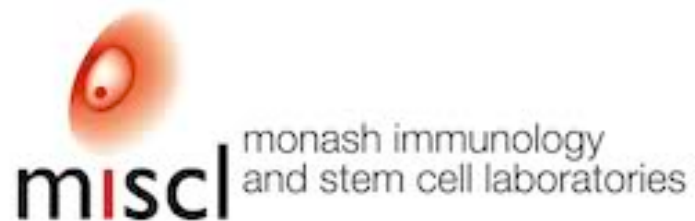
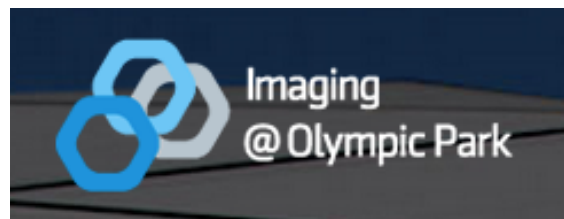


Biological Therapies for Osteoarthritis: Victorian Experience

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



Acknowledgements

- Monash Immunology and Stem Cell Laboratories
- ProStem Cell Hong Kong
- Australia Catholic University
- Victoria House Medical Imaging
- Imaging at Olympic Park
- Lakeside Sports Medicine Centre
- Clinical Intelligence

Financial Declaration

- Partner at Lakeside Sports Medicine Centre
- Partner in Cell Medicine Australia
- Will in the future hold shares in Magellan Stem Cells
- I have not been paid for this presentation

