Immunomodulatory Pathways in Atherosclerosis

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UNIVERSITY OF CAMBRIDGE

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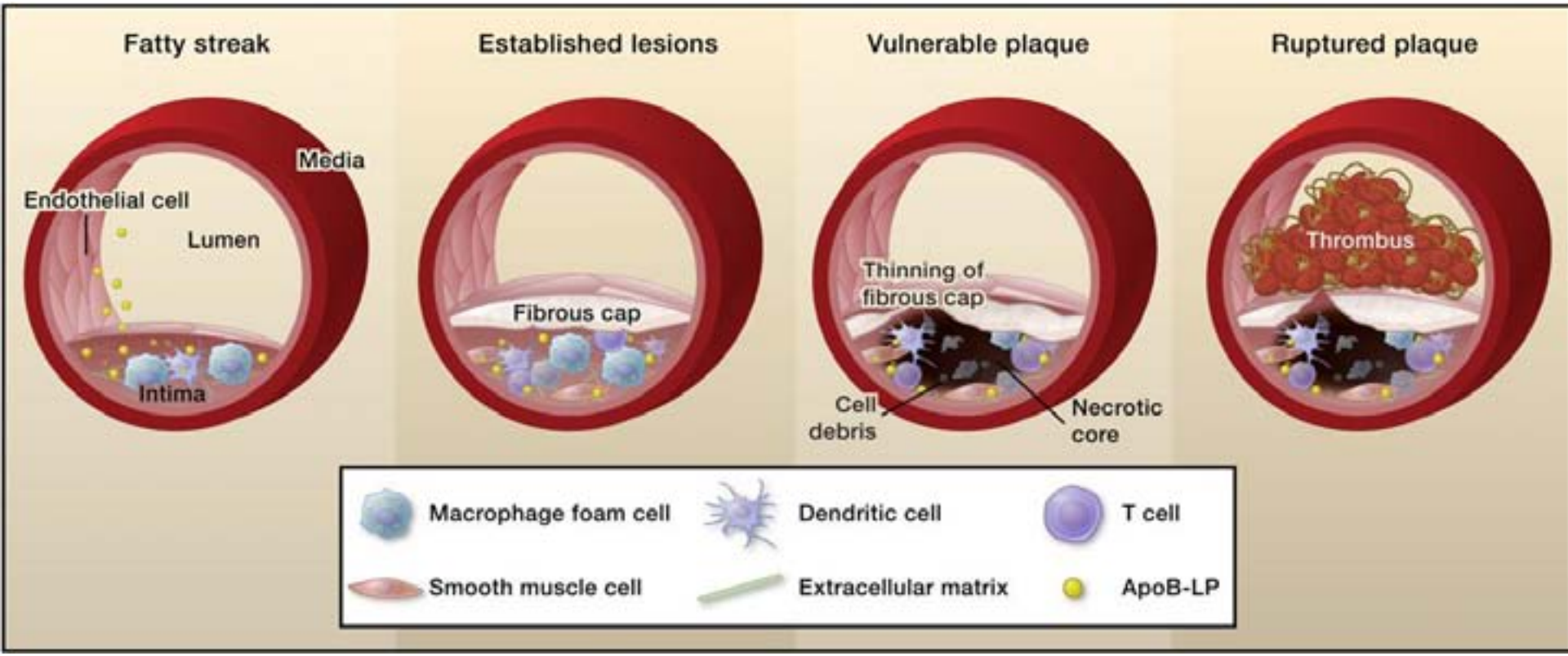
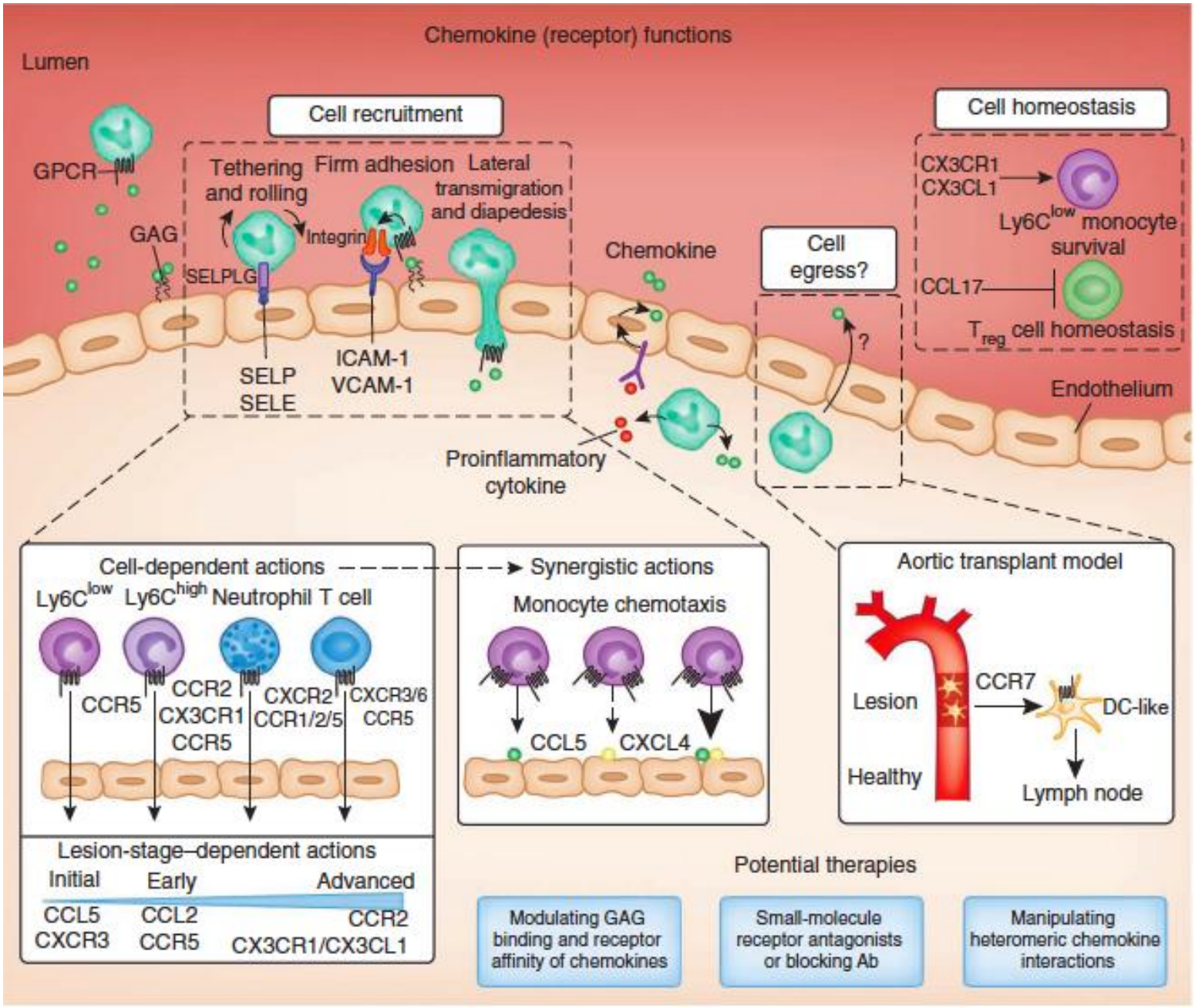
TOLERAGE

L·I·N·K IMMUNOREGULATORY NETWORK

Targeting the Immuno-Inflammatory Response In Atherosclerosis



Moore KJ & Tabas I.
Cell 2011

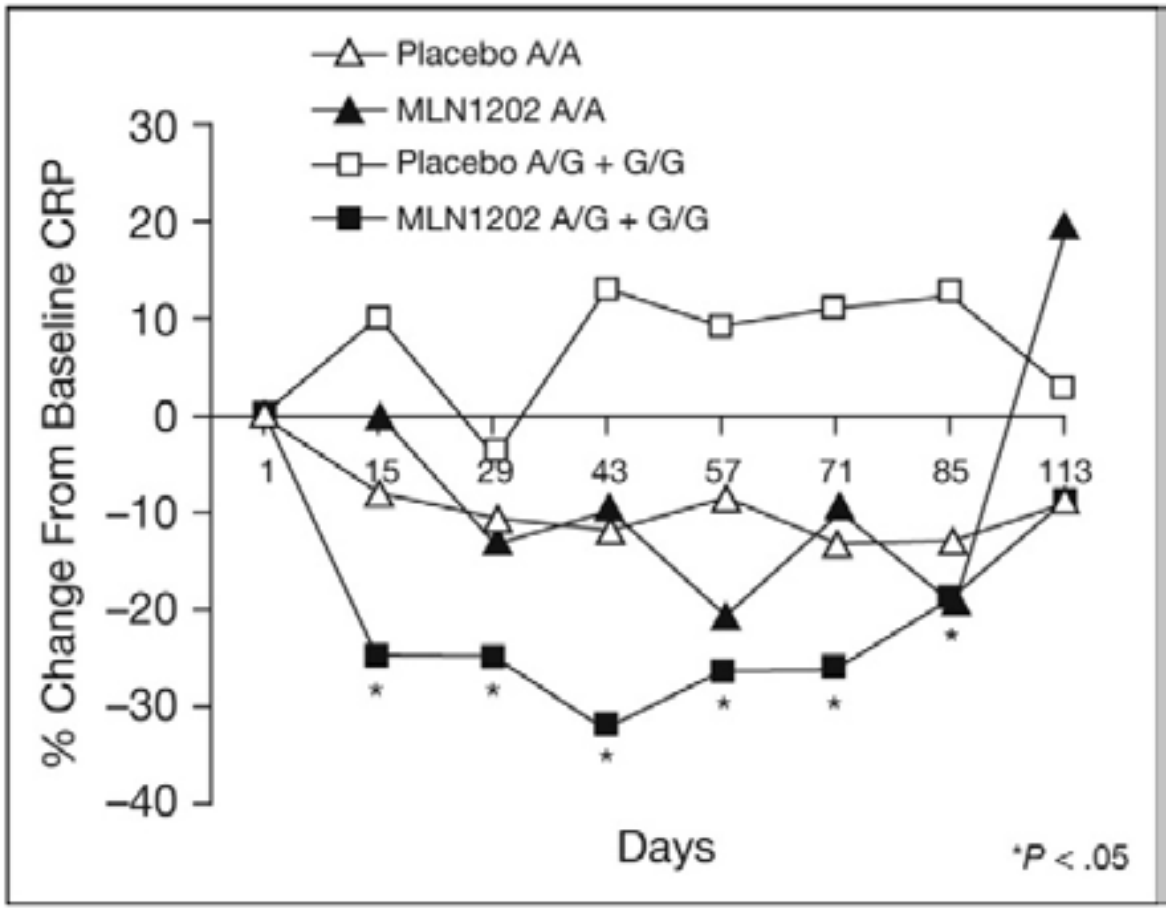


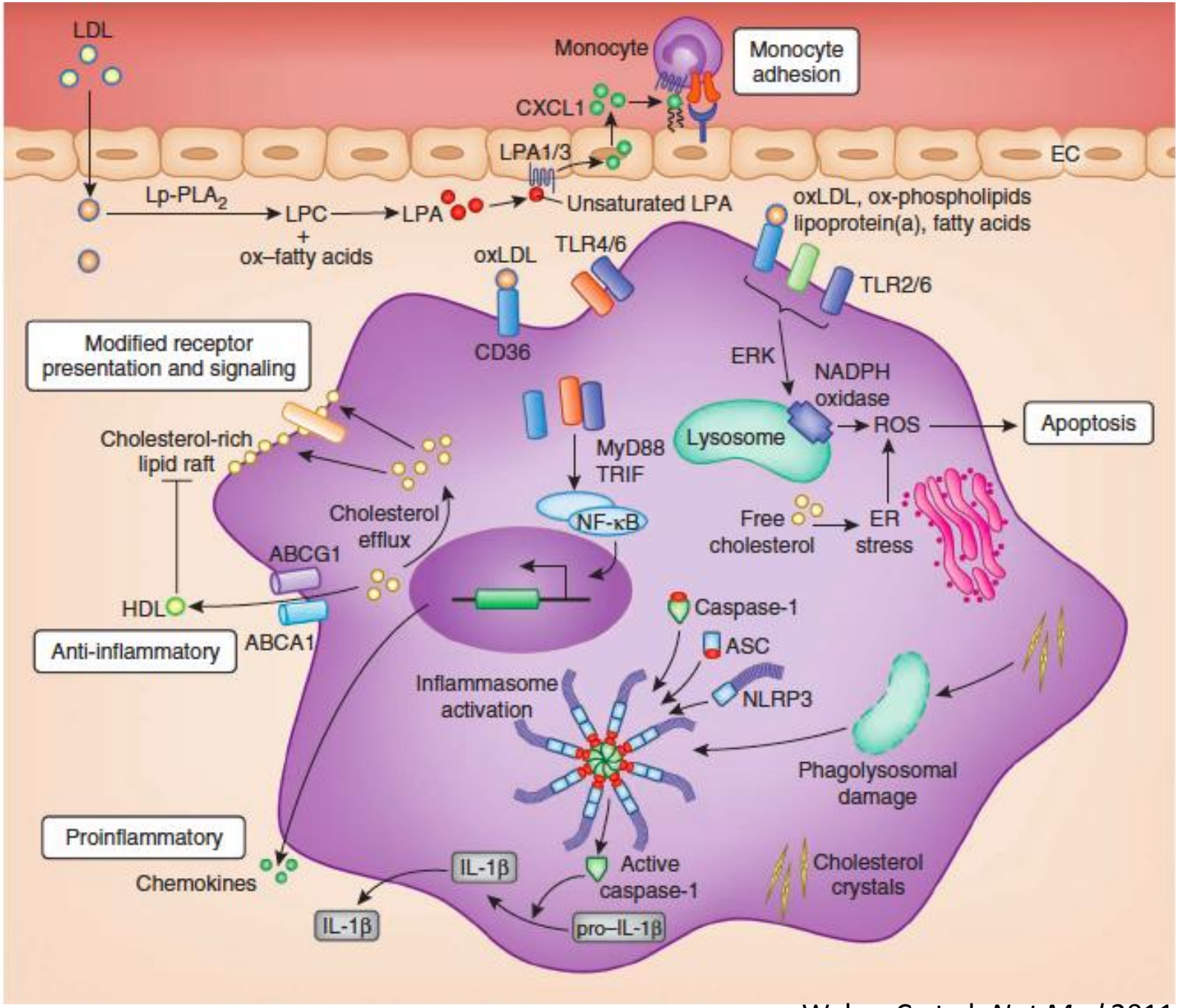
Weber C et al. *Nat Med* 2011

Effect of CC Chemokine Receptor 2 CCR2 Blockade on Serum C-Reactive Protein in Individuals at Atherosclerotic Risk and With a Single Nucleotide Polymorphism of the Monocyte Chemoattractant Protein-1 Promoter Region

Jim Gilbert, MD[a,*], Julie Lekstrom-Himes, MD[b], Debra Donaldson, MD[c], Yih Lee, PhD[d], Mingxiu Hu, PhD[d], Jing Xu, PhD[d], Tim Wyant, MD[d], and Michael Davidson, MD[e,f], for the MLN1202 Study Group[†]

(Am J Cardiol 2011;107:906–911)

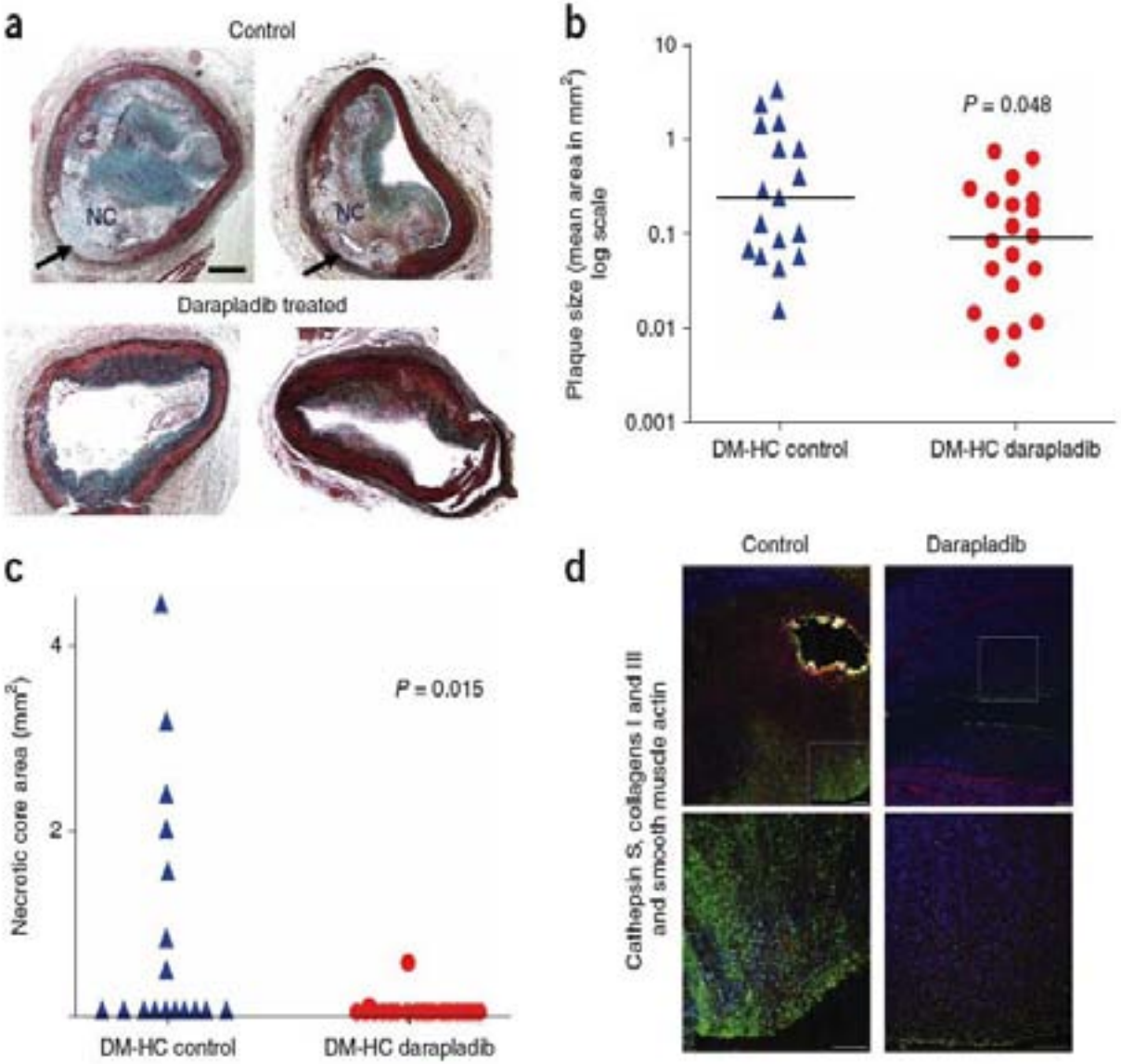




Weber C et al. *Nat Med* 2011

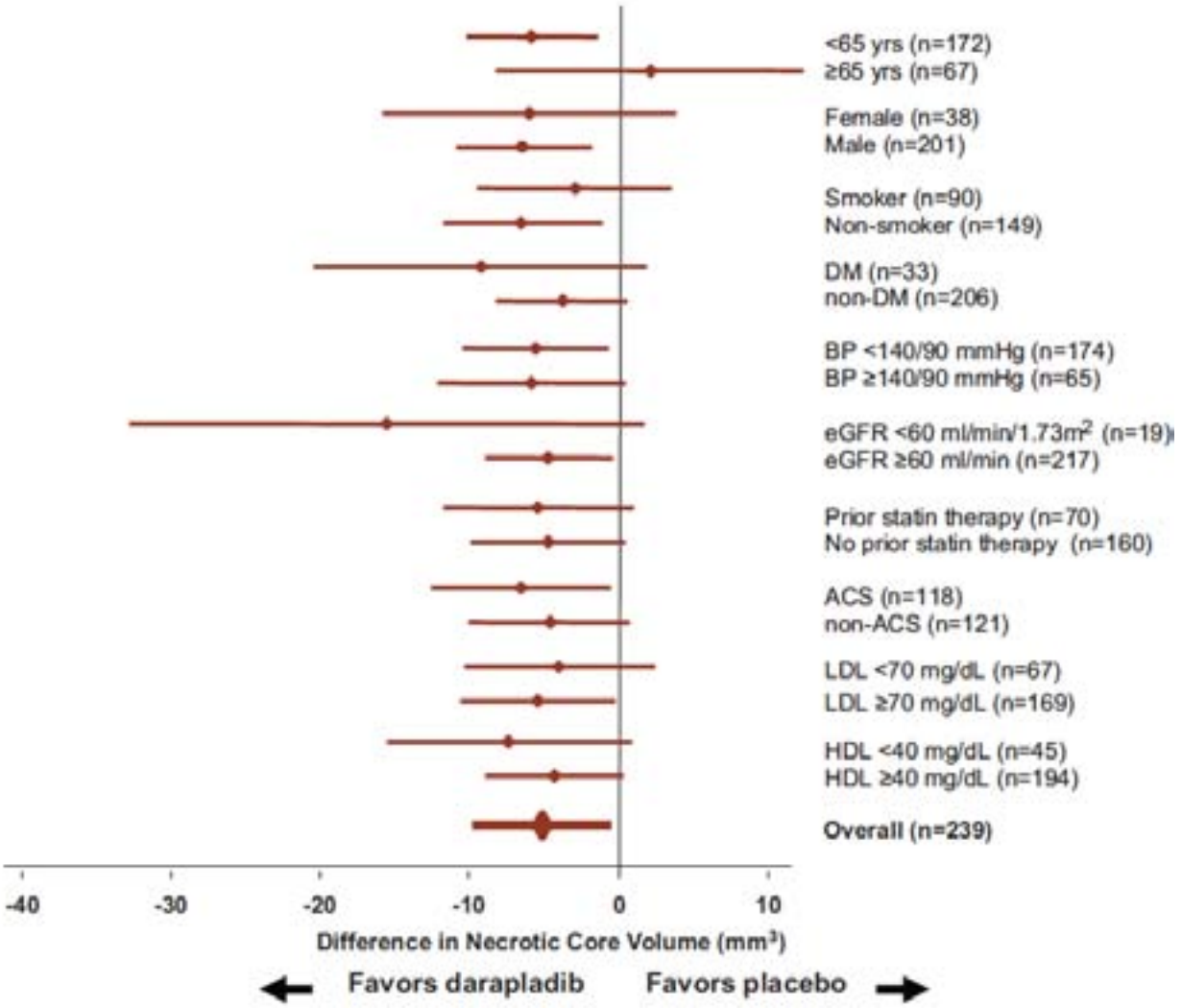
Inhibition of lipoprotein-associated phospholipase A_2 reduces complex coronary atherosclerotic plaque development

Wilensky RL et al., Nat Med 2008



Effects of the Direct Lipoprotein-Associated Phospholipase A_2 Inhibitor Darapladib on Human Coronary Atherosclerotic Plaque

Circulation



Serruys PW et al., Circulation 2008

The Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy Trial (STABILITY)

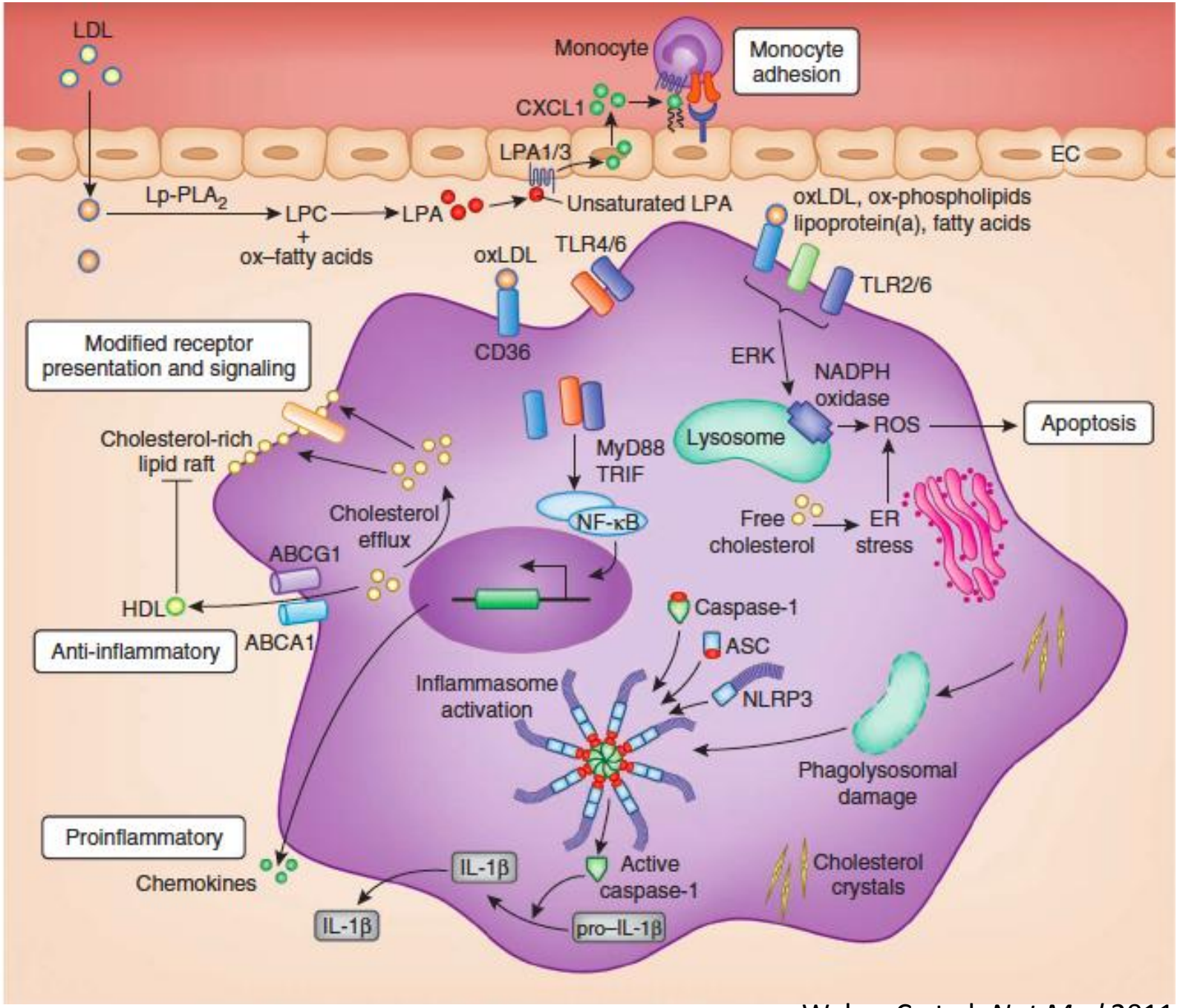
Study NCT00799903 Information provided by GlaxoSmithKline

Brief Title ICMJE	The Stabilization of Atherosclerotic Plaque by Initiation of **Darapladib** Therapy Trial
Official Title ICMJE	LPL100601, A Clinical Outcomes Study of **Darapladib** Versus Placebo in Subjects With Chronic Coronary Heart Disease to Compare the Incidence of Major Adverse Cardiovascular Events (MACE)
Brief Summary	This study will test whether **darapladib** can safely lower the chances of having a cardiovascular event (such as a heart attack or stroke) in people with coronary heart disease.
Detailed Description	Subjects who qualify for the study will be randomized 1:1 to either darapladib or placebo administered in addition to standard therapy. Following the baseline visit, subjects will be expected to return for clinic visits at 1 month, 3 months, and every 6 months until the end of the study. Average time in the study for an individual subject is expected to be about 3 years.
Study Type ICMJE	Interventional
Study Phase	Phase III
Current Primary Outcome Measures ICMJE (submitted: November 28, 2008)	Time to the first occurrence of any component of the composite of Major Adverse Cardiovascular Events [MACE: CV death (death due to a cardiovasacular cause), non-fatal myocardial infarction, non-fatal stroke] [Time Frame: Patients will remain in the study until a specified number of MACE events have occurred. It is anticipated that patients will be in the study about 3 years.] [Designated as safety issue: No]

The Stabilization Of pLaques usIng Darapladib-Thrombolysis In Myocardial Infarction 52 Trial (SOLID-TIMI 52)

Study NCT01000727 Information provided by GlaxoSmithKline

Brief Title ICMJE	The Stabilization Of pLaques usIng **Darapladib**-Thrombolysis In Myocardial Infarction 52 Trial
Official Title ICMJE	A Clinical Outcomes Study of **Darapladib** Versus Placebo in Subjects Following Acute Coronary Syndrome to Compare the Incidence of Major Adverse Cardiovascular Events (MACE).
Brief Summary	This study will test whether **darapladib** can safely lower the chances of having a cardiovascular event (such as a heart attack or stroke) when treatment is started within 30 days after an acute coronary syndrome (also called ACS).
Detailed Description	Subjects who qualify for the study will be randomized 1:1 to either darapladib or placebo administered in addition to standard therapy. Following the baseline visit, subjects will be expected to return for clinic visits at 1 month, 3 months, 6 months and every 6 months until the end of the study.
Study Type ICMJE	Interventional
Study Phase	Phase III
Current Primary Outcome Measures ICMJE (submitted: October 22, 2009)	Time to the first occurrence of any component of the composite of Major Adverse Cardiovascular Events [MACE: CV death (death due to a cardiovascular cause), non-fatal myocardial infarction, non-fatal stroke]. [Time Frame: Through the end of the study.] [Designated as safety issue: No]



Weber C et al. *Nat Med* 2011

Cardiovascular Risk Reduction Study (Reduction in Recurrent Major CV Disease Events)

This study is currently recruiting participants.
Verified November 2011 by Novartis

Study NCT01327846 Information provided by Novartis

Brief Title ICMJE
Cardiovascular Risk Reduction Study (Reduction in Recurrent Major CV Disease Events)

Official Title ICMJE
A Randomized, Double-blind, Placebo-controlled, Event Driven Trial of Quarterly Subcutaneous **Canakinumab** in the Prevention of Recurrent Cardiovascular Events Among Stable Post-myocardial Infarction Patients With Elevated hsCRP

Brief Summary
The purpose of this trial is to test the hypothesis that **canakinumab** treatment of patients with MI at least one month prior to study entry and elevated hsCRP will prevent recurrent cardiovascular events.

