



Per la promozione della ricerca sulle malattie da arteriosclerosi

Project Title

**“EFFECT OF JAK-STAT INHIBITION
ON MACROPHAGE CHOLESTEROL METABOLISM AND ATHEROSCLEROSIS”**

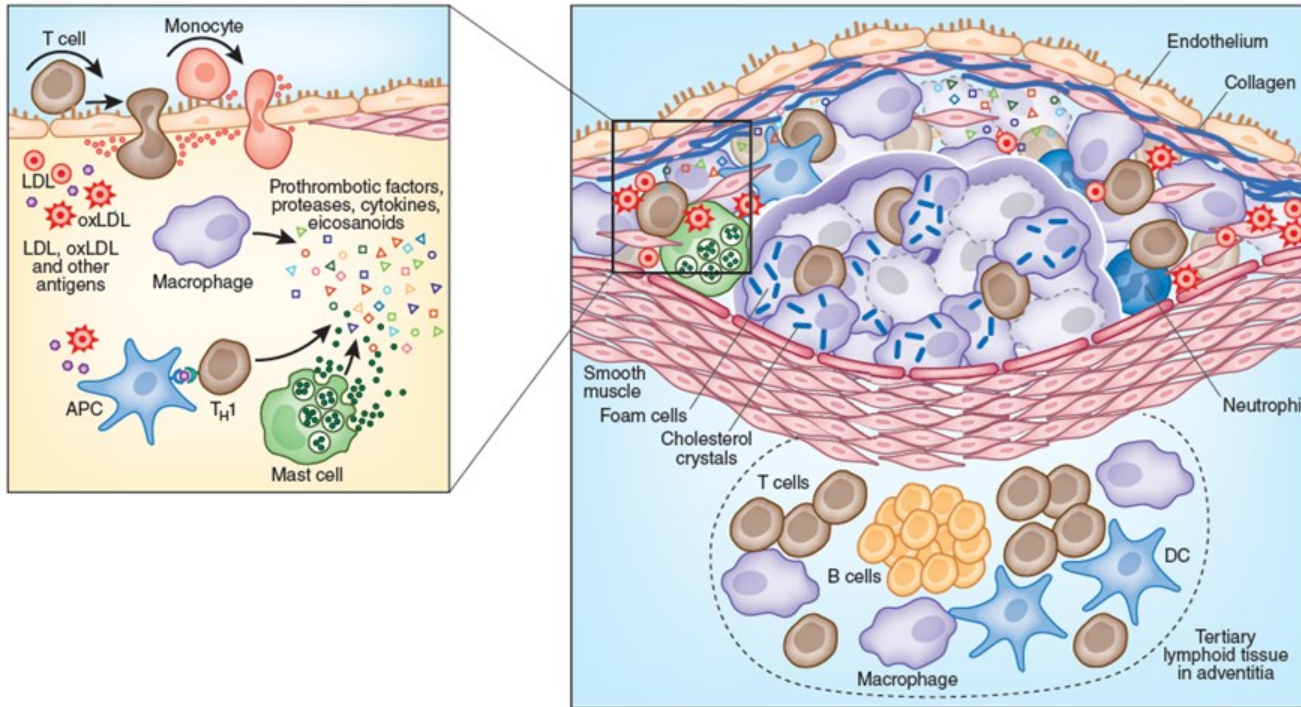
Maria Pia Adorni

Laboratorio di Farmacologia dei Lipidi

Dipartimento di Farmacia

Università degli Studi di Parma

Atherosclerosis

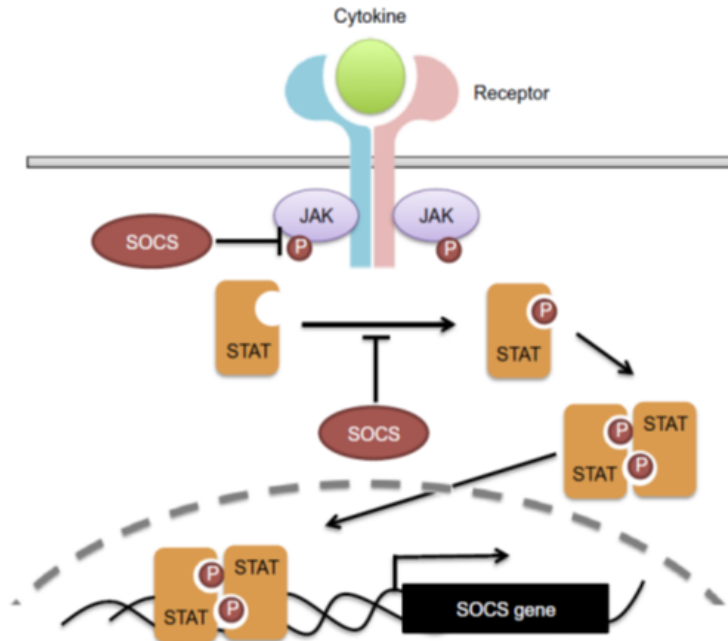


Pathogenesis of atherosclerosis is a complex process that involves extensive interplay between various elements of inflammation and of the innate and adaptive immune systems

Systemic inflammatory and autoimmune diseases are associated with accelerated atherosclerosis and increased cardiovascular risk

- **Systemic Inflammation impairs reverse cholesterol transport in vivo (McGillicuddy F.C. et al., Circulation 2009 3;119(8):1135-45)**
- **Plasma from rheumatoid arthritis patients promotes proatherogenic cholesterol transport gene expression in THP-1 human macrophages (downregulating the cholesterol efflux proteins ABCA1, ABCG1 while upregulating the scavenger receptors CD36, LOX1 and CXCL16) and promotes foam cell transformation in THP-1 macrophages (Voloshyna et al. Exp Biol Med (Maywood). 2013; 238(10)).**
- **Autoimmune diseases (including rheumatoid arthritis) are associated to an alteration of plasma lipoprotein functions related to macrophage cholesterol metabolism (Ronda et al Ann Rheum Dis. 2014)**

Janus Kinase/signal transducers and activators of transcription (JAK/STAT) pathway

