permissive gene expression signature. One such set of markers is shown in WO 2017218757 A1. Gene expression signatures of the tumor will give actionable information. However, it is static, and therefore cannot take into account changing circumstances that may arise during treatment. In addition, gene expression signature cannot factor in tumor burden.

[0011] Thus, there is a need for real time measurement and monitoring in a dynamic clinical environment, and adapting the treatment decisions based on the individual response and changing circumstances in each patient.

SUMMARY

[0012] The present disclosure generally relates to a method of diagnosis. In certain examples, the disclosure relates to methods of determining the likelihood that a cancerous tissue in a subject having the cancerous tissue will respond to administration of a cancer therapy regimen is provided. The methods generally comprise (a) administering intratumorally to the cancerous tissue a subtherapeutic diagnostic dose of an oncolytic virus probe that comprises a nucleic acid that codes for soluble interferon beta (IFNβ), and (b) measuring the circulating level of IFNβ in the subject after administration of the oncolytic virus to determine if the cancerous tissue is a strong responder, an intermediate responder, a low responder or a non-responder.

[0012a] In one aspect, the present disclosure refers to a method of determining the likelihood that a cancerous tissue in a subject having the cancerous tissue will respond to administration of a cancer therapy regimen, the method comprising measuring the circulating level of interferon beta (IFNβ) in the subject between 12 hours to 45 days after intratumoral administration of a subtherapeutic diagnostic dose of an oncolytic virus probe to the cancerous tissue, wherein the subtherapeutic dose is from 10^5 $TCID_{50}$ to $3X10^9$ $TCID_{50}$, and wherein the oncolytic virus probe comprises a nucleic acid that codes for soluble IFNβ, to determine if the cancerous tissue is present in (a) a strong responder having a plasma IFNβ level greater than 1000 pg/mL, (b) an intermediate responder having a plasma IFNβ level between 10 pg/mL and 1000 pg/mL, or (c) a low responder or a non-responder having a plasma IFNβ level less than 10 pg/mL.

[0013] The present disclosure also relates to methods of treating a subject having been diagnosed with cancer. The treatment methods comprise: (a) administering to the subject a first dose of an oncolytic virus cancer therapy regimen that comprises a nucleic acid encoding interferon beta (IFNβ), and (b) administering at least a second dose of the oncolytic virus cancer therapy regimen if the subject has been identified as a strong responder or an intermediate responder to the oncolytic virus cancer therapy regimen.

[0013a] In one aspect, the present disclosure refers to use of an oncolytic virus in the manufacture of a medicament for treating cancer in a subject, wherein:
(a) the oncolytic virus is the same oncolytic virus as the oncolytic virus probe administered intratumorally according to the invention, (b) the subject is selected as having cancerous tissue determined, according to the method of any of the preceding claims, to be a strong or intermediate responder to the oncolytic virus and (c) wherein the medicament is to be administered intratumorally as a therapeutic dose of said oncolytic virus as part of a cancer therapy regimen.

[0013b] In one aspect, the present disclosure refers to use of an oncolytic virus that comprises a nucleic acid encoding interferon beta (IFNβ) in the manufacture of a medicament for treating a subject having been diagnosed with cancer, wherein: a first dose of said oncolytic virus is to be administered intratumorally to the subject, wherein the first dose of the oncolytic virus is a non-therapeutic and non-toxic dose of the oncolytic virus, wherein the non-therapeutic and non-toxic dose is from 10^5 $TCID_{50}$ to $3X10^9$ $TCID_{50}$, and wherein the level of IFNβ is assessed between 0.5 to 45 days after administration of the first dose of the oncolytic virus; and at least a second dose of the oncolytic virus is to be administered to the subject if the subject has been identified as a strong responder or an intermediate responder to the first dose of the oncolytic virus, wherein the strong responder has a plasma IFNβ level greater than 1000 pg/mL after administration of the first dose of the oncolytic virus, and wherein the intermediate responder has a plasma IFNβ level between 10 pg/mL and 1000 pg/mL after administration of the first dose of the oncolytic virus.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] **Figure 1** shows that intratumorally injected Voyager-V1 virus concentration correlates with response. IFNβ levels predict patient's response to Voyager-V1.

[0015] **Figure 2** shows the plasma IFNβ levels in patients administered with dose level (DL) 1, 2, or 3 of Voyager-V1. DL1, DL2, and DL3 correspond to $5x10^9$, $1.7x10^{10}$, and $5x10^{10}$ $TCID_{50}$, respectively. SD indicates stable disease. PR indicate partial response.

[0016] **Figure 3** shows a plot of plasma IFNβ level at day 2 (24 hours post administration) against anti-VSV antibody titer at day 29 (day 28 post administration).

[0017] **Figures 4A-4F** show the comparison of relative IFNβ and IFNα trends in patients. **Figures 4A-4C** show that the IFNβ level (the dark line) increases at 24 hours post administration. **Figures 4D-4F** show that the IFNα level (the dark line) decreases at 24 hours post administration. The data indicate that IFNβ transgene levels can serve as a biomarker of viral infection.

