat side effects [135].

GCSF is effective in raising Absolute Neutrophil Count (ANC) when interferon doses are giving in HCV therapy [137-138].Since defective synthesis of endogenous GCSF during HCV treatment with Combination therapy contributes to Neutropenia [139].

Role of GCSF in Neuropathic pain

Neuropathic pain arises from a direct consequence of lesion or disease with the involvement of peripheral and central nervous system (CNS). Neuropathic pain involves the interaction between leukocyte derived opioid peptides and their receptors on peripheral sensory neurons. Studies showed that GCSF can increase the number of opioid

contained polymorphonuclear cells and significantly relieve the pain.

GCSF is a potential mediator of cytokines, chemokines and CD34+ adhesion molecules and has a direct or indirect role in controlling the pain. GCSF can stimulate bone marrow to produce more polymorphonuclear cells; these are a kind of granulocytes which secretes opioid peptides [140]. GCSF therapy has proven to be innovative strategy for neuropathic pain treatment.

GCSF produces an analgesic effect by two major biological and molecular functions.

The exogenous single GCSF dose can increase the circulating WBC, PMNs [141] and plays an important role in peripheral analgesia by producing opoids.

GCSF has direct effect on CD34+ cells to increase the anti-inflammatory [142] cytokine expression [143] by cytokine modulation leads to analgesic effect.

It not only alleviates neuropathic pain but also repairs the injured sites/lesion of infection, ischemia, tumor growth or an auto immune process.

Conclusion

GCSF has found tremendous applications in various therapeutic conditions viz., cancer therapy, myeloablative therapy, Neutropenia, bone marrow suppression, stem cell transplantation and in immuno regulatory disorder like Crohn's disease, EAE, autoimmune neutropenia etc. GCSF is also used in central nervous system disorders like cerebral ischemia and stroke, myocardial infarctions and liver failure conditions, owing to its repair and regenerating functions. GCSF is used in liver damage for regeneration of hepatic tissue and further improvement of neutrophil dysfunction and for prevention of multi organ failure. Apart from this GCSF is used to relieve neuropathic pain by opoid producing polymorphonuclear cells (PMNs) which have analgesic effect.

GCSF can modulate autoimmune processes in autoimmune neutropenia but it has not been proven. The potential for flare up of rheumatic disease means that judicious use of growth factors like GCSF; it can be seen in Felty's syndrome (FD) and Systemic Lupus Erythematosus (SLE). GCSF have promising applications in neural disorders like stroke by its neuroprotective effects.

References:

1.Schabitz W. R., Steigleder T, Cooper-Kuhn C.M, Schwab S., et al . Intravenous brain-derived neurotrophic factor enhances poststroke sensorimotor recovery and stimulates neurogenesis.Stroke 2007; 38(7): 2165–2172.

2. Schabitz W.R., Kollmar R, Schwaninger M, Juettler E, Bardutzky J, Scholzke M.N, Sommer C and S.Schwab . Neuroprotective effect of granulocyte colony-stimulating factor after focal cerebral ischemia. Stroke 2003; 34:745-751.

3.Metcalf D. The molecular control of cell division, differentiation,commitment and maturation in haematopoietic cells. Nature 1989; 339:27–30.

4.Tsuchiya M., Asano S., Kaziro Y, and S.Nagata . Isolation and characterization of the cDNA for murine granulocyte colony-stimulating factor. Proc Natl Acad Sci 1986; 83:7633–7637.

5.Nicola N.A., Begley C.G, and D.Metcalf . Identification of the human analogue of a regulator that induces differentiation in murine leukemia cells. Nature1985 ; 314: 625–628.

6.Welte K., Bonilla M.A., Gillio A.P., Boone T.C., Potter G.K., Gabrilove J.L,et al. Recombinant human granulocyte colony-stimulating factor. Effects on hematopoiesis in normal and cyclophosphamide-treated primates. J Exp Med 1987; 165:941–948.

7.Nagata S., Tsuchiya M., Asano S., Kaziro Y., Yamazaki T., Yamamoto O., Hirata Y., Kubota N.,Oheda M, and H. Nomura H. Molecular cloning and expression of cDNA for human granulocyte colony-stimulating factor. Nature 1986; 319:415-418.

8.Burgess A. W . Growth factors and cancer. Aust. NZ J. Surg 1985; 55:105-110.