Osteoarthritis

NSAIDS
Panadol

Increase
exercise

Decrease
weight

Decrease
pain

2008

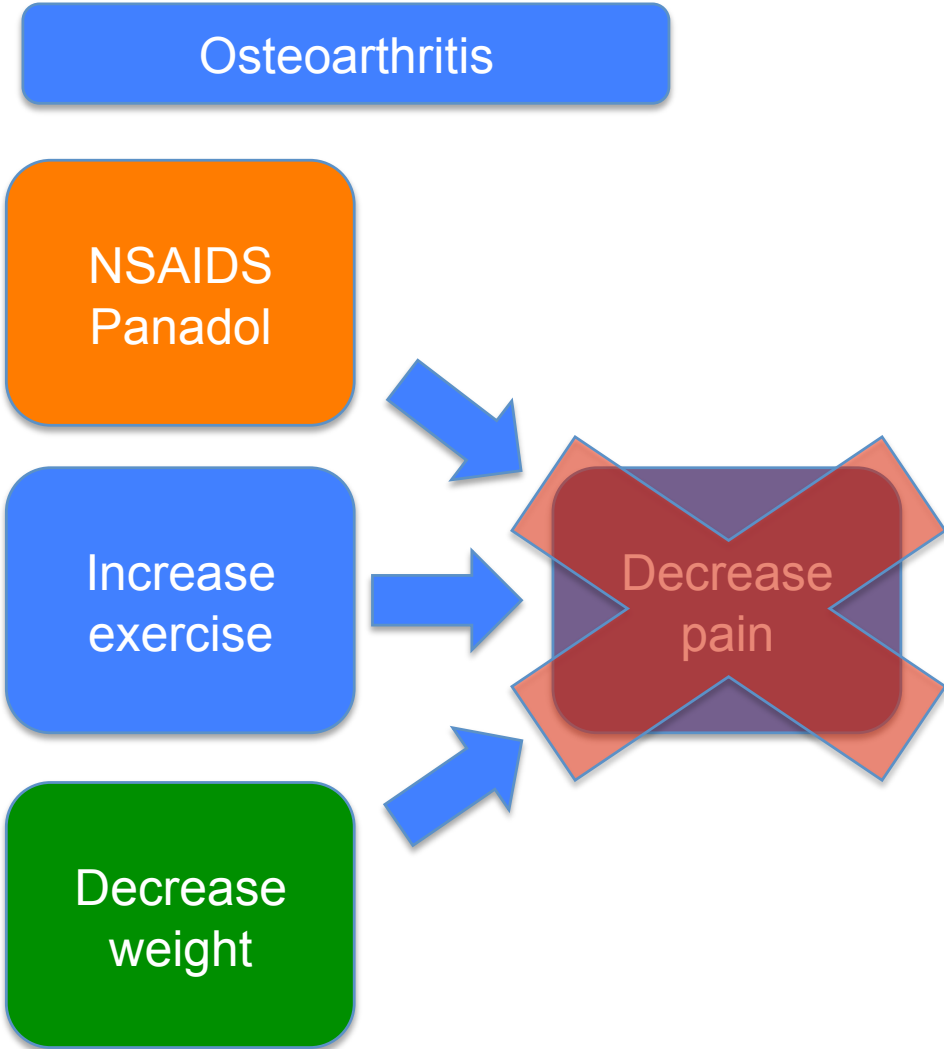
Osteoarthritis

NSAIDS
Panadol

Increase
exercise

Decrease
weight

Decrease
pain



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graph LR; A[NSAIDS Panadol] --> D[Decrease pain]; B[Increase exercise] --> D; C[Decrease weight] --> D;
```

Osteoarthritis

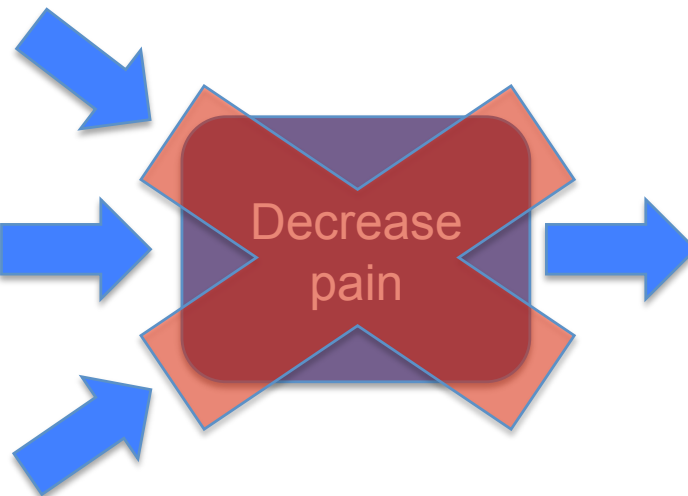
NSAIDS
Panadol

Increase
exercise

Decrease
weight

Decrease
pain

Arthroscope



Osteoarthritis

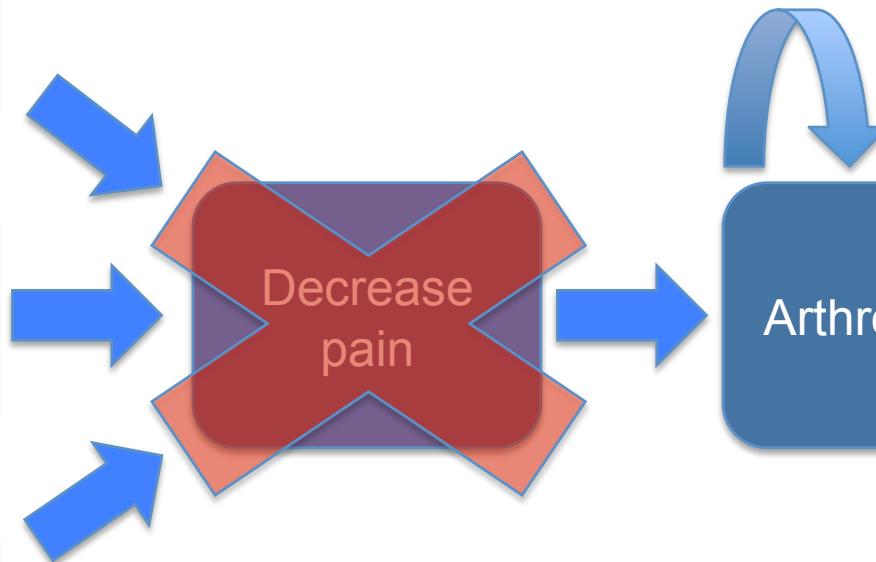
NSAIDS
Panadol

Increase
exercise

Decrease
weight

Decrease
pain

Arthroscope



