

# TRANSLATIONAL RESEARCH IN ATHEROSCLEROSIS

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## Learning outcomes

- ✿ To outline the fundamental mechanisms involved in the pathogenesis of cardiovascular disease
- ✿ To illustrate an example of grant writing

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## Plan of the lecture

- ✿ Myth busting on atherosclerosis
- ✿ Tips on “grant writing”

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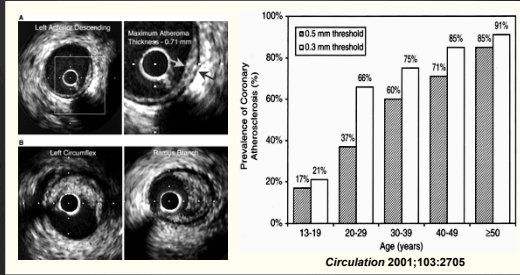
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## Atherosclerosis is the most prevalent chronic disease




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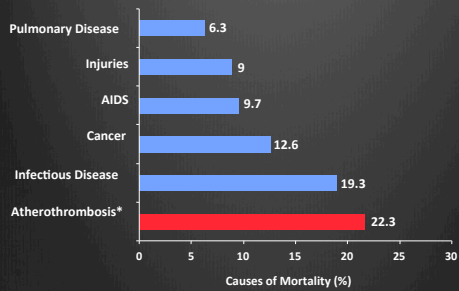
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## Atherothrombosis\* is the Leading Cause of Death Worldwide<sup>1</sup>



\* Atherothrombosis defined as ischemic heart disease and cerebrovascular disease.  
<sup>1</sup> The World Health Report 2001, Geneva, WHO, 2001.

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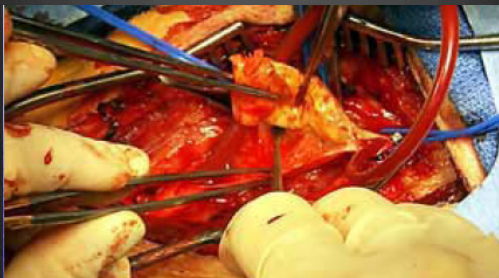
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## What is atherosclerosis?




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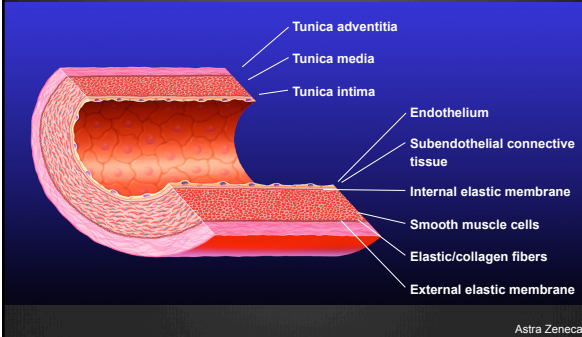
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## Normal Arterial Wall



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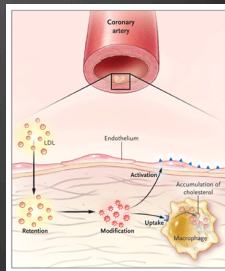
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## Lipids

- ✧ Endothelium activation
- ✧ Accumulation of low-density lipoproteins
- ✧ Oxidation of LDL
- ✧ Development of "foam cells"
- ✧ Development of fatty plaques



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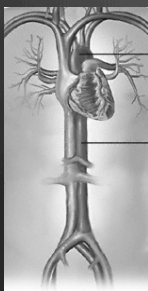
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## Fatty Streak in Aorta



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**Experimental models of atherosclerosis: hyperlipidemia**

