

## Supporting Information for

Antibody-guided proteases enable selective and catalytic degradation of challenging therapeutic targets

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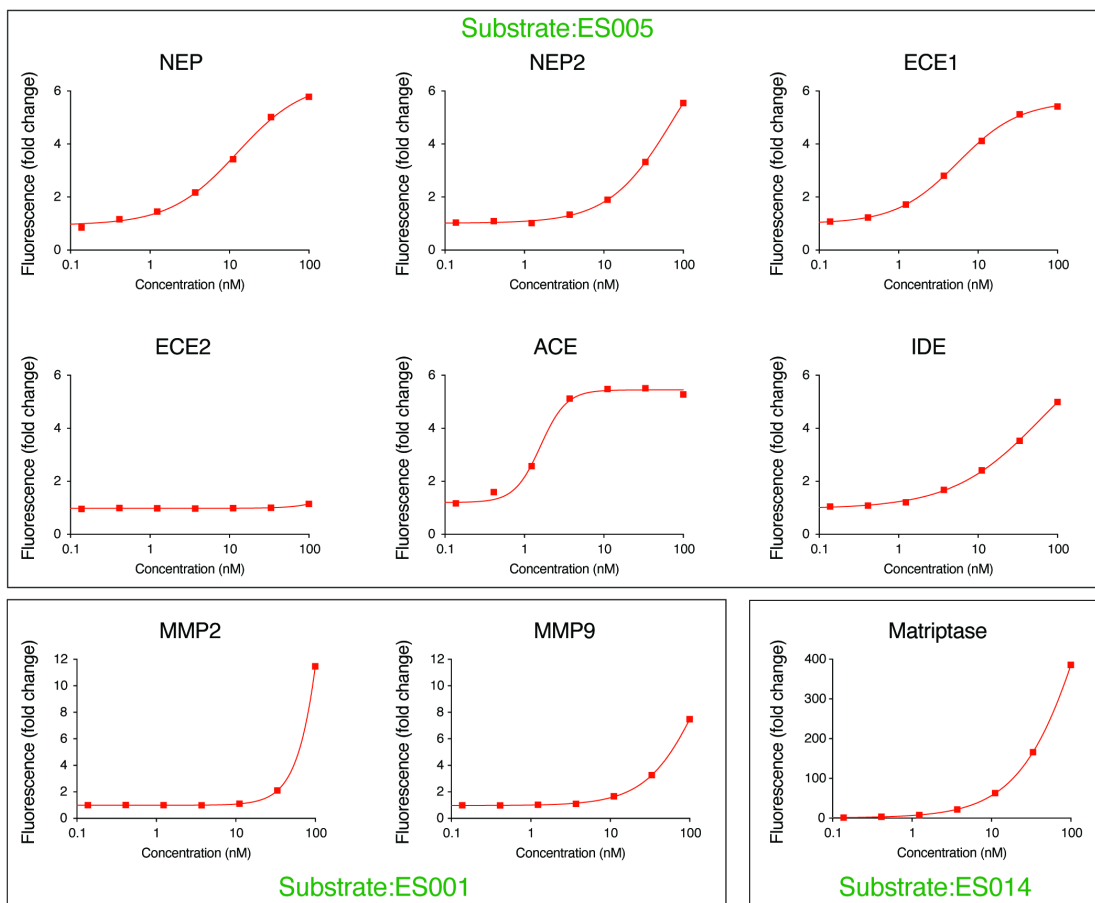
<sup>1</sup>These authors contributed equally to this work

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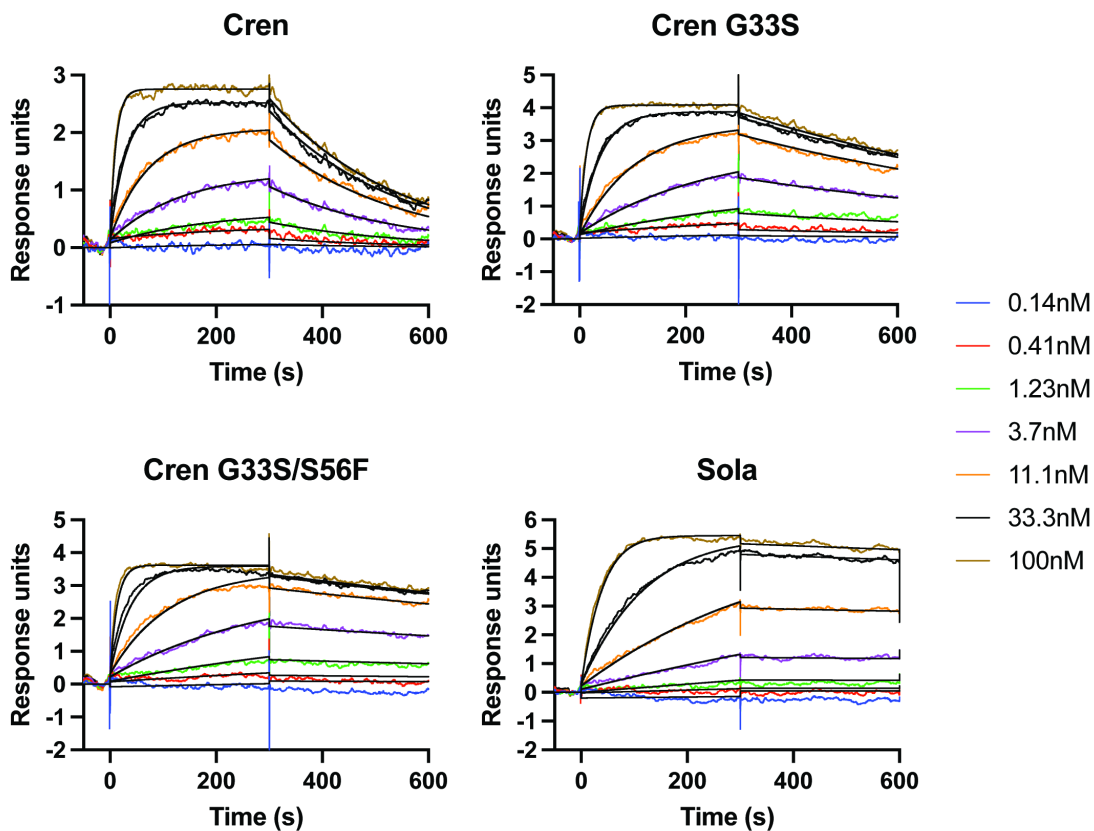
This supporting information file contains:

Figures S1 – S10

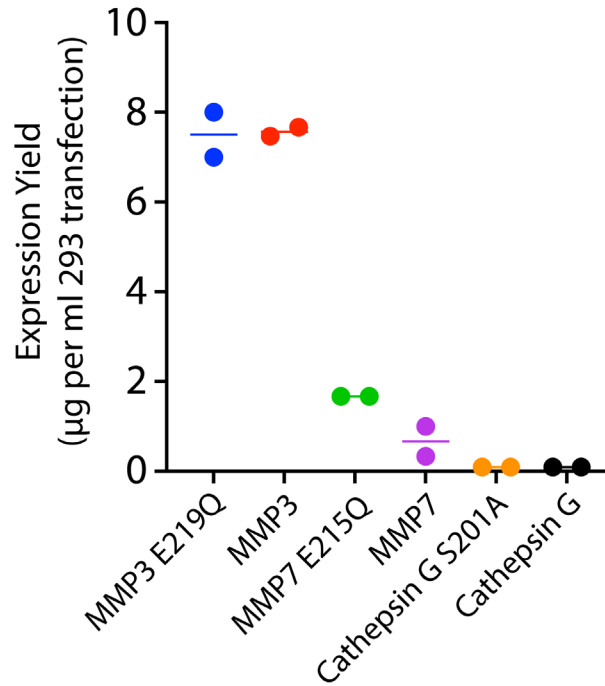
Supporting Text S1



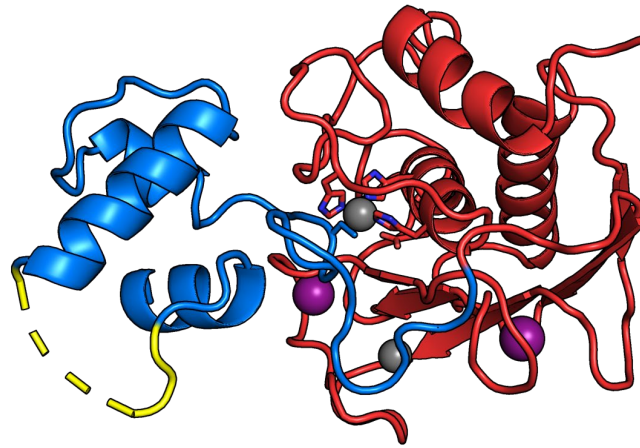
**Figure S1.** Activity of an A $\beta$  protease panel on control substrates. The activity of 9 proteases previously shown to cleave A $\beta$  was tested on one of three fluorescence resonance energy transfer (FRET) control substrates. Cleavage of the substrate results in increased fluorescence and is reported as fold change over no protease. The catalog name of each substrate is indicated in green within each box.



