University of BRISTOL

Imperial College London

British Heart Foundation

Post-ischemic neovascularization:

basic concept and new treatment options

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ESC Summer school, Nice 16 June 2013

Index of this Lecture

- Introduction to ischemia and post-ischemic neovascularisation
- Research Models
- Therapeutic angiogenesis research: past, present and future
- microRNAs in post-ischaemic vascular regeneration
- Novel stem cell products: Empowered EPCs, Pericyte progenitor cells

Ischemic Disease

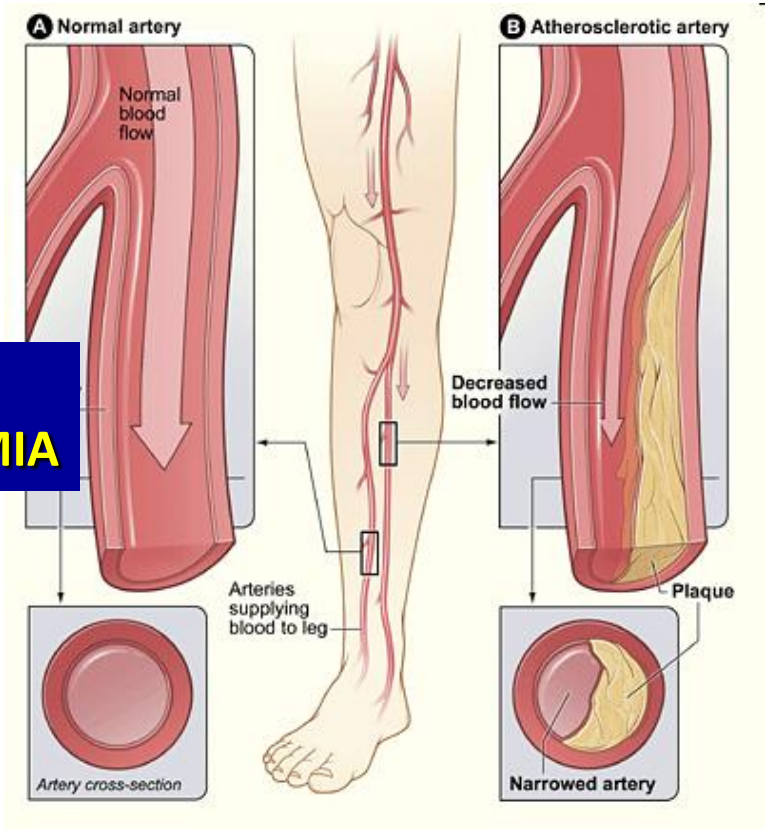
- Tissue ischaemia is caused by poor blood flow supply, which impairs the delivery of oxygen (creating hypoxia) and nutrients (creating tissue starvation)

- Ischaemic disease is favoured by atherosclerosis, diabetes, aging and a series of cardiovascular risk factors

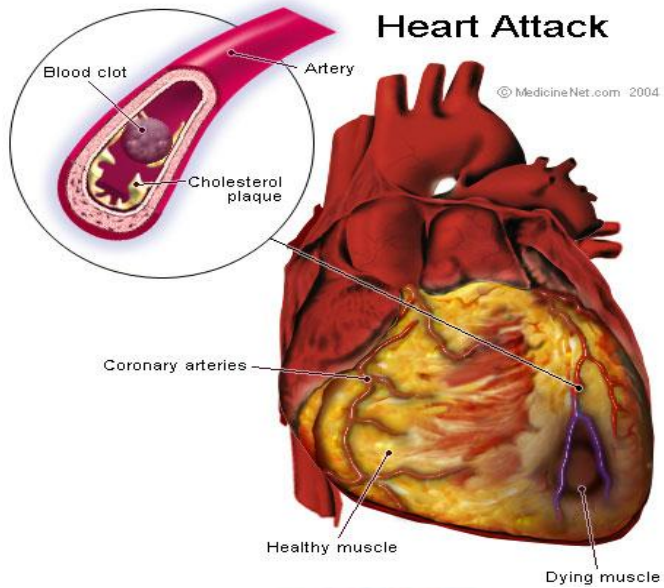
- Ischaemic disease is one of the biggest medical epidemic worldwide and its treatment is still an umet clinical need.

Post-Ischaemic Vascular Regeneration: the Medical Need

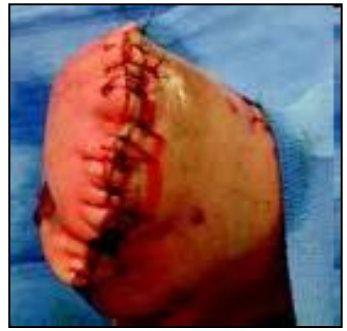
LIMB ISCHAEMIA



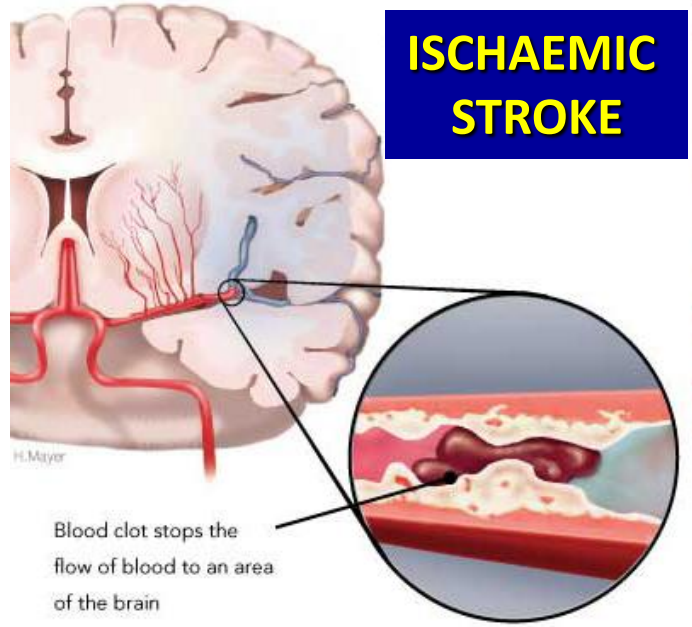
MYOCARDIAL INFARCT



CRITICAL LIMB ISCHAEMIA

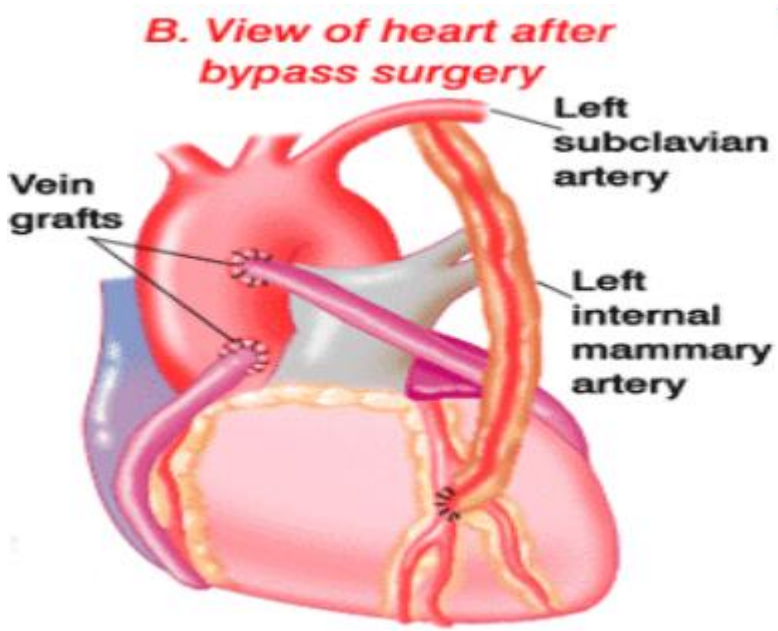


ISCHAEMIC STROKE



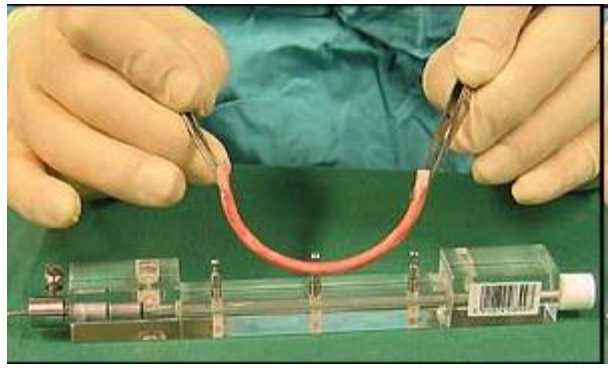
Vascular Regeneration: what can we try?

Substituting the diseased (large) vessel

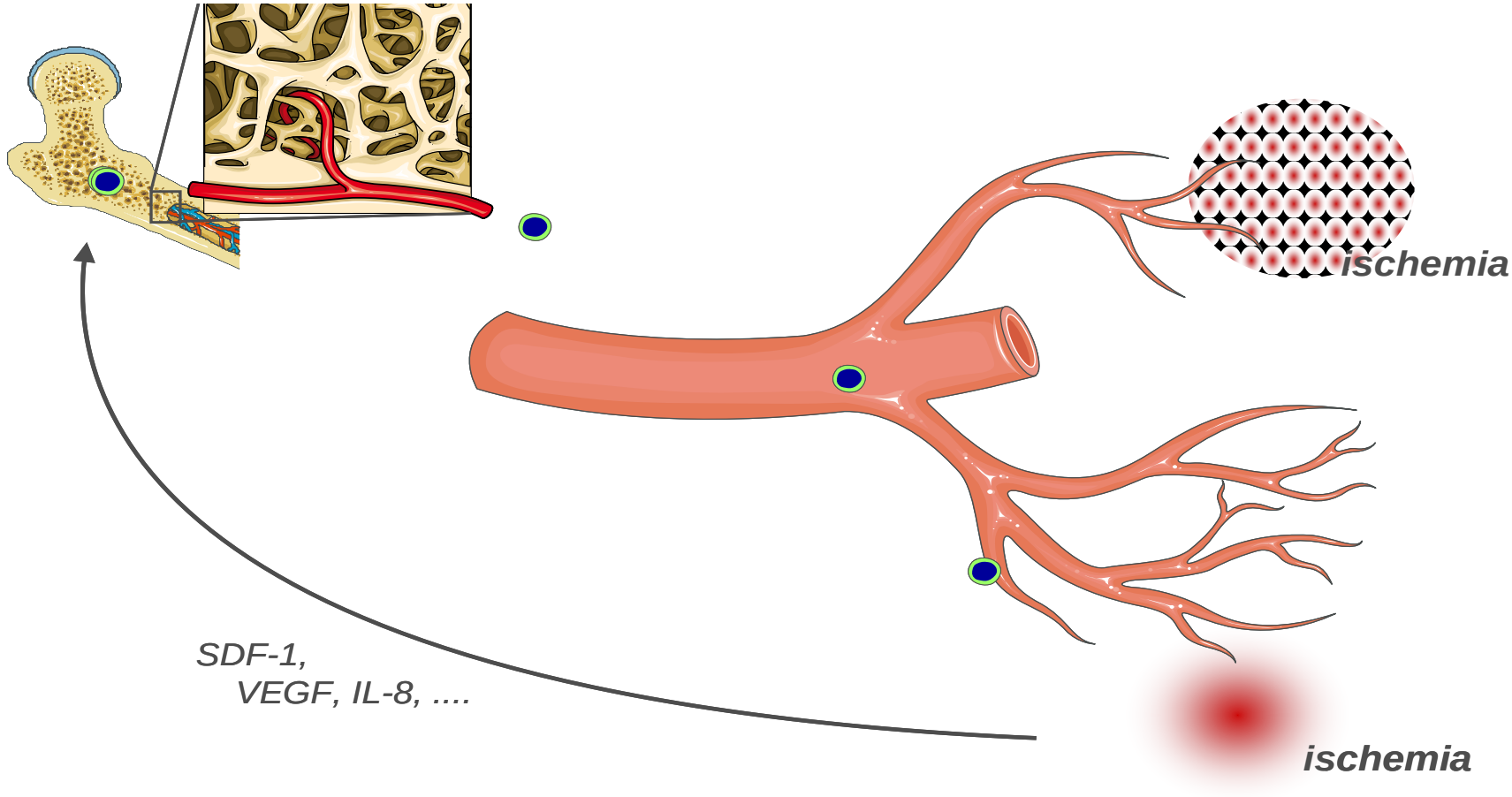


By-pass grafting with pieces of patient own vessels
(vena saphena and/or mammary artery)

By-pass grafting with “artificial” vessels created in the laboratory



Therapeutic Neovascularization



Strategies for Post-Ischemic Neovascularisation

- Increase the expression/activity of endogenous "pro-angiogenic" factors in ischemic tissues
- Contrast "anti-angiogenic" molecular signatures induced by pathology and/or risks factors
- Stimulate endogenous stem and progenitor cells with various pro-angiogenic capacities
- Transplantation of vascular stem and progenitor cells with pro-angiogenic capacities

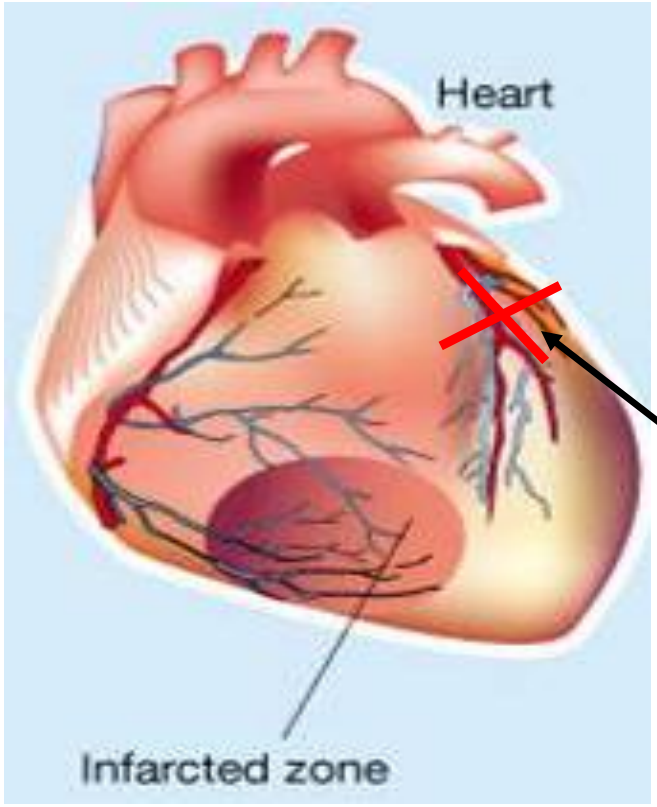
In Vivo Research Models

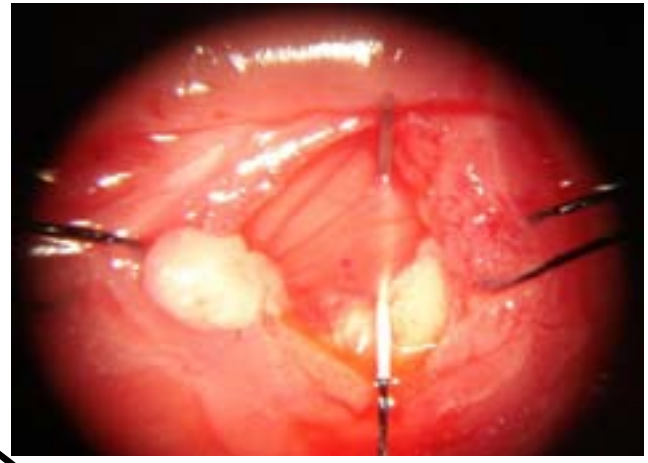
Animal Models of Ischemia: MI

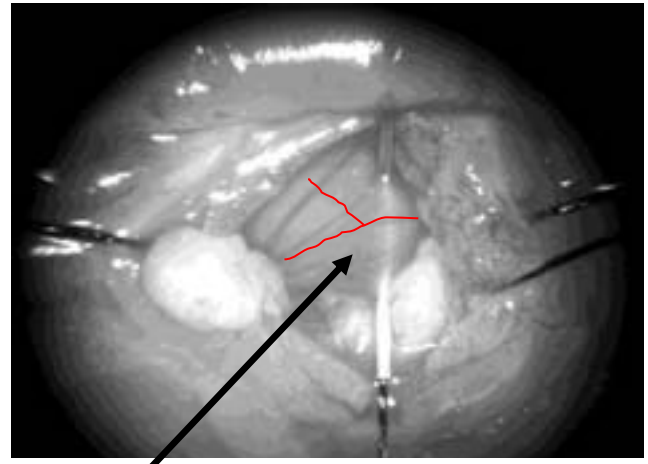
Experimental models of myocardial infarction (MI) are routinely performed in Rodents.

- Permanent ligation of LAD

- Ischemia/reperfusion





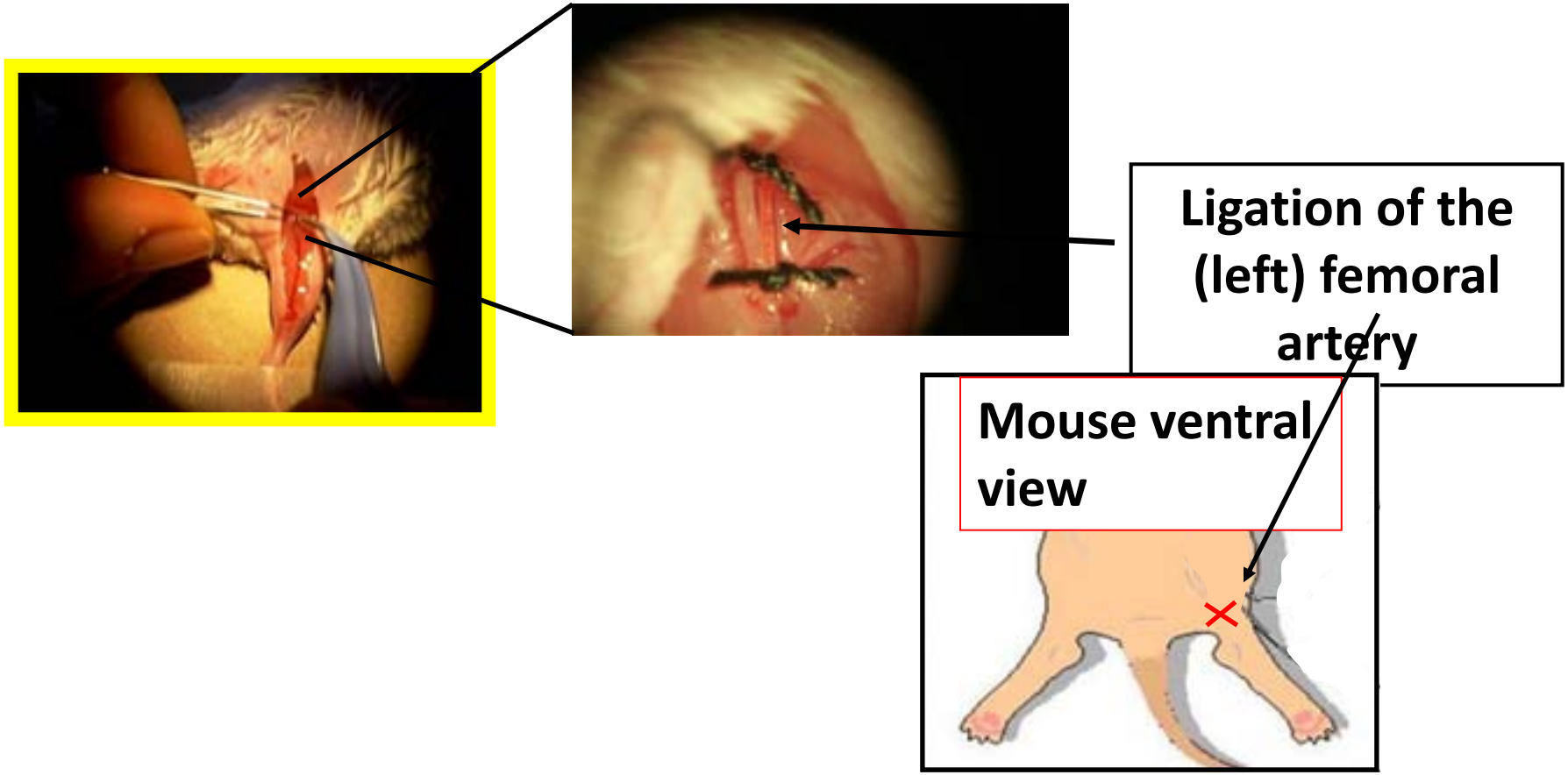


Occlusion of LAD

Mouse model of myocardial infarct

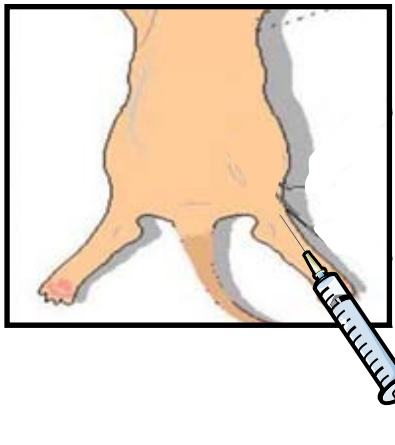
Animal Models of Ischemia: LI

Experimental models of limb ischemia (LI) is used in mice to mimic a situation comparable to peripheral artery disease. Since peripheral artery disease is often associated with diabetes, this model is also performed in diabetic mice. LI is performed by permanent ligation of one femoral artery.



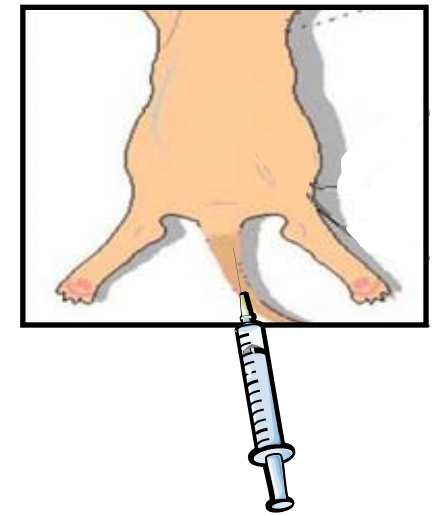
Systemic Gene/Cell Delivery

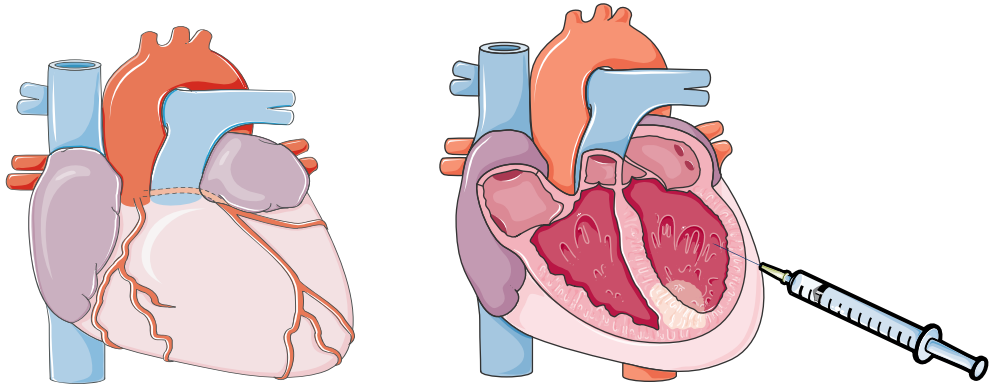
Intravenous infusion of stem cells/genes:



through the femoral vein

through the tail vein





through the left ventricular cavity

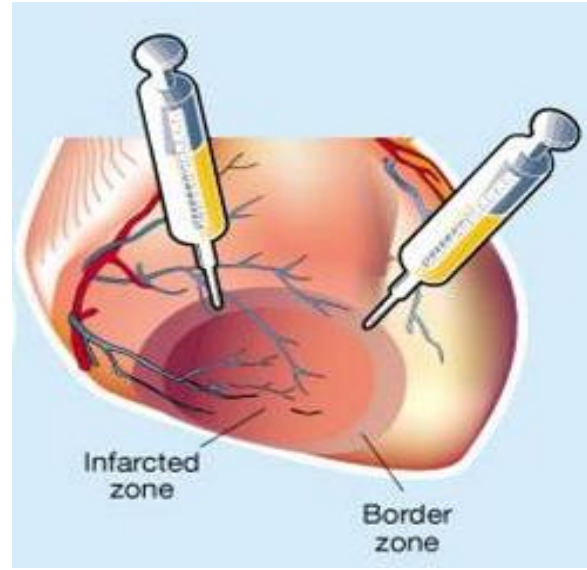
Limits of systemic delivery:

- Not possible to target a specific organ
- (Loss of cell number)
- (Loss of cell viability)

Local Gene/Cell Delivery

Cardiac:

1. **Endomyocardial needle injection**
2. **Catheter delivery (large animals)**
3. **Intracoronary infusion (large animals/humans)**
4. **Intrapericardial (large animals)**

