Abstract:

The instant invention relates to compounds, compositions and methods provided for prevention and treatment of various forms of graft-versus-host disease (GvHD) comprising or using Cilengitide, a cyclic arginine-glycine-aspartic acid containing pentapeptide, and/or pharmaceutically acceptable derivates, solvates and/or salts thereof. Moreover, various dosing regimens and/or combinations comprising or using Cilengitide and/or pharmaceutically acceptable derivatives, solvates and/or salts thereof are provided, preferably for the treatment of humans in vivo and preferably as well for ex vivo conditioning of organ transplants in order to suppress immune responses and preferably also other adverse effects resulting in GvHD and related inflammatory processes.
Compounds, compositions and methods are provided for prevention and treatment of various forms of graft-versus-host disease (GvHD) comprising or using Cilengitide, a cyclic arginine-glycine-aspartic acid containing pentapeptide, and/or pharmaceutically acceptable derivatives, solvates and/or salts thereof. Moreover, various dosing regimens and/or combinations comprising or using Cilengitide and/or pharmaceutically acceptable derivatives, solvates and/or salts thereof are provided, preferably for the treatment of humans in vivo and preferably as well for ex vivo conditioning of organ transplants in order to suppress immune responses and preferably also other adverse effects resulting in GvHD and related inflammatory processes.

Graft-versus-host disease (GvHD) is a common complication of allogeneic bone marrow transplantation in which functional immune cells in the transplanted marrow recognize the recipient as "foreign" and mount an immunologic attack. It can also take place in a blood transfusion under certain circumstances.

According to the 1966 Billingham Criteria, 3 criteria are typical for GvHD to occur:

- An immunocompetent graft is administered, with viable and functional immune cells.
- The recipient is immunologically disparate - histoincompatible.
- The recipient is immunocompromised and therefore cannot destroy or inactivate the transplanted cells.

After bone marrow transplantation, T cells present in the graft, either as contaminants or intentionally introduced into the host, attack the tissues of the transplant recipient after perceiving host tissues as antigenically foreign. The T cells produce an excess of cytokines, including TNF-a and interferon-gamma (IFN\textgamma). A wide range of host antigens can initiate graft-versus-host-
among them the human leukocyte antigens (HLAs). However, graft-versus-host disease can occur even when HLA-identical siblings are the donors. HLA-identical siblings or HLA-identical unrelated donors often have genetically different proteins (called minor histocompatibility antigens) that can be presented by MHC molecules to the donor's T-cells, which see these antigens as foreign and so mount an immune response. While donor T-cells are undesirable as effector cells of graft-versus-host-disease, they are valuable for engraftment by preventing the recipient's residual immune system from rejecting the bone marrow graft (host-versus-graft). In addition, as bone marrow transplantation is frequently used to treat cancer, mainly leukemias, donor T-cells have proven to have a valuable graft-versus-tumor effect. A great deal of current research on allogeneic bone marrow transplantation involves attempts to separate the undesirable graft-vs-host-disease aspects of T-cell physiology from the desirable graft-versus-tumor effect.

In the clinical setting, graft-versus-host-disease is divided into acute and chronic forms:

- The acute or fulminant form of the disease (aGvHD) is normally observed within the first 100 days post-transplant and is a major challenge to transplants owing to associated morbidity and mortality
- The chronic form of graft-versus-host-disease (cGvHD) normally occurs after 100 days. The appearance of moderate to severe cases of cGvHD adversely influences long-term survival.[4]

This distinction is not arbitrary: Acute and chronic graft-versus-host-disease appear to involve different immune cell subsets, different cytokine profiles, somewhat different host targets, and respond differently to treatment. Brandon Schmidt has been credited with first discovering Graft Versus Host Disease in 1927. Later, in 1987, the disease was further described with genetic explanation by Kevin Smith in 'IJ ed. 867-5309'.

In the classical sense, acute graft-versus-host-disease is characterized by selective damage to the liver, skin and mucosa, and the gastrointestinal tract. Newer research indicates that other graft-versus-host-disease target organs
include the immune system (the hematopoietic system, e.g., the bone marrow and the thymus) itself, and the lungs in the form of idiopathic pneumonitis. Chronic graft-versus-host-disease also attacks the above organs, but over its long-term course can also cause damage to the connective tissue and exocrine glands.

Acute GvHD of the GI tract can result in severe intestinal inflammation, sloughing of the mucosal membrane, severe diarrhea, abdominal pain, nausea, and vomiting. This is typically diagnosed via intestinal biopsy. Liver GvHD is measured by the bilirubin level in acute patients. Skin GvHD results in a diffuse maculopapular rash, sometimes in a lacy pattern.

Acute GvHD is preferably staged as follows: overall grade (skin-liver-gut) with each organ staged individually from a low of 1 to a high of 4 (or I to IV). Patients with grade IV GvHD usually have a poor prognosis. If the GvHD is severe and requires intense immunosuppression involving steroids and additional agents to get under control, the patient may develop severe infections as a result of the immunosuppression and may die of infection.

Transfusion-associated graft versus host disease is typically associated with transfusion of un-irradiated blood to immunocompromised recipients. It can also occur in situations in which the blood donor is homozygous and the recipient is heterozygous for an HLA haplotype. It is associated with higher mortality (80-90%) due to involvement of bone marrow lymphoid tissue, however the clinical manifestations are similar to GvHD resulting from bone marrow transplantation. Transfusion-associated GvHD is rare in modern medicine. It is almost entirely preventable by controlled irradiation of blood products to inactivate the white blood cells (including lymphocytes) within.

Thymus transplantation may be said to be able to cause a special type of GvHD because the recipients thymocytes would use the donor thymus cells as models when going through the negative selection to recognize self-antigens, and could therefore still mistake own structures in the rest of the body for being non-self. This is a rather indirect GvHD because it is not directly cells in the graft itself that causes it but cells in the graft that make the recipient's T cells act like donor T cells. It can be seen as a multiple-organ
autoimmunity in xenotransplantation experiments of the thymus between different species. Autoimmune disease is a frequent complication after human allogeneic thymus transplantation, found in 42% of subjects over 1 year post transplantation. However, this is partially explained by the fact that the indication itself, that is, complete DiGeorge syndrome, increases the risk of autoimmune disease.

For dysfunctional and/or diseased organs of the body, besides therapeutic invention with drugs, organ transplantation is an alternative, sometimes the last resort in the treatment of the patient. Particularly for patients with leukemia, end-stage renal, cardiac, pulmonary or hepatic failure, organ transplantation is quite commonly used in the treatment. For example, allografts (organ grafts harvested from donors other than the patient him/herself or host/recipient of the graft) of various types, e.g. kidney, heart, lung, liver, bone marrow, pancreas, cornea, small intestine and skin (e.g. epidermal sheets) are currently routinely performed. Xenografts (organ grafts harvested from non-human animals), such as porcine heart valves, are also being used clinically to replace their dysfunctional human counterparts.

To ensure successful organ transplantation, it can be desirable to obtain the graft from the patient’s identical twin or his/her immediate family member. This is because organ transplants evoke a variety of immune responses in the host, which potentially result in rejection of the graft and/or graft-versus-host disease (herein referred to as "GvHD").

The immune response is believed to be primarily triggered by T cells through recognition of alloantigens, and the major targets in transplant rejection are non-self allelic forms of class I and class II Major Histocompatibility Complex (MHC) antigens. In acute rejection, donor’s antigen-presenting cells such as dendritic cells and monocytes migrate from the allograft to the regional lymph nodes, where they are recognized as foreign by the recipient’s CD4+ T H cells, stimulating T H cell proliferation. Following T H cells proliferation, a population of effector cells (including cytotoxic CD8+ T cells and CD4+ T cells) is
generated, which migrates and infiltrates to the graft and mediates graft rejection (Noelle et al. (1991) FASEB 5(13):2770).

Whereas acute rejection is believed to be a T cell-dependent process, a broad array of effector mechanisms appears to participate in graft destruction. Through the release of cytokines and cell-to-cell interactions, a diverse assembly of lymphocytes including CD4+ T cells, CD8+ cytotoxic T cells, antibody-forming B cells and other proinflammatory leukocytes, can be recruited into the anti-allograft response. Antigen-presenting graft cells can be destroyed directly by cytotoxic CD8+ T cells. Activated CD4+ T cells are found to produce interleukin-2 (hereinafter, referred to as "IL-2"), which is found to be essential to the activation of both CD8+ T cells and B cells. Additionally, CD4+ T cells can produce other cytokines such as IFN-γ and IL-4 that are also believed to contribute to the destruction of allograft.

Furthermore, interferon-γ (hereinafter, referred to as "IFN-γ") can induce increased expression of class I and class II MHC molecules on graft tissue, which then can be more readily attacked by alloreactive effector cells. IFN-γ potentially enhances macrophage activity and thus potentially affects many inflammatory cells that can lead to delayed-type-hypersensitivity reactions and inflammation causing nonspecific damage to the graft. These reactions appear to be among the primary causes of the early acute rejection that may occur within the first few weeks after transplant. If untreated, acute rejection progresses to a rapid and severe process that can cause the destruction of the transplant within a few days.

On the other hand, when a T-lymphocyte from the donor recognizes the differences based on a set of genetic markers, generally referred to as human leukocyte antigens (HLA), it can start to attack the new body, i.e., the patient's body. Routinely, patients and donors are matched as closely as possible for HLA markers. Many minor markers, however, differ between donors and patients except when the patient and donor are identical twins. Before a transplant, extensive typing of the donor and recipient is often performed to make sure that the donor and recipient are as close
immunologically as possible. Despite this typing, there typically are immunological differences that can often not be detected, but that the T-lymphocytes in the donor graft can be capable of detecting. As a result, the donor T-lymphocytes can start to attack the patient's body and cause GvHD. There are two forms of GvHD: the acute and chronic GvHD. Acute GvHD usually occurs within the first three months following a transplant. T-cells present in the donor's bone marrow at the time of transplant attack the patient's skin, liver, stomach, and/or intestines. The earliest signs of acute GvHD are usually a skin rash that appears on the hand, feet and face. Other than blistering skin, patients with severe GvHD also develop large amounts of watery or bloody diarrhea with cramping due to the donor's T-cells' attack on the stomach and intestines. Jaundice (yellowing of the skin and eyes) is the usual indication that GvHD disease involves the liver. The more organs involved and the worse the symptoms, the worse the GvHD disease.


To protect patients from such fatal damages, various immunosuppressive agents have been employed. Currently, allograft rejection is controlled using immunosuppressive agents such as cyclosporin A, azathioprine, corticosteroids, including prednisone and methylprednisolone, cyclophosphamide, and FK506. Cyclosporin A, the most powerful and most frequently used immunosuppressant, revolutionized the field of organ transplant surgery. Other immunosuppressive agents such as FK506, rapamycin, mycophenolic acid, 15-deoxyspergualin, mimoribine, misoprostol, OKT3 and anti-IL-2 receptor antibodies, have been used in the treatment
and/or prevention of organ transplantation rejection (see, e.g., Briggs, Immunology letters, 29(1-2), 89-94, 1991; FASEB 3:341 t, 1989). Although the development of new immunosuppressive drugs has led to substantial improvement in the survival of patients, these drugs are often associated with a high incidence of side effects such as nephrotoxicity and/or hepatotoxicity. For example, cyclosporin A has associated toxicities and side effects when used even at therapeutic doses. Although FK506 is about 10 to 100 times more potent than cyclosporin A in inhibiting activation-induced IL-2 transcription in vitro and graft rejection in vivo, it also shows side effects such as neurotoxicity and nephrotoxicity. Thus, there still exists the need for treatment and prophylaxis for GvHD with improved toxicity profiles.

However, even though chemotherapy in combination with radiotherapy and bone marrow transplantation (BMT) has been explored over the past 30-40 years for some metabolic and hematopoietic disorders, it became evident rather a decade ago that the therapeutic effect is only partially caused by the eradication of leukemia cells using high-dose chemotherapy and irradiation. Numerous clinical observations provide over-convincing evidence that, moreover, (donor T cell) immune responses contribute substantially to the elimination of residual cancerous cells and especially to the subsequent long-term success of BMT-based therapies. In retrospect, the standard therapeutic strategy in BMT overestimated the anticancer potential of even very high doses of chemotherapy and radiotherapy and underestimated the efficacy of immunotherapy mediated by BMT-derived allogeneic donor lymphocytes.