**Diet**  
(Primates, Rabbit, Pig, Mice)

**High Cholesterol**  
Weeks to months

Foam cell-rich **Fatty Streaks**

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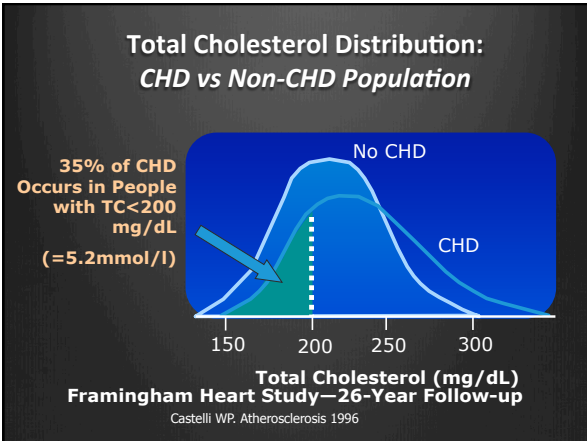
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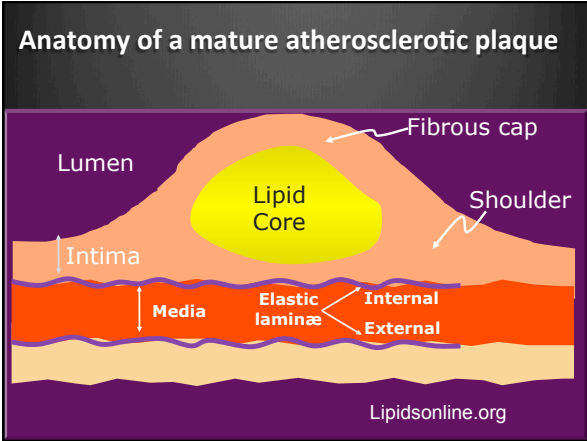
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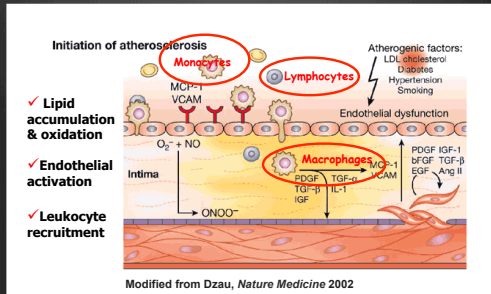
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## Atherosclerosis - I




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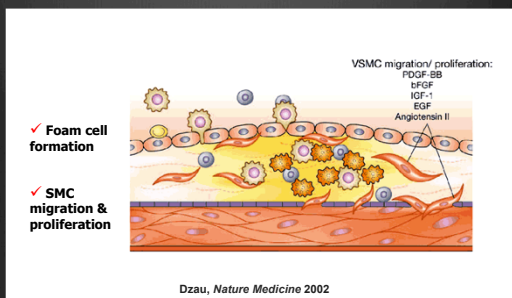
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## Atherosclerosis - II




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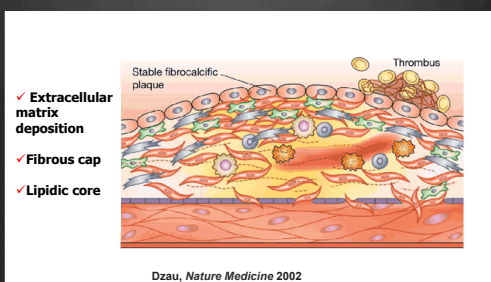
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## Atherosclerosis - III




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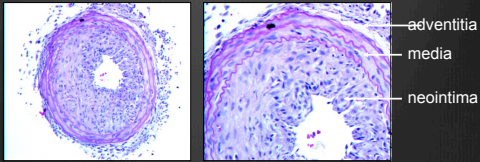
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### Neointima formation after collar injury



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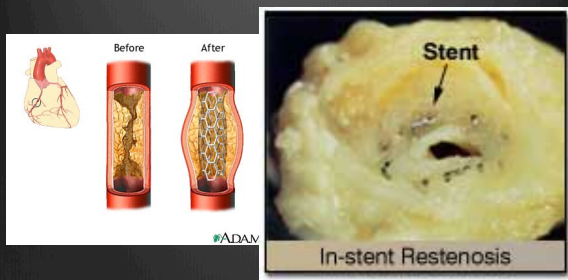
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### Restenosis reduces the success of interventions



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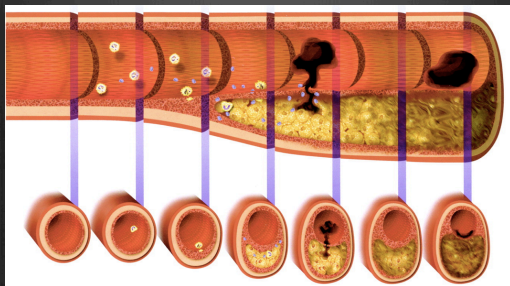
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### The paradox of atherosclerosis: a chronic process ....



Libby P Circulation 2001

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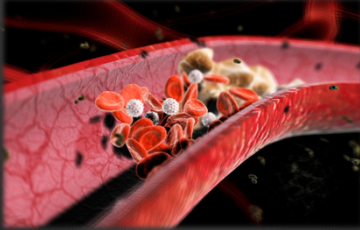
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... with acute clinical manifestations!!