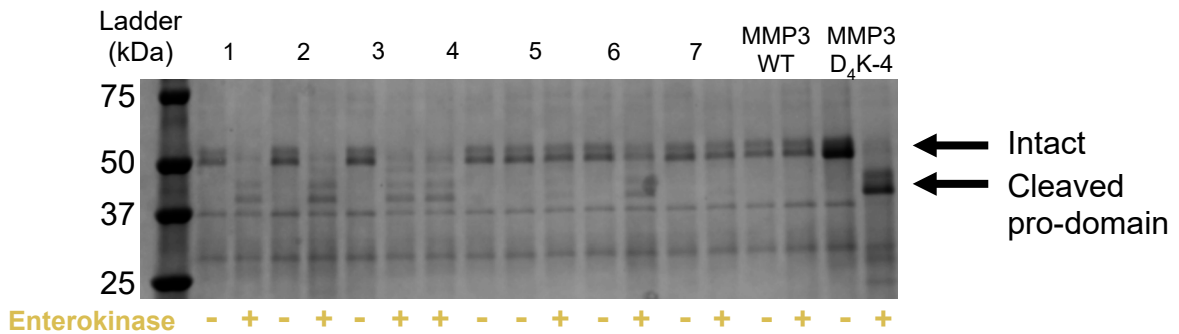
**Figure S2.** SPR kinetic analysis for the binding of crenezumab, crenezumab point mutants, and solanezumab to Aβ(1-28) (see Methods). A summary of the kinetic parameters derived from the sensogram fitting is shown in Fig. 4A. The chi-squared ( $\chi^2$ ) values for all fits shown here are less than 5% of the  $R_{\max}$  values, which confirms the high quality of the fits and strong confidence in the kinetic parameters shown in Fig. 4A.



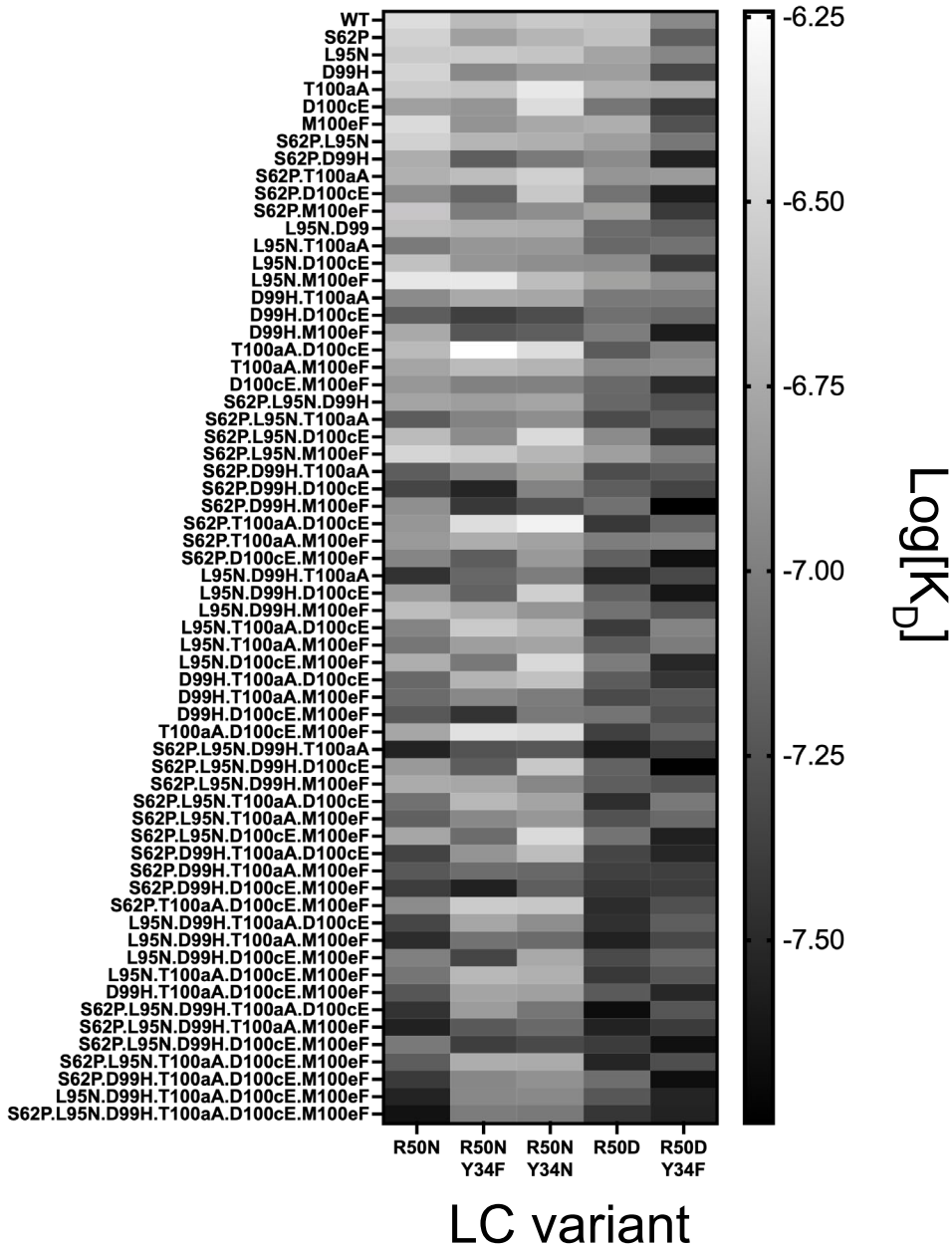
**Figure S3.** Expression of three proteases previously shown to cleave within the IgG hinge: matrix metalloproteinase 3 (MMP3), matrix metalloproteinase 7 (MMP7), and cathepsin G. Expression yield per ml HEK293 transfection shows little to no expression yield for MMP7 or cathepsin G. MMP3 E219Q, MMP7 E215Q, and cathepsin G S201A are inactive forms of the proteases with point mutations to residues essential for catalytic activity. These mutants will not be impacted by autocatalytic activity. Improved expression for MMP7 E215Q compared to MMP7 suggests instability due to autodegradation, which could in part account for the low expression yields.



