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Identification of Hyperreactive Cysteines within Ryanodine Receptor Type 1 by Mass Spectrometry*[S]

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The skeletal-type ryanodine receptor (RyR1) undergoes covalent adduction by nitric oxide (NO), redox-induced shifts in cation regulation, and non-covalent interactions driven by the transmembrane redox potential that enable redox sensing. Tight redox regulation of RyR1 is thought to be primarily mediated through highly reactive (hyperreactive) cysteines. Of the 100 cysteines per subunit of RyR1, ~25–50 are reduced, with 6–8 considered hyperreactive. Thus far, only Cys-3635, which undergoes selective adduction by NO, has been identified. In this report, RyR1-enriched junctional sarcoplasmic reticulum is labeled with 7-diethylamino-3-(4′-maleimidylphenyl)-4-methylcoumarin (CPM, 1 pmol/μg of protein) in the presence of 10 mM Mg^{2+}, conditions previously shown to selectively label hyperreactive sulfhydryls and eliminate redox sensing. The CPM-adducted RyR1 is separated by gel electrophoresis and subjected to in-gel tryptic digestion. Isolation of CPM-adducted peptides is achieved by analytical and microbore high-performance liquid chromatography utilizing fluorescence and UV detection. Subsequent analysis using two direct and one tandem mass spectrometry methods results in peptide masses and sequence data that, compared with the known primary sequence of RyR1, enable unequivocal identification of CPM-adducted cysteines. This work is the first to directly identify seven hyperreactive cysteines: 1040, 1303, 2436, 2565, 2606, 2611, and 3635 of RyR1. In addition to Cys-3635, the nitrosylation site, six additional cysteines may contribute toward redox regulation of the RyR1 complex.

Redox modulation of proteins and ion channels through critical cysteines is thought to underlie the regulation of many intracellular signaling pathways. Initial studies of redox in biological systems focused on correlations of oxidative stress to the gross pathology of stroke (1, 2), atherosclerosis (3), and aging and neurodegeneration (4, 5). However, the study of redox has grown to include discrete and reversible regulation of cell physiology, often through high affinity signaling molecules such as H_2O_2 and NO (6). In biological systems, NO is broadly used for signaling by binding to specific cysteine sulfhydryls on target proteins. The high reactivity of NO toward protein sulfhydryls and heme groups may severely limit its free diffusion in biological systems, thus requiring a NO translocation and delivery system mediated by critical (reactive) protein sulfhydryls (7, 8). Examples of the many proteins NO is known to modulate include guanylate cyclase (9, 10), a Ca^{2+}-dependent potassium channel (11), *N*-methyl-D-aspartate receptors (12, 13), and ryanodine receptors (RyRs)[1] (14, 15).

The skeletal type RyR (RyR1) is a large (2.3-MDa) homotetrameric Ca^{2+} release channel of the sarcoplasmic reticulum that is subject to tight, multifaceted redox regulation, including oxidative activation and inhibition (16–19), subunit coordination (20), pO_2-dependent NO activation, possibly through reduced calmodulin inhibition (14), and transmembrane redox sensing capabilities (21–23). Additionally, Ca^{2+} release and single channel experiments suggest that oxidation, *S*-nitrosylation, and *S*-glutathionylation alter RyR1 sensitivity to Ca^{2+} and Mg^{2+} (24–26). All of these redox interactions are thought to be mediated by cysteines, of which there are 100 per monomer of RyR1. It is thought that ~25–50 of these cysteines are free and, based on reactivity, are commonly segregated into three to four classes (27–29). Of these, Cys-3635 has been shown to be selectively nitrosylated (15); whereas additional, yet unidentified cysteines are involved in redox regulation of the channel complex.

Biochemical evidence using the fluorogenic sulfhydryl probe 7-diethylamino-3-(4′-maleimidylphenyl)-4-methylcoumarin (CPM) to label junctional sarcoplasmic reticulum (JSR) preparations (0.1–1.0 pmol of CPM/μg of JSR protein) indicate, based on the labeling kinetics and pattern of proteins adducted, that RyR1 contains a group or class of hyperreactive sulfhydryls that are conformationally sensitive and exhibit the greatest reactivity in the closed state of the channel (30, 31). Additional biochemical and biophysical techniques indicate that this group of six to eight hyperreactive or critical cysteines bestow sensitivity to oxygen tension that is important in NO binding of Cys-3635 (14, 15, 29), determine RyR1 responsiveness to channel modulators (32), and confer the transmembrane redox sensing ability (21). The reversibility of RyR1 activation by redox potential changes and physiological levels of NO implies a delicate intracellular redox signaling mechanism. These functional data illustrate the critical role hyperreactive sulfhydryls play in redox regulation of RyR1; however, aside from the NO and calmodulin binding site of Cys-3635, the identity of

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[S] The online version of this article (available at http://www.jbc.org) contains additional text, Table S1, and Figs. S1–S10.

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[1] The abbreviations used are: RyR, ryanodine receptor; RyR1, skeletal-type ryanodine receptor; CPM, 7-diethylamino-3-(4′-maleimidylphenyl)-4-methylcoumarin; JSR, junctional sarcoplasmic reticulum; HPLC, high-pressure liquid chromatography; MS, mass spectrometry; MALDI, matrix-assisted laser desorption/ionization time-of-flight; ESI, electrospray ionization; MH, malignant hyperthermia; MHS, malignant hyperthermia susceptibility; CCD, central core disease; MOPS, 4-morpholinepropanesulfonic acid; TPCK, L-1-tosylamido-2-phenylethyl chloromethyl ketone.

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the additional hyperreactive or critical cysteines remains uncertain.

This report identifies the hyperreactive sulfhydryls of RyR1 via post-translational modification with CPM and a mass spectrometric methodology. Labeling of JSR vesicles is performed with discriminating concentrations of CPM under conditions favoring RyR1 channel closure, which has been previously shown to specifically label hyperreactive cysteines within the channel complex and selectively eliminate its redox sensing capabilities (21, 30, 31, 33). Subsequent to this labeling reaction, the CPM-adducted RyR1 is subjected to tryptic digestion, sequential HPLC steps, and two methods of mass spectrometry. This methodology yields RyR1 sequence data and exact peptide masses corresponding to calculated CPM and hydrolyzed-CPM-adducted molecular masses, enabling the identification of 7 CPM-adducted cysteines of RyR1, including the NO binding site of Cys-3635. This work provides the first structural elucidation of most, and possibly all hyperreactive sulfhydryls of RyR1 that may regulate channel activity in response to changes in the local redox environment. A method is outlined that may have general applicability for identification of critical cysteines within redox-regulated proteins.

EXPERIMENTAL PROCEDURES

Materials—For sulfhydryl labeling, KCl and MOPS (>99.5%) were obtained from Sigma-Aldrich, $MgCl_2 \cdot 6H_2O$ from EM Scientific (Gibbstown, NJ), and CPM from Molecular Probes (Eugene, OR). JSR membrane preparation, CPM labeling, and electrophoresis were performed using NANOpure water from a Barnstead International purifier (model D4751, Dubuque, IA). Solvents for tryptic digestion and HPLC were High Purity Solvents from Burdick and Jackson (Muskegon, MI). Ammonium acetate (HPLC grade) and trifluoroacetic acid (protein sequence analysis grade) used in HPLC mobile phases were obtained from Fluka BioChemika (Bucks SG, Switzerland). Ultra Smooth Polypropylene or Low Retention Microcentrifuge Tubes (0.65 or 1.5 ml, Island Scientific, Bainbridge Island, WA) were used during tryptic digestion and manual collection of HPLC fractions. Concentrations during in-gel digestion and of HPLC fractions were performed using an SVC-200H Savant SpeedVac concentrator system (GMI, Inc., Albertville, MN). Electrophoresis gels were cast with 30% Duracryl (Genomic Solutions, Ann Arbor, MI). Protein assays were based on the method described in Lowry *et al.* (34).

Membrane Preparation—JSR was isolated from male New Zealand White rabbit fast-twitch skeletal muscle using the method previously described in Saito *et al.* (35).

CPM Labeling of JSR—CPM was prepared and used as described in Liu *et al.* (30). The labeling of the most reactive cysteines present in JSR was performed as previously described, with solutions degassed under vacuum. JSR vesicles were incubated while continuously stirring in RyR closed buffer (100 mM KCl, 20 mM MOPS, and 10 mM $MgCl_2$, pH 7.4) and 1 μg/ml leupeptin from Sigma-Aldrich at 37 °C for 3–5 min prior to addition of CPM (1 pmol/μg of JSR protein) to a final volume of 25 ml. The reaction proceeded for 1 min before being placed on ice, a time previously shown under closed conditions to complete the reaction (30). CPM-labeled JSR was pelleted at 146,000 × *g* ($r_{average}$) and 4 °C for 3 h using a Ti-50.2 rotor (Beckman) and resuspended in RyR closed buffer.

Gel Electrophoresis—Ensuing protein denaturation in Laemmli Sample Buffer from Bio-Rad Laboratories (Hercules, CA) at 37 °C for 1 h, CPM-RyR1 was isolated from labeled JSR vesicles using SDS-PAGE in large format gels (20 × 20 × 0.1 cm) under constant 25 mA. The resolving gel (pH 8.8) consisted of a two-phase composition, the bottom 60% consisting of 10% acrylamide and the top 40% consisting of 3–10%; a 10-well 3% stacking gel (pH 6.8) was also used.

CPM-RyR Digestion—In-gel tryptic digestion procedures were based on methods described in Shevchenko *et al.* (36) and Wilm *et al.* (37). CPM-labeled RyR1 excised from each SDS-PAGE gel was washed thoroughly four times (15 min each) with water, diced into approximately 1-mm squares, and dried via the SpeedVac in 1.5-ml microcentrifuge tubes (3–6 tubes). Gel pieces were subsequently reduced with 10 mM dithiothreitol in 100 mM NH_4HCO_3 (pH 8, 55 °C) for 1 h and alkylated with 55 mM iodoacetamide in 100 mM NH_4HCO_3 for 45 min in the dark at room temperature. Gel pieces were washed with 100 mM NH_4HCO_3 and partially dehydrated with acetonitrile before complete dehydration via SpeedVac. Finally, the CPM-RyR1 was digested in 50% NH_4HCO_3, pH 7.8–8.0, containing sequence grade TPCK-modified trypsin (catalog no. V5111, Promega, Madison, WI) at a final concentration range of 10 to 25 ng/μl (37 °C) for 24 h. Peptides were extracted once each with 0.1% trifluoroacetic acid and then 5% formic acid-acetonitrile (50:50). The digested CPM-RyR1 from each gel was then combined and concentrated by SpeedVac to 100 μl for analytical HPLC analysis.

Sequential HPLC—Initial separation of tryptic digested CPM-labeled RyR was performed using a Vydac (catalog no. 218TP52, Hesperia, CA) analytical C-18 reverse phase HPLC column (2.1-mm inner diameter × 25-cm length) on a Waters 600 system (Milford, MA). Separations were performed at 0.5 ml/min using mobile phases A (25 mM ammonium acetate in 10% acetonitrile) and B (22.5 mM ammonium acetate in 80% acetonitrile) with initial conditions of 83% A and 17% B that changed linearly to 70% A and 30% B over 80 min, then to 100% B over 10 min. Separation was completed with 100% B for 10 min. The eluant was monitored with a variable wavelength Hewlett-Packard (Palo Alto, CA) 1100 UV detector monitoring absorbance at UV 214 nm for peptide detection and a Shimadzu (Kyoto, Japan) 535 fluorescence detector with a standard flow cell (12 μl) monitoring emission at 469 nm from excitation at 384 nm for detection of CPM-adducted peptides.

Fluorescence fractions from analytical HPLC were subjected to additional separation using a Vydac (catalog no. 218TP51) microbore C-18 reverse phase HPLC column (1.0-mm inner diameter × 25-cm length) with an ABI model 140B Solvent Delivery System. Separations were performed at 80 μl/min using mobile phase A (0.1% trifluoroacetic acid) and B (0.085% trifluoroacetic acid in 70% acetonitrile) with an initial condition of 95% A that decreased linearly to 65% over 10 min, then to 40% over 50 min, and then to 5% over 10 min. Separation was completed with 5% A for 5 min. Samples were loaded in multiple injections under the initial conditions, and the signal was allowed to return to baseline before onset of the run. A dual detection system was again employed, using an ABI model 785A Programmable Absorbance Detector monitoring absorbance at UV 214 nm for peptide detection and a Shimadzu (Kyoto, Japan) 535 fluorescence detector with a 2-μl semi-micro flow cell (catalog no. 20662817) monitoring emission at 469 nm from excitation at 384 nm for detection of CPM-adducted peptides.

Mass Spectrometry—Samples were analyzed in a matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometer (Biflex III, Bruker Daltonics, Bremen, Germany) and in a quadrupole orthogonal time-of-flight mass spectrometer with *QqT* geometry, where *Q* is the quadrupole analyzer, *q* is the R_F-only quadrupole, and *T* is the time-of-flight analyzer (QSTAR, Applied Biosystems, Foster City, CA) for direct electrospray MS (ESI) and tandem ESI (ESI MS/MS) experiments. In both cases the spectra were generated in positive ion mode.

The MALDI-TOF instrument was equipped with a nitrogen laser operating at an output of 337.1 nm with a pulse width of 3 ns and a repetition rate of 6 Hz. The instrument was operated in reflector mode, 19.3-kV acceleration potential, 20.0-kV reflector potential, 2- to 4-ns time base, and 10- to 30-ms delay. The output signal of the detector was digitized at a sampling rate of 500 MHz/channel using a 1-GHz Lecroy digitizer. A camera mounted on a microscope allowed inspection of the sample crystallization. The crystals on the target were sampled randomly, with major coverage of the spot. External calibration was performed with angiotensin II (Sigma, A9525) and somatostatin 28 (Sigma, S6135) with molecular masses according to the $(M+H)^+$ ions at *m/z* 1046.53 Da (angiotensin II, monoisotopic mass), *m/z* 3147.47 Da (somatostatin 28, monoisotopic mass). For analysis, first a 0.5-μl matrix solution, α-cyano-4-hydroxycinnamic acid (Hewlett Packard, part number G2054-85010) then 0.5 μl of the sample (protein digest) were spotted onto the stainless steel tip and allowed to dry at room temperature.

The quadrupole orthogonal time-of-flight mass spectrometer was controlled by Analyst-QS version 1.0 software with Service Pack 3 installed. This instrument was equipped with a nano-spray ionization source (Protana, Odense, Denmark). Voltage on the Protana "medium" capillary tips was 900 V. External two-point calibration was performed using the singly charged ions of CsI and a peptide with nominal mass of 828.5 Da. Mass accuracy was typically better than 10 ppm, and resolution was typically better than 7000 full-width half-maximum. The flow rate of the nanospray source was ~25–50 nl/min. Nitrogen was employed as the curtain gas at 25 arbitrary units. The orifice voltage was set at 80 V for all samples, whereas the focusing ring was set to 250 V and the skimmer was kept at 30 V. The TOF analyzer was set to acquire spectra at a rate of 7 kHz over the mass range 100–3000 Da. The resultant spectra are the averages of 100–300 consecutive spectra.

MS Data Analysis—The generated mass spectral data were transformed into ASCI format for analysis using MassLynx 4.0 software,

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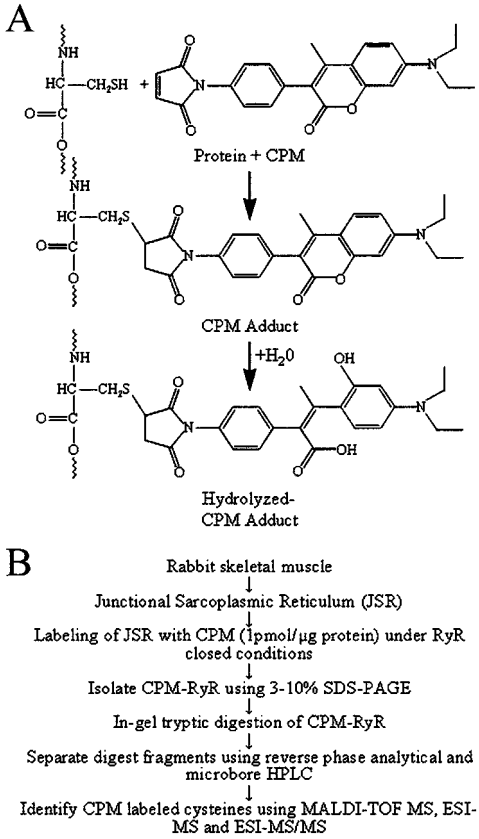

FIG. 1. **Chemistry of CPM adduct formation and procedural outline for identification of CPM adducts.** *A*, chemical reaction illustrating CPM forming a Michael adduct with a protein sulfhydryl and undergoing a subsequent hydrolysis of the chromen ring. *B*, a schematic outlining the mass spectrometric methodology to identify CPM-adducted sulfhydryls of RyR1.

including the MaxEnt module for signal reconstruction (Waters/Micromass, Manchester, UK). Theoretical masses for 0, 1, 2, and 3 positively charged peptides from full tryptic digestion of RyR1 were generated using the MassLynx 4.0 protein peptide editor module. Additional peptide masses were calculated for all cysteine containing peptides based on adduction by the 402.16-Da CPM and 420.17-Da hydrolyzed-CPM (see Fig. 1*A*). For peptides containing two cysteine residues, CPM modifications are assumed identical. Additionally, peptides with one uncleaved Arg or Lys were allowed (first order incompletion). The mass calculations for unmodified RyR1 peptides containing cysteines and all modified RyR1 peptides were merged into one Microsoft Excel data base used to screen masses generated by MS. Peptide sequence information obtained from MS/MS experiments facilitates the data base mass comparisons and was used whenever possible. A detailed description of the data base generation and the data base, are given in the Supplemental Material.

RESULTS

CPM Labeling, SDS-PAGE, and In-gel Tryptic Digestion—A schematic illustrating the identification procedure is included in Fig. 1*B*. The paramount first step in the identification of RyR1 hyperreactive sulfhydryls is their specific labeling by CPM under physiologically relevant, well characterized conditions. To achieve this, RyR1 hyperreactive sulfhydryls were labeled as described under "Experimental Procedures" using discriminating amounts of CPM to label JSR (1 pmol of CPM/μg of protein), a membrane fraction containing proteins, and cellular components necessary for normal RyR1 function. The CPM labeling of JSR was performed 24 times over a period of 2 days, yielding ~15 mg of CPM-labeled JSR protein. At 1 pmol of CPM/μg of protein, the JSR used in this procedure produced CPM labeling rate constants under RyR1 open (20 μM Ca^{2+}) and closed (10 mM Mg^{2+}) of 0.00156 ± 0.00003 and 0.04469 ± 0.00016 s^{-1}, respectively. The significantly faster rate of thioether adduct formation under channel-closed conditions was consistent with previously reported results (30, 31). Additionally, CPM labeling of JSR under the RyR1 closed conditions used in this procedure has been previously shown to selectively eliminate RyR1 redox sensing (21) through specific binding of hyperreactive sulfhydryls (30, 31, 33).

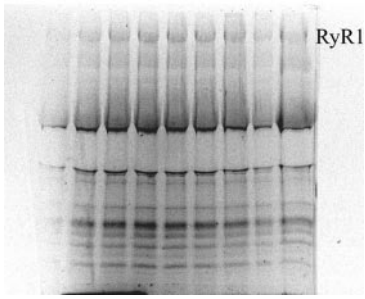

FIG. 2. **Fluorescent profile of SDS-PAGE.** A fluorescence image of a representative SDS-PAGE separation of CPM-labeled JSR, with CPM-labeled RyR1 representing the lowest mobility band that was subsequently excised for in-gel tryptic digestion.

Size separation of CPM-RyR1 thioether adducts from the other JSR proteins was achieved using SDS-PAGE (a total of nine gels). A representative gel image illustrating the CPM fluorescence pattern is shown in Fig. 2, which is consistent with previously reported results (30, 31). The additional fluorescent bands are currently under a similar investigation. In addition to providing clean separation of the CPM-RyR1 adducts, SDS-PAGE provides an excellent medium for full tryptic digestion, which generally yields doubly charged cationic peptides that are highly amenable to MS sequencing. Digested peptides were extracted from the gel matrix, frozen with liquid N_2, and stored at −80 °C until separated by analytical HPLC. Successful tryptic digestion was verified in subsequent HPLC profiles.

HPLC Separations—A monomer of RyR1 (5037 amino acids) generates 505 predicted tryptic cleavage products that can be separated using sequential steps of analytical and microbore HPLC. For each large format gel (nine total), the digested RyR1 peptides were subjected to C-18 reverse phase analytical HPLC. Fluorescence detection of CPM-adducted peptides using 384-nm excitation and 469-nm emission wavelengths generated a similar pattern for all nine analytical HPLC separations; a representative chromatogram is included in Fig. 3*A*. Each analytical HPLC chromatogram contained seven to eight dominant fluorescence peaks that were combined and concentrated into groups A, B, and C based on retention times: group A containing two to three peaks and eluting from 23 to 31 min, group B containing one peak eluting from 31 to 38 min, and group C containing three to four peaks eluting from 49 to 64 min (Fig. 3*A*). Several smaller fluorescence peaks were routinely observed between groups B and C (44–48 min), which were not analyzed due to their relatively low intensity and variable profile. Of the total fluorescence signal, groups A, B, and C represent 60–70%, with the variable peaks between groups B and C contributing ~10%. Minor peaks and a slightly increasing baseline constitute the remaining fluorescence signal.

To achieve greater resolution of the CPM-adducted RyR1 peptides, a microbore HPLC separation was performed on the pooled and concentrated analytical HPLC groups, monitoring fluorescence and UV absorbance. A representative chromatogram of group C in Fig. 3*B* illustrates improved, but incomplete resolution of the fluorescence peaks. Complete resolution of individual CPM-adducted RyR1 peptides occurred in subsequent MS analysis. One microbore separation was performed

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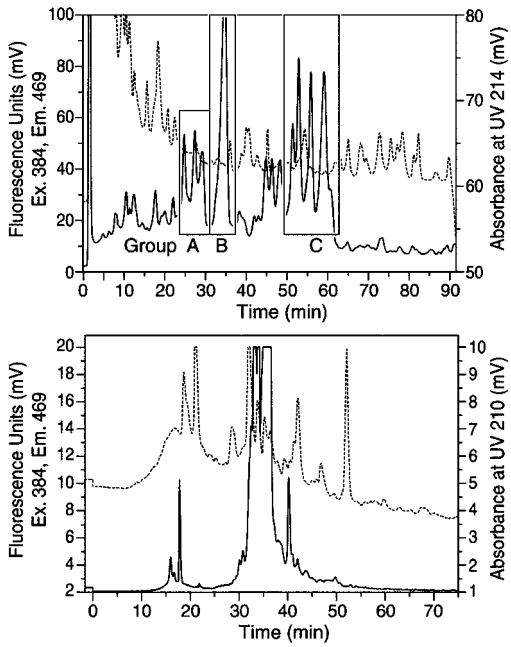

FIG. 3. **Sequential reverse phase HPLC separation of CPM-adducted RyR1 tryptic peptides.** Representative analytical (*A*) and microbore (*B*) HPLC chromatograms illustrating the fluorescence due to CPM (*solid line*) and absorbance at 214 nm for analytical and 210 nm for microbore (*dashed line*) HPLC.

on Group B, whereas two were performed on groups A and C. The second group C chromatogram is included in Fig. 3*B*. To possibly facilitate MS ionization, each fluorescent microbore fraction was partially hydrolyzed in 1% formic acid for 1 week under the storage conditions of 4 °C. Prior to MS analysis, samples were concentrated via SpeedVac to ~10 μl, and acetonitrile was added to improve spray ionization efficiency.

