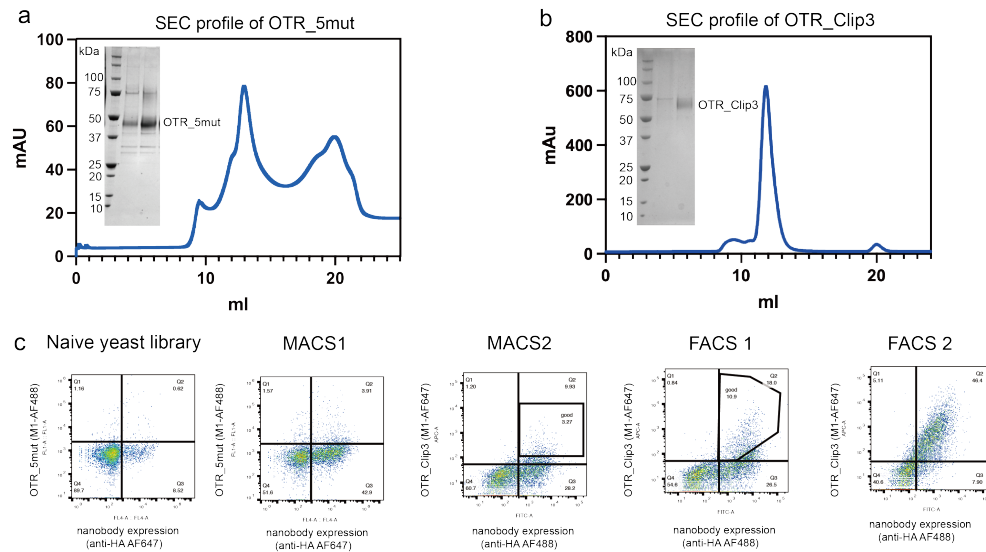
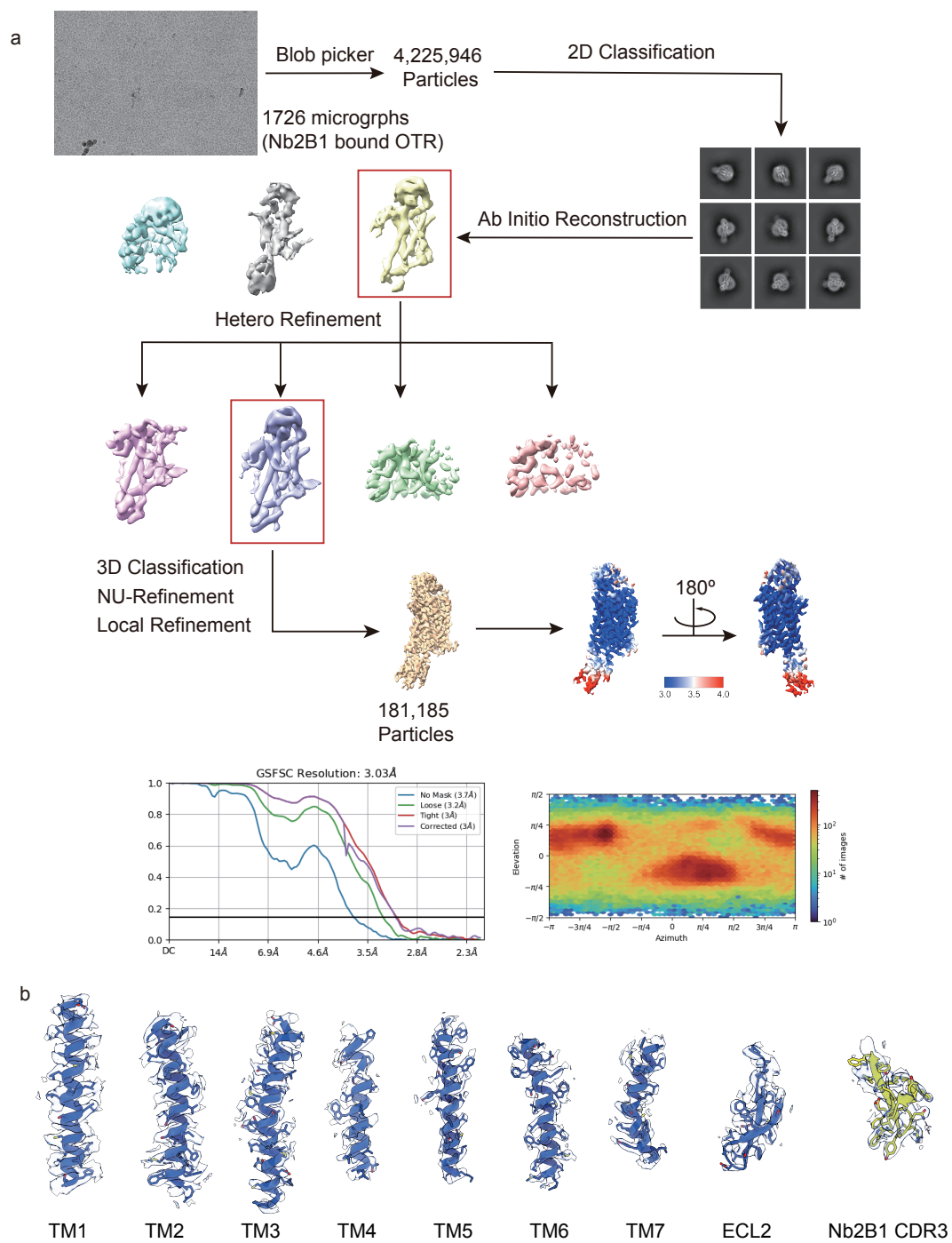


