Supporting Information for

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

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This supporting information file contains:

Figures S1 – S10

Supporting Text S1

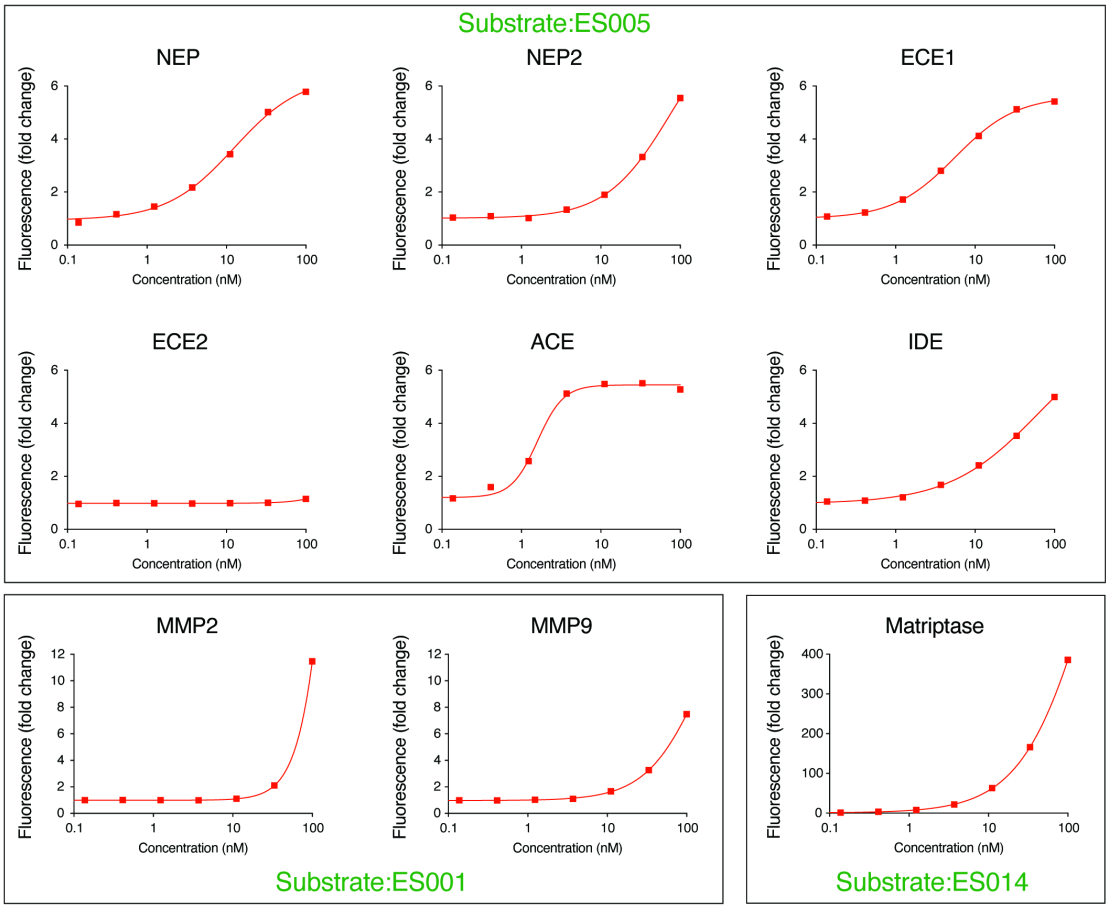


Figure S1. Activity of an Aβ protease panel on control substrates. The activity of 9 proteases previously shown to cleave Aβ was tested on one of three fluorescence resonance energy transfer (FRET) control substrates. Cleavage of the substrate results in increased fluorescence and is reported as fold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

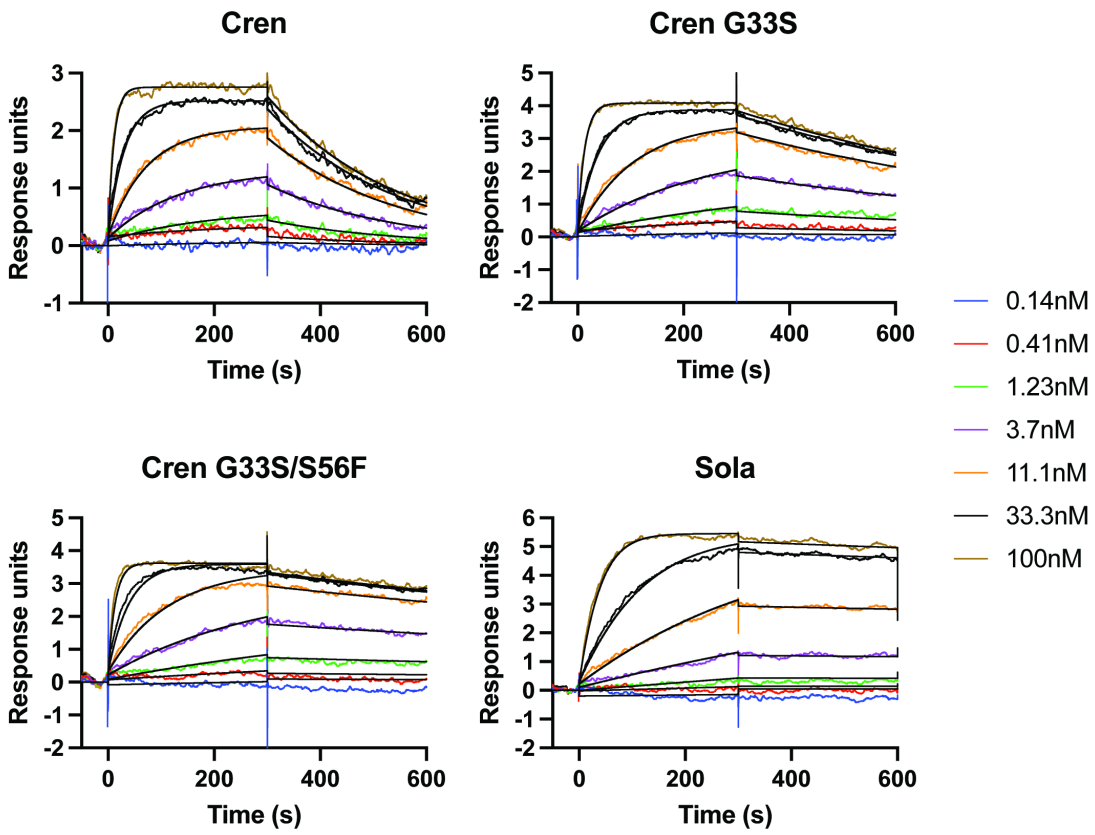


Figure S2. SPR kinetic analysis for the binding of crenezumab, crenezumab point mutants, and solanezumab to Aβ(1-28) (see Methods). A summary of the kinetic parameters derived from the sensogram fitting is shown in Fig. 4A. The chi-squared (χ^2) values for all fits shown here are less than 5% of the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

