emulsified in polyvinyl alcohol with stirring at 400 rpm using a propeller-type agitator with 3 blades (Heidon 600G, Shinto Scientific, Tokyo, Japan). After the system was agitated for 2 hours under reduced pressure at 40°C, the entire suspension was centrifuged (20,000 x *g* for 20 minutes at -20°C). After the supernatant was removed, purified water was added and mixed with the sediment. The wet mixture was then centrifuged again to remove excess polyvinyl alcohol and the unencapsulated reagent that could not adsorb onto the surfaces of the nanoparticles. After this process was repeated, the resultant dispersion was freeze-dried under the same conditions. The FITC-, pitavastatin-, or 7ND-loaded PLGA nanoparticles contained 5.0% (w/v) FITC, 12.0% (w/v) pitavastatin, or 0.40% (w/v) 7ND, respectively. The average diameters of the PLGA-NPs were 231 nm, 159 nm, and 290 nm for the FITC-NP, pitavastatin-NP, and 7ND-NP, respectively. The surface charges (zeta potential) analyzed by Zetasizer Nano (Sysmex, Hyogo, Japan) were -16.7 mV, -4 mV, and 8.1 mV, respectively.

Cellular uptake and in vitro kinetics of the nanoparticles

Murine peritoneal macrophages were obtained from wild-type mice that were injected intraperitoneally with 2 ml of 0.05% thioglycollate 72 hours before the extraction. The cells were centrifuged at 1,000 rpm for 5 minutes at 4°C, suspended in lysis buffer and washed twice with phosphate-buffered saline (PBS) for 5 minutes at 4°C. The cell pellets were suspended in DMEM plus 10% FBS and 1% PS at an initial concentration of 5.0×10^5 cells/ml in a 35 mm culture dish. FITC-NPs were added to the dish (1.0 mg PLGA/ml) and incubated at 37°C in a 5% CO_2 environment overnight. After two washes with PBS for 5 minutes at room temperature, the cells were fixed with methanol and counterstained with propidium iodide (Vector Laboratories Inc., Burlingame, CA, USA). The intracellular uptake of FITC-NP was evaluated by fluorescence microscopy (BX50,

Olympus, Tokyo, Japan) and confocal microscopy (FV1000-D, Olympus). RAW264.7, a murine macrophage cell line, was purchased from the American Type Culture Collection (ATCC; Manassas, VA, USA). The cells were seeded on 6-well-chamber slides and incubated at 37°C in a 5% CO_2 environment until they were subconfluent. The growth medium was replaced with 2 ml of an OsO_4-NP suspension medium (1.0 mg PLGA/ml), incubated for 6 hours and fixed with 2.5% glutaraldehyde. The intracellular uptake of OsO_4-NPs was observed by transmission electronic microscopy (Hitachi H7000E, Tokyo, Japan). To examine the FITC kinetics of cultured macrophages, confluent RAW264.7 cells were incubated with FITC-NP or FITC only at the indicated concentrations (1, 3, 10, 30, and 100 μM). After 2 hours of incubation, extracellular FITC-NPs or FITC was washed out, and FITC with diffuse interference contrast image was observed by confocal laser microscopy (Nikon A1R, Tokyo, Japan) at the indicated time points (days 0, 1, 4, and 7). The average fluorescent intensity of FITC was analyzed using the National Institutes of Health Image Software.

In vivo kinetics of the nanoparticles

The whole aortas of $ApoE^{-/-}$ mice that were fed with HFD and infused with angiotensin II were excised 24 hours after an intravenous injection of the FITC-NPs. The excised aortas were evaluated by stereoscopic and fluorescence microscopy (Nikon SMZ1500 equipped with Nikon HB-10103AF and appropriate fluorescence filter sets, Tokyo, Japan). The brachiocephalic arteries were fixed with 3.7% formaldehyde and embedded in OCT compound. Sections were cut at lengths of 5 μm and evaluated by fluorescence microscopy (BX50, Olympus). The nuclei were stained with propidium iodide (Vector Laboratories Inc., Burlingame, CA, USA). Serial sections were stained with hematoxylin-eosin.