1 Supplementary figure

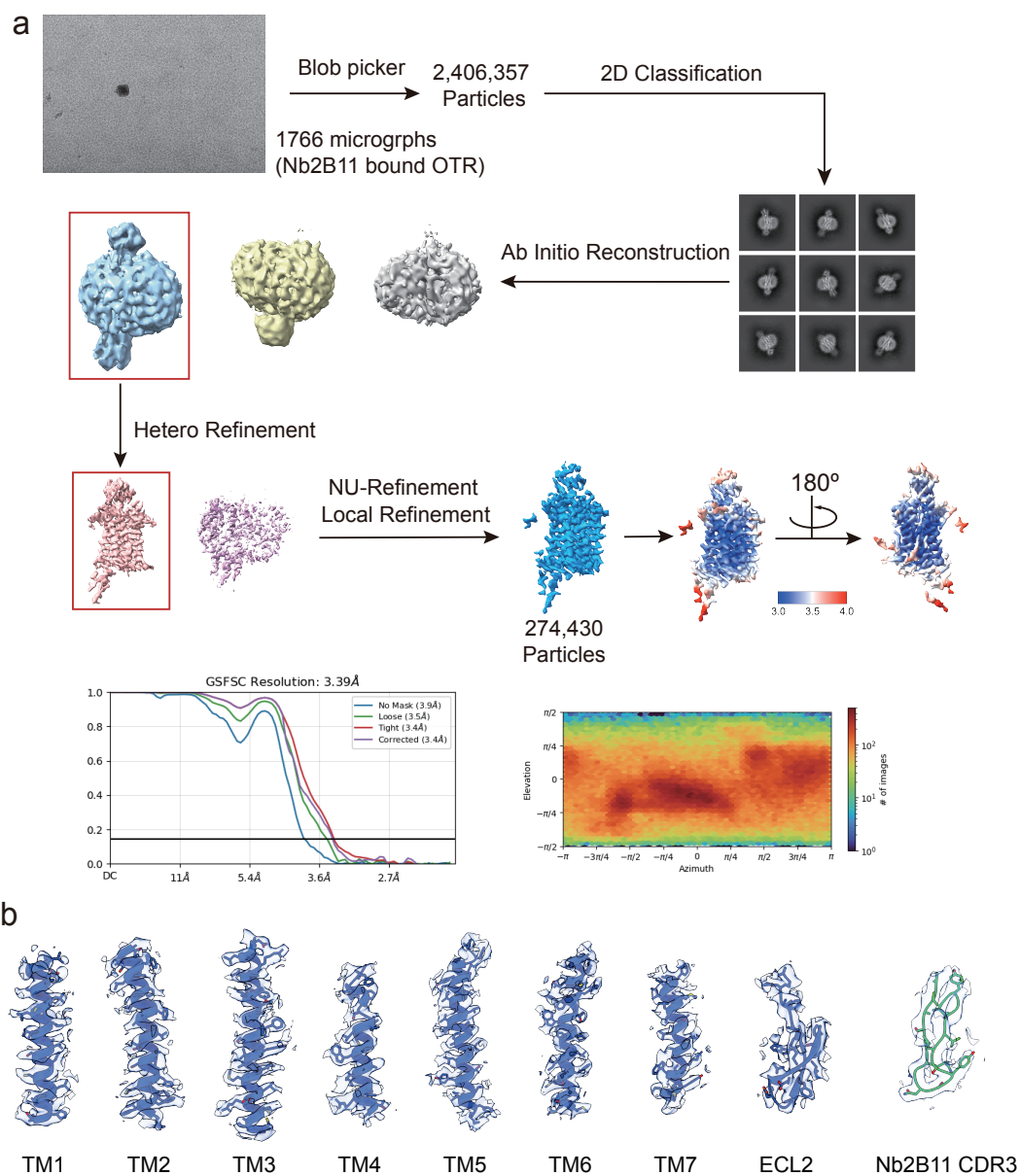


2
3 **Supplementary Fig. 1: Preparation of OTR proteins and Flow cytometry for nanobody**
4 **antagonist selection.**
5 **a-b** SEC profiles and Coomassie blue-stained SDS-PAGE gels of OTR_5mut (a) and
6 OTR_Clip3 (b). **c** Binding of yeast display library to FLAG-OTR after each selection round,
7 and FACS plot of the population was collected containing the high affinity OTR binders.