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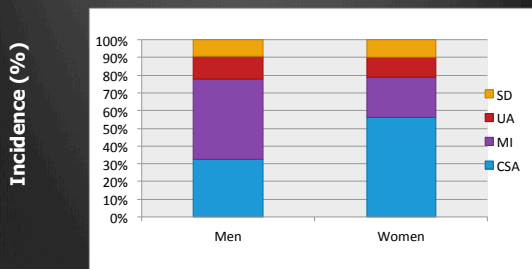
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### Mode of first presentation of IHD



Framingham study Kannel WB Am J Card 1976; 329:1442

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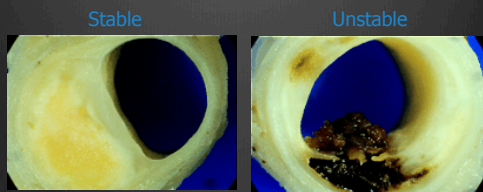
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### The two facets of atherosclerosis



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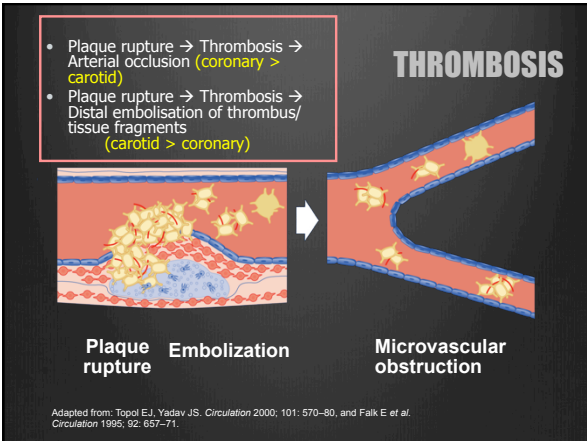
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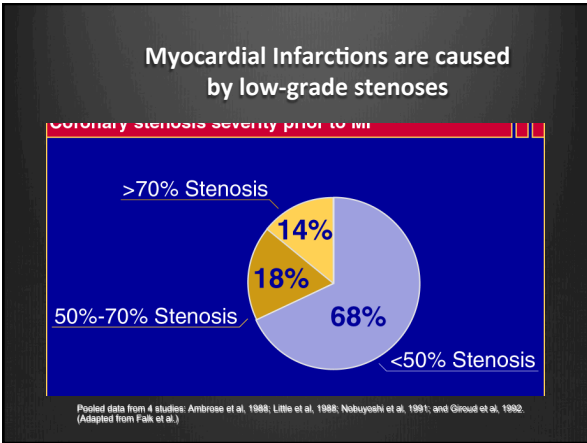
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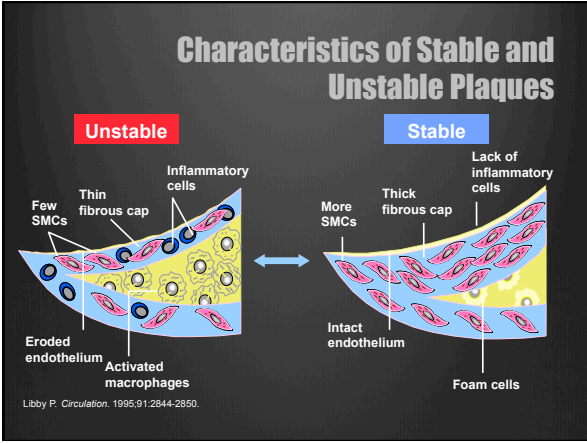
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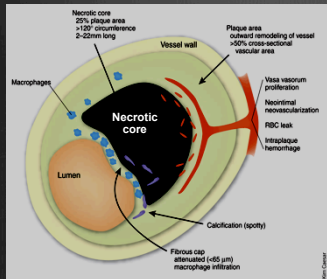
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## Hallmarks of high risk atherosclerotic plaques



- ✓ Inflammation
- ✓ Matrix degradation
- ✓ Neovascularisation

*Nature Medicine* (2007) The popcorn plaques J Narula & H W Strauss

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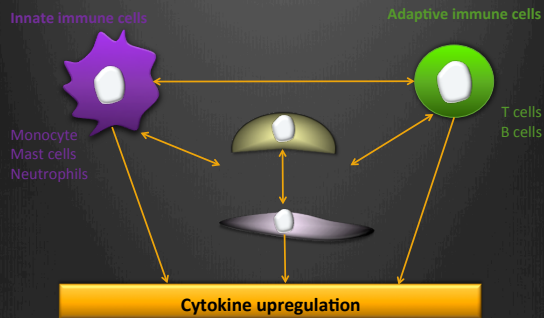
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## Both innate and adaptive immunity play a role in atherosclerosis