Detailed Description

Study Type ICMJE
Interventional

Study Phase
Phase III

Study Design ICMJE
Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

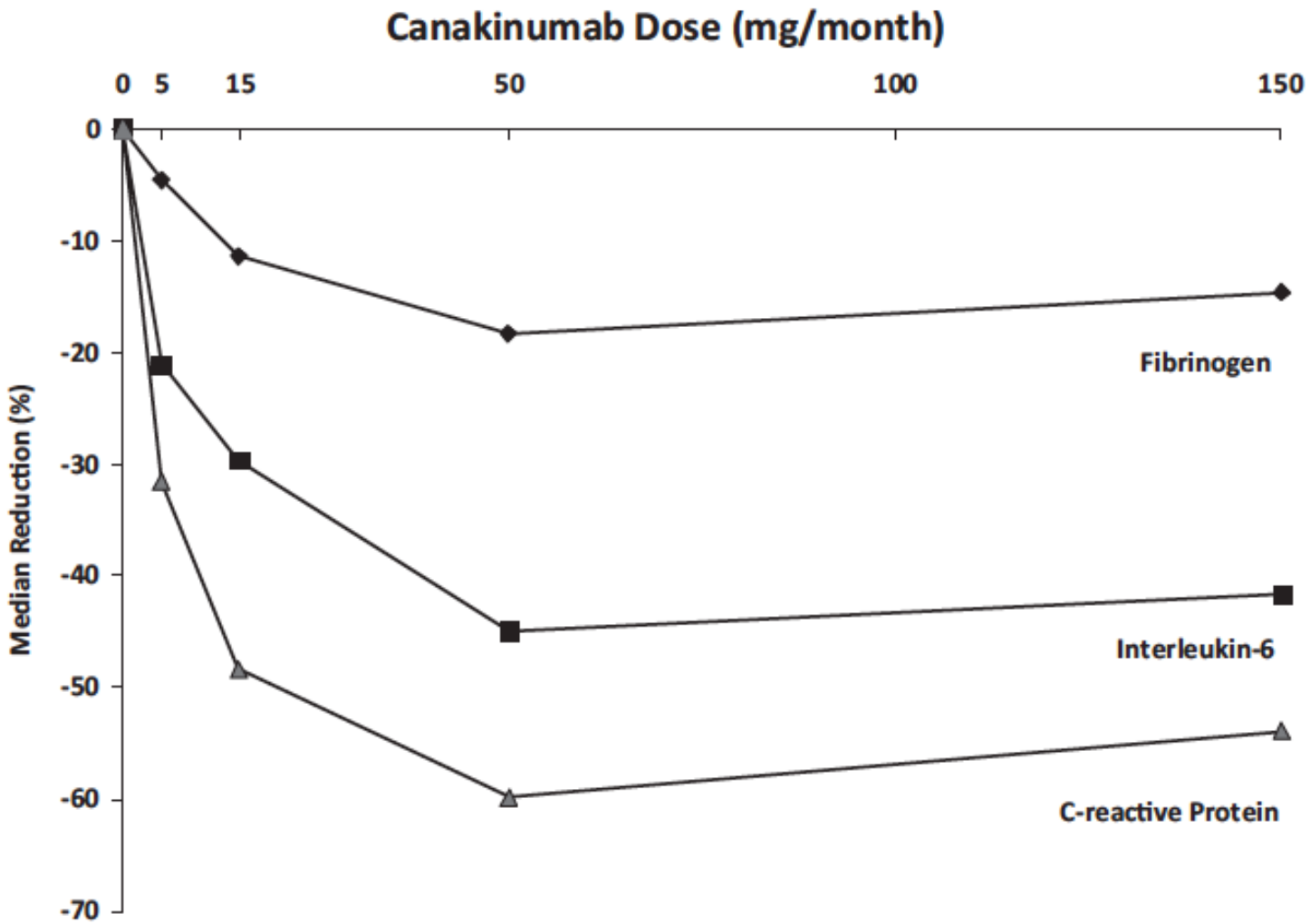
Current Primary Outcome Measures
Time to first occurrence of a major adverse cardiovascular event, which is a composite endpoint consisting of cardiovascular death, non-fatal MI, and stroke. [Time Frame: 36 Months] [Designated as safety issue: No]

Current Secondary Outcome Measures ICMJE
(submitted: March 31, 2011)

- Time to the first occurrence of the composite cardiovascular endpoint consisting of cardiovascular death, non-fatal MI, stroke, and hospitalization for unstable angina requiring unplanned revascularization. [Time Frame: 36 Months] [Designated as safety issue: No]
- Time to new onset type 2 diabetes among those with pre-diabetes at randomization. [Time Frame: 36 Months] [Designated as safety issue: No]
- Time to first occurrence of non-fatal MI, stroke, and all-cause mortality composite. [Time Frame: 36 Months] [Designated as safety issue: No]
- Time to all-cause mortality. [Time Frame: 36 Months] [Designated as safety issue: No]

Effects of Interleukin-1β Inhibition With Canakinumab on Hemoglobin A1c, Lipids, C-Reactive Protein, Interleukin-6, and Fibrinogen

A Phase IIb Randomized, Placebo-Controlled Trial

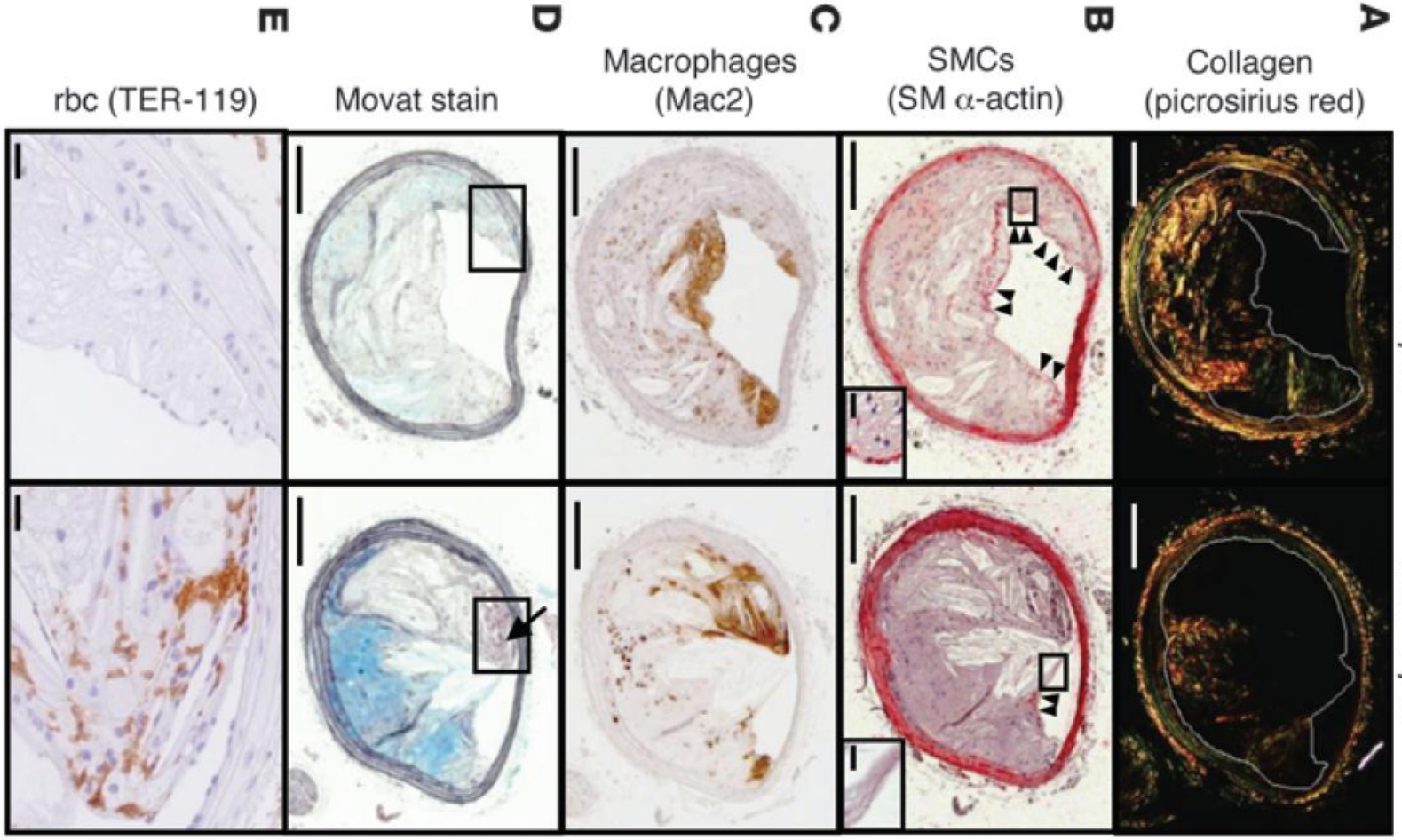


Ridker PM et al. *Circulation* 2011

Genetic inactivation of IL-1 signaling enhances atherosclerotic plaque instability and reduces outward vessel remodeling in advanced atherosclerosis in mice

JCI 2012

Matthew R. Alexander,[1,2] Christopher W. Moehle,[1,2] Jason L. Johnson,[3] Zhengyu Yang,[4] Jae K. Lee,[4] Christopher L. Jackson,[3] and Gary K. Owens[1,2]



Testing the inflammatory hypothesis of atherothrombosis: scientific rationale for the cardiovascular inflammation reduction trial (CIRT)

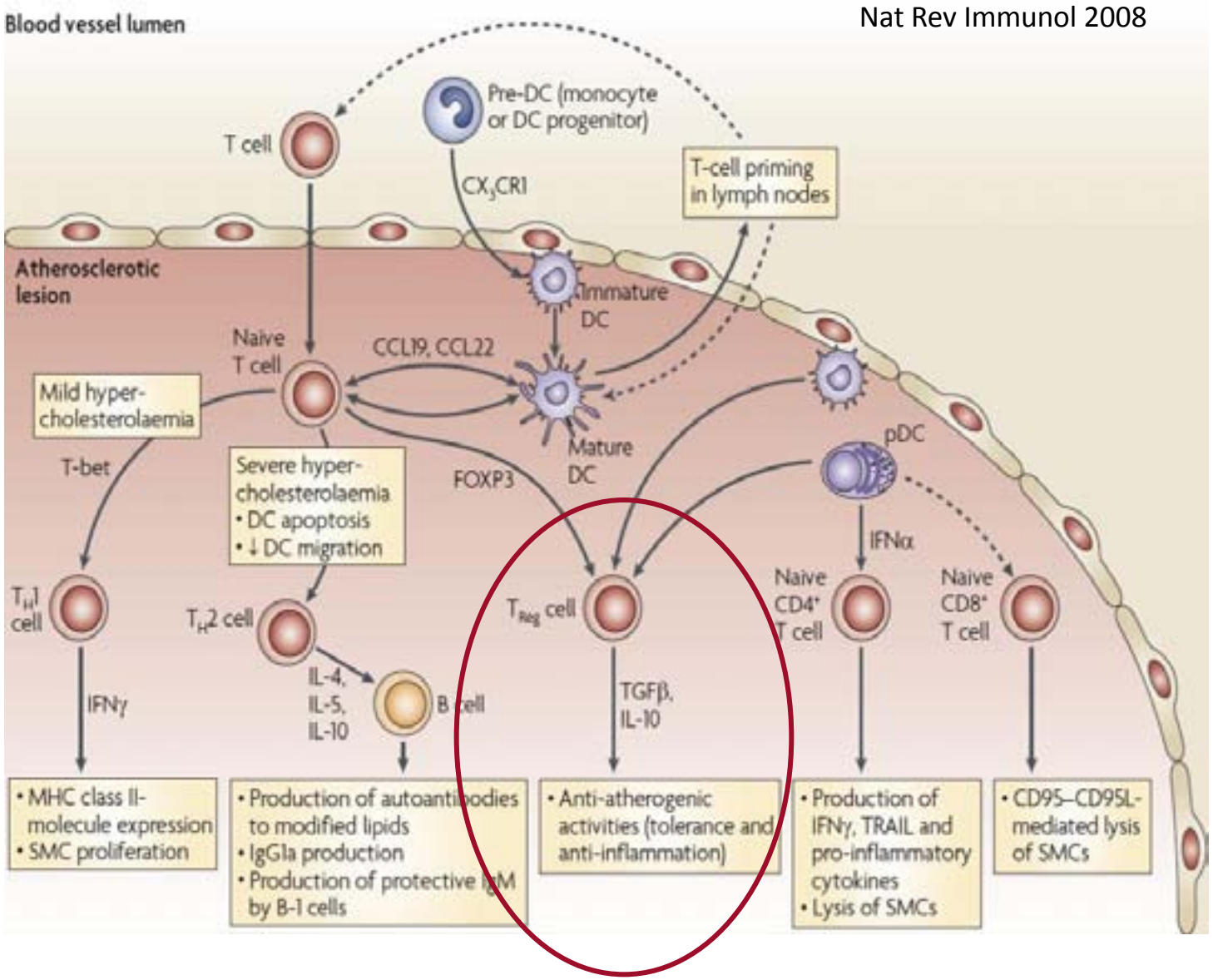
PAUL M. RIDKER

Low dose methotrexate and CVD: observational evidence

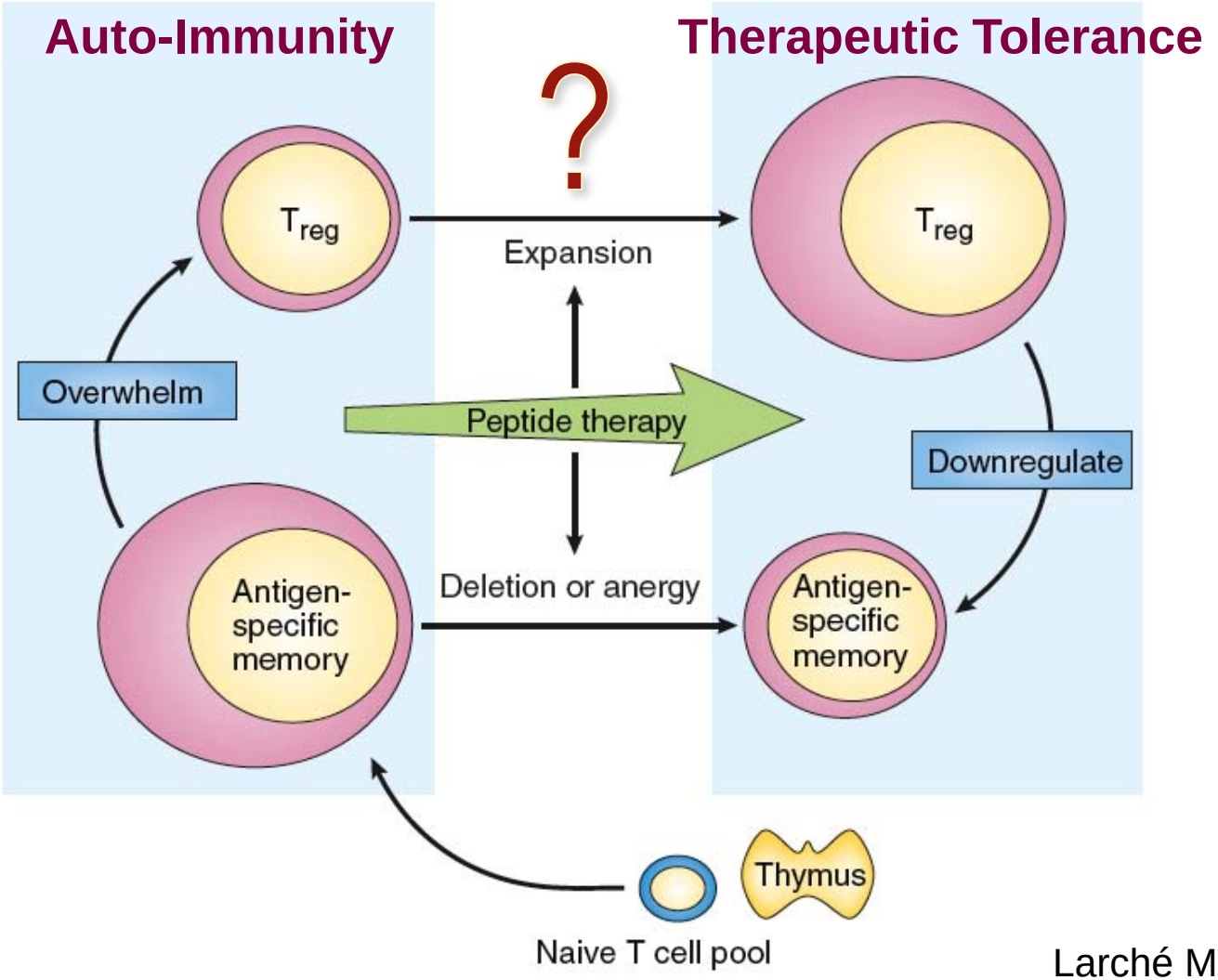
Cohort	Group	HR* (95% CI)	Endpoint	Exposure
Wichita Choi 2002	RA	0.4 (0.2–0.8) 0.3 (0.2–0.7) 0.4 (0.3–0.8)	Total mortality CV mortality CV mortality	LDM LDM LDM < 15 mg wk^{-1}
Netherlands van Helm 2006	RA	0.3 (0.1–0.7) 0.2 (0.1–0.5) 0.2 (0.1–1.2) 0.2 (0.1–0.5)	CVD CVD CVD CVD	LDM only LDM + SSZ LDM + HCQ LDM + SSZ + HCQ
Miami VA Pradanovich 2005	Psoriasis RA 	0.7 (0.6–0.9) 0.5 (0.3–0.8) 0.8 (0.7–1.0) 0.6 (0.5–0.8)	CVD CVD CVD CVD	LDM LDM < 15 mg wk^{-1} LDM LDM < 15 mg wk^{-1}
CORRONA Solomon 2006	RA	0.6 (0.3–1.2) 0.4 (0.2–0.8)	CVD CVD	LDM TNF-inhibitor
QUEST-RA Narango 2008	RA	0.85 (0.8–0.9) 0.82 (0.7–0.9) 0.89 (0.8–1.0)	CVD MI Stroke	LDM LDM LDM
UK Norfolk 2008	RA, PSA	0.6 (0.4–1.0) 0.5 (0.3–1.1)	Total mortality CV mortality	LDM LDM

to allocate 7000 stable coronary artery disease patients with persistent elevations of hsCRP to placebo or very-low-dose-methotrexate (VLDM, 10 mg weekly), a proven anti-inflammatory regimen that reduces TNFα, IL-6, and CRP levels and is in wide use among rheumatoid arthritis patients.

Weber C et al.
Nat Rev Immunol 2008

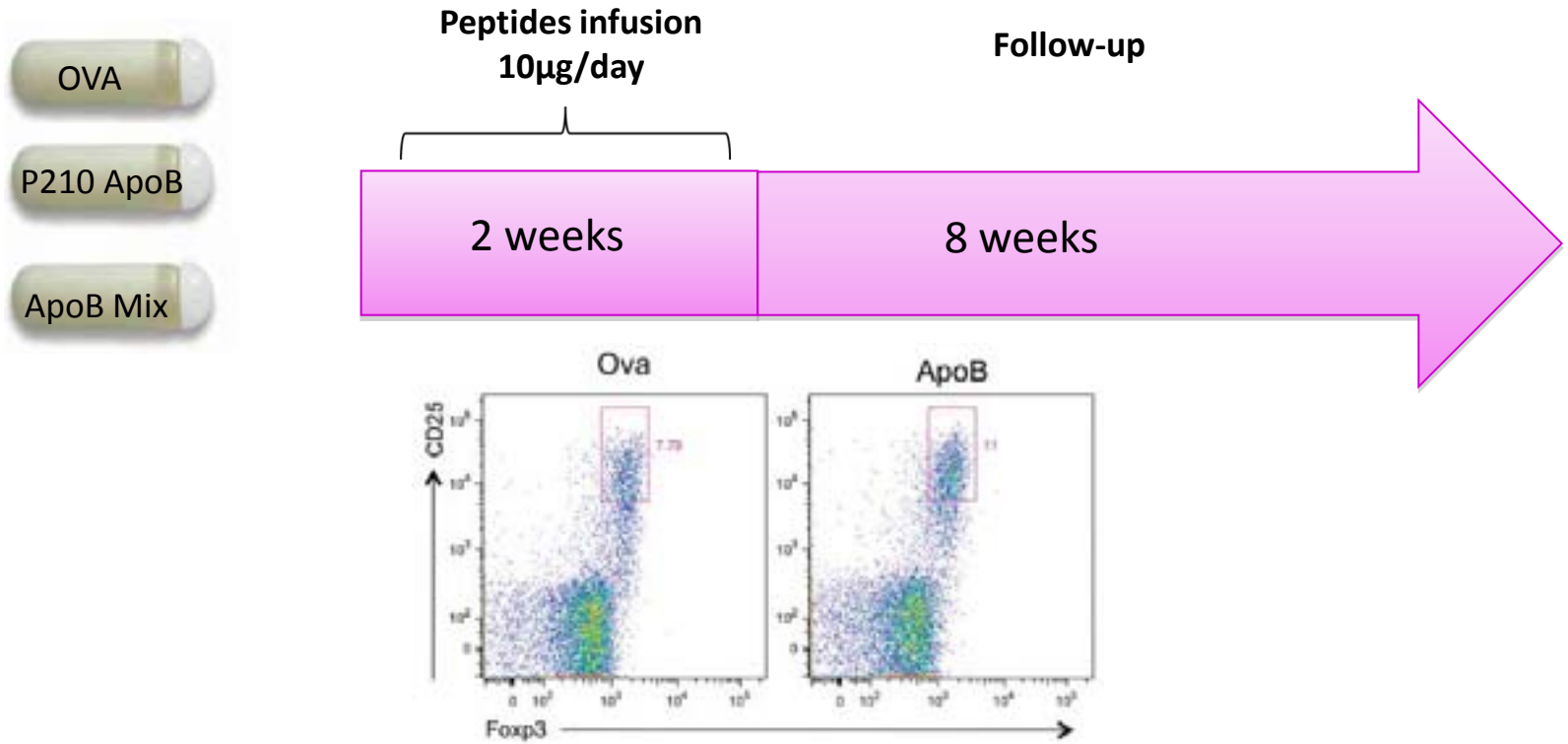


Peptide-based Therapeutic Vaccination



Larché M & Wraith DC
Nat Med 2005

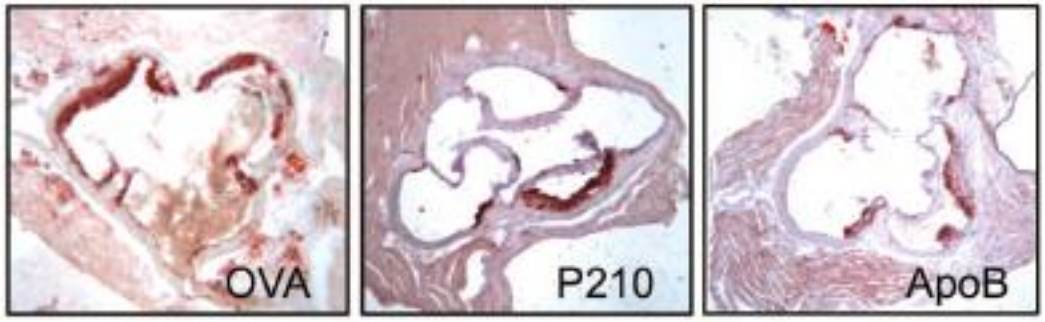
Inducing tolerance to lipoproteins: Atherosclerosis Vaccine?

