Professor Richard Boyd

Monash University

Australia

Professor Martin Pera

Stem Cell Sciences

University of Melbourne

The Practical use of Stem Cell Therapy in a Clinical Setting - Concurrent Workshop

Saturday, 22 June 2013 Start 4:30pm Duration: 60mins Kandinsky

Stem Cell Therapies:
The path to helping patients…

Richard Boyd

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CALIFORNIA INSTITUTE FOR CIRM REGENERATIVE MEDICINE

MAGELLAN STEM CELLS

GENESIS STEMCELL 领航干细胞 Life is Valuble

Australian Stem Cell Centre

norwood immunology

monash immunology and stem cell laboratories

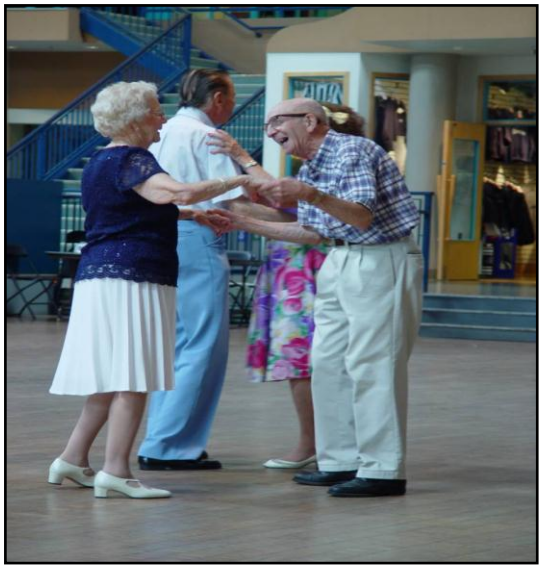
ProStemCell 保信幹細胞

Hong Kong Stem Cell bank and clinic

Why the need for stem cells?

Now….

Next….



- Knee cartilage performs essential mechanical function.
- Cartilage damage and pain control are major clinical challenges
- New technologies or therapies are urgently needed.

HOPES: Diseases for stem cell treatment..

- **Osteoarthritis "wear and tear" from aging and sport**
- **Neurotrauma – Alzheimers, Parkinson's, spinal cord injury, motor neurone disease, stroke**
- **Cardiovascular**
- **Repair of Immune system**
  - **Immune deficiency**
    - **Cancer – chemotherapy, radiation induced immunodeficiency**
    - **Aging**
    - **Chronic infection**
  - **Autoimmune disease (type 1 diabetes, MS, rheumatoid arthritis)**
  - **Transplantation tolerance**
- **Skin - burns, wounds**
- **Lung (COPD, asthma, allergies)**
- **Kidney disease**
- **Diabetes……**
- **Healthy start to life – cerebral palsy, lung, kidney**

HURDLES

- **Ethical**
  - **Strict Government regulations now in place**
  - **Human ES cells can only be developed under license from NH&MRC; obtained from discard IVF embryos under strict informed consent**
  - **Human cloning banned**
  - **Creating and destroying human life soley for research or therapy banned**
  - **1000+ ES lines so no new ones needed**
  - **iPS – also large number of lines**
    - **Age, environment, disease type, geographical**

HURDLES

- **Safety**
  - **Must have pre-clinical animal data, preferably large animals (more realistic models for human disease**

- **Practical**
  - **Which stem cells to use?**
  - **Your own or someone else's?**
  - **Stem cell banking – for one or for all in the family?**
    - **Is this financially justifiable**
  - **Commercial IP – who owns it?**

Why are stem cells different?

- Perceived as the body repair kit
- Natural healers – Body's ambulance
- Life is short
- Hurting ain't fun
- World is small
- People are "rich"
- People are impatient

"Stem cells - The Gold Rush of medicines"

Stem cell tourism – beware the bad guys

"Good guy" – stem cell clinics

- **Safety first**
- **Pre-clinical data**
- **Conduct properly sanctioned clinical trials**
- **Registered with TGA/FDA**
- **Support underlying research**
- **Every patient enlisted on trial**
- **Thorough analysis of what is injected and where and what is the outcome**
- **Realistic, non-opportunistic funding**
- **PATIENT CARE and FOLLOW-UP**

Stem cell therapies: Our code of ethics

We have formed an entity "Australian Autologous Cell Therapies Group"

- ***Academic, clinical and commercial "clinical groups"***
- ***make certain there is maximal patient safety; clinical rigour,***
- ***evidence based,***
- ***appropriate thorough patient follow-up;***
- ***on-line data management (we are working with "Clinical Intelligence Pty Ltd. Melb)***
- ***Peer group evaluation of data; international presentations and publications***
- ***Everyone wins?!?!?***

The Funding dilemma: A practical solution?

Alternative ***additional strategy to meet clinical integrity and patient needs (prevent medical tourism)***

- ***Phase I funded by commercial entity***
  - ***When clinicians satisfied….***
- ***Dual Phase II strategy:***
  - » ***RCT (patients don't pay but have 1 in 2 chance of getting "drug"***
  - » ***If it is a cross-over trial (recommended) placebo's now get test 'drug' and vice versa usually after ~ 6 month***
- ***BUT – many patients don't want this***
  - ***They are actually in pain and would rather "pay for procedure" knowing that some good may occur because of previous pre-clinical data and hope to relieve pain***

The Funding dilemma: RCT and "user pays"

SO: This becomes a Case Series – ***patients offered the option of paying for stem cell therapy***

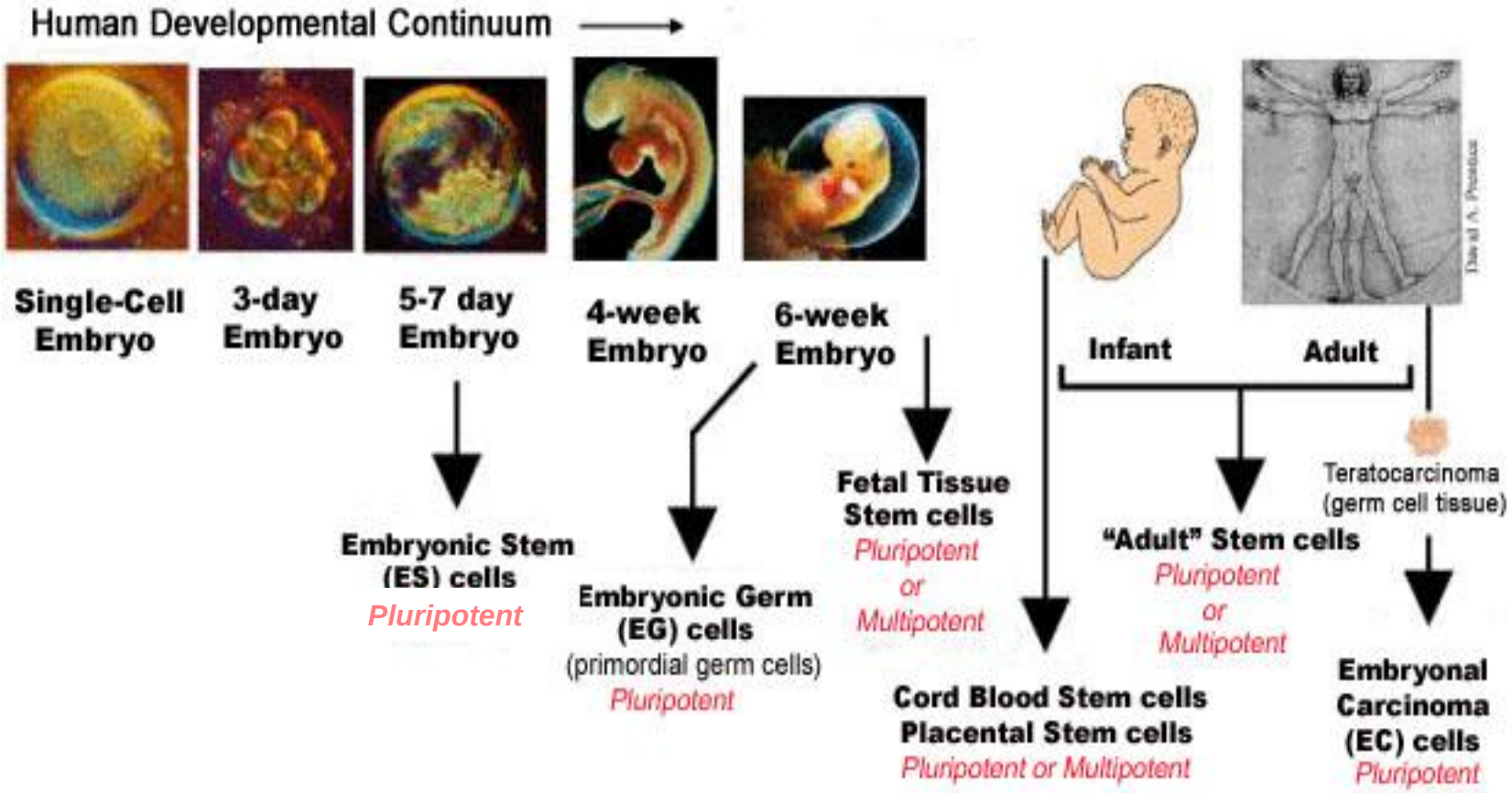
- **Companies thus receive compensation for their outlay in the RCT**
  - **No need for patients to travel to less regulated clinics and pay $30-50k CONTROL OF ROGUE CLINICS**
- **Strict clinical appraisal and follow-up**
- **Strict analysis of what is being injected**
  - **Effectively multi-centre trials**
  - **Data (good, bad or otherwise) published in reputable journals;**

NOTE AND VIP!

All patients must be enrolled in a trial; this is experimental medicine!

Which stem cells to choose..??

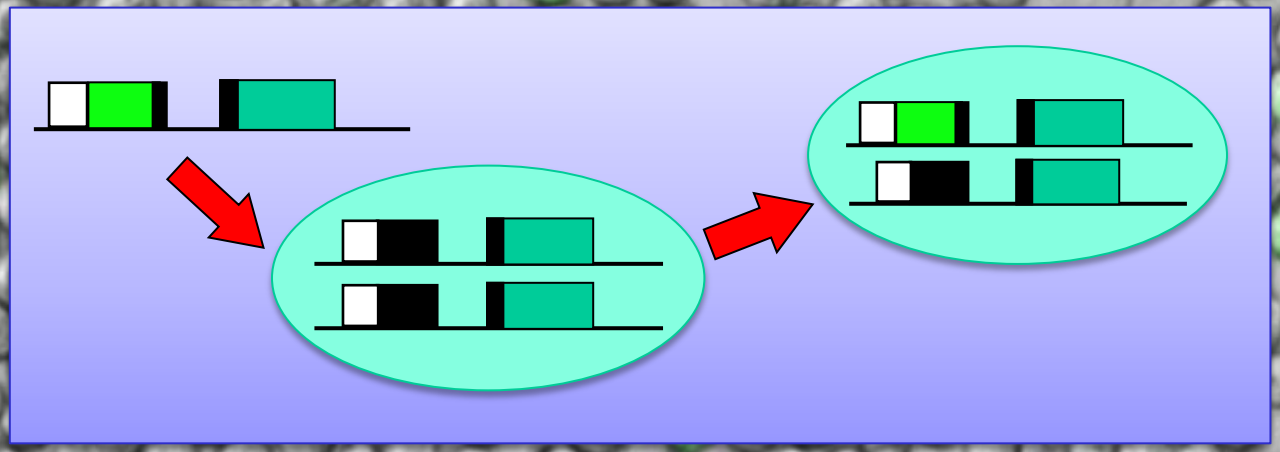
Many Types of Stem Cells!



Another HURDLE:
How do I know my stem cell is heading along the right pathway??

Genetic modification of embryonic stem cells. *Andrew Elefanty, Ed Stanley*

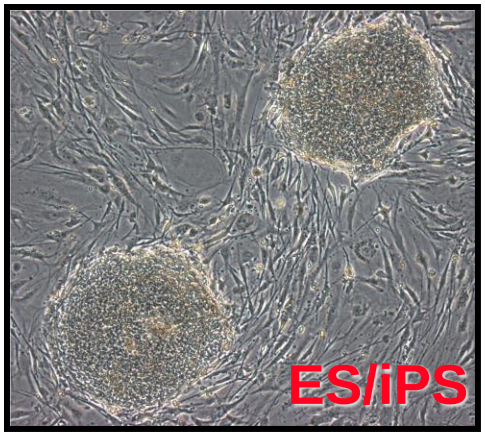
Replace one copy of a gene with a fluorescent gene

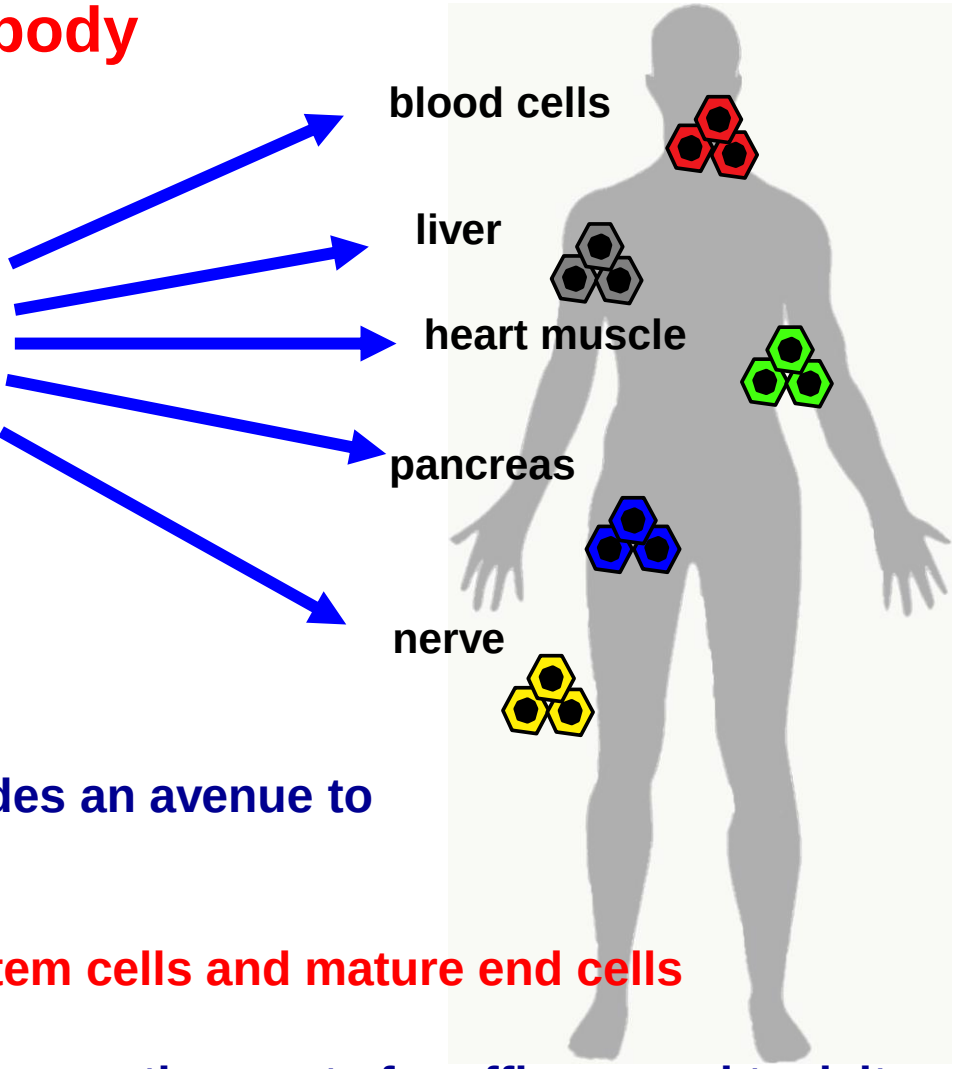


Whenever the modified gene is expressed, the cell will fluoresce

Provides ability to identify the cells of interest when they appear

ES/iPS cells can differentiate into all the cell types in the body



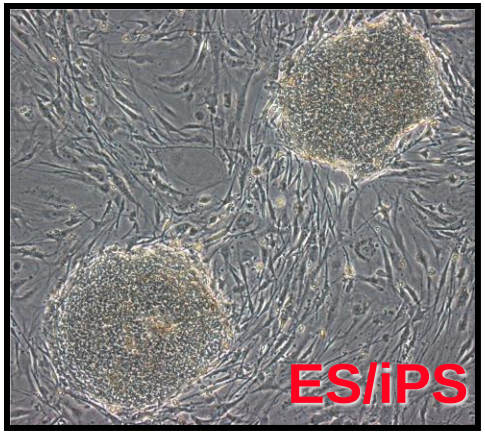


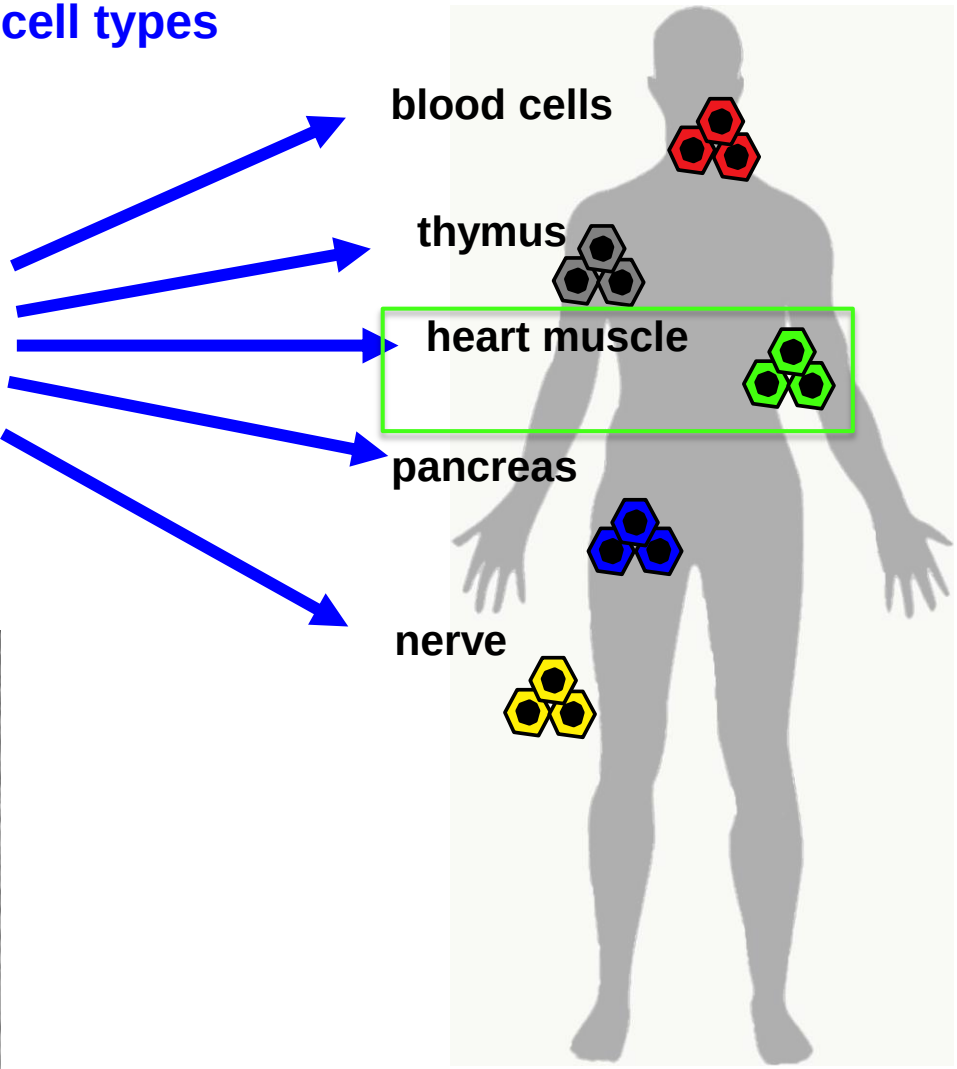
Differentiation of ES/iPS cells provides an avenue to

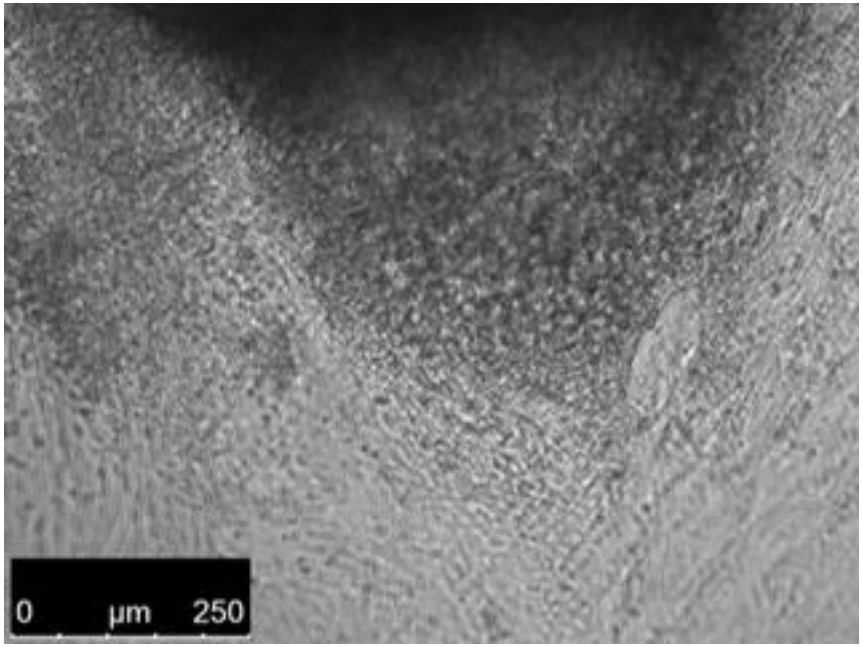
- **study early development**

- **generate tissue specific stem cells and mature end cells**
  - **to study disease**
  - **to screen drugs/therapeutic agents for efficacy and toxicity**
  - **for cell therapies**

Human ES cells with fluorescent reporters allow visualization of multiple different cell types

