**Supplementary Table S1.** Reagents and resources used.

| **Reagent or resource (abbreviation)** | **Obtained from (vendor)** | **Catalog number** |
|---|---|---|
| DSPE-PEG(2000) Carboxylic Acid (DSPE-PEG-CO2H) | Avanti Polar Lipids | 880135P |
| DSPE-PEG(2000) Maleimide (DSPE-PEG-MAL) | Avanti Polar Lipids | 880135P |
| 18:1 Liss Rhod PE (Rhodamine-PE) | Avanti Polar Lipids | 810150P |
| 18:0 PE-DTPA (Gd) | Avanti Polar Lipids | 791275 |
| trFluor™ Eu-Cryptate succinimidyl ester | Aat Bioquest | 1430 |
| N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC) | Sigma Aldrich | E6383 |
| N-Hydroxysulfosuccinimide sodium salt (sulfo-NHS) | Sigma Aldrich | 56485 |
| 2-Mercaptoethanol | Sigma Aldrich | M6250 |
| Hydroxylamine hydrochloride ($NH_2OH$) | Sigma Aldrich | 379921 |
| Sepharose 4B | Sigma Aldrich | 4B200 |
| RAW-Blue™ Cells | Invivogen | raw-sp |
| Dexamethasone (Dex) | MP Biomedicals | 02150154-CF |
| N-Acetyl-L-cysteine (NAC) | Sigma Aldrich | A9165 |
| Nunc MaxiSorp 96-well plates | Thermo Fisher | 44-2404-21 |
| CCR2 (Human) Recombinant Protein | Abnova | H00729230-G01 |
| Recombinant Human CCL2/MCP-1 Protein | R&D Systems | 279-MC-050 |
| Recombinant Mouse CCL2/MCP-1 Protein | R&D Systems | 479-JE-010 |
| Liberase | Roche | 5401119001 |
| Deoxyribonuclease I (Dnase I) | Roche | 04536282001 |
| Hyaluronidase | Sigma Aldrich | H3506 |
| Lympholyte-M | Cedarlane | CL5030 |
| RPMI-1640 | Thermo Fisher | 11875085 |
| Fetal Bovine Serum (FBS) | Gemini Bio-Products | 100-106 |
| 1,4-Dithiothreitol (DTT) | Roche | 11583786001 |
| Bio Rad TGX Criterion precast gels | Bio Rad | 5671083 |

| **Supplementary Table S1 (continuation)** | | |
|---|---|---|
| **Reagent or resource (abbreviation)** | **Obtained from (vendor)** | **Catalog number** |
| AquaBlock | EastCoast Bio, Inc. | PP82 |
| SIGMAFAST OPD | Sigma Aldrich | P9187-5SET |
| RAW 264.7 cells | ATCC | TIB-71 |
| J774A.1 cells | ATCC | TIB-67 |
| Mouse Interleukin-1ß (IL-1ß) AlphaLISA Detection Kit | Perkin Elmer | al503c |
| TNFα (mouse) AlphaLISA Detection Kit | Perkin Elmer | al505c |
| Streptavidin-HRP | Thermo Fisher | 21132 |
| anti-NLRP3/NALP3, used at 1:5000 for Western blot | Adipogen | AG-20B-0014-C100 |
| anti-Caspase-1 (p10), used at 1:500 for Western blot | Adipogen | AG-20B-0044-C100 |
| Biotin anti-human MCP-1 Antibody | BioLegend, Inc. | 502609 |
| Anti-F4/80 antibody [CI:A3-1] (ab6640), used at 1:250 for IHC | Abcam | ab6640 |
| Cleaved Caspase-1, used at 1:1000 for Western blot | Cell Signalling | 67314S |
| GAPDH-HRP, used at 1:2000 for Western blot | Cell Signalling | 8884S |
| IL-1-Beta, used at 1:5000 for Western blot | Cell Signalling | 31202S |
| Caspase-3, used at 1:1000 for Western blot | Cell Signalling | 14220S |
| HO-1, used at 1:10,000 for Western blot | Cell Signalling | 82206S |
| ASC/TMS1, used at 1:1000 for Western blot | Cell Signalling | 67824T |
| beta Actin Polyclonal Antibody, used at 1:30,000 for Western blot | Thermo Fisher | PA1-16889 |
| CD11b, used at 1 µL per $10^6$ cells in flow cytometry | BioLegend, Inc. | 101211 |
| CD11c used at 1 µL per $10^6$ cells in flow cytometry | BioLegend, Inc. | 117321 |
| CCR2 used at 1 µL per $10^6$ cells in flow cytometry | BioLegend, Inc. | 150609 |
| Ly6C used at 1 µL per $10^6$ cells in flow cytometry | BioLegend, Inc. | 128021 |
| Goat anti-Mouse IgG (H+L), Superclonal Recombinant Secondary Antibody, HRP, at 1:50,000 for Western blot | Thermo Fisher | A28177 |
| Goat anti-Rabbit IgG (H+L), Superclonal™ Recombinant Secondary Antibody, HRP, at 1:50,000 for Western blot | Thermo FIsher | A27036 |
| µ-Slide Chemotaxis | IBIDI | 80326 |
| ibidi Heating System | IBIDI | 10918 |

| **Supplementary Table S1 (continuation)** | | |
|---|---|---|
| **Reagent or resource (abbreviation)** | **Obtained from (vendor)** | **Catalog number** |
| Alexa Fluor 633 Phalloidin | Thermo FIsher | A22284 |
| Qiagen RNeasy Mini Kit | Qiagen | 74104 |
| High-Capacity cDNA Reverse Transcription Kit | Thermo FIsher | 4368814 |
| Mrc1 TaqMan | Thermo FIsher | Mm01329632_m1 |
| Nos2 TaqMan | Thermo FIsher | Mm00440502_m1 |
| IL6 TaqMan | Thermo FIsher | Mm00446190_m1 |
| TNF TaqMan | Thermo FIsher | Mm00443258_m1 |
| IL1b TaqMan | Thermo FIsher | Mm00434228_m1 |
| Teklad Custom Diet | ENVIGO | TD.02028 |
| Alfalfa-free diet | ENVIGO | TD.97184 |
| DAB Peroxidase (HRP) Substrate Kit | Vactor Labs | SK-4100 |
| Nigericin | Invivogen | tlrl-nig |
| Adenosine 5′-triphosphate (ATP) | Sigma Aldrich | A1852 |
| nCounter Inflammation Panel | Nanostring | XT-CSO-MIN2-12 |
| Mouse Cytokine Array - Eve Technologies | EVE technologies | MD31 |
| GSH/GSSG-Glo Assay | Promega | V6611 |
| DCFDA / H2DCFDA - Cellular ROS Assay Kit | Abcam | ab113851 |
| LDH-Glo Cytotoxicity Assay | Promega | J2380 |
| B6.129P2-Apoe$^{tm1Unc}$/J mice | The Jackson Laboratory | Stock No: 002052 |
| B6.129S4-Ccr2$^{tm1Ifc}$/J mice | The Jackson Laboratory | Stock No: 004999 |
| BMS CCR2 22 | Tocris | Cat. No. 3129 |
| ULTRA PURE LPS from *Salmonella minnesota* R595 (Re) | List Biological Laboratories | 434 |
| ACK lysis buffer | Thermo FIsher | A1049201 |