9. Burgess A. W. and N.A.Nicola . Growth Factors and Stem Cells. New York: Academic Press. 1983.

10.Arai K., Yokota T., Miyajima A., Arai N. and F. Lee. Molecular biology of T-cell derived lymphokines: a model system for proliferation and differentiation of hemopoietic cells. Bioessays 1986; 5: 166-171.

11.Cesaro S., Chinello P, De Silvestro G, Marson P, Picco G,Varotto S et al. Granulocyte transfusions from G-CSF stimulated donors for the treatment of severe infections in neutropenic pediatric patients with onco-hematological diseases, Support Care Cancer 2003;11:101-106.

12.Wang C.Z., Liu J.F, Geng X.D. Refolding with Simultaneous Purification of Recombinant Human (GCSF) from *E. coli* Using Strong Anion Exchange Chromatography. Chinese Chem. Lett 2005; 16(3):389-392.

13.Abolghasemi D.S., Babaeipour V, Mofid M.R, Divsalar A, Faraji F. An efficient purification method for high recovery of Recombinant Human Granulocyte Colony Stimulating Factor from recombinant *E. coli*. International J. Environ. Sci. Dev 2010; 1 & 2.

14.Nagata S. Gene structure and function of granulocyte colony-stimulating factor.*Bio Essays* 1989; 10(4): 113-117.

15.Faraji F., Mofid M.R, Babaeipour.V, Divsalar A, and S.Abolghasemi Dehaghani . The Structural Characterization of Recombinant Human Granulocyte Colony Stimulating Factor. International Journal of Environmental Science and Development 2010; 1 (1).

16.Welte K., Gabrilove J, Bronchud M.H, Platzer E, and G.Morstyn . *Filgrastim (r-metHuG-CSF): the first 10 years. Blood* 1996; *88: 1907–1929.*

17.Bergley C., Lopez A., Nicola N., Warren D., Vadas M., Sanderson C, and D.Metcalf . Purified colony-stimulating factors enhance the survival of human neutrophils and eosinophils in vitro: A rapid and sensitive micro-assay for colony-stimulating factors. Blood 1986; 68: 162-166.

18.Clark S.C, and R. Kamer . The hematopoietic colony-stimulating factors. Science 1987 ; 236: 1229–1237.

19.Avalos B., Gasson J., Hedvat C., Quan S., Baldwin G., Weisbart R.,Williams R., Golde D, and J.DiPersio. Human granulocyte colonystimulating factor: biologic activities and receptor characterization on hematopoietic cells and small cell lung cancer cell lines. Blood 1990;75:851-857.

20.Demetri G.D, and Griffin J.D. Granulocyte colony-stimulating factor and its receptor. Blood 1991;78: 2791-2808.

21.Wells J.A., de Vos A.M . Hematopoietic receptor complexes. Annu Rev Biochem1996 ; 65:609-634.

22.Hanazono Y., Hosoi T., Kuwaki T., Matsuki S., Miyazono K., Miyagawa K, and F.Takaku. Structural analysis of the receptors for granulocyte colony-stimulating factor on neutrophils. Exp Hematol 1990; 18:1097-1103.

23.Shimoda K., Okamura S, Harada N, Kondo S, Okamura T, and Niho Y. Identification of a functional receptor for granulocyte colony-stimulating factor on platelets. J Clin Invest 1993; 91:1310-1313.