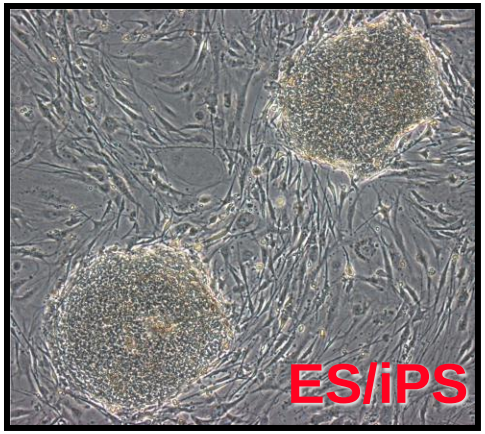






Green fluorescent beating human cardiomyocytes

Human ES cells with fluorescent reporters allow visualization of multiple different cell types



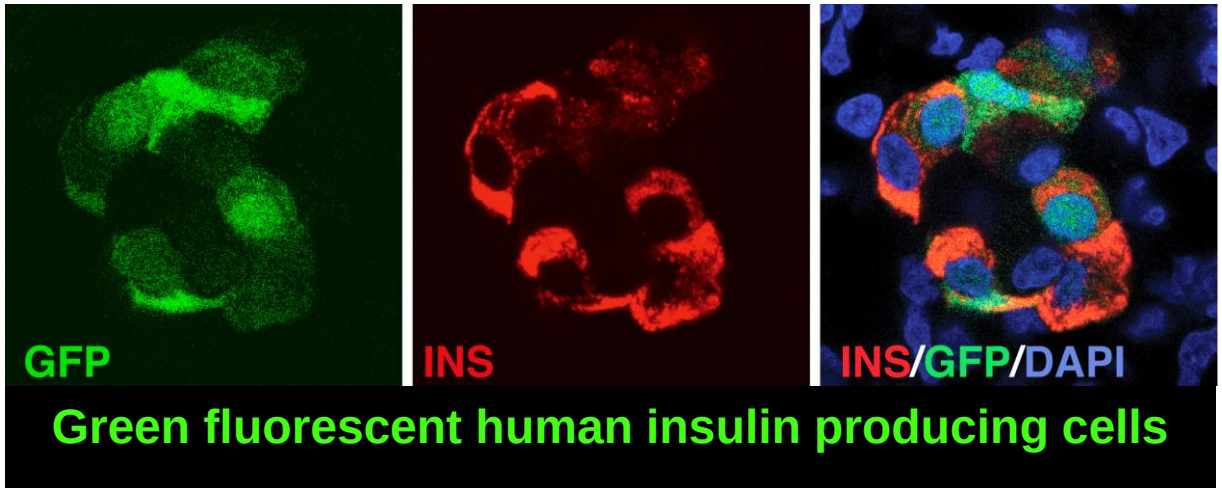
blood cells

thymus

heart muscle

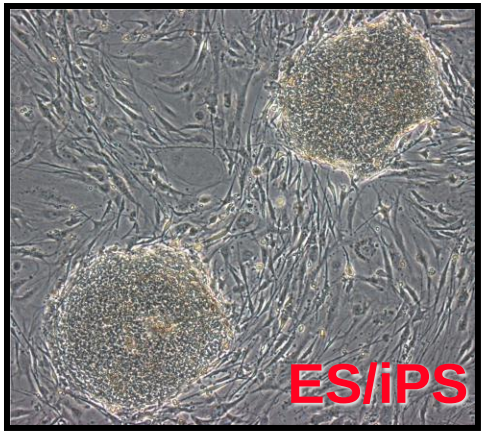
pancreas

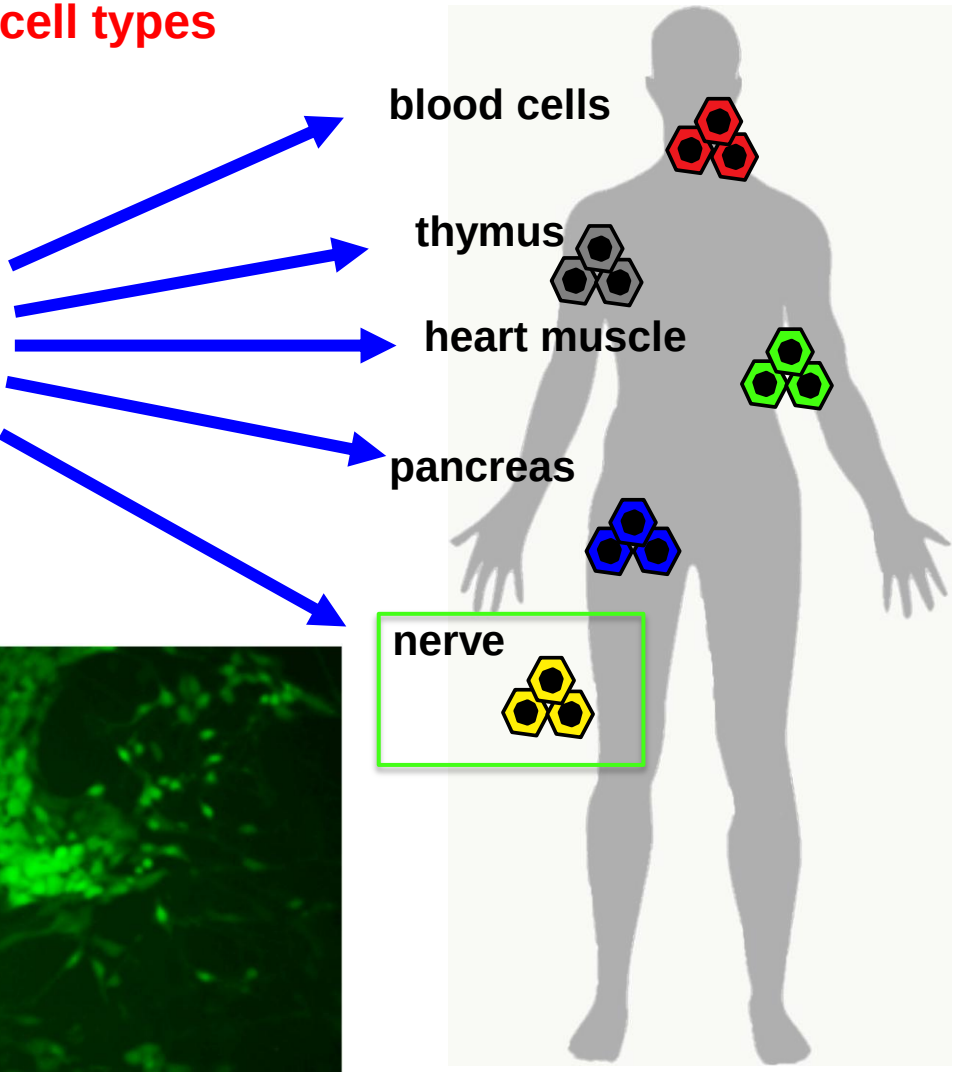
nerve

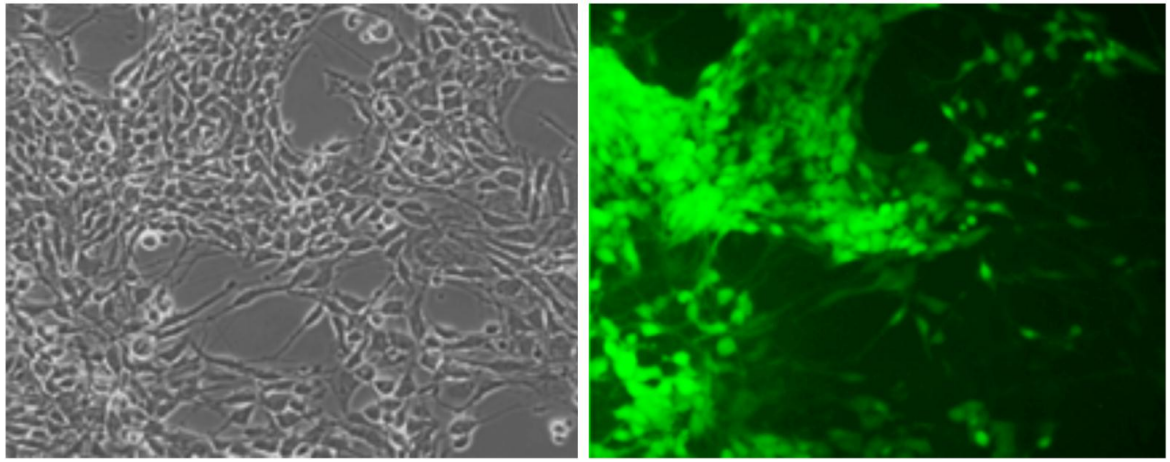


Green fluorescent human insulin producing cells

Human ES cells with fluorescent reporters allow visualization of multiple different cell types

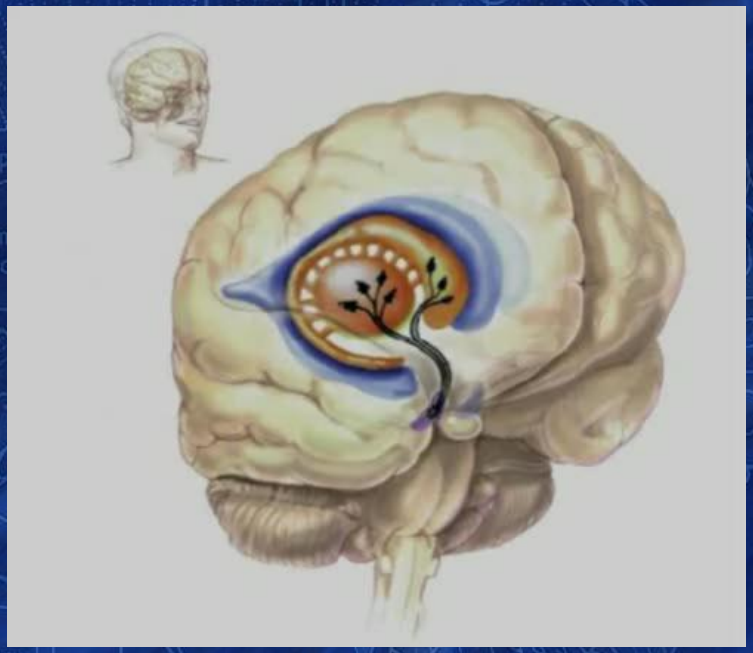






Green fluorescent human neural cells

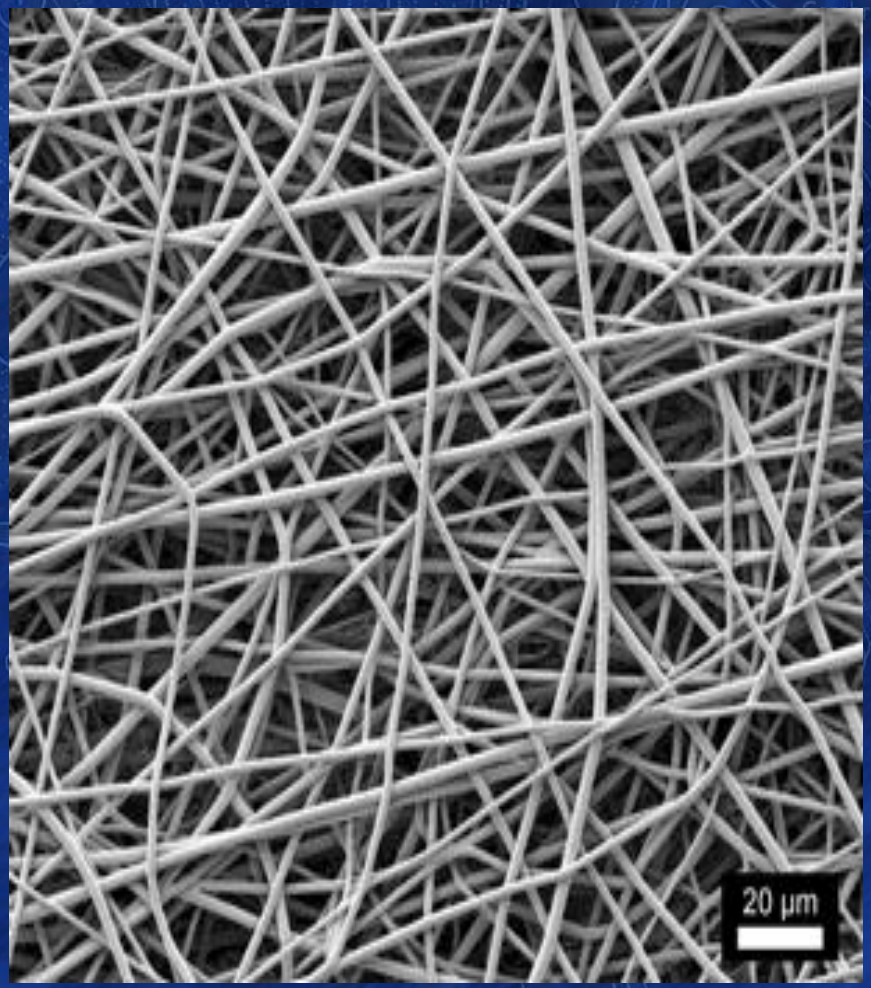
Neural Tissue Engineering using nanobiotechnology



David Nisbet
John Forsythe
Monash Engineering

1. Engineer scaffolds that promote neurite/nerve extension
2. Fabricate “smart” scaffolds that can instruct stem cells.
3. Future work towards cell replacement strategies using stem cells.

Tissue Engineering Scaffolds

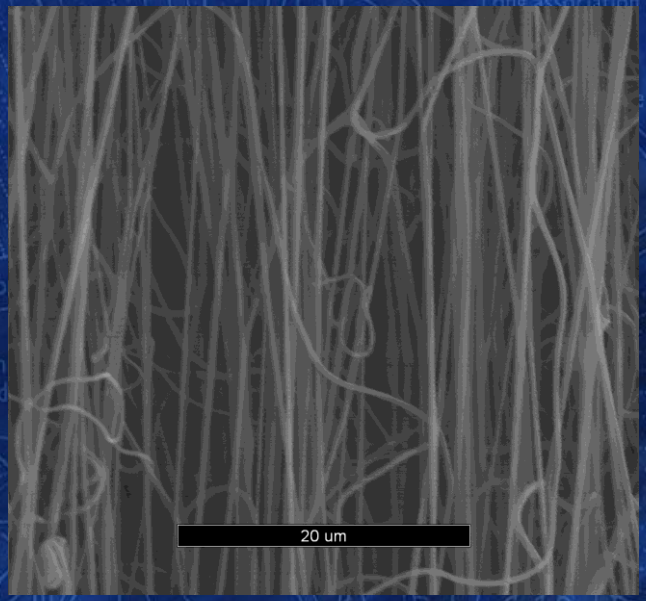


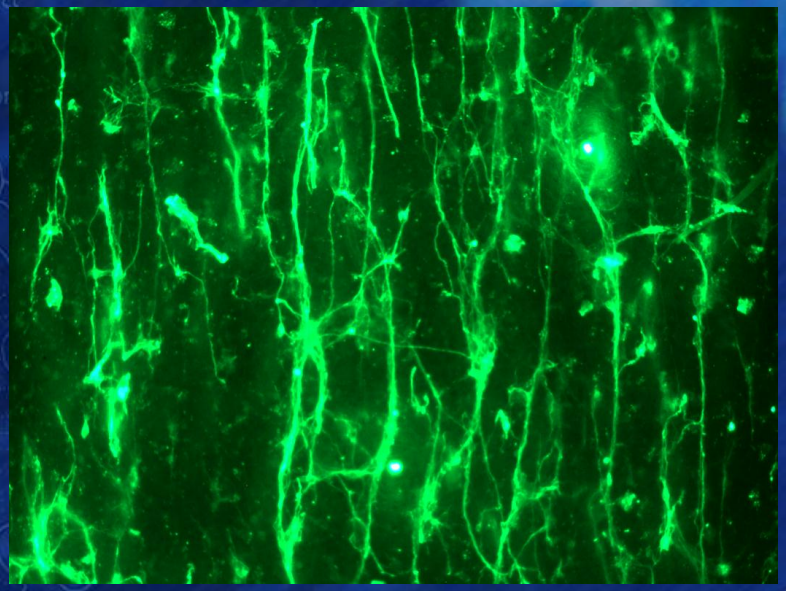
Important Features

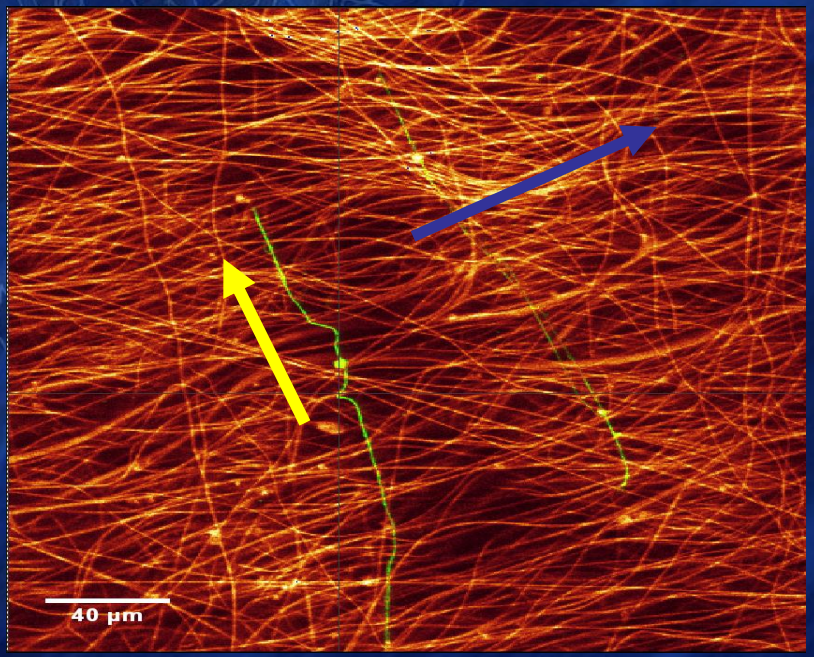
- Interfiber distance
- Surface functionality