1 - LENYYDL **DDDDK**QFVRRKDSGPVVKK  
 2 - LENYYDLK **DDDDK**FVRRKDSGPVVKK  
 3 - LENYYDLKKD **DDDDK**RRKDSGPVVKK  
 4 - LENYYDLKKDV **DDDDK**RKDSGPVVKK  
 5 - LENYYDLKKDVK **DDDDK**KDSGPVVKK  
 6 - LENYYDLKKDVKQ **DDDDK**KDSGPVVKK  
 7 - LENYYDLKKDVKQF **DDDDK**SGPVVKK  
 MMP3 WT - LENYYDLKKDVKQFVRRKDSGPVVKK  
 MMP3-D<sub>4</sub>K-4 - LENYYDLKK **DDDDK**VRRKDSGPVVKK

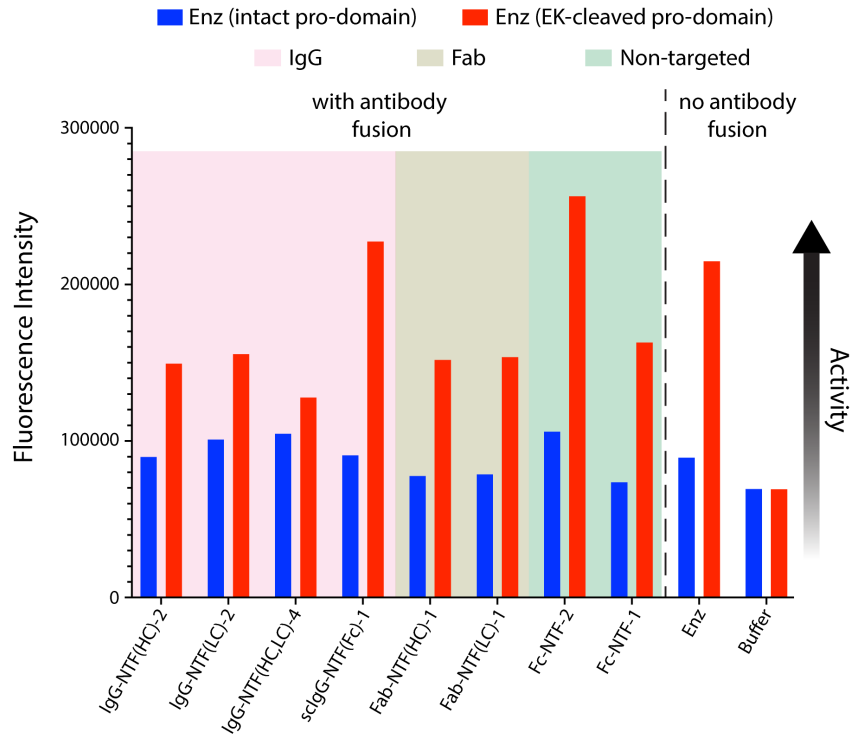


**Figure S4.** Insertion of an enterokinase cleavage sequence within the pro-domain of MMP3. After testing protease site substitutions at four locations within the pro-domain of MMP3, the most promising variant had an enterokinase site substitution at position 4 (Figs. 5B and 5C). We then sought to optimize the MMP3-D<sub>4</sub>K-4 variant by “walking” the enterokinase cleavage site around position 4 one residue at a time. The coverage of the enterokinase cleavage sites for the eight MMP3 variants is shown with a structural (top) and sequence (middle) representation in yellow. SDS-PAGE of the MMP3 variants with and without exposure to enterokinase (bottom) shows no improvements in stability or activation efficiency from variants 1-7 over the original MMP3-D<sub>4</sub>K-4.

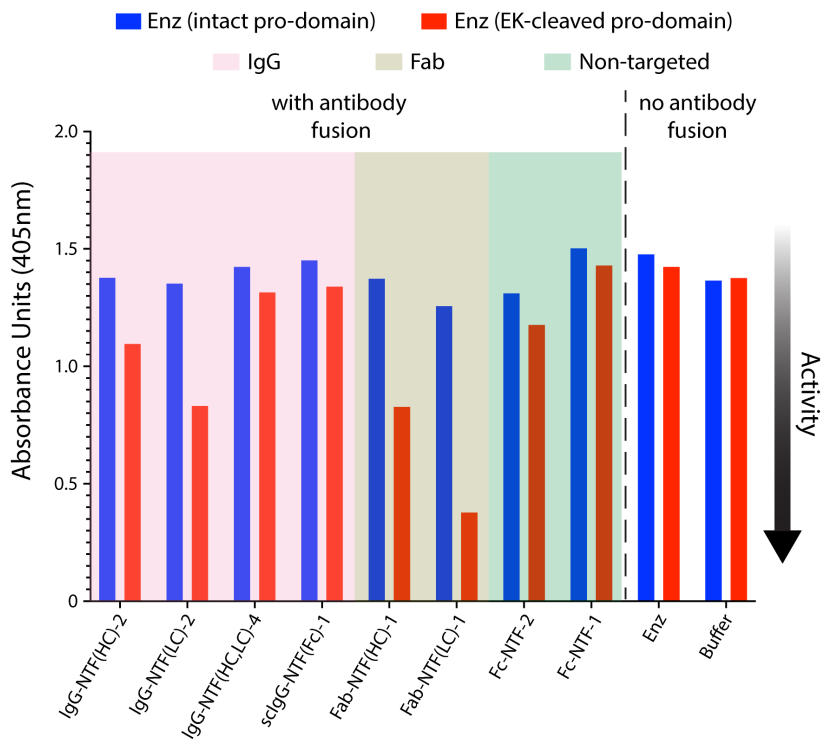


**Figure S5.** Heat map summarizing affinity of RF61 variants to human IgG1 Fc from round 3 of affinity maturation. Each row and column are different heavy and light chain variants, respectively. Residues are numbered according to Kabat convention. Affinity is represented as the log of the  $K_D$  value obtained via SPR.