Mass Spectrometry—To identify the specific cysteines adducted by CPM, the fluorescence eluant from microbore HPLC was subjected to MS analysis using two methods, direct MALDI-TOF MS (MALDI) and ESI MS/MS (ESI). Both provide accurate peptide mass determinations with mass accuracies of 50 ppm for MALDI and better than 10 ppm for ESI. The ESI was the primary choice due to the higher mass accuracy and sequencing capabilities. Analysis of all fluorescent microbore eluants required 12 MALDI, 11 direct ESI, and 67 ESI product ion MS experiments. The charge state of the ions measured by MS are denoted by $(M+nH)^{n+}$, where n is the charge of the ion due to the addition of protons. In total, 7 CPM-adducted cysteines were identified from 6 digested peptides (one containing two cysteines), summarized in Table I and outlined as follows: 1) Cys-3635 (peptide 3631–3637) adducted by hydrolyzed-CPM was found in three microbore HPLC fractions of group C based on the theoretical peptide mass of $(M+H)^+$ 1185.58 Da and MS/MS sequence identification. The peptide fragment was found in MALDI as a high intensity signal at $(M+H)^+$ 1185.71 Da (Fig. 4*A*) and in direct ESI by a low intensity signal at $(M+2H)^{2+}$ 593.24 Da that corresponds to the predicted value of $(M+H)^+$ 1185.58 Da (Fig. 4*B*). This ion was selected for ESI MS/MS analysis and produced a fragmentation pattern indicating CPM adduction of peptide 3631–3637 (Fig. 4*C*). 2) Cys-1303 (peptide 1303–1324) adducted by CPM and hydrolyzed-CPM was found in microbore HPLC fractions of group C (two fractions) and B (one fraction), respectively. Identification was based on the theoretical peptide masses of $(M+H)^+$ 2564.21 Da (CPM adduct) and $(M+H)^+$ 2582.22 Da (hydrolyzed-CPM adduct) and achieved through MALDI, ESI, and ESI MS/MS. For the group B fraction, Fig. 4*D* illustrates the MALDI spectrum with a low intensity signal at $(M+H)^+$ 2582.26 Da. In Fig. 4*E*, the direct ESI spectrum contains low intensity signals at $(M+3H)^{3+}$ 861.44 Da and $(M+4H)^{4+}$ 646.32 Da that correspond to the predicted value of $(M+H)^+$ 2582.22 Da. The ESI MS/MS spectrum of the $(M+3H)^{3+}$ 861.44-Da peptide yields a fragmentation pattern that indicates peptide 1303–1324 adducted by hydrolyzed-CPM (Fig. 4*F*). For microbore HPLC group C, the MALDI spectra do not contain useful information about this peptide due to low ionization efficiency and/or concentration. However, a direct ESI experiment produces a strong signal at $(M+3H)^{3+}$ 855.40 Da that corresponds to the predicted value of $(M+H)^+$ 2564.21 Da for CPM-adducted peptide 1303–1324 (Supplemental Fig. 1). ESI MS/MS analysis of this triply charged ion produced a fragmentation pattern further indicating CPM adduction of Cys-1303 in the 1303–1324 peptide (Supplemental Fig. 2). 3) Cys-2565 (peptide 2565–2575) adducted by CPM was detected in one microbore HPLC fraction of group C based on the theoretical peptide mass of $(M+H)^+$ 1603.74 Da and MS/MS sequence identification. The MALDI spectrum in Fig. 4*A* illustrates a high intensity signal corresponding to $(M+H)^+$ 1604.09 Da. In Fig 4*B*, direct ESI reveals strong signals at $(M+2H)^{2+}$ 802.40 Da and $(M+3H)^{3+}$ 534.91 Da, respectively. ESI MS/MS analysis of the $(M+3H)^{3+}$ 534.91 Da peptide illustrates a fragmentation pattern that matches the theoretical decomposition for peptide 2565–2575 (Supplemental Fig. 3). 4) Cys-2606 and Cys-2611 (peptide 2598–2612) with both cysteines adducted by hydrolyzed-CPM was detected in one microbore HPLC fractions of group A based on the theoretical peptide mass of $(M+H)^+$ 2576.17 Da. The fraction yielded a MALDI spectrum with a low intensity peak at $(M+H)^+$ 2576.30 Da, corresponding to the predicted $(M+H)^+$ 2576.17 Da for hydrolyzed-CPM adduction of Cys-2606 and Cys-2611 (Supplemental Fig. 4). A direct ESI spectrum transformed to show the single charge state and reduce the noise illustrates an intense signal at $(M+H)^+$ 2576.21 Da, corresponding to the predicted $(M+H)^+$ 2576.17 Da (Supplemental Fig. 5). 5) Cys-1040 (peptide 1037–1044) adducted by hydrolyzed-CPM was detected in two microbore HPLC fractions of group A based on the theoretical peptide mass of $(M+H)^+$ 1311.60 Da. Each fraction yielded a separate MALDI spectrum, one indicating a strong signal at $(M+H)^+$ 1311.47 Da (Supplemental Fig. 6) and the other a strong signal at $(M+H)^+$ 1311.60 Da (Supplemental Fig. 7). 6) Cys-2436 (peptide 2436–2447) adducted by CPM was detected in one microbore HPLC fraction of group B based on the theoretical peptide mass of $(M+H)^+$ 1699.80 Da. A direct ESI spectrum transformed to the single charge state illustrates a strong signal at $(M+H)^+$ 1699.99 Da (Supplemental Fig. 8).

These cysteines represent high probability matches to theoretical predictions of CPM- or hydrolyzed-CPM-adducted peptides of RyR1. To further ensure proper identification, the obtained masses are also screened against theoretical digests of unlabeled RyR1 and the TPCK-modified porcine trypsin (Swiss-Prot P00761, with lysines methylated) used for digestion. The peptide masses obtained do not match any of these theoretical digests masses. Cysteines identified with the highest probability are 1303, 2565, and 3635, which are detected by MALDI, direct ESI, and ESI MS/MS. Cysteines 2606 and 2611 also represent high probability matches being identified by both MALDI and direct ESI. Although still with high probability, cysteines 1040 and 2436 are identified by MALDI and direct ESI, respectively.

Two additional cysteines were also tentatively identified. Direct ESI transformed to the single charge state detected what appears to be two overlapping signals yielding a mass $(M+H)^+$ of 2139.29 Da (Supplemental Fig. 9), closely matching

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TABLE I

Summary of MS results, listing the seven redox-sensing cysteines identified

Listed are the cysteines identified by amino acid number, the corresponding RyR1 peptide sequence with the modified cysteines in bold and underlined (**C**), whether the cysteine modification was by CPM or hydrolyzed CPM (Hyd-CPM), the analytical HPLC group containing the CPM-adducted peptide (A, B, or C) and the MS methodology detecting the CPM-adducted peptide, including direct MALDI-TOF (MALDI), direct ESI (ESI), and tandem ESI (MS/MS). For direct MALDI and ESI, the theoretical (in parentheses) and obtained ion masses (Da) are listed next to the analytical HPLC group. The multiple listing for most cysteines indicate the corresponding peptide was detected in multiple microbore HPLC fractions, each one listed.

Cys position	RyR1 segment	Modification	Analytical HPLC group, $(M+H)^+$ found (theoretical)		
			MALDI	ESI	MS/MS
			Da		
1040	DSL**C**QAVR	Hyd-CPM	A, 1311.61 (1311.60)		
		Hyd-CPM	A, 1311.47 (1311.60)		
1303	**C**TAGATPLAPPGLQPPAEDEAR	Hyd-CPM	B, 2582.21 (2582.22)	B, 2582.22 (2582.22)	B
		CPM		C, 2564.21 (2564.21)	C
		CPM		C, 2564.14 (2564.21)	
		CPM		C, 2564.20 (2564.21)	
2436	**C**APEMHLIQAGK	CPM		B, 1699.99 (1699.80)	
2565	**C**APLFAGTEHR	CPM	C, 1604.09 (1603.74)	C, 1603.82 (1603.74)	C
2606 and 2611	AQRDVIED**C**LMAL**C**R	Hyd-CPM	A, 2576.30 (2576.17)	A, 2576.21 (2576.17)	
3635	AVVA**C**FR	Hyd-CPM	C, 1185.71 (1185.58)	C, 1185.66 (1185.58)	C
		Hyd-CPM	C, 1185.73 (1185.58)	C, 1185.58 (1185.58)	
		Hyd-CPM	C, 1185.91 (1185.58)		

the predicted peptide mass of $(M+H)^+$ 2138.96 Da for CPM adducted Cys-120 in peptide 116–130. Similarly, ESI also detected another set of overlapping signals indicating a mass of $(M+H)^+$ 2334.46 Da (Supplemental Fig. 10), possibly corresponding to the predicted mass of $(M+H)^+$ 2335.19 Da for CPM-adducted Cys-3193 in peptide 3180–3196. These obtained masses do not match theoretical peptide masses from tryptic digestion of unmodified RyR1 or self-digestion of TPCK modified trypsin. However, these cysteines are presented with a caveat due to mass ambiguity and that neither MALDI nor ESI MS/MS analysis supported the identifications.

DISCUSSION

Several lines of biochemical and biophysical evidence indicate the central role 6–8 critical or hyperreactive sulfhydryls of RyR1 play in conferring channel sensitivity to modulators and in sensing O_2 tension and transmembrane redox potentials (14, 21, 25, 26). Identification of Cys-3635 as the only sulfhydryl adducted by NO under physiological conditions is heretofore the only structural information regarding the hyperreactive sulfhydryls of RyR1 (15). The scarcity of structural information likely results from difficulties in isolating and digesting the large (~2.3 MDa tetramer), membrane-bound RyR1, which contains 100 cysteines per monomer. In addition, specific labeling of hyperreactive sulfhydryls requires fully functional RyR1, conditions that include discriminating, undisruptive concentrations of labeling reagent and a membrane fraction containing the numerous RyR1 accessory proteins. This work uncovers the primary sequence location of seven hyperreactive sulfhydryls that may be involved in conferring redox-sensing properties to the RyR1 channel complex and describes the mass spectrometric methodology based on post-translational modification employed in the identification.

Initial challenges in identifying the hyperreactive sulfhydryls include labeling RyR1 in a physiologically relevant environment containing the necessary accessory proteins and subsequently isolating the CPM-RyR1 from this milieu. Adherence to conditions previously described in the initial detection of hyperreactive sulfhydryls (30, 31) and the characterization of the transmembrane redox sensor (21) ensure the specific CPM labeling of redox-sensitive sulfhydryls. Isolation of CPM-RyR1 monomers is achieved using multiple large format SDS-PAGE, all yielding a similar fluorescent labeling pattern that is consistent with profiles generated in the initial detection of RyR1 hyperreactive sulfhydryls (30, 31), indicating successful labeling and repeatability of the SDS-PAGE separation. The lowest mobility fluorescence band from SDS-PAGE is excised, and the final peptide mass and sequence information confirm the excision of only RyR1.

SDS-PAGE also provides a good medium for full tryptic digestion of the CPM-RyR1, generating numerous peptides that are separated using sequential analytical and microbore HPLC. Tryptic digestion, a well documented method (36, 37), generates doubly charged cationic peptides, which generally fragment predictably in tandem mass spectrometric systems. Analytical HPLC separation generates a repeatable pattern of fluorescence peaks that are sequestered and concentrated into three groups, A, B, and C. The UV 214 absorbance profiles reveal numerous peaks, as expected from the 505 possible tryptic cleavage products of RyR1. The presence of a few, repeatable fluorescence peaks that do not overlap UV peaks attests to the specificity of CPM labeling and the selective, biologically relevant quantities of CPM used. The analytical HPLC groups A, B, and C contain several non-CPM-labeled RyR1 peptides, thus requiring an additional separation step achieved with microbore HPLC.

Fluorescence fractions from microbore HPLC are subjected to mass spectrometric analysis by two ionization methods (MALDI and ESI) to increase the chance of detection, because derivatized peptides often exhibit unpredictable and variable ionization behavior under different ionization techniques. Additionally, results supported by multiple MS methodologies increase the probability of successful identification.

The stringent criteria for mass comparisons between measured and theoretical masses (0.35 Da being the greatest difference in a peptide that was identified by MALDI and ESI), verification by multiple MS methodologies for five of seven cysteines, and the detection of the same CPM-adducted peptide in multiple HPLC fractions enables us to present the seven cysteines in Table I with very little uncertainty. For these seven cysteines, the probabilities presented may not correlate with the level of cysteine reactivity, because frequency and intensity of the MS signal may only be a function of gel extraction or ionization efficiency. However, the frequent position of the CPM-adducted cysteines near arginine or lysine residues may contribute to their hyperreactivity.

This possible of generation of cysteine hyperreactivity by juxtapositional arginines or lysines has potential implications for the lethal pharmacogenetic disorder malignant hyperther-

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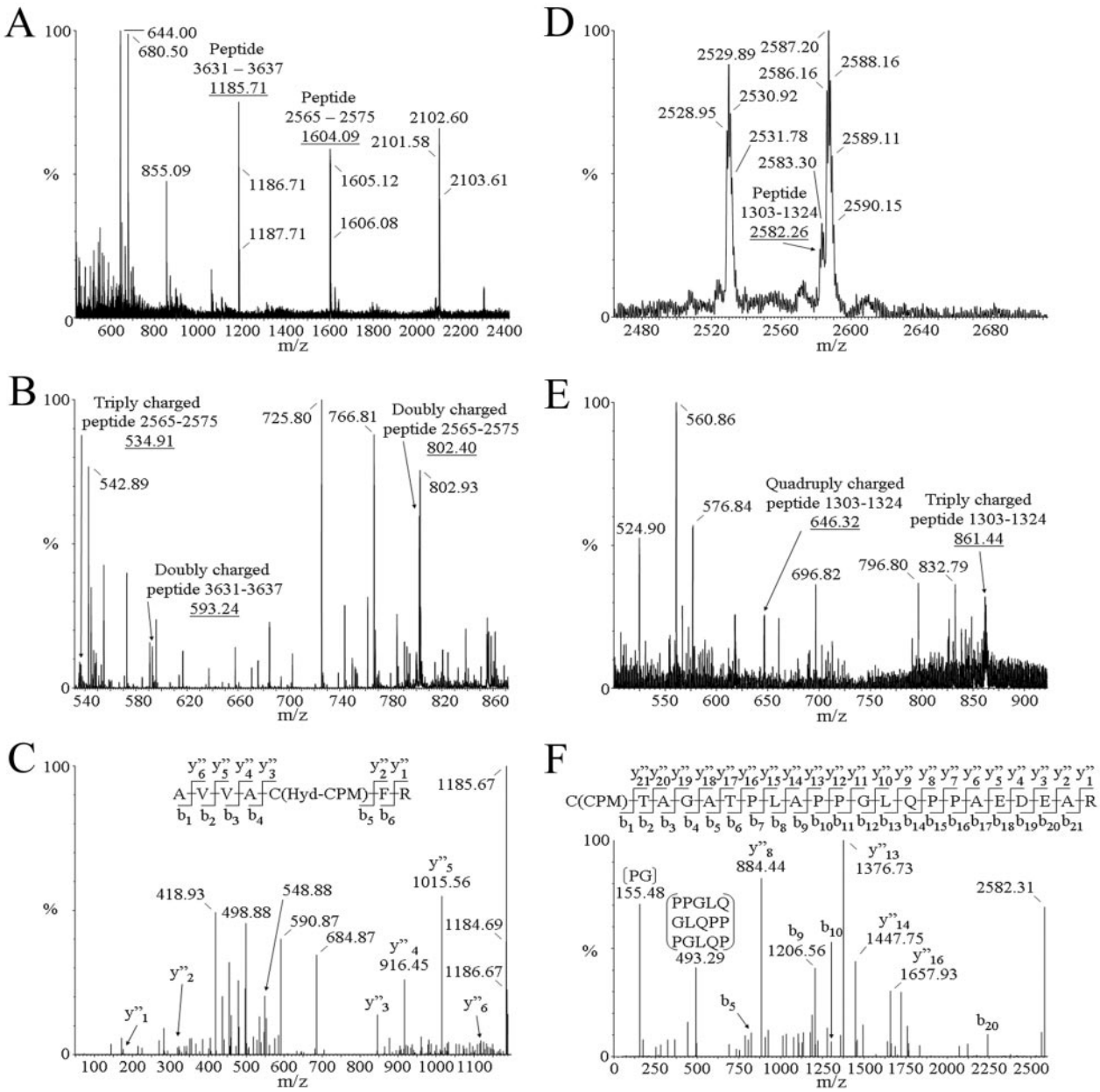

FIG. 4. **Mass spectrometry.** *A*, MALDI-TOF spectrum indicating monoisotopic masses that correspond to RyR1 peptide 3631–3637 with Cys-3635 adducted by hydrolyzed-CPM and peptide 2565–2575 with Cys-2565 adducted by CPM. *B*, direct ESI spectrum identifying doubly and triply charged ions corresponding to peptide 3631–3635 with Cys-3635 adducted by hydrolyzed-CPM and a doubly charged ion corresponding to peptide 2565–2575 with Cys-2565 adducted by CPM. *C*, an ESI MS/MS spectrum of the triply charged peptide from *part B*, which produces a fragmentation pattern that matches the predicted profile for peptide 3631–3637 with Cys-3635 adducted by hydrolyzed-CPM. *D*, MALDI-TOF spectrum indicating a monoisotopic mass that correspond to RyR1 peptide 1303–1324 with Cys-1303 adducted by hydrolyzed-CPM. *E*, direct ESI spectrum identifying triply and quadruply charged ions corresponding to peptide 1303–1324 with Cys-1303 adducted by hydrolyzed-CPM. *F*, an ESI MS/MS spectrum of the triply charged peptide from *part E*, which produces a fragmentation pattern that matches the predicted profile for peptide 1303–1324 with Cys-1303 adducted by hydrolyzed-CPM.

mia (MH) and the closely related central core disease (CCD), which are both linked to mutations in the *RyR1* gene. Human RyR1 R2435H/L mutations are associated with MH susceptibility (MHS) and CCD (38, 39), whereas R2454H/C (38, 40) and R2458H/C (41) mutations are associated with only MHS. Furthermore, a recent genetic and biochemical analysis of post-MH episode horse tissue reveals the point mutation R2454G (42). These arginine residues are vicinal to and possibly induce hyperreactivity in Cys-2436, the human analogue to rabbit Cys-2436 identified in this report. Non-arginine mutations vicinal to human Cys-2436 and linked to MHS include G2435H (40, 43, 44) and I2453T (45). Cys-2436 lies within a RyR1 MH/CCD region 2 (amino acids 2163–2458) that is often mutated in MHS or CCD patients; similarly, Cys-120, potentially identified here as a hyperreactive cysteine, lies within a RyR1 MH/CCD region 1 (amino acids 35–614) (46, 47). Although not necessarily related to MHS or CCD, the hyperreactivity, based on identification here, and the vicinal nature of cysteines of 2606 and 2611 suggest they may contribute the recently reported NADH-dependent oxidoreductase activity of RyR (48, 49).

This work presents the identification of hyperreactive sulfhydryls of RyR1 that may contribute to redox sensing and outlines a mass spectrometric methodology to identify reactive protein cysteines. Successful identification is derived from using a JSR preparation assayed for normal RyR1 function and

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CPM labeling kinetics, employing a CPM-labeling procedure previously shown to selectively eliminate the RyR1 transmembrane redox sensor, SDS-PAGE fluorescence profiles matching the initial discovery of RyR1-hyperreactive sulfhydryls, repeatable analytical HPLC chromatograms with only six to eight fluorescence peaks, and the same CPM-adducted cysteines identified in multiple microbore HPLC fractions and via multiple MS methodologies. The possibility exists that the list of cysteines presented is not comprehensive, resulting from inefficient MS ionization or peptide extraction from the gel matrix. However, the seven hyperreactive cysteines identified in the present study provide a basis for focusing future molecular analysis using expression of Cys point mutations to unravel the redox-sensing mechanisms regulating the RyR1 complex. In addition, RyR1 mutations lacking inherent redox-sensing capabilities may help elucidate cell signaling cascades regulated by redox and better understand the physiological role of redox signaling.

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Supplemental Data

This data section is a two-part supplement to the primary manuscript. The first section provides additional insight into the construction of the database used to analyze the MS results and the actual database. The final section includes additional mass spectra used to identify the hyperreactive cysteines.

The RyR1 sequence (Swiss-Prot # P11716) used for this analysis contains 5037 amino acid residues, of which 100 are cysteine residues. From this sequence, a database was created based on digestion with trypsin to account for cysteine containing peptides that are unmodified and those that are modified at the cysteine residue by CPM or hydrolyzed-CPM. Trypsin hydrolysis of the peptide occurs C-terminal to Lys (K) and Arg (R) residues. Theoretically, trypsin generates 505 peptide fragments, 81 of which contain cysteines (some peptides contain multiple cysteine residues). Additionally, if one K or R are uncleaved by trypsin (first order incompletion), 998 peptides are possible, with 217 containing one or more cysteines. As each cysteine containing peptide can be unmodified, adducted with CPM, or adducted with hydrolyzed-CPM, 651 possible peptides were accounted for (assuming peptides with multiple cysteines undergo identical modification, i.e. each modification is by CPM or hydrolyzed-CPM). For each peptide, masses are shown for the 0, 1, 2, and 3 charged states (see database below).

The MassLynx 4.0 program was set to calculate the monoisotopic mass for peptides < 3500 Da and the average mass for peptides > 3500 Da. To account for this, obtained peptides masses > 3500 Da are analyzed manually in addition to database and amino acid sequence comparisons to prevent misidentification.

Creating database:

1. Perform theoretical digest the native protein

2. Modify the Cys residue in the native protein to account for adduction by CPM, rename it "B" and define the elementary composition of "B" (creating new artificial residue). Replace all the Cys residues with "B" and theoretically digest the protein.
3. Modify the Cys residue in the native protein to account for adduction by hydrolyzed-CPM, rename it "Z", and define the elementary composition of "Z" (creating a new artificial residue). Replace all the Cys residues with "Z" and theoretically digest the protein.
4. Merge the resulting files and short by the fragment masses.
5. Delete all the fragments in the database which do not contain C, B or Z residues.

