

# Targeting cell metabolism to decrease the pro-inflammatory state in high CV-risk patients: Lp(a)

Nederlandse Lipiden Academie:

4e Nationale Lipidendag  
17 mei 2018, Paushuize, Utrecht

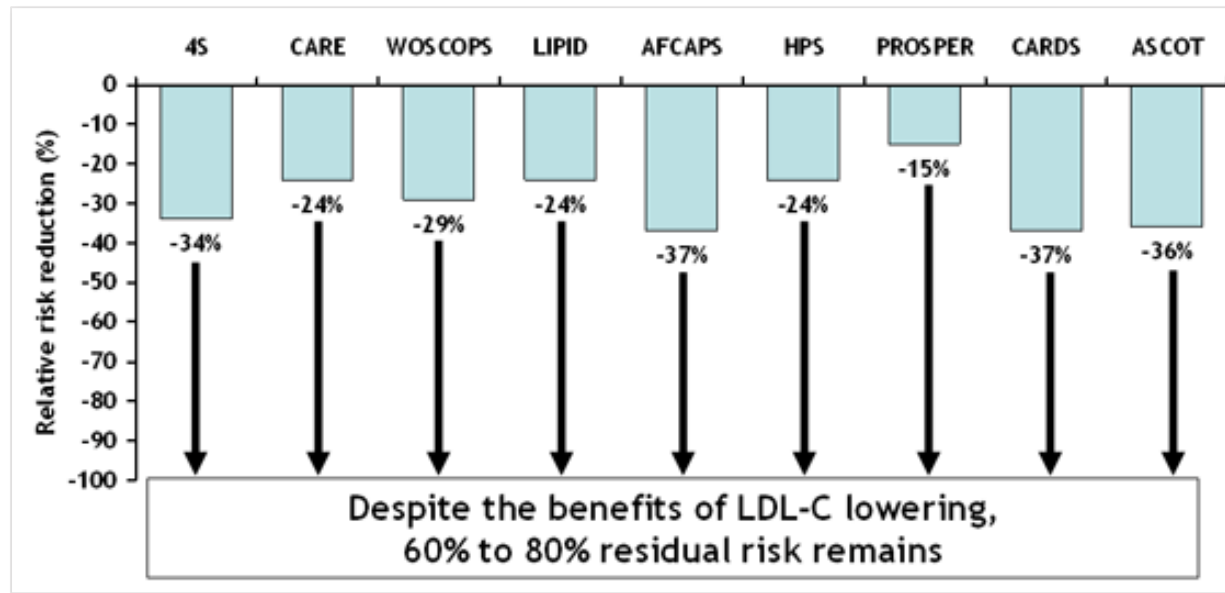
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## ***Disclosures***

None

# *Lipids in cardiovascular disease*

- LDL-c lowering leads to reduction in CV events
- However, not all events can be prevented by only LDL-c lowering



- Not only lipids, but also inflammation plays a crucial role in disease progression

# ***Inflammation and atherosclerosis***

Atherosclerotic lesions are characterized by inflammation

*Surgeon J. Hudson, 1805*

Discussion of inflammatory nature of atherosclerosis reopened in 1999,  
with first significant review:

## *Mechanisms of Disease*

FRANKLIN H. EPSTEIN, M.D., *Editor*

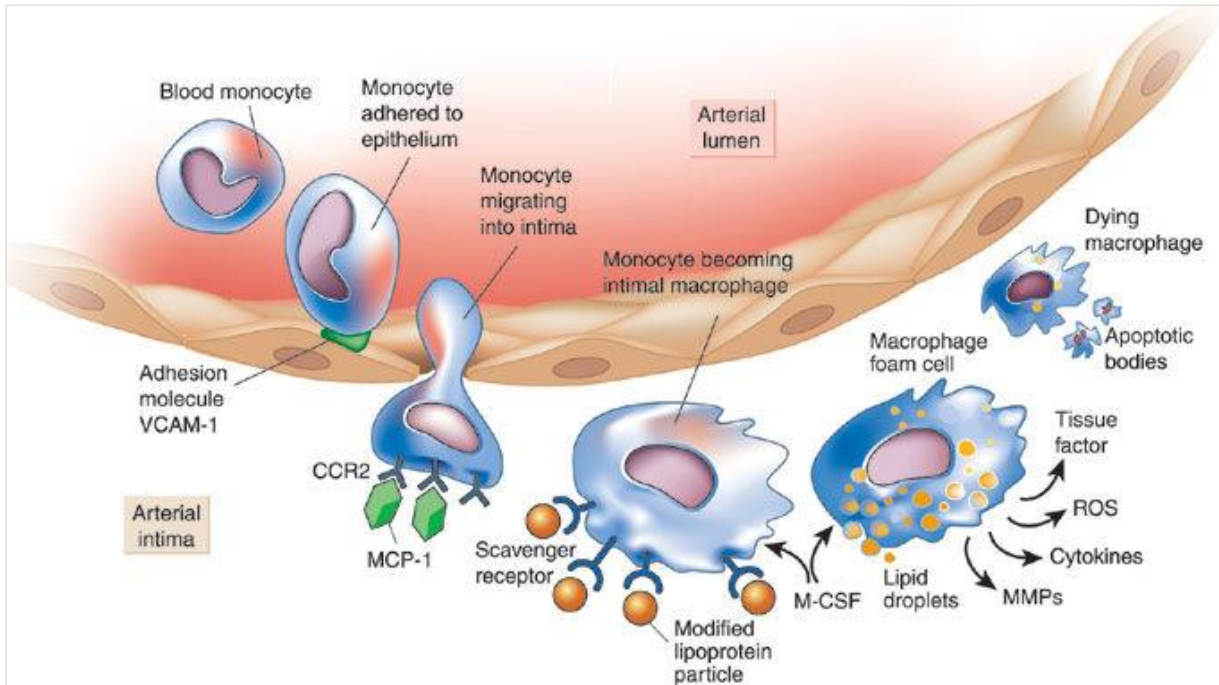
### **ATHEROSCLEROSIS — AN INFLAMMATORY DISEASE**

RUSSELL ROSS, Ph.D.

**Cited > 28.000 times**

# *Inflammation in the driver's seat*

Atherosclerosis is characterized by chronic low grade inflammation



Libbey. Nature. 2002

- Arterial sites of disturbed laminar flow
- Subendothelial accumulation lipoproteins
- Inflammatory mØ predominant cells