# Fluorogenic peptide substrate

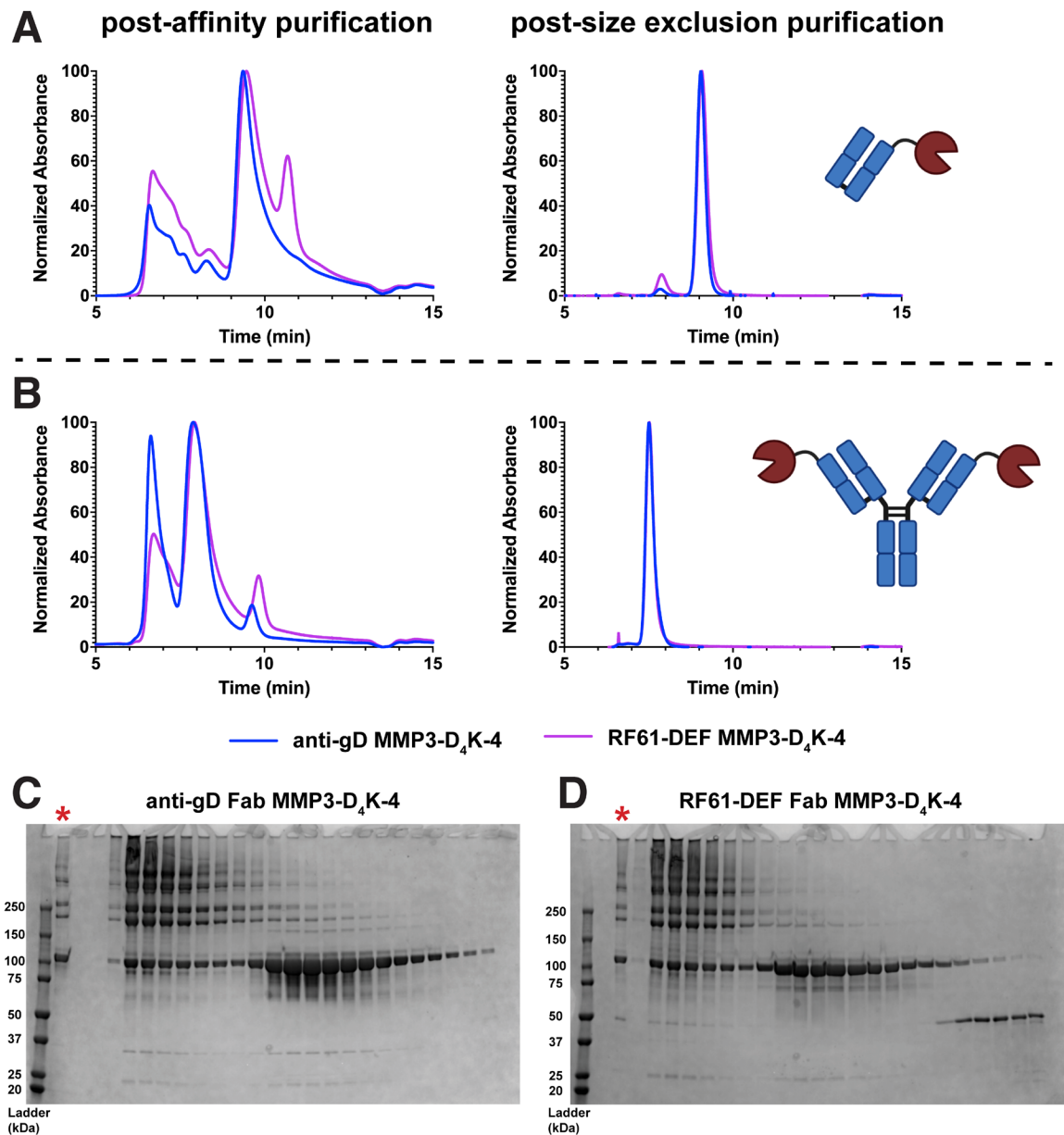


# IgG substrate



**Figure S6.** Antibody-MMP3-D<sub>4</sub>K-4 fusion format expression and activity screen. After affinity column purification, eluate from each sample was incubated with enterokinase at room temperature overnight, then MMP3-D<sub>4</sub>K-4 activity was tested using a fluorogenic peptide substrate (top) and IgG (bottom). Blue and red bars represent samples without and with incubation with enterokinase to cleave the pro-domain, respectively. Background color shading differentiates between IgG and Fab formats, as well as non-targeted formats. Formats with and without antibody domain fusions are separated by a dashed black line. Activity against the peptide substrate (top) demonstrates presence of active MMP3-D<sub>4</sub>K-4. All samples containing MMP3 showed some level of enzyme activity. Activity against IgG (bottom) as measured by ELISA denotes antibody-guided proteolytic activity. Little to no activity was observed for non-targeted formats, while targeted MMP3-D<sub>4</sub>K-4 formats cleaved IgG. The varying extents of activity can be explained by different sample concentrations and purity, as the samples for this initial screening attempt were not normalized or further purified with size exclusion chromatography.

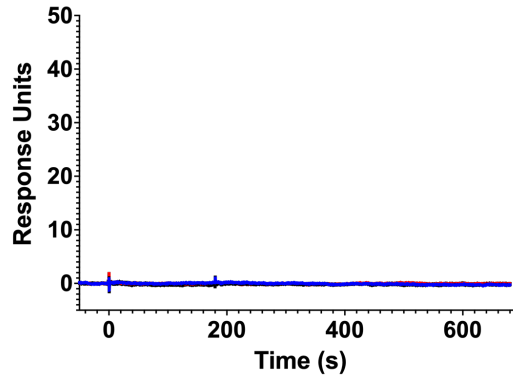




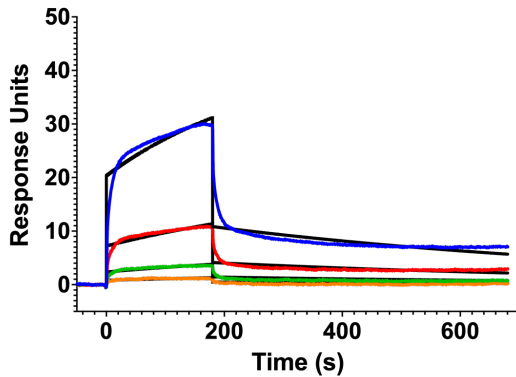
**Figure S7.** Purification summary for both Fab-MMP3-D<sub>4</sub>K-4 (A) and IgG-MMP3-D<sub>4</sub>K-4 (B) fusion proteins. Representative samples shown include the anti-gD fusions (blue) and the RF61-DEF fusions (magenta). The transfection supernatants were first purified using affinity chromatography with GammaBind Plus resin (Fab fusions) or MabSelect SuRe resin (IgG fusions). Analytical SEC chromatograms after the affinity purification step are shown on the left. High molecular weight aggregates and low molecular weight fragments are observed in most samples. Isolation of the desired fusion proteins was performed using size exclusion chromatography. Analytical SEC chromatograms of the purified

species are shown on the right. The Fab fusions were purified to >92% monomer (a small percentage of non-covalent dimer was present in the final sample), and the IgG fusions were purified to >98% monomer. C) and D) Non-reduced SDS-PAGE analysis of the fractions from the SEC purification shown on the left of (A) for the anti-gD and RF61-DEF Fab fusions, respectively. The red asterisks highlight the lanes containing the pooled affinity-purified material. The mass of the desired Fab-protease fusion protein is approximately 100 kDa and corresponds to the SEC elution peak between 9 and 10 minutes. The high molecular weight peaks from the SEC chromatogram correspond to higher order aggregates of the fusion protein. For the RF61-DEF fusion protein specifically, there is a lower molecular weight peak that corresponds to Fab alone. Although the MMP3-D<sub>4</sub>K-4 is a similar mass as the non-reduced Fab, the affinity purification step would remove any cleaved protease, leaving only the Fab at 50 kDa. Similar patterns are observed (higher order aggregates, lower molecular weight truncations, and/or mispaired knob/hole Fc homodimers) for the anti-A $\beta$  NEP fusions (Fig. 2C) and the IgG-MMP3-D<sub>4</sub>K-4 fusions (Fig. S7B).