Definitions:

Residue #	Amino acid numbering starting from the N-terminal of the protein
C	Cysteine residue
B	Cysteine residue modified by CPM (1-(4-(7-(diethylamino)-4-methyl-2-oxo-2H-chromen-3-yl)phenyl)-1H-pyrrole-2,5-dione), which modifies the mass with 402.16 Da.
Z	Cysteine residue modified by hydrolyzed-CPM, the "chromen" ring of the CPM opens by one molecule of water which increases the mass to 420.17 Da.
Da	Dalton is the unit describing the mass of a neutral molecule. The Da is synonymous with amu (atomic mass unit), which equals 1/12 mass of C^{12}, or $1.6605387313 \times 10^{-24}$ g.
$(M+nH)^{n+}$	Symbol of the molecular or pseudo molecular ion in case of multiple charged species, where n = the charge of the ion due to the addition of protons to the analite molecule.

Supplemental Table 1. **Database used for MS screening**

Residue #	Theoretical Mass (Da)	$[M+H]^{+}$ (Da)	$[M+2H]^{2+}$ (Da)	$[M+3H]^{3+}$ (Da)	Sequence
2651-2653	435.19	436.2	218.6	146.07	(R)**C**WK(Y)
3631-3637	764.4	765.41	383.21	255.81	(R)AVVA**C**FR(M)
2228-2234	798.32	799.33	400.17	267.11	(K)MVTS**CC**R(F)
311-317	830.37	831.38	416.2	277.8	(K)ATSF**C**FR(V)
2651-2653	837.35	838.36	419.68	280.13	(R)**B**WK(Y)
2651-2653	855.36	856.37	428.69	286.13	(R)**Z**WK(Y)
1037-1044	890.43	891.44	446.22	297.82	(R)DSL**C**QAVR(T)
1672-1680	916.45	917.46	459.24	306.49	(R)AV**C**ALGNNR(V)
3630-3637	920.5	921.51	461.26	307.84	(R)RAVVA**C**FR(M)
2235-2241	950.41	951.42	476.21	317.81	(R)FL**C**YF**C**R(I)
3396-3403	967.44	968.45	484.73	323.49	(R)DEFSVL**C**R(D)
1586-1594	978.47	979.48	490.24	327.16	(K)NPAPQ**C**PPR(L)
3037-3045	1070.51	1071.52	536.26	357.85	(K)EMITSLF**C**K(L)
1585-1594	1106.57	1107.57	554.29	369.86	(R)KNPAPQ**C**PPR(L)
2360-2369	1116.58	1117.58	559.3	373.2	(R)KPE**C**FGPALR(G)
311-320	1144.57	1145.58	573.29	382.53	(K)ATSF**C**FRVSK(E)
393-402	1148.49	1149.5	575.25	383.84	(R)**C**QQEESQAAR(M)
35-45	1149.56	1150.57	575.79	384.19	(K)L**C**LAAEGFGNR(L)
3631-3637	1166.56	1167.57	584.29	389.86	(R)AVVA**B**FR(M)
2225-2234	1170.53	1171.54	586.28	391.19	(R)FPKMVTS**CC**R(F)
116-125	1173.55	1174.56	587.78	392.19	(R)MYLS**C**LTTSR(S)
3631-3637	1184.57	1185.58	593.29	395.86	(R)AVVA**Z**FR(M)
3186-3196	1197.67	1198.67	599.84	400.23	(K)LRPALGE**C**LAR(L)
2565-2575	1200.57	1201.58	601.29	401.2	(K)**C**APLFAGTEHR(A)
3649-3658	1204.53	1205.53	603.27	402.52	(R)A**C**NMFLESYK(A)
1647-1656	1207.56	1208.57	604.79	403.53	(R)**C**MDILELSER(L)
311-317	1232.53	1233.54	617.27	411.85	(K)ATSF**B**FR(V)
1034-1044	1247.6	1248.61	624.81	416.88	(R)SNRDSL**C**QAVR(T)
311-317	1250.54	1251.55	626.28	417.86	(K)ATSF**Z**FR(V)
307-317	1267.61	1268.62	634.81	423.55	(K)AHTKATSF**C**FR(V)
3168-3179	1285.66	1286.67	643.84	429.56	(R)TL**C**SIYSLGTTK(N)
1037-1044	1292.59	1293.59	647.3	431.87	(R)DSL**B**QAVR(T)
2436-2447	1296.63	1297.64	649.32	433.22	(R)**C**APEMHLIQAGK(G)
1260-1271	1303.59	1304.6	652.8	435.54	(R)MDGTVDTPP**C**LR(L)
2235-2244	1306.63	1307.64	654.32	436.55	(R)FL**C**YF**C**RISR(Q)
1037-1044	1310.6	1311.6	656.31	437.87	(R)DSL**Z**QAVR(T)
1672-1680	1318.61	1319.62	660.31	440.55	(R)AV**B**ALGNNR(V)
3630-3637	1322.66	1323.67	662.34	441.89	(R)RAVVA**B**FR(M)
3035-3045	1327.65	1328.66	664.83	443.56	(K)EKEMITSLF**C**K(L)
1672-1680	1336.62	1337.63	669.32	446.55	(R)AV**Z**ALGNNR(V)
3630-3637	1340.67	1341.68	671.34	447.9	(R)RAVVA**Z**FR(M)
2553-2564	1345.8	1346.81	673.91	449.61	(R)YL**C**LAVLPLITK(**C**)
1669-1680	1348.7	1349.71	675.36	450.58	(R)LYRAV**C**ALGNNR(V)
3396-3403	1369.6	1370.61	685.81	457.54	(R)DEFSVL**B**R(D)

2601-2612	1379.62	1380.63	690.82	460.88	(R)DVIED**C**LMAL**C**R(Y)
1586-1594	1380.63	1381.64	691.32	461.22	(K)NPAPQ**B**PPR(L)
3396-3403	1387.61	1388.62	694.81	463.55	(R)DEFSVL**Z**R(D)
1586-1594	1398.64	1399.65	700.33	467.22	(K)NPAPQ**Z**PPR(L)
3774-3787	1450.7	1451.71	726.36	484.57	(R)GAAEMVLQMISA**C**K(G)
2643-2653	1461.72	1462.73	731.87	488.25	(K)LLTNHYER**C**WK(Y)
5018-5029	1462.58	1463.59	732.3	488.53	(R)**C**WDFFPAGD**C**FR(K)
3037-3045	1472.67	1473.68	737.34	491.9	(K)EMITSLF**B**K(L)
3037-3045	1490.68	1491.69	746.35	497.9	(K)EMITSLF**Z**K(L)
1585-1594	1508.72	1509.73	755.37	503.92	(R)KNPAPQ**B**PPR(L)
2360-2369	1518.73	1519.74	760.37	507.25	(R)KPE**B**FGPALR(G)
2317-2330	1519.65	1520.66	760.83	507.56	(K)GYPDIGWNP**C**GGER(Y)
1585-1594	1526.73	1527.74	764.37	509.92	(R)KNPAPQ**Z**PPR(L)
2360-2369	1536.74	1537.75	769.38	513.26	(R)KPE**Z**FGPALR(G)
244-257	1537.73	1538.74	769.88	513.59	(R)LVYYEGGAV**C**THAR(S)
311-320	1546.73	1547.74	774.37	516.58	(K)ATSF**B**FRVSK(E)
393-402	1550.65	1551.65	776.33	517.89	(R)**B**QQEESQAAR(M)
35-45	1551.72	1552.73	776.87	518.25	(K)L**B**LAAEGFGNR(L)
931-945	1556.77	1557.78	779.39	519.93	(K)TLLALG**C**HVGMADEK(A)
311-320	1564.74	1565.75	783.38	522.59	(K)ATSF**Z**FRVSK(E)
393-402	1568.66	1569.66	785.34	523.89	(R)**Z**QQEESQAAR(M)
35-45	1569.73	1570.74	785.87	524.25	(K)L**Z**LAAEGFGNR(L)
116-125	1575.71	1576.72	788.86	526.24	(R)MYLS**B**LTTSR(S)
116-125	1593.72	1594.73	797.87	532.25	(R)MYLS**Z**LTTSR(S)
3186-3196	1599.82	1600.83	800.92	534.28	(K)LRPALGE**B**LAR(L)
2228-2234	1602.63	1603.64	802.33	535.22	(K)MVTS**BB**R(F)
2565-2575	1602.73	1603.74	802.37	535.25	(K)**B**APLFAGTEHR(A)
3649-3658	1606.68	1607.69	804.35	536.57	(R)A**B**NMFLESYK(A)
1647-1656	1609.72	1610.72	805.87	537.58	(R)**B**MDILELSER(L)
2356-2369	1611.93	1612.94	806.97	538.32	(R)LLIRKPE**C**FGPALR(G)
3186-3196	1617.83	1618.84	809.92	540.29	(K)LRPALGE**Z**LAR(L)
16-30	1619.81	1620.82	810.91	540.94	(R)TDDEVVLQ**C**SATVLK(E)
2565-2575	1620.74	1621.75	811.38	541.25	(K)**Z**APLFAGTEHR(A)
3649-3658	1624.69	1625.7	813.35	542.57	(R)A**Z**NMFLESYK(A)
1647-1656	1627.73	1628.73	814.87	543.58	(R)**Z**MDILELSER(L)
2228-2234	1638.66	1639.66	820.34	547.23	(K)MVTS**ZZ**R(F)
31-45	1647.84	1648.85	824.93	550.29	(K)EQLKL**C**LAAEGFGNR(L)
1034-1044	1649.76	1650.77	825.89	550.93	(R)SNRDSL**B**QAVR(T)
1034-1044	1667.77	1668.78	834.89	556.93	(R)SNRDSL**Z**QAVR(T)
307-317	1669.77	1670.78	835.89	557.6	(K)AHTKATSF**B**FR(V)
307-317	1687.78	1688.79	844.9	563.6	(K)AHTKATSF**Z**FR(V)
3168-3179	1687.82	1688.82	844.92	563.61	(R)TL**B**SIYSLGTTK(N)
243-257	1693.84	1694.84	847.93	565.62	(R)RLVYYEGGAV**C**THAR(S)
3037-3051	1693.93	1694.93	847.97	565.65	(K)EMITSLF**C**KLAALVR(H)
2436-2447	1698.79	1699.8	850.4	567.27	(R)**B**APEMHLIQAGK(G)
1260-1271	1705.75	1706.76	853.88	569.59	(R)MDGTVDTPP**B**LR(L)
3168-3179	1705.83	1706.84	853.92	569.62	(R)TL**Z**SIYSLGTTK(N)
2436-2447	1716.8	1717.81	859.41	573.27	(R)**Z**APEMHLIQAGK(G)

1260-1271	1723.76	1724.77	862.89	575.59	(R)MDGTVDTPP**Z**LR(L)
3035-3045	1729.81	1730.82	865.91	577.61	(K)EKEMITSLF**B**K(L)
2228-2241	1730.72	1731.73	866.37	577.92	(K)MVTS**CC**RFL**C**YF**C**R(I)
2598-2612	1734.82	1735.83	868.42	579.28	(K)AQRDVIED**C**LMAL**C**R(Y)
116-130	1735.79	1736.8	868.9	579.61	(R)MYLS**C**LTTSRSMTDK(L)
2014-2028	1744.71	1745.72	873.36	582.58	(K)DEADEED**C**PLPEDIR(Q)
3035-3045	1747.82	1748.83	874.92	583.61	(K)EKEMITSLF**Z**K(L)
2553-2564	1747.96	1748.97	874.99	583.66	(R)YL**B**LAVLPLITK(**B**)
1669-1680	1750.86	1751.87	876.44	584.63	(R)LYRAV**B**ALGNNR(V)
2235-2241	1754.73	1755.74	878.37	585.92	(R)FL**B**YF**B**R(I)
111-125	1761.84	1762.85	881.93	588.29	(R)HAHSRMYLS**C**LTTSR(S)
599-615	1761.89	1762.9	881.95	588.31	(K)VLDVL**C**SL**C**V**C**NGVAVR(S)
2553-2564	1765.97	1766.98	883.99	589.67	(R)YL**Z**LAVLPLITK(**Z**)
535-550	1766.87	1767.87	884.44	589.96	(R)AN**C**ALFSTNLDWVVSK(L)
1669-1680	1768.87	1769.88	885.44	590.63	(R)LYRAV**Z**ALGNNR(V)
1260-1275	1780.87	1781.88	891.44	594.63	(R)MDGTVDTPP**C**LRLAHR(T)
2235-2241	1790.75	1791.76	896.38	597.92	(R)FL**Z**YF**Z**R(I)
2436-2452	1822.92	1823.93	912.47	608.65	(R)**C**APEMHLIQAGKGEALR(I)
1647-1661	1832.91	1833.92	917.46	611.98	(R)**C**MDILELSERLDLQR(F)
290-306	1835.93	1836.94	918.97	612.99	(R)YLALTEDQGLVVVDA**C**K(A)
3774-3787	1852.86	1853.86	927.44	618.63	(R)GAAEMVLQMISA**B**K(G)
802-818	1862.95	1863.96	932.48	621.99	(K)FLPPPGYAP**C**HEAVLPR(E)
2643-2653	1863.88	1864.88	932.95	622.3	(K)LLTNHYER**B**WK(Y)
3774-3787	1870.87	1871.87	936.44	624.63	(R)GAAEMVLQMISA**Z**K(G)
2643-2653	1881.89	1882.9	941.95	628.3	(K)LLTNHYER**Z**WK(Y)
903-918	1886.95	1887.95	944.48	629.99	(R)LHP**C**LVNFHSLPEPER(N)
2317-2330	1921.81	1922.82	961.91	641.61	(K)GYPDIGWNP**B**GGER(Y)
1709-1725	1922.96	1923.96	962.49	641.99	(R)AGYYDLLISIHLESA**C**R(S)
3180-3196	1932.03	1933.03	967.02	645.02	(K)NTYVEKLRPALGE**C**LAR(L)
2317-2330	1939.82	1940.83	970.92	647.61	(K)GYPDIGWNP**Z**GGER(Y)
244-257	1939.89	1940.9	970.95	647.64	(R)LVYYEGGAV**B**THAR(S)
2298-2316	1951.99	1953	977	651.67	(K)VVSYLAG**C**GLQS**C**PMLLAK(G)
244-257	1957.9	1958.91	979.96	653.64	(R)LVYYEGGAV**Z**THAR(S)
3770-3787	1957.99	1959.00	980	653.67	(R)LHTRGAAEMVLQMISA**C**K(G)
931-945	1958.93	1959.93	980.47	653.98	(K)TLLALG**B**HVGMADEK(A)
2225-2234	1974.85	1975.86	988.43	659.29	(R)FPKMVTS**BB**R(F)
931-945	1976.94	1977.95	989.48	659.99	(K)TLLALG**Z**HVGMADEK(A)
2225-2234	2010.87	2011.88	1006.44	671.3	(R)FPKMVTS**ZZ**R(F)
2356-2369	2014.09	2015.09	1008.05	672.37	(R)LLIRKPE**B**FGPALR(G)
3168-3185	2020.02	2021.03	1011.02	674.35	(R)TL**C**SIYSLGTTKNTYVEK(L)
16-30	2021.97	2022.97	1011.99	675	(R)TDDEVVLQ**B**SATVLK(E)
2356-2369	2032.1	2033.10	1017.06	678.37	(R)LLIRKPE**Z**FGPALR(G)
16-30	2039.98	2040.98	1021	681	(R)TDDEVVLQ**Z**SATVLK(E)
902-918	2043.05	2044.06	1022.53	682.02	(K)RLHP**C**LVNFHSLPEPER(N)
31-45	2050	2051.01	1026.01	684.34	(K)EQLKL**B**LAAEGFGNR(L)
31-45	2068.01	2069.02	1035.01	690.34	(K)EQLKL**Z**LAAEGFGNR(L)
244-261	2080.03	2081.04	1041.02	694.35	(R)LVYYEGGAV**C**THARSLWR(L)
4876-4892	2082.85	2083.86	1042.43	695.29	(K)**C**DDMMT**C**YLFHMYVGVR(A)

3631-3648	2088.08	2089.08	1045.05	697.03	(R)AVVA**C**FRMTPLYNLPTHR(A)
532-550	2094.03	2095.04	1048.02	699.02	(R)GNRAN**C**ALFSTNLDWVVSK(L)
3054-3073	2095.12	2096.13	1048.57	699.38	(R)VSLFGTDAPAVVN**C**LHILAR(S)
243-257	2095.99	2097.00	1049	699.67	(R)RLVYYEGGAV**B**THAR(S)
3037-3051	2096.08	2097.09	1049.05	699.7	(K)EMITSLF**B**KLAALVR(H)
2235-2244	2110.95	2111.96	1056.48	704.66	(R)FL**B**YF**B**RISR(Q)
243-257	2114	2115.01	1058.01	705.68	(R)RLVYYEGGAV**Z**THAR(S)
3037-3051	2114.09	2115.1	1058.06	705.71	(K)EMITSLF**Z**KLAALVR(H)
16-34	2118.09	2119.1	1060.05	707.04	(R)TDDEVVLQ**C**SATVLKEQLK(L)
116-130	2137.95	2138.96	1069.98	713.66	(R)MYLS**B**LTTSRSMTDK(L)
596-615	2141.09	2142.1	1071.55	714.7	(R)NHKVLDVL**C**SL**C**V**C**NGV
2014-2028	2146.87	2147.88	1074.44	716.63	(K)DEADEED**B**PLPEDIR(Q)
2235-2244	2146.97	2147.98	1074.49	716.66	(R)FL**Z**YF**Z**RISR(Q)
802-820	2148.09	2149.1	1075.05	717.04	(K)FLPPPGYAP**C**HEAVLPRER(L)
535-553	2151.08	2152.09	1076.55	718.03	(R)AN**C**ALFSTNLDWVVSKLDR(L)
116-130	2155.96	2156.97	1078.99	719.66	(R)MYLS**Z**LTTSRSMTDK(L)
1303-1324	2161.05	2162.06	1081.53	721.36	(R)**C**TAGATPLAPPGLQPPAEDEAR(A)
111-125	2164	2165.01	1083.01	722.34	(R)HAHSRMYLS**B**LTTSR(S)
3385-3403	2164.05	2165.05	1083.03	722.36	(K)AEAEEGELLVRDEFSVL**C**R(D)
2014-2028	2164.88	2165.89	1083.45	722.63	(K)DEADEED**Z**PLPEDIR(Q)
1709-1727	2166.09	2167.1	1084.05	723.04	(R)AGYYDLLISIHLESA**C**RSR(R)
535-550	2169.02	2170.03	1085.52	724.02	(R)AN**B**ALFSTNLDWVVSK(L)
111-125	2182.01	2183.02	1092.01	728.34	(R)HAHSRMYLS**Z**LTTSR(S)
1260-1275	2183.03	2184.04	1092.52	728.68	(R)MDGTVDTPP**B**LRLAHR(T)
2601-2612	2183.94	2184.95	1092.98	728.99	(R)DVIED**B**LMAL**B**R(Y)
535-550	2187.03	2188.04	1094.53	730.02	(R)AN**Z**ALFSTNLDWVVSK(L)
1489-1508	2189.91	2190.92	1095.96	730.98	(K)**C**SN**C**YMVWGGDFVSPGQQGR(I)
475-493	2194.08	2195.08	1098.05	732.37	(R)QSLFQEEGMLSLVLN**C**IDR(L)
1260-1275	2201.04	2202.05	1101.53	734.69	(R)MDGTVDTPP**Z**LRLAHR(T)
2601-2612	2219.96	2220.97	1110.99	741	(R)DVIED**Z**LMAL**Z**R(Y)
3887-3904	2223.05	2224.06	1112.53	742.03	(R)FLQLL**C**EGHNNDFQNYLR(T)
2436-2452	2225.08	2226.08	1113.55	742.7	(R)**B**APEMHLIQAGKGEALR(I)
931-951	2227.1	2228.11	1114.56	743.37	(K)TLLALG**C**HVGMADEKAEDNLK(K)
1647-1661	2235.07	2236.08	1118.54	746.03	(R)**B**MDILELSERLDLQR(F)
290-306	2238.09	2239.1	1120.05	747.04	(R)YLALTEDQGLVVVDA**B**K(A)
2436-2452	2243.09	2244.09	1122.55	748.7	(R)**Z**APEMHLIQAGKGEALR(I)
1647-1661	2253.08	2254.09	1127.55	752.03	(R)**Z**MDILELSERLDLQR(F)
290-306	2256.1	2257.11	1129.06	753.04	(R)YLALTEDQGLVVVDA**Z**K(A)
802-818	2265.11	2266.12	1133.56	756.04	(K)FLPPPGYAP**B**HEAVLPR(E)
5018-5029	2266.9	2267.9	1134.46	756.64	(R)**B**WDFFPAGD**B**FR(K)
290-310	2273.17	2274.18	1137.59	758.73	(R)YLALTEDQGLVVVDA**C**KAHTK(A)
3228-3248	2280.15	2281.16	1141.08	761.06	(R)AILGLPNSVEEM**C**PDIPVLDR(L)
1937-1954	2282.03	2283.04	1142.02	761.68	(K)LQM**C**NLLEYF**C**DQELQHR(V)
802-818	2283.12	2284.13	1142.57	762.05	(K)FLPPPGYAP**Z**HEAVLPR(E)
3517-3537	2287.14	2288.15	1144.58	763.39	(K)MLPIGLNM**C**APTDQDLIMLAK(T)
903-918	2289.1	2290.11	1145.56	764.04	(R)LHP**B**LVNFHSLPEPER(N)
3396-3414	2298.21	2299.22	1150.11	767.08	(R)DEFSVL**C**RDLYALYPLLIR(Y)
5018-5029	2302.92	2303.92	1152.47	768.65	(R)**Z**WDFFPAGD**Z**FR(K)