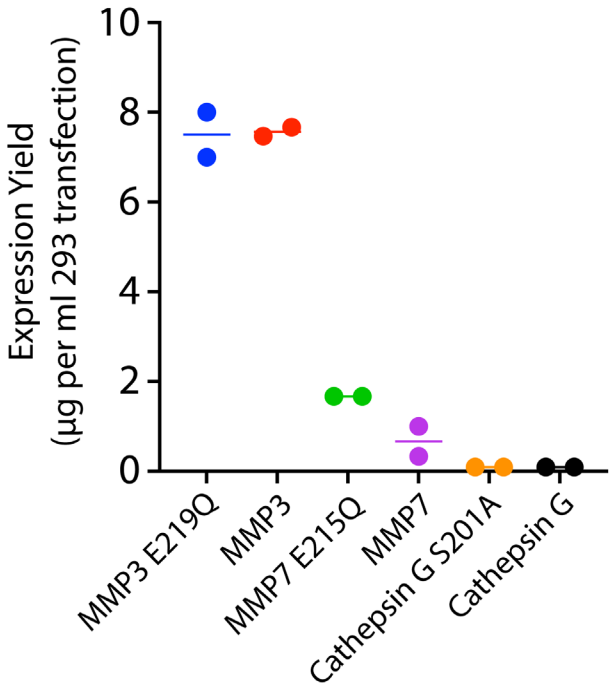


Figure S3. Expression of three proteases previously shown to cleave within the IgG hinge: matrix metalloproteinase 3 (MMP3), matrix metalloproteinase 7 (MMP7), and cathepsin G. Expression yield per ml HEK293 transfection shows little to no expression yield for MMP7 or cathepsin G. MMP3 E219Q, MMP7 E215Q, 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.

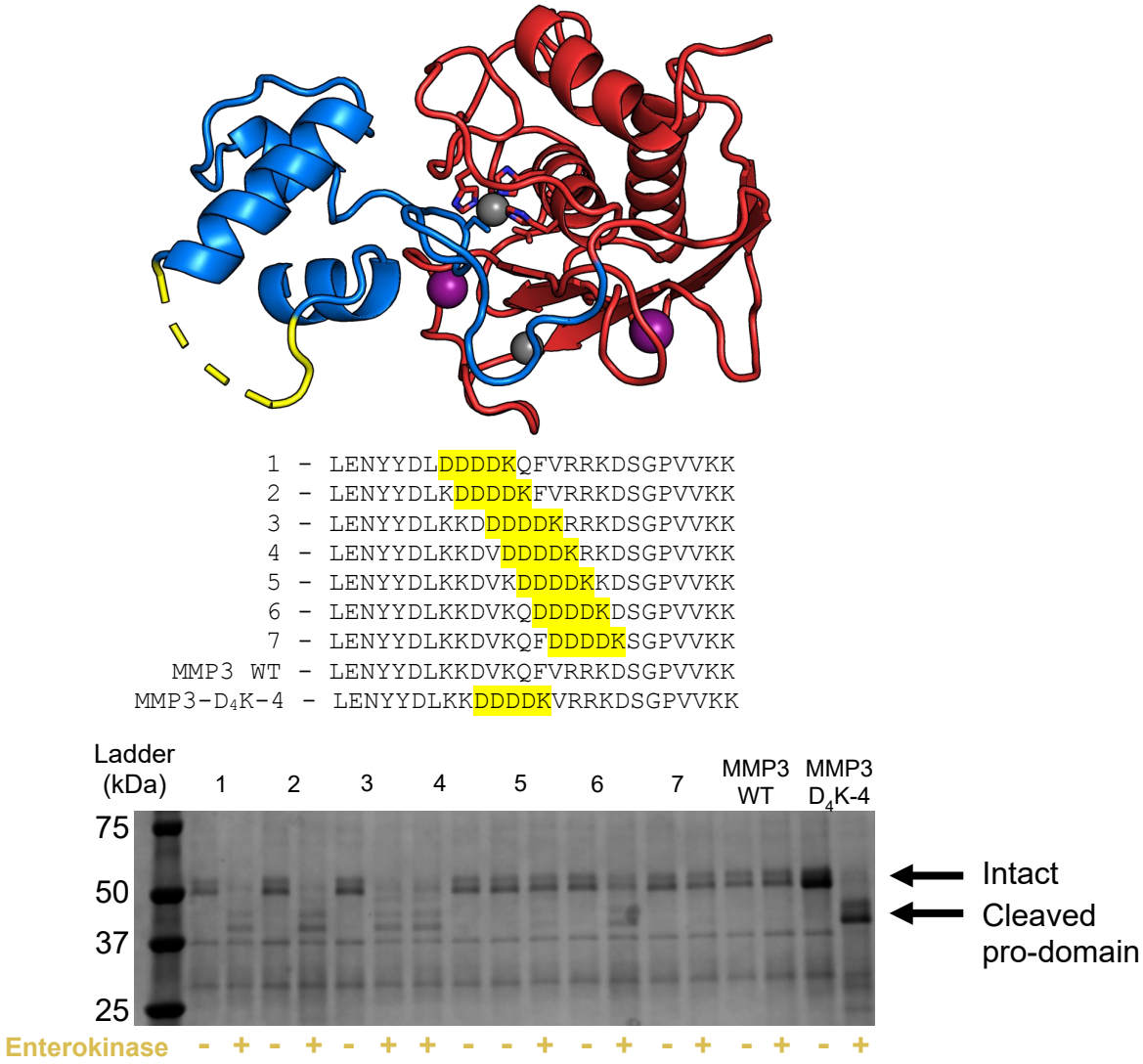


Figure S4. Insertion of an enterokinase cleavage sequence within the pro-domain of MMP3. After testing protease site substitutions at four locations within the pro-domain of MMP3, the most promising variant had an enterokinase site substitution at position 4 (Figs. 5B and 5C). We then sought to optimize the MMP3-D$_4$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$_4$K-4.

