169-174, Mattiuzzi *et al.* (2003) *Clinical Cancer Research* 9: 976-980, Dworkin *et al.* (2003) *Neurology* 60: 1274-1283.) such as meningoencephalitis (Tauro *et al.* (2000) *Bone Marrow Transplant* 26: 795-796), transverse myelitis, visual impairment (Walton *et al.* (1999) *Bone Marrow Transplant* 23: 1317-1320), pneumonitis (Wacker *et al.* (1989) *Bone Marrow Transplant* 4: 191-194), hepatitis (Rogers *et al.* (1995) *Bone Marrow Transplant* 15: 805-807; Schiller *et al.* (1991) *Bone Marrow Transplant* 7: 489-491), bacterial superinfection, cutaneous scarring and disfigurement (Schuchter *et al.* (1989) *Blood* 74: 1424-1427). Despite the high risk of morbidity and mortality associated with HZ in immunocompromised individuals, this population is not eligible for vaccination with a live attenuated vaccine against HZ such as ZOSTAVAX®. Thus, there is a significant need for a vaccine that would be safe and effective in immunocompromised patient populations to prevent HZ or reduce the severity or duration of HZ or associated complications.

Safety concerns regarding immunocompromised patients have led researchers to investigate the use of non-replicating vaccines against viral pathogens such as subunit vaccines, virus-like particle vaccines and inactivated whole vaccines. Many approved inactivated vaccines contain viruses that are inactivated using formalin, including hepatitis A, polio, and Japanese encephalitis vaccines. For HZ, it has been suggested that a safer vaccine for immunocompromised subjects could be developed through heat inactivation of the VZV or through the use of a subunit vaccine (Cohen, J.I., (2008) *J. Infect. Dis.* 197(Suppl 2): S237-S241). Redman *et al.* (*J. Infectious Diseases* (1997) 176: 578-85) describe an inactivated VZV vaccine which was inactivated by heating at 50°C, resulting in an infectious virus content of $\leq$ 1.2 pfu/0.5 mL. This level of infectivity would not be desirable for a product to be administered to immunocompromised patients. US Patent Nos. 6,214,354 and 5,997,880 also mention the potential of using an inactivated VZV vaccine and disclose an example of the production and testing of a heat-treated vaccine.

It would meet a significant medical need if a method of inactivating VZV were developed that resulted in a VZV sample that was safe and effective in immunocompromised patients, i.e., lacked residual infectivity but retained the immunogenicity and antigenicity of a non-inactivated sample.

SUMMARY

It has been shown herein that a VZV sample can be inactivated with gamma irradiation so that the infectivity of the VZV in the sample is at an undetectable level; however, there is no significant loss in immunogenicity and/or antigenicity and no significant change in structure of the VZV upon inactivation by the methods described herein relative to a VZV sample that has not been inactivated.

In the present disclosure, there is provided an inactivated varicella zoster virus (VZV), wherein the infectivity of the VZV is undetectable and wherein the inactivated VZV induces an immune response against VZV when administered to a patient. Also provided is a pharmaceutical composition/vaccine comprising a therapeutically effective amount of the inactivated VZV and a pharmaceutically acceptable carrier. The compositions of the present disclosure are either liquid or in a frozen state, e.g. lyophilized. In some embodiments of the compositions described herein, the VZV is inactivated with gamma radiation.

In an aspect, there is provided a pharmaceutical composition comprising therapeutically effective amount of an inactivated varicella zoster virus (VZV) and a pharmaceutically acceptable carrier, wherein the VZV is inactivated by 5-25 kGy of gamma irradiation and wherein the infectivity of the VZV is $\leq$0.040 plaque-forming units (PFU's)/mL and wherein the inactivated VZV induces an immune response against VZV when administered to a patient.

In the present disclosure, there is provided a method of preparing an inactivated VZV vaccine, the method comprising gamma irradiating a sample comprising a VZV using from about 5 kGy to about 50 kGy of gamma radiation. In preferred embodiments, the source of gamma radiation is ^{60}Co, although other isotopes known in the art may also be useful in this regard. In some embodiments of the method of preparation disclosed herein, the sample is lyophilized prior to irradiating. In alternative embodiments, a liquid bulk is exposed to the gamma radiation, without first being lyophilized.

In another aspect, there is provided a method of preparing an inactivated varicella zoster virus (VZV) comprising gamma irradiating a sample comprising a VZV using from 5 to 25 kGy of gamma radiation.

In another aspect, there is provided an inactivated VZV produced or obtainable by the method as defined herein.

In another aspect, there is provided a vaccine comprising a therapeutically effective amount of the inactivated VZV as defined herein and a pharmaceutically acceptable carrier.

The present disclosure also provides a method of treatment of or immunization against HZ or other disease associated with reactivation of VZV, the method comprising administering to a subject a vaccine or pharmaceutical composition comprising a therapeutically effective amount of an inactivated VZV and a pharmaceutically acceptable carrier, wherein the VZV is inactivated by gamma irradiation. In some embodiments of the methods of treatment described herein, the route of administration of the composition/vaccine is subcutaneous or intramuscular. In specific embodiments of this disclosure, the patient is 50 years of age or older and/or immunocompromised.

In another aspect, there is provided the use of an inactivated varicella zoster virus (VZV) for the manufacture of medicament for the treatment of herps zoster in a subject, wherein the VZV is inactivated with 5-25 kGy of gamma irradiation.

As used throughout the specification and in the appended claims, the singular forms "a," "an," and "the" include the plural reference unless the context clearly dictates otherwise.

As used throughout the specification and appended claims, the following definitions and abbreviations apply:

The term "treatment" refers to both therapeutic treatment and prophylactic or preventative measures. Individuals in need of treatment include those already with the disorder as well as those prone to have the disorder or those in which the disorder is to be prevented. Treatment of a patient with the inactivated VZV of the invention includes one or more of the following: inducing/increasing an immune response against VZV in the patient, preventing, ameliorating, abrogating, or reducing the likelihood of reactivation of VZV in patients who have been infected with varicella or received a live VZV vaccine, preventing or reducing the likelihood of developing HZ and/or other disease or complication associated with VZV reactivation such as PHN, reducing the severity or duration of HZ and/or other disease or complication associated with the reactivation of VZV, such as PHN.