Osteoarthritis

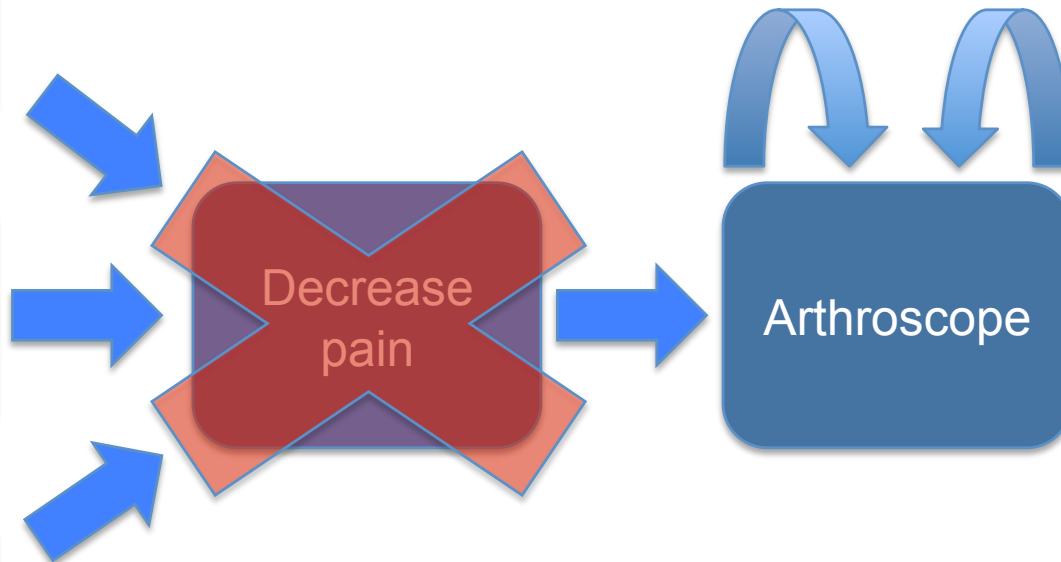
NSAIDS
Panadol

Increase
exercise

Decrease
weight

Decrease
pain

Arthroscope



Osteoarthritis

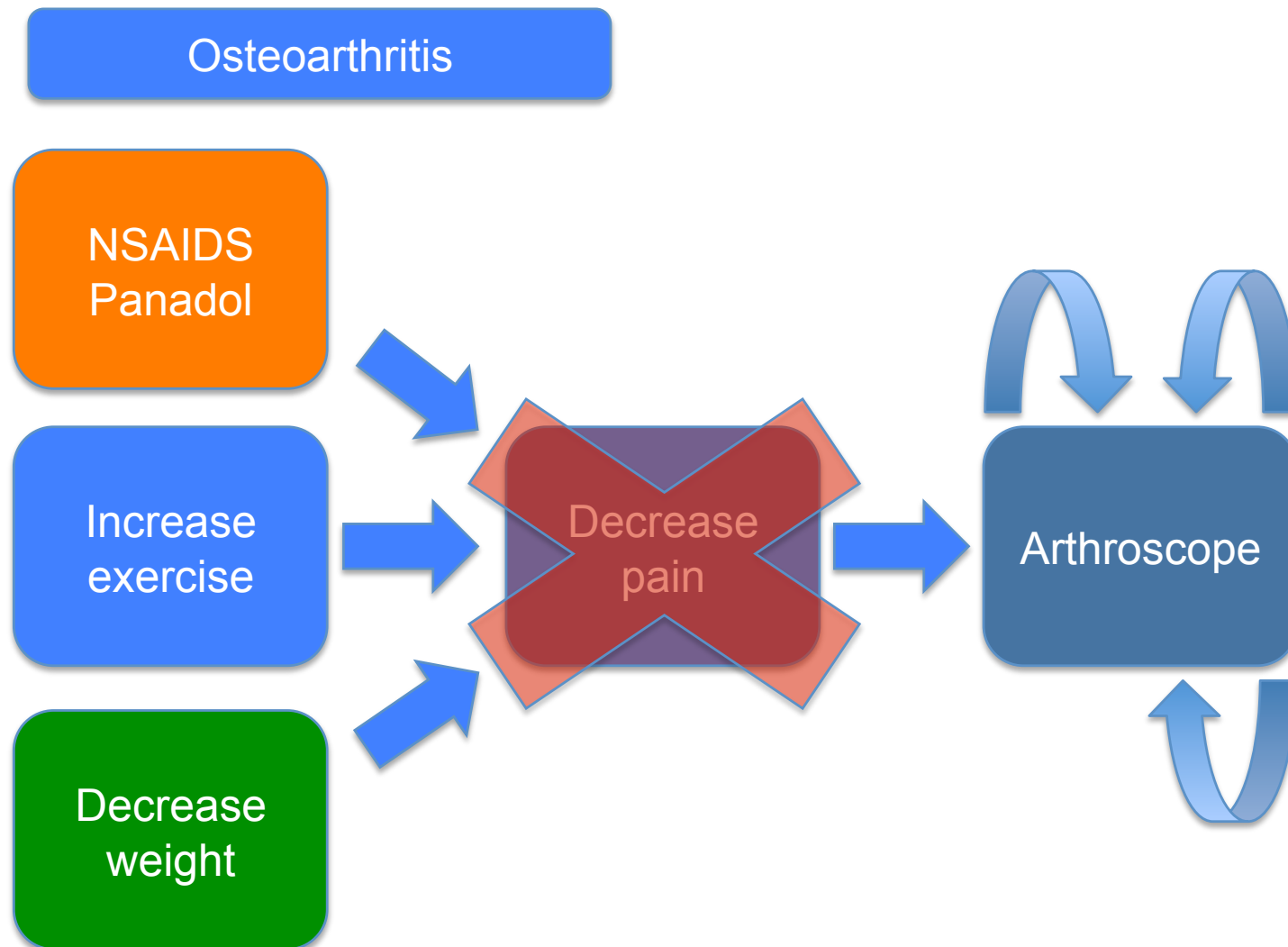
NSAIDS
Panadol

Increase
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Decrease
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Decrease
pain

Arthroscope



Osteoarthritis

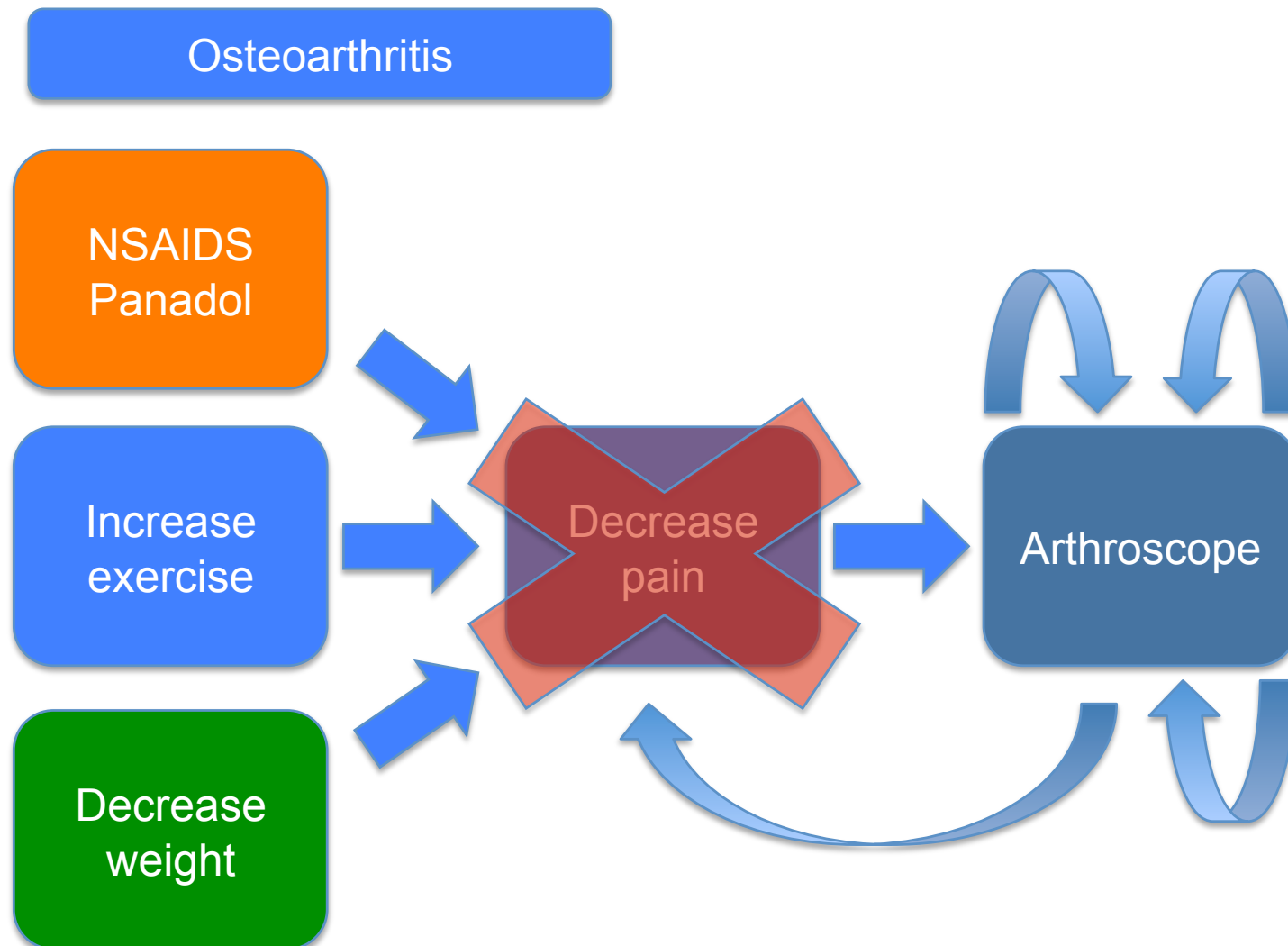
NSAIDS
Panadol

Increase
exercise

Decrease
weight

Decrease
pain

Arthroscope



Osteoarthritis

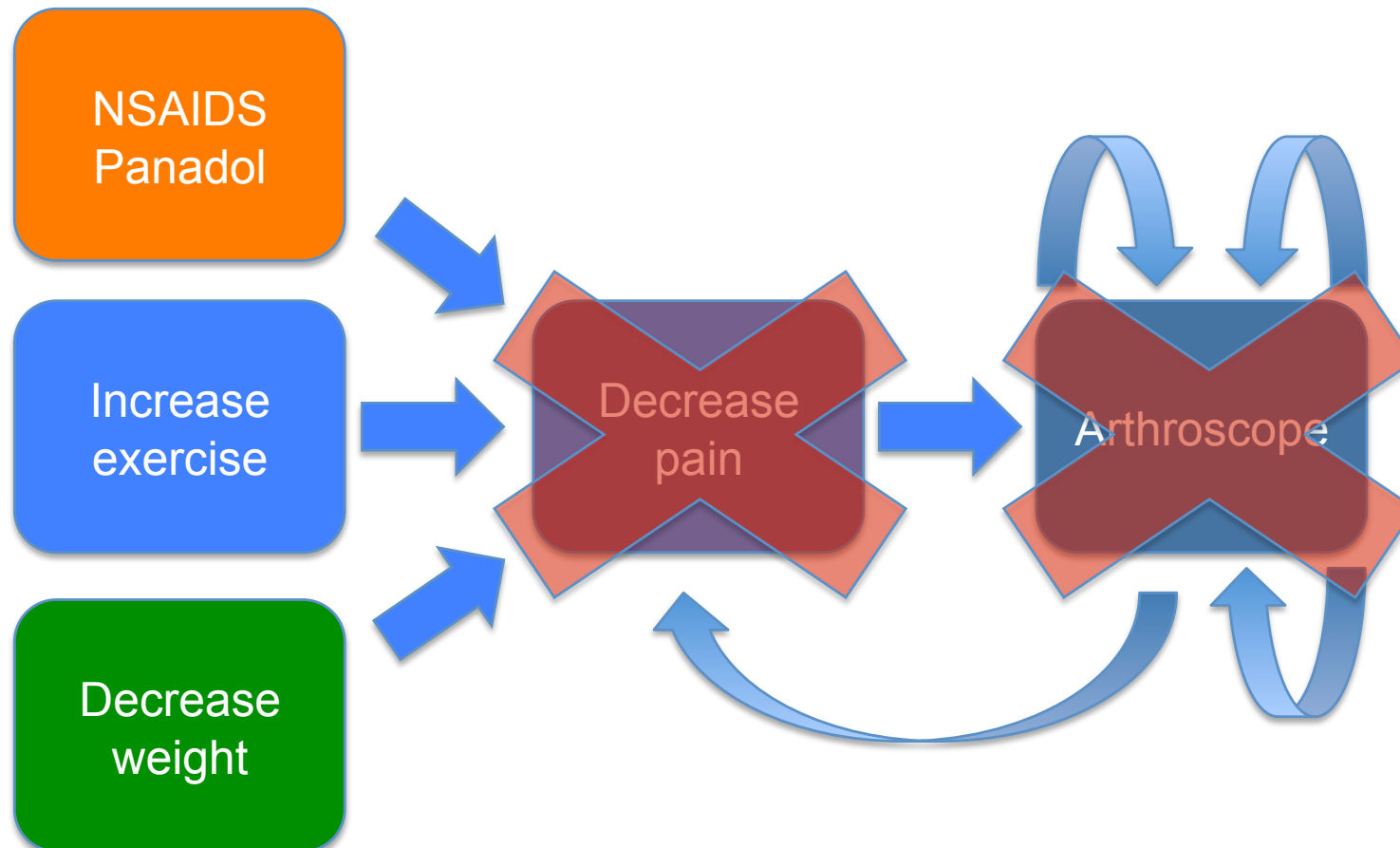
NSAIDS
Panadol

Increase
exercise

Decrease
weight

Decrease
pain

Arthroscopy



Osteoarthritis

