Professor Harvey White

Interventional Cardiologist

Auckland

Stem Cells and the Heart - Main Programme

Friday, 21 June 2013 | Start 5:10pm | Duration: 20mins | Baytrust

Stem cells and the heart

Harvey White
Director of Coronary Care Unit and
Cardiovascular Research Unit
Green Lane Cardiovascular Service
Auckland City Hospital, Auckland

In gerbils, stemcells boost hopes of ending deafness

AFP
September 13, 2012
11:38AM

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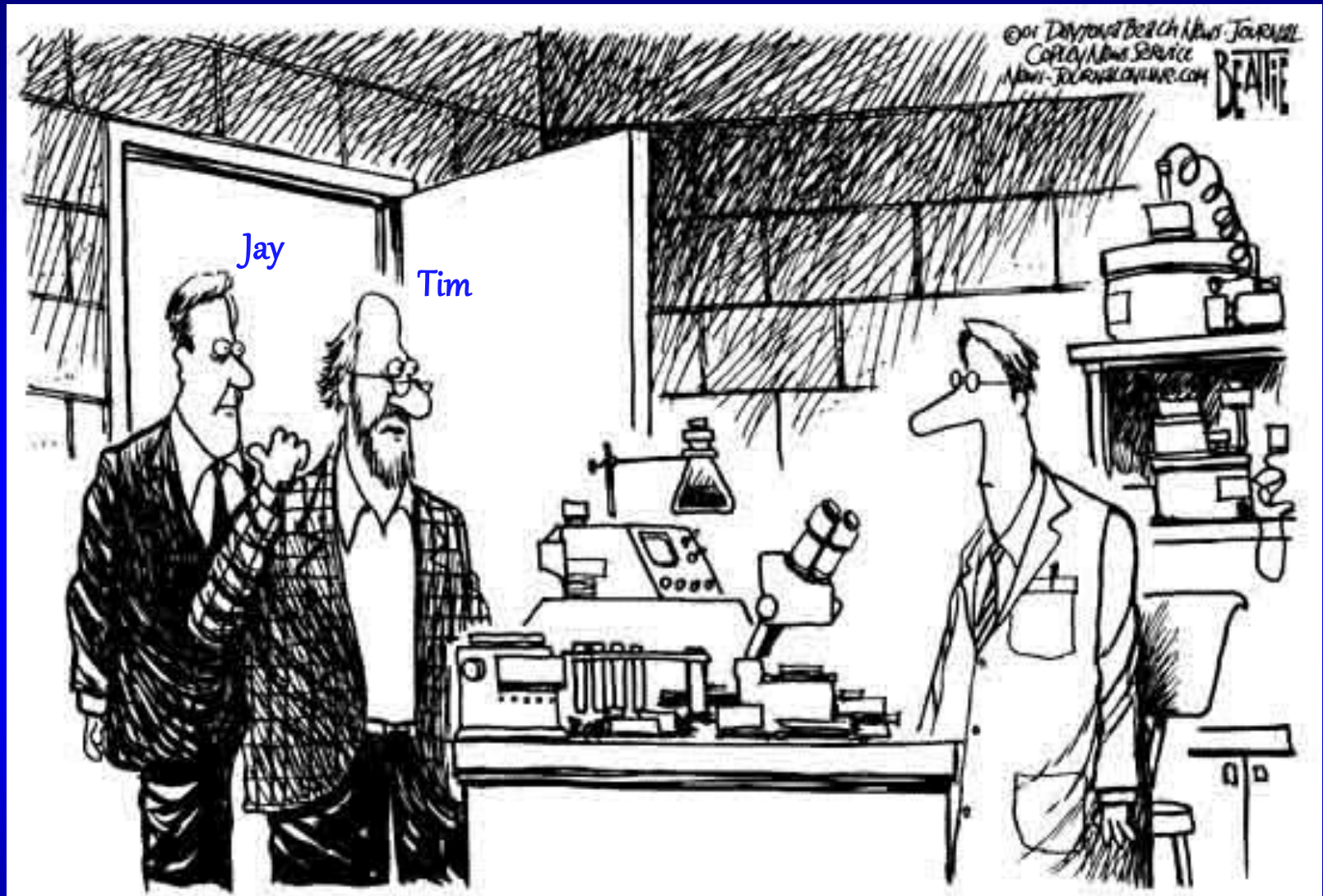
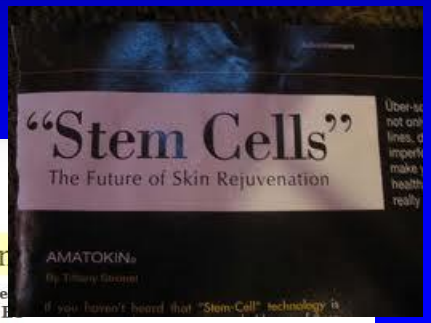


"We're here to help with your stem cell research. I'm a philosopher and he's a politician."

The Hope of Stem Cells



LIVE SCIENCE

Scientists Create Sten

By Stephanie Nano, Associated Pre
posted: 08 August 2008 09:22 am E

NEW YORK (AP) -- Harvard scientists say they have created stems cells for 10 genetic disorders, which will allow researchers to watch the diseases develop in a lab dish.

This early step, using a new technique, could help speed up efforts to
of the most confounding ailments, the scientists said.

The new work was reported online Thursday in the journal *Cell*, and th
plan to make the cell lines readily available to other scientists.

the Harvard Stem Cell Institute
variety of diseases, including Par
em cells.

"watch the disease progress in
on, co-director of the institute, s

his opens the door to a new wa

iving them the chameleon-like c
ds of tissue, such as heart, ner
eed medical research.

n were the first to report last November that they had
cells had behaved like stem cells in a series of lab tests.
of scientists said they reprogrammed skin cells from two
g's disease, and grew them into nerve cells.

THE INDEPENDENT ON SUNDAY SCIEN

Home > News > Science

Stem cells: the fi

Revolutionary treatment usi

By Steve Connor, Science Ed

Friday, 20 November 2009

People suffering from a form
ndness could soon becom
the world to benefit from
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macular
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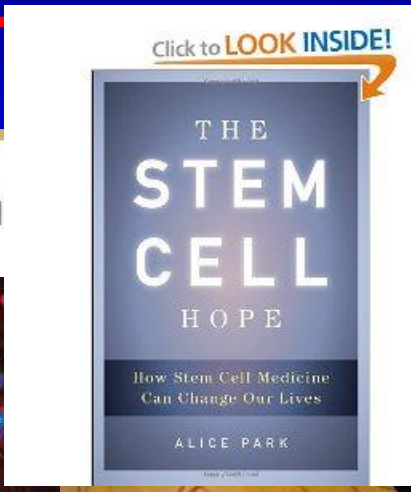


onSUNDAY

g researcher's sten
r Parkinson's cure

Too Much Controversy!

