

# Verschillen tussen vrouwen en mannen met hart- en vaatziekten

**Prof. dr. ir. Hester den Ruijter**

Hoogleraar hart- en vaatziekten bij vrouwen, UMC Utrecht



# Disclosures

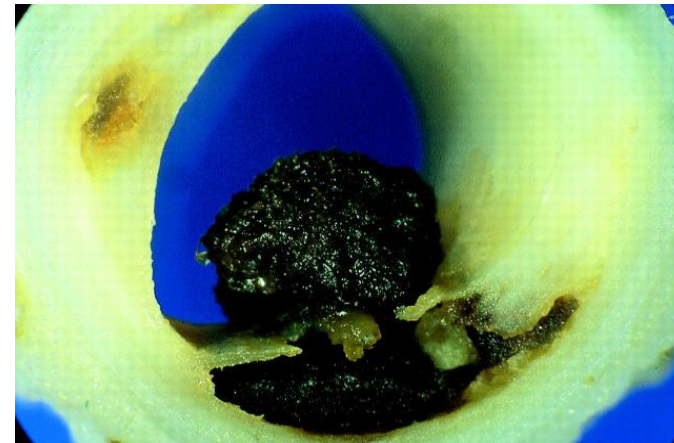
Potentiële belangenverstrengeling	geen
Voor presentatie mogelijk relevante relaties:	
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Honorarium of andere (financiële) vergoeding	
Aandeelhouder	
Andere relatie, namelijk ...	

# Scope

- This presentation explores the influence of sex-assigned-at-birth on atherosclerotic mechanisms
- The terms “female” and “women” are used in reference to sex-assigned-at-birth.
- Efforts to better understand the influence of gender identification and gender-affirming therapies on atherosclerosis are also important but will not be covered today.

# Sex-based differences in atherosclerosis

Plaque erosion common in younger women  
Plaque rupture more common in men



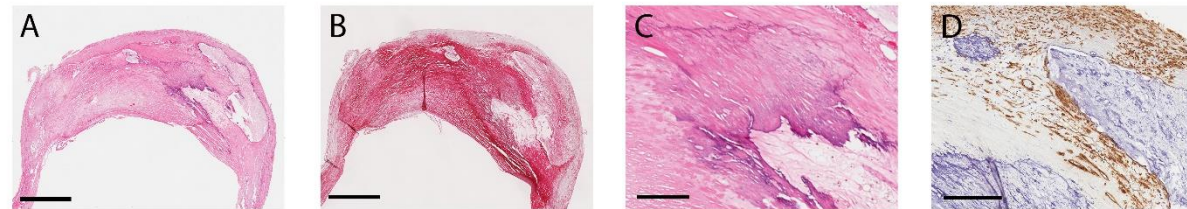
*Sato et al. Curr Atheroscler Rep 2022, Lee et al. JACC Cardiovasc Imaging 2020, Yagahi et al. Atherosclerosis 2015, Farb et al. Circulation 1996*

# Atherosclerotic lesions

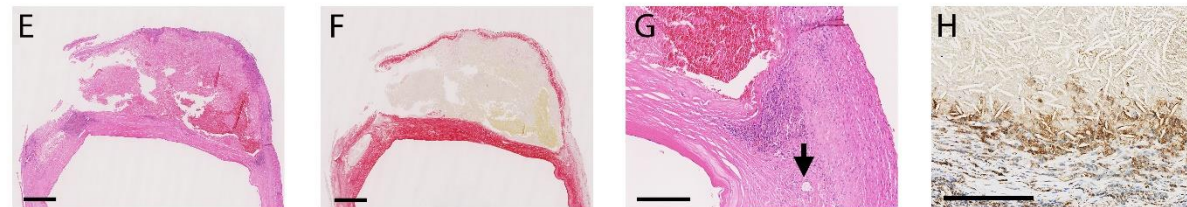
Stable is more common among women, yet symptomatic.  
Overall, in recent years the proportion of stable lesions has changed

*(den Ruijter et al. Circulation 2012 & Pasterkamp, den Ruijter, Libby, Nature Reviews Cardiology 2017)*

Stable plaque



Instable plaque



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## Research questions:

Are there sex differences gene regulation of atherosclerosis?