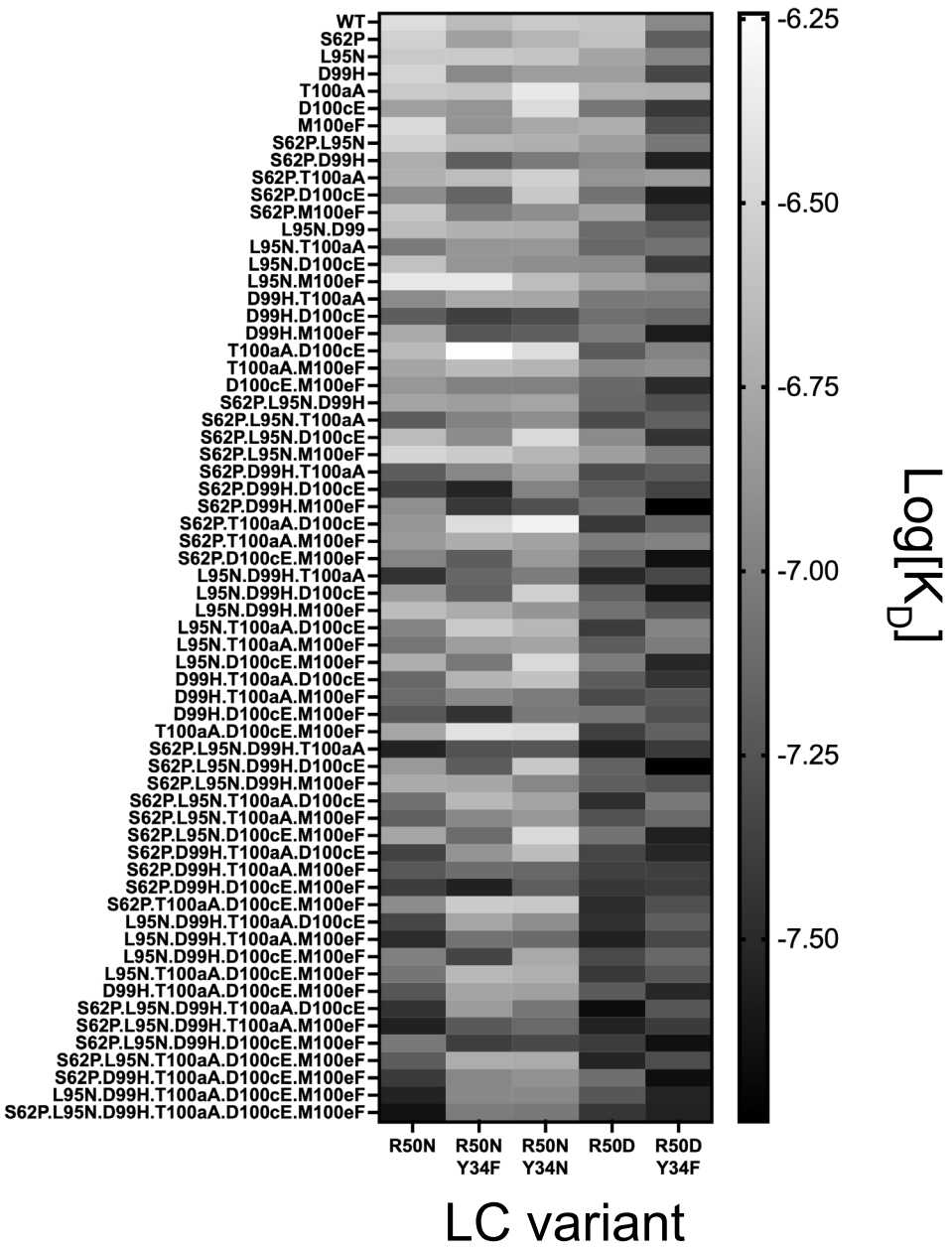
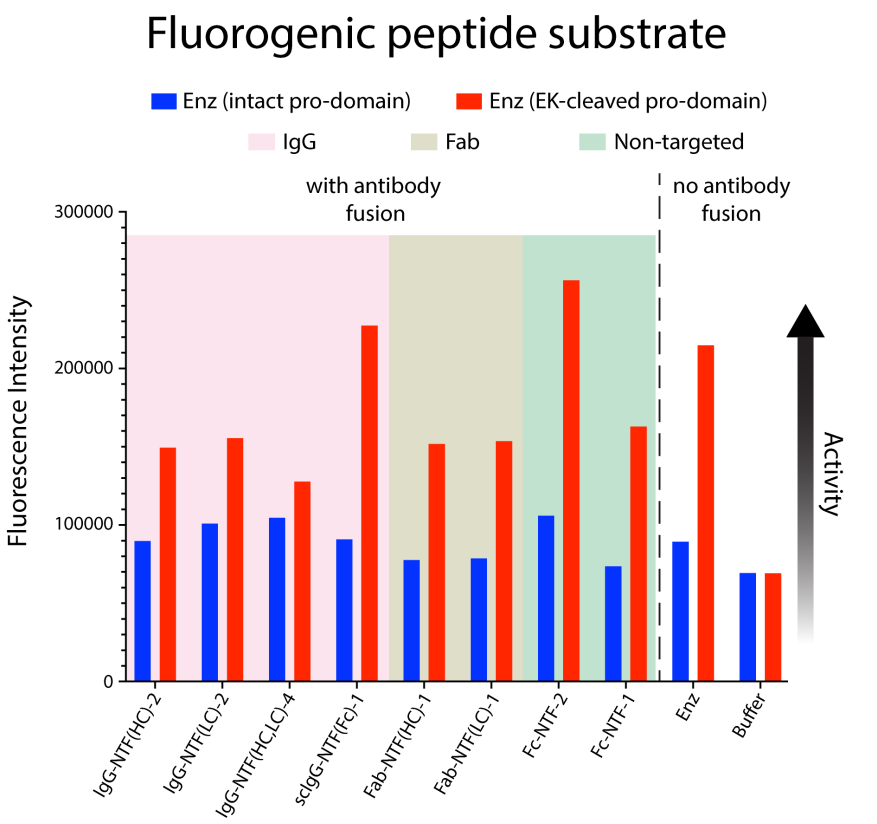


Figure S5. Heat map summarizing affinity of RF61 variants to human IgG1 Fc from round 3 of affinity maturation. Each row and column are different heavy and light chain variants, respectively. Residues are numbered according to Kabat convention. Affinity is represented as the log of the K_D value obtained via SPR.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Enz (EK-cleaved pro-domain)
IgG
Fab
Non-targeted
with antibody fusion
no antibody fusion
Fluorescence Intensity
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200000
100000
0
Activity
IgG-NTF(HC)-2
IgG-NTF(LC)-2
IgG-NTF(HC,LC)-4
scIgG-NTF(Fc)-1
Fab-NTF(HC)-1
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Enz
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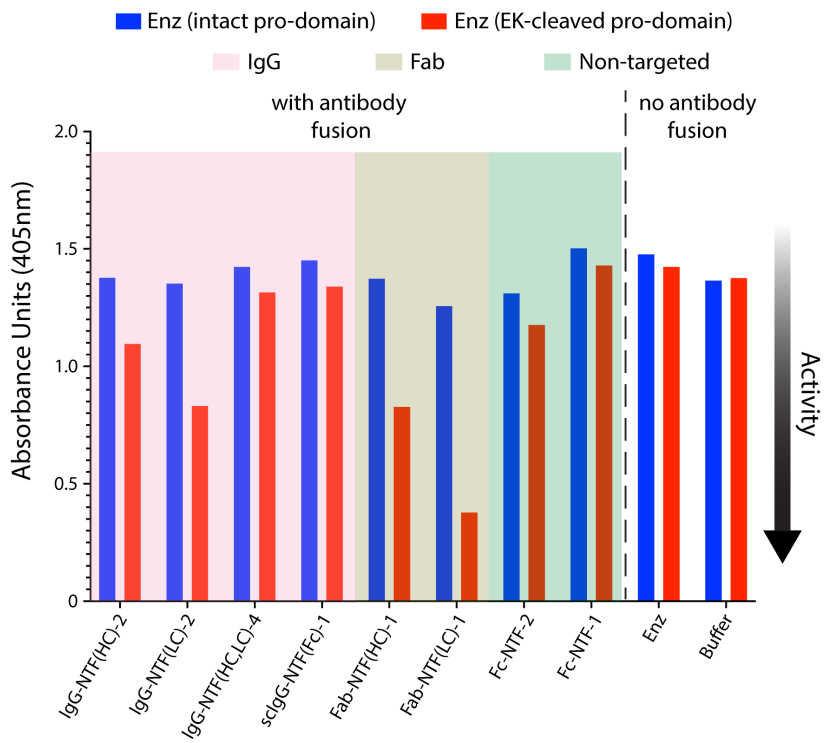
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Enz (EK-cleaved pro-domain)
IgG
Fab
Non-targeted
with antibody fusion
no antibody fusion
Absorbance Units (405nm)
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1.5
1.0
0.5
0
Activity
IgG-NTF(HC)-2
IgG-NTF(LC)-2
IgG-NTF(HC,LC)-4
scIgG-NTF(Fc)-1
Fab-NTF(HC)-1
Fab-NTF(LC)-1
Fc-NTF-2
Fc-NTF-1
Enz
Buffer

Figure S6. Antibody-MMP3-D_4K-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_4K-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_4K-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_4K-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.