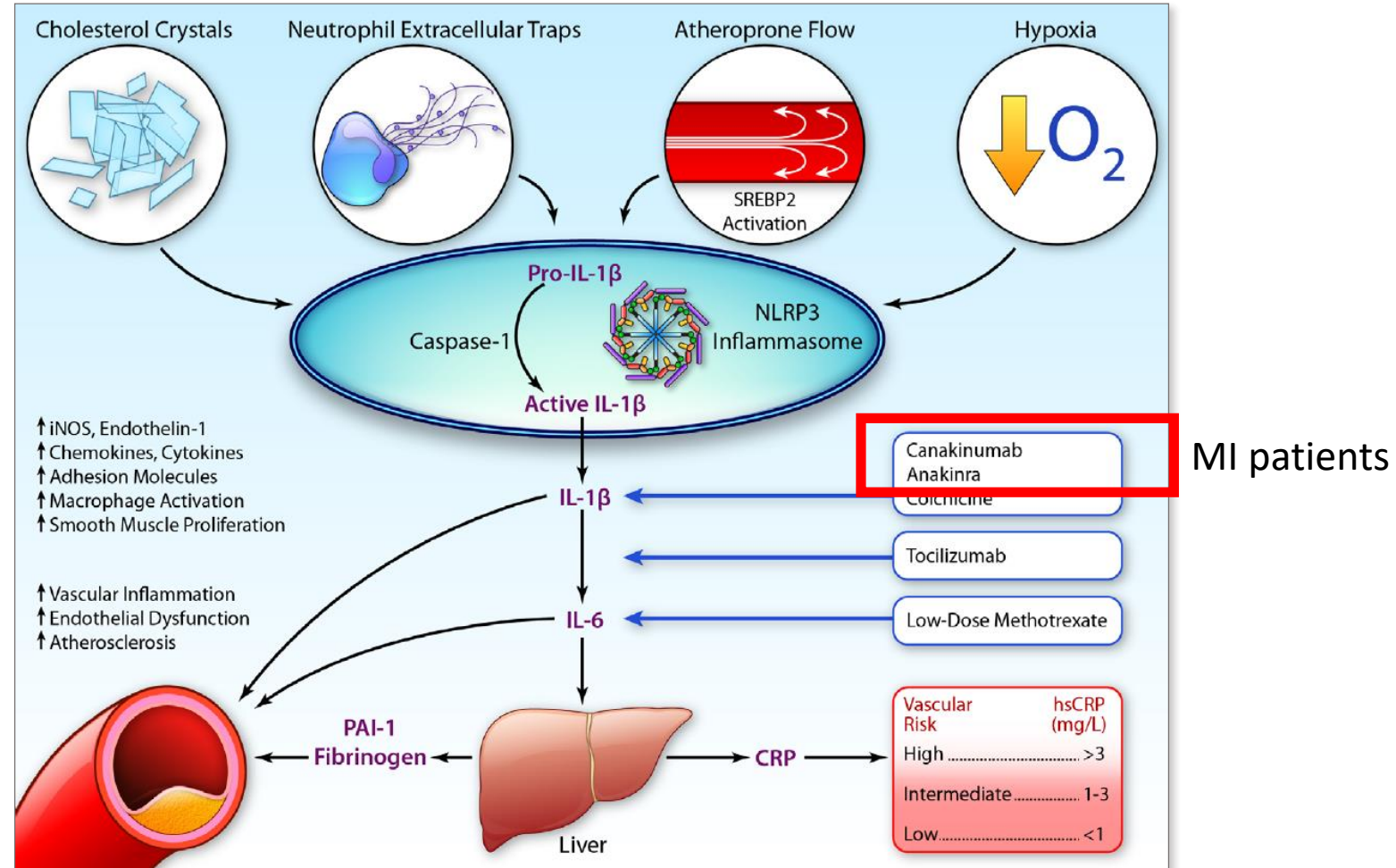
**CRP clinically useful as biomarker  
for risk prediction**



**Inhibiting inflammation the  
key to the future?**

# ***IL-1 $\beta$ inhibition as target for atheroprotection***

Upstream of CRP  $\rightarrow$  IL-1 $\beta$



Ridker PM. Circ Res 2016;118:145-156.

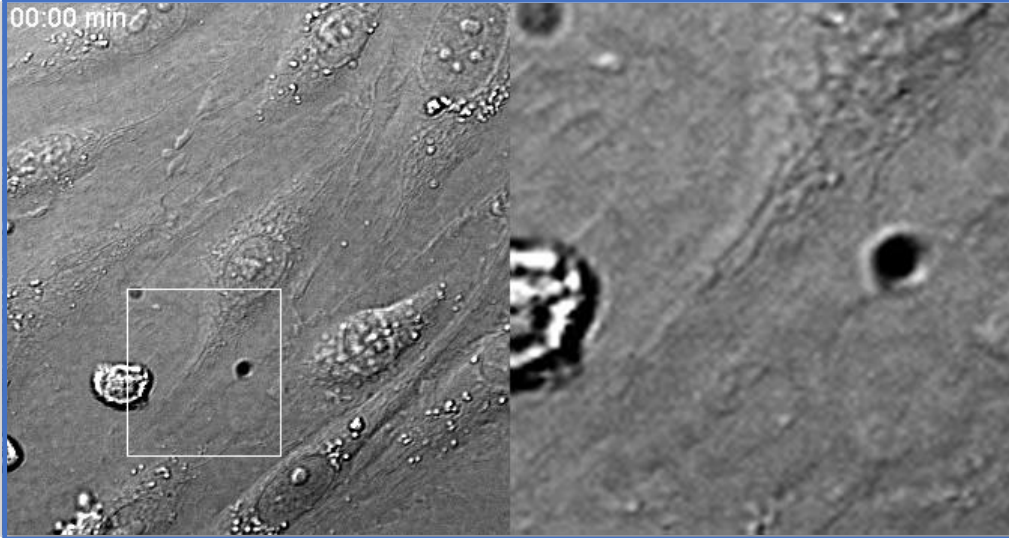
Antiinflammatory therapy targeting led to a significantly lower rate of recurrent cardiovascular events, independent of lipid-level lowering.

# *What if we go further upstream...?*

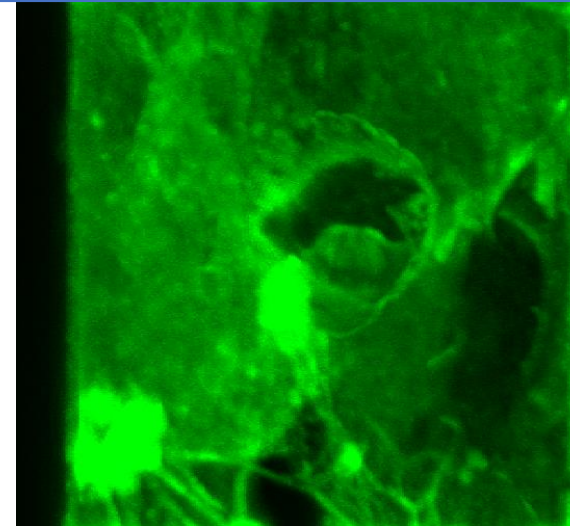
Induction of inflammation and production of inflammatory mediators costs energy



Monocyte transendothelial migration



Endothelial remodeling during migration



Cytoskeleton (actin)  
endothelium



Chemo/cytokines



(e.g. IL-1 $\beta$ )

Lipids — **(Immuno)metabolism** — Inflammation — Cytokine production, migration



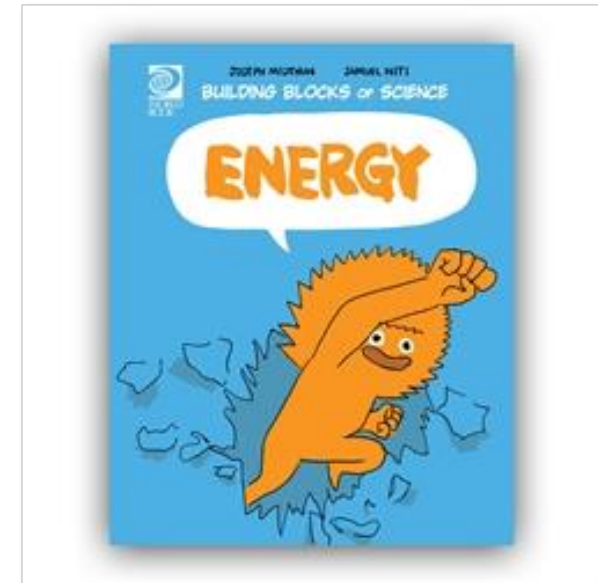
# *Immunometabolism*

## Immunometabolism:

The changes in intracellular metabolic pathways in immune cells that alter their function

3 major metabolic pathways involved:

- Glycolysis
- Tricarboxylic Acid (TCA) cycle
- Fatty acid oxidation



→ **Complex interplay between metabolic reprogramming and immunity**



*Aerobic  
Respiration*

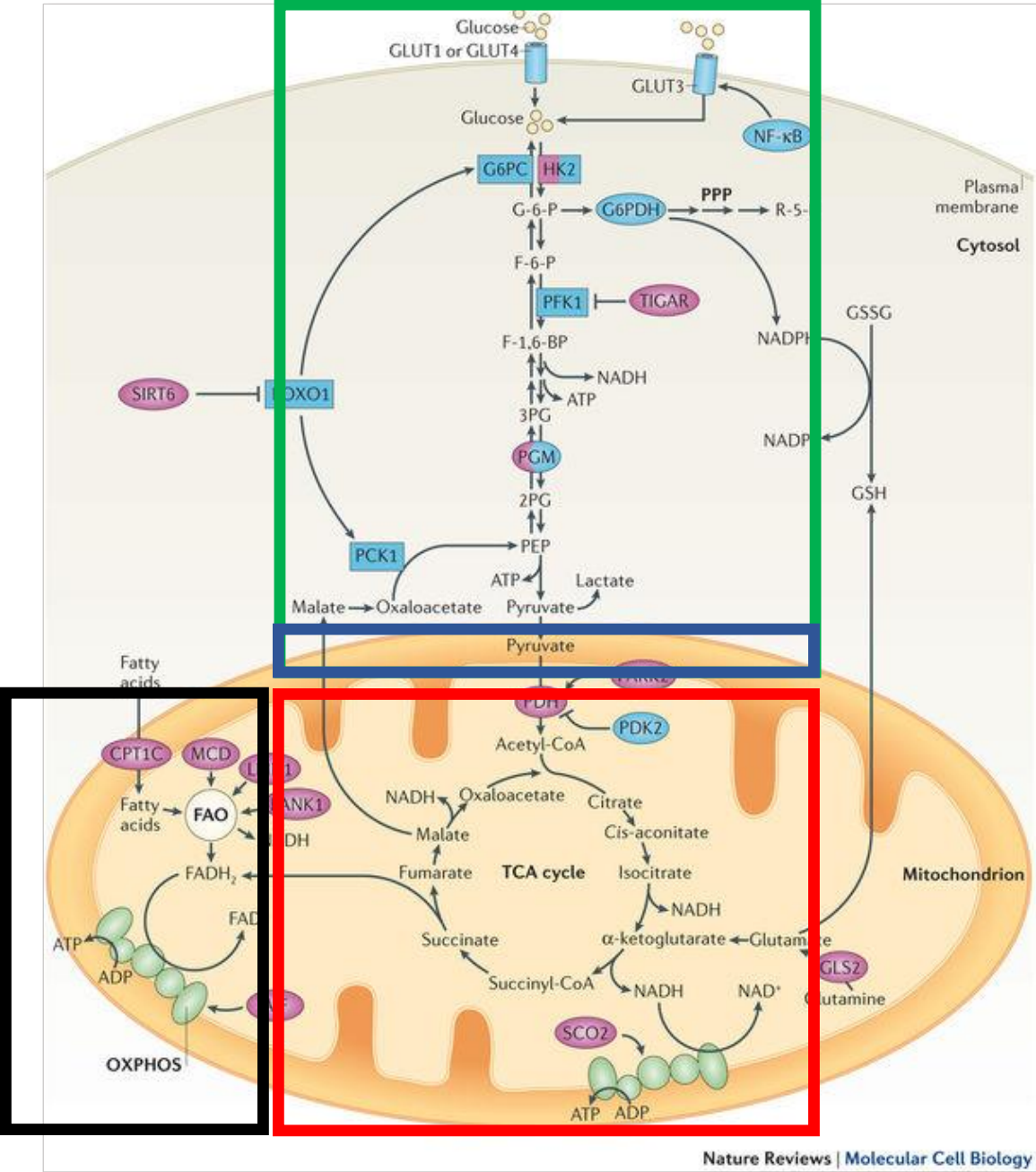
Glycoylsis

2 ATP