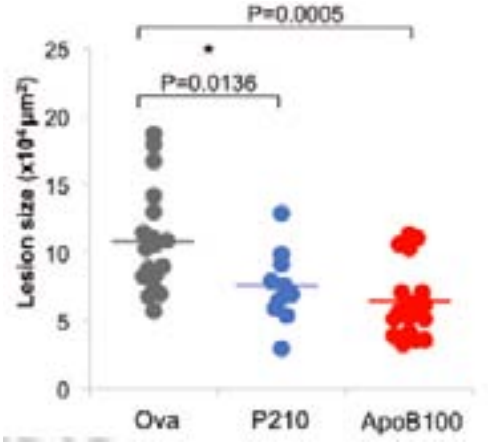


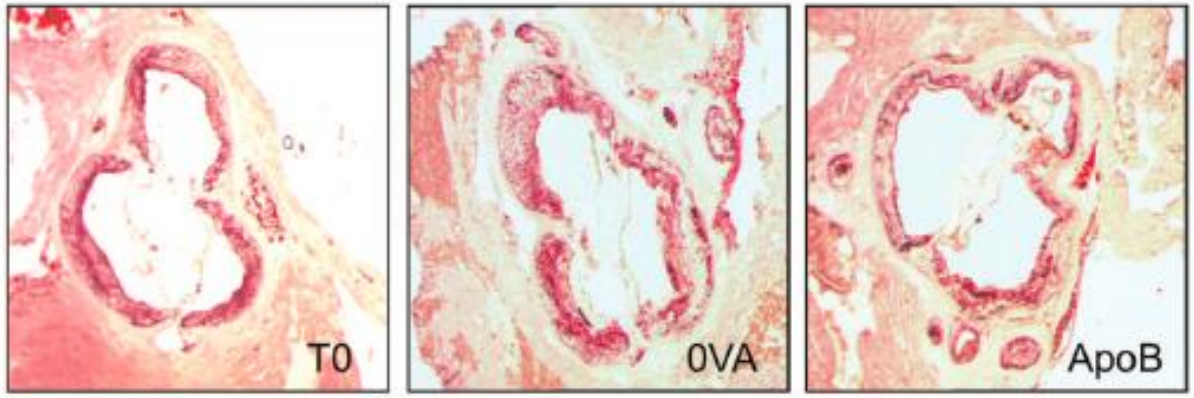
ApoB peptide-based vaccination reduces atherosclerosis by inducing a specific Treg cell response

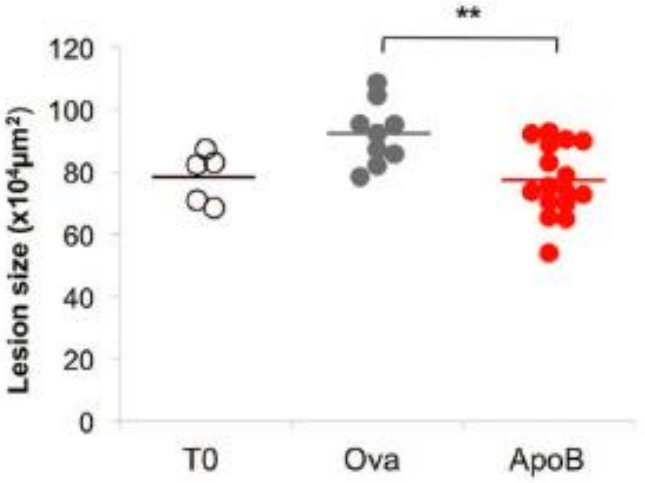
Regulatory T-Cell Response to Apolipoprotein B100–Derived Peptides Reduces the Development and Progression of Atherosclerosis in Mice

Olivier Herbin, Hafid Ait-Oufella, Wang Yu, Gunilla Nordin Fredrikson, Benjamin Aubier, Nicolas Perez, Véronique Barateau, Jan Nilsson, Alain Tedgui, Ziad Mallat







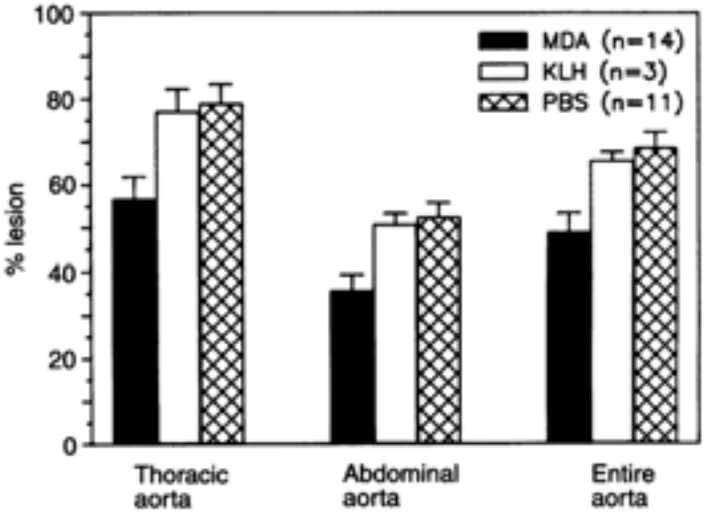


(*Arterioscler Thromb Vasc Biol.* 2012;32:00-00.)

Immunization of low density lipoprotein (LDL) receptor-deficient rabbits with homologous malondialdehyde-modified LDL reduces atherogenesis

(modified lipoproteins/oxidation/autoantibodies/atherosclerosis/immune system)

WULF PALINSKI, ELIZABETH MILLER, AND JOSEPH L. WITZTUM

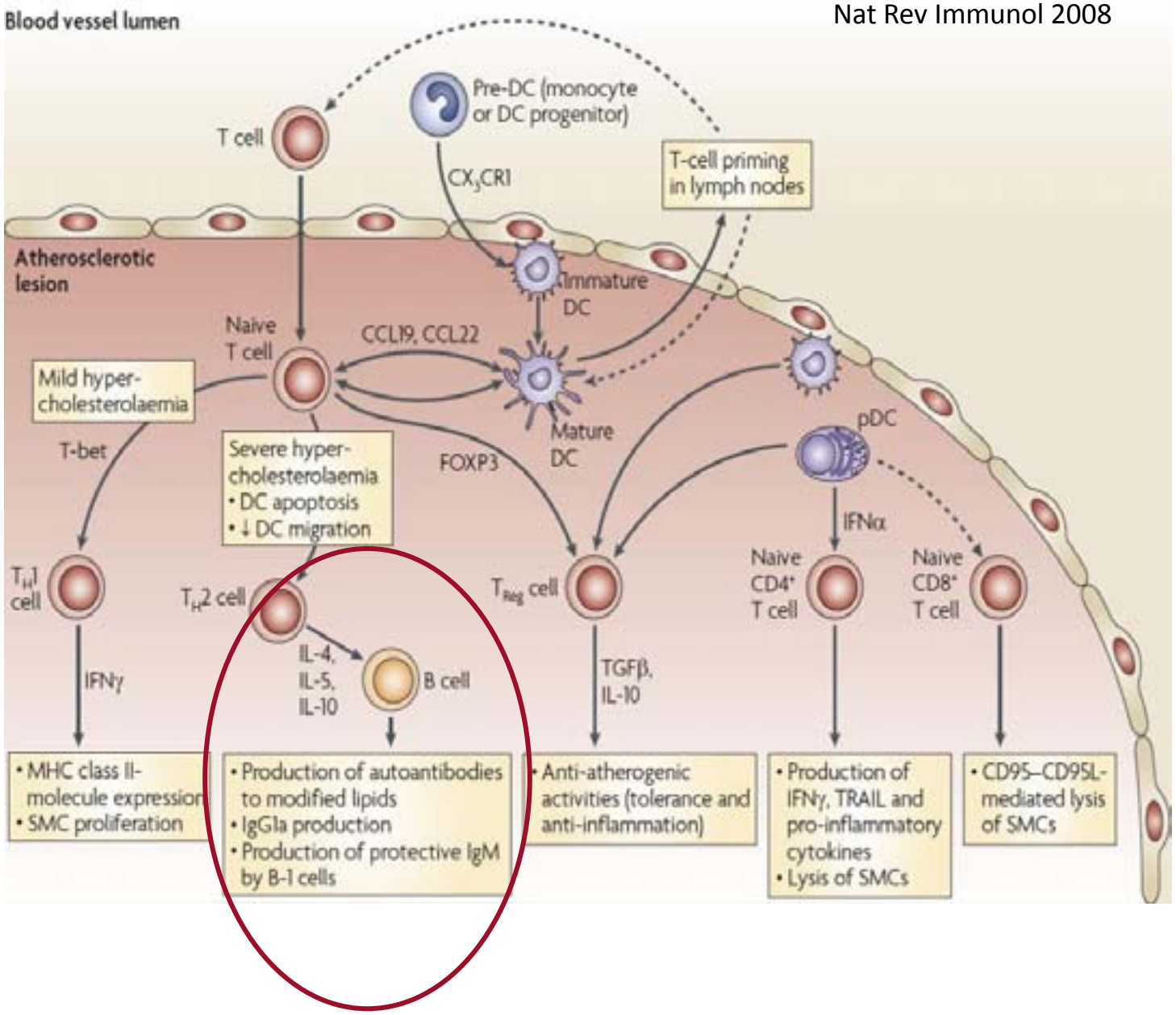


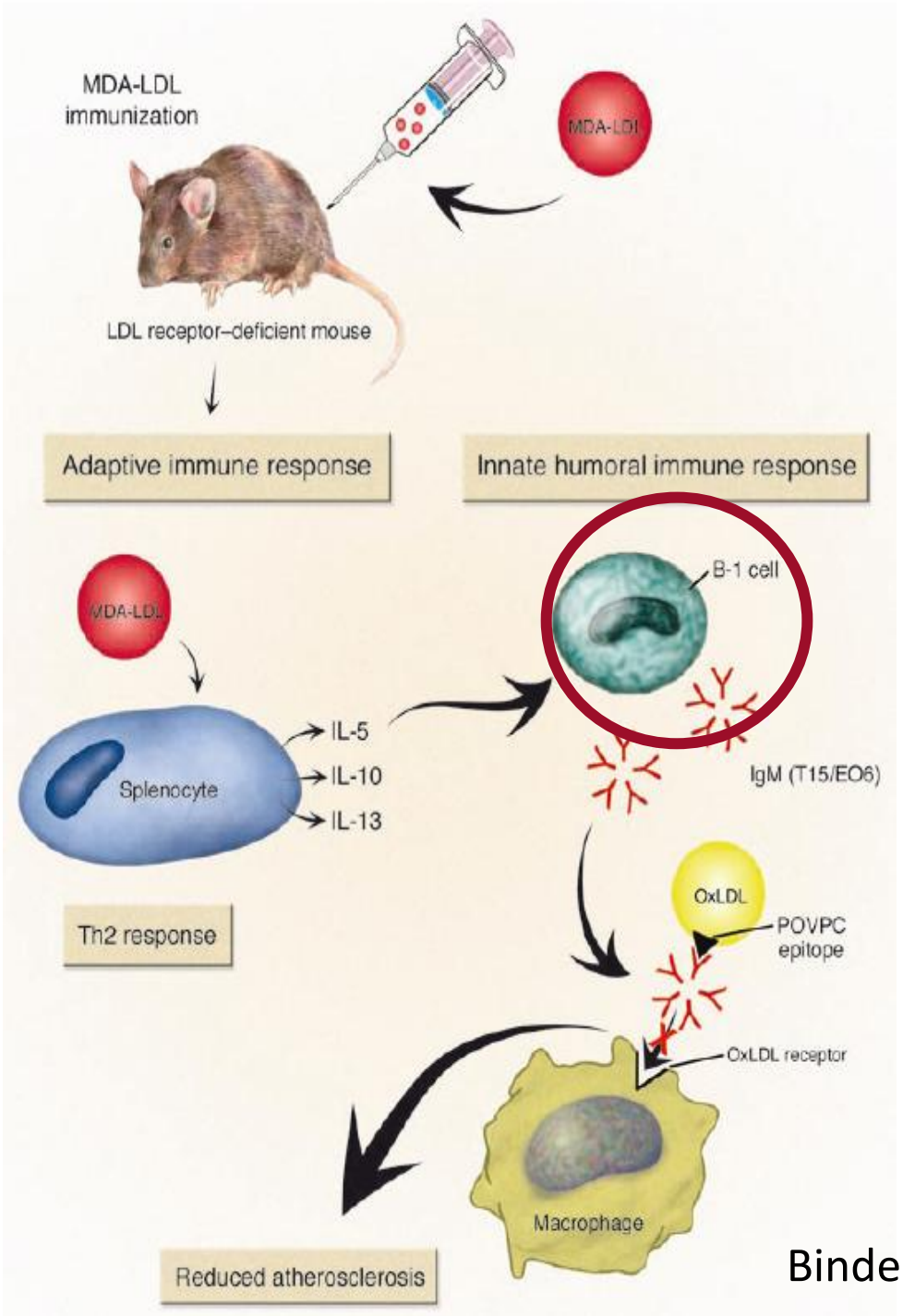
Recombinant Human Antibodies Against Aldehyde-Modified Apolipoprotein B-100 Peptide Sequences Inhibit Atherosclerosis

Alexandru Schiopu, MD; Jenny Bengtsson, PhD; Ingrid Söderberg, BSI; Sabina Janciauskiene, PhD; Stefan Lindgren, MD, PhD; Mikko P.S. Ares, PhD; Prediman K. Shah, MD; Roland Carlsson, PhD; Jan Nilsson, MD, PhD; Gunilla Nordin Fredrikson, PhD

Circulation. 2004

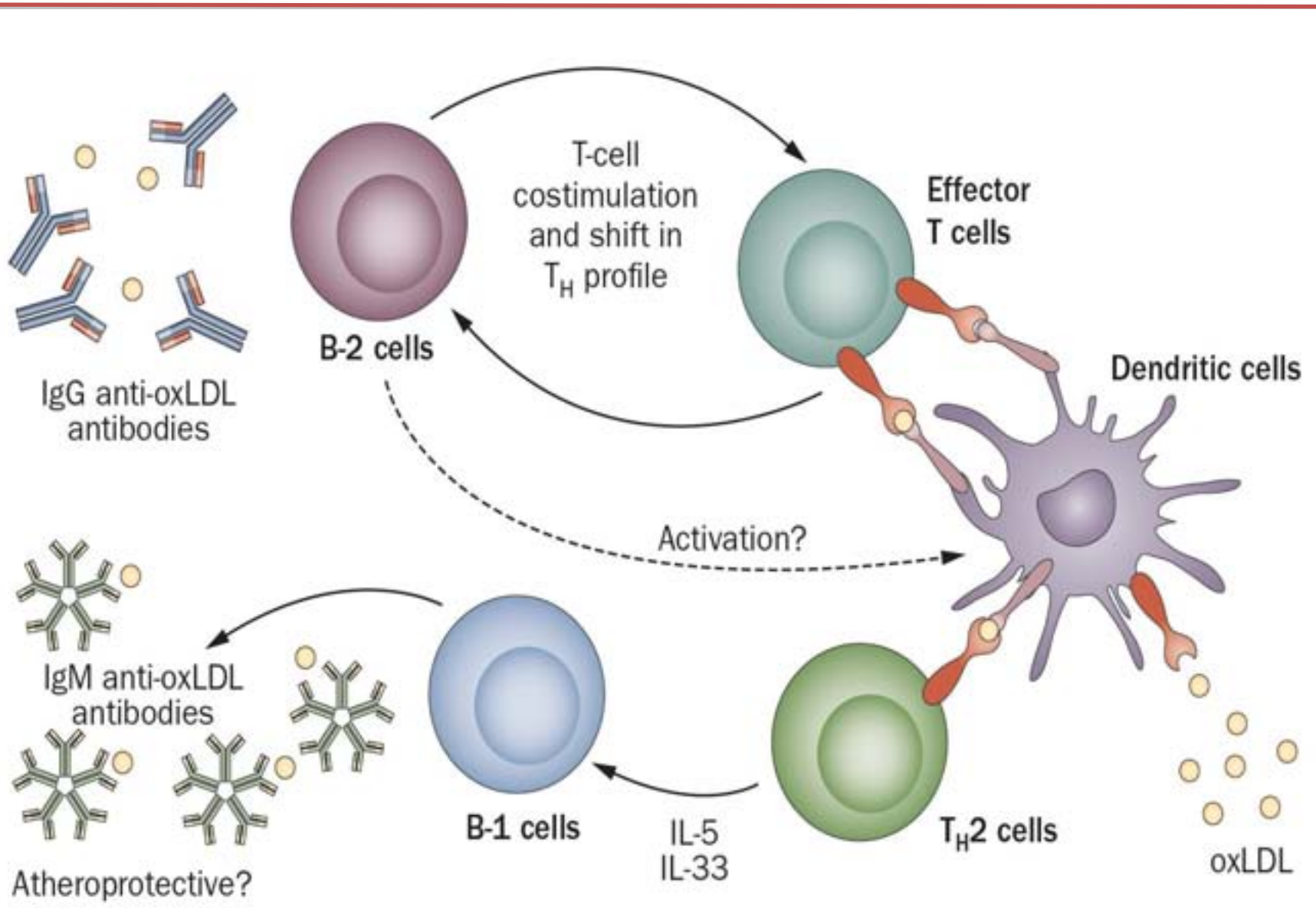
Weber C et al.
Nat Rev Immunol 2008





Binder CJ et al., *JCI* 2004

B cell pathways in atherosclerosis



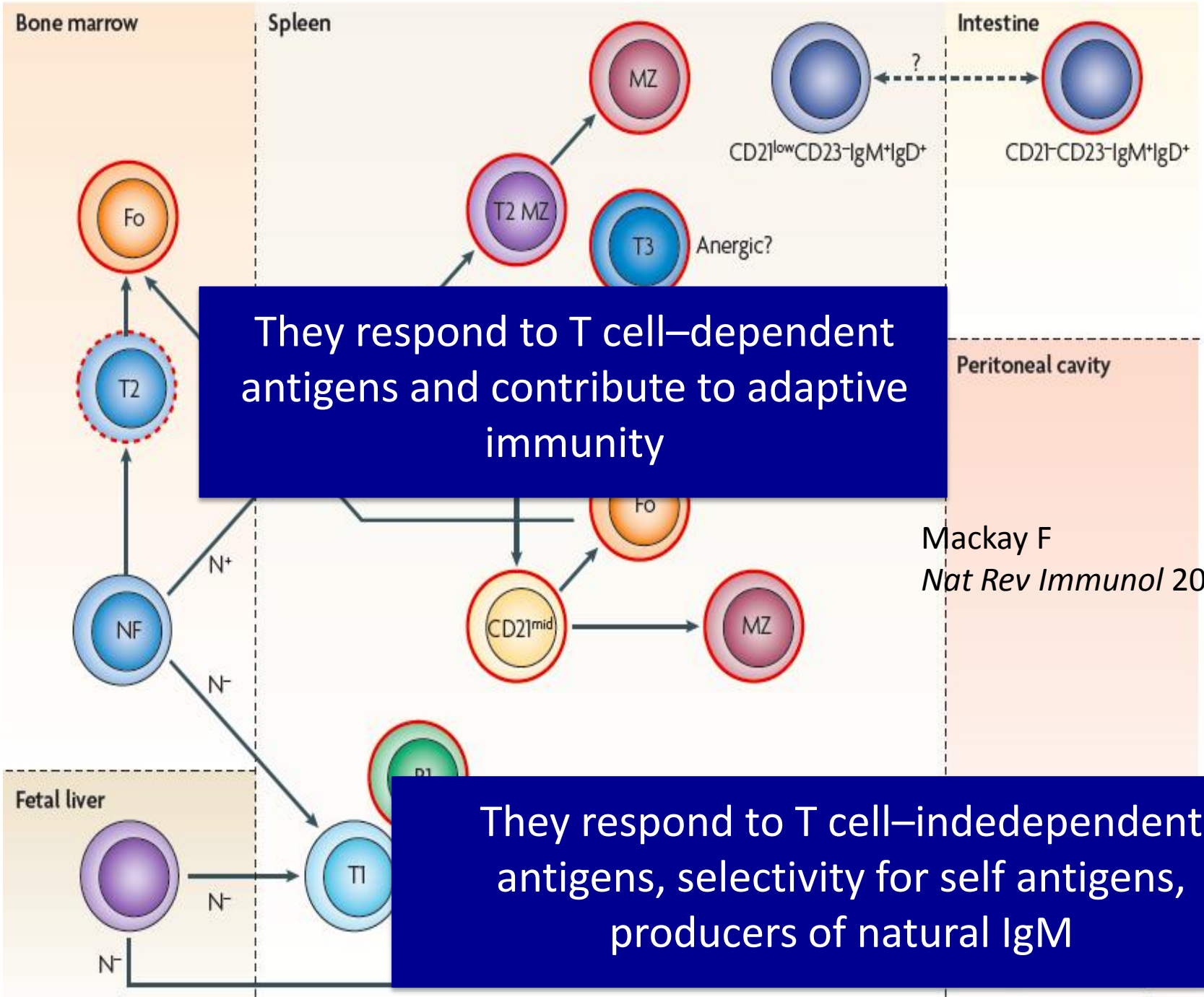
Lahoute et al. *Nat Rev Cardiol*, 2011;8:348-58.

A Study to Evaluate the Safety, Tolerability, and Activity of Intravenous MLDL1278A in Patients on Standard-of-Care Therapy for Stable Atherosclerotic Cardiovascular Disease

This study is currently recruiting participants.
Verified November 2011 by Genentech

Study NCT01258907 Information provided by Genentech

Brief Title ICMJE	A Study to Evaluate the Safety, Tolerability, and Activity of Intravenous **MLDL1278A** in Patients on Standard-of-Care Therapy for Stable Atherosclerotic Cardiovascular Disease
Official Title ICMJE	A Multicenter, Randomized, Double Blind, Placebo-Controlled Phase II Study to Evaluate the Safety, Tolerability, and Activity of Intravenous **MLDL1278A** in Patients on Standard-of-Care Therapy for Stable Atherosclerotic Cardiovascular Disease
Brief Summary	This is a Phase II (proof-of-activity), double-blind, placebo-controlled, randomized, multicenter study of **MLDL1278A** (also known as BI-204) involving patients on standard-of-care therapy for atherosclerotic cardiovascular disease with evidence of vascular inflammation, as quantified by FDG-PET/CT.
Detailed Description	
Study Type ICMJE	Interventional
Study Phase	Phase II
Study Design ICMJE	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double Blind (Subject, Investigator) Primary Purpose: Treatment
Current Primary Outcome Measures	Change in TBR as measured by FDG-PET/CT [Time Frame: Baseline to Week 12] [Designated as safety issue: No]
Current Secondary Outcome Measures ICMJE (submitted: December 10, 2010)	• Incidence and severity of adverse events and clinical laboratory abnormalities as a measure of safety and tolerability of MLDL1278A [Time Frame: Throughout study or until early discontinuation] [Designated as safety issue: No]

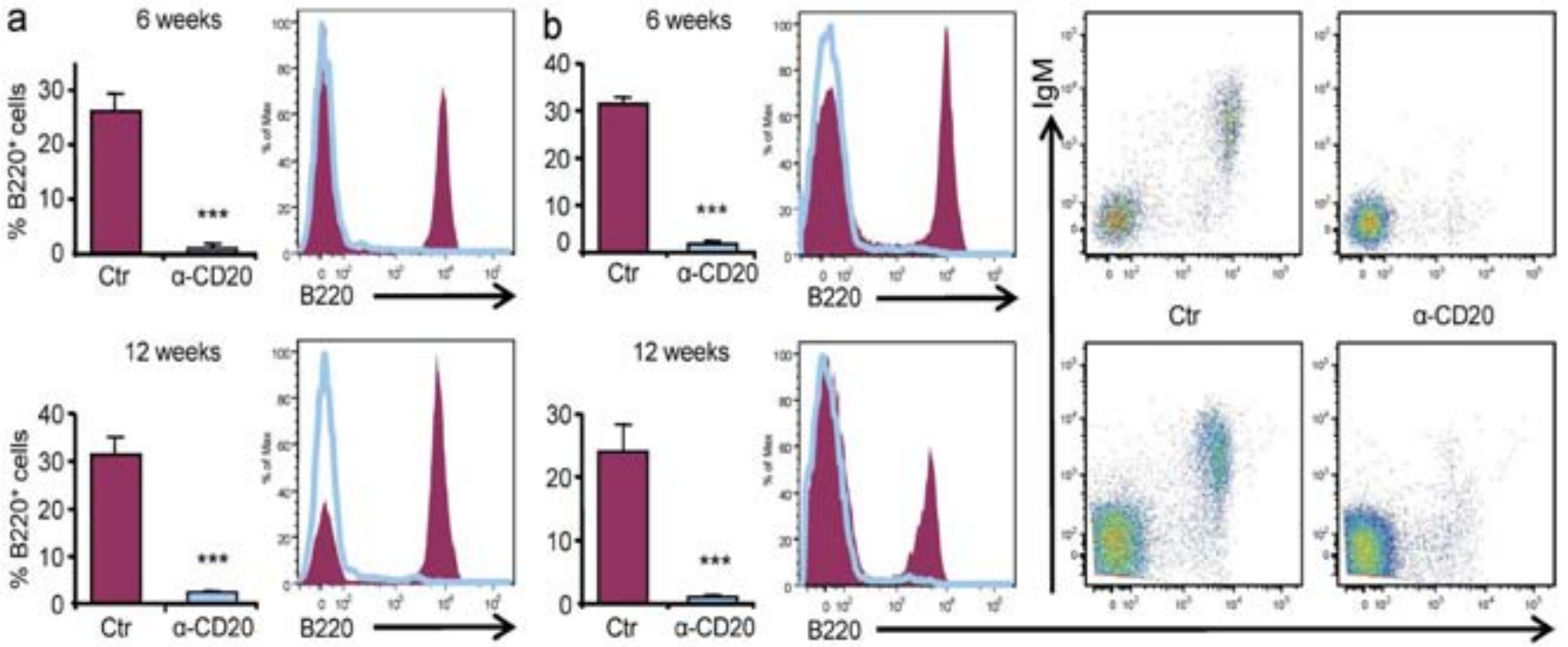


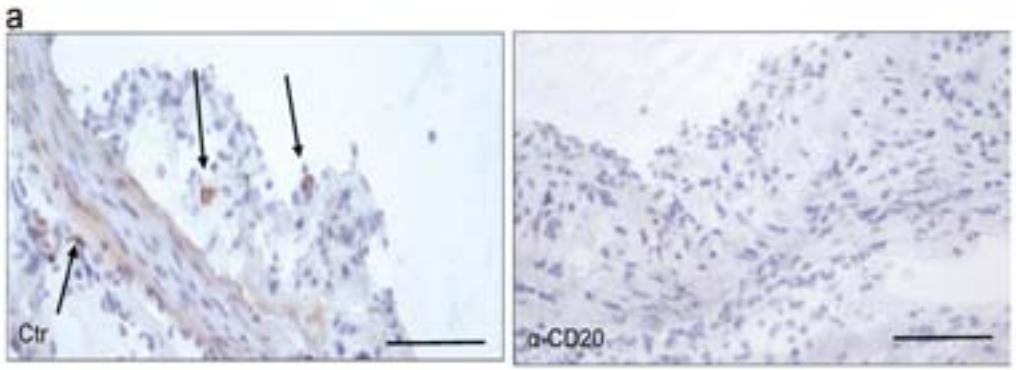
They respond to T cell–dependent antigens and contribute to adaptive immunity