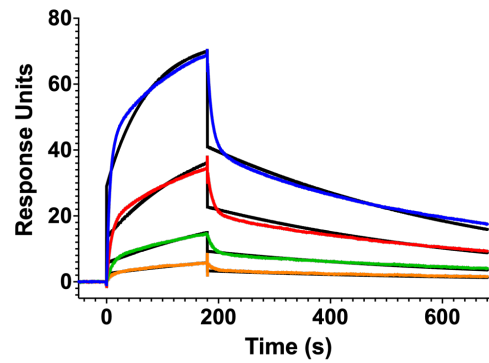
### RF61 WT Fab MMP3-D<sub>4</sub>K-4



### RF61-D Fab MMP3-D<sub>4</sub>K-4



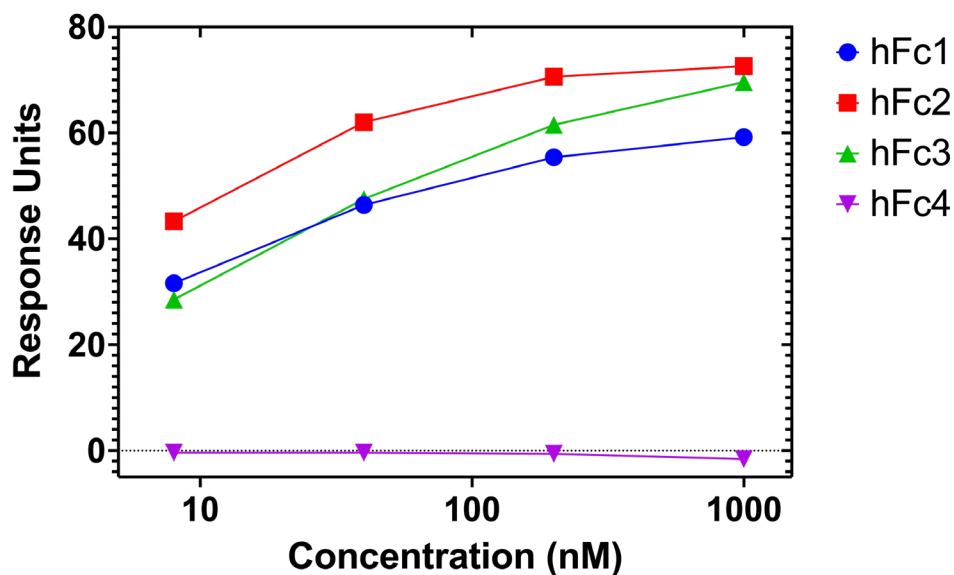
### RF61-DEF Fab MMP3-D<sub>4</sub>K-4



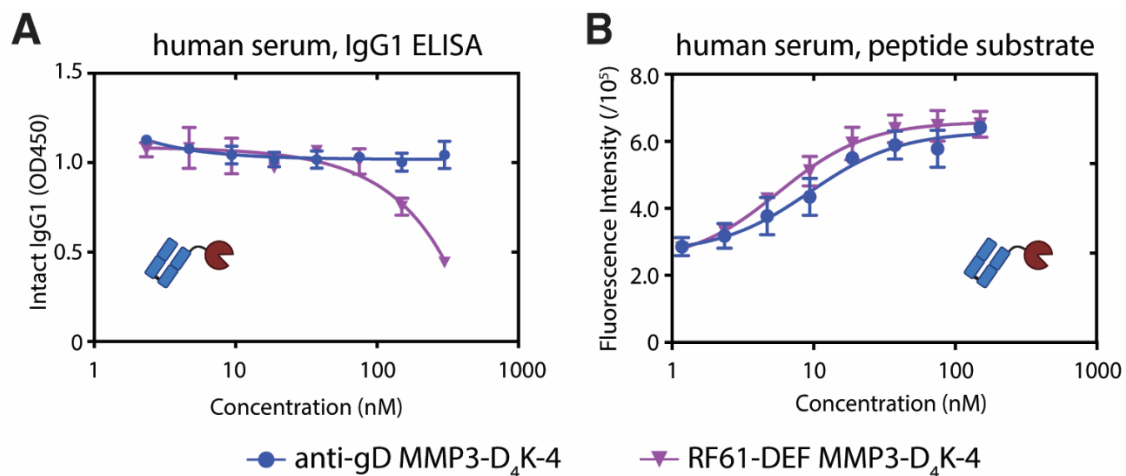
	$R_{max}$ (RU)	$k_a$ (1/Ms/10000)	$k_d$ (1000/s)	$K_D$ (nM)
<b>RF61 WT Fab MMP3-D<sub>4</sub>K-4</b>	-	-	-	-
<b>RF61-D Fab MMP3-D<sub>4</sub>K-4</b>	33.5	1.26	1.31	104
<b>RF61-DEF Fab MMP3-D<sub>4</sub>K-4</b>	52.2	5.83	1.90	32.5

**Figure S8.** SPR kinetic analysis for the binding of RF61 Fab-MMP3-D<sub>4</sub>K-4 fusion proteins to the Fc domain of human IgG1 (see Methods). RF61 WT Fab showed no detectable binding with these parameters (up to 5  $\mu$ g/ml concentration of capture solution and up to 200 nM concentration of analyte). RF61-DEF binds approximately 3-fold tighter to IgG1 than RF61-D. Kinetic parameters are summarized in the table. The anti-gD-MMP3-D<sub>4</sub>K-4 fusion protein was not used as a negative control in this assay due to the affinity of its kappa light chain to the Protein L chip, although in other formats, no binding was observed between the anti-gD antibody and human IgG1. The chi-squared ( $\chi^2$ )

values for the fits shown here with detectable binding to the Fc domain are less than 5% of the  $R_{\max}$  values, which confirms the high quality of the fits and strong confidence in the kinetic parameters shown in the table.



**Figure S9.** RF61 binding to all human IgG subtypes. The RF61-DEF variant from round 3 of saturation mutagenesis was screened for binding to the Fc domain of the four human IgG subtypes using SPR. Strong and similar binding was observed to the Fc domains of IgG1, IgG2, and IgG3, while no detectable binding to IgG4 was found. IgG4 has a Glu at residue 355, while IgG1, IgG2, and IgG3 have an Arg. The binding ablation variants shown in Fig. 6C suggest R355 is crucial for strong binding of RF61 to Fc.



**Figure S10.** Cleavage assays measuring the proteolytic activity in human serum of targeted (purple) and non-targeted (blue) MMP3-D<sub>4</sub>K-4 against human IgG1 (A) and a fluorogenic MMP3 peptide substrate (B) after 24 hours at 37°C. The targeted MMP3-D<sub>4</sub>K-4 construct contains the anti-IgG Fab RF61-DEF, while the non-targeted construct contains an anti-gD Fab (see Fig. 7B).

## Supporting Text S1. Nucleotide sequences for select constructs expressed in this work.

### Anti-A $\beta$

#### IgG-CTF-2 format, neprolysin, anti-gD, heavy chain:

ATGGGATGGTCATGTATCATCCTTTTCTAGTAGCAACTGCAACCGGTGTACATTGAGAAGTTCAGCTGGTGGAGTCTGGCGGTGGCCT  
GGTGCAGCCAGGGGCTCACTCCGTTTGTCTGTGCCGCTTCTGGCTACTCCATCACCTCCGACTTTGCCTGGAAGTGGGTCGGTCAGG  
CCCCGGTAAGGGCTGGAATGGGTTGGATACATTAGTTACTCTGGAACCCTAGCTATAACCCTAGCTGAAAGTCCCGTATCACTATA  
AGTCGCGACAATTCCAAAAACACATTCTACCTGCAGATGAACAGCCTGCGTGTGAGGACTGCGCTTATTATTGTGCTCGAGAAAA  
CTACTATGGCCGTTCTCACGTTGGTACTTTCGACGTCTGGGGTCAAGGAACCTGGTACCCTCTCGAGTGCCTCCACCAAGGGCCCAT  
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GTGACGGTGTGCTGGAAGTCAAGGCGCCTGACCAGCGCGGTGCACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTACTCCCTCAG  
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TTCCACTGCAGAAAGAACAGCTACATGAACCCCCGAGAAGAAGTGCAGAGTGTGGTGA

### IgG-CTF-2 format, neprolysin, anti-gD, light chain:

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GTCTGCATCTGTAGGAGACAGAGTACCATCACTTGCCGGGCAAGTGCCTGTGACTCTTACGGTAACAGCTTTATACATTGGTATC  
AGCAGAAACCAGGGAAAGCCCCAAGCTCCTGATCTATCGTGCATCCGATTTGGAAAGTGGGGTCCCATCAAGGTTCAAGTGGCAGTGGGA  
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AATCTGGAAGTCTTCTGTGTGTGCCTGCTGAATACTTCTATCCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAA  
TCGGGTAAGTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAAGCAGA  
CTACGAGAAACAAAGTCTACGCCTGCGAAGTCAACCATCAGGGCCTGAGCTCGCCCGTCAAAAGAGCTTCAACAGGGGAGAGTGT  
AA

### IgG-CTF-2 format, neprolysin, crenezumab, heavy chain:

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCAGAAGTTCAGCTGGTTCGAGTCTGGGGGAGGCTT  
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### IgG-CTF-2 format, neprolysin, crenezumab, light chain:

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### IgG-CTF-2 format, neprolysin, solanezumab, heavy chain:

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CACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCAAATCTTGTGACAAAATC  
ACACATGCCACCGTGCACAGCCTGAACTCCTGGGGGACCGTCACTCTTCTTCCCCAAAACCAAGGACACCCCTCATGATC  
TCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCAGAACCCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGG  
GGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCAGTACCGTGTGGTCAAGCTCCTCAGGCTCCTCAGGCTCCTGACAGGACT  
GGTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAGCCCTCCAGCCCCATCGAGAAAACCATCTCCAAGCCAAAGGGCAG  
CCCCGAGAACCACAGGTGTACACCCCTGCCCATCCCGGAAGAGATGACCAAGAACCAGGTACGCTGACCTGCCTGGTCAAAGGCTT  
CTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAACAACACTACAAGACCAGCCTCCCGTGTGGACTCCGACG  
GCTCCTTCTTCTTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT  
CTGCACAACCACTACACGAGAAAGAGCCTCTCCTGTCTCCGGTGGCGGCGGGATCCTACGACGAGGCATCTGCAAGAGCAGCGA  
CTGCATCAAGAGCGCCGACACTGATCCAGAATGGACGCCACCACCGAGCCCTGCACCGACTTCTCAAGTACGCTGCGGCGGCT  
GGCTGAAGAGAAACGTGATCCCGAGACCAGCAGCAGATACGGCAACTTCGACATCCTGAGAGACGAGCTGGAGGTGGTGTGAAGGAT  
GTGCTGCAGGAGCCAAAGACCGAGGACATCGTGGCCGTGCAGAAAGCCCTGTACAGAAGCTGCATCAACGAGAGCGCCATCGA  
CAGCAGAGGCGGAGCCCTGCTGAAGCTGCTGCCGACATCTACGGTGGCCCGTGGCCACCGAGAACTGGGAGCAGAAGTACGGCG  
CCAGCTGGACCGCCGAGAAGGCCATCGCCAGCTGAACAGCAAGTACGGCAAGAAGGTGCTGATCAACCTGTTCTGGGACCGCAGC  
AAGAACAGCGTGAACACGTGATCCACATCGACCAGCCAGACTGGGCTGCCAGCAGAGACTACTACGAGTGCACCGGCATCTACAA