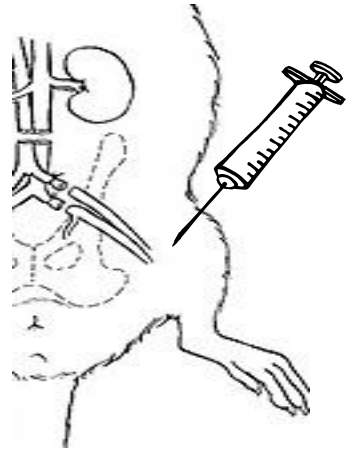


Cells/Genes are directly injected into the infarcted border zone

Injection is often performed immediately after MI

Lower limb

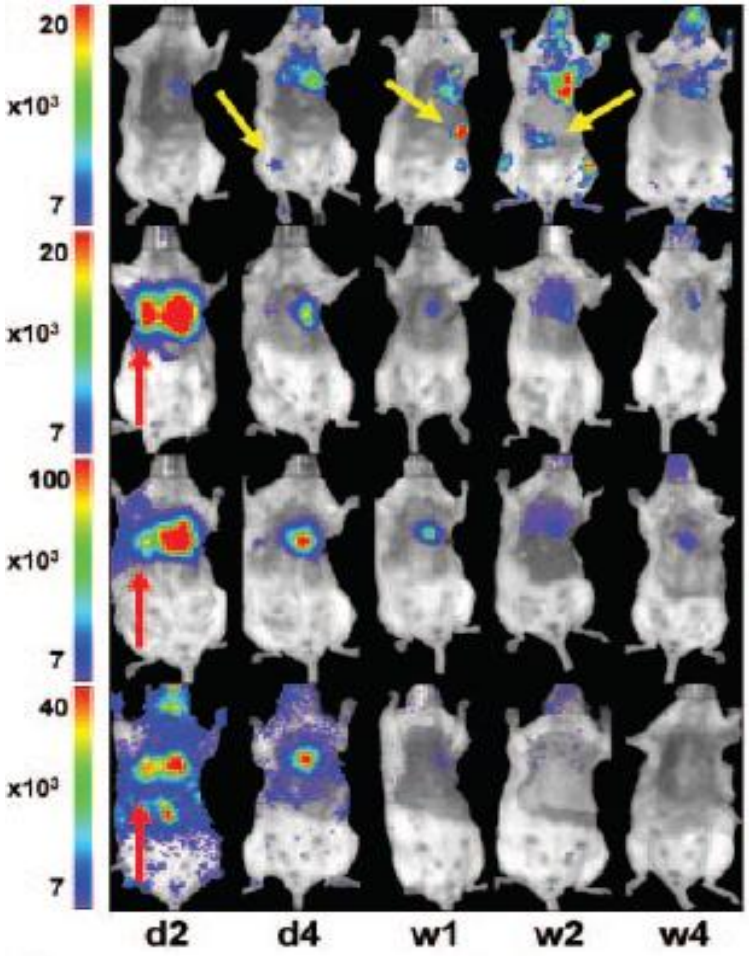
1. **Direct intramuscular injection**
2. **Intra-arterial infusion**



Cells/genes are directly injected into the adductor muscle often immediately after ischemia

Transgene/ Cell Tracking after Local Delivery

In vivo optical bioluminescence imaging (by using luminescence protein)



BM-derived mononuclear cells

Skeletal myoblasts

Mesenchymal stem cells

Fibroblasts

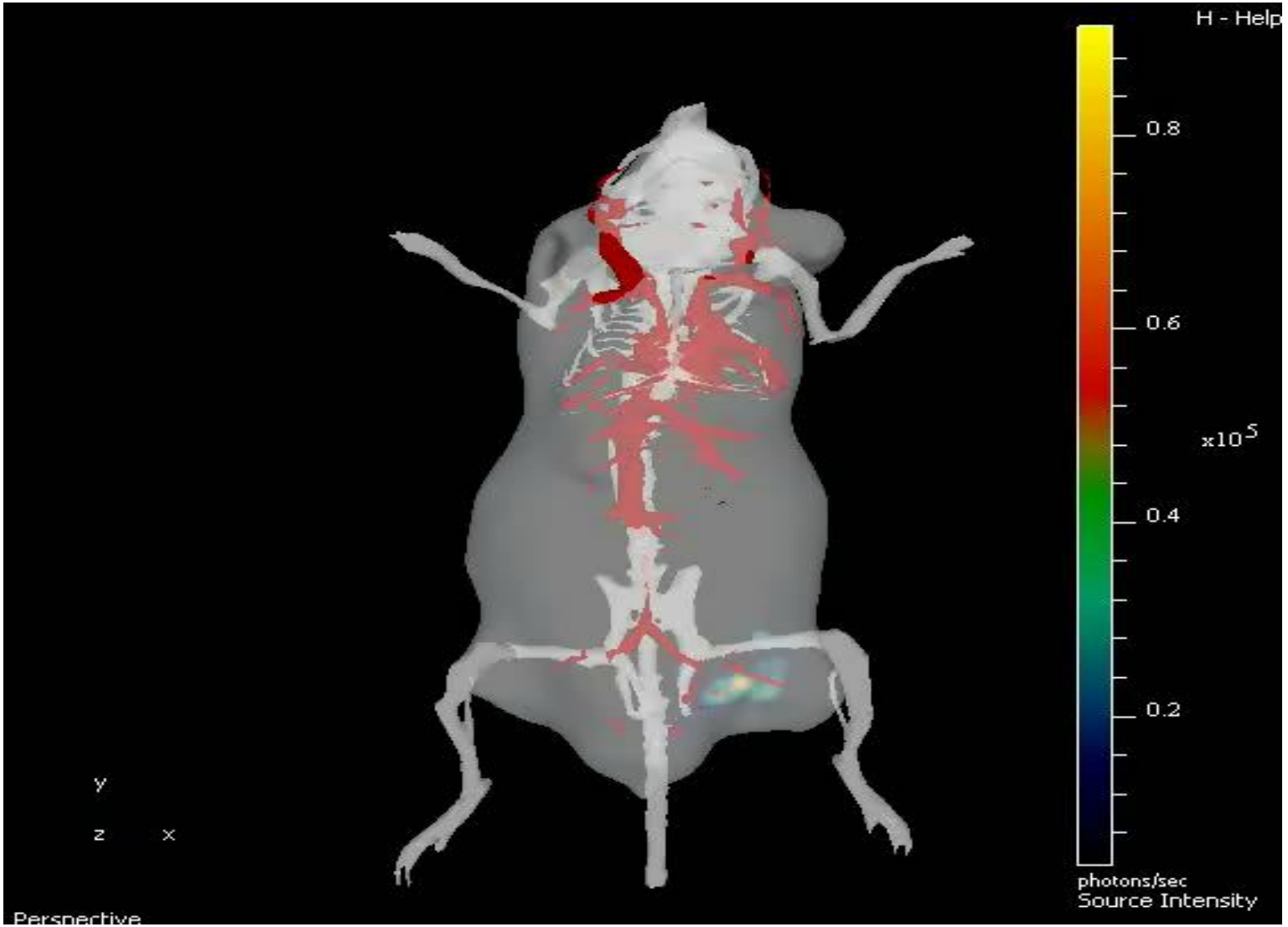
Types of injected stem cells

Body distribution of cells labelled with D-luciferin after intracardiac injection of different types of stem cells

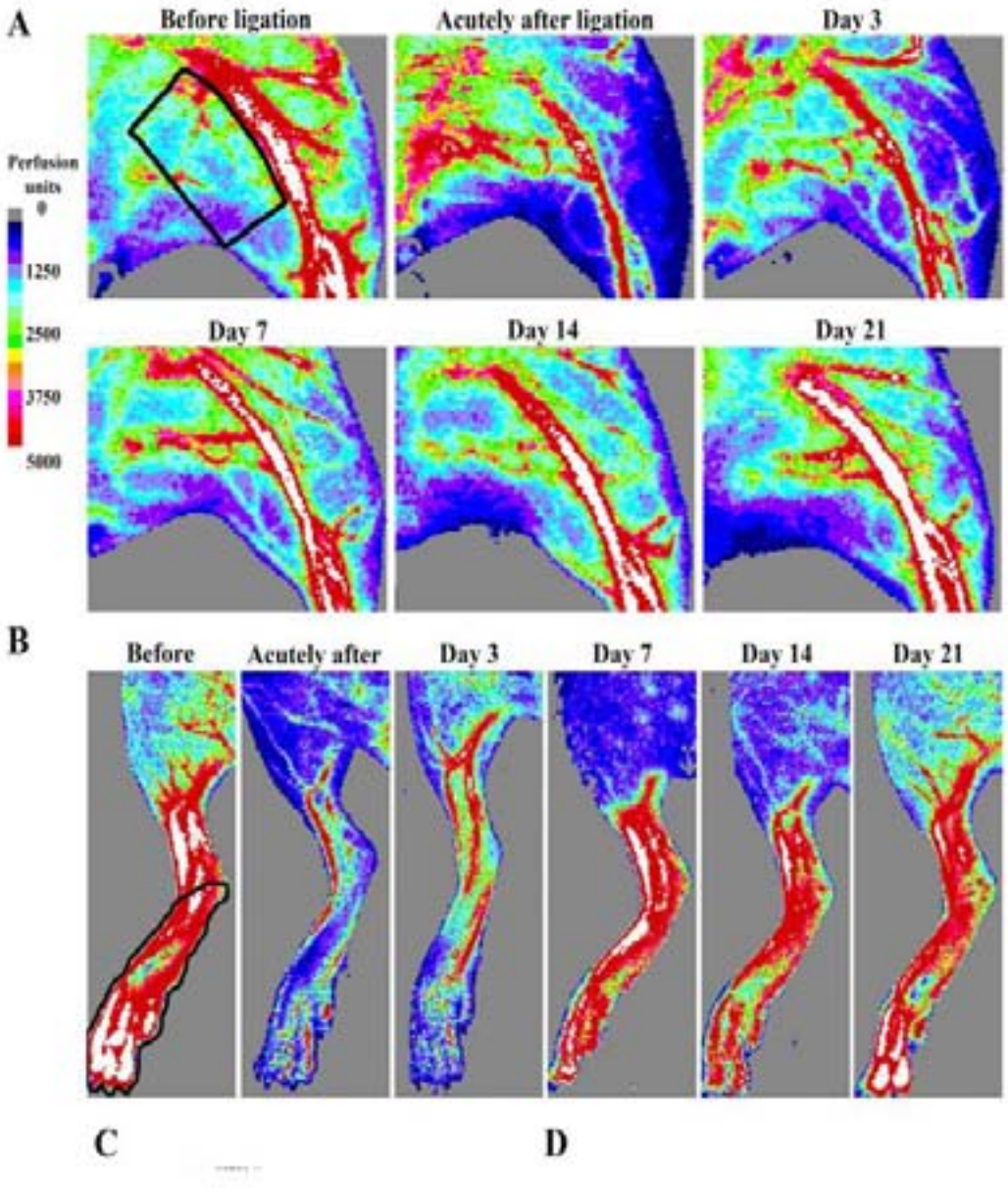
Van der Bogt et al, Circulation 2008

Time after cell injection

New 3D bioluminescent IVIS system (Caliper)

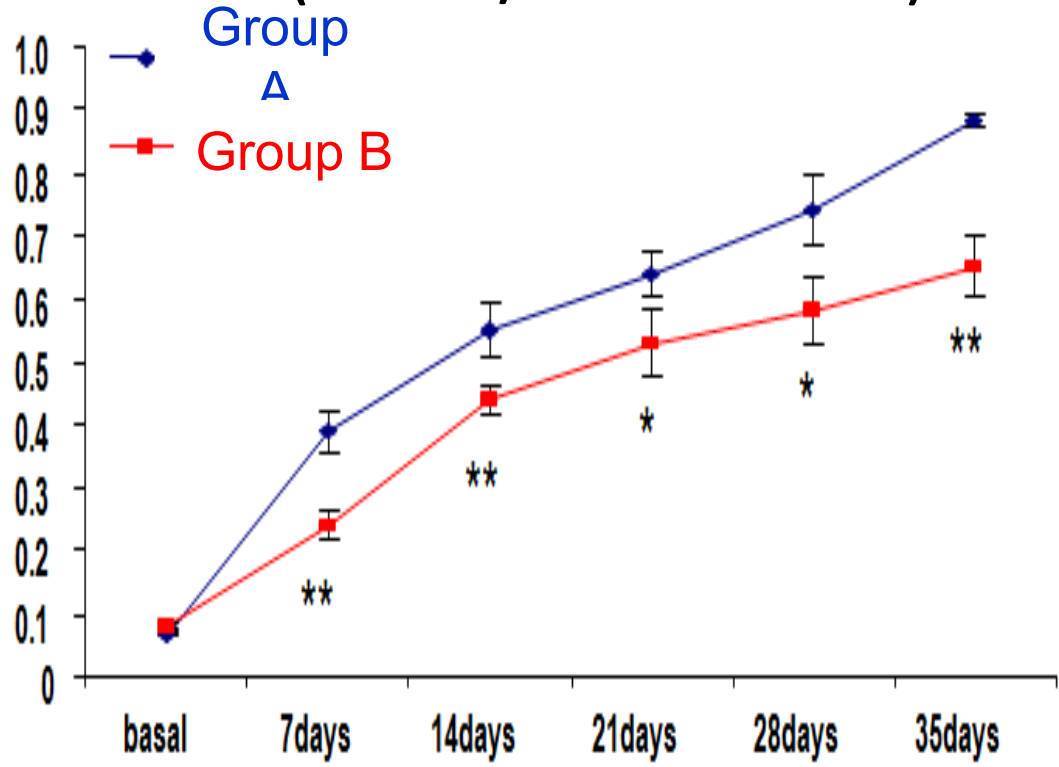


Non Invasive Colour Laser Doppler

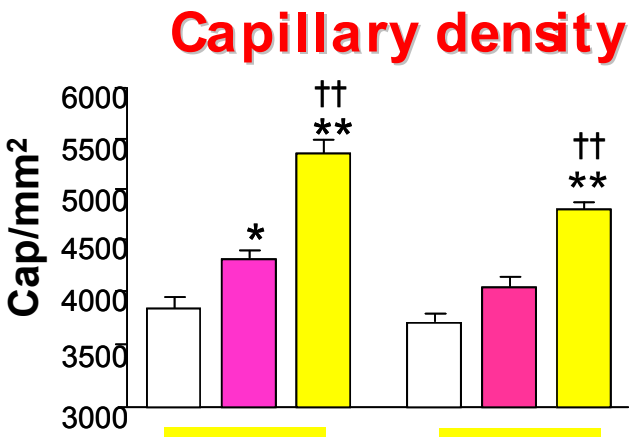


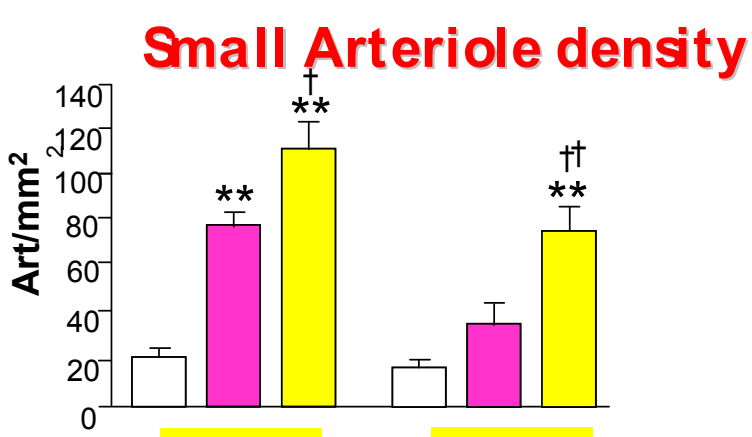
Blood Flow Recovery

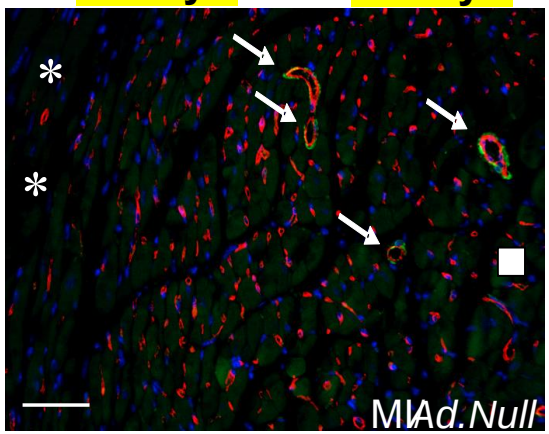
Blood flow ratio (ischemic/contralateral foot)

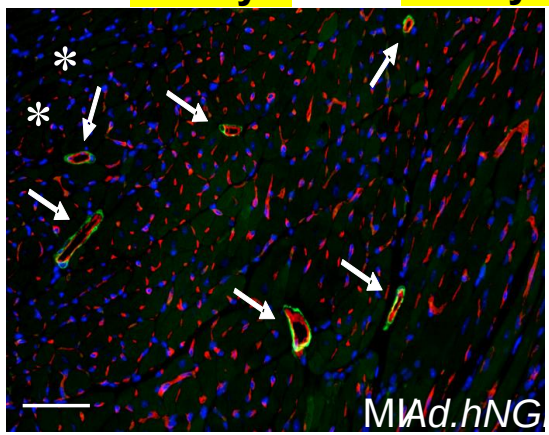


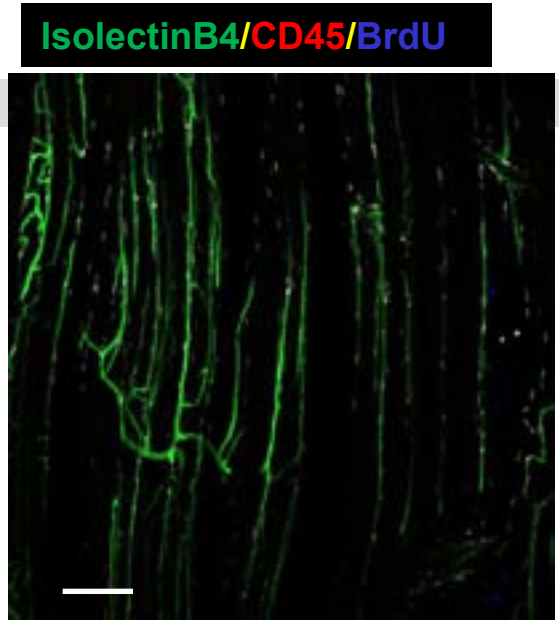
Histology /IHC for vessel analyzes

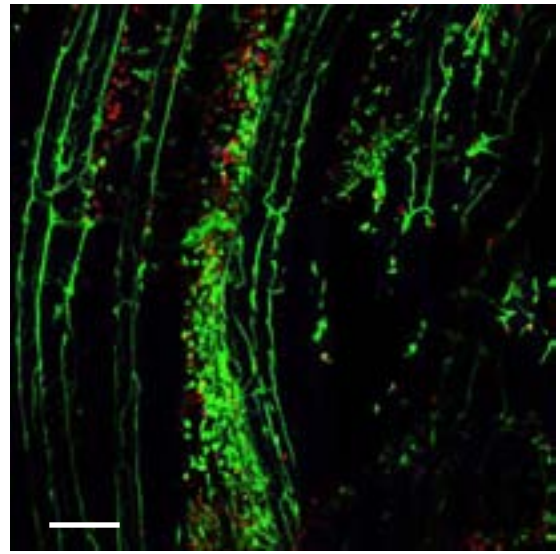






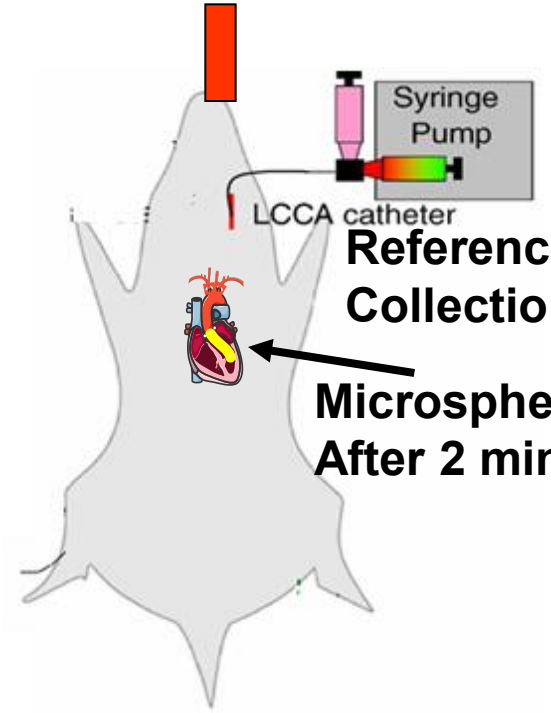






Absolute Blood Flow Measurement in Tissues

Artificial Respiration

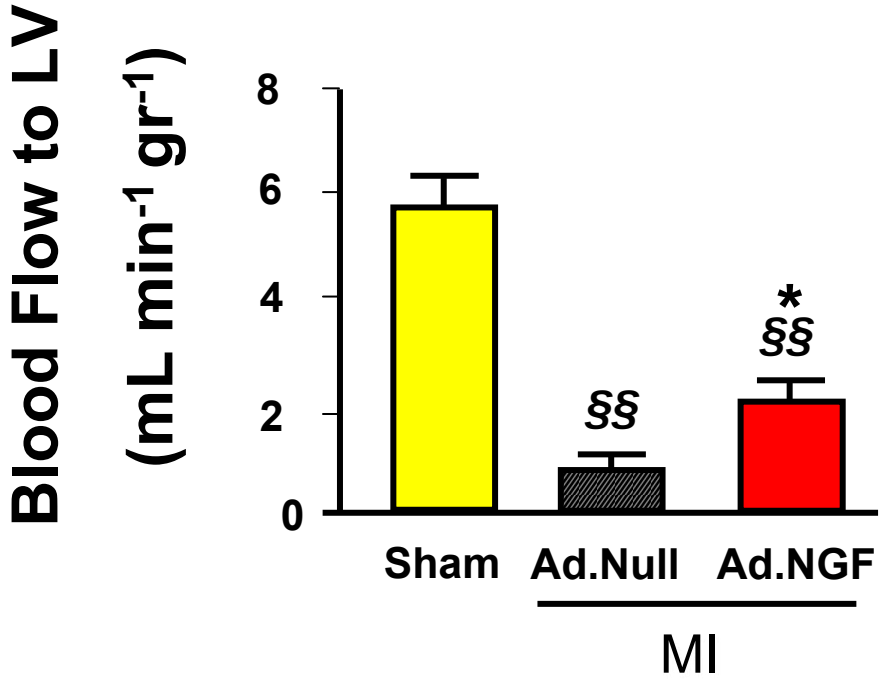


Reference Blood Flow Collection (170μl/min)

Microsphere injection in LV. After 2 minutes, collect tissues

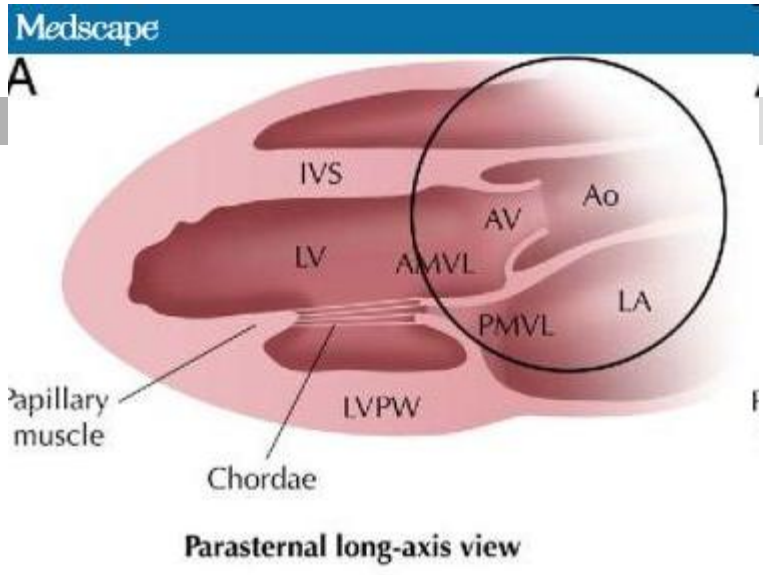
$$\text{BF (mL/min/gr)} = \frac{\text{R x (fl tissues/ fl ref blood)}}{\text{gr of tissue}}$$

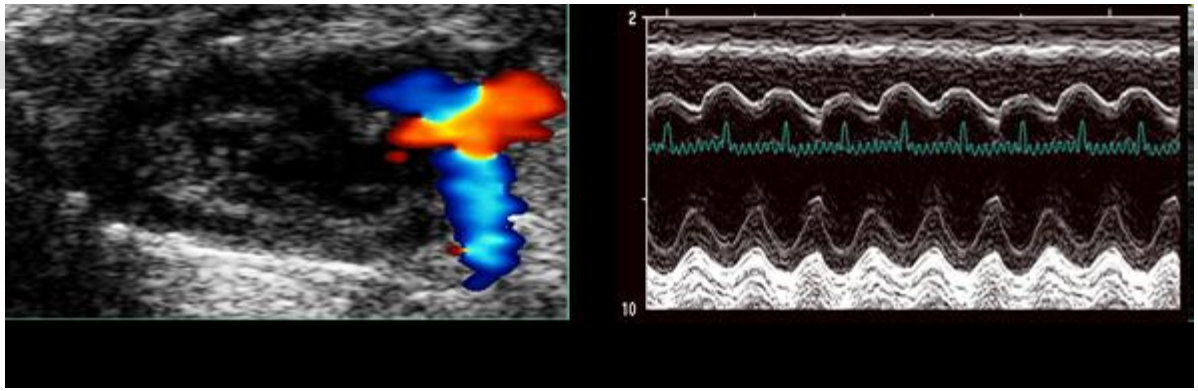
R = rate (mL/min) of ref blood withdrawal

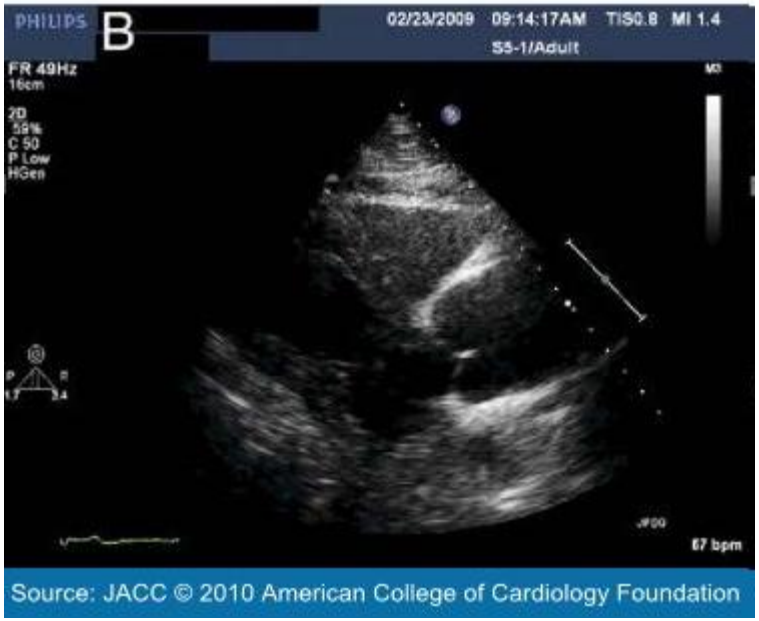


Meloni et al. Circ Res, 2010

Mouse Echocardiography







Large animal models for translational research

Arrival From Farm

Day -7

Myocardial Infarction (n=45)

