KING'S BHF CENTRE OF RESEARCH EXCELLENCE

kcl.ac.uk/schools/medicine/research/cardio/bhfcentre/

Prospective Study on Circulating MicroRNAs and Risk of Myocardial Infarction

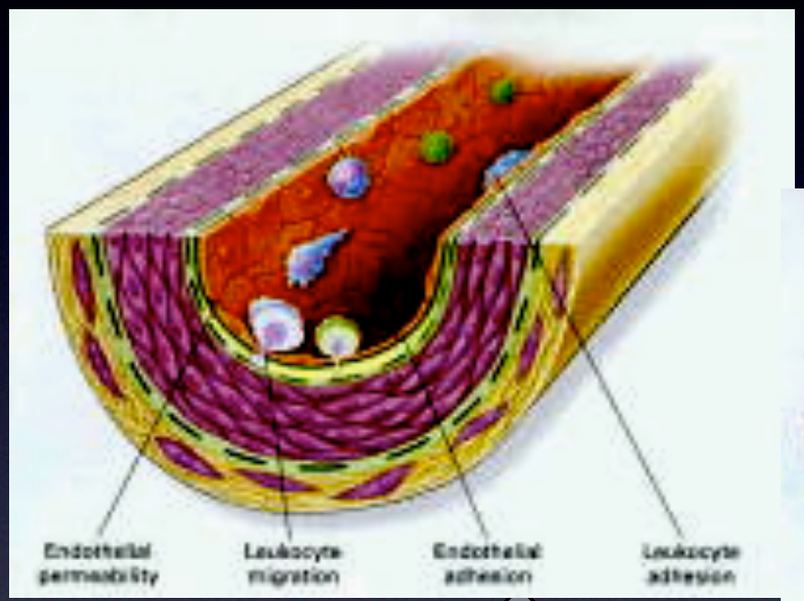
Manuel MAYR, MD, PhD
Professor of Cardiovascular Proteomics
British Heart Foundation Centre

British Heart Foundation

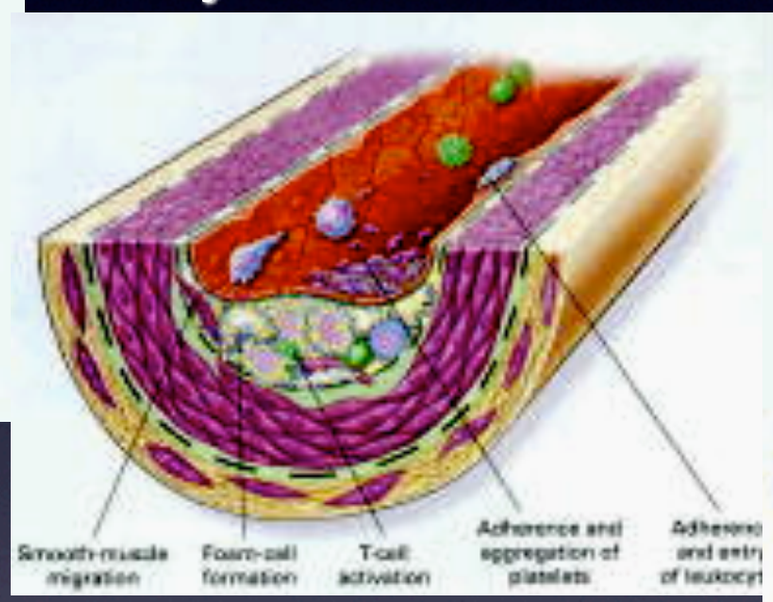
KING'S College LONDON

Strategies to deliver new vascular biomarkers ?