Can we identify (female-specific) key driver genes responsible for progression towards stable plaques and plaque erosion?

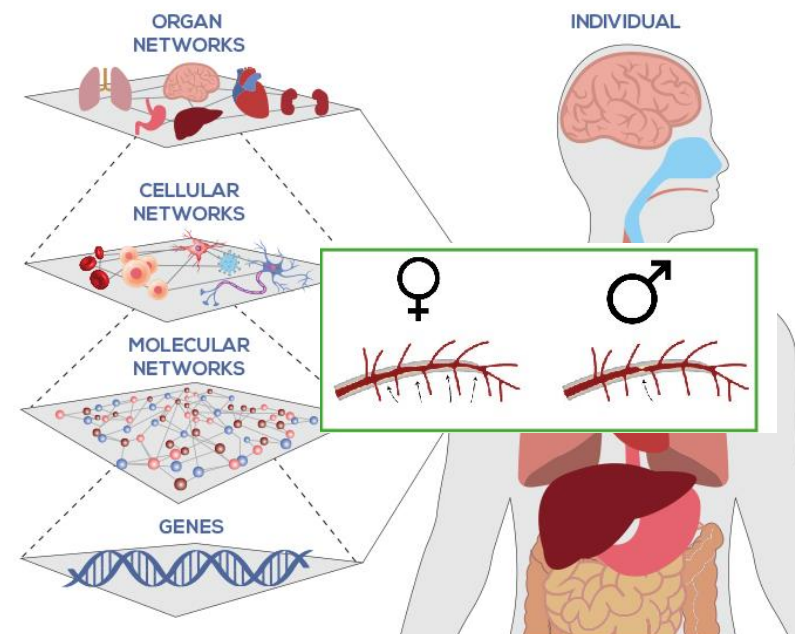


# Molecular networks of atherosclerosis

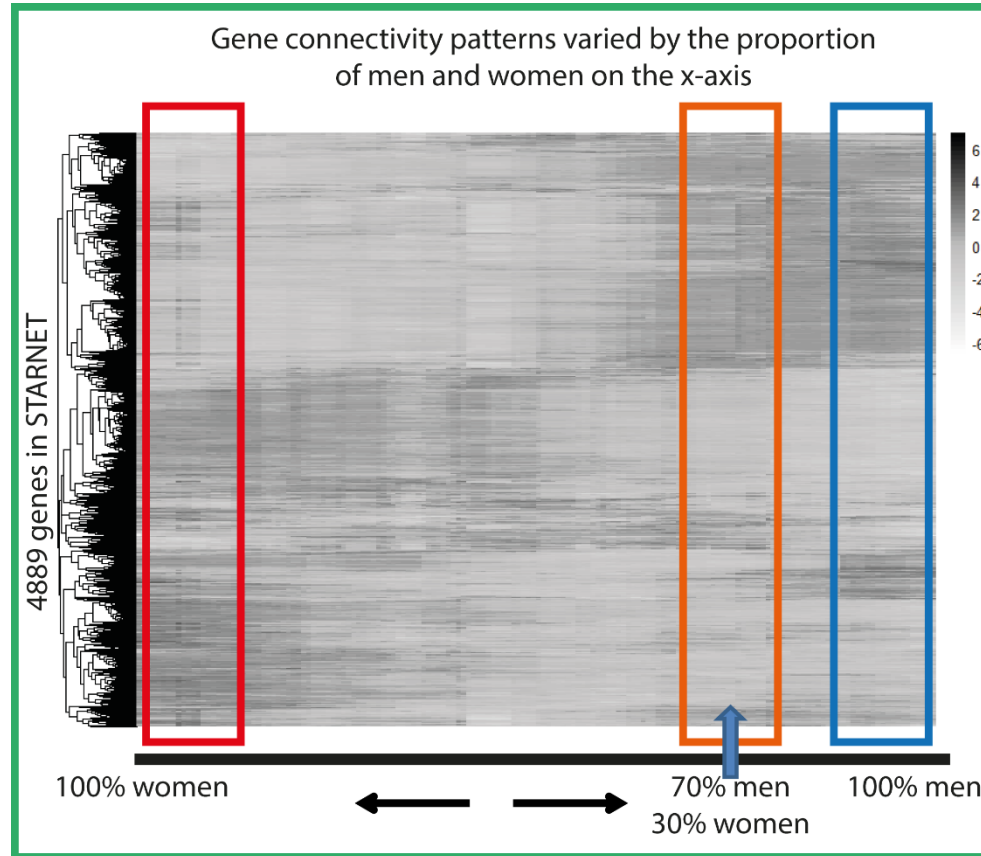
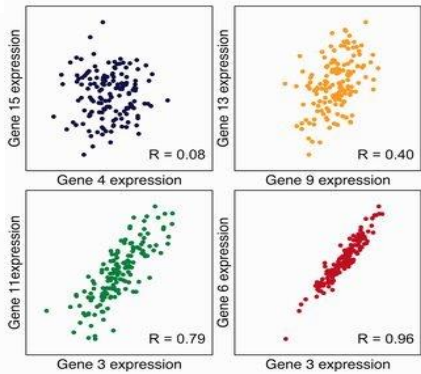
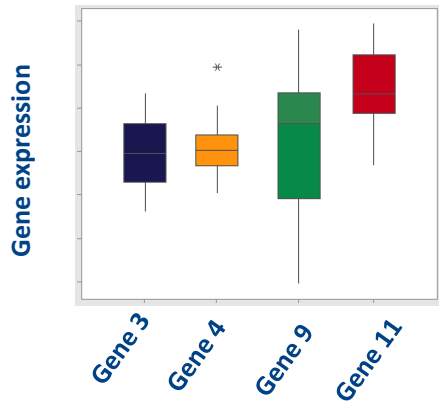
The CABG population consists of 31% women