Day 0

Randomization to:**
- **Group A (n=13)**
- **Group B (n=13)**
- **Group C (n=13)**

Day 14

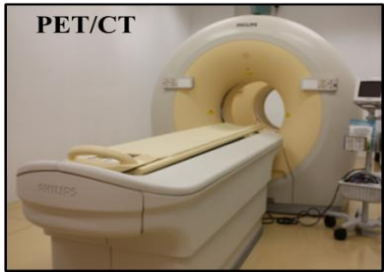
Day 15

***Randomization will be based on baseline LVEF by MRI.**

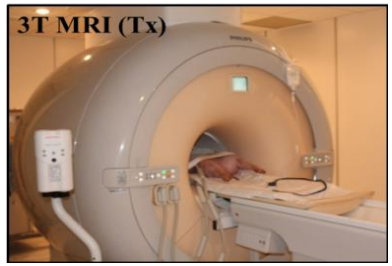
Day 28

Day 56

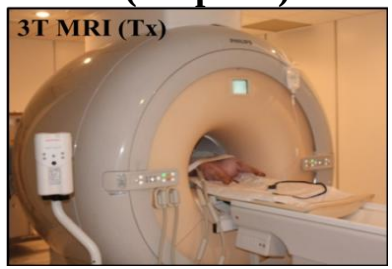
BASELINE IMAGING

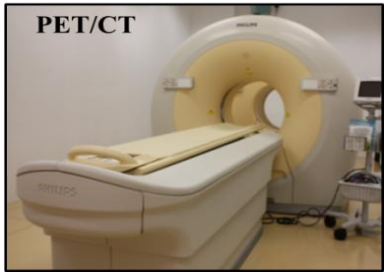


intermediate IMAGING



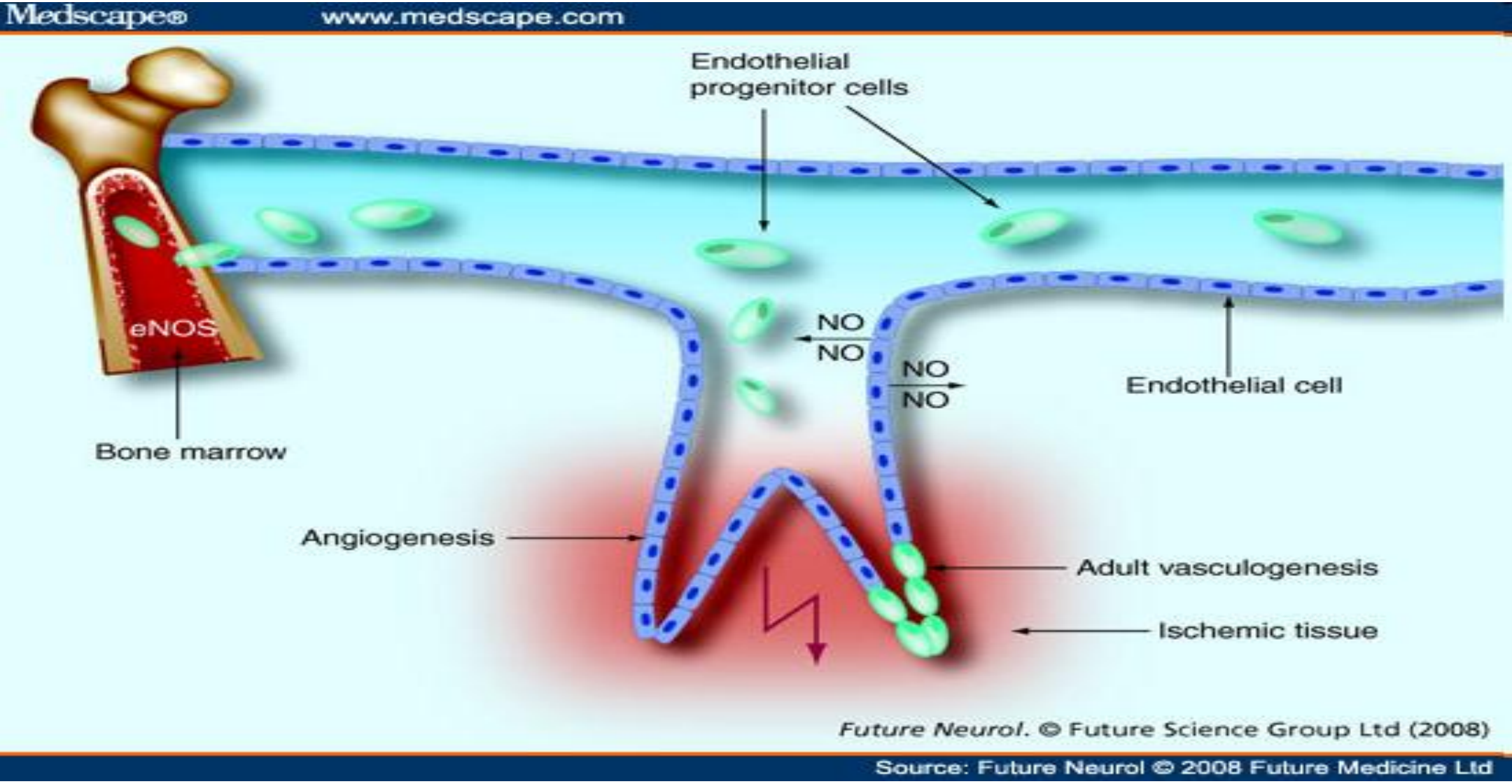
FINAL IMAGING (endpoint)





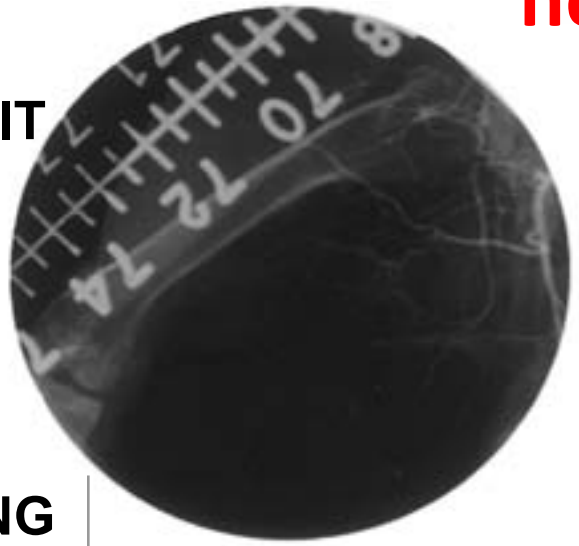
From Dr Borja Ibanez, CNIC-Madrid

Spontaneous post-ischemic neovascularization process

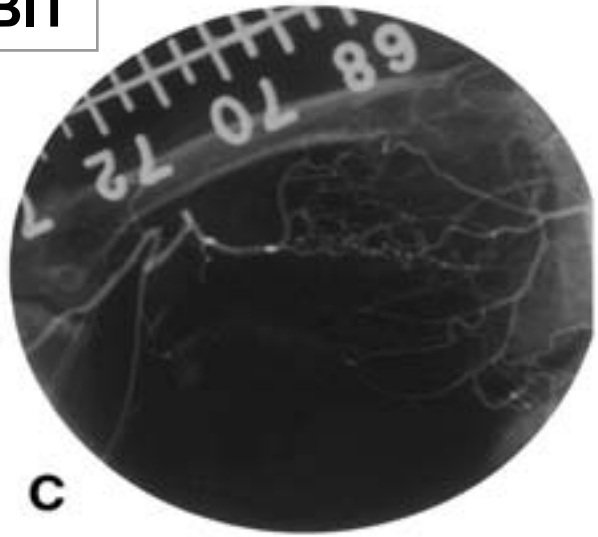


Aging impairs post-ischemic collateral formation and healing in limbs

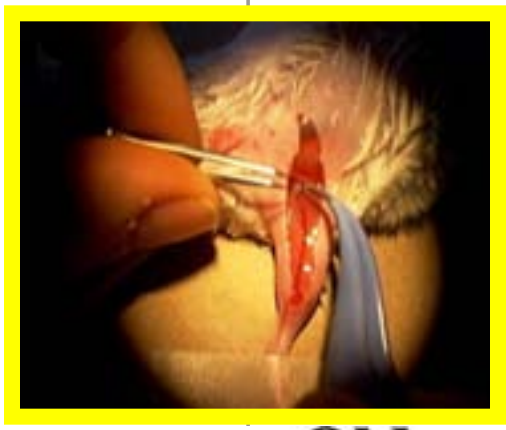
OLD RABBIT



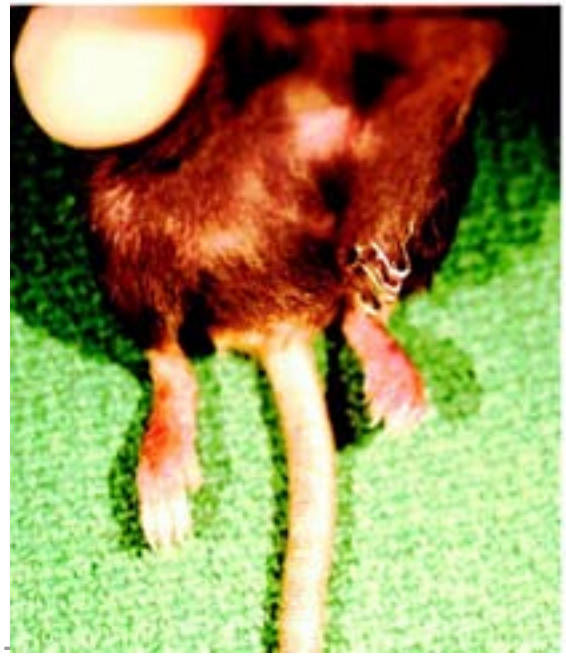
YOUNG RABBIT



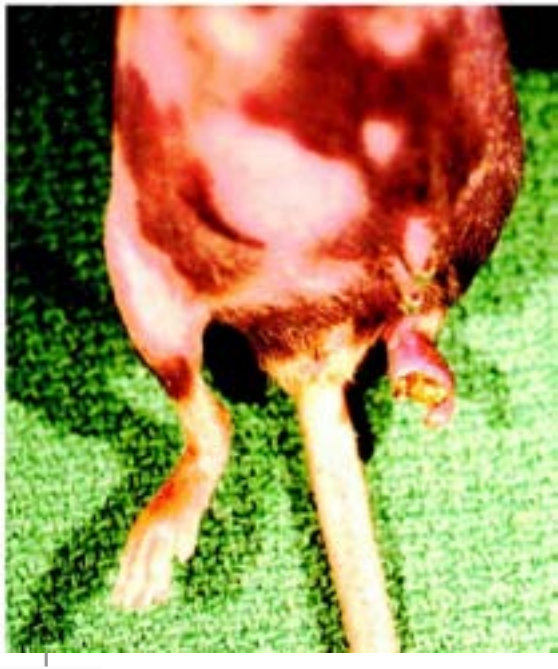
Experimental limb ischemia



Young



Old

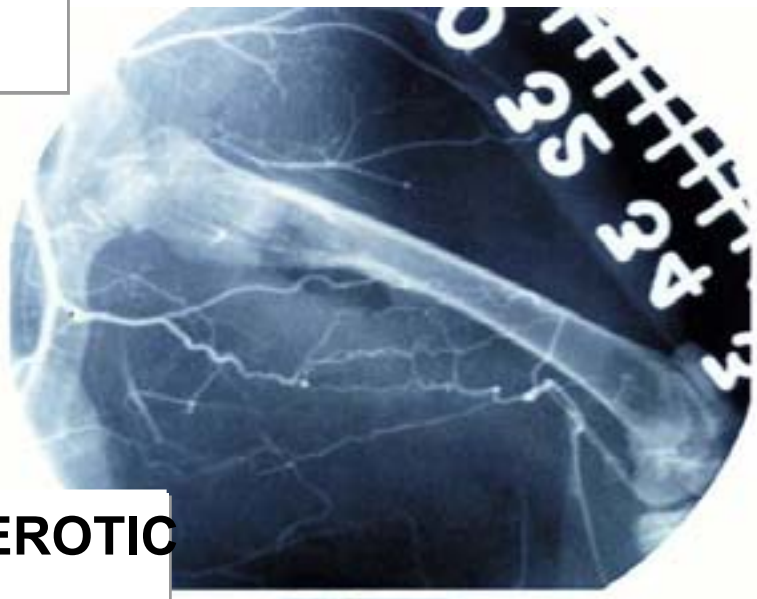


MICE

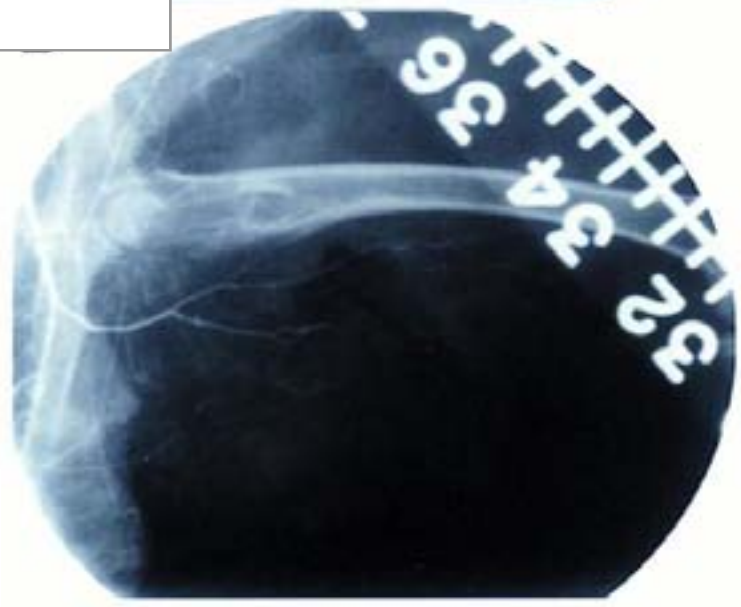
Rivard & Isner, Circulation, 1999

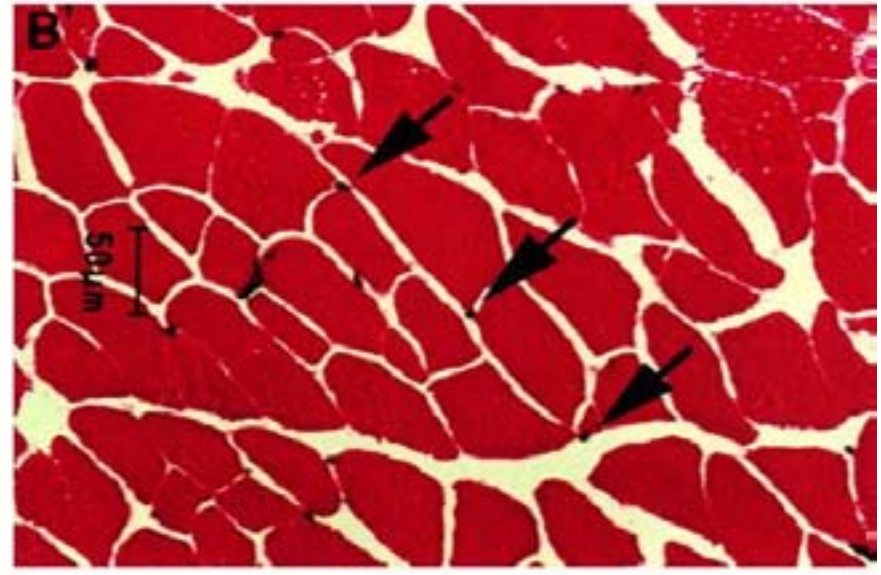
Hypercholesterolemia attenuates post-ischemic angiogenesis in limbs

NORMAL RABBIT



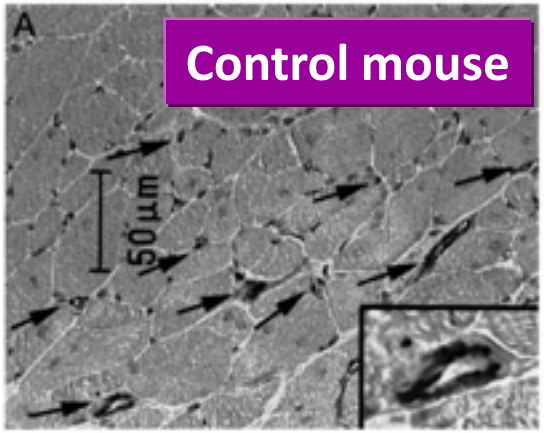
ATHEROSCLEROTIC RABBIT

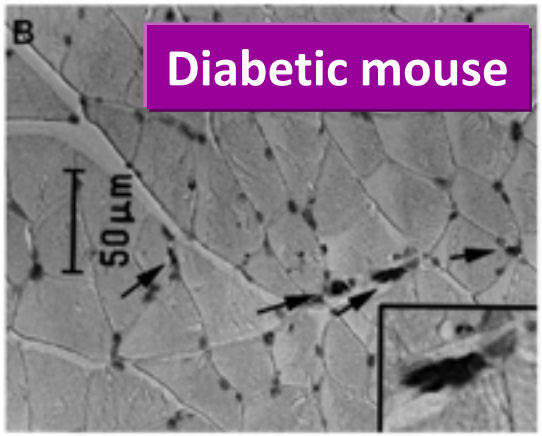


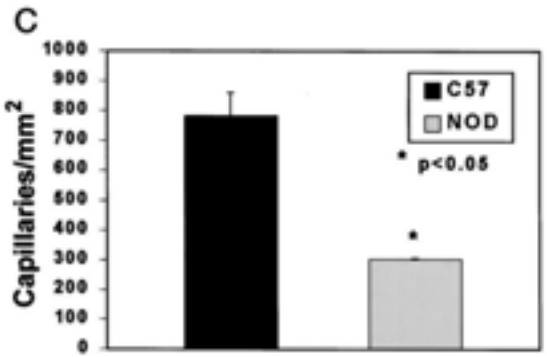


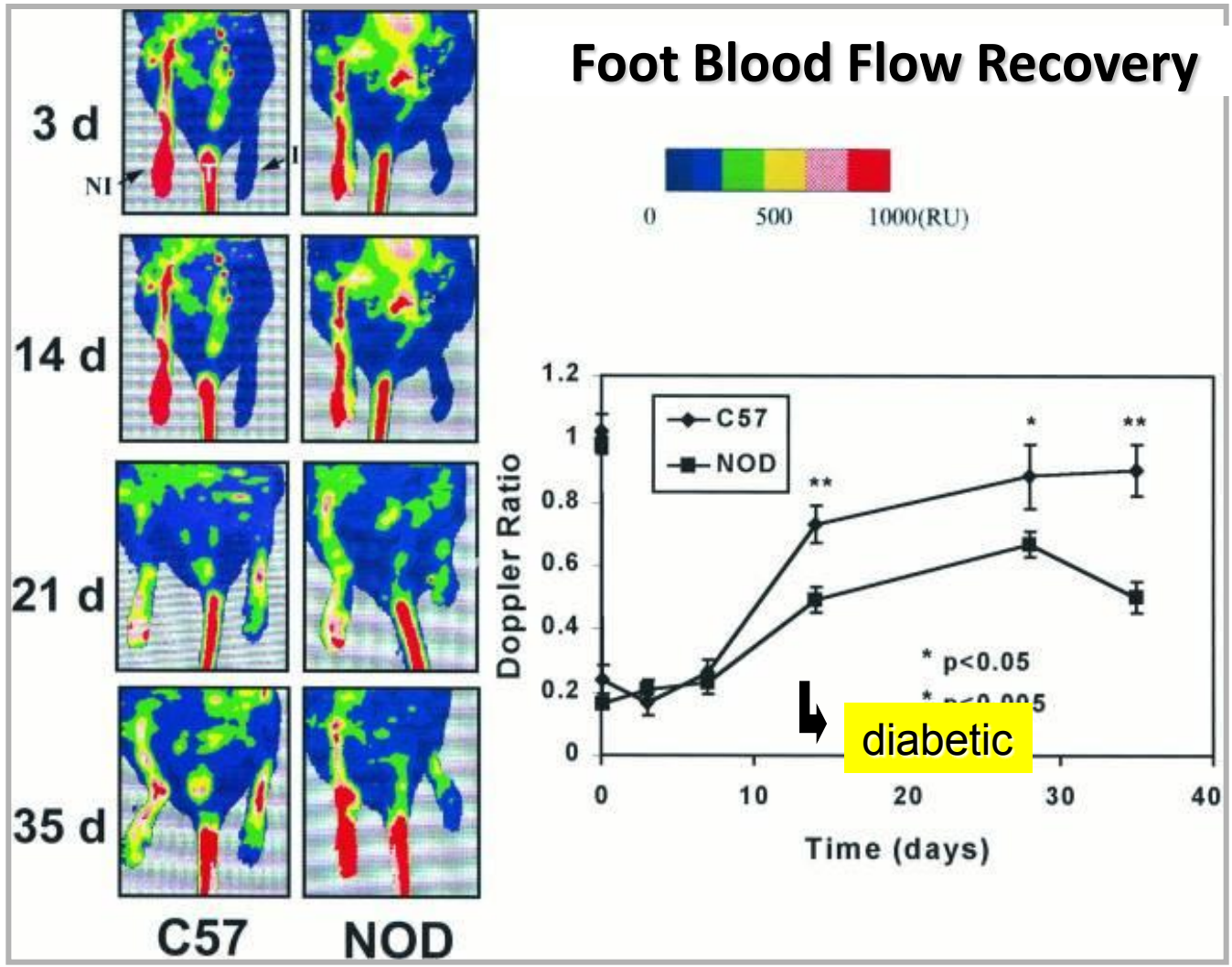
Van Belle, & Isner
Circulation 1997

Diabetes impairs post-ischamic angiogenesis and blood flow recovery





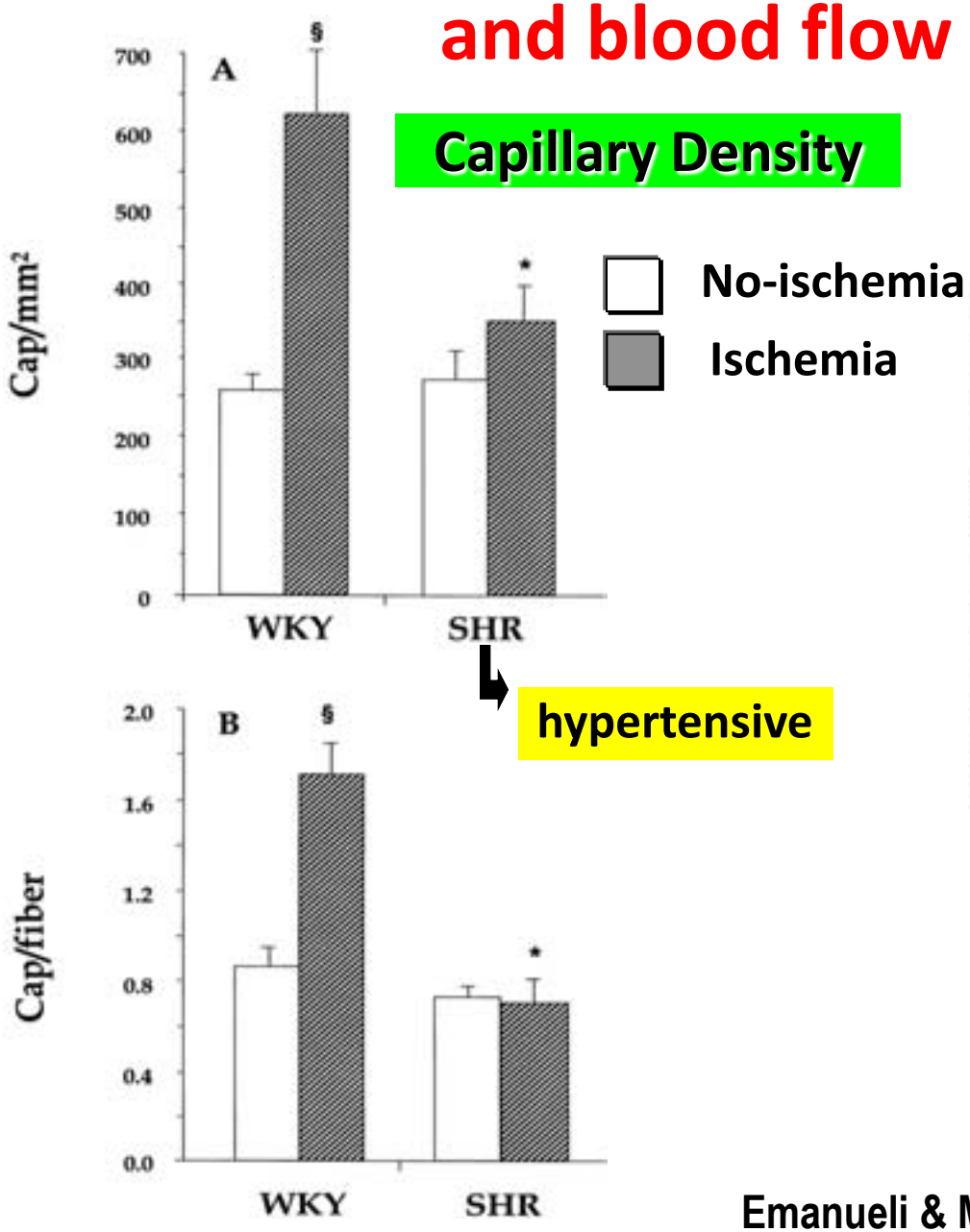




diabetic

Rivard & Isner, Am J Pathol, 1999

High blood pressure impairs post-ischemic angiogenesis and blood flow recovery in rats