Cardiovascular Disease Targets

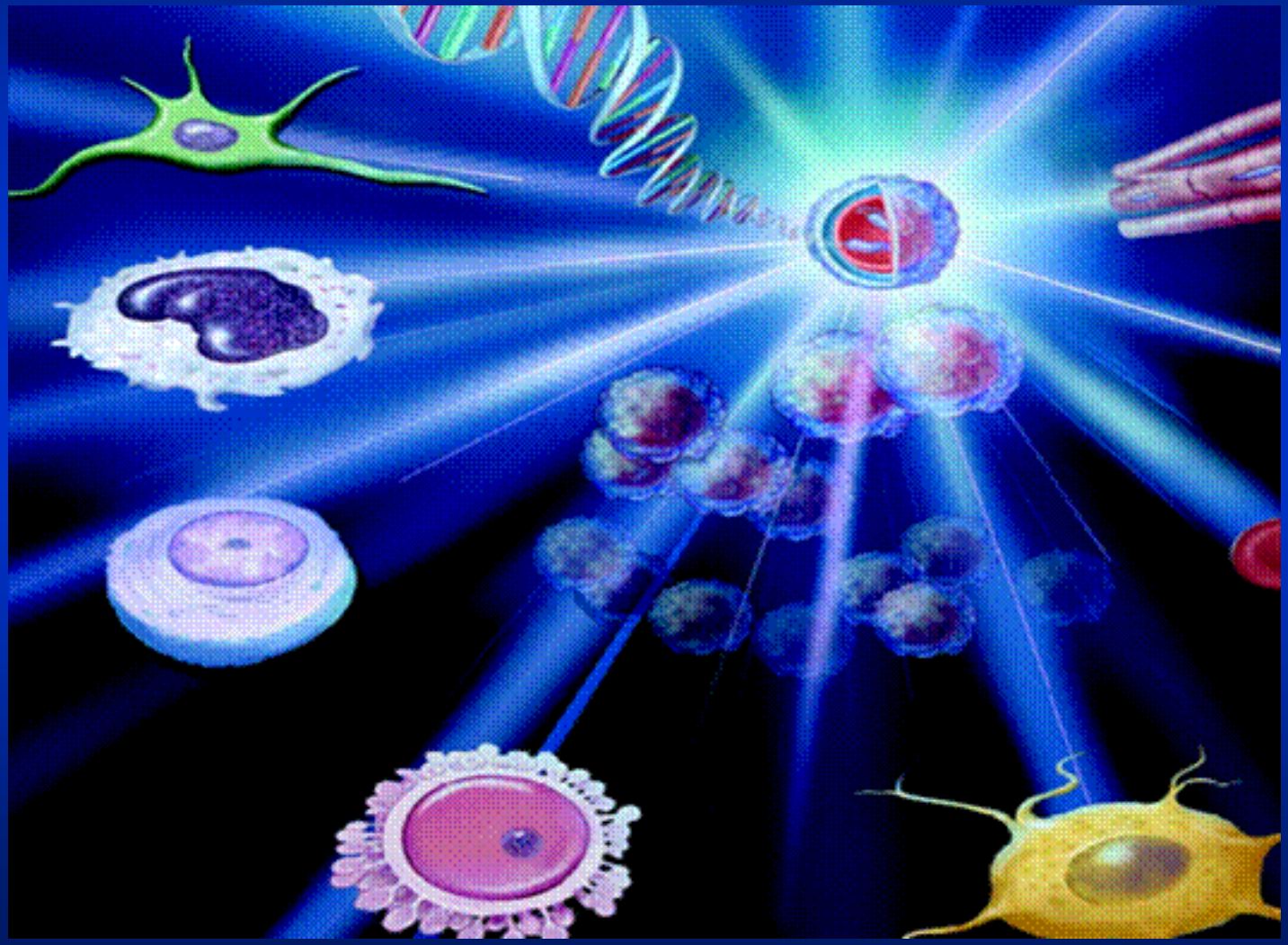
- Refractory angina
- Acute myocardial infarction
- Congestive heart failure
  - Ongoing ischemia
  - Previous MI
  - Nonischaemic
- Peripheral arterial disease

Which Cell is the BEST Cell?

Cell Therapy

- Embryonic stem cells
- Cord blood stem cells
- Adult stem cells
  - Circulating
  - Bone marrow
    - Hematopoietic
    - Mesenchymal
  - Tissue specific
    - Fat, Muscle, etc

Angiogenesis in coronary artery disease

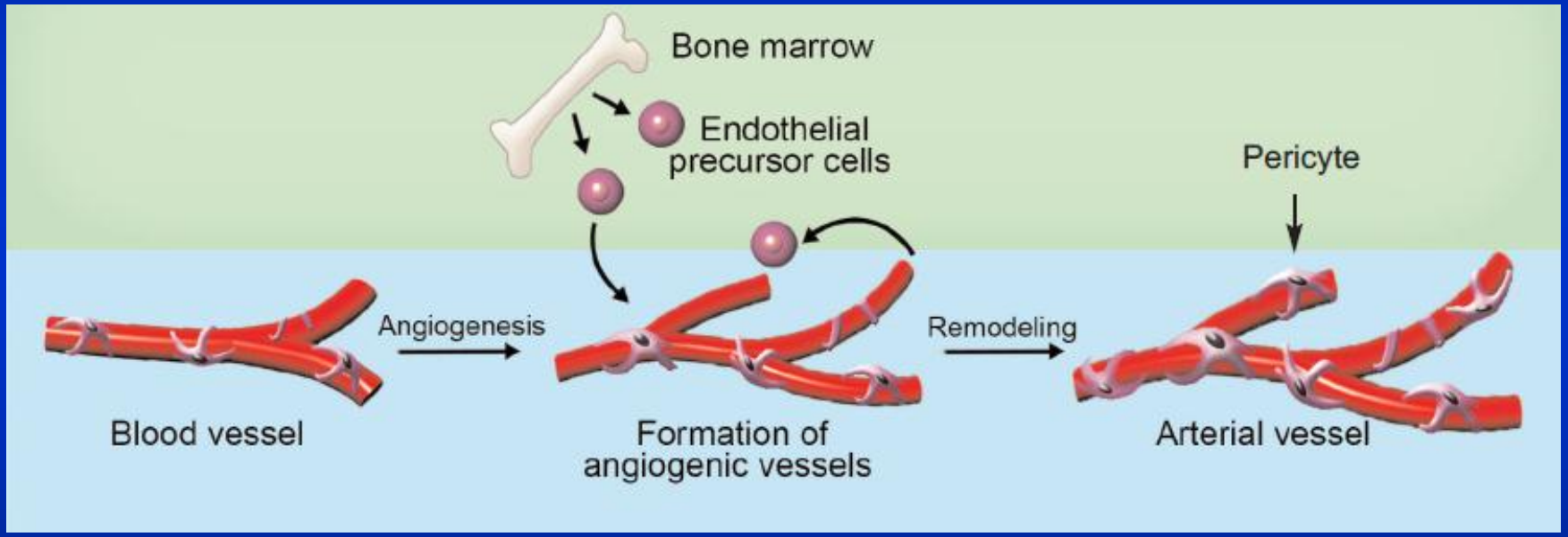


Therapeutic Angiogenesis

Angiogenic growth factors (or genes that encode) (or cell therapy) to promote or enhance the natural process of collateral blood vessel developmen

Can We Really Grow New Blood Vessels?

Formation of arterial networks. Angiogenesis and vasculogenesis are key processes of blood vessel formation which involves endothelial cell differentiation, proliferation, migration, and tubular organization. Establishment of an arterial network requires vascular remodeling by perivascular mural cells including pericytes and vascular smooth muscle cells.