The clinical successes observed after the treatment of hematopoietic disorders (leukemia) with allogeneic bone-marrow transplants (allo-BMT) have to a large extent fulfilled the fundamentals of a curative immunotherapy. The term allogeneic is used to describe a situation in which the donor and recipient is a different individual, compared to the term syngeneic in which the donor and recipient are identical twins and have an identical tissue type.
since their genetic make-up is the same. Autologous transplants are derived from an individual which later in the process gets his or her own cells back. But, strictly speaking, this is not a transplantation since no immunologic transplantation barriers exist.

There are two types of allogeneic donors: related, usually sibling donors, and unrelated, usually found from very large pools of volunteers and matched to a tissue type that is the same as the patient's. Allogeneic transplantation, whether from a related or unrelated donor, differs from either syngeneic or autologous transplantation in that the potential exists for immune rejection of the donated stem cells by the recipient (host-versus-graft effect) and the immune reaction by the donor's immune cells against the tissues of the recipient (graft-versus-host disease). The immune rejection is usually prevented by intensive treatment of the recipient before the transplantation (conditioning) to suppress the immune system. Conditioning schemes vary according to the transplantation center and the malignancy involved. For instance in treatment of leukemia, the patient is undergoing myeloablative conditioning comprising a combination of high-dose cyclophosphamide and total body irradiation prior to BMT. Post-transplantation the immune reaction is combated by giving immune suppressive drugs, including methotrexate, glucocorticoid hormones (steroids), cyclosporine or a microemulsion thereof (Neoral®), tacrolimus (Prograf®) and mycophenolate mofetil (Cellcept®), for a limited time period in order to prevent acute attack and injure of the patient's tissues. Improvements of supportive care in addition to controlled immunosuppression have reduced toxicity of the conditioning and the post-BMT immune reaction substantially. However, severe complications still occur at oropharynx, gastrointestinal tract, liver, lung, skin, kidney, urinary tract and nervous system and, consequently, allo-BMT is limited to younger, medically fit patients. In the art, it is generally accepted that hematological cancers cannot always be eradicated by high doses of chemotherapy-radiation conditioning only, but
need allo-BMT in addition. Thus, conventional allo-BMT-based therapies have become a standard procedure for the treatment of many human hematological malignancies and provide the benchmark for all immunotherapies - the possibility of a "cure".

Donors for allo-BMT are selected according to their expression of major histocompatibility complex (MHC) molecules: the human leukocyte antigens (HLA). HLA types are genetically determined. Thus, an individual's HLA type is inherited from his or her parents. There are three major genes in a cluster that seem to be particularly important in transplantation: HLA-A, HLA-B, and HLA-DR. Each individual carries two copies of each of to the genes in the HLA cluster. In addition, many allelic versions correspond each of the HLA genes.

To get an ideal 6-out-of-6 match, two people have to carry, the same alleles at each of their two HLA-A, HLA-B, and HLA-DR genes and there is a 1 in 200 chance that a parent and child will be HLA-matched.

When a HLA-matched relative is unavailable and there is time to conduct a search, an unrelated donor is usually considered. The chance of any 2 unrelated individuals being matched for all 6 HLA genes is 1 in a million.

Because of the polymorphism of the HLA system, the ethnic background and the median age at diagnosis, transplants from HLA-matched related donors are currently available to 15-60% of newly diagnosed patients. Alternative donors include relatives with minor degrees of incompatibility and HLA-compatible unrelated volunteers. The probability of finding suitable unrelated donors, matched or partially mismatched, has increased with the development of a network of registries now containing more than 4.7 million donors worldwide and with access to other sources such as fetal cord blood.

A bone-marrow transplant mainly consists of hematopoetic stem cells which may be obtained from the bone marrow, blood or fetal cord blood. The hematopoetic stem cells are usually aspirated from the bone marrow. An alternative procedures involves a 3- to 5-days treatment of donors with granulocyte colony-stimulating factor (G-CSF) to mobilize stem cells and
progenitor cells from the marrow into the blood. The appropriate cells are then collected from the donor by leukapheresis. Blood contained in the placenta and umbilical cord of newborn babies is emerging as a new source of stem cells. Cord blood contains significant numbers of stem cells; it has advantages over BMT or adult blood stem cell transplantation for certain patients and may be considered if a matched unrelated marrow stem cell donor is unavailable. One advantage of using umbilical cord blood is that it does not need to be a perfect tissue match with the recipient.

Patients preconditioned as described above receive the stem cell preparation and two to five weeks after transplantation, the engraftment of donated cells becomes apparent by the emergence of normal white cells in the blood of the patient. Red cells and platelets are transfused periodically until marrow function is restored by the transplanted stem cells. The time to hematopoietic recovery is shorter with blood stem cells than with bone marrow cells. Some of the new chimerical immune cells recognize the host as foreign and are going to produce a graft-versus-leukemia effect, hereinafter referred to as graft-versus-tumor (GVT) activity which is usually accompanied by graft-versus-host disease (GvHD). The GvHD reaction occurs when the donor’s immune cells, especially the T lymphocytes, recognize that the host cells are different from themselves.

Allo-BMT-induced GvHD is an immune function closely related to GVT which may occur soon after the transplanted cells begin to appear in the recipient. Both types of immune responses are mediated by T cells recognizing cells that are not genetically identical and this could explain the historical finding that transplants between identical twins are less successful than those between matched siblings in the treatment of chronic myeloid leukemia (CML) (Gale et al., Ann. Intern. Med. 1994, 120: 646-652). In the case of stem cell transplantation, the donor cells carefully inspect the cells of the recipient’s tissue for signs of differences and attack them if they find significant variations. In the initial phase after transplantation, for instance, residual patient-derived APC are present and will be scanned by donor-
derived T cells for differences based on polymorphic genes. A cytotoxic response will be initiated if the donated T cells recognize host cells presenting foreign antigens, which are basically all the immune cells. Whether the T-cell response turns into a dreadful GvHD or a beneficial GVT is determined by the fact that the genetically manifested differences are either presented in the context of cells that belong to the cancerous tissues or organs or, worse, are part of essential non-diseased organs such as skin, joints, lung, liver or kidney. Depending on the importance of the affected organ, GvHD ranges in severity from only small rash to life-threatening illness. Allo-BMT in general remains a somewhat crude approach, with significant transplant-related morbidity and mortality. A recent compilation of reports places the risk of death at 20-41%, and, despite the availability of potent immunosuppressive drugs, up to 70% of the treated patients still suffer from GvHD. The broad identification of allo-antigens that are responsible for a disease-promoting process as well as the definition of allo-antigens that are useful for the disease-fighting option is therefore the central aspect of the present invention.

Nonetheless, immunotherapy based on BMT offers up to 70% of the patients a leukemia-free survival after transplantation (Clift et al. Haematol. 1997, 10: 319-336). However, more than 60% of CML patients do not receive allo-BMT owing to disease status, advanced age or lack of a suitable donor. BMT and/or stem cell transplantation are accepted treatment options for acute myeloid leukemia (AML) in first or subsequent complete remission, AML early relapse or induction failure, acute lymphoblastic leukemia (ALL) in first or subsequent complete remission, ALL in early relapse or induction failure, CML, myelodysplasia, aplastic anemia, Hodgkin's disease sensitive and resistant relapse, aggressive lymphoma sensitive and resistant relapse, and low grade lymphoma.

Graft-versus-host reaction results when the donor's immune cells, especially the T lymphocytes, sense that the host cells are different from themselves. The differences may involve a broad spectrum of proteins that are not detected by HLA typing, or there may be faint differences in HLA type that
permit transplantation but not without engendering the reaction. The differences reflect more limited polymorphism in individual codons of the corresponding HLA molecules outside the codons used for HLA typing and matching. It is known that, with the exception of identical twins, some incompatibility will exist even though HLA testing indicates sufficient similarity to permit a transplant to be successful. HLA-typing methods do only cover polymorphisms that have empirically been screened as important. With the growing information coming in from HLA sequencing, new allelic variants are continuously being discovered which in part may be recognized as foreign. Variations also become evident when the donor and the recipient have a different sex. In summary, the severity of immune reactions such as GvHD depends on the type and degree of molecularly defined protein differences between the patient and the donor that are presented by the patient's cells. The GVT activity has been best studied in CML patients, where the recognition and eradication of residual tumor cells by donor immune cells cytotoxic T cells (CTLs) appears to be essential for inducing long-lasting molecular remission. Further insight into the mechanisms of immune regulation in CML has been gained by the observation that there is an increased risk of relapse following T-cell depletion of the grafts. The risk of relapse is also increased in the absence of GvHD (Goldman et al., Ann. Intern. Med. 1988, 108: 806-814; Horowitz et al., Blood 1990, 75: 555-562.). Moreover, syngeneic twin BMT is much less effective than matched sibling BMT. Together, these findings indicate that T-cell recognition of tumor cells is an essential prerequisite of the therapeutic effect.

When disease reappears after an apparently successful transplantation, complete remission can be achieved by withdrawal of immunosuppressive drugs or, more impressively, by additional donor T lymphocyte infusion. Thus, the GVT effect related to allo-BMT represents the most conclusive evidence that the immune system can cure cancer in humans and it has to be emphasized that the powerful anti-leukemia effect is generated by cytotoxic T cells transferred to the recipient.
Donor T lymphocytes destroy the recurrent leukemia cells by the GVT effect and, presumably, T cells of both the CD4+ and CD8+ subpopulations in the allograft contribute to this phenomenon. CD4+ T cells often have a helper function for antibody- or cell-mediated immune responses and are MHC class II-restricted. CD8+ T cells often have a cytotoxic function and are usually MHC class I-restricted. The relevant antigens (tumor-expressed antigens, the recipient's histocompatibility antigens, or both) have not been identified yet and it is the objective of the present invention to identify and define the antigens involved.

It is striking that T cell-depleted grafts are associated with an increased risk of relapse in CML (Goldman et al., Ann. Intern. Med. 1988, 108: 806-814; Horowitz et al., Blood 1990, 75: 555-562). As described above, anti-leukemia effects may be generated by allo-BMT, when donor lymphocyte infusion (DLI) is performed. In this setting, DLI can reinstate durable molecular remission in up to 70% of cases. However, DLI can as well be associated with significant toxicity caused by GvHD, which frequently accompany a graft-versus-leukemia effect, with significant mortality from marrow aplasia and/or systemic GvHD occurring in 50-90% of cases (S. MacKinnon, Br. J. Haematol. 2000, 110: 12-17).

To overcome the shortcomings related to the toxicity of the "traditional" allo-BMT protocol, a conditioning model comprising immunosuppression with mycophenolate mofetil (Cellcept®) and cyclosporine in combination with minimally toxic low-dose total-body irradiation has been suggested. However, because of the less rigorous conditioning, a pronounced graft-versus-host response has been observed. Depleting T cells from the transplant prior to infusion may prevent GvHD in this situation. A modified type of transplantation procedure, sometimes called "minitransplant", is currently developed based on these observations. The hazards of graft rejection and a higher relapse rate can be avoided by maintaining only a portion of the T cells in the graft. The positive selection of CD34+ cells from peripheral blood preparations provides an approximately 1000-fold reduction of T-cells. These purified CD34+ cells containing committed and pluripotent stem cells are
suitable for allogeneic transplantation. In CML, the administration of incrementally increasing T-cell doses has been used to partially circumvent the GvHD problem (MacKinnon et al., Blood 1995, 86: 1261-1268) and to increase the GVT effect at the same time.

The role of integrins in this context, however, is largely unknown. Integrins are known to be receptors that mediate cell signaling, cell mobility, extracellular matrix (ECM) interaction and cell cycle regulation. More specifically, the integrins ανβ3 and ανβ5 are receptors that are known to regulate cell adhesion to ECM, which is a prerequisite for endothelial cells (EC) during vascularization (Eliceiri 1999). While under physiological conditions vascularization is found during embryogenesis, pathological neovascularization is observed in growing tumors and different inflammatory diseases (Firestein 1999; Danese 2007; Halin 2008; Szekanecz 2009; Penack 2010). Therefore, local inflammation may be controlled by interfering with integrin mediated neovascularization which is dependent on the migration and proliferation of EC.