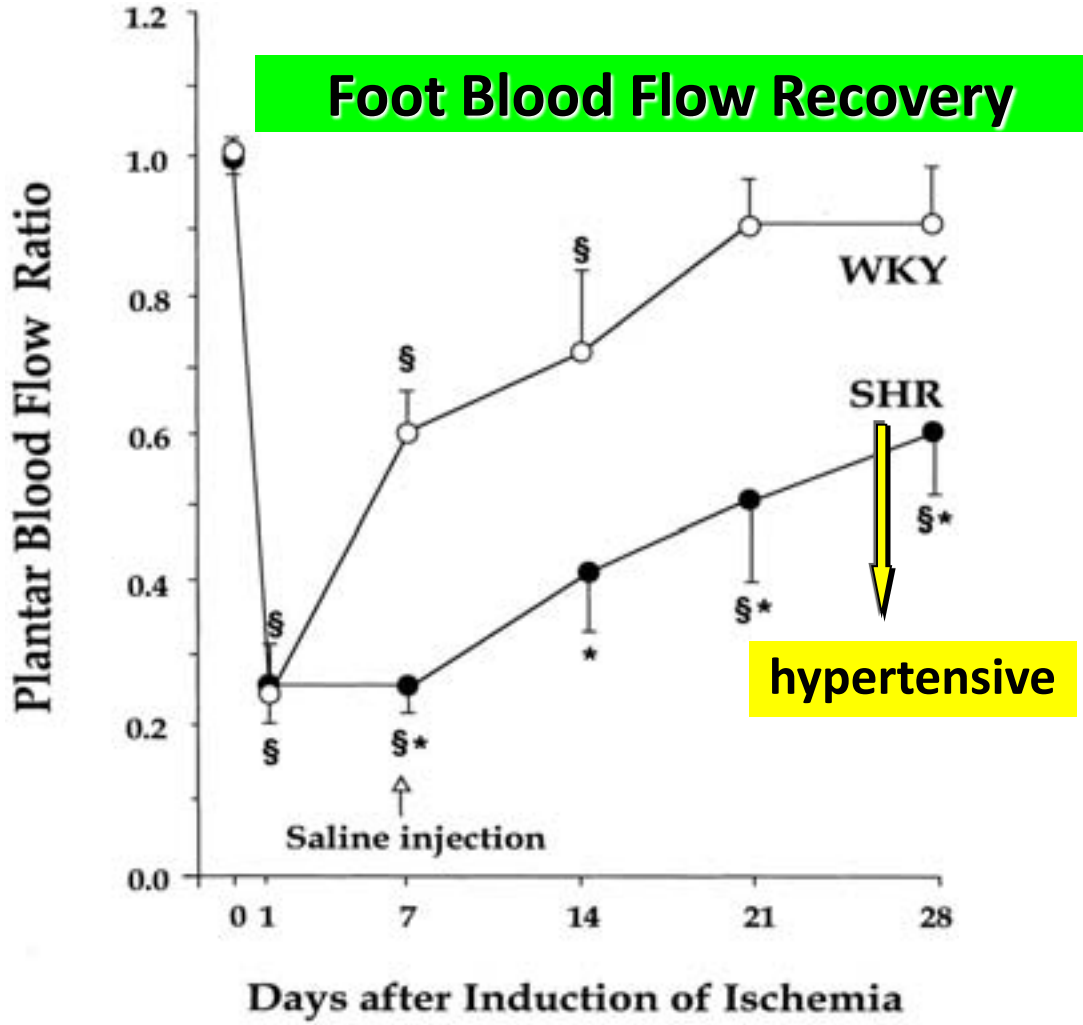
Capillary Density

No-ischemia

Ischemia

hypertensive

Foot Blood Flow Recovery



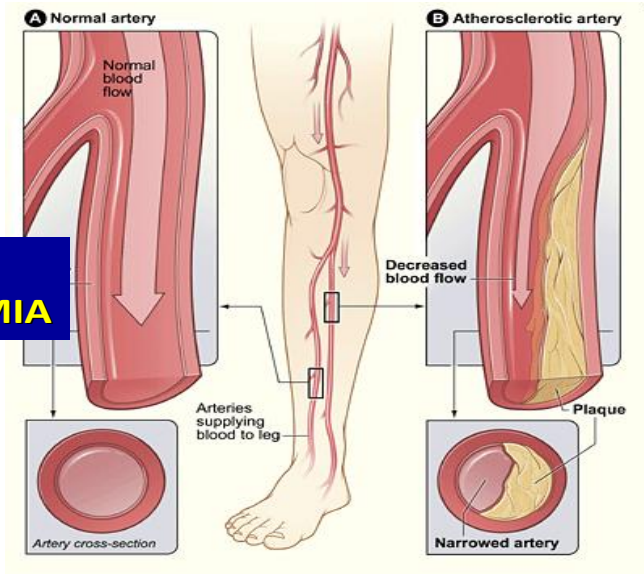
hypertensive

Emanueli & Madeddu. Hypertension 2001

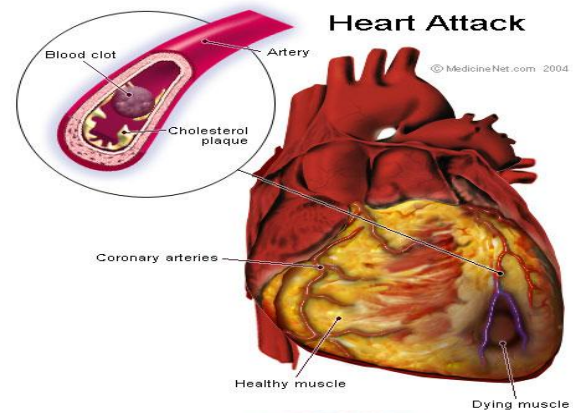
Ischemic patients have at least one of these aforementioned conditions and often all of them plus additional risk factors (obesity, "wrong" genetic and epigenetic backgrounds, smoke, etc) to prevent spontaneous healing.

They need some help to fight ischaemia!

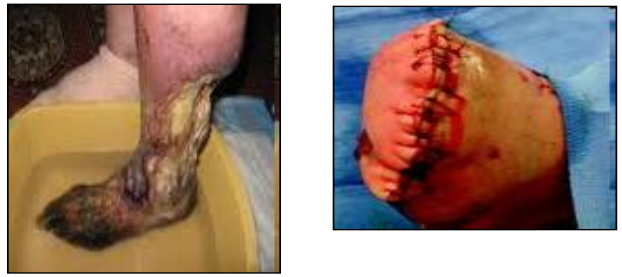
LIMB ISCHAEMIA



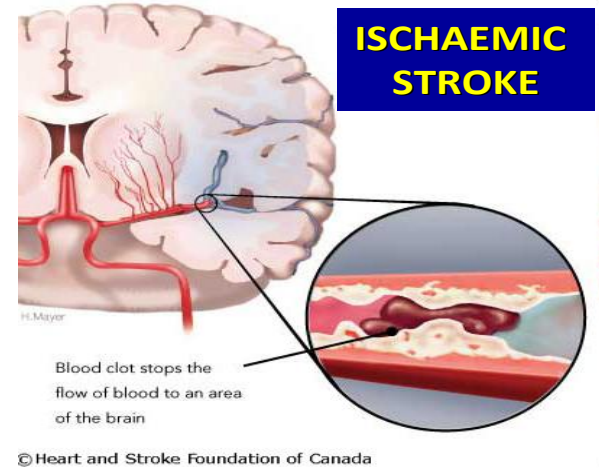
MYOCARDIAL INFARCT



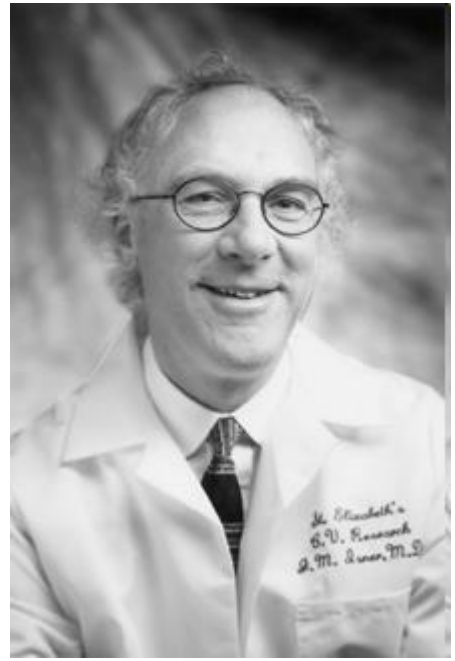
CRITICAL LIMB ISCHAEMIA



ISCHAEMIC STROKE



Therapeutic Neovascularisation of Cardiac and Peripheral Ischaemia



Jeff Isner

First Stretegic Mind to use Angiogenesis as a Therapy

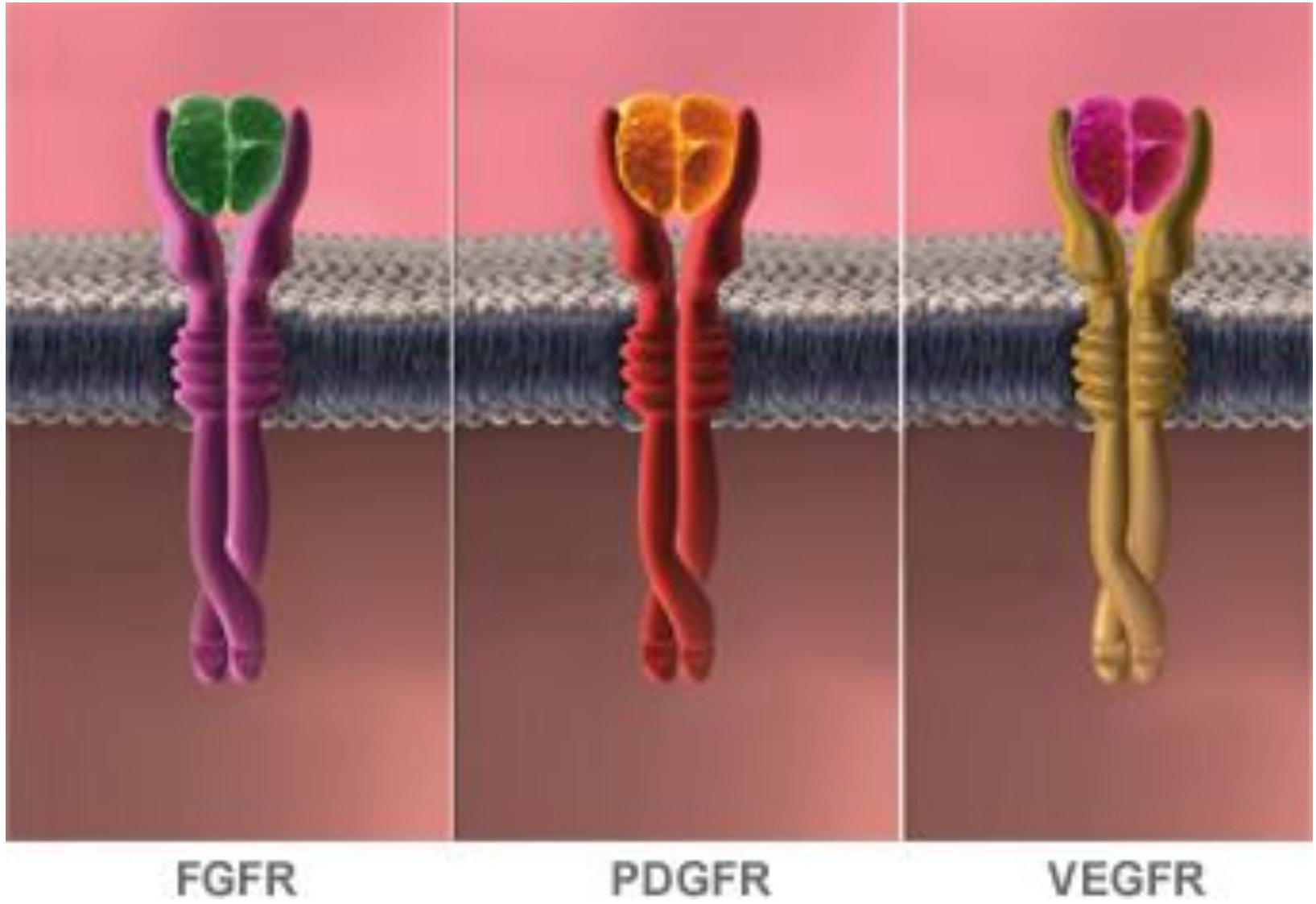
- First attempt

To increase the expression of the prototypical **pro-angiogenic factor VEGF-A** in ischaemic tissues using a supply-side approach, mainly by **gene therapy *via* plasmids and first generation adenoviruses**

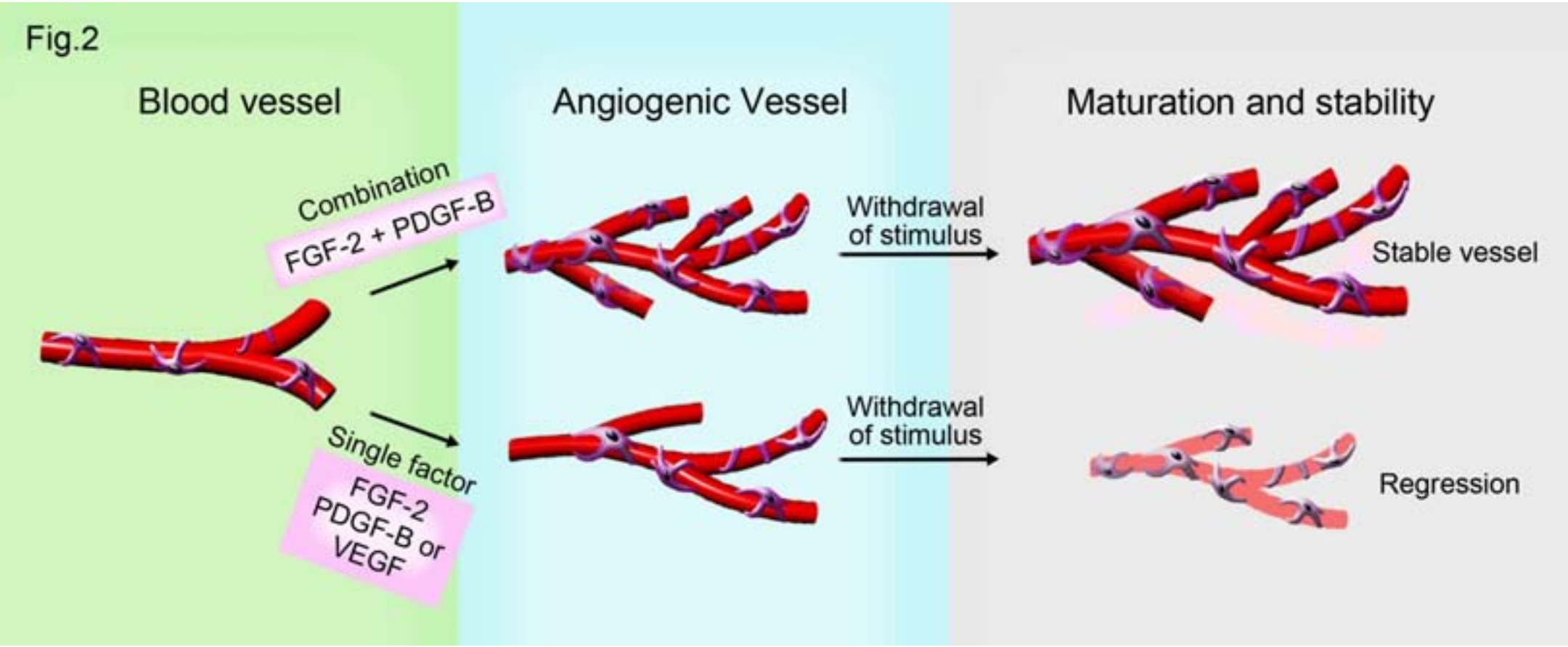
- Second attempt

Transplantation of **endothelial progenitor cells** (**EPCs)** in ischaemic tissues. Done in collaboration with Prof Asahara then a fellow of Isner. This approach was then clinically translated by others (mainly in Frankfurt and Japan)

“Classical” pro-angiogenic factors in mono-therapies



Vascular stabilisation vs vascular regression



Effect of fibroblast growth factor NV1FGF on amputation and death: a randomised placebo-controlled trial of gene therapy in critical limb ischaemia

Jill Belch, William R Hiatt, Iris Baumgartner, I Vickie Driver, Sigrid Nikol, Lars Norgren, Eric Van Belle, on behalf of the TAMARIS Committees and Investigators

Lancet 2011; 377: 1929–37

Published Online
May 31, 2011
DOI:10.1016/S0140-6736(11)60394-2

Summary

Background Patients with critical limb ischaemia have a high rate of amputation and mortality. We tested the hypothesis that non-viral 1 fibroblast growth factor (NV1FGF) would improve amputation-free survival.

Methods In this phase 3 trial (EFC6145/TAMARIS), 525 patients with critical limb ischaemia unsuitable for revascularisation were enrolled from 171 sites in 30 countries. All had ischaemic ulcer in legs or minor skin gangrene and met haemodynamic criteria (ankle pressure <70 mm Hg or a toe pressure <50 mm Hg, or both, or a transcutaneous oxygen pressure <30 mm Hg on the treated leg). Patients were randomly assigned to either NV1FGF at 0·2 mg/mL or matching placebo (visually identical) in a 1:1 ratio. Randomisation was done with a central interactive voice response system by block size 4 and was stratified by diabetes status and country. Investigators, patients, and study teams were masked to treatment. Patients received eight intramuscular injections of their assigned treatment in the index leg on days 1, 15, 29, and 43. The primary endpoint was time to major amputation or death at 1 year analysed by intention to treat with a log-rank test using a multivariate Cox proportional hazard model. This trial is registered with ClinicalTrials.gov, number NCT00566657.

Findings 259 patients were assigned to NV1FGF and 266 to placebo. All 525 patients were analysed. The mean age was 70 years (range 50–92), 365 (70%) were men, 280 (53%) had diabetes, and 248 (47%) had a history of coronary artery disease. The primary endpoint or components of the primary did not differ between treatment groups, with major amputation or death in 86 patients (33%) in the placebo group, and 96 (36%) in the active group (hazard ratio 1·11, 95% CI 0·83–1·49; p=0·48). No significant safety issues were recorded.

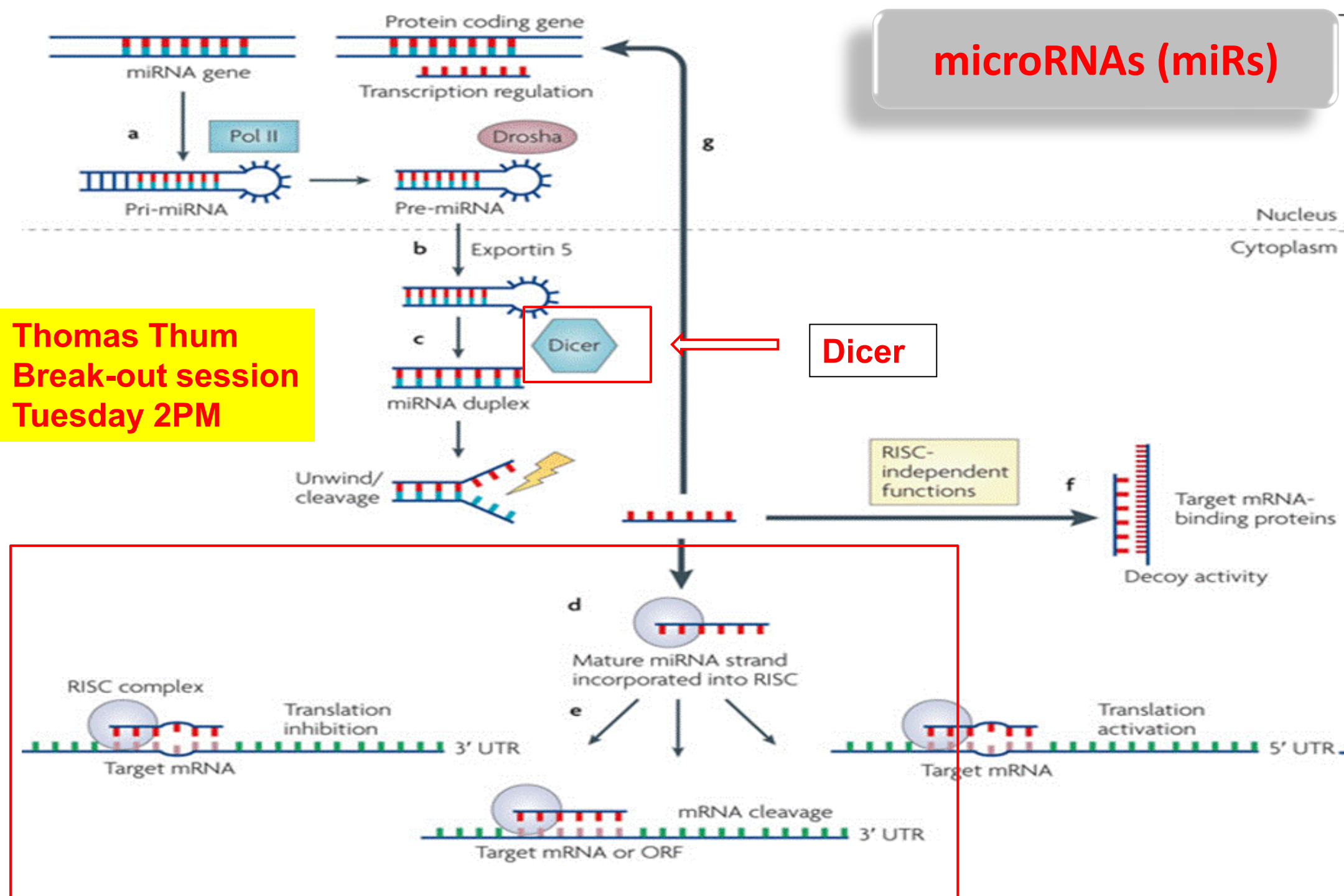
Interpretation TAMARIS provided no evidence that NV1FGF is effective in reduction of amputation or death in patients with critical limb ischaemia. Thus, this group of patients remains a major therapeutic challenge for the clinician.

Options for Improving Traditional Post-Ischaemic Neovascularisation Therapeutics

- More basic science to understand all the players in the angiogenesis and anti-angiogensis orchestras
- Test different angiogenesis modulator factors (growth factors and more)
- Combinatory approaches
- More severity in preclinical testing (large animal models, risk factors associated to experimental ischemia, etc)
- Work at gene vectors
- Success in *in vivo* small vessel imaging
- Design better clinical trials

- Do not give up!

microRNAs (miRs)

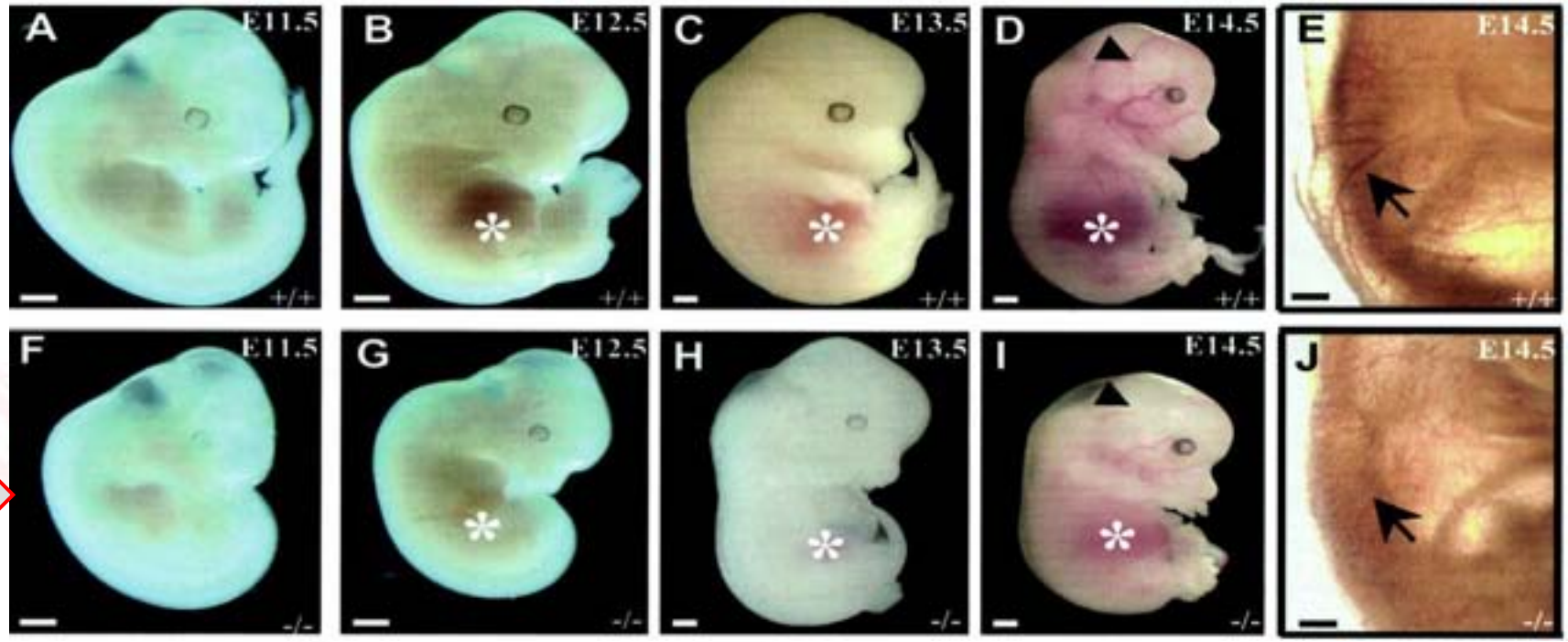


Thomas Thum
Break-out session
Tuesday 2PM

Dicer

First evidence for a regulatory role of miRs in vascular development

Mice homozygous for a hypomorphic allele of *Dicer* showed impaired developmental angiogenesis and died at days 12.5 - 14.5 of gestation

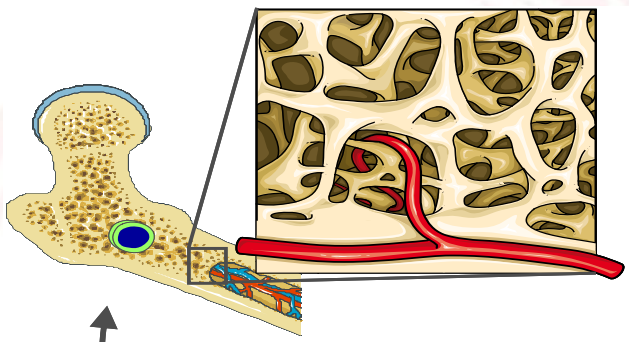


Low Dicer

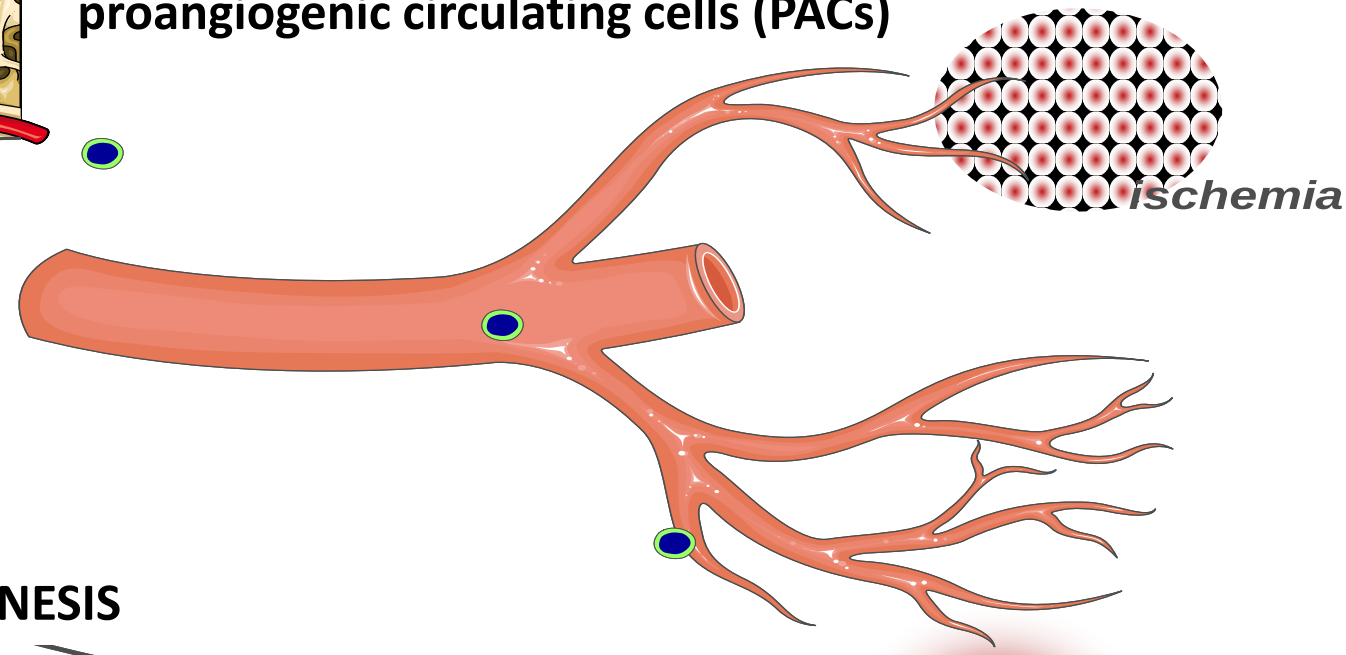
Dicer generates short interfering RNAs (including miRNAs) from longer double-stranded RNAs.