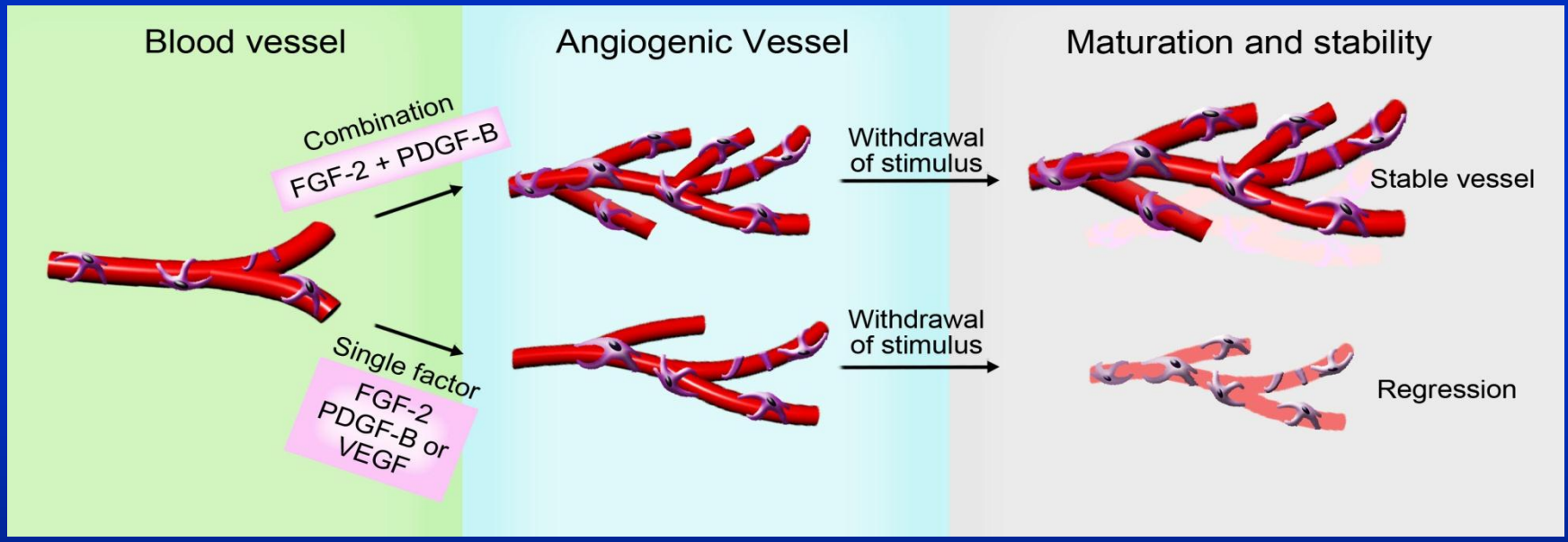


Cao. Discovery Medicine 2010

Fate of vasculature induced by single or combination factors.

FGF-2 and PDGF-B synergistically induce angiogenesis and the newly formed vasculature becomes stabilized even after withdrawal of stimuli. Exposure of dual factors to angiogenic vessels leads to vascular maturation and remodeling with arterial features.

Conversely, delivery of single angiogenic factors such as FGF-2, PDGF-B, or VEGF to ischemic tissues only transiently promotes angiogenesis and blood vessels remain unstable.



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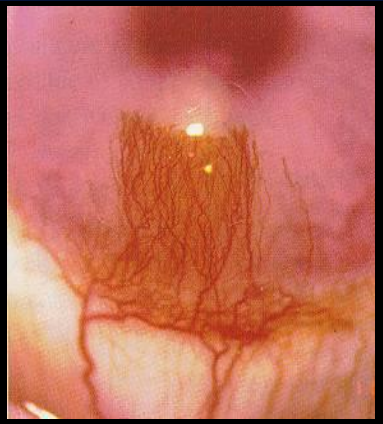
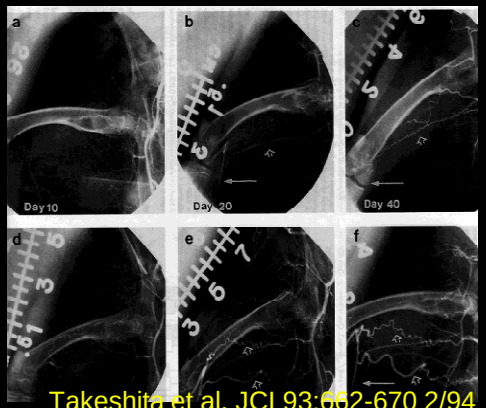
Angiogenesis does work

Chick Allantoic Membrane

Rabbit Cornea

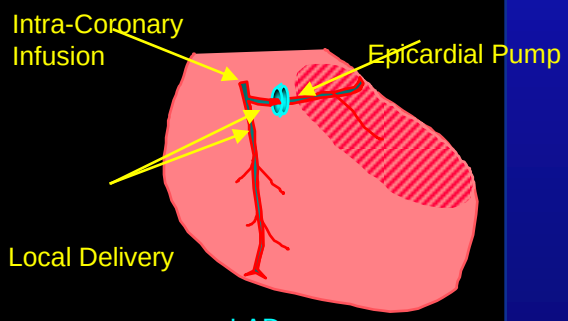


Rabbit Hindlimb



Takeshita et al. JCI 93:662-670 2/94

Ameroid Pig Heart



Angiogenesis

Stimulator	Mechanism
FGF	Promotes proliferation & differentiation of endothelial cells, smooth muscle cells, and fibroblasts
VEGF	Affects permeability
VEGF and NRP-1	Integrate survival signals
Ang1 and Ang2	Stabilize vessels
PDGF (BB-homodimer) and PDGFR	recruit smooth muscle cells
TGF-β, endoglin an TGF- β receptors	↑extracellular matrix production
MCP-1	
Integrins αVβ3, αVβ5 and α5β1	Bind matrix macromolecules and proteinases
VE-cadherinand CD31	endothelial junctional molecules
Ephrin	Determine formation of arteries or veins
Plasminogen activators	remodels extracellular matrix, releases and activates growth factors
Plasminogen activator inhibitor-1	stabilizes nearby vessels
eNOS and COX-2	
AC133	regulates angioblast differentiation
Id1/Id3	Regulates endothelial transdifferentiation

Autologous, Catheter-based, IM Transplantation of EPCs

Transplantation of EPC-Enriched (NA/ CD31+) Fraction Attenuates Chronic Myocardial Ischemia in Swine

