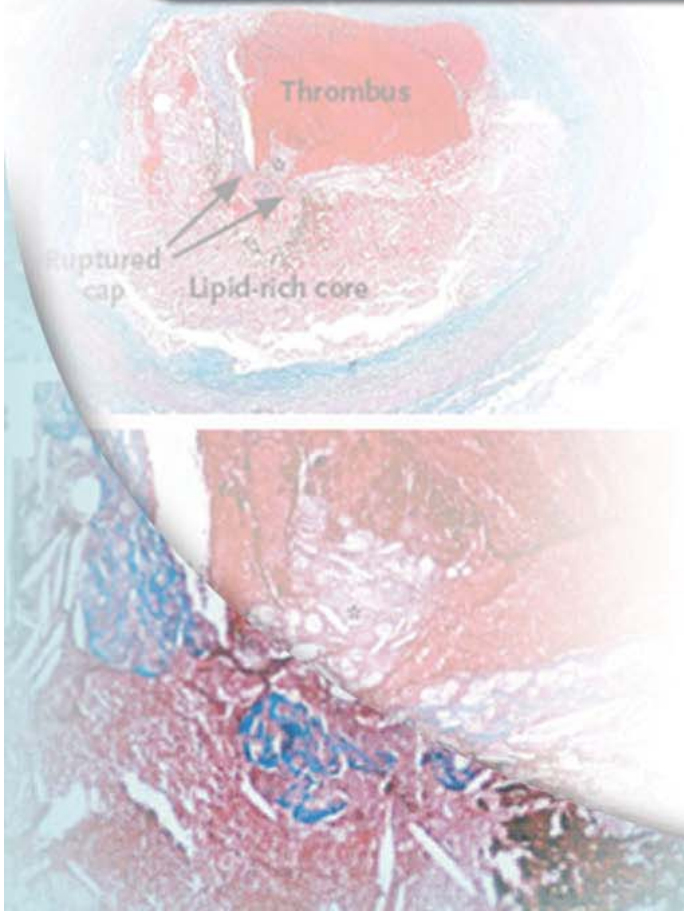
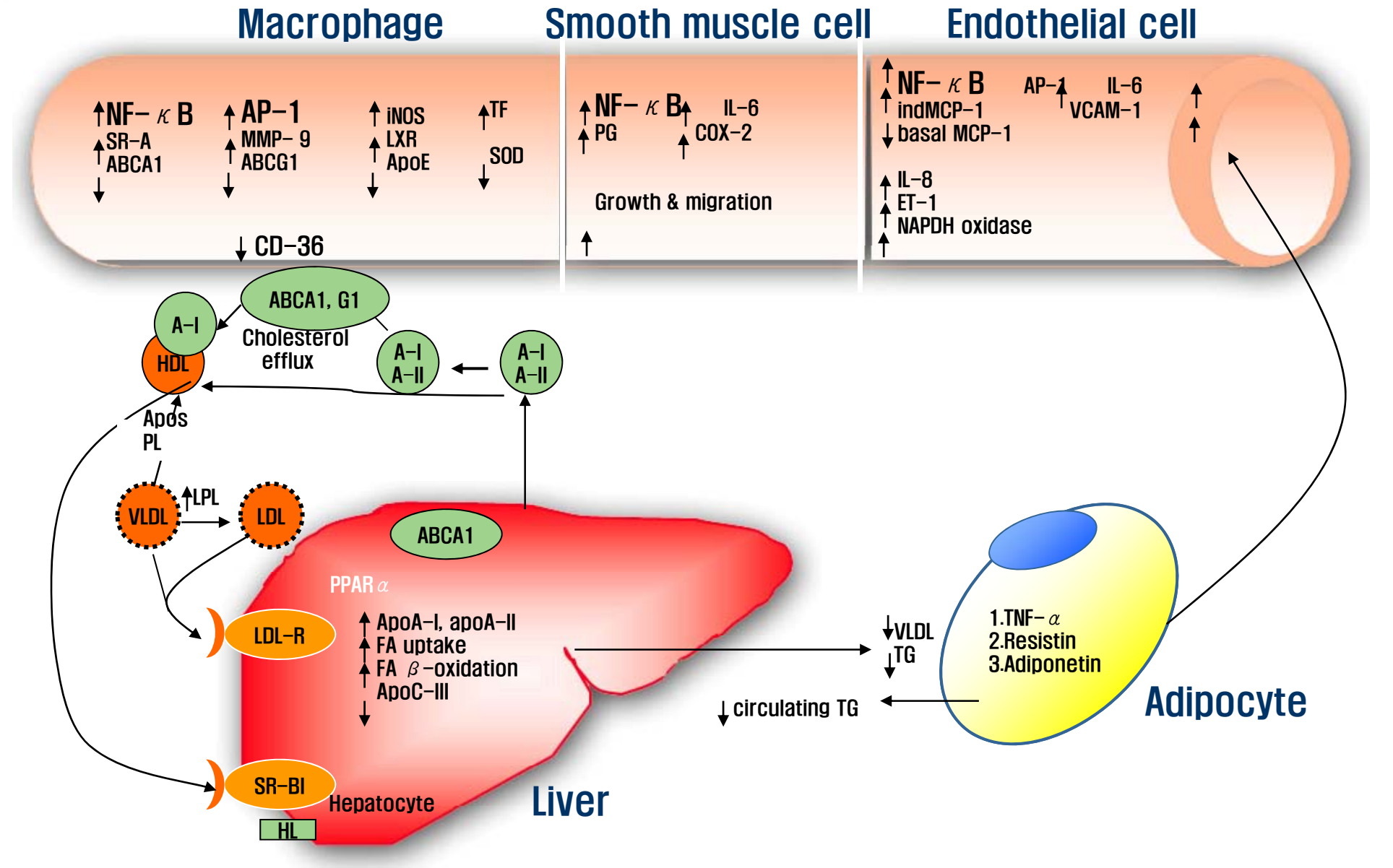
CD137(4-1BB), a TNF Receptor Superfamily, Deficiency Reduces Atherosclerosis in Hyperlipidemic Mice

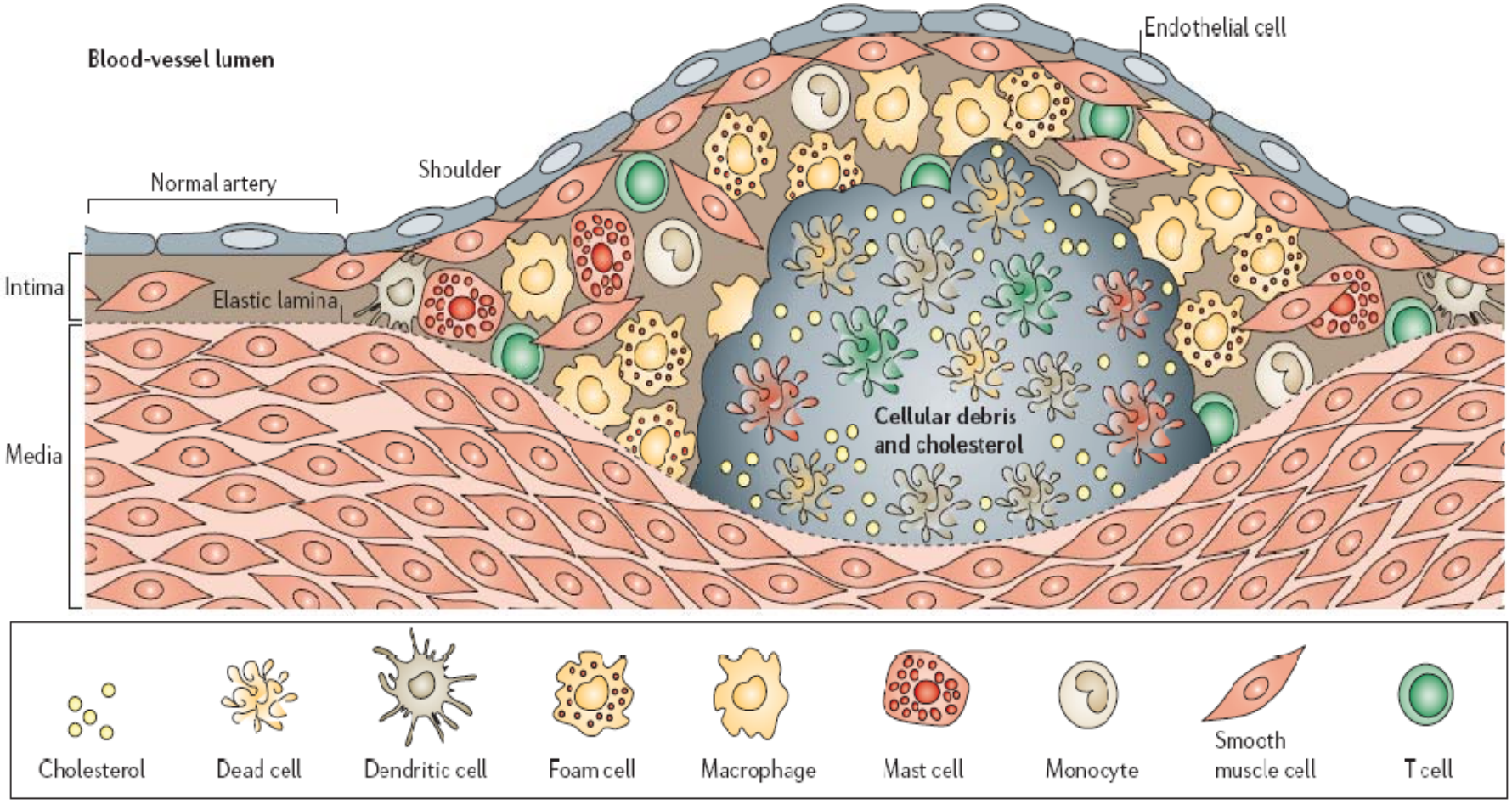


Goo Taeg Oh, DVM., PhD
Laboratory of Cardiovascular Genomics
Division of Molecular Life Sciences
Ewha Womans University
gootaeg@ewha.ac.kr

Atherosclerosis is a Systemic Inflammatory Disease

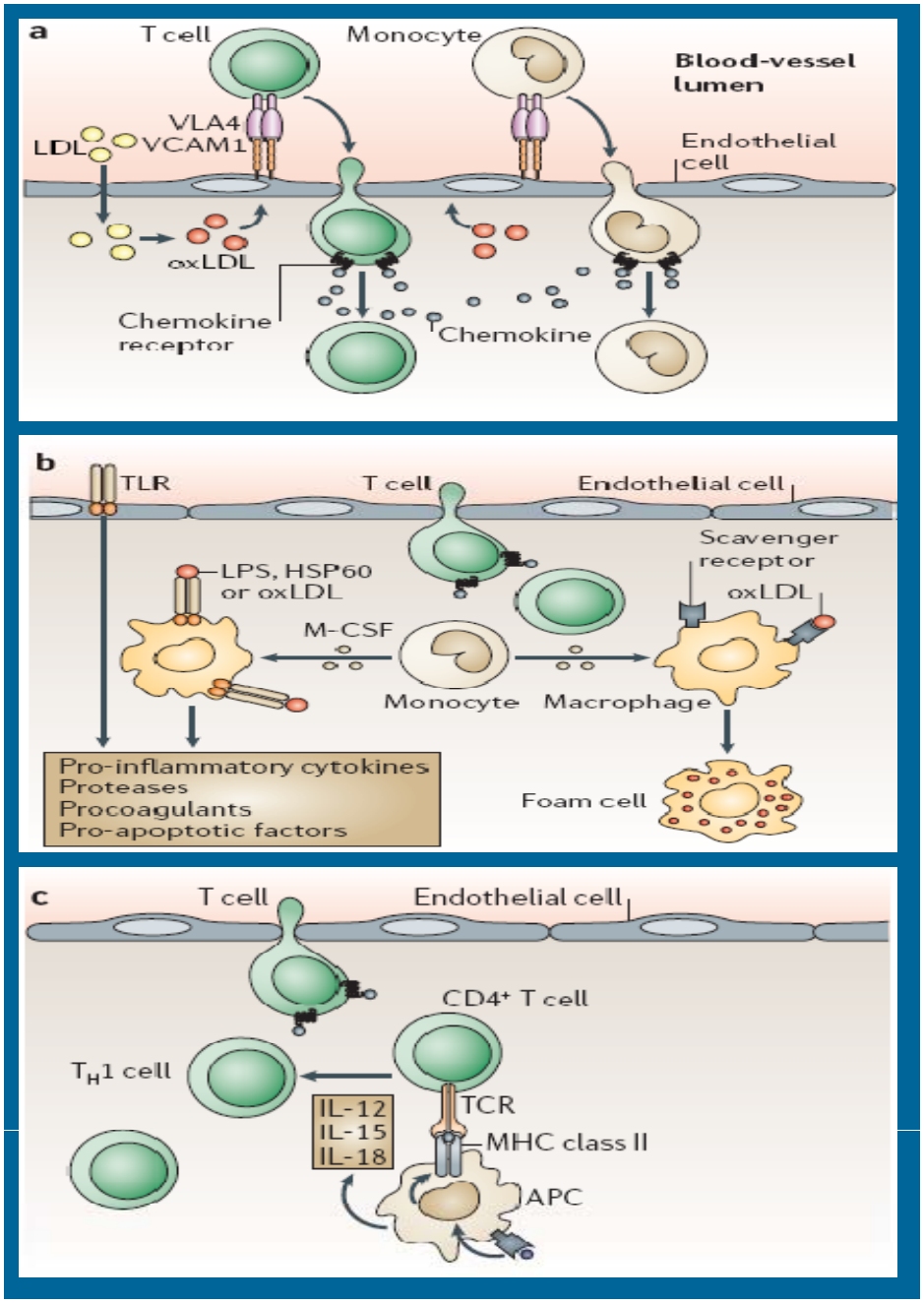


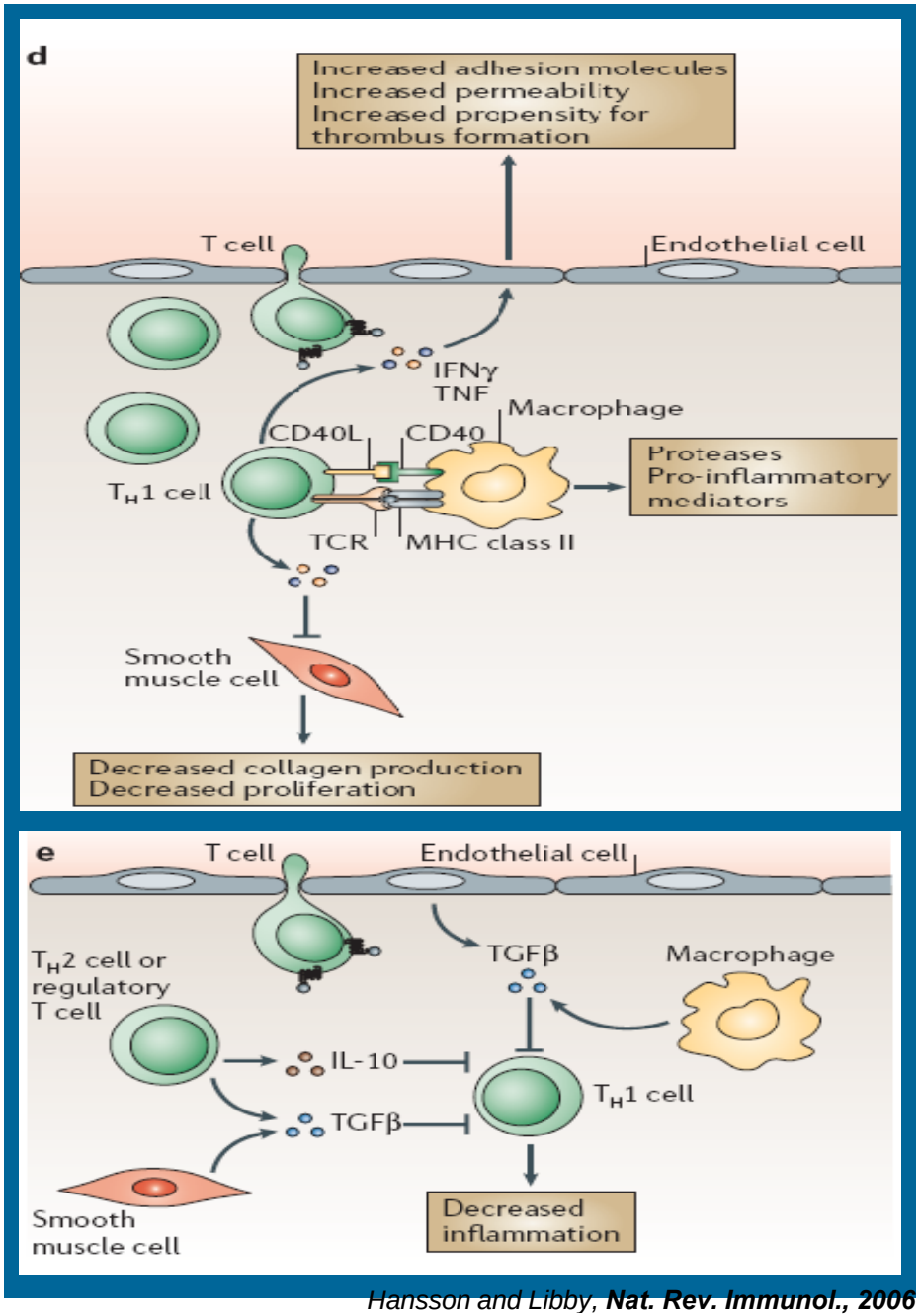
Cellular Composition of Atherosclerotic Plaque