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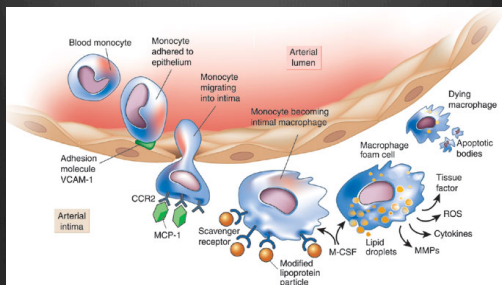
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## Monocyte-macrophages



Libby P. Inflammation in atherosclerosis. *Nature*. 2002 19-26;420(6917):868-74

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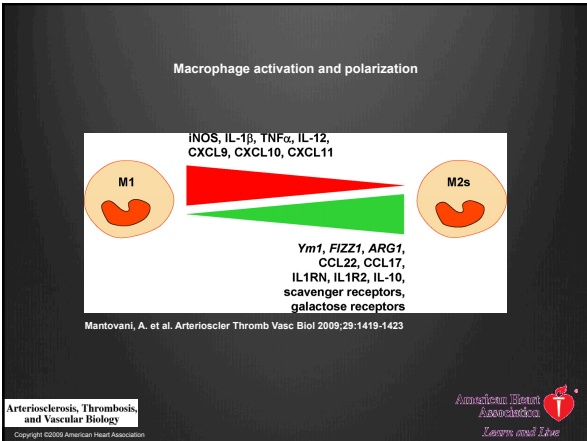
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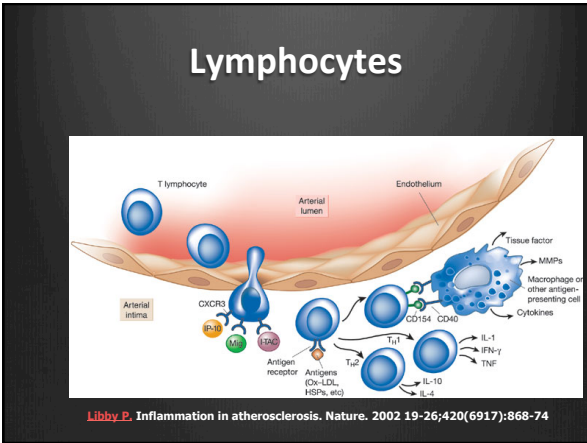
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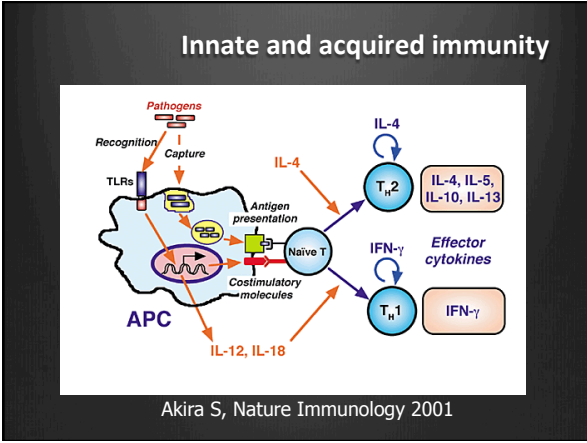
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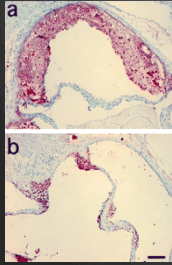
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## Recruitment of inflammatory cells is a key step in atherosclerosis



Mol Cell. 1998 Aug;2(2):275-81.  
Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low density lipoprotein receptor-deficient mice. Gu L, Okada Y, Clinton SK, Gerard C, Sukhova GK, Libby P, Rollins BJ.