903-918	2307.11	2308.12	1154.57	770.05	(R)LHP**Z**LVNFHSLPEPER(N)
1709-1725	2325.11	2326.12	1163.56	776.05	(R)AGYYDLLISIHLESA**B**R(S)
2317-2336	2327.08	2328.09	1164.55	776.7	(K)GYPDIGWNP**C**GGERYLDFLR(F)
3180-3196	2334.18	2335.19	1168.1	779.07	(K)NTYVEKLRPALGE**B**LAR(L)
1709-1725	2343.12	2344.13	1172.57	782.05	(R)AGYYDLLISIHLESA**Z**R(S)
3180-3196	2352.19	2353.2	1177.1	785.07	(K)NTYVEKLRPALGE**Z**LAR(L)
3905-3925	2352.24	2353.24	1177.13	785.09	(R)TQTGNTTTINIII**C**TVDYLLR(L)
222-242	2360.02	2361.02	1181.02	787.68	(R)LFHGHMDE**C**LTISAADSDDQR(R)
3770-3787	2360.15	2361.16	1181.08	787.72	(R)LHTRGAAEMVLQMISA**B**K(G)
3770-3787	2378.16	2379.17	1190.09	793.73	(R)LHTRGAAEMVLQMISA**Z**K(G)
3052-3073	2388.28	2389.29	1195.15	797.1	(R)HRVSLFGTDAPAVVN**C**LHILAR(S)
3516-3537	2415.24	2416.25	1208.63	806.09	(K)KMLPIGLNM**C**APTDQDLIMLAK(T)
3168-3185	2422.18	2423.18	1212.1	808.4	(R)TL**B**SIYSLGTTKNTYVEK(L)
3168-3185	2440.19	2441.2	1221.1	814.4	(R)TL**Z**SIYSLGTTKNTYVEK(L)
902-918	2445.21	2446.21	1223.61	816.08	(K)RLHP**B**LVNFHSLPEPER(N)
797-818	2461.24	2462.24	1231.63	821.42	(R)HGEFKFLPPPGYAP**C**HEAVLPR(E)
902-918	2463.22	2464.22	1232.62	822.08	(K)RLHP**Z**LVNFHSLPEPER(N)
473-493	2464.22	2465.23	1233.12	822.41	(R)NRQSLFQEEGMLSLVLN**C**IDR(L)
244-261	2482.19	2483.2	1242.1	828.4	(R)LVYYEGGAV**B**THARSLWR(L)
284-306	2487.28	2488.29	1244.65	830.1	(R)HVTTGRYLALTEDQGLVVVDA**C**K(A)
3631-3648	2490.23	2491.24	1246.12	831.09	(R)AVVA**B**FRMTPLYNLPTHR(A)
532-550	2496.19	2497.2	1249.1	833.07	(R)GNRAN**B**ALFSTNLDWVVSK(L)
3054-3073	2497.28	2498.29	1249.65	833.44	(R)VSLFGTDAPAVVN**B**LHILAR(S)
244-261	2500.2	2501.21	1251.11	834.41	(R)LVYYEGGAV**Z**THARSLWR(L)
3263-3283	2505.25	2506.25	1253.63	836.09	(R)YTEMPHVIEITLPML**C**SYLPR(W)
3631-3648	2508.24	2509.25	1255.13	837.09	(R)AVVA**Z**FRMTPLYNLPTHR(A)
2141-2163	2512.22	2513.23	1257.12	838.41	(R)AYTISPSSVEDTMSLLE**C**LGQIR(S)
532-550	2514.2	2515.21	1258.11	839.07	(R)GNRAN**Z**ALFSTNLDWVVSK(L)
3054-3073	2515.29	2516.3	1258.65	839.44	(R)VSLFGTDAPAVVN**Z**LHILAR(S)
222-243	2516.12	2517.13	1259.07	839.71	(R)LFHGHMDE**C**LTISAADSDDQRR(L)
16-34	2520.25	2521.25	1261.13	841.09	(R)TDDEVVLQ**B**SATVLKEQLK(L)
3638-3658	2528.2	2529.21	1265.11	843.74	(R)MTPLYNLPTHRA**C**NMFLESYK(A)
2553-2575	2528.36	2529.37	1265.19	843.8	(R)YL**C**LAVLPLITK**C**APLFAGTEHR(A)
1586-1607	2535.25	2536.26	1268.64	846.09	(K)NPAPQ**C**PPRLEVQMLMPVSWSR(M)
16-34	2538.26	2539.26	1270.14	847.09	(R)TDDEVVLQ**Z**SATVLKEQLK(L)
2598-2612	2539.14	2540.15	1270.58	847.39	(K)AQRDVIED**B**LMAL**B**R(Y)
3517-3539	2544.29	2545.3	1273.15	849.11	(K)MLPIGLNM**C**APTDQDLIMLAKTR(Y)
802-820	2550.25	2551.26	1276.13	851.09	(K)FLPPPGYAP**B**HEAVLPR
535-553	2553.24	2554.24	1277.63	852.09	(R)AN**B**ALFSTNLDWVVSKLDR(L)
1303-1324	2563.21	2564.21	1282.61	855.41	(R)**B**TAGATPLAPPGLQPPAEDEAR(A)
3226-3248	2565.29	2566.3	1283.65	856.11	(R)ERAILGLPNSVEEM**C**PDIPVLDR(L)
3385-3403	2566.2	2567.21	1284.11	856.41	(K)AEAEEGELLVRDEFSVL**B**R(D)
1709-1727	2568.25	2569.25	1285.13	857.09	(R)AGYYDLLISIHLESA**B**RSR(R)
802-820	2568.26	2569.27	1285.14	857.1	(K)FLPPPGYAP**Z**HEAVLPRER(L)
535-553	2571.25	2572.25	1286.63	858.09	(R)AN**Z**ALFSTNLDWVVSKLDR(L)
2698-2722	2573.17	2574.18	1287.59	858.73	(R)MAMP**C**L**C**AIAGALPPDYVDASYSSK(A)

2598-2612	2575.16	2576.17	1288.59	859.39	(K)AQRDVIED**Z**LMAL**Z**R(Y)
1303-1324	2581.22	2582.22	1291.62	861.41	(R)**Z**TAGATPLAPPGLQPPAEDEAR(A)
3385-3403	2584.22	2585.22	1293.12	862.41	(K)AEAEEGELLVRDEFSVL**Z**R(D)
1709-1727	2586.26	2587.27	1294.14	863.09	(R)AGYYDLLISIHLESA**Z**RSR(R)
475-493	2596.23	2597.24	1299.12	866.42	(R)QSLFQEEGMLSLVLN**B**IDR(L)
3774-3799	2612.27	2613.28	1307.14	871.76	(R)GAAEMVLQMISA**C**KGETGAMVSSTLK(L)
475-493	2614.24	2615.25	1308.13	872.42	(R)QSLFQEEGMLSLVLN**Z**IDR(L)
3887-3904	2625.21	2626.22	1313.61	876.08	(R)FLQLL**B**EGHNNDFQNYLR(T)
931-951	2629.26	2630.26	1315.64	877.43	(K)TLLALG**B**HVGMADEKAEDNLK(K)
3054-3078	2637.41	2638.41	1319.71	880.14	(R)VSLFGTDAPAVVN**C**LHILARSLDAR(T)
2360-2385	2640.37	2641.38	1321.19	881.13	(R)KPE**C**FGPALRGEGGSGLLAAIEEAIR(I)
3887-3904	2643.22	2644.23	1322.62	882.08	(R)FLQLL**Z**EGHNNDFQNYLR(T)
931-951	2647.27	2648.27	1324.64	883.43	(K)TLLALG**Z**HVGMADEKAEDNLK(K)
1624-1646	2651.27	2652.27	1326.64	884.76	(R)LGWAVQ**C**QDPLTMMALHIPEENR(**C**)
290-310	2675.33	2676.34	1338.67	892.78	(R)YLALTEDQGLVVVDA**B**KAHTK(A)
3228-3248	2682.31	2683.32	1342.16	895.11	(R)AILGLPNSVEEM**B**PDIPVLDR(L)
2654-2676	2685.25	2686.26	1343.63	896.09	(K)YY**C**LPTGWANFGVTSEEELHLTR(K)
3517-3537	2689.3	2690.31	1345.66	897.44	(K)MLPIGLNM**B**APTDQDLIMLAK(T)
1509-1534	2689.38	2690.39	1345.7	897.47	(R)ISHTDLVIG**C**LVDLATGLMTFTANGK(E)
290-310	2693.34	2694.35	1347.68	898.79	(R)YLALTEDQGLVVVDA**Z**KAHTK(A)
3228-3248	2700.32	2701.33	1351.17	901.11	(R)AILGLPNSVEEM**Z**PDIPVLDR(L)
3396-3414	2700.37	2701.37	1351.19	901.13	(R)DEFSVL**B**RDLYALYPLLIR(Y)
3517-3537	2707.31	2708.32	1354.66	903.45	(K)MLPIGLNM**Z**APTDQDLIMLAK(T)
3001-3023	2708.44	2709.45	1355.23	903.82	(K)ILLPLINQYFTNH**C**LYFLSTPAK(V)
2565-2588	2717.32	2718.33	1359.67	906.78	(K)**C**APLFAGTEHRAIMVDSMLHTVYR(L)
3396-3414	2718.38	2719.38	1360.2	907.13	(R)DEFSVL**Z**RDLYALYPLLIR(Y)
2317-2336	2729.24	2730.25	1365.63	910.75	(K)GYPDIGWNP**B**GGERYLDFLR(F)
2317-2336	2747.25	2748.26	1374.63	916.76	(K)GYPDIGWNP**Z**GGERYLDFLR(F)
341-365	2751.34	2752.34	1376.68	918.12	(K)YGESL**C**FVQHVASGLWLTYAAPDPK(A)
393-416	2752.31	2753.31	1377.16	918.44	(R)**C**QQEESQAARMIHSTAGLYNQFIK(G)
3905-3925	2754.39	2755.4	1378.2	919.14	(R)TQTGNTTTINIII**B**TVDYLLR(L)
2298-2316	2756.31	2757.32	1379.16	919.78	(K)VVSYLAG**B**GLQS**B**PMLLAK(G)
222-242	2762.17	2763.18	1382.09	921.73	(R)LFHGHMDE**B**LTISAADSDDQR(R)
131-155	2762.25	2763.25	1382.13	921.76	(K)LAFDVGLQEDATGEA**C**WWTMHPASK(Q)
3905-3925	2772.4	2773.41	1387.21	925.14	(R)TQTGNTTTINIII**Z**TVDYLLR(L)
3960-3984	2777.32	2778.33	1389.67	926.78	(K)QVFNSLTEYIQGP**C**TGNQQSLAHSR(L)
222-242	2780.18	2781.19	1391.1	927.74	(R)LFHGHMDE**Z**LTISAADSDDQR(R)
3052-3073	2790.44	2791.45	1396.23	931.16	(R)HRVSLFGTDAPAVVN**B**LHILAR(S)
2298-2316	2792.33	2793.34	1397.17	931.78	(K)VVSYLAG**Z**GLQS**Z**PMLLAK(G)
3732-3756	2794.14	2795.15	1398.08	932.39	(K)S**C**HLEEGGENGEAEEEEVEVSFEEK

					(E)
3052-3073	2808.45	2809.46	1405.23	937.16	(R)HRVSLFGTDAPAVVN**Z**LHILAR(S)
2654-2677	2813.35	2814.36	1407.68	938.79	(K)YY**C**LPTGWANFGVTSEEELHLTRK(L)
845-869	2814.42	2815.43	1408.22	939.15	(R)**C**LSHTDFVP**C**PVDTVQIVLPPHLER(I)
3516-3537	2817.4	2818.41	1409.71	940.14	(K)KMLPIGLNM**B**APTDQDLIMLAK(T)
3516-3537	2835.41	2836.42	1418.71	946.14	(K)KMLPIGLNM**Z**APTDQDLIMLAK(T)
3197-3222	2843.39	2844.4	1422.7	948.8	(R)LAAAMPVAFLEPQLNEYNA**C**SVYTTK(S)
3825-3849	2845.38	2846.39	1423.7	949.47	(K)EVGFFQSIQALMQT**C**SVLDLNAFER(Q)
797-818	2863.39	2864.4	1432.71	955.47	(R)HGEFKFLPPPGYAP**B**HEAVLPR(E)
473-493	2866.38	2867.39	1434.2	956.47	(R)NRQSLFQEEGMLSLVLN**B**IDR(L)
3649-3672	2875.29	2876.3	1438.66	959.44	(R)A**C**NMFLESYKAAWILTEDHSFEDR(M)
797-818	2881.41	2882.41	1441.71	961.48	(R)HGEFKFLPPPGYAP**Z**HEAVLPR(E)
473-493	2884.39	2885.4	1443.2	962.47	(R)NRQSLFQEEGMLSLVLN**Z**IDR(L)
4876-4892	2887.17	2888.17	1444.59	963.4	(K)**B**DDMMT**B**YLFHMYVGVR(A)
2601-2624	2887.47	2888.48	1444.74	963.5	(R)DVIED**C**LMAL**C**RYIRPSMLQHLLR(R)
284-306	2889.44	2890.44	1445.73	964.15	(R)HVTTGRYLALTEDQGLVVVDA**B**K(A)
2698-2725	2901.34	2902.35	1451.68	968.12	(R)MAMP**C**L**C**AIAGALPPDYVDASYSSKAEK(K)
3263-3283	2907.4	2908.41	1454.71	970.14	(R)YTEMPHVIEITLPML**B**SYLPR(W)
284-306	2907.45	2908.46	1454.73	970.16	(R)HVTTGRYLALTEDQGLVVVDA**Z**K(A)
2141-2163	2914.38	2915.38	1458.2	972.47	(R)AYTISPSSVEDTMSLLE**B**LGQIR(S)
222-243	2918.28	2919.28	1460.15	973.77	(R)LFHGHMDE**B**LTISAADSDDQRR(L)
4876-4892	2923.19	2924.19	1462.6	975.4	(K)**Z**DDMMT**Z**YLFHMYVGVR(A)
3263-3283	2925.42	2926.42	1463.72	976.15	(R)YTEMPHVIEITLPML**Z**SYLPR(W)
3638-3658	2930.36	2931.37	1466.19	977.79	(R)MTPLYNLPTHRA**B**NMFLESYK(A)
2141-2163	2932.39	2933.4	1467.2	978.47	(R)AYTISPSSVEDTMSLLE**Z**LGQIR(S)
1931-1954	2935.4	2936.41	1468.71	979.48	(K)LPESVKLQM**C**NLLEYF**C**DQELQHR(V)
919-945	2935.42	2936.43	1468.72	979.48	(R)NYNLQMSGETLKTLLALG**C**HVGMADEK(A)
222-243	2936.29	2937.29	1469.15	979.77	(R)LFHGHMDE**Z**LTISAADSDDQRR(L)
1586-1607	2937.41	2938.42	1469.71	980.15	(K)NPAPQ**B**PPRLEVQMLMPVSWSR(M)
3517-3539	2946.45	2947.46	1474.23	983.16	(K)MLPIGLNM**B**APTDQDLIMLAKTR(Y)
3638-3658	2948.37	2949.38	1475.19	983.8	(R)MTPLYNLPTHRA**Z**NMFLESYK(A)
2137-2163	2949.49	2950.5	1475.75	984.17	(R)ALPRAYTISPSSVEDTMSLLE**C**LGQIR(S)
1586-1607	2955.42	2956.43	1478.72	986.15	(K)NPAPQ**Z**PPRLEVQMLMPVSWSR(M)
3517-3539	2964.46	2965.47	1483.24	989.16	(K)MLPIGLNM**Z**APTDQDLIMLAKTR(Y)
3226-3248	2967.45	2968.46	1484.73	990.16	(R)ERAILGLPNSVEEM**B**PDIPVLDR(L)
599-615	2968.37	2969.38	1485.19	990.46	(K)VLDVL**B**SL**B**V**B**NGVAVR(S)

3824-3849	2973.47	2974.48	1487.74	992.17	(K)KEVGFFQSIQALMQT**C**SVLDLNAFER(Q)
3226-3248	2985.46	2986.47	1493.74	996.16	(R)ERAILGLPNSVEEM**Z**PDIPVLDR(L)
1489-1508	2994.22	2995.23	1498.12	999.08	(K)**B**SN**B**YMVWGGDFVSPGQQGR(I)
1681-1708	3010.56	3011.56	1506.29	1004.53	(R)VAHAL**C**SHVDQAQLLHALEDAHLPGPLR(A)
3774-3799	3014.43	3015.43	1508.22	1005.82	(R)GAAEMVLQMISA**B**KGETGAMVSSTLK(L)
599-615	3022.4	3023.41	1512.21	1008.47	(K)VLDVL**Z**SL**Z**V**Z**NGVAVR(S)
1489-1508	3030.25	3031.25	1516.13	1011.09	(K)**Z**SN**Z**YMVWGGDFVSPGQQGR(I)
3774-3799	3032.44	3033.44	1517.23	1011.82	(R)GAAEMVLQMISA**Z**KGETGAMVSSTLK(L)
3054-3078	3039.56	3040.57	1520.79	1014.2	(R)VSLFGTDAPAVVN**B**LHILARSLDAR(T)
2360-2385	3042.53	3043.54	1522.27	1015.18	(R)KPE**B**FGPALRGEGGSGLLAAIEEAIR(I)
131-157	3046.41	3047.41	1524.21	1016.48	(K)LAFDVGLQEDATGEA**C**WWTMHPASKQR(S)
1624-1646	3053.42	3054.43	1527.72	1018.82	(R)LGWAVQ**B**QDPLTMMALHIPEENR(**B**)
3054-3078	3057.57	3058.58	1529.8	1020.2	(R)VSLFGTDAPAVVN**Z**LHILARSLDAR(T)
2360-2385	3060.54	3061.55	1531.28	1021.19	(R)KPE**Z**FGPALRGEGGSGLLAAIEEAIR(I)
1620-1646	3064.47	3065.48	1533.24	1022.5	(R)AGERLGWAVQ**C**QDPLTMMALHIPEENR(**C**)
1624-1646	3071.43	3072.44	1536.73	1024.82	(R)LGWAVQ**Z**QDPLTMMALHIPEENR(**Z**)
845-871	3083.6	3084.61	1542.81	1028.88	(R)**C**LSHTDFVP**C**PVDTVQIVLPPHLERIR(E)
1937-1954	3086.34	3087.35	1544.18	1029.79	(K)LQM**B**NLLEYF**B**DQELQHR(V)
2654-2676	3087.41	3088.42	1544.71	1030.14	(K)YY**B**LPTGWANFGVTSEEELHLTR(K)
1509-1534	3091.54	3092.55	1546.78	1031.52	(R)ISHTDLVIG**B**LVDLATGLMTFTANGK(E)
341-368	3091.56	3092.57	1546.79	1031.53	(K)YGESL**C**FVQHVASGLWLTYAAPDPKALR(L)
376-402	3096.45	3097.46	1549.23	1033.16	(K)AILHQEGHMDDALFLTR**C**QQEESQAAR(M)
2651-2676	3102.44	3103.44	1552.23	1035.15	(R)**C**WKYY**C**LPTGWANFGVTSEEELHLTR(K)
2654-2676	3105.42	3106.43	1553.72	1036.15	(K)YY**Z**LPTGWANFGVTSEEELHLTR(K)
1509-1534	3109.55	3110.56	1555.78	1037.52	(R)ISHTDLVIG**Z**LVDLATGLMTFTANGK(E)
3001-3023	3110.6	3111.61	1556.31	1037.87	(K)ILLPLINQYFTNH**B**LYFLSTPAK(V)
2565-2588	3119.48	3120.49	1560.75	1040.84	(K)**B**APLFAGTEHRAIMVDSMLHTVYR(L)
1937-1954	3122.37	3123.37	1562.19	1041.8	(K)LQM**Z**NLLEYF**Z**DQELQHR(V)
3001-3023	3128.61	3129.62	1565.31	1043.88	(K)ILLPLINQYFTNH**Z**LYFLSTPAK(V)
2565-2588	3137.49	3138.5	1569.75	1046.84	(K)**Z**APLFAGTEHRAIMVDSMLHTVYR(L)
341-365	3153.49	3154.5	1577.76	1052.17	(K)YGESL**B**FVQHVASGLWLTYAAPDP

					K(A)
393-416	3154.46	3155.47	1578.24	1052.5	(R)**B**QQEESQAARMIHSTAGLYNQFIK(G)
759-788	3157.59	3158.6	1579.81	1053.54	(R)ING**C**PVQGVFEAFNLDGLFFPVVSFSAGVK(V)
3263-3287	3162.55	3163.56	1582.28	1055.19	(R)YTEMPHVIEITLPML**C**SYLPRWWER(G)
131-155	3164.4	3165.41	1583.21	1055.81	(K)LAFDVGLQEDATGEA**B**WWTMHPASK(Q)
341-365	3171.51	3172.51	1586.76	1058.18	(K)YGESL**Z**FVQHVASGLWLTYAAPDPK(A)
393-416	3172.47	3173.48	1587.25	1058.5	(R)**Z**QQEESQAARMIHSTAGLYNQFIK(G)
3960-3984	3179.48	3180.48	1590.75	1060.83	(K)QVFNSLTEYIQGP**B**TGNQQSLAHSR(L)
131-155	3182.42	3183.42	1592.22	1061.81	(K)LAFDVGLQEDATGEA**Z**WWTMHPASK(Q)
3197-3225	3183.57	3184.58	1592.79	1062.2	(R)LAAAMPVAFLEPQLNEYNA**C**SVYTTKSPR(E)
3732-3756	3196.3	3197.31	1599.16	1066.44	(K)S**B**HLEEGGENGEAEEEEVEVSFEEK(E)
3960-3984	3197.49	3198.5	1599.75	1066.84	(K)QVFNSLTEYIQGP**Z**TGNQQSLAHSR(L)
2997-3023	3201.71	3202.72	1601.86	1068.24	(K)FFAKILLPLINQYFTNH**C**LYFLSTPAK(V)
3732-3756	3214.31	3215.32	1608.16	1072.44	(K)S**Z**HLEEGGENGEAEEEEVEVSFEEK(E)
2654-2677	3215.51	3216.51	1608.76	1072.84	(K)YY**B**LPTGWANFGVTSEEELHLTRK(L)
3825-3852	3215.57	3216.58	1608.8	1072.87	(K)EVGFFQSIQALMQT**C**SVLDLNAFERQNK(A)
2654-2677	3233.52	3234.52	1617.77	1078.85	(K)YY**Z**LPTGWANFGVTSEEELHLTRK(L)
1-30	3239.5	3240.5	1620.76	1080.84	(-)MGDGGEGEDEVQFLRTDDEVVLQ**C**SATVLK(E)
3197-3222	3245.55	3246.55	1623.78	1082.86	(R)LAAAMPVAFLEPQLNEYNA**B**SVYTTK(S)
3825-3849	3247.54	3248.54	1624.78	1083.52	(K)EVGFFQSIQALMQT**B**SVLDLNAFER(Q)
3197-3222	3263.56	3264.56	1632.79	1088.86	(R)LAAAMPVAFLEPQLNEYNA**Z**SVYTTK(S)
1213-1240	3263.59	3264.6	1632.8	1088.87	(R)FFAI**C**GLQEGFEPFAINMQRPVTTWFSK(S)
3825-3849	3265.55	3266.55	1633.78	1089.52	(K)EVGFFQSIQALMQT**Z**SVLDLNAFER(Q)
903-930	3265.6	3266.61	1633.81	1089.54	(R)LHP**C**LVNFHSLPEPERNYNLQMSGETLK(T)
3649-3672	3277.45	3278.46	1639.73	1093.49	(R)A**B**NMFLESYKAAWILTEDHSFEDR(M)
3649-3672	3295.46	3296.47	1648.74	1099.5	(R)A**Z**NMFLESYKAAWILTEDHSFEDR(M)
1181-1212	3305.67	3306.68	1653.84	1102.9	(R)EIEIGDGFLPV**C**SLGPGQVGHLNLGQDVSSLR(F)
3732-3760	3311.36	3312.37	1656.69	1104.79	(K)S**C**HLEEGGENGEAEEEEVEVSFEEK