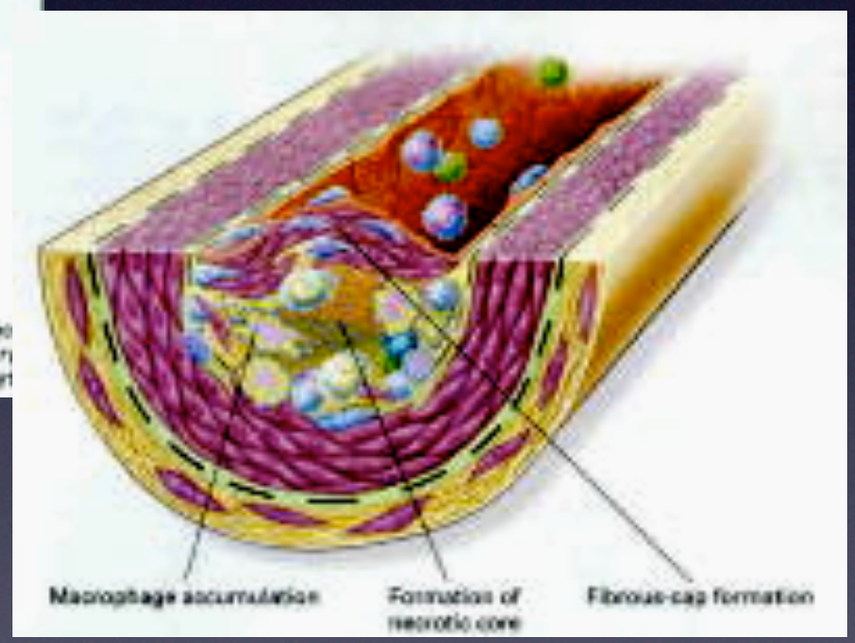
Endothelial dysfunction



Fatty streak formation



Advanced lesion



MiRNAs

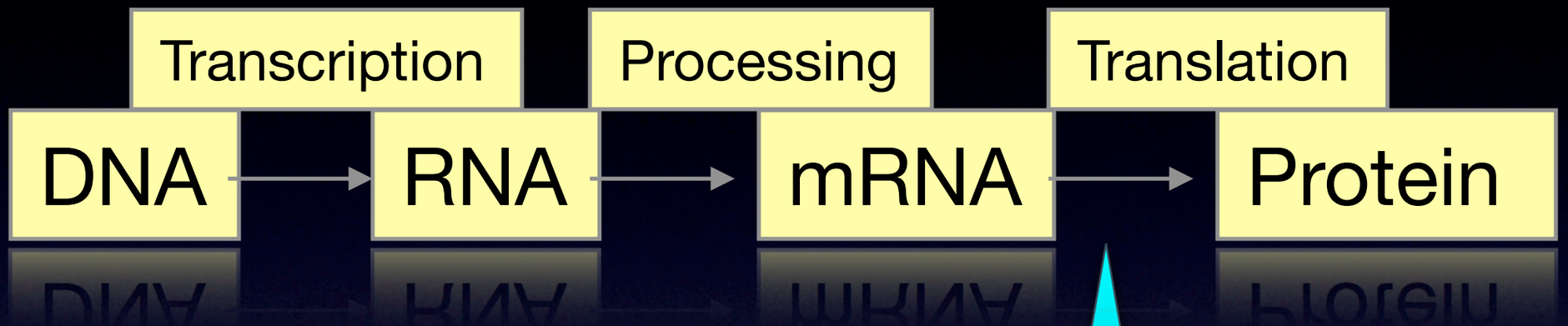
Dr. A. Zampetaki

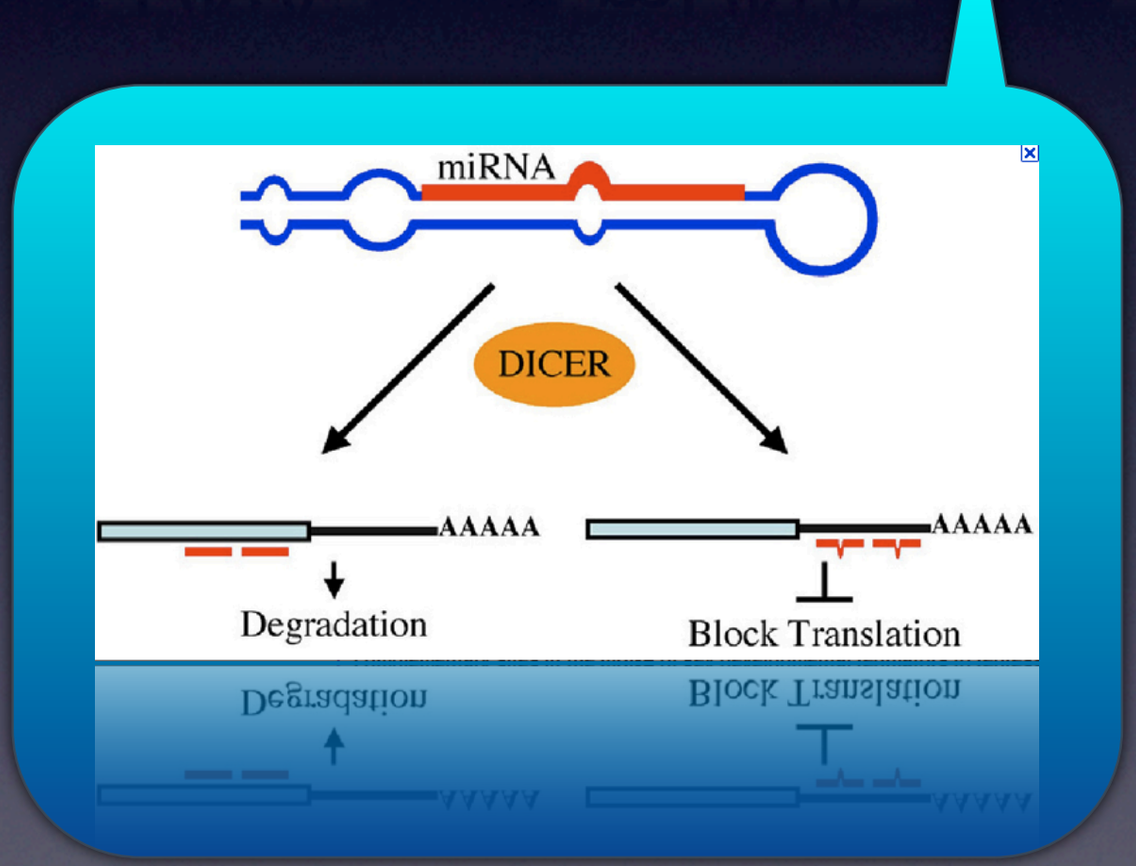
Lipidomics

Proteomics

MicroRNAs

Small Non-Coding RNAs

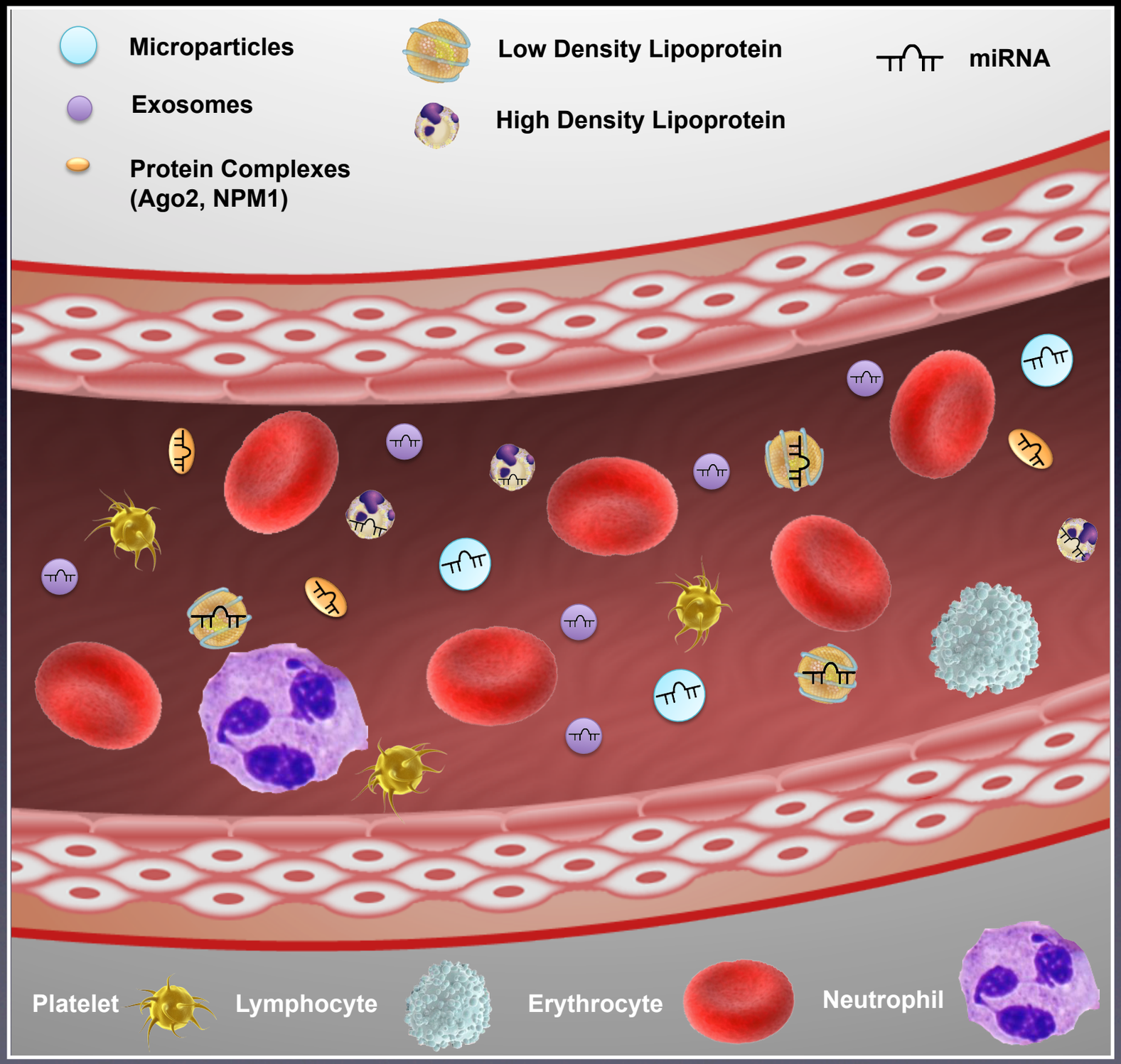




Another layer of complexity for regulating gene expression

Circulating MicroRNAs

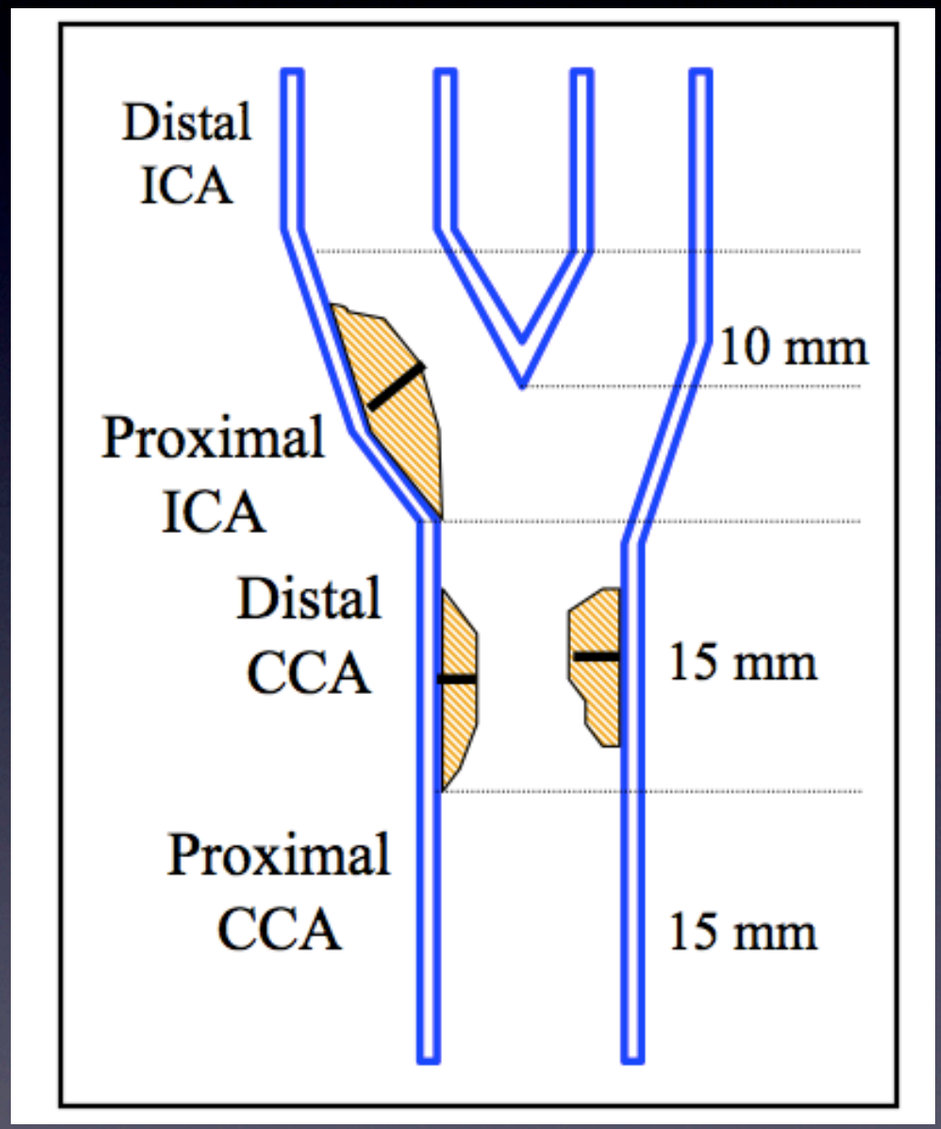
New Biomarkers for Cardiovascular Disease ?



