We claim:

1. A method of assessing the activity of a tau-targeting reagent, comprising:

(a) administering the tau-targeting reagent to a cell comprising a four-repeat (4R) tau isoform linked to a first reporter protein and a three-repeat (3R) tau isoform linked to a second reporter protein that is different from the first reporter protein; and

(b) assessing the activity of the tau-targeting reagent in the cell, wherein:

(I) the assessing comprises measuring 4R tau isoform messenger RNA expression and second reporter protein messenger RNA expression, wherein a larger relative decrease in 4R tau isoform messenger RNA expression compared to second reporter protein messenger RNA expression after administering the tau-targeting reagent to the cell indicates that the tau-targeting reagent is a 4R-preferential tau targeting reagent;

(II) the assessing comprises measuring first reporter protein messenger RNA expression and second reporter protein messenger RNA expression, wherein a larger relative decrease in first reporter protein messenger RNA expression compared to second reporter protein messenger RNA expression after administering the tau-targeting reagent to the cell indicates that the tau-targeting reagent is a 4R-preferential tau targeting reagent; or

(III) the assessing comprises measuring first reporter protein expression and second reporter protein expression, wherein a larger relative decrease in first reporter protein expression compared to second reporter protein expression after administering the tau-targeting reagent to the cell indicates that the tau-targeting reagent is a 4R-preferential tau targeting reagent.

2. The method of claim 1, wherein the activity of the tau-targeting reagent is assessed compared to a control cell that is not administered the tau-targeting reagent or is assessed compared to prior to administering the tau-targeting reagent.

3. The method of claim 1 or 2, wherein:

(I) a decrease of at least 70% in 4R tau isoform messenger RNA expression and a decrease of no more than 30% in second reporter protein messenger RNA expression after administering the tau-targeting reagent to the cell indicates that the tau-targeting reagent is a 4R-preferential tau targeting reagent;

(II) a decrease of at least 70% in first reporter protein messenger RNA expression and a decrease of no more than 30% in second reporter protein messenger RNA expression after administering the tau-targeting reagent to the cell indicates that the tau-targeting reagent is a 4R-preferential tau targeting reagent; or

(III) a decrease of at least 70% in first reporter protein expression and a decrease of no more than 30% in second reporter protein expression after administering the tau-targeting reagent to the cell indicates that the tau-targeting reagent is a 4R-preferential tau targeting reagent.

4. The method of any one of claims 1-3, wherein:

(I) the 4R tau isoform and the 3R tau isoform are human; and/or

(II) (a) the cell comprises a first fusion protein comprising the 4R tau isoform fused to the first reporter protein and a second fusion protein comprising the 3R tau isoform fused to the second reporter protein,

optionally wherein the cell comprises a first nucleic acid encoding the first fusion protein and a second nucleic acid encoding the second fusion protein, wherein the cell expresses the first fusion protein and the second fusion protein; or

(b) the cell comprises a first nucleic acid comprising a coding sequence for the 4R tau isoform and a coding sequence for the first reporter protein and a second nucleic acid comprising a coding sequence for the 3R tau isoform and a coding sequence for the second reporter protein, wherein the cell expresses the 4R tau isoform, the 3R tau isoform, the first reporter protein, and the second reporter protein,

optionally wherein the coding sequence for the 4R tau isoform and the coding sequence for the first reporter protein are separated by a coding sequence for a first 2A peptide, and the coding sequence for the 3R tau isoform and the coding sequence for the second reporter protein are separated by a coding sequence for a second 2A peptide,

optionally wherein the first 2A peptide is a first P2A peptide, and the second 2A peptide is a second P2A peptide.

5. The method of claim 4, wherein:

(I) the first nucleic acid and the second nucleic acid are integrated into the genome of the cell; and/or

(II) (a) the cell comprises a viral vector comprising the first nucleic acid and the second nucleic acid,

optionally wherein the viral vector is a lentivirus vector or an adeno-associated virus (AAV) vector; or

(b) the cell comprises a first viral vector comprising the first nucleic acid and a second viral vector comprising the second nucleic acid,

optionally wherein the first viral vector and the second viral vector are lentivirus vectors or adeno-associated virus (AAV) vectors.

6. The method of any one of claims 1-5, wherein the cell is a mammalian cell, optionally wherein the cell is a human cell, the cell is an immortalized cell, and/or the cell is a HEK293 cell.

7. The method of any one of claims 1-6, wherein:

(I) the first reporter protein is a first fluorescent reporter protein, and the second reporter protein is a second fluorescent reporter protein, and the assessing in step (b) comprises immunofluorescence staining or flow cytometry;

(II) the assessing in step (b) comprises assessing tau hyperphosphorylation or tau aggregation;

(III) the tau-targeting reagent is an RNAi agent or an antisense oligonucleotide;

(IV) the tau-targeting reagent is an intrabody; or

(V) the tau-targeting reagent is a nuclease agent, optionally wherein the nuclease agent comprises a Cas protein and a guide RNA designed to target a guide RNA target sequence in a tau coding sequence.

8. The method of any one of claims 1-7, wherein:

(I) the first reporter protein is a first fluorescent reporter protein, and the second reporter protein is a second fluorescent reporter protein,

optionally wherein the first reporter protein is eYFP, and the second reporter protein is mCherry; and/or

(II) (a) the 4R tau isoform is a 2N4R tau isoform, and wherein the 3R tau isoform is a 2N3R tau isoform,

optionally wherein the 4R tau isoform comprises the sequence set forth in SEQ ID NO: 13, and the 3R tau isoform comprises the sequence set forth in SEQ ID NO: 14; or

(b) the 4R tau isoform is a 1N4R tau isoform, and wherein the 3R tau isoform is a 1N3R tau isoform,

optionally wherein the 4R tau isoform comprises the sequence set forth in SEQ ID NO: 23, 27, 31, or 47, and the 3R tau isoform comprises the sequence set forth in SEQ ID NO: 24, 28, 32, or 49.