Yang W J et al. J. Biol. Chem. 2005;280:9330-9335

Spontaneous post-ischemic neovascularization process



Bone marrow-derived endothelial progenitor cells (EPCs)/ proangiogenic circulating cells (PACs)



VASCULOGENESIS

VEGF, IL-8, ...

ANGIOGENESIS

<u>Scientific Questions</u>:

Do miRs modulate it? What miRs? At what levels?

Therapeutic exploitation of miRs?

miR expression is regulated by hypoxia and ischemia

Hypoxia

Table 1 Compilation of microRNAs associated with the hypoxia response by recent publications

MicroRNAs upregulated by hypoxia		MicroRNAs downregulated by hypoxia	
Mir-7	3	Mir-15b	2
Mir-15a	3	Mir-16	2
mir-21	1	Mir-19a	3
mir-23a	1	Mir-20a	2
Mir-23b	1	Mir-20b	2
Mir-24	1	Mir-26b	2
Mir-26a	1	Mir-29b	3
Mir-26b	1	Mir-30b	2
Mir-27a	1	Mir-30e-5p	3
Mir-30b	1, 3	Mir-101	3
Mir-30d	2	Mir-122a	3
Mir-93	1, 4	Mir-141	3
Mir-98	3	Mir-186	3
Mir-103	1	Mir-195	3
Mir-106a	1	Mir-197	3
Mir-107	1	Mir-224	2
Mir-125b	1	Mir-320	3
Mir-148a	3	Mir-374	3
Mir-148b	3	Mir-422b	3
Mir-151	2	Mir-424	3, 4
Mir-155	2	Mir-565	3
Mir-181a	1	Let-7-a	2
Mir-181b	1, 2	Let-7-c	2
Mir-181c	1	Let-7-d	2
Mir-188	2	Let-7-e	2
Mir-191	3	Let-7-f	2
Mir-192	1	Let-7-g	2
Mir-195	1		
Mir-200a	3		
Mir-210	1, 2, 3		
Mir-213	1		
Mir-214	3		
Mir-373	3		
Mir-429	3		
Mir-498	3		
Mir-563	3		
Mir-572	3		
Mir-628	3		
Mir-637	3		
Let-7-e	3		
Let-7-g	3		
Let-7-i	3		

Study cited, and corresponding cell types and conditions: (1) Kulshreshtha *et*

Kulshreshtha &, Ivan, CDD, 2008.

Mouse limb ischaemia model

Table 1. Top 15 Upregulated MIRNAs

miRNA	FC at Day 3	Expression Baseline	6 h	24 h	3 d	7 d	14 d	Function
Mmu-miR-223	7.79	1392	3606	5208	10 841	2663	2143	Hematopoietic lineage differentiation
Mmu-miR-342	5.49	1608	1728	2712	8825	2954	2463	Unknown
Mmu-miR-720	5.07	868	1237	1338	4405	895	1410	Unknown
Mmu-miR-21	3.54	16 240	17 365	23 919	57 514	29 067	31 587	VSMC proliferation
Mmu-miR-20a	2.99	1440	1106	1442	4299	1231	1646	Part of the miR-17–92 cluster
Mmu-miR-221	2.89	954	665	995	2757	1281	1837	Inhibits angiogenesis
Mmu-miR-15b	2.79	3128	5258	6146	8738	4786	3383	Potential inhibitor of VEGF
Mmu-miR-762	2.46	1890	15 718	3852	4649	4372	2758	Unknown
Mmu-miR-17-5p	2.33	905	587	833	2106	700	980	Part of the miR-17–92 cluster
Mmu-miR-214	2.17	3334	3247	2431	7219	5222	5974	Potential inhibitor of angiogenesis
Mmu-miR-181a	1.84	3195	3113	3737	5870	4006	3940	Regulates myoblast differentiation
Mmu-miR-92	1.79	3914	3544	4567	7007	3821	2729	Strong inhibitor of angiogenesis
Mmu-miR-29a	1.57	22 294	15 958	20 328	35 051	21 583	25 449	Unknown
Mmu-miR-25	1.50	3497	3206	5039	5232	3773	3540	Unknown
Mmu-miR-191	1.46	10 260	8896	11 265	15 030	11 026	10 404	Induced by VEGF in endothelial cells

Table 2. Top 15 Downregulated MIRNAs

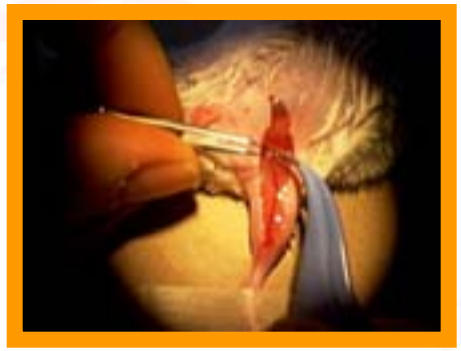
miRNA	FC at Day 3	Expression Baseline	6 h	24 h	3 d	7 d	14 d	Function
Mmu-miR-196a	−9.08	2078	5319	3680	229	2957	1315	Mesenchymal stem cell differentiation
Mmu-miR-98	−6.32	3160	9812	5172	500	5289	1209	Unknown
Mmu-let-7e	−3.98	11 433	20 092	17 674	2875	14 206	11 220	Part of the let-7 family*
Mmu-miR-30a3p	−3.25	3343	3727	2939	1028	2440	1924	Predicted targets include VEGF
Mmu-let-7b	−2.29	22 955	25 181	22 522	10 028	22 084	26 826	Part of the let-7 family*
Mmu-let-7g	−1.99	19 036	22 295	21 157	9563	20 524	21 034	Part of the let-7 family*
Mmu-let-7 days	−1.96	25 651	27 387	24 953	13 104	24 780	27 348	Part of the let-7 family*
Mmu-let-7c	−1.89	26 411	26 846	24 973	14 002	24 774	30 647	Part of the let-7 family*
Mmu-miR-100	−1.81	4949	3903	3122	2728	3557	3736	Unknown
Mmu-let-7a	−1.77	31 665	31 916	29 922	17 873	30 531	34 355	Part of the let-7 family*
Mmu-miR-805	−1.76	6035	9591	8618	3426	6468	4708	Unknown
Mmu-let-7f	−1.75	28 348	30 789	28 893	16 230	28 697	31 142	Part of the let-7 family*
Mmu-miR-365	−1.67	8257	6057	6496	4936	7592	2710	Unknown
Mmu-let-7i	−1.61	14 023	15 620	15 048	8689	15 276	18 171	Part of the let-7 family*
Mmu-miR-143	−1.59	11 126	7527	9446	7019	9640	10 678	Regulate smooth muscle cell fate

FC indicates fold change; VSMC, vascular smooth muscle cell; and VEGF, vascular endothelial growth factor.
*The let-7 family targets thrombospondin-1.

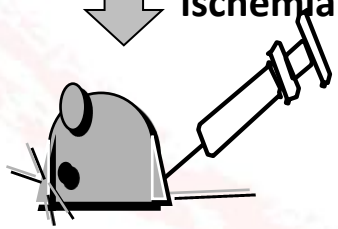
Grundmann & Moser, Circ , 2011

miR-92a: first example of mIR targeting for post-ischemic angiogenesis

Systemic miR-92a inhibition stimulates recovery after hind limb ischaemia



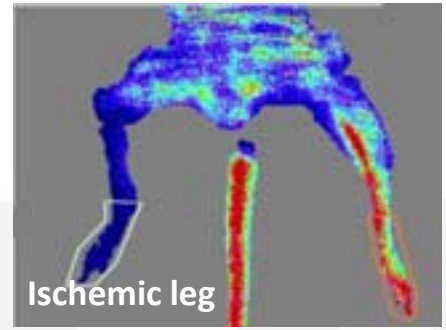
Hind limb ischemia



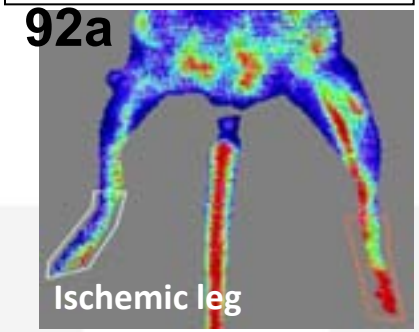
Day 0,2,4,7, and 9
Antagomir 92a or Co

Blood flow
Microvessel density

Antagomir-Co

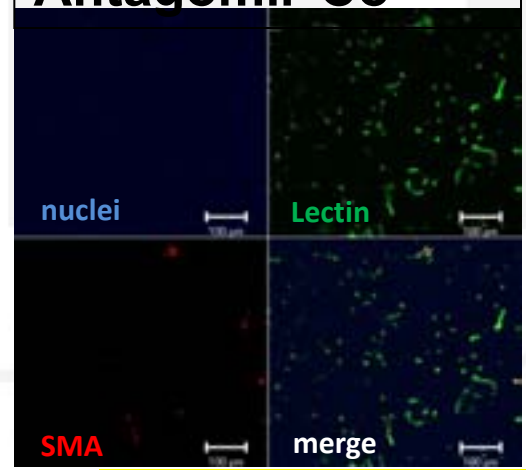


Antagomir-92a

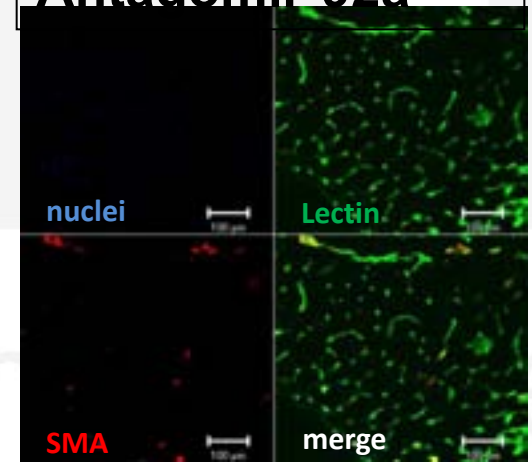


Bonauer& Dimmeler, Science, 2009

Antagomir-Co



Antagomir-92a



Slide kindly provided by Stefanie Dimmeler

Example for miR targeting and contrasting anti-angiogenic factors

miR-503: how we joined the miR club!

Andrea Caporali

Circulation 2011
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Molecular Cardiology

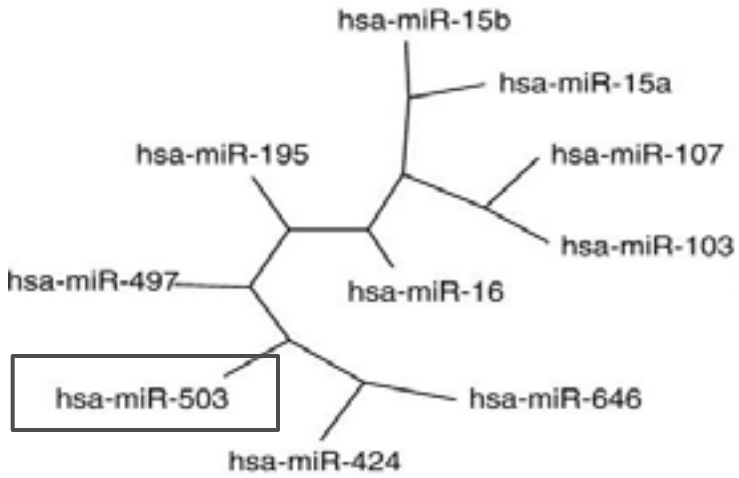
Deregulation of microRNA-503 Contributes to Diabetes Mellitus–Induced Impairment of Endothelial Function and Reparative Angiogenesis After Limb Ischemia

Andrea Caporali, PhD; Marco Meloni, PhD; Christine Völlenkle, PhD; Desiree Bonci, PhD; Graciela B. Sala-Newby, PhD; Roberta Addis, BSc; Gaia Spinetti, PhD; Sergio Losa, MD; Rachel Masson, PhD; Andrew H. Baker, PhD; Reuven Agami, PhD; Carlos le Sage, PhD; Gianluigi Condorelli, MD, PhD; Paolo Madeddu, MD; Fabio Martelli, PhD; Costanza Emanueli, PhD

miR-503

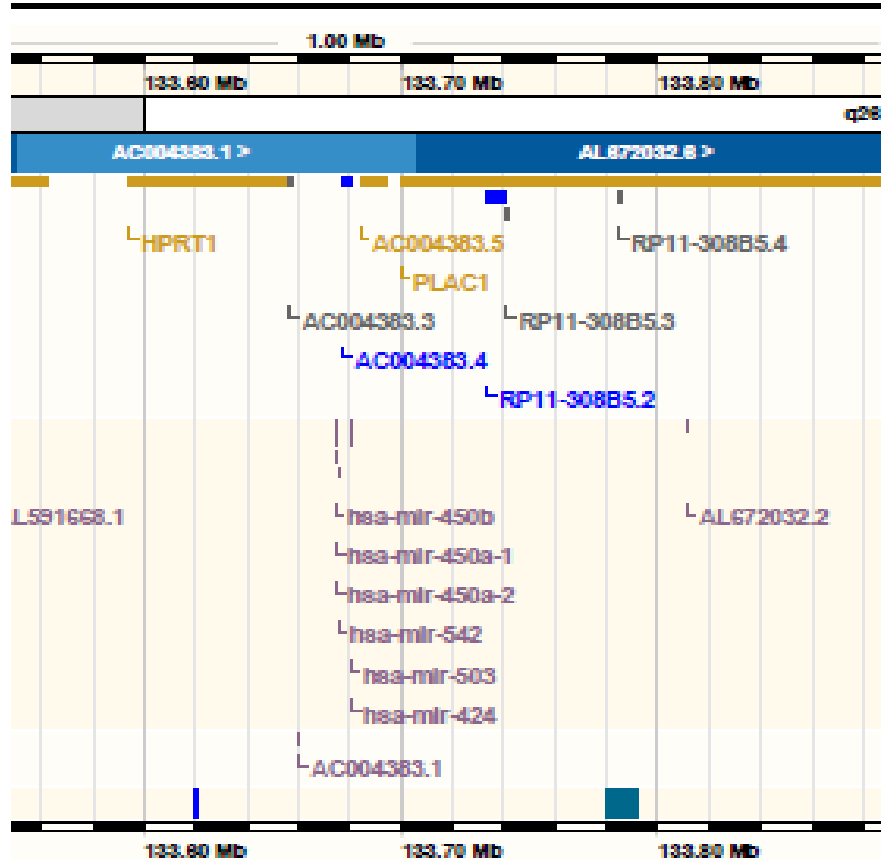
Member of miR-15/107 group:
AGCAGC seed sequence

hsa-miR-107	AGCAGC	AUUGUACAGGGCUAUCA
hsa-miR-103	AGCAGC	AUUGUACAGGGCUAUGA
hsa-miR-15a U	AGCAGC	ACAUAAUGGUUUGUG
hsa-miR-15b U	AGCAGC	ACAUCAUGGUUUACA
hsa-miR-16 U	AGCAGC	ACGUAAAUAUUGGCG
hsa-miR-195 U	AGCAGC	ACAGAAAUAUUGGCC
hsa-miR-497 C	AGCAGC	ACACUGUGGUUUGU
hsa-miR-503 U	AGCAGC	GGGAACAGUUCUGCAG
hsa-miR-424 C	AGCAGC	AAUUCAUGUUUUGAA
hsa-miR-646 A	AGCAGC	UGCCUCUGAGGC



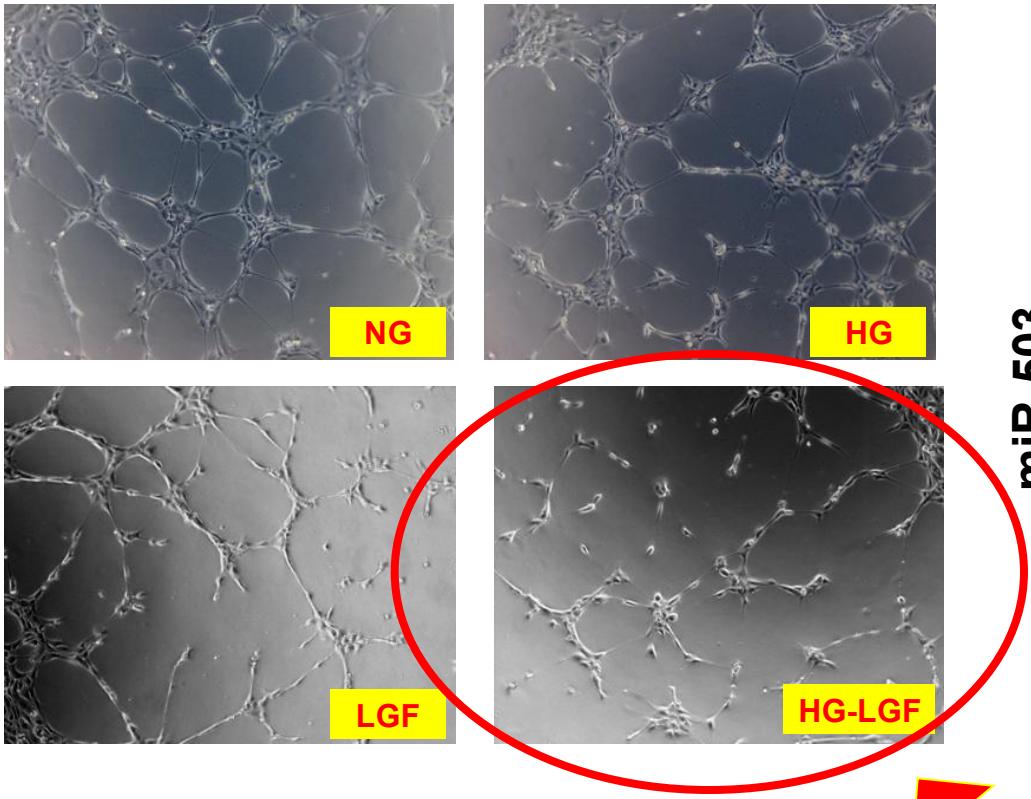
Finnerty JR et al. JMB 2010

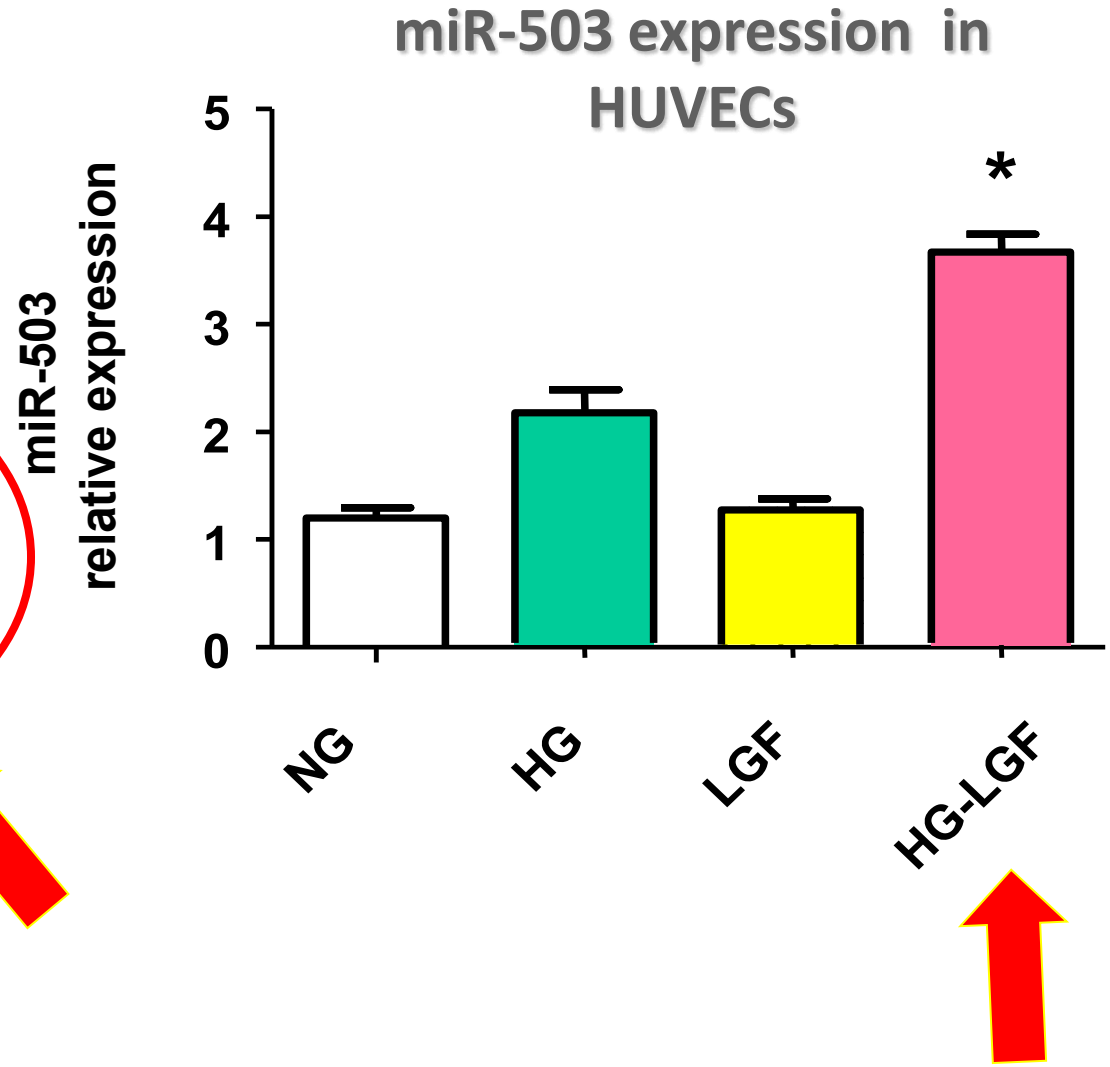
Chr X; intergenic
Cluster: miR-424-503



Examination of the mir-424 and mir-503 loci showed that they are separated by 383 bases on the genome and derived from the same primary transcript

miR-503 expression in ECs is increased by culture conditions mimicking hyperglycaemia and ischemia