In situ zymography

Gelatinase (MMP-2/gelatinase-A and MMP-9/gelatinase-B) activity was measured in unfixed frozen sections (6 μm thick) using quenched fluorescein-labeled gelatinase substrate (DQ gelatin, Invitrogen, Eugene, OR, USA).[14] The fluorescent area produced by the proteolytic digestion of quenched fluorescein-labeled gelatin was recognized as combined gelatinase activity (MMP-2 + MMP-9). The brachiocephalic artery sections were incubated at 37°C for 30 minutes according to the manufacturer's protocol. Fluorescent microscopy was used to detect gelatinase activity as green fluorescence. Negative control zymograms were incubated in the presence of 20 mM EDTA. The specific removal of essential divalent cations resulted in no detectable gelatinolytic activity.

Gelatin zymography

The RAW264.7 cells were prepared as described above. The growth medium was replaced with pitavastatin at 0.01, 0.1, or 1 μM; pitavastatin-incorporated NPs containing 0.0367, 0.367, or 3.67 μg/mL of PLGA and 0.01, 0.1, or 1 μM of pitavastatin; FITC-incorporated NPs containing 3.67 μg/mL of PLGA-NP; or the vehicle alone. When the medium was replaced, LPS was added at 25 ng/mL to each well. Twenty-four hours after the LPS stimulation, the culture supernatant was obtained. The supernatant was subjected to gelatin zymography using the Gelatin Zymo-Electrophoresis Kit (Primary Cell, Hokkaido, Japan) according to the manufacturer's directions.

Real-time quantitative RT PCR

Real-time PCR amplification was performed with the mouse cDNA with the use of the ABI PRISM 7000 Sequence Detection System (Applied Biosystems), as described previously.[15] For mouse MCP-1, the sense and antisense PCR primers were

5'-CCTGGATCGGA-ACCAAATGA-3' and 5'-CGGGTCAACTTCA-CATTCAAAG-3', respectively, and the probe oligonucleotide was 5'-AACT-GCATCTGCCCTAAGG-TCTTCAGCA-3'. For mouse CCR2, the sense and antisense primers were 5'-CCTTGGGA-ATGAGTAACTGTGTGAT-3' and 5'-ATGGA-GAGATACCTTCGGAACTTCT-3', and the probe oligonucleotide was 5'-CACTTAGACCAGGCCATGCAGGT-GACA-3'. The GAPDH probe was purchased from Applied Biosystems.

Chemotaxis assay

THP-1, the human monocyte cell line, was obtained from the German Collection of Micro-organisms and Cell Cultures (DSMZ; Brauschweig, Germany). The cells were cultured in RPMI 1640 with 10% FBS and 37°C in a 5% CO_2 environment until they were subconfluent. The growth medium was replaced with starvation medium with pitavastatin-NPs containing 0.00367 to 36.7 μg/mL of PLGA and 0.001 to 10 μM of pitavastatin, FITC-NPs containing 36.7 μg/mL of PLGA, or vehicle alone for 24 hours. The chemotactic activity of THP-1 cells in response to 10 ng/mL MCP-1 was measured in a 96-well microchemotaxis Boyden chamber (ChemoTx; Neuroprobe), as described previously.[16] Monocytes that had transmigrated through the micropore were stained with trypan blue. The number of monocytes that migrated in response to MCP-1 was counted.

Measurements of statin concentration in plasma

Pitavastatin concentrations in plasma were measured at predetermined time points by liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS). Briefly, the high-performance liquid chromatography (HPLC) analysis was performed using Agilent 1100 series system (Agilent Technologies, Inc, Santa Clara, CA, USA). The column temperature was maintained at 40 °C. The flow rate was 0.3 mL/min. Pre-prepared plasma

solutions were injected from the autosampler into the HPLC system. The turbo ion spray interface was operated in the positive ion mode at 4800 V and 550 °C. The analytical data were processed using Analyst software (version 1.4, Applied Biosystems, Foster City, CA, USA).

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Supplementary Figure Legends

Supplementary Figure 1. Experimental protocols for the treatments in $ApoE^{-/-}$ mice. At 16-18 weeks of age, mice began receiving the HFD. After 4 weeks of the experimental diet, all mice were infused with angiotensin II dissolved in phosphate-buffered saline (PBS) at 1.9 mg/kg per day.