Hansson and Libby, ***Nat. Rev. Immunol., 2006***

Recruitment and Activation of Immune Cells in Atherosclerotic Plaques

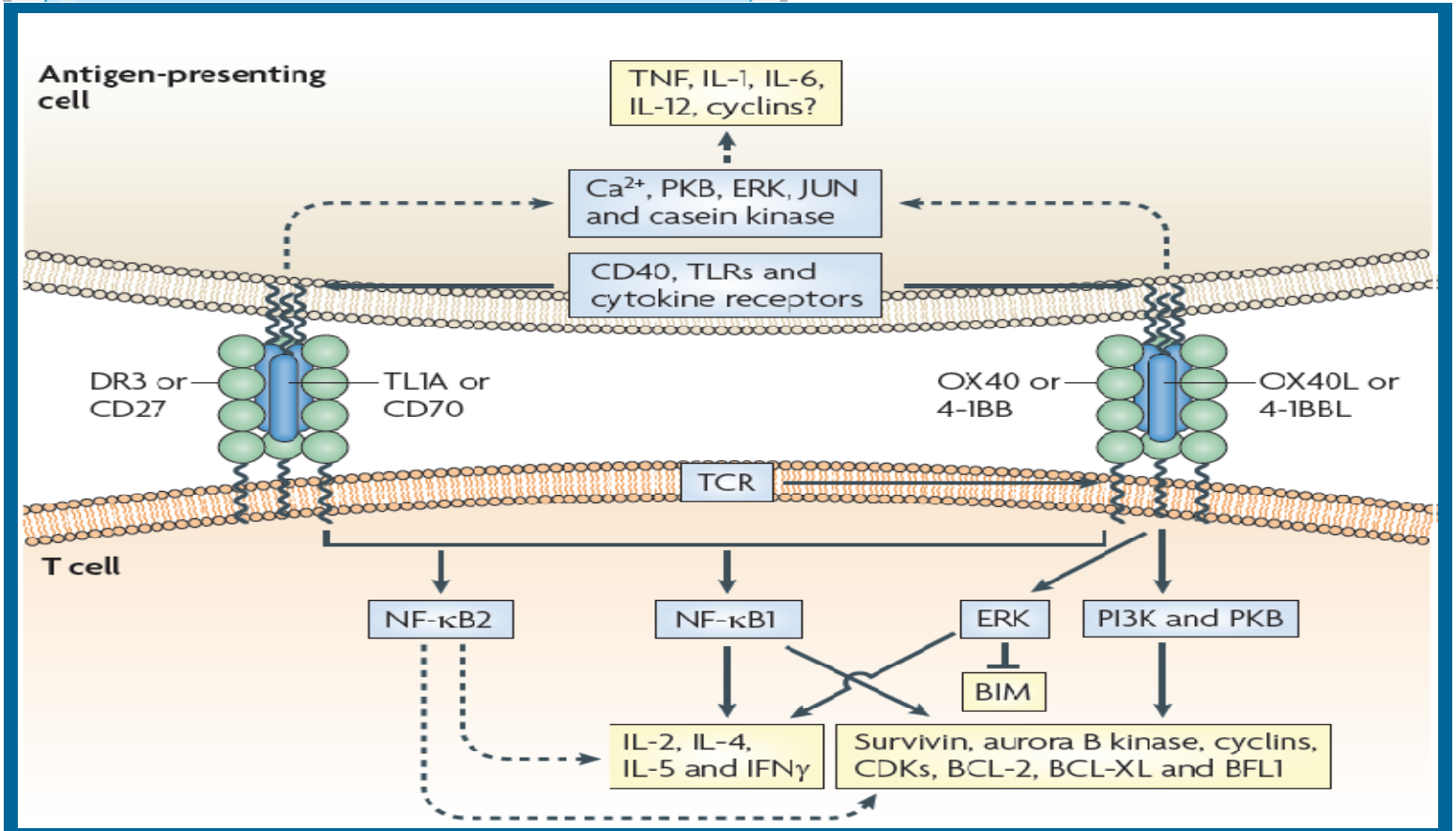




Hansson and Libby, ***Nat. Rev. Immunol., 2006***

T cell Mediated Immune Response in Atherosclerosis

Co-stimulatory Molecules on T-cell

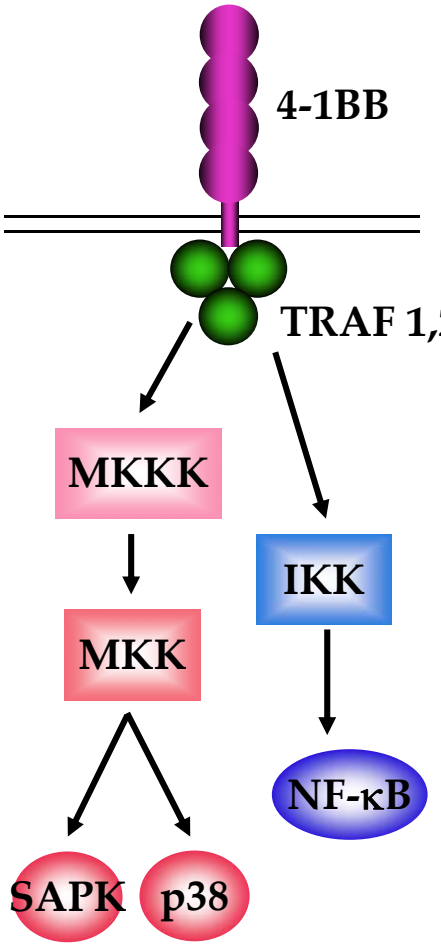


1. Reduction of atherosclerosis in mice by inhibition of CD40 signaling.
Nature 1998; 394:200–203.

2. Requirement for CD154(CD40L) in the progression of atherosclerosis.
Nat Med 1999; 5:1313–1316.

M.Croft, Nature. Rev. Immunol., 2009

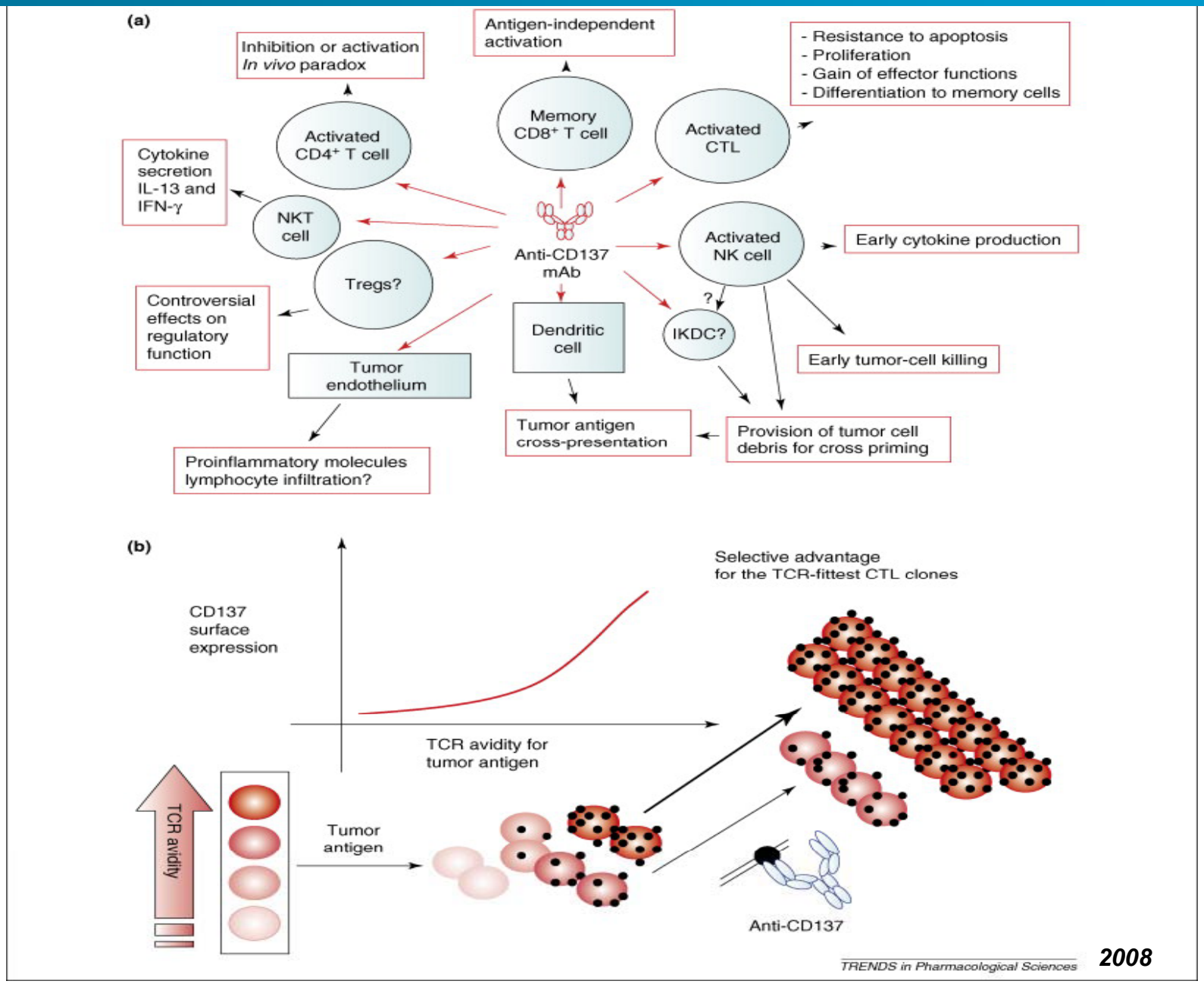
4-1BB (CD137) on T cell Surface



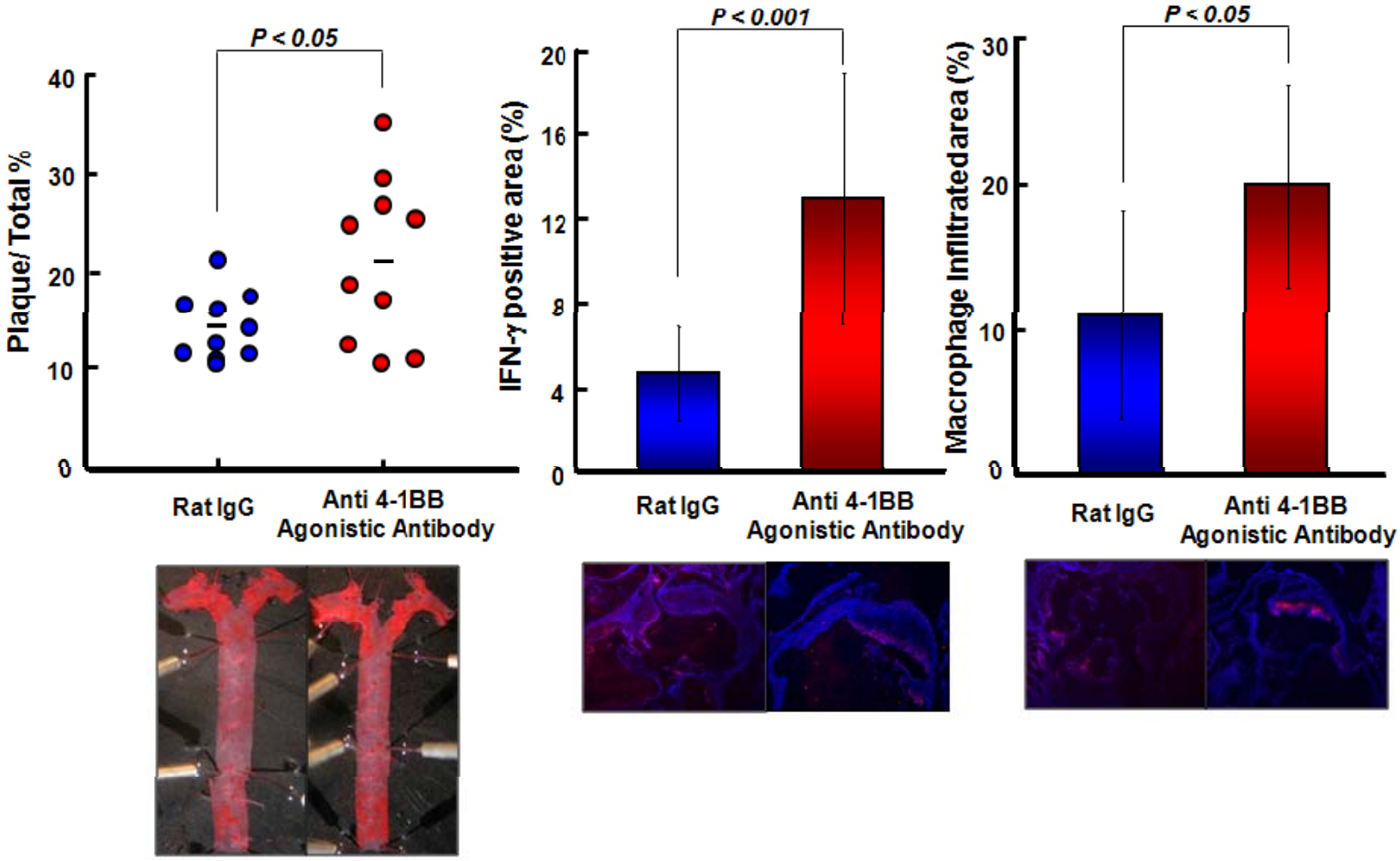
- **A positive costimulatory role for 4-1BB on CD4 T cells.**
  - The 4-1BBL augmented primary responses of CD4 T cells in the absence of CD28 signaling, and 4-1BB agonistic Ab enhanced CD4 T cell responses *in vitro* and *in vivo*.
- In contrast, it has been reported that 4-1BB ligation has either no specific role or even a negative role in regulating CD4 T cells.
  - 4-1BBL-/- mice generated normal CD4 T cell responses after lymphocytic choriomeningitis virus and influenza infection, although CD8 T cell responses were down-regulated in those mice.
- In addition, 4-1BB agonistic Ab treatment unexpectedly led to suppressed pathogenic CD4 T cell responses in several autoimmune disease models, including experimental autoimmune encephalomyelitis, lupus, and collagen-induced arthritis.

Therefore, 4-1BB may be involved in atherogenesis through its modulatory effect on T cell activation.

The Strong Preclinical Potency of anti-CD137 Treatment



Effect of *4-1bb* Agonistic Antibody on Atherosclerotic Plaque Formation in *Ldlr* Knock-Out Mice



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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CD137 Is Expressed in Human Atherosclerosis and Promotes Development of Plaque Inflammation in Hypercholesterolemic Mice

Peder S. Olofsson, Leif Å. Söderström, Dick Wågsäter, Yuri Sheikine, Pauline Ocaya, François Lang, Catherine Rabu, Lieping Chen, Mats Rudling, Pål Aukrust, Ulf Hedin, Gabrielle Paulsson-Berne, Allan Sirsjö and Göran K. Hansson

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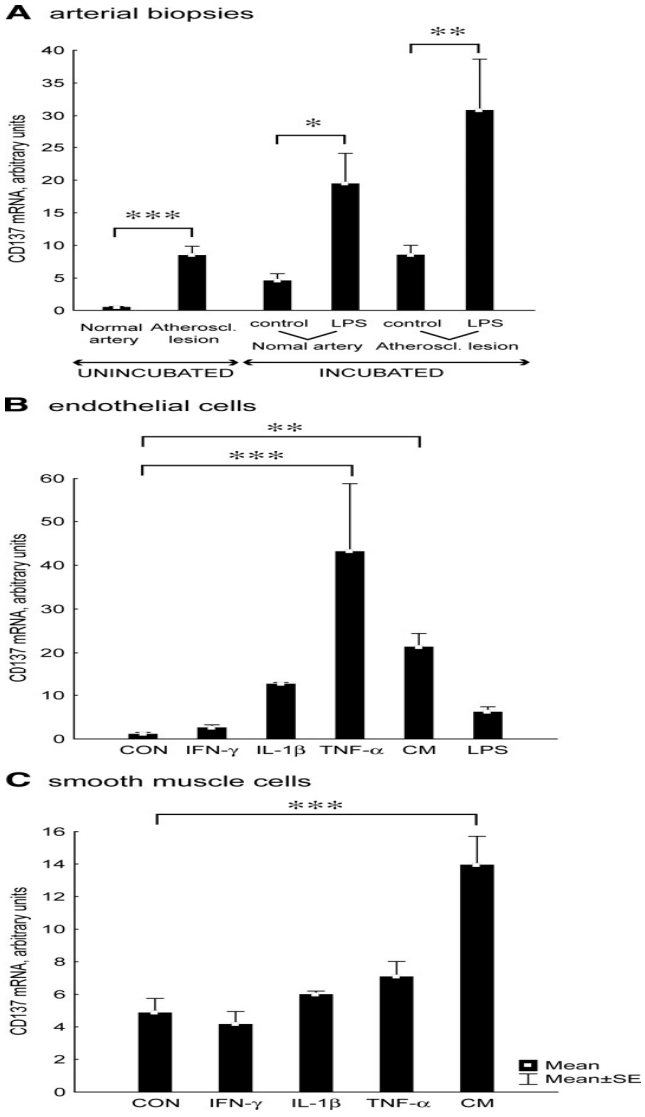
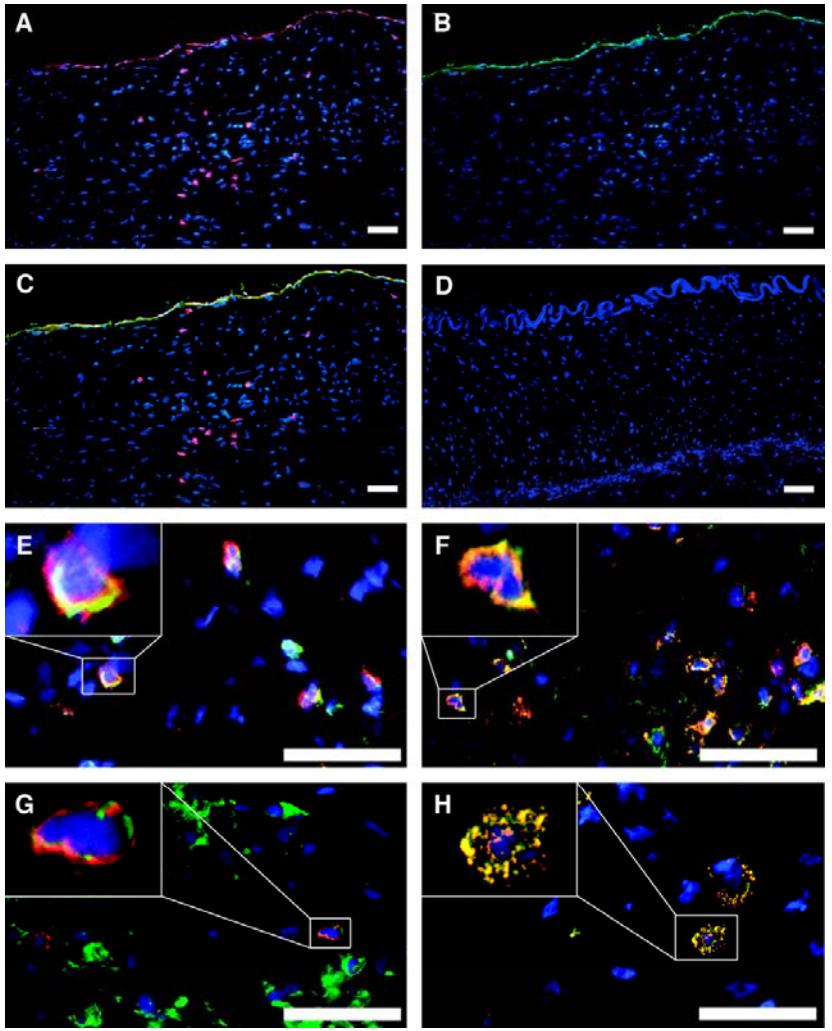
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