**Supplementary Table S2.** Peptides Scanned from Original Protein.
MKVSAALLCLLLIAATFIPQGLAQPDAINAPVTCCYNFTNRKISVQRLASYRRITSSKCPKEAVIFKTIVAKEICADP
KQKWVQDSMDHLDKQTQTPKT

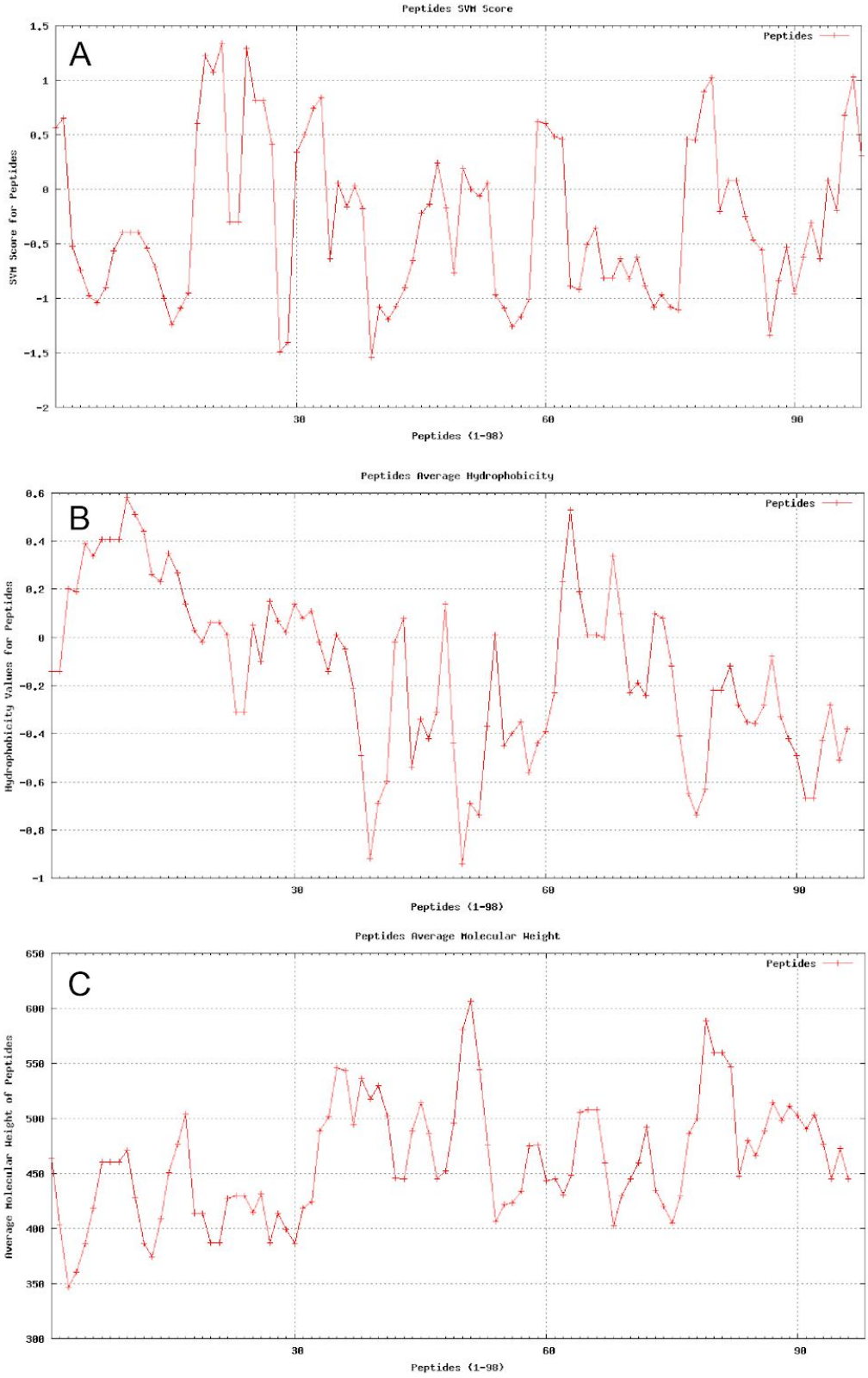
| Peptide Sequence | SVM score | Prediction | Hydrophobicity | Hydropathicity | Hydrophilicity | Charge | Mol wt |
|---|---|---|---|---|---|---|---|
| RLAS | -0.77 | AHT | -0.31 | 0.07 | 0.25 | 1 | 445.55 |
| KVSA | -0.74 | AHT | -0.14 | 0.33 | 0.33 | 1 | 403.52 |
| LLIA | -0.71 | AHT | 0.51 | 3.48 | -1.48 | 0 | 428.6 |
| KISV | -0.65 | AHT | -0.02 | 1 | 0 | 1 | 445.6 |
| **VTCC** | **-0.64** | **AHT** | **0.11** | **2.12** | **-0.97** | **0** | **424.57** |
| KTIV | -0.64 | AHT | 0 | 1.03 | -0.17 | 1 | 459.63 |
| DKQT | -0.64 | AHT | -0.67 | -2.9 | 1.45 | 0 | 490.56 |
| IVAK | -0.62 | AHT | 0.1 | 1.65 | -0.2 | 1 | 429.6 |
| HLDK | -0.62 | AHT | -0.42 | -1.7 | 0.93 | 0 | 511.62 |
| ALLC | -0.56 | AHT | 0.34 | 2.97 | -1.27 | 0 | 418.58 |
| QDSM | -0.55 | AHT | -0.35 | -1.48 | 0.55 | -1 | 479.55 |
| LLLI | -0.54 | AHT | 0.58 | 3.97 | -1.8 | 0 | 470.68 |
| MKVS | -0.53 | AHT | -0.14 | 0.35 | 0.12 | 1 | 463.64 |
| MDHL | -0.53 | AHT | -0.08 | -0.25 | -0.15 | -1 | 514.64 |