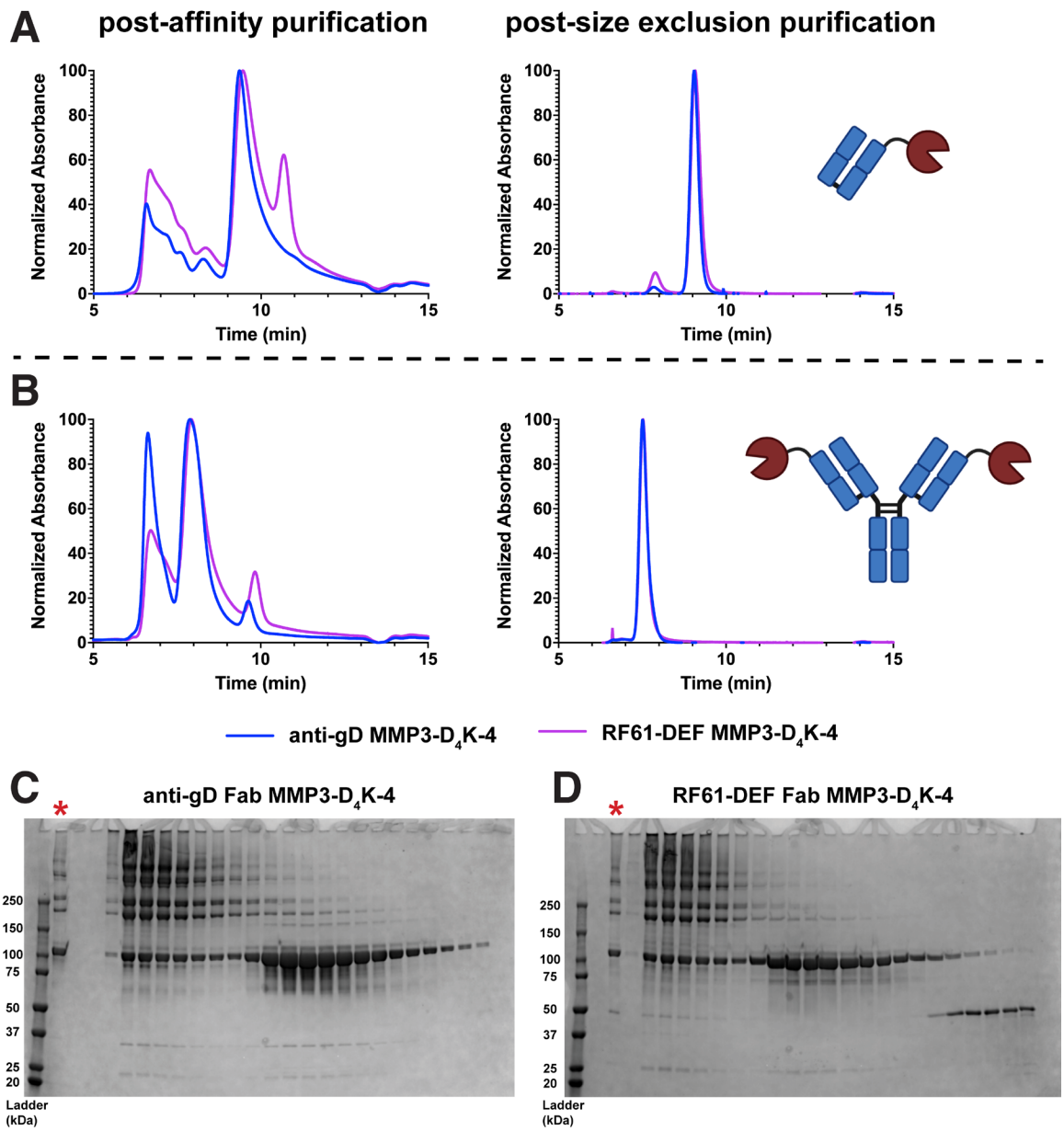
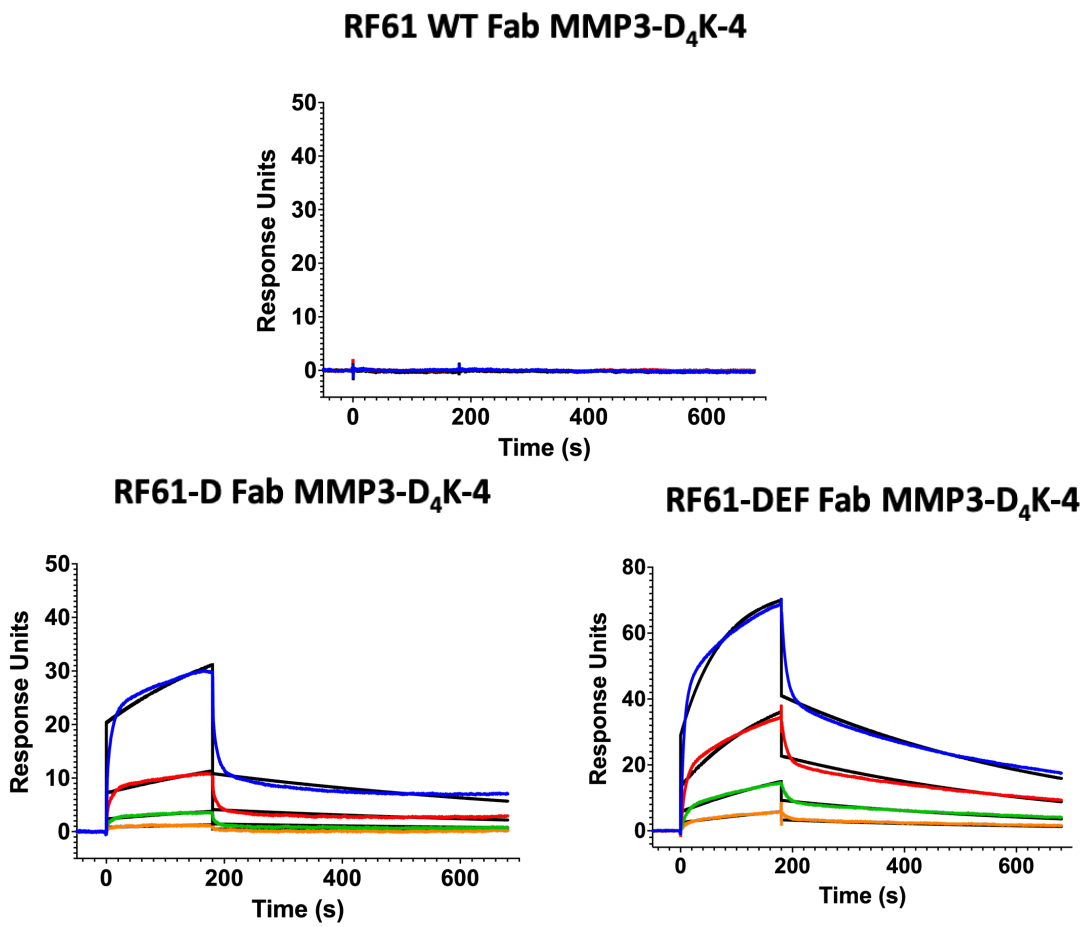


Figure S7. Purification summary for both Fab-MMP3-D4K-4 (*A*) and IgG-MMP3-D4K-4 (*B*) fusion proteins. Representative samples shown include the anti-gD fusions (blue) and the RF61-DEF fusions (magenta). The transfection supernatants were first purified using affinity chromatography with GammaBind Plus 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_4K-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-Aβ NEP fusions (Fig. 2C) and the IgG-MMP3-D_4K-4 fusions (Fig. S7B).