24.Morikawa K., Morikawa S, Nakamura M, Miyawaki T. Characterization of granulocyte colony-stimulating factor receptor expressed on human lymphocytes. Br J Haematol 2002; 118:296-304.
25.Avalos B.R. Molecular analysis of the granulocyte colonystimulating factor receptor. Blood 1996; 88:761-777.
26.Bussolino F., Wang J.M., Defilippi P., Turrini F., Sanavio F., Edgell C.S., Aglietta M., Arese P, and A.Mantovani. Granulocyte- and granulocyte-macrophage colony-stimulating factors induce humanendothelial cells to migrate and proliferate. Nature 1989; 337: 471–473.
27.Renee Beekman., Marijke G. Valkhof, Mathijs A. Sanders, Paulette M. H. van Strien, Jurgen R. Haanstra, Lianne Broeders, Wendy M. Geertsma-Kleinekoort, Anjo J. P. Veerman, Peter J. M. Valk1, Roel G. Verhaak, Bob Lowenberg, and Ivo P. Touw. Sequential gain of mutations in severe congenital neutropenia progressing to acute myeloid leukemia. American Society of Hematology.,Blood 2012; 119:5063-5064.
28.Tian S.S., Lamb P, Seidel H.M, Stein R.B,and J. Rosen . Rapid activation of the STAT3 transcription factor by granulocyte colony-stimulating factor. Blood 1994; 84:1760-1764.
29.Shimoda K., Feng J, Murakami H, Nagata S, Watling D, Rogers N.C, Stark G.R, Kerr I.M, and J.N Ihle . Jak1 plays an essential role for receptor phosphorylation and Stat activation in response to granulocyte colony-stimulating factor. Blood 1997; 90:597-604.
30.Hunter M.G., and Avalos B.R . Phosphatidylinositol 3'-kinase and SH2-containing inositol phosphatase (SHIP) are recruited by distinct positive and negative growth-regulatory domains in the granulocyte colony-stimulating factor receptor. J Immunol 1998; 160:4979-4987.
31.Dong F., Larner A.C. Activation of Akt kinase by granulocyte colony-stimulating factor (GCSF): evidence for the role of a tyrosine kinase activity distinct from the Janus kinases. Blood 2000; 95:1656-1662.
32.Ward A.C., Loeb D.M, Soede-Bobok A.A, Touw I.P, Friedman A.D . Regulation of granulopoiesis by transcription factors and cytokine signals. Leukemia 2000; 14:973-990.
33.Schneider A., Kruger C, Steigleder T, Weber D, Pitzer C, Laage R, Aronowski J, Maurer M.H, Gassler N, Mier W, Hasselblatt M, Kollmar R, Schwab S, Sommer C, Bach A, Kuhn H.G, Schabitz W.R. The hematopoietic factor G-CSF is a neuronal ligand that counteracts programmed cell death and drives neurogenesis. J Clin Invest 2005; 115:2083-2098.
34.Takano H., Ohtsuka M, Akazawa H, Toko H, Harada M, Hasegawa H, Nagai T, Komuro I . Pleiotropic effects of cytokines on acute myocardial infarction: G-CSF as a novel therapy for acute myocardial infarction. Current pharmaceutical design2003; 9:1121-1127.
35.Kuethe F., Figulla H.R, Voth M, Richartz B.M, Opfermann T, Sayer H.G, Krack A,Fritzenwanger M, Hoffken K, Gottschild D, Werner G.S . Mobilization of stem cells by granulocyte colony-stimulating factor for the regeneration of myocardial tissue after myocardial infarction. Dtsch Med Wochenschr 2004; 129:424-428.
36.Nienaber C.A., Petzsch M, Kleine H.D, Eckard H, Freund M, Ince H . Effects of granulocytecolony stimulating factor on mobilization of bone-marrow-derived stem cells after myocardial infarction in humans. Nat Clin Pract Cardiovasc Med 2006; 3 (1):S73-77.
37.Ripa R.S., Jorgensen E, Wang Y, Thune J.J, Nilsson J.C, Sondergaard L, Johnsen H.E, Kober L,Grande P, Kastrup J. Stem cell mobilization induced by subcutaneous granulocytecolony stimulating factor to improve cardiac regeneration after acute ST-elevation
myocardial infarction: result of the double-blind, randomized, placebo-controlled stem
cells in myocardial infarction (STEMMI) trial. Circulation 2006; 113:1983-1992.
38.Suzuki K., Nagashima K, Arai M, Uno Y, Misao Y, Takemura G, Nishigaki K, Minatoguchi S, Watanabe S, Tei C, Fujiwara H. Effect of granulocyte colony-stimulating factor treatment at a low dose but for a long duration in patients with coronary heart disease. Circ J 2006; 70:430-437.