Nisbet DR, Forsythe JS, et al. J. Biomater. App. 2009

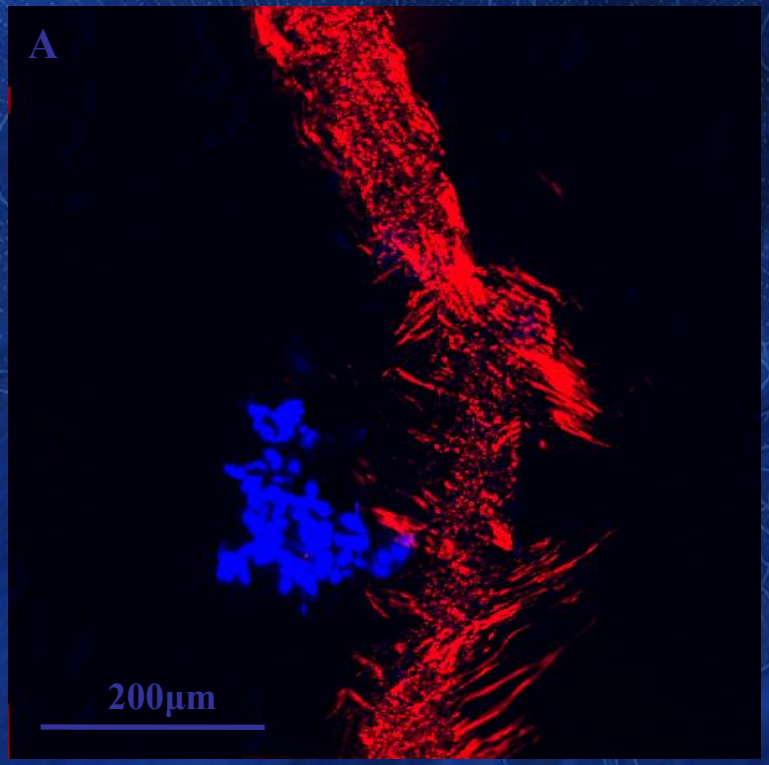
Factors Controlling Nerve Growth



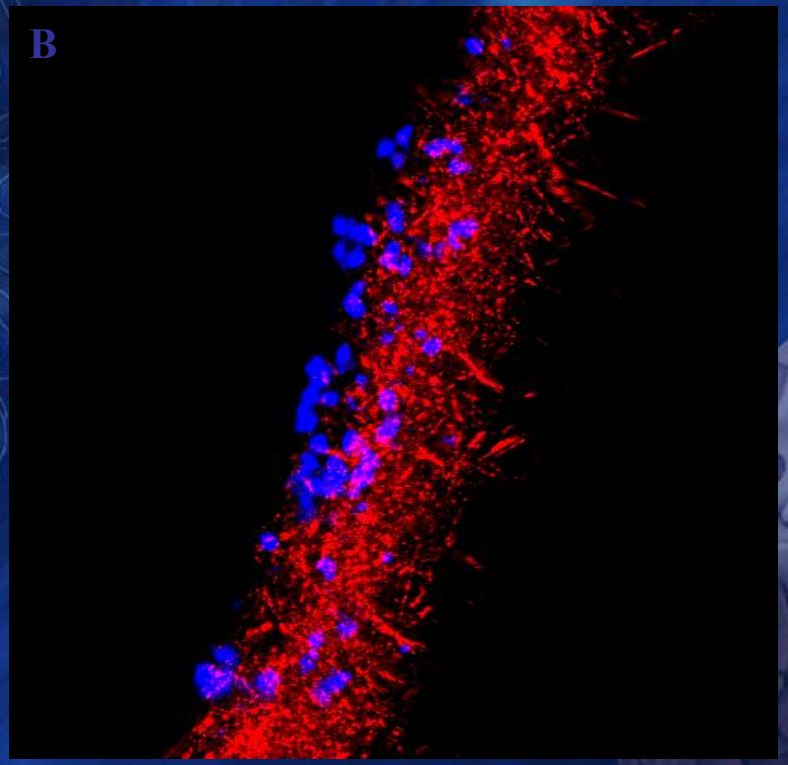




Interaction of Stem Cells with Nanofibrous Scaffolds



Unmodified nanofibrous scaffold



PCL nanofibrous scaffold surface modified

Nisbet DR, Forsythe JS, et al. J. Bio. Sci. Poly. Ed. 2008

A HURDLE

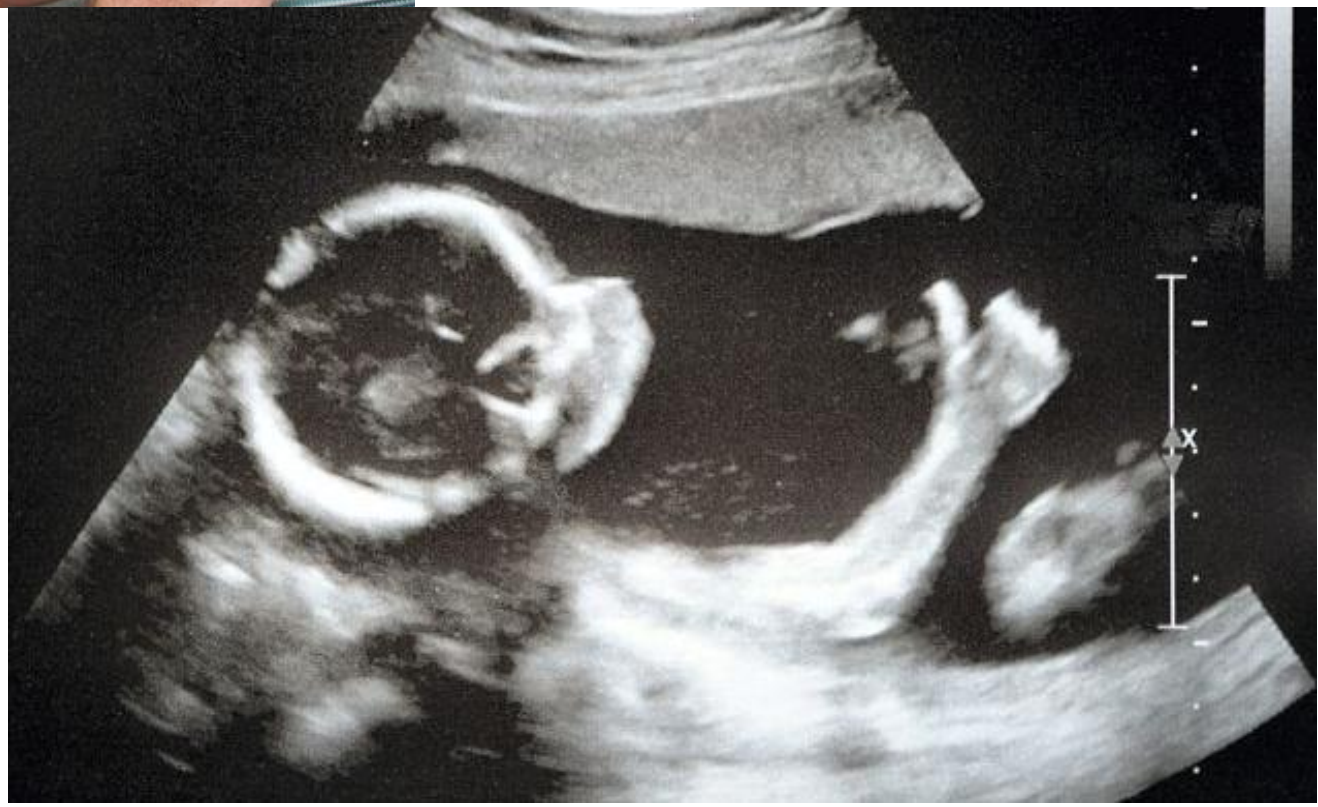
Stem Cell are very exciting but

back to the BIGGEST PRACTICAL PROBLEM….

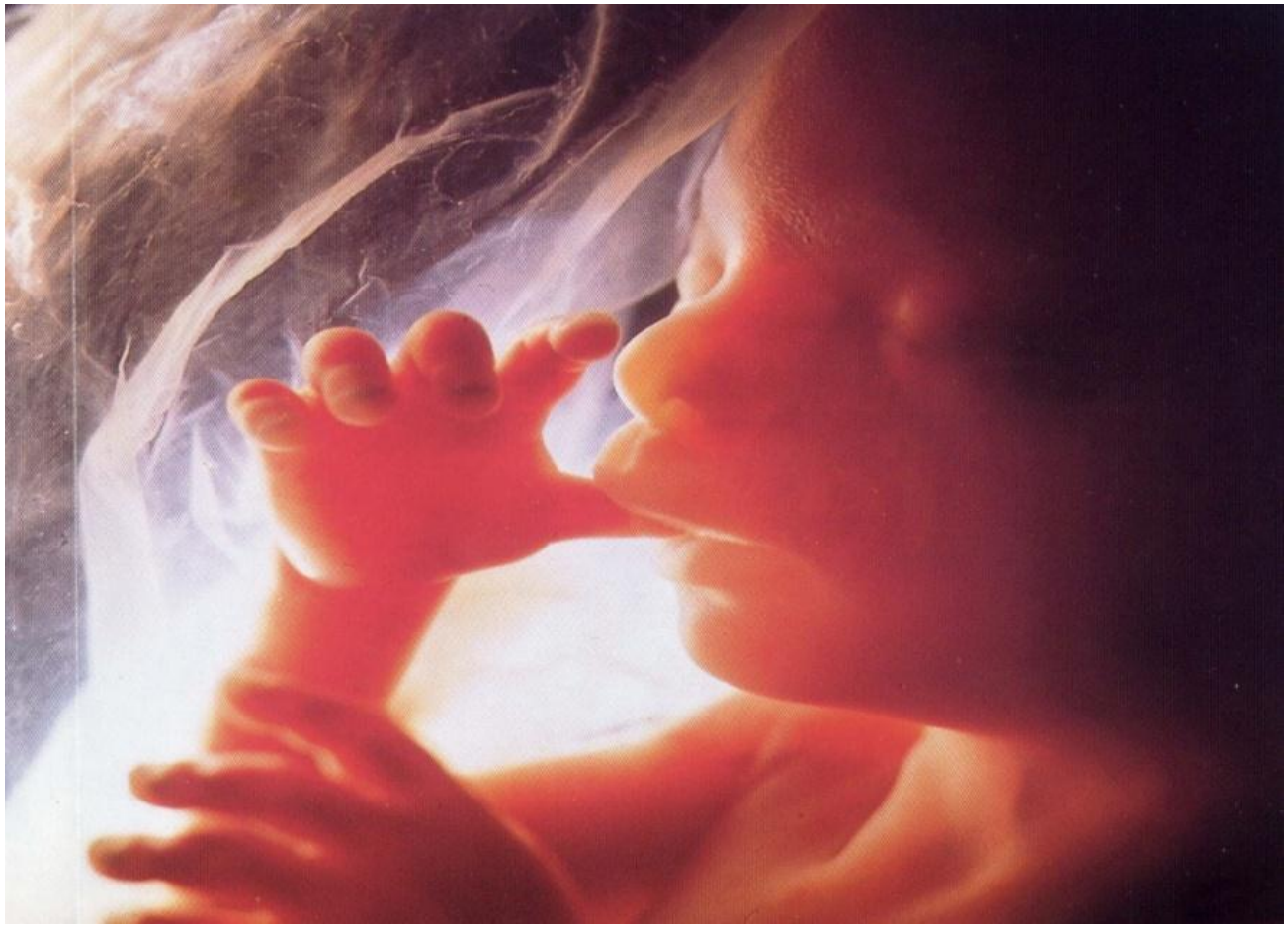
- **How can we find a source of our own multipotential/pluripotential stem cells, that are safe, ethical and effective in treating a wide range of diseases ?**

Worry!

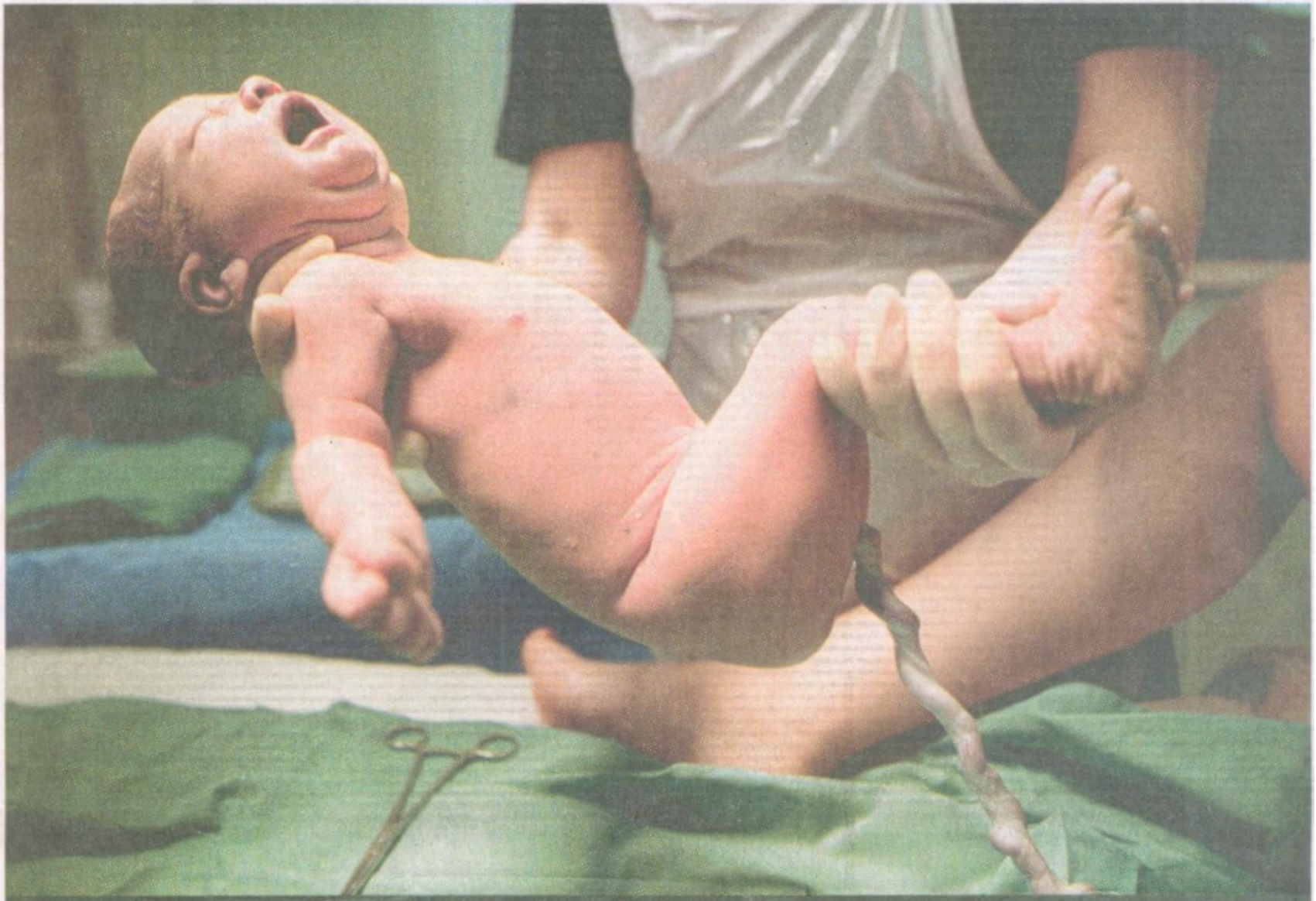
Relief…



Miracles in motion…



A once in a lifetime chance



Frozen blood from this baby's umbilical cord could one day save its life. A medical revolution revealed: **NEWS 8**

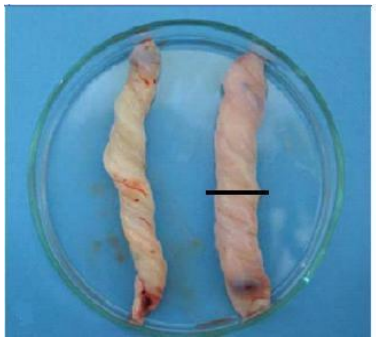
Picture: SIMON O'DWYER

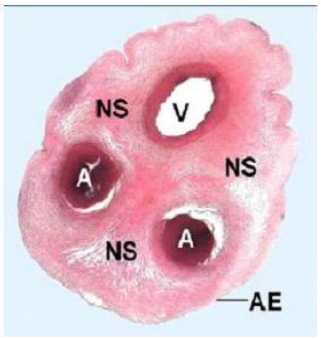
Sources of stem cells in new born…

www.healthystarttolife.monash.org/

- **Umbilical Cord**
  - **Haemopoietic stem cells (HSC)**

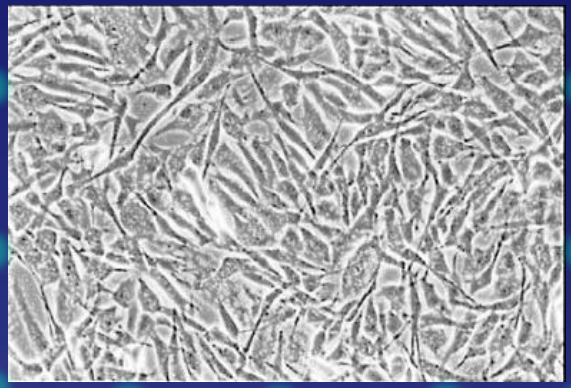
"Wharton's Jelly"
  - **Mesenchymal Stem Cells (MSC)**



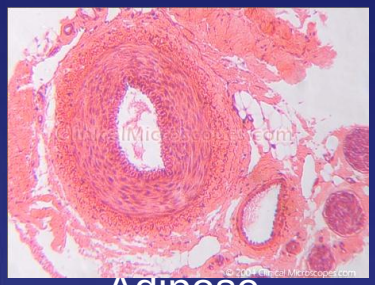


Capabilities of MSC

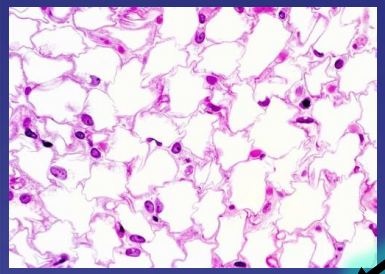
MESENCHYMAL STEM CELLS



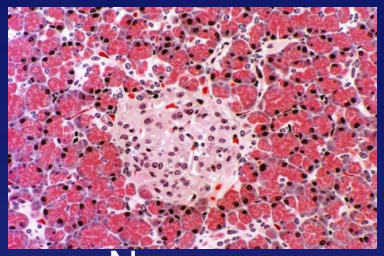
Endothelium



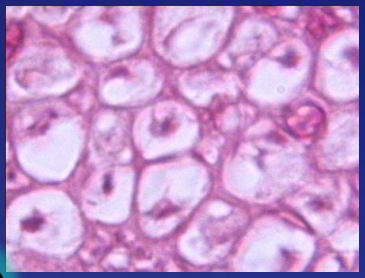
Adipose

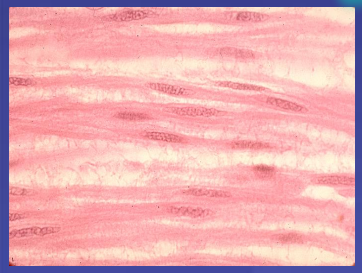


Pancreas



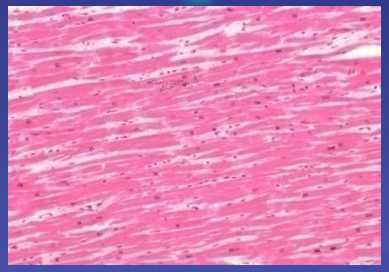
Neuron



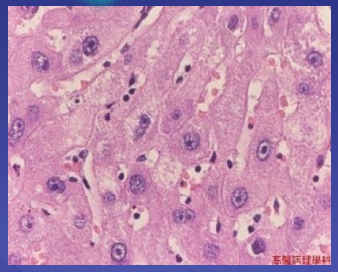


Muscle

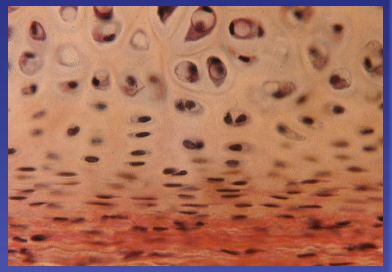
Bone



Myocardium



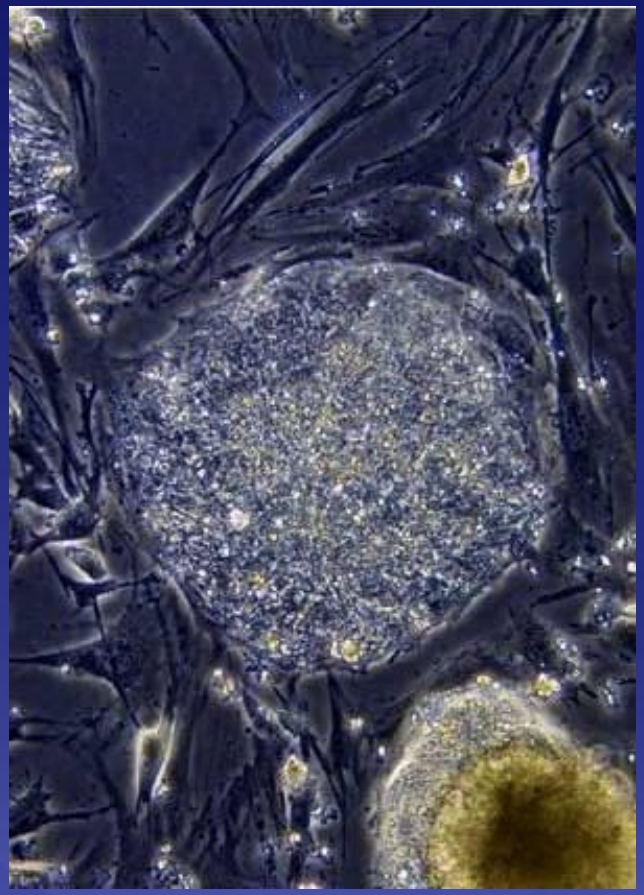
Liver



Cartilage

Mode(s) of action

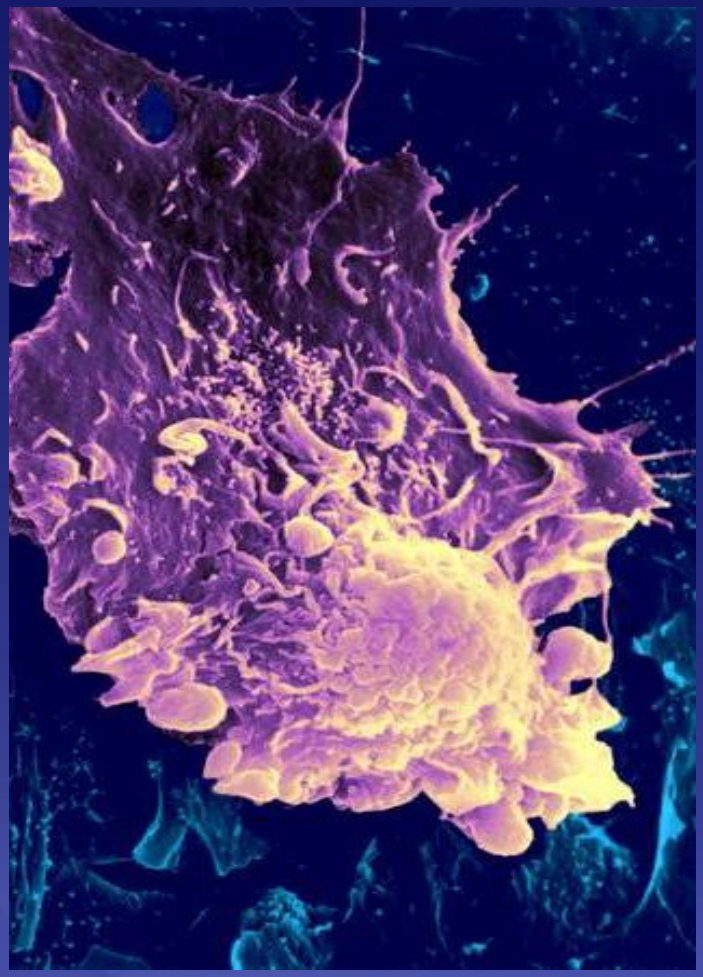
- Cell differentiation
- Anti inflammatory
- Immunomodulatory



MSC Anti-inflammatory & immunomodulatory effects

Cytokine mediated:

- **MSCs**
  - IL-1ra (Volarrvic et al, Autoimmunity, 2010)
  - Down regulate pro-inflammatory IFN, IL-12 and TNF-Alpha (Abdi et al, Diabetes, 2008)
  - Promote reparatory M2 macrophages (Kim, Exp Haematol, 2009)
  - HGF, IL-10 and TGF-beta (Puissant et al, Br J Haematol, 2005)
- MSC act on Macrophages
  - IL-1ra (Danis, Clin Exp Immunol, 1995)



Amnion Stem Cells

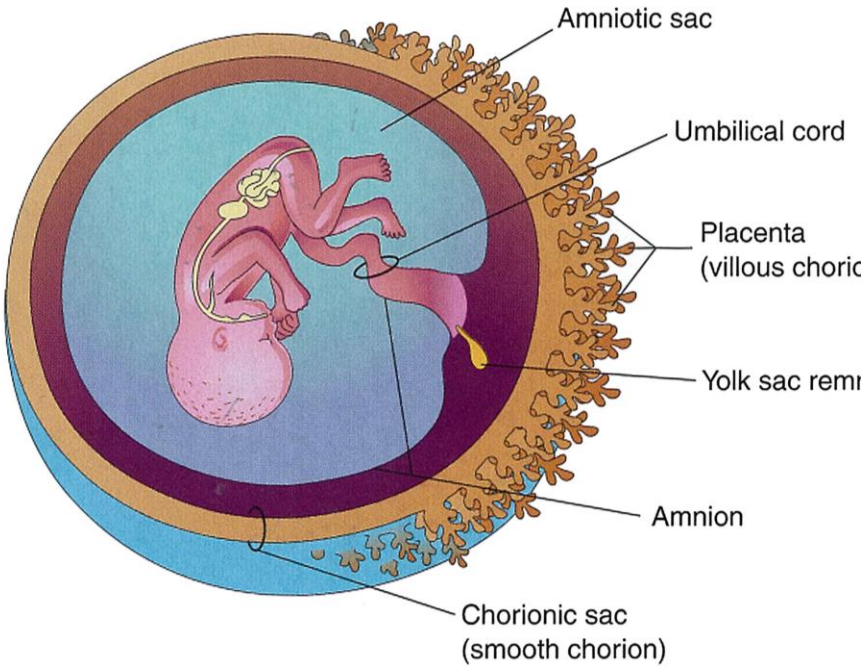
Made by the baby for the baby.

