IN THE PATENT OFFICE AT CHENNAI

ORDER (No.113/2023)

(Under Section 25(1) and Rule 55)

In the matter of the application for Patent 201747022885 filed by MERCK SHARP & DOHME LLC

And

In the matter of representation by way of opposition u/s 25(1) to the grant of patent thereon by Dr. C. Manivannan

Merck Sharp & Dohme Corp.
126 East Lincoln Avenue, Rahway,
New Jersey 07065-0907,
United States of America …… **APPLICANT**

Dr. C. Manivannan
3A, Chinna Andaar Street, Kulithalai (TK), Karur (Dt),
Tamil Nadu - 639104, India …… **OPPONENT**

The applicant has filed a patent application number 201747022885 on 29/06/2017 for granting of a patent for their invention titled "CRYSTALS OF ANTI HUMAN PD 1 MONOCLONAL ANTIBODIES". A request for examination was filed by the applicant on 17/01/2019. The application was published on 28/07/2017. The first examination report (FER) was issued on 16/02/2021 and the applicant's agent replied to the FER on 16/08/2021.

ORIGINAL CLAIMS at the date of filing of the application:

WHAT IS CLAIMED IS:

1. A crystal of an anti-PD-1 monoclonal antibody (mAb), wherein the anti-PD-1 mAb is pembrolizumab or a pembrolizumab variant or the antibody in a pembrolizumab biosimilar.

2. The crystal of claim 1, wherein the crystal is characterized by having a length in a range selected from the group consisting of: 1 to 200 microns, 1 to 100 microns, 1 to 20 microns, 5 to 100 microns, 5 to 50 microns 5 to 40 microns, 5 to 30 microns, 5 to 20 microns, 5 to 10 microns, 10 to 100 microns, 10 to 50 microns and 10 to 20 microns.

3. The crystal of claim 2, wherein the crystal is characterized by having a length of 5 to 10 microns, 5 to 20 microns, 5 to 40 microns or 50 to 100 microns.

4. The crystal of any one of claims 1 to 3, wherein the anti-PD-1 mAb is pembrolizumab and the crystal is characterized by unit cell dimensions of a = 63.5 to 78.9 A, b = 110.2 to 112.2 A, c = 262.5 to 306 A, a =90, β =90, γ = 90° and a space group of P2,2i2i.

5. The crystal of any one of claims 1 to 4, which is capable of diffracting X-rays to a resolution selected from the group consisting of 2.3 Ato 3.5 A, 2.3 Ato 3.0 A, 2.3 Ato 2.75 A, 2.3 Ato 2.5 Aand 2.3 A.

6. A method for producing crystals of an anti-PD-1 monoclonal antibody (mAb), wherein the anti-PD-1 mAb is pembrolizumab, a pembrolizumab variant, or the antibody in a pembrolizumab biosimilar and the method comprises exposing a solution comprising the antiPD-1 mAb to a precipitant solution at a temperature that is at least 25°C and is no greater than 50°C for a time sufficient for crystal formation, wherein the precipitant solution has a pH of 4.0 to 5.0 and comprises 1.0 M to 2.5 M ammonium dihydrogen phosphate.

7. The method of claim 6, wherein the exposing step comprises mixing the antibody solution and the precipitant solution to form a crystallization mixture and applying a crystallization process to the mixture, wherein the crystallization process is selected from the group consisting of hanging drop vapor diffusion, sitting drop vapor diffusion and batch.

8. The method of claim 7, wherein the crystallization process is a batch process and the method further comprises seeding the crystallization mixture with crystals of the anti-PD-1 mAb.

9. The method of any one of claims 6 to 8, wherein the antibody solution comprises the

anti-PD-1 mAb at a concentration of 2 to 200 mg/ml, 3 to 100 mg/ml, 10 to 90 mg/ml, 20 to80 mg/ml, 30 to 70 mg/ml, 40 to 60 mg/ml or about 50 mg/ml and the precipitant solution has a pH selected from the group consisting of 4.2 to 4.8, 4.4 to 4.6 and 4.5.

10. The method of any one of claims 6 to 9, wherein the precipitant solution comprises (a) 1.5 M to 2.0 M ammonium dihydrogen phosphate and 100 to 120 mM Tris-HCl or (b) 1.9 M ammonium dihydrogen phosphate and 0.09 M ammonium hydrogen phosphate.

11. The method of any one of claims 6 to 10, wherein the exposing step is performed for at least 3, 4 or 5 days at a temperature of about 30°C.

12. A method for crystallizing an anti-PD-1 monoclonal antibody (mAb) from a solution comprising the anti-PD-1 mAb, wherein the antibody is pembrolizumab, a pembrolizumab variant, or the antibody in a pembrolizumab biosimilar and the method comprises: (a) combining the anti-PD-1 mAb solution with a precipitant solution and seed crystals of the anti-PD-1 mAb to produce a seeded crystallization mixture; (b) incubating the seeded crystallization mixture at a temperature of at least 20°C and no greater than about 40°C; and (c) harvesting the crystals, wherein the seed crystals are from a seed stock of crystals of the anti-PD-1 mAb that were produced by a method of any one of claims 1 to 11.