Protocol 1. Animals were divided into 2 groups at the beginning of angiotensin II infusion: (i) adoptively transferred $CCR2^{+/+}$-inflammatory macrophages from $ApoE^{-/-}$ mice (1×10^6 cells/ 200 μl PBS) and (ii) adoptively transferred $CCR2^{-/-}$-leukocytes from $ApoE^{-/-}CCR2^{-/-}$ mice (1×10^6 cells/ 200 μl PBS).

Protocol 2. Animals were divided into 2 groups at the beginning of angiotensin II infusion: (i) the FITC-incorporated NP group (1.3 mg PLGA/ 200 μl PBS) and (ii) the 7ND-incorporated NP group (5 μg 7ND plasmid/ 200 μl PBS). NPs were administered by weekly intravenous injection.

Protocol 3. Animals were divided into 4 groups at the beginning of angiotensin II infusion: (i) the no treatment group, (ii) the FITC-incorporated NP group (0.1 mg PLGA/ 200 μl PBS), (iii) the pitavastatin-only group (0.012 mg pitavastatin/ 200 μl PBS), and (iv) the pitavastatin-incorporated NP group (0.1 mg PLGA/ 0.012 mg pitavastatin/ 200 μl PBS). NPs were administered by weekly intravenous injection.

Protocol 4. Animals were divided into 2 groups at the beginning of angiotensin II infusion: (i) oral daily administration of pitavastatin at a low dose (0.1 mg/kg/day) and (ii) oral daily administration of pitavastatin at a high dose (1.0 mg/kg/day). Pitavastatin was daily administered by oral gavage.

The no treatment group in protocol 2 was also used as the control group in protocols 1. and 4.

Supplementary Figure 2. Characteristics and kinetics of adoptive transferred macrophages. (**A**) Quantitative flow cytometric analysis of the number of $F4/80^+CD115^+$ macrophages in the peritoneal cavities of $ApoE^{-/-}$ or $ApoE^{-/-}CCR2^{-/-}$ mice induced by intraperitoneal injection of thioglycollate (TG). (**B**) Quantitative analysis of the mean

fluorescence intensity (MFI) of Ly-6C expression in the $F4/80^{+}CD115^{+}$ macrophages from the peritoneal cavities of the $ApoE^{-/-}$ mice. The data are reported as the mean±SEM. (**C**) Left panel: A fluorescence photomicrograph of the brachiocephalic artery of an $ApoE^{-/-}$ mouse from the no treatment group. Upper middle and right panel: PKH fluorescence photomicrographs of the brachiocephalic artery of an $ApoE^{-/-}$ mouse transferred with PKH-labeled activated macrophages. Lower middle and right panel: FITC autofluorescence photomicrographs of the brachiocephalic artery of an $ApoE^{-/-}$ mouse transferred with PKH-labeled activated macrophages. Right panel: An expanded image of the red square area in the middle panel. The nuclei were stained with DAPI. The scale bar indicates 100 μm.

Supplementary Figure 3. The adoptive transfer of splenic monocytes accelerates plaque destabilization and rupture in the brachiocephalic arteries. (A) Left panel: Representative flow cytometry dot plots of splenic leukocytes from $ApoE^{-/-}$ mice. Middle panel: The Representative flow cytometry dot plots of splenic leukocytes negatively selected with antibodies against the leukocytes other than monocytes from $ApoE^{-/-}$ mice. Right panel: The Representative histogram of Ly-6C expression on negatively selected splenic monocytes. (B) Upper panel: Photomicrographs of atherosclerotic plaques in the brachiocephalic artery stained with elastica van Gieson (EVG) in the No Treatment (N) and the Monocytes (M) groups. Arrowheads indicate disrupted/buried fibrous caps. The scale bar indicates 100 μm. Lower panel: Quantitation of the number of disrupted/buried fibrous caps and fibrous cap thickness. The data are reported as the mean±SEM. $*P<0.05$ versus the No Treatment group. There were no statistically significant differences in fibrous cap thickness between the two groups.

