

Sequence Listing

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on June 24, 2020, is named 8555_039Z_SL.txt and is 29,049 bytes in size.

BACKGROUND OF THE DISCLOSURE

[0001] Rett syndrome (RTT) is a neurodevelopmental disorder that is mostly caused by mutations in the X-linked gene Methyl CpG-binding Protein 2 (MECP2). Rett syndrome predominantly affects girls and is the second most common cause of severe intellectual disability after Down syndrome, with an incident of 1:10,000 live births. Patients suffer from cognitive and physical disabilities, with most of them wheel chair bound and requiring full time care. There is no cure to date, however, the late onset from 6-18 months of life provides a valuable window of opportunity for therapeutic intervention. An experimental model, *Mecp2*-deficient mice, is available for preclinical research. A significant contribution to research in RTT is the proof of concept demonstration that re-expression of MeCP2 in *Mecp2*-deficient mice, preferentially in astrocytes, significantly improved locomotion and anxiety levels, restored respiratory abnormalities to a normal pattern, and greatly prolonged lifespan compared to globally null mice. These studies showed that glia, like neurons, are integral components of the neuropathology of RTT. (Lioy et al., Nature, 475(7357):497-500 (2012)) This landmark achievement, whereby *Mecp2* expression was restored in the mutant mice, leading to a dramatic recovery from their "Rett-like phenotype," has increased the motivation to find a cure. However, there remains a need for treatments for Rett syndrome that alleviate the symptoms associated with the disorder.

BRIEF SUMMARY OF THE DISCLOSURE

[0002] Methods for using semaphorin 4D (SEMA4D) binding molecules to alleviate symptoms in a subject with Rett syndrome are disclosed herein. In one aspect, the present disclosure provides a use of an isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D) for use in the manufacture of a medicament for treating Rett syndrome in a subject in need thereof. According to ~~aspeet~~examples of the disclosure illustrated herein, there is provided a method for improving symptoms in a subject with Rett syndrome including administering to the subject an effective amount of an isolated binding molecule which specifically binds to SEMA4D and inhibits, suppresses, prevents, reverses or slows the effect of SEMA4D on disease progression.

[0003] According to ~~aspeet~~examples illustrated herein, there is provided a method of treating a subject with Rett syndrome including administering to the subject an effective amount of an isolated binding molecule which specifically binds to SEMA4D, wherein the binding to SEMA4D acts to improve symptoms associated with the disorder.

[0004] Methods of alleviating symptoms in a subject having Rett syndrome are provided, comprising administering to that subject an effective amount of an isolated binding

| molecule which specifically binds to SEMA4D. In certain embodimentexamples of the
| methods, the binding molecule inhibits SEMA4D interaction with its receptor or a portion
| of its receptor. In certain embodimentexamples of the methods, the receptor is selected
from the group

consisting of Plexin-B1, Plexin-B2 and CD72. In certain [embodimentexamples](#) of the methods, the binding molecule inhibits SEMA4D-mediated Plexin-B1 signal transduction. In certain [embodimentexamples](#) of the methods, the isolated binding molecule specifically binds to the same SEMA4D epitope as a reference monoclonal antibody selected from the group consisting of VX15/2503, Mab D2517, D2585, and MAb 67. In certain [embodimentexamples](#) of the methods, the isolated binding molecule competitively inhibits a reference monoclonal antibody selected from the group consisting of VX15/2503, Mab D2517, D285, and MAb 67 from specifically binding to SEMA4D. In certain [embodimentexamples](#) of the methods, the isolated binding molecule comprises an antibody or antigen-binding fragment thereof. In certain [embodimentexamples](#) of the methods, the antibody or antigen-binding fragment thereof is monoclonal antibody VX15/2503 or MAb 67. In certain [embodimentexamples](#) of the methods, the antibody or antigen-binding fragment thereof comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID NOs 3, 4, and 5, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 8, 9, and 10, respectively. In certain [embodimentexamples](#) of the methods, the VH and VL comprise, respectively, SEQ ID NO: 6 and SEQ ID NO: 11, SEQ ID NO: 7 and SEQ ID NO: 12, or SEQ ID NO: 21 and SEQ ID NO: 25. In certain [embodimentexamples](#) of the methods, the antibody or antigen-binding fragment thereof comprises a variable heavy chain comprising VHCDRs 1-3 comprising SEQ ID NO: 22, SEQ ID NO: 23, and SEQ ID NO: 24, respectively, and a variable light chain comprising VLCDRs 1-3 comprising SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28, respectively.

[0005] In certain [embodimentexamples](#) of any one of the aforementioned methods, the symptoms treated are selected from a group consisting of neuropsychiatric symptoms, cognitive symptoms, motor dysfunction, and any combination thereof. In certain [embodimentexamples](#) of any of the aforementioned methods, the subject has stage I Rett syndrome. In certain [embodimentexamples](#), alleviation of the neuropsychiatric symptoms includes reducing anxiety-like behavior, decreasing sleep disturbances, reducing agitation, reducing restlessness, and any combination thereof. In certain [embodimentexamples](#), the symptoms that are alleviated are selected from the group consisting of neuropsychiatric symptoms, cognitive symptoms, delayed physical development, delayed communication development, loss of communication skills, motor dysfunction, sleep disturbances, irregular heartbeat, repetitive jerky movements, body tremors, and any combination thereof. In certain [embodimentexamples](#), alleviating symptoms comprises preventing or reducing anxiety-like behavior, increasing cognition, increasing coordination, increasing locomotion, progressing physical development, decreasing body tremors, decreasing repetitive movements, increasing motor skills, increasing communication skills, decreasing sleep disturbances, decreasing agitation, decreasing restlessness, and any combination thereof.