					EMEK(Q)
599-629	3312.7	3313.71	1657.36	1105.24	(K)VLDVL**C**SL**C**V**C**NGVAVRSNQDLIT ENLLPGR(E)
126-155	3324.49	3325.5	1663.25	1109.17	(R)SMTDKLAFDVGLQEDATGEA**C**WW TMHPASK(Q)
2553-2575	3332.68	3333.69	1667.35	1111.9	(R)YL**B**LAVLPLITK**B**APLFAGTEHR(A)
919-945	3337.58	3338.59	1669.8	1113.54	(R)NYNLQMSGETLKTLLALG**B**HVGM ADEK(A)
2228-2241	3339.35	3340.36	1670.68	1114.13	(K)MVTS**BB**RFL**B**YF**B**R(I)
3288-3321	3342.74	3343.75	1672.38	1115.25	(R)GPEAPPPALPAGAPPP**C**TAVTSDHL NSLLGNILR(I)
596-615	3347.56	3348.57	1674.79	1116.86	(R)NHKVLDVL**B**SL**B**V**B**NGVAVR(S)
2137-2163	3351.65	3352.66	1676.83	1118.23	(R)ALPRAYTISPSSVEDTMSLLE**B**LGQI R(S)
1937-1964	3355.58	3356.59	1678.8	1119.53	(K)LQM**C**NLLEYF**C**DQELQHRVESLAA FAER(Y)
919-945	3355.59	3356.6	1678.8	1119.54	(R)NYNLQMSGETLKTLLALG**Z**HVGM ADEK(A)
3954-3984	3364.63	3365.64	1683.32	1122.55	(K)AMSVAKQVFNSLTEYIQGP**C**TGNQ QSLAHSR(L)
2553-2575	3368.7	3369.71	1685.36	1123.91	(R)YL**Z**LAVLPLITK**Z**APLFAGTEHR(A)
2137-2163	3369.66	3370.67	1685.84	1124.23	(R)ALPRAYTISPSSVEDTMSLLE**Z**LGQI R(S)
3824-3849	3375.63	3376.64	1688.82	1126.22	(K)KEVGFFQSIQALMQT**B**SVLDLNAFE R(Q)
2698-2722	3377.48	3378.49	1689.75	1126.84	(R)MAMP**B**L**B**AIAGALPPDYVDASYSS K(A)
3824-3849	3393.64	3394.65	1697.83	1132.22	(K)KEVGFFQSIQALMQT**Z**SVLDLNAFE R(Q)
596-615	3401.6	3402.6	1701.81	1134.87	(R)NHKVLDVL**Z**SL**Z**V**Z**NGVAVR(S)
2000-2028	3407.56	3408.57	1704.79	1136.86	(R)SPPQEQINMLLHFKDEADEED**C**PLP EDIR(Q)
46-76	3407.66	3408.66	1704.84	1136.89	(R)L**C**FLEPTSNAQNVPPDLAI**CC**FTLE QSLSVR(A)
2228-2241	3411.4	3412.4	1706.71	1138.14	(K)MVTS**ZZ**RFL**Z**YF**Z**R(I)
1681-1708	3412.71	3413.72	1707.36	1138.58	(R)VAHAL**B**SHVDQAQLLHALEDAHLP GPLR(A)
759-790	3412.76	3413.77	1707.39	1138.6	(R)ING**C**PVQGVFEAFNLDGLFFPVVSF SAGVKVR(F)
2698-2722	3413.5	3414.51	1707.76	1138.84	(R)MAMP**Z**L**Z**AIAGALPPDYVDASYSS K(A)
1681-1708	3430.72	3431.73	1716.37	1144.58	(R)VAHAL**Z**SHVDQAQLLHALEDAHLP GPLR(A)
131-157	3448.56	3449.57	1725.29	1150.53	(K)LAFDVGLQEDATGEA**B**WWTMHPA SKQR(S)
2298-2330	3453.63	3454.64	1727.82	1152.22	(K)VVSYLAG**C**GLQS**C**PMLLAKGYPDI GWNP**C**GGER(Y)
554-584	3464.85	3465.86	1733.43	1155.96	(R)LEASSGILEVLY**C**VLIESPEVLNIIQE NHIK(S)
131-157	3466.58	3467.58	1734.3	1156.53	(K)LAFDVGLQEDATGEA**Z**WWTMHPA SKQR(S)
1620-1646	3466.63	3467.63	1734.32	1156.55	(R)AGERLGWAVQ**B**QDPLTMMALHIPE ENR(**B**)

2416-2447	3474.81	3475.82	1738.41	1159.28	(R)VHLGHAIMSFYAALIDLLGR**C**APE MHLIQAGK(G)
2532-2564	3481.86	3482.86	1741.94	1161.63	(R)AAASLDTATFSTTEMALALNRYL**C** LAVLPLITK(**C**)
1620-1646	3484.64	3485.64	1743.33	1162.55	(R)AGERLGWAVQ**Z**QDPLTMMALHIPE ENR(**Z**)
1439-1468	3491.57	3492.58	1746.79	1164.86	(R)VFAGQEPS**C**VWVGWVTPDYHQHD MNFDLSK(V)
341-368	3493.72	3494.72	1747.87	1165.58	(K)YGESL**B**FVQHVASGLWLTYAAPDP KALR(L)
376-402	3498.61	3499.62	1750.31	1167.21	(K)AILHQEGHMDDALFLTR**B**QQEESQ AAR(M)
4102-4131	3509.83	3510.84	1755.92	1170.95	(K)QFTGPEIQFLLS**C**SEADENEMINFEE FANR(F)
341-368	3514.02	3515.03	1758.02	1172.35	(K)YGESL**Z**FVQHVASGLWLTYAAPDP KALR(L)
1241-1271	3515.98	3516.98	1759	1173	(K)SLPQFEPVPPEHPHYEVARMDGTV DTPP**C**LR(L)
376-402	3518.89	3519.9	1760.45	1173.97	(K)AILHQEGHMDDALFLTR**Z**QQEESQ AAR(M)
1303-1336	3533.84	3534.84	1767.93	1178.95	(R)**C**TAGATPLAPPGLQPPAEDEARAAE PDPDYENLR(R)
2691-2722	3543.08	3544.09	1772.55	1182.04	(K)YDQELYRMAMP**C**L**C**AIAGALPPDY VDASYSSK(A)
759-788	3562.11	3563.11	1782.06	1188.38	(R)ING**B**PVQGVFEAFNLDGLFFPVVSF SAGVK(V)
3263-3287	3567.22	3568.23	1784.62	1190.08	(R)YTEMPHVIEITLPML**B**SYLPRWWER (G)
759-788	3580.12	3581.13	1791.07	1194.38	(R)ING**Z**PVQGVFEAFNLDGLFFPVVSF SAGVK(V)
3263-3287	3585.23	3586.24	1793.62	1196.09	(R)YTEMPHVIEITLPML**Z**SYLPRWWER (G)
3197-3225	3588.12	3589.13	1795.07	1197.05	(R)LAAAMPVAFLEPQLNEYNA**B**SVYT TKSPR(E)
3197-3225	3606.14	3607.15	1804.08	1203.05	(R)LAAAMPVAFLEPQLNEYNA**Z**SVYT TKSPR(E)
2997-3023	3606.29	3607.3	1804.15	1203.11	(K)FFAKILLPLINQYFTNH**B**LYFLSTPA K(V)
1037-1068	3607.92	3608.93	1804.97	1203.65	(R)DSL**C**QAVRTLLGYGYNIEPPDQEPS QVENQSR(W)
3825-3852	3620.13	3621.13	1811.07	1207.72	(K)EVGFFQSIQALMQT**B**SVLDLNAFER QNK(A)
845-869	3621.2	3622.21	1811.61	1208.07	(R)**B**LSHTDFVP**B**PVDTVQIVLPPHLER(I)
3228-3262	3624.22	3625.23	1813.12	1209.08	(R)AILGLPNSVEEM**C**PDIPVLDRLMAD IGGLAESGAR(Y)
2997-3023	3624.31	3625.32	1813.16	1209.11	(K)FFAKILLPLINQYFTNH**Z**LYFLSTPA K(V)
3825-3852	3638.14	3639.15	1820.08	1213.72	(K)EVGFFQSIQALMQT**Z**SVLDLNAFER QNK(A)
1-30	3644.01	3645.02	1823.01	1215.68	(-)MGDGGEGEDEVQFLRTDD EVVLQ**B**SATVLK(E)
1291-1324	3653.14	3654.15	1827.58	1218.72	(R)LSLPVQFHQHFR**C**TAGATPLAPPGL

					QPPAEDEAR(A)
845-869	3657.23	3658.24	1829.62	1220.08	(R)**Z**LSHTDFVP**Z**PVDTVQIVLPPHLER(I)
1-30	3662.02	3663.03	1832.02	1221.68	(-)MGDGGEGEDEVQFLRTDDEVVLQ**Z**SATVLK(E)
1213-1240	3668.26	3669.27	1835.14	1223.76	(R)FFAI**B**GLQEGFEPFAINMQRPVTTWFSK(S)
903-930	3670.19	3671.2	1836.1	1224.4	(R)LHP**B**LVNFHSLPEPERNYNLQMSGETLK(T)
1213-1240	3686.27	3687.28	1844.14	1229.77	(R)FFAI**Z**GLQEGFEPFAINMQRPVTTWFSK(S)
903-930	3688.2	3689.21	1845.11	1230.41	(R)LHP**Z**LVNFHSLPEPERNYNLQMSGETLK(T)
2601-2624	3694.43	3695.44	1848.22	1232.48	(R)DVIED**B**LMAL**B**RYIRPSMLQHLLR(R)
2698-2725	3708.32	3709.32	1855.17	1237.11	(R)MAMP**B**L**B**AIAGALPPDYVDASYSSKAEK(K)
1181-1212	3710.18	3711.19	1856.1	1237.74	(R)EIEIGDGFLPV**B**SLGPGQVGHLNLGQDVSSLR(F)
3732-3760	3715.9	3716.9	1858.96	1239.64	(K)S**B**HLEEGGENGEAEEEEVEVSFEEKEMEK(Q)
836-869	3717.34	3718.34	1859.68	1240.12	(R)GPHLVGPSR**C**LSHTDFVP**C**PVDTVQIVLPPHLER(I)
3001-3034	3718.34	3719.35	1860.18	1240.45	(K)ILLPLINQYFTNH**C**LYFLSTPAKVLGSGGHASNK(E)
1181-1212	3728.2	3729.21	1865.11	1243.74	(R)EIEIGDGFLPV**Z**SLGPGQVGHLNLGQDVSSLR(F)
126-155	3729.19	3730.19	1865.6	1244.07	(R)SMTDKLAFDVGLQEDATGEA**B**WWTMHPASK(Q)
2601-2624	3730.46	3731.47	1866.24	1244.49	(R)DVIED**Z**LMAL**Z**RYIRPSMLQHLLR(R)
3732-3760	3733.91	3734.92	1867.96	1245.65	(K)S**Z**HLEEGGENGEAEEEEVEVSFEEKEMEK(Q)
1931-1954	3742.32	3743.32	1872.17	1248.45	(K)LPESVKLQM**B**NLLEYF**B**DQELQHR(V)
2698-2725	3744.35	3745.35	1873.18	1249.12	(R)MAMP**Z**L**Z**AIAGALPPDYVDASYSSKAEK(K)
126-155	3747.2	3748.21	1874.61	1250.08	(R)SMTDKLAFDVGLQEDATGEA**Z**WWTMHPASK(Q)
3288-3321	3747.29	3748.3	1874.65	1250.1	(R)GPEAPPPALPAGAPPP**B**TAVTSDHLNSLLGNILR(I)
1439-1470	3749.21	3750.21	1875.61	1250.74	(R)VFAGQEPS**C**VWVGWVTPDYHQHDMNFDLSKVR(A)
3288-3321	3765.31	3766.31	1883.66	1256.11	(R)GPEAPPPALPAGAPPP**Z**TAVTSDHLNSLLGNILR(I)
3954-3984	3769.23	3770.24	1885.63	1257.42	(K)AMSVAKQVFNSLTEYIQGP**B**TGNQQSLAHSR(L)
1931-1954	3778.35	3779.35	1890.18	1260.46	(K)LPESVKLQM**Z**NLLEYF**Z**DQELQHR(V)
1760-1797	3786.38	3787.39	1894.2	1263.13	(R)HGLPGVGVTTSLRPPHHFSPP**C**FVAALPAAGVAEAPAR(L)
3954-3984	3787.25	3788.26	1894.63	1263.42	(K)AMSVAKQVFNSLTEYIQGP**Z**TGNQQSLAHSR(L)
3874-3904	3793.21	3794.22	1897.61	1265.41	(K)VMADDEFTQDLFRFLQLL**C**EGHNN

					DFQNYLR(T)
2000-2028	3812.21	3813.22	1907.11	1271.74	(R)SPPQEQINMLLHFKDEADEED**B**PLPEDIR(Q)
759-790	3817.43	3818.43	1909.72	1273.48	(R)ING**B**PVQGVFEAFNLDGLFFPVVSFSAGVKVR(F)
2000-2028	3830.22	3831.23	1916.12	1277.75	(R)SPPQEQINMLLHFKDEADEED**Z**PLPEDIR(Q)
759-790	3835.44	3836.45	1918.73	1279.49	(R)ING**Z**PVQGVFEAFNLDGLFFPVVSFSAGVKVR(F)
1624-1656	3843.51	3844.52	1922.76	1282.18	(R)LGWAVQ**C**QDPLTMMALHIPEENR**C**MDILELSER(L)
3249-3283	3849.58	3850.59	1925.8	1284.2	(R)LMADIGGLAESGARYTEMPHVIEITLPML**C**SYLPR(W)
551-584	3851.48	3852.49	1926.75	1284.83	(K)LDRLEASSGILEVLY**C**VLIESPEVLNIIQENHIK(S)
554-584	3869.49	3870.5	1935.75	1290.84	(R)LEASSGILEVLY**B**VLIESPEVLNIIQENHIK(S)
2416-2447	3879.63	3880.64	1940.82	1294.22	(R)VHLGHAIMSFYAALIDLLGR**B**APEMHLIQAGK(G)
2532-2564	3886.59	3887.6	1944.3	1296.54	(R)AAASLDTATFSTTEMALALNRYL**B**LAVLPLITK(**B**)
554-584	3887.51	3888.52	1944.76	1296.84	(R)LEASSGILEVLY**Z**VLIESPEVLNIIQENHIK(S)
845-871	3890.55	3891.55	1946.28	1297.86	(R)**B**LSHTDFVP**B**PVDTVQIVLPPHLERIR(E)
1439-1468	3896.34	3897.34	1949.18	1299.79	(R)VFAGQEPS**B**VWVGWVTPDYHQHDMNFDLSK(V)
2416-2447	3897.65	3898.66	1949.83	1300.22	(R)VHLGHAIMSFYAALIDLLGR**Z**APEMHLIQAGK(G)
2532-2564	3904.61	3905.61	1953.31	1302.54	(R)AAASLDTATFSTTEMALALNRYL**Z**LAVLPLITK(**Z**)
330-365	3906.45	3907.46	1954.23	1303.16	(R)DVEGMGPPEIKYGESL**C**FVQHVASGLWLTYAAPDPK(A)
2651-2676	3909.42	3910.43	1955.72	1304.15	(R)**B**WKYY**B**LPTGWANFGVTSEEELHLTR(K)
1672-1708	3911.49	3912.5	1956.75	1304.84	(R)AV**C**ALGNNRVAHAL**C**SHVDQAQLLHALEDAHLPGPLR(A)
4102-4131	3912.28	3913.29	1957.15	1305.1	(K)QFTGPEIQFLLS**B**SEADENEMINFEEFANR(F)
2029-2062	3913.12	3914.12	1957.57	1305.38	(R)QDLQDFHQDLLAH**C**GIQLEGEEEEPEEETSLSSR(L)
1439-1468	3914.35	3915.36	1958.18	1305.79	(R)VFAGQEPS**Z**VWVGWVTPDYHQHDMNFDLSK(V)
1241-1271	3918.43	3919.43	1960.22	1307.15	(K)SLPQFEPVPPEHPHYEVARMDGTVDTPP**B**LR(L)
845-871	3926.58	3927.58	1964.3	1309.87	(R)**Z**LSHTDFVP**Z**PVDTVQIVLPPHLERIR(E)
4102-4131	3930.3	3931.31	1966.16	1311.11	(K)QFTGPEIQFLLS**Z**SEADENEMINFEEFANR(F)
1303-1336	3936.29	3937.29	1969.15	1313.1	(R)**B**TAGATPLAPPGLQPPAEDEARAAEPDPDYENLR(R)
1241-1271	3936.44	3937.45	1969.23	1313.16	(K)SLPQFEPVPPEHPHYEVARMDGTVDTPP**Z**LR(L)
1759-1797	3942.57	3943.58	1972.29	1315.2	(R)RHGLPGVGVTTSLRPPHHFSPP**C**FV

					AALPAAGVAEAPAR(L)
2651-2676	3945.45	3946.46	1973.73	1316.16	(R)**Z**WKYY**Z**LPTGWANFGVTSEEELHLTR(K)
1303-1336	3954.3	3955.31	1978.16	1319.11	(R)**Z**TAGATPLAPPGLQPPAEDEARAAEPDPDYENLR(R)
3284-3321	4002.57	4003.58	2002.29	1335.2	(R)WWERGPEAPPPALPAGAPPP**C**TAVTSDHLNSLLGNILR(I)
1037-1068	4010.37	4011.38	2006.19	1337.8	(R)DSL**B**QAVRTLLGYGYNIEPPDQEPSQVENQSR(W)
3186-3222	4025.73	4026.74	2013.87	1342.92	(K)LRPALGE**C**LARLAAAMPVAFLEPQLNEYNA**C**SVYTTK(S)
3228-3262	4026.67	4027.68	2014.34	1343.23	(R)AILGLPNSVEEM**B**PDIPVLDRLMADIGGLAESGAR(Y)
1037-1068	4028.38	4029.39	2015.2	1343.8	(R)DSL**Z**QAVRTLLGYGYNIEPPDQEPSQVENQSR(W)
3228-3262	4044.68	4045.69	2023.35	1349.24	(R)AILGLPNSVEEM**Z**PDIPVLDRLMADIGGLAESGAR(Y)
1471-1508	4046.52	4047.53	2024.27	1349.85	(R)AVTVTMGDEQGNVHSSLK**C**SN**C**YMVWGGDFVSPGQQGR(I)
1291-1324	4055.59	4056.6	2028.8	1352.87	(R)LSLPVQFHQHFR**B**TAGATPLAPPGLQPPAEDEAR(A)
1291-1324	4073.61	4074.61	2037.81	1358.88	(R)LSLPVQFHQHFR**Z**TAGATPLAPPGLQPPAEDEAR(A)
3001-3034	4120.79	4121.8	2061.4	1374.6	(K)ILLPLINQYFTNH**B**LYFLSTPAKVLGSGGHASNK(E)
3001-3034	4138.8	4139.81	2070.41	1380.61	(K)ILLPLINQYFTNH**Z**LYFLSTPAKVLGSGGHASNK(E)
1439-1470	4151.66	4152.66	2076.84	1384.89	(R)VFAGQEPS**B**VWVGWVTPDYHQHDMNFDLSKVR(A)
1937-1964	4162.74	4163.75	2082.38	1388.59	(K)LQM**B**NLLEYF**B**DQELQHRVESLAAFAER(Y)
1439-1470	4169.67	4170.68	2085.84	1390.9	(R)VFAGQEPS**Z**VWVGWVTPDYHQHDMNFDLSKVR(A)
4096-4131	4170.58	4171.59	2086.3	1391.2	(K)AMDSQKQFTGPEIQFLLS**C**SEADENEMINFEEFANR(F)
2029-2064	4182.46	4183.47	2092.24	1395.16	(R)QDLQDFHQDLLAH**C**GIQLEGEEEEPEEETSLSSRLR(S)
1760-1797	4188.83	4189.84	2095.42	1397.28	(R)HGLPGVGVTTSLRPPHHFSPP**B**FVAALPAAGVAEAPAR(L)
3874-3904	4195.66	4196.67	2098.84	1399.56	(K)VMADDEFTQDLFRFLQLL**B**EGHNNDFQNYLR(T)
1937-1964	4198.77	4199.78	2100.39	1400.6	(K)LQM**Z**NLLEYF**Z**DQELQHRVESLAAFAER(Y)
1760-1797	4206.85	4207.85	2104.43	1403.29	(R)HGLPGVGVTTSLRPPHHFSPP**Z**FVAALPAAGVAEAPAR(L)
3874-3904	4213.68	4214.69	2107.85	1405.57	(K)VMADDEFTQDLFRFLQLL**Z**EGHNNDFQNYLR(T)
1509-1547	4213.8	4214.81	2107.91	1405.61	(R)ISHTDLVIG**C**LVDLATGLMTFTANGKESNTFFQVEPNTK(L)
3905-3940	4221.76	4222.76	2111.89	1408.26	(R)TQTGNTTTINIII**C**TVDYLLRLQESISDFYWYYSGK(D)
4102-4137	4238.64	4239.65	2120.33	1413.89	(K)QFTGPEIQFLLS**C**SEADENEMINFEEFANRFQEPAR(D)
3249-3283	4252.03	4253.04	2127.02	1418.35	(R)LMADIGGLAESGARYTEMPHVIEIT