Supplementary Figure 4. Cellular uptake and *in vitro* kinetics of the NPs in macrophages. (**A**) Fluorescence photomicrographs of murine peritoneal macrophages incubated with FITC-NPs for 24 hours. An inset depicts a photomicrograph of macrophages incubated without FITC-NPs. (**B**) A fluorescence confocal microscopy image of RAW264.7 cells

incubated with FITC-NPs for 24 hours. (**C**) Electron microscopy image of RAW264.7 cells incubated with OsO_4-NPs for 24 hours. (**D**) Upper panel: Time course of the FITC signal retained in RAW264.7 cells after a 2-hour incubation with FITC-NPs or FITC (0.3, 1, 3, 10, 30, 100 μM) followed by a washout period. Cells were observed at 0, 24, 72 hours, and 1 week of washout. Lower panel: Quantitative analysis of relative fluorescence units (RFUs) of RAW264.7 cells incubated with FITC-NPs (green lines) or FITC (blue lines). *P<0.01 and **P<0.001 versus FITC (N = 4 per group). Data were compared using two-way ANOVA followed by Bonferroni's multiple comparison tests.

Supplementary Figure 5. Effects of daily oral administration of pitavastatin (0.1 or 1.0 mg/kg per day) on atherosclerotic plaque rupture in the brachiocephalic arteries. (**A**) Upper panel: Photomicrographs of atherosclerotic plaques stained with elastica van Gieson (EVG), Mac3 or MCP-1 in the No Treatment (N), pitavastatin 0.1 mg/kg (0.1), and pitavastatin 1.0 mg/kg (1.0) groups. Arrowheads indicate disrupted/buried fibrous caps. The scale bar indicates 100 μm. Lower panel: Quantitation of the number of disrupted/buried fibrous caps, fibrous cap thickness and Mac3- and MCP-1-positive areas. The data are reported as the mean±SEM. †P<0.05 versus the No Treatment group using one-way ANOVA followed by Dunnett's multiple comparison tests. **P<0.01 versus the No Treatment group using one-way ANOVA followed by Bonferroni's multiple comparison tests. (**B**) Upper panel: Photomicrographs of the intraluminal surface of the total aorta stained with oil red O. Lower panel: Quantitation of the percentage of the plaque area compared with the total luminal surface area. The data are reported as the mean±SEM. *P<0.05 versus the No Treatment group. (C) Upper panel: Photomicrographs of atherosclerotic plaques in the aortic root stained with EVG or Mac3. Lower panel: Quantitation of plaque size and Mac3-positive areas. The scale bar indicates 200 μm. The data are reported as the mean±SEM. †P<0.05 versus the No Treatment group using one-way ANOVA followed by Dunnett's multiple comparison tests.

Supplementary Tables

Supplementary Table 1. Body weight, heart rate, systolic blood pressure, and lipid profiles in the no treatment, $CCR2^{+/+}$ inflammatory macrophage, and $CCR2^{-/-}$ leukocyte groups.

	No Treatment (N= 9)	$CCR2^{+/+}$ Inflammatory Macrophage (N= 5)	$CCR2^{-/-}$ Leukocyte (N= 8)
Body Weight (g)	33±1	35±3	34±3
Heart Rate (beat/min)	650±20	640±40	580±40
Systolic Blood Pressure (mmHg)	120±2	112±8	115±9
Total Cholesterol (mg/dl)	660±30	710±100	720±60
Triglyceride (mg/dl)	65±9	74±16	69±5

The data are expressed as the mean±SEM. The mean values were compared using ANOVA and Bonferroni's multiple comparison tests, and there are no significant differences for any of these parameters among these groups.

Supplementary Table 2. Body weight, heart rate, systolic blood pressure, and lipid profiles in the no treatment, FITC-NP, pitavastatin, and pitavastatin-NP groups.

	No Treatment (N= 9)	FITC-NP (N= 7)	Pitava (N= 6)	Pitava-NP (N= 10)
Body Weight (g)	33±1	30±1	34±1	32±1

Heart Rate (beat/min)	650±20	630±30	650±20	590±20
Systolic Blood Pressure (mmHg)	120±0	110±10	12±10	120±0
Total Cholesterol (mg/dl)	660±30	670±50	610±50	710±40
Triglyceride (mg/dl)	65±9	60±5	53±5	70±6

The data are expressed as the mean±SEM. The mean values were compared using ANOVA and Bonferroni's multiple comparison tests, and there are no significant differences for any of these parameters compared with the No Treatment group.