**Supplementary Table S3.** Physico-chemical properties of synthesized nanoparticles.

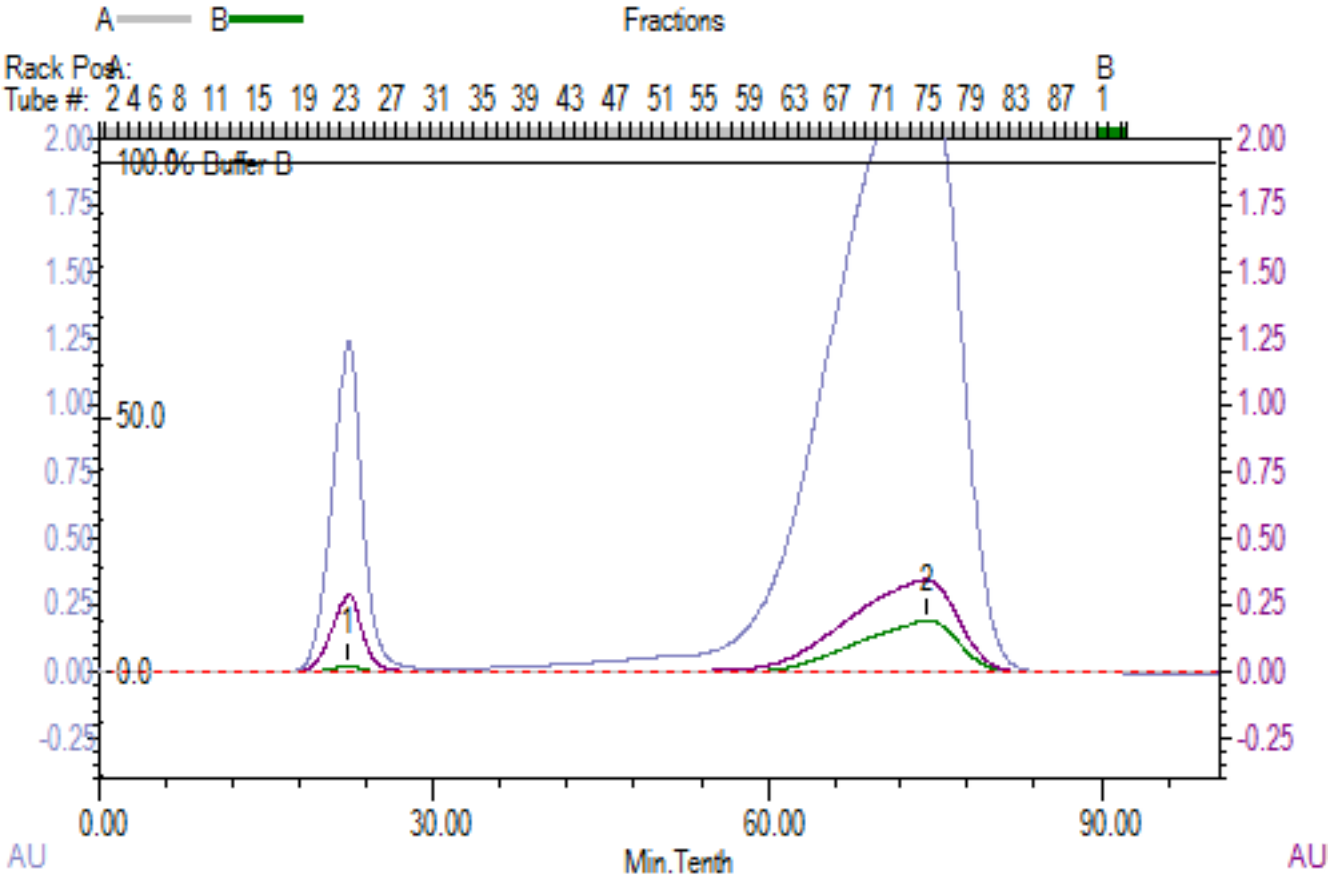
| NP ID | Conjugated Peptide | Conjugation end N-Term or SH type | Size (Mean Z average), nm | Size Standard Deviation | Mean Polydispersity Index (PDI) |
|---|---|---|---|---|---|
| A1 | RLAS | N | 93 | 11 | 0.198 |
| A2 | KVSA | N | 110 | 32 | 0.124 |
| A3 | LLIA | N | 134 | 42 | 0.162 |
| A4 | KISV | N | 114 | 42 | 0.09 |
| A5 | VTCC | N | 76 | 10 | 0.141 |
| A6 | KTIV | N | 142 | 32 | 0.054 |
| B1 | DKQT | N | 204 | 54 | 0.176 |
| B2 | IVAK | N | 53 | 5 | 0.058 |
| B3 | HLDK | N | 61 | 12 | 0.257 |
| B4 | ALLC | N | 86 | 14 | 0.151 |
| B5 | QDSM | N | 198 | 65 | 0.169 |
| B6 | LLLI | N | 223 | 32 | 0.152 |
| C1 | MKVS | N | 189 | 23 | 0.159 |
| C2 | MDHL | N | 134 | 13 | 0.111 |
| C3 | VTCC | SH | 167 | 64 | 0.148 |
| C4 | ALLC | SH | 79 | 23 | 0.002 |