NSAIDS
Panadol

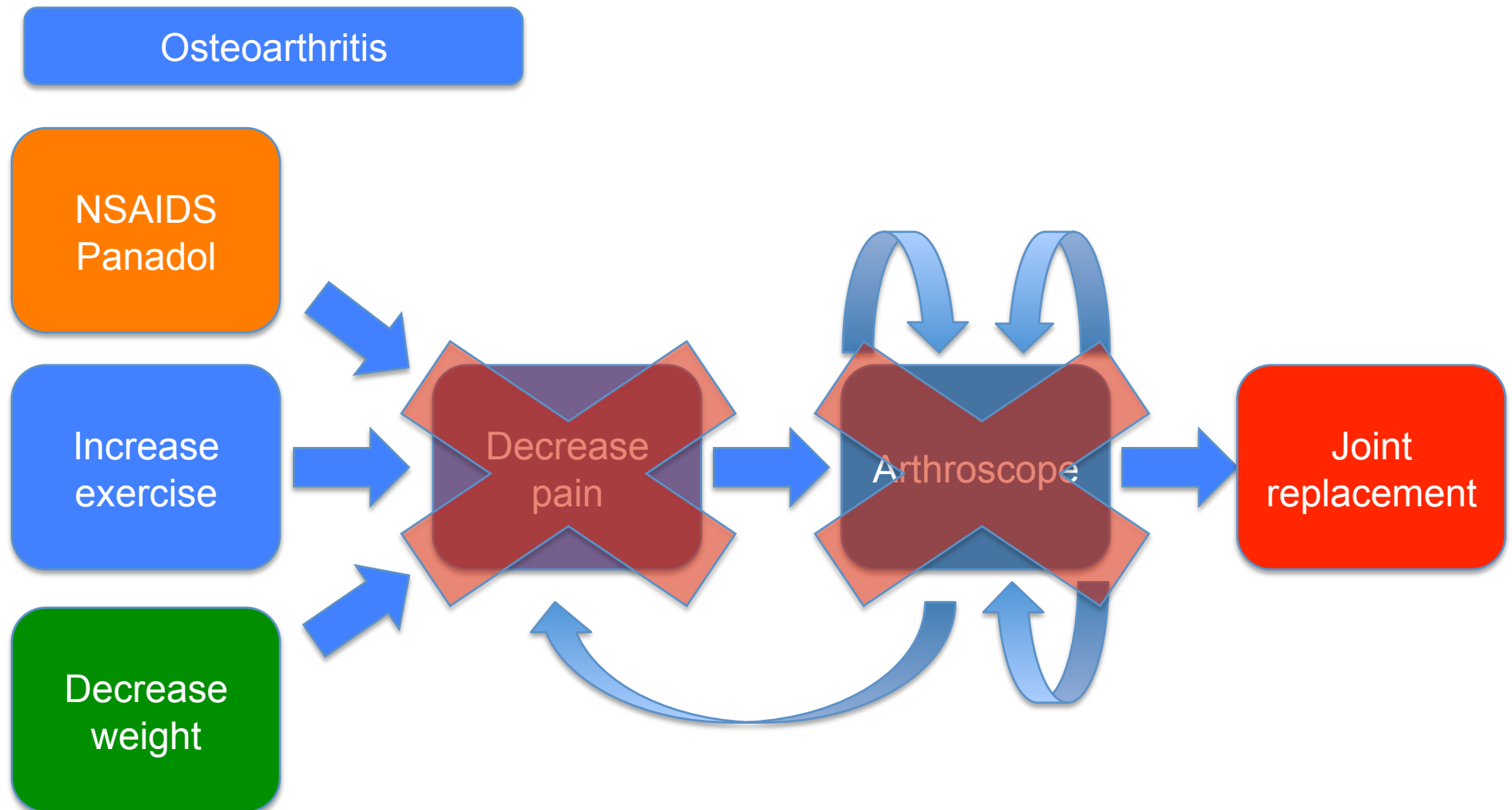
Increase
exercise

Decrease
weight

Decrease
pain

Arthroscope

Joint
replacement



Osteoarthritis

NSAIDS
Panadol

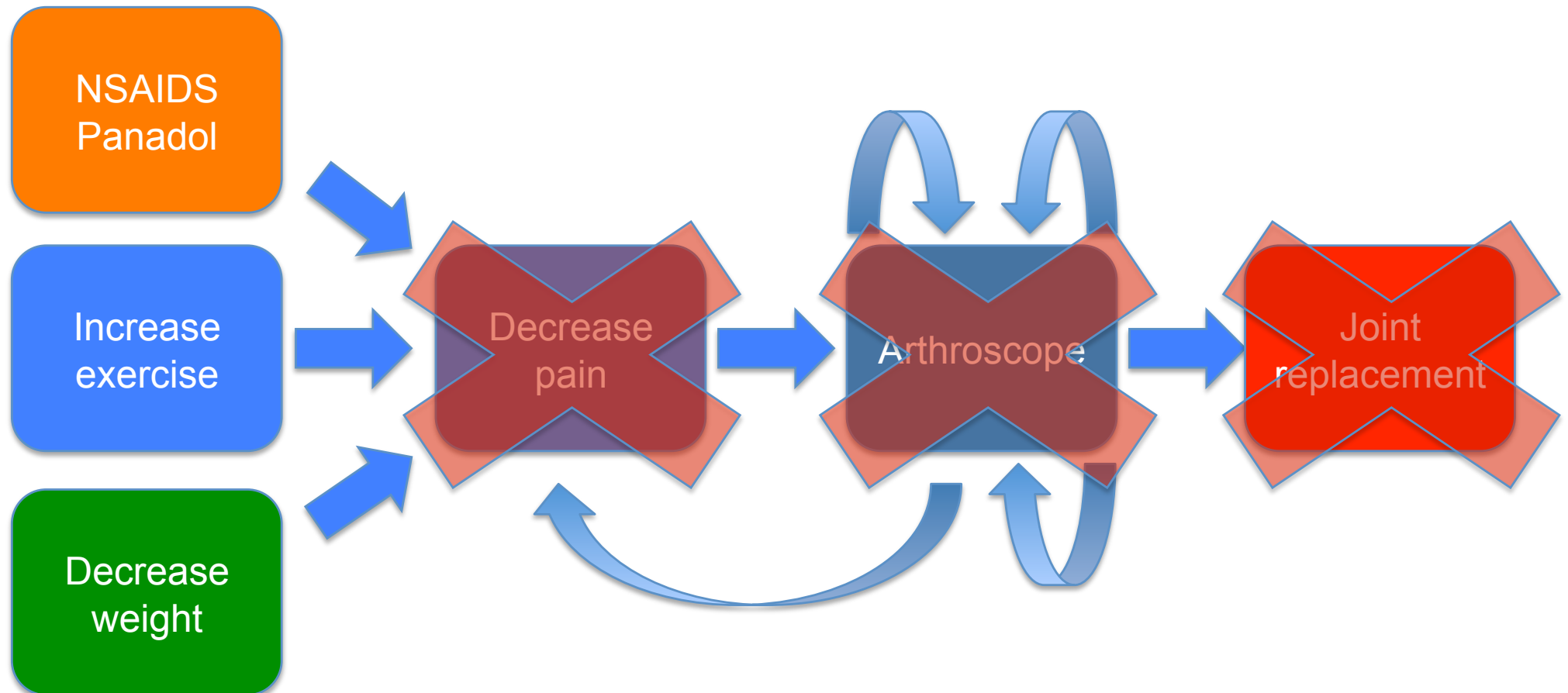
Increase
exercise

Decrease
weight

Decrease
pain

Arthroscopy

Joint
replacement



Osteoarthritis

NSAIDS
Panadol

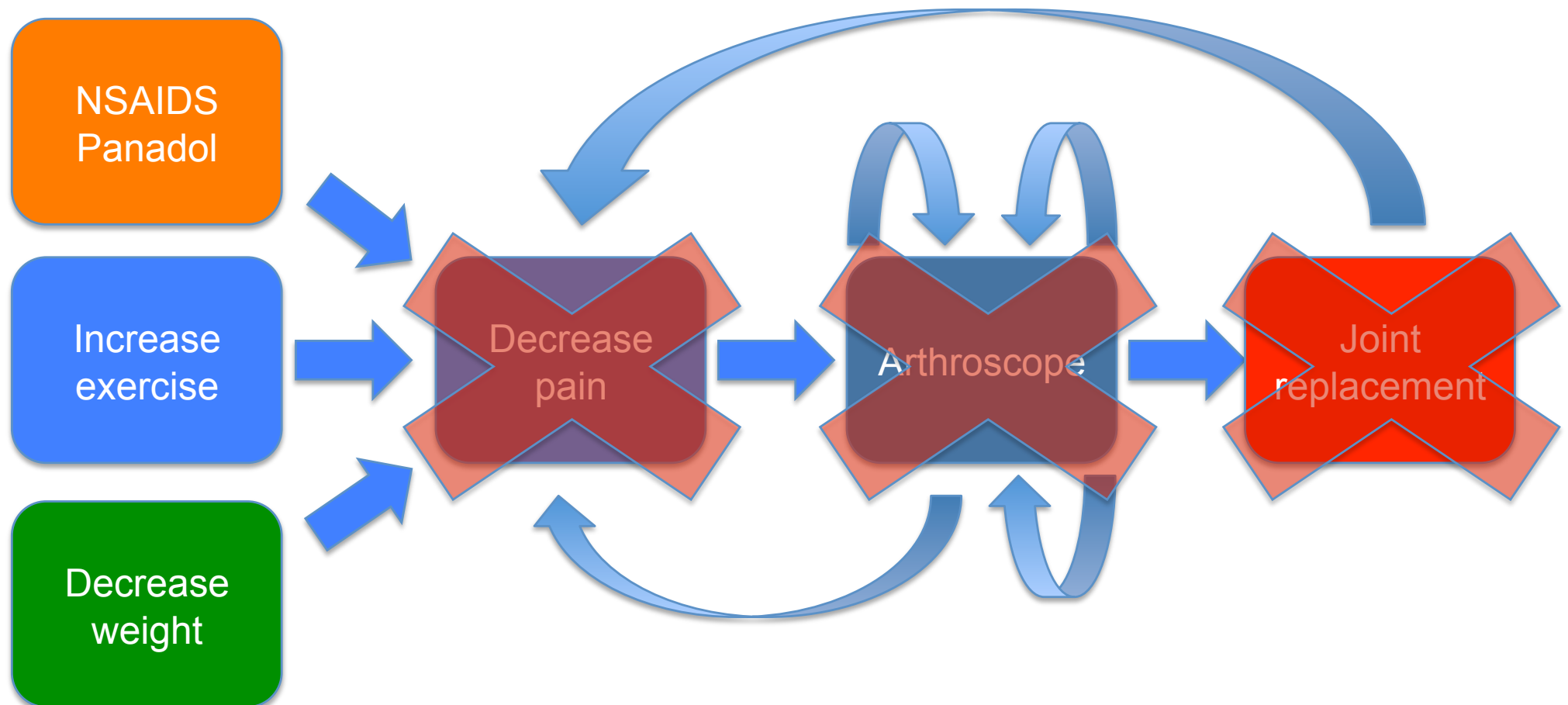
Increase
exercise

Decrease
weight

Decrease
pain

Arthroscopy

Joint
replacement



Osteoarthritis

NSAIDS
Panadol

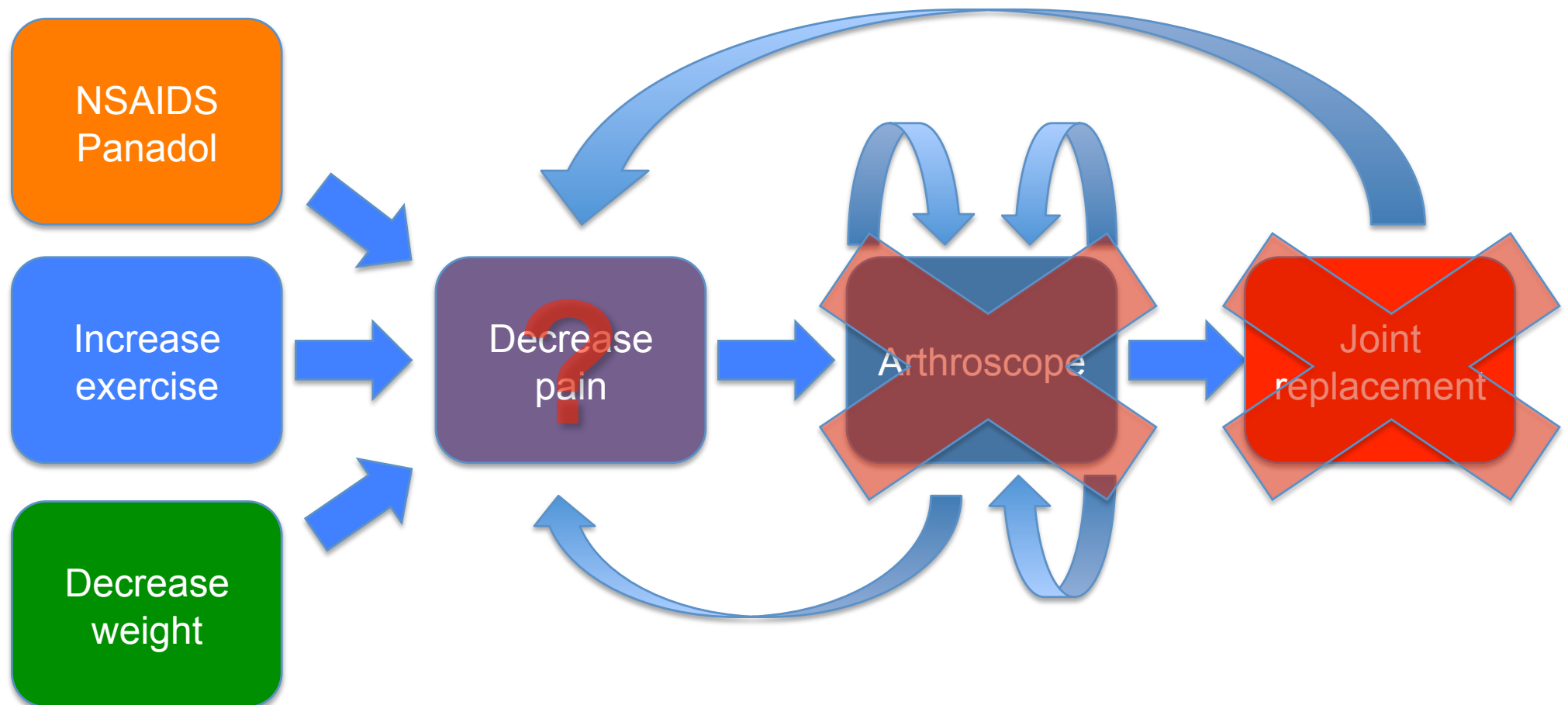
Increase
exercise

Decrease
weight

Decrease
pain

Arthroscopy

Joint
replacement



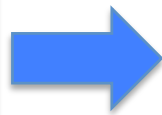