Towards a cure

Sean Murphy

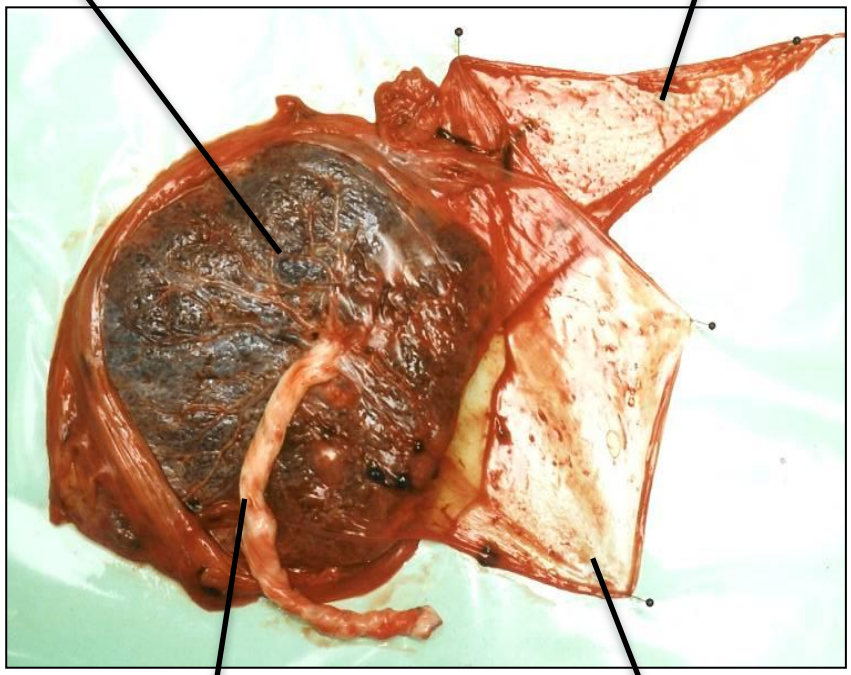
Placental tissue Stem Cells

Ann Chidgey



Placenta: Placenta derived stem cells

Chorion
Mesenchymal Stem Cells

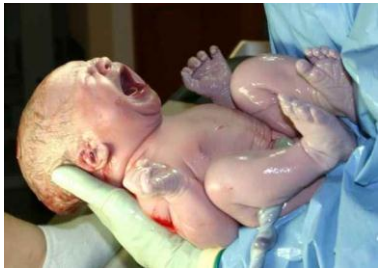


Umbilical Cord
Hematopoietic Stem Cells
Mesenchymal Stem Cells

Amnion membrane
Mesenchymal Stem Cells
Amnion Epithelial Cells

Isolation of amnion epithelial cells

Baby delivered by Caeserian section



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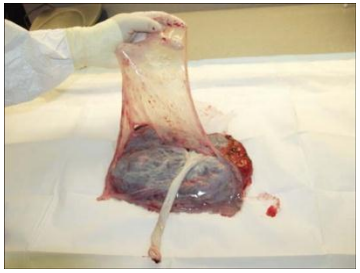
Amnion is peeled from chorion and cut into pieces



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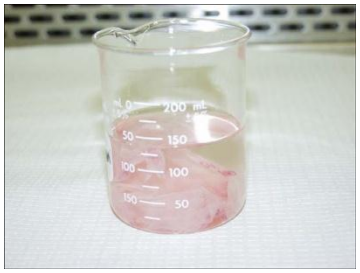
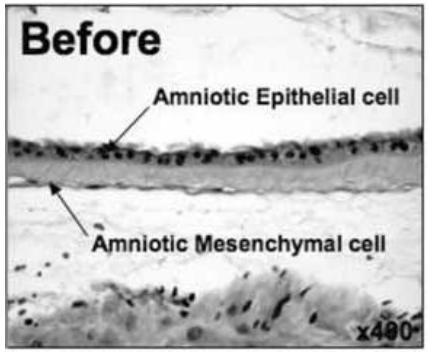
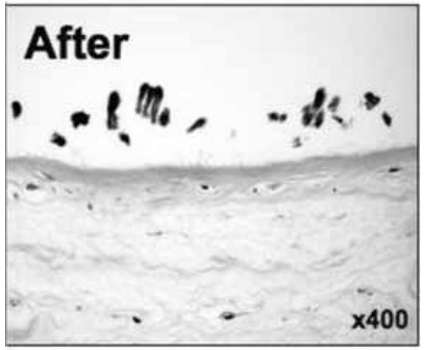
Washed several times to remove blood/blood clots; Membrane digested in trypsin







Cells are collected by filtration

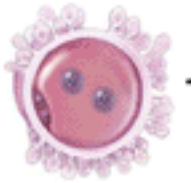
↓

Trypsin is inhibited

↓

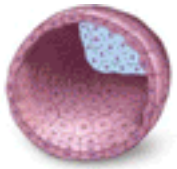
Cells cryopreserved, cultured or used for experiments

AEC formed from the Epiblast - multipotent stem cells



ZYGOTE

BLASTOCYST



Embryonic Stem Cells

Hypoblast

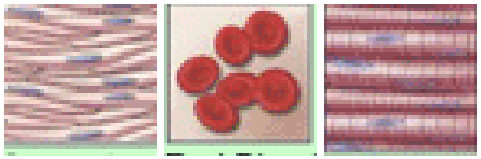
Epiblast

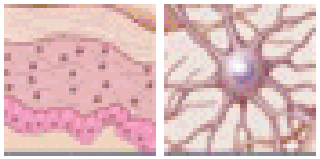
Amnion Epithelial Cells

Endoderm

Mesoderm

Ectoderm





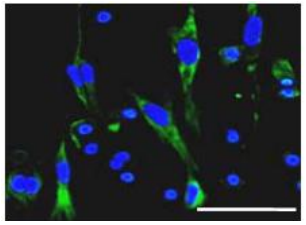
WEEK 1

WEEK 2

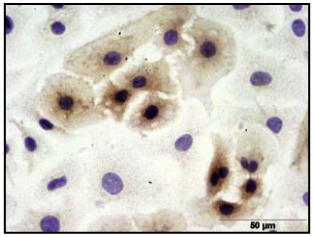
WEEK 3

AEC can differentiate into mesodermal, endodermal and ectodermal derived tissues

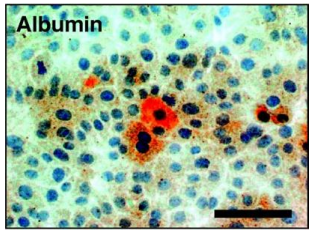
Neurons



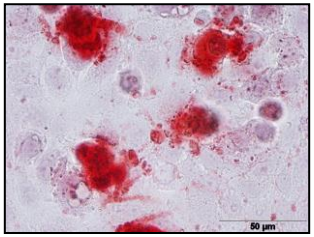
Lung Epithelium

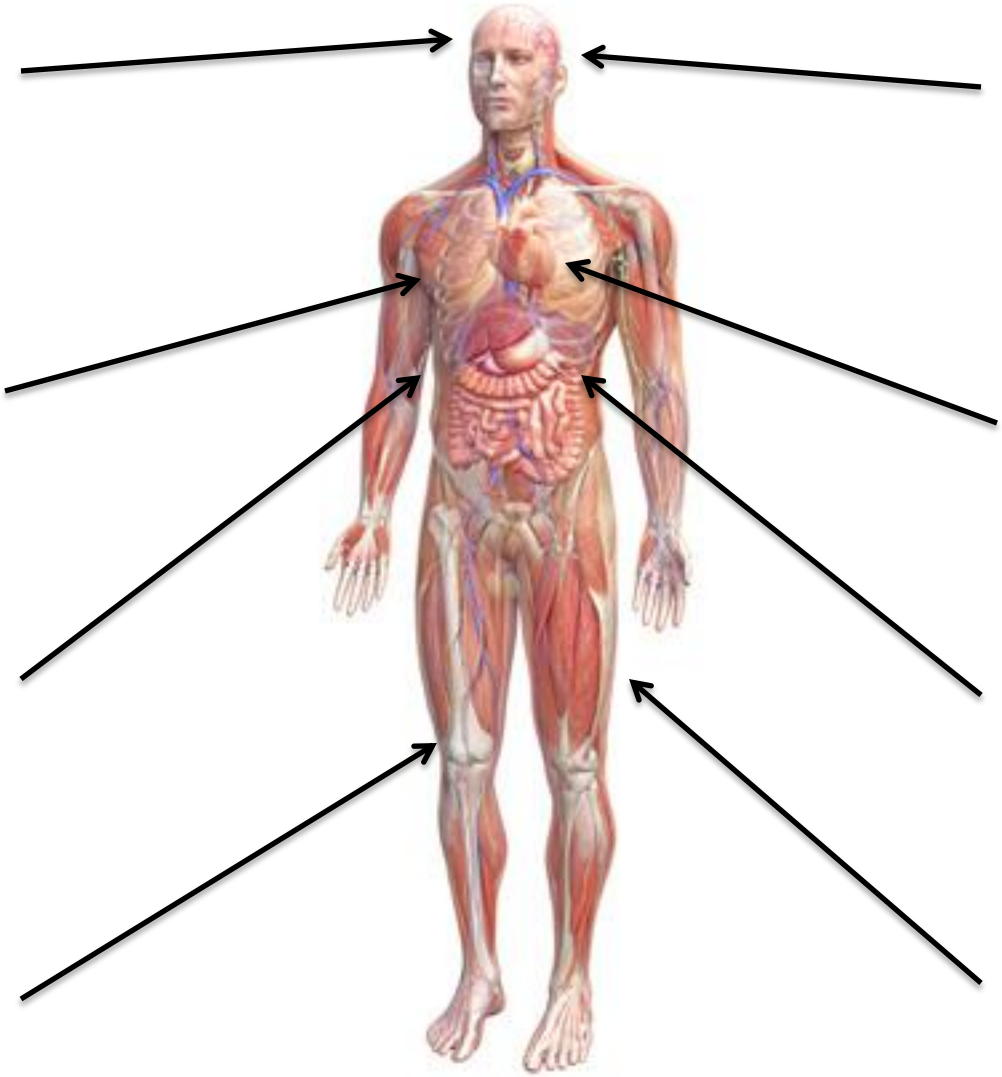


Hepatocytes

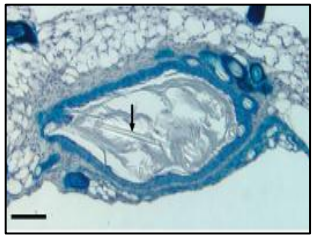


Osteocytes

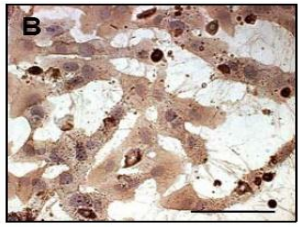




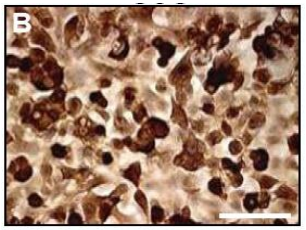
Hair and skin



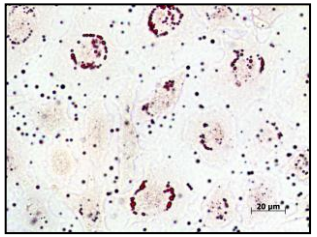
Cardiomyocytes



Pancreatic cells



Adipocytes



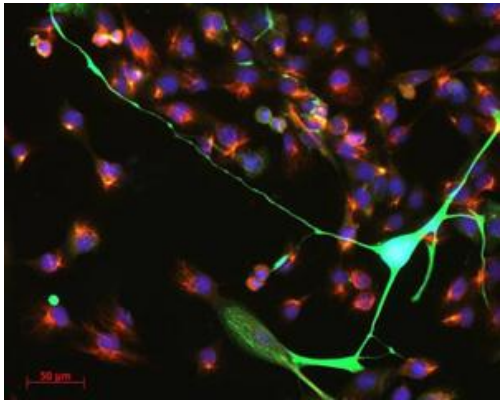
Fliniaux, 2004, Miki *et al.* 2005, Murphy *et al.* 2010

Breast milk – natures “jewel” for health

The Value of **Maternal** Stem Cells at birth

Placental, chorion, decidual tissue

- Maternal Mesenchymal Stem Cells for maternal use!
- Females have higher incidence of autoimmune disease!



Breast milk!

- Contains ~1 million cells/ml
- Mixture of:

  Immunity- Type II macrophages, T regulatory cells

  -> key elements in preventing maternal-fetal rejection

  also Ab and T cell based immunity

  Stem Cells - breast duct -derived **<u>pluripotential</u>**

  "epithelial" stem cells; Mesenchymal Stem Cells

- **Present as long as lactating; increased with feeding**

These newborn stem cells are so valuable! - should be banked

- **Nature's whole body repair kit**
- **ProStemCell Pty Ltd Hong Kong**
- **State of the art stem cell bank!**
  - **World's first comprehensive stem cell bank**
  - **Sponsored research with our lab; $500k**
    - **3 research programs**
    - **Optimising cryopreservation**
    - **Amnion for skin wounds**
    - **Cord MSC and amnion for immune system repair**
  - **Partner for ARC Linkage grant ~$600k**

Hong Kong Stem Cell Bank and clinic

Professional
Stem Cell
Processing • Storage • Therapeutic

ProStemCell

Professional
Stem Cell

Processing • Storage • Therapeutic

ProStemCell

The Value of Stem Cell Family Banking

Cord blood

HSC - compatible for parent or sibling transplant (haplo – 'close"); even blood relative

Cord Tissue

MSC from Wharton's jelly for regenerative medicine and inhibiting inflammatory diseases – autoimmunity, asthma, allergies, arthritis

MSC can be expaned in culture

Amnion

Pluripotential epithelial stem cells for potential repair of "all" tissues and organs

Placental, chorion, decidual tissue

HSC

Maternal MSC for maternal and sibling use

Females have higher incidence of autoimmune disease!

Breast milk

- Stem cells and immunity for mother and child

New Born Stem Cell Banking – a logical choice

Bank it

Donate it

BUT don’t discard it.

It just makes sense!

HOPES

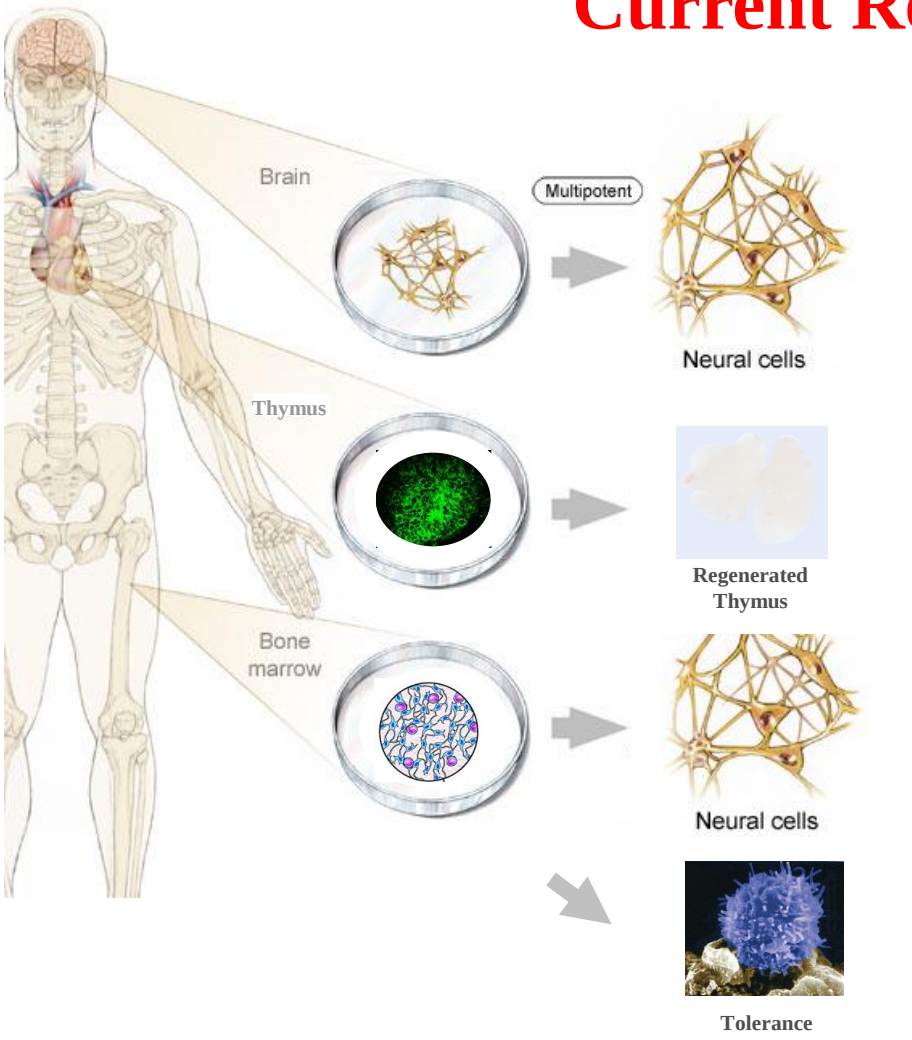
Can stem cells fix diseases - safely?

Multiple Sclerosis (Claude Bernard Group)

miscl

Monash Immunology and Stem Cell Laboratories

Current Research



Endogenous Neural Stem Cell Mobilisation

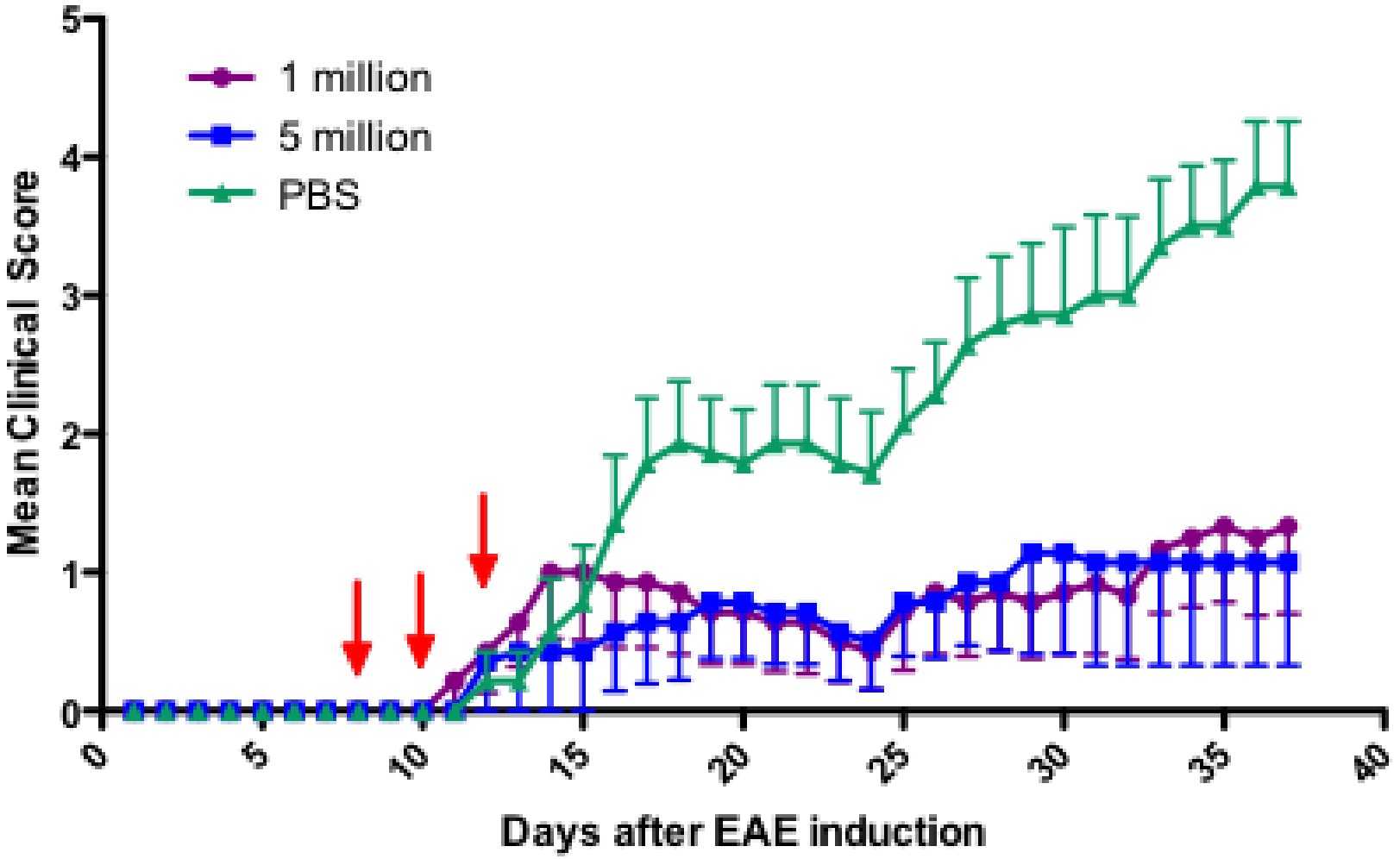
Thymic Regeneration – Reprogramming the Immune system