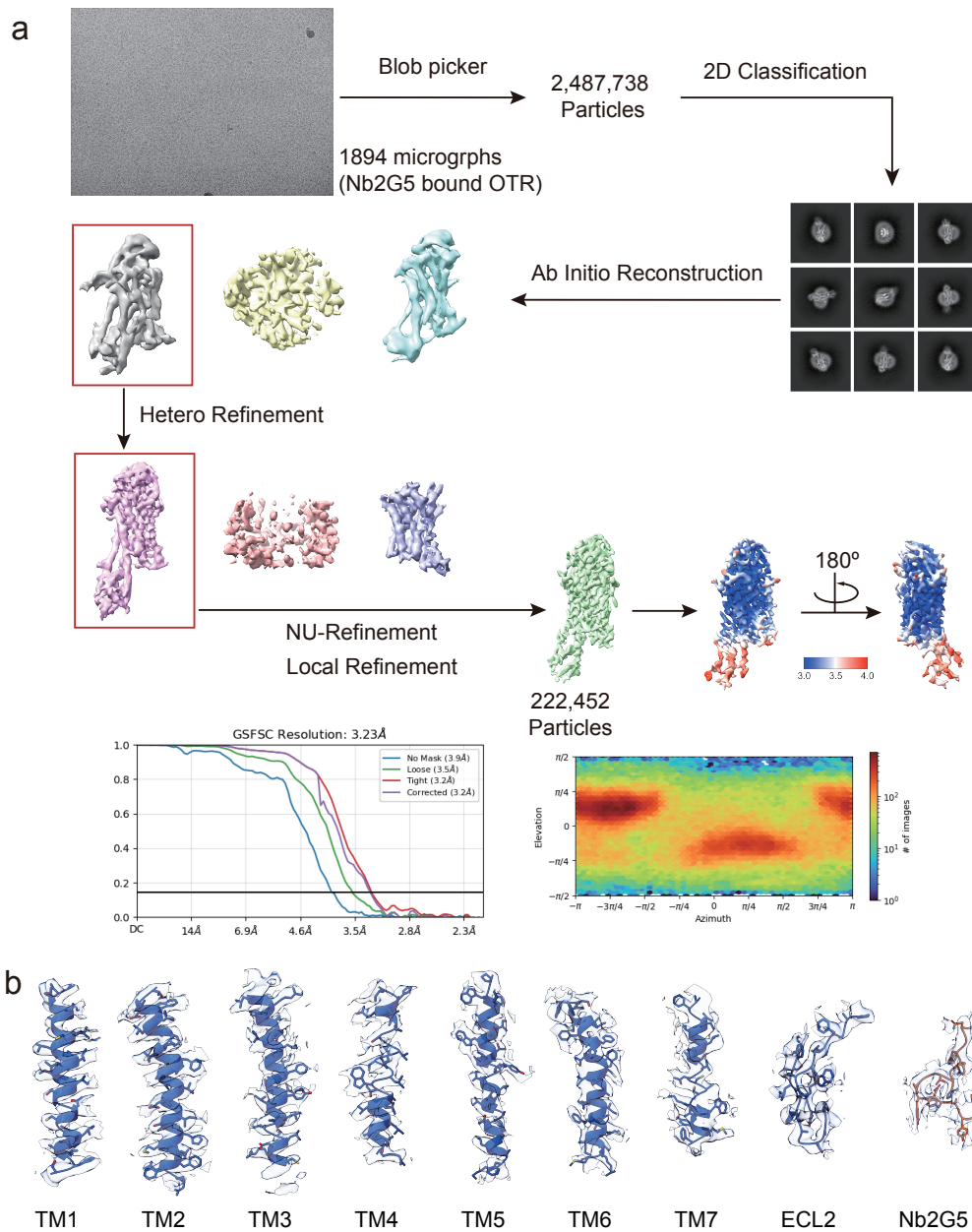
Supplementary Fig.2: Cryo-EM data processing of Nb2B1 bound OTR_Clip3 complex.

a Cryo-EM data processing workflow for Nb2B1 bound OTR_Clip3 complex. **b** Cryo-EM density map and model of Nb2B1 bound OTR_Clip3 are shown for all transmembrane helices, ECL2 of OTR, CDR3 of Nb2B1.