**Supplementary Table S4.** Alignment of CCTV filtered by *mus musculus*.

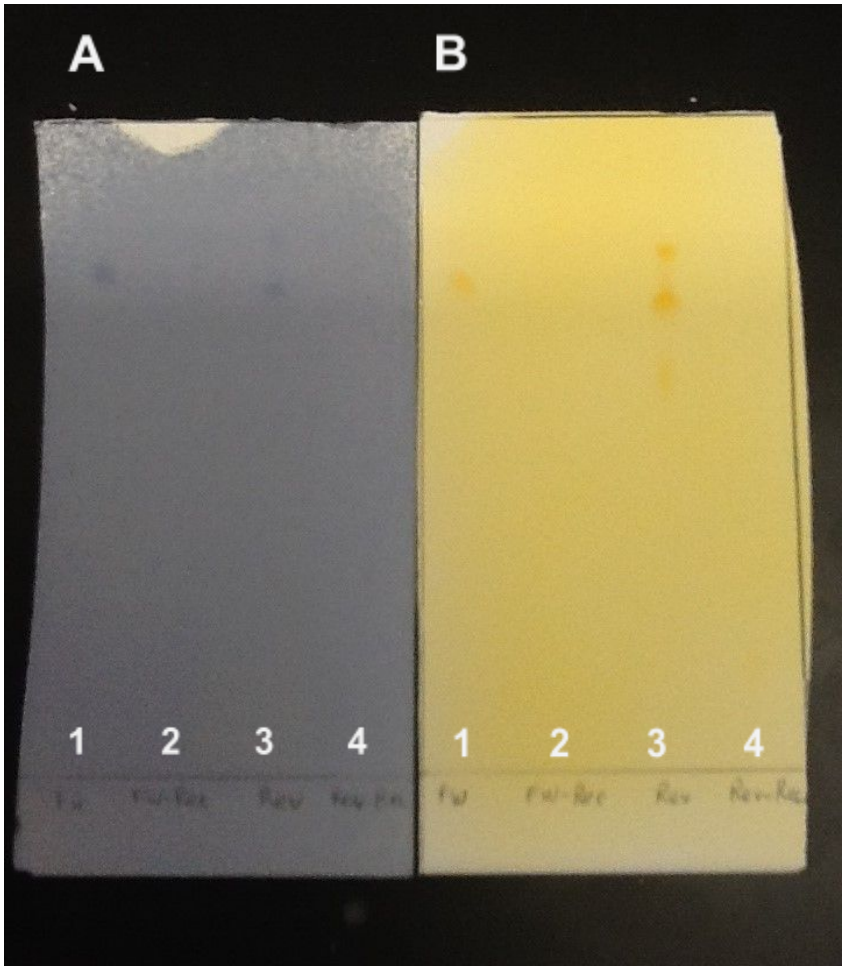
| Sequence ID | Start | End | Organism | Protein |
|---|---|---|---|---|
| NP_038658.2 | 3,273 | 3,276 | *Mus musculus* | polycystin-1 precursor |
| NP_076055.3 | 1,533 | 1,536 | *Mus musculus* | mucin-2 precursor |
| NP_001240786.1 | 1,641 | 1,644 | *Mus musculus* | methylcytosine dioxygenase TET1 isoform 1 |
| NP_082290.2 | 1,000 | 1,003 | *Mus musculus* | transmembrane protein 94 |
| NP_001116066.2 | 978 | 981 | *Mus musculus* | PH domain leucine-rich repeat-containing protein phosphatase 2 |
| NP_001076811.1 | 553 | 556 | *Mus musculus* | protein dispatched homolog 3 |
| NP_001074813.2 | 400 | 403 | *Mus musculus* | syntaxin-binding protein 5 |
| NP_780465.4 | 971 | 974 | *Mus musculus* | protein HEG homolog 1 precursor |
| NP_666151.3 | 642 | 645 | *Mus musculus* | WD repeat-containing protein 60 |
| NP_899006.1 | 174 | 177 | *Mus musculus* | G protein-regulated inducer of neurite outgrowth 3 |
| NP_941052.1 | 340 | 343 | *Mus musculus* | solute carrier family 22 member 20 |
| NP_032568.3 | 123 | 126 | *Mus musculus* | mothers against decapentaplegic homolog 6 |
| NP_033332.1 | 72 | 75 | *Mus musculus* | synaptotagmin-1 isoform 1 |
| NP_001239271.1 | 72 | 75 | *Mus musculus* | synaptotagmin-1 isoform 2 |
| NP_032132.1 | 220 | 223 | *Mus musculus* | medium-wave-sensitive opsin 1 |
| NP_796007.1 | 18 | 21 | *Mus musculus* | brorin precursor |
| NP_666413.1 | 143 | 146 | *Mus musculus* | olfactory receptor 1475 |
| NP_997015.2 | 143 | 146 | *Mus musculus* | olfactory receptor 1471 |
| NP_666901.2 | 143 | 146 | *Mus musculus* | olfactory receptor 1472 |
| NP_071297.1 | 148 | 151 | *Mus musculus* | fructosamine-3-kinase isoform a |
| NP_852085.2 | 148 | 151 | *Mus musculus* | ketosamine-3-kinase |
| NP_001033788.1 | 148 | 151 | *Mus musculus* | fructosamine-3-kinase isoform b |
| NP_061262.1 | 94 | 97 | *Mus musculus* | spermatid-specific linker histone H1-like protein |
| NP_035461.2 | 31 | 34 | *Mus musculus* | **C-C motif chemokine 12 precursor** |
| NP_067418.1 | 30 | 33 | *Mus musculus* | **C-C motif chemokine 8 precursor** |