[0018] **Figures 5A-5F** show that the circulating levels of IFNβ detected in serum is an indicator of variability in Voyager-V1 infection and spread in individual patients. In particular, **Figures 5A-5C** show that the circulating levels of IFNβ can be detected in patients with intratumoral injection of doses in the range from approximately 10^6 to 10^8 TCID50.

[0019] **Figure 6** shows an illustration of the construct of Voyager-V1 (VSV-IFNβ-NIS, VV1)

[0020] **Figure 7** shows a flow chart summary of the method used in the Voyager-V1 systemic virotherapy study as provided in Example 1.

[0021] **Figures 8A and 8B** show the clinical activity after one intravenous dose of Voyager-V1. Specifically, **Figure 8A** shows the CT scans of pre-treatment and 3 months after Voyager-V1 treatment in a subject with endometrial cancer. The overall tumor reduction is 16.5% in diameter at day 29. **Figure 8B** shows there is a 75% reduction in tumor diameters in a subject with T-cell lymphoma.

[0022] **Figures 9A and 9B** show that NIS imaging confirms infection of tumor by Voyager-V1 in two subject, Subject 105-021 (**Figure 9A**) and Subject 105-020 (**Figure 9B**).

[0023] **Figures 10A and 10B** show that Voyager-V1 treatment increases CD8 tumor infiltrating cells one month after with intravenous injection (subject 6, **Figure 10A**) or intratumoral injection (subject 103-014, **Figure 10B**).

DETAILED DESCRIPTION OF THE INVENTION

[0024] The present invention generally relates to a method of diagnosis. In certain embodiments, the invention relates to methods of determining the likelihood that a cancerous tissue in a subject having the cancerous tissue will respond to administration of a cancer therapy regimen is provided. The methods generally comprise (a) administering intratumorally to the cancerous tissue a subtherapeutic diagnostic dose of an oncolytic virus probe that comprises a nucleic acid that codes for soluble interferon beta (IFNβ), and (b) measuring the circulating level of IFNβ in the subject after

WHAT IS CLAIMED

1. A method of determining the likelihood that a cancerous tissue in a subject having the cancerous tissue will respond to administration of a cancer therapy regimen, the method comprising measuring the circulating level of interferon beta (IFNβ) in the subject between 12 hours to 45 days after intratumoral administration of a subtherapeutic diagnostic dose of an oncolytic virus probe to the cancerous tissue, wherein the subtherapeutic dose is from 10^5 $TCID_{50}$ to $3X10^9$ $TCID_{50}$, and wherein the oncolytic virus probe comprises a nucleic acid that codes for soluble IFNβ, to determine if the cancerous tissue is present in (a) a strong responder having a plasma IFNβ level greater than 1000 pg/mL, (b) an intermediate responder having a plasma IFNβ level between 10 pg/mL and 1000 pg/mL, or (c) a low responder or a non-responder having a plasma IFNβ level less than 10 pg/mL.

2. The method of claim 1, wherein the cancer therapy regimen comprises administration of a therapeutic dose of the same oncolytic virus of said oncolytic virus probe administered intratumorally if said cancerous tissue is said strong responder or said intermediate responder.

3. The method of claim 1, wherein the cancer therapy regimen comprises administration of a different oncolytic virus than said oncolytic virus probe administered intratumorally if said cancerous tissue is said low responder or said non-responder.

4. The method of claim 1, wherein, when said cancerous tissue is said low responder or said non-responder, the cancer therapy regimen is an immuno-oncolytic therapy.

5. The method of claim 1, wherein, when said cancerous tissue is said low responder or said non-responder, the cancer therapy regimen is an antibody or small molecule anti-cancer treatment.

6. The method of claim 1, wherein the subtherapeutic diagnostic dose is a non-toxic and non-therapeutic dose.

7. The method of claim 6, wherein the non-therapeutic and non-toxic dose is from 10^8 $TCID_{50}$ to $5X10^8$ $TCID_{50}$.

8. The method of claim 1, wherein the oncolytic virus probe is a GMP grade virus.

9. The method of any one of the preceding claims, wherein the oncolytic virus probe is a vesicular stomatitis virus (VSV).

10. The method of claim 9, wherein the oncolytic virus probe further comprises a nucleic acid encoding a sodium iodine symporter (NIS).

11. The method of claim 10, wherein the oncolytic virus probe has the construct of N-P-M-IFNβ-G-NIS-L.

12. The method of any one of the preceding claims, wherein the circulating level of IFNβ is measured in the subject between 12 hours to 3 days after administration of the oncolytic virus probe.

13. The method of claim 12, wherein the circulating level of IFNβ is measured in the subject about 48 hours after administration of the oncolytic virus probe.

14. The method of claim 12, wherein the circulating level of IFNβ is measured in the subject about 24 hours after administration of the oncolytic virus probe.

15. The method of any one of the preceding claims, wherein the circulating level of IFNβ is measured by an immunological assay.