Osteoarthritis

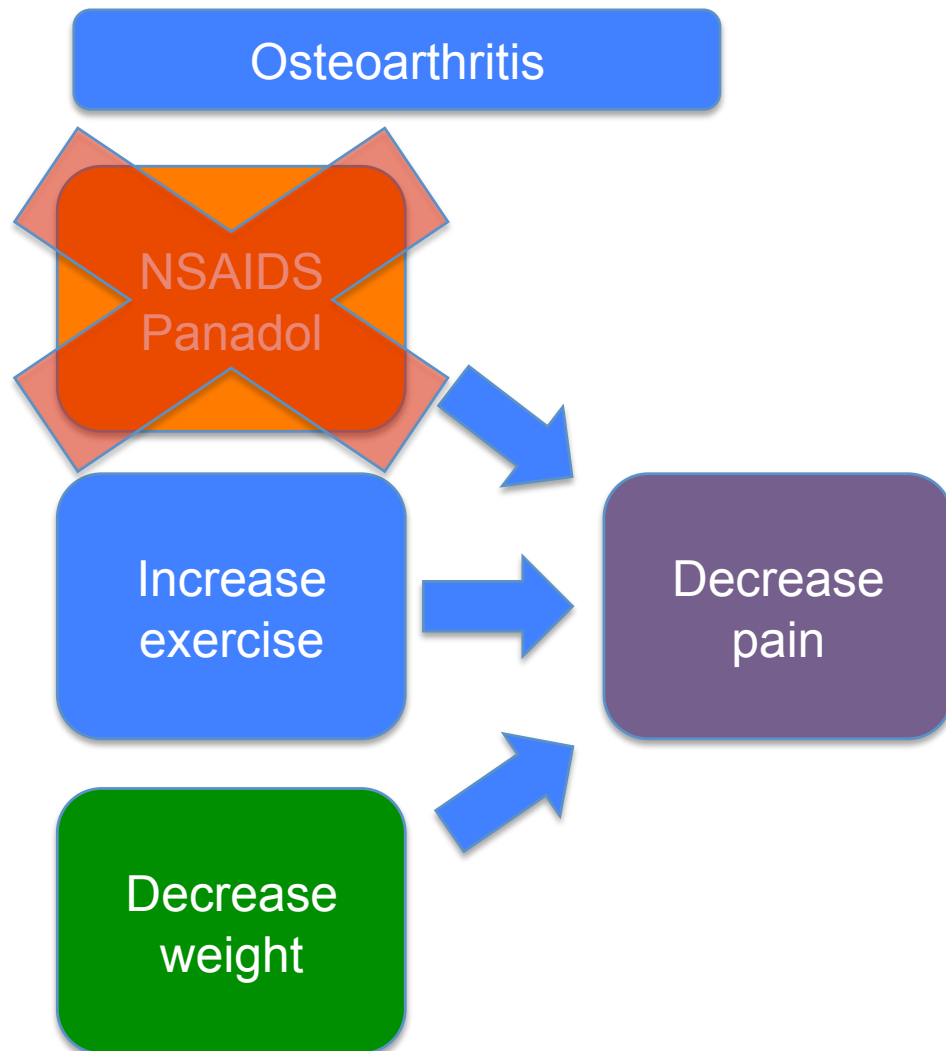
NSAIDS
Panadol

Increase
exercise

Decrease
weight

Decrease
pain







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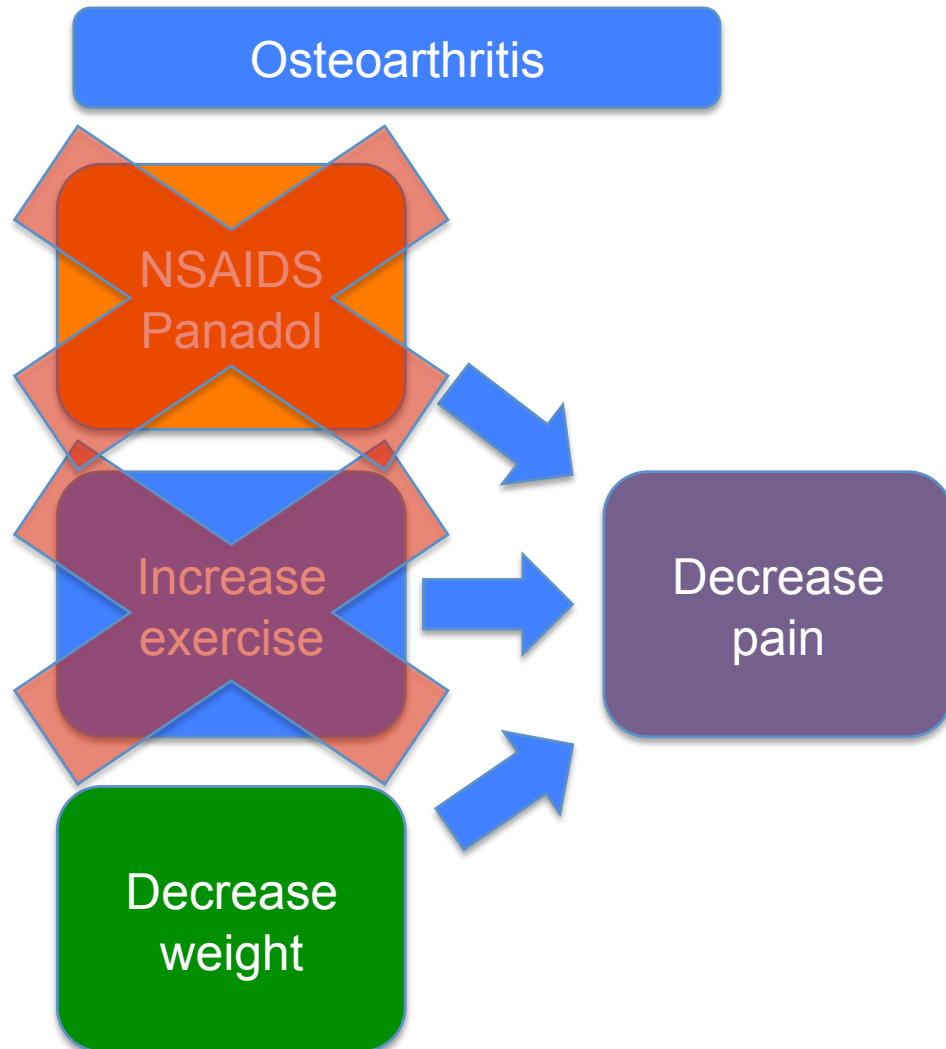
Osteoarthritis

NSAIDS
Panadol

Increase
exercise

Decrease
weight

Decrease
pain





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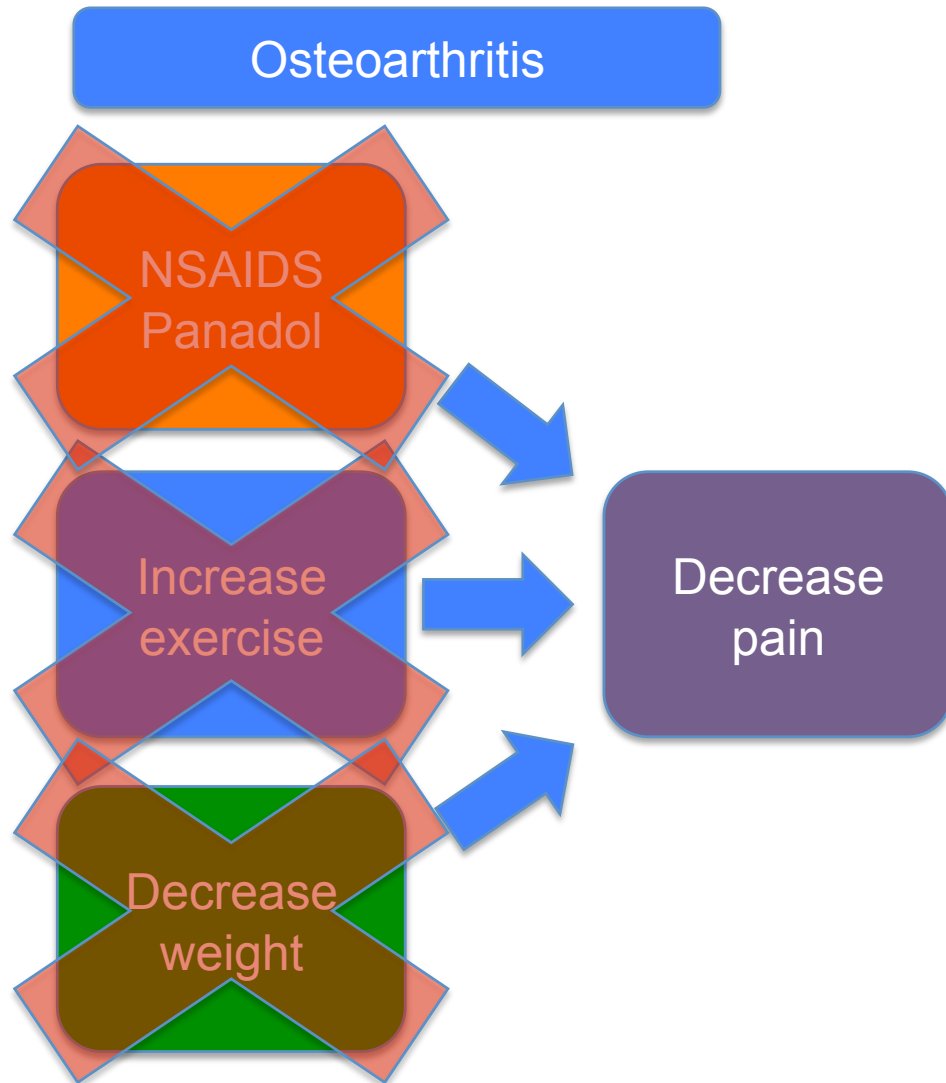
Osteoarthritis

NSAIDS
Panadol

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pain





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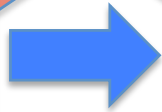
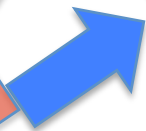
Osteoarthritis

