predominant antigen presenting cell. It is also well known that tumors and infectious agents create an immunosuppressive environment which is not optimal for a strong primary immune response. Alternatively, if a dominant antigen results in cells which are reacting to self, tolerance is broken and autoimmunity ensues. Such tolerance could be broken by the presence of a chronic or latent virus leading to a response (even chronically to weak subdominant antigens). There are multiple associations of viruses with autoimmunity. The inflammation at the site leads to release of other antigens while the viral antigens provide help to the T cells responsive to the organ, causing autoimmunity. After the dominance hierarchy is established in the primary response and reinforced by memory, the immune system in the patient will effectively replicate the same response each time the antigen is present.

[0007] An ongoing immune response against a dominant epitope can diminish the response to a subdominant epitope (Wolpert EZ 1998, Kedl RM 2003). The dominance/ subdominance hierarchy can be somewhat fluid. For instance, deleting or silencing T cell responses against a dominant epitope can lead to the appearance of a previously undetectable response against subdominant epitopes (Van derMost RG et al. 1997, Andreansky SS et al. 2005). Similarly, removal of a dominant sequence in an epitope does not eliminate the response to the antigen but rather results in the host responding more strongly to a previously subdominant epitope (Allan JE and Doherty PC 1985, Mylin LM et al. 2000).

SUMMARY ~~OF THE INVENTION~~

[0008] The present ~~invention~~disclosure relates to a novel therapeutic for cancer, chronic infections, autoimmune diseases, and transplantation based upon the modification of the immunodominance hierarch by therapeutic manipulation of cellular homeostasis.

[0009] Disclosed is a novel approach to rebalance the immune response to antigens to provide significant therapeutic benefit in, among others, cancer, chronic and latent infection, autoimmunity and transplantation. By generating immune responses to subdominant epitopes and subdominant antigens in a controlled microenvironment, the ~~invention~~disclosure fundamentally changes the nature of the immune response to the disease to one that provides therapeutic

benefit. It can change the balance of the immune response before or after a prior immune response has occurred to the antigen or even if there is one ongoing.

[0010] The present ~~invention~~disclosure features a method comprising identifying a dominant antigen or epitope and a subdominant antigen or epitope in a patient sample, cultivating a T cell capable of recognizing the subdominant antigen or epitope, and treating a patient with an effective number of the T cells to alter the immunodominance hierarchy of the patient.

[0011] The present ~~invention~~disclosure also features methods for altering the immunodominance hierarchy of a patient comprising identifying at least one subdominant antigen or epitope in a patient sample, cultivating a T cell capable of recognizing the subdominant antigen or epitope, and treating the patient with an effective number of those T cells to provide therapeutic benefit.

[0012] In some ~~aspect~~examples, the ~~invention~~disclosure further comprises cultivating a T cell in the absence of a dominant antigen or epitope. In other ~~aspect~~examples, the ~~invention~~disclosure further comprises cultivating a T cell in the absence or presence of agents that enrich suppressive T cells or responsive T cells. Such agents can include, but are not limited to, growth factors, hormones, or other immune cells.

[0013] In some ~~aspect~~examples, the ~~invention~~disclosure further comprises administering the effective number of T cells via intradermal administration.

[0014] In other ~~aspect~~examples, the ~~invention~~disclosure further comprises pre-treating the patient with a conditioning agent to reduce the number of endogenous T cells prior to treating the patient with the cultivated T cells. The conditioning agent can be, but is not limited to, a chemotherapeutic agent.

[0015] In some ~~aspect~~examples, the T cell is provided *ex vivo* from a patient.

[0016] The subdominant antigen or subdominant epitope is, for example, an antigen or epitope to which a cellular or humoral immune response is not detectable or is only detectable at a low level. Alternatively, the subdominant antigen or subdominant epitope is an antigen or epitope that evokes a weaker tolerance or immune response than that of a dominant antigen or

dominant epitope. The subdominant antigen is, for example, a viral antigen, a fungal antigen, a bacterial antigen, a parasitic antigen, a prion antigen, a tumor antigen, or an antigen associated with autoimmunity, allergy, inflammation, organ transplant rejection, or graft versus host disease. The viral antigen is, for example, a chronic or latent viral antigen. The viral antigen is be from EBV, HPV, HSV, VZV, Hepatitis B, Hepatitis C, HIV, HTLV, CMV, RSV, or influenza. The tumor antigen is, for example, a tumor-associated antigen, a tumor specific antigen, or an antigen associated with cancer stem cells or metastasis.