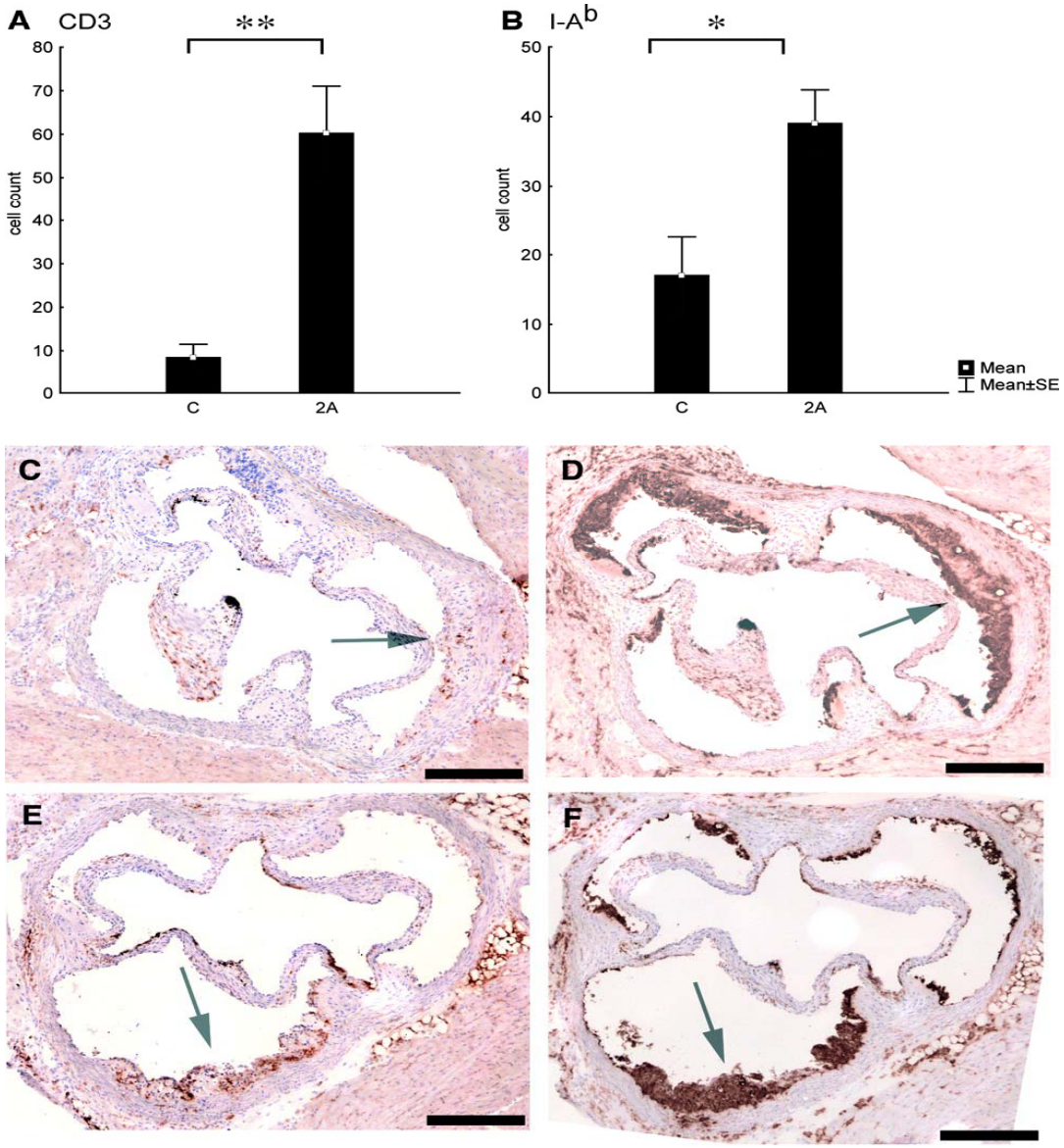
Expression of CD137 on Human Atherosclerosis





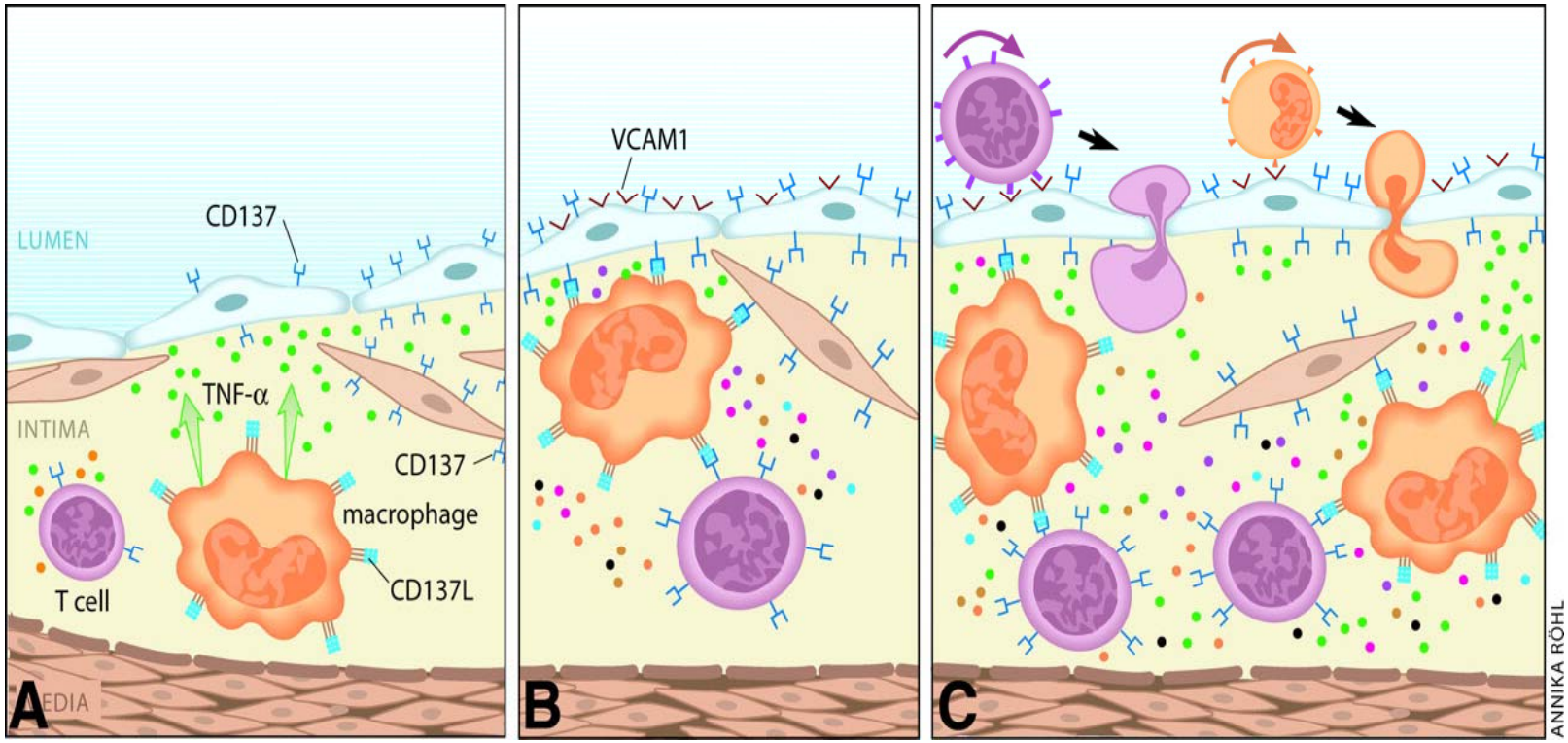
Olofsson, P. S. et al. ***Circulation 2008;117:1292-1301***

CD3 and I-Ab immunostaining in atherosclerotic lesions of Apoe-/- mice



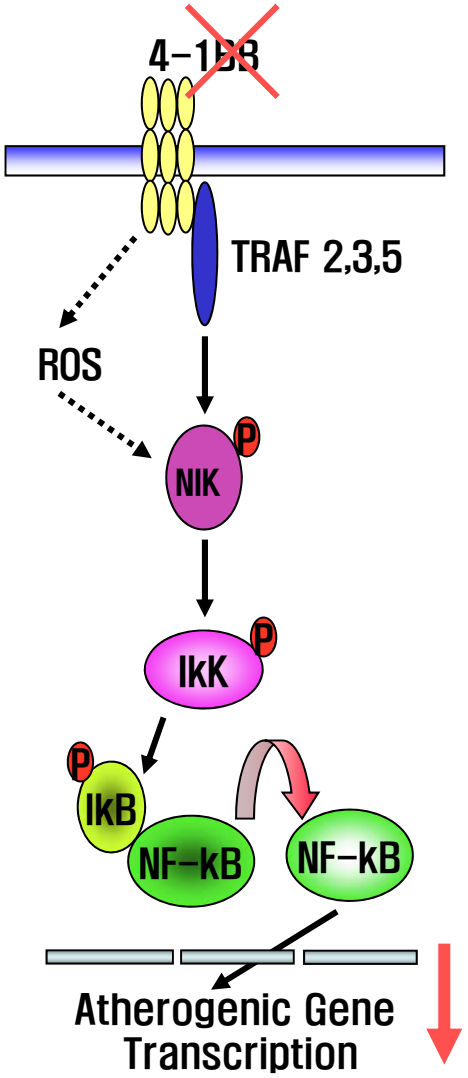
Olofsson, P. S. et al. ***Circulation 2008;117:1292-1301***

Proposed model for CD137 in atherosclerosis

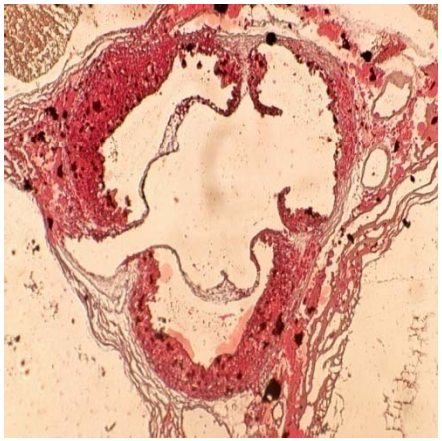


Olofsson, P. S. et al. ***Circulation 2008;117:1292-1301***

Hypothesis



ApoE-/- or Ldlr-/-



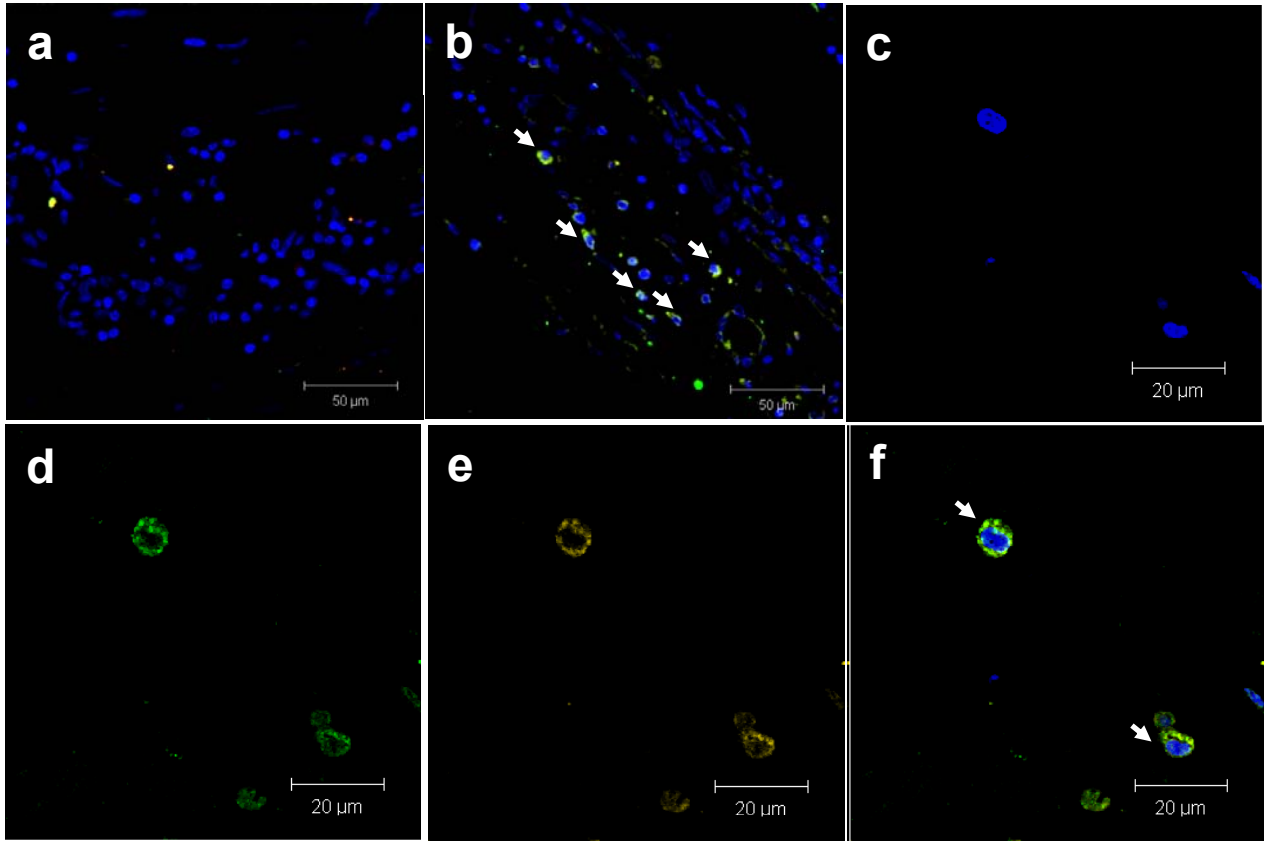
4-1bb-/-

Double Knock-out

Found it !
Removed it !
Proved it !

Find it !