16. The method of any one of the preceding claims, wherein the cancerous tissue is a solid tumor or a hematological malignancy.

17. The method of any one of the preceding claims, wherein the cancerous tissue is a head and neck cancer, colon cancer, rectal cancer, pancreatic cancer, bladder cancer, breast cancer, hepatocellular cancer, lung cancer, medulloblastoma, atypical teratoid/rhabdoid tumor, a leukemia, a lymphoma, or a myeloma.

18. Use of an oncolytic virus in the manufacture of a medicament for treating cancer in a subject, wherein:
    (a) the oncolytic virus is the same oncolytic virus as the oncolytic virus probe administered intratumorally according to claim 1,

(b) the subject is selected as having cancerous tissue determined, according to the method of any of the preceding claims, to be a strong or intermediate responder to the oncolytic virus, and

(c) wherein the medicament is to be administered intratumorally as a therapeutic dose of said oncolytic virus as part of a cancer therapy regimen.

19. The use of claim 18, wherein the cancer therapy regimen comprises more than one anti-cancer composition.

20. The use of claim 18, wherein the cancerous tissue is a solid tumor and the cancer therapy regimen is an oncolytic virus that is to be administered intratumorally at a dose that is based upon the number of viral particles per unit volume of tumor.

21. The use of claim 20, wherein the therapeutic dose of the oncolytic virus to be administered intratumorally is given in a standard dose range.

22. The use of claim 18, wherein the cancer therapy regimen is an oncolytic virus that is to be administered intravenously.

23. Use of an oncolytic virus that comprises a nucleic acid encoding interferon beta (IFNβ) in the manufacture of a medicament for treating a subject having been diagnosed with cancer, wherein:

a first dose of said oncolytic virus is to be administered intratumorally to the subject, wherein the first dose of the oncolytic virus is a non-therapeutic and non-toxic dose of the oncolytic virus, wherein the non-therapeutic and non-toxic dose is from 10^5 $TCID_{50}$ to $3X10^9$ $TCID_{50}$, and wherein the level of IFNβ is assessed between 0.5 to 45 days after administration of the first dose of the oncolytic virus; and

at least a second dose of the oncolytic virus is to be administered to the subject if the subject has been identified as a strong responder or an intermediate responder to the first dose of the oncolytic virus, wherein the strong responder has a plasma IFNβ level greater than 1000 pg/mL after administration of the first dose of the oncolytic virus, and wherein the intermediate responder has a plasma IFNβ level between 10 pg/mL and 1000 pg/mL after administration of the first dose of the oncolytic virus.

24. The use of claim 23, wherein the second dose of the oncolytic virus is an intravenous administration or an intratumoral administration.

25. The use of claim 23 or 24, wherein the oncolytic virus comprises a nucleic acid encoding a sodium iodine symporter (NIS).

26. The use of any one of claims 23-25, wherein the oncolytic virus is an RNA virus.

27. The use of any one of claims 23-26, wherein the oncolytic virus is a vesicular stomatitis virus (VSV).

28. The use of claim 27, wherein the VSV has the construct of N-P-M-IFNβ-G-NIS-L.

29. The use of any one of claims 23-28, wherein one or more additional immune-oncology therapy agents are to be further administered to the subject if the subject has been identified as an intermediate responder to the oncolytic virus.

30. The use of any one of claims 23-29, wherein a janus kinase inhibitor (JAK inhibitor) inhibitor is to be further administered to the subject if the subject has been identified as a strong responder to the oncolytic virus.

31. The use of claim 30, wherein the JAK inhibitor is ruxolitinib.

32. The use of any one of claims 23-31, wherein the level of IFNβ is assessed between 0.5 to 3 days after administration of the first dose of the oncolytic virus.

33. The use of any one of claims 23-32, wherein the second dose of the oncolytic virus is to be administered within 1-10 days after administration of the first dose of the oncolytic virus.

34. The use of claim 33, wherein the circulating levels of IFNβ are assessed within 12-24 hours after administration of the first dose of the oncolytic virus.

35. The use of any one of claims 23-34, wherein the circulating level of IFNβ is assessed by an immunological assay.

36. The use of any one of claims 23-35, wherein the cancer is a solid tumor or a hematological malignancy.

37. The use of claim 36, wherein the solid tumor is a head and neck cancer, colon cancer, rectal cancer, pancreatic cancer, bladder cancer, breast cancer, hepatocellular cancer, lung cancer, medulloblastoma, or atypical teratoid/rhabdoid tumor.

38. The use of claim 36, wherein the hematological malignancy is a leukemia, a lymphoma, or a myeloma.

39. The use of any one of claims 23-37, wherein the second administration of the oncolytic virus is by intratumoral injection.

40. The use of claim 39, where in the second intratumoral injection is to be administered to the subject based on the number of viral particles per unit volume of tumor.

41. The use of claim 40, wherein second intratumoral injection is to be administered to the subject in a standard dose range.

42. The use of any one of claims 23-38, wherein the second dose of the oncolytic virus is to be administered intravenously.