39.Sanchez-Ramos et al. The potential of hematopoietic growth factors for treatment of Alzheimer's disease. a mini-review*Neuroscience* 2008; **9**(2):S3.
40**.**Germeshausen M**.**, Skokowa J, Ballmaier M, Zeidler C, Welte K. G-CSF receptor mutations in patients with congenital neutropenia.Curr Opin Hematol 2008; 15(4):332-337.
41. Karolien Beel., and Peter Vandenberghe . G-CSF receptor (*CSF3R*) mutations in X-linked neutropenia evolving to acute myeloid leukemia or myelodysplasia. *Haematologica* 2009; *94:1449-1452.*
42. Moore MA. The clinical use of colony-stimulating factors. Annu Rev Immunol 1991; 9:159–191.
43. Morstyn G., Campbell L., Lieschke G., Layton J.E., Maher D., O Connor M., Green M.,Sheridan W., Vincent M., Alton K, et al. Treatment of chemotherapy-induced neutropenia by subcutaneously administered granulocyte colony-stimulating factor with optimization of dose and duration of therapy. J Clin Oncol 1989; 7:1554-1562.
44. Pitzer C., Krüger C, Plaas C, Kirsch F, Dittgen T, Müller R, Laage R, Kastner S, Suess S, Spoelgen R, Henriques A, Ehrenreich H, Schäbitz WR, Bach A, Schneider A . Granu locyte-colony stimulating factor improves outcome in a mouse model of amyotrophic lateral sclerosis. *Brain.* 2008; 131 (12): 3335–3347.
45. Y-C Su et al. G-CSF downregulates natural killer cell-mediated cytotoxicity in donors for hematopoietic SCT. Bone Marrow Transplantation 2012; 47:73–81.
46. Weitz-Schmidt G., Chreng S, and S.Riek . Allosteric LFA-1 inhibitors modulate natural killer cell function. Mol Pharmacol2009; 75: 355–362.
47. Link D.C. Mechanisms of granulocyte colony-stimulating factor induced hematopoietic progenitor-cell mobilization. Seminar Hematol 2000; 37(2): 25–32.
48.Vose J.M., Ho A.D, Coiffier B, Corradini P, Khouri I, Sureda A et al. Advances in mobilization for the optimization of autologous stem cell transplantation. Leuk Lymphoma2009 ; 50: 1412–1421.
49.Lieschke G.J, Grail D, Hodgson G, Metcalf D, Stanley E, Cheers C,et al. Mice lacking granulocyte colony-stimulating factor have chronic neutropenia, granulocyte and macrophage progenitor cell deficiency, and impaired neutrophil mobilization. Blood 1994; 84: 1737–1746.
50.Liu F., Wu H, Wesselschmidt R, Kornaga T, Link D. Impaired production and increased apoptosis of neutrophils in granulocyte colony-stimulating factor receptor-deficient mice. Immunity 1996; 5:491–501.
51.Anderlini P., Przepiorka D, Champlin R, and Korbling M. Biologic and Clinical Effects of Granulocyte Colony-Stimulating Factor in Normal Individuals. *Blood* 1996; 88 (8) : 2819-2825.
52.Hara et al. G-CSF influences mouse skeletal muscle development and regeneration by stimulating myoblast proliferation. J. Exp. Med. 2011; 208 (4): 715-727.
53.Takayama H., Miyake Y, Nouso K, Ikeda F, Shiraha H, Takaki A,Kobashi H and K.Yamamoto . Serum levels of platelet-derived growth factor-BB and vascular endothelial growth factor as prognostic factors for patients with fulminant hepatic failure. J. Gastroenterol. Hepatol 2011; 26: 116–121.
54.Long-Sun Ro, et al. Review-The Potential Application of Granulocyte Colony Stimulating Factor Therapy on Neuropathic Pain, , Department of Neurology, Chang Gung Memorial Hospital. 5, Fusing St., GueishanTownship, Taiwan (R.O.C.) 2008.
55.Ozer H., Armitage J.O, Bennett C.L, et al. update of recommendations for the use of hematopoietic colony-stimulating factors: Evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. J Clin Oncol 2000; 18:3558-3585.
56.Jones S.E, Schottstaedt M.W, Duncan L.A, et al. Randomized double-blind prospective trial to evaluate the effects of sargramostim versus placebo in a moderate-dose fluorouracil, doxorubicin, and