Besides their role in EC, different types of integrins are believed to play a role in immune cells. αυβ3 integrin was shown to be expressed on activated T cells (Luzina 2009) and dendritic cells (DC) (Rubartelli 1997). T cells expressing αυβ3 integrins were shown to contribute to pulmonary inflammation (Luzina 2009) and DC require αυβ3 integrins to phagocytose antigen (Rubartelli 1997). Data derived from murine models of graft-versus-host disease (GvHD) demonstrate that the αυβ7 integrin plays a central role in the homing of T cells to the gut and that βυ− donor T cells induced significantly less severe GvHD than wild-type (WT) T cells (Waldmann 2006). Conversely, βυ− donor T cells were fully functional with respect to proliferation, cytokine production and leukemia rejection in vivo (Waldmann 2006). A more recent study demonstrated that recipients of donor T cells deficient for the βυ integrin member LFA-1 (CD18) had significantly less GvHD mortality as compared with recipients of WT donor T cells (Liang 2008).
After allogeneic hematopoietic cell transplantation (alloHCT) bone marrow derived hematopoietic stem cells can function as endothelial progenitor cells (Shi 1998). This cell type is recruited to sites of inflammation where it differentiates into EC and may support the inflammatory process of GvHD by facilitating neovascularization.

Cilengitide (EMD 121974; Merck KgaA, Darmstadt, Germany) is a cyclic arginine-glycine-aspartic acid pentapeptide, that selectively binds the cell surface receptors $\alpha\nu\beta_3$ and $\alpha\nu\beta_5$, which are expressed on activated endothelial cells during angiogenesis (Goodman 2002). The drug induces programmed cell death in angiogenic blood vessels by preventing interaction of their cell surface av-integrins with specific matrix ligands, such as vitronectin, tenascin, and fibronectin (MacDonald 2001) and it inhibits the proliferation and differentiation of human endothelial progenitor cells (Loges 2007).

Thus, the potential role of av integrins in the immune cell compartment and inflammatory neoangiogenesis mediated by bone marrow derived EC and the impact of Cilengitide on this system was studied in a GvHD model.


The above cited references are incorporated into this application by reference in their entirety.
It was found that Cilengitide and preferably also its pharmaceutically acceptable derivatives, solvates and/or salts is able to prevent, treat and/or ameliorate GvHD and related inflammatory processes.

However, the administration of Cilengitide (or Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and preferably also its pharmaceutically acceptable derivatives, solvates and/or salts preferably does not adversely affect the normal function or desired response of the immune system, such as the Graft-versus-Tumor (GVT) reaction, or only to a minor, not relevant extent.

Thus, preferred subject of the instant invention relates to compounds, compositions and methods comprising or using Cilengitide and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof for the prevention, amelioration and/or treatment of various forms of graft-versus-host disease (GvHD) and related inflammatory processes, preferably including acute graft-versus-host disease and/or chronic graft-versus-host disease.

Furthermore, a preferred subject of the instant invention relates to compounds, compositions and methods comprising or using Cilengitide and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof for the prevention and/or clinical treatment of graft-versus-host disease (GvHD), preferably including acute graft-versus-host disease and/or chronic graft-versus-host disease. In particular, compounds, compositions and methods comprising or using Cilengitide and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof are provided for the treatment of humans in vivo. Additionally, compounds, compositions and methods comprising or using Cilengitide and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof are provided for the ex vivo conditioning of organ transplants in order to minimise the risk and/or severity of unwanted graft-versus-host reactions and related inflammatory processes, preferably including the suppression T-lymphocyte mediated
immune responses. Preferably, the compounds, compositions and methods according to the invention advanatagously enhance the efficacy of coadministered immunosuppressive agents and/or coadministered anti-GvHD agents and/or help to minimize the adverse effects and/or systemic toxicity of the respective co-administered agents.

In one aspect, a method is provided for treating a patient having graft-versus-host disease. The method comprises: administering to the patient Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, in a pharmaceutically effective amount, preferably in an amount and/or regimen as described herein. The patient may have acute or chronic graft-versus-host disease, and may have also failed at least one immunosuppressive regimen such as a regimen including steroids (e.g., prednisone and methylprednisolone), cyclophosphamide, cyclosporin A, FK506, thalidomide, azathioprine, and daclizumab.

In one embodiment, the method is used to treat hematopoietic stem cell transplant (HSCT) patients manifesting grade 2 or greater acute GvHD. In one embodiment, the method is used to treat hematopoietic stem cell transplant (HSCT) patients manifesting grade 2 or greater acute GvHD, who have failed to respond to treatment with at least 2 mg/kg of methylprednisolone or equivalent corticosteroid or other salvage therapy. For example, the HSCT patient may be treated with pentostatin at 0.25-1 mg/m²/day as a 20 minute intravenous (IV) infusion on days 1, 2 and 3. The method may further comprise: monitoring the improvement of the GvHD symptoms in the skin, mouth, fascia, and liver. Treatment with pentostatin may be repeated to further reduce the symptoms or to prevent recurrence of the disease.

In another embodiment, the method is used to treat steroid-refractory chronic graft vs host disease (cGvHD). For example, recipients of allogeneic HSCT developing cGvHD who have failed to respond to treatment with at least 2
mg/kg of methylprednisolone or equivalent corticosteroid or other salvage therapy may be treated with Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably in a pharmaceutically active amount and more preferably in an amount and/or regimen as described herein.

In another aspect, a method is provided for preventing or reducing the risk of developing graft-versus-host disease in a recipient of an organ or tissue transplant. The method comprises: administering to the transplant recipient Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably in a pharmaceutically active amount, more preferably within a predetermined time window before or after the transplantation and even more preferably in an amount, regimen and/or a predetermined time window before after the transplantation as described herein. Preferably, the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof is administered to the transplant recipient 3 or 2 days before and/or after the transplantation. Even more preferably, it is administered to the transplant recipient, e.g. by IV infusion, at a dose as described herein. Alternatively preferably, it is administered to the transplant recipient, e.g. by IV infusion, at a lower dose than 1000 mg/m², and preferably at a dose higher than 10 mg/m².

In a variation of the embodiment, the transplant recipient is transplanted with hematopoietic stem cells and treated in a myeloablative conditioning regimen. Additionally to the administration of the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, the recipient may be treated with with high dose cyclophosphamide and/or busulfan and/or melphalan and/or 1200-1800 cGy irradiation prior to stem cell infusion, preferably as is known in the art and even more preferably as is described herein. Post transplantation the recipient may preferably be treated with Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val)
and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof on one or more days, more preferably several days and even more preferably several consecutive days.

In another embodiment, Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof may be administered to a transplant recipient after the transplantation on one or more days, more preferably several days and even more preferably several consecutive days.

The above methods may further comprise: administering to the GvHD patient or the transplant recipient an immunosuppressive and/or anti-inflammatory agent, preferably selected from the immunosuppressant and/or anti-inflammatory agents described herein and even more preferably an immunosuppressive and/or anti-inflammatory agent selected from the group consisting of prednisone, methylprednisolone, cyclophosphamide, cyclosporin A, FK506, thalidomide, azathioprine, Daclizumab, Infliximab, MEDI-205, abx-cbl and ATG.

In yet another aspect, a method is provided for ex vivo or in vitro treatment of blood derived cells, bone marrow transplants, or other organ transplants. The method comprises: treating a tissue or organ transplant with Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof. Preferably, the method comprises: treating a tissue or organ transplant with Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof in an effective amount, even more preferably in an effective amount as described herein and especially preferably in an amount such that activity of T-lymphocytes therein is substantially inhibited, preferably by at least 50% reduction in activity, more preferably by at least 80% reduction in activity, and most preferably by at least 90% reduction in activity.

Preferably, said treatment or conditioning of a tissue or organ transplant with Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof takes place by perfusion and/or
bath. Preferably, said treatment or conditioning of a tissue or organ transplant with Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof is preferably performed at a concentration between 1 micromolar and 100 micromolar, more preferably 2 micromolar and 50 micromolar, even more preferably 2 micromolar and 40 micromolar and especially 2 micromolar and 10 micromolar of the with Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof. Preferably, the timeframe for the exposure of said tissue or organ transplant will generally be in the range between 1 hour and 48 hours, more preferably 2 to 24 hours and especially 4 to 24 hours.

Examples of the tissue or organ transplant include, but are not limited to, stem cells, bone marrow, heart, liver, kidney, lung, pancreas, small intestine, cornea, and skin. In this method, the tissue or organ transplant can be additionally treated with an ADA inhibitor, preferably an ADA inhibitor as described herein and especially preferably an ADA inhibitor selected from the group consisting of pentostatin, fludarabine monophosphate, and cladribine. In one embodiment, the transplant is stored in a preservation solution containing Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably in an effective amount, even more preferably in an effective amount as described herein and especially in an amount sufficient to inhibit activity of T-lymphocytes of the transplant. As a basis for said preservation solution containing Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, commercially available preservation solutions can be used. An example of commercially available preservation solutions is Plegisol (Abbott). The preservation solution may also contain conventional co-solvents, excipients, stabilizing agents and/or buffering agents. In another embodiment, the transplant is washed with a buffer containing Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof prior to storage or transplantation.
this way, the risk of developing acute GvHD upon transplantation should be significantly reduced, and the host is not only protected from GvHD, but preferably also from potential side effects of agents other than Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof potentially contained in said buffer and/or preservation solution.

The present invention provides methods for prevention and clinical treatment of various forms of graft-versus-host disease (GvHD) by using Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof. In particular, novel formulations and dosing regimens of other than Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof are provided for the treatment various forms of graft-versus-host disease (GvHD), preferably comprising specific suppression of the T-lymphocyte mediated immune responses, preferably while minimizing systemic toxicity of other coadministered drugs, and especially preferably myelosuppression.

With the methods according to the invention, patients with acute or chronic GvHD can be treated with Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, optionally in combination with one or more of immunosuppressive and/or anti-inflammatory agents, to reduce the pathological symptoms with minimal myelosuppression. In addition, the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof may preferably be used for ex vivo treatment or conditioning of transplants for positively affecting the rate of engraftment.

The ADA inhibitor as referred to herein is preferably a compound or an agent that has an inhibitory effect on biochemical activity of adenosine deaminase (ADA). Suitable ADA inhibitors for use in accordance with the instant invention are known in the art. Preferred examples of the ADA inhibitors include, but are not limited to, pentostatin, fludarabine monophosphate, and
cladribine. Other ADA inhibitor may be adenosine analogs that compete with adenosine for binding to ADA such as 2'-deoxyadenosine, 3'-deoxyadenosine, and dideoxyadenosine. Suitable ADA inhibitors, suitable formulations of ADA inhibitors, including formulations for oral use, suitable dosings, dosing regimens and treatment regimen using such ADA inhibitors are known in the art, for example from US 7,037,900 (DiMartino et al.), the disclosure of which is incorporated into this application in its entirety by reference.

Thus, subject of the instant invention is:

[1] A Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), for use in the treatment, prevention and/or prophylaxis, preferably treatment and/or prophylaxis and especially preferably treatment, of Graft-versus-Host Disease (GvHD).

The use of a Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), for the manufacture of a medicament for use in the treatment, prevention and/or prophylaxis, preferably treatment and/or prophylaxis and especially preferably treatment, of Graft-versus-Host Disease (GvHD).

A method for the treatment, prevention and/or prophylaxis, preferably treatment and/or prophylaxis and especially preferably treatment, of Graft-versus-Host Disease (GvHD), comprising administering to a subject, preferably a human subject, a Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), preferably in a pharmaceutically effective amount and more preferably in an amount and/or regimen or schedule as described herein.
The meaning of the term Graft-versus-Host Disease (GvHD) is well known and understood in the art and preferably used herein in accordance with the art. Preferably, in the context of the instant invention, it is understood as discussed herein.

Peptide, use or method as described above and/or below, wherein Graft-versus-Host Disease comprises acute Graft-versus-Host Disease and/or chronic Graft-versus-Host Disease, more preferably acute Graft-versus-Host Disease.

Peptide, use or method as described above and/or below, wherein Graft-versus-Host Disease emerges in the context or results from the context of:

a) allogenic marrow transplantation and/or allogenic bone marrow transplantation (allo-BMT),
b) allogenic hematopoetic cell transplantation (alloHCT or allo-HCT),
c) transplantation of one or more organs or tissues, selected from the group consisting of bone marrow, stem cells, bones, cornea, skin, heart valves, veins, liver, lung, skin, kidney, heart, pancreas, intestine and thymus.

Peptide, use or method as described above and/or below, wherein the treatment of the GvHD takes place after:

a) allogenic marrow transplantation and/or allogenic bone marrow transplantation (allo-BMT),
b) allogenic hematopoetic cell transplantation (alloHCT or allo-HCT),
c) transplantation of one or more organs or tissues, selected from the group consisting of bone marrow, stem cells, bones, cornea, skin, heart valves, veins, liver, lung, skin, kidney, heart, pancreas, intestine and thymus.