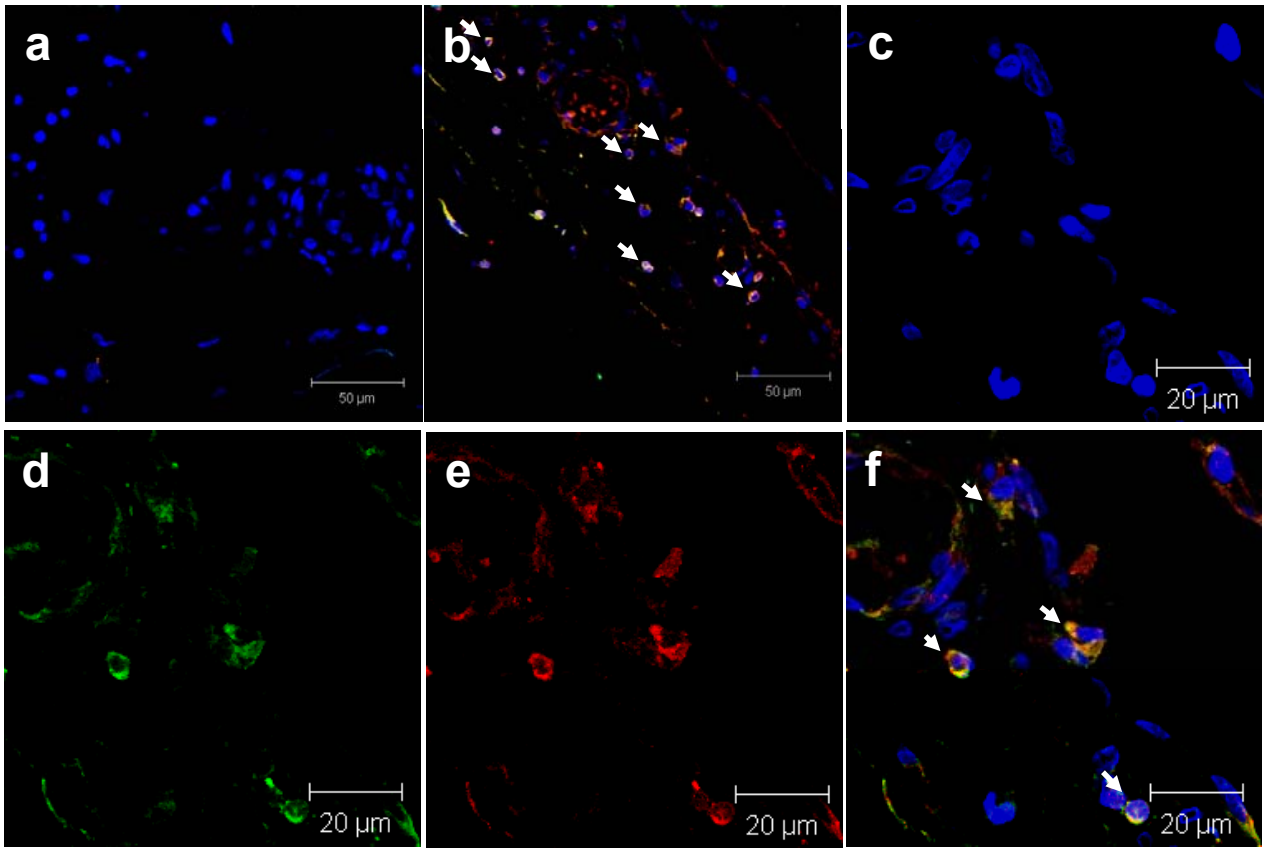
Expression of 4-1BB in infiltrated T cells in human atheroma



4-1BB (green)

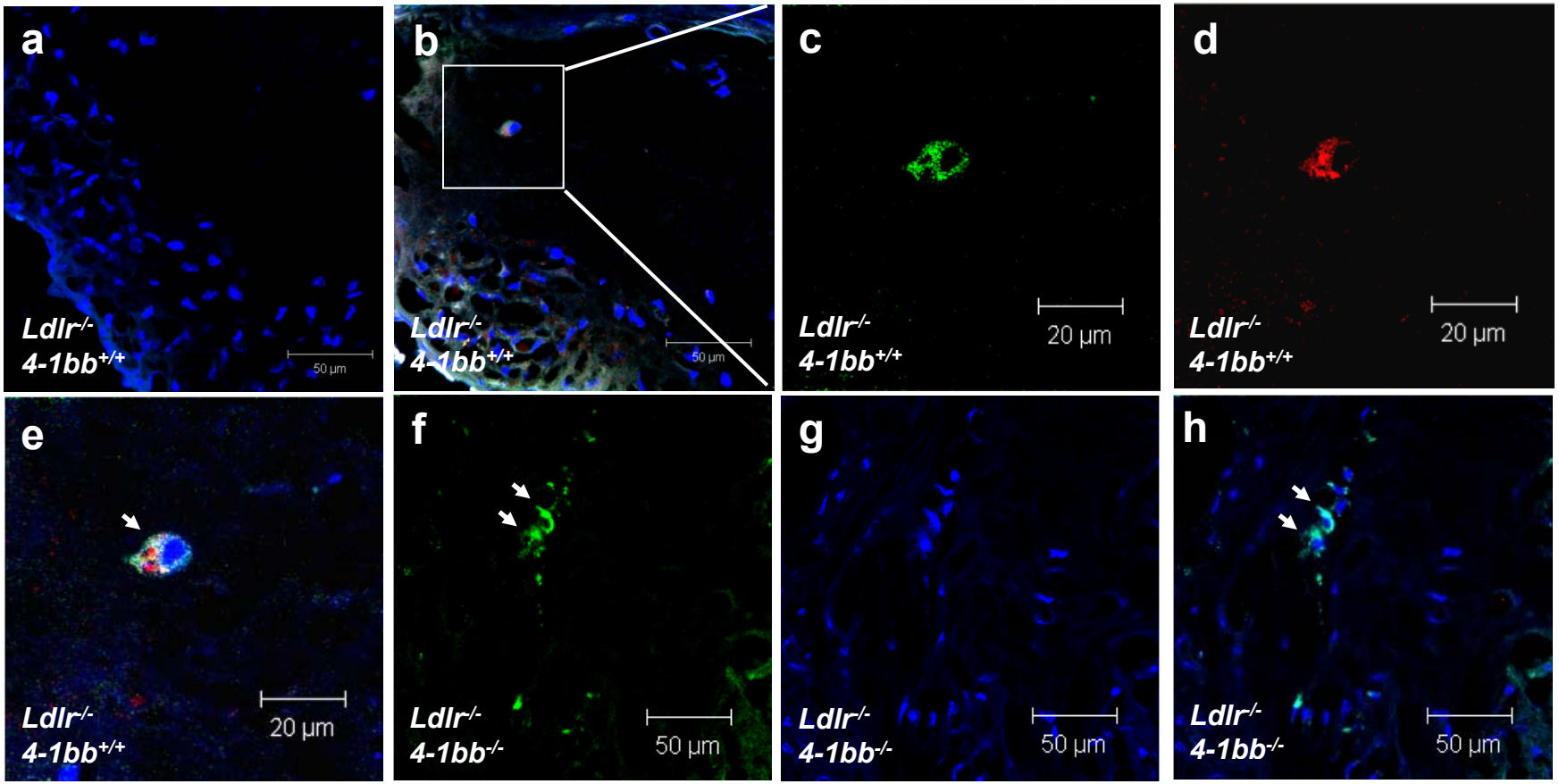
CD3 (yellow)

Expression of 4-1BBL in Infiltrated Monocyte/Macrophage in Human Atheroma



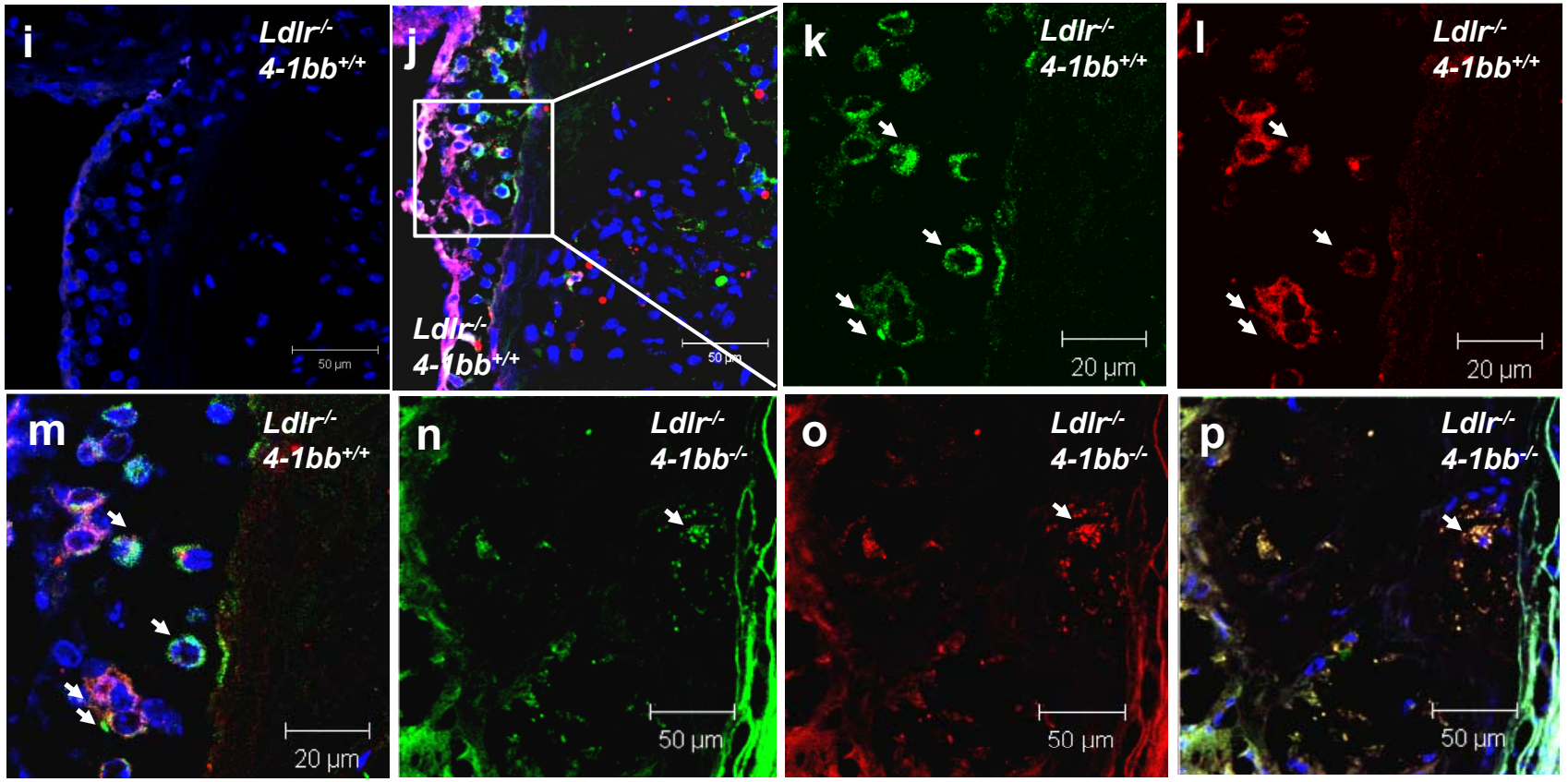
CD68 (green) *4-1BBL (red)*

4-1BB expression of T cells in Mouse Atherosclerotic Lesion



Triple immunostain for nuclei (blue), CD3 (green), 4-1bb (red).

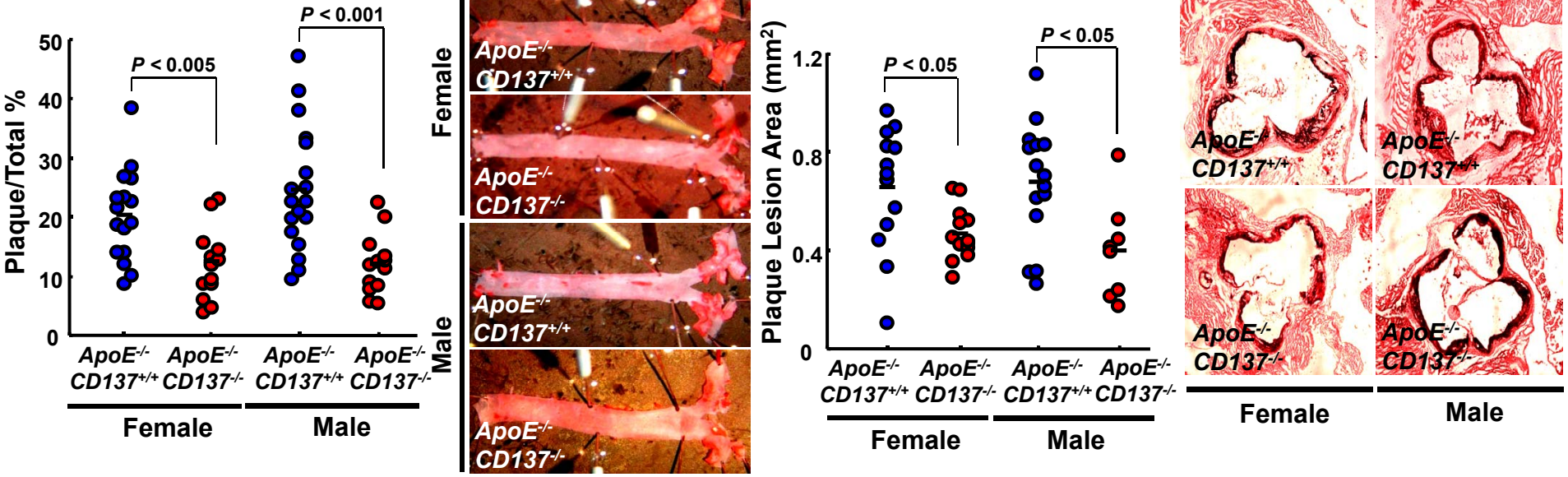
4-1BBL Expression of Macrophages in Mouse Atherosclerotic Lesion



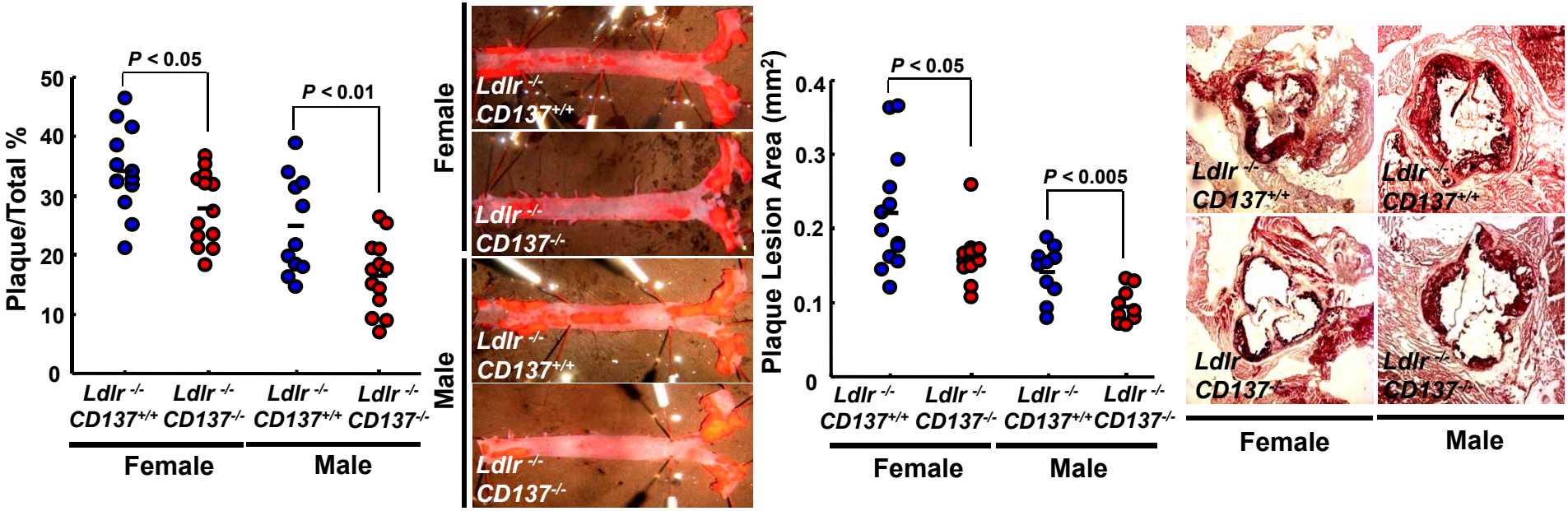
Triple immunostain for nuclei (blue), CD68 (green), 4-1bbl (red)

Remove it !