cyclophosphamide adjuvant chemotherapy program for stage II and III breast cancer. J Clin Oncol 1996; 14:2976-2983.
57.Beveridge R.A., Miller J.A, Kales A.N, et al. A comparison of efficacy of sargramostim (yeastderived Rhu GM- CSF) and filgrastim (bacteria-derived RhuG-CSF) in the therapeutic setting of chemotherapy-induced myelosuppression. Cancer Invest 1998; 16:366-373.
58.Hughes W.T., Armstrong D, Bodey G.P, et al. Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002; 34:730–751.
59.Lyman G.H. Risks and consequences of chemotherapyinduced neutropenia. Clin Cornerstone 2006; 8: S12–S18.
60.Greil R. and O. Psenak ESMO Guidelines Working group. Hematopoietic growth factors: ESMO recommendations for the application. Ann Oncol 2007 ; (18): ii89–ii91.
61.Perez Velasco. Review of granulocyte colony-stimulating factors in the treatment of established febrile neutropenia. J Oncol Pharm Practice 2010 ; 17(3) 225–232.
62.BEEKMAN and TOUW. G-CSF and its receptor in myeloid malignancy, BLOOD 2010 ;115(25).
63.Garcia-Carbonero R., Mayordomo J.I, Tornamira M.V,et al. Granulocyte colony-stimulating factor in the treatment of high-risk febrile neutropenia: a multicenter randomized trial. J Natl Cancer Inst 2001; 93: 31–38.
64.Ozkaynak M.F, Krailo M, Zhengjia C, et al . Randomized comparison of antibiotics with and without granulocyte colony-stimulating factor in children with chemotherapy-induced febrile neutropenia: a report from the Children's Oncology Group. Pediatr Blood Cancer 2005 ; 45: 274–280.
65.Forrest G.N., Schimpff and A.Cross . Febrile neutropenia, colony-stimulating factors and therapy: time for a new methodology? Support Care Cancer 2002;10:177–180.
66.MARY L. DISIS. Clinical Use of Subcutaneous G-CSF or GM-CSF in Malignancy. Oncology 2005; 19 (42).
67.Frasci G. Treatment of breast cancer with chemotherapy in combination with filgrastim: Approaches to improving therapeutic outcome. Drugs 2002; 62 (1):17-31.
68.Hall D.J., Martin D.A, Kincaid K. Filgrastim support during combination chemotherapy using cisplatin, doxorubicin, and cyclophosphamide to treat advanced or recurrent endometrial cancer: A clinical study and literature review. Eur J Gynaecol Oncol 2003; 24:481-489.
69.Wolf T., Densmore J.J: Pegfilgrastim . use during chemotherapy: Current and future applications. Curr Hematol Rep 2004; 3:419-423.
70.Crawford J. Once-per-cycle pegfilgrastim (Neulasta) for the management of chemotherapy induced neutropenia. Semin Oncol. 2003;30(13):24-30.
71.Fain K., Moore MAS., Clarkson B., Oettgen H.F., Alton K., Welte K, and L.Souza. Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium.NEngl J Med 1988; 318: 1414-1422.
72.Gabrilove J.L., Jakobowski A., Scher H., Sternberg C., Wong G., Grous J., Yagoda A., Fain K., Moore MAS., Clarkson B., Oettgen H.F., Alton K., Welte K, and L.Souza. Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium.NEngl J Med 1988; 318: 1414-1422.
73.Hernandez Bronchud M.H., Scargge J.H., Thatcher N., Crowther D., Souza L.M., Alton N.K., Testa N.G, and T.M.Dexter. Phase 1/11 study of recombinant human granulocyte colony-stimulating factor in patients receiving intensive chemotherapy for small cell lung cancer. Br J Cancer 1987; 56: 809-813.
74.Cooper et al. Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy systematic review and meta-analysis. BMC Cancer 2011; 11:404.
75.Nehal Masood., et al. Splenic rupture, secondary to G-CSF use for chemotherapy induced neutropenia. a case report and review of literature.**,** BioMed Central Ltd., *Cases Journal* 2008; **1**:418.
76.Boxer L. G-CSF associated with more live births in women with severe neutropenia. HEMATOLOGY 2010; #1490. Presented at: 52nd ASH Annual Meeting; Dec. 4-7, ; Orlando, Fla.
77.Chemotherapy Principles . An In depth Discussion of the Techniques And Its Role in Cancer Treatment. American Cancer Society 2011.
78.Venkata Samavedi., MBBS, MD Internist in Houston, TX . Hematopoietic Stem Cell Transplantation. Drugs2011; Diseases& Procedures.
79.Schmitz N., Linch D C, Dreger P. et al. Randomised trial of filgrastim-mobilised peripheral blood progenitor cell transplantation versus autologous bone-marrow transplantation in lymphoma patients. Lancet 1996; 347:353–357. [PubMed].
80.Schiffer C.A . Hematopoietic growth factors as adjuncts to the treatment of acute myeloid leukemia. Blood 1996; 88:3675–3685. [PubMed].
81.Irandoust M.I., Aarts L.H, Roovers O, Gits J, Erkeland S.J and I.P Touw . Suppressor of cytokine signaling3 controls lysosomal routing of G-CSF receptor. *EMBOJ* 2007; 26(7):1782-1793.
82.Panopoulos A.D. and S.S Watowich. Granulocyte colony-stimulating factor: molecular mechanisms of action during steady state and emergency hematopoiesis. *Cytokine* 2008; 42(3):277-288.
83.Wolfler A., Irandoust M, Meenhuis A, Gits J,Roovers O, Touw I.P . Site-specific ubiquitination determines lysosomal sorting and signal attenuation of the granulocyte colony-stimulating factor receptor. *Traffic*2009; 10(8):1168-1179.
84.Nagoya **.** USE OF GRANULOCYTE COLONY-STIMULATING FACTOR FOR TREATMENT OF APLASTIC ANEMIA**.** J. Med. Sci. 1999; 62. 77 – 82.
85.Christopher et al. Expression of the G-CSF receptor in monocyticcells is sufficient to mediate hematopoietic progenitor mobilization by G-CSF in mice. J. Exp. Med 2011; 208 (2):251-260.
86.Orlic D., *et al.* Mobilized bone marrow cells repair the infarcted heart, improving function and survival. Proc. Natl. Acad. Sci *2001;* 98: 10344-10349.
87.Six.I, *et al.* Beneficial effect of pharmacological mobilization of bone marrow in experimental cerebral ischemia , Eur. J. Pharmacol*2003;* 458 : 327–328.
88.Ince. H., et al . G-CSF in the setting of acute myocardial infarction. European Heart Journal Supplements 2006; 8 (H): H40–H45.
89.Kleinschnitz C. et al. Induction of granulocyte colony-stimulating factor mRNA by focal cerebral ischemia and cortical spreading depression. Brain Res. Mol. Brain Res 2004; 131:73-78.
90.Chuan-Zhen Lu., and Bao-Guo Xiao. Neuroprotection of G-CSF in cerebral ischemia. Frontiers in Bioscience 2007; (12): 2869-2875.
91.Bao-Guo Xiao. Cell biology and clinical promise of G-CSF: immunomodulation and neuroprotection. *J. Cell. Mol. Med 2007; 11(6): 1272-1290.*
92.England T. J.., Gibson C. L., and P. M. W. Bath. Granulocytecolony stimulating factor in experimental stroke and its effects on infarct size and functional outcome. a systematic review,*Brain Research Reviews* 2009; 62(1): 71–82.
93.Solaroglu I., Cahill J, T. Tsubokawa, E. Beskonakli, and J. H.Zhang . Granulocyte colony-stimulating factor protects the brain against experimental stroke via inhibition of apoptosis and inflammation. *Neurological Research* 2009; 31 (2):167–172.
94.Jung KH., *et al.* G-CSF protects human cerebral hybrid neurons against *in vitro* ischemia.Neurosci. Lett *2006;* 394 :168–173.

