CLAIMS

1. A modified poxvirus which genome comprises in the native (wild-type) context a M2L locus encoding a functional m2 poxviral protein and which is modified to be defective for the said m2 function; wherein said functional M2 poxviral protein is able to bind CD80 or CD86 co-stimulatory ligands or both CD80 and CD86 co-stimulatory ligands and wherein said defective m2 function is unable to bind said CD80 and CD86 co-stimulatory ligands.

2. The modified poxvirus of claim 1, wherein the modified poxvirus is generated or obtained from a *Chordopoxvirinae*, preferably selected from the group of genus consisting of Avipoxvirus, Capripoxvirus, Leporipoxvirus, Molluscipoxvirus, Orthopoxvirus, Parapoxvirus, Suipoxvirus, Cervidpoxvirus and Yatapoxvirus.

3. The modified poxvirus of claim 2, wherein the modified poxvirus is a member of the Orthopoxvirus genus, preferably selected from the group consisting of vaccinia virus (VV), cowpox (CPXV), raccoonpox (RCN), rabbitpox, Monkeypox, Horsepox, Volepox, Skunkpox, variola virus (or smallpox) and Camelpox; or a member of the *Leporipoxvirus* genus, with a preference for myxoma virus.

4. The modified poxvirus of claim 3, wherein the modified poxvirus is a vaccinia virus preferably selected from the group consisting of Western Reserve (WR), Copenhagen (Cop), Lister, LIVP, Wyeth, Tashkent, Tian Tan, Brighton, Ankara, LC16M8, LC16M0 strains, etc., with a specific preference for WR, Copenhagen and Wyeth strains.

5. The modified poxvirus of any one of claims 1 to 4, wherein the inability to bind said CD80 and CD86 co-stimulatory ligands originates from a genetic lesion within the M2L locus or from an abnormal interaction impairing the m2 function either directly or indirectly.

6. The modified poxvirus of claim 5, wherein said genetic lesion(s) of the M2L locus include partial or total deletion and/or one or more non-silent mutation(s) either within the m2-coding sequence or in the regulatory elements controlling M2L expression,

preferably leading to the synthesis of a defective m2 protein or to the lack of m2 synthesis.

7. The modified poxvirus of claim 6, wherein said genetic lesion is a partial or entire deletion of the M2L locus.

8. The modified poxvirus of any one of claims 1 to 7, wherein the modified poxvirus is further modified in a region other than M2L locus.

9. The modified poxvirus of claim 8, wherein the modified poxvirus is further modified in the J2R locus resulting in a modified poxvirus defective for both m2 and tk functions.

10. The modified poxvirus of claim 8 or 9, wherein the modified poxvirus is further modified in the I4L and/or F4L locus/loci, resulting in a modified poxvirus defective for both m2 and rr functions.

11. The modified poxvirus of any one of claims 8 to 10, wherein the modified poxvirus is further modified in the J2R and I4L/F4L loci, resulting in a modified poxvirus defective for m2, tk and rr activities.

12. The modified poxvirus of any one of claims 1 to 11, wherein the modified poxvirus is oncolytic and/or recombinant.

13. The modified poxvirus of claim 12, wherein the modified poxvirus is recombinant and is engineered to express at least one polypeptide selected from the group consisting of antigenic polypeptides, polypeptides having nucleos/tide pool modulating function and immunomodulatory polypeptides.

14. The modified poxvirus of claim 13, wherein said immunomodulatory polypeptide is selected from the group consisting of cytokines, chemokines, ligands and antibodies or any combination thereof.

15. The modified poxvirus of claim 14, wherein said cytokine is selected from the group consisting of IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-36, IFNa, IFNg, and granulocyte macrophage colony stimulating factor (GM-CSF).