					LPML**B**SYLPR(W)
551-584	4253.93	4254.94	2127.97	1418.98	(K)LDRLEASSGILEVLY**B**VLIESPEVLNIIQENHIK(S)
3249-3283	4270.04	4271.05	2136.03	1424.36	(R)LMADIGGLAESGARYTEMPHVIEITLPML**Z**SYLPR(W)
551-584	4271.94	4272.95	2136.98	1424.99	(K)LDRLEASSGILEVLY**Z**VLIESPEVLNIIQENHIK(S)
330-365	4308.9	4309.91	2155.46	1437.31	(R)DVEGMGPPEIKYGESL**B**FVQHVASGLWLTYAAPDPK(A)
2029-2062	4315.57	4316.57	2158.79	1439.53	(R)QDLQDFHQDLLAH**B**GIQLEGEEEEPEEETSLSSR(L)
330-365	4326.92	4327.93	2164.47	1443.31	(R)DVEGMGPPEIKYGESL**Z**FVQHVASGLWLTYAAPDPK(A)
2029-2062	4333.58	4334.59	2167.8	1445.54	(R)QDLQDFHQDLLAH**Z**GIQLEGEEEEPEEETSLSSR(L)
554-592	4337.1	4338.11	2169.56	1446.71	(R)LEASSGILEVLY**C**VLIESPEVLNIIQENHIKSIISLLDK(H)
1759-1797	4345.02	4346.03	2173.52	1449.35	(R)RHGLPGVGVTTSLRPPHHFSPP**B**FVAALPAAGVAEAPAR(L)
2691-2722	4347.98	4348.99	2175	1450.34	(K)YDQELYRMAMP**B**L**B**AIAGALPPDYVDASYSSK(A)
1759-1797	4363.03	4364.04	2182.52	1455.35	(R)RHGLPGVGVTTSLRPPHHFSPP**Z**FVAALPAAGVAEAPAR(L)
2691-2722	4384.01	4385.02	2193.01	1462.35	(K)YDQELYRMAMP**Z**L**Z**AIAGALPPDYVDASYSSK(A)
3284-3321	4405.02	4406.03	2203.52	1469.35	(R)WWERGPEAPPPALPAGAPPP**B**TAVTSDHLNSLLGNILR(I)
3284-3321	4423.04	4424.04	2212.53	1475.35	(R)WWERGPEAPPPALPAGAPPP**Z**TAVTSDHLNSLLGNILR(I)
836-869	4522.23	4523.24	2262.13	1508.42	(R)GPHLVGPSR**B**LSHTDFVP**B**PVDTVQIVLPPHLER(I)
599-629	4522.25	4523.26	2262.13	1508.42	(K)VLDVL**B**SL**B**V**B**NGVAVRSNQDLITENLLPGR(E)
35-76	4542.26	4543.27	2272.14	1515.1	(K)L**C**LAAEGFGNRL**C**FLEPTSNAQNVPPDLAI**CC**FTLEQSLSVR(A)
836-869	4558.27	4559.27	2280.14	1520.43	(R)GPHLVGPSR**Z**LSHTDFVP**Z**PVDTVQIVLPPHLER(I)
3887-3925	4560.19	4561.2	2281.1	1521.07	(R)FLQLL**C**EGHNNDFQNYLRTQTGNTTTINIII**C**TVDYLLR(L)
4096-4131	4573.03	4574.04	2287.52	1525.35	(K)AMDSQKQFTGPEIQFLLS**B**SEADENEMINFEEFANR(F)
599-629	4576.3	4577.3	2289.16	1526.44	(K)VLDVL**Z**SL**Z**V**Z**NGVAVRSNQDLITENLLPGR(E)
2029-2064	4584.91	4585.92	2293.46	1529.31	(R)QDLQDFHQDLLAH**B**GIQLEGEEEEPEEETSLSSRLR(S)
4096-4131	4591.05	4592.06	2296.53	1531.36	(K)AMDSQKQFTGPEIQFLLS**Z**SEADENEMINFEEFANR(F)
2029-2064	4602.93	4603.94	2302.47	1535.32	(R)QDLQDFHQDLLAH**Z**GIQLEGEEEEPEEETSLSSRLR(S)
1509-1547	4616.25	4617.26	2309.13	1539.76	(R)ISHTDLVIG**B**LVDLATGLMTFTANGKESNTFFQVEPNTK(L)
46-76	4617.3	4618.31	2309.66	1540.11	(R)L**B**FLEPTSNAQNVPPDLAI**BB**FTLEQSLSVR(A)
3905-3940	4624.21	4625.21	2313.11	1542.41	(R)TQTGNTTTINIII**B**TVDYLLRLQESIS

					DFYWYYSGK(D)
1509-1547	4634.27	4635.27	2318.14	1545.76	(R)ISHTDLVIG**Z**LVDLATGLMTFTANGKESNTFFQVEPNTK(L)
4102-4137	4641.09	4642.1	2321.55	1548.04	(K)QFTGPEIQFLLS**B**SEADENEMINFEEFANRFQEPAR(D)
3905-3940	4642.22	4643.23	2322.12	1548.41	(R)TQTGNTTTINIII**Z**TVDYLLRLQESISDFYWYYSGK(D)
1624-1656	4648.41	4649.42	2325.21	1550.48	(R)LGWAVQ**B**QDPLTMMALHIPEENR**B**MDILELSER(L)
4102-4137	4659.1	4660.11	2330.56	1554.04	(K)QFTGPEIQFLLS**Z**SEADENEMINFEEFANRFQEPAR(D)
2298-2330	4663.4	4664.41	2332.71	1555.48	(K)VVSYLAG**B**GLQS**B**PMLLAKGYPDIGWNP**B**GGER(Y)
46-76	4671.35	4672.36	2336.68	1558.12	(R)L**Z**FLEPTSNAQNVPPDLAI**ZZ**FTLEQSLSVR(A)
1624-1656	4684.44	4685.45	2343.23	1562.49	(R)LGWAVQ**Z**QDPLTMMALHIPEENR**Z**MDILELSER(L)
3716-3756	4703.04	4704.05	2352.53	1568.69	(K)LDEDYLYMAYADIMAKS**C**HLEEGGENGEAEEEEVEVSFEEK(E)
1672-1708	4716.39	4717.4	2359.2	1573.14	(R)AV**B**ALGNNRVAHAL**B**SHVDQAQLLHALEDAHLPGPLR(A)
2298-2330	4717.45	4718.46	2359.73	1573.49	(K)VVSYLAG**Z**GLQS**Z**PMLLAKGYPDIGWNP**Z**GGER(Y)
475-516	4736.28	4737.28	2369.15	1579.77	(R)QSLFQEEGMLSLVLN**C**IDRLNVYTTAAHFAEYAGEEAAESWK(E)
554-592	4739.55	4740.56	2370.78	1580.86	(R)LEASSGILEVLY**B**VLIESPEVLNIIQENHIKSIISLLDK(H)
1672-1708	4752.42	4753.43	2377.22	1585.15	(R)AV**Z**ALGNNRVAHAL**Z**SHVDQAQLLHALEDAHLPGPLR(A)
554-592	4757.56	4758.57	2379.79	1586.86	(R)LEASSGILEVLY**Z**VLIESPEVLNIIQENHIKSIISLLDK(H)
179-221	4762.43	4763.44	2382.22	1588.48	(R)YLHLSTASGELQVDASFMQTLWNMNPI**C**S**CC**EEGYVTGGHVLR(L)
3186-3222	4830.63	4831.64	2416.32	1611.22	(K)LRPALGE**B**LARLAAAMPVAFLEPQLNEYNA**B**SVYTTK(S)
4958-4998	4834.51	4835.52	2418.26	1612.51	(K)**C**FI**C**GIGSDYFDTTPHGFETHTLEEHNLANYMFFLMYLINK(D)
1471-1508	4851.42	4852.42	2426.72	1618.15	(R)AVTVTMGDEQGNVHSSLK**B**SN**B**YMVWGGDFVSPGQQGR(I)
1489-1534	4864.61	4865.62	2433.31	1622.54	(K)**C**SN**C**YMVWGGDFVSPGQQGRISHTDLVIG**C**LVDLATGLMTFTANGK(E)
3186-3222	4866.66	4867.67	2434.34	1623.23	(K)LRPALGE**Z**LARLAAAMPVAFLEPQLNEYNA**Z**SVYTTK(S)
1471-1508	4887.45	4888.46	2444.73	1630.16	(R)AVTVTMGDEQGNVHSSLK**Z**SN**Z**YMVWGGDFVSPGQQGR(I)
3124-3167	4890.55	4891.56	2446.28	1631.19	(K)GVGQNLTYTTVALLPVLTTLFQHIAQHQFGDDVILDDVQVS**C**YR(T)
3960-4002	4893.68	4894.69	2447.85	1632.23	(K)QVFNSLTEYIQGP**C**TGNQQSLAHSRLWDAVVGFLHVFAHMMMK(L)
1681-1725	4918.64	4919.65	2460.33	1640.55	(R)VAHAL**C**SHVDQAQLLHALEDAHLPGPLRAGYYDLLISIHLESA**C**R(S)
1760-1808	4947.79	4948.8	2474.9	1650.27	(R)HGLPGVGVTTSLRPPHHFSPP**C**FVAALPAAGVAEAPARLSPAIPLEALR(D)
3288-3336	5043.85	5044.85	2522.93	1682.29	(R)GPEAPPPALPAGAPPP**C**TAVTSDHL

					NSLLGNILRIIVNNLGIDEATWMK(R)
3716-3756	5105.49	5106.5	2553.75	1702.84	(K)LDEDYLYMAYADIMAKS**B**HLEEGG ENGEAEEEEVEVSFEEK(E)
3716-3756	5123.5	5124.51	2562.76	1708.84	(K)LDEDYLYMAYADIMAKS**Z**HLEEGG ENGEAEEEEVEVSFEEK(E)
475-516	5138.73	5139.73	2570.37	1713.92	(R)QSLFQEEGMLSLVLN**B**IDRLNVYTT AAHFAEYAGEEAAESWK(E)
475-516	5156.74	5157.75	2579.38	1719.92	(R)QSLFQEEGMLSLVLN**Z**IDRLNVYTT AAHFAEYAGEEAAESWK(E)
3124-3167	5293	5294.01	2647.51	1765.34	(K)GVGQNLTYTTVALLPVLTTLFQHIA QHQFGDDVILDDVQVS**B**YR(T)
3960-4002	5296.13	5297.14	2649.07	1766.38	(K)QVFNSLTEYIQGP**B**TGNQQSLAHSR LWDAVVGFLHVFAHMMMK(L)
3124-3167	5311.02	5312.03	2656.52	1771.35	(K)GVGQNLTYTTVALLPVLTTLFQHIA QHQFGDDVILDDVQVS**Z**YR(T)
3960-4002	5314.14	5315.15	2658.08	1772.39	(K)QVFNSLTEYIQGP**Z**TGNQQSLAHSR LWDAVVGFLHVFAHMMMK(L)
3120-3167	5347.1	5348.1	2674.56	1783.37	(R)TQVKGVGQNLTYTTVALLPVLTTL FQHIAQHQFGDDVILDDVQVS**C**YR(T)
1760-1808	5350.24	5351.25	2676.13	1784.42	(R)HGLPGVGVTTSLRPPHHFSPP**B**FVA ALPAAGVAEAPARLSPAIPLEALR(D)
3887-3925	5365.09	5366.1	2683.55	1789.37	(R)FLQLL**B**EGHNNDFQNYLRTQTGNT TTINIII**B**TVDYLLR(L)
1760-1808	5368.26	5369.26	2685.14	1790.43	(R)HGLPGVGVTTSLRPPHHFSPP**Z**FVA ALPAAGVAEAPARLSPAIPLEALR(D)
3887-3925	5401.12	5402.13	2701.57	1801.38	(R)FLQLL**Z**EGHNNDFQNYLRTQTGNT TTINIII**Z**TVDYLLR(L)
1132-1180	5402.05	5403.05	2702.03	1801.69	(R)WHLGSEPFGRPWQSGDVVG**C**MIDL TENTIIFTLNGEVLMSDSGSETAFR(E)
2141-2189	5411.31	5412.32	2706.66	1804.78	(R)AYTISPSSVEDTMSLLE**C**LGQIRSLLI VQMGPQEENLMIQSIGNIMNNK(V)
3288-3336	5446.3	5447.3	2724.16	1816.44	(R)GPEAPPPALPAGAPPP**B**TAVTSDHL NSLLGNILRIIVNNLGIDEATWMK(R)
3288-3336	5464.31	5465.32	2733.16	1822.44	(R)GPEAPPPALPAGAPPP**Z**TAVTSDHL NSLLGNILRIIVNNLGIDEATWMK(R)
1213-1259	5477.27	5478.28	2739.64	1826.77	(R)FFAI**C**GLQEGFEPFAINMQRPVTTW FSKSLPQFEPVPPEHPHYEVAR(M)
1422-1468	5539.12	5540.13	2770.57	1847.38	(R)DDPEIILNTTTYYYSVRVFAGQEPS**C** VWVGWVTPDYHQHDMNFDLSK(V)
4958-4998	5639.41	5640.42	2820.71	1880.81	(K)**B**FI**B**GIGSDYFDTTPHGFETHTLEEH NLANYMFFLMYLINK(D)
2014-2062	5640.9	5641.9	2821.46	1881.31	(K)DEADEED**C**PLPEDIRQDLQDFHQDL LAH**C**GIQLEGEEEEPEEETSLSSR(L)
4958-4998	5675.44	5676.45	2838.73	1892.82	(K)**Z**FI**Z**GIGSDYFDTTPHGFETHTLEEH NLANYMFFLMYLINK(D)
1681-1725	5723.54	5724.55	2862.78	1908.85	(R)VAHAL**B**SHVDQAQLLHALEDAHLP GPLRAGYYDLLISIHLESA**B**R(S)
46-99	5733.48	5734.49	2867.75	1912.17	(R)L**C**FLEPTSNAQNVPPDLAI**CC**FTLE QSLSVRALQEMLANTVEAGVESSQGG GHR(T)
1129-1180	5743.42	5744.43	2872.72	1915.48	(R)GQRWHLGSEPFGRPWQSGDVVG**C** MIDLTENTIIFTLNGEVLMSDSGSETAF R(E)

3120-3167	5749.55	5750.55	2875.78	1917.52	(R)TQVKGVGQNLTYTTVALLPVLTTLFQHIAQHQFGDDVILDDVQVS**B**YR(T)
1681-1725	5759.57	5760.58	2880.79	1920.86	(R)VAHAL**Z**SHVDQAQLLHALEDAHLPGPLRAGYYDLLISIHLESA**Z**R(S)
3120-3167	5767.56	5768.57	2884.79	1923.53	(R)TQVKGVGQNLTYTTVALLPVLTTLFQHIAQHQFGDDVILDDVQVS**Z**YR(T)
1132-1180	5804.5	5805.5	2903.26	1935.84	(R)WHLGSEPFGRPWQSGDVVG**B**MIDLTENTIIFTLNGEVLMSDSGSETAFR(E)
2141-2189	5813.76	5814.77	2907.89	1938.93	(R)AYTISPSSVEDTMSLLE**B**LGQIRSLLIVQMGPQEENLMIQSIGNIMNNK(V)
1132-1180	5822.51	5823.52	2912.26	1941.85	(R)WHLGSEPFGRPWQSGDVVG**Z**MIDLTENTIIFTLNGEVLMSDSGSETAFR(E)
2141-2189	5831.77	5832.78	2916.89	1944.93	(R)AYTISPSSVEDTMSLLE**Z**LGQIRSLLIVQMGPQEENLMIQSIGNIMNNK(V)
1213-1259	5879.72	5880.73	2940.87	1960.92	(R)FFAI**B**GLQEGFEPFAINMQRPVTTWFSKSLPQFEPVPPEHPHYEVAR(M)
1213-1259	5897.74	5898.75	2949.88	1966.92	(R)FFAI**Z**GLQEGFEPFAINMQRPVTTWFSKSLPQFEPVPPEHPHYEVAR(M)
1422-1468	5941.57	5942.58	2971.79	1981.53	(R)DDPEIILNTTTYYYSVRVFAGQEPS**B**VWVGWVTPDYHQHDMNFDLSK(V)
1422-1468	5959.58	5960.59	2980.8	1987.54	(R)DDPEIILNTTTYYYSVRVFAGQEPS**Z**VWVGWVTPDYHQHDMNFDLSK(V)
179-221	5969.78	5970.79	2985.9	1990.93	(R)YLHLSTASGELQVDASFMQTLWNMNPI**B**S**BB**EEGYVTGGHVLR(L)
179-221	6023.82	6024.83	3012.92	2008.95	(R)YLHLSTASGELQVDASFMQTLWNMNPI**Z**S**ZZ**EEGYVTGGHVLR(L)
1489-1534	6071.96	6072.97	3036.99	2024.99	(K)**B**SN**B**YMVWGGDFVSPGQQGRISHTDLVIG**B**LVDLATGLMTFTANGK(E)
1489-1534	6126	6127.01	3064.01	2043.01	(K)**Z**SN**Z**YMVWGGDFVSPGQQGRISHTDLVIG**Z**LVDLATGLMTFTANGK(E)
1129-1180	6145.87	6146.87	3073.94	2049.63	(R)GQRWHLGSEPFGRPWQSGDVVG**B**MIDLTENTIIFTLNGEVLMSDSGSETAFR(E)
35-76	6152.06	6153.07	3077.04	2051.7	(K)L**B**LAAEGFGNRL**B**FLEPTSNAQNVPPDLAI**BB**FTLEQSLSVR(A)
3124-3179	6159.05	6160.06	3080.53	2054.02	(K)GVGQNLTYTTVALLPVLTTLFQHIAQHQFGDDVILDDVQVS**C**YRTL**C**SIYSLGTTK(N)
1129-1180	6163.88	6164.89	3082.95	2055.64	(R)GQRWHLGSEPFGRPWQSGDVVG**Z**MIDLTENTIIFTLNGEVLMSDSGSETAFR(E)
35-76	6224.12	6225.13	3113.07	2075.72	(K)L**Z**LAAEGFGNRL**Z**FLEPTSNAQNVPPDLAI**ZZ**FTLEQSLSVR(A)
165-221	6233.07	6234.08	3117.54	2078.7	(R)VGDDLILVSVSSERYLHLSTASGELQVDASFMQTLWNMNPI**C**S**CC**EEGYVTGGHVLR(L)
2014-2062	6445.8	6446.8	3223.91	2149.61	(K)DEADEED**B**PLPEDIRQDLQDFHQDLLAH**B**GIQLEGEEEEPEEETSLSSR(L)
2014-2062	6481.83	6482.83	3241.92	2161.62	(K)DEADEED**Z**PLPEDIRQDLQDFHQDLLAH**Z**GIQLEGEEEEPEEETSLSSR(L)

4231-4295	6494.96	6495.96	3248.49	2165.99	(K)MELFVSF**C**EDTIFEMQIAAQISEPEGEPEADEDEGMGEAAAEGAEEGAAGAEGAAGTVAAGATAR(L)
1181-1240	6555.53	6556.53	3278.77	2186.18	(R)EIEIGDGFLPV**C**SLGPGQVGHLNLGQDVSSLRFFAI**C**GLQEGFEPFAINMQRPVTTWFSK(S)
4231-4295	6897.41	6898.41	3449.71	2300.14	(K)MELFVSF**B**EDTIFEMQIAAQISEPEGEPEADEDEGMGEAAAEGAEEGAAGAEGAAGTVAAGATAR(L)
4231-4295	6915.42	6916.43	3458.72	2306.15	(K)MELFVSF**Z**EDTIFEMQIAAQISEPEGEPEADEDEGMGEAAAEGAEEGAAGAEGAAGTVAAGATAR(L)
46-99	6940.83	6941.84	3471.42	2314.62	(R)L**B**FLEPTSNAQNVPPDLAI**BB**FTLEQSLSVRALQEMLANTVEAGVESSQGGGHR(T)
3124-3179	6963.95	6964.96	3482.98	2322.32	(K)GVGQNLTYTTVALLPVLTTLFQHIAQHQFGDDVILDDVQVS**B**YRTL**B**SIYSLGTTK(N)
46-99	6994.88	6995.89	3498.45	2332.63	(R)L**Z**FLEPTSNAQNVPPDLAI**ZZ**FTLEQSLSVRALQEMLANTVEAGVESSQGGGHR(T)
3124-3179	6999.98	7000.99	3501	2334.33	(K)GVGQNLTYTTVALLPVLTTLFQHIAQHQFGDDVILDDVQVS**Z**YRTL**Z**SIYSLGTTK(N)
179-242	7105.97	7106.98	3553.99	2369.66	(R)YLHLSTASGELQVDASFMQTLWNMNPI**C**S**CC**EEGYVTGGHVLRLFHGHMDE**C**LTISAADSDDQR(R)
4231-4302	7119.7	7120.7	3560.86	2374.24	(K)MELFVSF**C**EDTIFEMQIAAQISEPEGEPEADEDEGMGEAAAEGAEEGAAGAEGAAGTVAAGATARLAAAAAR(A)
2249-2316	7155.24	7156.25	3578.63	2386.09	(R)SMFDHLSYLLENSGIGLGMQGSTPLDVAAASVIDNNELALALQEQDLEKVVSYLAG**C**GLQS**C**PMLLAK(G)
1181-1240	7360.43	7361.43	3681.22	2454.48	(R)EIEIGDGFLPV**B**SLGPGQVGHLNLGQDVSSLRFFAI**B**GLQEGFEPFAINMQRPVTTWFSK(S)
1181-1240	7396.46	7397.46	3699.24	2466.49	(R)EIEIGDGFLPV**Z**SLGPGQVGHLNLGQDVSSLRFFAI**Z**GLQEGFEPFAINMQRPVTTWFSK(S)
165-221	7440.42	7441.43	3721.22	2481.15	(R)VGDDLILVSVSSERYLHLSTASGELQVDASFMQTLWNMNPI**B**S**BB**EEGYVTGGHVLR(L)
165-221	7494.47	7495.48	3748.24	2499.16	(R)VGDDLILVSVSSERYLHLSTASGELQVDASFMQTLWNMNPI**Z**S**ZZ**EEGYVTGGHVLR(L)
4231-4302	7522.15	7523.15	3762.08	2508.39	(K)MELFVSF**B**EDTIFEMQIAAQISEPEGEPEADEDEGMGEAAAEGAEEGAAGAEGAAGTVAAGATARLAAAAAR(A)
4231-4302	7540.16	7541.17	3771.09	2514.4	(K)MELFVSF**Z**EDTIFEMQIAAQISEPEGEPEADEDEGMGEAAAEGAEEGAAGAEGAAGTVAAGATARLAAAAAR(A)
684-758	7878.72	7879.72	3940.37	2627.25	(R)VGWALTEGYSPYPGGGEGWGGNGVGDDLYSYGFDGLHLWTGHVARPVTSPGQHLLAPEDVVS**CC**LDLSVPSISFR(I)

