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**Supplemental Information**

**EMC Is Required to Initiate Accurate**

**Membrane Protein Topogenesis**

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| name         | sequence   | hydro. (TM tend.) | charge $\Delta(C-N)$ |
|--------------|--|-------------------|----------------------|
| LepB         | <u>ANMFALILVIATLVTGILWSVDKFFFPAPKRRE</u> RQAAAQ            | 21.9              | +3                   |
| ASGR1        | PPPPQPMLQRLSSGPR <u>LLLLSLGLSLLLLLVVSVIGSQNSQLQEELR</u>    | 23.5              | -3                   |
| V1BR         | <u>ATTPWMGRDEELAKVEIGVLATVVLVATGGNLAVLLTLGQLGRKRSRM</u>    | 17.1              | +5                   |
| VN1R5        | <u>LKLVIENMAEIMLFSLDLLLFSTDILSFNFPSKMIKLPG</u>             | 13.7              | 0                    |
| MTR1L        | <u>GSIGSKLPQPEYPPALIIFMFSAMVITIVVDLIGNSMVILAVTKNKKL</u>    | 17.7              | +3                   |
| OR3A2        | <u>AEFILLGLVQTEEMQPVVVLLLLFAYLVTTGGNLSILAAVLVEPKLHA</u>    | 21.2              | +4                   |
| OR2L5        | <u>ILLGLFPFSKIGLFLFILFVLIFFLMALIGNLSMILLIFLDTHLHTPMY</u>   | 34.6              | -2                   |
| ACM1         | <u>PQITVLAPGKGPWQVAFIGITTGLLSLATVTGNLLVLI SFKVNTTELKT</u>  | 18.0              | 0                    |
| O52N2        | <u>GFFILNGVPGLEATHIWIWISLPFSFMYIIAVVGN SGLISLISHEEALHR</u> | 17.6              | 0                    |
| $\beta_1$ AR | <u>RQVSAELLSQQWEAGMSLLMALVVLLIVAGNVLVIAAIGSTQRLQTLT</u>    | 21.1              | +1                   |
| ACTHR        | <u>QNTARQNSDSPRVVMPEEIFFTISIVGVLENLIVLLAVFKNKNLQAPM</u>    | 17.3              | +1                   |
| ADRB1        | <u>PASESPEPLSQQWNTAGMGLLMALIVLLIVAGNVLVIVAIAKTPRLQTL</u>   | 28.0              | 0                    |
| CNR2         | <u>SNPMKDYMILSGPQKTAVAVLCTLLGLLSALENVAVLYLILSSHQLRR</u>    | 20.0              | +1                   |
| O56A3        | <u>NSFVRSPSWQHWSLPLSLLFLLAVGANTTLLMTIWL EASLHQPLYL</u>     | 17.2              | -1                   |
| NK1R         | <u>TSEPNQFVQPAWQMVWAAAYTVIVVTSVVG NVVVMWII LAHKRMRTV</u>   | 20.5              | +4                   |
| CCKAR        | <u>SLDQPRPSKEWQPAMQILLYSLIFLLSVLGNTLVITVLI RNKRMRTVT</u>   | 25.8              | +4                   |
| TAAR5        | <u>VQGSSPRTVHTLGIQLVIYLASAAGMLIIVLGNV FVAFVSYFKALHT</u>    | 21.7              | 0                    |
| ADA1A        | <u>SQSTQPPAPVQMSKAILLGVILGGLILFGVLGNILVILSVASHRHLHS</u>    | 27.2              | 0                    |
| AGTR2        | <u>STLQSSQKPSDKHMDAIPILYIIFVIGFLVNI VVVTLFSSQKGPKKV</u>    | 27.3              | +3                   |

**Table S1 - Sequences of TMD regions analyzed in this study (related to Fig. 4).** The GPCR-TMD1 cassette depicted in Fig. 3A was populated with the first TMD and adjacent flanking regions (~10 residues on either side) of the indicated GPCRs. The TMD regions of the model proteins bacterial leader peptidase (LepB) and ASGR1 are shown for comparison. The TMD region (as annotated by Uniprot) is underlined, and flanking basic and acidic residues are shown in red and blue, respectively. The calculated TM tendency score and charge difference are indicated for each TMD region. Note that the Uniprot annotated TMD may not be precise in defining the boundaries, so parameters such as TMD length and hydrophobicity should be interpreted with this caveat in mind.