Peptide, use or method as described above and/or below, wherein prevention and/or prophylaxis of the GvHD takes place prior to a
a) allogenic marrow transplantation and/or allogenic bone marrow transplantation (allo-BMT),
b) allogenic hematopoietic cell transplantation (alloHCT or allo-HCT),
c) transplantation of one or more organs or tissues, selected from the group consisting of bone marrow, stem cells, bones, cornea, skin, heart valves, veins, liver, lung, skin, kidney, heart, pancreas, intestine, and thymus.

Peptide, use or method as described above and/or below, wherein the GvHD is selected from steroid-refractory Graft-versus-Host Disease, steroid-refractory chronic Graft-versus-Host Disease, steroid-resistant Graft-versus-Host Disease and steroid-refractory acute Graft-versus-Host Disease.

Peptide, use or method as described above and/or below, wherein organs and/or tissues of the subject, selected from the group consisting of oropharynx, gastrointestinal tract, liver, lung, skin, kidney, urinary tract and nervous system, more preferably selected from the group consisting of gastrointestinal tract, liver, lung and skin, and even more preferably selected from gastrointestinal tract, liver and skin, are afflicted with GvHD and/or symptoms related to GvHD, preferably including GvHD induced inflammation.

The severity of the GvHD, preferably including acute and/or chronic GvHD, is preferably classified according to grades 1 to 4 (or I to IV). Preferably, all grades can be ameliorated, prevented and/or treated by the Peptide, use or method for the prevention, prophylaxis and/or treatment as described herein.

Preferably, the acute GvHD is classified according to grades 1 to 4 (or I to IV). Preferably, all grades of the acute GvHD can be ameliorated, prevented and/or treated by the Peptide, use or method for the prevention, prophylaxis and/or treatment as described herein. Especially preferably, the clinical symptoms of

a) the skin, preferably including the exanthem of the skin and especially the maculopapular exanthem of the skin, and/or blistering of the skin
b) the liver, preferably including the rise of the bilirubin values and/or the jaundice, and/or
c) the gastrointestinal tract, preferably including diarrhoea, severe diarrhoea, nausea and/or ileus,
can be preferably ameliorated, prevented and/or treated according to the methods comprising the administering of said Peptide as described herein. Preferably, all grades and especially grades I-III can be treated according to the methods comprising the administering of said Peptide as described herein.

Preferably, also the chronic GvHD is classified according to grades 1 to 4 (or I to IV). Preferably, all grades of the chronic GvHD can be ameliorated, prevented and/or treated by the Peptide, use or method for the prevention, prophylaxis and/or treatment as described herein. Especially preferably, the clinical symptoms of

a) the skin, preferably including the exanthem of the skin and especially the maculopapular exanthem of the skin, and/or blistering of the skin
b) the liver, preferably including the rise of the bilirubin values, jaundice, hepatitis and/or cirrhosis,
c) the gastrointestinal tract, preferably including diarrhoea, severe diarrhoea, nausea and/or ileus,

and/or
d) the xerothalmia and/or xerostomia,
can be preferably ameliorated, prevented and/or treated according to the methods comprising the administering of said Peptide as described herein. Preferably, all grades and especially grades I-III can be treated according to the methods comprising the administering of said Peptide as described herein.

Dosings and standard administration schedules or regimen for the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives,
solvates and/or salts thereof are preferably known in the art. Preferred dosings and standard administration schedules regimen for the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivates, solvates and/or salts thereof are described herein above and/or below or can preferably be readily deducted by the skilled artisan from the disclosure given herein.

For use in the treatment, prevention and/or prophylaxis, preferably treatment and/or prophylaxis and especially preferably treatment, of Graft-versus-Host Disease (GvHD) as described herein, said treatment preferably comprises the administration of the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivates, solvates and/or salts thereof to said subject in an amount of 50 mg to 15000 mg per week (and per human), more preferably in an amount of 500 mg to 12000 mg per week (and per human), even more preferably 1500 mg to 11000 mg per week (and per human), even more preferably 2500 mg to 10000 mg per week (and per human) and especially 3000 mg to 5000 mg per week (and per human), such as about 800 mg per week, about 1600 mg per week, about 2500 mg per week, about 4000 mg per week, about 8000 mg per week, about 10000 mg a week or about 12000 mg a week. The given amounts are preferably to be regarded as "flat" amounts, i.e. without an adaptation or factor regarding the size, body weight and/or body surface of the subject to be treated. Preferably, the above given amounts are administered to human subjects 12 years or older, more preferably 16 years or older and especially 18 years or older. Especially preferably, the given amounts are suitable for adult human subjects. If the Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) is applied, partially or totally, as a pharmaceutically acceptable derivative, solvate and/or salt thereof, said amounts are is preferably calculated on the amount of Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained in said pharmaceutically acceptable derivative, solvate and/or salt thereof.
Alternatively preferably, for use in the treatment, prevention and/or prophylaxis, preferably treatment and/or prophylaxis and especially preferably treatment, of Graft-versus-Host Disease (GvHD) as described herein, said treatment preferably comprises the administration of the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof to said subject in an amount of 1 mg/kg to 150 mg/kg per day, preferably 2 mg/kg to 100 mg/kg per day, more preferably 5 mg/kg to 80 mg/kg per day, even more preferably 10 mg/kg to 60 mg/kg per day and especially preferably 10 mg/kg to 30 milligrams/kg, for example about 1.5 mg/kg, about 2.5 mg/kg, about 7.5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 50 mg/kg, about 75 mg/kg or about 100 mg/kg, per day.

The amount of the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof administered to said subject per day can be given as one single dose on the respective day, or can be divided into one or more administrations, such as divided into twice a day or three times a day administrations.

Peptide, use or method as described above and/or below, wherein the prevention, prophylaxis and/or treatment comprises the administration of the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof to said subject in an amount of 50 mg to 14,000 mg per week, preferably 100 mg to 12,500 mg per week, more preferably 500 mg to 10,000 mg per week, even more preferably 1000 mg to 10,000 mg per week and especially 2000 mg to 10,000 mg per week, for example about 100 mg per week, about 250 mg per week, about 500 mg per week, about 1000 mg per week, about 2000 mg per week, about 4000 mg per week, about 6000 mg per week, about 8000 mg per week, about 10,000 mg per week or about 12,000 mg per week. Said amounts per week are preferably administered to a subject for a time period of at least one week, more preferably at least two weeks even more preferably at least four weeks.
and even more preferably at least eight weeks. Thus, said amounts per week are preferably administered to a subject for a time period between between one week and 52 weeks, more preferably for the time period between two weeks and 26 weeks, even more preferably for a time period between four weeks and 26 weeks, and especially preferably for a time period between eight weeks and 20 weeks. The given time periods are especially preferred with respect to acute GvHD.

In the case of chronic GvHD, the administration periods for the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof preferably are unlimited. Accordingly, the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof can be administered to the subject as long as a benefit is obtained. Even administration periods of several years are possible.

Thus, a preferred subject of the instant invention relates to a Peptide, use or method as described above and/or below, wherein the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof is administered to a subject in an amount of 1000 mg to 12500 mg per week for a time period between 4 and 20 weeks.

Thus, a preferred subject of the instant invention relates to a Peptide, use or method as described above and/or below, wherein the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof is administered to a subject in a once weekly to seven times weekly administration scheme consisting of about 100 mg to about 2000 mg per day and/or per administration.

The amounts of the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof in
milligrams/kg for the administration to a subject per day can preferably also employed in the conditioning of tissue and/or organs prior to transplantation.

Preferably, the conditioning of tissue and/or organs prior to transplantation is to be regarded as a preferred form of prophylaxis and/or prevention of Graft-versus-Host Disease (GvHD) as described herein.

In the treatment, prevention and/or prophylaxis, preferably treatment and/or prophylaxis and especially preferably treatment, of Graft-versus-Host Disease (GvHD) as described herein, it can be advantageous to additionally administer to the subject one or more cotherapeutic agents, preferably one, two or three cotherapeutic agents, other than the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof.

Preferably, said one or more cotherapeutic agents (other than the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof) are preferably selected from the group of immunosuppressive agents (immunosuppressants) and/or anti-inflammatory agents.

Suitable immunosuppressive and/or anti-inflammatory agents (other than the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof) that can be employed in the context of the instant invention are known in the art.

One group of immunosuppressive and/or anti-inflammatory agents, preferably immunosuppressive agents (or immunosuppressants), are compounds, substances or agents that perform immunosuppression of the immune system of an animal, preferably the human animal. They may be either exogenous, as immunosuppressive drugs, or endogenous, as, e. g.,
testosterone. Preferred in the context of the instant invention are exogenous compounds, substances or agents. Such compounds are known in the art.

Examples of immunosuppressive and/or anti-inflammatory agents, preferably immunosuppressive agents (or immunosuppressants), comprise

a) antimetabolites, such as
   i) purine synthesis inhibitors, e.g. Azathioprine and/or Mycophenolic acid,
   ii) pyrimidine synthesis inhibitors, e.g. Leflunomide and/or Teriflunomide, and
   iii) antifolates, e.g. methotrexate;

b) macrolides, such as FKBP/Cyclophilin/Calcineurin, e.g. Tacrolimus, Ciclosporin and/or Pimecrolimus;

c) (other) IL-2 inhibitors, such as Abetimus and/or Gusperimus;

d) TNF alpha inhibitors, such as Thalidomide and/or Lenalidomide;

e) IL-1 receptor antagonists, such as Anakinra;

f) mTOR inhibitors, such as Sirolimus, Deforolimus, Everolimus, Temsirolimus, Zotarolimus and/or Biolimus A9;

g) immunosuppressive Antibodies, Fusionproteins and/or Globulins, such as Eculizumab, Infliximab, Adalimumab, Certolizumab, Certolizumab pegol, Afelimomab, Golimumab, Mepolizumab, Omalizumab, Nerelimumab, Faralimomab, Elsilimomab, Lebrikizumab, Ustekinumab, Muromonab, Muromonab-CD3, Otelixizumab, Teplizumab, Visilizumab, Clenoliximab, Keliximab, Zanolimumab, Efalizumab, Erlizumab, Aftuzumab, Rituximab, Ocrelizumab, Pascolizumab, Lumiliximab, Teneliximab, Toralizumab, Aselizumab, Galiximab, Gavilimomab, Ruplizumab, Belimumab, Iplilimumab, Tremelimumab, Bertilimumab, Lerdelimumab, Metelimumab, Natalizumab, Tocilizumab, Odulimumab, Basiliximab, Daclizumab, Inolimumab, Zolimomab aritox, Atorolimumab, Cedeлизumab, Dorlixizumab, Fontolizumab,

Gantenerumab, Gomiliximab, Maslimomab, Morolimumab, Pexelizumab, Reslizumab, Rovelizumab, Siplizumab, Talizumab, Telimomab aritox, Vapaliximab, Vepalimomab, Anti-thymocyte globulin, Anti-lymphocyte
globulin, Abatacept, Belatacept, Etanercept, Pegsunercept, Aflibercept, Alefacept and/or Rilonacept; and the pharmaceutically acceptable derivatives, salts and/or solvates thereof.

Preferred as immunosuppressive and/or anti-inflammatory agents, preferably immunosuppressive agents (or immunosuppressants) are one or more agents, selected from the group consisting of: Azathioprine, Mycophenolic acid, methotrexate, Tacrolimus, Ciclosporin, Pimecrolimus, Thalidomide, Lenalidomide, Sirolimus, Deforolimus, Temsirolimus, Everolimus, Infliximab, Adalimumab, Certolizumab, Certolizumab pegol, Afelimomab, Golimumab, Muromonab, Muromonab-CD3, Otelixizumab, Teplizumab, Visilizumab, Basiliximab, Daclizumab, Inolimomab, Anti-thymocyte globulin, Anti-lymphocyte globulin, Etanercept and/or Pegsunercept; and the pharmaceutically acceptable derivatives, salts and/or solvates thereof.

Even more preferred as immunosuppressive and/or anti-inflammatory agents, preferably immunosuppressive agents (or immunosuppressants) are one or more agents, selected from the group consisting of: Azathioprine, Mycophenolic acid, methotrexate, Tacrolimus, Ciclosporin, Thalidomide, Lenalidomide, Sirolimus, Everolimus, Infliximab, Muromonab, Muromonab-CD3, Basiliximab, Daclizumab, Inolimomab, Anti-thymocyte globulin, Anti-lymphocyte globulin, Etanercept and/or Pegsunercept; and the pharmaceutically acceptable derivatives, salts and/or solvates thereof.