Response to Cardiovascular Risk Factors

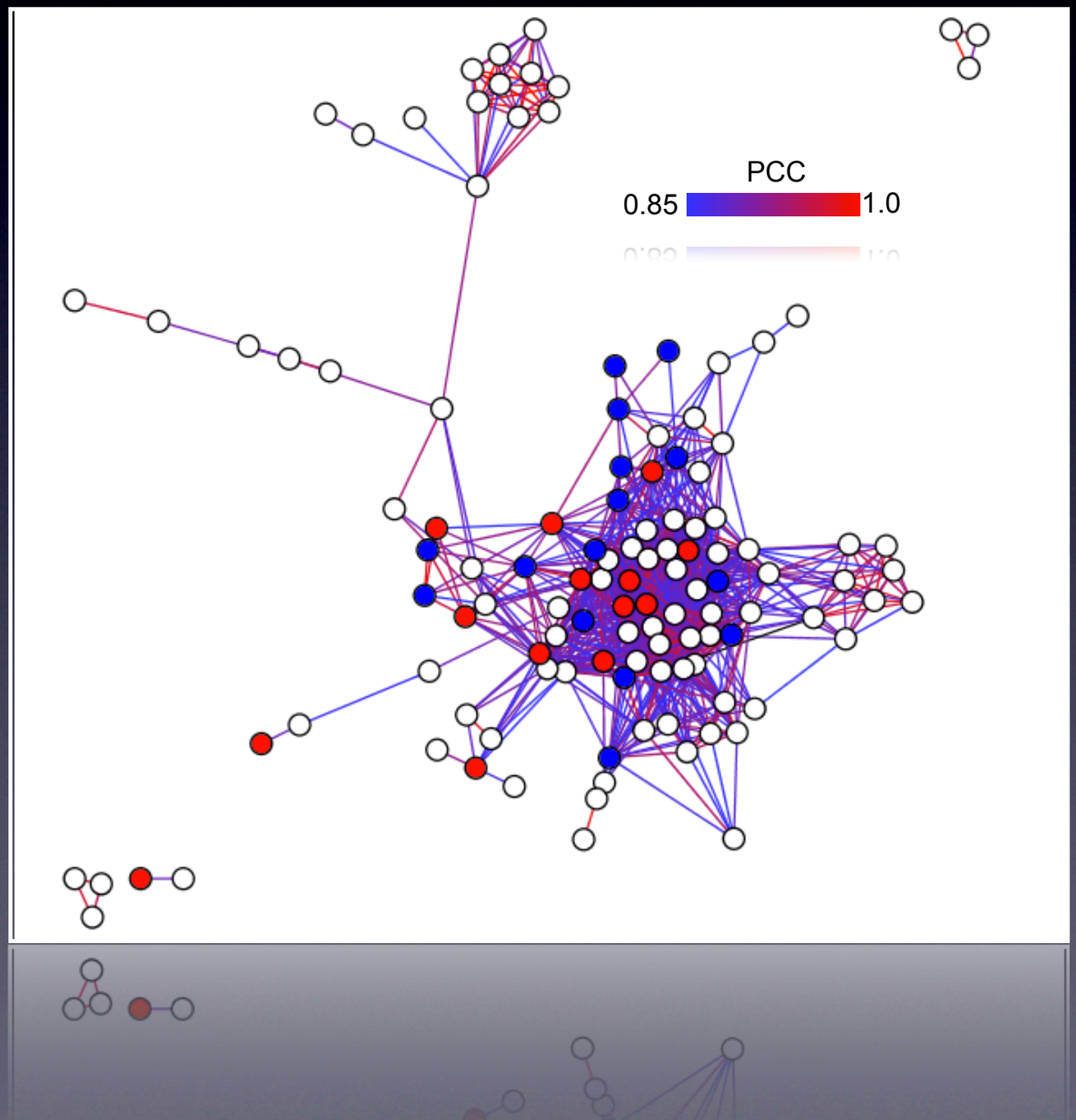
Bruneck Study

- Population-based (n=1000)
- Prospective (1990-2010)
- Assessment every 5 years
- Follow-up >90%
- Person-based progression model
- Age 40-79 years at baseline



Concepts of Network Topology

- Human Taqman miRNA arrays for 754 small non-coding RNAs
- 12 pooled samples (n=60)
- Common cardiovascular risk factors (RR, smoking, DM, LDL)
- 120 miRNAs and 1020 co-expression links