13. A pharmaceutical composition comprising (a) crystals of an anti-PD-1 monoclonal antibody (mAb), wherein the antibody is pembrolizumab, a pembrolizumab variant, or the antibody in a pembrolizumab biosimilar and (b) at least one pharmaceutically acceptable excipient.

14. The composition of claim 13, wherein each of the anti-PD-1 mAb crystals in the composition is a crystal as defined in any one of claims 1 to 5 or produced by a method of any one of claims 6 to 10.

15. The composition of claim 3 or 14, herein the anti-PD-1 mAb crystals are suspended in a liquid and the anti-PD-1 mAb concentration in the composition is at least 50 mg/ml, at least 100 mg/ml, at least 200 mg/ml or at least 250 mg/ml.

16. The composition of claim 13 or 14, which is a solid.

17. A method of treating a human subject for a cancer, which comprises administering to the patient a therapeutically effective amount of a pharmaceutical composition of any one of claims 13 to 16.

18. The method of claim 17, wherein the cancer is bladder cancer, breast cancer, clear cell kidney cancer, head/neck squamous cell carcinoma, lung squamous cell carcinoma, malignantmelanoma, non-small-cell lung cancer (NSCLC), ovarian cancer, pancreatic cancer, prostate cancer, renal cell cancer, small-cell lung cancer (SCLC), triple negative breast cancer, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), diffuse large B-cell lymphoma (DLBCL), EBV-positive DLBCL, primary mediastinal large B-cell lymphoma, T-cell/histiocyte-rich large B-cell lymphoma, follicular lymphoma, Hodgkin's lymphoma (HL), mantle cell lymphoma (MCL), multiple myeloma (MM), myeloid cell leukemia- 1 protein (Mcl-1), myelodysplasia syndrome (MDS), non-Hodgkin's lymphoma (NHL), or small lymphocytic lymphoma (SLL).

19. The method of claim 18, wherein the pharmaceutical composition comprises at least 200 mg/ml of the mAb and is administered subcutaneously.
20. The method of claim 18 or 19, wherein the cancer is a solid tumor and a tissue section of the cancer removed from the subject prior to a first administration of the pharmaceutical composition tested positive for expression of one or both of PD-L1 and PD-L2.

A pre-grant representation u/s 25(1) of The Patents Act, 1970 was filed for patent application 201747022885 by Dr. C. Manivannan on 22/04/2022.

GROUNDS FOR PRE-GRANT OPPOSITION:
i. **Section 25(1)(e)**– that the invention claimed in the impugned application is obvious and clearly does not involve any inventive step.
ii. **Section 25(1)(f)**– that the subject of any claim of the complete specification is not an invention within the meaning of this act or is not patentable under this act.
iii. **Section 25(1)(g)**– that the complete specification of the impugned application does not sufficiently and clearly describe the invention or the method by which it is to be performed.

A pre-grant opposition u/s 25 (1) intimation for patent application 201747022885 was issued to the applicant on 7.2.2023. However, the applicant has not made any statement and evidence within three months from the date of this notice as per Rule 55 of the Patent Rules, 2003.

A pre-grant hearing notice was issued to applicant and opponent through office letter dated 31.05.2023 offering a hearing on 27/06/2023 at 14:30 HRS(IST) for (1h 30 Mins). Further, the hearing has been rescheduled to 12/07/2023 / 09:00 HRS(IST) for (3h) due to technical issues in IPO module.

During the hearing held on 12/07/2023, only the Opponent's agent has attended and the applicant's agent for pre-grant opposition did not appear. Applicant's agent has informed that they will not be attending the hearing as they have not received the instructions from the applicant. Opponent's agent has made submission regarding the grounds for opposition to substantiate the arguments.

In view of the submissions, it is found that there are merits on the grounds for opposition in the Pre-grant representation filed u/s 25(1) of The Patents Act, 1970 and the application is NOT allowed to proceed further for grant.

(V.G.SARAVANA RAM PRASAD)
Deputy Controller of Patents & Designs

IN THE PATENT OFFICE AT CHENNAI

ORDER (No.113/2023)

(Under Section 15, THE PATENTS ACT, 1970)

The objections in First Examination Report (FER) under Section 12 and 13 of Patents Act were not complied within the prescribed period. An opportunity of hearing under Section 14 of Patents Act was offered to the applicant through office letter dated 13/07/2023. Applicant's agent has informed through letter dated 28.07.2023 that they will not be attending the hearing as they have not received the instructions from the applicant.

Consequently, the outstanding objections of the said hearing notice is maintained and found that the requirements for grant of patent are not met in accordance with provisions of the act.

This application for grant of patent is refused under Section 15, The Patents Act, 1970.

(V.G.SARAVANA RAM PRASAD)

Deputy Controller of Patents & Designs