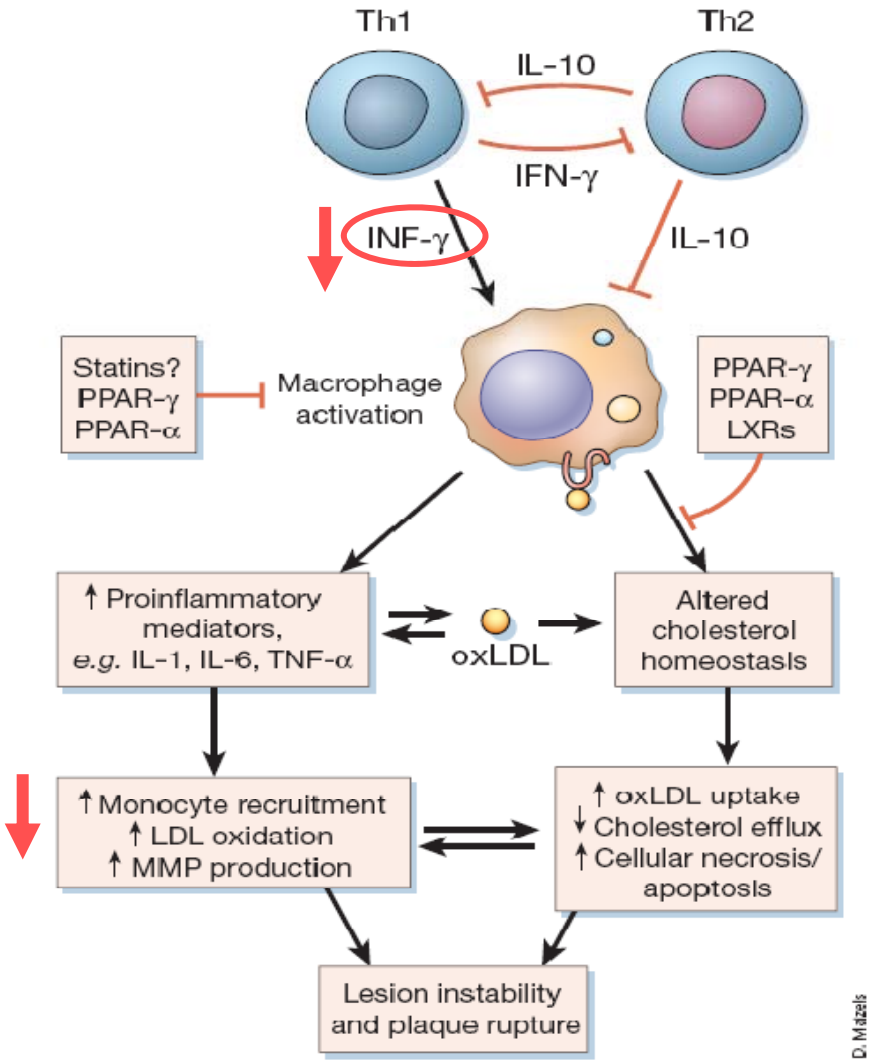
Removal of 4-1BB Reduced Atherosclerosis in Normal Diet *ApoE* Null Mice



Removal of 4-1BB Reduced Atherosclerosis in High Fat Diet *Ldlr* Null Mice

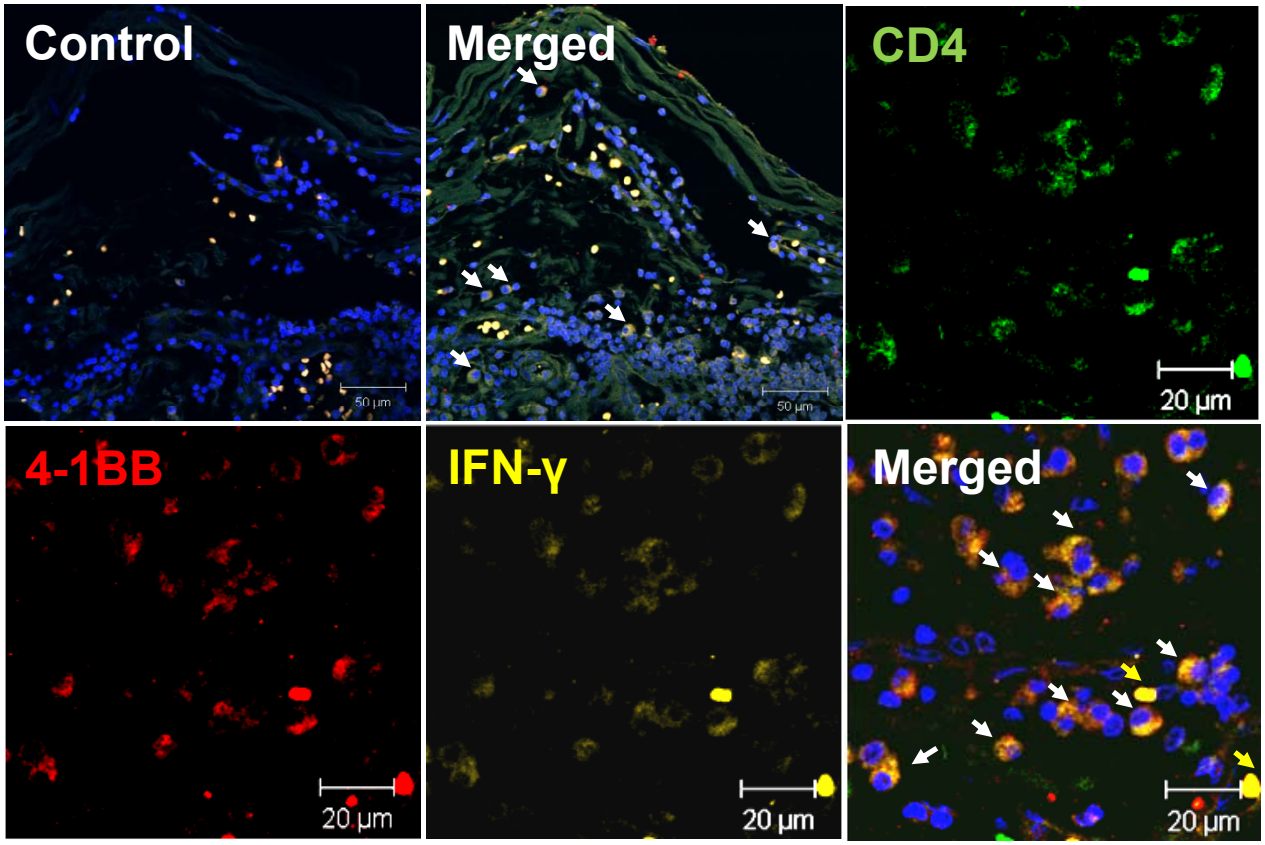


Prove it !

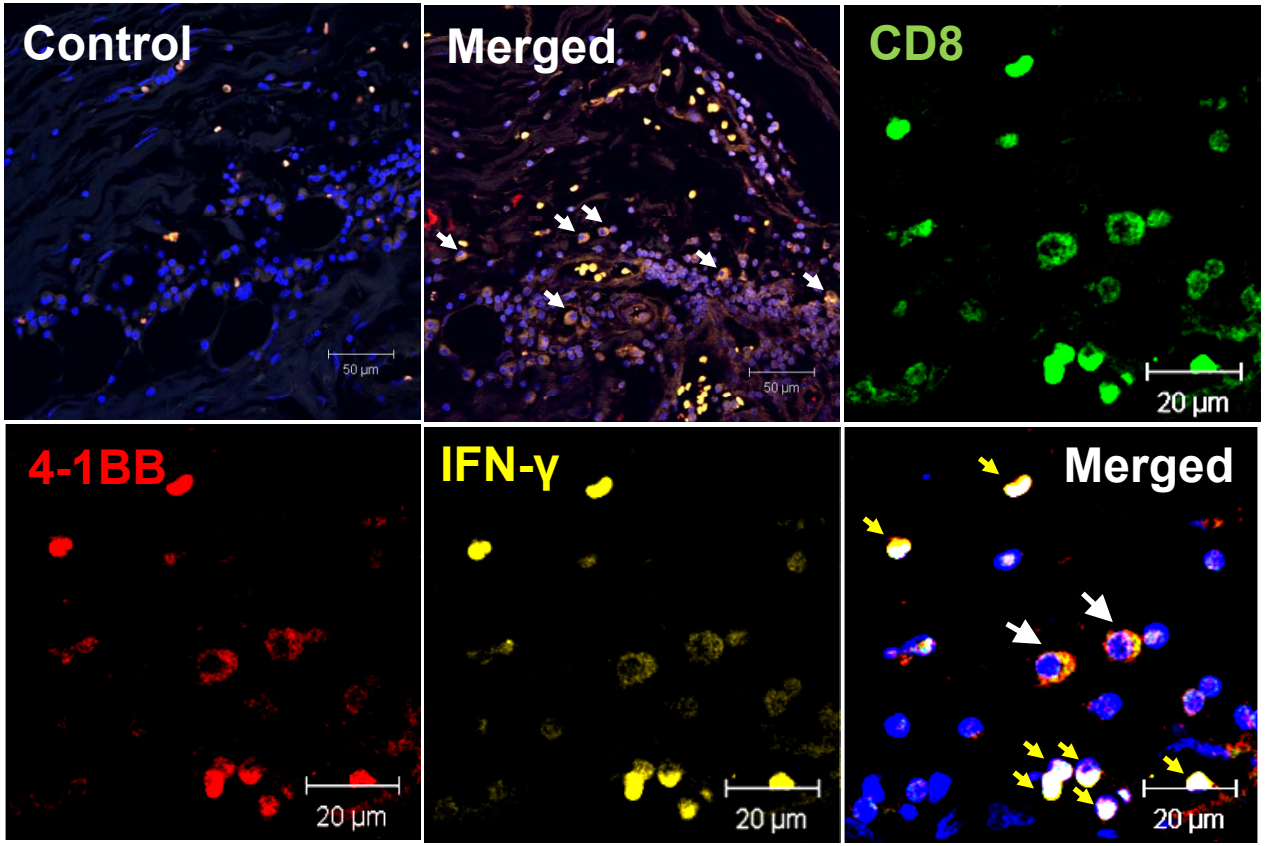


Nat. Med., 2002

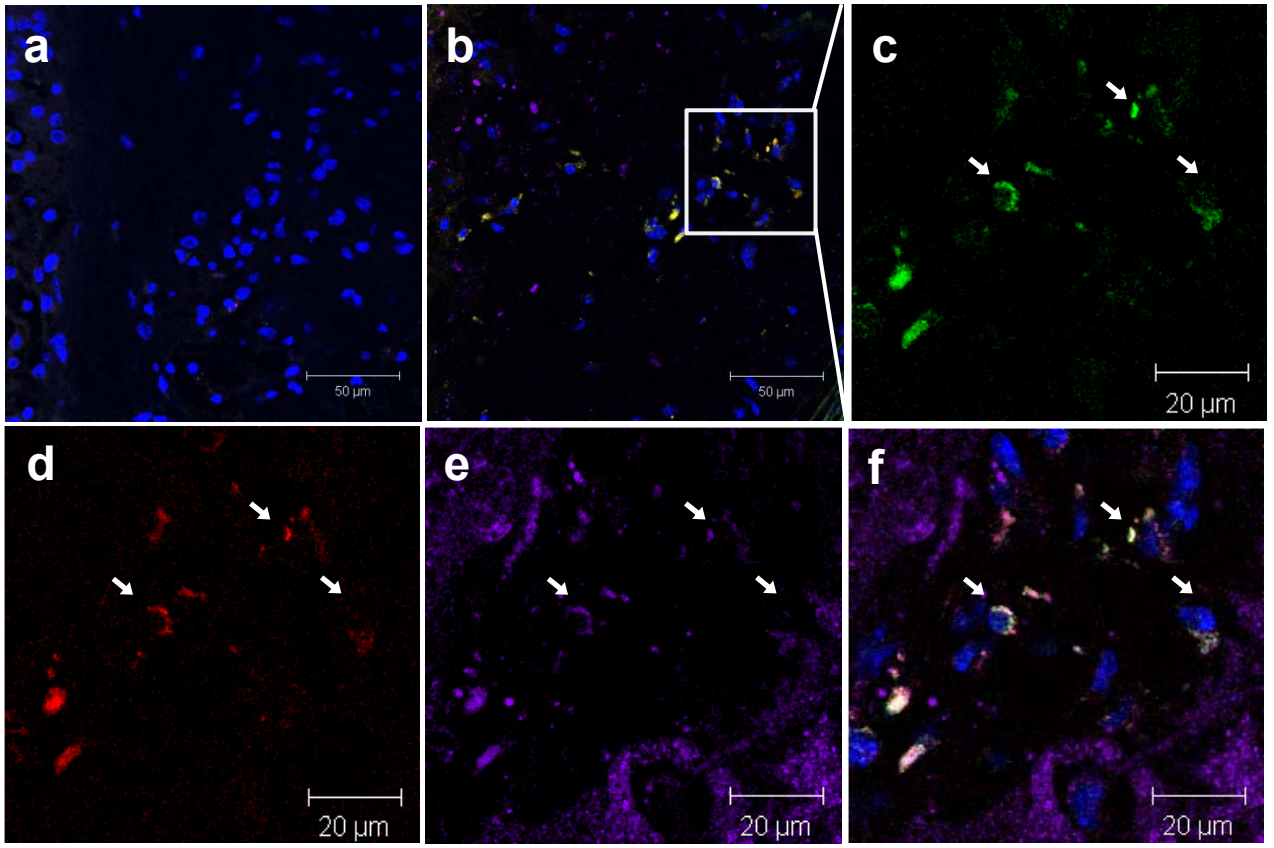
CD4 and IFN-γ Positive T cells are detected in Human Atheroma



CD8 and IFN-γ Positive T cells are Detected in Human Atheroma

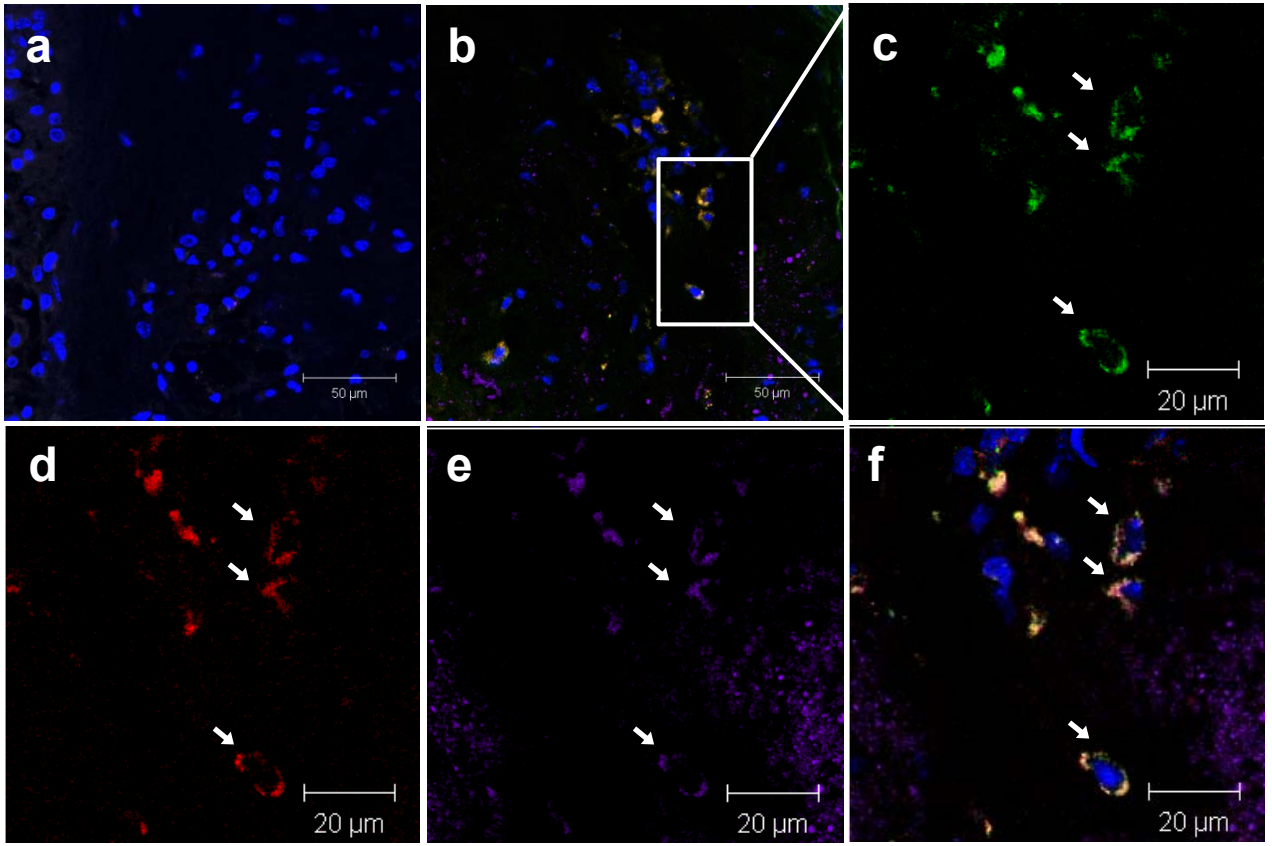


4-1BB expressing CD4^{+} T cells in Mouse Atherosclerotic Lesion Produce Interferon-γ



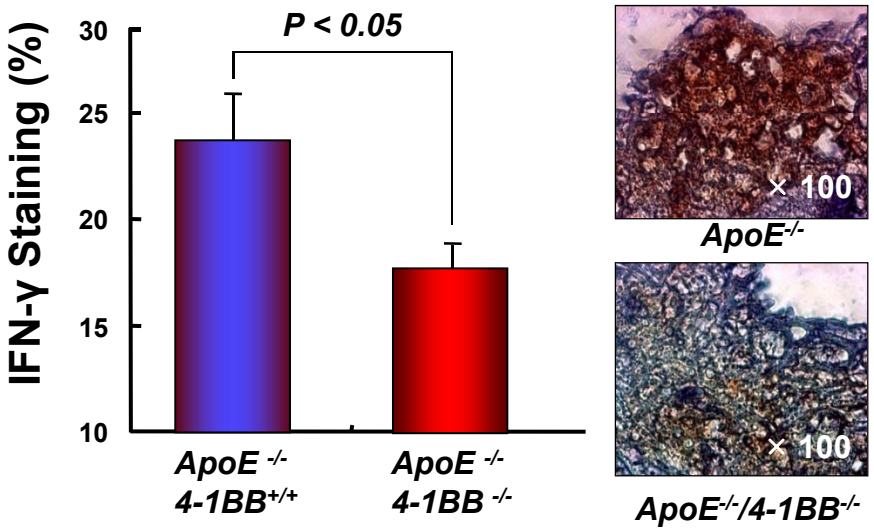
Quadruple immunostain for nuclei (blue), 4-1BB (green), CD4 (red), Interferon-γ (violet).