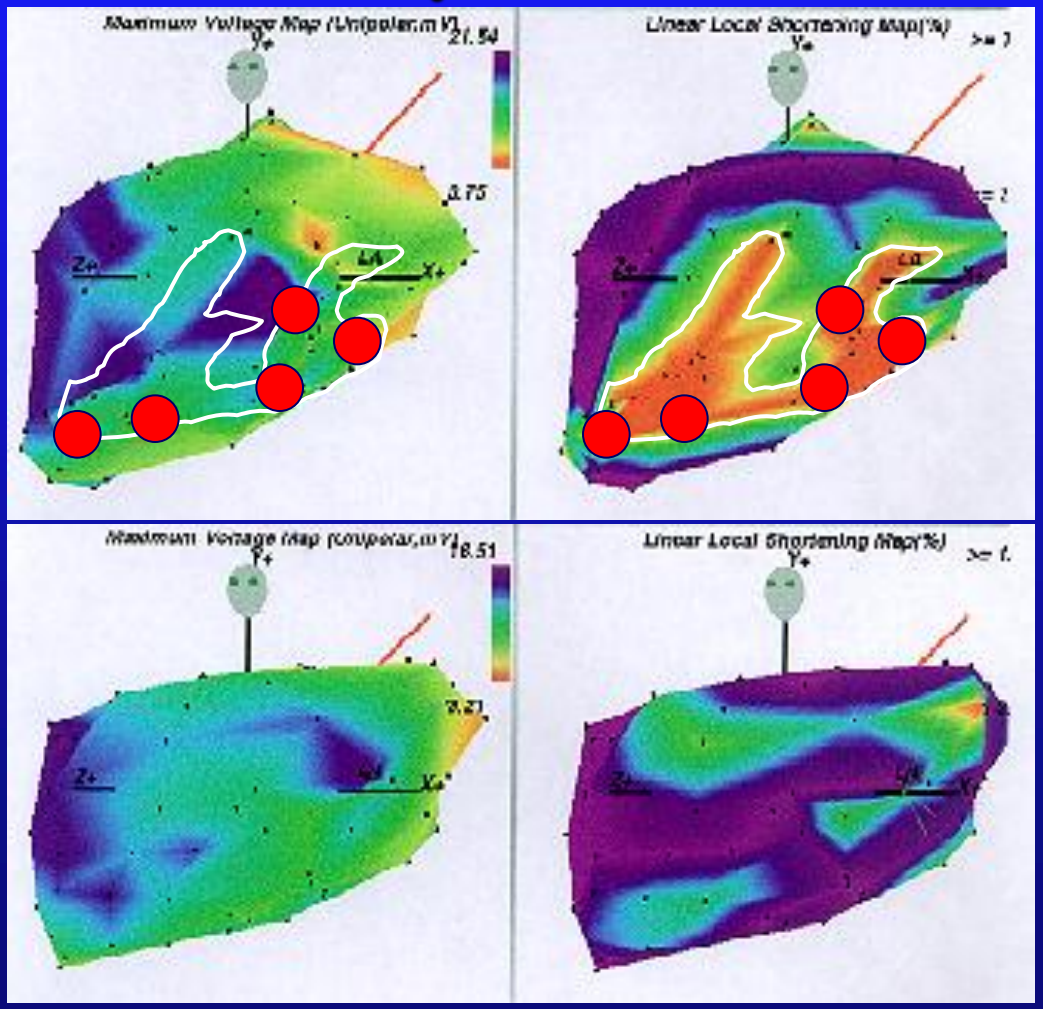
NA/ CD31+

Viability

Wall Motion

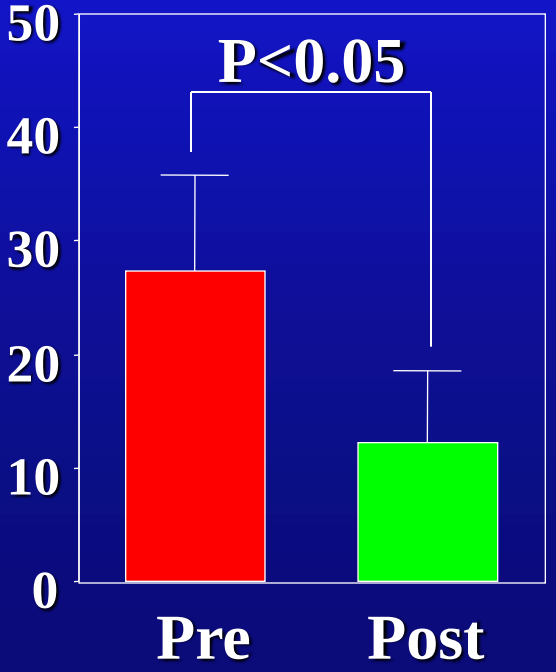
Pre Tx

4 weeks Post Tx



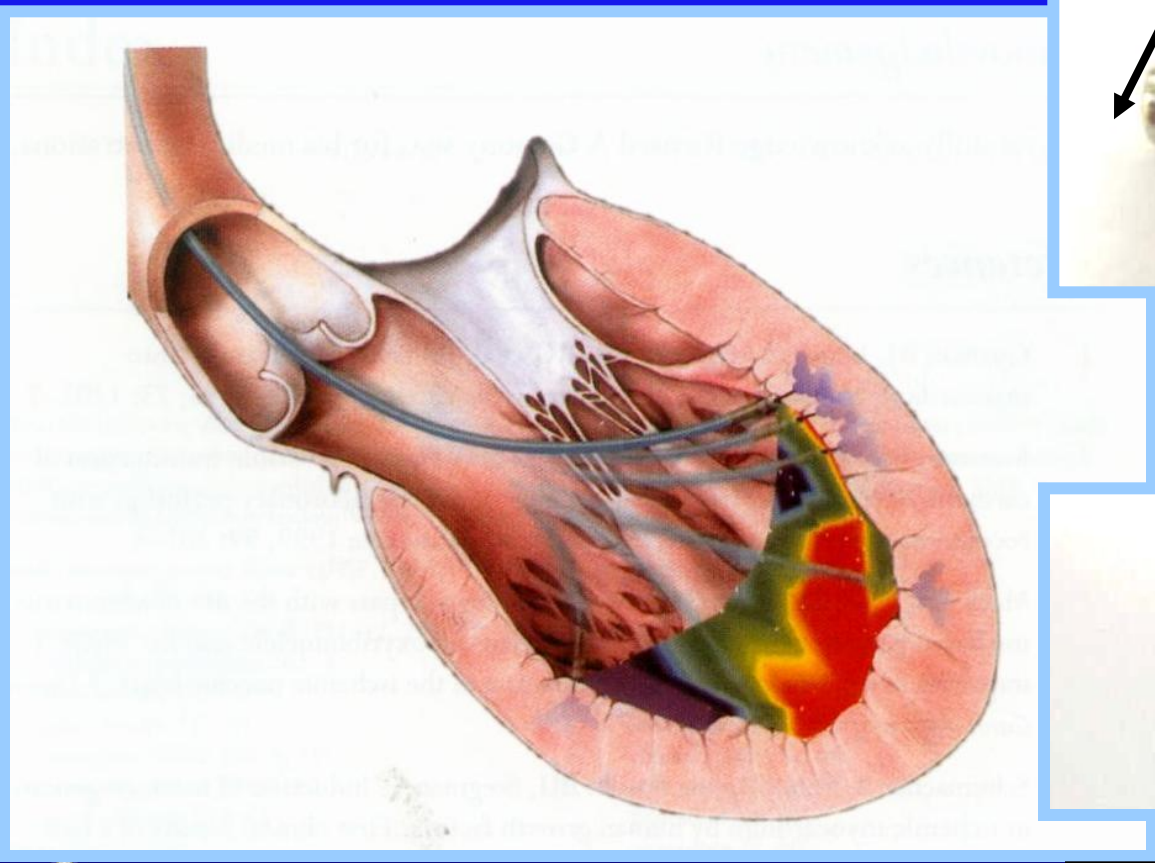
Injection sites

Ischemic area (%)