Aortic atherosclerosis gene expression data

We selected 160 women, and age-matched 160 men (~69 years)



# Gene connectivity in atherosclerosis

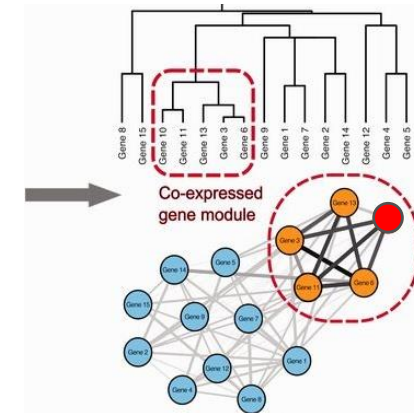
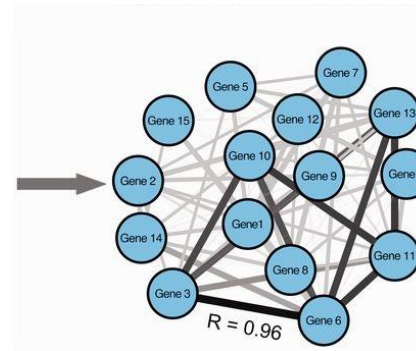
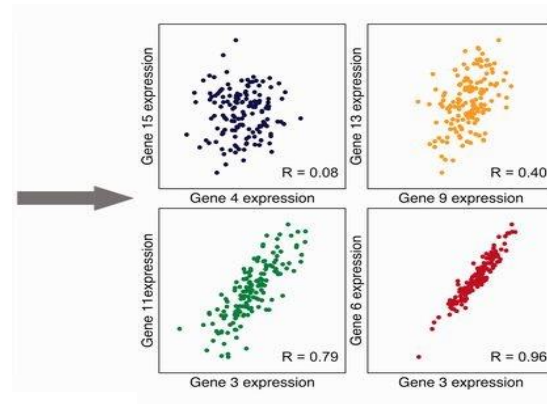
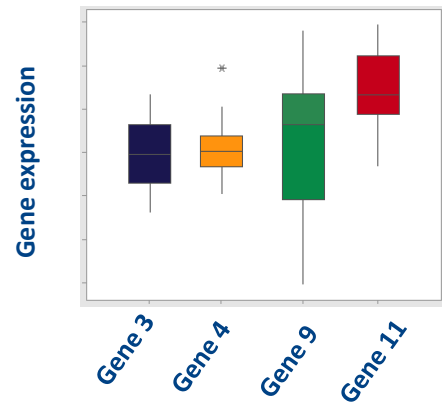


“Higher connectivity = more co-expression. Higher connected genes are more functional and more instrumental for disease biology.”