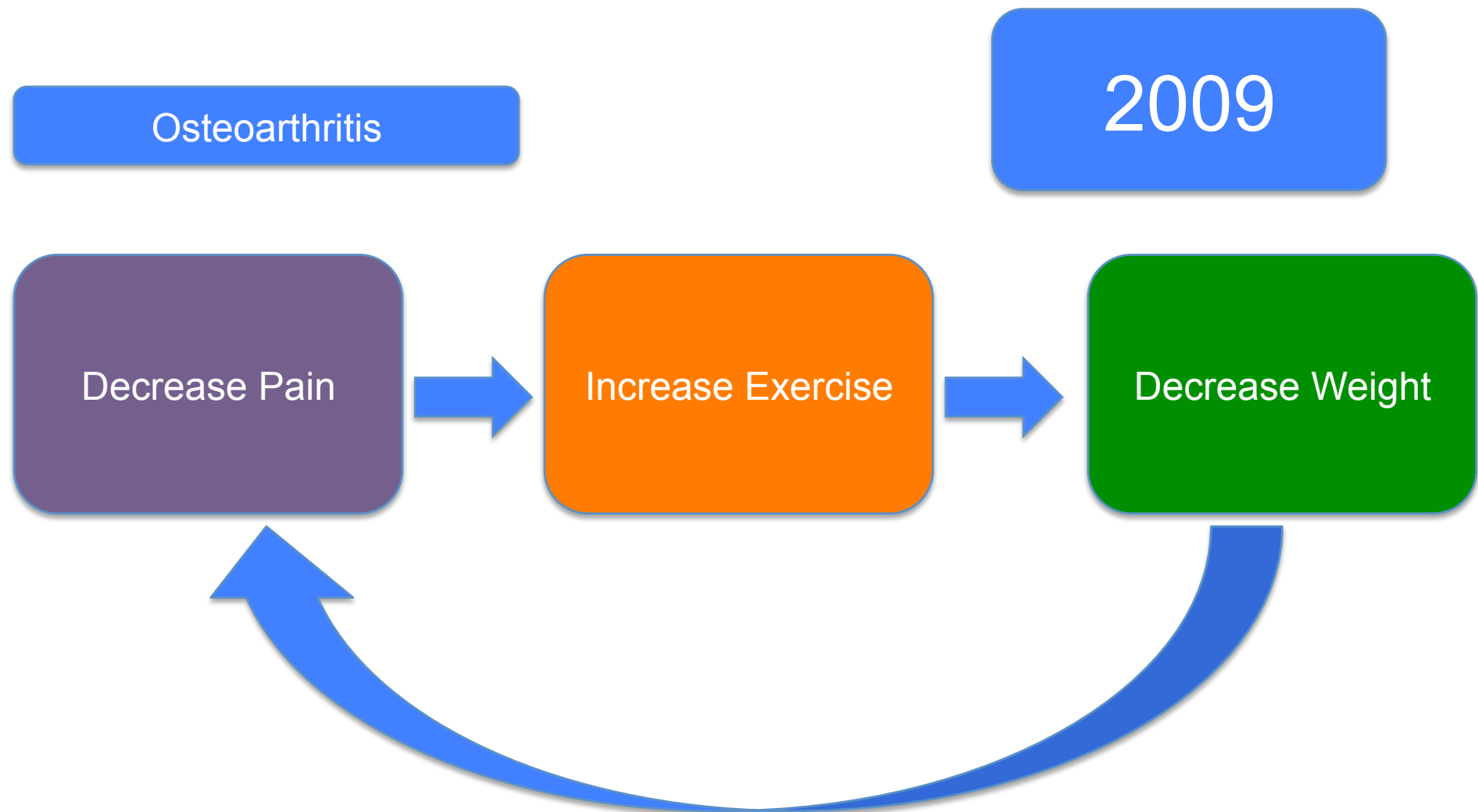
NSAIDS
Panadol

Increase
exercise

Decrease
weight

Decrease
pain





Osteoarthritis

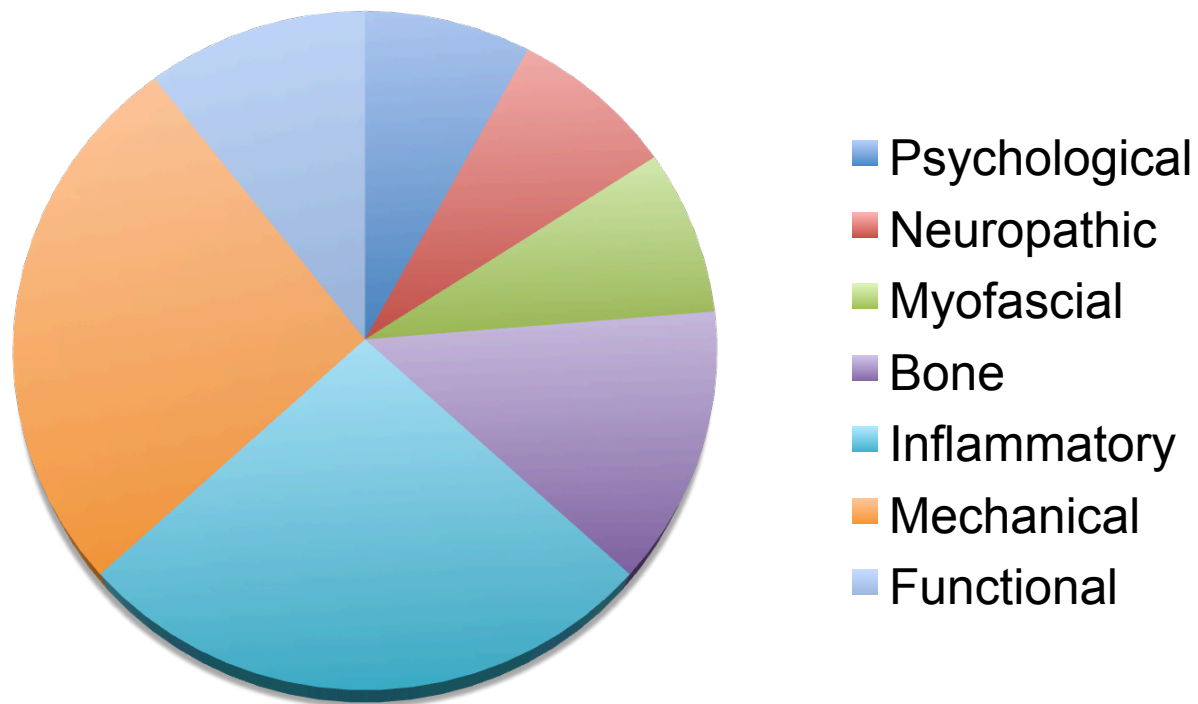
Decrease Pain

Increase Exercise

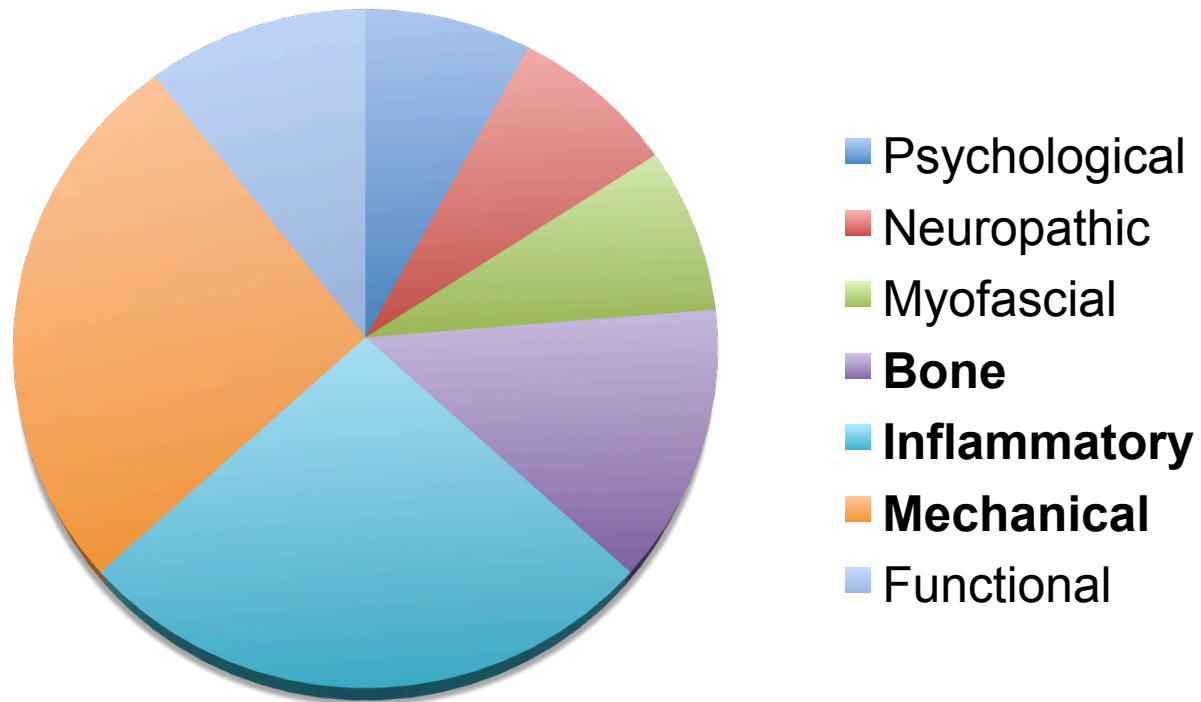
Decrease Weight

1kg = 2kg/step = 10 tons/day

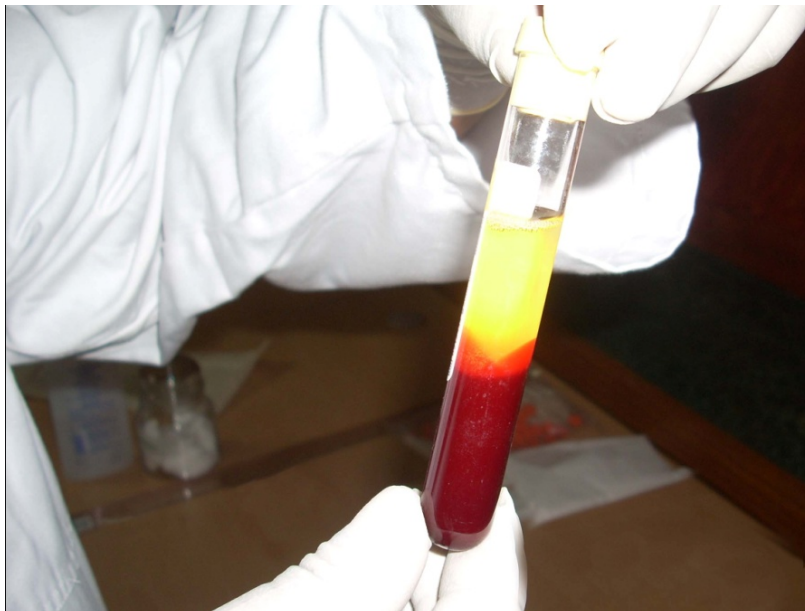
Pain in Osteoarthritis



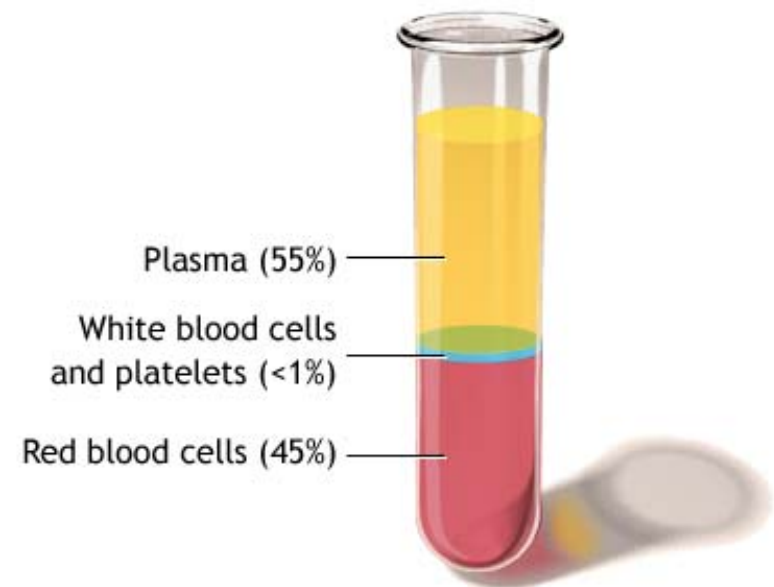
Pain in Osteoarthritis



Platelet rich plasma



2009



PRP for Osteoarthritis

2009

Author	Patients	Disease	Test	Follow-up	Symptom Improvement
Baltzer et al 2008	300	OA knee grade 1-3	ACS vs HA vs NS (RCT)	2 years	VAS 69 to 29* ACS Vs HA * ACS vs NS *