Supplementary Table 3. Body weight, heart rate, systolic blood pressure, and lipid profiles in the FITC-NP and 7ND-NP groups.

	FITC-NP (N= 9)	7ND-NP (N= 10)
Body Weight (g)	28±1	25±1
Heart Rate (beat/min)	640±30	680±10
Systolic Blood Pressure (mmHg)	130±10	120±10
Total Cholesterol (mg/dl)	720±60	730±20
Triglyceride (mg/dl)	47±11	53±18

The data are expressed as the mean±SEM. The mean values were compared using the unpaired *t*-test, and there are no significant differences for any of these parameters between these 2 groups.

Supplementary Table 4. Body weight, heart rate, systolic blood pressure, and lipid profiles in the no treatment, pitavastatin 0.1 mg/kg, and pitavastatin 1.0 mg/kg groups.

	No Treatment (N= 9)	Pitavastatin 0.1 mg/kg (N= 10)	Pitavastatin 1.0 mg/kg (N= 11)
Body Weight (g)	33±1	30±1*	32±0
Heart Rate (beat/min)	650±20	610±20	630±10
Systolic Blood Pressure (mmHg)	120±0	110±0	120±0
Total Cholesterol (mg/dl)	660±30	780±20	800±50
Triglyceride (mg/dl)	65±9	82±15	43±5

The data are expressed as the mean±SEM. *P<0.05 versus the No Treatment group. The data were compared using ANOVA followed by Bonferroni's multiple comparison tests.

Supplementary Table 5. Serum biomarkers in the no treatment, $CCR2^{+/+}$ inflammatory macrophage, and $CCR2^{-/-}$ leukocyte group.

		No Treatment (N= 7)	$CCR2^{+/+}$ Inflammatory Macrophage (N= 5)	$CCR2^{-/-}$ Leukocyte (N= 7)
Apo A1	**μg/mL**	48±6	39±6	38±3
CD40	**pg/mL**	87±9	160±40	75±9
CD40 Ligand	**pg/mL**	2600±300	5700±400**	4600±700*
CRP	**μg/mL**	11±1	10±1	11±2

EGF	**pg/mL**	16±1	23±1**	21±1**
Endothelin-1	**pg/mL**	18±1	21±2	17±2
Eotaxin	**pg/mL**	320±20	330±50	380±30
Factor VII	**ng/mL**	14±1	19±1*	18±1
FGF-basic	**ng/mL**	7.0±0.6	11±1*	9.0±0.8
GCP-2	**ng/mL**	31±7	13±7	5±1**
Haptoglobin	**μg/mL**	140±20	190±30	200±20
IFN-γ	**pg/mL**	N.D.	23±8	N.D.
IgA	**μg/mL**	42±5	52±9	60±7
IL-10	**pg/mL**	430±20	N.D.	N.D.
IL-11	**pg/mL**	N.D.	490±430	85±29
IL-17	**ng/mL**	N.D.	N.D.	0.01±0.00
IL-18	**ng/mL**	18±1	30±1***	27±0***
IL-1α	**pg/mL**	260±72	160±45	94±15
IL-1β	**ng/mL**	17±1	20±1	20±1
IL-5	**ng/mL**	N.D.	0.73±0.23	0.61±0.12
IL-6	**pg/mL**	11±2	15±4	N.D.
IL-7	**ng/mL**	0.18±0.06	0.22±0.12	0.18±0.07
IP-10	**pg/mL**	68±9	230±140	54±3
LIF	**pg/mL**	1200±0	1500±100	1200±100
Lymphotactin	**pg/mL**	120±50	180±40	100±20
MCP-1	**pg/mL**	130±10	220±30**	110±10
MCP-3	**pg/mL**	400±30	700±100**	490±40
MCP-5	**pg/mL**	21±2	49±6**	37±6