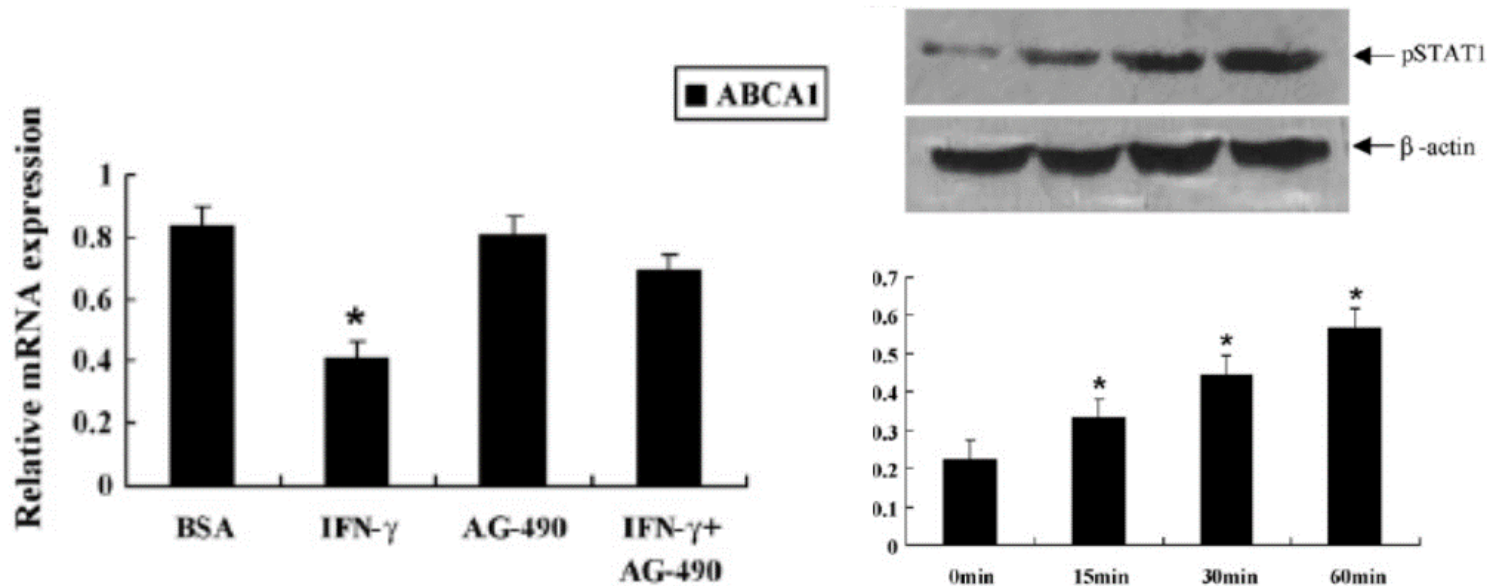


Essential intracellular signaling mechanism that regulates several cell functions and gene expression and plays a critical role in mediating inflammatory and immune responses (JAK3, TYK2)

ROLE IN ATHEROGENESIS

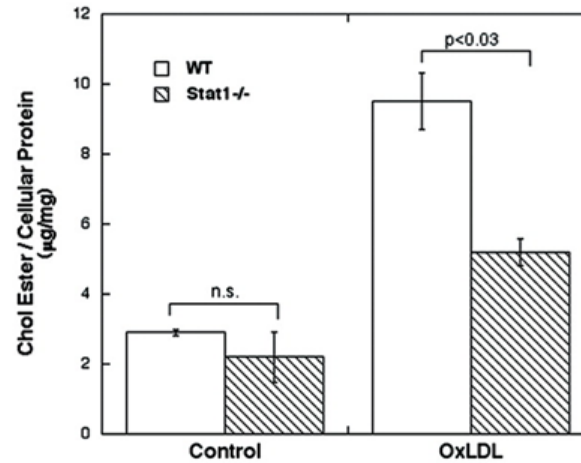
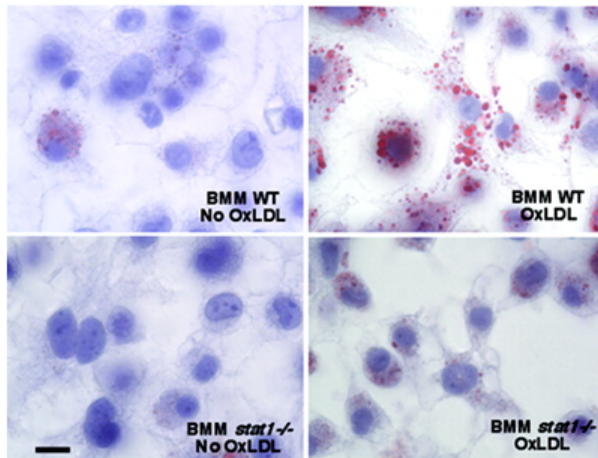
AOPPs inhibits cholesterol efflux by down regulating ABCA1 expression in a JAK/STAT signaling pathway-dependent manner (*J of Atheroscler Thromb* 2011)

IFN- γ down-regulates ABCA1 expression by inhibiting LXR in a JAK/STAT signaling pathway-dependent manner (*Atherosclerosis* 203 (2009) 417–428)