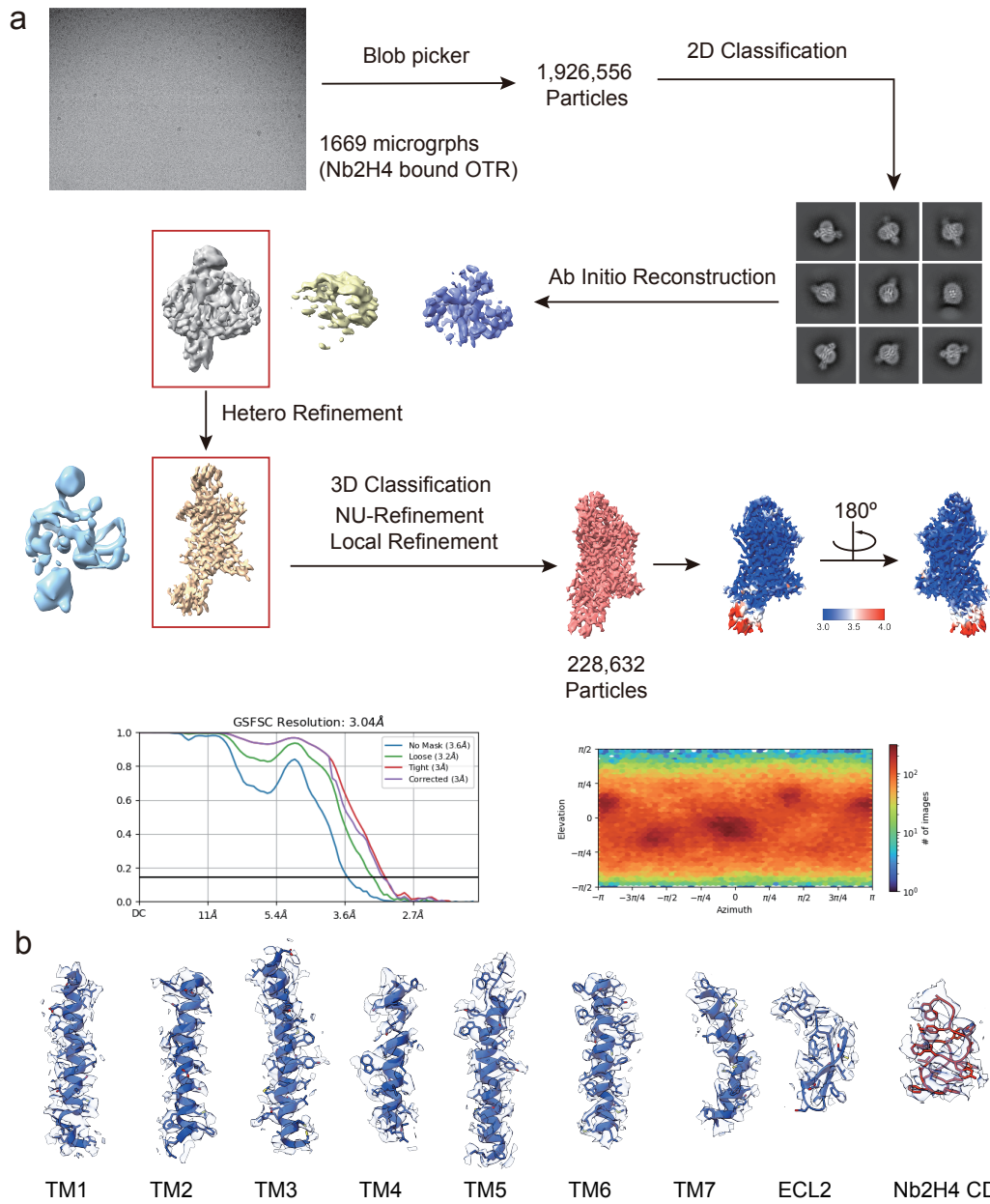
Supplementary Fig. 3: Cryo-EM data processing of Nb2B11 bound OTR_Clip3 complex.

a Cryo-EM data processing workflow for Nb2B11 bound OTR_Clip3 complex. **b** Cryo-EM density map and