M-CSF	**ng/mL**	5.2±0.3	8.2±0.4***	6.0±0.1
MDC	**pg/mL**	460±20	580±70	560±40
MIP-1α	**ng/mL**	2.4±0.3	4.1±0.2***	4.0±0.2***
MIP-1β	**pg/mL**	190±40	410±50**	280±20
MIP-1γ	**ng/mL**	50±3	67±7	52±7
MIP-2	**pg/mL**	18±4	28±3	21±2
MIP-3	**ng/mL**	2.3±0.2	3.5±0.3**	2.4±0.3
MMP-9	**ng/mL**	110±20	210±20**	140±20
MPO	**ng/mL**	110±20	200±10**	160±10*
Myoglobin	**ng/mL**	320±260	260±200	78±32
OSM	**ng/mL**	0.15±0.03	N.D.	0.03±0.01**
RANTES	**pg/mL**	0.64±0.20	N.D.	N.D.
SAP	**μg/mL**	47±2	35±1*	38±4
SCF	**pg/mL**	310±40	230±30	190±20*
SGOT	**μg/mL**	51±9	50±5	73±4
TIMP-1	**ng/mL**	4.9±0.7	5.2±0.9	4.7±0.6
Tissue Factor	**ng/mL**	8.6±0.3	11±2	7.5±1.0
TNF-α	**ng/mL**	0.11±0.02	N.D.	N.D.
TPO	**ng/mL**	110±10	150±10**	130±0*
VCAM-1	**ng/mL**	2200±100	3500±700*	2700±100
VEGF	**pg/mL**	290±40	200±10	190±10*
vWF	**ng/mL**	150±10	330±130	160±20

The data are expressed as the mean±SEM. The means were compared by means of

ANOVA and Bonferroni's multiple comparison tests. **P*<0.05 versus the No Treatment group, ***P*<0.01 versus the No Treatment group, ****P*<0.001 versus the No Treatment group. Multiplex immunoassay was performed using the Luminex LabMAP instruments by Charles River Inc. Apo A1 (Apolipoprotein A1), CD (Cluster of Differentiation), CRP (C Reactive Protein), EGF (Epidermal Growth Factor), FGF-9 (Fibroblast Growth Factor-9), FGF-basic (Fibroblast Growth Factor-basic), GCP-2 (Granulocyte Chemotactic Protein-2), GM-CSF (Granulocyte Macrophage-Colony Stimulating Factor), GST-α (Glutathione S-Transferase alpha), IFN-γ (Interferon-gamma), IgA (Immunoglobulin A), IL (Interleukin), IP-10 (Inducible Protein-10), KC/GROα (Melanoma Growth Stimulatory Activity Protein), LIF (Leukemia Inhibitory Factor), MCP (Monocyte Chemoattractant Protein), M-CSF (Macrophage Colony-Stimulating Factor), MDC (Macrophage-Derived Chemokine), MIP (Macrophage Inflammatory Protein), MMP-9 (Matrix Metalloproteinase-9), MPO (Myeloperoxidase), OSM (Oncostatin M), RANTES (Regulation Upon Activation, Normal T-Cell Expressed and Secreted), SAP (Serum Amyloid P), SCF (Stem Cell Factor), SGOT (Serum Glutamic-Oxaloacetic Transaminase), TIMP-1 (Tissue Inhibitor of Metalloproteinase Type-1), TNF-α (Tumor Necrosis Factor-alpha), TPO (Thrombopoietin), VCAM-1 (Vascular Cell Adhesion Molecule-1), VEGF (Vascular Endothelial Cell Growth Factor), vWF (von Willebrand Factor). N.D. (Not Detected).

Supplementary Table 6. Serum biomarkers in the FITC-NP and pitavastatin-NP groups.