Stem Cell Therapy and CNS Repair

Tolerance Induction and Immune Regulation

MSC and AMNION-DERIVED STEM CELLS SUPPRESS THE MULTIPLE SCLEROSIS-LIKE DISEASE IN MICE

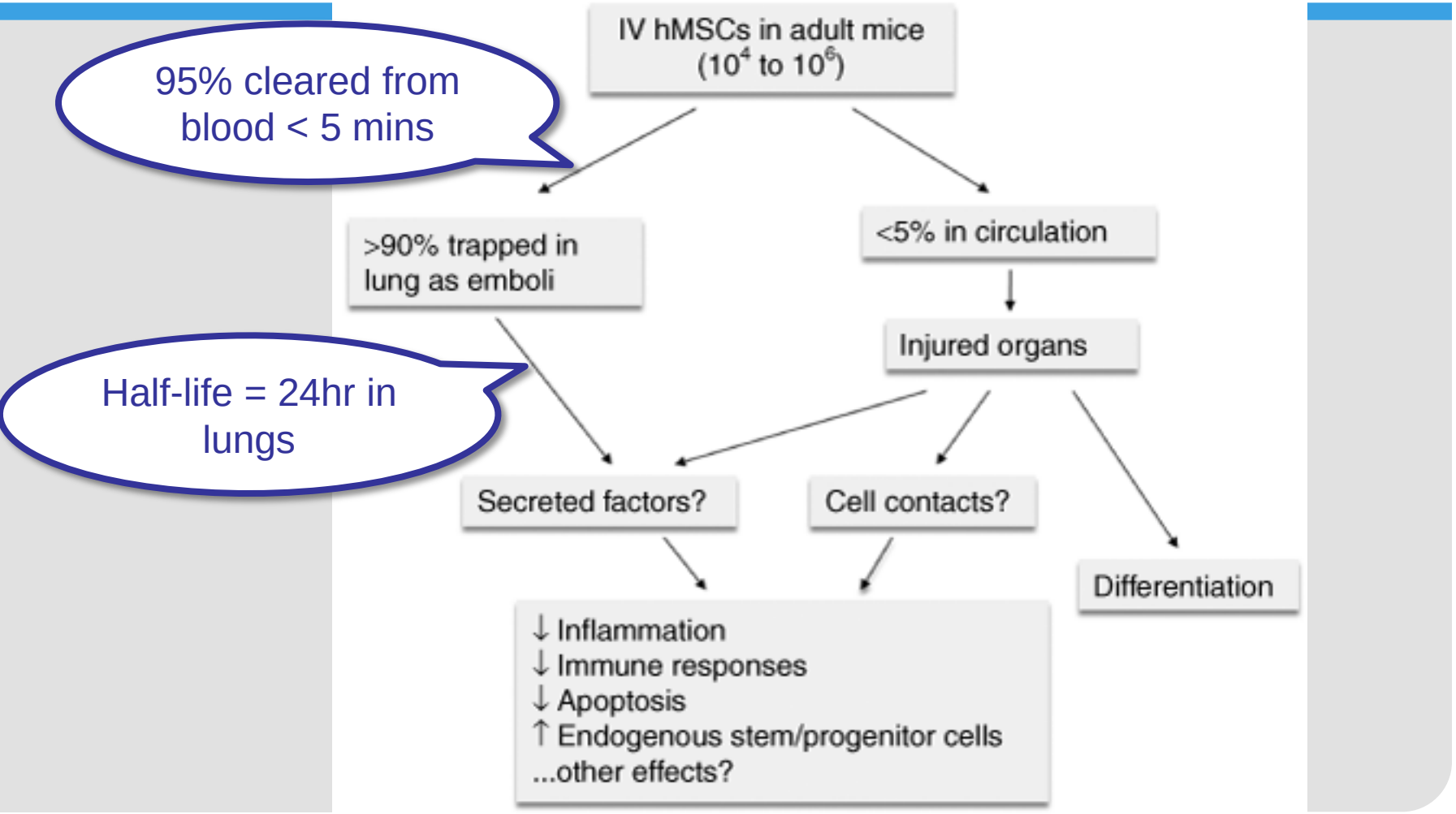
miscl



C. McDonald, G. Jenkin, C.C.A. Bernard

Lung disease optimal for MSC treatment

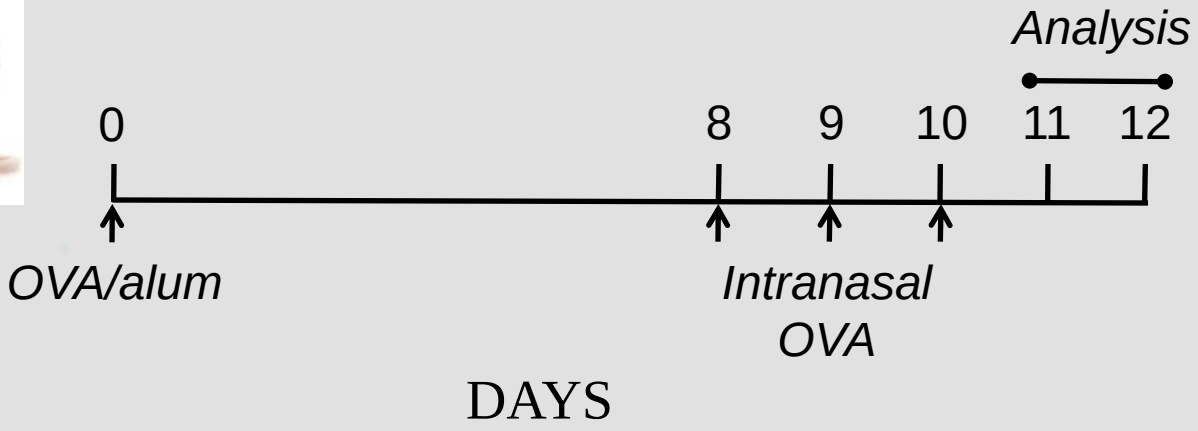
Tracy Heng



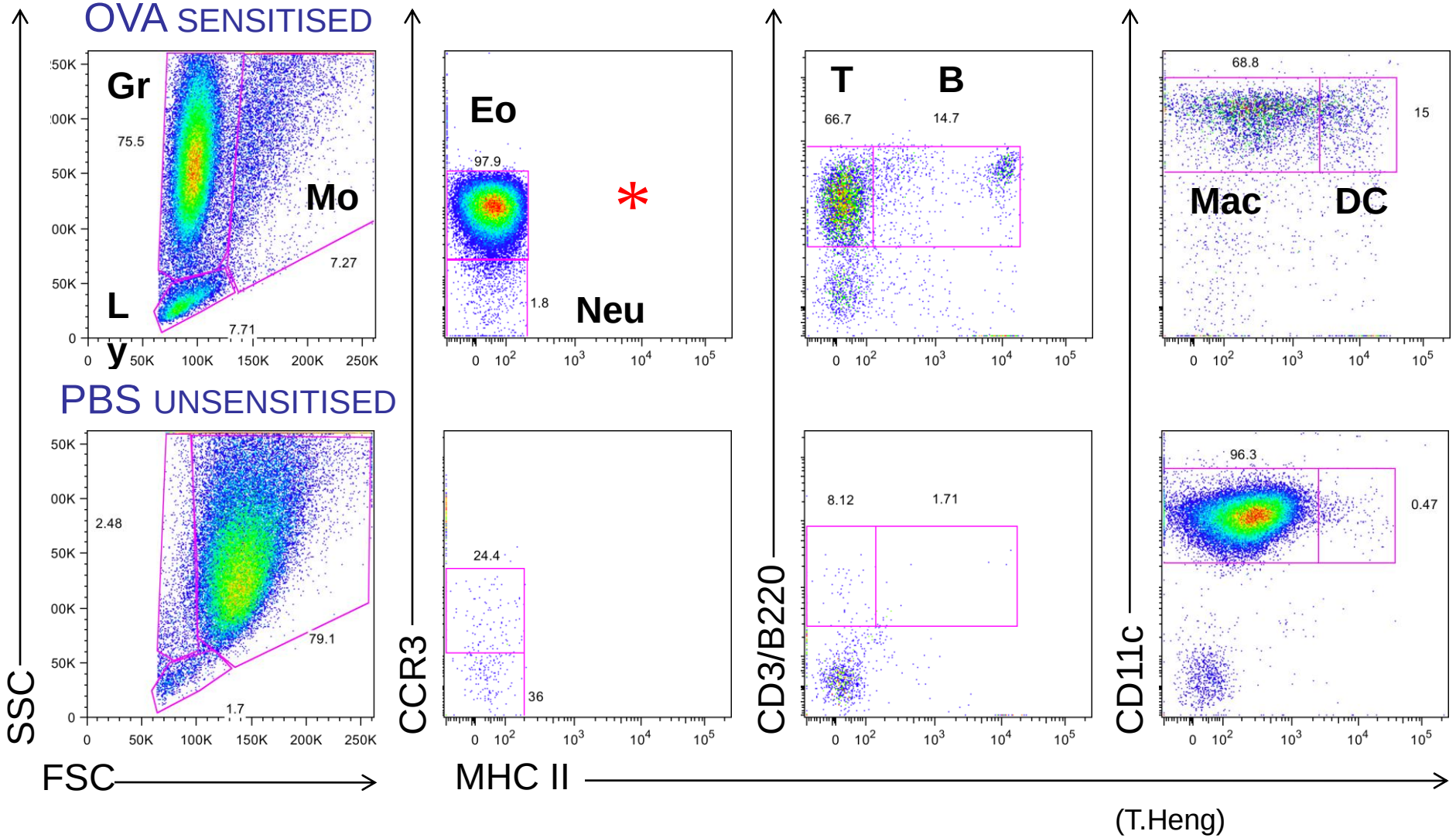
(D. Prockop 2009 *Mol Ther*)

Ovalbumin-induced asthma model

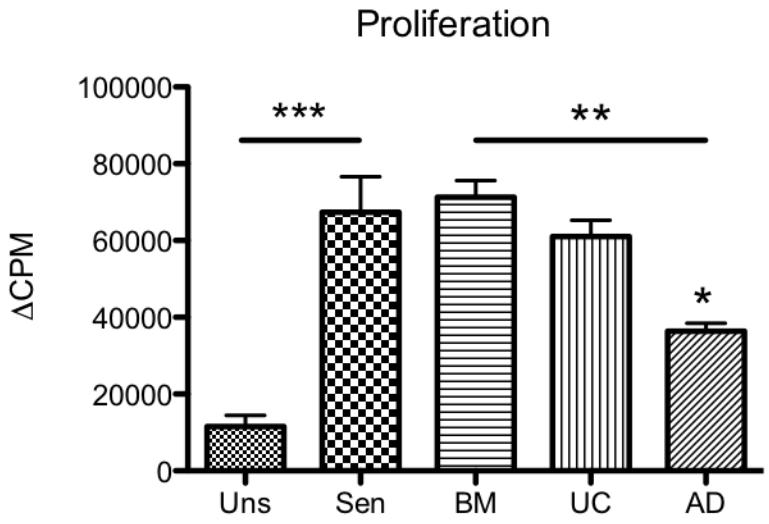
Tracy Heng

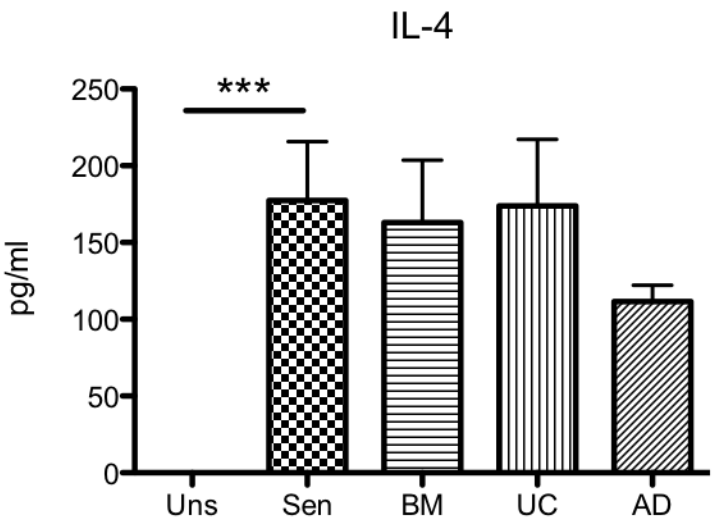


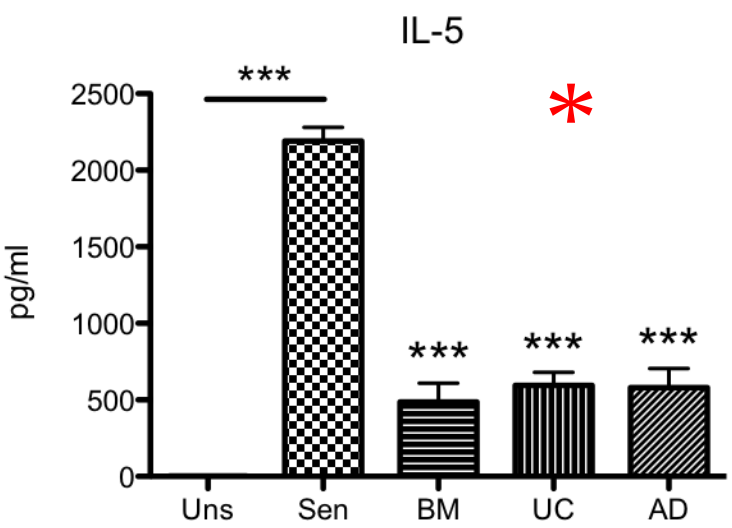
OVA-sensitised mice develop cellular infiltration of the airways

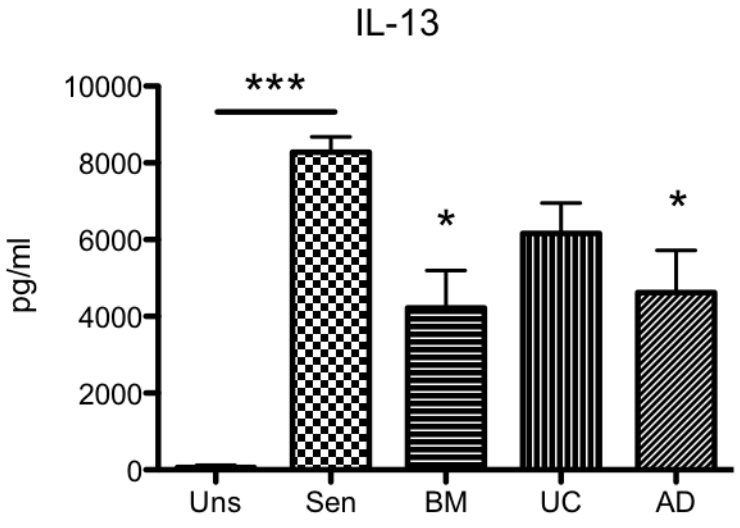


MSC treatment decreased OVA-specific T cell proliferation and cytokine production



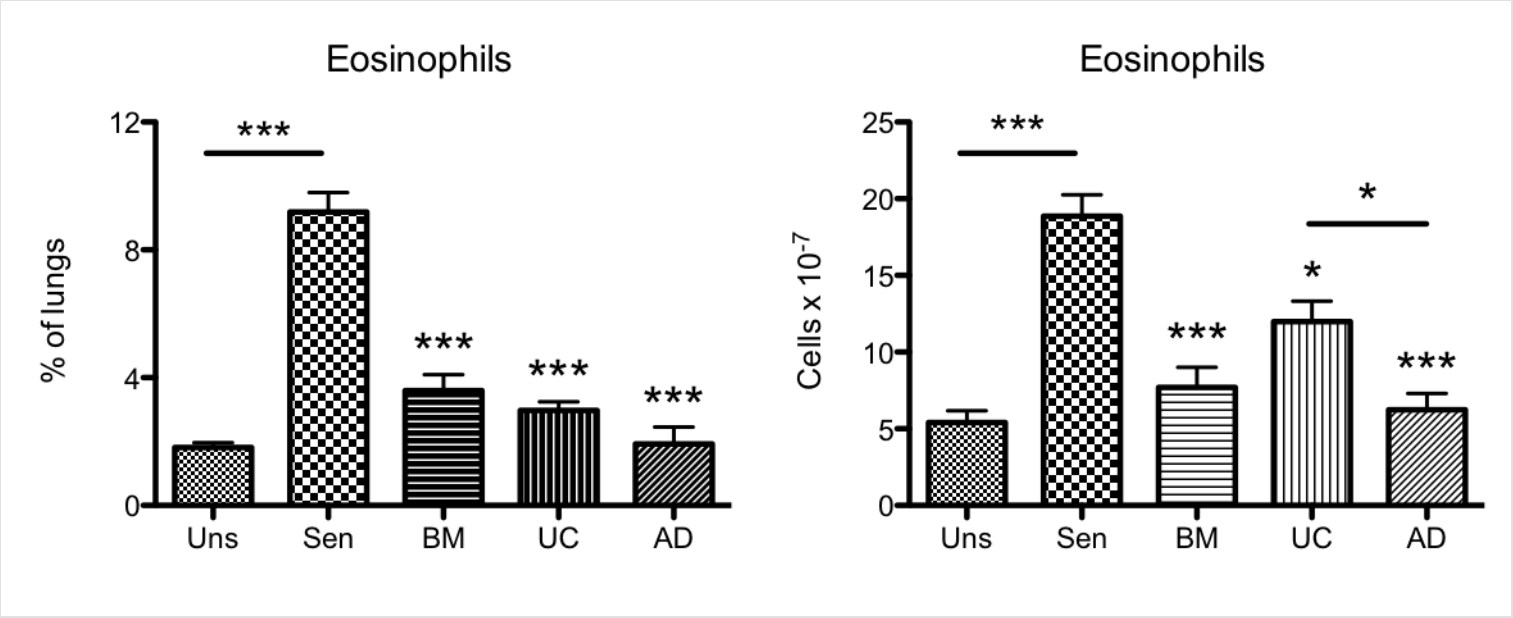






(T.Heng)

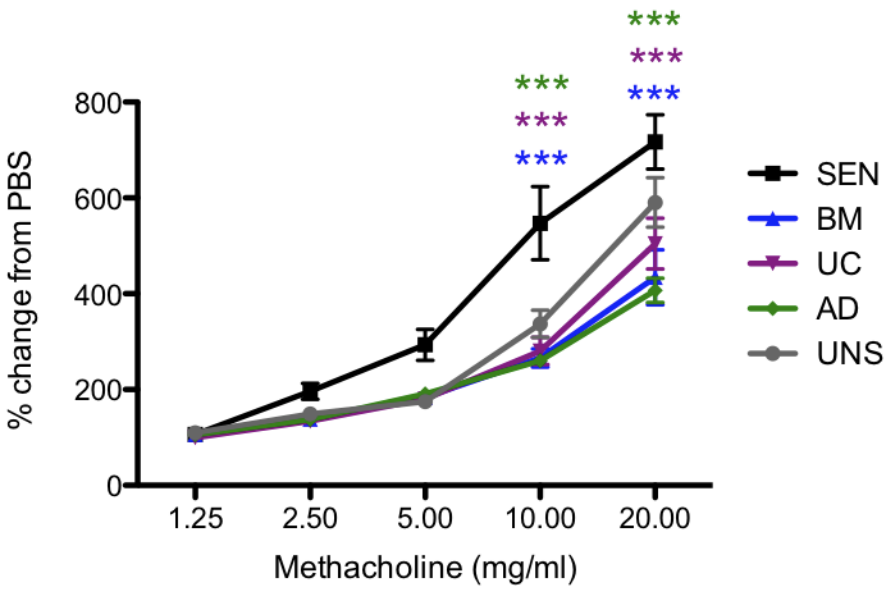
… MSC reduce eosinophils in asthma lungs



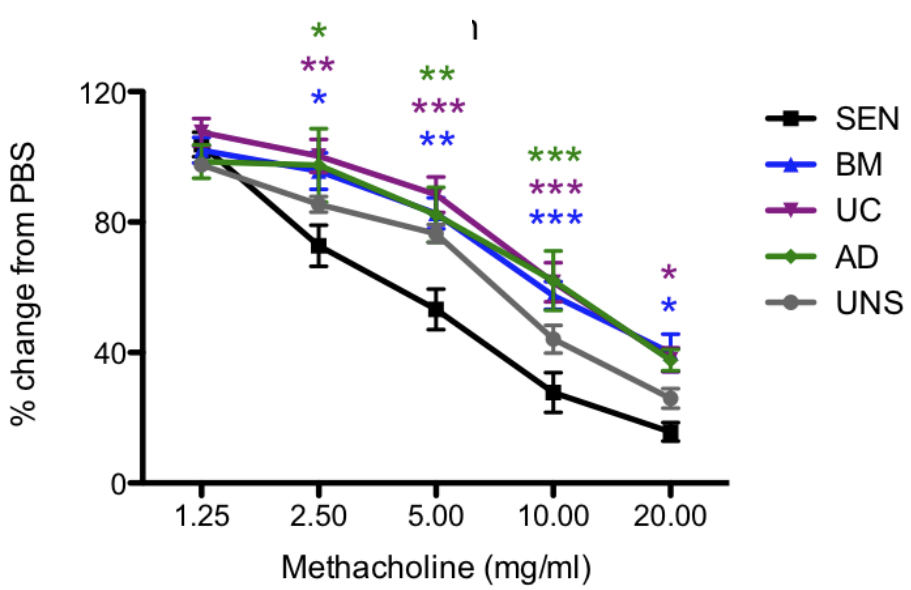
(T.Heng)

MSC treatment dramatically improved lung function

Airway Resistance (RI)



Dynamic Compliance (Cdyn)

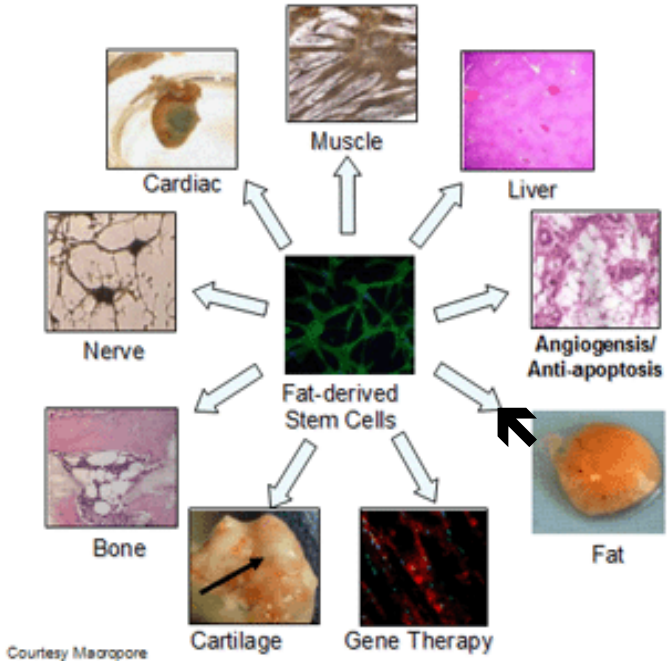


(T.Heng)

Veterinary applications

- to improve animal health; pre-clinical model for humans
- **Adipose-derived cells:**
  (A) Stromal vascular fraction (SVF)
  – MSC, Tregs, type II Macrophages
  – Pre-adipocytes, fibroblasts, endothelium
  (B) In vitro expanded MSC
  – Immunosuppressive; pro-repairing
- Horses with bowed tendons, ligament injuries, and fractures,
- Dogs with osteoarthritis
- More than 5,000 horses treated since 2003
- More than 4,500 dogs treated since 2006
- More than 350 dogs, cats, horses in Australia

(Australian Veterinary Stem Cells , Vet Stem)



Veterinary applications -

SVF

- *>70% of all animals responded*
- *No serious adverse effects*
- *Strong evidence of pain reduction and return of capacity*

Expanded MSC

- *>70% of all animals responded*
- *100% of younger dogs*

Osteoarthritis (most)

Chronic kidney failure

Cardiovascular disease (dilated cardiomyopathy)

(Australian Veterinary Stem Cells , Vet Stem)

Clinical Cases- “Sophie”

- NSAIDs and Cartrophen gave only mild relief, and “Sophie” had difficulty with steps, trotting, and getting in and out of the car.
- Now, 1 month after treatment, her owner says “I have my old dog back again!”
- “Sophie” can now jump into the car, and trots and runs with a new lease on life.
- THE FAMILY PET CAT ISN’T HAPPY!