[0006] In certain [embodimentexamples](#), the subject is in Stage II, Stage III, or Stage IV of Rett syndrome. In certain [embodimentexamples](#), the Stage II, Stage III, or Stage IV subject exhibits symptoms selected from the group consisting of neuropsychiatric symptoms, cognitive symptoms, delayed physical development, motor dysfunction, irregular heartbeat and breathing, decreased communication skills, scoliosis, sleep disturbances, seizures, gastrointestinal problems, repetitive jerky motions, body tremors, and any combination thereof. In certain [embodimentexamples](#), the alleviation of symptoms includes reducing anxiety-

What is claimed is:

1. ~~Use of a~~An isolated binding molecule which specifically binds to semaphorin-4D (SEMA4D) ~~for use in the manufacture of a medicament for~~ treating Rett syndrome in a subject in need thereof.
2. The ~~isolated binding molecule for the~~ use of claim 1, wherein the binding molecule competitively inhibits a reference monoclonal antibody selected from the group consisting of VX15/2503, D2517, D2585, and Mab 67 from specifically binding to SEMA4D.
3. The ~~isolated binding molecule for the~~ use of claim 1 or 2, wherein the binding molecule inhibits SEMA4D interaction with its receptor or a portion of its receptor.
4. The ~~isolated binding molecule for the~~ use of claim 3, wherein the receptor is selected from the group consisting of Plexin-B1 and Plexin-B2, and CD72.
5. The ~~isolated binding molecule for the~~ use of any one of claims 1 to 4, wherein the binding molecule inhibits SEMA4D receptor-mediated signal transduction.
6. The ~~isolated binding molecule for the~~ use of claim 1, wherein the isolated binding molecule specifically binds to the same SEMA4D epitope as a reference monoclonal antibody selected from the group consisting of VX15/2503, D2517, or Mab 67.
7. The ~~isolated binding molecule for the~~ use of any one of claims 1 to 6, wherein the isolated binding molecule comprises an antibody or antigen-binding fragment thereof.
8. The ~~isolated binding molecule for the~~ use of claim 7, wherein the antibody or antigen-binding fragment thereof is VX15/2503, D2517, or Mab 67.
9. The ~~isolated binding molecule for the~~ use of claim 7, wherein the antibody or antigen-binding fragment thereof comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID Nos 3, 4, and 5, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 8, 9, and 10, respectively.

10. The ~~isolated binding molecule for the~~ use of claim 9, wherein the VH and VL comprise, respectively, SEQ ID NO: 6 and SEQ ID NO: 11 or SEQ ID NO: 7 and SEQ ID NO: 12.
11. The ~~isolated binding molecule for the~~ use of claim 7, wherein the antibody or antigen-binding fragment thereof comprises a variable heavy chain (VH) comprising VHCDRs 1-3 comprising SEQ ID Nos 22, 23, and 24, respectively, and a variable light chain (VL) comprising VLCDRs 1-3 comprising SEQ ID NOs 26, 27, and 28, respectively.
12. The ~~isolated binding molecule for the~~ use of claim 11, wherein the VH and VL comprise, respectively, SEQ ID NO: 21 and SEQ ID NO: 25.
13. The ~~isolated binding molecule for the~~ use of any one of claims 1 to 12, wherein the subject is in Stage 1 of Rett syndrome.
14. The ~~isolated binding molecule for the~~ use of claim 13, ~~wherein said use for~~ alleviating Rett syndrome disease Stage symptoms selected from the group consisting of neuropsychiatric symptoms, cognitive symptoms, motor dysfunction, delayed physical development, delayed communication development, loss of communication skills, sleep disturbances, irregular heartbeat, irregular breathing patterns, repetitive jerky movements, body tremors, and any combination thereof.
15. The ~~isolated binding molecule for the~~ use of claim 14, wherein alleviating symptoms comprises preventing or reducing anxiety-like behaviour, increasing cognition, increasing coordination, increasing locomotion, progressing physical development, decreasing body tremors, decreasing repetitive movements, increasing motor skills, increasing communication skills, decreasing sleep disturbances, decreasing agitation, decreasing restlessness, decreasing breathing irregularities, and any combination thereof.
16. The ~~isolated binding molecule for the~~ use of any one of claims 1 to 12, wherein the subject is in Stage II, Stage III, or Stage IV of Rett syndrome.
17. The ~~isolated binding molecule for the~~ use of claim 16, ~~wherein the said use for~~ alleviates ~~alleviating~~ Rett syndrome symptoms selected from the group consisting of neuropsychiatric symptoms, cognitive symptoms, delayed physical development, motor

dysfunction, irregular heartbeat and breathing, decreased communication skills, scoliosis, sleep disturbances, seizures, gastrointestinal problems, repetitive jerky motions, body tremors, and any combination thereof.

18. The ~~isolated binding molecule for the~~ use of claim 17, wherein alleviating symptoms comprises reducing anxiety-like behaviour, increasing cognition, increasing coordination, increasing locomotion, progressing physical development, decreasing body tremors, decreasing repetitive motions, increasing motor skills, increasing communication skills, or any combination thereof.