One group of Immunosuppressive and/or anti-inflammatory agents, preferably anti-inflammatory agents, are compounds, substances or agents that reduce inflammation. Such compounds are known in the art.
One preferred subgroup of Immunosuppressive and/or anti-inflammatory agents, preferably anti-inflammatory agents, are selected from steroids, corticoids and/or corticosteroids, preferably corticoids and/or corticosteroids. Anti-inflammatory steroids, corticoids and/or corticosteroids in this regard are known in the art.

Preferably, corticoids and/or corticosteroids as used herein are preferably selected from natural and/or synthetical corticoids or corticosteroids.

More preferably, the corticoids or corticosteroids are selected from the group consisting Cortison, Corticosteron, Cortisol, Aldosteron, Desoxycorticosteron, Dehydroepiandrosteron, Fludrocortisone acetate, Deoxycorticosterone acetate, Prednison und Prednisolon, Methylprednisolon, Triamcinolon, Dexamethason, Betamethason and Paramethason, and/or preferably the pharmaceutically acceptable derivatives, salts and/or solvates thereof.

The corticoids or corticosteroids can be divided into various subgroups, said subgroups preferably including natural or naturally occurring corticoids or corticosteroids, synthetic corticoids or corticosteroids and/or Glucocorticoids.

Natural or naturally occurring corticoids or corticosteroids are preferably selected from the group consisting of Cortison, Corticosteron, Cortisol, Aldosteron, Desoxycorticosteron and Dehydroepiandrosteron, and/or preferably the pharmaceutically acceptable derivatives, salts and/or solvates thereof.

Synthetic corticoids or corticosteroids are preferably selected from the group consisting of Prednison und Prednisolon, Methylprednisolon, Triamcinolon, Dexamethason, Betamethason and Paramethason, and/or preferably the pharmaceutically acceptable derivatives, salts and/or solvates thereof.
Glucocorticoids are preferably selected from the group consisting of Hydrocortisone (Cortisol), Cortisone acetate, Prednisone, Prednisolone, Methylprednisolone, Dexamethasone, Betamethasone, Triamcinolone and Beclometasone, Fludrocortisone acetate, Deoxycorticosterone acetate and Aldosterone, and/or preferably the pharmaceutically acceptable derivatives, salts and/or solvates thereof.

Natural or naturally occurring Glucocorticoids are preferably selected from the group consisting of Cortison, Corticosteron und Cortisol, and/or preferably the pharmaceutically acceptable derivatives, salts and/or solvates thereof.

Synthetic Glucocorticoids are preferably selected from the group consisting of Prednisone, Prednisolone, Methylprednisolone, Dexamethasone, Betamethasone, Triamcinolone and Beclometasone, Fludrocortisone acetate, Deoxycorticosterone acetate and Aldosterone, more preferably from Prednisone, Prednisolone, Methylprednisolone, Dexamethasone, Betamethasone, Triamcinolone and Beclometasone, and especially from Prednisone, Prednisolone, Methylprednisolone and Dexamethasone, and/or preferably the pharmaceutically acceptable derivatives, salts and/or solvates thereof.

For example, the compound or agent Basiliximab (also available under the trade name Simulect) is a chimeric mouse-human monoclonal antibody to the α chain (CD25) of the IL-2 receptor of T cells. It can be used to prevent rejection in organ transplantation, especially in kidney transplants.

For example, the compound or agent Mycophenolic acid (INN) or mycophenolate is an immunosuppressant drug preferably used to prevent
rejection in organ transplantation. It was initially marketed as the prodrug mycophenolate mofetil (MMF) to improve oral bioavailability. More recently, the salt mycophenolate sodium has also been introduced. Mycophenolic acid is also commercially available under the trade names CellCept (mycophenolate mofetil; Roche) and Myfortic (mycophenolate sodium; Novartis).

For example, the compound or agent Azathioprine interferes with the synthesis of purines (adenine and guanine), which is required for DNA synthesis. Fast-growing cells, including T-cells and B-cells, are particularly affected by the inhibition of purine synthesis. It is a pro-drug, converted in the body to the active metabolites 6-mercaptopurine (6-MP) and 6-thioinosinic acid. Azathioprine is produced by a number of generic manufacturers and and commercially available under various brand names (e.g. Azasan by Salix in the U.S., Imuran by GlaxoSmithKline in Canada and the U.S., Australia and UK, Azamun in Finland and Imurel in Scandinavia and France).

Anti-thymocyte globulin (ATG), for example, is an infusion of horse or rabbit-derived antibodies against human T cells which can be used in the prevention and treatment of acute rejection in organ transplantation and therapy of aplastic anemia. At least two antithymocyte globulin (ATG) agents are licensed for clinical use in the United States, including Thymoglobulin (rabbit ATG, rATG, Genzyme) and Atgam (equine ATG, eATG, Pfizer). Thymoglobulin and Atgam are currently licensed for use in the treatment of renal allograft rejection; Atgam is additionally licensed for use in the treatment of aplastic anemia. Both drugs are used in off-label applications, especially as immunosuppression induction agents before and/or during kidney transplantation. An rATG product made by Fresenius is marketed outside of the United States.

Especially preferred as immunosuppressive and/or anti-inflammatory agents are preferably one or more agents, selected from the group consisting of:
cyclosporin A, azathioprine, prednisone, methylprednisolone, cyclophosphamide, FK506, rapamycin, mycophenolic acid, 15-deoxyspergualin, mimoribine, misoprostol, methotrexate, Tacrolimus, Thalidomide, Lenalidomide, Sirolimus, Everolimus, Infliximab, Muromonab, Muromonab-CD3, Basiliximab, Daclizumab, Inolimomab, Anti-thymocyte globulin, Anti-lymphocyte globulin, Etanercept and/or Pegasunercept; and the pharmaceutically acceptable derivatives, salts and/or solvates thereof, and even more preferably cyclosporin A, azathioprine, prednisone, methylprednisolone, cyclophosphamide, FK506, rapamycin, mycophenolic acid, methotrexate, Tacrolimus, Thalidomide, Lenalidomide, Sirolimus, Everolimus, Basiliximab, and/or Anti-lymphocyte globulin (ATG).

Thus, a preferred subject of the instant invention relates to a Peptide, use or method as described above and/or below, wherein said Peptide is used in combination with

a) one or more cotherapeutic agents that are immunosuppressants,

b) one or more cotherapeutic agents that are anti-inflammatory agents, and/or

c) radiotherapy.

The term radiotherapy and/or radiotherapy regimen is known and understood in the art. This holds also true for radiotherapy and/or radiotherapy regimen in connection with the prevention, prophylaxis and/or treatment of Graft-versus-Host Disease and/or the transplantation regimen that can lead to the versus-Host Disease. Suitable regimen regarding said radiotherapy and/or radiotherapy regimen are described herein. In the context of the instant invention, the radiotherapy applied or administered to the subject of the treatment is preferably selected from external beam radiotherapy/radiation, brachytherapy, and systemic radioisotope therapy. Preferred in this respect is external beam radiotherapy/external beam radiation.
In this context, radiation or radiotherapy preferably means external beam radiation and even more preferably external beam radiation of the whole body, also referred to as Total Body Irradiation (TBI). The total doses of such radiation or radiotherapy is generally in the range between 2 Gy and 30 Gy more preferably 6 to 25 Gy, even more preferably 8 to 20 Gy and especially 8 to 14 Gy or 12 to 18 Gy. In a myeloablate setting or regimen, the TBI is preferably in the range of 8 to 14 Gy or 12 to 18 Gy. Preferably, the myeloablate setting or regimen also comprises chemotherapy, for example chemotherapy as described herein. However suitable myeloablate settings or regimen are known in the art. Currently, who “reduced intensity” or “mini transplantation” settings or regimen are explored, wherein a rather low dose TBI (such as about 2 Gy, often as a single dose) is combined with chemotherapeutics, such as Fludarabine (e.g. 90-150mg/m²), often followed by an immunosuppressive regimen, preferably a high dosage immunosuppressive regimen, comprising e.g. cyclosporin and/or methotrexate. Also such regimens can be advantageously combined with the administration of the Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable deratives, solvates and/or salts thereof, preferably as described herein.

The compounds to be used according to the invention, preferably including the Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable deratives, solvates and/or salts thereof, and/or one or more cotherapeutic agents as defined herein, can generally be administered to the patient in a form and in a way or manner that is known in the art for the respective compounds or class of compounds, for example as described herein or as described in the literature cited herein.

Dosings and standard administration schedules for the above and/or below given coherapeutic agents and especially for the immunosuppressive and/or anti-inflammatory agents are preferably known in the art. Preferred dosings and standard administration schedules or regimen above and/or
below given cotherapeutic agents and especially for the immunosuppressive and/or anti-inflammatory agents are described herein above and/or below or can preferably be readily deducted by the skilled artisan from the disclosure given herein.

Preferably, the compounds, agents and/or compositions for use according to the invention and especially the compounds agents and/or compositions that do not comprise Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, can be administered to a subject as it is known in the art and more preferably as is described herein.

Preferably, the compounds, agents and/or compositions for use according to the invention and especially the compounds agents and/or compositions comprising Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, or compounds agents and/or compositions consisting of or essentially consisting of Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, can be administered to a subject as it is known in the art and more preferably as is described herein.

Preferred ways of administering such compounds, agents and/or compositions to patients include, but are not limited to oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) administration or administration methods. Suitable standard formulations for the respective administration or administration method are preferably either known in the art or can be prepared using all processes known in the pharmaceutical art by, for example, combining the active ingredient with the excipient(s) and/or adjuvant(s).
Preferably, the compounds, agents and/or compositions for use according to the invention and especially the compounds agents and/or compositions comprising Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, or compounds agents and/or compositions consisting of or essentially consisting of Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, are administered to the subject parentally. Preferably, such parenteral administration comprises IV (intravenous), IM (intramuscular) and/or SC (subcutaneous) administration. Currently preferred in this regard is intravenous administration, such as intravenous perfusion.

Preferably, each compound for use according to the invention and preferably also the derivatives and/or solvates thereof, can be also employed as a salt, or, if the compound given herein is already a salt, a different sort thereof.

Preferably, the salts of said compounds (or different salts thereof) are acid addition salts and/or base addition salts. The terms "acid addition salt" and "base addition salt" are known and understood in the art.

Generally, a compound having a basic group or center can be converted into an acid addition salt by the addition of an acid. Generally, a compound having an acidic group or center can be converted into a base addition salt by the addition of a base.

Methods for producing such acid addition salts and for producing such base addition salts and methods of converting one acid addition salt into a different acid addition salt and methods of converting one base addition salt into a different base addition salt are known in the art.

Preferably, the base edition salts include aluminium, ammonium, calcium, copper, iron(III), iron(II), lithium, magnesium, manganese(III), manganese(II), potassium, sodium and zinc salts, but this is not intended to represent a
restriction. Of the above-mentioned salts, preference is given to ammonium; the alkali metal salts sodium and potassium, and the alkaline earth metal salts calcium and magnesium. Salts of the compounds for use according to the invention which are derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines, also including naturally occurring substituted amines, cyclic amines, and basic ion exchanger resins, for example arginine, betaine, caffeine, chloroprocaine, choline, N,N'-dibenzylethlenediamine (benzathine), dicyclohexylamine, diethanolamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydabamine, isopropylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine and tris-(hydroxymethyl)methylamine (tromethamine), but this is not intended to represent a restriction.

Compounds for use according to the present invention which contain basic nitrogen-containing groups can be quaternised using agents such as (C1-C4)-alkyl halides, for example methyl, ethyl, isopropyl and tert-butyl chloride, bromide and iodide; di(C1-C4)alkyl sulfates, for example dimethyl, diethyl and diamyl sulfate; (C6-C18)alkyl halides, for example decyl, dodecyl, lauryl, myristyl and stearyl chloride, bromide and iodide; and aryl(C1-C4)alkyl halides, for example benzyl chloride and phenethyl bromide. Both water- and oil-soluble compounds for use according to the invention can be prepared using such salts.

The above-mentioned pharmaceutical salts which are preferred include acetate, trifluoracetate, besylate, citrate, fumarate, gluconate, hemisuccinate, hippurate, hydrochloride, hydrobromide, isethionate, mandelate, meglumine, nitrate, oleate, phosphonate, pivalate, sodium phosphate, stearate,
sulfate, sulfosalicylate, tartrate, thiomalate, tosylate and tromethamine, but this is not intended to represent a restriction.

Particular preference is given to hydrochloride, dihydrochloride, hydrobromide, maleate, mesylate, phosphate, sulfate and succinate.