	Pre-treatment	Day 30	Day 60	Day 90
Lameness- Walking				
Non-detectable				
Intermittent		x	x	x
Persistent	x			
Ambulatory only with assistance				
Non-ambulatory				
Lameness- Trotting				
Non-detectable				
Intermittent		x	x	x
Persistent	x			
Ambulatory only with assistance				
Non-ambulatory				
Pain on Manipulation				
No Pain		x	x	x
Mild pain				
Severe pain	x			
Range of Motion				
No limitation			x	x
Pain only at full flexion/extension		x		
Pain at less than full flexion/extension				
Pain at any attempt	x			
Functional Disability				
Normal activity				
Slightly stiff gait		x	x	x
Stiff gait				
Very stiff gait	x			

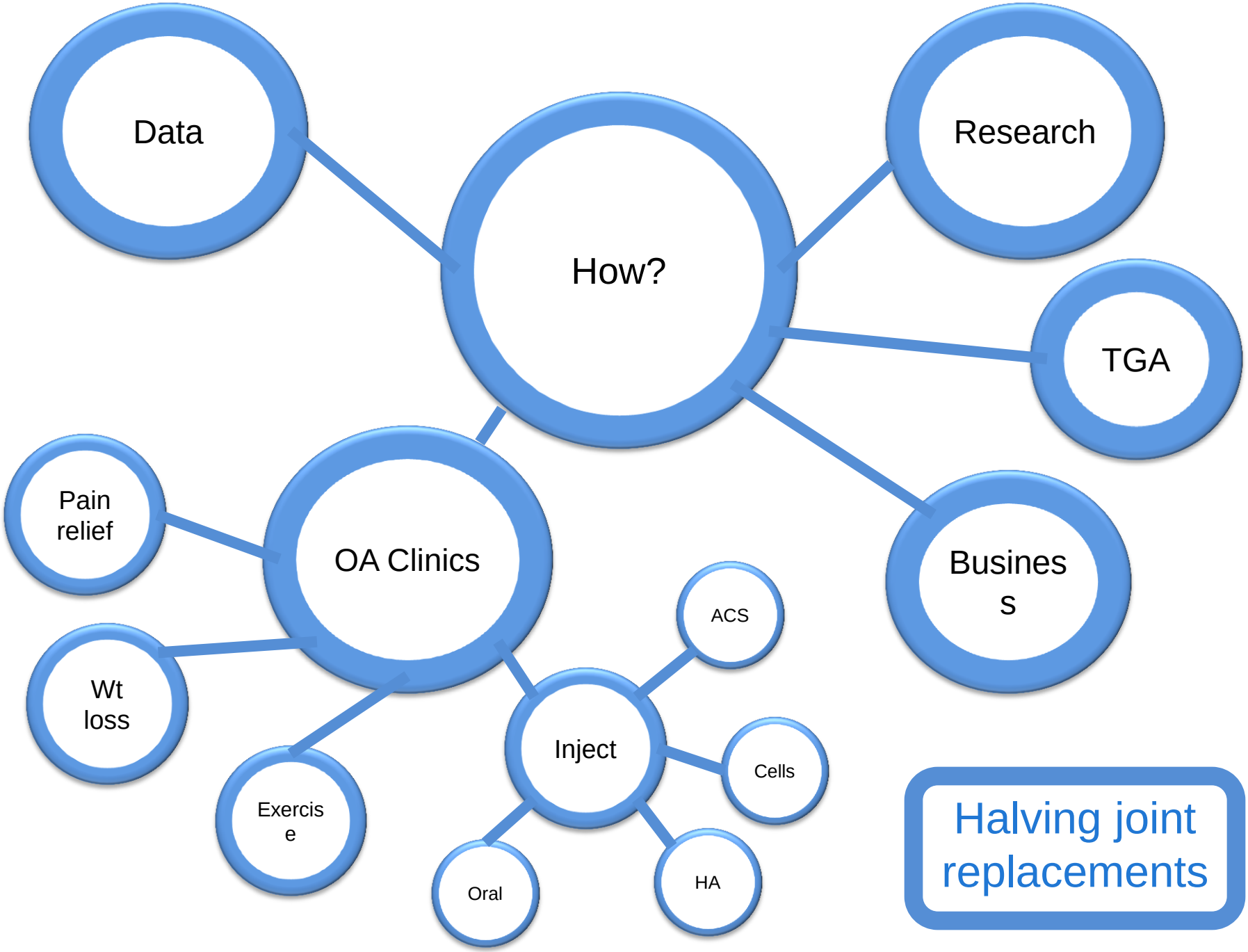
Clinical Cases- “Cooper”

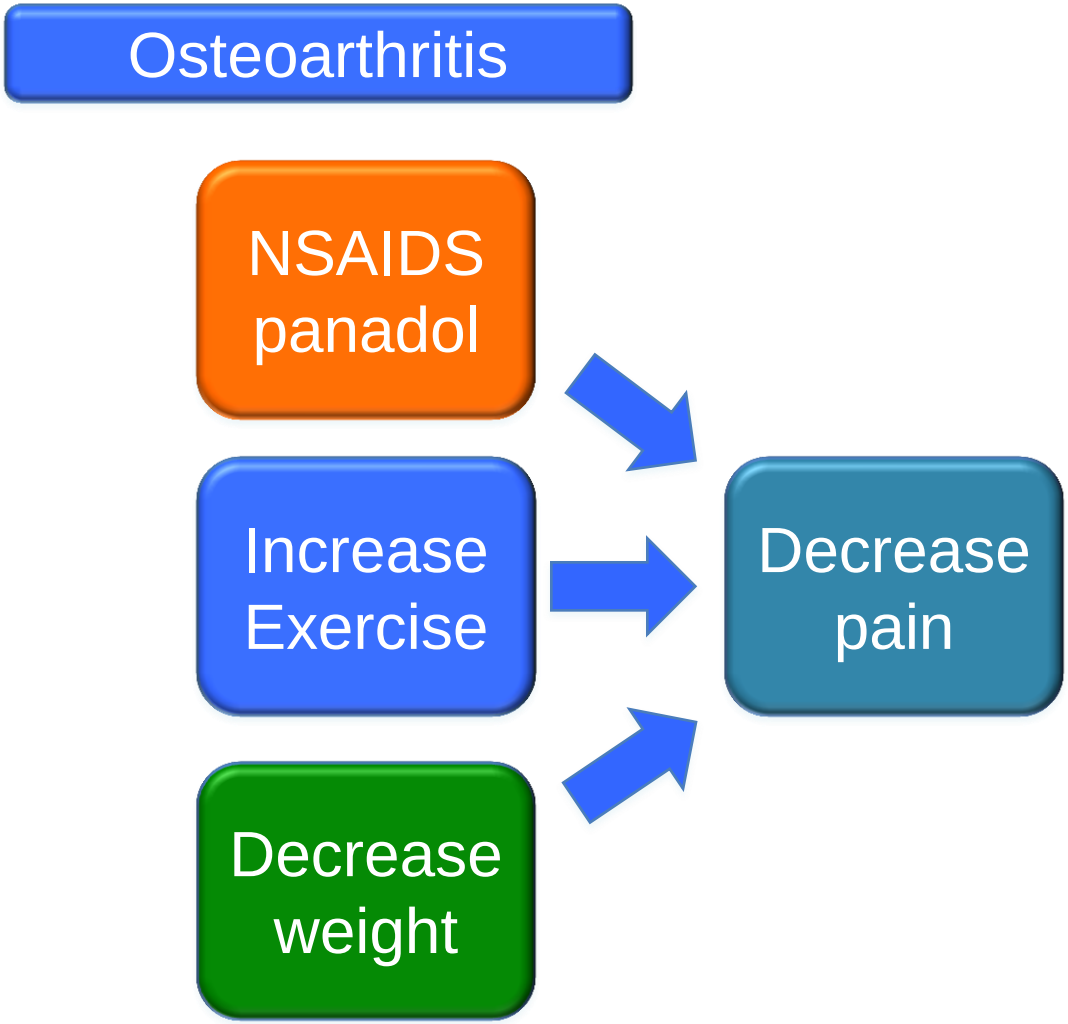
- “Cooper” was treated with allogeneic adult MSC
- injected into both hip joints
- great improvement within a month
- Owners comment “A dramatic improvement in climbing stairs and now playing with other dogs.”

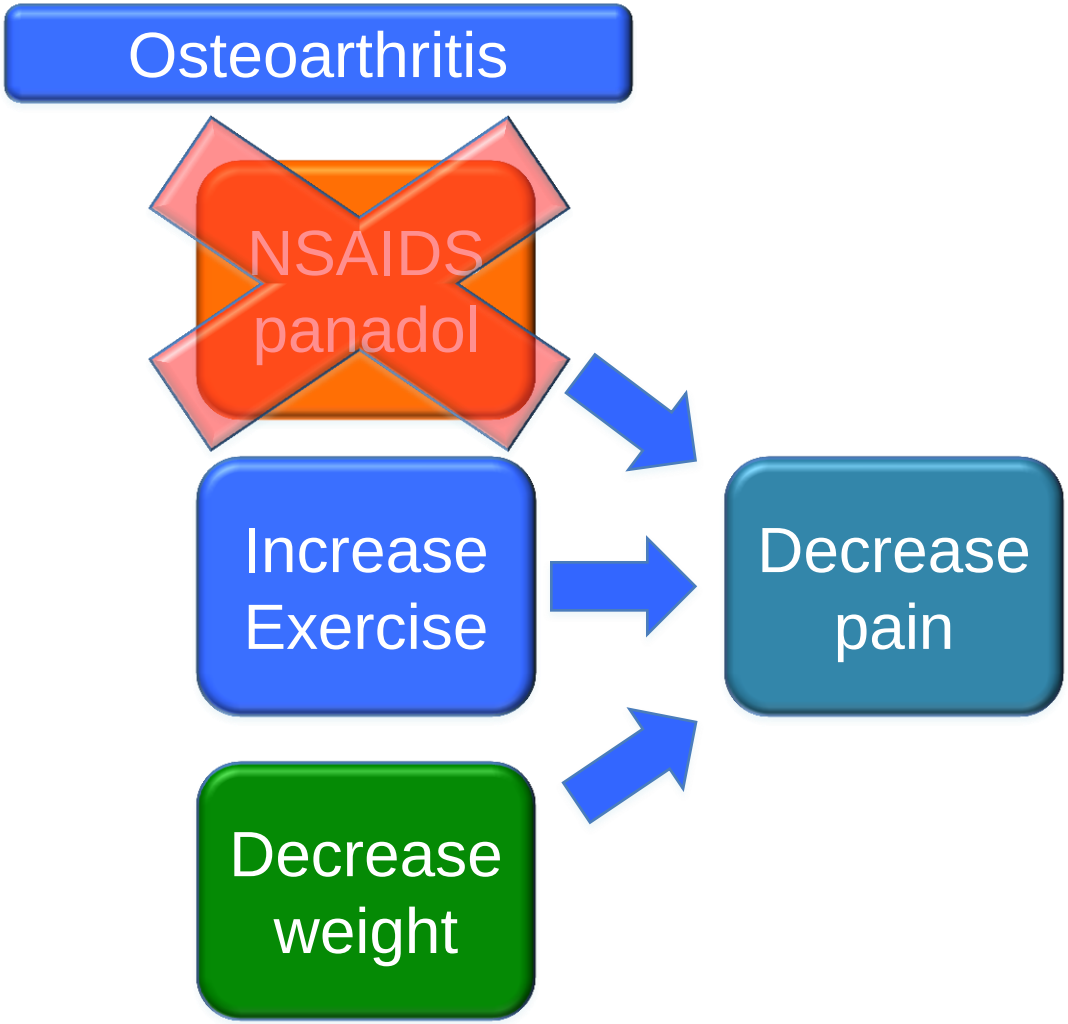
	Pre-treatment	Day 30	Day 60	Day 90
Lameness- Walking				
Non-detectable		x	x	X
Intermittent				
Persistent	x			
Ambulatory only with assistance				
Non-ambulatory				
Lameness- Trotting				
Non-detectable				
Intermittent		x	x	x
Persistent	x			
Ambulatory only with assistance				
Non-ambulatory				
Pain on Manipulation				
No Pain		x	x	x
Mild pain	x			
Severe pain				
Range of Motion				
No limitation			x	x
Pain only at full flexion/extension		x		
Pain at less than full flexion/extension	x			
Pain at any attempt				
Functional Disability				
Normal activity				
Slightly stiff gait		x	x	x
Stiff gait				
Very stiff gait	x			

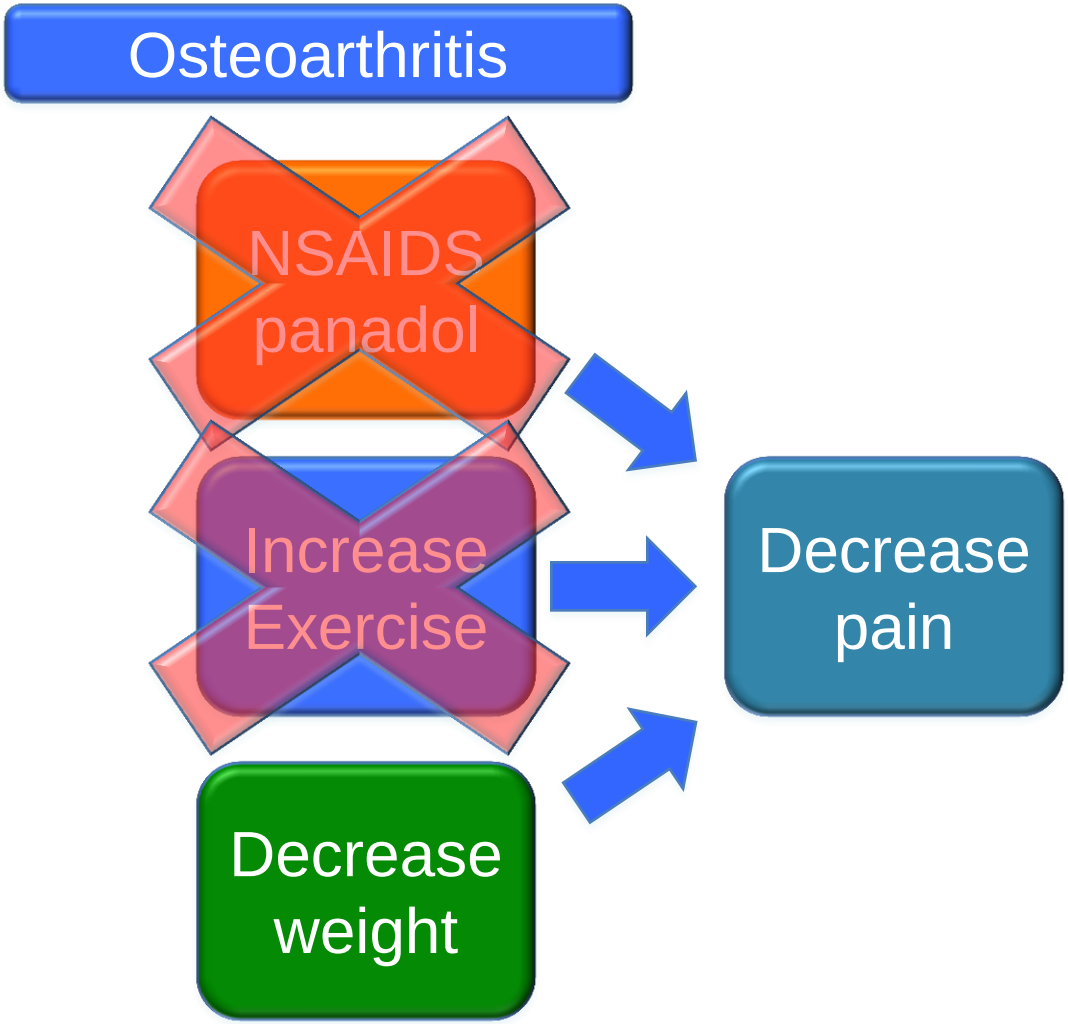
Solving Osteoarthritis

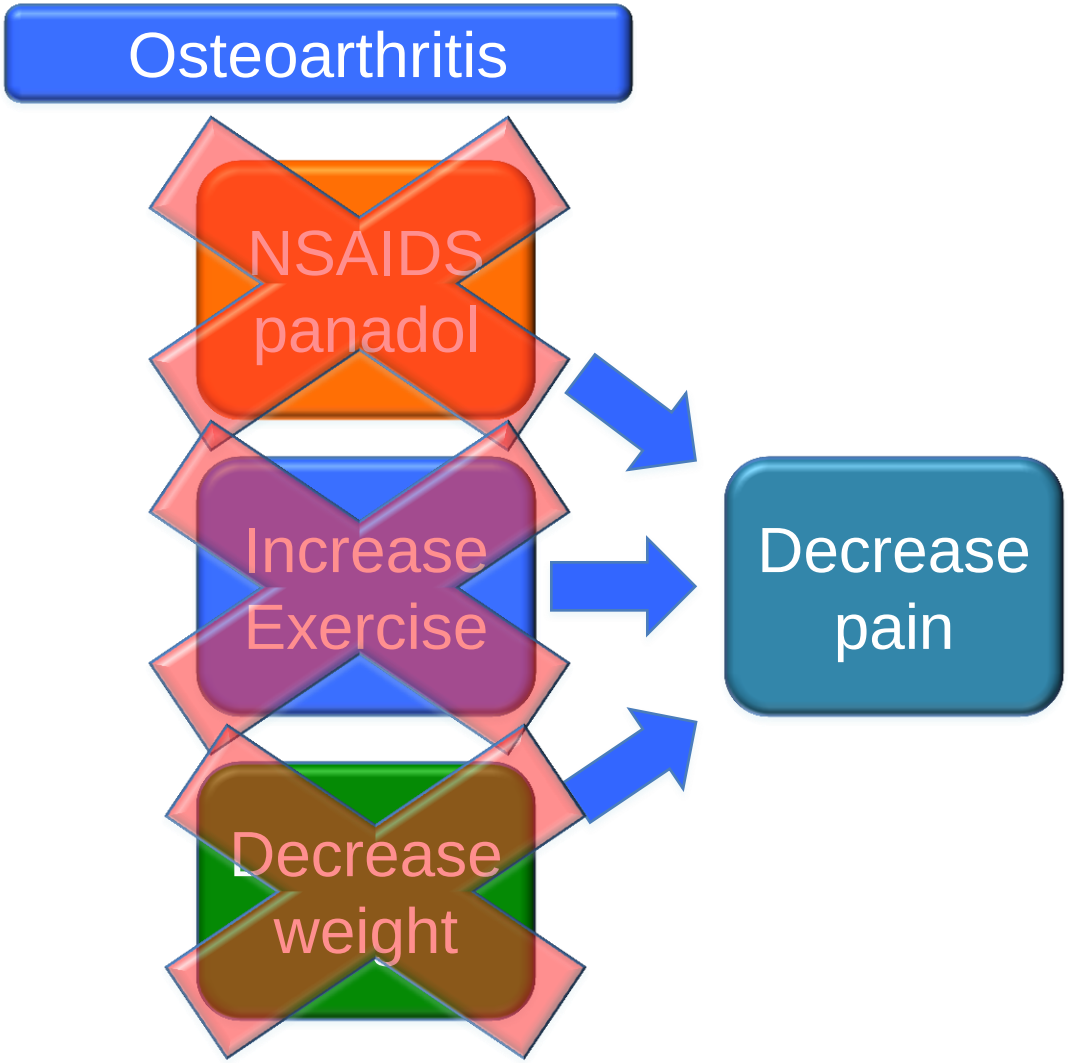
Dr Dan Bates
(BSc (Hons), B.Med)