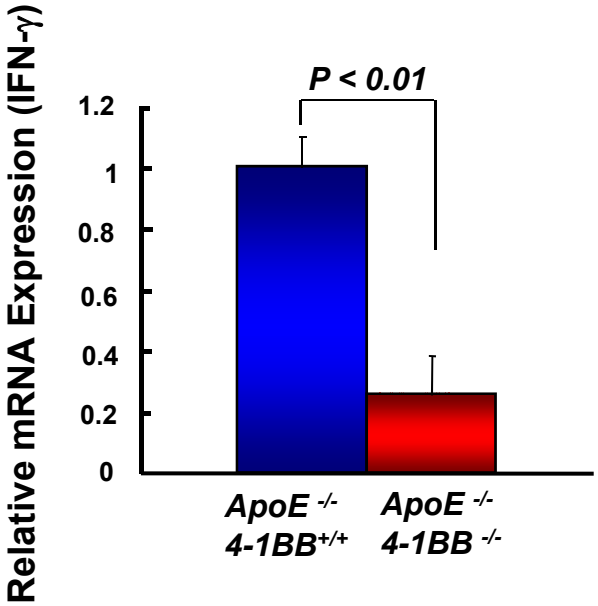
4-1BB Expressing CD8^{+} T cells in Mouse Atherosclerotic Lesion Produce Interferon-γ



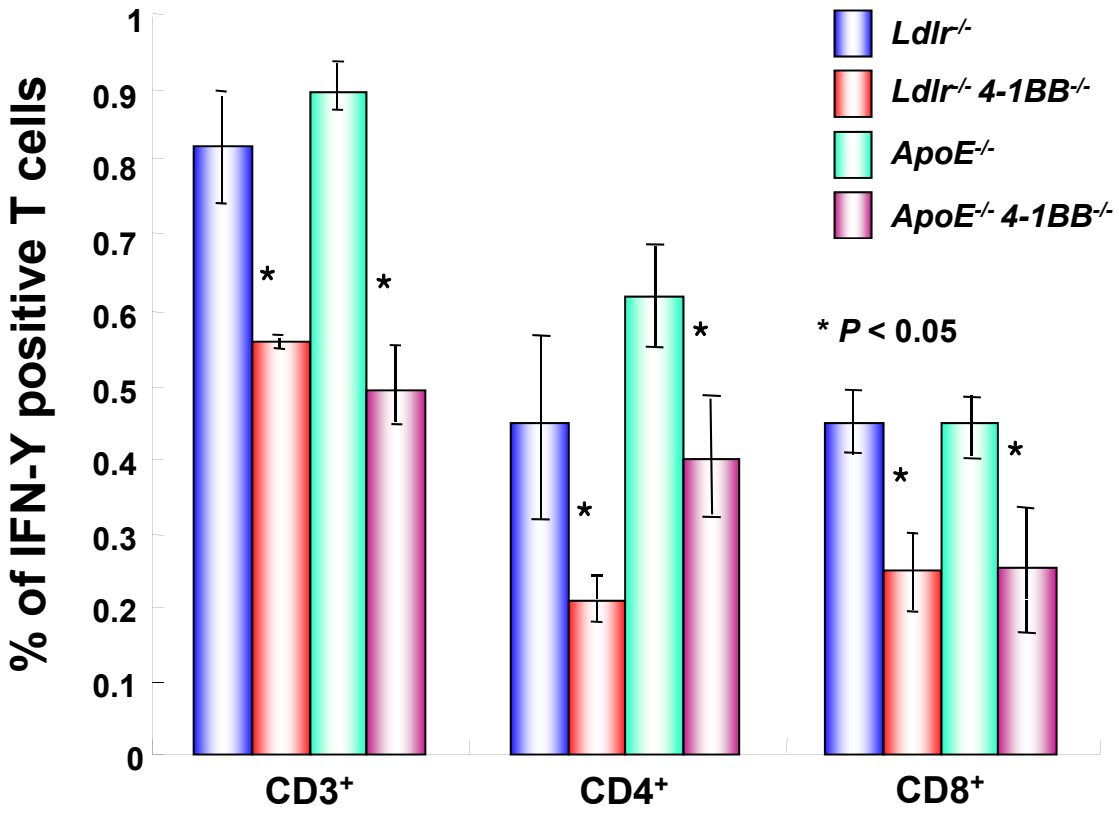
Quadruple immunostain for nuclei (blue), 4-1BB (green), CD8 (red), Interferon-γ (violet).

4-1BB Mediates IFN-γ Production in Atherosclerotic Lesion

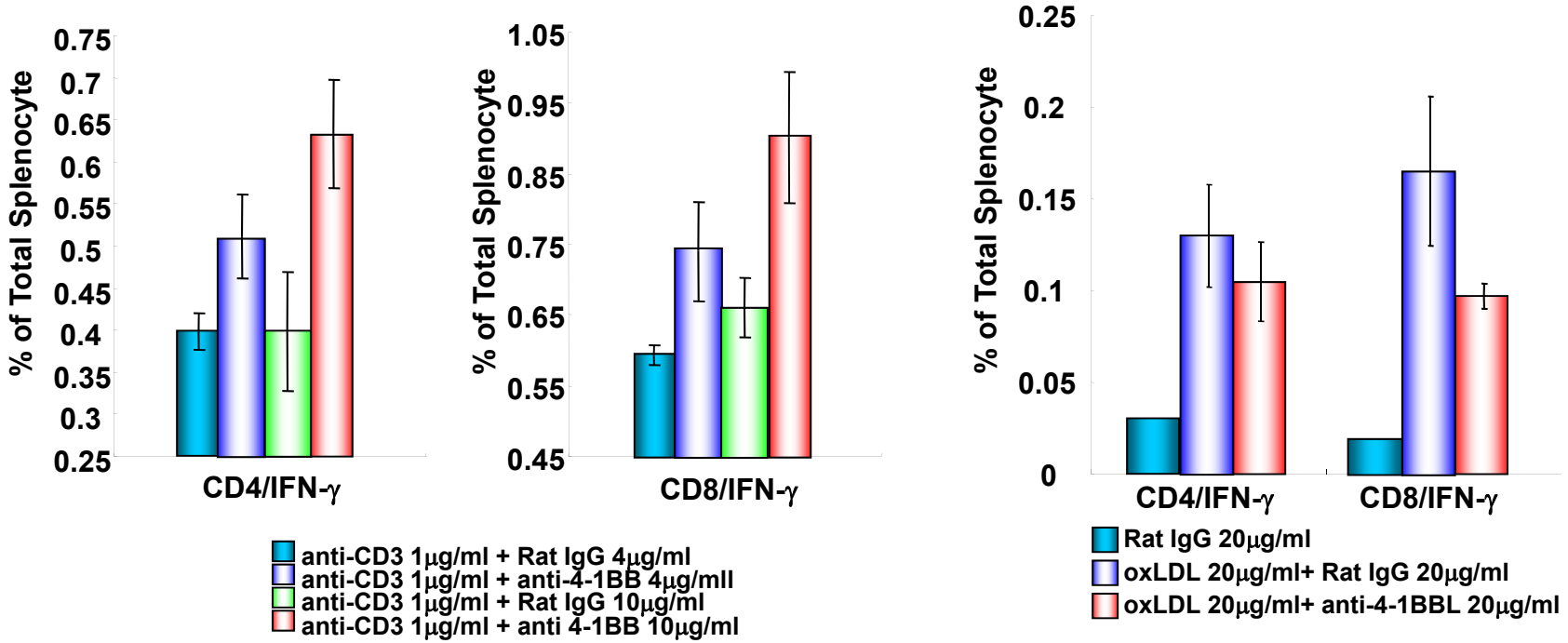




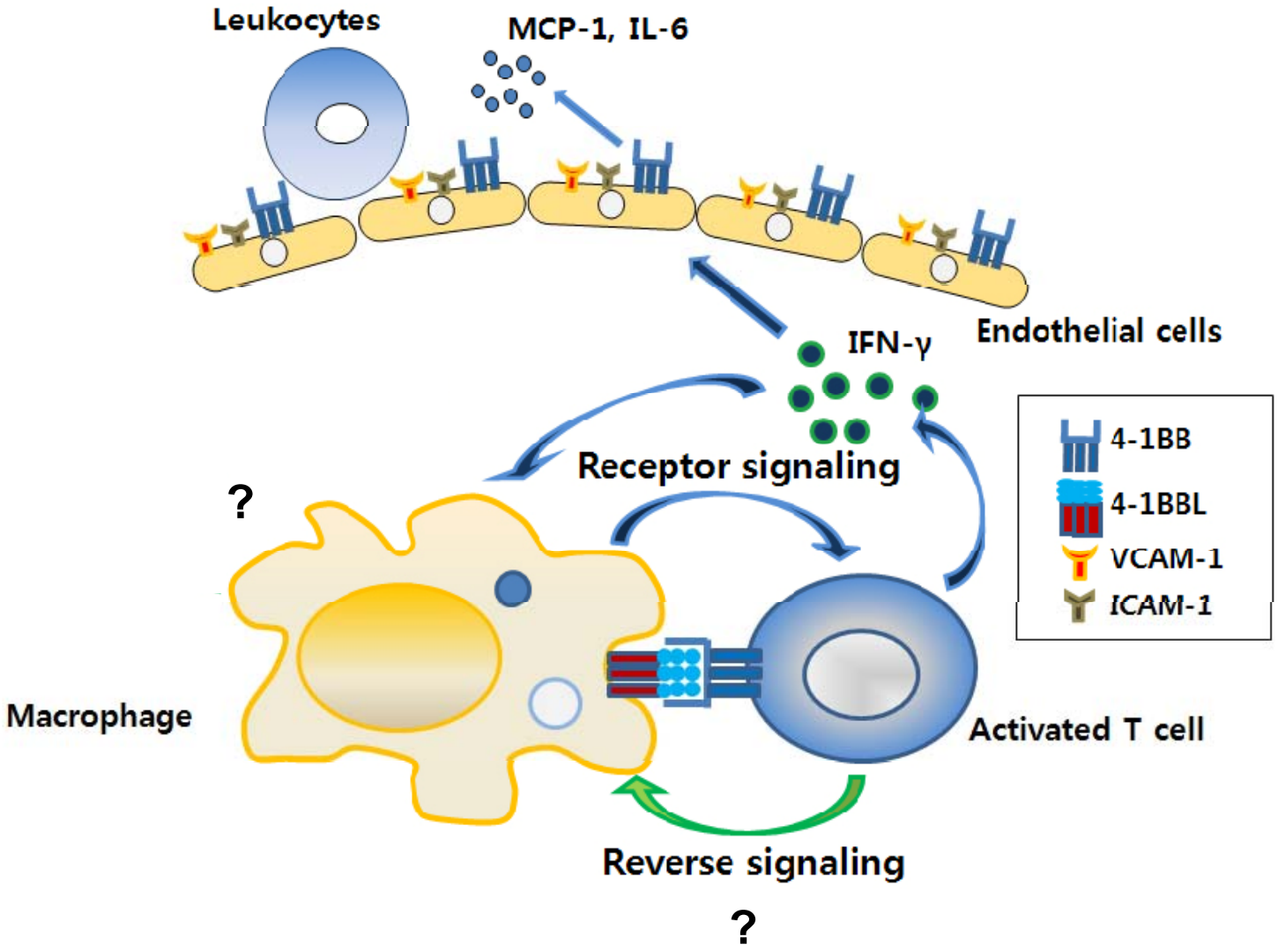
Removal of 4-1BB Reduced IFN-γ Production in Mouse T cell



Effect of 4-1BBL Antagonistic Antibody and *4-1BB* Agonistic Antibody on IFN-γ Production in Extracted Splenocyte



SUMMARY

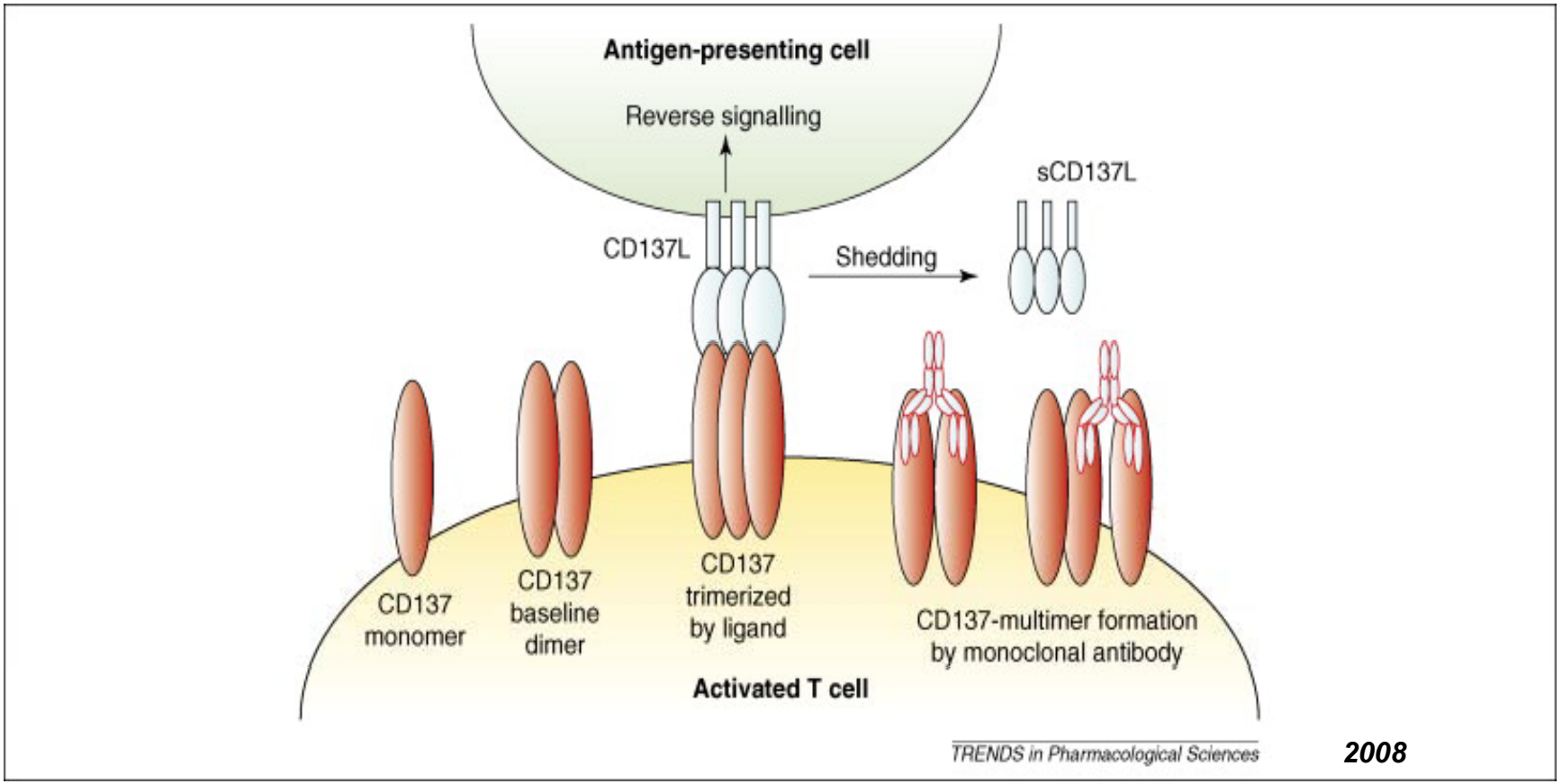

Leukocytes
MCP-1, IL-6
IFN-γ
Endothelial cells
Receptor signaling
?
4-1BB
4-1BBL
VCAM-1
ICAM-1
Macrophage
Activated T cell
Reverse signaling
?

Opinion

Cell PRESS

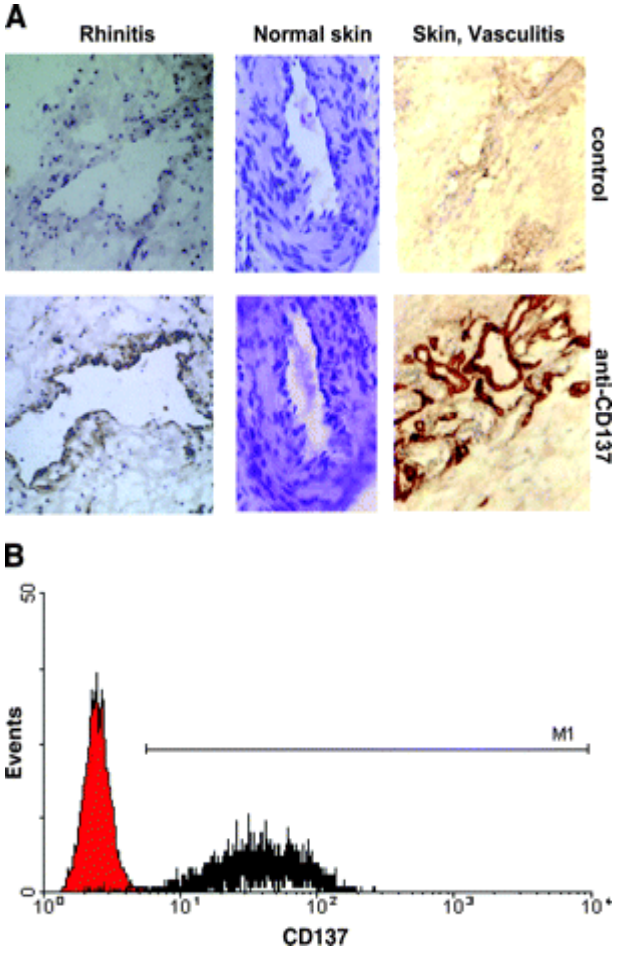
Multi-layered action mechanisms of CD137 (4-1BB)-targeted immunotherapies

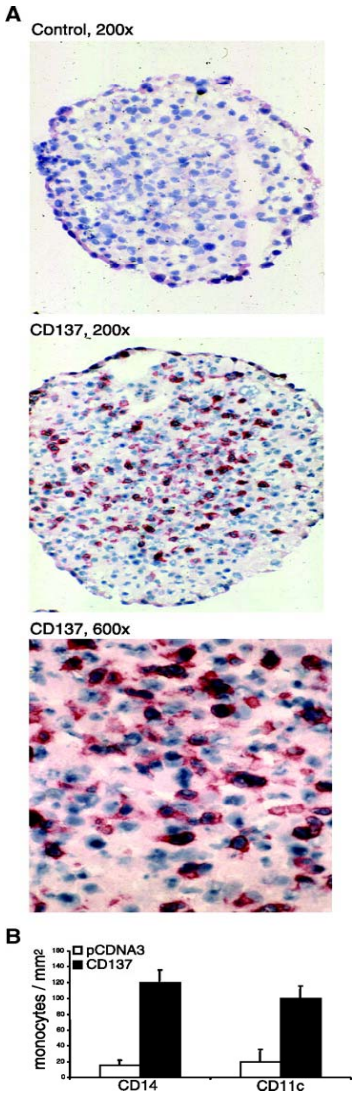
Multimerization of CD137 by natural ligand (CD137L) and agonist mAbs