	R_{max} (RU)	k_a (1/Ms/10000)	k_d (1000/s)	K_D (nM)
RF61 WT Fab MMP3-D_4K-4	-	-	-	-
RF61-D Fab MMP3-D_4K-4	33.5	1.26	1.31	104
RF61-DEF Fab MMP3-D_4K-4	52.2	5.83	1.90	32.5

Figure S8. SPR kinetic analysis for the binding of RF61 Fab-MMP3-D4K-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 µg/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-D4K-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 (χ^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.

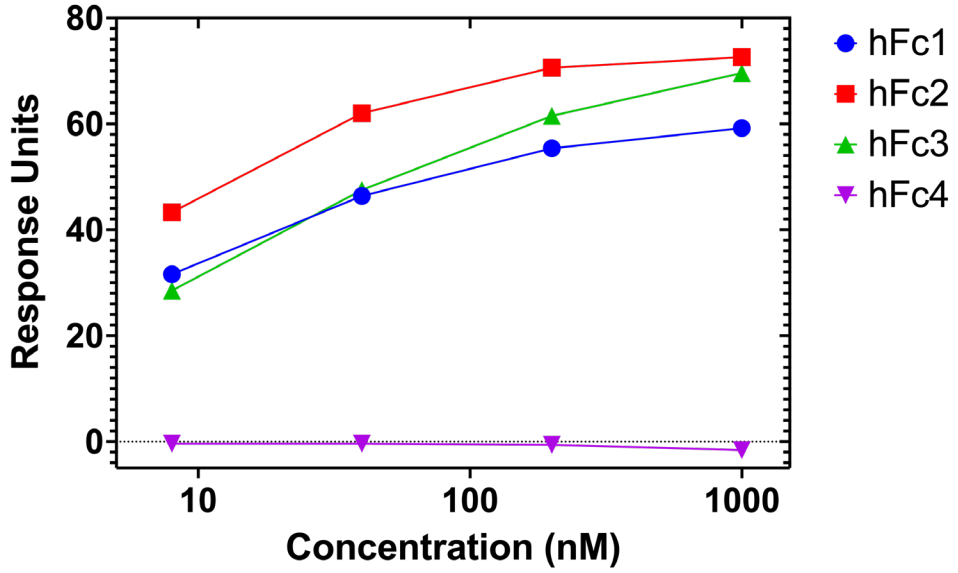


Figure S9. RF61 binding to all human IgG subtypes. The RF61-DEF variant from round 3 of saturation mutagenesis was screened for binding to the Fc domain of the four human IgG subtypes using SPR. Strong and similar binding was observed to the Fc domains of IgG1, IgG2, and IgG3, while no detectable binding 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.

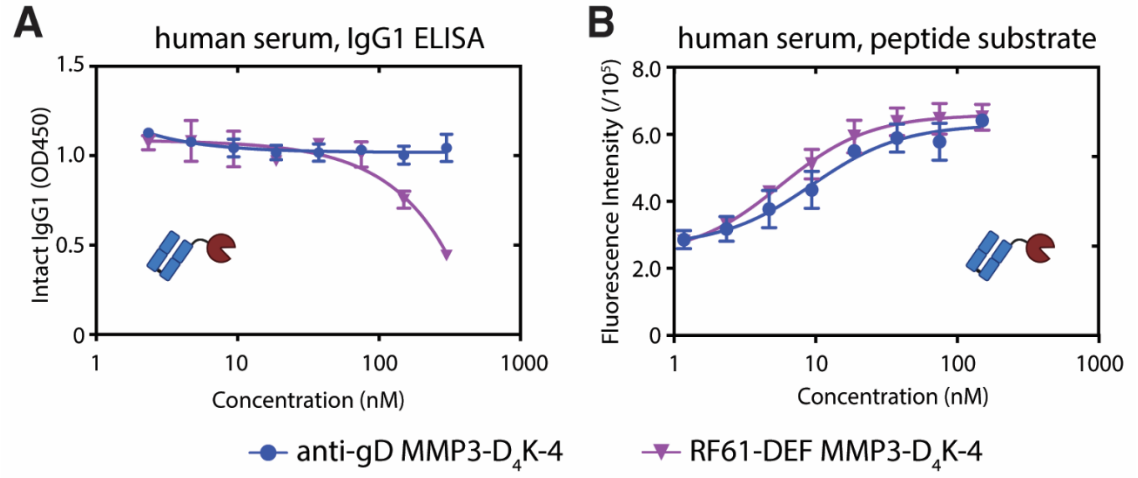


Figure S10. Cleavage assays measuring the proteolytic activity in human serum of targeted (purple) and non-targeted (blue) MMP3-D_4K-4 against human IgG1 (*A*) and a fluorogenic MMP3 peptide substrate (*B*) after 24 hours at 37°C. The targeted MMP3-D_4K-4 construct contains the anti-IgG Fab RF61-DEF, 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-Aβ

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

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

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

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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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CTACTGGGGCCAAGGAACCCTGGTCACCGTCTCGAGTGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCA
CCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACC
AGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACTGTGCCCTCTAGCAGCTTGGG
CACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTC
ACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATC
TCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGA
GGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACT
GGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG
CCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAAGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTT
CTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACG
GCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCT
CTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTGGCGGCGGCGGATCCTACGACGACGGCATCTGCAAGAGCAGCGA
CTGCATCAAGAGCGCCGCCAGACTGATCCAGAACATGGACGCCACCACCGAGCCCTGCACCGACTTCTTCAAGTACGCCTGCGGCGGCT
GGCTGAAGAGAAACGTGATCCCCGAGACCAGCAGCAGATACGGCAACTTCGACATCCTGAGAGACGAGCTGGAGGTGGTGCTGAAGGAT
GTGCTGCAGGAGCCCAAGACCGAGGACATCGTGGCCGTGCAGAAGGCCAAGGCCCTGTACAGAAGCTGCATCAACGAGAGCGCCATCGA
CAGCAGAGGCGGCGAGCCCCTGCTGAAGCTGCTGCCCGACATCTACGGCTGGCCCGTGGCCACCGAGAACTGGGAGCAGAAGTACGGCG
CCAGCTGGACCGCCGAGAAGGCCATCGCCCAGCTGAACAGCAAGTACGGCAAGAAGGTGCTGATCAACCTGTTCGTGGGCACCGACGAC
AAGAACAGCGTGAACCACGTGATCCACATCGACCAGCCCAGACTGGGCCTGCCCAGCAGAGACTACTACGAGTGCACCGGCATCTACAA