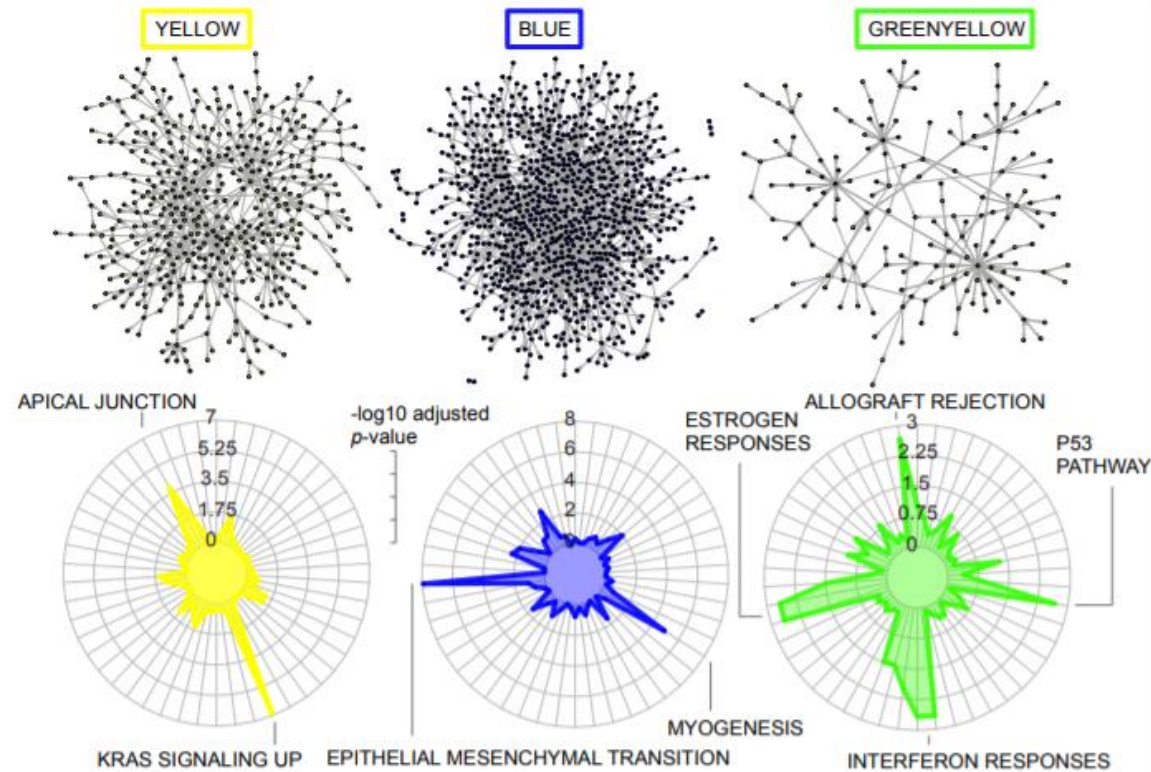
*Jeong et al 2001, Hartman et al. 2021*



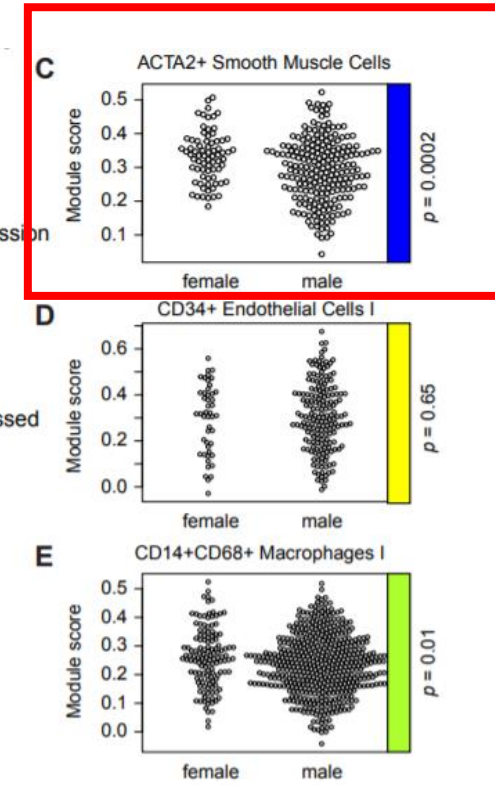