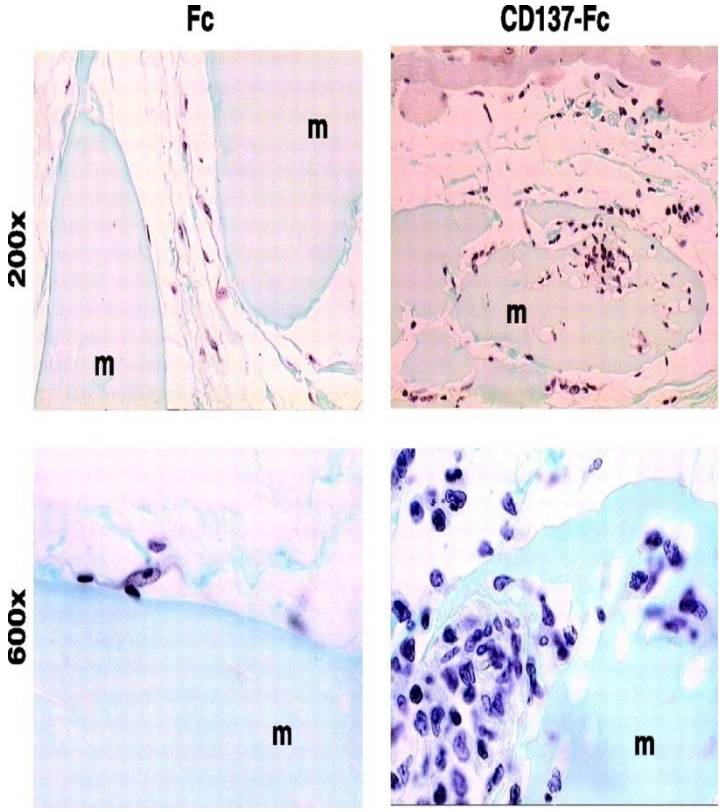


2008

Expression of 4-1BB on Blood Vessel Walls Induces Migration of Monocytes

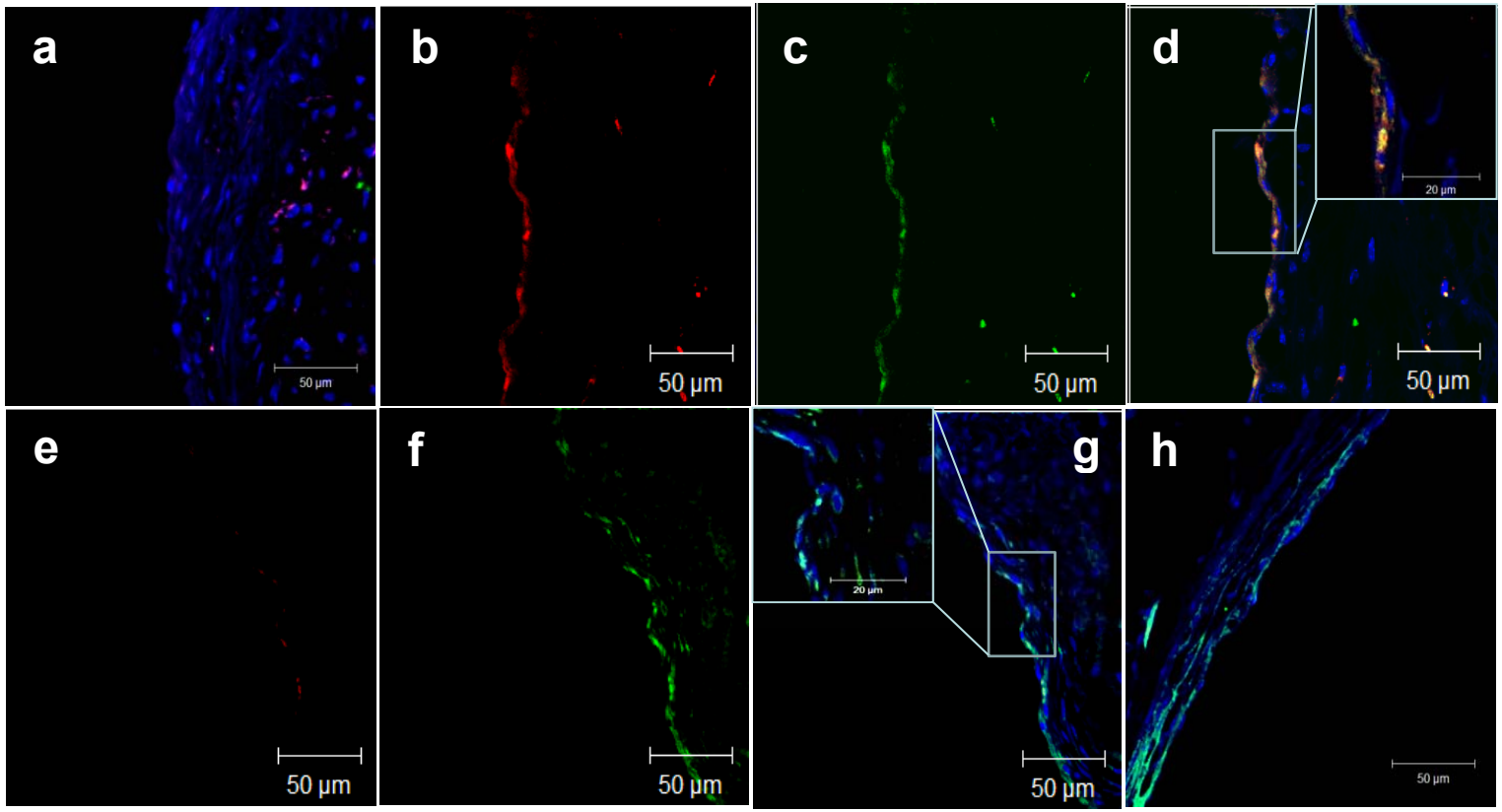






FASEB J. 21, 456–463 (2007)

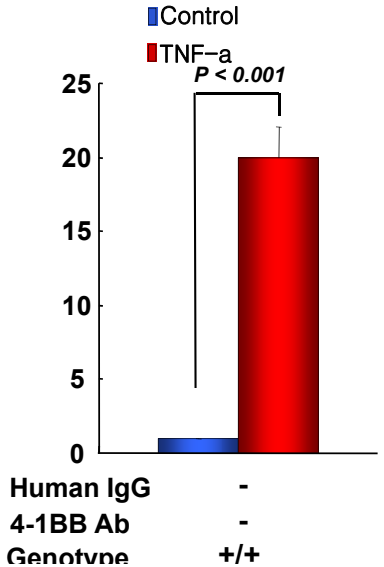
4-1BB is Expressed on the Endothelial Cells at the Site of Plaque Lesion

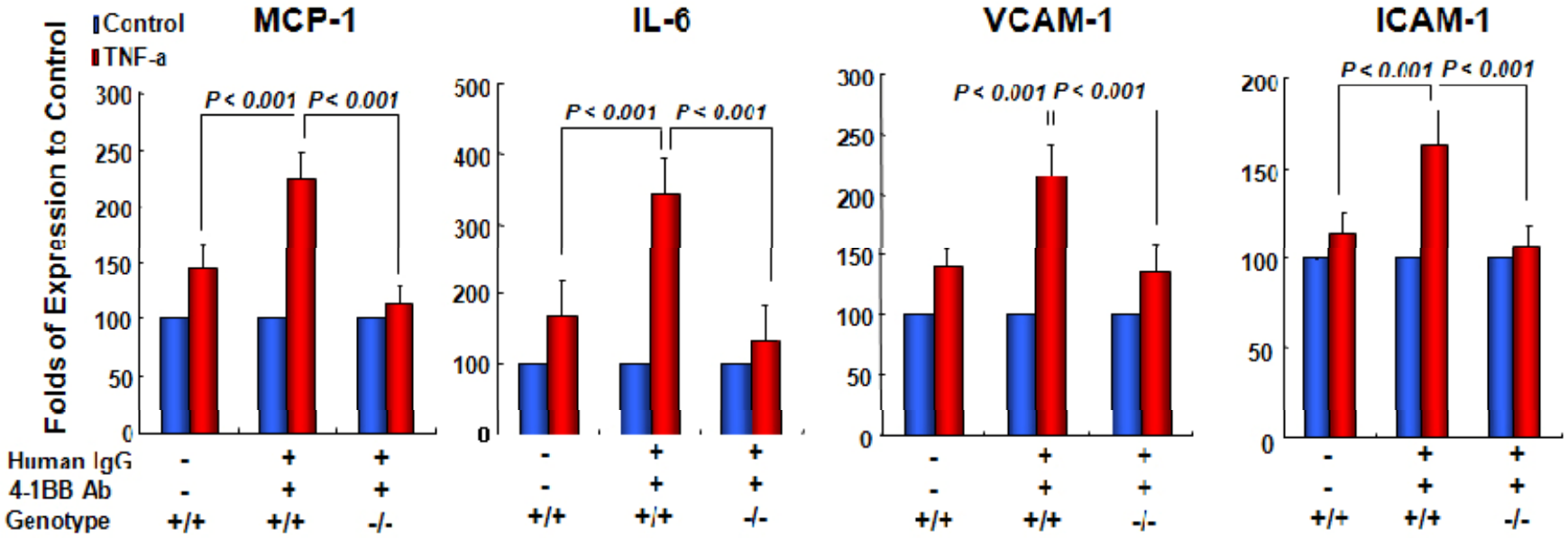


Normal vessel
(C57BL6/J)

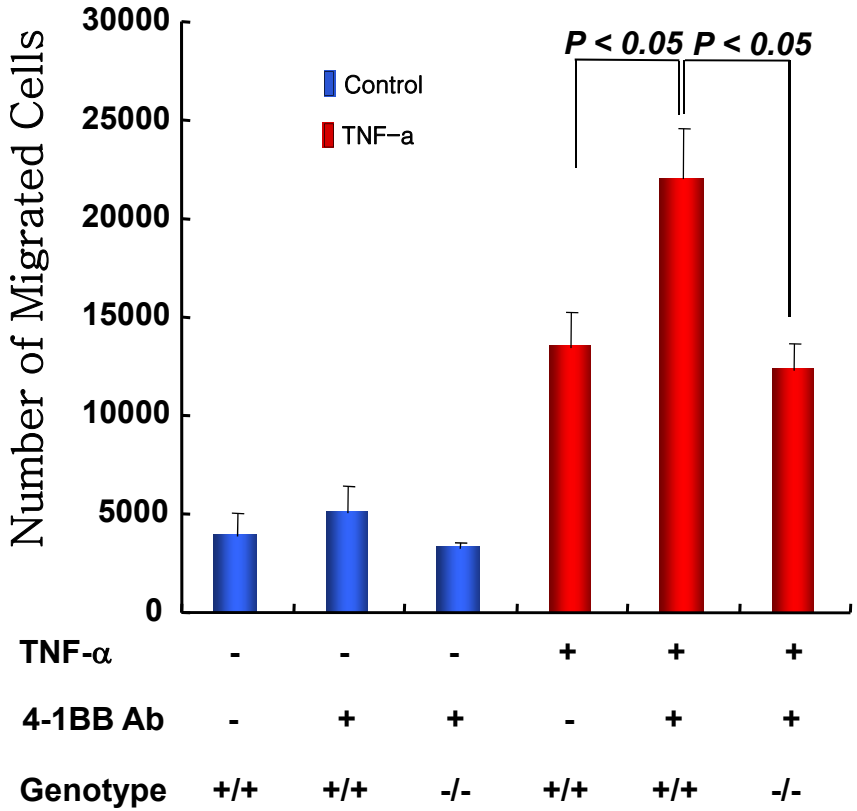
Triple immunostain for nuclei (blue), 4-1bb (red), CD31 (green).

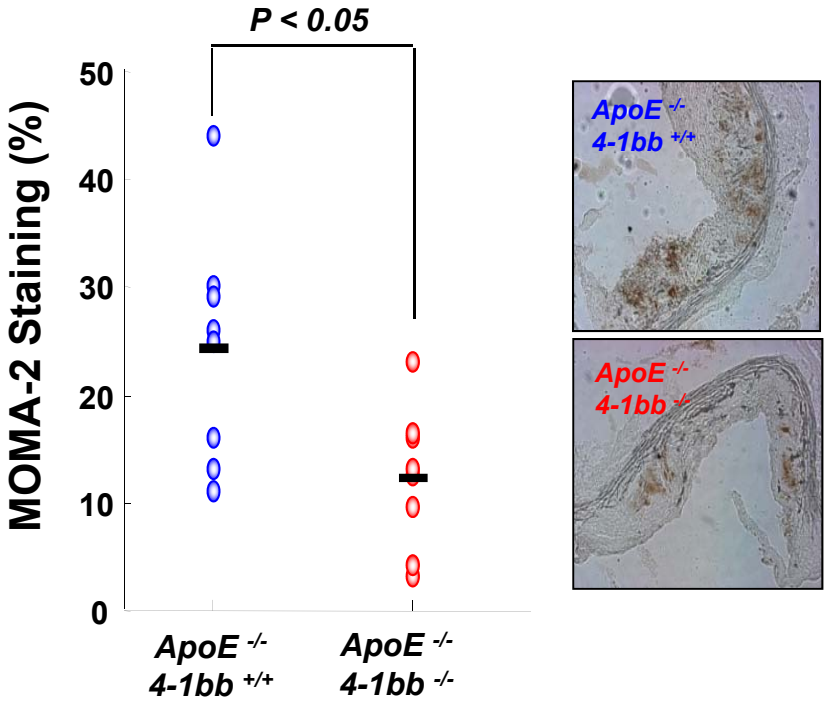
Endothelial 4-1BB Signaling Enhanced the Production of Pro-inflammatory Molecules





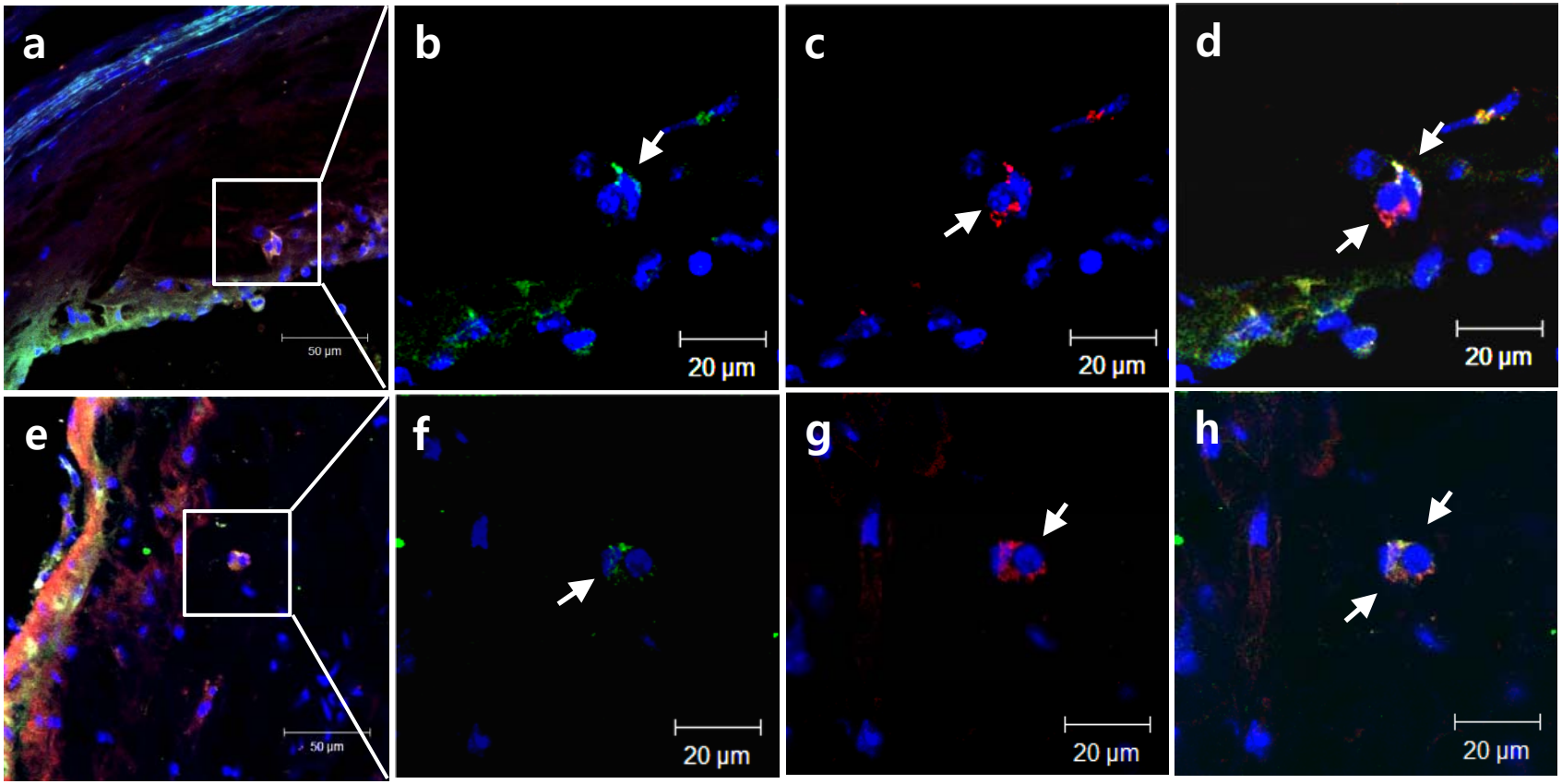
Removal of 4-1BB Reduced Macrophage Infiltration into Plaque Lesion





Co-localization of 4-1BB on the T cell and 4-1BBL on the Macrophage

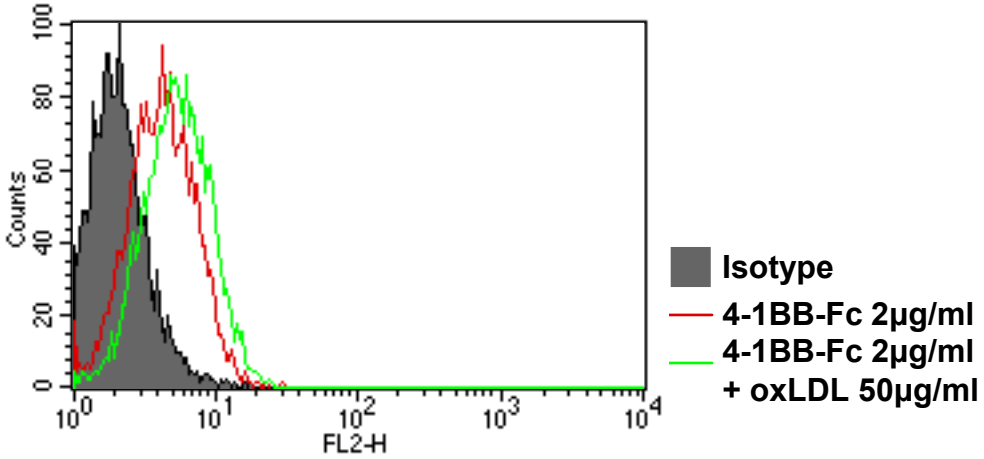
Triple immunostain for nuclei (blue), CD8(red), CD68(green).