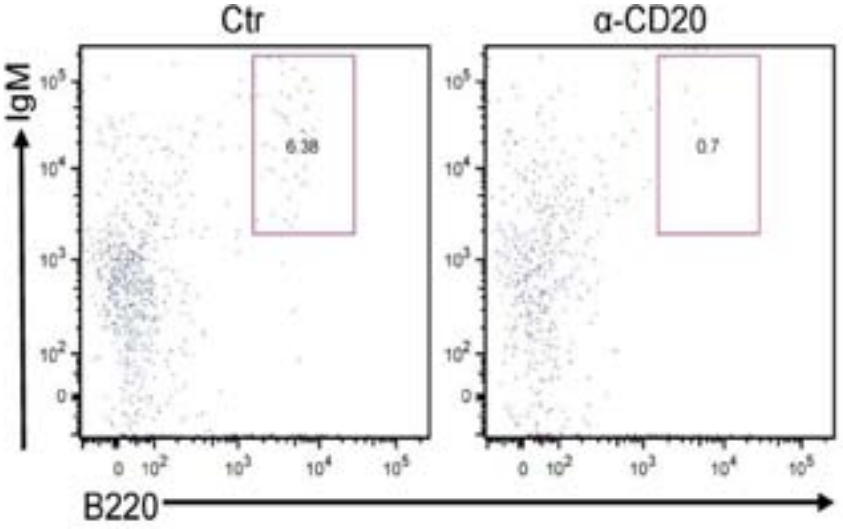
Mackay F
Nat Rev Immunol 2009

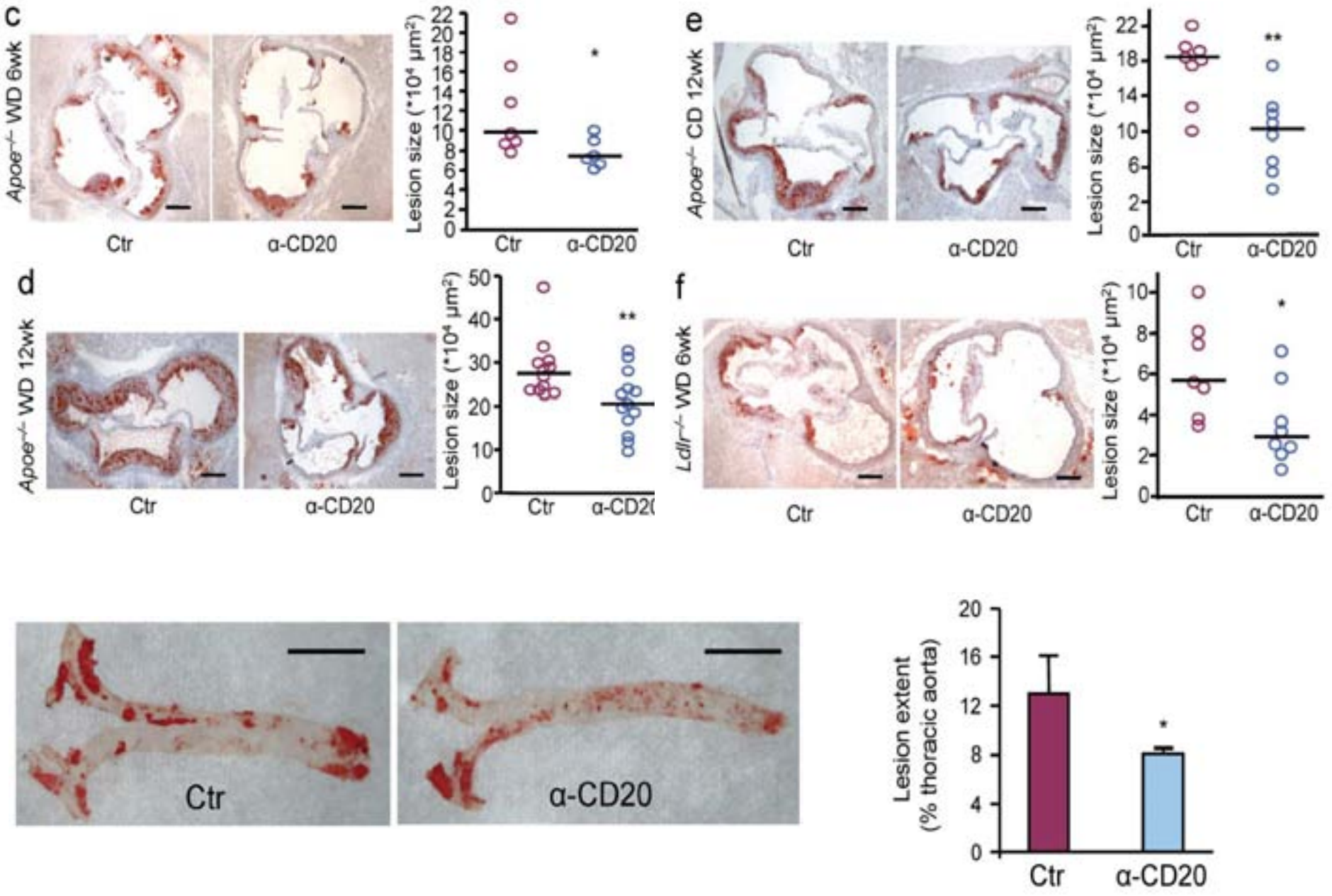
They respond to T cell–indedependent antigens, selectivity for self antigens, producers of natural IgM

CD20 mAb-mediated B Cell Depletion in Atherosclerosis

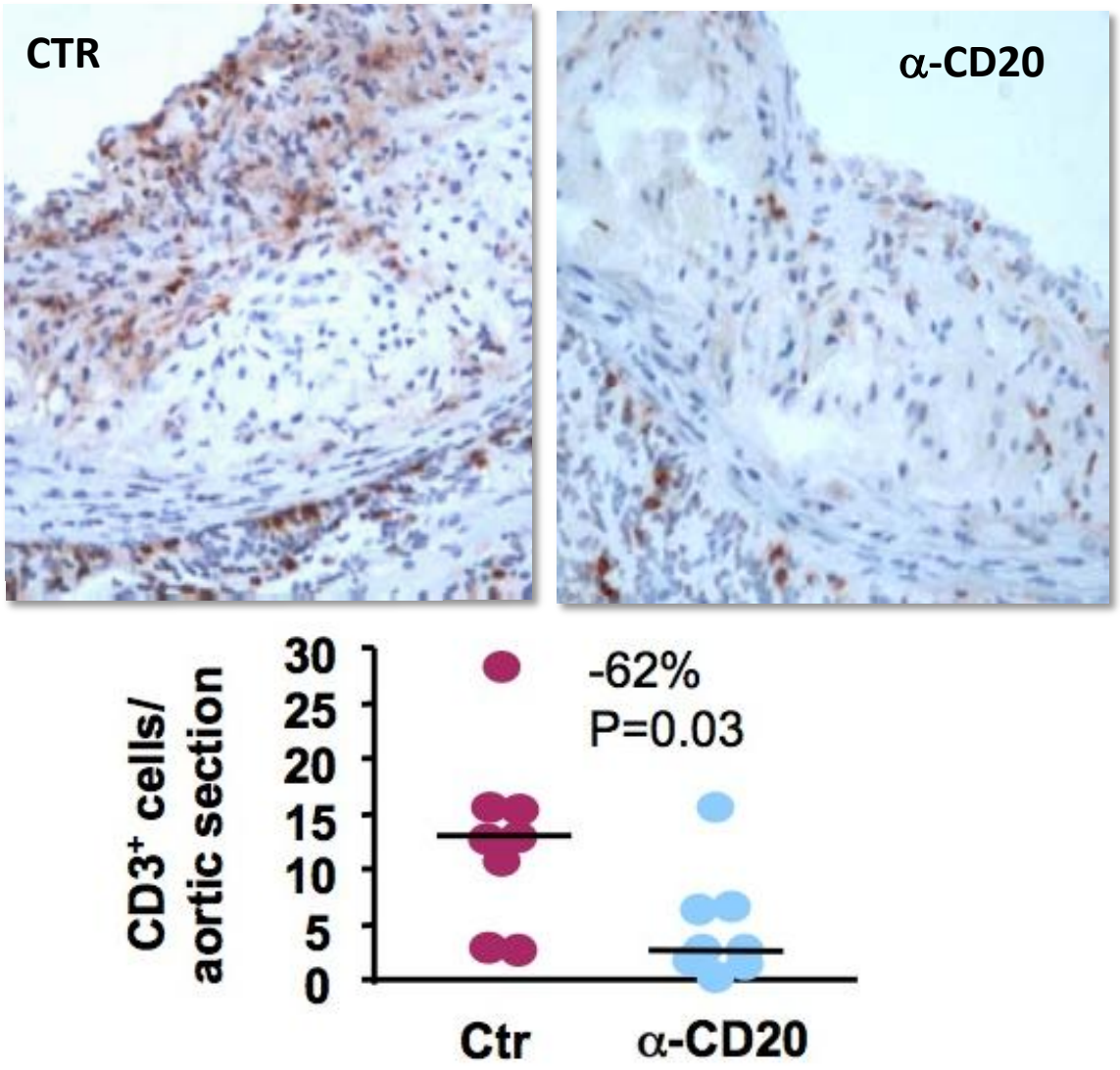







c
Apoe−/− WD 6wk
Ctr
α-CD20
Lesion size (*10⁴ µm²)
Ctr
α-CD20
d
Apoe−/− WD 12wk
Ctr
α-CD20
Lesion size (*10⁴ µm²)
Ctr
α-CD20
e
Apoe−/− CD 12wk
Ctr
α-CD20
Lesion size (*10⁴ µm²)
Ctr
α-CD20
f
Ldlr−/− WD 6wk
Ctr
α-CD20
Lesion size (*10⁴ µm²)
Ctr
α-CD20
Ctr
α-CD20
Lesion extent (% thoracic aorta)
Ctr
α-CD20

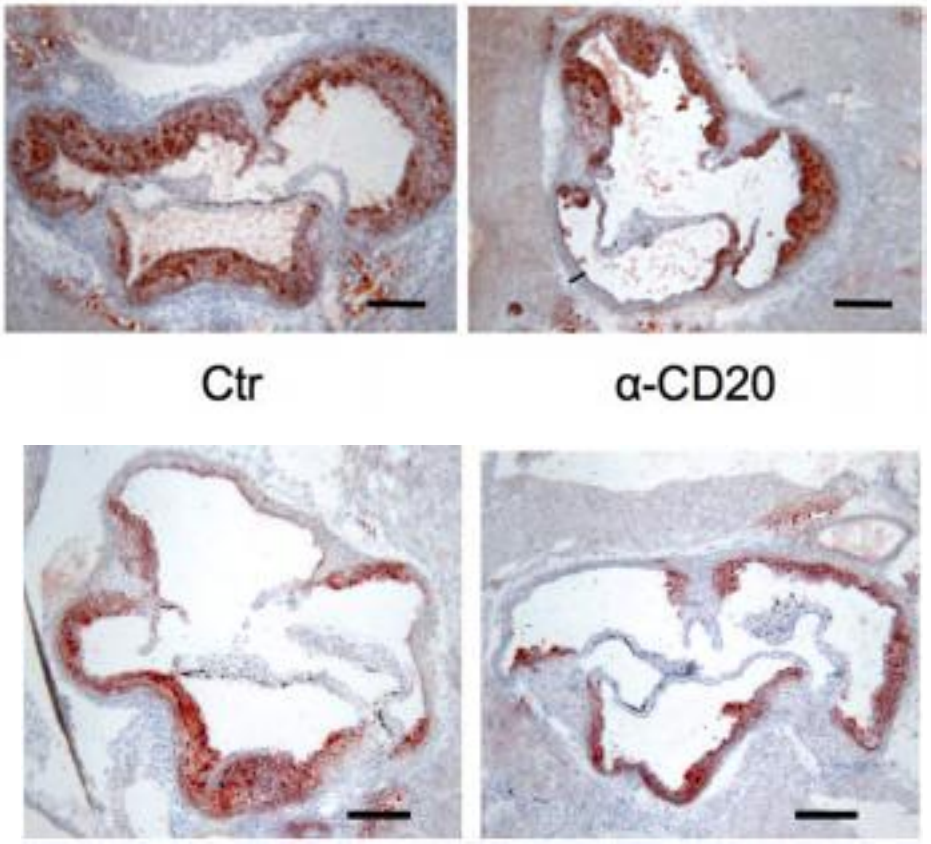
Decreased T cell infiltration after anti-CD20 therapy

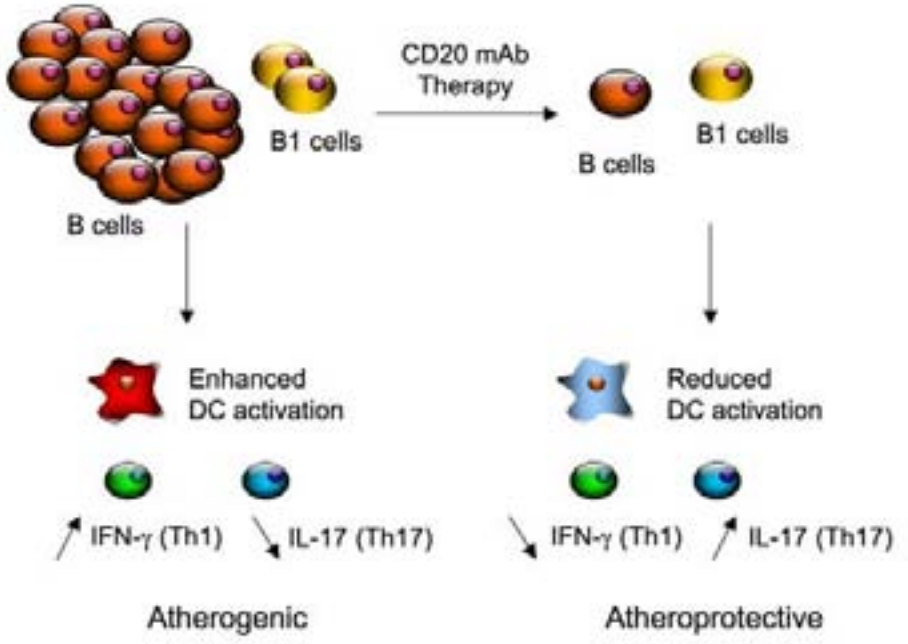


B cell depletion reduces the development of atherosclerosis in mice

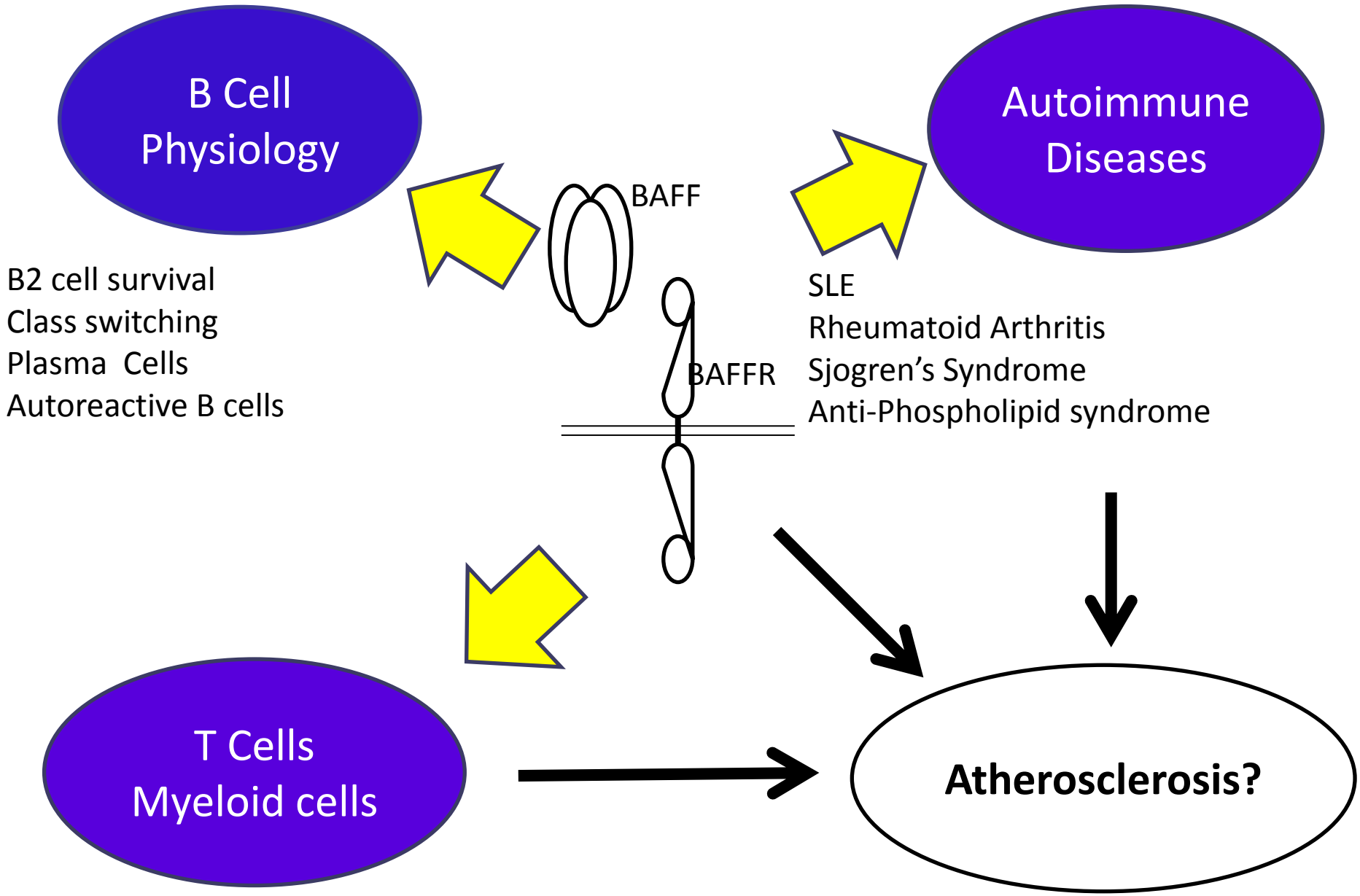
Ait-Oufella et al.

JEM 2010

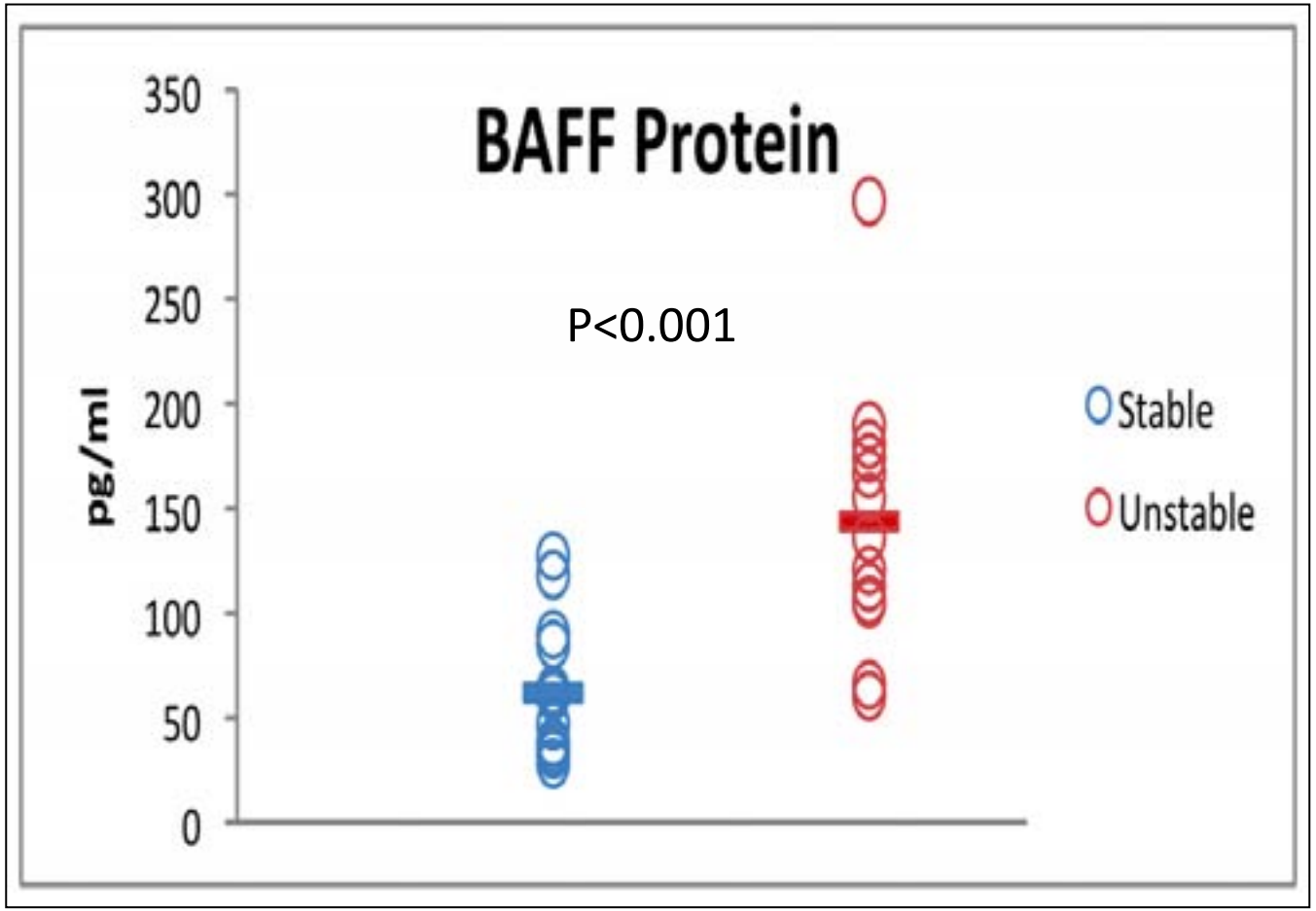




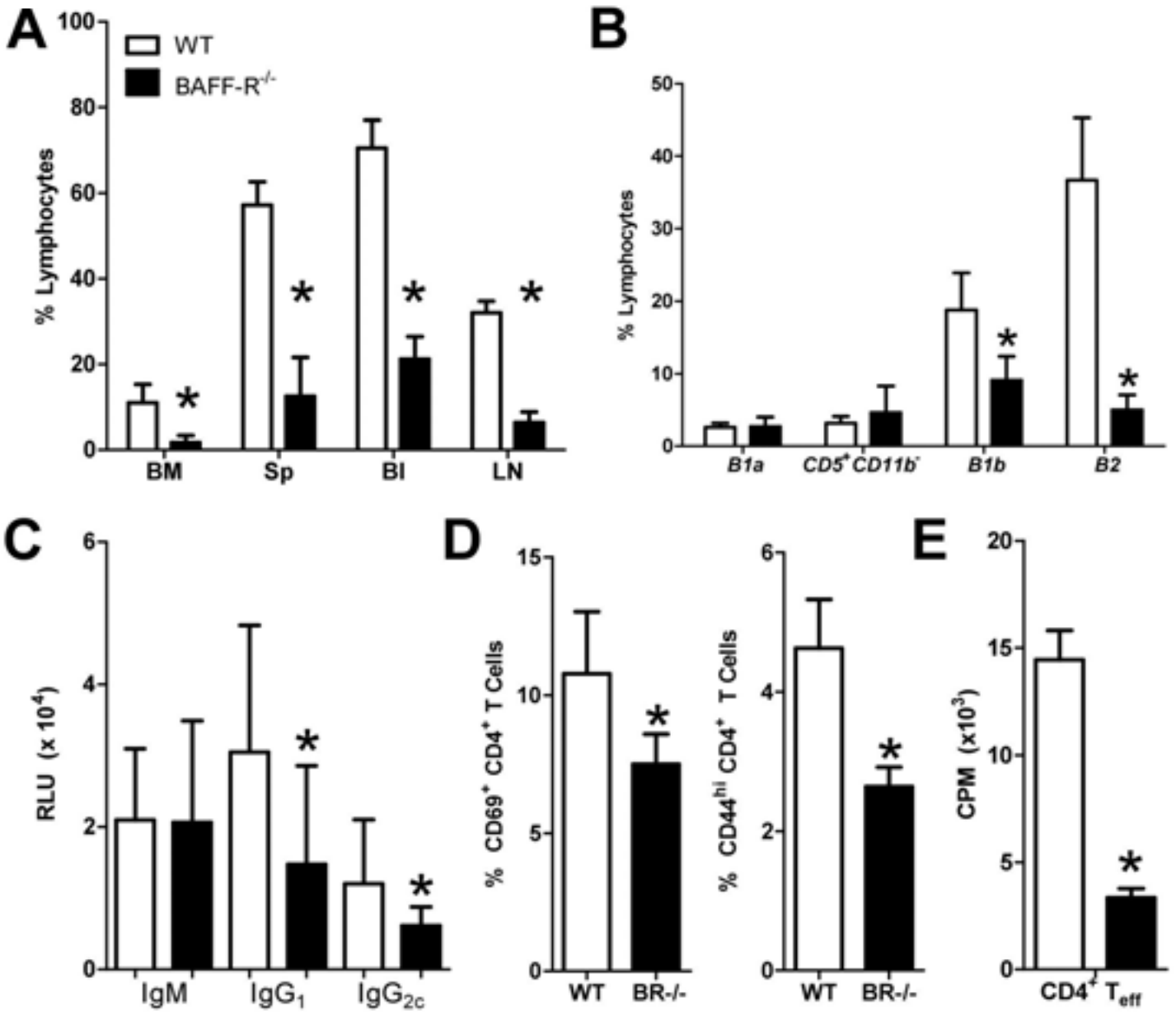
BAFF – B cell activating factor

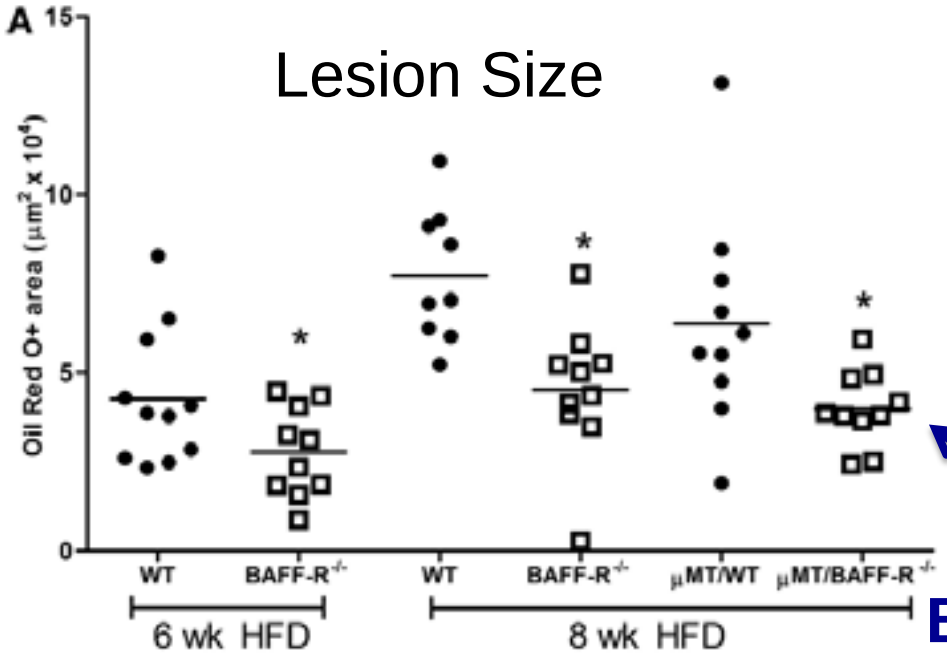


BAFF Levels in Human Carotid Lesions and Relation with Plaque Phenotype

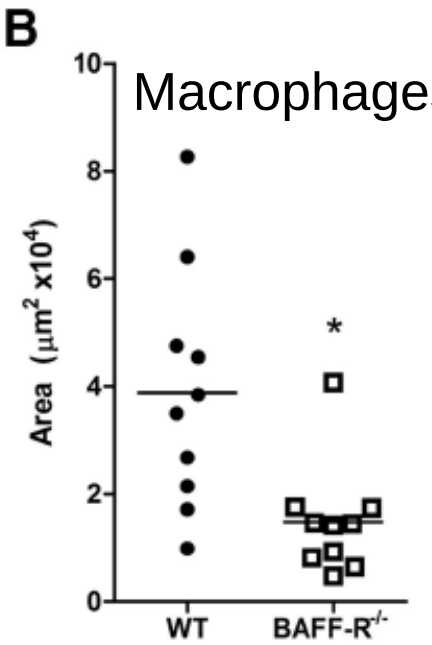


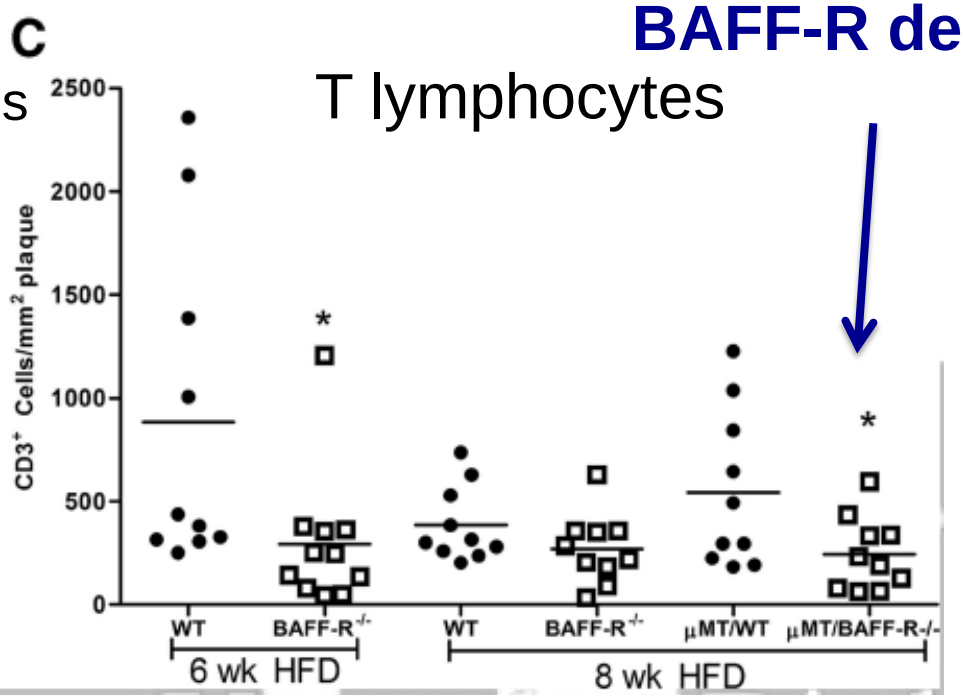
BAFF Receptor Deficiency Reduces the Development of Atherosclerosis in Mice