		FITC-NP (N= 6)	Pitava-NP (N= 9)
Apo A1	**μg/mL**	45±2	46±2

CD40	**pg/mL**	110±10	90±11
CD40 Ligand	**pg/mL**	1900±100	1400±100*
CRP	**μg/mL**	7.6±0.8	7.5±0.8
EGF	**pg/mL**	26±3	24±1
Endothelin-1	**pg/mL**	24±2	24±1
Eotaxin	**pg/mL**	370±10	420±20
Factor VII	**ng/mL**	28±2	28±1
FGF-basic	**ng/mL**	17±2	17±0
GCP-2	**ng/mL**	39±5	35±4
Haptoglobin	**μg/mL**	150±10	150±10
IgA	**μg/mL**	44±12	32±3
IL-10	**pg/mL**	N.D.	N.D.
IL-11	**pg/mL**	120±60	61±9
IL-18	**ng/mL**	18±1	16±1
IL-1α	**pg/mL**	440±130	200±40
IL-1β	**ng/mL**	7.9±0.3	7.8±0.6
IL-4	**pg/mL**	71±28	59±6
IL-5	**ng/mL**	0.80±0.12	1.1±0.2
IL-6	**pg/mL**	N.D.	12±4
IL-7	**ng/mL**	0.082±0.018	N.D.
IP-10	**pg/mL**	40±3	47±7
LIF	**pg/mL**	1900±100	1900±100
Lymphotactin	**pg/mL**	80±9	82±7
MCP-1	**pg/mL**	130±10	110±0*

MCP-3	**pg/mL**	380±30	320±20
MCP-5	**pg/mL**	28±4	30±2
M-CSF	**ng/mL**	7.3±0.1	7.5±0.2
MDC	**pg/mL**	650±40	840±70
MIP-1α	**ng/mL**	3.3±0.2	3.2±0.1
MIP-1β	**pg/mL**	200±30	180±10
MIP-1γ	**ng/mL**	54±4	45±3
MIP-2	**pg/mL**	28±2	22±2
MIP-3	**ng/mL**	2.0±0.1	2.1±0.1
MMP-9	**ng/mL**	130±10	120±10
MPO	**ng/mL**	140±20	120±10
Myoglobin	**ng/mL**	240±60	360±150
OSM	**ng/mL**	0.05±0.01	N.D.
SAP	**μg/mL**	32±2	30±2
SCF	**pg/mL**	280±10	240±10*
TIMP-1	**ng/mL**	5.0±0.7	4.3±0.5
Tissue Factor	**ng/mL**	14±1	12±0
TPO	**ng/mL**	30±3	32±2
VCAM-1	**ng/mL**	2600±100	2500±200
VEGF	**pg/mL**	200±20	150±10*
vWF	**ng/mL**	180±10	150±10*

The data are expressed as the mean±SEM. The mean values were compared using an unpaired *t*-test. *$P<0.05$ versus the FITC-NP group.

Supplementary Table 7. Plasma concentration of pitavastatin in the pitavastatin and pitavastatin-NP groups.

	2 hours	6 hours	24 hours
Pitavastatin (ng/mL)	1.3±0.2	N.D.	N.D.
Pitavastatin-NP (ng/mL)	2.5±0.2*	N.D.	N.D.

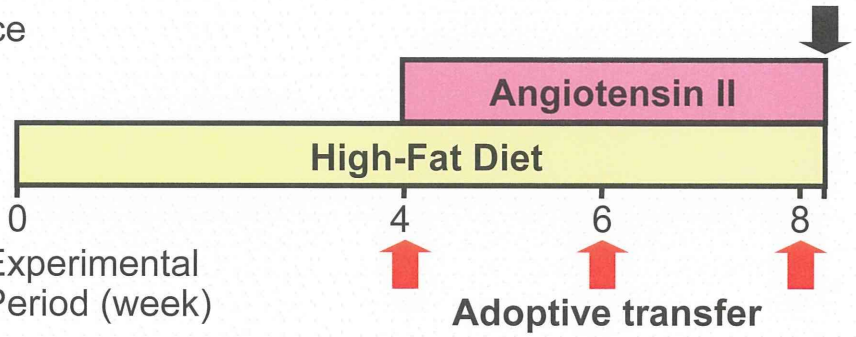
The data are expressed as the mean±SEM. The mean values were compared using an unpaired *t*-test. *$P<0.05$ versus the Pitavastatin group.