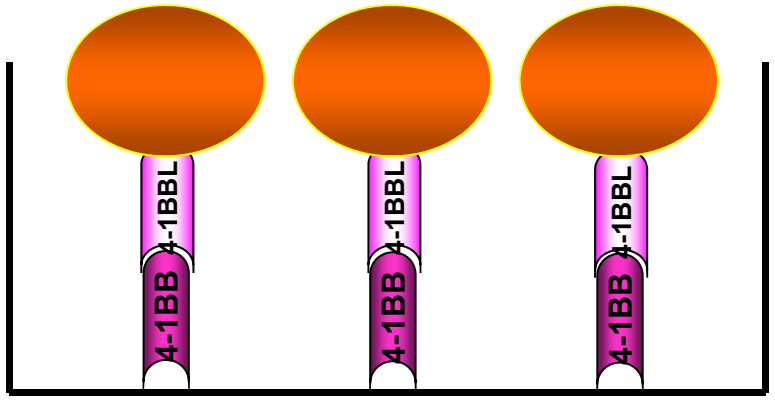
Triple immunostain for nuclei (blue), 4-1BB(green), 4-1BBL (red)

Monocyte Produced Atherogenic Factors by the Activation via 4-1BB

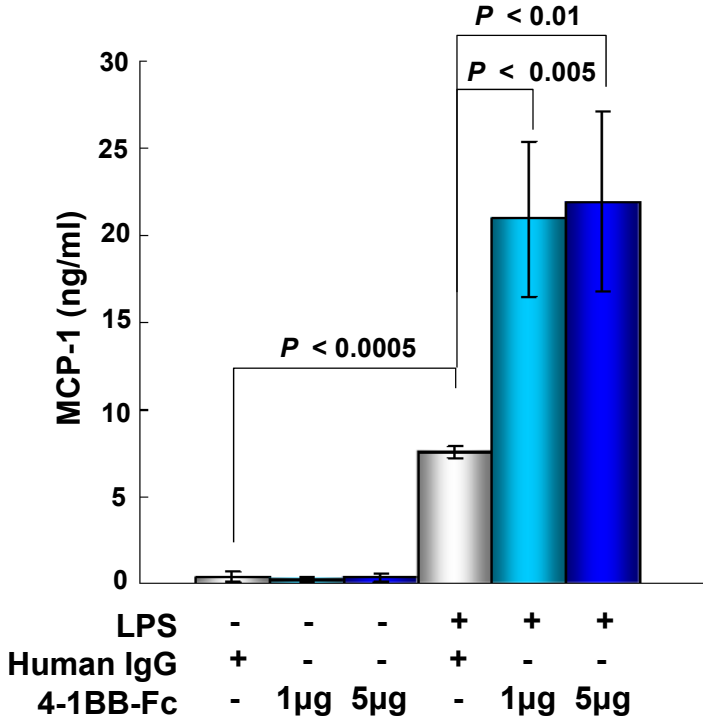
4-1BB-Fc induce 4-1BBL Expression



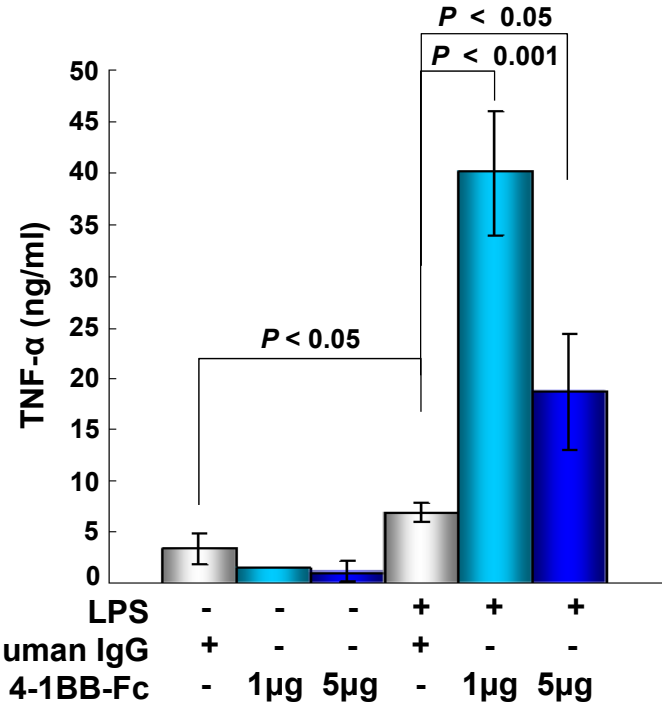
What kind of atherogenic factors?



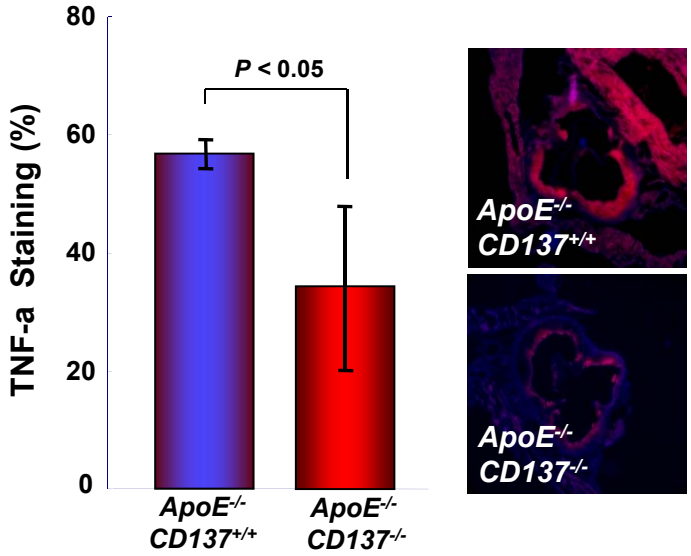
MCP-1 Production

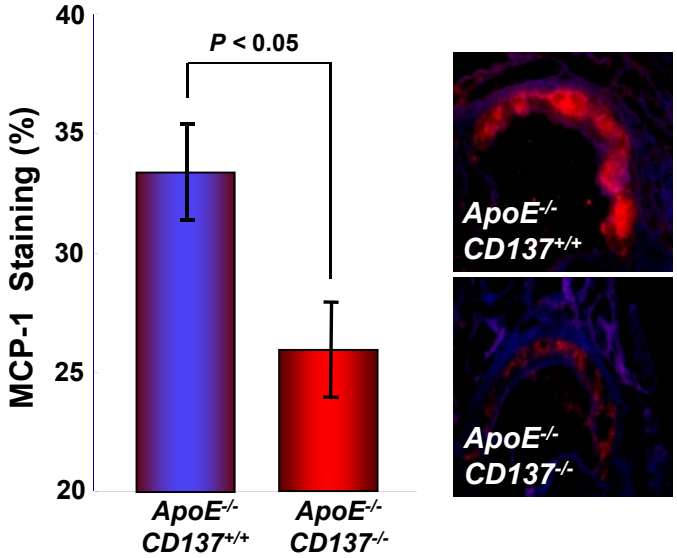


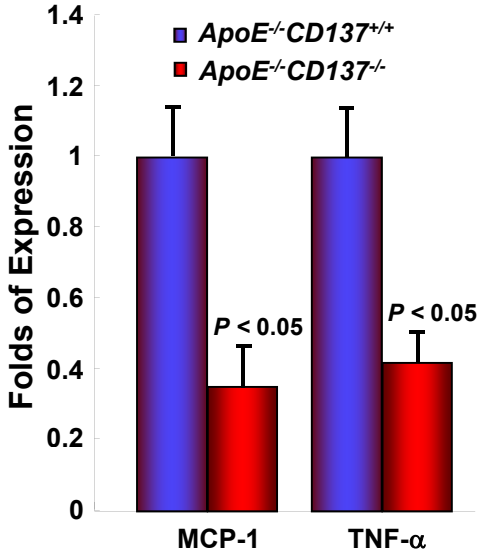
TNF-α Production



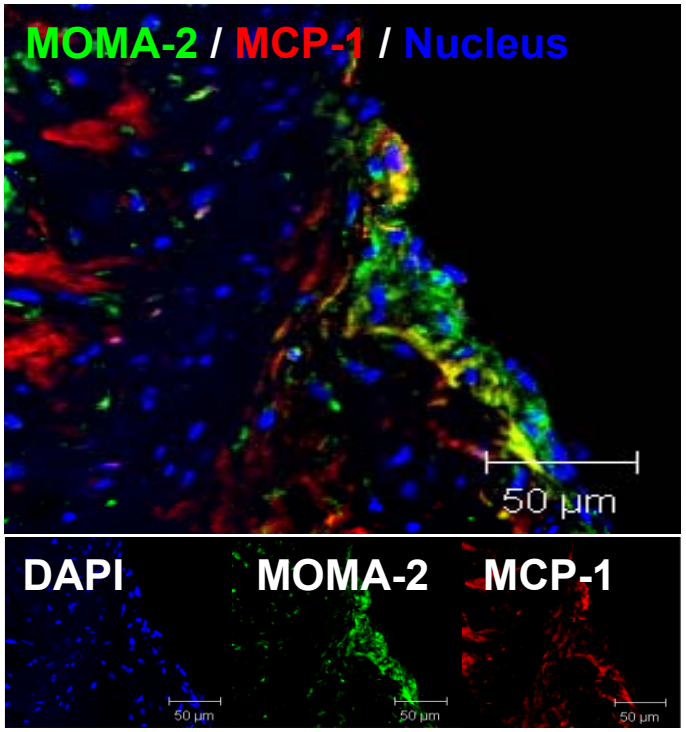
Removal of 4-1BB Reduced the Production of TNF-α and MCP-1 *in vivo*

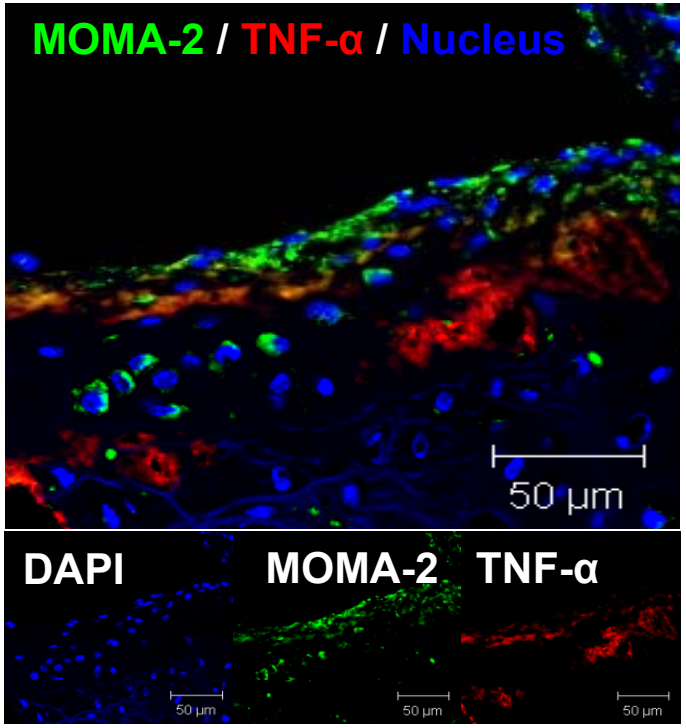




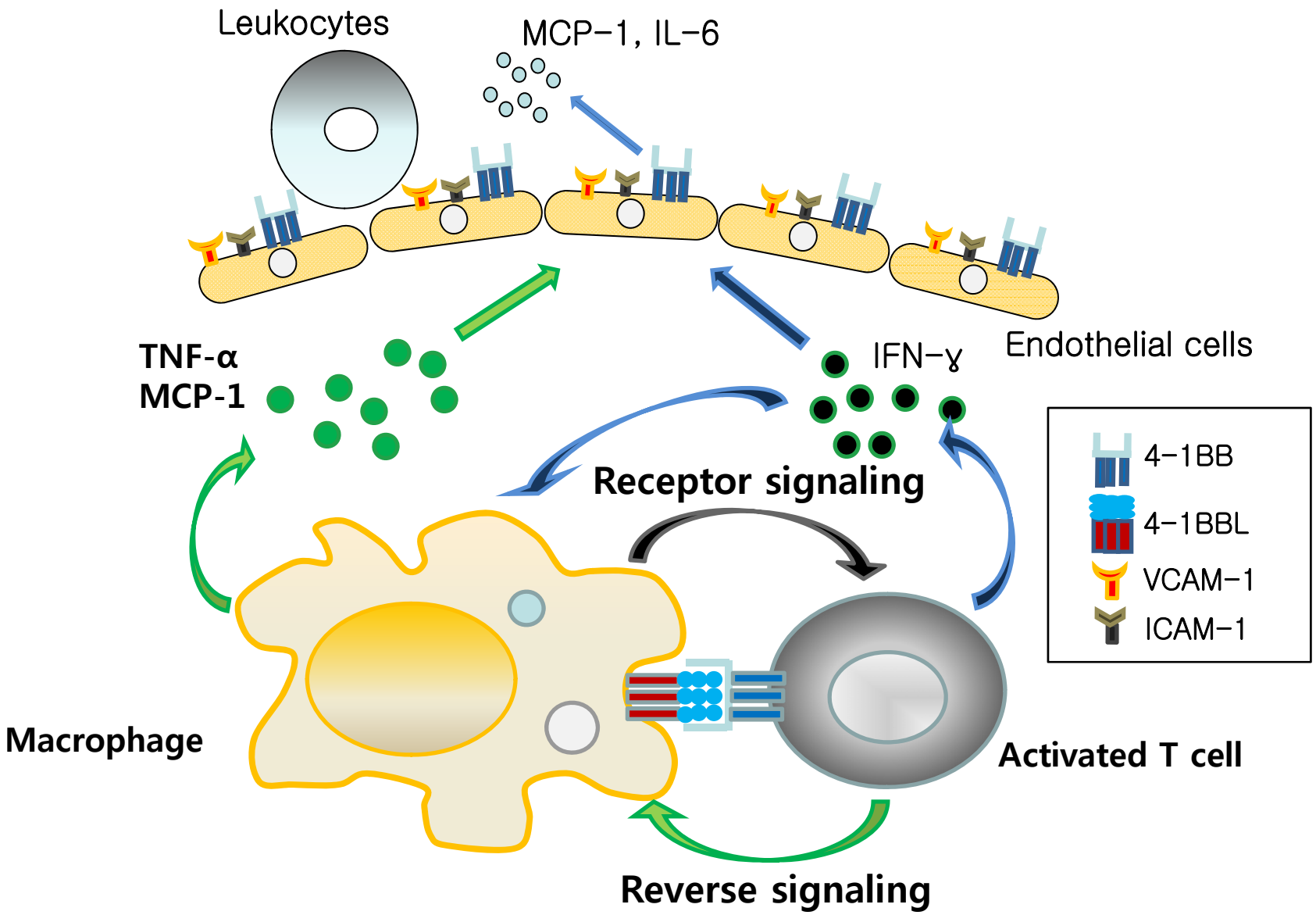


MCP-1, TNF-α Production in 4-1BB-Fc treated Atherosclerotic Plaque





CONCLUSION


Leukocytes
MCP-1, IL-6
TNF-α
MCP-1
IFN-γ
Endothelial cells
Receptor signaling
4-1BB
4-1BBL
VCAM-1
ICAM-1
Macrophage
Activated T cell
Reverse signaling

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Ewha Womans Univ.

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Soo Young Lee

감사합니다