GGAGGCCTGCACCGCCTACGTGGACTTCATGATCAGCGTGGCCAGACTGATCAGACAGGAGGAGAGACTGCCCATCGACGAGAACCAGC  
TGCCCTGGAGATGAACAAGGTGATGGAGCTGGAGAAGGAGATCGCCAACGCCACCGCAAGCCGAGGACAGAAACGACCCATGCTG  
CTGTACAACAAGATGACCCTGGCCAGATCCAGAACAACCTTCAGCCTGGAGATCAACGGCAAGCCCTTCAGCTGGCTGAACTTACCAA  
CGAGATCATGAGCACCGTGAACATCAGCATACCAACGAGGAGGATGTGGTGGTGTACGCCCCGAGTACCTGACCAAGCTGAAGCCCA  
TCCTGACCAAGTACAGCGCCAGAGACCTGCAGAACCTGATGAGCTGGAGATTATCATGACCTGGTGGAGCAGCCTGAGCAGAACCTAC  
AAGGAGAGCAGAAACGCCTTCAGAAAGGCCCTGTACGGCACCACCAGCGAGACCGCCACCTGGAGAAGATGCGCCAACTACGTGAACGG  
CAACATGGAGAACGCCGTGGGCAGACTGTACGTGGAGGCCGCTTCGCCGGCGAGAGCAAGCACGTGGTGGAGGACCTGATCGCCAGA  
TCAGAGAGGTGTTCATCCAGACCTGGACGACCTGACCTGGATGGACGCCGAGACCAAGAAGAGAGCCGAGGAGAAGGCCCTGGCCATC  
AAGGAGAGAATCGGCTACCCGACGACATCGTGAGCAACGACAACAAGCTGAACAACGAGTACCTGGAGCTGAACTACAAGGAGGACGA  
GTACTTCGAGAACATCATCCAGAACCTGAAGTTCAGCCAGAGCAAGCAGCTGAAGAAGCTGAGAGAGAAGGTGGACAAGGACGAGTGA  
TCAGCGGCGCCGCGTGGTGAACGCCTTCTACAGCAGCGGAGAAACAGATCGTGTTCGCCCGGCATCTGCAGCCCCCTTCTTC  
AGCGCCAGCAGAGCAACGCCTGAACCTACGGCGGCATCGGCATGGTGTACGGCCACGAGATCACCCACGGCTTCGACGACAACGGCAG  
AACTTCAACAAGGACGGCGACCTGGTGGACTGGTGGACCCAGCAGAGCGCCAGCAACTTCAAGGAGCAGAGCCAGTGCATGGTGTACC  
AGTACGGCAACTTCAGCTGGGACCTGGCCGGCGGCAGCACCTGAACGGCATCAACACCCCTGGGCGAGAATCGCCGACAACGGCGGC  
CTGGGCCAGGCCTACAGAGCCTACCAGAACTACATCAAGAAGAACGGCGAGGAGAAGCTGCTGCCCGCCTGGACCTGAACCAAGCA  
GCTGTCTTCTCCTGAACTTCGCCAGGTGTGGTGCAGCCTACAGACCCGAGTACGCCGTGAACAGCATCAAGACCGATGTGCACAGCC  
CCGGCAACTTCAGAATCATCGGCACCCTGCAGAACAGCGCCGAGTTCAGCGAGGCCCTCCACTGCAGAAAGAACAGTACATGAACCC  
GAGAAGAAGTGCAGAGTGTGGTGA

## IgG-CTF-2 format, neprolysin, solanezumab, light chain:

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTTCAGATGTTGTGATGACTCAATCTCCACTCTCCCT  
GCCCGTACCCTTGGACAGCCAGCCTCCATCTCATGCAGGAGTAGTCAAAGCCTCATATACAGTGTGGAAACGCCTACTTGCATTGGT  
TTCTCCAGAAGCCAGGCCAATCTCCAAGGCTCCTAATTTATAAGGTTTCTAACAGATCTCTGGCGTCCCAGACAGATTACGCGCAGT  
GGGTGAGCAGTATTTACACTGAAAATCAGCAGGGTGGAGGCTGAGGATGTTGGCGTGTATTACTGCTCGCAATCTACTCAGTTCC  
TTGGACGTTTCGGCAAGGTACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCTCCTCCCGCATCTGATGAGCAGT  
TGAAATCTGGAAGTCTCTGTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAAGGTGGATAACGCCCTC  
CAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGC  
AGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCAACCATCAGGGCCTGAGCTCGCCCGTCAACAAAGAGCTTCAACAGGGGAGAGT  
GTAA

## Anti-IgG

### IgG-NTF(LC)-2 format, MMP3-D4K-4, anti-gD, heavy chain:

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTTCAGAGGTTTCAGCTGGTGGAGTCTGGCGGTGGCCT  
GGTGCAGCCAGGGGCTCACTCCGTTTTGCTGTGCCGCTTCTGGCTACTCCATCACCTCCGACTTTGCCTGGAAGTGGGTCGGTCCAGG  
CCCCGGTAAGGGCCTGGAATGGGTGGATACATTAGTTACTCTGGAACCACTAGCTATAACCTTAGCCTGAAGTCCCGTATCACTATA  
AGTCGCGACAATTCAAAAACACATTTACTCTGCAGATGAACAGCCTGCGTGTGAGGACACTGCCGTCTATTATTGTGCTCGGGAAAA  
CTACTATGGCCGTTCTCAGGTTGGTACTTCGACGTCTGGGTCAGGAACCTGGTCAACGCTCTCGAGTGCCTCCACCAAGGGCCCAT  
CGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCG  
GTGACGGTGTGCTGGAAGTCAAGCGCCCTGACCAGCGCGTGCACACCTTCCCGCTGTCTACAGTCTCAGGACTCTACTCCCTCAG  
CAGCGTGGTGTGCTGTCCTTAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTTGAATCACAAGCCAGCAACCAAGGTGGACA  
AGAAAGTTGAGCCAAATCTTGTGACAAAACCTCACACATGCCACCGTGCAGCGGAGGCGGAGCCGGCGGGGACCGTCAAGTCTTCTC  
TTCCCCCAAAACCAAGGACACCCCTCATGATCTCCCGGACCCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCAGAAAGCCCTGA  
GGTCAAGTTCAACTGGTACGTGGACGGCTGGAGGTGCATAATGCCAAGACAAGCCGGGAGGAGCAGTACAACAGCACGTACCGTGT  
TGGTACAGCTCCTCACCCTGCACCCAGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGCCCTCGGAGCCCC

ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCATCCGAGGAAGAGATGACCAAGAA  
CCAGGTGAGCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACA  
ACAAGACCACGCTCCCGTGTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG  
AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGAGAAGAGCCTCTCCCTGTCTCCGGTTGA