The acid-addition salts of basic compounds for use according to the invention are preferably prepared by bringing the free base form into contact with a sufficient amount of the desired acid, causing the formation of the salt in a conventional manner. The free base can preferably be regenerated by bringing the salt form into contact with a base and isolating the free base in a conventional manner. The free base forms preferably differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free base forms thereof.

As mentioned, the pharmaceutically acceptable base-addition salts of the compounds for use according to the invention are preferably formed with metals or amines, such as alkali metals and alkaline earth metals or organic amines. Preferred metals are sodium, potassium, magnesium and calcium. Preferred organic amines are N,N'-dibenzylethlenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methyl-D-glucamine and procaine.

The base-addition salts of acidic compounds for use according to the invention are preferably prepared by bringing the free acid form into contact with a sufficient amount of the desired base, causing the formation of the salt in a conventional manner. The free acid can preferably be regenerated by bringing the salt form into contact with an acid and isolating the free acid in a conventional manner. The free acid forms preferably differ in a certain respect from the corresponding salt forms thereof with respect to certain
physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free acid forms thereof.

If a compound for use according to the invention contains more than one group or center which is capable of forming pharmaceutically acceptable salts of this type, the invention preferably also encompasses the use of such multiple salts. Typical multiple salt forms include, for example, bitartrate, diacetate, difumarate, dimeglumine, diphosphate, disodium and trihydrochloride, but this is not intended to represent a restriction.

With regard to that stated above, it can be seen that the expression "pharmaceutically acceptable salt" in the present connection is preferably taken to mean an active ingredient which comprises a compound for use according to the instant invention in the form of one of its salts, in particular if this salt form imparts improved pharmacokinetic properties on the active ingredient compared with the free form of the active ingredient or any other salt form of the active ingredient used earlier. The pharmaceutically acceptable salt form of the active ingredient can also provide this active ingredient for the first time with a desired pharmacokinetic property which it did not have earlier and can even have a positive influence on the pharmacodynamics of this active ingredient with respect to its therapeutic efficacy in the body.

The invention furthermore preferably relates to medicaments for use as described herein comprising one or more compounds for use according to the invention and/or pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

The invention furthermore relates to medicaments for use as described herein comprising Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically
acceptable derivatives, solvates and/or salts thereof, preferably including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

Pharmaceutical formulations can optionally be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Such a unit can comprise, for example, 0.5 mg to 3 g, preferably 1 mg to 2500 mg, particularly preferably 5 mg to 2000 mg, of a compound or agent for use according to the invention, depending on the condition treated, the severity of the condition treated, the method of administration and the age, weight and condition of the patient, or pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Preferred dosage unit formulations are preferably those which comprise a daily dose or part-dose, as indicated above, or a corresponding fraction thereof of an active ingredient. Furthermore, pharmaceutical formulations of this type can preferably be prepared using a process which is generally known in the pharmaceutical art.

Pharmaceutical formulations can preferably be adapted for administration via any desired suitable method, for example by oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) methods. Such formulations can preferably be prepared using all processes known in the pharmaceutical art by, for example, combining the active ingredient with the excipient(s) or adjuvant(s).

Pharmaceutical formulations adapted for oral administration can preferably be administered as separate units, such as, for example, capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or foam foods; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.
Thus, for example, in the case of oral administration in the form of a tablet or capsule, the active-ingredient component can preferably be combined with an oral, non-toxic and pharmaceutically acceptable inert excipient, such as, for example, ethanol, glycerol, water and the like. Powders are preferably prepared by comminuting the compound to a suitable fine size and preferably mixing it with a pharmaceutical excipient comminuted in a similar manner, such as, for example, an edible carbohydrate, such as, for example, starch or mannitol. A flavour, preservative, dispersant and dye may likewise be present.

Capsules are preferably produced by preparing a powder mixture as described above and filling shaped gelatine shells therewith. Glidants and lubricants, such as, for example, highly disperse silicic acid, talc, magnesium stearate, calcium stearate or polyethylene glycol in solid form, can be added to the powder mixture before the filling operation. A disintegrant or solubiliser, such as, for example, agar-agar, calcium carbonate or sodium carbonate, may likewise be added in order to improve the availability of the medicament after the capsule has been taken.

In addition, if desired or necessary, suitable binders, lubricants and disintegrants as well as dyes can likewise be incorporated into the mixture. Suitable binders include starch, gelatine, natural sugars, such as, for example, glucose or beta-lactose, sweeteners made from maize, natural and synthetic rubber, such as, for example, acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. The lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. The disintegrants include, without being restricted thereto, starch, methylcellulose, agar, bentonite, xanthan gum and the like. The tablets are formulated by, for example, preparing a powder mixture, granulating or dry-pressing the mixture, adding a lubricant and a disintegrant and pressing the entire mixture to give tablets. A powder mixture is prepared
by mixing the compound comminuted in a suitable manner with a diluent or a base, as described above, and optionally with a binder, such as, for example, carboxymethylcellulose, an alginate, gelatine or polyvinylpyrrolidone, a dissolution retardant, such as, for example, paraffin, an absorption accelerator, such as, for example, a quaternary salt, and/or an absorbant, such as, for example, bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting it with a binder, such as, for example, syrup, starch paste, acadia mucilage or solutions of cellulose or polymer materials and pressing it through a sieve. As an alternative to granulation, the powder mixture can be run through a tableting machine, giving lumps of non-uniform shape, which are broken up to form granules. The granules can be lubricated by addition of stearic acid, a stearate salt, talc or mineral oil in order to prevent sticking to the tablet casting moulds. The lubricated mixture is then pressed to give tablets. The compounds according to the invention can also be combined with a free-flowing inert excipient and then pressed directly to give tablets without carrying out the granulation or dry-pressing steps. A transparent or opaque protective layer consisting of a shellac sealing layer, a layer of sugar or polymer material and a gloss layer of wax may be present. Dyes can be added to these coatings in order to be able to differentiate between different dosage units.

The dosage unit formulations for oral administration can, if desired, be encapsulated in microcapsules. The formulation can also be prepared in such a way that the release is extended or retarded, such as, for example, by coating or embedding of particulate material in polymers, wax and the like.

Pharmaceutical formulations adapted for parenteral administration preferably include aqueous and non-aqueous sterile injection solutions, which optionally can comprise antioxidants, buffers, bacteriostatics and/or solutes, by means of which the formulation can optionally be rendered isotonic with the blood of the recipient to be treated; and aqueous and non-aqueous sterile suspensions, which may comprise suspension media and optionally
thickeners. The formulations can be preferably administered in single-dose or multidose containers, for example sealed ampoules and vials, and optionally stored in freeze-dried (lyophilised) state, so that only the addition of the sterile carrier liquid, for example water for injection purposes, immediately before use is necessary. Injection solutions and suspensions prepared in accordance with the recipe can preferably be prepared from sterile powders, granules and tablets.

It goes without saying that, in addition to the above particularly mentioned constituents, the formulations may optionally also comprise other agents usual in the art with respect to the particular type of formulation; thus, for example, formulations which are suitable for oral administration may comprise flavours.

A therapeutically effective amount of a compound for use according to the invention, preferably a compound for use according to the invention other than the Peptide according to formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, and especially a compound for use according to the invention is selected from immunosuppressive agents and/or anti-inflammatory agents, depends on a number of factors, including, for example, the age and weight of the animal, the precise condition that requires treatment, and its severity, the nature of the formulation and the method of administration, and is ultimately determined by the treating doctor or vet. However, an effective amount of a compound according to the invention for the treatment of neoplastic growth, for example colon or breast carcinoma, is generally in the range from 0.1 to 100 mg/kg of body weight of the recipient (mammal) per day, preferably in the range of from 1 to 30 mg/kg of body weight per day and particularly typically in the range from 1 to 10 mg/kg of body weight per day. Thus, the actual amount per day for an adult mammal weighing 70 kg is usually between between 70 and 2100 mg and especially between 70 and 700 mg, where this amount can be administered as a single dose per day or usually in
a series of part-doses (such as, for example, two, three, four, five or six) per day, so that the total daily dose is the same. An effective amount of a salt or solvate or of a physiologically functional derivative thereof can be determined as the fraction of the effective amount of the compound according to the invention per se. It can be assumed that similar doses are suitable for the treatment of other conditions mentioned above.

The invention preferably furthermore relates to medicaments comprising:

a) at least one Peptide according to formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates, salts and/or stereoisomers thereof, including mixtures thereof in all ratios, and optionally

b) at least one further medicament active ingredient, preferably a cotherapeutic agent as described herein and especially a cotherapeutic agent selected from the group consisting of immunosuppressive agents and anti-inflammatory agents, and even more preferably cotherapeutic agents selected from the group consisting of immunosuppressive agents and anti-inflammatory agents as described herein.

The invention preferably furthermore relates to compositions, preferably pharmaceutical compositions, comprising:

a) at least one Peptide according to formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates, salts and/or stereoisomers thereof, including mixtures thereof in all ratios, and

b) one or more pharmaceutically acceptable auxiliaries, excipients and/or adjuvants,

and optionally

c) at least one further medicament active ingredient, preferably a cotherapeutic agent as described herein and especially a cotherapeutic agent selected from the group consisting of immunosuppressive agents and anti-inflammatory agents, and even more preferably cotherapeutic
agents selected from the group consisting of immunosuppressive agents and anti-inflammatory agents as described herein.

Suitable pharmaceutically acceptable auxiliaries, excipients and/or adjuvants for said compositions are known in the art and/or described herein.

Typically, a therapeutically effective amount of an immunosuppressive and/or anti-inflammatory agent, preferably immunosuppressive agent, in the form of a, for example, antibody or antibody fragment or antibody conjugate and more preferably in form of an Antibody, Fusionprotein and/or Globulin is an amount such that when administered in physiologically tolerable composition is sufficient to achieve a plasma concentration of from about 0.01 microgram (g) per milliliter (ml) to about 100 µg/ml, preferably from about 1 µg/ml to about 5 µg/ml and usually about 5 µg/ml. Stated differently the dosage can vary from about 0.1 mg/kg to about 300 mg/kg, preferably from about 0.2 mg/kg to about 200 mg/kg, most preferably from about 0.5 mg/kg to about 20 mg/kg, in one or more dose administrations daily for one or several days. Where the immunosuppressive and/or anti-inflammatory agent, preferably immunosuppressive agent, is in the form of a fragment of a monoclonal antibody or a conjugate, the amount can readily be adjusted based on the mass of the fragment / conjugate relative to the mass of the whole antibody. A preferred plasma concentration in molarity is from about 2 micromolar (µM) to about 5 millimolar (mM) and preferably, about 100 µM to 1 mM antibody antagonist. A therapeutically effective amount of an agent according to this invention which is a non-immunotherapeutic peptide or a protein polypeptide (e.g. IFN-alpha), or other similarly-sized small molecule, is typically an amount of polypeptide such that when administered in a physiologically tolerable composition is sufficient to achieve a plasma concentration of from about 0.1 microgram (g) per milliliter (ml) to about 200 µg/ml, preferably from about 1 µg/ml to about 150 µg/ml. Based on a polypeptide having a mass of about 500 grams per mole, the preferred plasma concentration in molarity is from about 2 micromolar (µM) to about 5
millimolar (mM) and preferably about 100 \( \mu \)M to 1 mM polypeptide antagonist. The typical dosage of an active agent, preferably including the cotherapeutic agents described herein, which is a chemical antagonist or other (chemical) agent according to the invention (i.e. preferably neither an antibody, fusion protein or globulin nor any other polypeptide/protein) is 10 mg to 1000 mg, preferably about 20 to 200 mg, and more preferably 50 to 100 mg per kilogram body weight per day. The preferred dosage of such an active agent, which is a chemical antagonist or other (chemical) agent according to the invention (i.e. preferably neither an antibody, fusion protein or globulin nor any other polypeptide/protein) is 0.5 mg to 3000 mg per patient and day, more preferably 10 to 2500 mg per patient and per day, and especially 50 to 1000 mg per patient and per day, or, per kilogram body weight, preferably about 0.1 to 100 mg/kg, and more preferably 1 mg to 50 mg/kg, preferably per dosage unit and more preferably per day, or, per square meter of the bodysurface, preferably 0.5 mg to 2000 mg/m\(^2\), more preferably 5 to 1500 mg/m\(^2\), and especially 50 to 1000 mg/m\(^2\), preferably per dosage unit and more preferably per day.