GGAGGCCTGCACCGCCTACGTGGACTTCATGATCAGCGTGGCCAGACTGATCAGACAGGAGGAGAGACTGCCCATCGACGAGAACCAGC
TGGCCCTGGAGATGAACAAGGTGATGGAGCTGGAGAAGGAGATCGCCAACGCCACCGCCAAGCCCGAGGACAGAAACGACCCCATGCTG
CTGTACAACAAGATGACCCTGGCCCAGATCCAGAACAACTTCAGCCTGGAGATCAACGGCAAGCCCTTCAGCTGGCTGAACTTCACCAA
CGAGATCATGAGCACCGTGAACATCAGCATCACCAACGAGGAGGATGTGGTGGTGTACGCCCCCGAGTACCTGACCAAGCTGAAGCCCA
TCCTGACCAAGTACAGCGCCAGAGACCTGCAGAACCTGATGAGCTGGAGATTCATCATGGACCTGGTGAGCAGCCTGAGCAGAACCTAC
AAGGAGAGCAGAAACGCCTTCAGAAAGGCCCTGTACGGCACCACCAGCGAGACCGCCACCTGGAGAAGATGCGCCAACTACGTGAACGG
CAACATGGAGAACGCCGTGGGCAGACTGTACGTGGAGGCCGCCTTCGCCGGCGAGAGCAAGCACGTGGTGGAGGACCTGATCGCCCAGA
TCAGAGAGGTGTTCATCCAGACCCTGGACGACCTGACCTGGATGGACGCCGAGACCAAGAAGAGAGCCGAGGAGAAGGCCCTGGCCATC
AAGGAGAGAATCGGCTACCCCGACGACATCGTGAGCAACGACAACAAGCTGAACAACGAGTACCTGGAGCTGAACTACAAGGAGGACGA
GTACTTCGAGAACATCATCCAGAACCTGAAGTTCAGCCAGAGCAAGCAGCTGAAGAAGCTGAGAGAGAAGGTGGACAAGGACGAGTGGA
TCAGCGGCGCCGCCGTGGTGAACGCCTTCTACAGCAGCGGCAGAAACCAGATCGTGTTCCCCGCCGGCATCCTGCAGCCCCCCTTCTTC
AGCGCCCAGCAGAGCAACAGCCTGAACTACGGCGGCATCGGCATGGTGATCGGCCACGAGATCACCCACGGCTTCGACGACAACGGCAG
AAACTTCAACAAGGACGGCGACCTGGTGGACTGGTGGACCCAGCAGAGCGCCAGCAACTTCAAGGAGCAGAGCCAGTGCATGGTGTACC
AGTACGGCAACTTCAGCTGGGACCTGGCCGGCGGCCAGCACCTGAACGGCATCAACACCCTGGGCGAGAACATCGCCGACAACGGCGGC
CTGGGCCAGGCCTACAGAGCCTACCAGAACTACATCAAGAAGAACGGCGAGGAGAAGCTGCTGCCCGGCCTGGACCTGAACCACAAGCA
GCTGTTCTTCCTGAACTTCGCCCAGGTGTGGTGCGGCACCTACAGACCCGAGTACGCCGTGAACAGCATCAAGACCGATGTGCACAGCC
CCGGCAACTTCAGAATCATCGGCACCCTGCAGAACAGCGCCGAGTTCAGCGAGGCCTTCCACTGCAGAAAGAACAGCTACATGAACCCC
GAGAAGAAGTGCAGAGTGTGGTGA

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

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCAGATGTTGTGATGACTCAATCTCCACTCTCCCT
GCCCGTCACCCTTGGACAGCCAGCCTCCATCTCATGCAGGAGTAGTCAAAGCCTCATATACAGTGATGGAAACGCCTACTTGCATTGGT
TTCTCCAGAAGCCAGGCCAATCTCCAAGGCTCCTAATTTATAAGGTTTCTAACAGATTCTCTGGCGTCCCAGACAGATTCAGCGGCAGT
GGGTCAGGCACTGATTTCACACTGAAAATCAGCAGGGTGGAGGCTGAGGATGTTGGCGTGTATTACTGCTCGCAATCTACTCACGTTCC
TTGGACGTTCGGCCAAGGTACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGT
TGAAATCTGGAACTGCTTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTC
CAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGC
AGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGT
GTTAA

Anti-IgG

IgG-NTF(LC)-2 format, MMP3-D$_4$K-4, anti-gD, heavy chain:

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCAGAGGTTCAGCTGGTGGAGTCTGGCGGTGGCCT
GGTGCAGCCAGGGGGCTCACTCCGTTTGTCCTGTGCCGCTTCTGGCTACTCCATCACCTCCGACTTTGCCTGGAACTGGGTCCGTCAGG
CCCCGGGTAAGGGCCTGGAATGGGTTGGATACATTAGTTACTCTGGAACCACTAGCTATAACCCTAGCCTGAAGTCCCGTATCACTATA
AGTCGCGACAATTCCAAAAACACATTCTACCTGCAGATGAACAGCCTGCGTGCTGAGGACACTGCCGTCTATTATTGTGCTCGGGAAAA
CTACTATGGCCGTTCTCACGTTGGGTACTTCGACGTCTGGGGTCAAGGAACCCTGGTCACCGTCTCGAGTGCCTCCACCAAGGGCCCAT
CGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCG
GTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAG
CAGCGTGGTGACTGTGCCCTCTAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACA
AGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCGGCGGAGGCGGAGCCGGCGGGGGACCGTCAGTCTTCCTC
TTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGA
GGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTG
TGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCGGAGCCCCC

ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCGAGGAAGAGATGACCAAGAA
CCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACT
ACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG
AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTTGA

IgG-NTF(LC)-2 format, MMP3-D$_4$K-4, anti-gD, light chain:

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCATACCCCCTGGACGGCGCCGCTAGAGGCGAGGA
CACCAGCATGAACCTGGTGCAGAAGTACCTGGAGAACTACTATGACCTGAAGAAGGACGATGACGATAAGGTGAGAAGGAAGGACAGCG
GCCCCGTGGTCAAGAAGATCAGAGAGATGCAGAAGTTCCTGGGCCTGGAGGTGACCGGCAAGCTGGACAGCGACACCCTGGAGGTGATG
AGAAAGCCCAGATGCGGCGTGCCCGACGTGGGCCACTTCAGAACCTTCCCCGGCATCCCCAAGTGGAGAAAGACCCACCTGACCTACAG
AATCGTGAACTACACCCCCGACCTGCCCAAGGACGCCGTGGACAGCGCCGTGGAGAAGGCCCTGAAGGTGTGGGAGGAAGTGACCCCCC
TGACCTTCAGCAGACTGTACGAGGGCGAGGCCGACATCATGATCAGCTTCGCCGTGAGAGAGCACGGCGACTTCTACCCCTTCGACGGC
CCCGGCAACGTGCTGGCCCACGCCTACGCCCCCGGCCCCGGCATCAACGGCGACGCCCACTTCGACGATGACGAGCAGTGGACCAAGGA
CACCACAGGCACCAACCTGTTCCTGGTGGCCGCTCACGAGATCGGCCACAGCCTGGGCCTGTTCCACAGCGCCAACACCGAGGCCCTGA
TGTACCCCCTGTACCACAGCCTGACCGACCTGACCAGATTCAGACTGAGCCAGGACGATATCAACGGCATCCAGAGCCTGTACGGCCCT
CCACCTGACAGCCCCGAGACCCCCCTGGTGCCCACCGAGCCCGTGCCTCCAGAGCCCGGCACCCCCGCCAACTGCGACCCCGCCCTGAG
CTTCGACGCCGTGAGCACCCTGAGAGGCGAGATCCTGATCTTCAAGGACAGACACTTCTGGAGAAAGAGCCTGAGAAAGCTGGAGCCCG
AGCTGCACCTGATCAGCTCCTTCTGGCCCAGCCTGCCCAGCGGCGTGGACGCCGCTTACGAGGTGACCAGCAAGGACCTGGTGTTCATC
TTCAAGGGCAACCAGTTCTGGGCCATCAGAGGCAACGAGGTGAGAGCCGGCTACCCCAGAGGCATCCACACCCTGGGCTTCCCTCCAAC
CGTGAGAAAGATCGACGCCGCTATCAGCGACAAGGAGAAGAACAAGACCTACTTCTTCGTGGAGGACAAGTACTGGAGATTCGACGAGA
AGAGAAACAGCATGGAGCCCGGCTTCCCCAAGCAGATCGCCGAGGACTTCCCCGGCATCGACAGCAAGATCGACGCCGTGTTCGAGGAG
TTCGGCTTCTTCTACTTCTTCACCGGCAGCTCCCAGCTGGAGTTCGACCCCAACGCCAAGAAGGTGACCCACACCCTGAAGAGCAACAG
CTGGCTGAACTGCGGCGGAGGCGGAGCCGGCGGAGGCGGAGCCGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAG
GAGACAGAGTCACCATCACTTGCCGGGCAAGTGCGTCTGTTGACTCTTACGGTAACAGCTTTATACATTGGTATCAGCAGAAACCAGGG
AAAGCCCCTAAGCTCCTGATCTATCGTGCATCCGATTTGGAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTT
CACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAATTACGCTGACCCTTTCACGTTCGGCCAAG
GTACCAAGGTGGAGATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACTGCT
TCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCA
GGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACA
AAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

IgG-NTF(LC)-2 format, MMP3-D$_4$K-4, RF61 wild-type, heavy chain:

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCACAGCTGCAGCTGCAGGAGAGCGGCCCCGGCCT
GGTGAAGCCCAGCGAGACCCTGAGCCTGACCTGCACCGTGAGCGGCGGCAGCATCAGCAGAGGCAGCCACTACTGGGGCTGGATCAGAC
AGCCCCCCGGCAAGGGCCTGGAGTGGATCGGCAGCATCTACTACAGCGGCAACACCTACTTCAACCCCAGCCTGAAGAGCAGAGTGACC
ATCAGCGTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACCGCCGCCGACACCGCCGTGTACTACTGCGCCAGACT
GGGCCCCGACGACTACACCCTGGACGGCATGGACGTGTGGGGCCAGGGCACCACCGTGACCGTCTCGAGTGCCTCCACCAAGGGCCCAT
CGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCG
GTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAG
CAGCGTGGTGACTGTGCCCTCTAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACA
AGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCGGCGGAGGCGGAGCCGGCGGGGGACCGTCAGTCTTCCTC
TTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGA
GGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTG
TGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCGGAGCCCCC
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCGAGGAAGAGATGACCAAGAA

CCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACT
ACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG
AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTTGA

IgG-NTF(LC)-2 format, MMP3-D$_4$K-4, RF61 wild-type, light chain:

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCATACCCCCTGGACGGCGCCGCTAGAGGCGAGGA
CACCAGCATGAACCTGGTGCAGAAGTACCTGGAGAACTACTATGACCTGAAGAAGGACGATGACGATAAGGTGAGAAGGAAGGACAGCG
GCCCCGTGGTCAAGAAGATCAGAGAGATGCAGAAGTTCCTGGGCCTGGAGGTGACCGGCAAGCTGGACAGCGACACCCTGGAGGTGATG
AGAAAGCCCAGATGCGGCGTGCCCGACGTGGGCCACTTCAGAACCTTCCCCGGCATCCCCAAGTGGAGAAAGACCCACCTGACCTACAG
AATCGTGAACTACACCCCCGACCTGCCCAAGGACGCCGTGGACAGCGCCGTGGAGAAGGCCCTGAAGGTGTGGGAGGAAGTGACCCCCC
TGACCTTCAGCAGACTGTACGAGGGCGAGGCCGACATCATGATCAGCTTCGCCGTGAGAGAGCACGGCGACTTCTACCCCTTCGACGGC
CCCGGCAACGTGCTGGCCCACGCCTACGCCCCCGGCCCCGGCATCAACGGCGACGCCCACTTCGACGATGACGAGCAGTGGACCAAGGA
CACCACAGGCACCAACCTGTTCCTGGTGGCCGCTCACGAGATCGGCCACAGCCTGGGCCTGTTCCACAGCGCCAACACCGAGGCCCTGA
TGTACCCCCTGTACCACAGCCTGACCGACCTGACCAGATTCAGACTGAGCCAGGACGATATCAACGGCATCCAGAGCCTGTACGGCCCT
CCACCTGACAGCCCCGAGACCCCCCTGGTGCCCACCGAGCCCGTGCCTCCAGAGCCCGGCACCCCCGCCAACTGCGACCCCGCCCTGAG
CTTCGACGCCGTGAGCACCCTGAGAGGCGAGATCCTGATCTTCAAGGACAGACACTTCTGGAGAAAGAGCCTGAGAAAGCTGGAGCCCG
AGCTGCACCTGATCAGCTCCTTCTGGCCCAGCCTGCCCAGCGGCGTGGACGCCGCTTACGAGGTGACCAGCAAGGACCTGGTGTTCATC
TTCAAGGGCAACCAGTTCTGGGCCATCAGAGGCAACGAGGTGAGAGCCGGCTACCCCAGAGGCATCCACACCCTGGGCTTCCCTCCAAC
CGTGAGAAAGATCGACGCCGCTATCAGCGACAAGGAGAAGAACAAGACCTACTTCTTCGTGGAGGACAAGTACTGGAGATTCGACGAGA
AGAGAAACAGCATGGAGCCCGGCTTCCCCAAGCAGATCGCCGAGGACTTCCCCGGCATCGACAGCAAGATCGACGCCGTGTTCGAGGAG
TTCGGCTTCTTCTACTTCTTCACCGGCAGCTCCCAGCTGGAGTTCGACCCCAACGCCAAGAAGGTGACCCACACCCTGAAGAGCAACAG
CTGGCTGAACTGCGGCGGAGGCGGAGCCGGCGGAGGCGGAGCCCAGAGCGTGCTGACCCAGCCCCCCAGCGCCAGCGGCACCCCCGGCC
AGAGAGTGACCATCAGCTGCAGCGGCAGCAGCAGCAACATCGGCAGCAACTACGTGTACTGGTATCAGCAGCTGCCCGGCACCGCCCCC
AAGCTGCTGATCTACAGAAACAACCAGAGACCCAGCGGCGTGCCCGACAGATTCAGCGGCAGCAAGAGCGGCACCAGCGCCAGCCTGGC
CATCAGCGGCCTGAGAAGCGAGGACGAGGCCGACTACTACTGCGCCACCTGGGACGACAGCCTGAGCGCCGTGATCTTCGGCGGCGGTA
CCAAGCTGACCGTCCTTGGCCAACCTAAGGCTGCACCATCTGTCACCCTCTTCCCGCCATCTTCTGAGGAGTTGCAAGCTAACAAAGCC
ACTCTTGTGTGCCTGATCAGTGACTTCTATCCCGGAGCGGTCACAGTAGCGTGGAAGGCGGATAGCTCCCCCGTAAAGGCTGGCGTCGA
GACGACTACCCCTTCGAAGCAGAGCAACAACAAATACGCCGCCAGCAGCTACCTGTCGCTGACCCCAGAACAGTGGAAGAGCCACAAAA
GCTACTCCTGCCAAGTCACCCATGAGGGCTCGACCGTCGAAAAGACCGTCGCCCCGACAGAGTGTTCTTGA