2249-2316	7960.14	7961.15	3981.08	2654.39	(R)SMFDHLSYLLENSGIGLGMQGSTPLDVAAASVIDNNELALALQEQDLEKVVSYLAG**B**GLQS**B**PMLLAK(G)
2249-2316	7996.17	7997.18	3999.09	2666.4	(R)SMFDHLSYLLENSGIGLGMQGSTPLDVAAASVIDNNELALALQEQDLEKVVSYLAG**Z**GLQS**Z**PMLLAK(G)
4216-4295	8158.76	8159.77	4080.39	2720.59	(R)QFIFDVVNEGGEAEKMELFVSF**C**EDTIFEMQIAAQISEPEGEPEADEDEGMGEAAAEGAEEGAAGAEGAAGTVAAGATAR(L)
4216-4295	8561.21	8562.22	4281.61	2854.74	(R)QFIFDVVNEGGEAEKMELFVSF**B**EDTIFEMQIAAQISEPEGEPEADEDEGMGEAAAEGAEEGAAGAEGAAGTVAAGATAR(L)
4216-4295	8579.23	8580.23	4290.62	2860.75	(R)QFIFDVVNEGGEAEKMELFVSF**Z**EDTIFEMQIAAQISEPEGEPEADEDEGMGEAAAEGAEEGAAGAEGAAGTVAAGATAR(L)
4582-4665	8672.49	8673.5	4337.25	2891.84	(K)VSDSPPGEDDMEGSAAGDLAGAGSGGGSGWGSGAGEEAEGDEDENMVYYFLEESTGYMEPALW**C**LSLLHTLVAFL**C**IIGYN**C**LK(V)
684-758	8683.62	8684.62	4342.82	2895.55	(R)VGWALTEGYSPYPGGGEGWGGNGVGDDLYSYGFDGLHLWTGHVARPVTSPGQHLLAPEDVVS**BB**LDLSVPSISFR(I)
1132-1212	8691.76	8692.77	4346.89	2898.26	(R)WHLGSEPFGRPWQSGDVVG**C**MIDLTENTIIFTLNGEVLMSDSGSETAFREIEIGDGFLPV**C**SLGPGQVGHLNLGQDVSSLR(F)
179-242	8715.77	8716.78	4358.89	2906.26	(R)YLHLSTASGELQVDASFMQTLWNMNPI**B**S**BB**EEGYVTGGHVLRLFHGHMDE**B**LTISAADSDDQR(R)
684-758	8719.65	8720.65	4360.83	2907.56	(R)VGWALTEGYSPYPGGGEGWGGNGVGDDLYSYGFDGLHLWTGHVARPVTSPGQHLLAPEDVVS**ZZ**LDLSVPSISFR(I)
179-242	8787.83	8788.84	4394.92	2930.28	(R)YLHLSTASGELQVDASFMQTLWNMNPI**Z**S**ZZ**EEGYVTGGHVLRLFHGHMDE**Z**LTISAADSDDQR(R)
4582-4672	9469.54	9470.55	4735.78	3157.52	(K)VSDSPPGEDDMEGSAAGDLAGAGSGGGSGWGSGAGEEAEGDEDENMVYYFLEESTGYMEPALW**C**LSLLHTLVAFL**C**IIGYN**C**LKVPLVIFK(R)
1132-1212	9496.66	9497.67	4749.34	3166.56	(R)WHLGSEPFGRPWQSGDVVG**B**MIDLTENTIIFTLNGEVLMSDSGSETAFREIEIGDGFLPV**B**SLGPGQVGHLNLGQDVSSLR(F)
1132-1212	9532.7	9533.7	4767.36	3178.57	(R)WHLGSEPFGRPWQSGDVVG**Z**MIDLTENTIIFTLNGEVLMSDSGSETAFREIEIGDGFLPV**Z**SLGPGQVGHLNLGQDVSSLR(F)
4582-4665	9879.84	9880.85	4940.93	3294.29	(K)VSDSPPGEDDMEGSAAGDLAGAGSGGGSGWGSGAGEEAEGDEDENMVYYFLEESTGYMEPALW**B**LSLLHTLVAFL**B**IIGYN**B**LK(V)

4582-4665	9933.88	9934.89	4967.95	3312.3	(K)VSDSPPGEDDMEGSAAGDLAGAGSGGGSGWGSGAGEEAEGDEDENMVYYFLEESTGYMEPALW**Z**LSLLHTLVAFL**Z**IIGYN**Z**LK(V)
662-758	10512.77	10513.78	5257.39	3505.26	(K)WYFEVMVDEVVPFLTAQATHLRVGWALTEGYSPYPGGGEGWGGNGVGDDLYSYGFDGLHLWTGHVARPVTSPGQHLLAPEDVVS**CC**LDLSVPSISFR(I)
4582-4672	10676.89	10677.9	5339.45	3559.97	(K)VSDSPPGEDDMEGSAAGDLAGAGSGGGSGWGSGAGEEAEGDEDENMVYYFLEESTGYMEPALW**B**LSLLHTLVAFL**B**IIGYN**B**LKVPLVIFK(R)
4582-4672	10730.93	10731.94	5366.48	3577.99	(K)VSDSPPGEDDMEGSAAGDLAGAGSGGGSGWGSGAGEEAEGDEDENMVYYFLEESTGYMEPALW**Z**LSLLHTLVAFL**Z**IIGYN**Z**LKVPLVIFK(R)
4564-4665	10819.18	10820.19	5410.6	3607.4	(R)FLALFLAFAINFILLFYKVSDSPPGEDDMEGSAAGDLAGAGSGGGSGWGSGAGEEAEGDEDENMVYYFLEESTGYMEPALW**C**LSLLHTLVAFL**C**IIGYN**C**LK(V)
684-788	11020.36	11021.37	5511.19	3674.46	(R)VGWALTEGYSPYPGGGEGWGGNGVGDDLYSYGFDGLHLWTGHVARPVTSPGQHLLAPEDVVS**CC**LDLSVPSISFRING**C**PVQGVFEAFNLDGLFFPVVSFSAGVK(V)
662-758	11317.67	11318.68	5659.84	3773.56	(K)WYFEVMVDEVVPFLTAQATHLRVGWALTEGYSPYPGGGEGWGGNGVGDDLYSYGFDGLHLWTGHVARPVTSPGQHLLAPEDVVS**BB**LDLSVPSISFR(I)
662-758	11353.7	11354.71	5677.86	3785.57	(K)WYFEVMVDEVVPFLTAQATHLRVGWALTEGYSPYPGGGEGWGGNGVGDDLYSYGFDGLHLWTGHVARPVTSPGQHLLAPEDVVS**ZZ**LDLSVPSISFR(I)
4564-4665	12026.53	12027.54	6014.27	4009.85	(R)FLALFLAFAINFILLFYKVSDSPPGEDDMEGSAAGDLAGAGSGGGSGWGSGAGEEAEGDEDENMVYYFLEESTGYMEPALW**B**LSLLHTLVAFL**B**IIGYN**B**LK(V)
4564-4665	12080.57	12081.58	6041.29	4027.87	(R)FLALFLAFAINFILLFYKVSDSPPGEDDMEGSAAGDLAGAGSGGGSGWGSGAGEEAEGDEDENMVYYFLEESTGYMEPALW**Z**LSLLHTLVAFL**Z**IIGYN**Z**LK(V)
684-788	12227.71	12228.72	6114.86	4076.91	(R)VGWALTEGYSPYPGGGEGWGGNGVGDDLYSYGFDGLHLWTGHVARPVTSPGQHLLAPEDVVS**BB**LDLSVPSISFRING**B**PVQGVFEAFNLDGLFFPVVSFSAGVK(V)
684-788	12281.75	12282.76	6141.88	4094.93	(R)VGWALTEGYSPYPGGGEGWGGNGVGDDLYSYGFDGLHLWTGHVARPVTSPGQHLLAPEDVVS**ZZ**LDLSVPSISFRING**Z**PVQGVFEAFNLDGLFFPVVSFSAGVK(V)

Supplemental Figure Legends

Supplemental Fig. 1. **Direct ESI mass spectrum of peptide 1303 – 1324 with cys-1303 adducted by CPM.** A segment of the direct ESI spectrum is represented, indicating a strong signal for the triply charged 855.40 Da, which matches the theoretical monoisotopic mass value of 2561.21 Da for CPM adduction of cys-1303 in peptide 1303-1324.

Supplemental Fig. 2. **ESI MS/MS spectrum of peptide 1303 – 1324 with cys-1303 adducted by CPM.** ESI MS/MS spectrum of the triply charged 855.40 Da peptide in Supplemental Fig. 1, which produces a fragmentation pattern indicating CPM adduction of cys-1303 in peptide 1303 – 1321.

Supplemental Fig. 3. **ESI MS/MS spectrum of peptide 2565 – 2575 with cys-2565 adducted by CPM.** ESI MS/MS spectrum of the triply charged 534.91 Da peptide in Fig. 4B, which produces a fragmentation pattern indicating CPM adduction of cys-2565 in peptide 2565 – 2575.

Supplemental Fig. 4. **MALDI-TOF mass spectrum of peptide 2598 – 2616 with cys-2606 and -2611 adducted by hydrolyzed-CPM.** A segment of the MALDI-TOF mass spectra indicating a low intensity signal at monoisotopic 2576.30 Da, which corresponds to the theoretical value of 2576.17 Da for hydrolyzed-CPM adduction of cys-2606 and -2611 in peptide 2598 – 2616.

Supplemental Fig. 5. **Direct ESI MS of peptide 2598 – 2612 with cys-2606 and -2611 adducted by hydrolyzed-CPM.** A segment of the direct ESI mass spectrum transformed to the single charge state that produces a high intensity signal at 2576.21 Da, corresponding to the

predicted 2576.17 Da for hydrolyzed-CPM adduction of cys-2606 and -2611 in peptide 2598 – 2612.

Supplemental Fig. 6. **MALDI-TOF MS of peptide 1037 – 1044 with cys-1040 adducted by hydrolyzed-CPM.** A segment of the MALDI-TOF spectrum is represented, indicating a strong signal at monoisoptic 1311.47 Da, which corresponds to the theoretical value of 1311.60 Da for hydrolyzed-CPM adduction of cys-1040 in peptide 1037 – 1044.

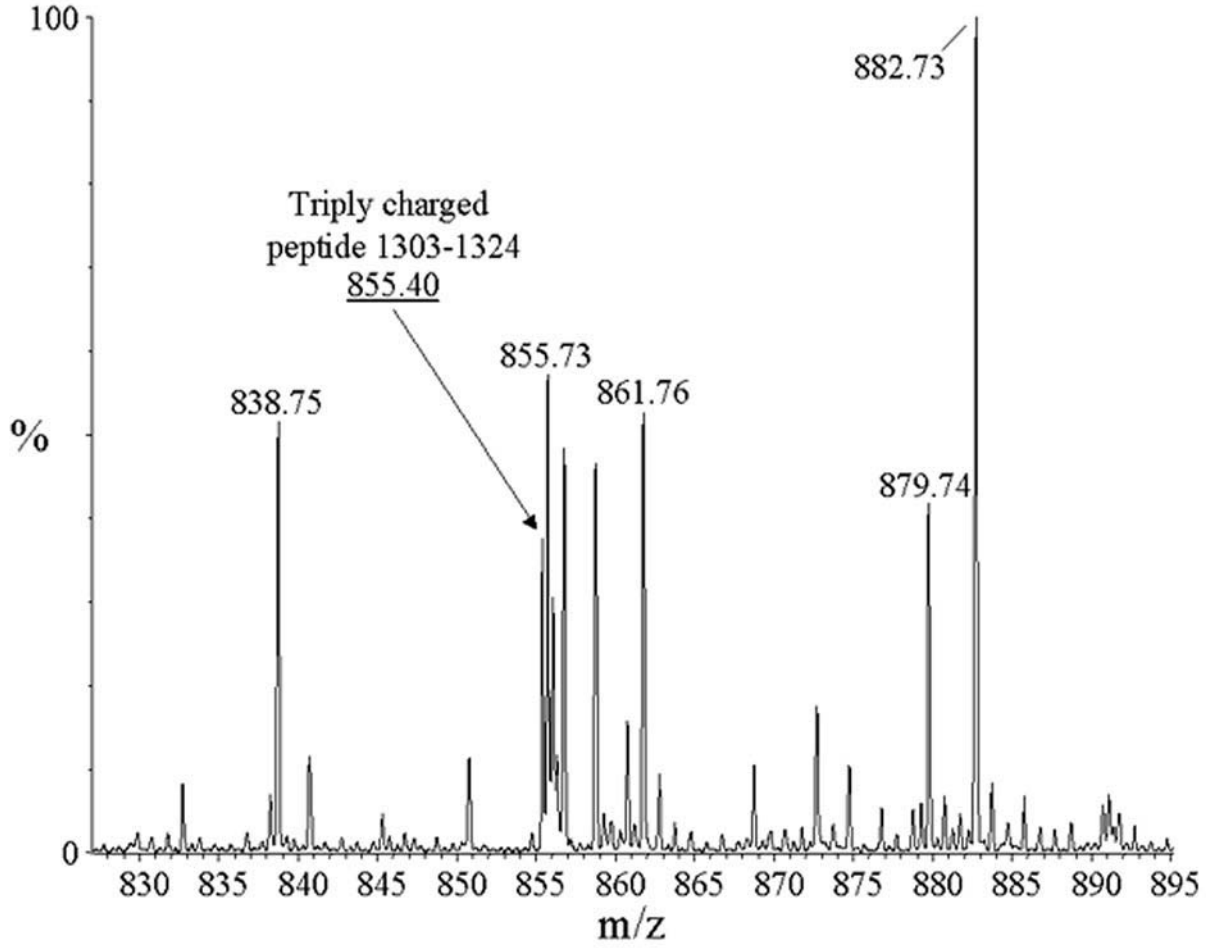
Supplemental Fig. 7. **MALDI-TOF MS of peptide 1037 – 1044 with cys-1040 adducted by hydrolyzed-CPM.** A MALDI-TOF spectrum is represented, indicating a signal at monoisotopic 1311.60 Da, which corresponds to the theoretical value of 1311.60 Da for hydrolyzed-CPM adduction of cys-1040 in peptide 1037 – 1044.

Supplemental Fig. 8. **Direct ESI MS of peptide 2436 – 2447 with cys-2436 adducted by CPM.** A direct ESI spectrum transformed to the single charge state produces a strong signal at 1699.99 Da, which corresponds to the theoretical 1699.80 Da for CPM adduction of cys-2436 in peptide 2436 – 2447.

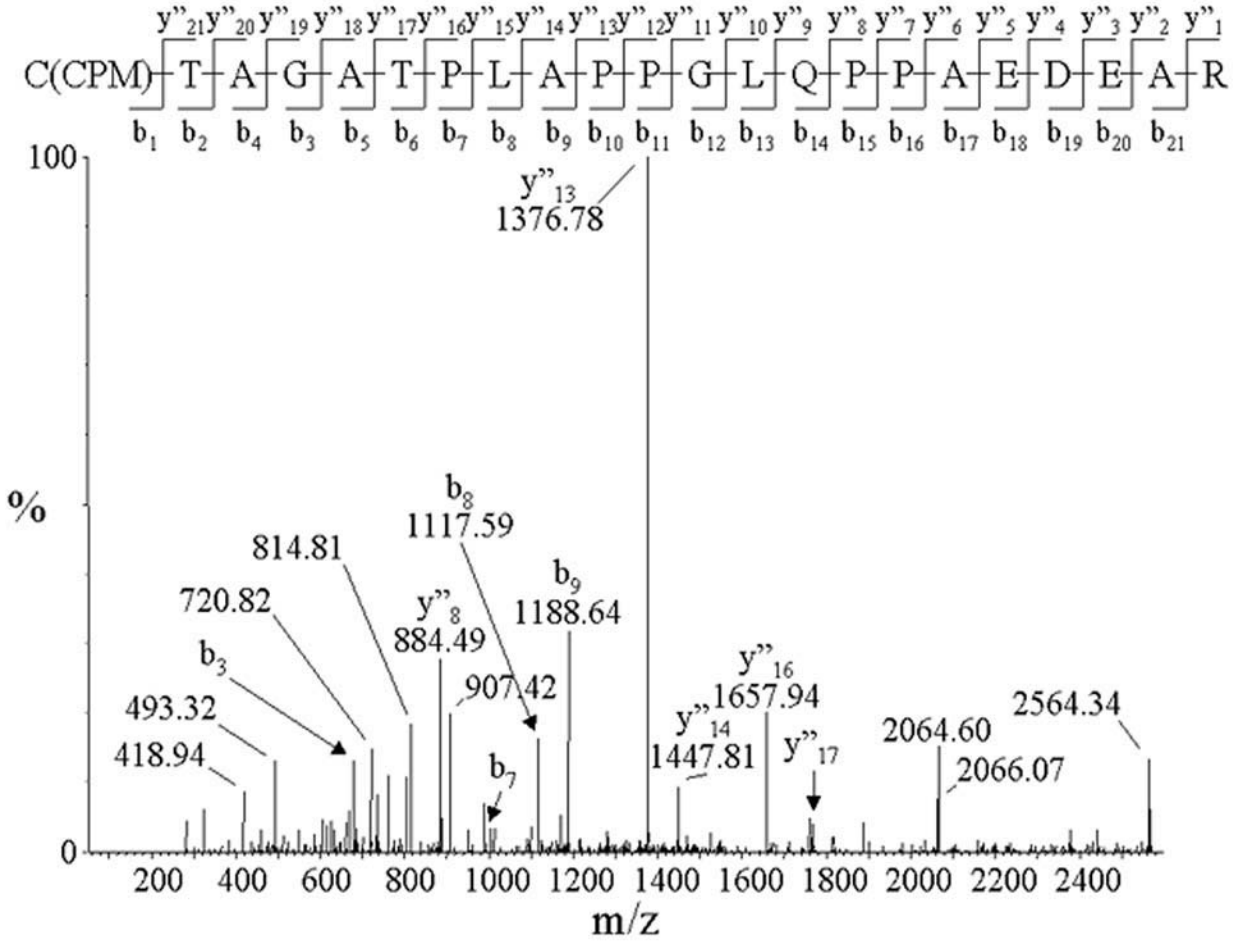
Supplemental Fig. 9. **Direct ESI MS tentatively identifying CPM-adduction of cys-120 in peptide 116 – 130.** A direct ESI spectrum transformed to the single charged state with two overlapping signals produces a high intensity signal at 2139.29 Da, which corresponds to the predicted 2138.96 Da for CPM adduction of cys-120 in peptide 116 – 130.

Supplemental Fig. 10. **Direct ESI MS tentatively identifying CPM-adduction of cys-3193 in peptide 3180 – 3196.** A direct ESI mass spectrum transformed to the single charged state with two overlapping signals produces a high intensity signal at 2334.46 Da, which corresponds to the theoretical 2335.19 Da for CPM adduction of cys-3193 in peptide 3180 – 3196.