Suitable dosings or dosing regimen for the anti-inflammatory agents and especially for the steroids, corticoids and/or corticosteroids are known in the art. Preferably, the anti-inflammatory agents and especially the steroids, corticoids and/or corticosteroids are administered to a subject in an amount, dosing or dosing regimen as described herein. Even more preferably, the anti-inflammatory agents and especially for the steroids, corticoids and/or corticosteroids are administered to the subject in an amount of 0.001 mg/kg to 50 mg/kg per day, preferably 0.01 mg/kg to 25 mg/kg per day, more preferably 0.1 mg/kg to 10 mg/kg per day, even more preferably 0.1 mg/kg to 5 mg/kg per day and especially preferably 0.5 mg/kg to 2.5 milligrams/kg, for example about 0.01 mg/kg, about 0.05 mg/kg, about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2.5 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg or about 25 mg/kg, per day.
The Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is preferably applied as a pharmaceutically acceptable salt, more preferably the pharmacologically acceptable hydrochloride salt, and especially preferably applied as the inner (or internal) salt, which is the compound cyclo-(Arg-Gly-Asp-DPhe-NMeVal) as such.

With regard to the Peptide of the formula cyclo-(Arg-Gly-Asp-DPhe-NMeVal), the following kinds of writing the name are preferably to be regarded as equivalent:

\[
\begin{align*}
\text{Cyclo-(Arg-Gly-Asp-DPhe-NMeVal)} & = \text{cyclo-(Arg-Gly-Asp-DPhe-NMeVal)} = \\
& = \text{cyclo-(Arg-Gly-Asp-DPhe-}[\text{NMe}]\text{Val)} = \text{cyclo-(Arg-Gly-Asp-DPhe-}[\text{NMe}])\text{-Val)} = \\
& = \text{cyclo}(\text{Arg-Gly-Asp-DPhe-NMeVal}) = \text{cyclo}(\text{Arg-Gly-Asp-DPhe-NMe-Val}) = \\
& = \text{cRGDfNMeV} = \text{c(RGDfNMeV)}.
\end{align*}
\]

The Peptide of the formula cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is also referred to as Cilengitide, which is the INN (International Non-propriety Name) of said compound.

The Peptide of the formula cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is also described in EP 0 770 622 A, US 6,001,961, WO 00/15244 and PCT/US07/01446 of the same applicant, the disclosure of which is explicitly incorporated into the instant application by reference.

Thus, a preferred subject of the instant invention relates to method for the prevention, prophylaxis and/or treatment of Graft-versus-Host Disease, comprising

a) administering to a subject a Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, and/or

b) conditioning a tissue or organ prior to transplantation into a subject with Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the
pharmaceutically acceptable derivatives, solvates and/or salts thereof.

A preferred subject of the instant invention relates to method for the prevention, prophylaxis and/or treatment of Graft-versus-Host Disease, comprising

a) administering to a subject a Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, and/or

b) conditioning a tissue or organ prior to transplantation into a subject with Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, wherein said Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof is employed in step a) and/or step b) in combination with one or more cotherapeutic agents as described above and/or below. Preferably, the one or more cotherapeutic agents for use in step a) and/or step b) are selected from the immunosuppressive agents and/or anti-inflammatory agents as described herein.

Preferably, said method can additionally the application of radiation or radiotherapy to said subject tissue and/or organ.

Preferably, said method can be used to the prevention, prophylaxis and/or treatment of acute Graft-versus-Host Disease and/or chronic Graft-versus-Host Disease.

Preferably, Graft-versus-Horst-Disease and more preferably acute Graft-versus-Horst-Disease, is characterised by a selective damage to organs, selected from liver, skin, mucosa and gastrointestinal tract, preferably triggered by the immune system of a subject and even more preferably triggered by the immune system of the subject after having received a transplantation. Additionally, target of the Graft-versus-Horst-Disease and
more preferably acute Graft-versus-Horst-Disease is typically the oropharynx, gastrointestinal tract, liver, lung, skin, kidney, urinary tract and/or nervous system of the subject afflicted with that disease.

More specifically, Graft-versus-Horst-Disease, more preferably acute Graft-versus-Horst-Disease, even more preferably Graft-versus-Horst-Disease of the GI tract and especially preferably acute Graft-versus-Horst-Disease of the GI tract preferably includes one or more clinical symptoms selected from the group consisting of (severe) intestinal inflammation, inflammation of the liver, sloughing of the mucosal membrane, (severe) diarrhoea, abdominal pain, nausea and vomiting. These clinical symptoms can be typically diagnosed by intestinal biopsy. Involvement of the liver can be measured by the bilirubin level in the respective patient. Preferably, one or more of these clinical symptoms are preferably triggered by the immune system of a subject and even more preferably triggered by the immune system of the subject after having received a transplantation.

Thus, a preferred subject of the instant invention relates to a method of treating Graft-versus-Horst-Disease, more preferably acute Graft-versus-Horst-Disease and/or chronic Graft-versus-Horst-Disease, in patients having undergone organ transplantation, more preferably patients with leukemia, end-stage renal, cardiac, pulmonary or hepatic failure having undergone subsequent organ transplantation, said method comprising the administration of a Peptide according to formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, said method more preferably comprising the administration of a Peptide according to formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof as described above and/or below, optionally in combination with the administration of one or more cotherapeutic agents, more preferably in combination with the administration of one or more cotherapeutic agents described herein and especially preferably in combination with the administration of one or more
cotherapeutic agents, selected from the group consisting of immunosuppressive agents and/or anti-inflammatory agents, preferably as described herein.

Transplantations in this regard preferably include organ transplantation and/or tissue transplantation. Such transplantations preferably include allografts (i.e. organ or tissue grafts harvested from donors other than the patient him or herself or host/recipient of the graft) of various types. Typical allografts in this regard refer to organs/tissues selected from the group consisting of kidney, heart, lung, liver, bone marrow, pancreas, cornea, small intestine and skin (e.g. epidermal sheets). Alternatively preferably, such transplantations preferably also include Seno crafts (i.e. organ or tissue grafts harvested from non-human animals. Such xenografts typically include, for example, porcine heart valves, or other organs that can be clinically used to replace their dysfunctional human counterparts.

Thus, a preferred subject of the instant invention relates to a method for the prevention, prophylaxis and/or treatment of Graft-versus-Horst-Disease, more preferably acute Graft-versus-Horst-Disease and/or chronic Graft-versus-Horst-Disease, in patients in the context of bone marrow transplantation, said method comprising the administration of a Peptide according to formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, said matters more preferably comprising the administration of a Peptide according to formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof as described above and/or below, optionally in combination with the administration of one or more cotherapeutic agents, more preferably in combination with the administration of one or more cotherapeutic agents described herein and especially preferably in combination with the administration of one or more cotherapeutic agents, selected from the group consisting of
immunosuppressive agents and/or anti-inflammatory agents, preferably as described herein.

Thus, a preferred subject of the instant invention relates to a method for the prevention, prophylaxis and/or treatment of Graft-versus-Horst-Disease, more preferably acute Graft-versus-Horst-Disease and/or chronic Graft-versus-Horst-Disease, in patients in the context of allogenic marrow transplantation or allogenic bone marrow transplantation, said method comprising the administration of a Peptide according to formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, said method more preferably comprising the administration of a Peptide according to formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof as described above and/or below, optionally in combination with the administration of one or more cotherapeutic agents, more preferably in combination with the administration of one or more cotherapeutic agents described herein and especially preferably in combination with the administration of one or more cotherapeutic agents, selected from the group consisting of immunosuppressive agents and/or anti-inflammatory agents, preferably as described herein.

Thus, an especially preferred subject of the instant invention relates to a method for the prevention, prophylaxis and/or treatment of Graft-versus-Horst-Disease, more preferably acute Graft-versus-Horst-Disease and/or chronic Graft-versus-Horst-Disease, in patients in the context of allogenic hematopoetic cell transplantation (alloHCT or allo-HCT), said method comprising the administration of a Peptide according to formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, said method more preferably comprising the administration of a Peptide according to formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof as described above and/or below, optionally in combination with the...
administration of one or more cotherapeutic agents, more preferably in combination with the administration of one or more cotherapeutic agents described herein and especially preferably in combination with the administration of one or more cotherapeutic agents, selected from the group consisting of immunosuppressive agents and/or anti-inflammatory agents, preferably as described herein.

A further preferred subject of the instant invention relates to a method for the prevention, prophylaxis and/or treatment of Graft-versus-Horst-Disease, more preferably acute Graft-versus-Horst-Disease and/or chronic Graft-versus-Horst-Disease, in patients in the context of allogenic marrow transplantation or allogenic bone marrow transplantation (allo-BMT), said method comprising the administration of a Peptide according to formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, said method more preferably comprising the administration of a Peptide according to formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof as described above and/or below, optionally in combination with the administration of one or more cotherapeutic agents, more preferably in combination with the administration of one or more cotherapeutic agents described herein and especially preferably in combination with the administration of one or more cotherapeutic agents, selected from the group consisting of immunosuppressive agents and/or anti-inflammatory agents, preferably as described herein.

A further preferred subject of the instant invention relates to a method for the prevention, prophylaxis and/or treatment of Graft-versus-Horst-Disease, more preferably acute Graft-versus-Horst-Disease and/or chronic Graft-versus-Horst-Disease, in one or more organs or tissues, selected from the group consisting of oropharynx, gastrointestinal tract, liver, lung, skin, kidney or in urinary tract and nervous system in patients in the context of allogenic marrow transplantation or allogenic bone marrow transplantation (allo-BMT),
said method comprising the administration of a Peptide according to formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, said method more preferably comprising the administration of a Peptide according to formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof as described above and/or below, optionally in combination with the administration of one or more cotherapeutic agents, more preferably in combination with the administration of one or more cotherapeutic agents described herein and especially preferably in combination with the administration of one or more cotherapeutic agents, selected from the group consisting of immunosuppressive agents and/or anti-inflammatory agents, preferably as described herein.

A convenient schedule for treating chronic GvHD in a subject would be a once weekly i.V. (or IV) infusion or a biweekly weekly i.V. (or IV) infusion of about 500 mg (flat), about 1000 mg (flat) or about 2000 mg (flat) per infusion. In the acute GvHD setting, this schedule can preferably also be applied to the subject, but a more often administration, such as every day or every second day or five times weekly can also be beneficial.

As used herein, the term "physiologically functional derivative" preferably refers to any pharmaceutically acceptable derivative of a compound to be used according to the present invention, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives.
As used herein, the term "pharmaceutically acceptable derivative" preferably refers to any compound that is a slightly modified compound or form of a compound to be used according to the instant invention. More preferably the term "pharmaceutically acceptable derivative", as used in connection with the compound Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), preferably refers to a compound of the same sequence, but being methylated or preferably N-methylated on a different amino acid than the valine amino acid (Val), or being completely unmethylated. Accordingly, an especially preferred pharmaceutically acceptable derivative of the compound Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) is a compound of the formula Cyclo-(Arg-Gly-Asp-DPhe-Val). Thus, a preferred subject of the instant invention is also a compound of the formula Cyclo-(Arg-Gly-Asp-DPhe-Val) (and, preferably, the pharmaceutically acceptable salts and solvates thereof) for the treatment of Graft-versus-Host Disease, preferably as described herein.

As used herein, the term "solvate" preferably refers to a complex of variable stoichiometry formed by a solute (in this invention, e.g. said Peptide (and/or a pharmaceutically acceptable derivative and/or salt thereof) and/or a cotherapeutic agent (or a salt or physiologically functional derivative thereof)) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably, the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Preferred examples of suitable pharmaceutically acceptable solvents are water and/or ethanol. Most preferably the solvent used is water. Pharmaceutically acceptable salts of compounds to be used according to the invention and their preparation is known in the art. If the compound itself is not a salt, it can be easily transferred into a salt by addition of a pharmaceutically acceptable acid or of a pharmaceutically acceptable base. Pharmaceutically acceptable acids and bases are known in the art, for example from the literature cited herein.
Preferably, a reference to "the Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val)" or the reference to "Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val)" includes also the pharmaceutically acceptable derivatives, solvates and/or salts thereof.

Preferably, a reference to "the Peptide" or "said Peptide" preferably means "the Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val)" and preferably also includes the pharmaceutically acceptable derivatives, solvates and/or salts thereof.

Thus, a reference to "the Peptide and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof" or to "said Peptide and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof" preferably refers to "the Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val)" and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof.

The term "without a pause" as used herein, especially used with respect to treatment regimens or treatment durations, is preferably understood to mean that said treatment regimens or durations are performed or applied in a consecutive order. For example, "2 to 8 weeks and especially 6 weeks, preferably without a pause" is preferably intended to mean "2 to 8 weeks and especially 6 weeks, preferably in a consecutive order".

