[0005] The same is true of chronic viral infection. The innate immune response is able to slow down viral replication and activate cytokines which trigger the synthesis of antiviral proteins. The adaptive immune system neutralizes virus particles and destroys infected cells. However, viruses have developed a number of countermeasures to avoid immune attack and stay moving targets for the immune system.

[0006] There is a need to provide an active immunotherapy that is capable of overcoming tumor and viral immunoavoidance mechanisms and to train the human immune system to perceive the threat/danger of human cancer cells and viral infected cells resulting in an immune response which can eradicate tumors or pathogen-infected cells wherever they might be located in the body.

SUMMARY

[0007] The present disclosure relates to methods and compositions for inducing a systemic, adaptive immune response against a tumor or pathogen. The method uses a combination of an allogeneic cell therapy and a method for subjecting the tumor or pathogen infected tissue to cellular distress, resulting in the liberation of tumor specific antigen(s) or pathogen specific antigen(s).

[0007a] In one aspect, there is provided the use of allogeneic cells in the manufacture of a medicament for inducing an adaptive immune response against a tumor or a pathogen in a patient, wherein the allogeneic cells are to be administered to be directed to the site of antigens generated in situ from the disease or pathogen infection, to thereby create an immune response that serves as an adjuvant to the uptake of antigens from the ablated tissue whereby subsequent maturation of the patient's antigen presenting cells systemically stimulate anti-tumor or anti-pathogen immunity.

[0008] In one ~~aspect~~embodiment, the present disclosure is a method for inducing an adaptive immune response against a tumor or a pathogen in a subject. The method includes the steps of: (1) administering to a subject with cancer or an infectious disease an aliquot of allogeneic cells that are designed to

be rejected by the subject immune system in a manner that induces anti-allogeneic Th1 immunity; (2) in the same subject, after allowing time for an anti-allogeneic Th1 immune memory to form (about 7 to 14 days), performing an *in situ* ablation of an accessible tumor lesion or pathogen-infected tissue with an ablation method which causes at least a portion of the tumor or infected tissue to die, preferably by necrosis, (e.g., by methods such as but not limited to electroporation, cryoablation, chemotherapy, radiation therapy, ultrasound therapy, ethanol chemoablation, microwave thermal ablation, radiofrequency energy or a

combination thereof); then; (3) injecting a second aliquot of the same allogeneic cells intralesionally (same cells as used to prime), preferably 2-24hrs after the ablation step, creating an immune response that serves as an adjuvant to the uptake of antigen(s) and the subsequent maturation of host antigen presenting cells (i.e., dendritic cells) responding to the necrotic or apoptotic tissue. Mature antigen presenting cells from the lesion then migrate to the lymph nodes and stimulate systemic anti-tumor or anti-pathogen immunity. In another ~~aspect~~embodiment, the priming step is omitted. The tissue from the tumor or the pathogen infected tissue is ablated *in situ* and an aliquot of the allogeneic cells are injected after the ablation to create the desired immune response.

[0009] In another ~~aspect~~embodiment, the present disclosure includes a vaccine for a patient against a tumor or a pathogen. The vaccine includes an antigenic composition comprising antigenic material from the tumor or pathogen and an aliquot of allogeneic cells wherein administration of the antigenic composition to the patient creates a rejection response and stimulates a delayed-type hypersensitivity response to the antigens thereby acting as an adjuvant to the stimulation of systemic anti-tumor or anti-pathogen immunity in the patient. The vaccine can also include a priming composition wherein the priming composition includes an aliquot of allogeneic cells.

[0010] In yet another ~~aspect~~embodiment, the present disclosure includes a method of vaccinating a patient. The method includes the steps of: (1) administering to the subject with cancer or an infectious disease a priming composition that includes an aliquot of allogeneic cells that are designed to be rejected by the subject immune system in a manner that induces anti-allogeneic Th1 immunity; (2) in the same subject, after allowing time for an anti-allogeneic Th1 immune memory to develop (about 7 to 14 days), injecting, preferably intradermally, an antigenic composition containing a source of tumor antigen or pathogen antigens (e.g., attenuated virus, tumor lysates, heat shock proteins), preferably containing from the same individual autologous lysates of the infected or cancerous tissue,

the lysates preferably containing chaperone proteins, and such lysates formulated with an aliquot of allogeneic cells (same cells used to prime the patient) to create a rejection response and stimulate a delayed-type hypersensitivity response to the alloantigens which serve to adjuvant the stimulation of systemic anti-tumor or anti-pathogen immunity. In a further ~~aspect~~embodiment, this method may be practiced without the priming step.

[0010a] In one aspect, there is provided a therapeutic composition for treating a tumor or pathogen in a patient comprising: allogeneic cells; and antigens comprising the product of tumor necrosis or pathogen infected tissue necrosis, wherein the antigens are generated in situ, whereby the allogeneic cells and the in situ generated antigens elicit an immune response by the patient to create an anti-tumor or anti-pathogen immunity.