model of Nb2B11 bound OTR_Clip3 are shown for all transmembrane helices, ECL2 of OTR, CDR3 of Nb2B11.



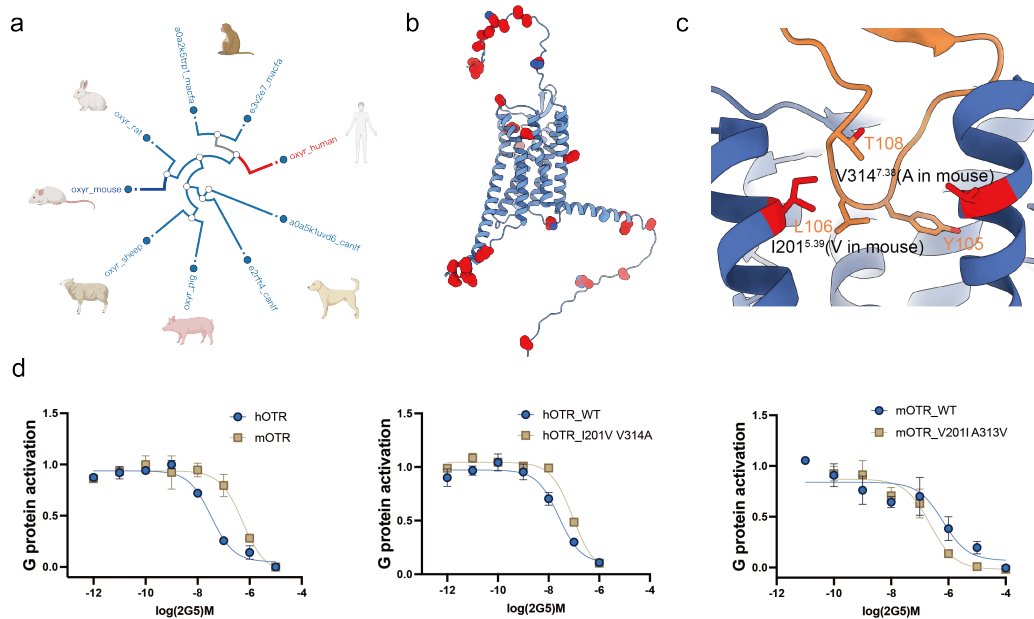
Supplementary Fig. 4: Cryo-EM data processing of Nb2G5 bound OTR_Clip3 complex.