**IgG-NTF(LC)-2 format, MMP3-D4K-4, anti-gD, light chain:**

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTACATACCCCTGGACGGCCCGCTAGAGGGCAGGA  
CACCAGCATGAACCTGGTGCAGAAGTACTGGAGAACTACTATGACCTGAAGAAGGACGATGACGATAAGGTGAGAAGGAAGGACAGCG  
GCCCGTGGTCAAGAAGATCAGAGAGATGCAGAAGTTCCTGGCCCTGGAGGTGACCGCAAGCTGGACAGCGACACCCTGGAGGTGATG  
AGAAAGCCAGATGCGCGTGCACGCTGGGCCACTTCAGAACCTTCCCGGCATCCCCAAGTGGAGAAAGACCCACTGACCTACAG  
AATCGTGAACCTACACCCCGACCTGCCAAGGACGCCGTGGACAGCGCCGTGGAGAAGGCCCTGAAGGTGTGGGAGGAAGTACCCCC  
TGACCTTACGACAGCTGTACGAGGGCGAGGCCGACATCATGATCAGCTTCGCGGTGAGAGAGCACGGCGACTTCTACCCCTTCGACGGC  
CCCGCAACGTGTGGCCACGCTACGCCCCGGCCCCGGCATCAACGGCGACGCCACTTCGACGATGACGAGCAGTGGACCAAGGA  
CACCACAGGCACCAACCTGTTCTGGTGGCCGCTCACGAGATCGGCCACAGCTGGCCCTGTTCCACAGCGCAACACCGAGGCCCTGA  
TGTAACCCCTGTACCACAGCCTGACCGACCTGACCAGATTGAGACTGAGCCAGGACGATATCAACGGCATCCAGAGCCTGTACGGCCCT  
CCACCTGACAGCCCCGAGACCCCTGGTGCACCGAGCCCGTGCCTCCAGAGCCCGCACCCCGCAACTGCGACCCCGCCTGAG  
CTTCGACGCCGTGACACCCCTGAGAGGGGAGATCCTGATCTTCAAGGACAGACACTTCTGGAGAAAGAGCCTGAGAAAGCTGGAGCCCG  
AGCTGCACCTGATCAGCTCCTTCTGGCCAGCCTGCCAGCGCGGTGGACGCCGCTTACGAGGTGACCAGCAAGGACCTGGTGTTCATC  
TTCAAGGGCAACCAAGTTCGGGCCATCAGAGGCAACGAGGTGAGAGCCGGCTACCCAGAGGCATCCACACCTGGGCTTCCCTCCAAC  
CGTGAGAAAGATCGACGCCGTATCAGCGACAAGGAGAAGAACAAGACTACTTCTTCTGAGGACAAAGTACTGGAGATTCGACGAGA  
AGAGAAACAGCATGGAGCCCGCTTCCCAAGCAGATCGCCGAGGACTTCCCGGCATCGACAGCAAGATCGACGCCGTGTTGAGGAG  
TTCGGCTTCTTCTACTTCTTACCGGCAGCTCCAGCTGGAGTTCGACCCCAAGCAAGGAGTACCCACACCCTGAAGAGCAACAG  
CTGGCTGAACTGCGCGGAGGGCGAGCCGGGAGCCGAGCCGACATCCAGATGACCCAGTCTCCATCCTCCTGTCTGCATCTGTAG  
GAGACAGAGTACCATCACTTGGCGGCAAGTGCCTGTGTTGACTCTTACGGTAACAGCTTTATACATTGGTATCAGCAGAAACAGGG  
AAAGCCCTAAGCTCCTGATCTATCGTGCATCCGATTTGGAAAGTGGGGTCCCATCAAGGTTCAAGTGGCAGTGGATCTGGGACAGATTT  
CACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGAACCTACTACTGTCAACAGAATTACGCTGACCCCTTTCAGTTCGGCCAAAG  
GTACCAAGGTGGAGATCAAACGAACCTGTGGCTGCACCATCTGTCTTATCTTCCCGCATCTGATGAGCAGTTGAAATCTGGAACCTGCT  
TCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAAGTGGATAACGCCCTCAATCGGGTAACTCCCA  
GGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACA  
AAGTCTACGCCTGCGAAGTACCCATCAGGGCTGAGCTCGCCCGTCAAAAGAGCTTCAACAGGGGAGAGTGTAA

**IgG-NTF(LC)-2 format, MMP3-D4K-4, RF61 wild-type, heavy chain:**

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTACAGCTGCAGCTGCAGGAGAGCGCCCCGGCCT  
GGTGAAGCCAGCGAGACCCTGAGCCTGACCTGCACCGTGGAGCGGGCAGCATCAGCAGAGGCAGCCACTACTGGGCTGGATCAGAC  
AGCCCCCGGCAAGGGCTGGAGTGGATCGGCAGCATCTACTACAGCGGCAACACTACTTCAACCCAGCCTGAAGAGCAGAGTGACC  
ATCAGCGTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACCGCCGCCACACCGCCGTACTACTGCGCCAGACT  
GGGCCCCGACGACTACACCCCTGGACGGCATGGACGTGTGGGGCAGGGCACCACCGTACCGTCTCGAGTGCCTCCACCAAGGGCCAT  
CGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGCAGCAGCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCGAGCCG  
GTGACGGTGTGTTGAACTCAGGCGCCCTGACCAGCGCGTGCACACCTTCCCGGCTGTCTTACAGTCTCAGGACTCTACTCCCTCAG  
CAGCGTGGTACTGTGCCCTTAGCAGCTGGGCACCAGACCTACATCTGCAACGTGAATCACAAGCCAGCAACCAAGGTGGACA  
AGAAAGTTGAGCCCAAATCTTGTGACAAAACCTACACATGCCACCGTGGCGGAGGGGAGCCGGGGGACCGTCACTTCTCTC  
TTCCCCCAAACCAAGGACACCCTCATGATCTCCCGGACCCTGAGGTACATGCGTGGTGGTGGACGTGAGCCAGAAAGACCCTGA  
GGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAGCCGGGAGGAGCAGTACAACAGCACGTACCGTG  
TGGTACGCTCCTCACCCTGCTGCACAGGACTGGCTGAATGGCAAGGAGTACAAGTGAAGGTCTCCAACAAGCCCTCGGAGCCCC  
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCATCCGAGGAAGAGATGACCAAGAA

CCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACA  
ACTACAAAGACCACGCTCCCGTGTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGG  
AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAAGAGCCTCTCCCTGTCTCCGGTTGA

### IgG-NTF(LC)-2 format, MMP3-D4K-4, RF61 wild-type, light chain:

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCATACCCCTGGACGGCGCCGCTAGAGGCGAGGA  
CACCAGCATGAACCTGGTGCAGAAGTACTGGAGAATACTATGACCTGAAGAAGGACGATGACGATAAGGTGAGAAGGAAGGACAGCG  
GCCCCGTGGTCAAGAAGATCAGAGAGATGCAGAAGTTCTGGGCTGGAGGTGACCGCAAGCTGGACAGCGACACCTGGAGGTGATG  
AGAAAGCCCAGATGCGGCGTGCAGGACTGGCCACTTCAGAACCTTCCCGGCATCCCAAGTGGAGAAAGACCCACCTGACCTACAG  
AATCGTGAACCTACACCCCGACCTGCCAAGGACGCGGTGGACAGCGCCGTGGAGAAGGCCCTGAAGGTGTGGGAGGAAGTACCCCC  
TGACCTTACAGCAGACTGTACGAGGGCGAGGCCGACATCATGATCAGCTTCGCCGTGAGAGAGCACGGCGACTTCTACCCCTTCGACGGC  
CCCGGCAACGTGTGGCCACGCTACGCCCCGGCCCCGGCATCAACGGCGACGCCCACTTCGACGATGACGAGCAGTGGACCAAGGA  
CACCACAGGCACCAACCTGTTCTGGTGGCCGCTCACGAGATCGGCCACAGCTGGGCTGTTCACAGCGCAACACCGAGGCCCTGA  
TGTACCCCTGTACCACAGCCTGACCGACTGACAGATTGACTGAGCCAGGACGATATCAACGGCATCCAGAGCCTGTACGGCCCT  
CCACCTGACAGCCCCGAGACCCCTGGTGCCACCGAGCCCGTGCCTCCAGAGCCCGCACCCCGCAACTGCGACCCCGCCCTGAG  
CTTCGACGCGTGTGACACCTGAGAGGCGAGATCCTGATCTTCAAGGACAGACACTTCTGGAGAAAGAGCCTGAGAAAGCTGGAGCCCG  
AGCTGCACCTGATCAGCTCCTTCTGGCCAGCCTGCCAGCGCGTGGACGCGCTTACGAGGTGACCAGCAAGGACCTGGTGTTCATC  
TTCAAGGGCAACAGTCTGGGCCATCAGAGGCAACGAGGTGAGAGCCGGCTACCCAGAGGCATCCACACCTGGGCTTCCCTCCAAC  
CGTGAGAAAGATCGACGCGCTATCAGCGACAAGGAGAAGAACAAGACCTACTTCTTCGTGGAGGACAAGTACTGGAGATTCGACGAGA  
AGAGAAACAGCATGGAGCCCGCTTCCCAAGCAGATCGCCGAGGACTTCCCGGCATCGACAGCAAGATCGACGCGCTGTTTCGAGGAG  
TTCGGCTTCTTCTACTTCTTACCAGGCTCCAGCTGGAGTTCGACCCCAACGCAAGAAGGTGACCCACACCTGAAGAGCAACAG  
CTGGCTGAACTGCGCGGAGGCGGAGCCGCGGAGGCCAGAGCGTGTGACCCAGCCCCAGCGCCAGCGGACCCCCGGCC  
AGAGAGTACCATCAGTGCAGCGGCAGCAGCAACATCGGCAGCAACTACGTGTACTGGTATCAGCAGTGCAGCGCACCGCCCC  
AAGCTGTGATCTACAGAAACAACAGAGACCCAGCGCGTGCCTGACAGATTCAGCGGCAGCAAGAGCGGCACAGCGCCAGCCTGGC  
CATCAGCGGCTGAGAAGCGAGGACGAGGCGGACTACTACTGCGCCACCTGGGACGACAGCCTGAGCGCCGTGATCTTCGGCGGCGGTA  
CCAAGCTGACCGTCTTGGCCAACCTAAGGCTGCACCATCTGTACCCCTTTCGCGCATCTTCTGAGGAGTTGCAAGCTAACAAAGCC  
ACTCTTGTGTGCCTGATCAGTGACTTCTATCCCGAGCGGTACAGTAGCGTGAAGGCGGATAGCTCCCCGTAAGGCTGGCGTTCGA  
GACGACTACCCCTTCGAAGCAGAGCAACAACAATACGCGCCAGCAGCTACCTGTCTGCTGACCCAGAACAGTGAAGAGCCACAAAA  
GCTACTCTGCCAAGTACCCATGAGGGCTCGACCGTCAAAAAGACCGTGCAGCCGACAGAGTGTCTTGA