~~15.~~16. The modified poxvirus of claim ~~14~~15, wherein said antibody specifically binds an immune checkpoint protein, preferably selected from the group consisting of CD3, 4-1BB, GITR, OX40, CD27, CD40, PD1, PDL1, CTLA4, Tim- 3, BTLA, Lag-3 and Tigit.

~~16.~~17. The modified poxvirus of claim ~~15~~16, wherein the modified poxvirus expresses an antagonist antibody that specifically binds to PD-L1 or CTLA4.

~~17.~~18. The modified poxvirus of claim ~~16~~17, wherein the modified poxvirus is selected from the group consisting of: a modified poxvirus defective for m2, tk and rr activities and encodes an anti-CTLA-4 antibody, with a preference for ipilimumab or tremelimumab; and a modified poxvirus is defective for m2, tk and rr activities and encodes an anti-PD-L1 antibody, with a preference for atezolizumab, durvalumab or avelumab.

~~18.~~19. A method for producing the modified poxvirus of any one of claims 1 to ~~17~~ 18 comprising the steps of a) preparing a producer cell line, b) transfecting or infecting the prepared producer cell line with the modified poxvirus, c) culturing the transfected or infected producer cell line under suitable conditions so as to allow the production of the virus, d) recovering the produced virus from the culture of said producer cell line and optionally e) purifying said recovered virus.

~~19.~~20. A composition comprising a therapeutically effective amount of the modified poxvirus of any one of claims 1 to ~~17~~ 18 and a pharmaceutically acceptable vehicle

~~20.~~21. The composition of claim ~~19~~ 20 comprising from ~~approximately~~ 10^3 to ~~approximately~~ 10^{12} pfu, advantageously from ~~approximately~~ 10^4 pfu to ~~approximately~~ 10^{11} pfu, preferably from ~~approximately~~ 10^5 pfu to ~~approximately~~ 10^{10} pfu; and more preferably from ~~approximately~~ 10^6 pfu to ~~approximately~~ 10^9 pfu of the modified poxvirus and notably individual doses of ~~approximately~~ 10^6, $5x10^6$, 10^7, $5x10^7$, 10^8 or $5x10^8$ pfu.

~~21.~~22. The composition of claim ~~19 or~~ 20 or 21, which is formulated for intravenous or intratumoral administration.

~~22.~~23. Use of the composition of any one of claims ~~19~~ 20 to ~~21~~100, in the manufacture of a medicament, for treating or preventing a proliferative disease selected from the group consisting of cancers as well as diseases associated to an increased osteoclast

activity such as rheumatoid arthritis and osteoporosis and cardiovascular diseases such as restenosis.

~~23.~~24. The use of claim ~~22~~23, wherein said cancer is selected from the group consisting of renal cancer, prostate cancer, breast cancer, colorectal cancer, lung cancer, liver cancer, gastric cancer, bile duct carcinoma, endometrial cancer, pancreatic cancer and ovarian cancer.

~~24.~~25. Use of the composition of any one of claims ~~19~~ 20 to ~~21~~11, in the manufacture of a medicament, for stimulating or improving an immune response selected from the group consisting of~~, and especially~~:

- for stimulating or improving a lymphocyte-mediated immune response (especially against an antigenic polypeptide);
- for stimulating or improving the activity of APC;
- for stimulating or improving an anti-tumoral response;
- for stimulating or improving the CD28-signalling pathway;
- for improving the therapeutic efficacy provided by the modified poxvirus described herein in a treated subject or a group of treated subjects; and/or
- for reducing the toxicity provided by the modified poxvirus described herein in a treated subject or a group of treated subjects.

~~25.~~26. The use of any one of claims ~~22~~ 23 to ~~24~~25, for use as stand-alone therapy or in conjunction with one or more additional therapies, preferably selected from the group consisting of surgery, radiotherapy, chemotherapy, cryotherapy, hormonal therapy, toxin therapy, immunotherapy, cytokine therapy, targeted cancer therapy, gene therapy, photodynamic therapy and transplantation.