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## Murine atherosclerosis is an inflammatory disease

Target/Intervention	Lesion size	Plaque composition
CCL2/CCR2	▼ (64-79%)	▼ M
CCL5/CCR5	▼ (44-53%)	▼ M&L
MyD88	▼ (59-62%)	▼ M
TLR-2	▼ (55%)	▼ M
TLR-4	▼ (24%)	▼ M
TNF $\alpha$	▼ (50-83%)	◄
IL-1/IL-1R	▼ (40-67%)	◄
IL-12	▼ (52-68%)	▼M&L ▲SMC/collagen
IL-10	▲ (2x)	▲ M&L ▼ SMC/collagen
IL-18	▼ (25-34%)	▼M&L ▲SMC/collagen
IFN $\gamma$ /IFN $\gamma$ R	▼ (59-75%)	▼ M&L
TGF $\beta$ RII on T cells	▲ (3x)	▼M&L ▲SMC/collagen
CD4 transfer	▲ (3x)	▲ L

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## Innate immunity vs. adaptive immunity

Table 1. Innate and adaptive immunity

Property	Innate Immune System	Adaptive Immune System
Receptors	Fixed in genome; rearrangement not necessary	Encoded in gene segments; rearrangement necessary
Distribution	Nonclonal; all cells of a class identical	Clonal; all cells of a class distinct
Recognition	Conserved molecular patterns (LPS, LTA, mannans, glycans)	Details of molecular structure (proteins, peptides, carbohydrates)
Self-non-self discrimination	Perfect: selected over evolutionary time	Imperfect: selected in individual somatic cells
Action time	Immediate activation of effectors	Delayed activation of effectors
Response	Costimulatory molecules; cytokines (IL-1 $\beta$ , IL-6); chemokines (IL-8)	Clonal expansion or anergy; IL-2; effector cytokines (IL-4, IFN- $\gamma$ )

Presidential Address to The American Association of Immunologists: The Road Less Traveled by The Role of Innate Immunity in the Adaptive Immune Response  
Charles A. Janeway, Jr.  
J Immunol 1998; 161:339-344

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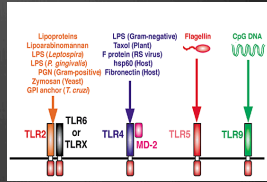
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# Toll-like Receptors (TLRs)

❖ TLRs are the receptors through which innate immunity senses pathogens in mammals




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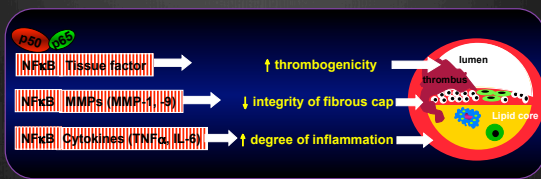
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# Innate immune signalling regulates the thrombotic potential of the atherosclerotic plaque




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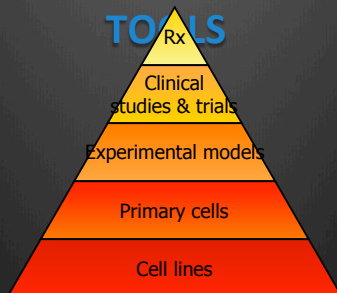
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# RESEARCH STRATEGY =




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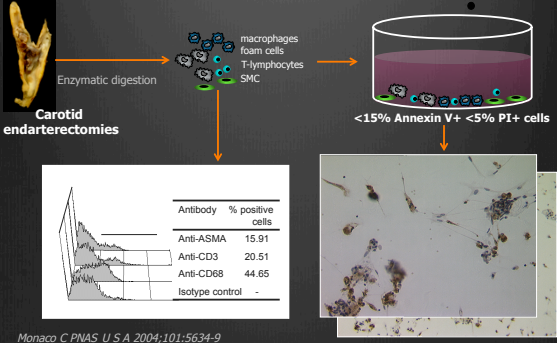
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### Functional studies in human atherosclerosis




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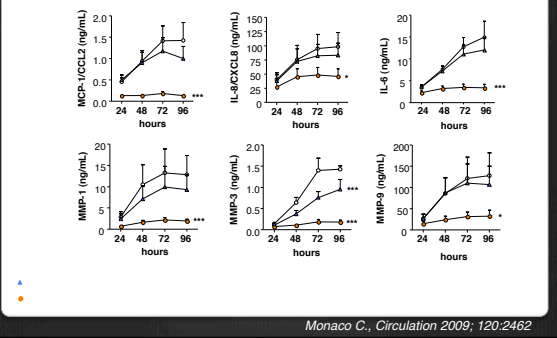
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### Persistent cytokine and MMP production in human atherosclerosis is driven by TLR2




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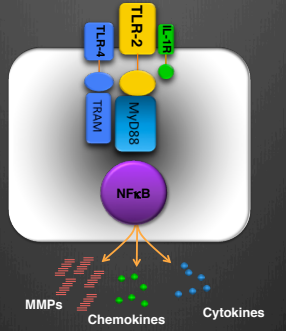
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TLRs drive local inflammation

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