### Fab-NTF(LC)-1 format, MMP3-D4K-4, RF61 wild-type, heavy chain:

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCACAGCTGCAGCTGCAGGAGAGCGGCCCGCCCT  
GGTGAAGCCAGCGAGACCTGAGCCTGACCTGCACCGTGGAGCGCGGAGCAGATCAGCAGAGGACGCACTACTGGGCTGGATCAGAC  
AGCCCCCGGCAAGGGCTGGAGTGGATCGGCAGCATCTACTACAGCGGCAACACCTACTTCAACCCAGCCTGAAGAGCAGAGTGACC  
ATCAGCGTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACCGCCGACACCGCGTGTACTACTGCGCCAGACT  
GGGCCCCGACGACTACACCTGGACGGCATGACGTGTGGGCCAGGGACACCGTGACCGTCTCGAGTGCCTCCACCAAGGGCCCAT  
CGGTCTTCCCCCTGGCACCCCTCCTCAAGAGCACCTCTGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCG  
GTGACCGTGTCTGGAACCTCAGGCGCCCTGACAGCGCGGTGCACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTACTCCCTCAG  
CAGCGTGGTGTGCTGTGACCTTAGCAGCTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGCAACCAAGGTGGACA  
AGAAAGTTGAGCCCAACTTGTGACAAAACCTACACAGATTATAAGGACGATGACGATAAATGA

### Fab-NTF(LC)-1 format, MMP3-D4K-4, RF61 wild-type, light chain:

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCATACCCCTGGACGGCGCCGCTAGAGGCGAGGA  
CACCAGCATGAACCTGGTGCAGAAGTACTGGAGAATACTATGACCTGAAGAAGGACGATGACGATAAGGTGAGAAGGAAGGACAGCG

GCCCCGTGGTCAAGAAGATCAGAGAGATGCAGAAGTTCTGGGCCTGGAGGTGACCGGCAAGCTGGACAGCGACACCCTGGAGGTGATG  
AGAAAGCCCAGATGCGGCGTGCCCCGACGTGGGCCACTTCAGAACCTTCCCCGGCATCCCCAAGTGGAGAAAGACCCACCTGACCTACAG  
AATCGTGAACCTACACCCCCGACCTGCCCAAGGACGCCGTGGACAGCGCCGTGGAGAAGGCCCTGAAGGTGTGGGAGGAAGTGACCCCC  
TGACCTTCAGCAGACTGTACGAGGGCGAGGCCGACATCATGATCAGCTTCGCCGTGAGAGAGCACGGCGACTTCTACCCCTTCGACGGC  
CCGGCAACGTGCTGGCCACGCCCTACGCCCCGGCCCCGGCATCAACGGCGACGCCCACTTCGACGATGACGAGCAGTGGACCAAGGA  
CACCACAGGCACCAACCTGTTCTGGTGGCCGCTCACGAGATCGGCCACAGCCTGGGCCTGTTCCACAGCGCCAACACCGAGGCCCTGA  
TGTACCCCTGTACCACAGCCTGACCGACCTGACCAGATTGACTGAGCCAGGACGATATCAACGGCATCCAGAGCCTGTACGGCCCT  
CCACCTGACAGCCCCGAGACCCCTGGTGCCACCCAGCCCGTGCCCTCCAGAGCCCGGCACCCCGCCAACCTGCGACCCCGCCCTGAG  
CTTCGACGCCGTGAGCACCTGAGAGGGGAGATCCTGATCTTCAAGGACAGACACTTCTGGAGAAAGAGCCTGAGAAAGCTGGAGCCCG  
AGCTGCACCTGATCAGCTCCTTCTGGCCAGCCTGCCAGCGCGGTGGACGCCGCTTACGAGGTGACCAGCAAGGACCTGGTGTTCATC  
TTCAAGGCAACCAGTTCTGGCCATCAGAGGCAACGAGGTGAGAGCCGGCTACCCAGAGGCATCCACACCTGGGCTTCCCTCCAAC  
CGTGAGAAAGATCGACGCGCTATCAGCGACAAGGAGAAGAACAAGACCTACTTCTTCGTGGAGACAAGTACTGGAGATTGACGAGA  
AGAGAAACAGCATGGAGCCCGCTTCCCAAGCAGATCGCCGAGGACTTCCCCGGCATCGACAGCAAGATCGACGCCGTGTTGAGGAG  
TTCGGCTTCTTCTACTTCTTACCGGCAGCTCCAGCTGGAGTTCGACCCCAACGCCAAGAAGGTGACCCACACCTGAAGAGCAACAG  
CTGGCTGAACTGCGGCGGAGGCCGAGCCGGCGGAGGCCGAGCCAGAGCGTGTGACCCAGCCCCCAGCGCCAGCGGCACCCCGGCC  
AGAGAGTGACCATCAGCTGCAGCGGCAGCAGCAACATCGGCAGCAACTACGTGTACTGGTATCAGCAGCTGCCCGGCACCGCCCC  
AAGCTGCTGATCTACAGAAACAACCAGAGACCAGCGCGGTGCCGACAGATTGAGCGGCAGCAAGAGCGGCACCAGCGCCAGCCTGGC  
CATCAGCGCCCTGAGAAGCGAGGACGAGGCCGACTACTACTGCGCCACCTGGGACGACAGCCTGAGCGCCGTGATCTTCGGCGGCGGTA  
CCAAGCTGACCGTCTTGGCCAACCTAAGGCTGACCATCTGTACCCCTCTTCCCGCATCTTCTGAGGAGTTGCAAGCTAACAAAGCC  
ACTCTTGTGTGCCTGATCAGTGACTTCTATCCCGGAGCGGTACAGTAGCGTGAAGCGGATAGCTCCCCGTAAGGCTGGCGTCTGA  
GACGACTACCCCTTCGAAGCAGAGCAACAACAATACGCCCGCAGCAGCTACCTGTGCTGACCCAGAACAGTGAAGAGCCACAAAA  
GCTACTCCTGCCAAGTCACCCATGAGGGCTCGACCGTCGAAAAGACCGTCGCCCCGACAGAGTGTCTTGA