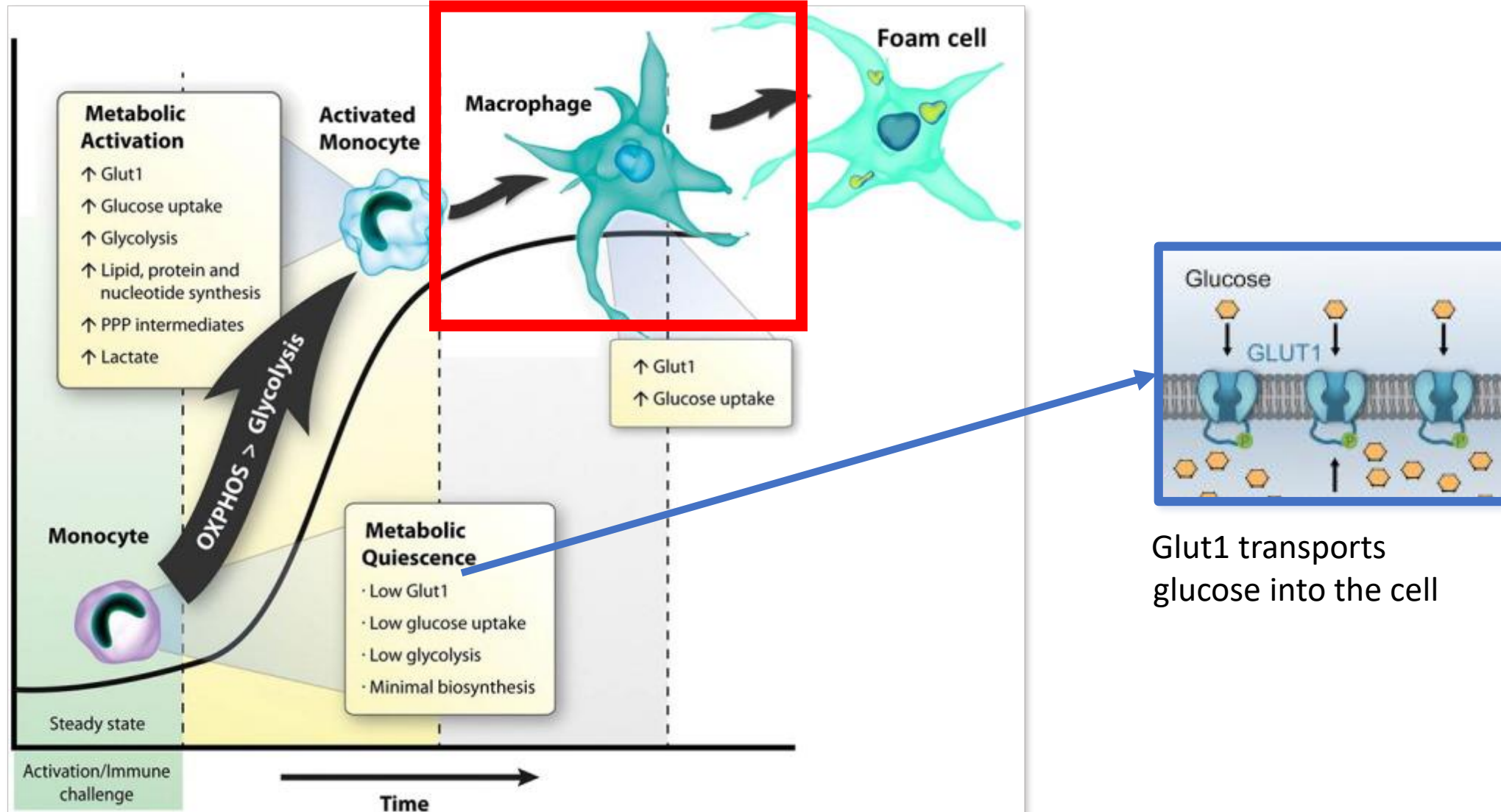
Link reaction

TCA cycle

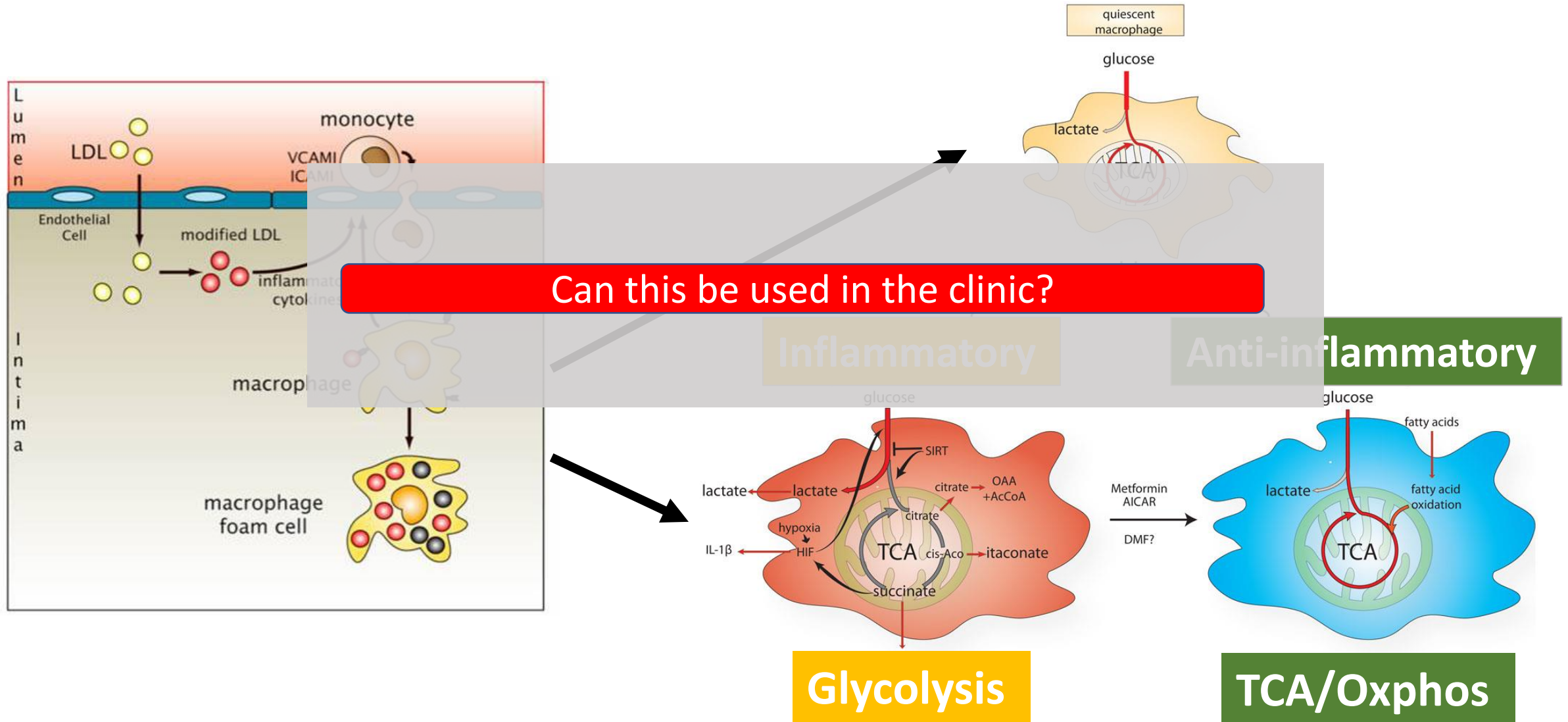
OXPHOS  
30 ATP



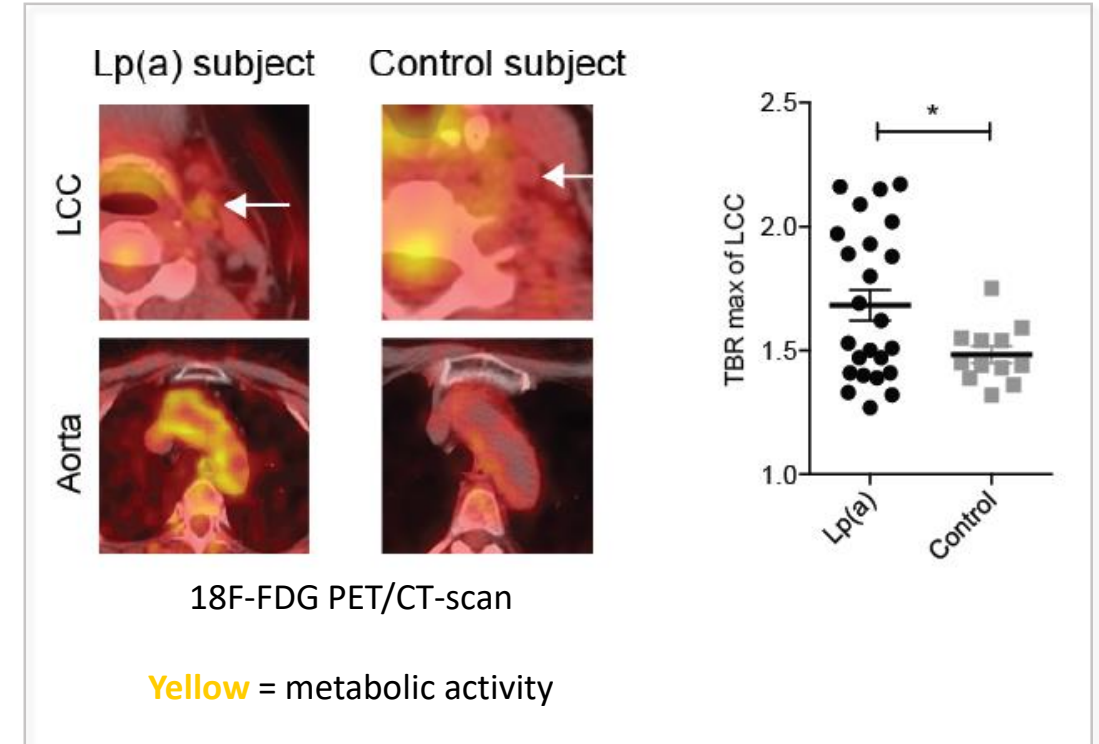
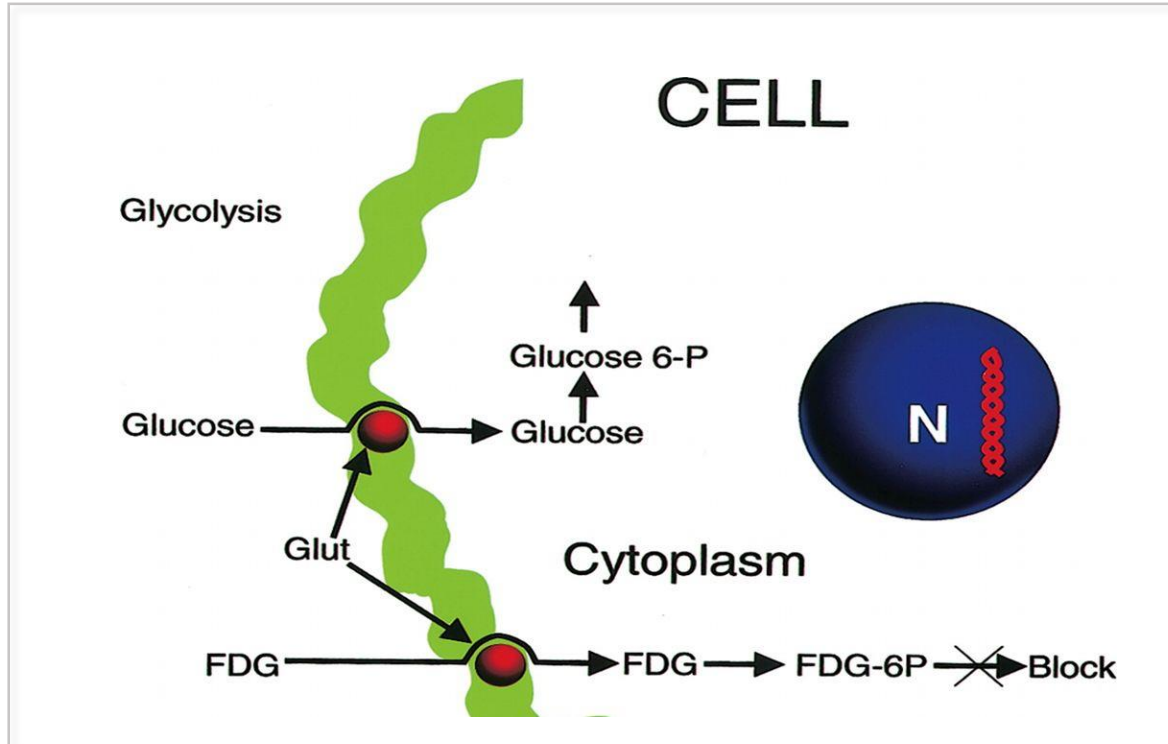
# *Different metabolic states during lifecycle*



