**Table S1:** Comparison of ADAM and BACE1 cleavage sites in described substrates. m: murine; h: human, aa: amino acids.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ADAM cleavage sites** | | | | | | | | | | | | | | |
| **Substrate** | **Species** | **Cons. (m/h)** | **Distance to**  **TMD (aa)** | | **P3** | **P2** | | **P1** | **-Cleavage sites-** | **P1‘** | | **P2‘** | **P3‘** | |
| EpCAM | m | no | 35 | | H | S | | S | K | | S | M | |
| App | h | yes | 12 | | H | Q | | K | L | | V | F | |
| AREG | h | no | 14 | | S | E | | K | S | | M | K | |
| AREG | m | no | 11 | | S | M | | K | T | | H | S | |
| TNF-α | h | no | 20 | | A | Q | | A | V | | R | S | |
| TNF-α | m | no | 23 | | T | L | | T | L | | R | S | |
| **BACE1 cleavage sites** | | | | | | | | | | | | | | |
| **Substrate** | **Species** | **Cons. (m/h)** | **Distance to**  **TMD (aa)** | **P3** | | **P2** | **P1** | | **-Cleavage sites-** | **P1‘** | **P2‘** | | **P3‘** |
| EpCAM | m | yes | 29 | L | | I | Y | | Y | V | | D |
| App | h | yes | 20 | V | | K | M | | D | A | | E |
| APLP1 | h | no | 29 | K | | V | N | | A | S | | V |
| APLP2 | h | yes | 28 | K | | E | M | | I | F | | N |
| CHL1 | h | yes | 20 | I | | F | Q | | D | V | | I |
| IL1R2 | h | no | 9 | L | | S | F | | Q | T | | L |
| L1 | h | no | 35 | T | | D | Y | | E | I | | H |
| NRG1 | h | yes | 10 | I | | E | F | | M | E | | A |
| NRG3 | h | yes | 10 | I | | E | F | | M | E | | S |
| PSLG-1 | h | no | 17 | S | | N | L | | S | V | | N |
| SCN1B | m | yes | 16 | I | | H | L | | E | V | | V |
| SCN2B | h | no | 15 | I | | H | L | | Q | V | | L |
| SCN2B | h | no | 12 | Q | | V | L | | M | E | | E |
| SCN2B | m | no | 14 | I | | Y | L | | Q | V | | L |
| SCN3B | m | yes | 32 | F | | E | F | | E | A | | H |
| SCN3B | m | yes | 6 | E | | D | F | | T | S | | V |
| SCN4B | m | yes | 13 | I | | F | L | | Q | V | | V |
| ST6GAL1 | m | no | 11 | L | | T | I | | Q | A | | K |
| SELPLG | h | no | 17 | S | | N | L | | S | V | | N |