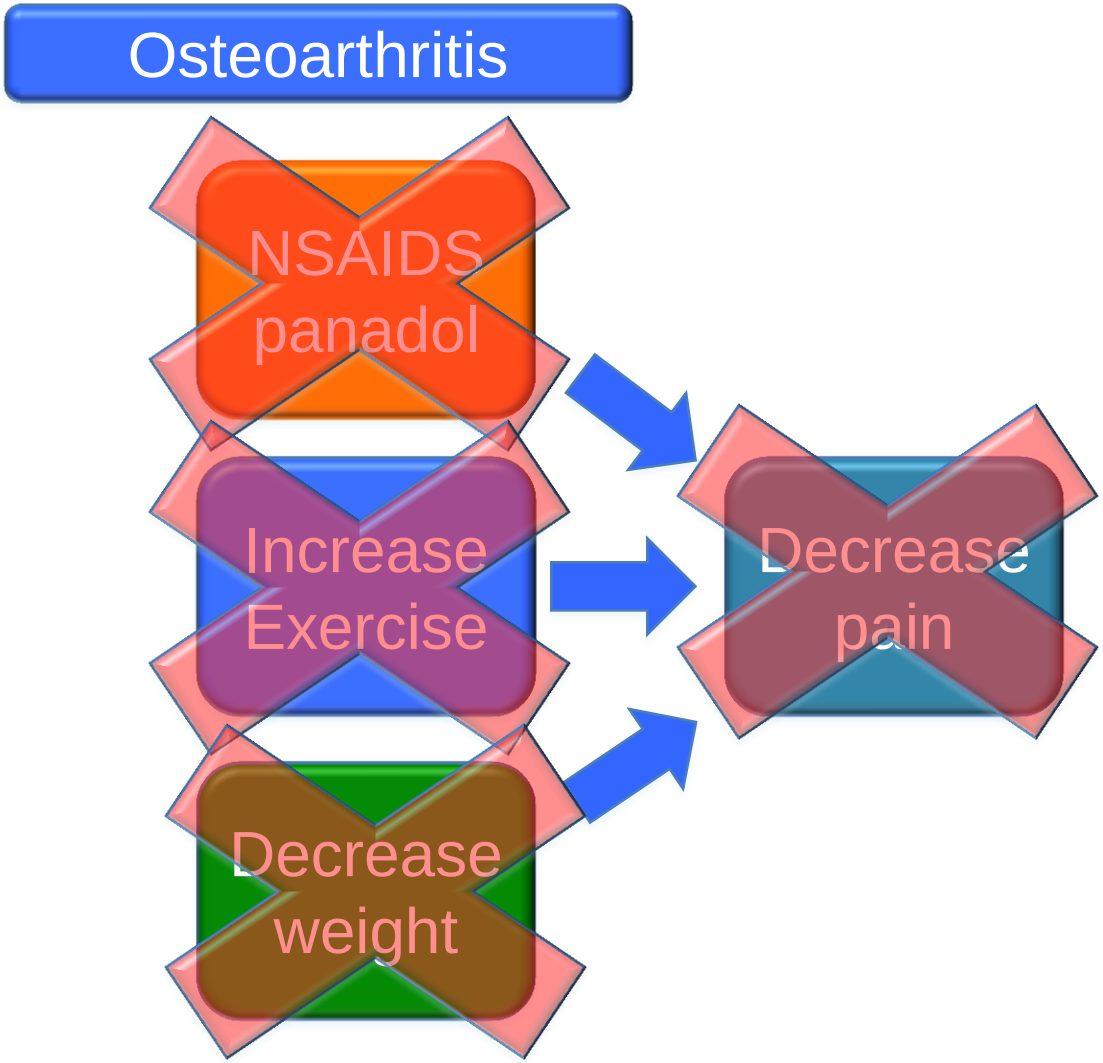

Data
How?
Research
TGA
Pain relief
OA Clinics
Business
Wt loss
ACS
Inject
Cells
Exercise
Oral
HA
Halving joint replacements

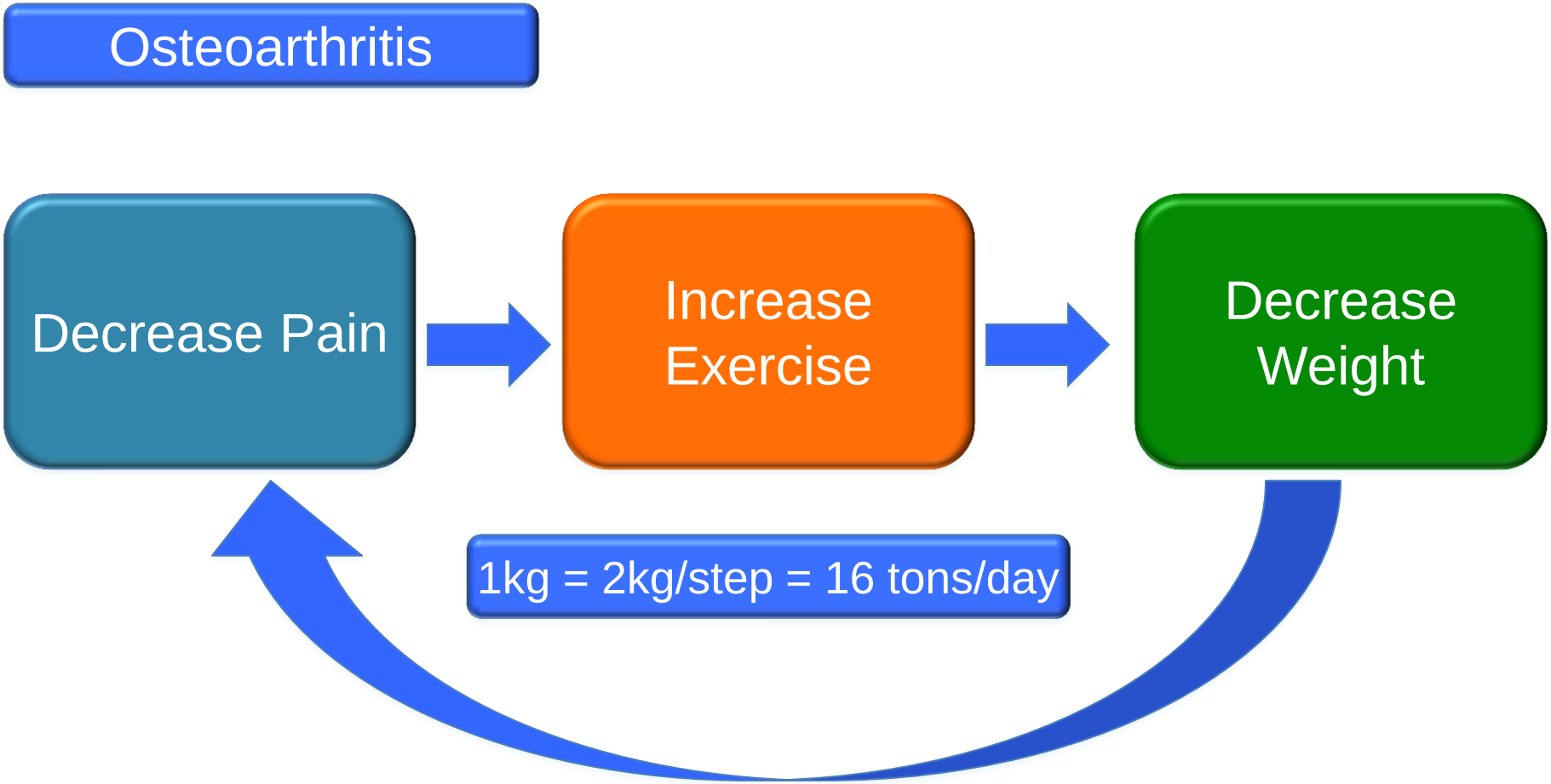

Osteoarthritis
NSAIDS
panadol
Increase
Exercise
Decrease
weight
Decrease
pain


Osteoarthritis
NSAIDS
panadol
Increase
Exercise
Decrease
weight
Decrease
pain

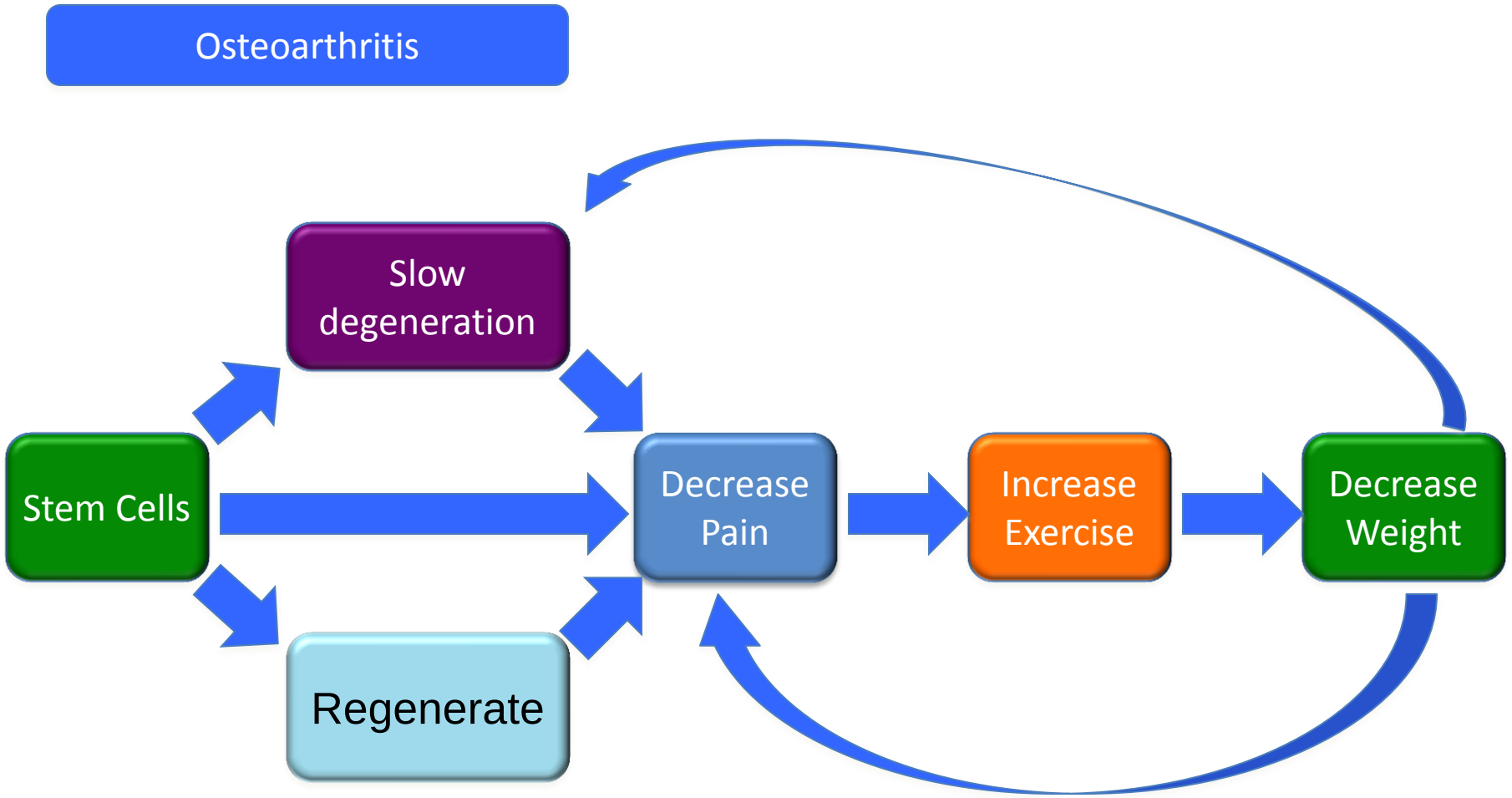

Osteoarthritis
NSAIDS
panadol
Increase
Exercise
Decrease
weight
Decrease
pain


Osteoarthritis
NSAIDS
panadol
Increase
Exercise
Decrease
weight
Decrease
pain


Osteoarthritis
NSAIDS
panadol
Increase
Exercise
Decrease
weight
Decrease
pain


Osteoarthritis
Decrease Pain
Increase Exercise
Decrease Weight
1kg = 2kg/step = 16 tons/day

Stem cells in osteoarthritis


Osteoarthritis
Slow degeneration
Stem Cells
Decrease Pain
Increase Exercise
Decrease Weight
Regenerate

Are they safe?

11687 horses and dogs
AE rate 1.28%
50+ animal studies

Gimble 2010

Vet-Stem

Multiple case series
503 published patients
Multiple diseases
Multiple injection sites

Rodrigeuz 2012

Centeno 2010

Wakitani 2011

Garcia olmo, 2009/ 2012

Mesimakl 2009

Riodan 2009

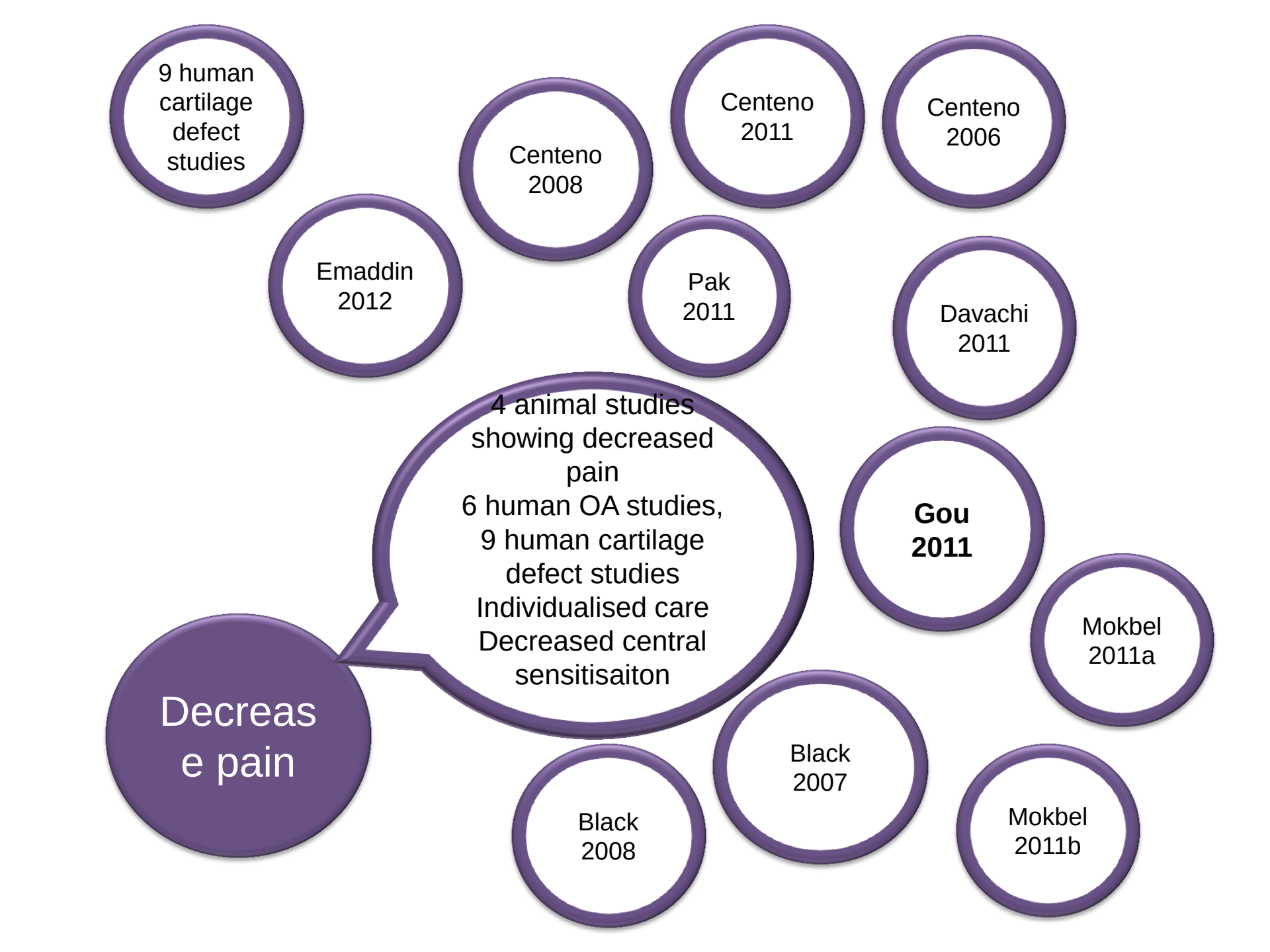
Lendekel 2004

Yoshimura 2008

Yoshimura 2007

Rigotti 2007

Yoshimura 2010


9 human cartilage defect studies
Centeno 2008
Centeno 2011
Centeno 2006
Emaddin 2012
Pak 2011
Davachi 2011
4 animal studies showing decreased pain
6 human OA studies,
9 human cartilage defect studies
Individualised care
Decreased central sensitisaiton
Gou 2011
Mokbel 2011a
Decreas e pain
Black 2007
Black 2008
Mokbel 2011b

Slowed Degeneration

Deikman 2012

Tograhi e 2012

Mokbel 2011a

8 Animal studies
Multiple mechanisms of joint damage
Slowed degeneration
No human evidence

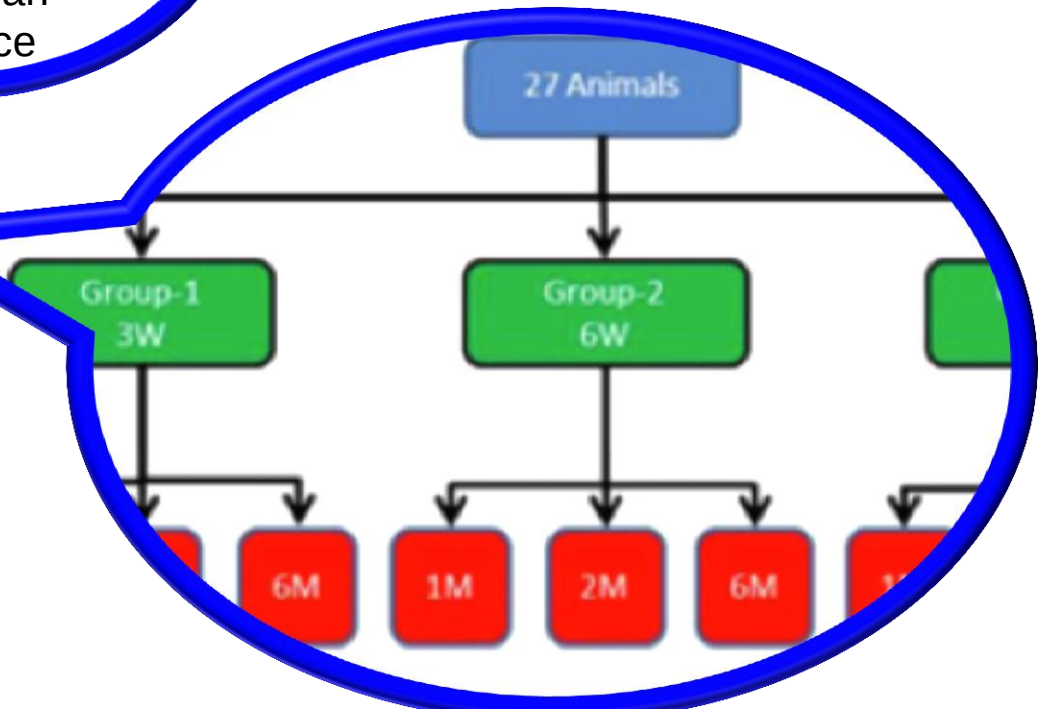
Sato 2012

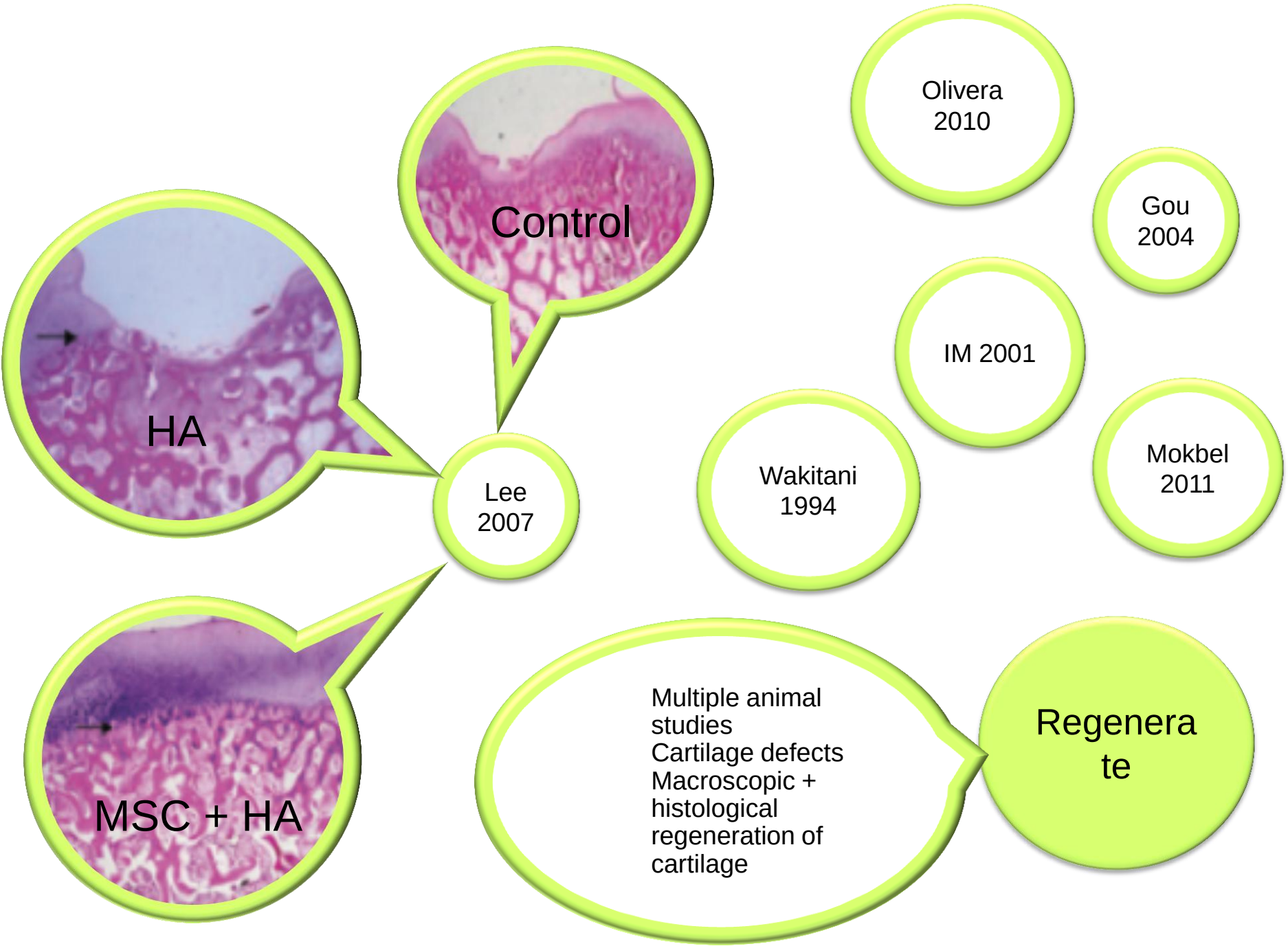
Murphy 2003

Matsumoto 2009

Mokbel 2011b

Mifume 2012




Olivera
2010
Gou
2004
Control
IM 2001
HA
Wakitani
1994
Mokbel
2011
Lee
2007
MSC + HA
Multiple animal studies
Cartilage defects
Macroscopic + histological regeneration of cartilage
Regenera
te