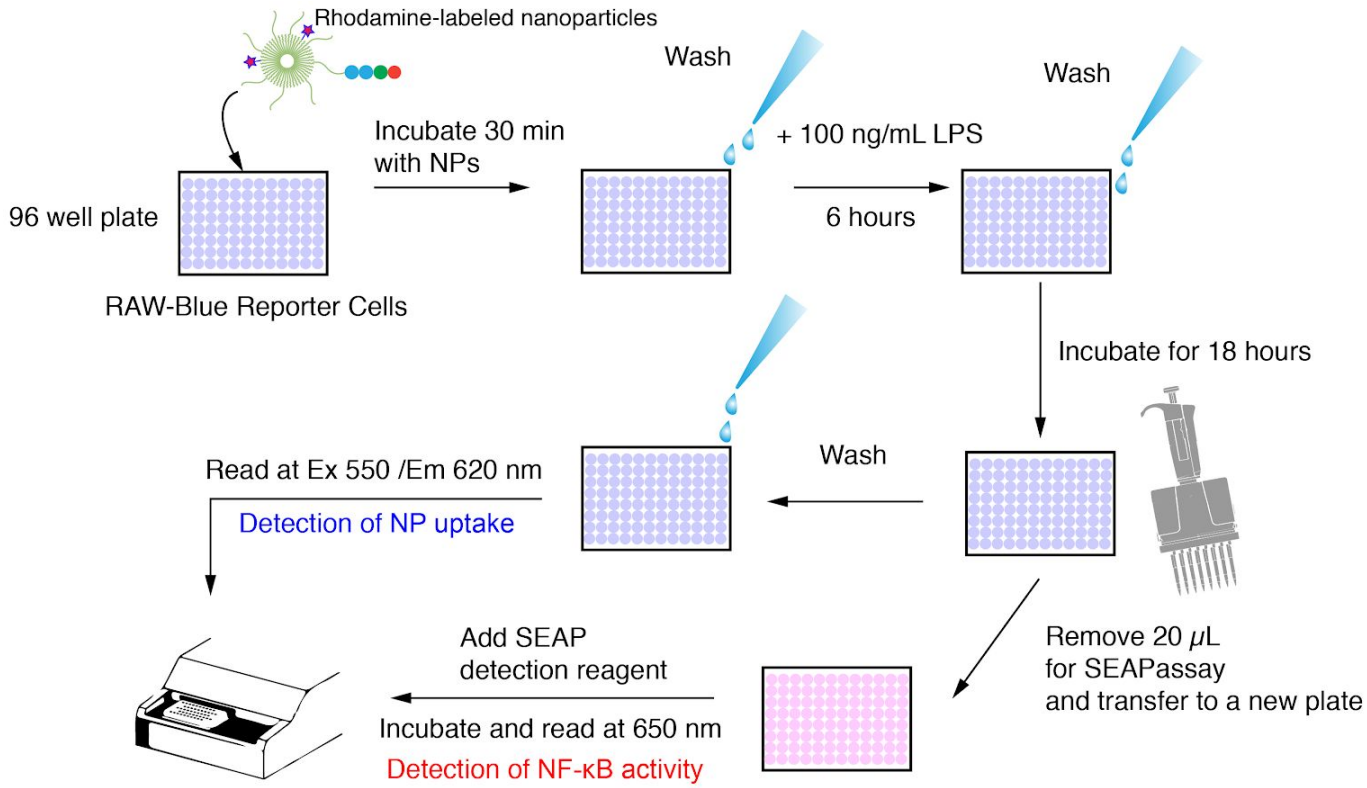

**Supplementary Figure S1.** Peptides and their characteristics predicted via Support Vector Machine (SVM) and the publicly available tool http://crdd.osdd.net/raghava/ahtpin. A) SVM scores for predicted peptides, B) Average hydrophobicity of predicted peptides, C) Average molecular weight of predicted peptides.




**Supplementary Figure S2.** Gel filtration purification of obtained nanoparticles. Fractions 15-31 (peak 1) were collected for further processing. Chromatogram traces of different colors represent different UV wavelengths of the detector.

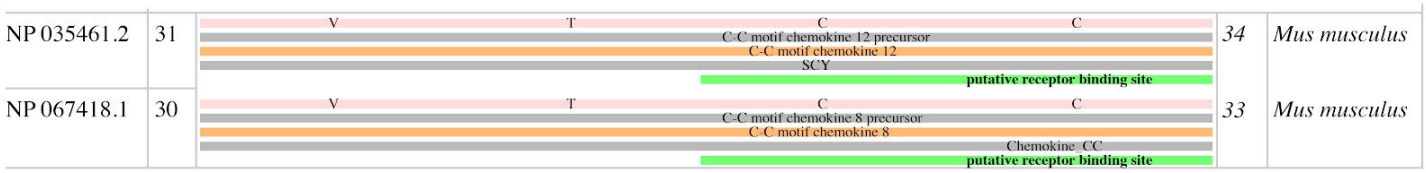



**Supplementary Figure S3.** TLC of obtained conjugation products. A) Molybdenum blue staining phosphates; B) Dragendorff reagent staining amines. 1: N-terminus CCTV conjugation; 2: reaction residue; 3: CCTV SH-conjugation; 4: reaction residue.