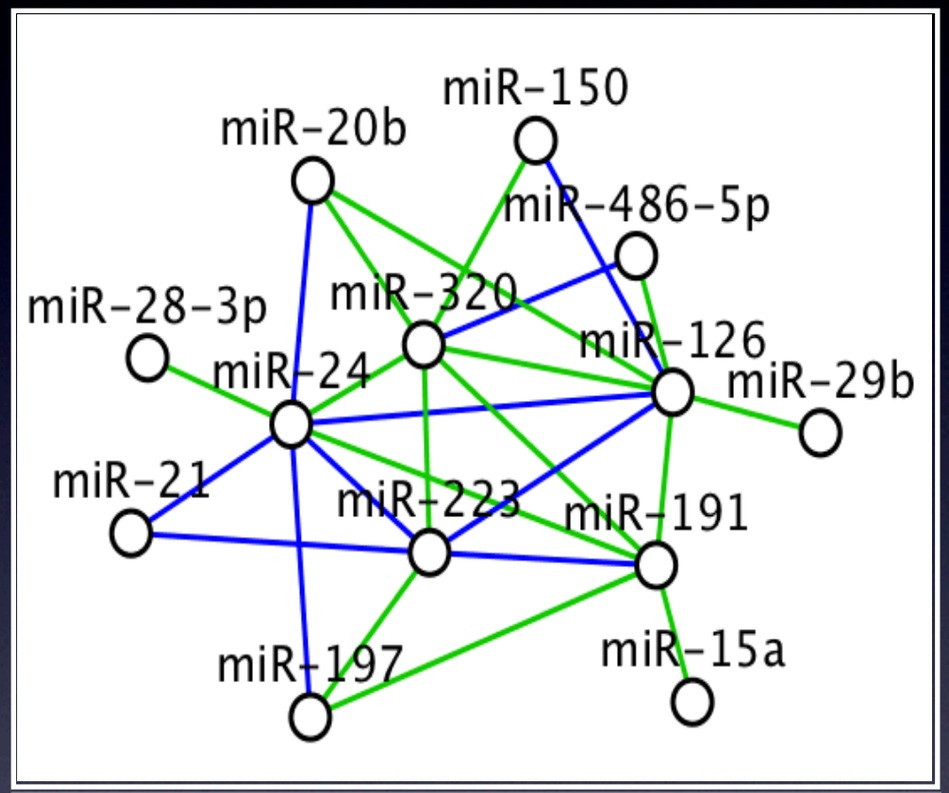


Editorial

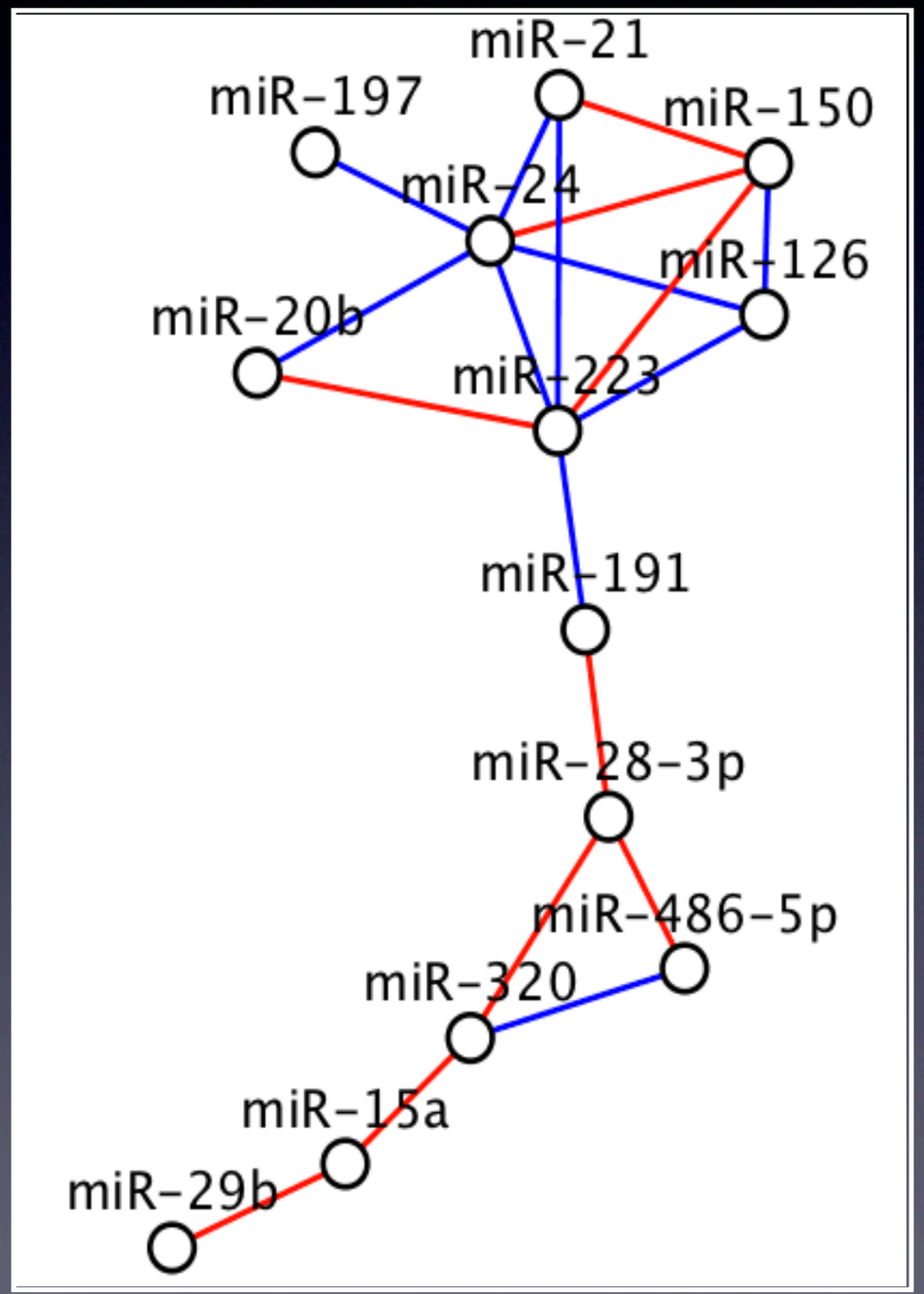
See related article, pages 810–817

Diabetes Mellitus Reveals Its Micro-Signature

Romano Regazzi



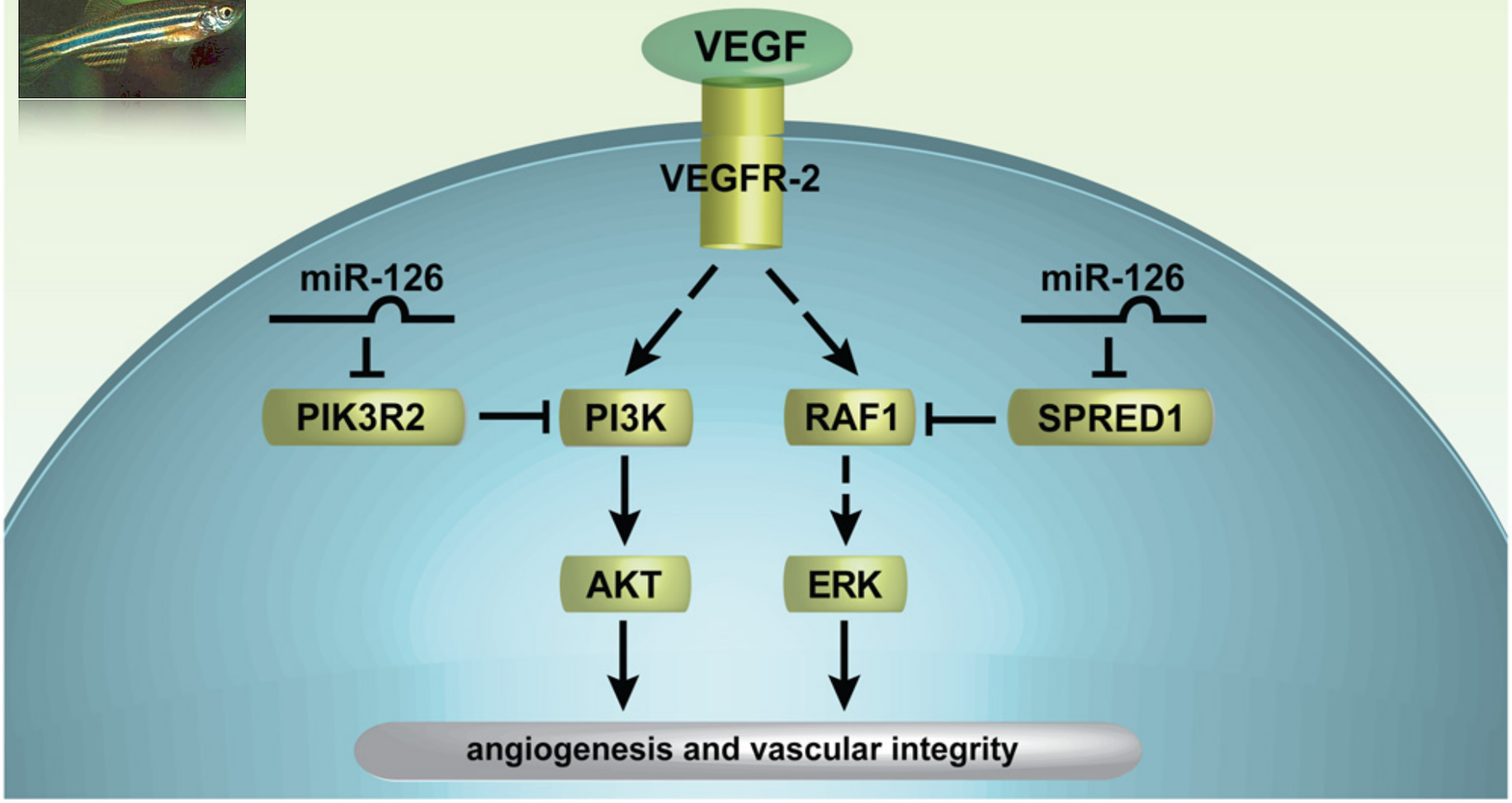
- Control network (green)
- Control & DM network (blue)
- DM network (red)