a Cryo-EM data processing workflow for Nb2G5 bound OTR_Clip3 complex. **b** Cryo-EM density map and model of Nb2G5 bound OTR_Clip3 are shown for all transmembrane helices, ECL2 of OTR, CDR3 of Nb2G5.

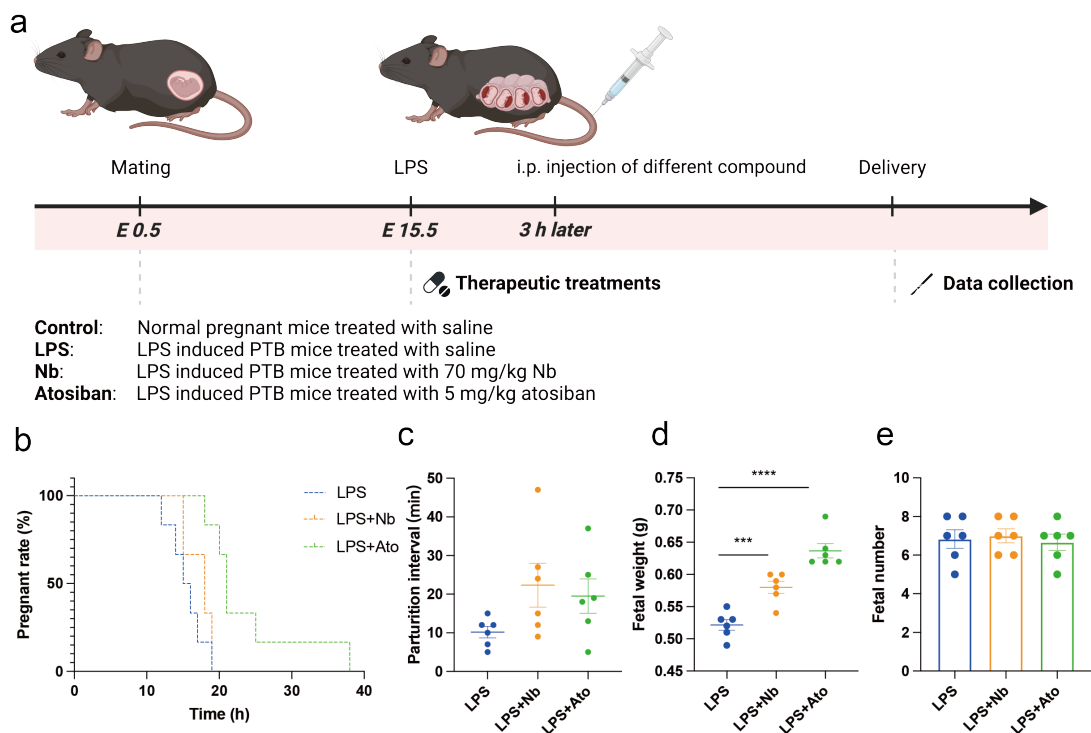


Supplementary Fig. 5: Cryo-EM data processing of Nb2H4 bound OTR_Clip3 complex.

a Cryo-EM data processing workflow for Nb2H4 bound OTR_Clip3 complex. **b** Cryo-EM density map and model of Nb2H4 bound OTR_Clip3 are shown for all transmembrane helices, ECL2 of OTR, CDR3 of Nb2H4.