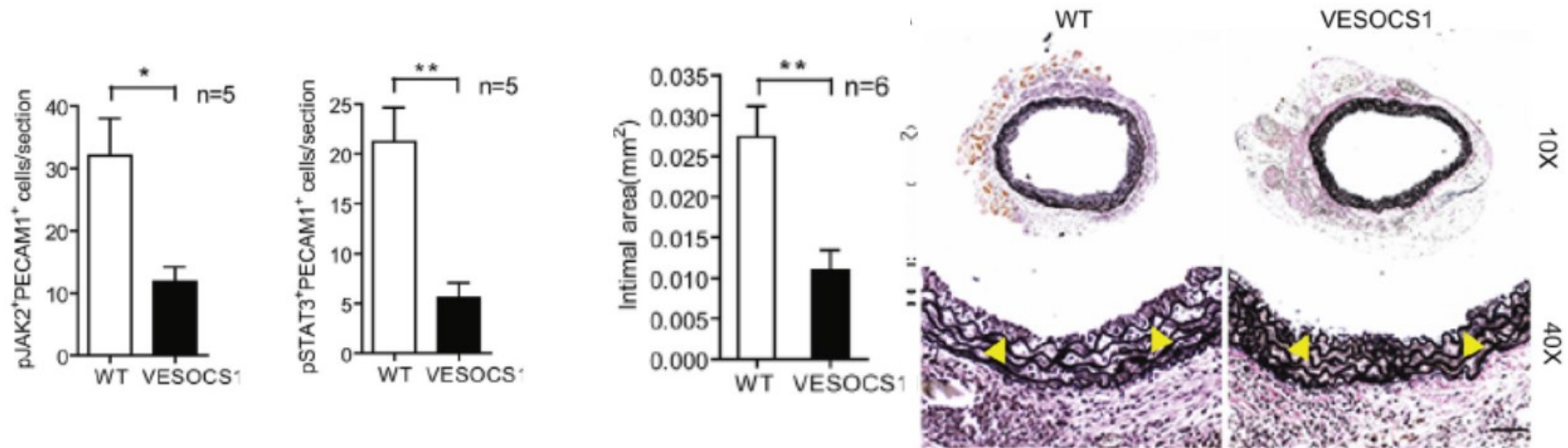


17 β estradiol reduces atherosclerosis in ApoE null mice associated with upregulating ABCA1 expression and cholesterol efflux, which are dependent on inhibition of JAK2/STAT3 phosphorylation (*Horm Metab Res* 2013)

Signal Transducer and Activator of Transcription 1 (STAT1) Is Required for Optimal Foam Cell Formation and Atherosclerotic Lesion Development (*Circulation* 2007;115:2939 –2947.)

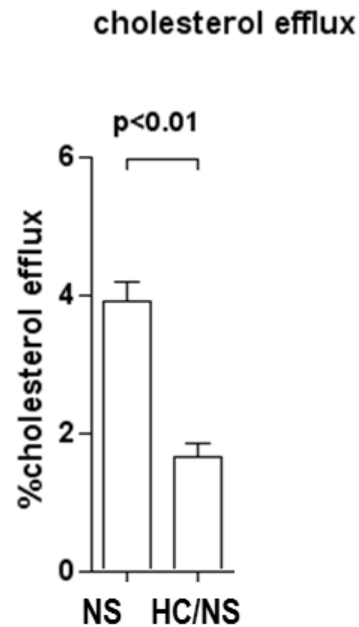
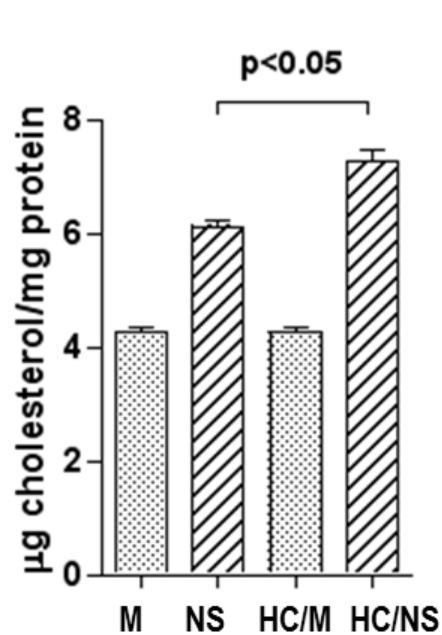


Endothelial cells-Specific Overexpression of SOCS1 Inhibits atherosclerosis in Mice