Centeno 2008

Amgad 2010

Nadiadnik 2010

Kasemkijw-attana 2010

Saw 2011

Wakitani 2007

Wakitani 2002

Wakitani 2004

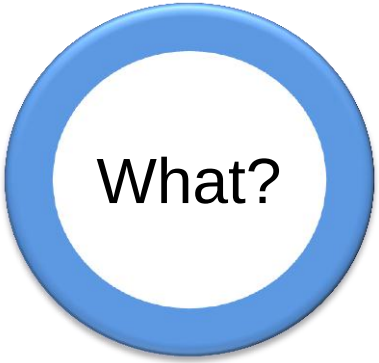
Korud a 2007

9 Human studies
Cartilage defects
286 patients
“Cartilage” regeneration

Regenera te

Human Evidence – MSC Safety

Author	Patients	Disease	Injection	Follow-up	Study	Symptom Improvement
Wakitani 2010	41	Knee Osteoarthritis	IA	11 years	Safety Study	No Cancer, No infections
Centeno 2010/2011	339	Knee, Back, Hips	IA, Paraspinal	2 years	Safety study	No Cancer, No infections
Rodrigeuz 2012	13	Rheumatoid Arthritis	IV and IA	13 months	Safety study	One episode of fever & myalgia
Guadalajada 2012	50	Perianal fistulas	Local	3 years	Safety and efficacy	No Cancer No injection



- Adipose derived stromal vascular fraction
  - 1 patient with cartilage defect
    - 4 years of pain
    - Refused surgery
    - Healthy
    - Competent
    - Fully informed and consented
  - 12 months follow up

2010

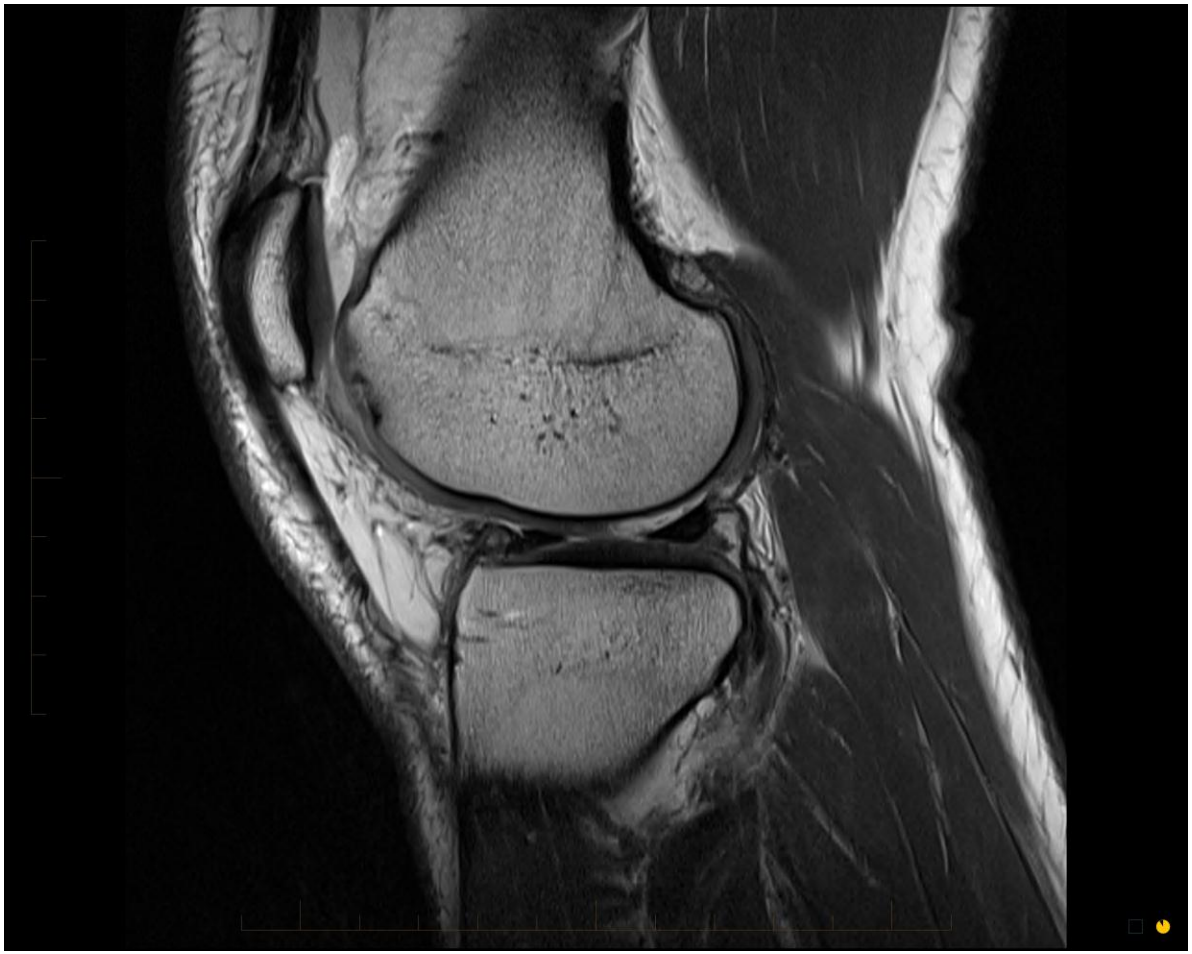
LAKESIDE
SPORTS MEDICINE CENTRE

Human Chondral Defects, OA

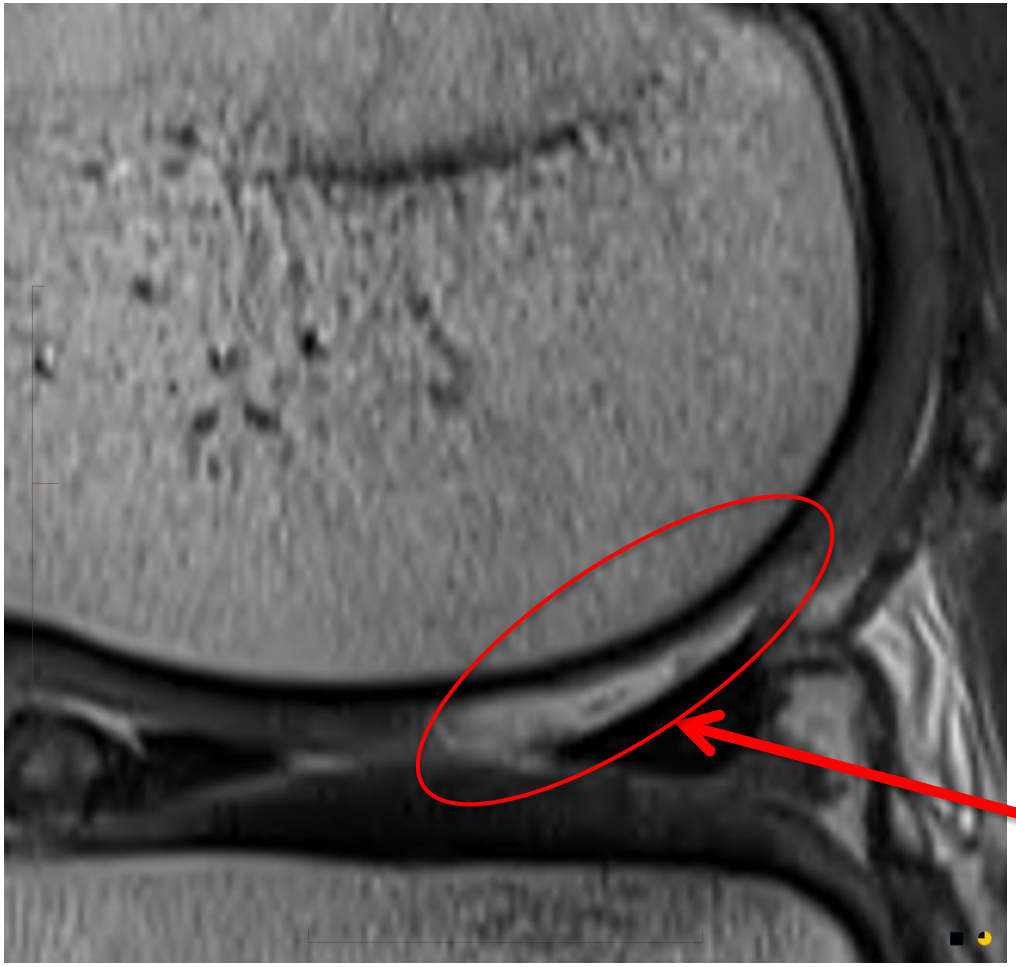
Dr DAN BATES

- 12% of the population will suffer chondral lesions
- These progress to osteoarthritis
- 15% of the Australian population suffer Osteoarthritis
- Costs 23 billion dollars per year to Australian economy

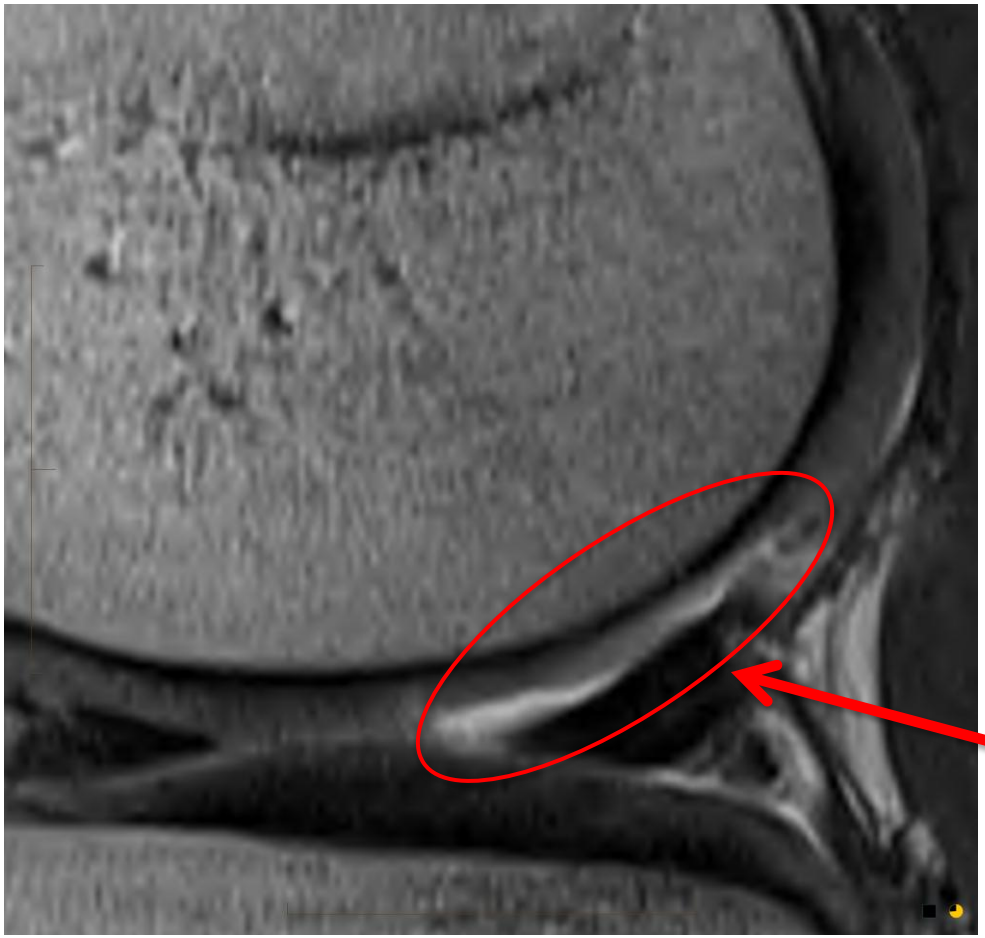
MRI – Left Knee 43 yo male



Left Lateral Femoral Condyle – Pre-treatment



12 Months post treatment

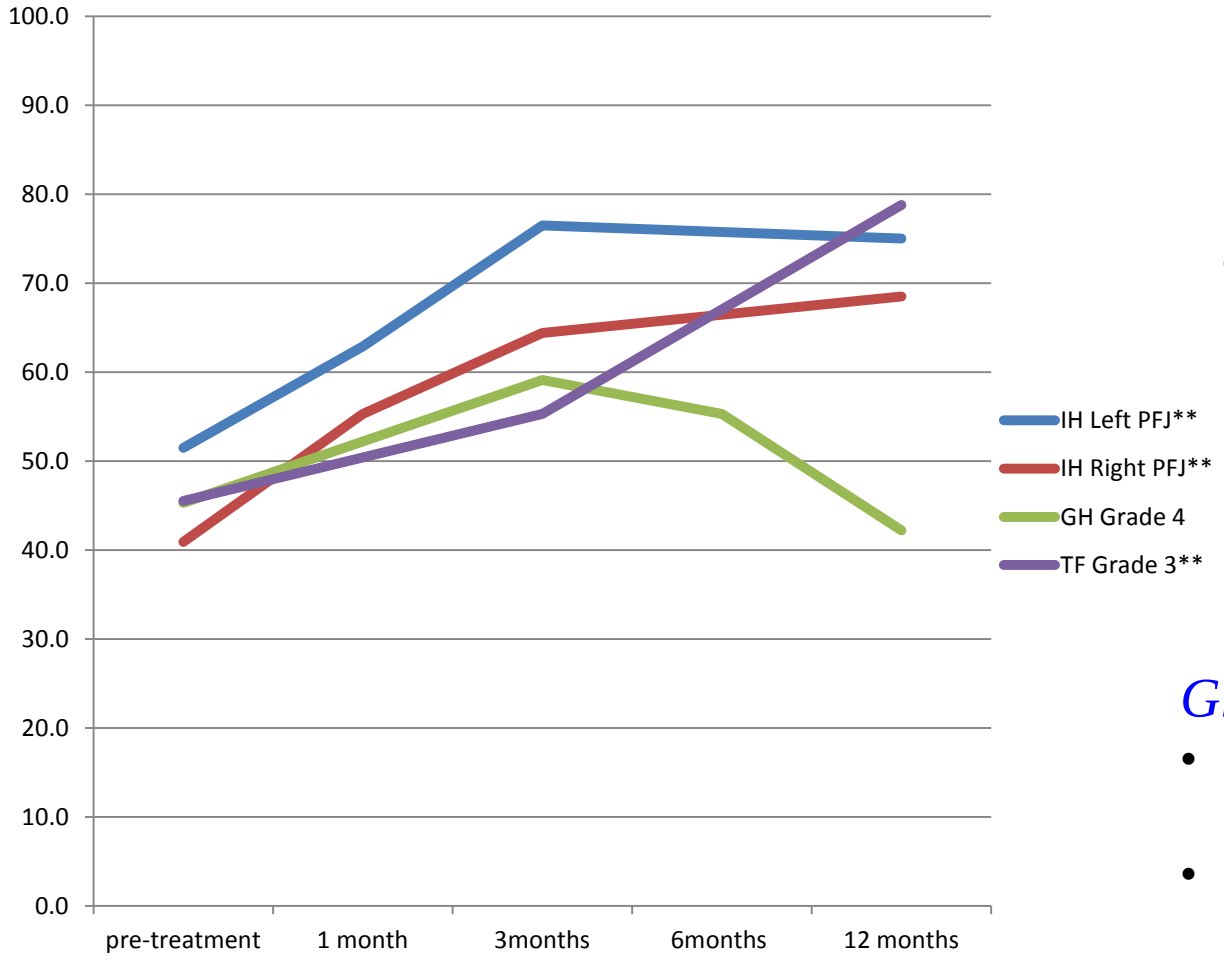


Defect Coverage at 12 months (Grey Line)

3 osteoarthritis patients

- Three patients - 4 Knees osteoarthritis
  - One Grade 4
  - One Grade 3
  - Two patellofemoral joint arthritis – same patient

Osteoarthritis Knee– WOMAC*



WOMAC
24 Questions on pain, disability, joint stiffness

Grade 4 OA

- *Need multiple injections*
- *Combination cell therapy*

Summary:

- Cell and animal data support cell medicine in osteoarthritis
- Early human studies have shown
  - Cartilage regeneration
  - Improved pain and function
- Regulators have supported the development of cell medicine

I’ll believe in stem cells when Panda’s can fly

WE CAN REBUILD HIM

We have the technology.

Acknowledgements

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Thymus regrowth and stem cells

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Neonatal stem cells

Immune Regeneration

MSC & AEC in Wound Repair

Standard Operating Procedures for isolation of AECs

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miscl monash immunology and stem cell laboratories

How do stem cells really work?

- Do they directly repair?
- Do they instruct endogenous cells to begin repair?
- Do they function by release of cytokines and growth factors?
  - *DOES it really matter to the patients?*
  - *They just want to become healthy again!*
  - *IT DOES matter to us, because we need to be able to provide best possible care NOT near enough is good enough*

How do stem cells really work?

- Will the ‘disease” environment influence the outcome
  - Inflammatory cytokines may switch off, dampen or even kill stem cells
  - In autoimmune disease – the same aggressive immune factors (cells, Abs) which triggered disease will attack stem cells of that same tissue type
- Age, general health

How do stem cells really work?

- Should we inject:
- Stem cells
  - GOOD will self renew, live a long time but
  - BAD may not actually fix the problem because they are still multipotential and not instructed to therapeutic need
- Progenitor cells
  - GOOD destined to become a defined cell type
  - BAD – won't self renew; may need multiple injections

How do stem cells really work?

- Therapeutic stem cell products
  - GOOD – should form into desired therapeutic cell
  - BAD – won't self renew

  (but if repair sufficient might be OK)

HURDLES

- **Funding – this is biggest problem**
  - **Government – who are we trying to kid?**
  - **Industry – do they own the IP?**
    - **Will the trials be successful?**
    - **Will the Govt's give rebates?**
    - **Will patients pay large sums (~$10k per treatment)**
  - **IP and "definition" world is messy**
    - **eg what is a mesenchymal stem cell versus stromal cell?**
    - **are the rules of stem cells being obeyed?**
    - **what are people really injecting?**

Must do clinical trials
The Funding dilemma

- **Normally:**
  - **A drug company develops a therapeutic product**
  - **Has Patent/ IP**
  - **Files for a Phase I – safety, dose escalation trial**
  - **Leads to Phase II Open label or better a**
  - **Randomised, placebo controlled, double blind efficacy trial (neither patient nor Doc know what is being injected)**
  - **Leads to "Licensing" Phase III trial (many 100's patients)**

Must do clinical trials
The Funding dilemma

- **Costs? $500m - $1b!**
- **Time 10 -15 years**
- **It is the ideal but this is an insurmountable hurdle for patients *and in reality patients may suffer because therapies won't be developed!***
- **People won't wait – but TRIALS are the key – otherwise how do we know the medicine works?**
- **Without trials and clinical proof we are just in the world of snake oil**
- **Can there be a compromise?**
- **A new practical solution to developing therapies?**

Developing new stem cell treatments: The Funding dilemma:

Take mesenchymal stem cells as an example:

Treatment of musculoskeletal /osteoarthritis

>11,000 large animals; pre-clinical

~1000 humans in "clinical treatment" studies, some random controlled trials (RCT)

- **Company X has some form of IP - usually on the source of the cells or method of "manufacture" – composition of matter Patent**
- **begins an Open label trial – case series ~15-30 patients**
- **Establishes proof of concept (don't do a trial you don't have a very good idea of the outcome!)**
- **Files for new IND (Investigative New Drug)**

Developing new stem cell treatments: The Funding dilemma:

- **Enrols patients (usually 50-100) in a randomised double-blind trial**
  - **What is the control?? Must be current best medical practice, standard of care; placebo probably saline**
- **When trial fully enrolled it is closed off till last patient through**
  - **Ethics 3-6 months**
  - **Usually at least 12 months of treatment analysis**
  - **Trial duration ~ 18 months to 2 years**
  - **If successful, leads to Phase III, 100- 300+ patients**
- **No further enrolments; patients have to wait…**

The Funding dilemma: A practical solution?

- **In Australia such treatments can be conducted under the TGA "Biological Exemption"**
  - **Basically states " Clinician takes full responsibility for what the patient receives, for one clinical treatment (can be multiple procedures but only for one treatment**
- **No need for Phase I, II, III to get a TGA registered product**
- **For "minimally manipulated procedures (cells not basically altered, no need for GMP**
- **For enzymically released cells and in vitro expanded, GMP conditions are also not mandatory but we have advised the TGA they should be!**

Stem cell therapies: A practical solution?

- *AUTOLOGOUS ! Safety first; no immune rejection*
- *ALLOGENEIC – may be desirable in the elderly, genetic disorders, evidence of disease susceptibility; immune rejection always an issue*
- *CODE OF ETHICS*
  - » *We have formed an entity "Australian Autologous Cell Therapies Group"*
  - » *Academic, clinical and commercial "clinical groups"*
  - » *Developing our own code of ethics to make certain there is maximal patient safety; clinical rigour, evidence based, appropriate thorough patient follow-up; on-line data management (we are working with "Clinical Intelligence Pty Ltd; Melb)*
  - » *peer group evaluation of data; international presentations and publications*
- *Everyone wins?!?!?*