# What they encounter determines “who” they becomes



# ***Lp(a) patients have increased vessel wall inflammation measured with 18F-FDG PET/CT-scan***

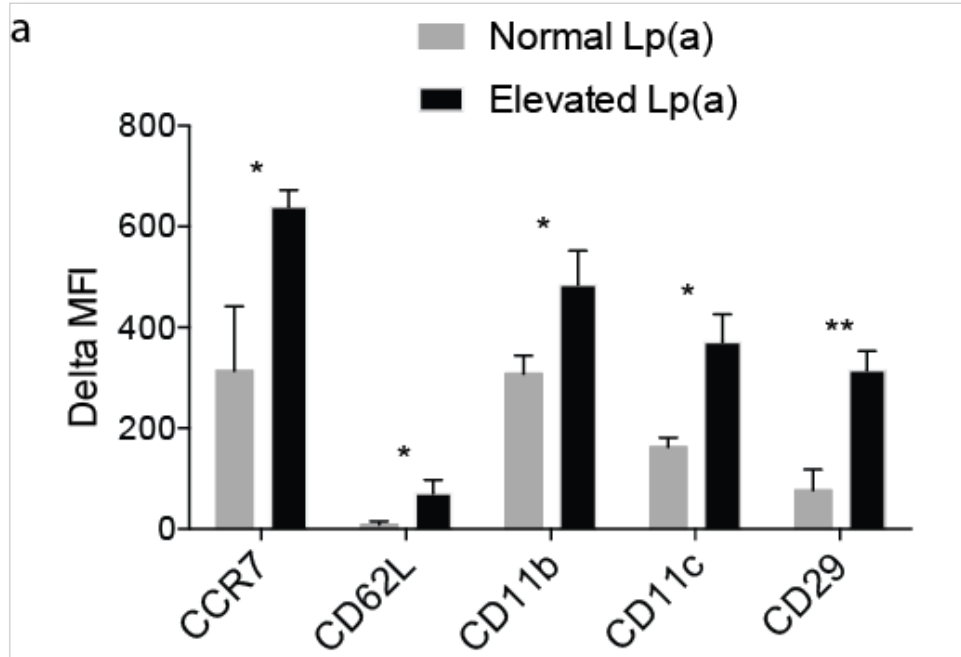


Van Der Valk et al. Circ 2016. 134(8):611-24

→ Increased glucose uptake in carotid and aorta  
(=increased glycolysis)

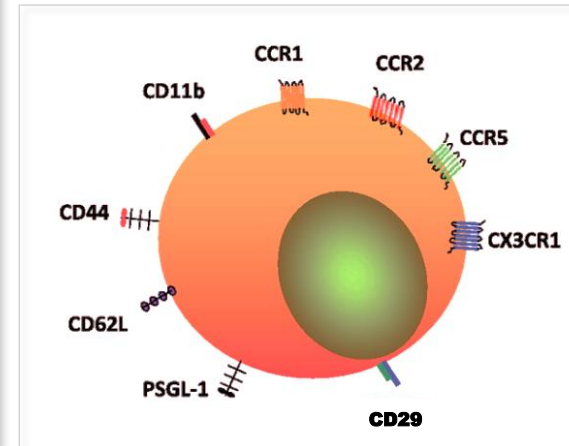
**What is the effect of this increased glycolysis?**

# *Lp(a) patients have 'pro-inflammatory' monocytes*



Increased expression of

- Chemokines
- Adhesion markers

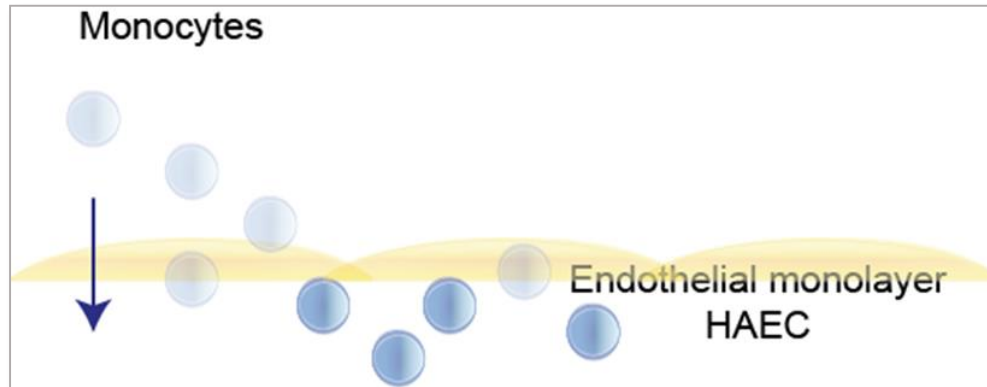


Van Der Valk et al. Circ 2016. 134(8):611-24

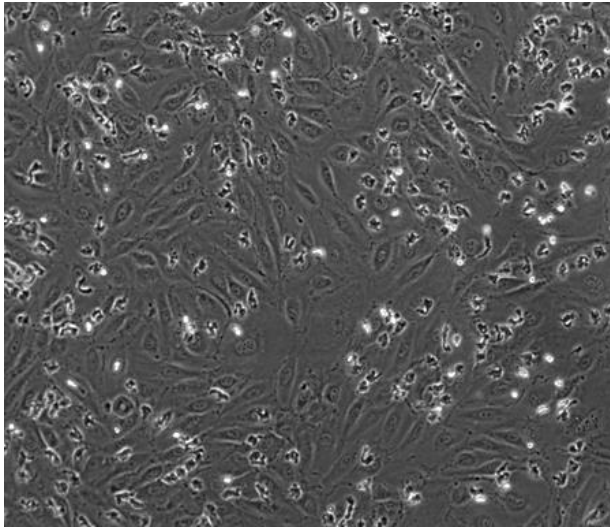
Functional differences in monocyte behavior?



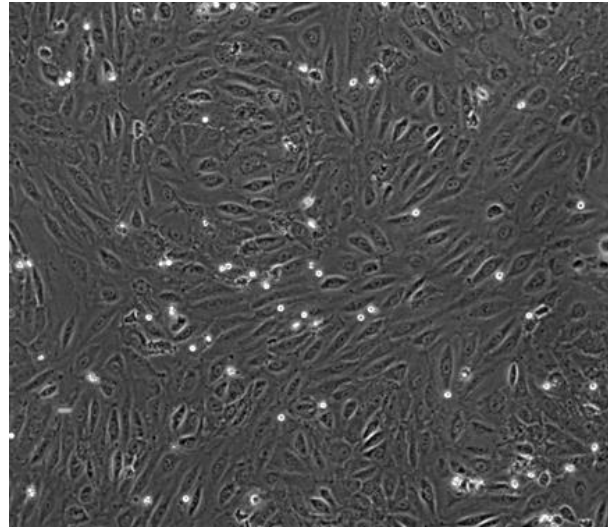
# *Lp(a) patients have 'pro-migratory' monocytes ex-vivo*



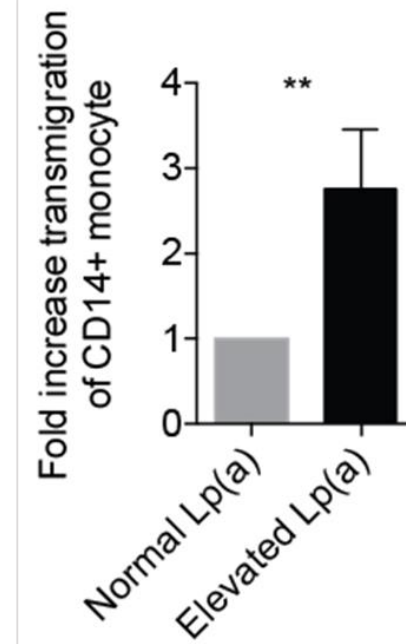
Hoog Lp(a)