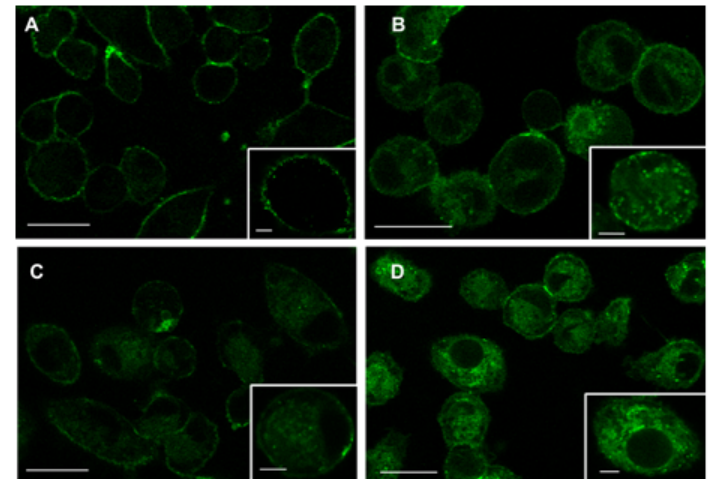


vascular endothelial SOCS1 (VESOCS1) transgenic mice

Macrophage cholesterol accumulation induced by hydrocortisone (HC)



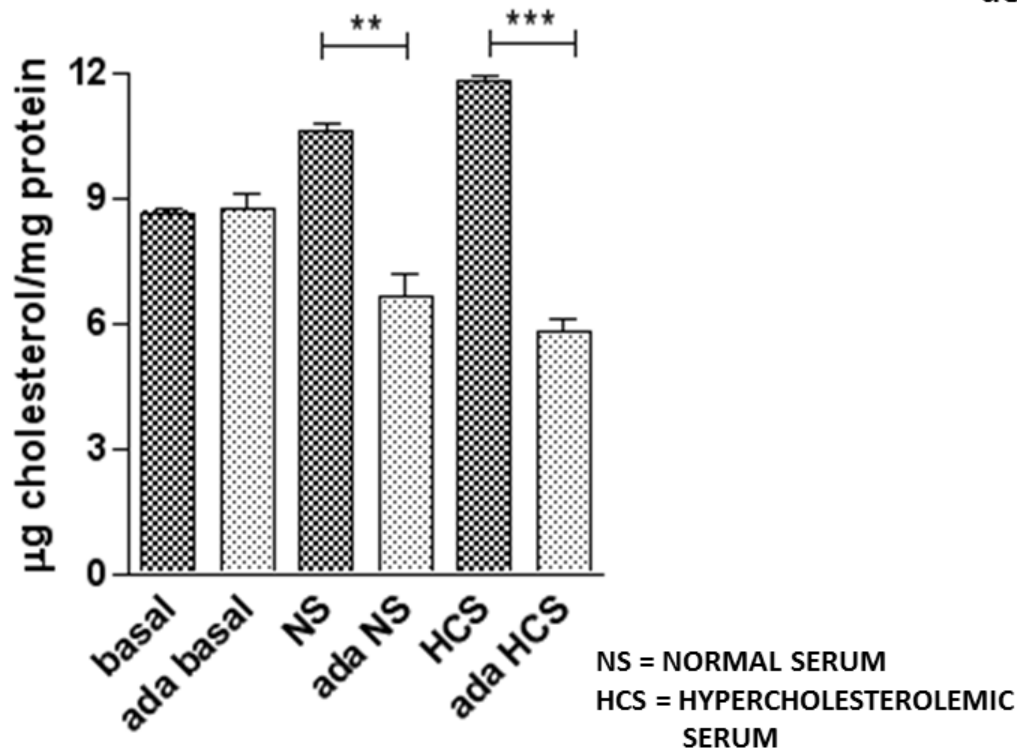
LDLr-mediated cholesterol influx



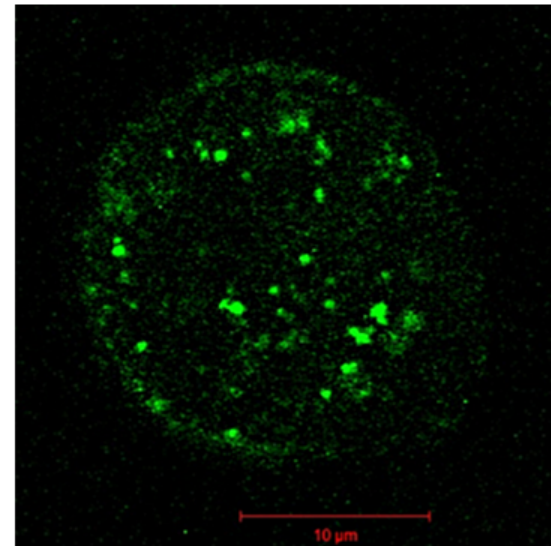
M = CULTURE MEDIUM
HC = HYDROCORTISONE
NS = NORMAL SERUM