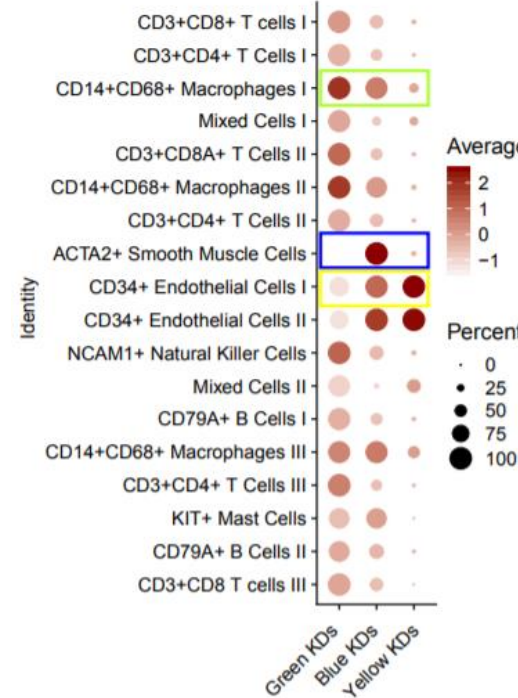
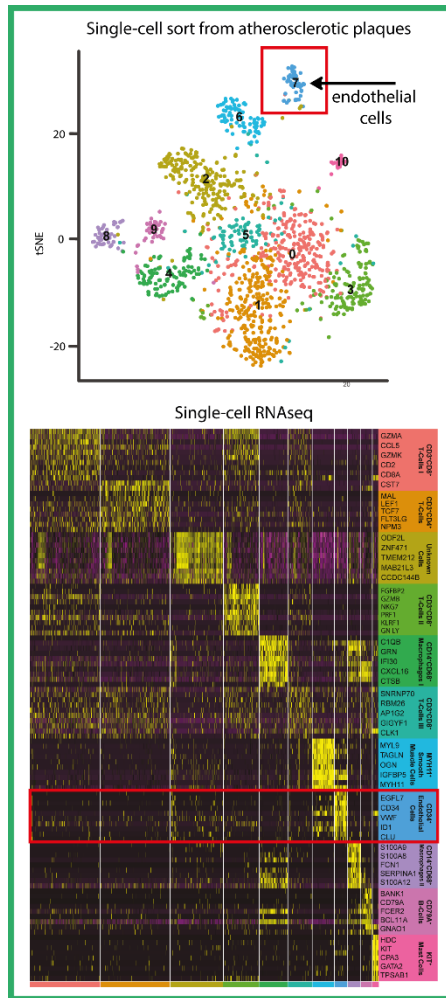
# Gene regulatory network (GRN) analysis