As used herein, the term "about" with respect to numbers, amounts, dosings, hours, times, timings, durations, and the like, is preferably understood to mean "approximately" with respect to said numbers, amounts, dosings, hours, times, timings, durations, and the like.

If not specified otherwise, amounts administered to a patient given in "mg", such as in 500 mg, 1000 mg, 2000 mg, 4000 mg, 6000 mg, 8000 mg, 10000
mg, 12000 mg and 14000 mg, are preferably intended to mean the respective amounts to be administered "flat", i.e. as a fixed dose that is not adjusted to the bodyweight and/or body surface of the respective patient.

If not explicitly indicated otherwise, the term "subject" as used herein with respect to the target of the administration of
a) the Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, and/or
b) the one or more cotherapeutic agents, preferably including the immunosuppressive and/or anti-inflammatory agents, as described herein,

preferably refers to a human animal and/or a nonhuman animal, preferably a human animal. Especially preferably, it refers to a patient, more preferably a human patient and especially a human patient in need of an administration and/or a treatment as described herein.

If not explicitly indicated otherwise, the term "one or more" as used herein, e.g. with respect to the number of compounds, agents, cancer cotherapeutic agents, cancer chemotherapeutic agents and the like, preferably means "one or more than one" and thus preferably includes "two or more" (or "two or more than two"), "three or more" (or "three or more than three") and/or "four more" (or "more or more than four"). Accordingly, the term "one or more" as used herein preferably includes the numbers one, two, three, four, five, six and/or higher numbers. With respect to the number of compounds, agents, cancer cotherapeutic agents, cancer chemotherapeutic agents, it especially preferably includes the numbers one, two, three, four and/or five, even more preferably the numbers one, two, three and/or four and especially the numbers one, two and/or three.

Preferably, especially preferred subjects of the instant invention relate to aspects, subjects, uses, methods and/or embodiments, wherein one or more
features of two or more of the herein described aspects, subjects, uses, methods and/or embodiments are combined in one subject.

The invention is explained in greater detail below by means of examples. The invention can be carried out throughout the range claimed and is not restricted to the examples given here.

Moreover, the following examples are given in order to assist the skilled artisan to better understand the present invention by way of exemplification. The examples are not intended to limit the scope of protection conferred by the claims. The features, properties and advantages exemplified for the compounds, compositions, methods and/or uses defined in the examples may be assigned to other compounds, compositions, methods and/or uses not specifically described and/or defined in the examples, but falling under the scope of what is defined in the claims.

Preferably, the features, properties and advantages exemplified for the compounds, compositions, methods and/or uses defined in the examples and/or claims may be assigned to other compounds, compositions, methods and/or uses not specifically described and/or defined in the examples and/or claims, but falling under the scope of what is defined in the specification and/or the claims.
Examples

The following examples are given in order to assist the skilled artisan to better understand the present invention by way of exemplification. The examples are not intended to limit the scope of protection conferred by the claims. The features, properties and advantages exemplified for the compounds and uses defined in the examples and/or the Figures related thereto may be assigned to other compounds and uses not specifically described and/or defined in the examples and/or the Figures related thereto, but falling under the scope of what is defined in the claims.

Example 1

5 Mio. bone marrow (BM) cells from C57Bl/6 mice (H-2k^b) are injected intravenously into Balb/c mice (H-2k^d) after lethal irradiation with 900 cGy. To induce GvHD, 3x10^5 CD4^+/CD8^+ T cells (Tc) are given and mice are treated either with the ανβ3 integrin inhibitor Cilengitide (75 mg/kg, i.p., n=12) or with PBS (control group, n=12) for 10 days. Imaging with the positron emission tomography (PET) is performed using a Ga-68 labelled RGD peptide and F-18-Fluorodesoxyglucose (FDG) twice per week for 26 days. Finally the PET scans are focused on days 11, 18 and 25 for FDG and 7, 21 and 26 for RGD. The application of the radiotracers is carried out intravenously. 40 min after injection of 7 - 10 MBq FDG (mice fasted for 2 - 3 h) or 60 min of 3 - 6 MBq RDG mice are scanned for 15 min or 30 min, respectively.

The experiment demonstrates increased ανβ3 integrin expression in the GIT following murine allogenic hematopoetic cell transplantation (alloHCT) when GvHD evolved. Pharmacological inhibition of ανβ3 integrin is able to abrogate the integrin ανβ3 signal in the GIT detected by PET within 10 min and the treatment with cilenitide leads to improved survival of mice after alloHCT with less severe GvHD histopathology score of the GIT. FDG-PET
shows also a decreased uptake in the GIT indicating a reduced inflammatory activity.

**Example 2**

5x10^6 bone marrow (BM) cells from C57Bl/6 mice (H-2k^b) are injected intravenously into Balb/c mice (H-2k^d) after lethal irradiation with 900 cGy. To induce GvHD, 3x10^5 CD4+/CD8+ T cells (Tc) are given and mice are treated with the ανβ3 integrin inhibitor Cilengitide (75 mg/kg, i.p., n=12) or with PBS (n=12) for 10 days. BM transplanted mice serve as the control group.

Imaging with the positron emission tomography (PET) is performed using a Ga-68 labelled RGD peptide and F-18-Fluorodeoxyglucose (FDG) twice per week for 26 days. Finally the PET scans are focused on days 11, 18 and 25 for FDG and 7, 21 and 26 for RGD. The application of the radiotracers is carried out intravenously. 40 min after injection of 7 - 10 MBq FDG (mice fasted for 2 - 3 h) or 60 min of 3 - 6 MBq RDG mice are scanned for 15 min or 30 min, respectively.

Performing the scans with RGD demonstrates a significant increase of ανβ3 integrin expression in the GIT following murine allogenic hematopoetic cell transplantation (alloHCT) when GvHD evolved (1.04 ± 0.18 %ID/g) compared to control (0.43 ± 0.13 %ID/g). Pharmacological inhibition of ανβ3 integrin is able to abrogate the integrin ανβ3 signal in the GIT detected by PET even within 10 min (data not shown) and the treatment leads to improved survival of mice after alloHCT with less severe GvHD histopathology score of the GIT.

FDG-PET shows also an increased uptake in the GIT indicating a raised inflammatory activity (4.93 ± 1.41 %ID/g) compared to ανβ3 integrin inhibitor treated mice (4.20 ± 1.51 %ID/g). With regard to the control group (3.1 1 ± 0.45 %ID/g) the inhibitory effect of the drug (Cilengitide) could also be confirmed.

These data indicate that ανβ3 integrins are a novel target to interfere with GvHD based on inhibition of inflammatory neovascularisation. Cilengitide
therefore provides a new strategy to reduce GvHD severity. The mode of action preferably includes the inhibition of neovascularization to ameliorate GvHD and spares T cell function against malignancies.
1.) Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof for use in the treatment and/or prophylaxis of Graft-versus-Host Disease.

2.) Peptide according to claim 1, wherein Graft-versus-Host Disease comprises acute Graft-versus-Host Disease and/or chronic Graft-versus-Host Disease.

3.) Peptide according to claim 1 and/or claim 2, wherein the treatment and/or prophylaxis comprises the administration of the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof to said a subject in an amount of 50 mg to 12500 mg per week.

4.) Peptide according to claim 1, 2 and/or 3, wherein the treatment and/or prophylaxis additionally comprises the administration of one or more cotherapeutic agents other than the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof.

5.) Peptide according to claim 4, wherein the one or more cotherapeutic agents other than the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof are selected from the group consisting of immunosuppressive and/or anti-inflammatory agents.

6.) Peptide according to claim 4, wherein said Peptide is used in combination with
a) one or more cotherapeutic agents that are immunosuppressants,
b) one or more cotherapeutic agents that are anti-inflammatory agents, and/or
c) radiotherapy.

7.) Peptide according to one or more of claims 4 to 6, wherein said Peptide is used in combination with one or more cotherapeutic agents, selected from the group consisting of:

a) antimetabolites,
b) macrolides,
c) IL-2 inhibitors,
d) TNF alpha inhibitors,
e) IL-1 receptor antagonists,
f) mTOR inhibitors, and
g) immunosuppressive Antibodies, Fusionproteins and/or Globulins.

8.) Peptide according to one or more of claims 4 to 7, wherein said Peptide is used in combination with one or more cotherapeutic agents, selected from the group consisting of Azathioprine, Mycophenolic acid, Methotrexate, Tacrolimus, Ciclosporin, Thalidomide, Lenalidomide, Sirolimus, Everolimus, Infliximab, Muromonab, Muromonab-CD3, Basiliximab, Daclizumab, Inolimomab, Anti-thymocyte globulin, Anti-lymphocyte globulin, Etanercept and/or Pegsunercept; and the pharmaceutically acceptable derivatives, salts and/or solvates thereof.

9.) Peptide according to one or more of claims 4 to 6, wherein said Peptide is used in combination with one or more cotherapeutic agents, selected from the group consisting of steroids, corticoids and/or corticosteroids.

10.) Peptide according to one or more of claims 4 to 6 and 9, wherein said Peptide is used in combination with one or more cotherapeutic agents, selected from the group consisting of Hydrocortisone (Cortisol),
Cortisone acetate, Prednisone, Prednisolone, Methylprednisolone, Dexamethasone, Betamethasone, Triamcinolone and Beclometasone, Fludrocortisone acetate, Deoxycorticosterone acetate and Aldosterone; and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof.

11.) Peptide according to one or more of claims 4 to 10, wherein said Peptide is used in combination with one or more cotherapeutic agents, selected from the group consisting of pentostatin, fludarabine monophosphate, cladribine, azathioprine, cyclosporin A, prednisone, methylprednisolone, cyclophosphamide, FK506, rapamycin, mycophenolic acid, 15-deoxyspergualin, mimoribine, misoprostol, methotrexate, Tacrolimus, Thalidomide, Lenalidomide, Sirolimus, Everolimus, Infliximab, Muromonab, Muromonab-CD3, Basiliximab, Daclizumab, Inolimomab, Anti-thymocyte globulin, Anti-lymphocyte globulin, Etanercept and/or Pegsunercept; and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof.

12.) Peptide according to one or more of the preceding claims, wherein the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof is administered to a subject in an amount of 1000 mg to 12500 mg per week for a time period between 4 and 20 weeks.

13.) Peptide according to one or more of the preceding claims, wherein the Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof is administered to a subject in a once weekly to seven times weekly administration scheme consisting of about 100 mg to about 2000 mg per day and/or per administration.

14.) A method for the prevention, prophylaxis and/or treatment of Graft-
versus-Host Disease, comprising
a) administering to a subject a Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof, and/or
b) conditioning a tissue or organ prior to transplantation into a subject with Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof.

15.) A method according to claim 14, wherein said Peptide of the formula Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the pharmaceutically acceptable derivatives, solvates and/or salts thereof is employed in combination with one or more cotherapeutic agents according to one or more of claims 4 to 11.

16.) A method according to one claim 14 and/or 15, wherein said method additionally comprises radiation or radiotherapy.

17.) A method according to one or more of claims 14 to 16, wherein the Graft-versus-Host Disease is selected from the group consisting of acute Graft-versus-Host Disease and chronic Graft-versus-Host Disease.
A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K38/12 A61P37/06 A61P29/00

ADD.

According to International Patent Classification (IPC) onto both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

Date of the actual completion of the international search

12 April 2012

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentilaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax. (+31-70) 340-3016

Date of mailing of the international search report

26/04/2012

Authorized officer

Cami 1leri, Alain
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>BURKE P A ET AL: &quot;Cilengitide Targeting of alphavbeta3 Integrin Receptor Synergies with Radioimmunotherapy to Increase Efficacy and Apoptosis in Breast Cancer Xenografts!&quot;. CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 62, no. 15, 1 August 2002 (2002-08-01), pages 4263-4272, XP002903574, abstract figures 1,2,4; tables 1,2</td>
<td>1-17</td>
</tr>
<tr>
<td>Category</td>
<td>Citation of document, with indication, where appropriate, of the relevant passages</td>
<td>Relevant to claim No.</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>A</td>
<td>L. BELVISI: &quot;Biological and molecular properties of a new v3/ v5 integrin antagonist&quot;, MOLECULAR CANCER THERAPEUTICS, vol. 4, no. 11, 1 November 2005 (2005-11-01), pages 1670-1680, XP55020573, ISSN: 1535-7163, DOI: 10.1158/1535-7163.MCT-05-0120 the whole document</td>
<td>1-17</td>
</tr>
<tr>
<td>Patent family cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>WO 2008122039</td>
<td>09-10-2008</td>
<td>A2</td>
</tr>
<tr>
<td>WO 2008122039</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>