Experiment Protocol 1

ApoE$^{-/-}$mice or ApoE$^{-/-}$CCR2$^{-/-}$mice
Thioglycollate-induced
peritoneal macrophages

↓

ApoE$^{-/-}$mice
18 weeks of age

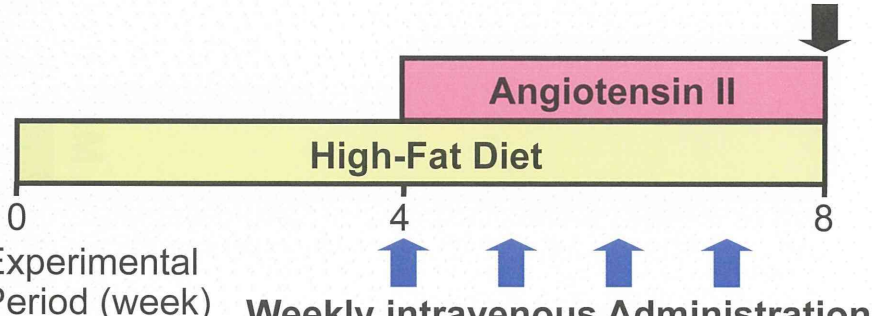


Treatment Group

1. CCR2$^{+/+}$-Inflammatory Macrophage (1x10^6 cells/ 200 μL PBS)
2. CCR2$^{-/-}$-Leukocyte (1x10^6 cells/ 200 μL PBS)

Experiment Protocol 2

ApoE$^{-/-}$mice
16 weeks of age

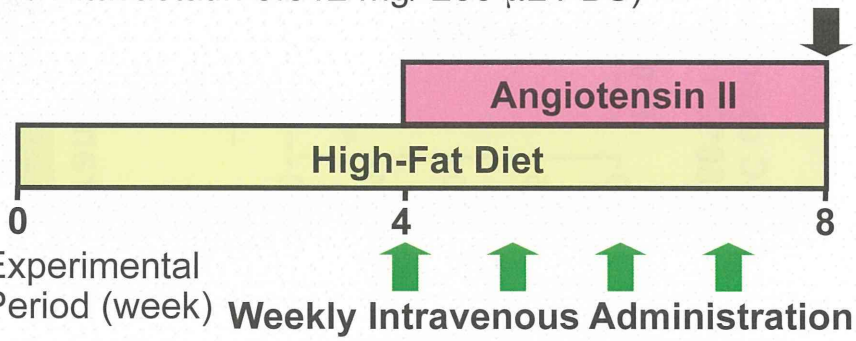


Treatment Group

1. No treatment
2. FITC-NP (0.1 mg PLGA/ 200 μL PBS)
3. Pitavastatin (Pitavastatin 0.012 mg/ 200 μL PBS)
4. Pitavastatin-NP (0.1 mg PLGA/ Pitavastatin 0.012 mg/ 200 μL PBS)

Experiment Protocol 3

ApoE$^{-/-}$mice
16 weeks of age

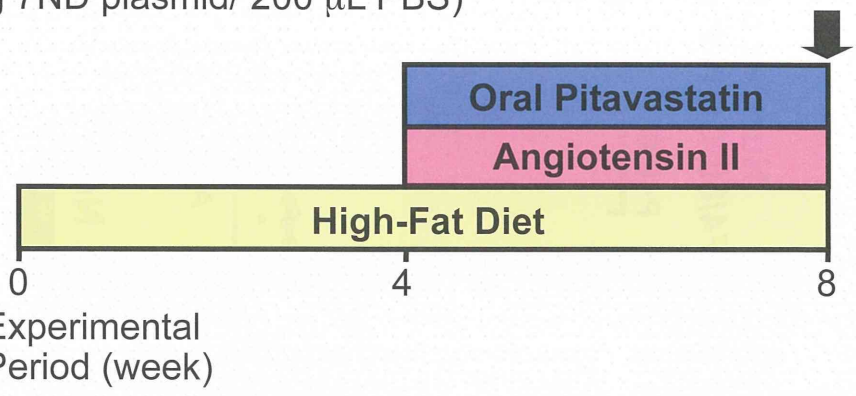


Treatment Group

1. FITC-NP (1.3 mg PLGA/ 200 μL PBS)
2. 7ND-NP (1.3 mg PLGA/ 5 μg 7ND plasmid/ 200 μL PBS)

Experiment Protocol 4

ApoE$^{-/-}$mice
16 weeks of age



Treatment Group

1. Pitavastatin (Lower dose: 0.1 mg/kg/day)
2. Pitavastatin (Higher dose: 1.0 mg/kg/day)