Catheter-based Cell Transplantation

Biosense Webster Injection Catheter

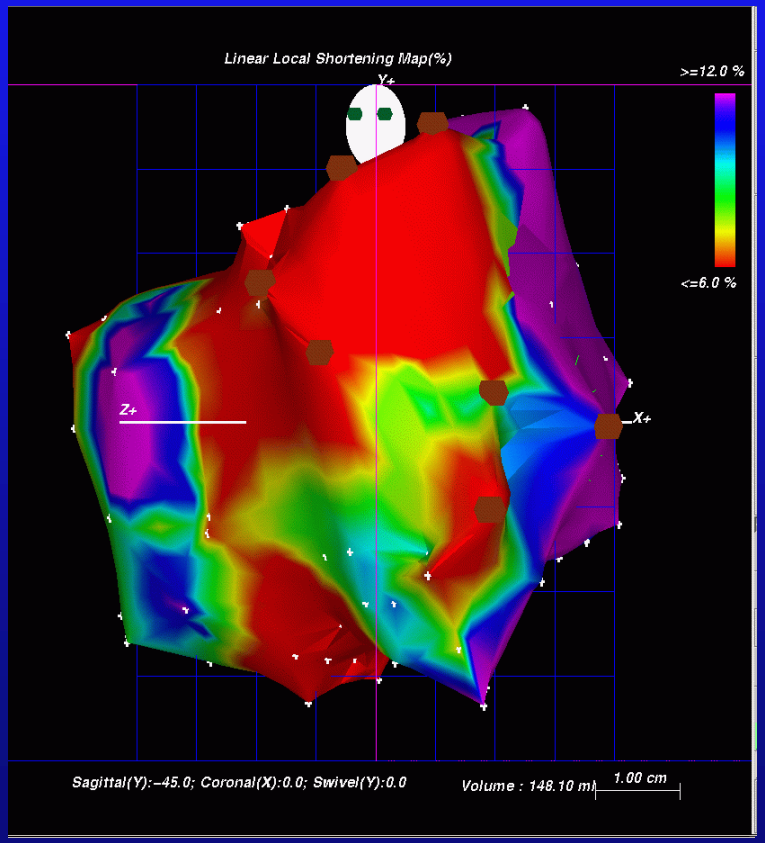


No Needle Extension

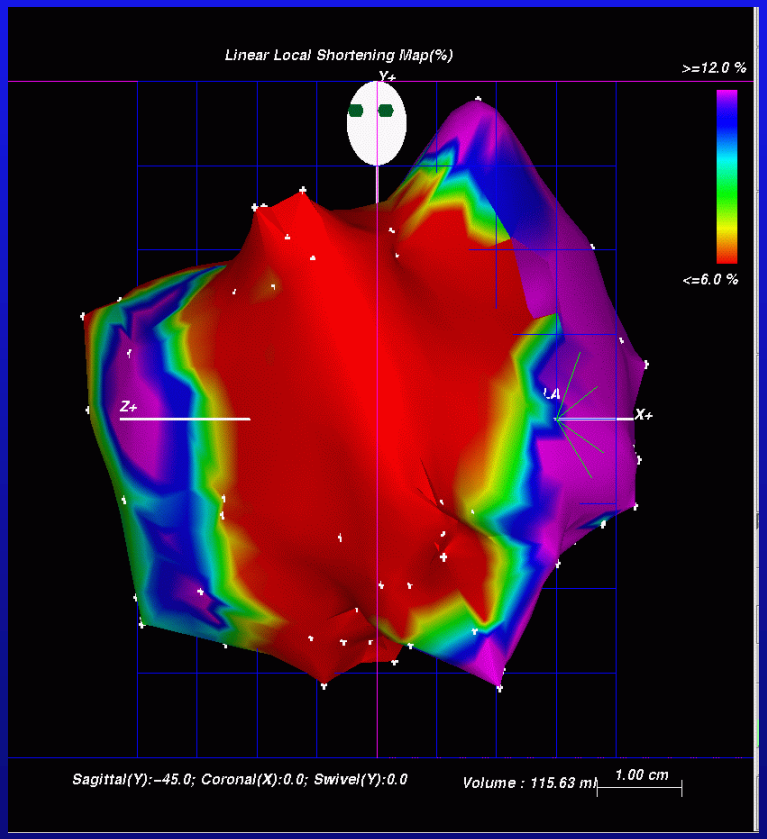
4-6mm Needle Extension

NOGA Mapping and Intramyocardial Injection

Intramyocardial injection sites



Local Linear Shortening - LAO

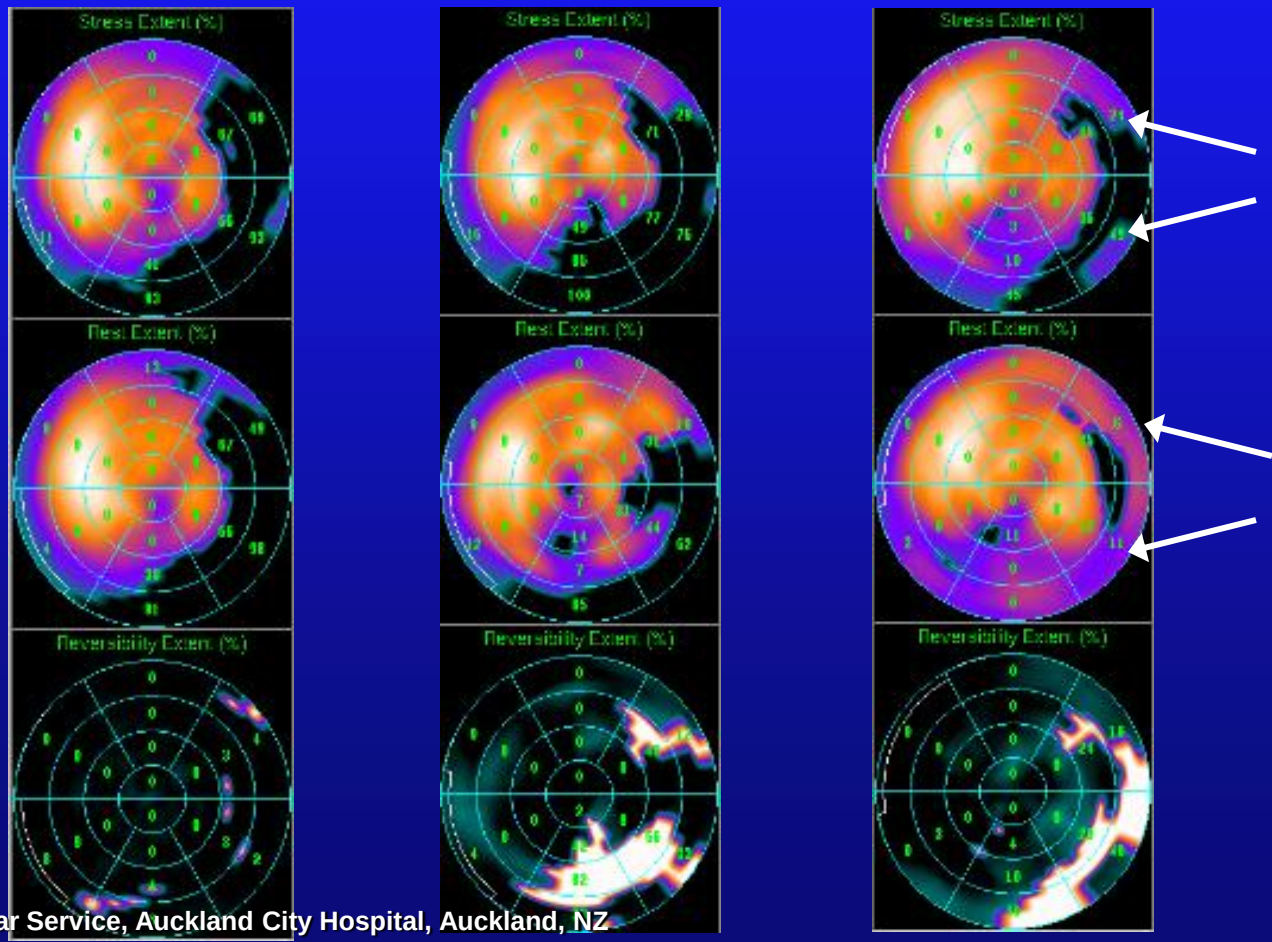


SPECT findings – Progressive Improvement in Perfusion At Rest and Post-stress Over 6 months