Function of MiR-126

Facilitator of VEGF Signalling

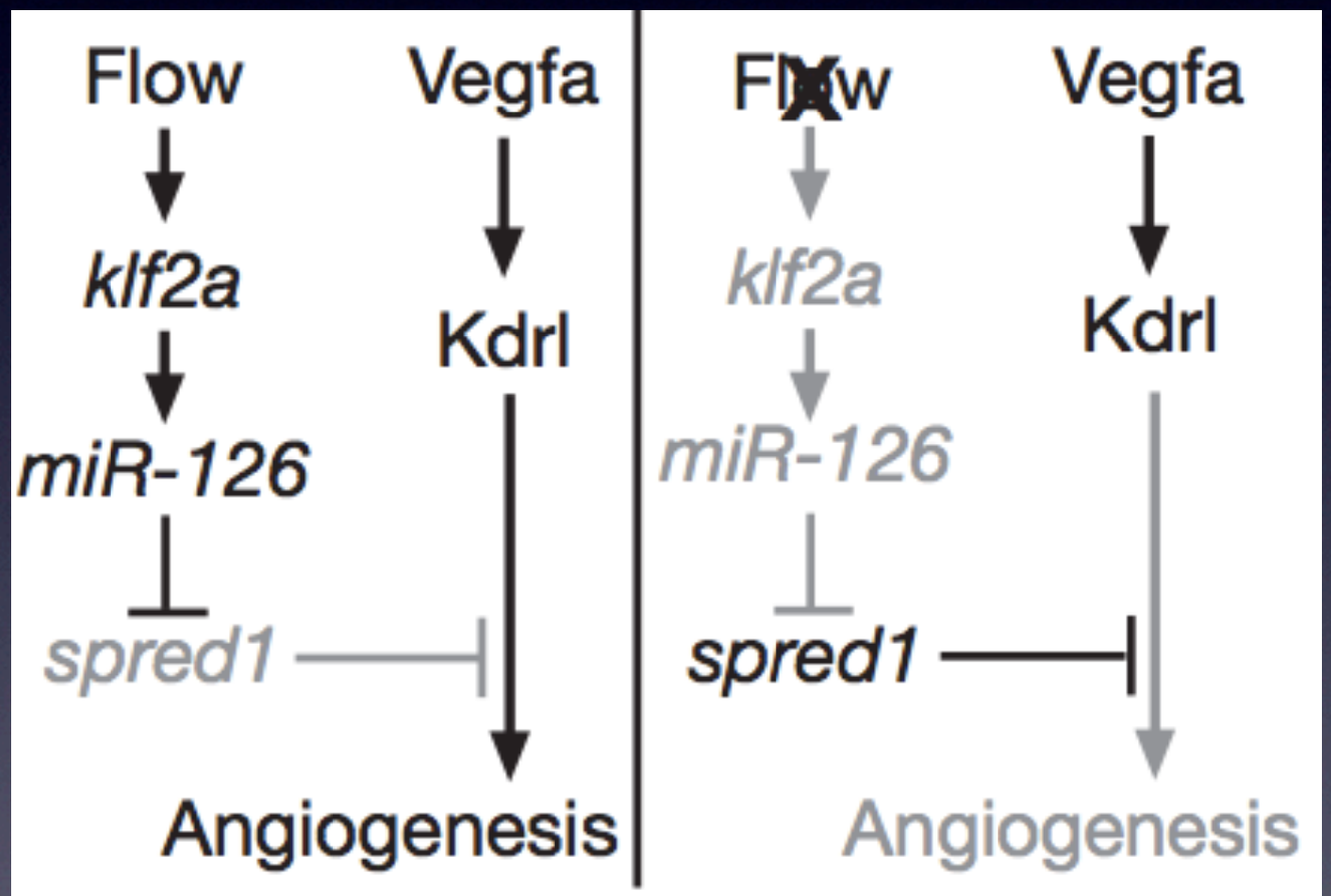
Fish et al Developmental Cell, 2008

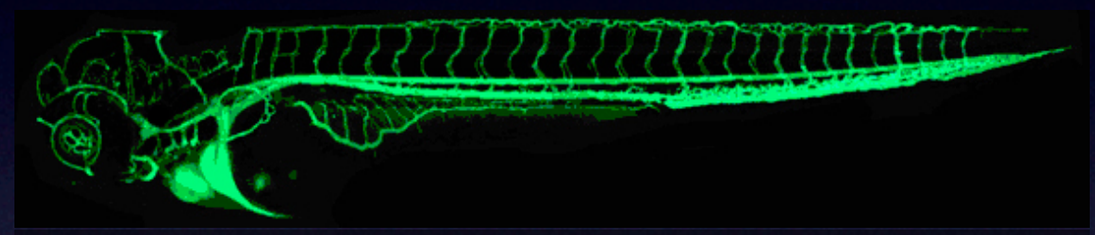


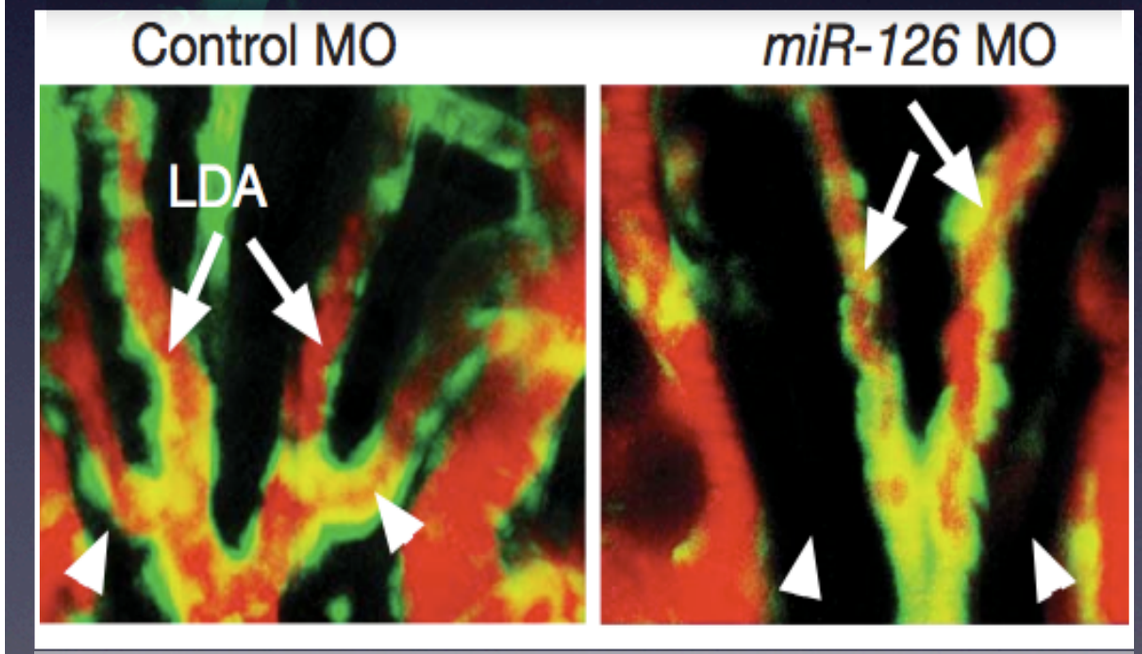
Function of MiR-126

Integration of Hemodynamics and VEGF Signaling

Nicoli et al, Nature, 2010



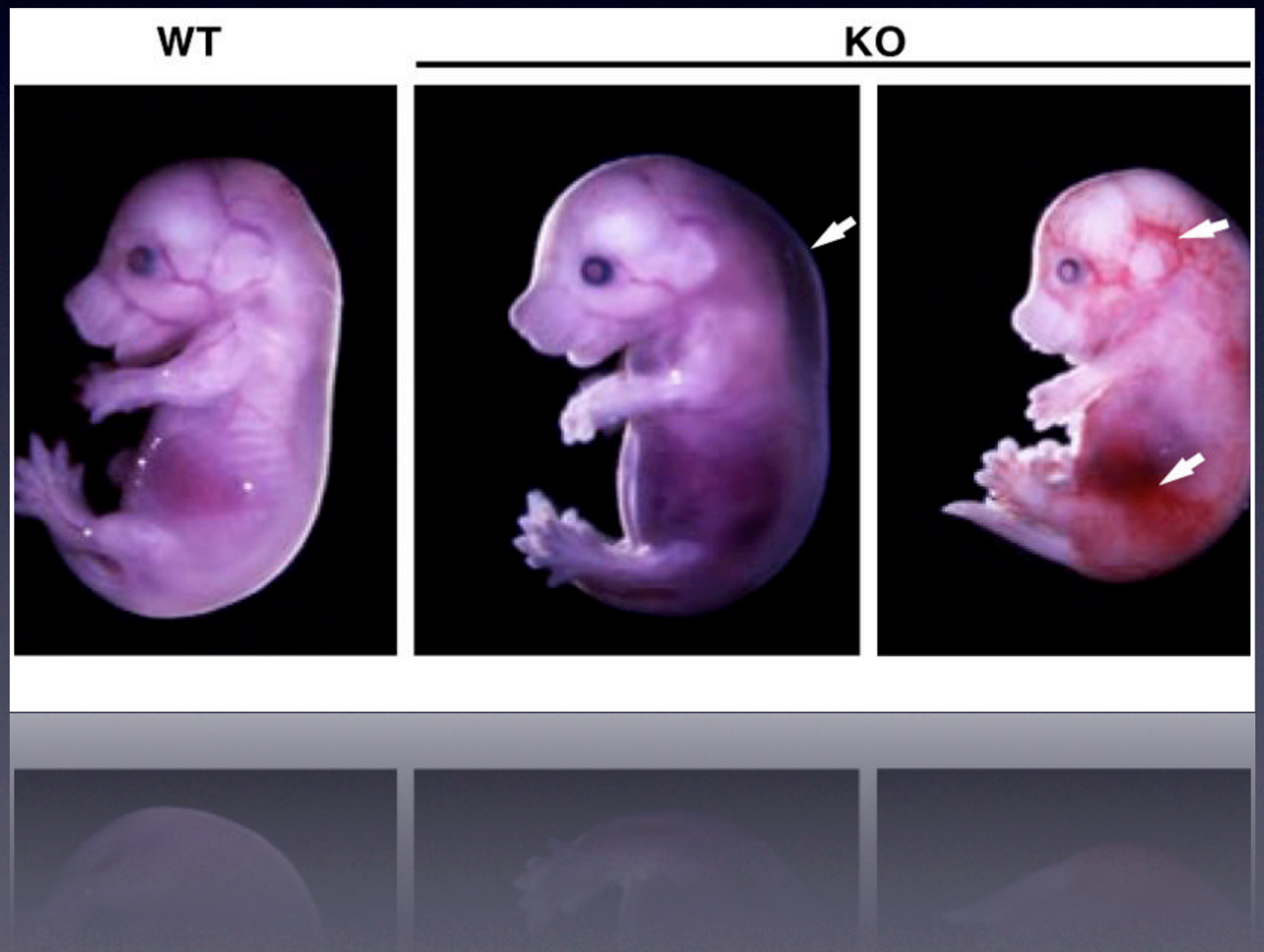




Function of MiR-126

Null Mice Prone to Vascular Leakage

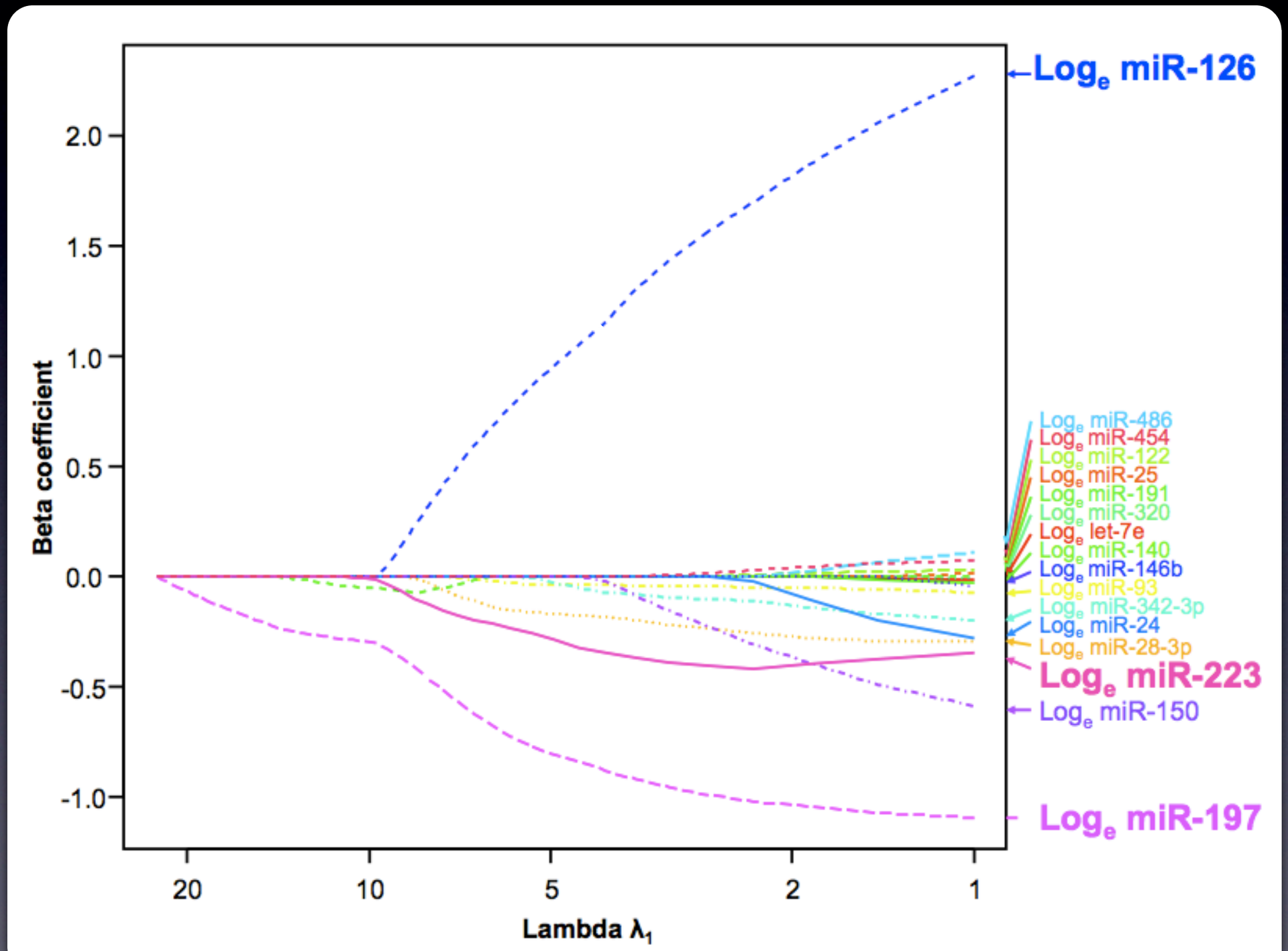
Wang et al, Developmental Cell, 2008



- 40% die during embryogenesis from vascular leakage.
- The mice that survive to adulthood are prone to vascular rupture and lethality following myocardial infarction.