95.Meuer K., *et al* . Granulocyte-colony stimulating factor is neuroprotective in a model of Parkinson's disease. J. Neurochem *2006;* 97: 675–686.
96.Ozceliket T., et al. Mobilization of PBSCs with chemotherapy and recombinant human G-CSF: a randomized evaluation of early vs late administration of recombinant human G-CSF. Bone Marrow Transplantation 2009; 44: 779–783.
97.Sprigg N., Bath P. M. and L Zhao et al . Granulocyte-colony stimulating factor mobilizes bone marrow stem cells in patients with subacute ischemic stroke: the Stem cell Trial of recovery EnhanceMent after Stroke (STEMS) pilot randomized,controlled trial (ISRCTN 16784092).*Stroke* 2006; 37 (12): 2979–2983.
98.Komine-Kobayashi M., Zhang N, Liu M, Tanaka R,Hara H, Osaka A, Mochizuki H, Mizuno Y,Urabe T. *Neuroprotective effect of recombinant human granulocyte colony-stimulating factor in transient focal ischemia of mice. J Cereb Blood Flow Metab* 2006; *26: 402-413.*
*99.*Kameshwar Prasad., et al. clinical study-Mobilization of StemCells Using G-CSF for Acute Ischemic Stroke: A Randomized Controlled, Pilot Study. Stroke Research and TreatmentVolume. 2011; Article ID 283473.
100.Kollmar R., *et al.* G-CSF, rt-PA and combination therapy after experimental thromboembolic stroke. *Experimental & Translational Stroke Medicine* 2010; **2**:9.
*101.*Martin D., Near S. L, A. Bendele, and Russell D. A. Inhibition of tumor necrosis factor is protective against neurologic dysfunction after active immunization of Lewis rats with myelin basic protein. *Exp. Neurol* 1995; *131:221.*
*102.*Armin Schneider., Hans-Georg Kuhn, Wolf-Rüdiger Schäbitz **.** A Role for GCSF (Granulocyte-Colony Stimulating Factor) in the Central Nervous System. Cell Cycle Landes Bioscience 2005; 4:12, 1753-1757.
103.Minnerup J., Heidrich J, Wellmann J, Rogalewski A, Schneider A, et al. Meta-analysis of the efficacy of granulocyte-colony stimulating factor in animal models of focal cerebral ischemia. Stroke 2008; 39(6): 1855–1861.
104.Minnerup J., Sevimli S, Schabitz W.R . Granulocyte-colony stimulating factor for stroke treatment: mechanisms of action and efficacy in preclinical studies. Exp Transl Stroke Med 2009; 1: 2.
105.Kai Diederich., et al. The Role of Granulocyte-Colony Stimulating Factor (G-CSF) in the Healthy Brain. A Characterization of G-CSF-Deficient Mice. The Journal of Neuroscience 2009; 29(37):11572–11581.
106.Floel et al. Granulocyte-Colony Stimulating Factor (G-CSF) in Stroke Patients with Concomitant Vascular Disease-ARandomized Controlled Trial. PLoS ONE 2011; 6-5.
107.Brown S.J. and Mayer L . The immune response in infl ammatory bowel disease. *Am J Gastroenterol* 2007; (102):2058–2069.
108.Rutella S. Granulocyte colony-stimulating factor for the induction of T-cell tolerance. *Transplantation* 2007; 84:S26–S30.
109.Rutella S., Pierelli L, Bonanno G, et al. Role for granulocyte colony-stimulating factor in the generation of human T regulatory type1 cells. *Blood* .2002; 100:2562–2571.
110.Korzenik J.R., Dieckgraefe B.K An open-labelled study of granulocyte colony-stimulating factor in the treatment of active Crohn's disease. *Aliment Pharmacol Ther* 2005; 21:391–400.
111.Luisa Guidi., et al. Review-Treatment of Crohn's disease with colony stimulating factors. An overview Therapeutics and Clinical Risk Management 2008; 4(5) 927–934.
112.Yamaguchi T., Ihara K, Matsumoto T, et al. Inflammatory bowel disease-like colitis in glycogen storage disease type 1b. *Inflamm Bowel Dis* 2001; 7:128–132.
113.Dieckgraefe B.K., Korzenik J.R. Treatment of active Crohn's disease with recombinant human granulocyte-macrophage colony-stimulating factor. *Lancet* 2002; 360:1478–1480.