Supplementary Fig. 6: Species selectivity of Nb2G5. **a** Phylogenetic tree of OTR sequences across various animal species. **b** Global polymorphic residue sites between human OTR and mouse OTR. **c** Polymorphic residue sites in the orthosteric pocket between human OTR and mouse OTR. **d** Glo-Sensor cAMP assay assessing Nb2G5 activity on hOTR, mOTR, and their respective mutants at orthosteric pocket polymorphic residues between human and mouse OTR. Values represent the means $\pm$ SEM of 3 independent samples.



38 **Supplementary Fig. 7: Nb2G5 exhibits moderate efficacy in mouse PTB model. a**
39 Establishment of an LPS-induced mouse PTB model. **b** Gestational delay time in preterm mice
40 following administration of Nb2G5 and atosiban. **c** Delivery interval time in preterm mice
41 treated with Nb2G5 and atosiban. **d-e** Pregnancy-related outcome measures of fetal weight (d)
42 and fetal number (e) in preterm mice treated with Nb2G5 and atosiban.
43

Construct	Sequence	Notes
OTR_WT	MEGALAANWSAEAAANASAAPPGAEGNRTAGPPRRNEA LARVEVAVLCLILLLALSGNACVLLALRTTRQKHSRLFFF MKHL SIADLVVAVFQVLPQLLWDITFRFYGPDLLCRLVK YLQVVGMFASTYLLLLMSLDRCLAICQPLRSLRRRTDRL AVLATWLGCLVASAPQVHIFSLREVADGVFDCWAVFIQP WGP KAYITWITLAVYIVPVIVLAACYGLISFKIWQNLRL KTA AAAAAEAEPEGAAAGDGGRVALARVSSVKLISKAKI RTVKMTFIIVLAFIVCWTPFFVQMWSVWDANAPKEAS AFIIVMLLASLNSCCNPWIYMLFTGHLFHELVQRFLCCS ASYLKGRRLGETSASKKSNSSSFVLSHRSSSQRSCSQPST A	
OTR_5mut	MEGALAANWSAEAAANASAAPPGAEGNRTAGPPRRNEA LARVEVAVLCLILLLALSGNACVLLALHTTRQKHSRLFFF FMKHL SIADLVVAVFQVLPQLLWDITFRFYGPDLLCRLV KYLQVVGMFASTYLLLLMSLDRCLAICQPLRSLRRRTAR LAVLATWLGCLVASAPQVHIFSLREVADGVFDCWAVFIQ PWGP KAYITWITLAVYIVPVIVLAACYGLIAFKIWQNLRL LKT AAAAAEAEPEGAAAGDGGRVALARVSSVKLISKAK IRTVKMTFIIVLAFIVCWTPFFVQMWSVWDANAPKEAS AFIIVMLLASLNSCCKPWIYMLFMGHLFHELVQRFLCCS ASYLKGRRLGETSASKKSNSSSFVLSHRSSSQRSCSQPST A	Five mutations (red)
OTR_Clip3	MEGALAANWSAEAAANASAAPPGAEGNRTAGPPRRNEA LARVEVAVLCLILLLALSGNACVLLALHTTRQKHSRLFFF FMKHL SIADLVVAVFQVLPQLLWDITFRFYGPDLLCRLV KYLQVVGMFASTYLLLLMSLDRCLAICQPLRSLRRRTAR LAVLATWLGCLVASAPQVHIFSLREVADGVFDCWAVFIQ PWGP KAYITWITLAVYIVPVIVLAACYGLIAFKIWQNAL GKELAAAFRKEMSLEEYKELLNALAERVGASEEAIEKA KKLLETYGAKKTPEEILIGRISAACYILADGAKRLGEPVA ILTLSFKNNLSPEDLELLKKAGEEDELAGEAYKGLEEGS KAGEATMRTVKMTFIIVLAFIVCWTPFFVQMWSVWDA NAPKEASAFIIVMLLASLNSCCKPWIYMLFMGHLFHELV QRFLCCSASYLKGRRLGETSASKKSNSSSFVLSHRSSSQ RSCSQPSTA	Five mutations (red), Clip3 (green)
Nb2B1	QVQLQESGGGLVQAGGSLRLSCAASGSGISDDAVMGWY RQAPGKERELVATISYGAITNYADSVKGRFTISRDNAKN TVY LQMNSLKPEDTAVYYCAASAAYRLETQYWRFLF YYWGQGTQVTVSS	
Nb2B11	QVQLQESGGGLVQAGGSLRLSCAASGSGISGITDMGWYR QAPGKEREFVASITYGGNTNYADSVKGRFTISRDNAKNT	