Risk of Myocardial Infarction

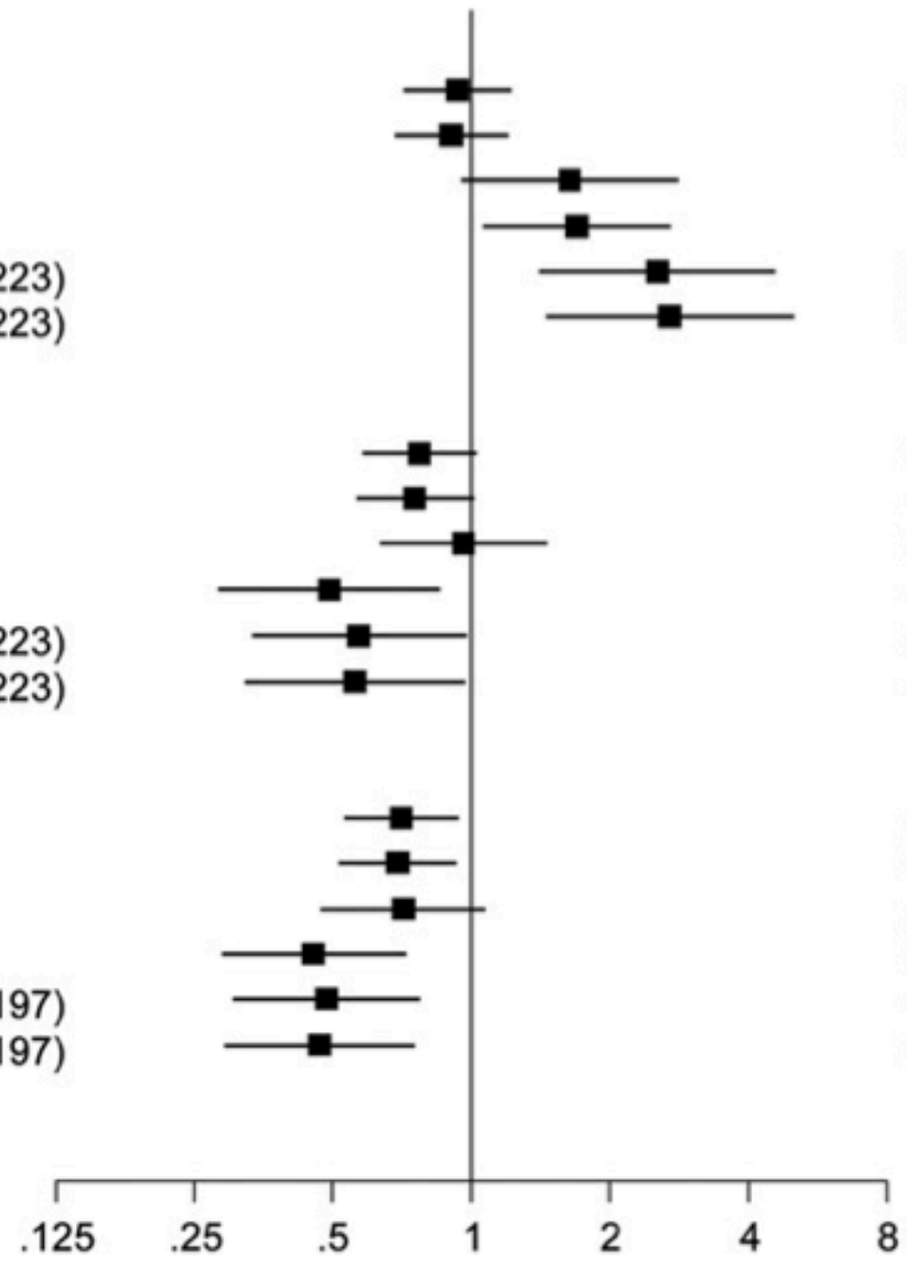
20 miRNAs, n=822, 10-year follow-up (1995-2005)



Risk of Myocardial Infarction

20 miRNAs, n=822, 10-year follow-up (1995-2005)

Adjustment	HR (95% CI)	P-value
MiR-126		
Age and sex	0.93 (0.71, 1.22)	0.606
Multivariable model 1	0.90 (0.68, 1.20)	0.483
+ miR-197	1.63 (0.95, 2.80)	0.076
+ miR-223	1.69 (1.06, 2.71)	0.029
Multivariable model 2 (+ miR-197, -223)	2.53 (1.40, 4.59)	0.002
Multivariable model 3 (+ miR-197, -223)	2.69 (1.45, 5.01)	0.002
MiR-197		
Age and sex	0.77 (0.58, 1.03)	0.076
Multivariable model 1	0.75 (0.56, 1.01)	0.061
+ miR-223	0.96 (0.63, 1.46)	0.856
+ miR-126	0.49 (0.28, 0.85)	0.012
Multivariable model 2 (+ miR-126, -223)	0.57 (0.33, 0.97)	0.037
Multivariable model 3 (+ miR-126, -223)	0.56 (0.32, 0.96)	0.036
MiR-223		
Age and sex	0.70 (0.53, 0.93)	0.015
Multivariable model 1	0.69 (0.52, 0.92)	0.013
+ miR-197	0.71 (0.47, 1.07)	0.101
+ miR-126	0.45 (0.29, 0.72)	0.001
Multivariable model 2 (+ miR-126, -197)	0.48 (0.30, 0.77)	0.002
Multivariable model 3 (+ miR-126, -197)	0.47 (0.29, 0.75)	0.002



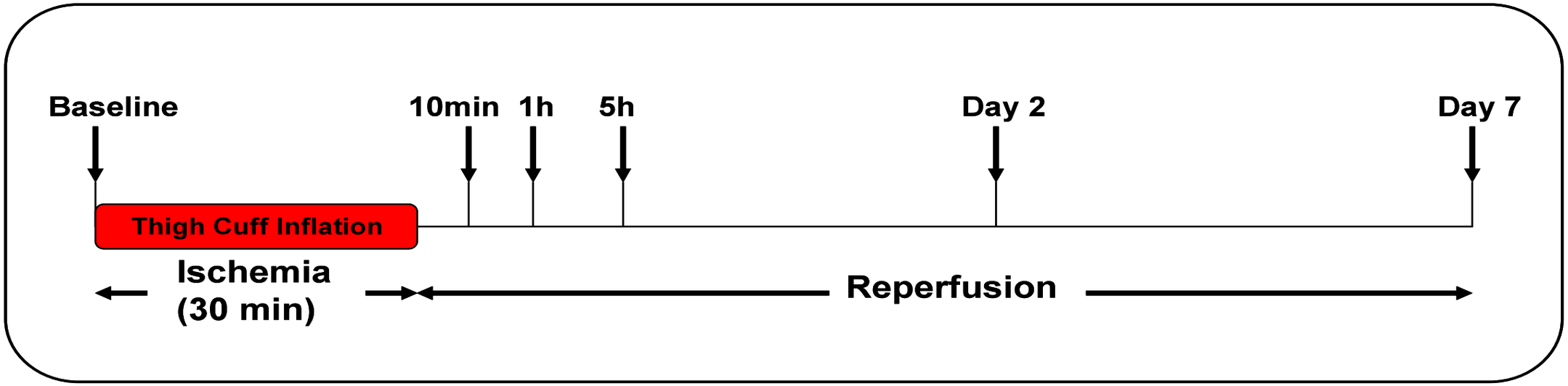
Integrated Discrimination Improvement
Upon addition of miRNAs to Framingham Risk Score

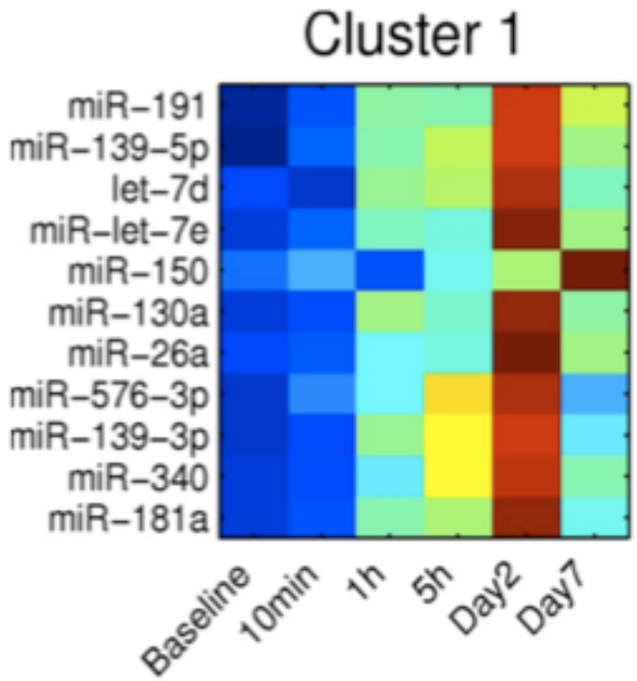
Table 2 **Summary Statistics of MI Risk Reclassification by Addition of miR-126, miR-197, and miR-223 to a Model With the FRS for Hard Coronary Heart Disease**

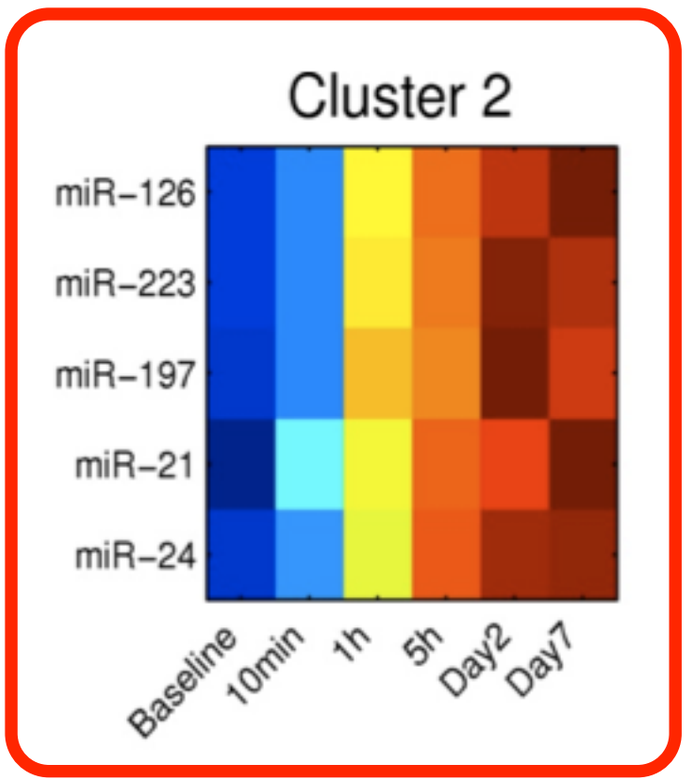
Statistic	Estimate	95% CI	p Value
Integrated discrimination improvement			
Controls	0.003331	0.000364–0.006297	0.028
Cases	0.043967	0.001742–0.086191	0.041
Overall	0.047297	0.004969–0.089626	0.029