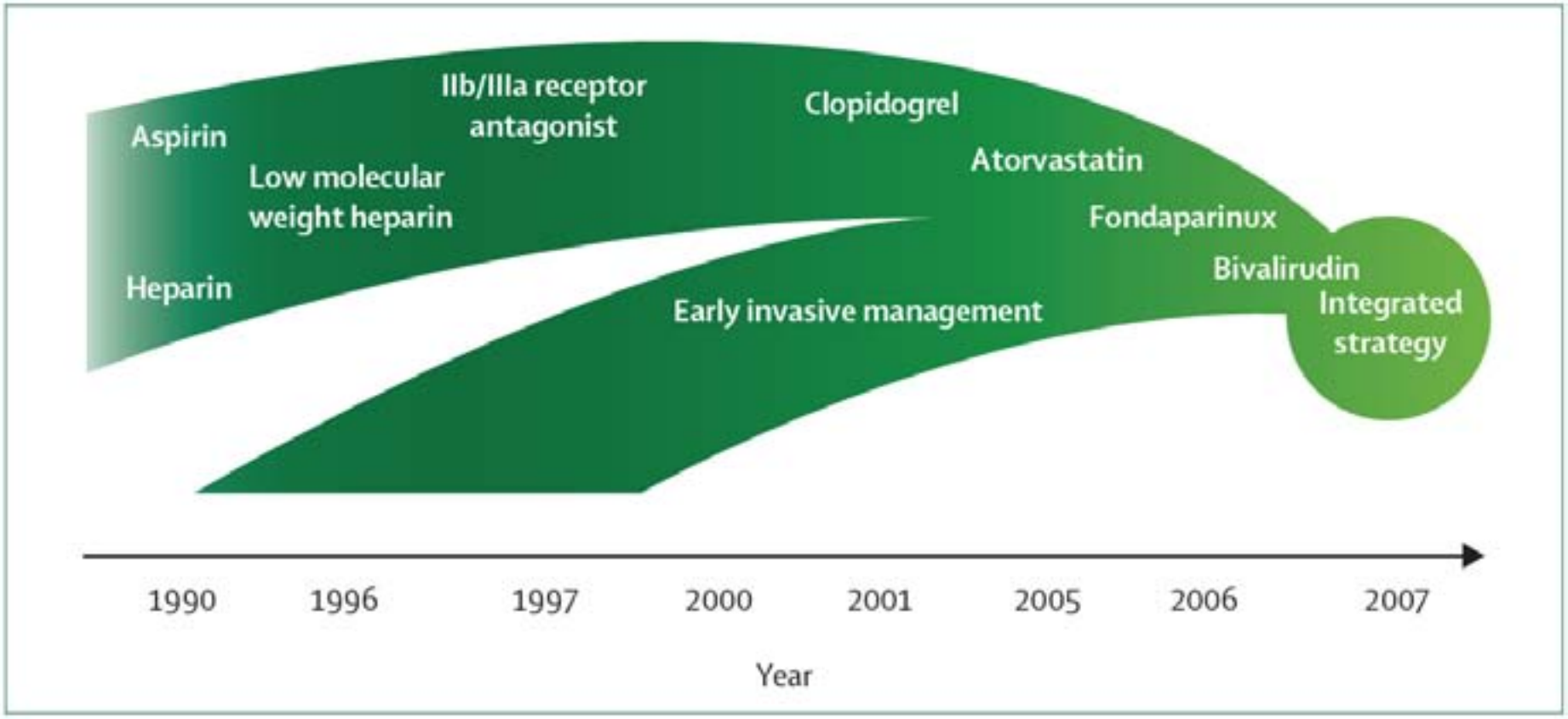


B cell-selective BAFF-R deletion





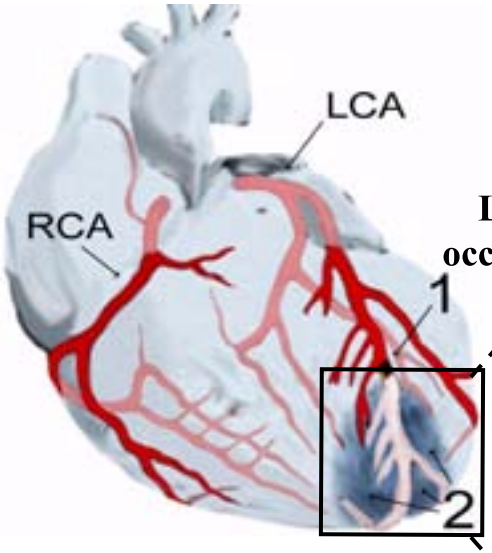
Acute Myocardial Infarction



Evolution of therapies in the management of acute coronary syndromes

White HD & Chew DP, *The Lancet* 2008

Post-MI Inflammation



LCA occlusion

Neutrophils

CD11b+

Ly6G+

Apoptosis → Adverse remodelling

Inflammatory Monocytes

Ly6C^{hi}

7/4^{hi}

CCR2+

CX3CR1^{lo}

Pro-Inflammatory cytokines
High Proteolysis → Adverse remodelling

Resident Monocytes

Ly6C^{lo}

7/4^{lo}

CX3CR1^{hi}

CCR2-

Anti-inflammatory cytokines
Angiogenesis → Myocardial healing

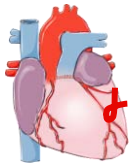
Chemokines release (CCL2, MIP-1α, CX3CL1)

Ischemic Myocardium

Blood

Role of B lymphocytes in immuno-inflammatory response and tissue remodelling after myocardial infarction

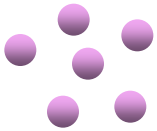
Kinetics of inflammatory cell infiltration after Myocardial Infarction



LCA ligation

Digestion

(Col I, XI, Hyaluronidase, DNase)

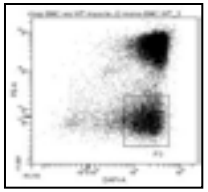


Gradient Density

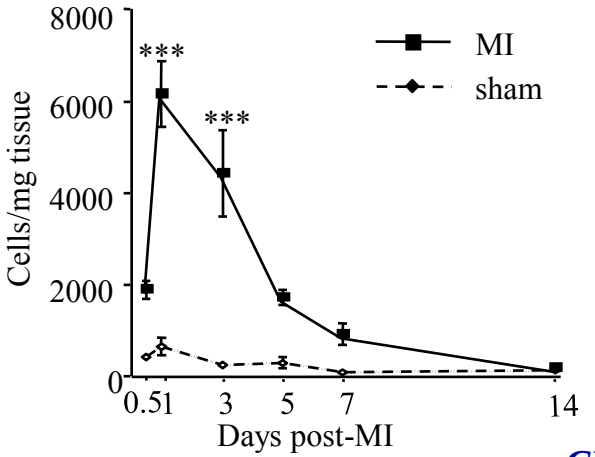
Centrifugation

FACS

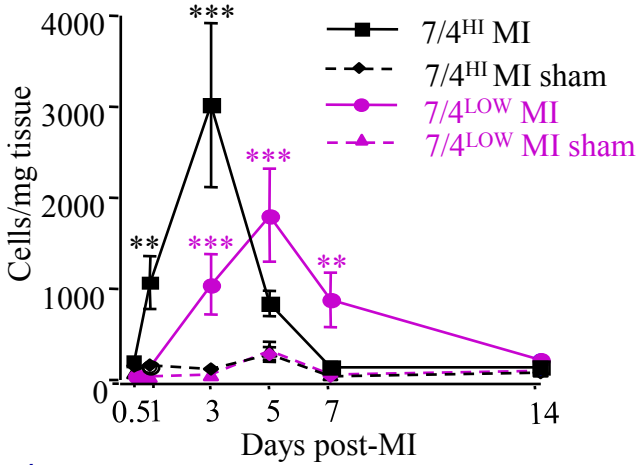
Analysis



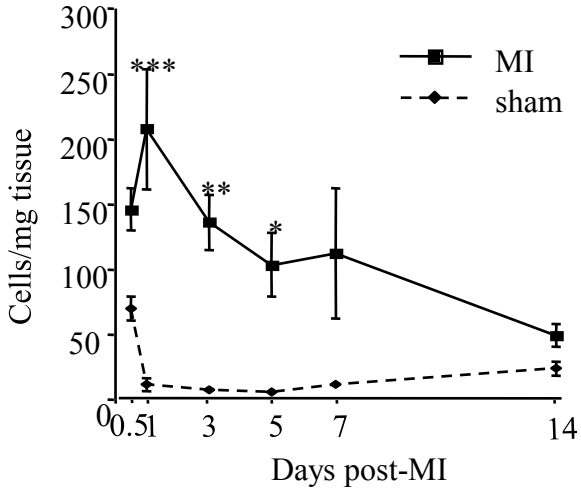
Neutrophils (CD11b⁺ Ly6G⁺ 7/4^{HI})



7/4^{HI} and 7/4^{LOW} Monocytes

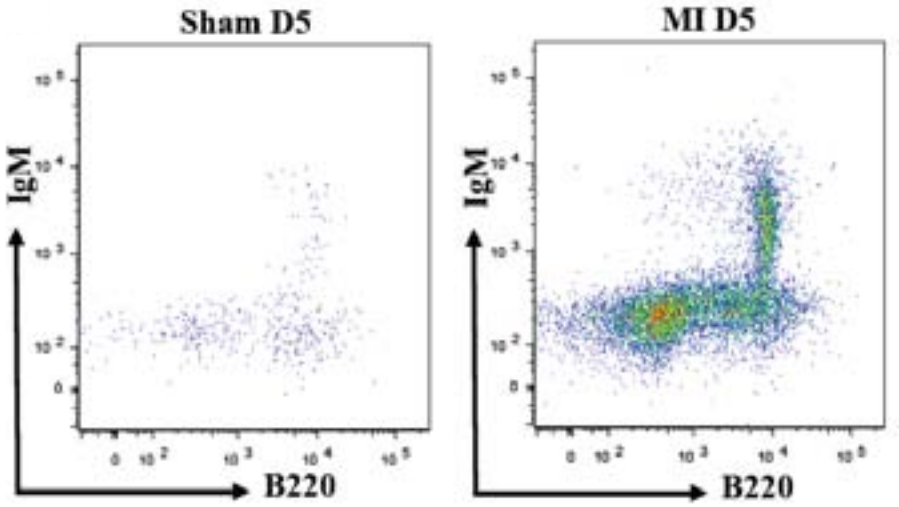


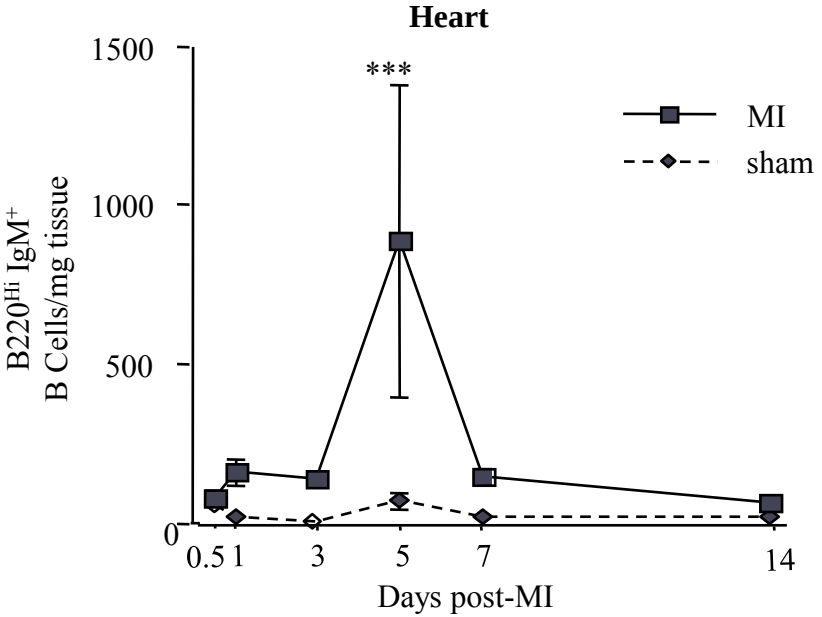
CD3⁺ T lymphocytes



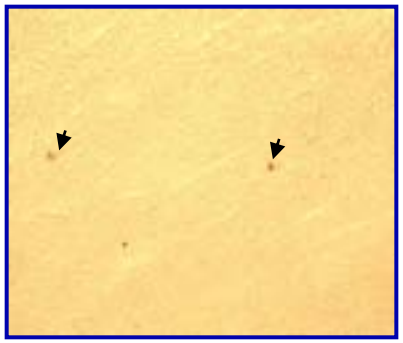
Kinetics of B lymphocytes infiltration after Myocardial Infarction

➢ ***Flow cytometry analysis***

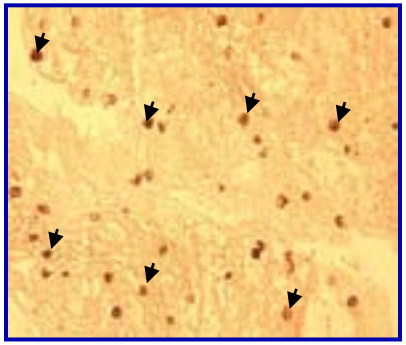




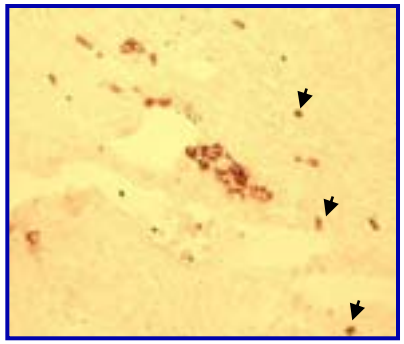
➢ ***B220 Immunostaining***



Sham D5

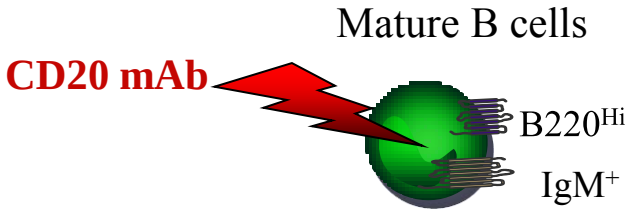


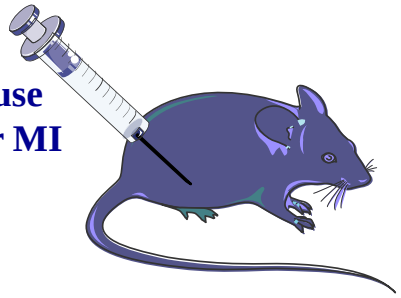
D5 after MI



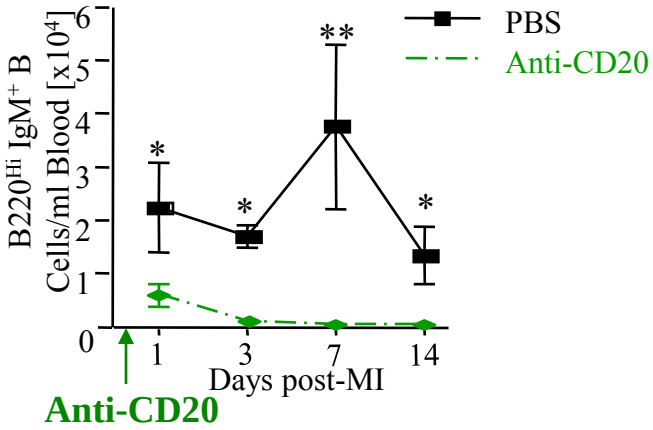
D14 after MI

Anti-CD20 antibody treatment reduces B lymphocyte levels

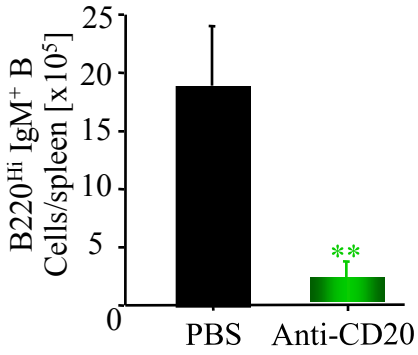


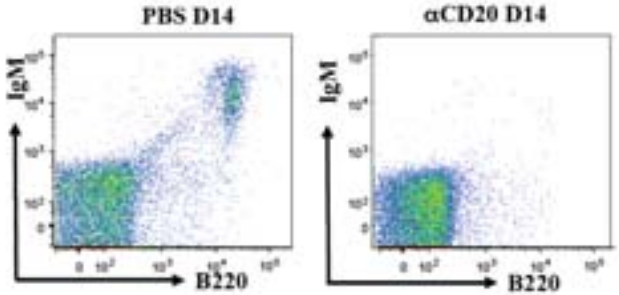


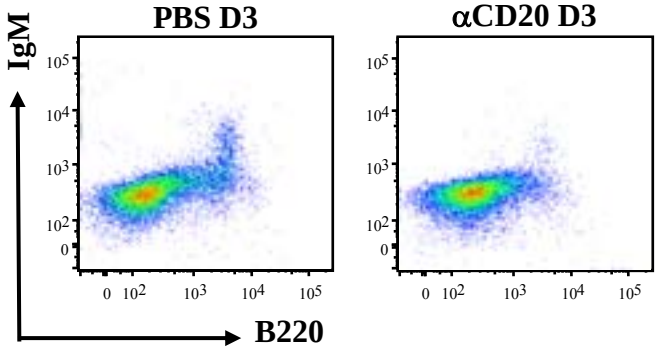
➢ ***Blood***



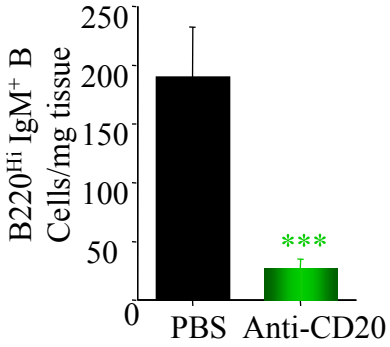
➢ ***Spleen D14***



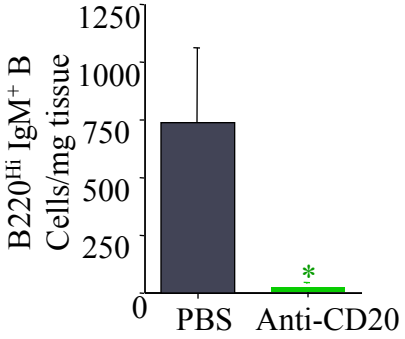




➢ ***Heart D3***

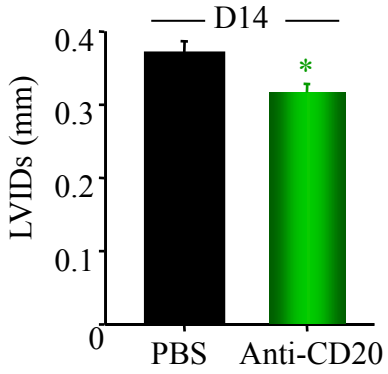


➢ ***Heart D5***

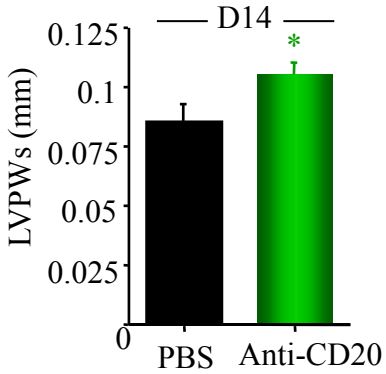


B lymphocyte depletion limits adverse LV remodelling

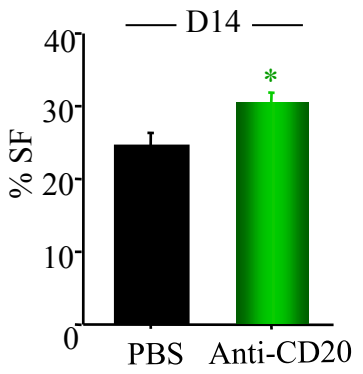
➢ ***LV internal dimension in diastole***



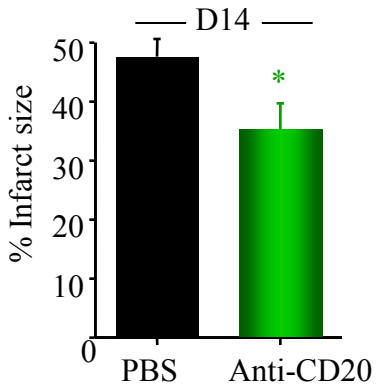
➢ ***LV Posterior Wall Thickness in systole***