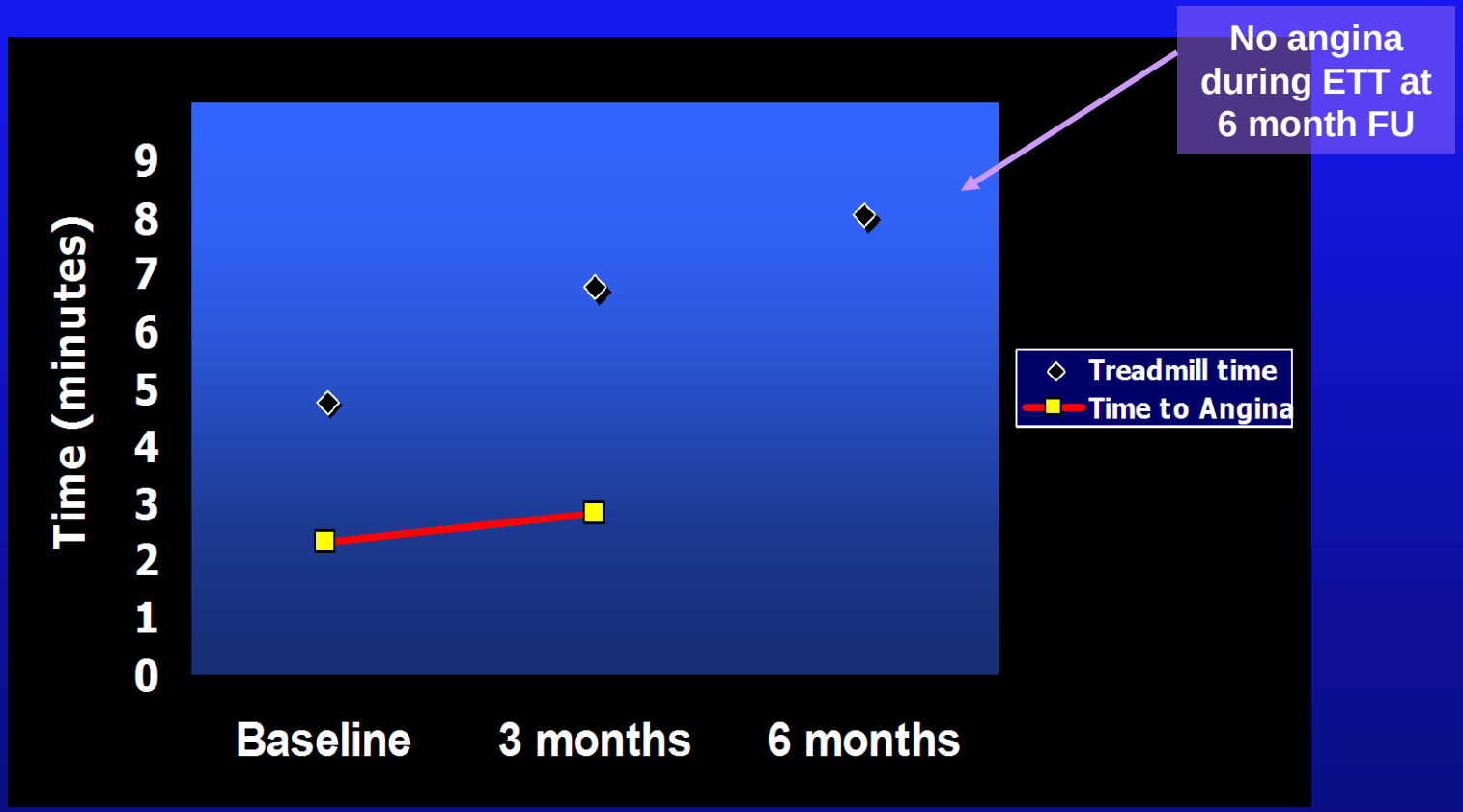
Baseline | 3 months | 6 months

Stress

Rest



Exercise times



Angiogenesis

Phase 1 unblinded Trials

- Protein: $VEGF_{165}$, FGF-2, FGF-1
- Gene: Adenovirus: FGF-4, $VEGF_{121}$, HIF-1∝
  Plasmid: VEGF-2, $VEGF_{165}$, FGF
- Cell: bone marrow

Placebo-controlled Trials

PROTEIN:	
VIVA: n=178	**IC VEGF-165**
FIRST: n=337	**IC FGF-2**
FGF CABG: n=40	IM FGF-1 with LIMA
FGF BEAD: n=24	Perivascular with CABG
GENE:	
AGENT 1/2: n= 79 + 52	**IC adFGF-4**
AGENT 3: n= 415	**IC adFGF-4**
VEGF-2: n= 9 + 19	**IM perc plVEGF-2**
EUROINJECT: n= 76	**IM perc plVEGF-A**
NOTHERN: n=93	**IM perc plVEGF-A**
CELL:	
ADVANCE: n=24	**IM CD34+ Cells**
FOCUS: n=30	**IM BM Cells**
ACT-34: n=162	**IM CD34+Cells**

Placebo Controlled Myocardial Angiogenesis Trials

- 1400 patients with 8 different agents and methods of delivery
- SAFE
- Prespecified, blinded secondary endpoints are positive
- Limited post hoc analysis suggests high risk subgroups benefit
- Modest efficacy

Clinical Events

Study	Placebo Patients (n)	Follow-up Time	Myocardial Infarction	Revascularization	Cancer	Death
UNGER	8	1 month	0	0	0	0
FIRST	86	6 months	5 (6%)	5 (6%)	1 (1%)	1 (1%)
VIVA	63	4 months	0	1 (2%)	3 (5%)	2 (3%)
AGENT 1	19	311 days	0 At 12 wks	4 (21%)*	0	0
AGENT 3	139	1 year	1 (1%)	24 (17%) Hosp & Revasc	4 (3%)	1 (1%)
LOSORDO	7	3 months	1 (14%)	1 (14%)	0	0
MUST-EECP	66	1 month	0	0	0	0
DIRECT	102	6 months	n/a	n/a	n/a	n/a
TOTAL	**490**		7 (2%)	35 (9%)	8 (2%)	4 (1%)

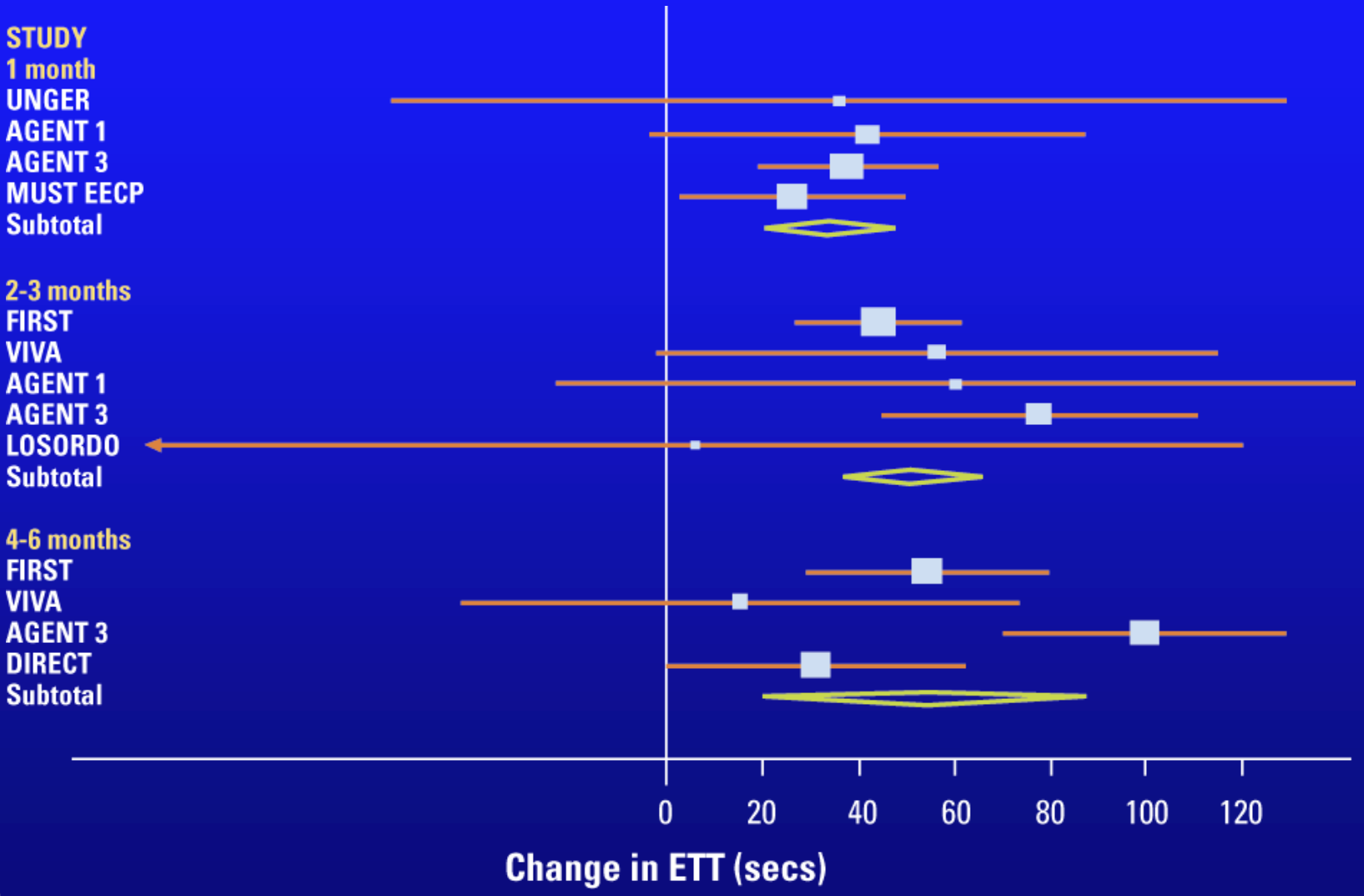
* = unstable angina

Angina

Study	Placebo Patients (n)	Angina Measurement	2-3 months	4-6 months	1 year	Compared to Treatment
UNGER	8	n/a	n/a	n/a	n/a	n/a
FIRST	86	CCS Angina Class SAQ	+	++	n/a	< *
VIVA	63	CCS Angina Class SAQ	++	++	+	< **
AGENT 1	19	n/a	n/a	n/a	n/a	n/a
AGENT 3	139	CCS Angina Class	+	+	+	< ***
LOSORDO	7	CCS Angina Class SAQ	0	n/a	n/a	< *
MUST-EECP	66	Angina Counts NTG use	0/+	n/a	n/a	< ****
DIRECT	102	CCS Angina Class	++	++	n/a	=