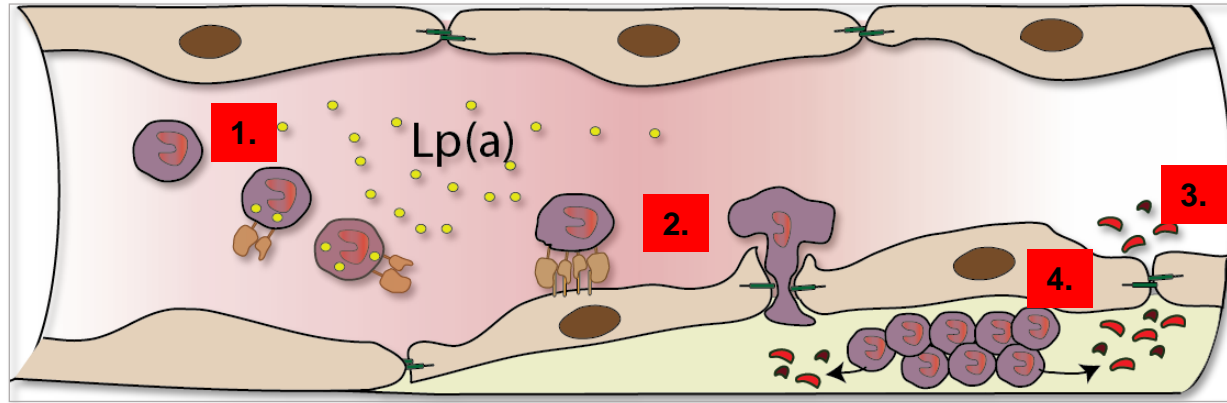
Laag Lp(a)



Van Der Valk et al. Circ 2016. 134(8):611-24



## *Sub-conclusion: Lp(a) & Inflammation*



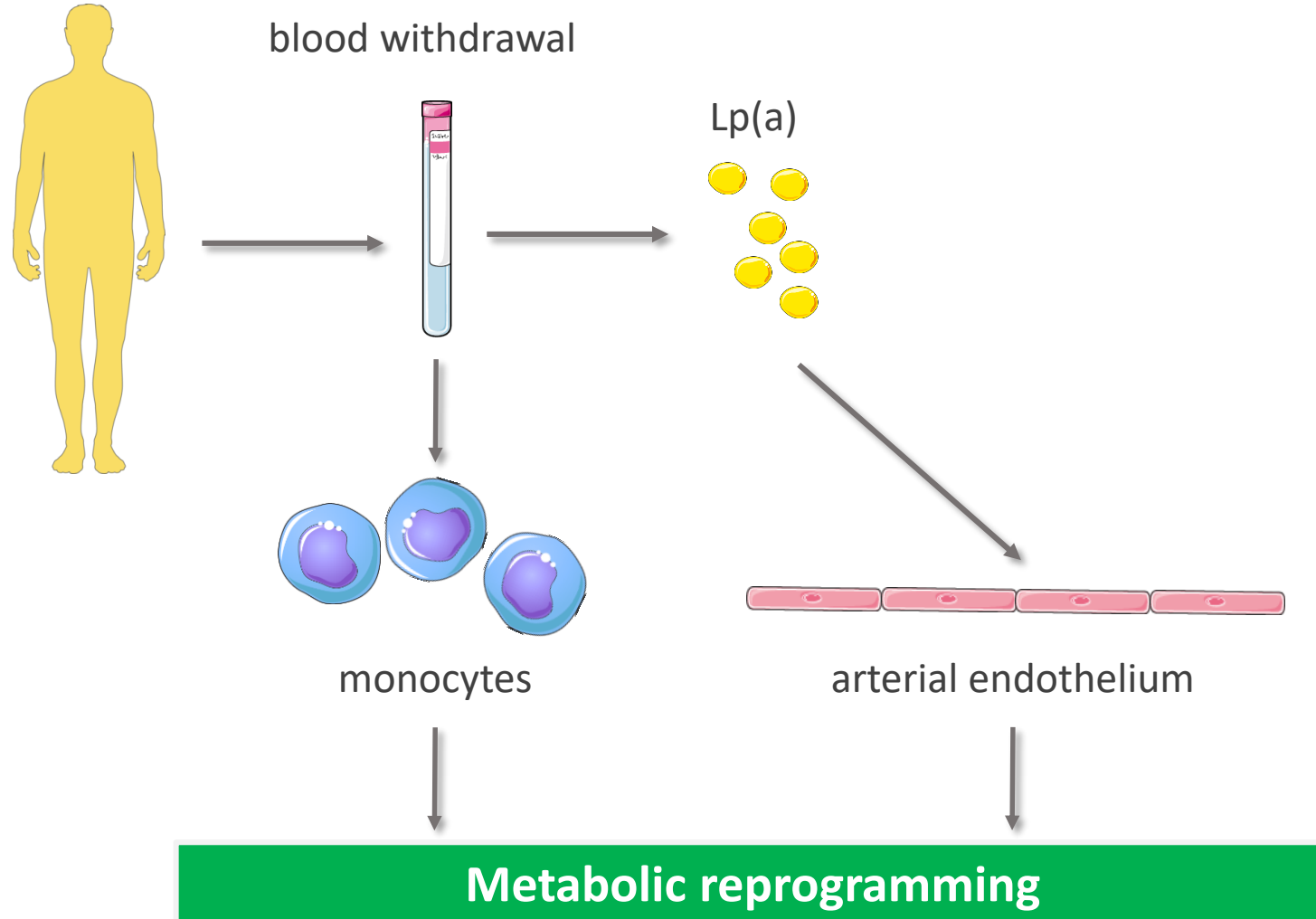
1. Increased monocyte activation
2. Enhanced adhesion and transmigration across the endothelium
3. Increased production of pro-inflammatory cytokines
4. Elevated inflammatory activity of the arterial wall (PET/CT)





# ***Lp(a)-induced metabolic reprogramming***

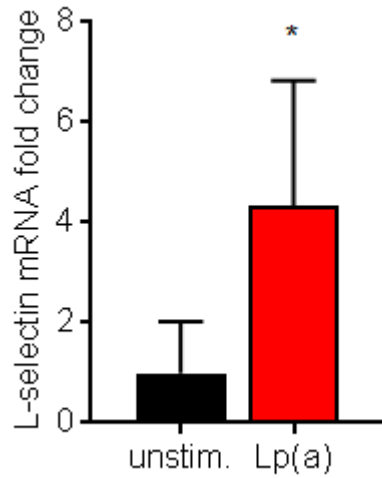
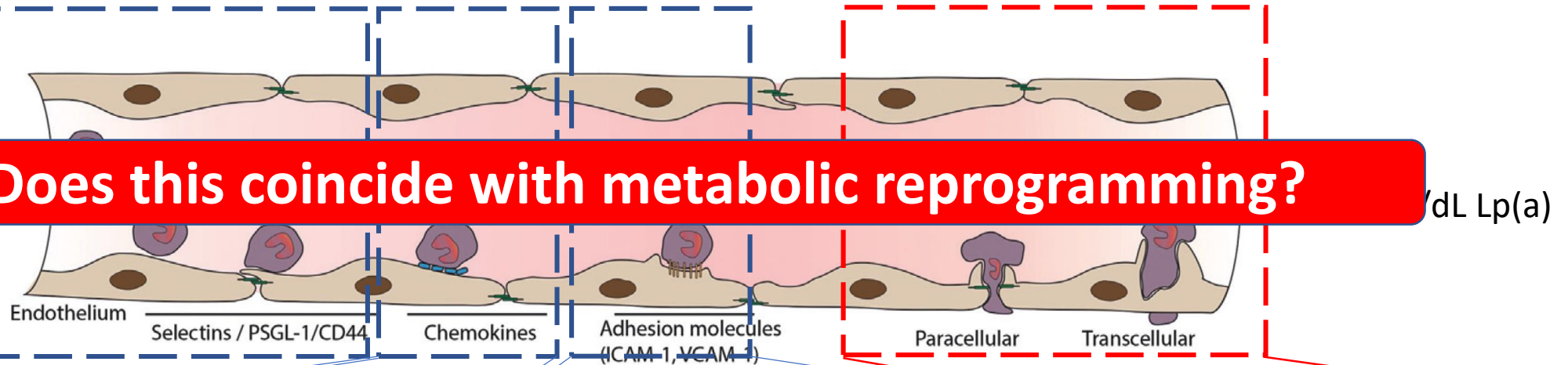
individual with elevated  
Lp(a) levels