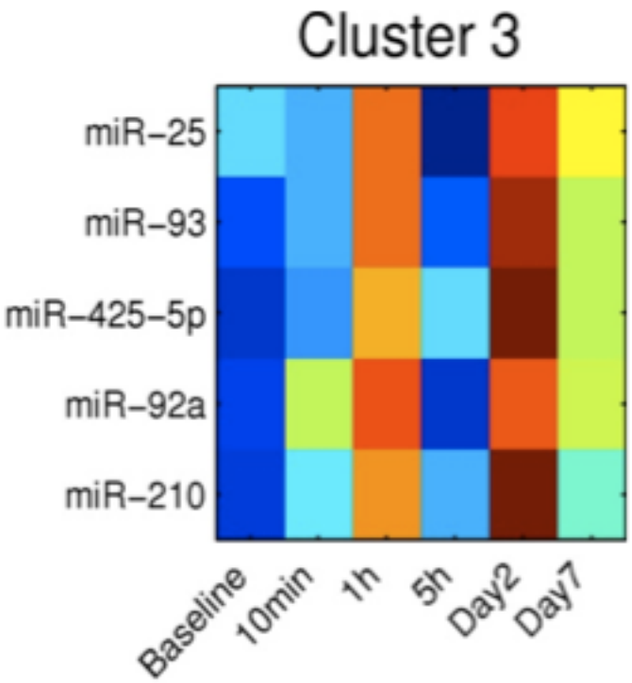
Cellular Origin ?

Ischemia/Reperfusion by Thigh Cuff Inflation (n=11)



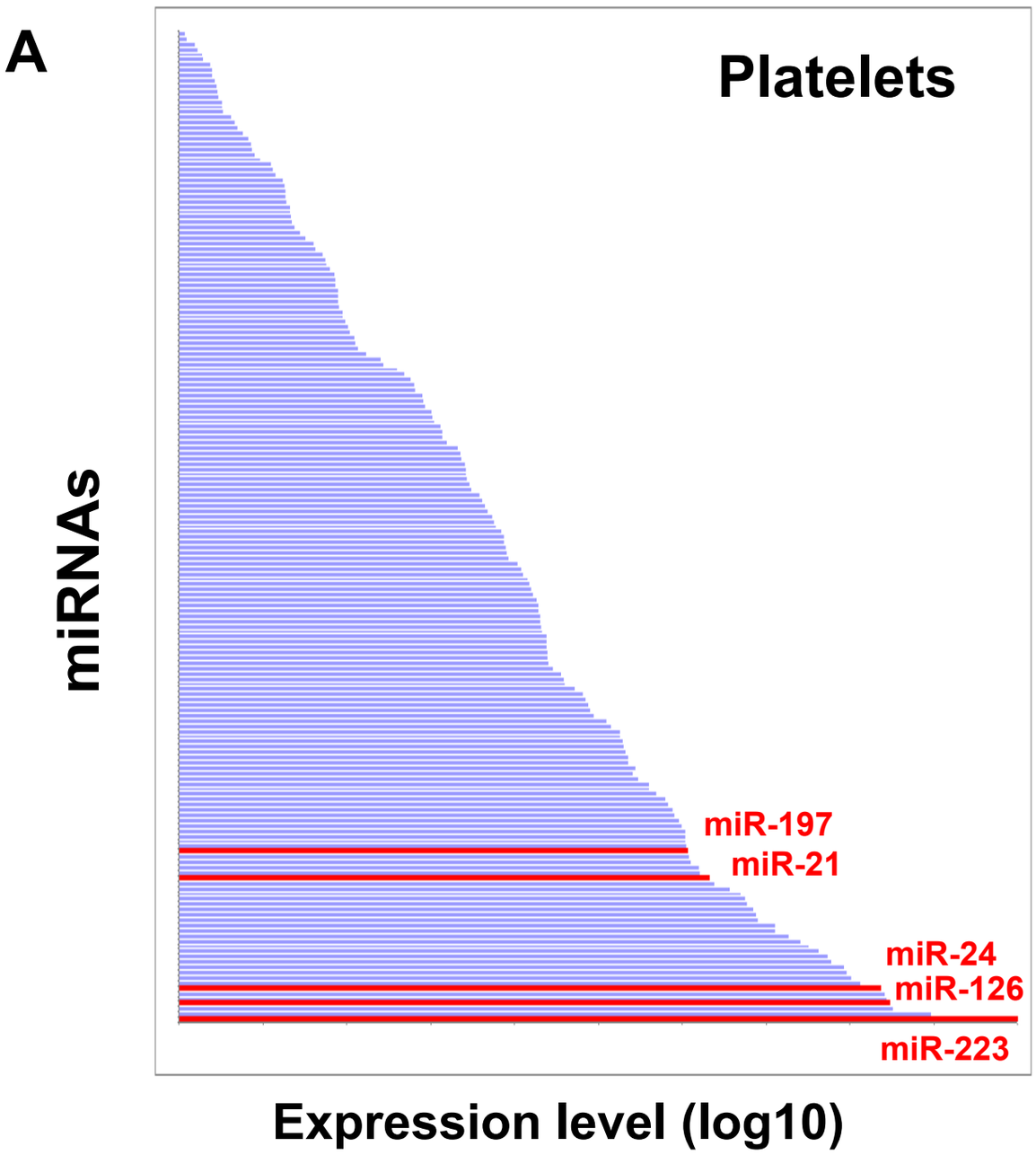


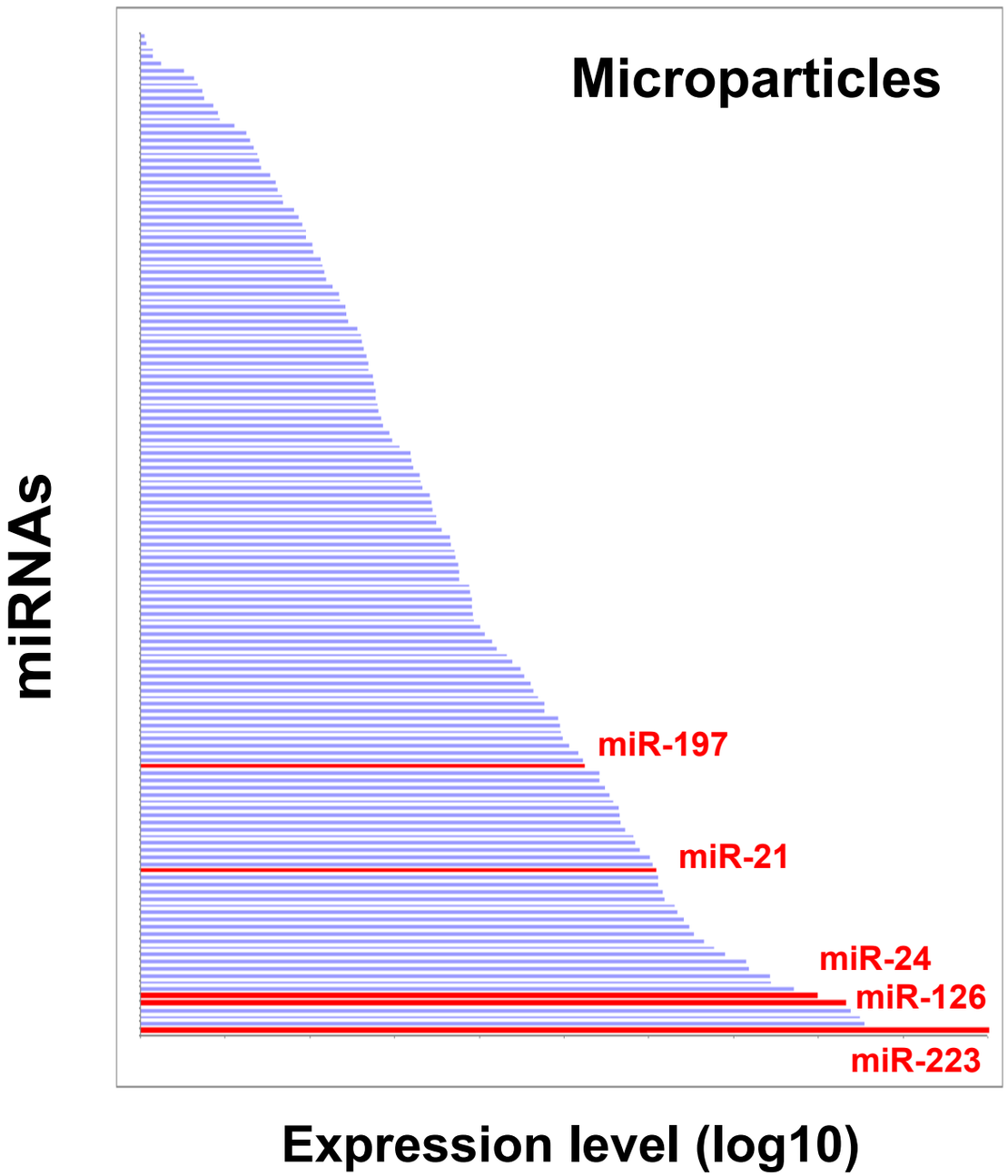




Cellular Origin ?