* Significant at 3 months ** Significant at 4 months *** Significant at 6 months **** Significant at 2 months

Exercise Treadmill Time



Angiogenesis for cardiovascular disease

- The primary endpoint for approval of an angiogenic agent must be an improvement in exercise performance of treated patients (FDA requirement)

- Several trials have had success in achieving various secondary or supportive endpoints, but failed when attempting to demonstrate a statistically significant improvement in exercise performance, typically done by a treadmill exercise test. This has been confounded by the placebo effect

Angiogenesis: Side effect profile

Plaque angiogenesis

- A theoretical concern associated with any angiogenic growth factor administration is the development of plaque angiogenesis that may precipitate plaque growth or destabilization due to broad-spectrum mitogenicity and chemotactic activity, especially toward macrophages.

- The latter possibility may be particularly relevant given the ability of FGFs and VEGFs to induce angiogenesis in vasa vasorum and the association between plaque angiogenesis and its growth and stability.

Simons. Circulation. 2000

Angiogenesis: Side effect profile

- **Proliferative retinopathy**
  Proliferative retinopathy has been associated with the expression and presence of angiogenic growth factors (predominantly VEGF) in the orbital fluid
- **Occult malignancies**
  The role of angiogenesis in tumor growth and metastasis is well documented and facilitation of this process may theoretically lead to accelerated primary tumor growth or stimulation of dormant metastases. To date, clinical experience with various growth factors has not substantiated these fears

Simons. Circulation. 2000

Angiogenesis: Failure of trials

- Biology is complex
- Combinations of angiogenic and anteriogenic factors may be required
- Combination therapy requires collaboration of pharmacological companies

Angiogenesis: Why has it largely failed to date?

- Optimal therapy may need combinations of angiogenic and anteriogenic factors
- VEGF increases permeability by leading to tissue oedema
- The newly formed vessels may be disorganized and primitive vessels such as those in tumour tissue
- Stimulation of new vessels is only part of the requirement. Maintenance and remodelling of the newly formed vessels is also needed

Therapeutic angiogenesis for ischemic myocardium

Promoting angiogenesis in ischemic cardiac tissue remains an undisputed therapeutic approach for the treatment of myocardium that lacks sufficient blood supply

Cao. Discovery Medicine 2010

Angiogenesis

- The concept of promoting angiogenesis in ischemic myocardium is worthy
- However most trials have been disappointing

Effect of Intracoronary Delivery of Autologous Bone Marrow Mononuclear Cells 2 to 3 Weeks Following Acute Myocardial Infarction on Left Ventricular Function

The LateTIME Randomized Trial

Jay H. Traverse, MD, Timothy D. Henry, MD, Stephen G. Ellis, MD, Carl J. Pepine, MD, James T. Willerson, MD, David X. M. Zhao, MD, John R. Forder, PhD, Barry J. Byrne, MD, PhD, Antonis K. Hatzopoulos, PhD, Marc S. Penn, MD, PhD, Emerson C. Perin, MD, PhD, Kenneth W. Baran, MD, Jeffrey Chambers, MD, Charles Lambert, MD, PhD, Ganesh Raveendran, MD, Daniel I. Simon, MD, Douglas E. Vaughan, MD, Lara M. Simpson, PhD, Adrian P. Gee, PhD, Doris A. Taylor, PhD, Christopher R. Cogle, MD, James D. Thomas, MD, Guilherme V. Silva, MD, Beth C. Jorgenson, RN, Rachel E. Olson, RN, MS, Sherry Bowman, RN, Judy Francescon, RN, Carrie Geither, RN, Eileen Handberg, PhD, Deirdre X. Smith, RN, Sarah Baraniuk, PhD, Linda B. Piller, MD, MPH, Catalin Loghin, MD, David Aguilar, MD, Sara Richman, Claudia Zierold, PhD, Judy Bettencourt, MPH, Shelly L. Sayre, MPH, Rachel W. Vojvodic, MPH, Sonia I. Skarlatos, PhD, David J. Gordon, MD, PhD, Ray F. Ebert, PhD, Minjung Kwak, PhD, Lemuel A. Moyé, MD, PhD, Robert D. Simari, MD

for the Cardiovascular Cell Therapy Research Network (CCTRN)

Context Clinical trial results suggest that intracoronary delivery of autologous bone marrow mononuclear cells (BMCs) may improve left ventricular (LV) function when administered within the first week following myocardial infarction (MI). However, because a substantial number of patients may not present for early cell delivery, the efficacy of autologous BMC delivery 2 to 3 weeks post-MI warrants investigation.

Objective To determine if intracoronary delivery of autologous BMCs improves global and regional LV function when delivered 2 to 3 weeks following first MI.

Design, Setting, and Patients A randomized, double-blind, placebo-controlled trial (LateTIME) of the National Heart, Lung, and Blood Institute–sponsored Cardiovascular Cell Therapy Research Network of 87 patients with significant LV dysfunction (LV ejection fraction [LVEF] ≤45%) following successful primary percutaneous coronary intervention (PCI) between July 8, 2008, and February 28, 2011.

Interventions Intracoronary infusion of 150×10^6 autologous BMCs (total nucleated cells) or placebo (BMC:placebo, 2:1) was performed within 12 hours of bone marrow aspiration after local automated cell processing.

Main Outcome Measures Changes in global (LVEF) and regional (wall motion) LV function in the infarct and border zone between baseline and 6 months, measured by cardiac magnetic resonance imaging. Secondary end points included changes in LV volumes and infarct size.

Results A total of 87 patients were randomized (mean [SD] age, 57 [11] years; 83% men). Harvesting, processing, and intracoronary delivery of BMCs in this setting was feasible. Change between baseline and 6 months in the BMC group vs placebo for mean LVEF (48.7% to 49.2% vs 45.3% to 48.8%; between-group mean difference, −3.00; 95% CI, −7.05 to 0.95), wall motion in the infarct zone (6.2 to 6.5 mm vs 4.9 to 5.9 mm; between-group mean difference, −0.70; 95% CI, −2.78 to 1.34), and wall motion in the border zone (16.0 to 16.6 mm vs 16.1 to 19.3 mm; between-group mean difference, −2.60; 95% CI, −6.03 to 0.77) were not statistically significant. No significant change in LV volumes and infarct volumes was observed; both groups decreased by a similar amount at 6 months vs baseline.

Conclusion Among patients with MI and LV dysfunction following reperfusion with PCI, intracoronary infusion of autologous BMCs vs intracoronary placebo infusion, 2 to 3 weeks after PCI, did not improve global or regional function at 6 months.

Trial Registration clinicaltrials.gov Identifier: NCT00684060.