114.Visser G., Rake J.P, Labrune P, et al. Granulocyte colony-stimulating factor in glycogen storage disease type 1b. Results of the European Study on Glycogen Storage Disease Type 1. *Eur J Pediatr*2002; 161(1): 83–87.
115.Anke Franzke., The role of G-CSF in adaptive immunity. Cytokine & Growth Factor Reviews 2006; 17: 235–244.
116.Flora Zavala. G-CSF Therapy of Ongoing Experimental Allergic Encephalomyelitis Via Chemokine- and Cytokine-Based Immune Deviation, *The Journal of Immunology* 2002; 168: 2011–2019.
117.Antel J. P., and T. Owens. Immune regulation and CNS autoimmune disease. *J. Neuroimmunol* 1999; *100:181.*
118.Selmaj K., Papierz W, Glabinski A, and Kohno T. Prevention of chronic relapsing experimental autoimmune encephalomyelitis by soluble tumor necrosis factor receptor .I. *J. Neuroimmunol* 1995; *56:135.*
119.Korner H., Riminton D.S, Strickland D.H, Lemckert F. A. Pollard J. D, and J. D. Sedgwick . Critical points of tumor necrosis factor action in central nervous system autoimmune inflammation defined by gene targeting. *J. Exp. Med* 1997; *186:1585.*
120.Karine Hadaya., Hassen Kared, Annie Masson, Lucienne Chatenoud, Flora Zavala . G-CSF treatment prevents cyclophosphamide acceleration of autoimmune diabetes in the NOD mouse., Journal of Autoimmunity 2005; 24: 125-134.
121.Choi M.F., Mant M.J, Turner A.R, Akubutu J.J, and S.L Aaron. Successful reversal of neutropenia in Felty's syndrome with recombinant granulocyte colony-stimulating factor. British Journal of Haematology 1994; 86:663–664.
122.Cooper D.L., Henderson-Bakas M, and N.Berliner . Lymphoproliferative disorder of granular lymphocytes associated with severe neutropenia. Response to granulocyte colony stimulating factor. Cancer 1993;72:1607-1611.
123.Ann L. Cornish., Ian K. Campbell, Brent S. McKenzie, Simon Chatfield & Ian P. Wicks. G-CSF and GM-CSF as therapeutic targets in rheumatoid arthritis. *Nature Reviews Rheumatology* 2009; **5:** 554-559.
124.*Laurence Boxer and David C. Dale.* Neutropenia: Causes and Consequences. *Seminars in Hematology 2002; 39(2): 75-81.*
125.Smith M.A. and J.G Smith . The use of granulocyte colony stimulating factor for treatment of autoimmune neutropenia.Current Opinion in Hematology 2001; 8:165–169.
126.SMITH M.A., and J.G. SMITH . Clinical experience with the use of rhG-CSF in secondary autoimmune neutropenia. Clin. Lab. Haem 2002; 24: 93–97.
127.GARG ET AL. Granulocyte Colony–Stimulating Factor Mobilizes CD34 Cells and improves Survival of Patients With Acute-on-Chronic Liver Failure. GASTROENTEROLOGY 2012; 142:505–512.
128.Garg H.K., Sarin S.K, Kumar A, et al. Tenofovir reduces morbidity and mortality in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure (ACLF): a randomized placebo controlled trial. Hepatology 2011; 53:774–780.
129.Sell S. Heterogeneity and plasticity of hepatocyte lineage cells. Hepatology 2001; 133:738–750.
130.Grove J.E., Bruscia E, Krause D.S . Plasticity of bone marrow-derived stem cells. Stem Cells 2004; 22:487–500.
131.Spahr L, Lambert JF, Brandt LR, et al. Granulocyte-colony stimulating factor induces proliferation of hepatic progenitors in alcoholic steatohepatitis: a randomized trial. Hepatology 2008; 48:221–229.
132.Durdi Qujeq Roya Abassi,Farideh Faeizi et al. Assessment effect of granulocyte colony –stimulating factor in experimental models of liver injury. Scientific research and Essays 2011; 6(21):4646-4650.
133.Manns M.P., McHutchison J.G, Gordon S.C, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001; 358: 958–965.