➢ ***Shortening Fraction***

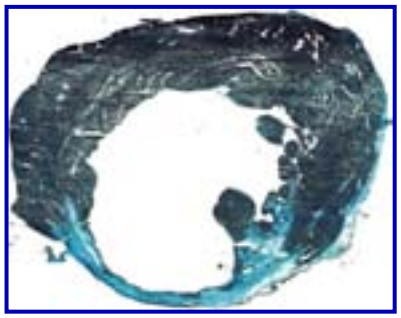


➢ ***Infarct Size (Masson Trichrome staining)***



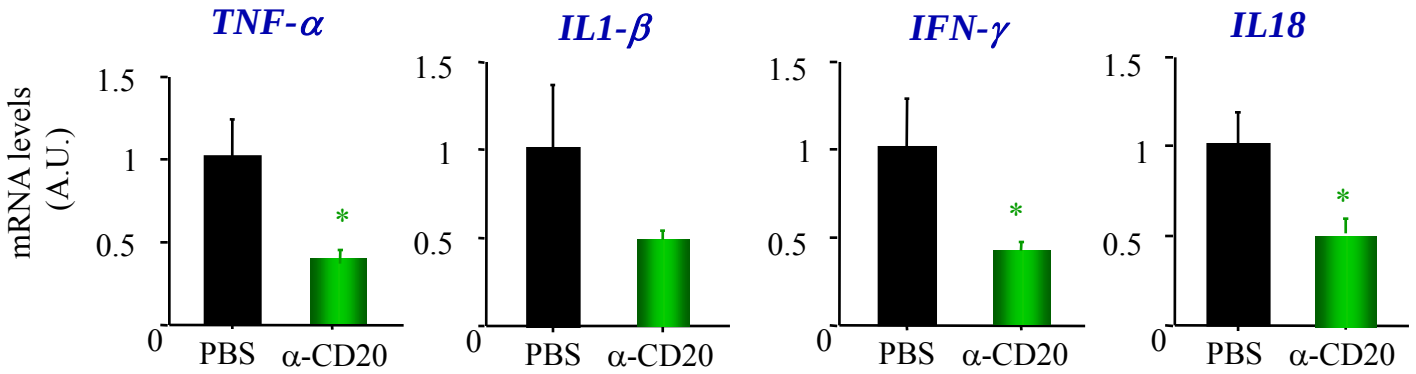
PBS

Anti-CD20

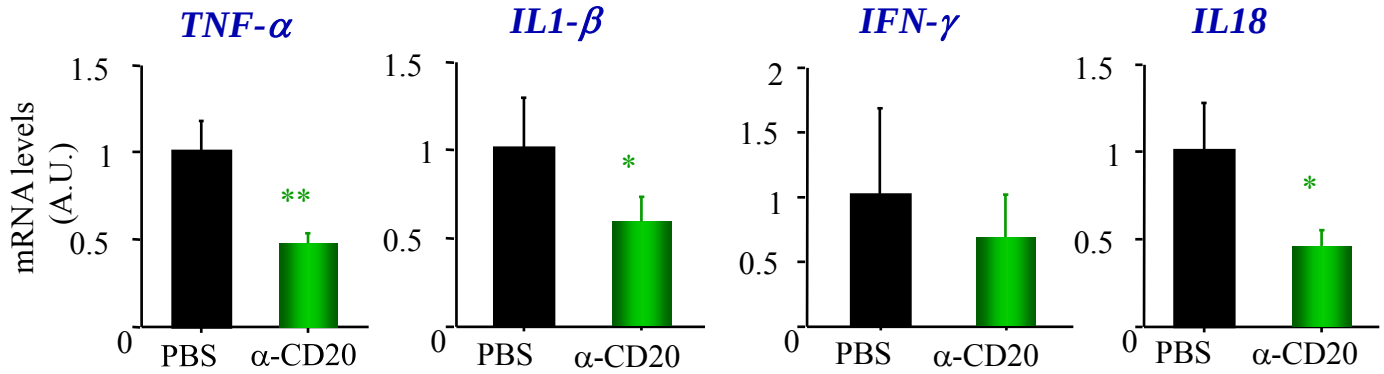


B lymphocyte depletion reduces systemic and local post-MI inflammation

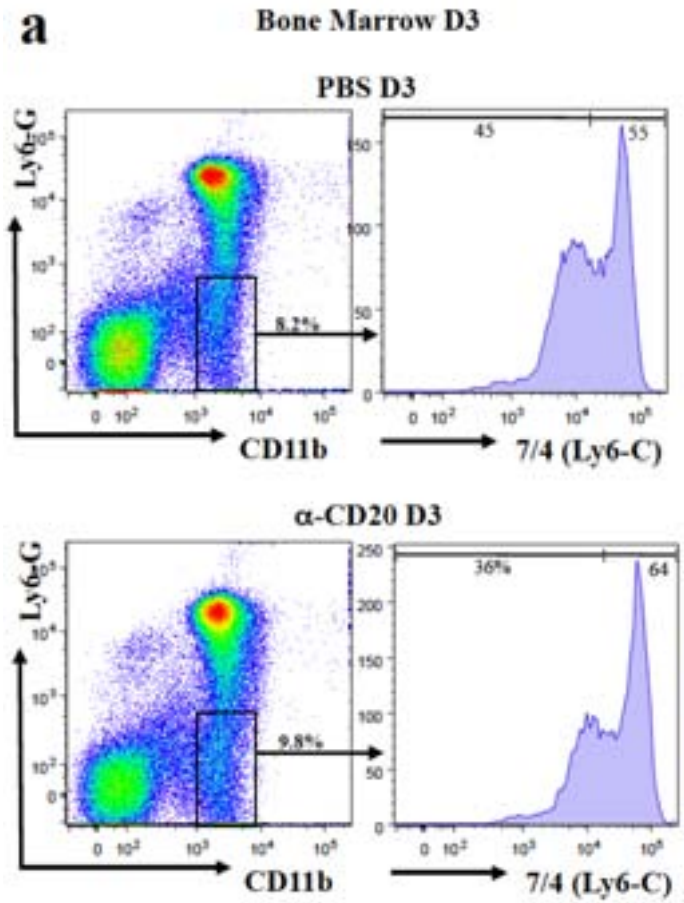
➢ ***Spleen D14***

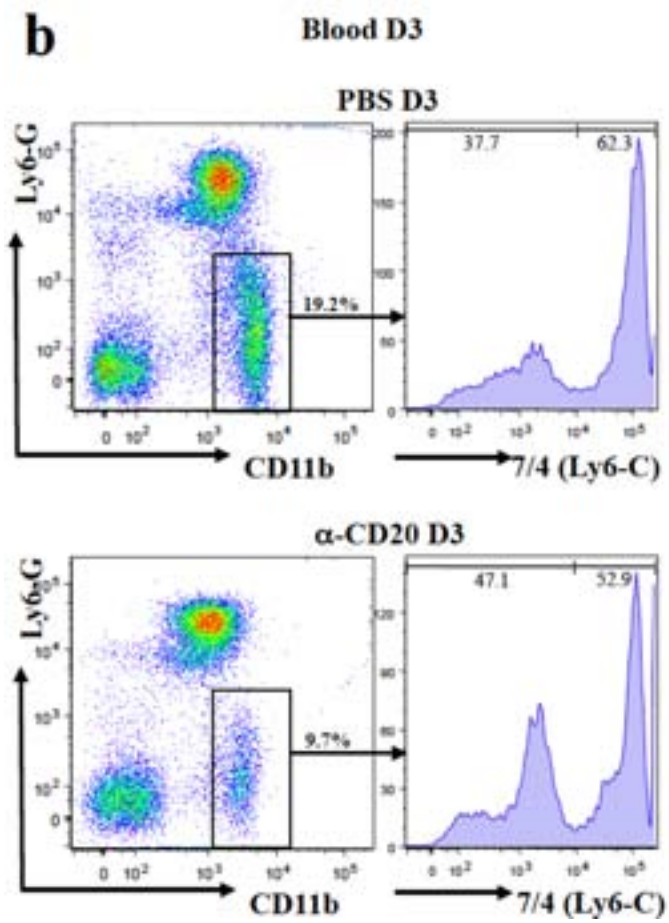


➢ ***Heart D14***

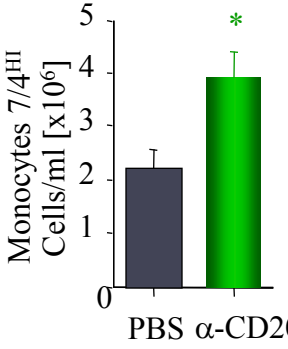


B lymphocyte depletion alters monocyte distribution in post-MI setting

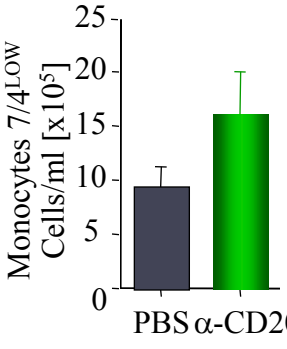




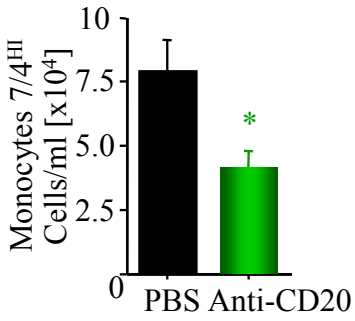
Monocytes 7/4^{HI}



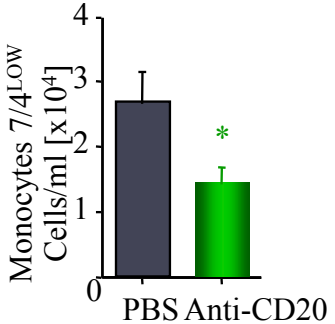
Monocytes 7/4^{Lo}



Monocytes 7/4^{HI}

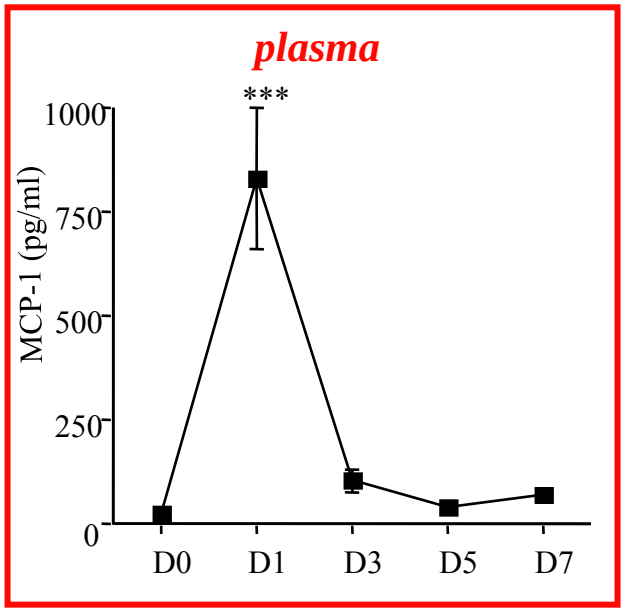


Monocytes 7/4^{Lo}

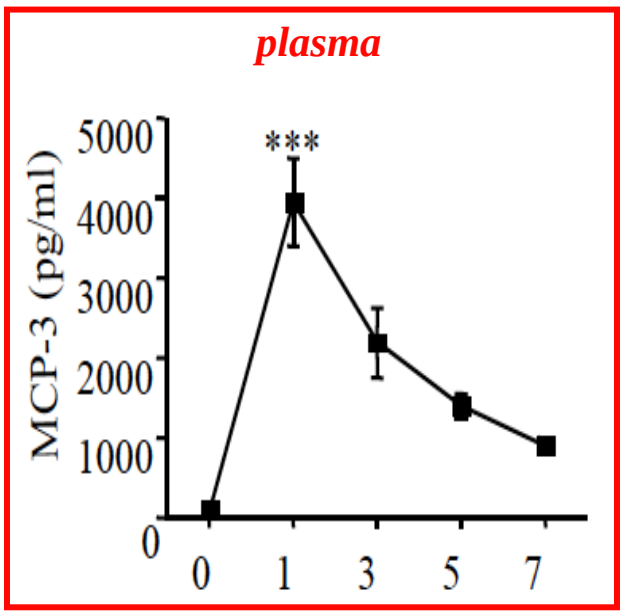


B lymphocyte depletion selectively reduces MCP-3 levels in post-MI

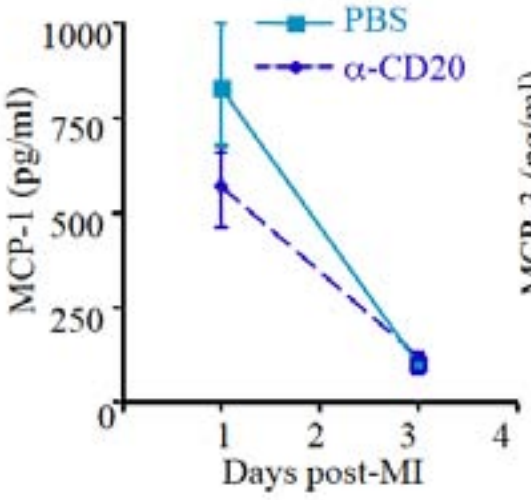
➢ ***MCP-1/CCL2***

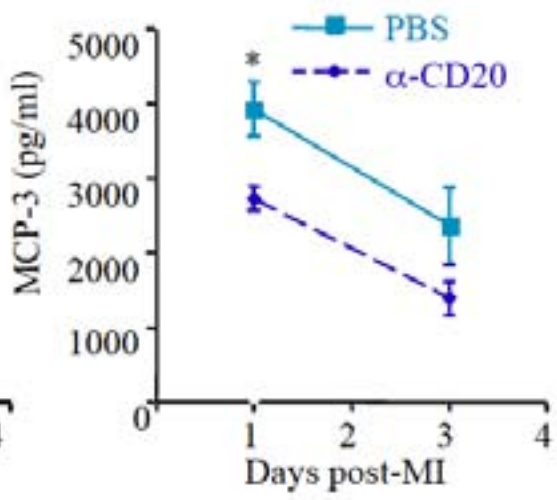


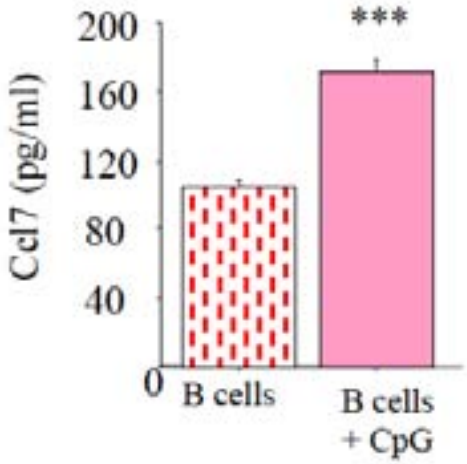
➢ ***MCP-3/CCL7***



MCP-1/CCL2
Not Detected in
B cell supernatants



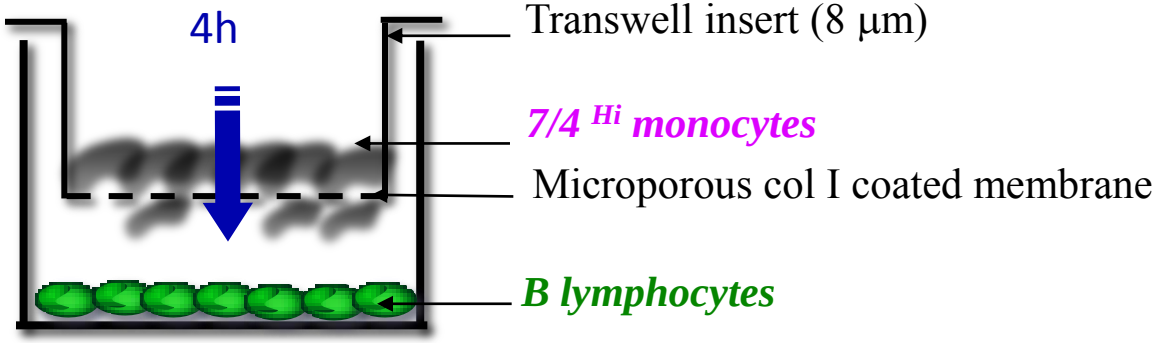


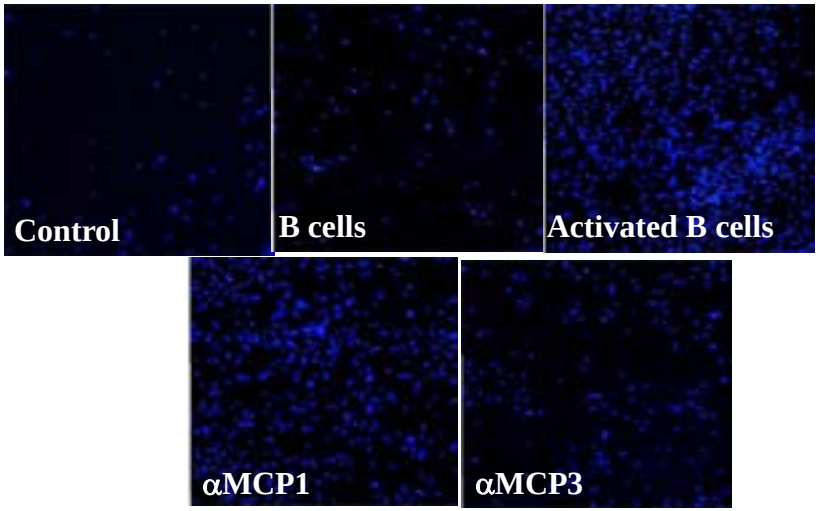


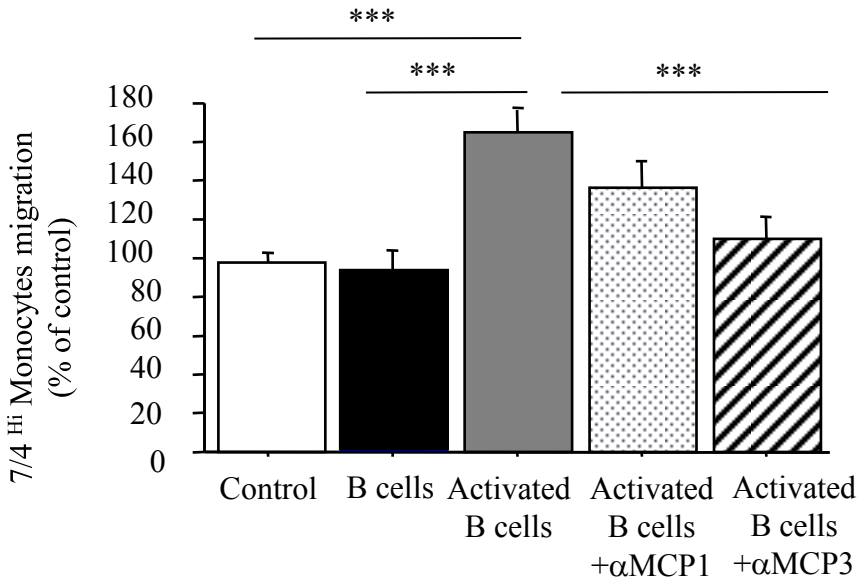
B lymphocytes trigger 7/4 ^{Hi} monocytes migration

➢ *7/4 ^{Hi} Monocytes transmigration assay*

Lower compartment :
- *Medium RPMI 10% SVF*
- *B cells (2.10^6)*
- *α-CD40 and IgM-treated B lymphocytes*

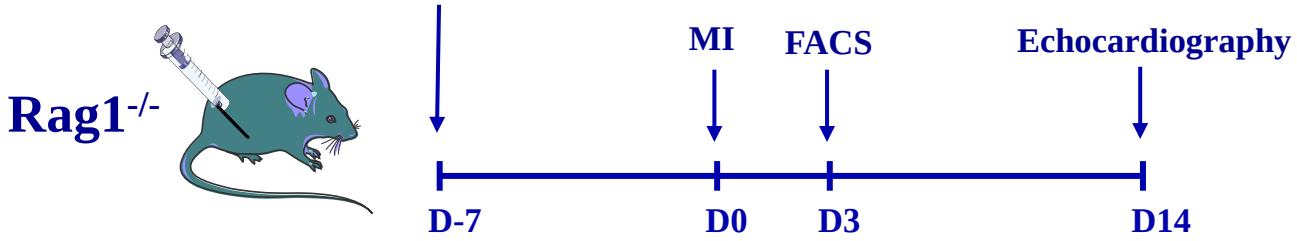




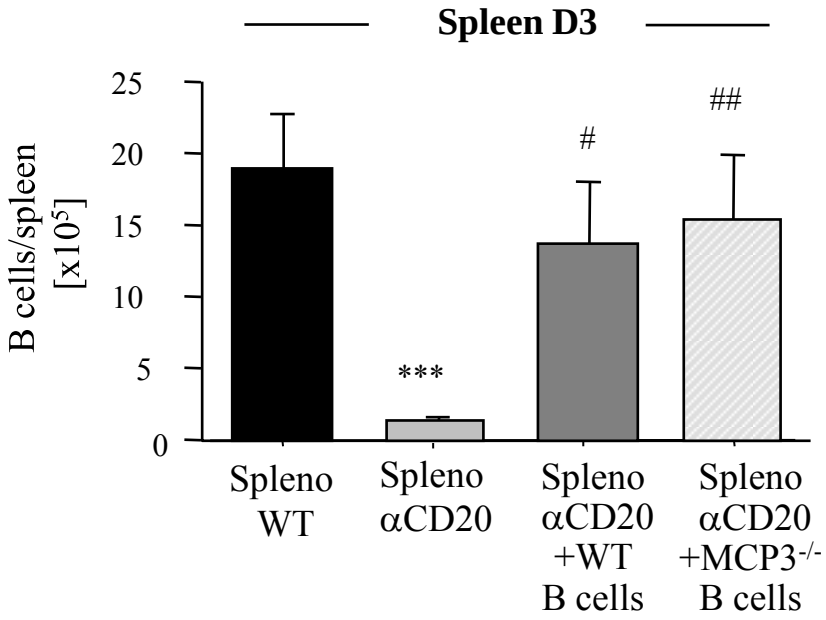


Exogenous administration of B lymphocytes promotes adverse LV remodelling

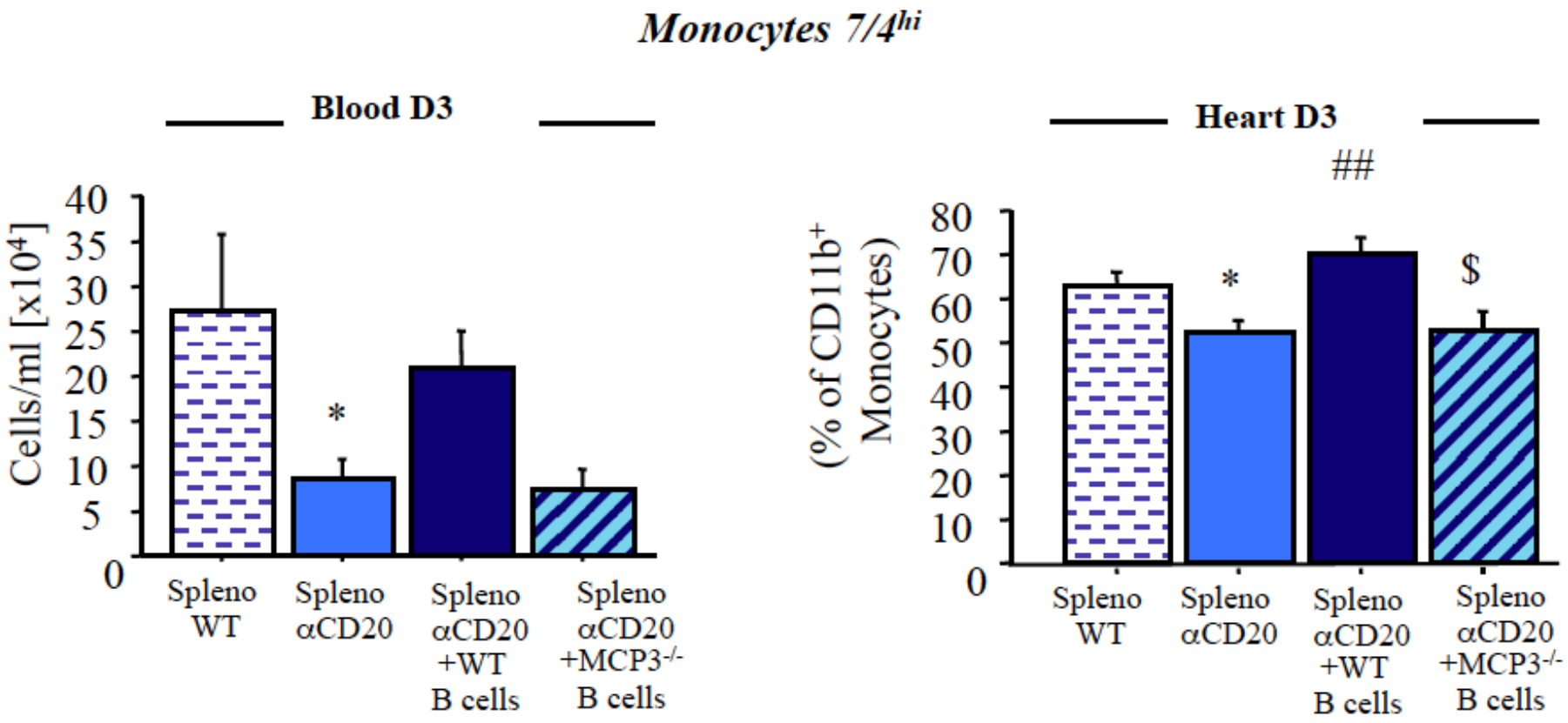
Injection splenocytes WT,
B cell-depleted splenocytes ±
WT or MCP-3-deficient B cells



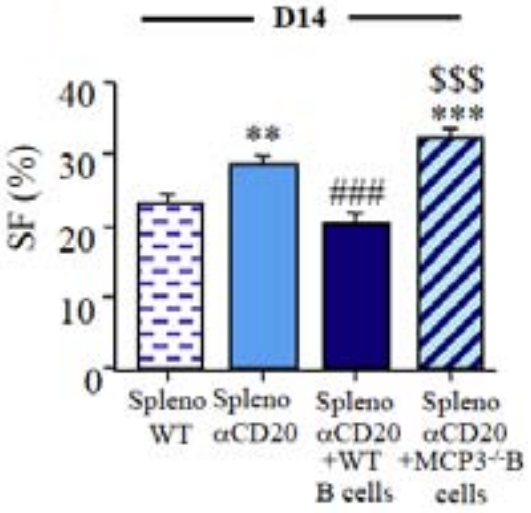
➢ ***B cells levels***

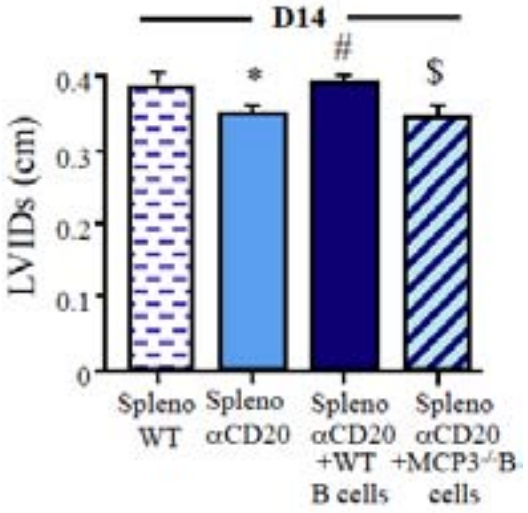


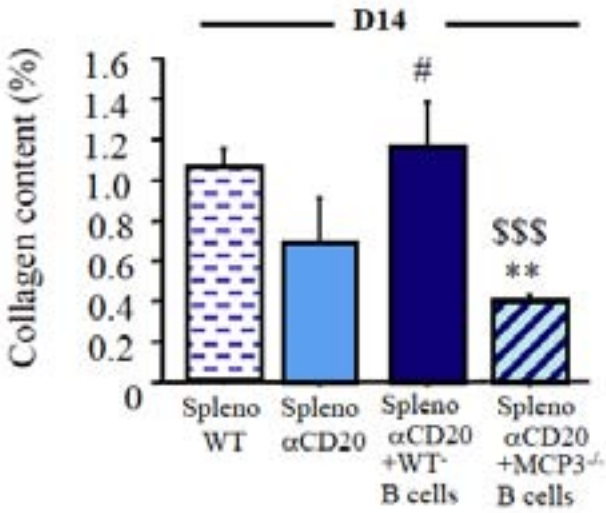
Exogenous administration of B lymphocytes enhances 7/4^{Hi} monocytes mobilisation and infiltration into the ischemic heart

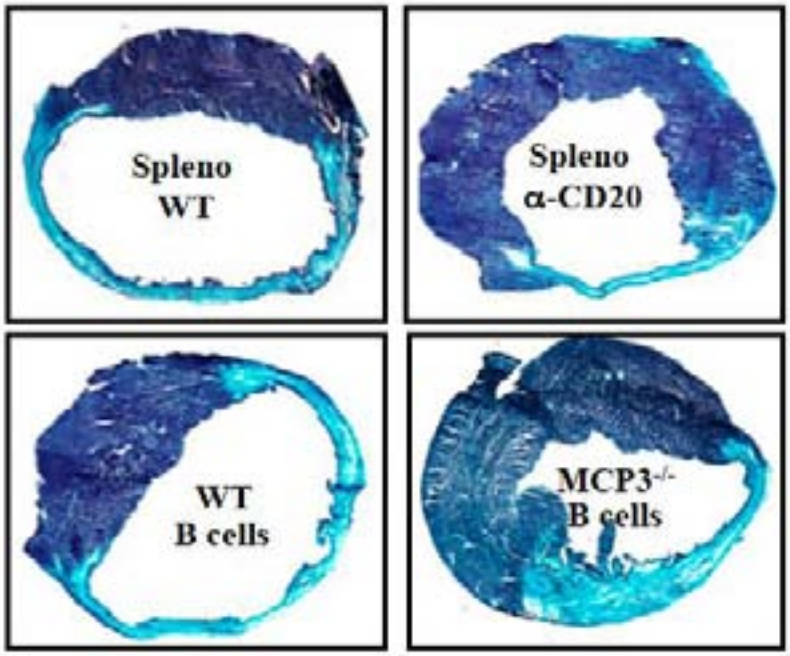


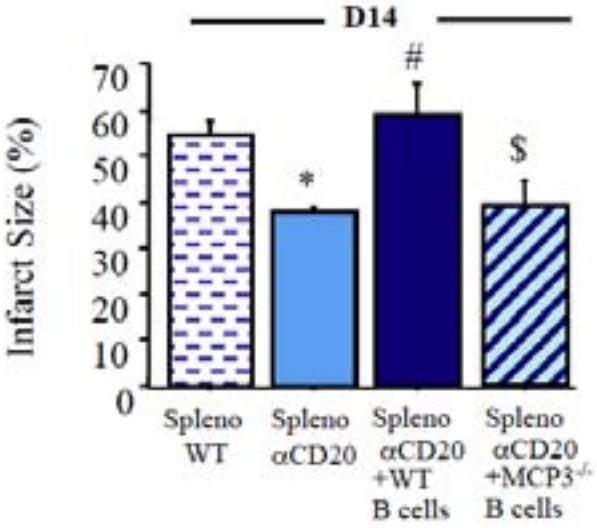
Exogenous administration of B lymphocytes promotes adverse LV remodelling











FAST-MI

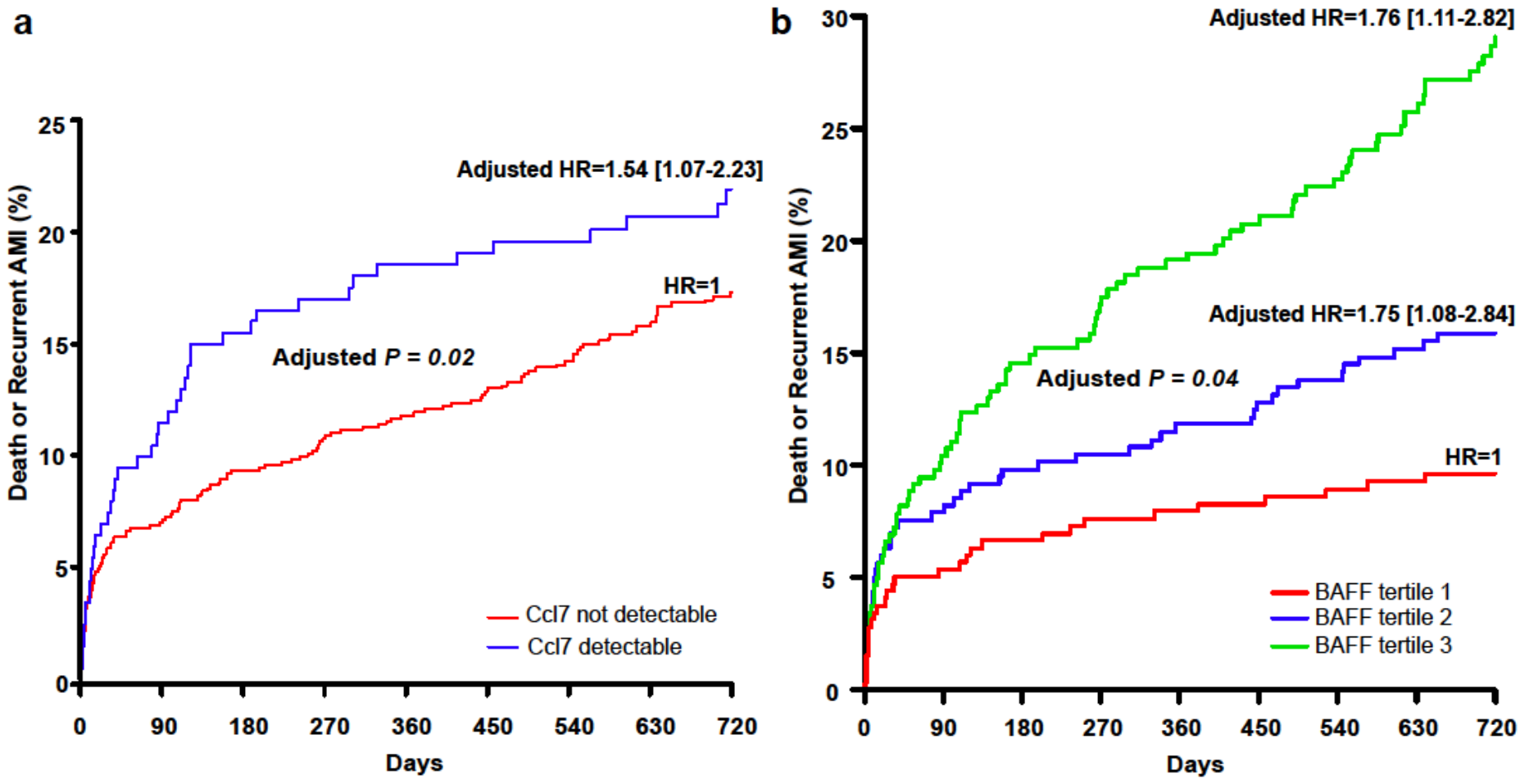
Impact of circulating levels of BAFF/CCL7 on 24 months-survival, recurrent myocardial infarction and incident stroke in patients with acute MI