# Gene regulatory networks in female tissues

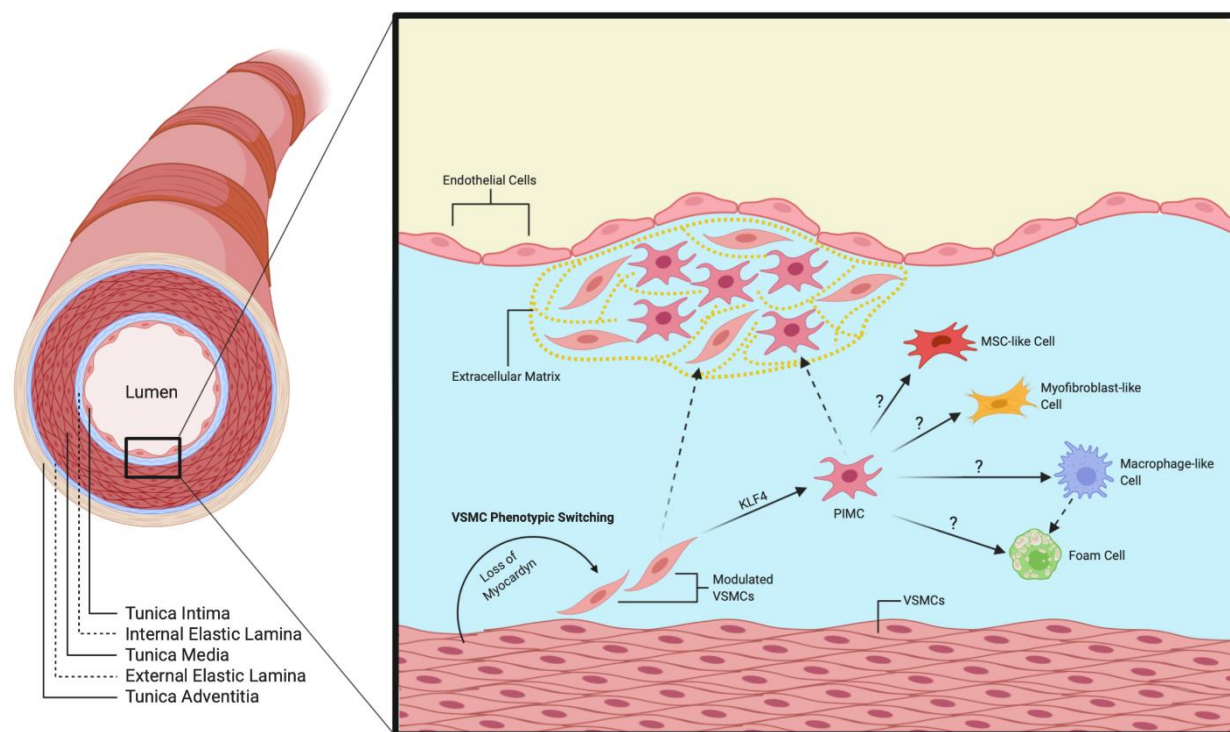


# What cell types represent these networks?



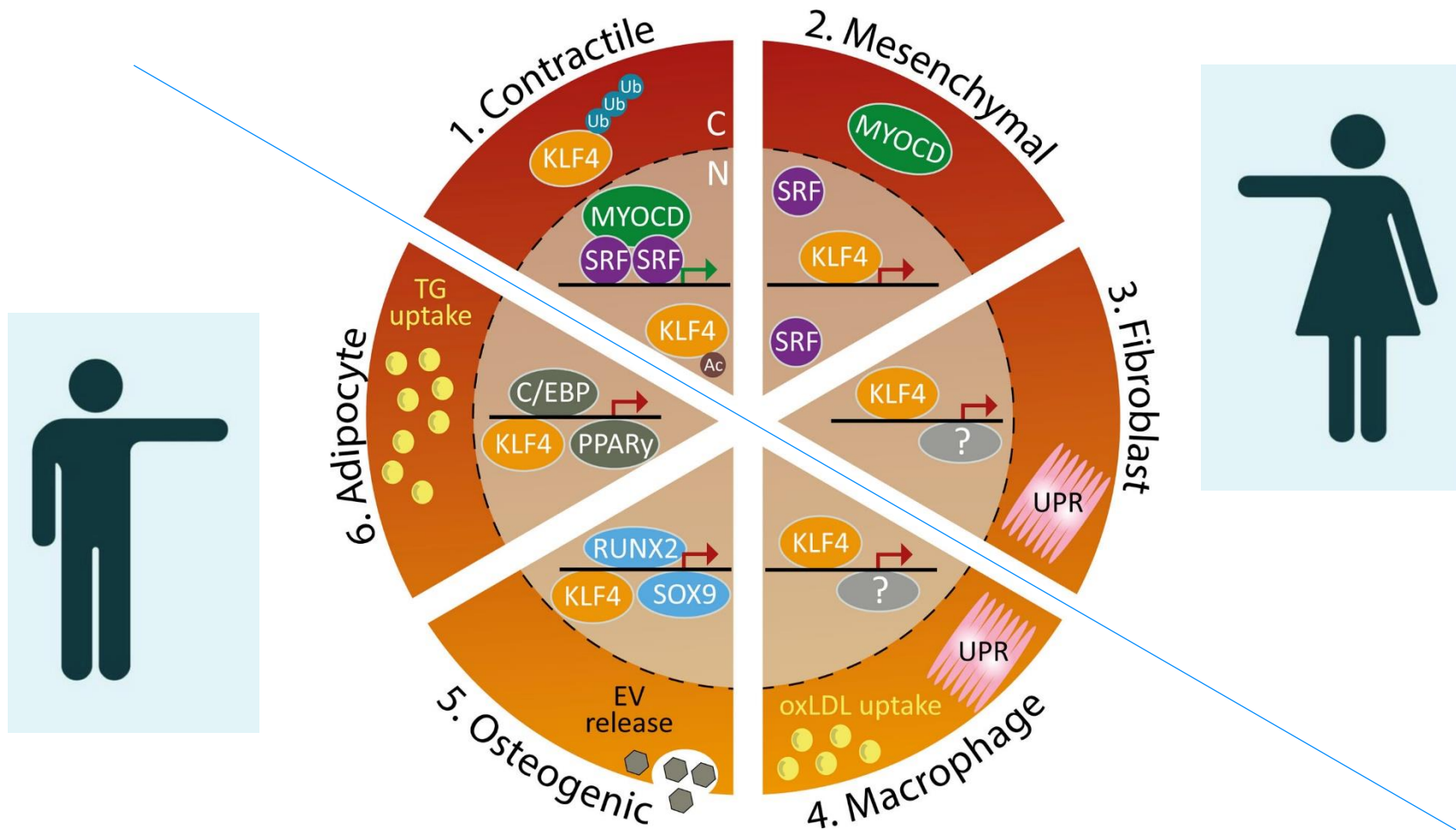


# Blue points to SMC phenotype switching



# Smooth muscle cells: sex-specific players

Dr. Ernest Diez Benavente

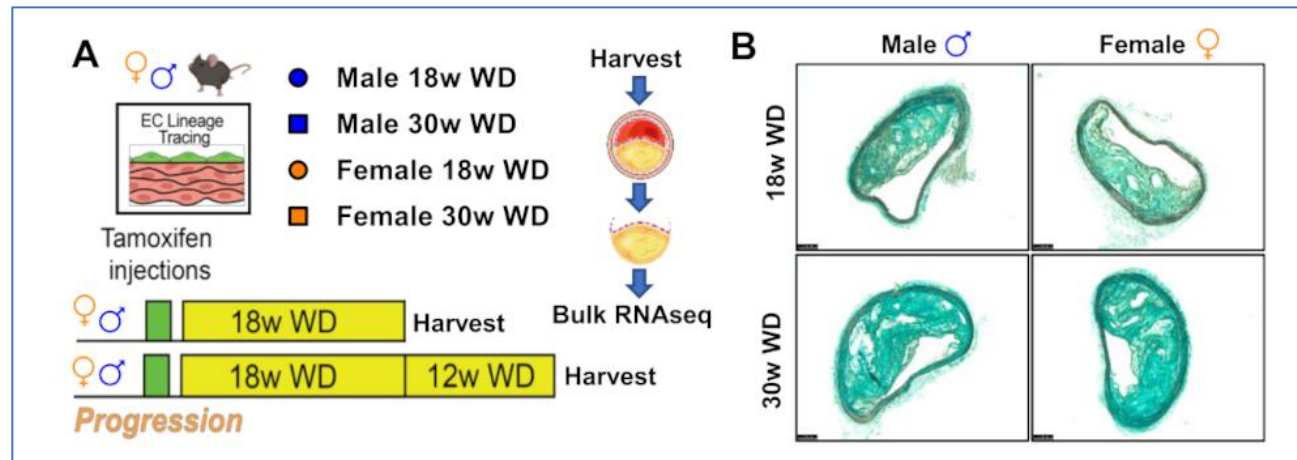