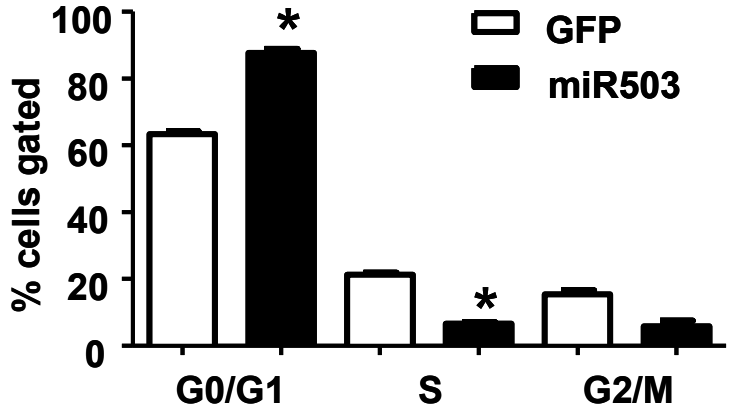
NG= normal glucose, 5 mM

HG= high glucose, 25 mM

LGF = reduced growth factors

Consequences of miR-503 overexpression in endothelial cells

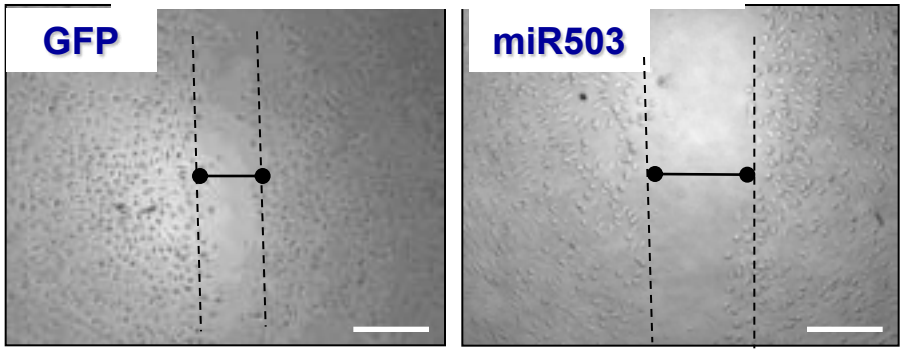
Impaired EC cycle



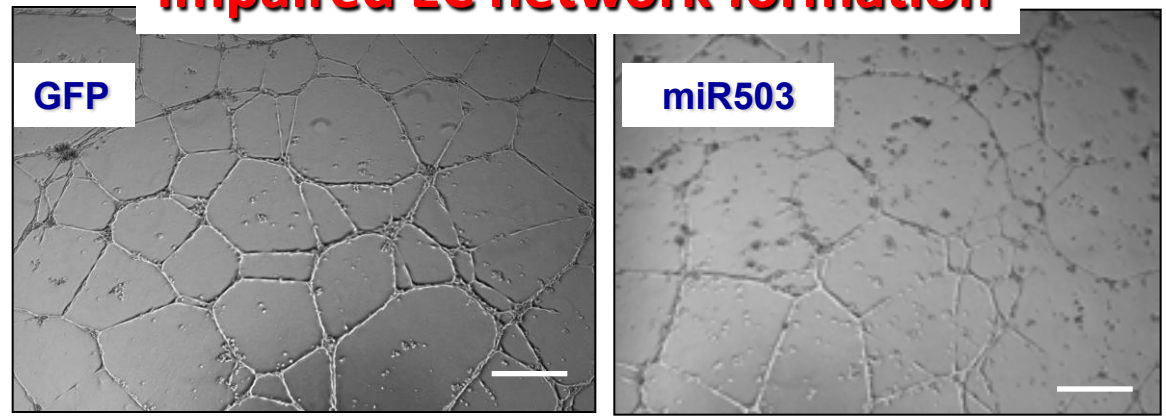
miR-503 target genes

```
675-682 cdc25A 3'UTR   5'  ...CGCUGUGGUACUGGGGCUGCUGCUAU...
                               |||  | ||||   |:||||||
          has-miR-503      3'      GACGUCUUGACAAGGGCGACGAU

248-254 CCNE1 3'UTR    5'  ...GUGCGUGCUCCCGAUGCUGCUAU...
                                          ||||||
          has-miR-503      3'      GACGUCUUGACAAGGGCGACGAU

486-492 CCNE1 3'UTR    5'  ...AACUGUUUUGUAAGUGCUGCUAU...
                               |||||||          ||||||
          has-miR-503      3' GACGUCUUGACAAGGG-----CGACGAU
```

Impaired EC migration

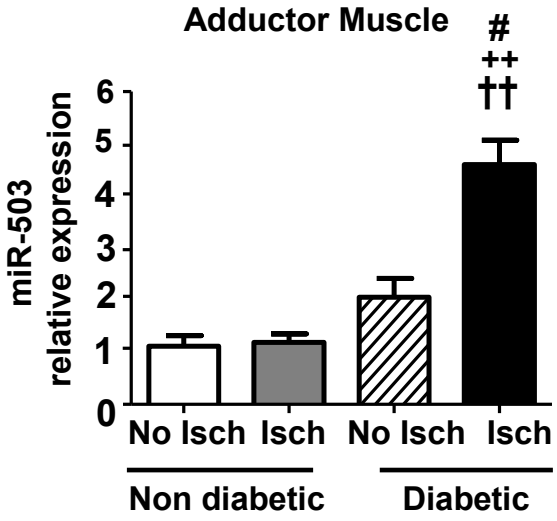


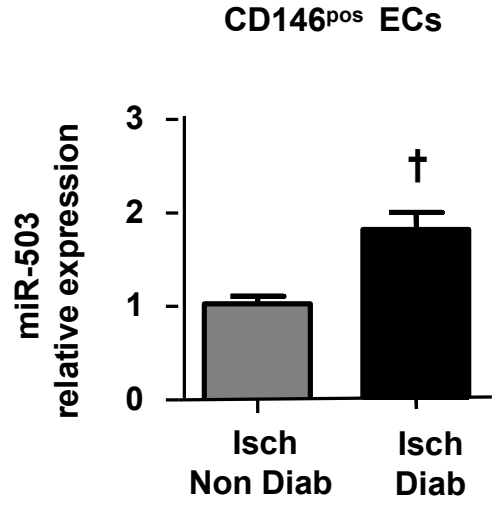
Impaired EC network formation



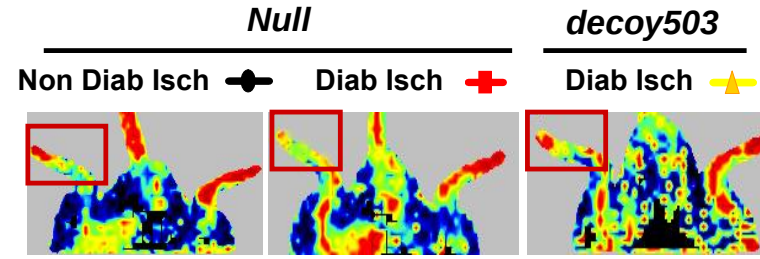
Local gene therapy with a decoy for miR-503 improves post-ischaemic angiogenesis in diabetic mice

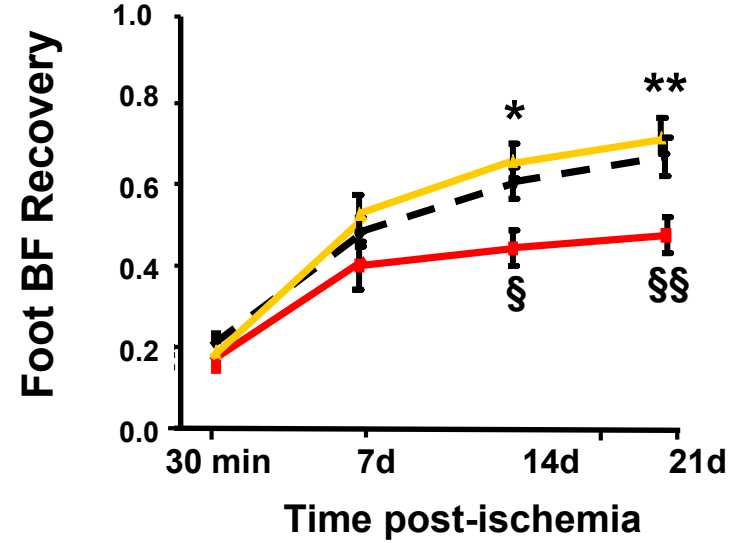
miR-503 expression



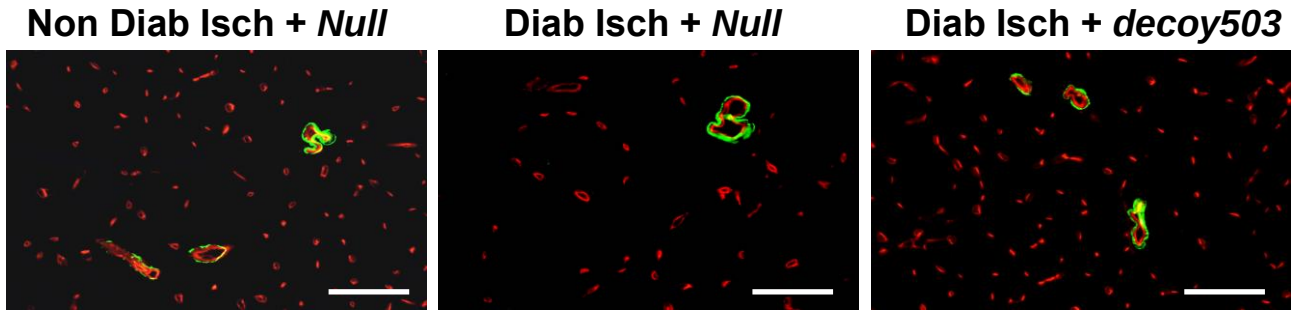


Blood flow recovery





Limb microvessels



New cell therapy products

Human circulating pro-angiogenic cells: PACs

HISTOPAQUE
MNC SEPARATION

Plasma

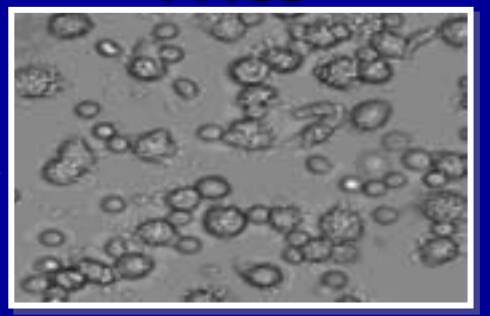
MNCs

erythrocytes

ADHERENCE ENRICHMENT
ON FIBRONECTIN

4 DAYS CULTURE IN EC
MEDIUM

PACs

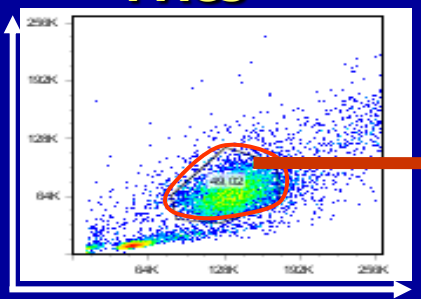


FLOATING

ADHERENT CELLS

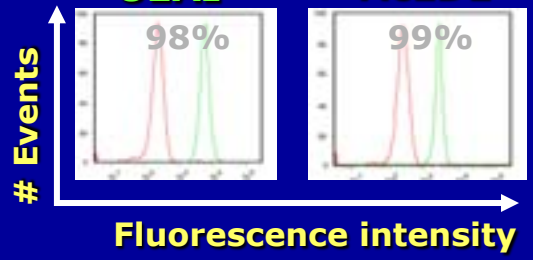
Isolation and culture

PACs



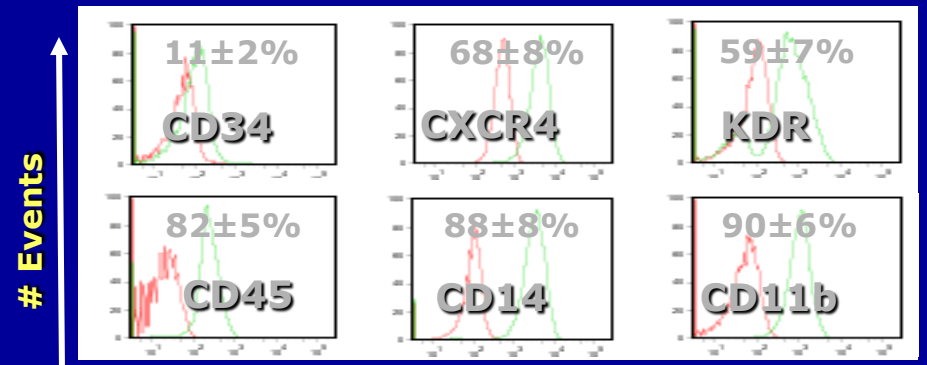
UEAI

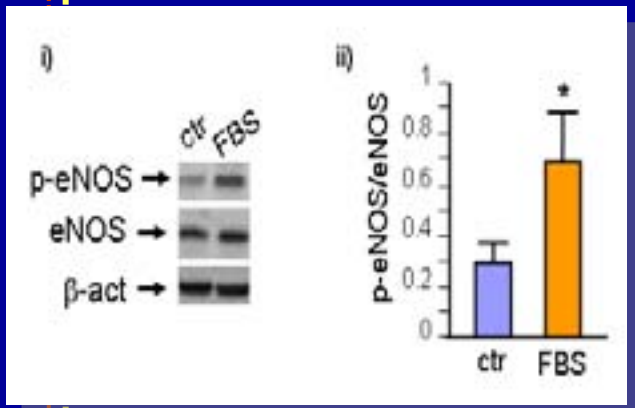
AcLDL



Negative control

Specific marker



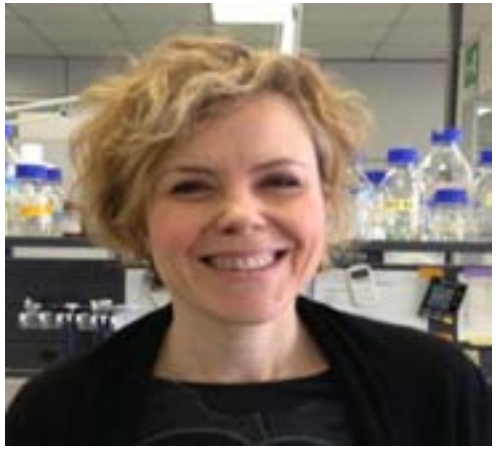


Phenotypic characterization

Circ Res, 2013

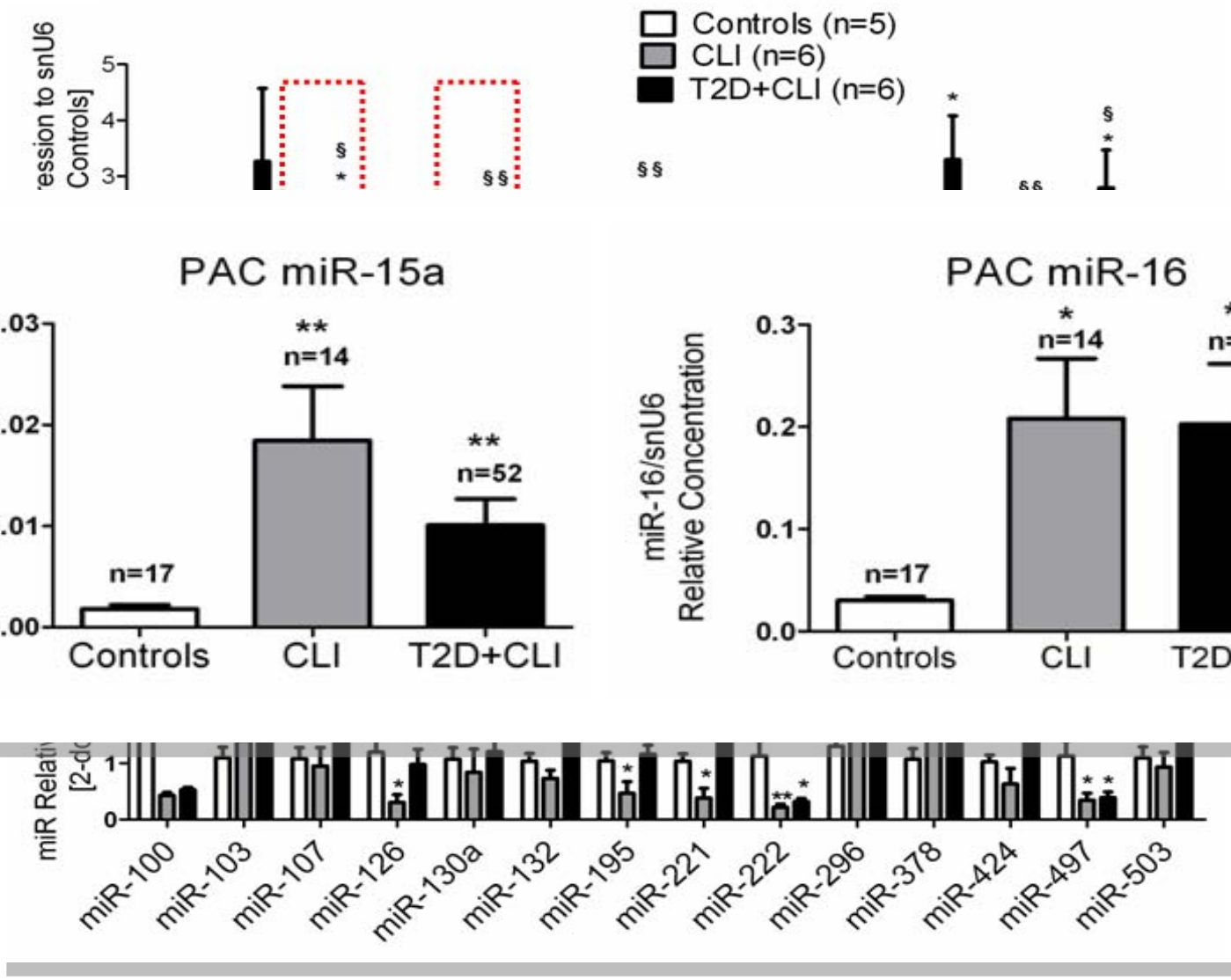
MicroRNA-15a and MicroRNA-16 Impair Human Circulating Proangiogenic Cell Functions and Are Increased in the Proangiogenic Cells and Serum of Patients With Critical Limb Ischemia

Gaia Spinetti, Orazio Fortunato, Andrea Caporali, Saran Shantikumar, Micol Marchetti, Marco Meloni, Betty Descamps, Ilaria Floris, Elena Sangalli, Rosa Vono, Ezio Faglia, Claudia Specchia, Gianfranco Pintus, Paolo Madeddu, Costanza Emanueli

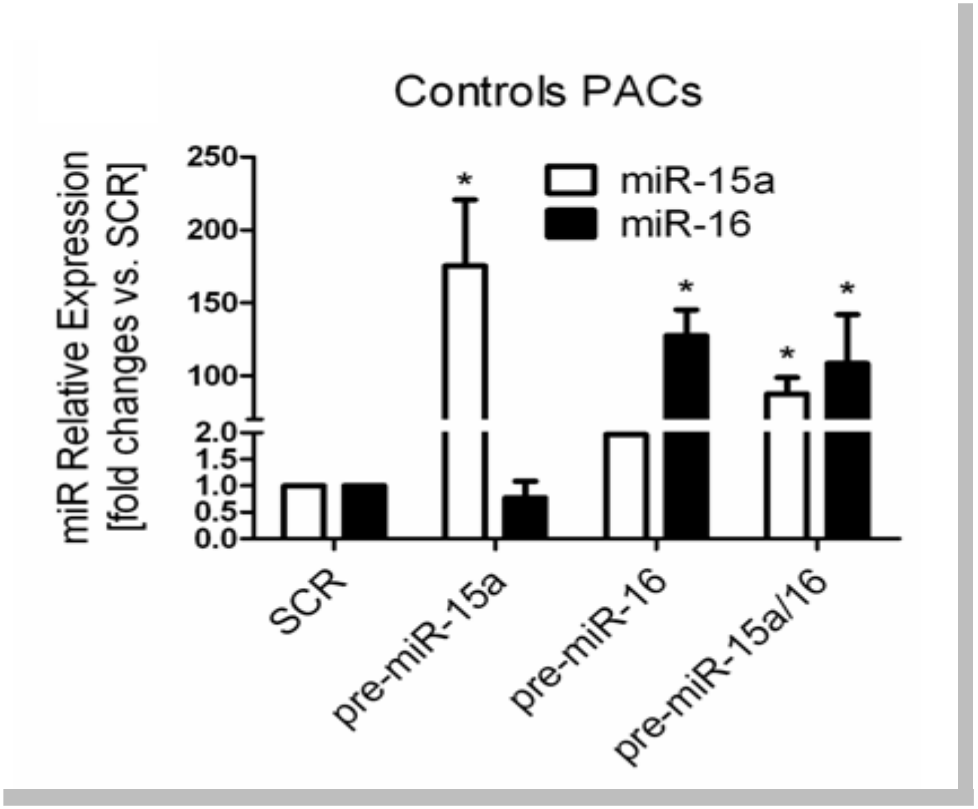


Gaia Spinetti

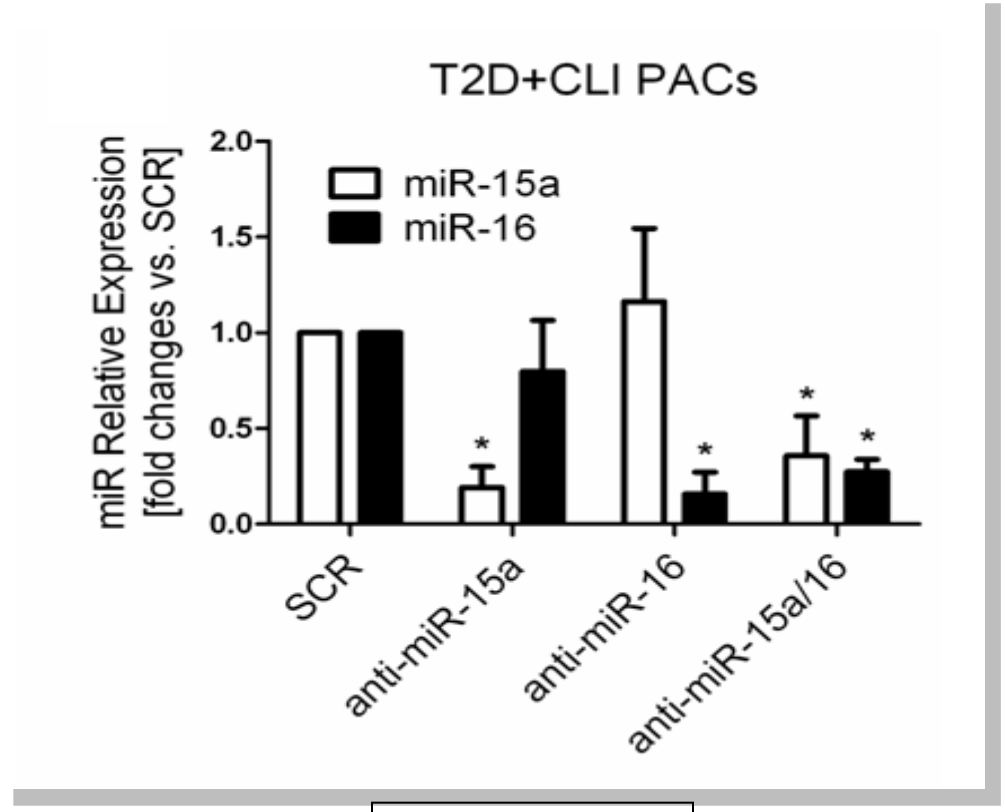
miR screening in blood PACs of CLI Patients with/out Diabetes