Fab-NTF(LC)-1 format, MMP3-D$_4$K-4, RF61 wild-type, heavy chain:

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCACAGCTGCAGCTGCAGGAGAGCGGCCCCGGCCT
GGTGAAGCCCAGCGAGACCCTGAGCCTGACCTGCACCGTGAGCGGCGGCAGCATCAGCAGAGGCAGCCACTACTGGGGCTGGATCAGAC
AGCCCCCCGGCAAGGGCCTGGAGTGGATCGGCAGCATCTACTACAGCGGCAACACCTACTTCAACCCCAGCCTGAAGAGCAGAGTGACC
ATCAGCGTGGACACCAGCAAGAACCAGTTCAGCCTGAAGCTGAGCAGCGTGACCGCCGCCGACACCGCCGTGTACTACTGCGCCAGACT
GGGCCCCGACGACTACACCCTGGACGGCATGGACGTGTGGGGCCAGGGCACCACCGTGACCGTCTCGAGTGCCTCCACCAAGGGCCCAT
CGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCG
GTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAG
CAGCGTGGTGACTGTGCCCTCTAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACA
AGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACACAGATTATAAGGACGATGACGATAAATGA

Fab-NTF(LC)-1 format, MMP3-D$_4$K-4, RF61 wild-type, light chain:

ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACATTCATACCCCCTGGACGGCGCCGCTAGAGGCGAGGA
CACCAGCATGAACCTGGTGCAGAAGTACCTGGAGAACTACTATGACCTGAAGAAGGACGATGACGATAAGGTGAGAAGGAAGGACAGCG

GCCCCGTGGTCAAGAAGATCAGAGAGATGCAGAAGTTCCTGGGCCTGGAGGTGACCGGCAAGCTGGACAGCGACACCCTGGAGGTGATG
AGAAAGCCCAGATGCGGCGTGCCCGACGTGGGCCACTTCAGAACCTTCCCCGGCATCCCCAAGTGGAGAAAGACCCACCTGACCTACAG
AATCGTGAACTACACCCCCGACCTGCCCAAGGACGCCGTGGACAGCGCCGTGGAGAAGGCCCTGAAGGTGTGGGAGGAAGTGACCCCCC
TGACCTTCAGCAGACTGTACGAGGGCGAGGCCGACATCATGATCAGCTTCGCCGTGAGAGAGCACGGCGACTTCTACCCCTTCGACGGC
CCCGGCAACGTGCTGGCCCACGCCTACGCCCCCGGCCCCGGCATCAACGGCGACGCCCACTTCGACGATGACGAGCAGTGGACCAAGGA
CACCACAGGCACCAACCTGTTCCTGGTGGCCGCTCACGAGATCGGCCACAGCCTGGGCCTGTTCCACAGCGCCAACACCGAGGCCCTGA
TGTACCCCCTGTACCACAGCCTGACCGACCTGACCAGATTCAGACTGAGCCAGGACGATATCAACGGCATCCAGAGCCTGTACGGCCCT
CCACCTGACAGCCCCGAGACCCCCCTGGTGCCCACCGAGCCCGTGCCTCCAGAGCCCGGCACCCCCGCCAACTGCGACCCCGCCCTGAG
CTTCGACGCCGTGAGCACCCTGAGAGGCGAGATCCTGATCTTCAAGGACAGACACTTCTGGAGAAAGAGCCTGAGAAAGCTGGAGCCCG
AGCTGCACCTGATCAGCTCCTTCTGGCCCAGCCTGCCCAGCGGCGTGGACGCCGCTTACGAGGTGACCAGCAAGGACCTGGTGTTCATC
TTCAAGGGCAACCAGTTCTGGGCCATCAGAGGCAACGAGGTGAGAGCCGGCTACCCCAGAGGCATCCACACCCTGGGCTTCCCTCCAAC
CGTGAGAAAGATCGACGCCGCTATCAGCGACAAGGAGAAGAACAAGACCTACTTCTTCGTGGAGGACAAGTACTGGAGATTCGACGAGA
AGAGAAACAGCATGGAGCCCGGCTTCCCCAAGCAGATCGCCGAGGACTTCCCCGGCATCGACAGCAAGATCGACGCCGTGTTCGAGGAG
TTCGGCTTCTTCTACTTCTTCACCGGCAGCTCCCAGCTGGAGTTCGACCCCAACGCCAAGAAGGTGACCCACACCCTGAAGAGCAACAG
CTGGCTGAACTGCGGCGGAGGCGGAGCCGGCGGAGGCGGAGCCCAGAGCGTGCTGACCCAGCCCCCCAGCGCCAGCGGCACCCCCGGCC
AGAGAGTGACCATCAGCTGCAGCGGCAGCAGCAGCAACATCGGCAGCAACTACGTGTACTGGTATCAGCAGCTGCCCGGCACCGCCCCC
AAGCTGCTGATCTACAGAAACAACCAGAGACCCAGCGGCGTGCCCGACAGATTCAGCGGCAGCAAGAGCGGCACCAGCGCCAGCCTGGC
CATCAGCGGCCTGAGAAGCGAGGACGAGGCCGACTACTACTGCGCCACCTGGGACGACAGCCTGAGCGCCGTGATCTTCGGCGGCGGTA
CCAAGCTGACCGTCCTTGGCCAACCTAAGGCTGCACCATCTGTCACCCTCTTCCCGCCATCTTCTGAGGAGTTGCAAGCTAACAAAGCC
ACTCTTGTGTGCCTGATCAGTGACTTCTATCCCGGAGCGGTCACAGTAGCGTGGAAGGCGGATAGCTCCCCCGTAAAGGCTGGCGTCGA
GACGACTACCCCTTCGAAGCAGAGCAACAACAAATACGCCGCCAGCAGCTACCTGTCGCTGACCCCAGAACAGTGGAAGAGCCACAAAA
GCTACTCCTGCCAAGTCACCCATGAGGGCTCGACCGTCGAAAAGACCGTCGCCCCGACAGAGTGTTCTTGA