- **FAST-MI is a nationwide French registry carried out in 3059 consecutive pts with AMI admitted in 223 CCUs**

- **100 centers, which included 1036 patients, participated in the serum databank.**

- **Outcome events were defined as all-cause death, recurrent AMI and incident stroke**

- **The 24-month follow-up of mortality was complete for 95% of patients**
  170 events occurred during follow-up


a
Death or Recurrent AMI (%)
25
20
15
10
5
0
Adjusted HR=1.54 [1.07-2.23]
HR=1
Adjusted P = 0.02
Ccl7 not detectable
Ccl7 detectable
0
90
180
270
360
450
540
630
720
Days
b
Death or Recurrent AMI (%)
30
25
20
15
10
5
0
Adjusted HR=1.76 [1.11-2.82]
Adjusted HR=1.75 [1.08-2.84]
Adjusted P = 0.04
HR=1
BAFF tertile 1
BAFF tertile 2
BAFF tertile 3
0
90
180
270
360
450
540
630
720
Days

B Lymphocytes Trigger CCL7-Dependent Monocyte Mobilisation and Promote Adverse Ventricular Remodelling after Acute Myocardial Infarction

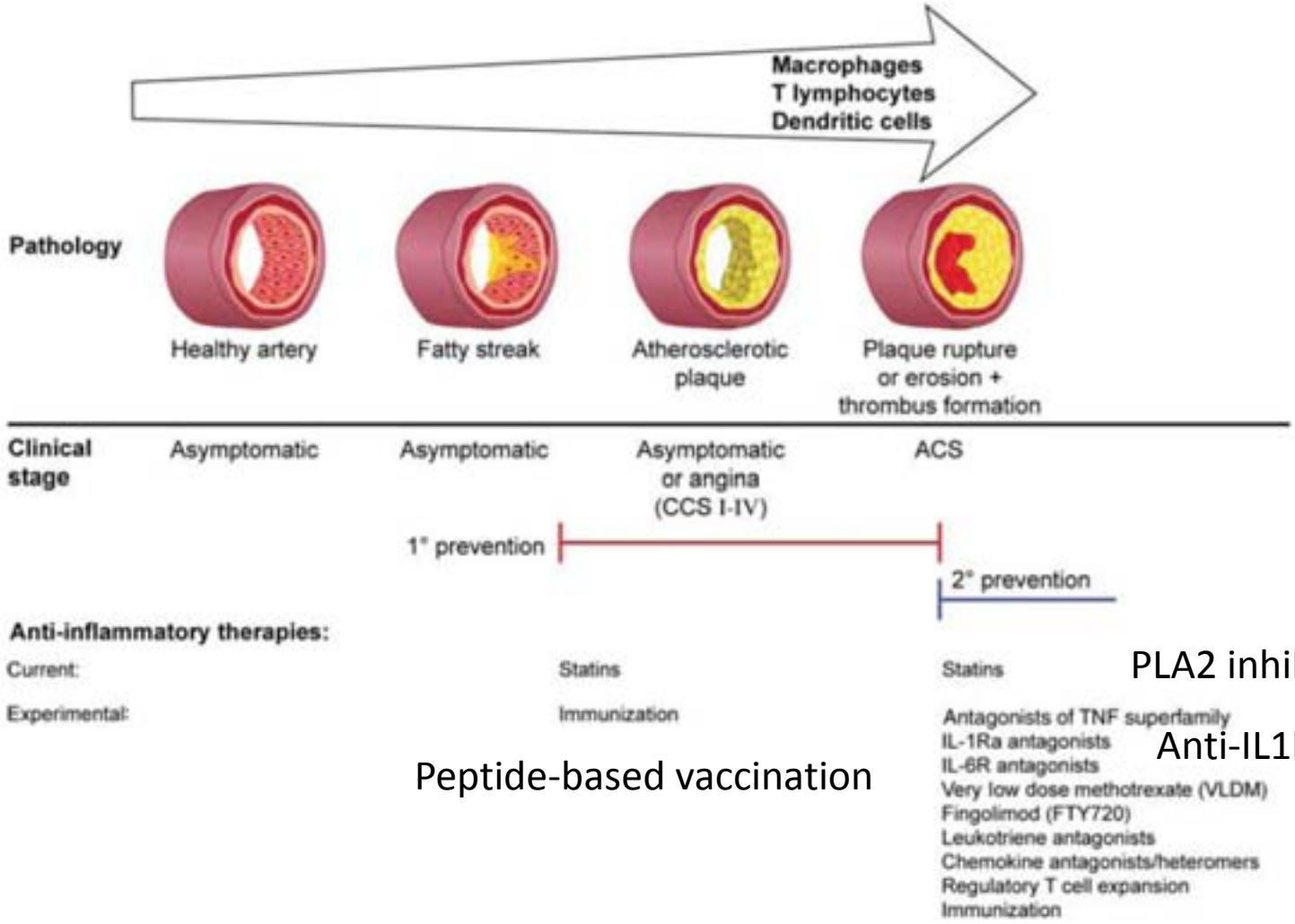
B cell depleting and CCL7-targeting therapies may be cardioprotective

Zouggari Y et al., *Nature Medicine*, In Press

Treating inflammation in atherosclerotic cardiovascular disease: emerging therapies

Roland Klingenberg[1,2*] and Göran K. Hansson[2]

European Heart Journal (2009) **30**, 2838–2844



PLA2 inhibitors

Anti-IL1beta

Peptide-based vaccination

B2 cell depleting agents

University of Cambridge
British Heart Foundation

Andy SAGE
Xuan LI
Deirdre MURPHY
Lauren BAKER
James HARRISON
Leanne MASTERS

Inserm U970
Alain TEDGUI
Hafid AIT-OUFELLA
Olivier HERBIN
Patrick BRUNEVAL

Jean-Sébastien SILVESTRE
Yasmine ZOUGGARI

CeMM, Medical University of Vienna, Austria
Christoph J. BINDER

AP-HP, Pierre et Marie Curie University
Tabassome SIMON

Duke University, USA
Thomas F. TEDDER

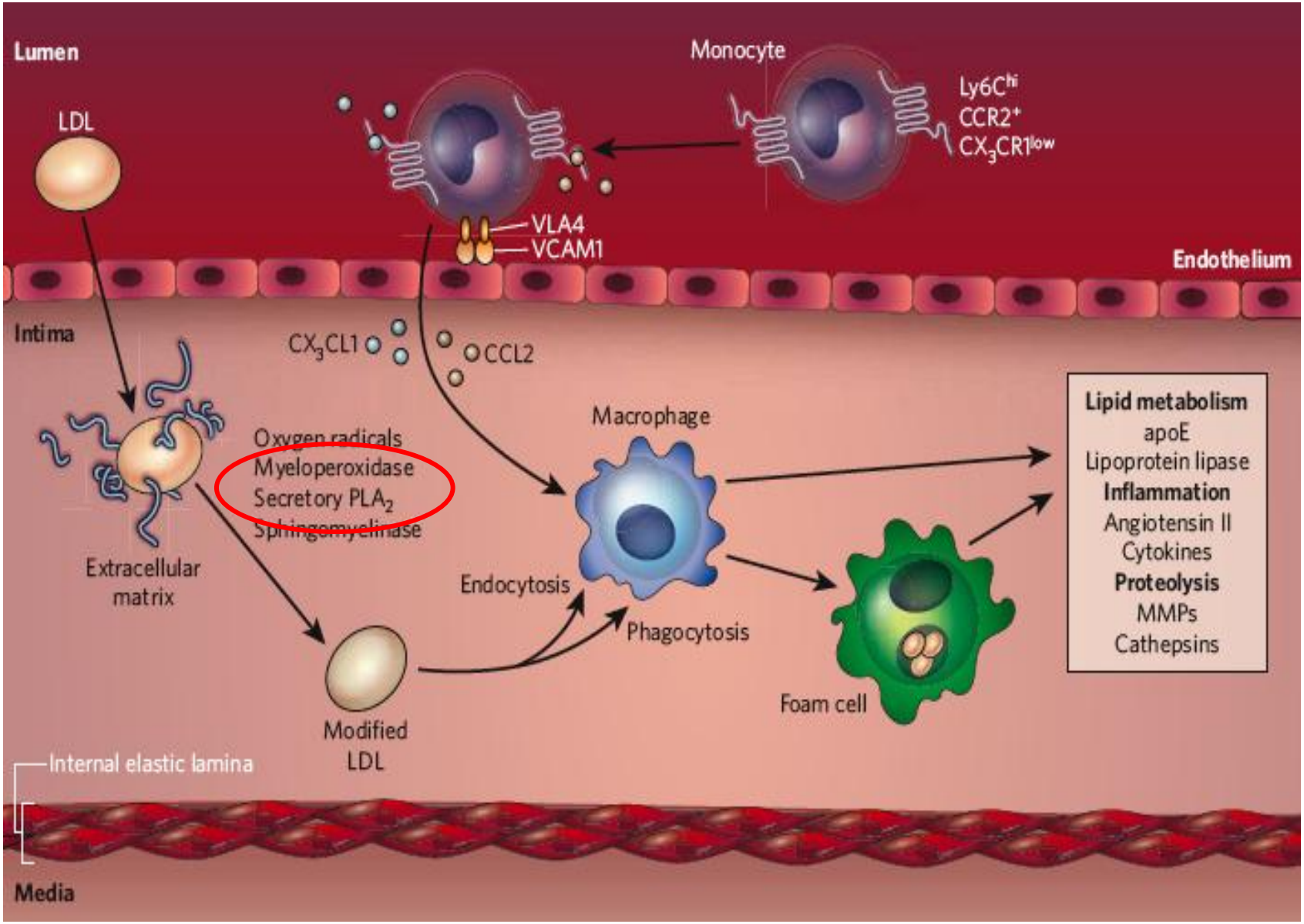
UCSF, USA
Israel F. CHARO

University of Utrecht, The Netherlands
Gerard PASTERKAMP

TOLERAGE

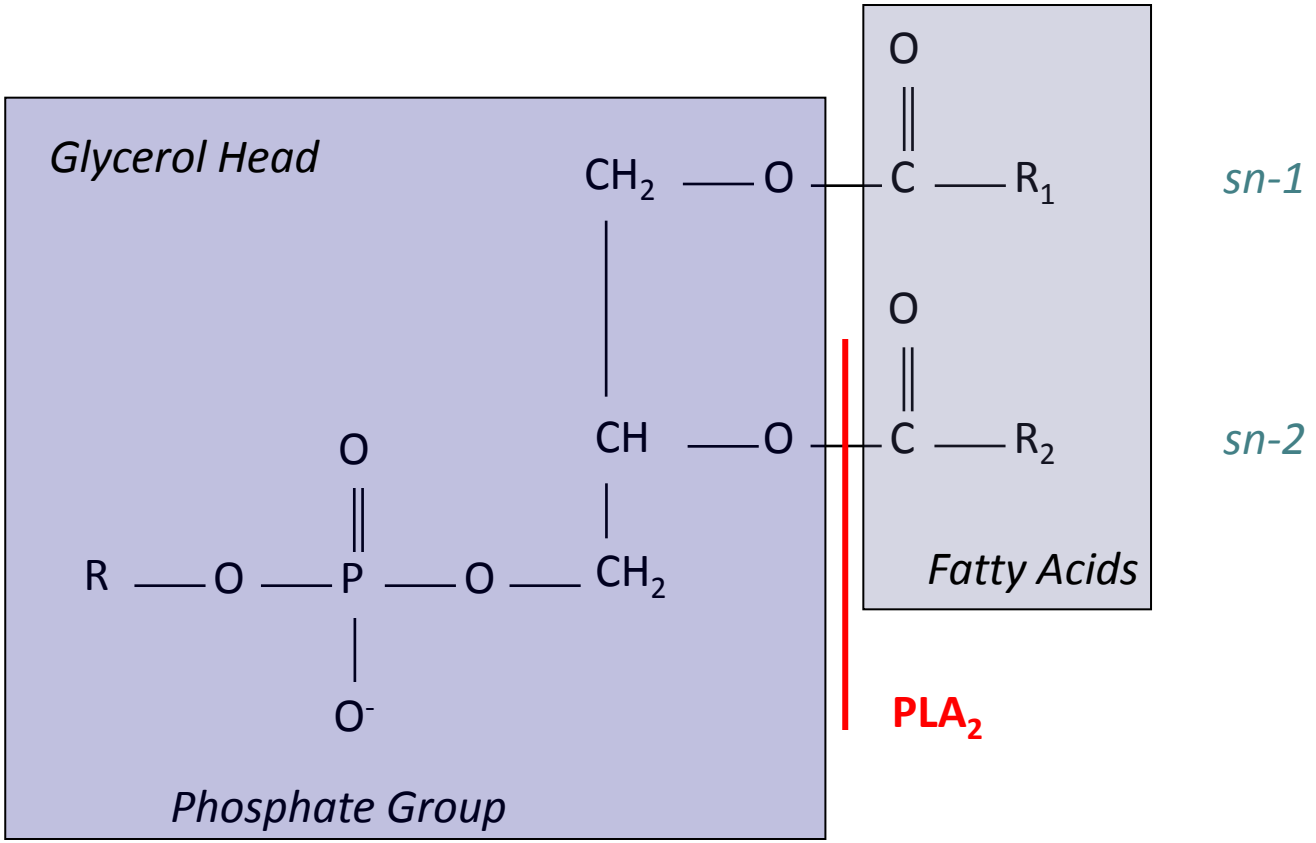
L·I·N·K LEDUCQ IMMUNOREGULATORY NETWORK

erc 2007 - 2012 5 Years



Rader DJ & Daugherty A. Nature 2008

PLA2 enzymes hydrolyze phospholipids at the *sn-2* position to generate lysophospholipids and fatty acids

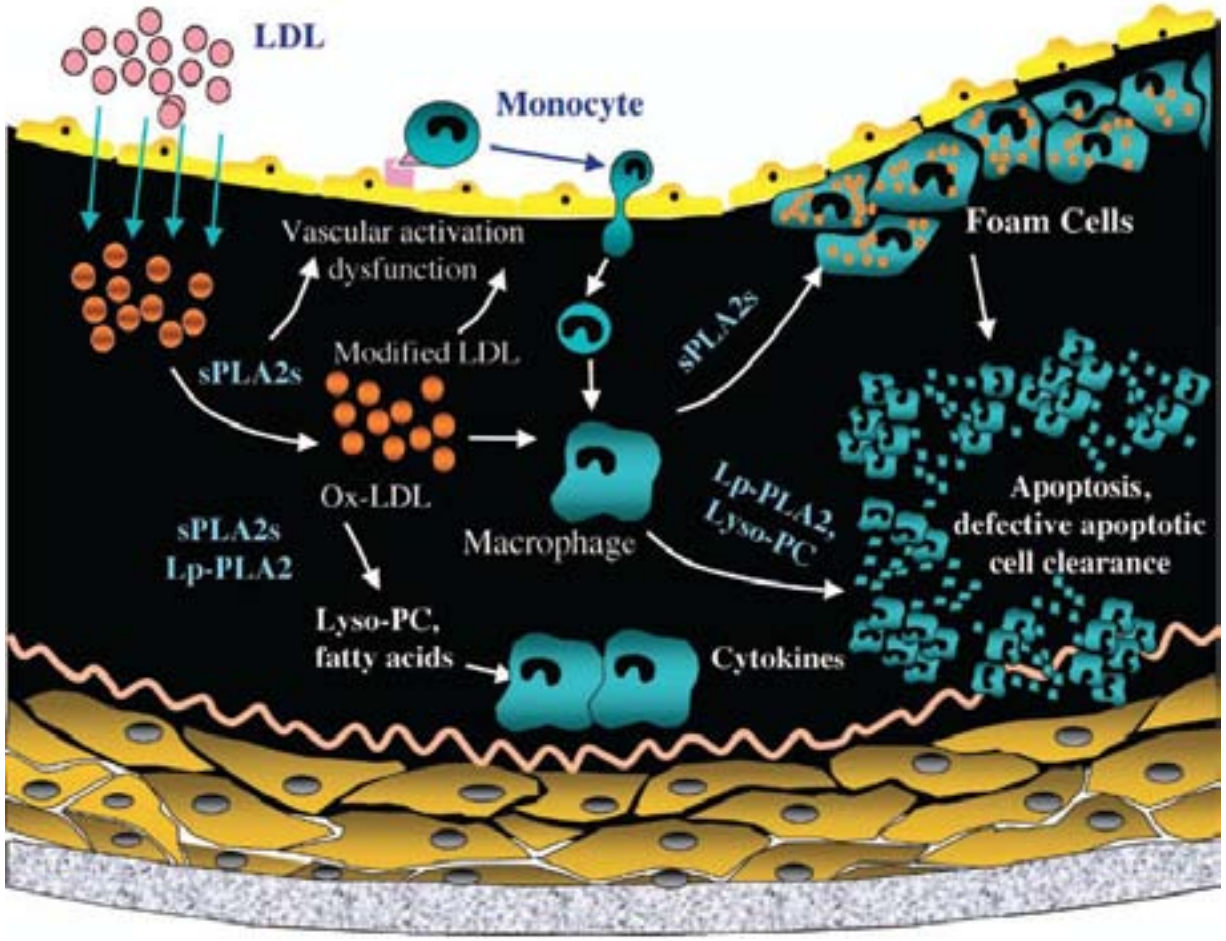


Lipoprotein-Associated and Secreted Phospholipases A_2 in Cardiovascular Disease

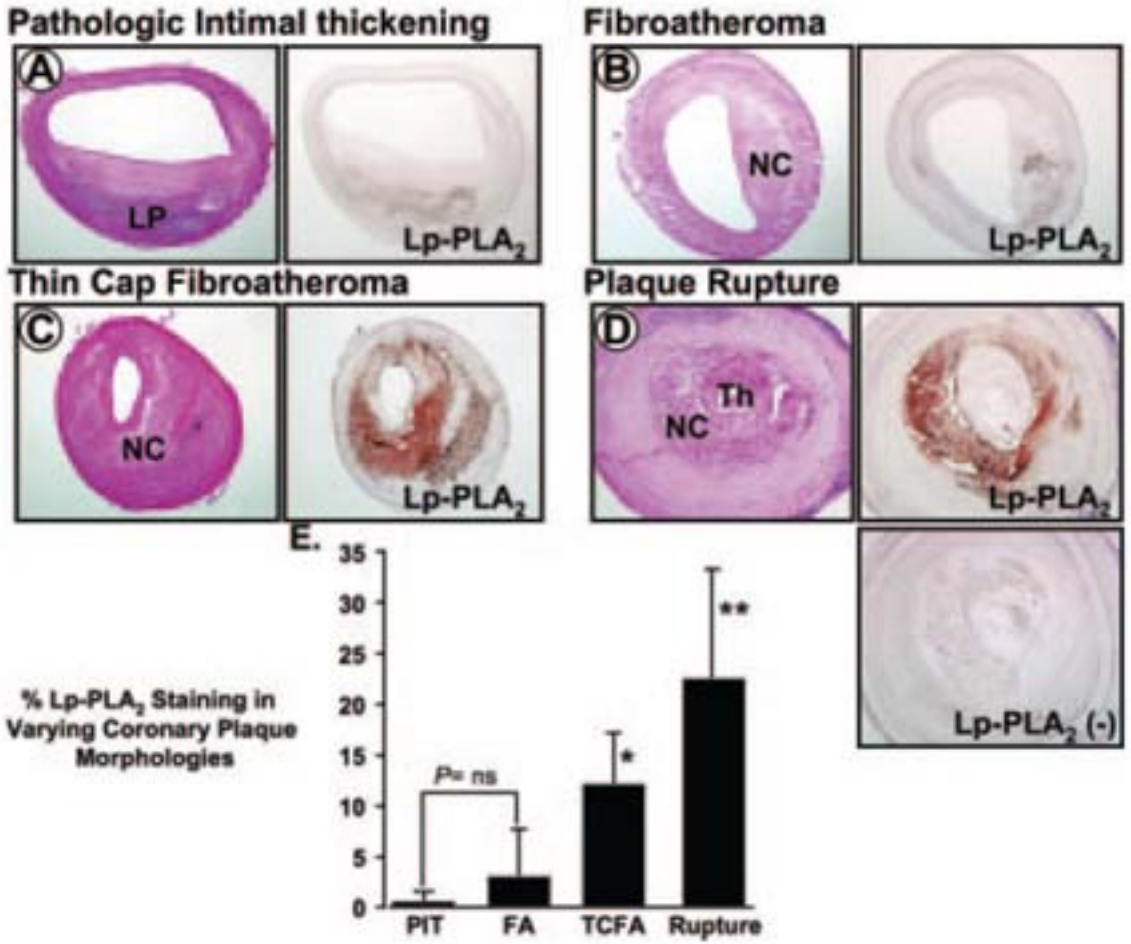
Roles as Biological Effectors and Biomarkers

Circulation

Ziad Mallat, MD, PhD; Gérard Lambeau, PhD; Alain Tedgui, PhD



Lipoprotein-Associated Phospholipase A_2 Protein Expression in the Natural Progression of Human Coronary Atherosclerosis

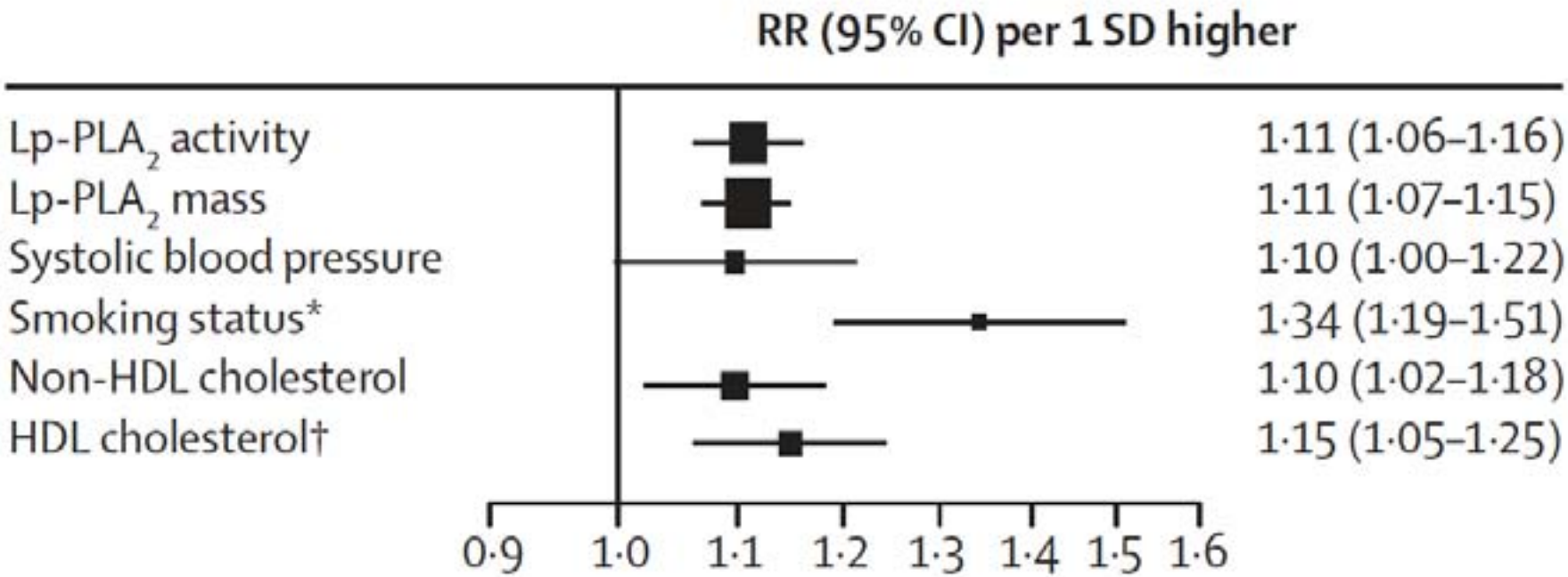


Kolodgie et al., Arterioscler Thromb Vasc Biol 2006

Lipoprotein-associated phospholipase A_2 and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies

*The Lp-PLA$_2$ Studies Collaboration**

Lancet 2010; 375: 1536–44



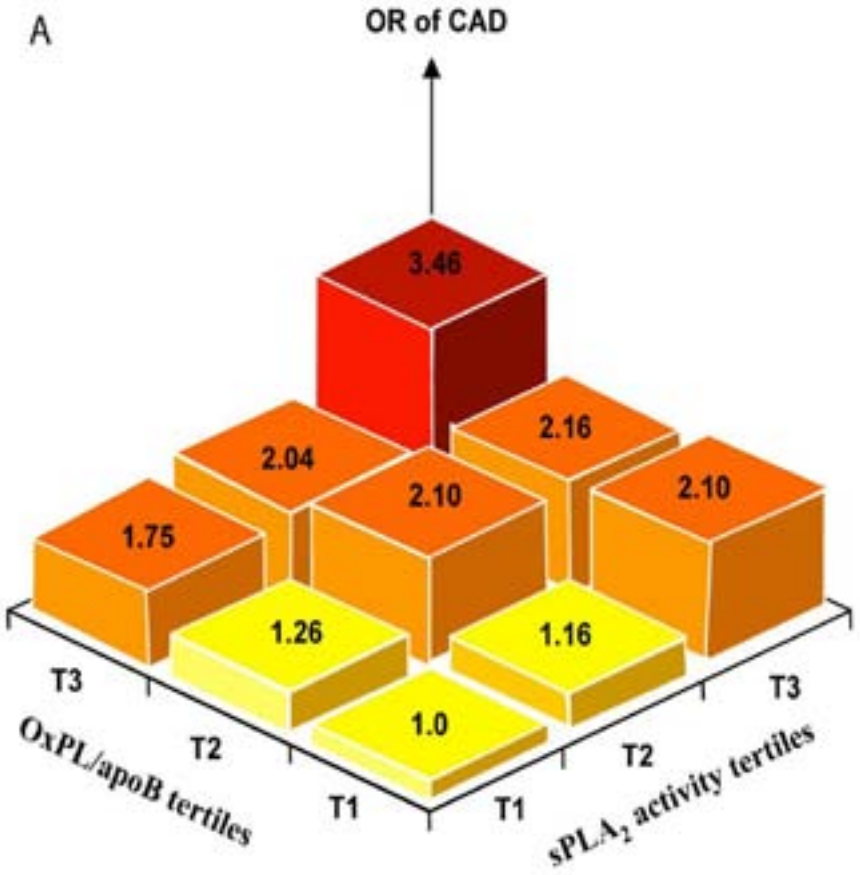
Oxidation-Specific Biomarkers, Lipoprotein(a), and Risk of Fatal and Nonfatal Coronary Events

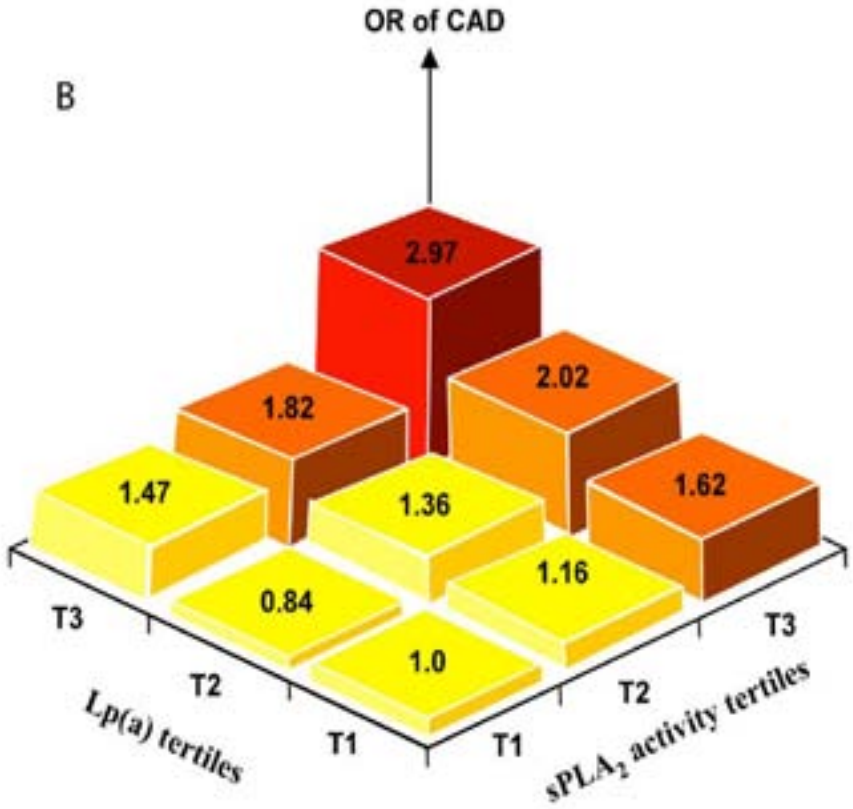
Sotirios Tsimikas, MD,* Ziad Mallat, MD, PHD,† Philippa J. Talmud, DSC,‡
John J. P. Kastelein, MD, PHD,¶ Nicholas J. Wareham, MBBS, PHD,§ Manjinder S. Sandhu, PHD,‖
Elizabeth R. Miller, BS,* Joelle Benessiano, MD, PHD,† Alain Tedgui, PHD,†
Joseph L. Witztum, MD,* Kay-Tee Khaw, MBBCHIR,‖ S. Matthijs Boekholdt, MD, PHD¶

La Jolla, California; Paris, France; London and Cambridge, United Kingdom; and Amsterdam, the Netherlands

Results After adjusting for age, smoking, diabetes, low- and high-density lipoprotein cholesterol, and systolic blood pressure, the highest tertiles of oxidized phospholipids on apolipoprotein B-100 particles and Lp(a) were associated with a significantly higher risk of CAD events (odds ratios: 1.67 and 1.64, respectively; $p < 0.001$) compared with the lowest tertiles. The odds ratio of CAD events associated with the highest tertiles of oxidized phospholipids on apolipoprotein B-100 particles or Lp(a) was significantly potentiated (approximately doubled) by the highest tertiles of secretory phospholipase A_2 activity and mass but less so for myeloperoxidase and lipoprotein-associated phospholipase A_2 activity. The odds ratios for fatal CAD were higher than for the combined end point. After taking into account the Framingham Risk Score, *c*-index values progressively increased when oxidative biomarkers were added to the model.