PAC miR-15a and -16 expression can be manipulated ex vivo

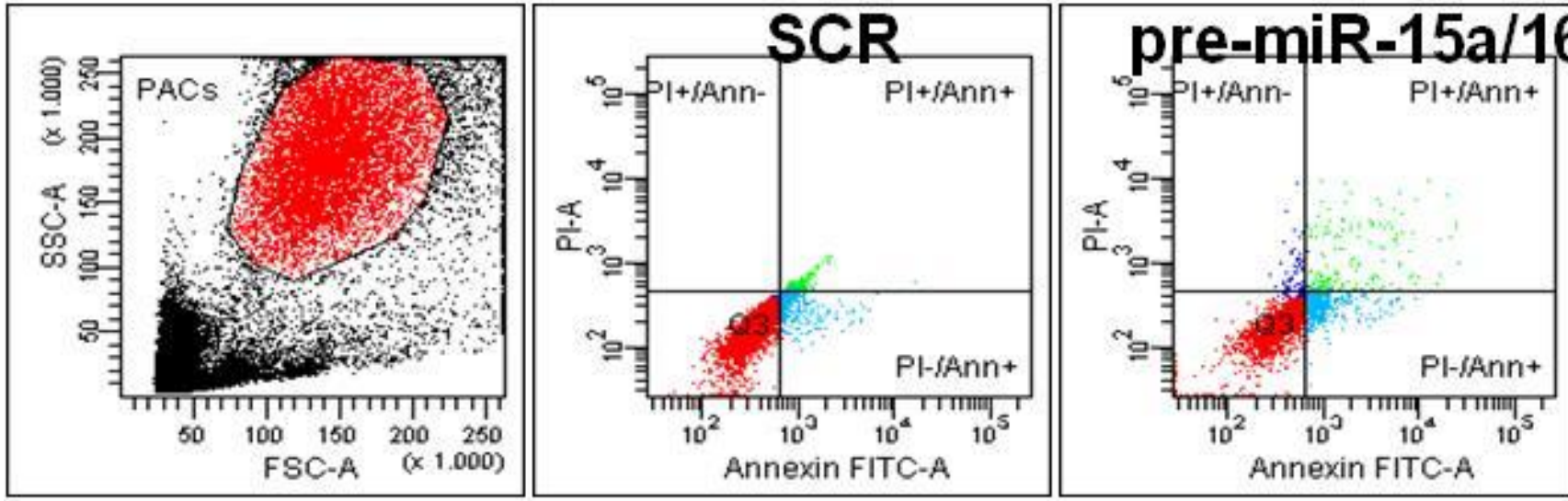


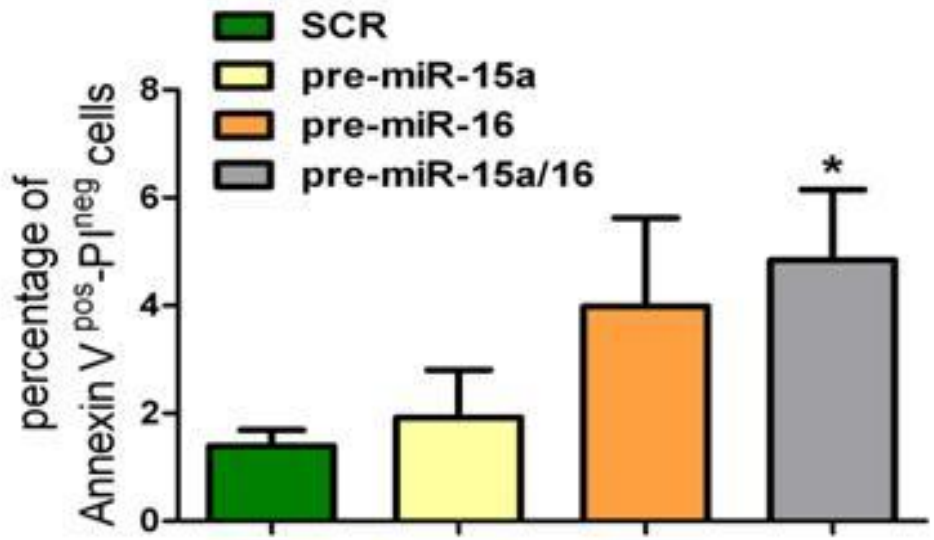
Pre-miR



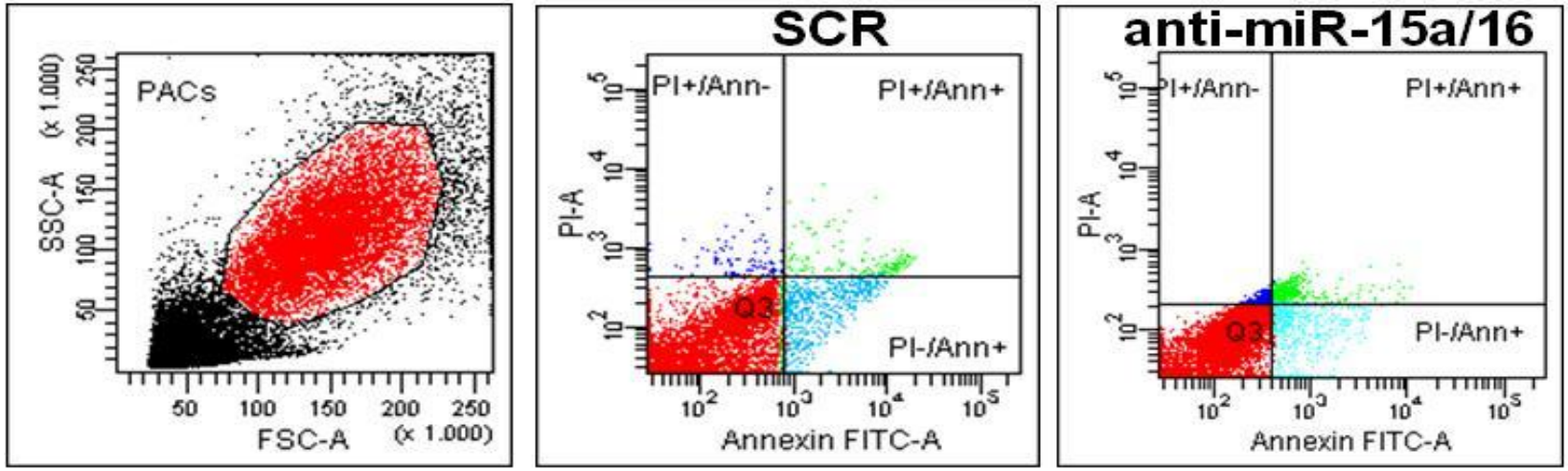
Anti-miR

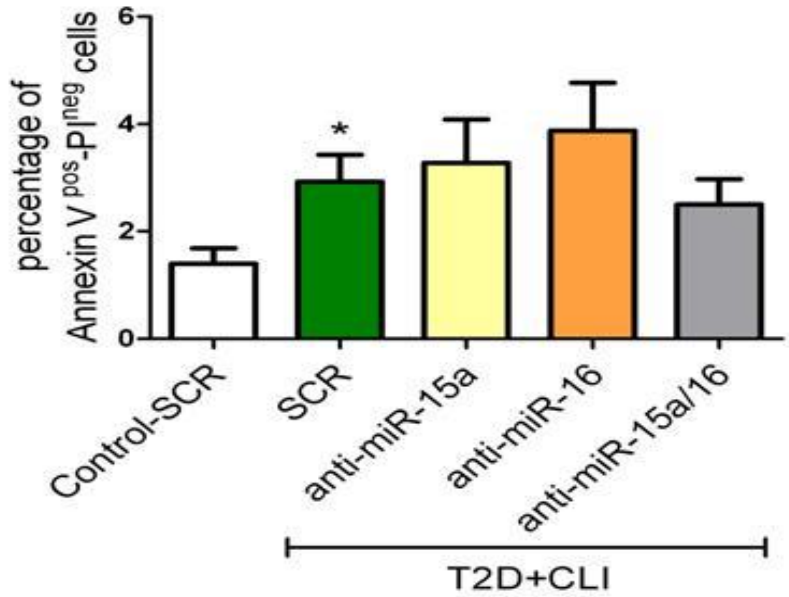
miR-15a and -16 overexpression increases apoptosis of "healthy" PACs



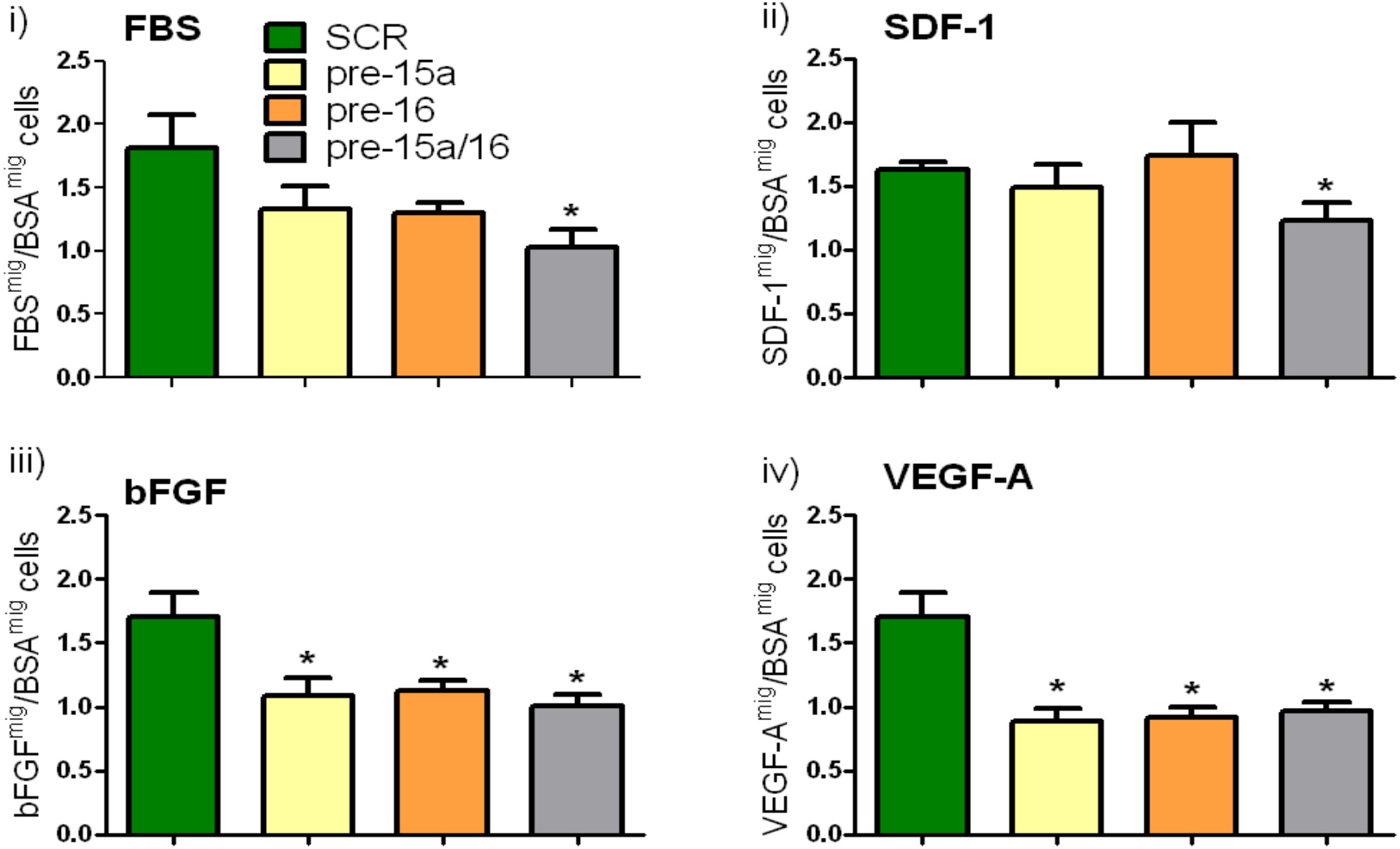


miR-15a and -16 inhibition improves survival of patient-derived PACs

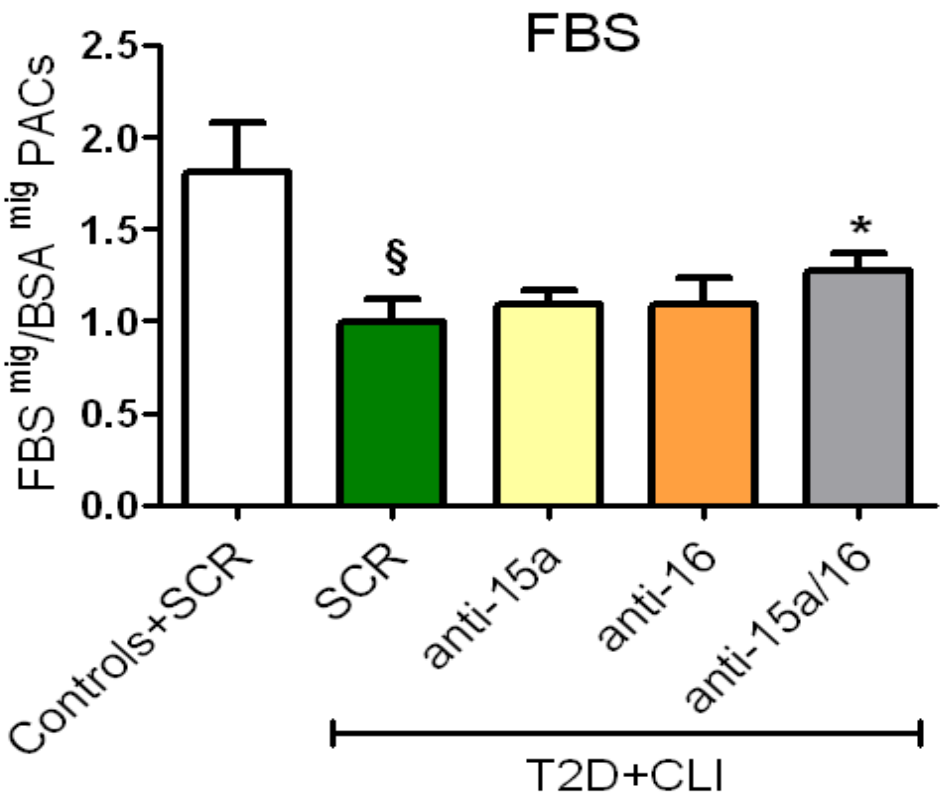


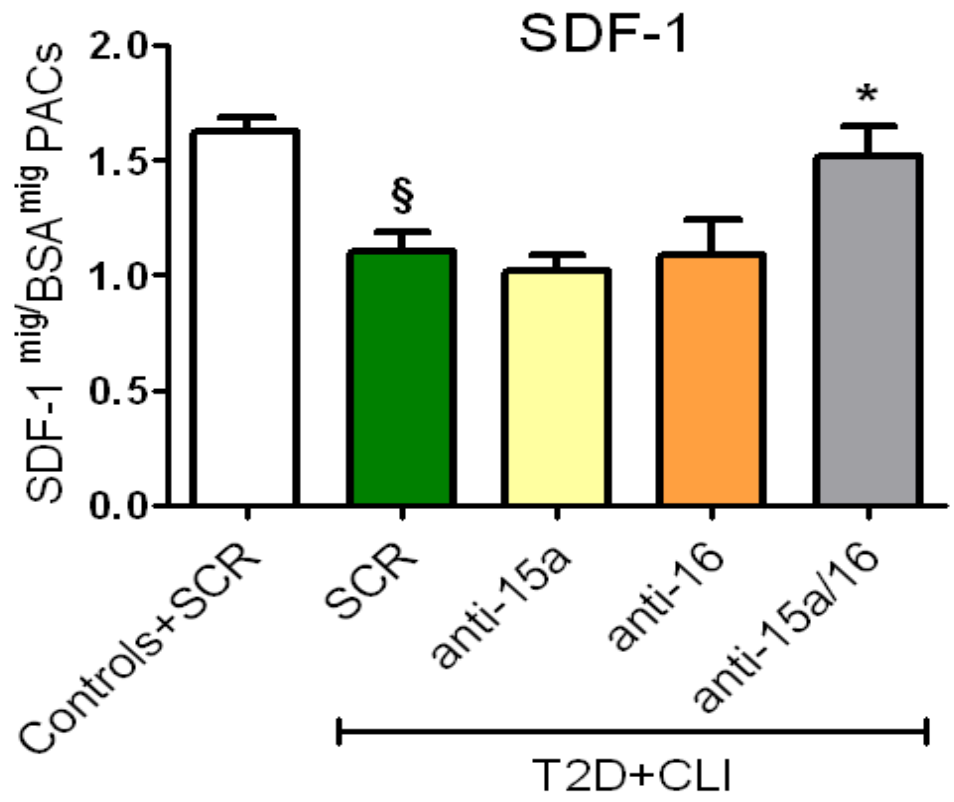


Overexpressing miR-15a and miR-16 inhibits the migratory capacity of healthy PACs



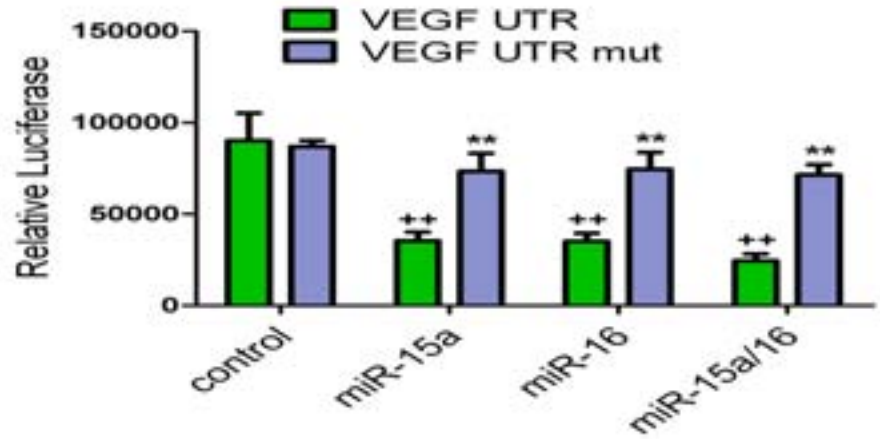
Inhibition of miR-15a together with miR-16 improves the migratory capacity of diseased PACs

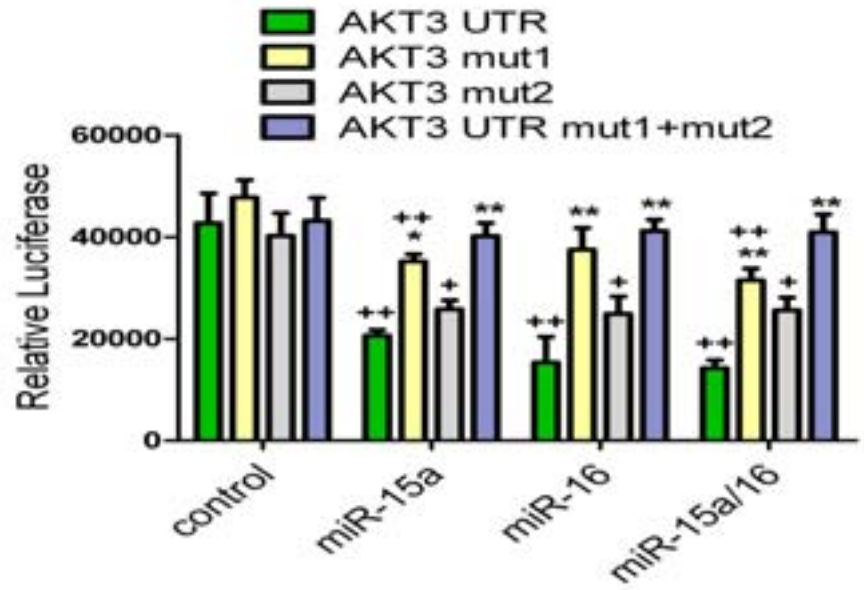




miR-15a and miR-16 target VEGF-A and AKT-3

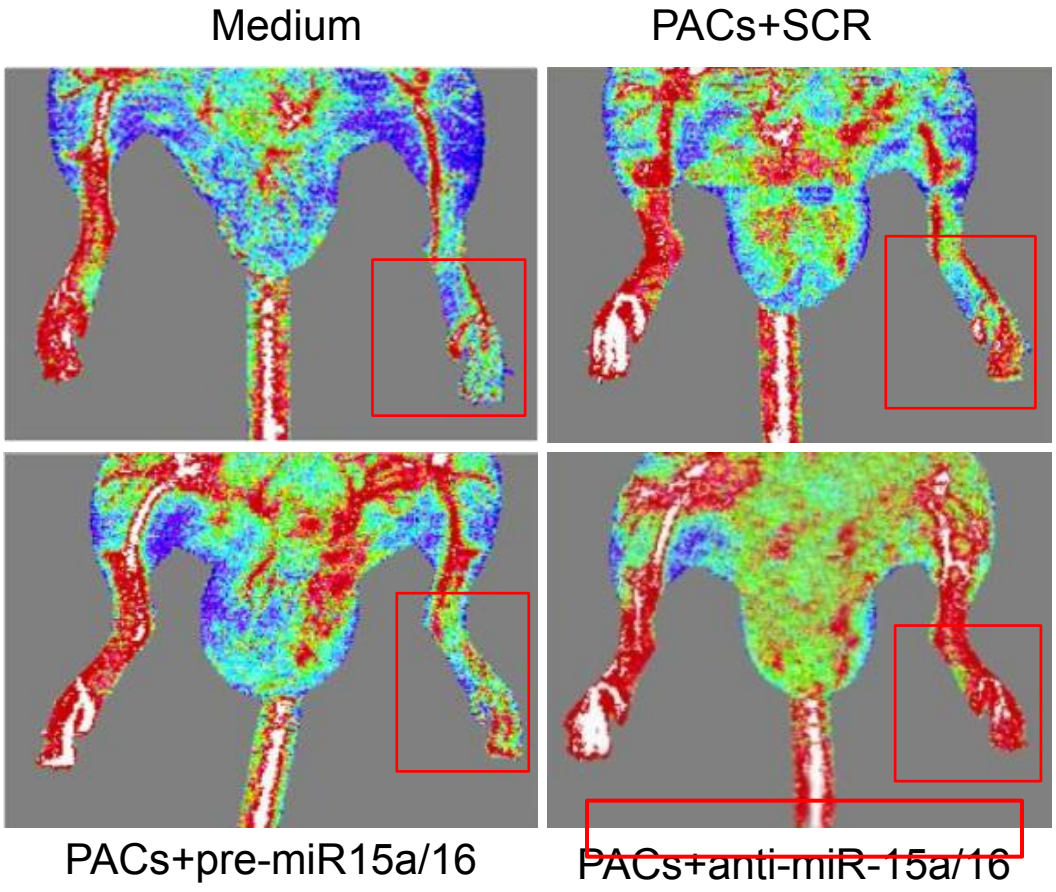
3'UTR luciferase activity assays

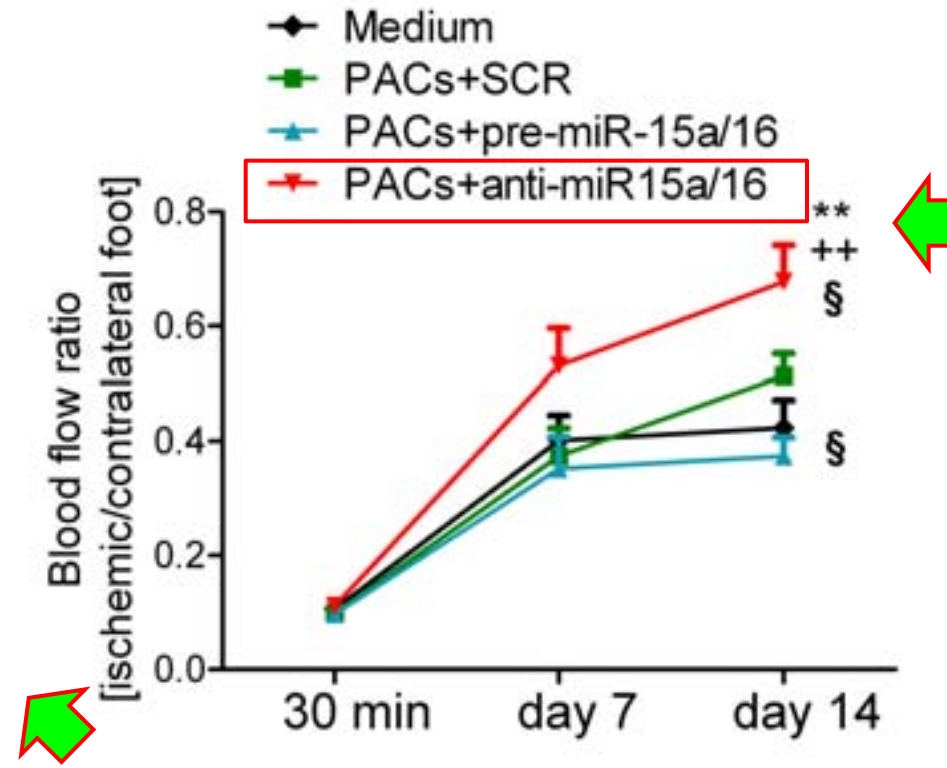




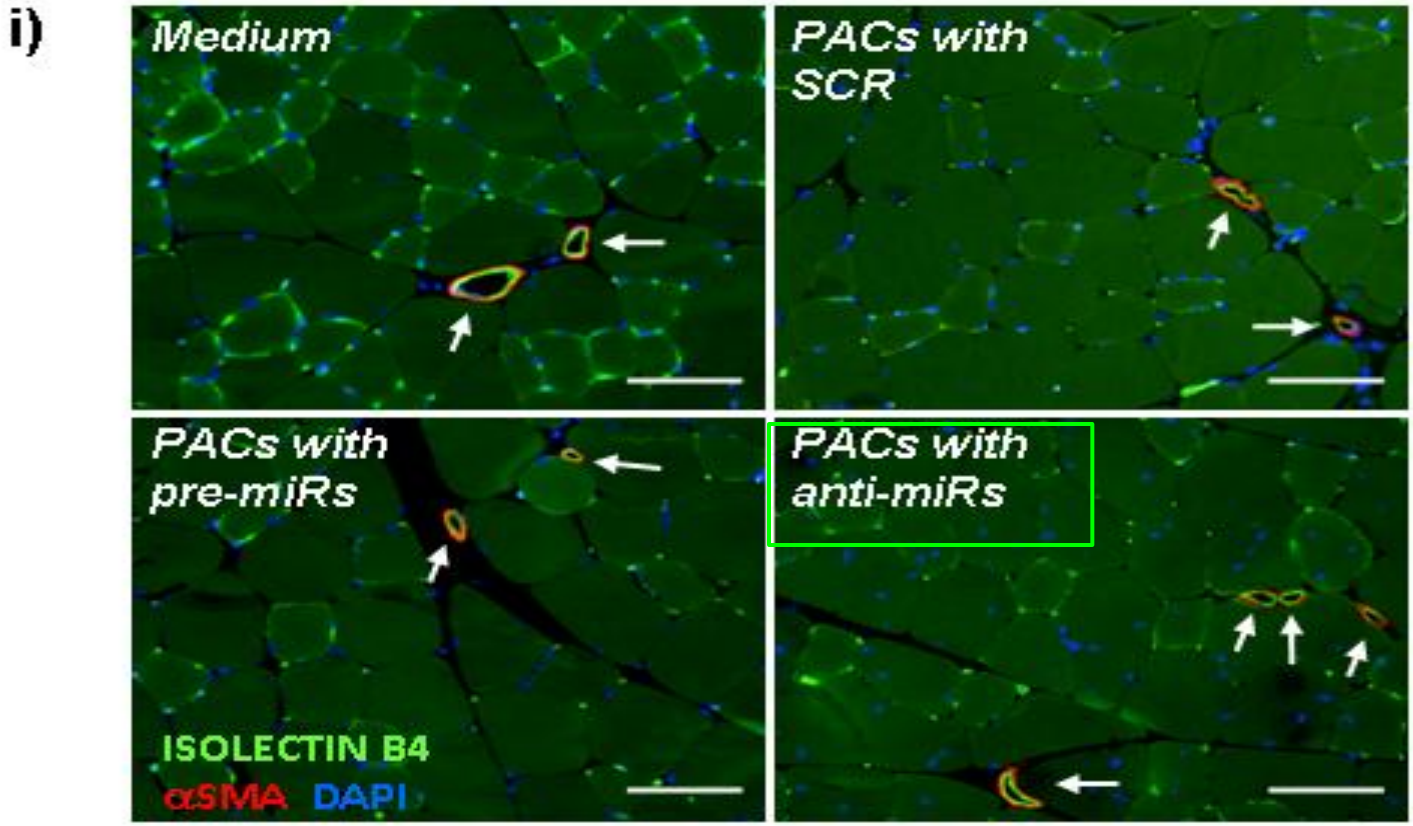
Ex-vivo miR-15a and miR-16 inhibition in PACs increases their regenerative potential:

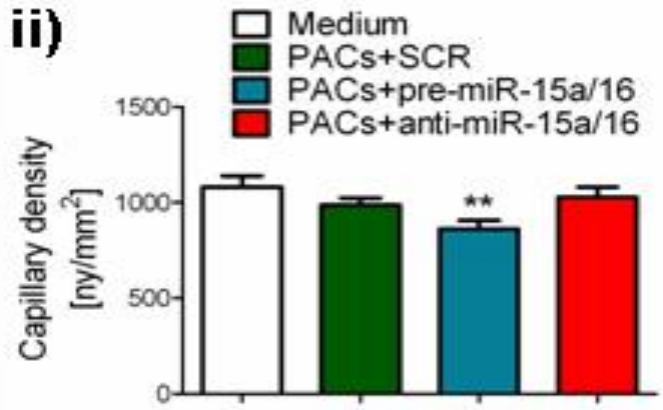
Foot Blood flow….