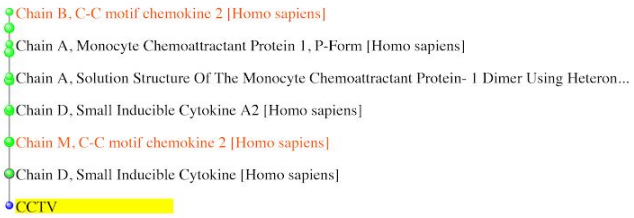



**Supplementary Figure S4.** Schematic representation of screening.

**Mouse alignment**

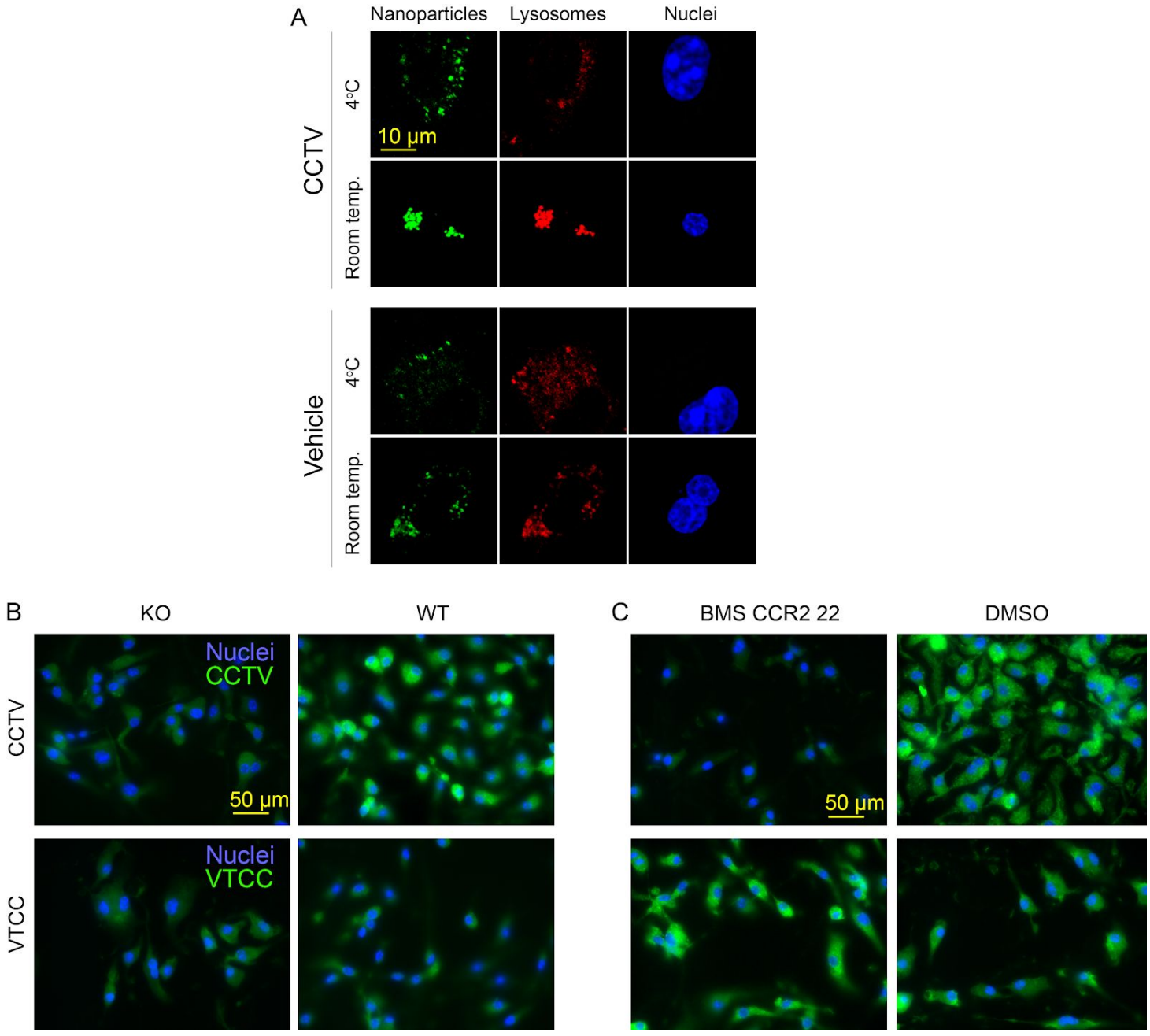



**Human alignment**

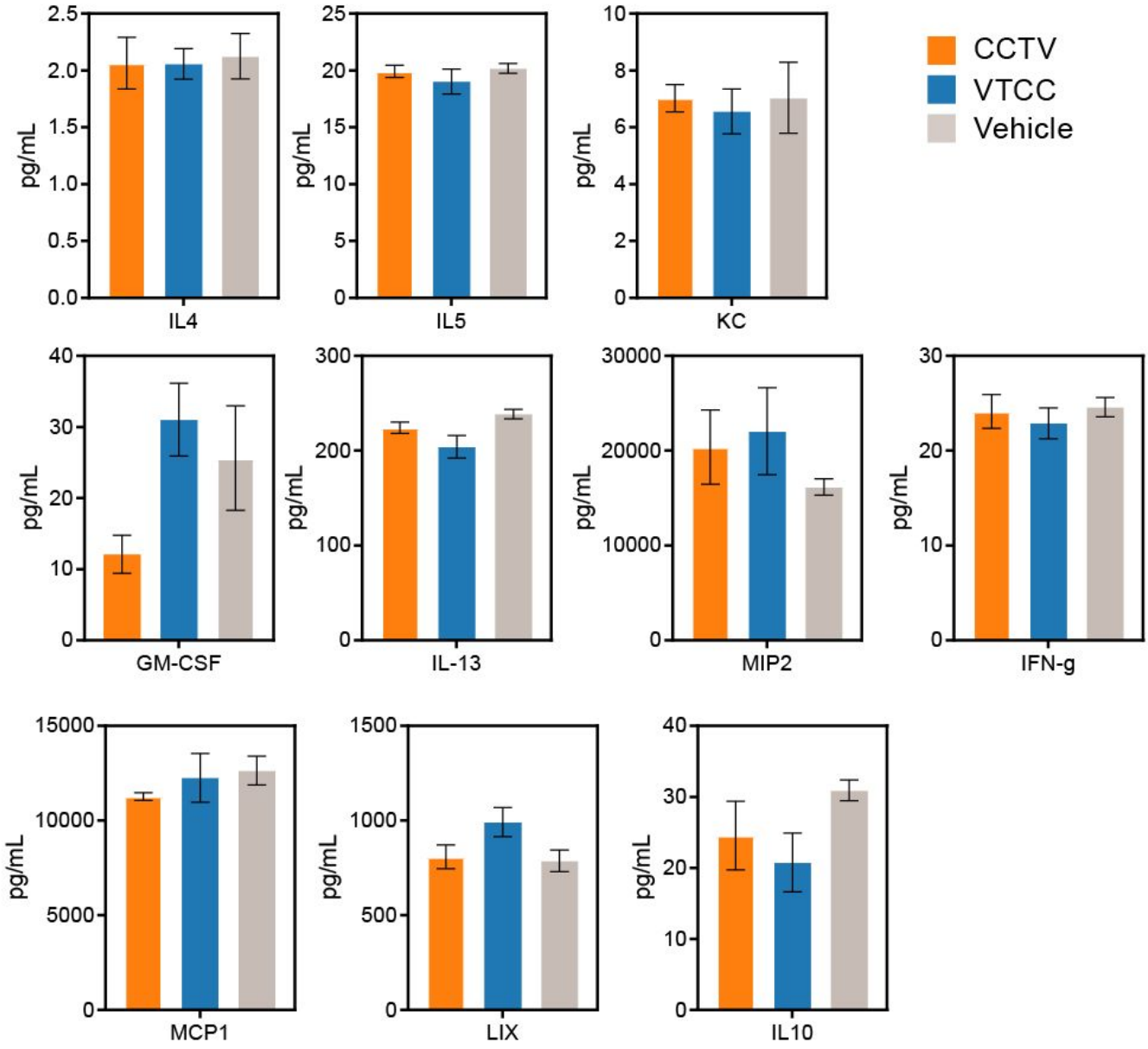



>pdb|4ZK9|B
-QPDAINAPVTCCYNFTNRKISVQRLASYRRITSSKCPKEAVIFKTIVAKEICADPKQKW
VQDSMDHLDKQTQTPKTHHHHHHH
>pdb|1DOK|A
MQPDAINAPVTCCYNFTNRKISVQRLASYRRITSSKCPKEAVIFKTIVAKEICADPKQKW
VQDSMDHLDKQTQTPKT-------
>pdb|1DOM|A
-QPDAINAPVTCCYNFTNRKISVQRLASYRRITSSKCPKEAVIFKTIVAKEICADPKQKW
VQDSMDHLDKQTQTPKT-------
>pdb|2NZ1|D
-QPDAINAPVTCCYNFTNRKISVQRLASYRRITSSKCPKEAVIFKTIVAKEICADPKQKW