# Female networks in atherosclerosis progression

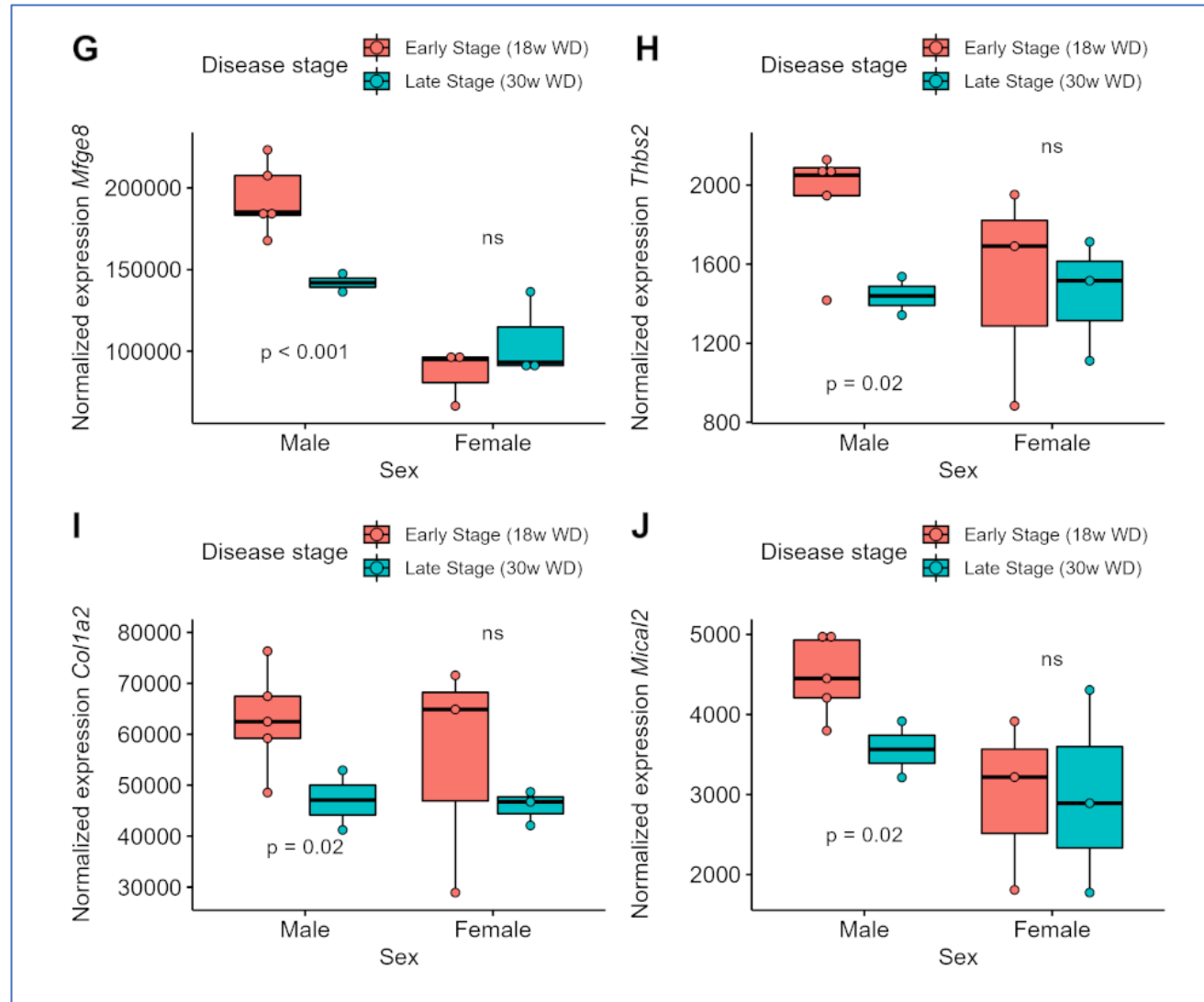


Dr. Santosh  
Karnewar

Female and male  $Apoe^{-/-}$  mice (n = 9 and 13, respectively). Mice were fed a western diet for 18 weeks (early-stage atherosclerosis) or 30 weeks (late-stage atherosclerosis)



# Male-specific downregulation of female network genes



# Conclusions

Gene regulatory networks in atherosclerosis depend on sex

Female atherosclerosis is characterized by phenotypic modulation of SMCs and driven by gene regulatory networks that promote a fibrous vulnerable plaques

The key driver genes of these female networks seem to be downregulated in males over atherosclerosis progression



# Acknowledgements

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