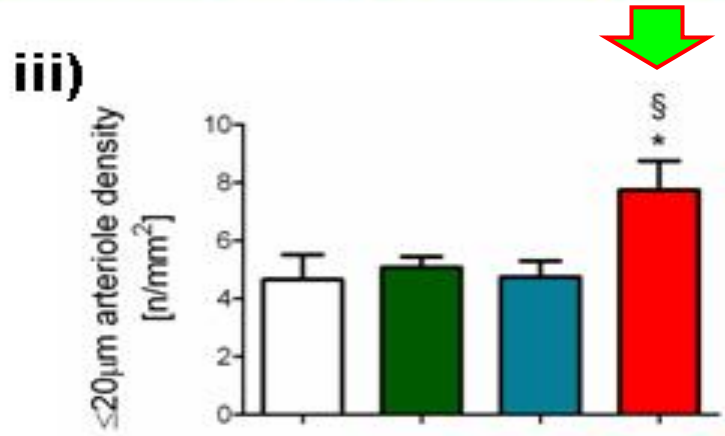


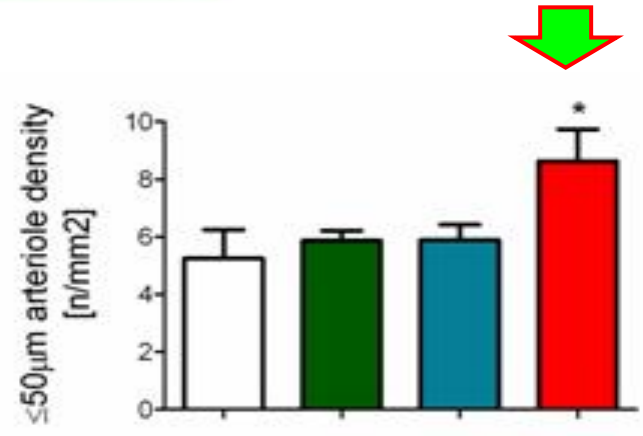


.... Microvascular Density

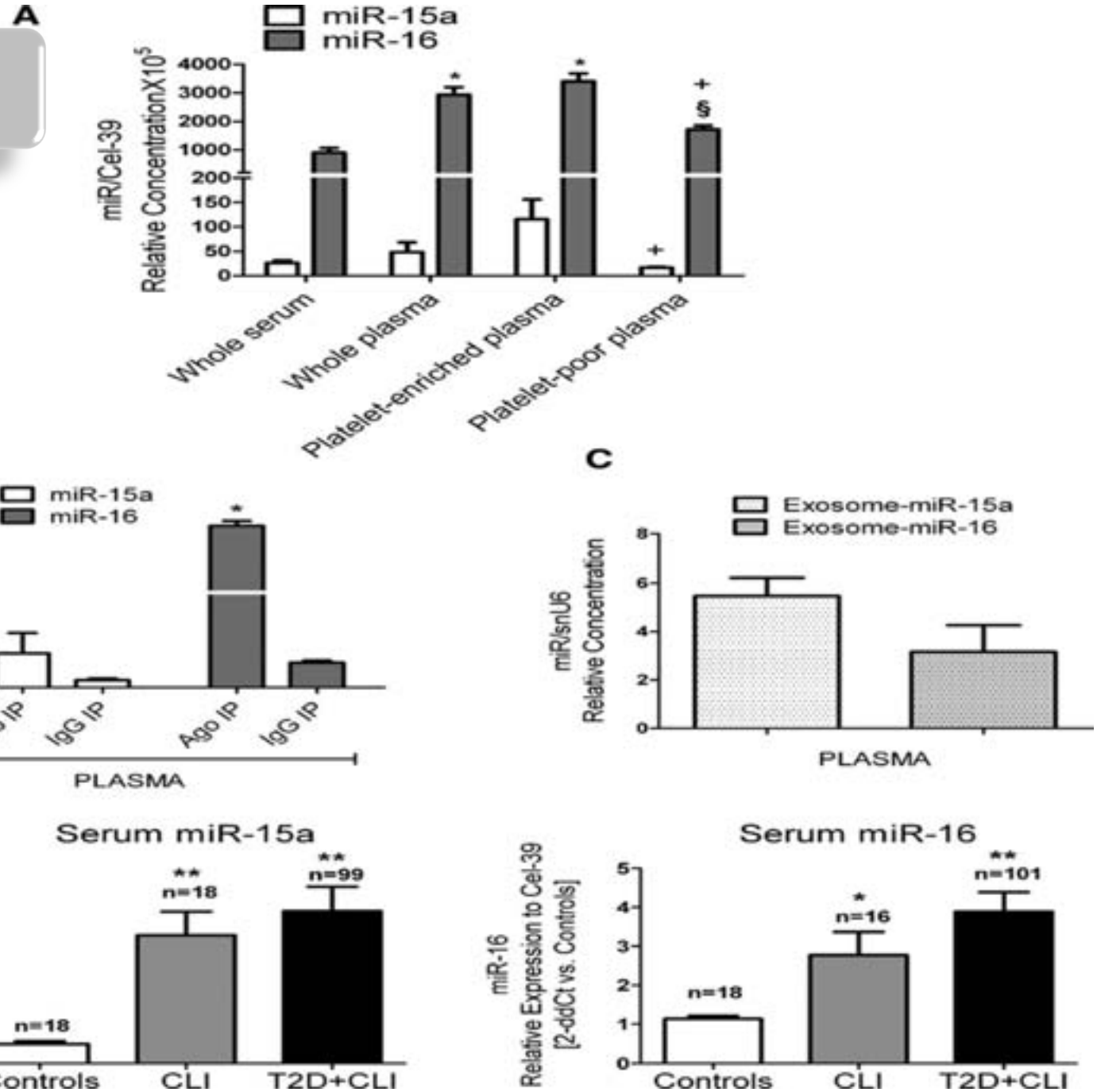








Blood circulating miR-15a and -16



Spinetti G et al.
Circ Res, 2013

CLI patients with DM undergoing PTA

Online Table III. Age, gender and clinical characteristics of type-2 diabetic patients a the moment they underwent angioplasty for critical limb ischemia

	T2D+CLI (n=122)
Age (years)	71.2 (9.3)
Gender (% males)	67
CAD (%)	48
Hypertension (%)	65
Neuropathy (%)	21
Retinopathy (%)	20
Ictus (%)	12
Active smoker (%)	13
HbA1c (%Hb)	7.8±1.5
Oral anti-diabetic drugs (%)	36
Insulin therapy (%)	64
Diet (%)	22
Aspirin therapy (%)	67
Clopidogrel therapy (%)	7
Anticoagulant therapy (%)	20
Statin therapy (%)	41

Quantitative data are expressed as mean and standard deviation (SD).
T2D= type2 diabetes, CLI=critical limb ischemia, CAD=coronary artery disease.

Association between serum miR-15 or miR-16 at revascularization and restenosis/amputation at follow up (1 year)

Online Table IV. Incidence of adverse events at one year follow up after angioplasty in type 2 diabetic patients described in Online Table IV (Total patients: N=122).

	N (%)
Any event	61 (50%)
Death (only)	17
Restenosis (only)	20
Amputation (only)	2
Restenosis and death	8
Restenosis and amputation	13
Restenosis and amputation and death	1
No event	61 (50%)

Online Table V. Association between miR expression and adverse events (restenosis and amputation)

Event	miR (2-ddCT)	OR*	95% CI	P-value
Restenosis (first event)	circulating miR-15a	1.28	1.01-1.61	0.04
	circulating miR-16	0.96	0.73-1.26	0.75
	PAC miR-15a	1.26	0.72-2.19	0.42
	PAC miR-16	0.79	0.51-1.23	0.30
Restenosis plus amputation	circulating miR-15a	2.10	1.32-3.36	0.002
	circulating miR-16	2.07	1.17-3.63	0.012
	PAC miR-15a	1.74	0.70-4.30	0.229
	PAC miR-16	0.70	0.35-1.41	0.315

*for 1 unit increase in log2

miRNA Summary and Perspective

- miRs modulate the post-ischemic neovascularization responses at multiple levels

- miR therapeutic can directly target ischemic tissues in vivo and be used for ex-vivo enhancement of the proangiogenic capacities of stem and progenitor cells

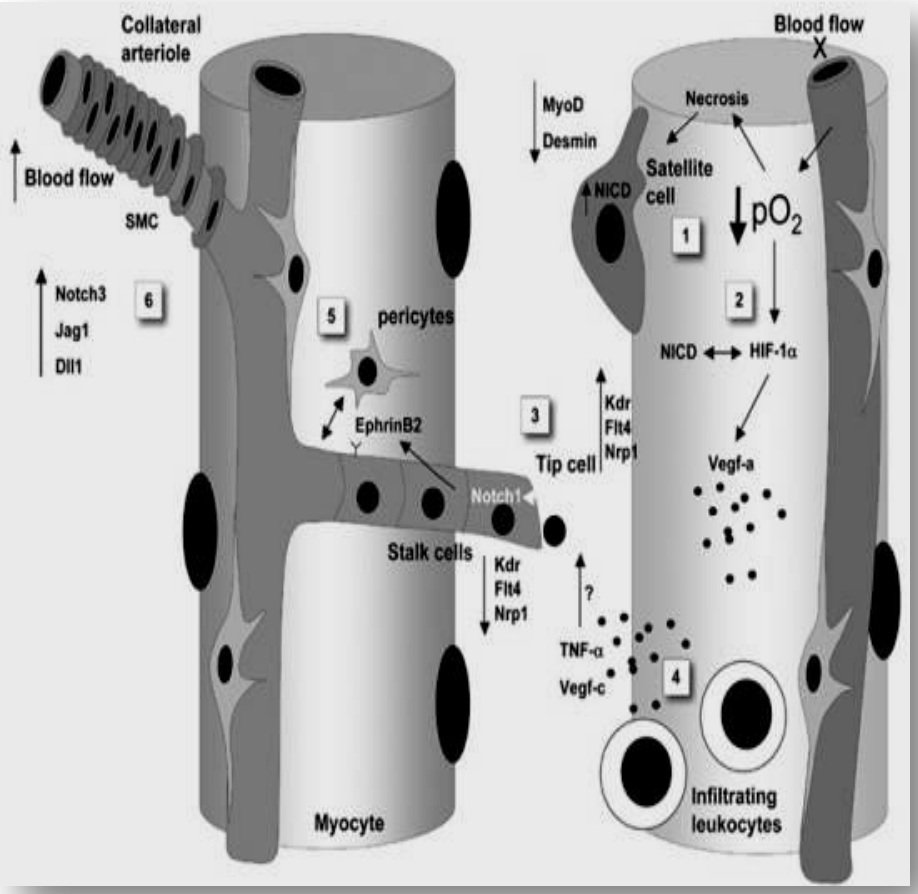
- Circulating miRs might be novel predictive and pognostic markers in ischemic patients

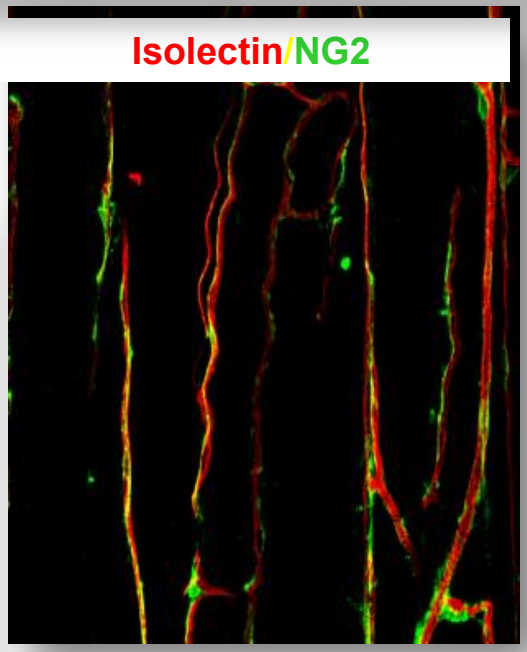
- There is a huge potential for miR translational research

Bristol Vena Saphena derived-Pericyte Progenitor Cells (SVPs)

Paolo Madeddu-Wednesday AM

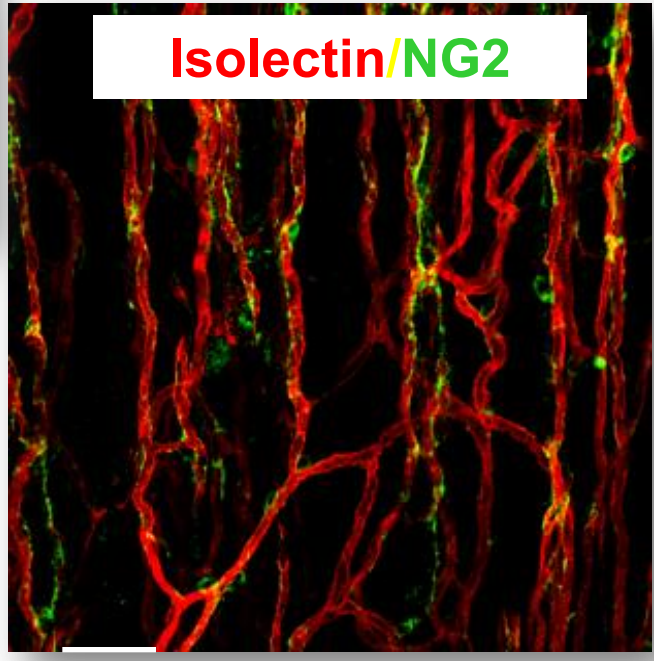
Pericyte coverage of is essential for microvessel maturation and stabilisation, including during post-ischemic vascular repair





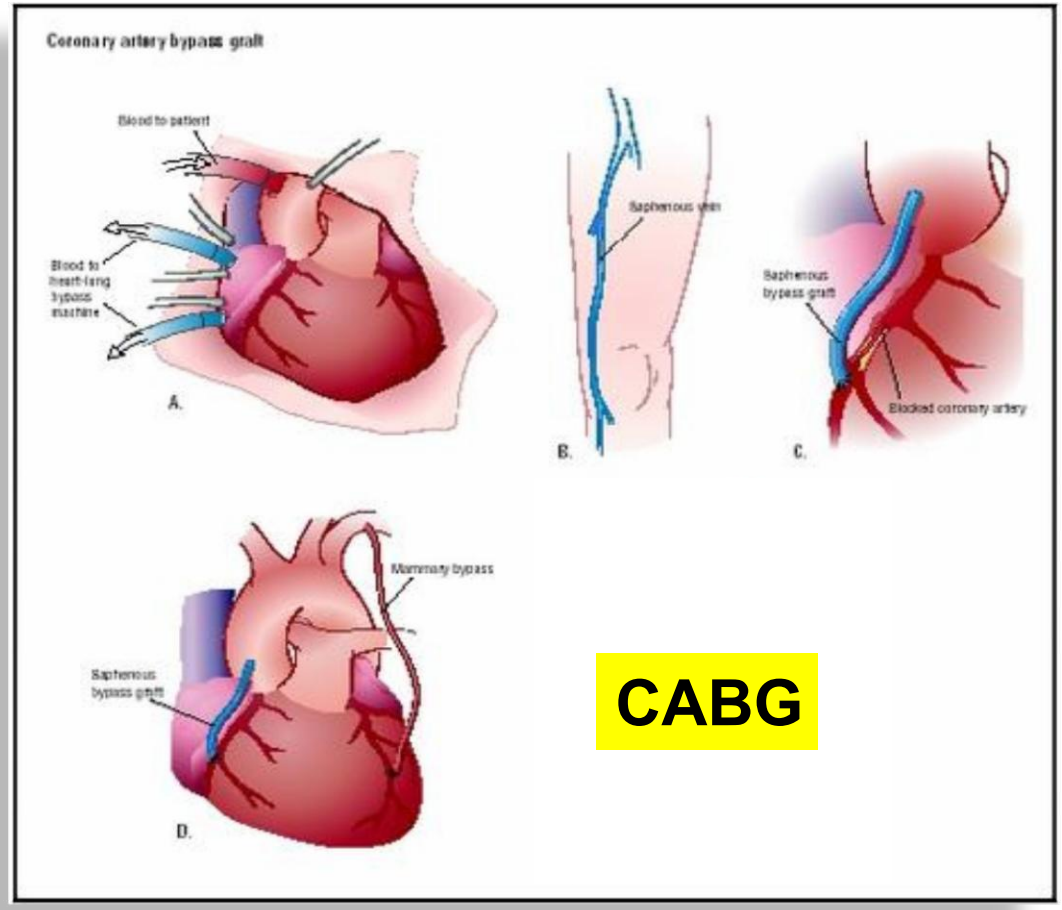
Limb muscle, basal conditions

NG2^{pos} pericytes around neovessels



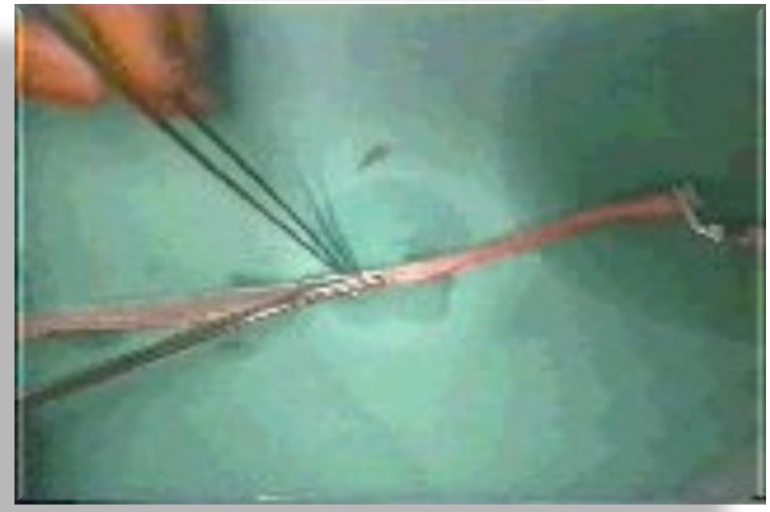
2 weeks post-ischemia

The saphenous vein: a convenient source of pericyte progenitor cells



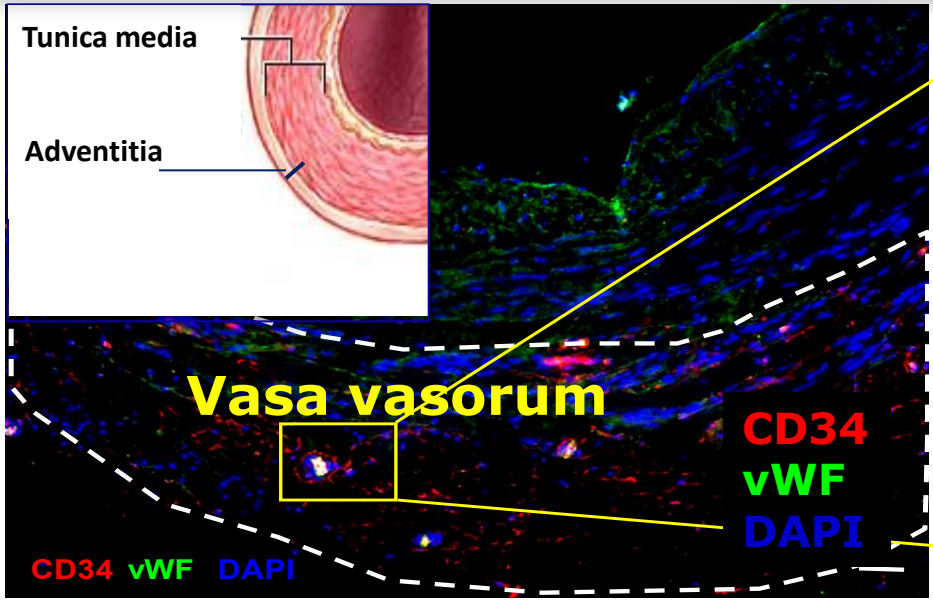
CABG

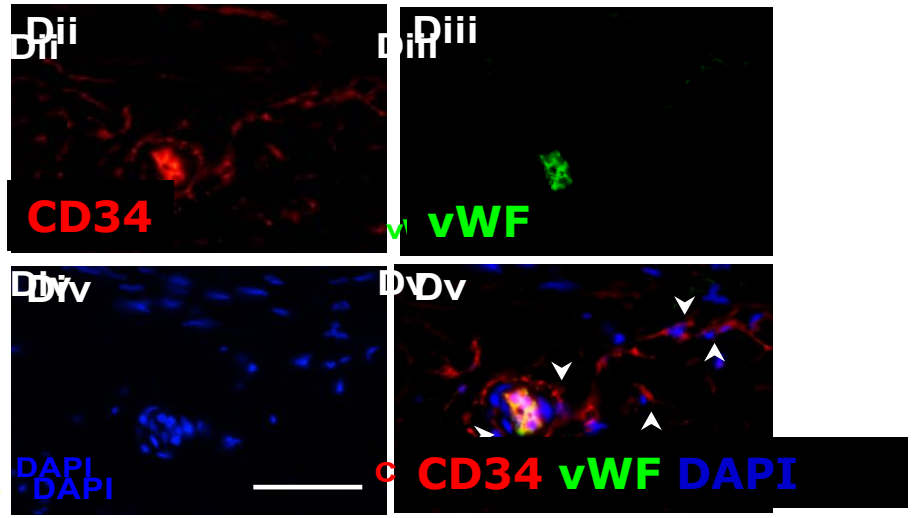
Vein leftover

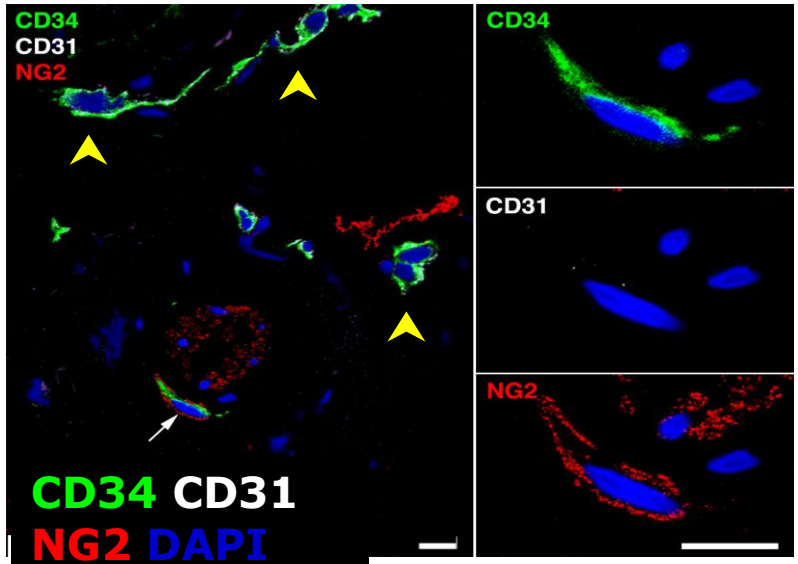


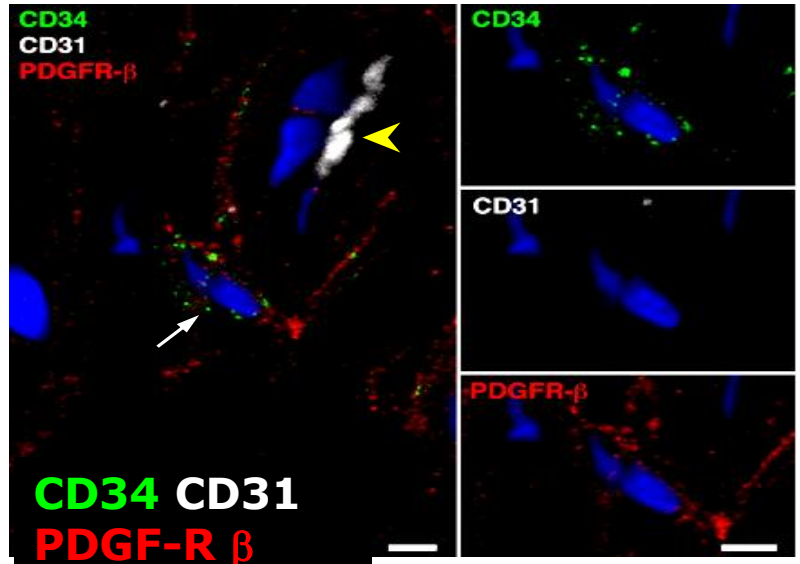
Campagnolo et al, Circulation, 2010

Identification of pericytes in human saphenous vein vasa vasorum









Campagnolo et al. Circulation 2010

Conclusions

- Myocardial and limb ischaemia are still unmet medical needs
- Novel options and revisited approaches hold therapeutic potential to treat limb and myocardial ischaemia
- This area of research can deliver disappointments as well as huge satisfaction
- Basic science and translational approaches must progress together to the ultimate clinical goal.

Main collaborators

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Micol Marchetti
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Bruno Peault
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Yale
Bill Sessa
Carlos Fernandez

Umass
Nathan Lawson

Madrid
Integromics

Vienna
Klemens Verlienger

Emanueli & Madeddu Labs in Bristol

We are currently recruiting and always happy to host visiting PhD students and sponsor excellent candidates for fellowship applications

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