[0017] The present ~~invention~~disclosure also features methods for identifying a dominant antigen or epitope and/or a subdominant antigen or epitope in a patient sample, cultivating a T cell capable of recognizing the subdominant antigen or epitope, wherein the T cell is a suppressive T cell, and treating a patient with an effective number of said T cell to alter the immunodominance hierarchy of the patient, thereby inducing tolerance in the patient for treatment or prevention of an autoimmune disease, allergy, inflammation, organ transplantation rejection, or graft versus host disease.

[0018] The present ~~invention~~disclosure also features methods for identifying a dominant antigen or epitope and/or a subdominant antigen or epitope in a patient sample, cultivating a T cell capable of recognizing the subdominant antigen or epitope, wherein the T cell is a responsive T cell, and treating a patient with an effective number of said T cell to alter the immunodominance hierarchy of the patient, thereby inducing a cytotoxic immune response in the patient for treatment or prevention of an infection or cancer. The infection is, for example, a bacterial, viral, parasitic, or prion infection.

[0019] In any of the methods of the present ~~invention~~disclosure, treatment or prevention of a disease, infection, cancer, or medical condition includes alleviating or ameliorating at least one symptom of a disease, infection, cancer, or medical condition. Therapeutic benefit includes any alleviation, amerlioration, improvement, prevention, or treatment of at least one symptom of a disease, infection, cancer, or medical condition.

[0020] In some ~~aspect~~examples, the patient sample is a blood sample.

[0021] The present ~~invention~~disclosure also features a method further comprising re-profiling of the patient by assaying for a tolerance or humoral or cellular immune response in response to the subdominant antigen or epitope to determine if the therapy successfully rebalanced the immune response.

[0022] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this ~~invention~~disclosure pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice of the present ~~invention~~disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety. In cases of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples described herein are illustrative only and are not intended to be limiting.

[0023] Other features and advantages of the ~~invention~~disclosure will be apparent from and encompassed by the following detailed description and claims.

[0023a] In one aspect, the present disclosure refers to a T cell capable of recognizing a subdominant antigen or epitope in a patient for use in a method of altering the immunodominance hierarchy of the patient. In another aspect, the present disclosure refers to a T cell for the use as disclosed herein, wherein the T cell is obtained by: a) identifying at least one subdominant antigen or epitope in a sample obtained from the patient, and b) cultivating a T cell capable of recognizing said subdominant antigen or epitope. In another aspect, the present disclosure refers to a T cell for the use as disclosed herein, wherein altering the immunodominance hierarchy treats/prevents/alleviates an infection, cancer, inflammation, organ transplantation rejection, or graft versus host disease in the patient. In another aspect, the present disclosure refers to use of a T cell capable of recognizing a subdominant antigen or epitope in a patient in the manufacture of a medicament for altering the immunodominance hierarchy of the patient. In another aspect, the present disclosure refers to a use according to claim 4, wherein the T cell is obtained by: a) identifying at least one subdominant antigen or epitope in a sample obtained from the patient, and b) cultivating a T cell capable of recognizing said subdominant antigen or epitope. In another aspect, the present disclosure refers to a use as disclosed herein, wherein altering the immunodominance hierarchy treats/prevents/alleviates an infection, cancer, inflammation, organ transplantation rejection, or graft versus host disease in the patient. In another aspect, the present disclosure refers to a T cell population for use in altering the immunodominance hierarchy of a patient obtainable by identifying at least one subdominant antigen or epitope in a sample obtained from the patient and cultivating a T cell population capable of recognizing said subdominant antigen or epitope. In another aspect, the present disclosure refers to a T cell population as disclosed herein for use in therapy. In yet another aspect, the present disclosure refers to a method comprising the steps of: a) identifying a dominant antigen or epitope and a subdominant antigen or epitope in a patient sample; b) cultivating a T cell capable of recognizing said subdominant antigen or epitope; c) treating a patient with an effective number of said T cell to alter the immunodominance hierarchy of the patient. In another aspect, the present disclosure refers to a method comprising the steps of: a) identifying at least one subdominant antigen or epitope in a patient sample; b) cultivating a T cell capable of recognizing said subdominant antigen or epitope; and c) treating a patient with an effective number of said T cell to alter the immunodominance hierarchy of the patient.