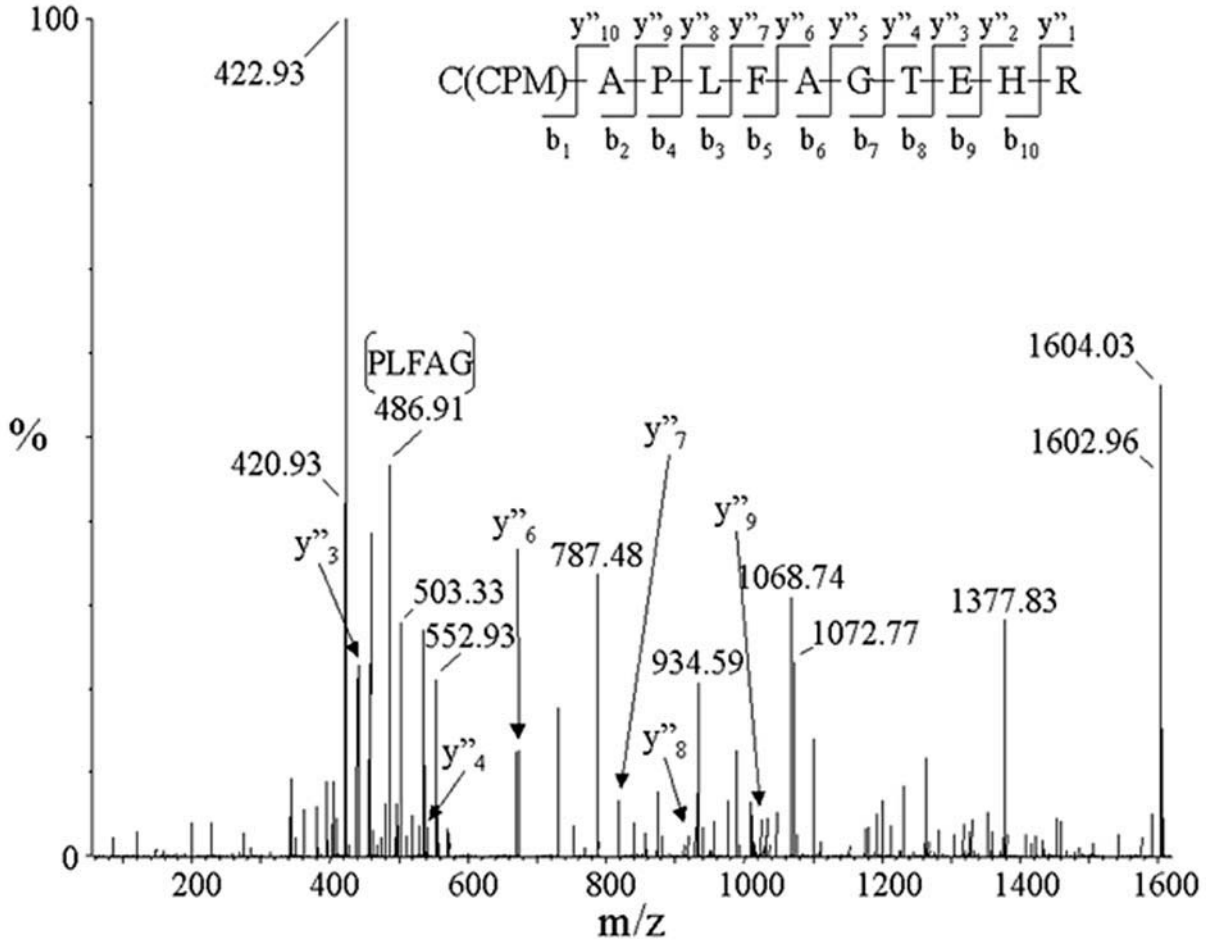
Supplemental Fig. 1



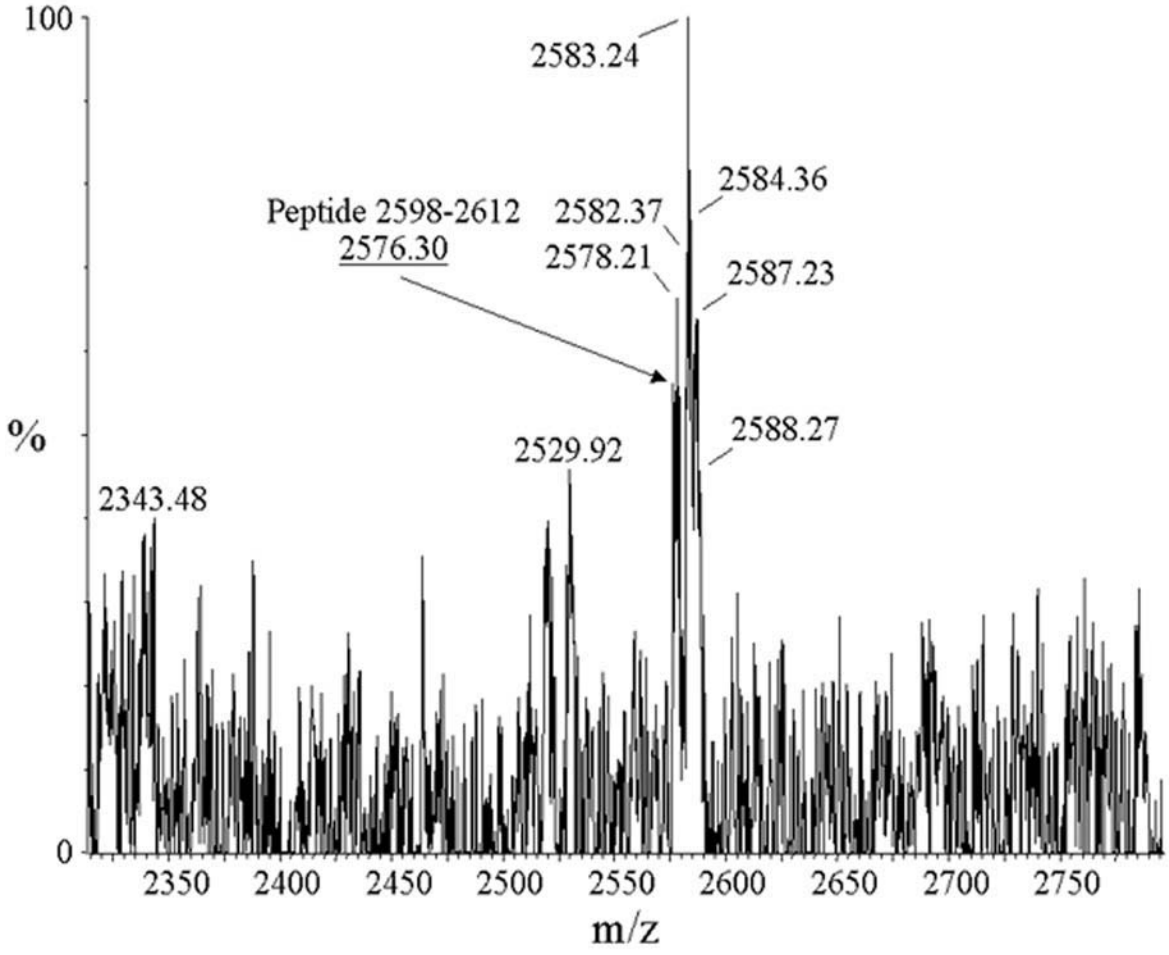
Supplemental Fig. 2



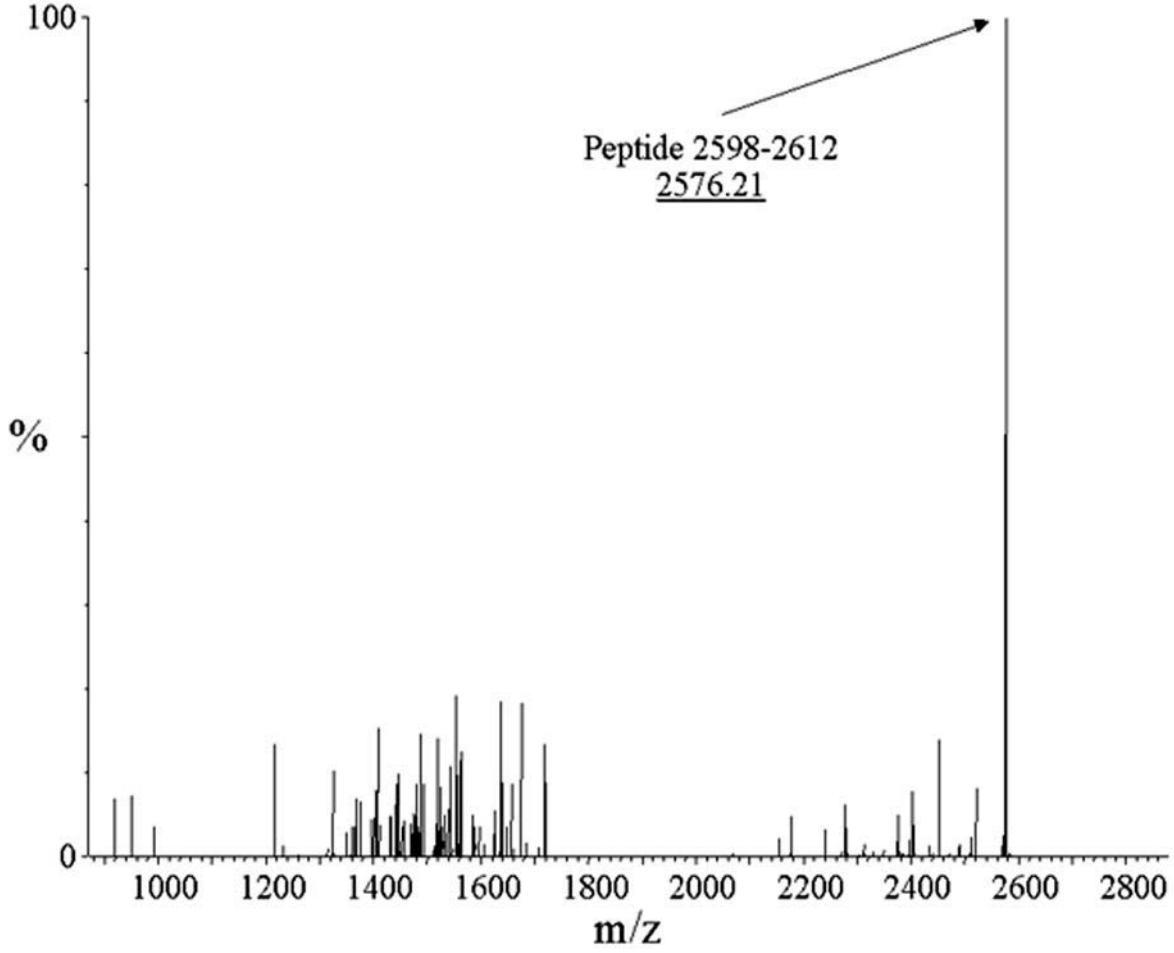
Supplemental Fig. 3



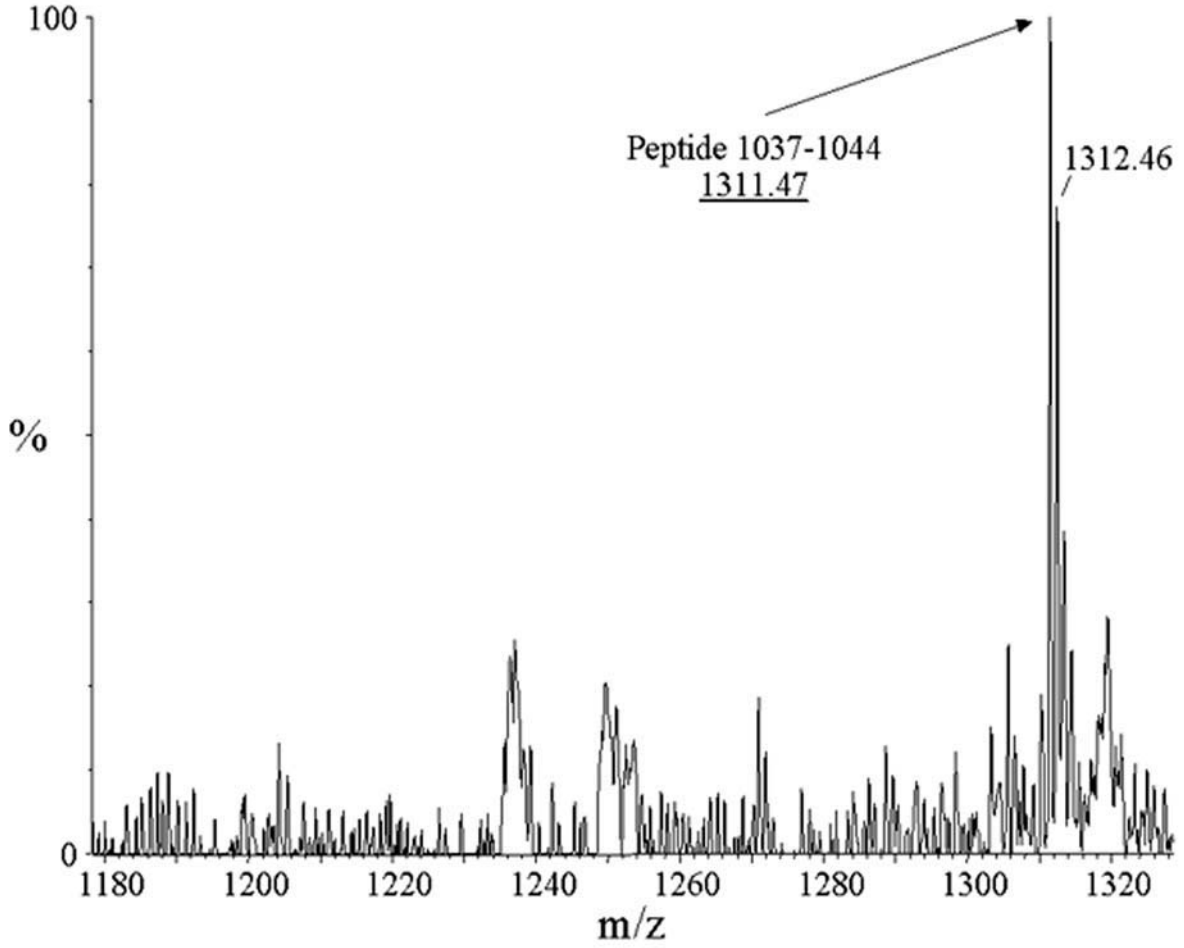
Supplemental Fig. 4



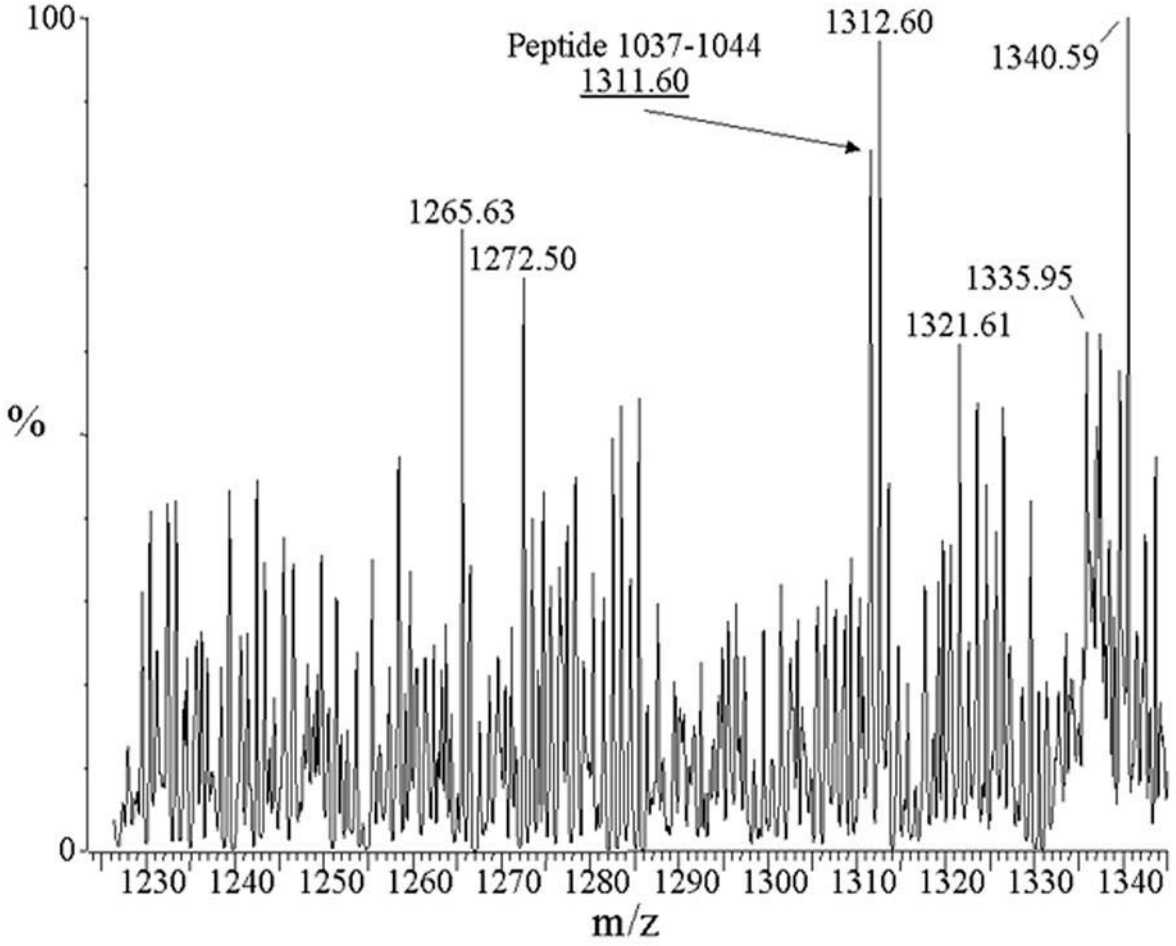
Supplemental Fig. 5



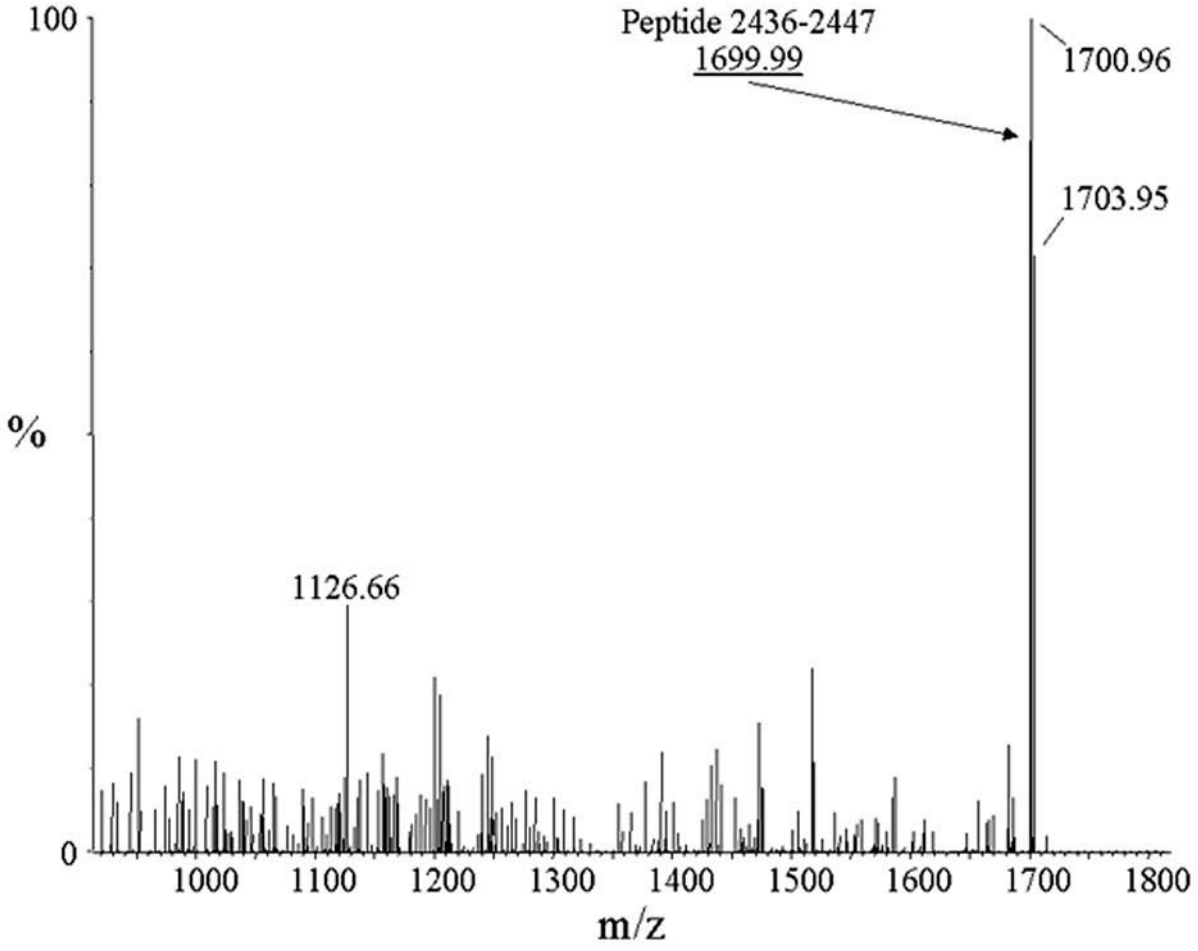
Supplemental Fig. 6



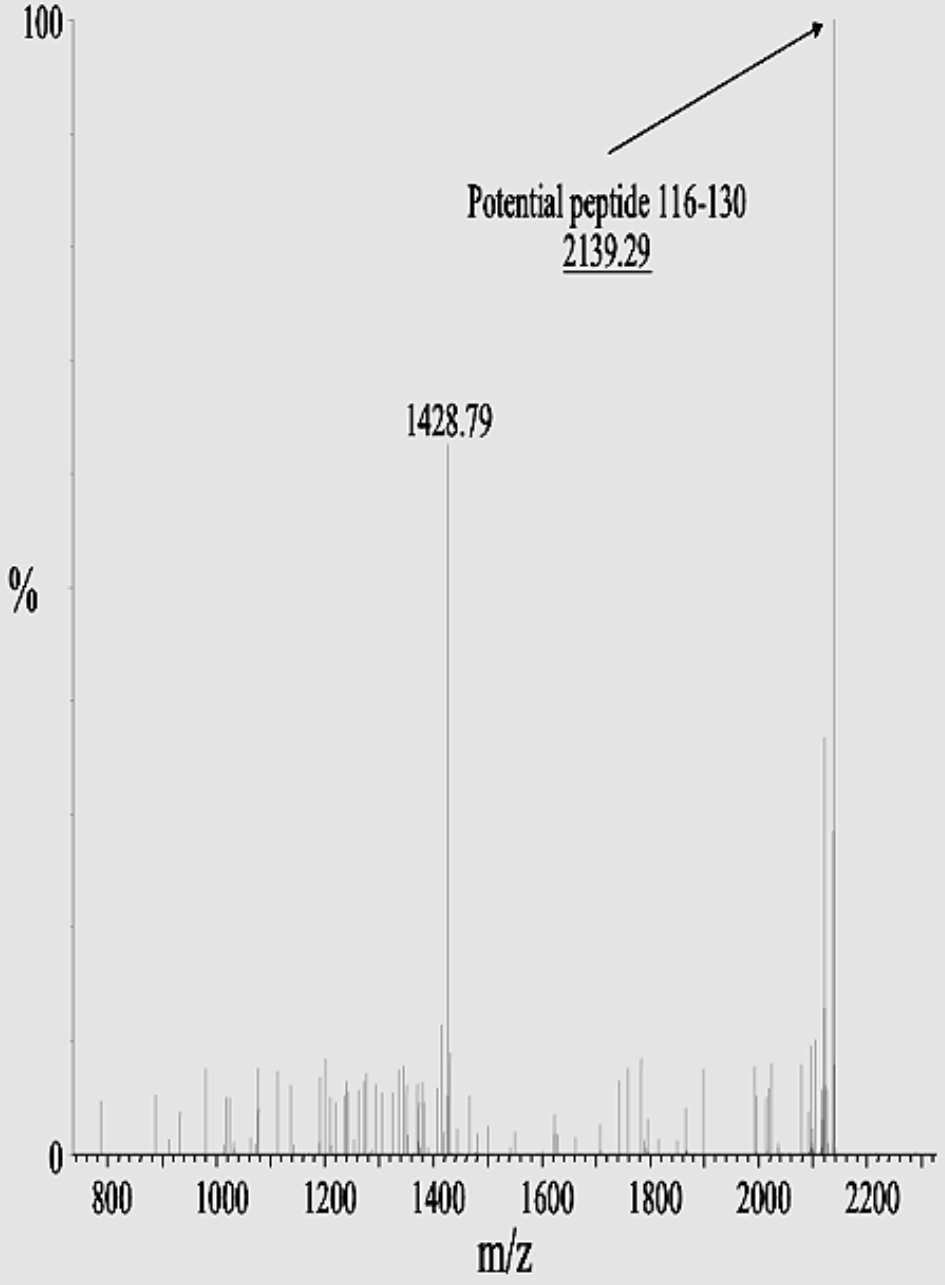
Supplemental Fig. 7



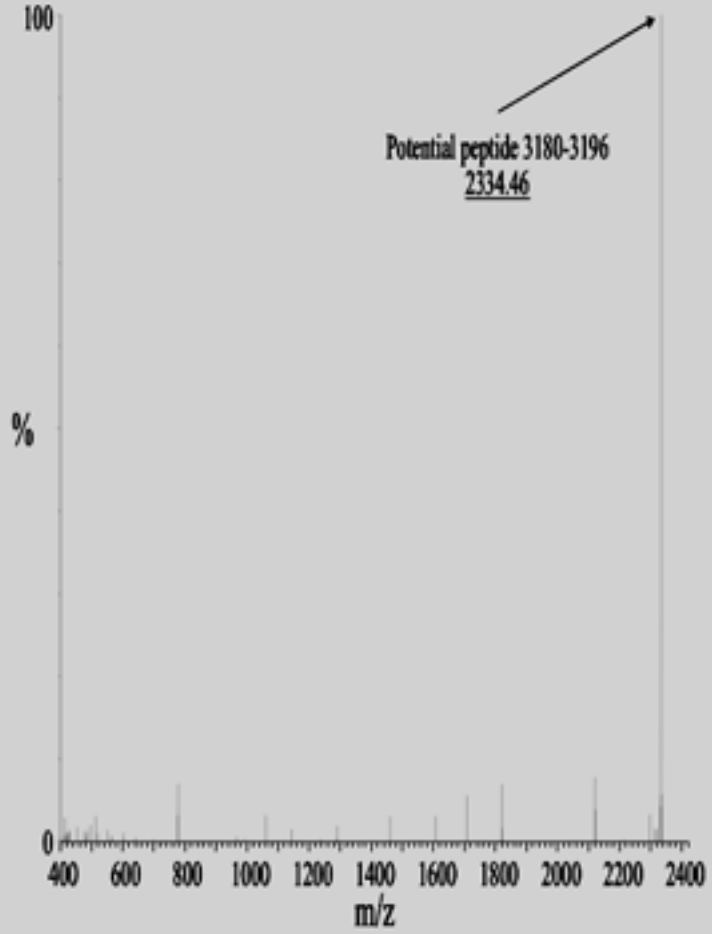
Supplemental Fig. 8



Supplemental Fig. 9



Supplemental Fig. 10



Identification of Hyperreactive Cysteines within Ryanodine Receptor Type 1 by Mass Spectrometry

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