JAMA. 2011;306(19):2110-2119
Published online November 14, 2011. doi:10.1001/jama.2011.1670 www.jama.com

SEVERAL RANDOMIZED TRIALS have demonstrated that administration of autologous bone marrow mononuclear cells (BMCs) following acute myocardial in-

Stem cells and the heart

Intracoronary injection of Bone Marrow derived mononuclear cells after myocardial infarction:

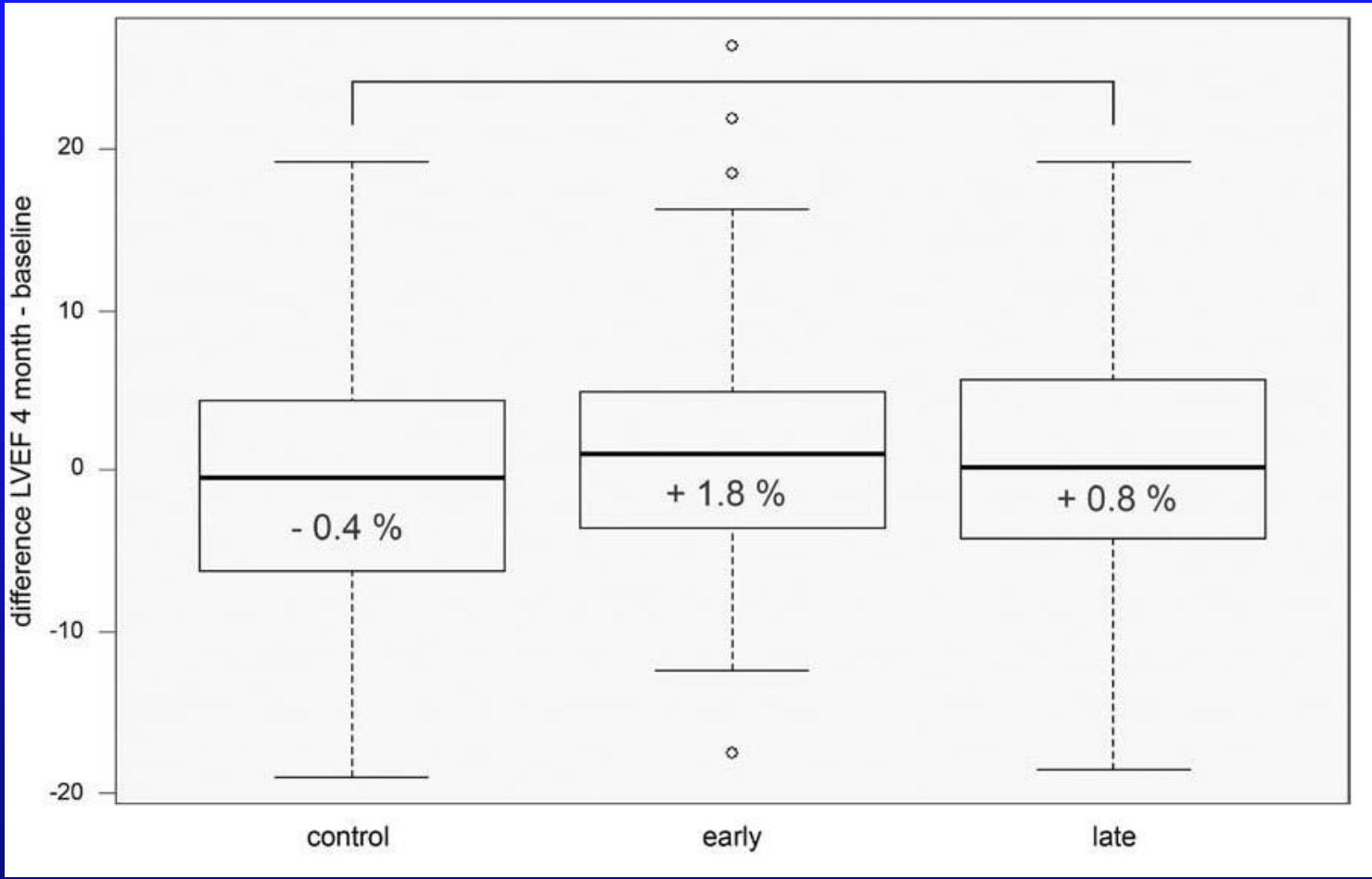
Several studies show an improvement in ejection fraction;
Others show no improvement;
Why the difference –

- Different study design
- Different cell isolation
-Protocols potentially leading to differences in cell functionality
- Different measurement of endpoint

- **Meta-analysis shows potential benefit**
- **Larger event driven trials are required**

The early euphoria of the clinical application of progenitor cell-based research has been reduced by recent negative trials

Bone Marrow-derived mononuclear cell treatment and ejection fraction



Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, NZ

Surder D *et al* Circ aha 2013: 127 1968

Stem Cells And The Heart

The early euphoria of the clinical application of progenitor cell-based research has been reduced by recent negative trials

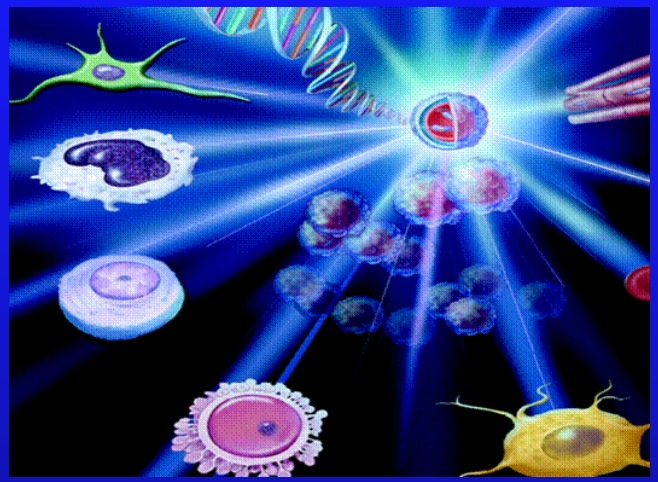
The future

- Ideal Growth Factor or Combination
- Protein, Gene, HIF-1. EPC, BM or stem cells
- Ideal Dose and Route of administration
- Ideal Patient: responders/non responders
- Ideal time points
- Ideal Endpoint
- Targeted treatment strategy

Strategies to Enhance Cell Therapy

1. Increase the number of cells (autologous)
   - Whole bone marrow (Harvest)
2. Selected cells (autologous)
   - Adipose derived cells (Cytori)
   - CD34+ cells (Baxter)
   - ALD-bright (Aldagen)
3. Expand and/or enhanced cells (autologous)
   - Aastrom Biosciences
   - C-Cure
4. Allogeneic
   - MPC (Mesoblast-Teva)
   - MSC (Osiris)
   - MAPC (Athersys)
5. Cardiac derived
   - Caduceus (Capricor)
   - SCIPIO

Stem Cells And The Heart
Are we ready?



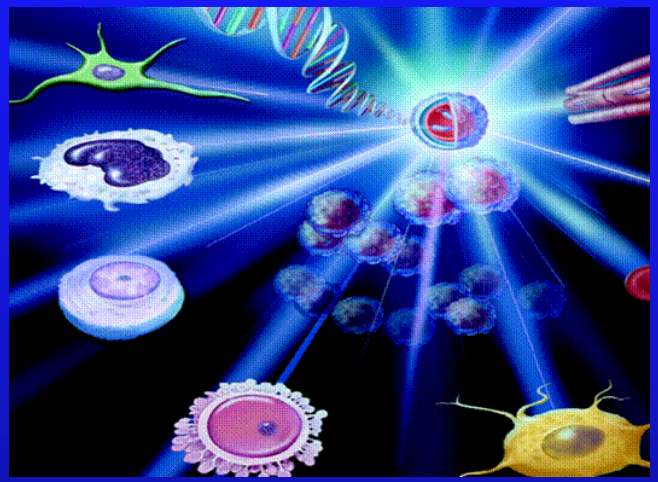
Harvey White

Green Lane Cardiovascular Service and

Cardiovascular Research Unit

Auckland City Hospital; Auckland, New Zealand

Stem Cells And The Heart
Are we ready? Not yet



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Auckland City Hospital; Auckland, New Zealand

Still not available at the florist yet…. GETTING CLOSER!