Conclusions This EPIC-Norfolk study links pathophysiologically related oxidation-specific biomarkers and Lp(a) with CAD events. Oxidation-specific biomarkers provide cumulative predictive value when added to traditional cardiovascular risk factors. (J Am Coll Cardiol 2010;56:946–55)


A
OR of CAD
3.46
2.04
2.16
2.10
2.10
1.75
1.26
1.16
1.0
T3
T2
T1
OxPL/apoB tertiles
T1
T2
T3
sPLA2 activity tertiles


B
OR of CAD
2.97
1.82
2.02
1.47
1.36
1.62
1.16
0.84
1.0
T3
T2
T1
Lp(a) tertiles
T1
T2
T3
sPLA2 activity tertiles

Prognostic Utility of Secretory Phospholipase A_2 in Patients with Stable Coronary Artery Disease

Michelle L. O'Donoghue,[1*] Ziad Mallat,[2,3] David A. Morrow,[1] Joelle Benessiano,[4] Sarah Sloan,[1] Torbjørn Omland,[5] Scott D. Solomon,[6] Eugene Braunwald,[1] Alain Tedgui,[2,3] and Marc S. Sabatine[1]

BACKGROUND: Secretory phospholipase A_2 ($sPLA_2$) may contribute to atherogenesis. To date, few prospective studies have examined the utility of $sPLA_2$ for risk stratification in coronary artery disease (CAD).

METHODS: We measured plasma $sPLA_2$ activity at baseline in 3708 subjects in the PEACE randomized trial of trandolapril vs placebo in stable CAD. Median follow-up was 4.8 years. We used Cox regression to adjust for demographics, clinical risk factors, apolipoprotein B, apolipoprotein A1, and medications.

RESULTS: After multivariable adjustment, $sPLA_2$ was associated with an increased risk of cardiovascular death, myocardial infarction, or stroke (adjusted hazard ratio Q4:Q1 1.55, 95% CI 1.13–2.14) and cardiovascular death or heart failure (1.91, 1.20–3.03). In further multivariable assessment, increased activity levels of $sPLA_2$ were associated with the risk of cardiovascular death, myocardial infarction, or stroke (adjusted hazard ratio 1.47, 95% CI 1.06–2.04), independent of lipoprotein-associated phospholipase A_2 mass and C-reactive protein, and modestly improved the area under the curve (AUC) beyond established clinical risk factors (AUC 0.668–0.675, $P = 0.01$). $sPLA_2$, N-terminal pro-B-type natriuretic peptide, and high-sensitivity cardiac troponin T all were independently associated with cardiovascular death or heart failure, and each improved risk discrimination ($P = 0.02$, $P < 0.001$, $P < 0.001$, respectively).

CONCLUSIONS: $sPLA_2$ activity provides independent prognostic information beyond established risk markers in patients with stable CAD. These data are encouraging for studies designed to evaluate the role of $sPLA_2$ as a therapeutic target.

Clinical Chemistry 57:9
1311–1317 (2011)

Type II Secretory Phospholipase A_2 and Prognosis in Patients with Stable Coronary Heart Disease: Mendelian Randomization Study

Lutz P. Breitling[1]*, Wolfgang Koenig[2], Marcus Fischer[3], Ziad Mallat[4], Christian Hengstenberg[3], Dietrich Rothenbacher[1,5], Hermann Brenner[1]

Abstract

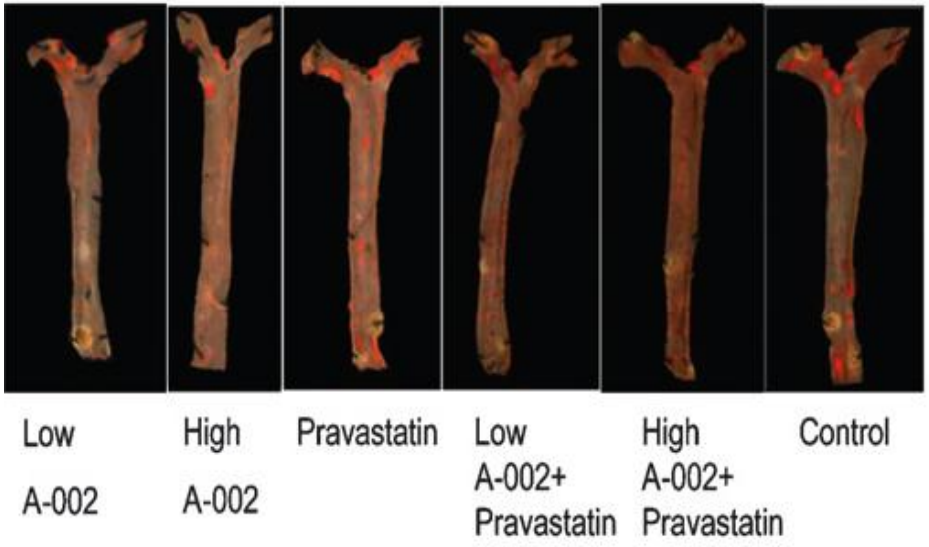
Background: Serum type II secretory phospholipase A_2 ($sPLA_2$-IIa) has been found to be predictive of adverse outcomes in patients with stable coronary heart disease. Compounds targeting $sPLA_2$-IIa are already under development. This study investigated if an association of $sPLA_2$-IIa with secondary cardiovascular disease (CVD) events may be of causal nature or mainly a matter of confounding by correlated cardiovascular risk markers.

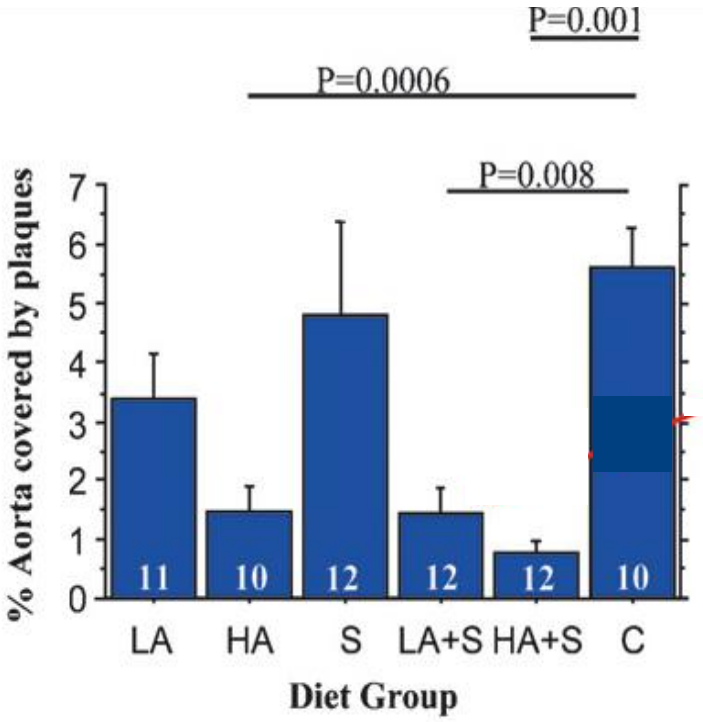
Methodology/Principal Findings: Eight-year follow-up data of a prospective cohort study (KAROLA) of patients who underwent in-patient rehabilitation after an acute cardiovascular event were analysed. Associations of polymorphisms (SNP) in the $sPLA_2$-IIa-coding gene *PLA2G2A* with serum $sPLA_2$-IIa and secondary fatal or non-fatal CVD events were examined by multiple regression. Hazard ratios (HR) were compared with those expected if the association between $sPLA_2$-IIa and CVD were causal. The strongest determinants of $sPLA_2$-IIa (rs4744 and rs10732279) were associated with an increase of serum concentrations by 81% and 73% per variant allele. HRs (95% confidence intervals) estimating the associations of the SNPs with secondary CVD events were increased, but not statistically significant (1.16 [0.89–1.51] and 1.18 [0.91–1.52] per variant allele, respectively). However, these estimates were very similar to those expected when assuming causality (1.18 and 1.17), based on an association of natural log-transformed $sPLA_2$-IIa concentration with secondary events with HR = 1.33 per unit.

Conclusion: The present findings regarding genetic polymorphisms, determination of serum $sPLA_2$-IIa, and prognosis in CVD patients are consistent with a genuine causal relationship and thus might point to a valid drug target for prevention of secondary CVD events.

sPLA2 inhibitor acts synergistically with statin to decrease atherosclerosis

apoE-/- mice treated with varespladib (A-002) +/- pravastatin





Shaposhnik et al. *J Lipid Res*, 2009, 50: 623–629.

Effects of 1-H-indole-3-glyoxamide (A-002, (Varespladib, Anthera Pharmaceuticals) on concentration of sPLA2 (PLASMA study): a phase II double-blind, randomised, placebo-controlled trial

393 patients randomly assigned received placebo (n=79) or the sPLA2 inhibitor, A-002: 50 mg (n=79), 100 mg (n=80), 250 mg (n=78), or 500 mg (n=77) twice daily, for 8 weeks.

Primary endpoint:
change in sPLA2 IIA concentration or activity from baseline to week 8

Results: Dose dependent reduction in sPLA2-IIA concentration in the A-002 groups (from 69±2% in the 50 mg group to 95 ± 8% in the 500 mg group), significantly different from placebo ($p<0.0001$)

Rosenson et al. Lancet, Vol 373 February 21, 2009

VISTA-16 Trial: Evaluation of Safety and Efficacy of Short-term A-002 Treatment in Subjects With Acute Coronary Syndrome

This study is currently recruiting participants.

Verified January 2012 by Anthera Pharmaceuticals

Study NCT01130246 Information provided by Anthera Pharmaceuticals

Detailed Description

A double-blind randomized parallel group placebo controlled study in subjects presenting with an ACS. Up to 6500 subjects will be randomized to receive either A-002 500 mg once daily (QD) or placebo tablets in addition to atorvastatin QD and standard of care. Treatment will be 16 weeks in duration. The dose of atorvastatin shall be adjusted after 8 weeks if subject's LDL-C is ≥100 mg/dL, but otherwise must remain stable throughout the16-week duration of study. The survival status for all enrolled subjects will be ascertained 6 months after they complete the study.

Randomization must occur within ≤96 hours of hospitalization for the index ACS event, or if already hospitalized, within ≤96 hours of index event diagnosis. Follow-up visits will occur on Weeks 1, 2, 4, 8, and 16. A 6 month follow-up visit will also occur.

The primary objective of the study is to determine whether 16 weeks of treatment with A-002 plus atorvastatin and standard of care is superior to placebo plus atorvastatin and standard of care for reducing the hazard of the first occurrence of the combined endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or documented unstable angina with objective evidence of ischemia requiring hospitalization.

LEUKOTRIENE MODIFIERS AS POTENTIAL THERAPEUTICS FOR CARDIOVASCULAR DISEASE

NATURE REVIEWS | DRUG DISCOVERY

Colin D. Funk

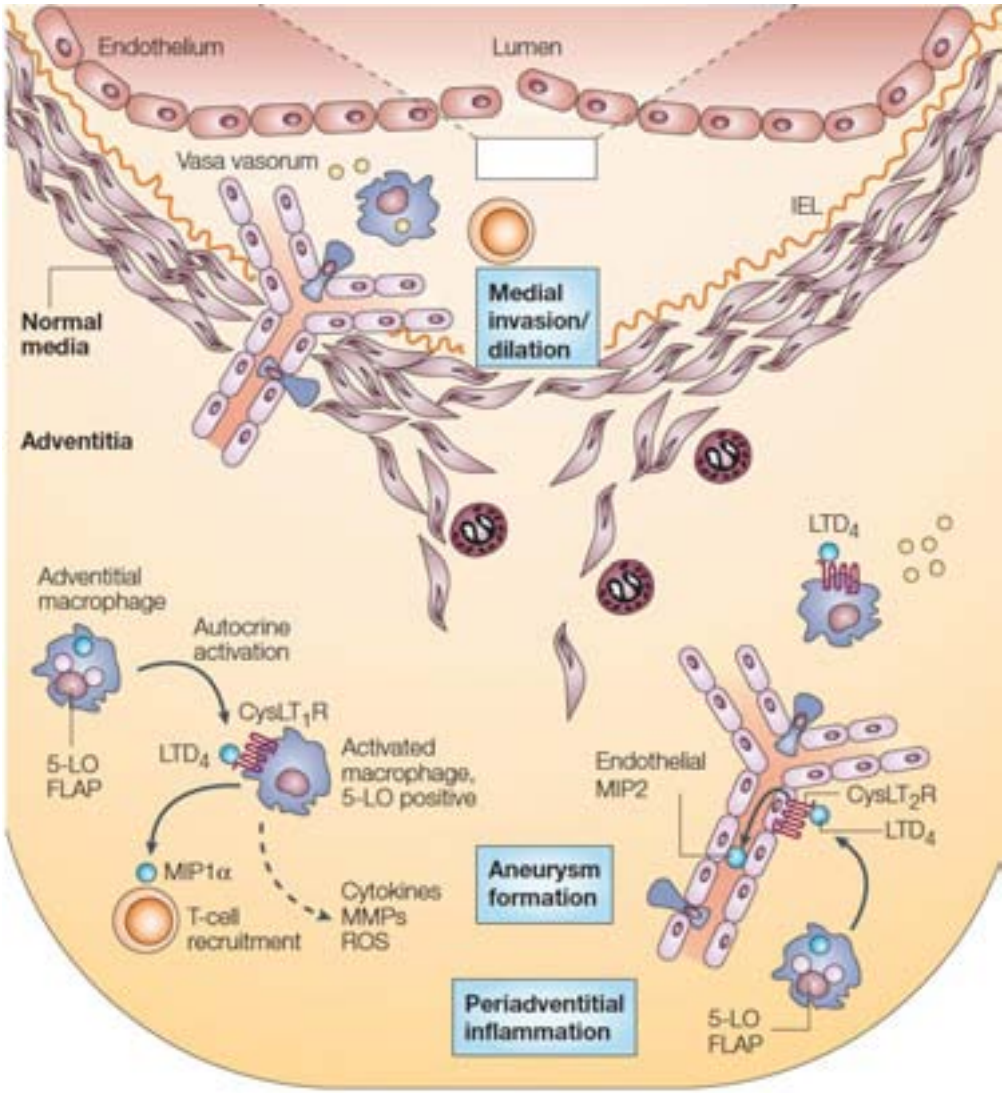
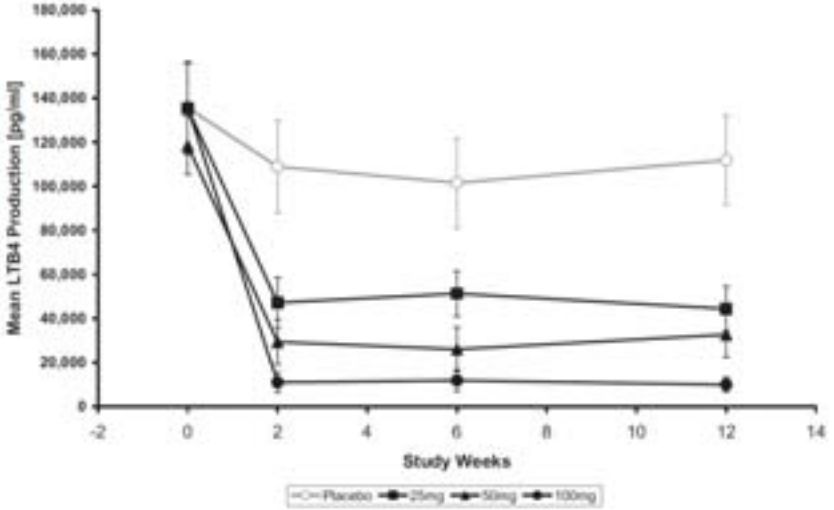


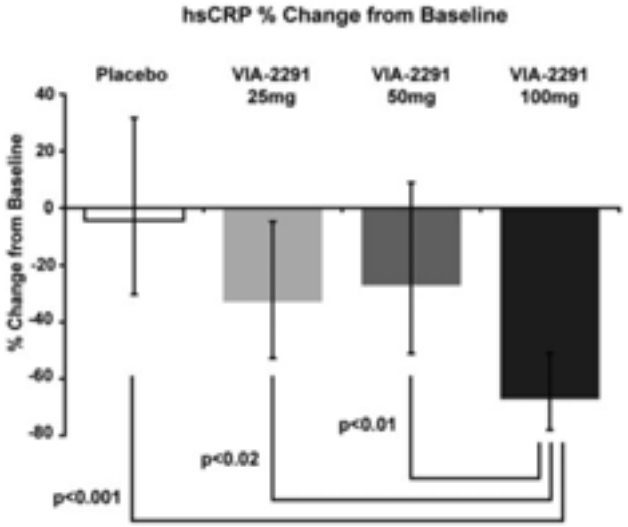
Table 2 | **Genetics of 5-lipoxygenase/leukotriene pathway and CVD**

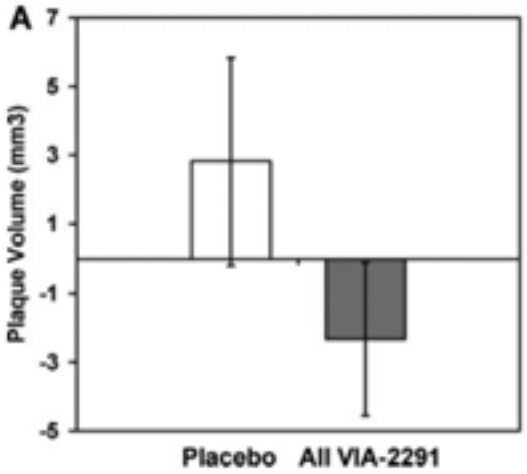
Genotype/ haplotype	Population (size)	Endpoint	*p* value	RR/ OR	Reference
Add/del allele 5-LO promoter (*ALOX5*)	USA (Los Angeles; 470	Carotid intima-media thickness	<0.001	3.7	36
HapA *ALOX5AP*	Iceland (779)	Myocardial infarction, stroke	<0.0001	1.6–1.80	37
HapA *ALOX5AP*	Scotland (450)	Ischaemic stroke	0.007	1.36	93
HapA *ALOX5AP*	Germany (639)	Stroke	NS	–	94
HapB *ALOX5AP*	United Kingdom (753)	Myocardial infarction	<0.005	1.95	37
HapB *ALOX5AP*	Scotland (450)	Ischaemic stroke	NS	1.20	93
HapB *ALOX5AP*	Germany (639)	Stroke	NS	–	94
SG13S114 SNP *ALOX5AP*	Germany (639)	Stroke	0.017	1.24	94
SG13S100 SNP *ALOX5AP*	Germany (639)	Stroke	0.024	1.26	94

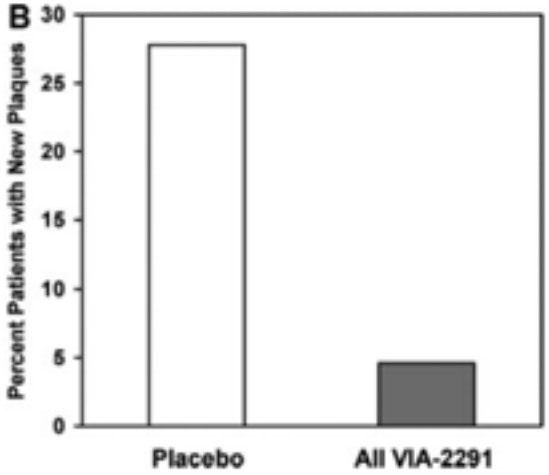
Treatment With 5-Lipoxygenase Inhibitor VIA-2291 (Atreleuton) in Patients With Recent Acute Coronary Syndrome

Jean-Claude Tardif, MD; Philippe L. L'Allier, MD; Reda Ibrahim, MD; Jean C. Grégoire, MD; Anna Nozza, MSc; Mariève Cossette, MSc; Simon Kouz, MD; Marc-André Lavoie, MD; Janie Paquin, RT; Tilmann M. Brotz, PhD; Rebecca Taub, MD; Josephine Pressacco, MD, PhD





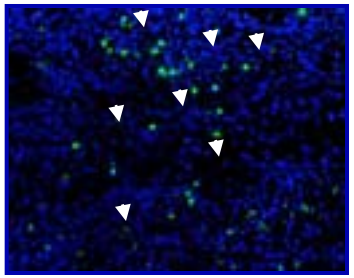




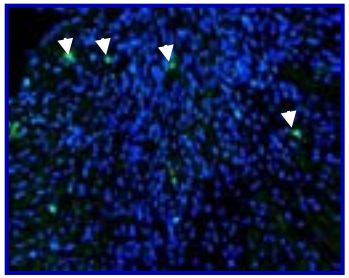
B lymphocyte depletion limits adverse LV remodelling

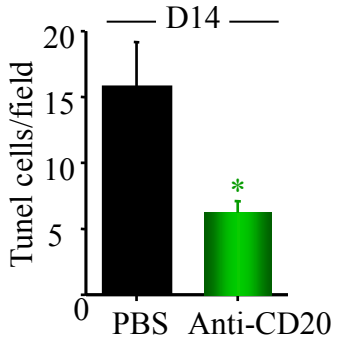
➢ ***Apoptotic cells number (Tunel)***

PBS



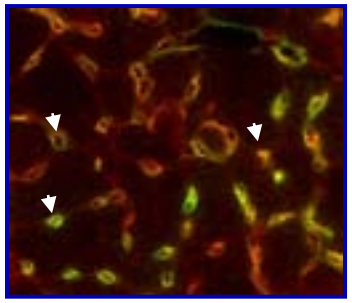
Anti-CD20



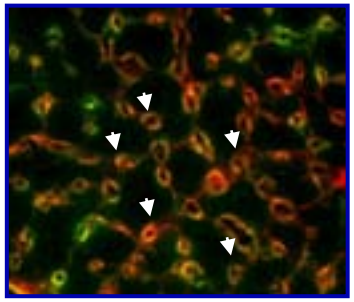


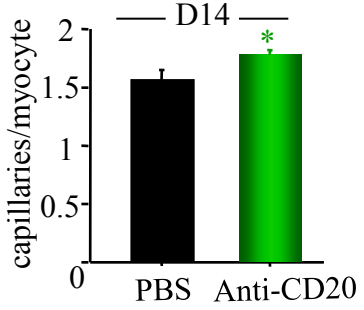
➢ ***Capillary Density (BS1 lectin, WGA)***

PBS



Anti-CD20

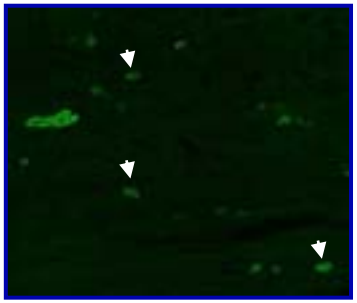


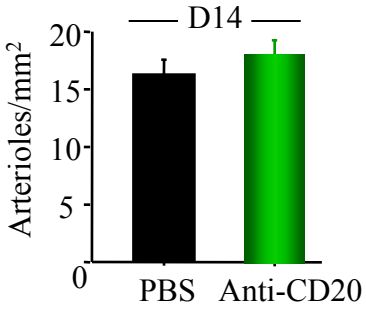


➢ ***Arteriolar Density (α-actin)***

PBS

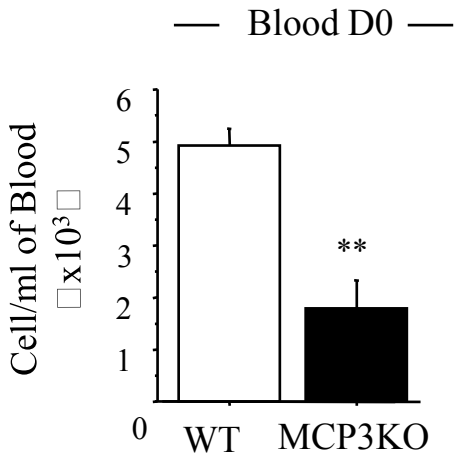
Anti-CD20

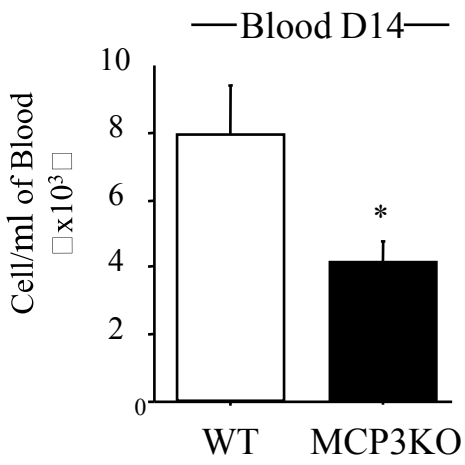


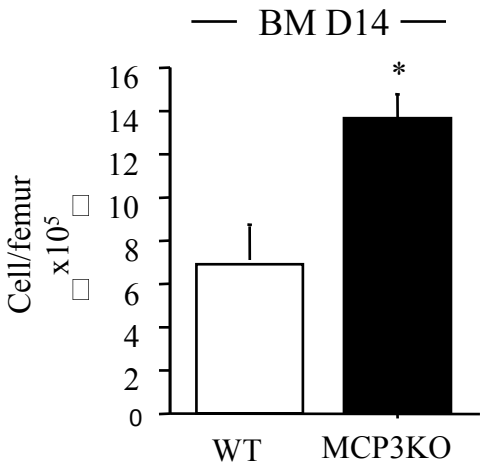


MCP-3 deficiency preserves LV function after acute MI

Monocytes 7/4^{HI}







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➢ ***Shortening Fraction***