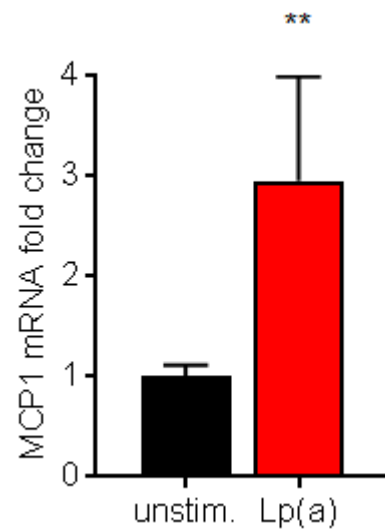
# *Lp(a) induces endothelial cell inflammation and monocyte migration*

**Does this coincide with metabolic reprogramming?**

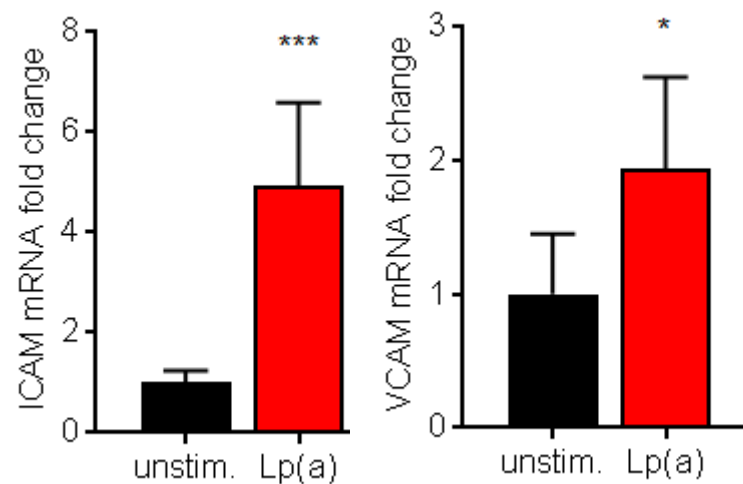
Kroon et al. *Int. Rev. Cell. Mol. Biol.* **2016**



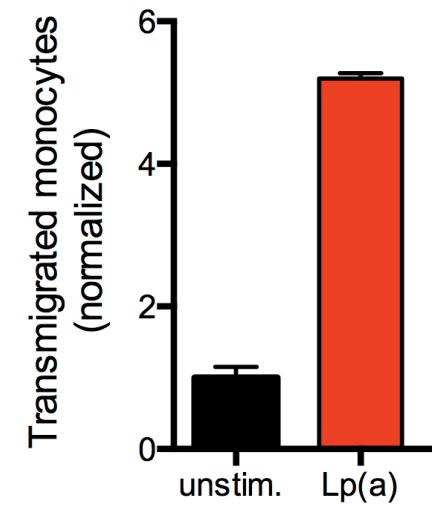
**Rolling**



**Chemokine activation**

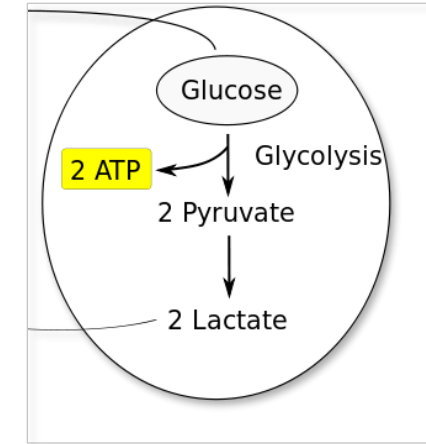
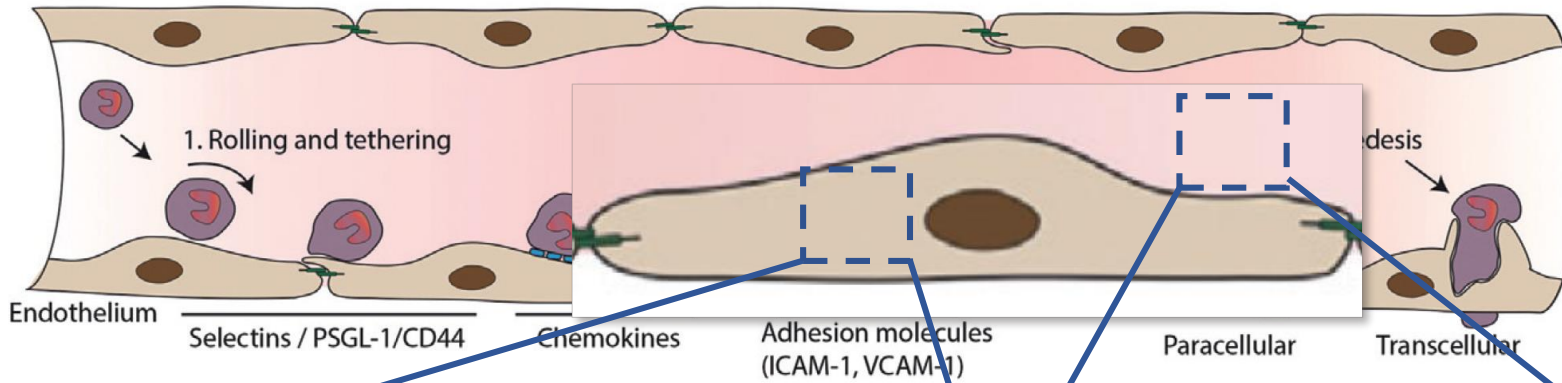


**Firm adhesion**

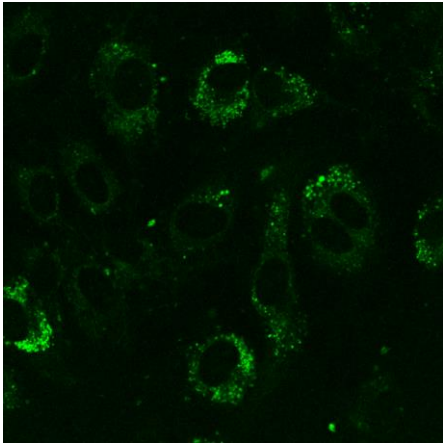


**Migration**

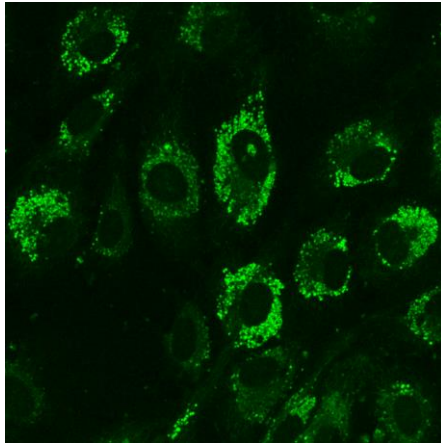
# *Lp(a) induces endothelial cell metabolic reprogramming*



Green labeled glucose

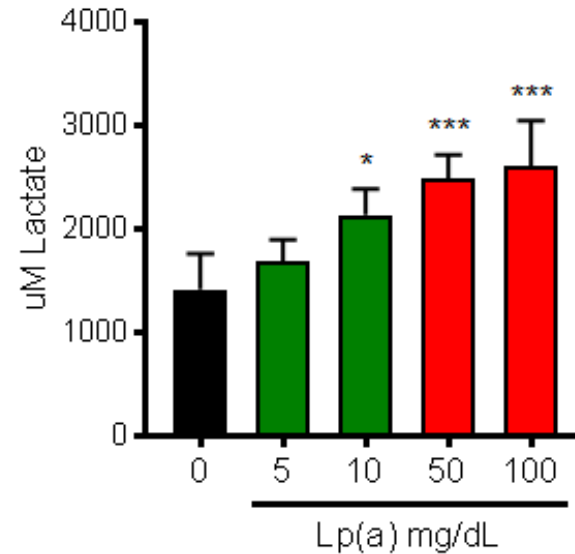


unstim.