VQDSIDHLDKQTQTPKT-------
>pdb|4DN4|M
-QPDAINAAVTCCYNFTNRKISVQRLASYRRITSSKCPKEAVIFKTIVAKEICADPKQKW
VQDSMDHLDKQTQTPKT-------
>pdb|1ML0|D
-QPDAINAAVTCCYNFTNRKISVQRLASYRRITSSKCPKEAVIFKTIVAKEICADPKQKW
VQDSIDHLDKQTQTPKT-------

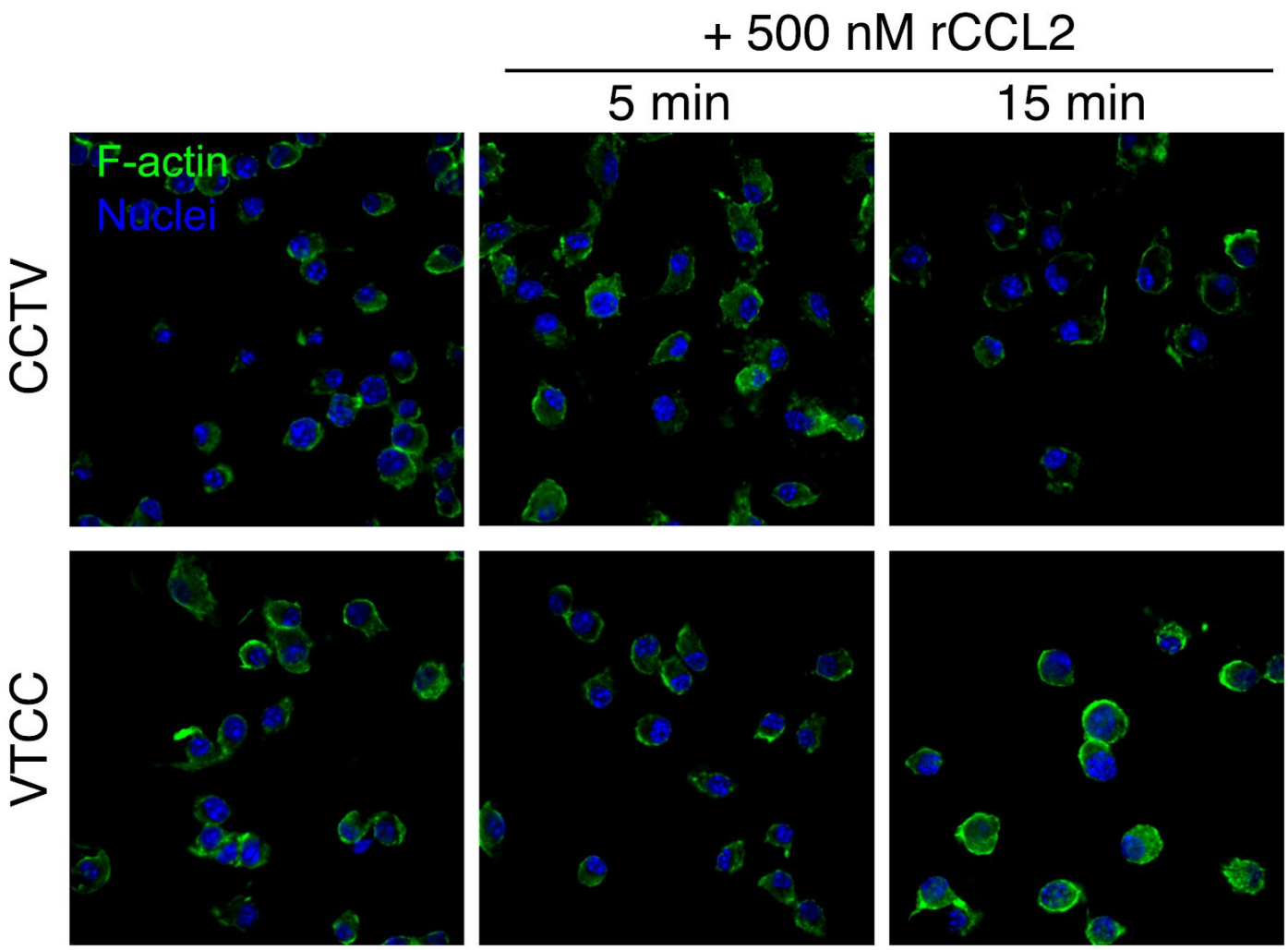
**Supplementary Figure S5.** FASTA alignment of the CCTV sequence using a constraint-based multiple alignment tool (https://www.ncbi.nlm.nih.gov/tools/cobalt/) demonstrated alignment of CCTV with putative receptor binding sites in CC motif chemokine 12 and 8 in mouse sequences and with CC motif chemokine 2 in human sequences.