134.Fried M.W., Shiffman M.L, Reddy K.R, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975–982.
135.MAC NICHOLAS R & S. NORRIS. optimizing SVR and management of the haematological side effects of peginterferon / ribavirin antiviral therapy for HCV – the role of epoetin, G-CSF and novel agents.Aliment Pharmacol Ther 2010; 31: 929–937.
136.Russo M.W. and Fried M.W. Side effects of therapy for chronic hepatitis C. Gastroenterology 2003; 124: 1711–1719.
137.Dieterich D.T., Spivak J.L. Hematologic disorders associated with hepatitis C virus
infection and their management. Clin Infect Dis 2003; 37:533–541.
138.Koirala J. Gandotra S.D, Rao S, et al . Granulocyte colony-stimulating factor
dosing in pegylated interferon alphainduced neutropenia and its impact on outcome of anti-HCV therapy. J Viral .Hepat 2007 ; (14): 782–787.
139.Durante-Mangoni E., Iardino P, Utili R,et al. Defective synthesis of granulocytecolony stimulating factor in pegylated interferon-alpha treated chronic hepatitis C patients with declining leukocyte counts. Antivir Ther 2006; 11: 637–640.
140.Brack A., Rittner H.L, Machelska H, Beschmann K, Sitte N, Schafer M, Stein C. Mobilization of opioid-containing polymorphonuclear cells by hematopoietic growth factors
British Journal of Haematology 2004; 86:663–664.
141.Bodine D.M., Seidel N.E, and D.Orlic . Bone marrow collected 14 days after in vivo administration of granulocyte colony-stimulating factor and stem cell factor to mice has 10-fold more repopulating ability than untreated bone marrow. Blood 1996; 88:89-97.
142.Gorgen I., Hartung T, Leist M, Niehorster M, Tiegs G, Uhlig S, Weitzel F, and A.Wendel . Granulocyte colony-stimulating factor treatment protects rodents against lipopolysaccharide-induced toxicity via suppression of systemic tumor necrosis factor-alpha. J Immunol 1992; 149:918-924.
143.Sloand E.M., Kim S, Maciejewski J.P, Van Rhee F,Chaudhuri A, Barrett J, and N.S.Young. Pharmacologic doses of granulocyte colony-stimulating factor affect cytokine production by lymphocytes in vitro and in vivo. Blood 2000; 95: 2269-2274.

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