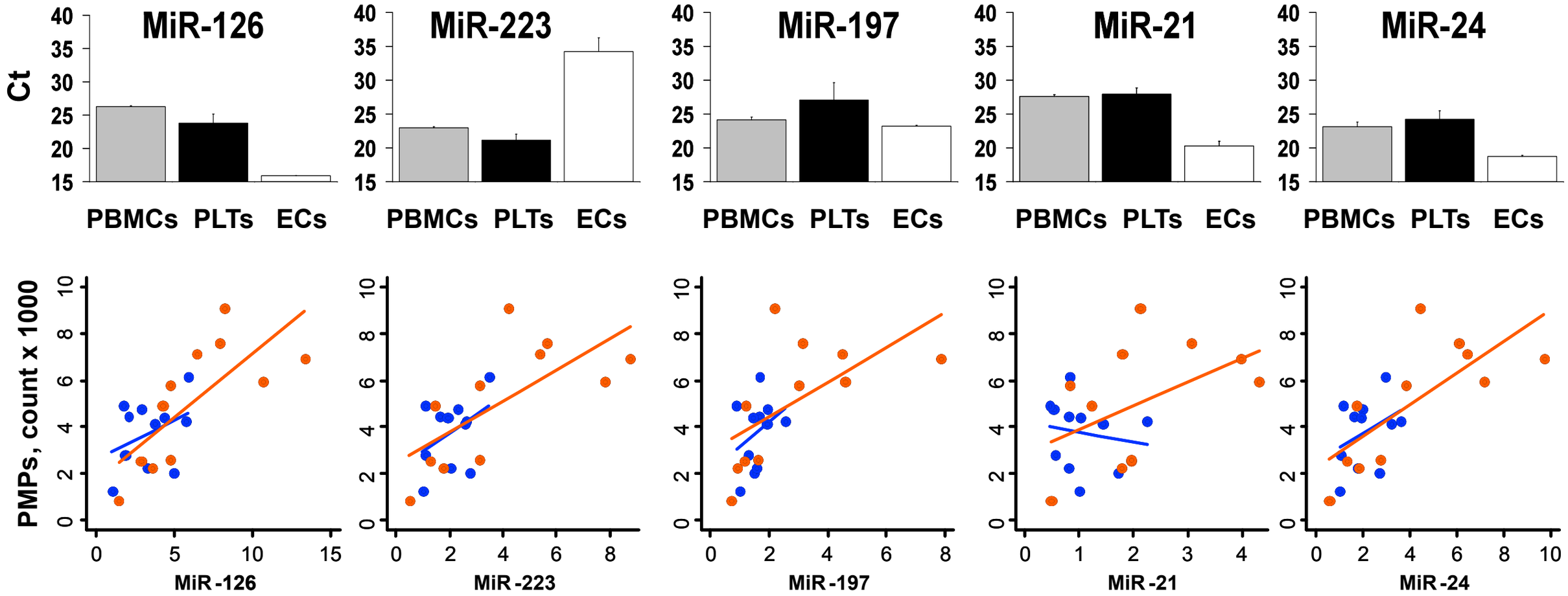
Presence in Platelets and Platelet Microparticles





Platelet Contribution

Correlation of MiRNAs to Platelet Microparticles

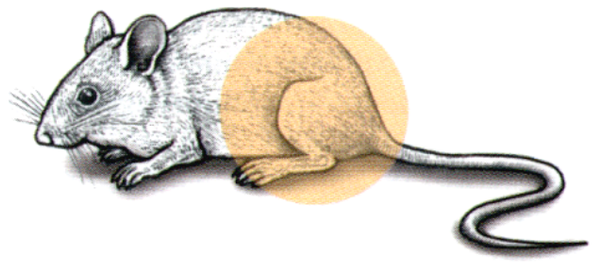


Baseline versus Day 2 post ischemia/reperfusion

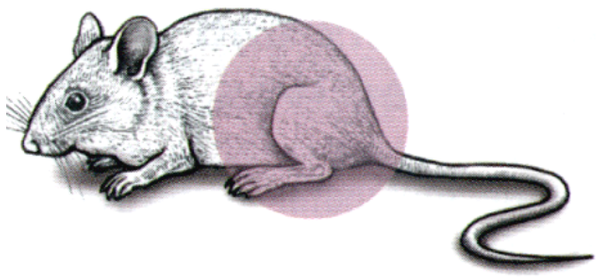
MicroRNAs in Vascular and Metabolic Disease

Anna Zampetaki, Manuel Mayr

Circulation Research 2012, 110:508-522

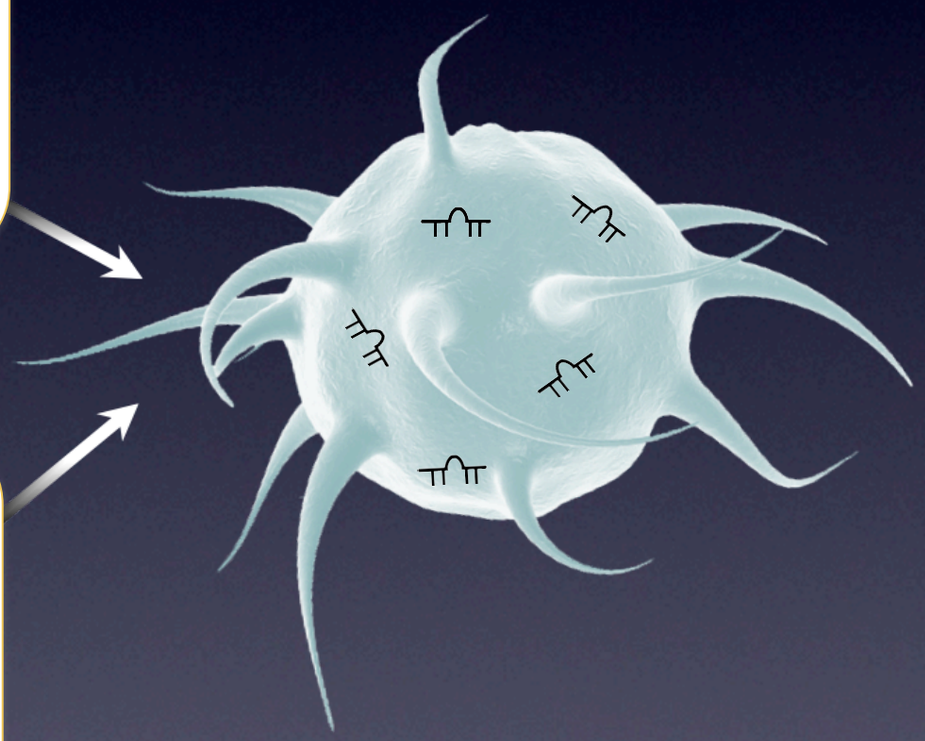


Global Knock-out



Systemic Inhibitors

Platelet Contribution ?

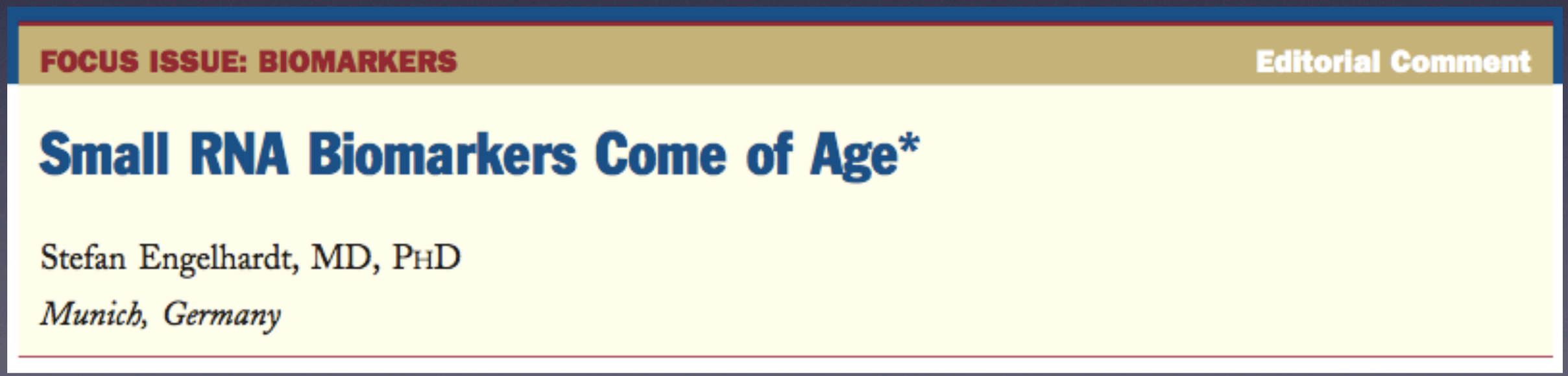


- miR-223
- miR-126
- miR-103
- Let-7
- miR-21
- miR-107
- miR-24
- miR-222

Conclusions

Validation in Independent Cohorts

- This is the first population-based study on circulating miRNAs.
- We identified a miRNA signature for DM and risk of MI.
- Currently, we monitor cardiovascular risk factors, but there is no good soluble biomarker to directly assess the health of blood vessels and identify "vulnerable" patients.



FOCUS ISSUE: BIOMARKERS Editorial Comment

Small RNA Biomarkers Come of Age*

Stefan Engelhardt, MD, PhD

Munich, Germany

KING'S BHF CENTRE OF RESEARCH EXCELLENCE

kcl.ac.uk/schools/medicine/research/cardio/bhfcentre/

Dr. Anna Zampetaki
Dr. Xiaoke Yin
Dr. Philipp Skroblin
Dr. Sarah Langley
Dr. Javier Barallobre-Barreiro
Dr. Katarzyna Dudek
Dr. Ursula Mayr

Ms. Patricia Gyambibi-Barnett
Mrs. Coral Xing
Mr. Ignat Drozdov

Dr. Lindsey Tilling
Prof. Phil Chowiencyzk
Prof. Ajay Shah

Innsbruck (A):
Prof. Stefan Kiechl
Dr. Peter Willeit
Prof. Johann Willeit

Paris (F):
Dr. Chantal Boulanger

ARTS

King's BRC Strategic Initiative

Diabetes UK
The charity for people with diabetes

JDRF Juvenile Diabetes Research Foundation International

British Heart Foundation