Lp(a)

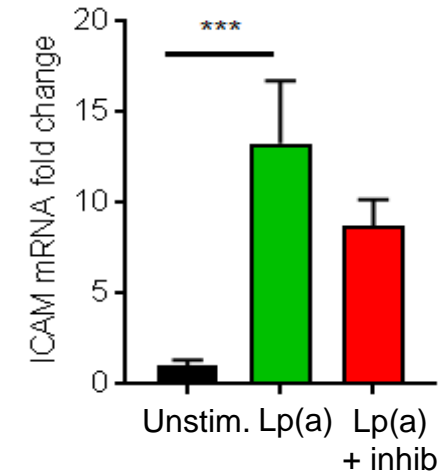
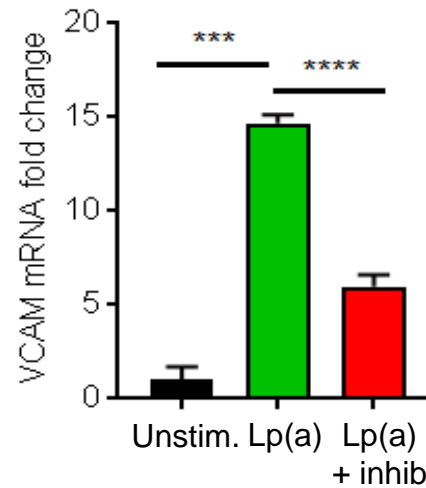
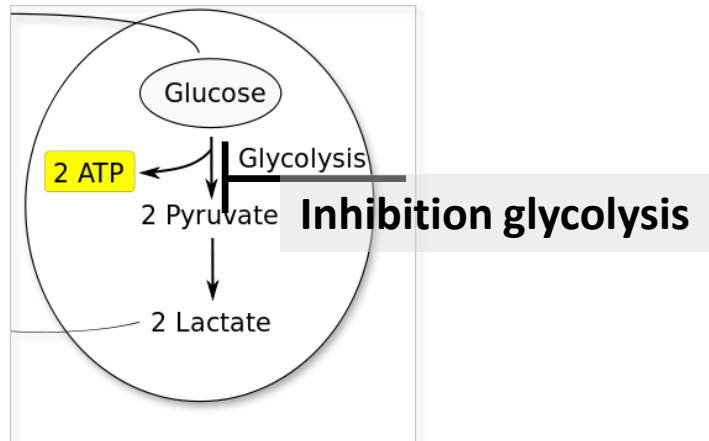
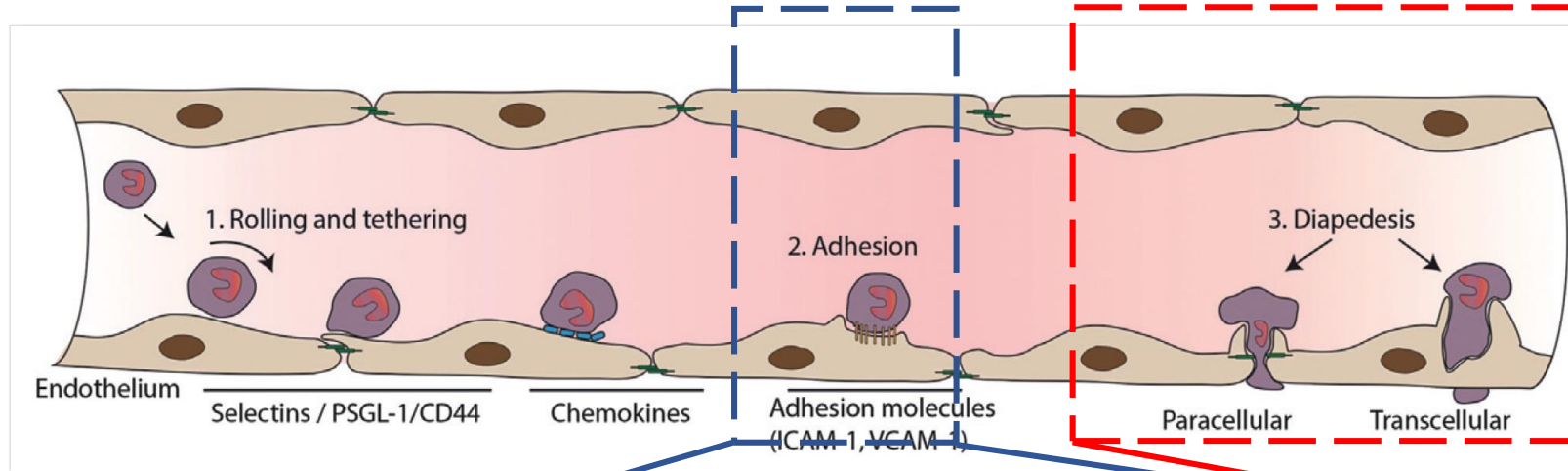
Glucose uptake



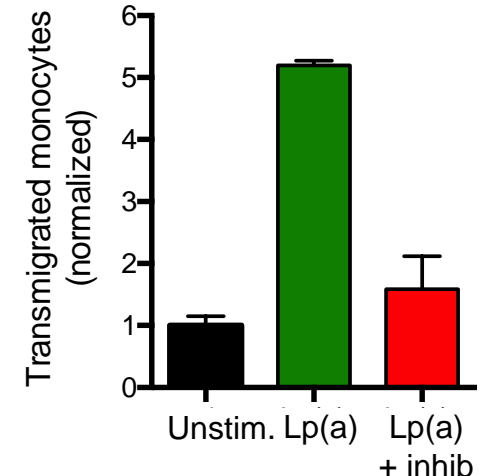
Lactate production

Inhibition?

# Targeting cell metabolism decreases inflammation and migration



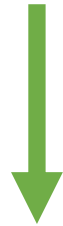
Firm adhesion



Migration

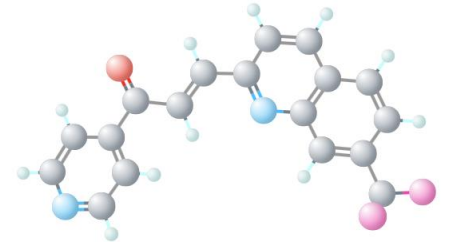
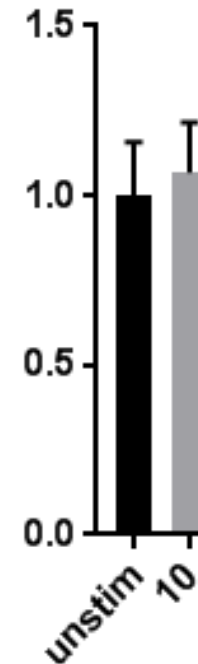
# ***Clinical perspective of inhibition of inducible glycolysis***

- Selective inhibitor of inducible glycolysis: basal glycolytic rate not affected
- Promising completed phase I trial in cancer patients with various solid tumors. No side effects reported



**Possibly the new era of  
cardiovascular intervention**

**Endothelial viability  
after 24h of inhibitor**



**PFK-158**



# Acknowledgements

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