	VYLQMNSLKPEDTAVYYCAVASSRGNSYSLLGGYILTY WGQGTQVTVSS	
Nb2G5	QVQLQESGGGLVQAGGSLRLSCAASGSISPGYWMGWY RQAPGKEREFVASIDLGGTTYADSVKGRFTISRDNANKN TVYLQMNSLKPEDTAVYYCAARIQYAYDYLGTHGYWG QGTQVTVSS	
Nb2H4	QVQLQESGGGLVQAGGSLRLSCAASGNIFIKYAMGWYR QAPGKERELVASINDGTTTNYADSVKGRFTISRDNANKNT VYLQMNSLKPEDTAVYYCAASVIYYLRDFFATWYIHYY WGQGTQVTVSS	

45

46

47 **Supplementary Table 2**

	OTR-Nb2G5 (EMDB- 64382) (PDB 9UOT)	OTR-Nb2B1 (EMDB- 64495) (PDB 9UTO)	OTR-Nb2B11 (EMDB- 64496) (PDB 9UTP)	OTR-Nb2H4 (EMDB- 64535) (PDB 9UVQ)
Data collection and processing				
Magnification	39000	39000	39000	39000
Voltage (kV)	300	300	300	300
Electron exposure (e-/Å ²)	50	50	50	50
Defocus range (μm)	1.1-1.8	1.1-1.8	1.1-1.8	1.1-1.8
Pixel size (Å)	1.08	1.08	1.08	1.08
Symmetry imposed	C1	C1	C1	C1
Initial particle images (no.)	2,487,738	4,225,946	2,406,357	1,926,556
Final particle images (no.)	222,454	181,185	274,430	228,632
Map resolution (Å)	3.3	3.0	3.4	3.0
FSC threshold	0.143	0.143	0.143	0.143
Refinement				
Initial model used	AlphaFold2 structures			
Model resolution (Å)	3.3	3.0	3.4	3.0
FSC threshold	0.143	0.143	0.143	0.143
Map sharpening <i>B</i> factor (Å ²)	-158.7	-89.2	-155	-104.9
Model composition				
Non-hydrogen atoms	2524	2671	1939	1616
Protein residues	338	341	266	248
Ligands	0	0	0	0
<i>B</i> factors (Å ²)				
Protein	73.17	67.61	101.55	42.39
R.m.s. deviations				
Bond lengths (Å)	0.004	0.004	0.004	0.002
Bond angles (°)	1.06	1.0	1.034	0.568
Validation				
MolProbity score	2.05	2.47	1.62	1.63
Clashscore	7.86	12.58	5.22	5.61
Poor rotamers (%)	0	0	0	0
Ramachandran plot				
Favored (%)	95.34	95.38	95.00	95.30
Allowed (%)	4.35	4.62	5.00	4.70
Disallowed (%)	0	0	0	0

48 **Supplementary Table 2: Data collection and refinement statistics.** The data collection and
49 refinement statistics of OTR-Nb2G5, OTR-Nb2B1, OTR-Nb2B11 and OTR-Nb2H4 structures.