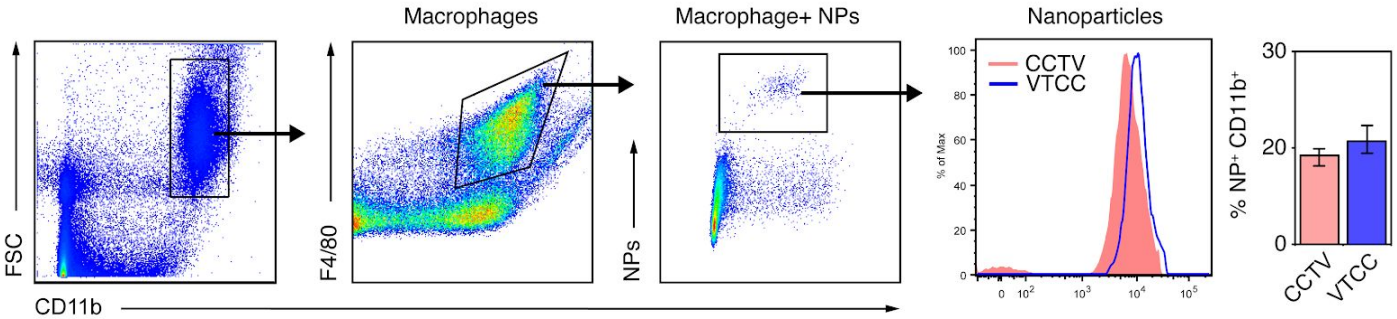

**Supplementary Figure S6. A)** Separate channels for main manuscript Figure 1B.
Uptake of carboxyfluorescein-labeled CCTV or VTCC in cultured bone marrow derived macrophages from **B)** CCR2 knockout (KO, B6.129S4-Ccr2$^{tm1Ifc}$/J) or wild-type (WT) mice; **C)** wild-type mouse-derived macrophages pre-treated (6 h) with CCR2 inhibitor BMS CCR2 22 (10 nM) or DMSO as vehicle control. **C)**



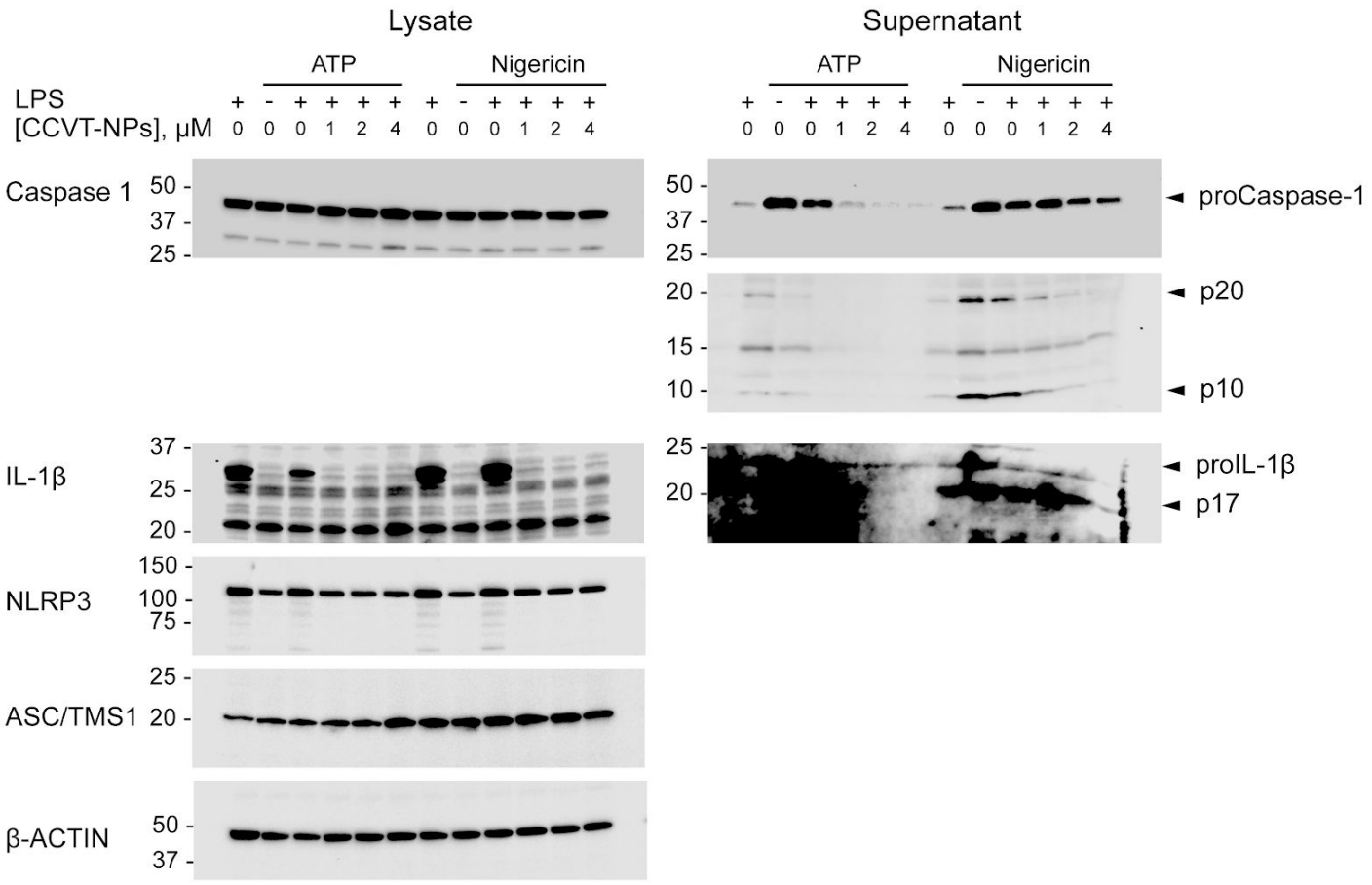

**Supplementary Figure S7.** Cytokines in supernatants from RAW cells stimulated with lipopolysaccharide (100 ng/mL) and treated with CCTV, VTCC or vehicle nanoparticles.




**Supplementary Figure S8.** Actin polymerization assays in bone marrow derived monocytes isolated from CCR2 knockout mice (B6.129S4-Ccr2$^{tm1Ifc}$/J). The experiments were performed as described in Methods and main text. Green: phalloidin staining of actin, blue: nuclei stained with Hoechst 33342.




**Supplementary Figure S9.** Flow cytometry analysis of total macrophage-specific accumulation of CCTV or VTCC in blood of Apoe$^{-/-}$ nanoparticle injected mice. The percent of macrophages that engulfed either nanoparticle was the same. Total blood macrophages were identified as F4/80 positive and CD11b positive.




**Supplementary Figure S10.** Inflammasome activation assays in J774 cells. The cells were treated as described in Methods and main text Figure 5 legend, plus additional inflammasome activator ATP that was added at 1 mM. Immunoblot was performed as described in methods.