Adalimumab, an anti-TNF α antibody, is able to bind to membrane TNF on macrophages and to inhibit cholesterol uptake, possibly through a reverse signaling

Cell cholesterol uptake



Binding and internalization of adalimumab in living THP-1 derived macrophages pretreated with LPS



Ronda N et al., Arthritis Rheumatol. 2015 May;67(5):1155-64

Hypothesis of the Study

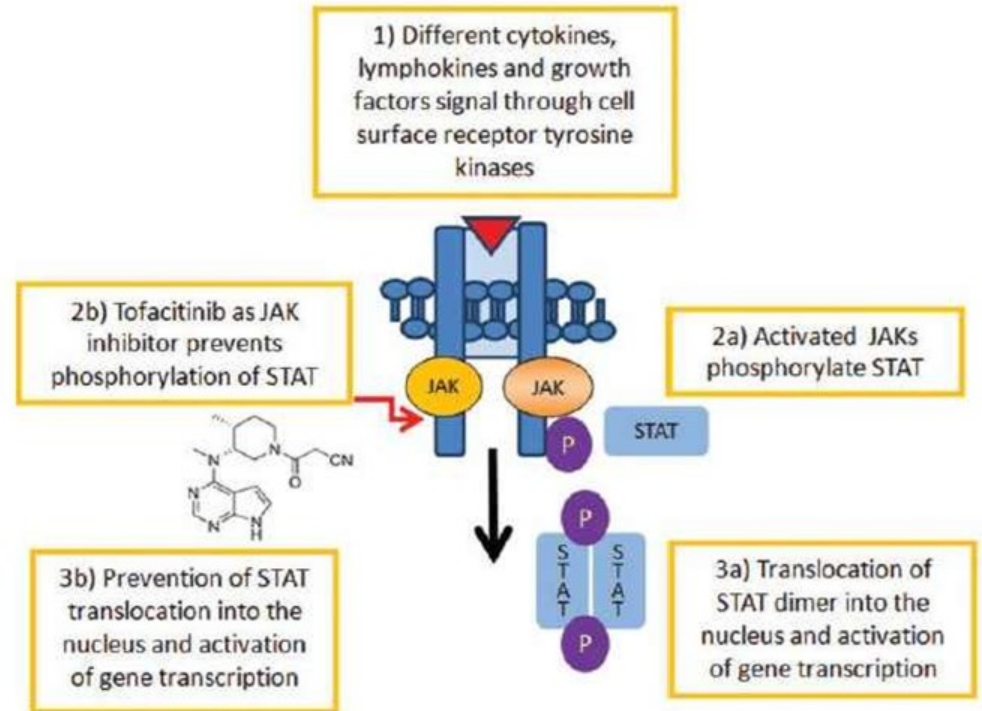
Inhibition of JAK/STAT signaling pathway with **tofacitinib
influences macrophage cholesterol metabolism
and macrophage pro-inflammatory phenotype**

TOFACITINIB

Janus kinase (JAK) inhibitor by Pfizer
JAK1, JAK3

Approved by FDA in 2012 for oral
treatment of AR

European Medicines Agency accepted for
Review Its Marketing Authorization
Application for XELJANZ® (Tofacitinib
Citrate) for the Treatment of Moderate to
Severe RA



Expected Results

Inhibition of JAK/STAT pathway may positively modulate macrophage cholesterol metabolism and macrophage inflammatory function.

Inhibition of JAK/STAT pathway may compensate the described defective capacity to promote cholesterol efflux of sera from patients with autoimmune and systemic inflammatory diseases and attenuating the pro-atherogenic potential of sera from these patients.

**Inhibition of JAK/STAT further define JAK-STAT signaling pathway
as a possible pharmacological target to reduce also atherosclerosis development**