[0011] In another ~~aspect~~embodiment, the present disclosure includes a therapeutic composition for treating a tumor or a pathogen in a patient comprising tumor antigens or pathogen antigens generated *in situ* and allogeneic cells, wherein the allogeneic cells and the *in situ* generated antigens elicit an immune response whereby subsequent maturation of the patient's antigen presenting cells systemically stimulate anti-tumor or anti pathogen immunity. The tumor antigens or pathogen antigens are generated *in situ* from necrosis of the tumor or the pathogen infected tissue. The therapeutic composition may also include a priming composition containing allogeneic cells. The allogeneic cells in the priming composition and in the antigenic composition may include between about 1×10^8 and about 1×10^{10} cells.

[0011a] In one aspect, there is provided a vaccine composition comprising: an adjuvant comprising allogeneic cells; and antigens generated in situ by necrosis of diseased cells or tissue, wherein the presence of the adjuvant at the necrotic site along with the in situ generated antigens elicit an immune response by the patient to create immunity against the disease.

[0012] In yet a further ~~aspect~~embodiment, the present description includes a vaccine composition for treating a tumor or a pathogen in a patient comprising antigens generated *in situ* that include tumor antigens or pathogen antigens and allogeneic cells wherein injecting the patient with the allogeneic cells in the presence of *in situ* generated antigens creates an immune response whereby subsequent maturation of the patient's antigen presenting cells systemically stimulate anti-tumor or anti pathogen immunity. The tumor antigens in the composition are derived from *in situ* necrosis of the tumor. The pathogen antigens in the composition are derived from *in situ* necrosis of the pathogen infected tissue. The composition may also include a priming composition containing allogeneic cells. The allogeneic cells in the priming composition and

in the vaccine composition may include between about 1 x 10^8 and about 1 x 10^{10} cells.

[0013] In a further ~~aspect~~embodiment, the present disclosure includes a method of vaccinating a patient. The method includes the steps of: (1) administering to the subject with cancer or an infectious disease a priming composition that includes an aliquot of allogeneic cells that are designed to be rejected by the subject immune system in a manner that induces anti-allogeneic Th1 immunity; (2) in the same subject, after allowing time for an anti-allogeneic Th1 immune memory to develop (about 7 to 14 days), ablating the tumor or pathogen infected tissue *in situ* to release tumor antigens or pathogen antigens (3) administering a composition of allogeneic cells (same cells used to prime the patient) to create a rejection response and stimulate a delayed-type hypersensitivity response to the alloantigens which serve to adjuvant the stimulation of systemic anti-tumor or anti-pathogen immunity. In a further ~~aspect~~embodiment, this method may be practiced without the priming step.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0014] The present disclosure includes a method for stimulating anti-tumor or anti-pathogen immunity in patients. The method involves first "priming" of the patient to develop Th1 anti-alloantigen immune memory by infusion of an aliquot of allogeneic cells. It is desired that the infusion of allogeneic cells stimulates the patient's immune system to react against the allogeneic cells. A time period is allowed to elapse until the patient's immune system is allowed to form an anti-allogeneic memory. In some embodiments, a patient may need a booster of allogeneic cells to develop the appropriate Th1 immune memory.

[0015] Patient as used herein includes not only mice but also humans. Th1 response as used herein refers to production of a cytokine profile that activates T-cells and macrophages. Th1 response is to be distinguished from Th2

11. ~~A method of~~Use of allogeneic cells in the manufacture of a medicament for inducing an adaptive immune response against a tumor or a pathogen in a patient, ~~the method comprising:~~wherein

~~generating antigens from the disease or pathogen infection *in situ*; and~~

~~administering~~ the allogeneic cells are to be administered to be directed to the site of ~~the *in situ* generated~~ antigens generated in situ from the disease or pathogen infection, to thereby create~~creating~~ an immune response that serves as an adjuvant to the uptake of antigens from the ablated tissue whereby subsequent maturation of the patient's antigen presenting cells systemically stimulate anti-tumor or anti-pathogen immunity.

12. The ~~method~~ use of claim 11, ~~further comprising:~~ wherein

~~administering to the patient~~ a priming composition is to be administerd to a patient prior to the generation of antigens *in situ*, the priming composition comprising allogeneic T-cells to be rejected by the patient's immune system in a manner that induces an allogeneic Th1 immunity ; and

permitting the patient's immune system to form anti-allogeneic Th1 immune memory prior to the generation of *in situ* antigens.

13. The ~~method~~ use of claim 11 wherein the antigens are generated *in situ* by ablation of the tumor or pathogen infected tissue.

14. The method of claim 13 wherein the ablation is by cryoablation.

15. The ~~method~~ use of claim 13 wherein the ablation is by electroporation.

16. The ~~method~~ use of claim 11 wherein the antigens comprise tumor or pathogen antigens, heat shock proteins and combinations thereof.

17. The ~~method~~ use of claim 11 wherein the allogeneic cells are allogeneic T-cells.

18. The ~~method~~ use of claim 11 wherein the allogeneic cells express high levels of Type 1 cytokines.

19. The ~~method~~ use of claim 11 wherein the allogeneic cells express a high density of CD40L, TRAIL, FasL and combinations thereof on the cell surface.