Sanchez et al 2008	30	OA knee	PRGF vs HA (retrospective)	12months	PRGF vs HA * WOMAC *

PRP for Osteoarthritis

2012

Author	Patients	Disease	Test	Follow-up	Symptom Improvement
Baltzer et al 2008	300	OA knee grade 1-3	ACS vs HA vs NS (RCT)	2 years	VAS 69 to 29* ACS Vs HA * ACS vs NS *
Sanchez et al 2008	30	OA knee	PRGF vs HA (retrospective)	12months	PRGF vs HA * WOMAC *
Kon et al 2009	115 Knees	OA knee	PRP (Case series)	12 months	EQ VAS 50-69.5* IKDC *
Kon et al 2011	114 Knees	OA Knee	PRP (Case series)	24months	IKDC 67-59 *
Kon et al 2011	150	Chondral defects and OA knees	PRP vs HA (Cohort)	12 months	EQ Vas 53-72* PRP Vs HA young * Old *
Sampson et al 2010	14	OA knee	PRP (Case Series)	12 months	VAS 2.5 to 0.8*
Wang Sauguesa et al, 2011	261	OA knee	PRGF (Cohort)	12 months	VAS 4.8 to 3.2* WOMAC *
Spakova et al, 2012	120	OA Knee	PRP vs HA (Cohort)	12 months	WOMAC *
Mei Dan et al, 2012	32	Chondral defect ankle	PRP vs HA (RCT)	12 months	VAS 4.1 -.9 AHFS * PRP vs HA *
Sanchez et al 2012	40	Hip OA	PRGF (Case Series)	12 months	WOMAC * Harris hip score *

Osteoarthritis

Decrease Pain

Increase Exercise

Decrease Weight



Osteoarthritis

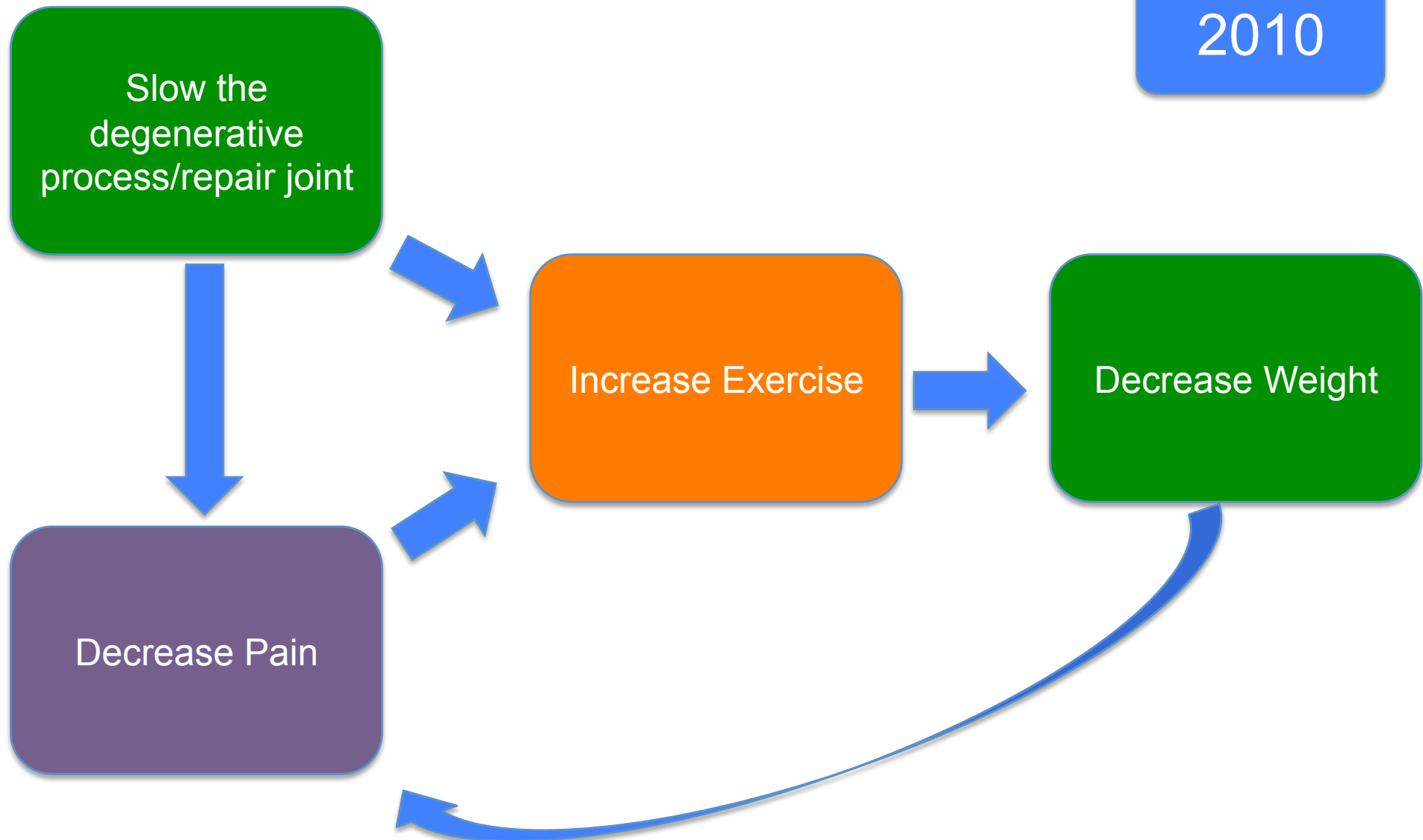
Decrease Pain

Increase Exercise

Decrease Weight



2010





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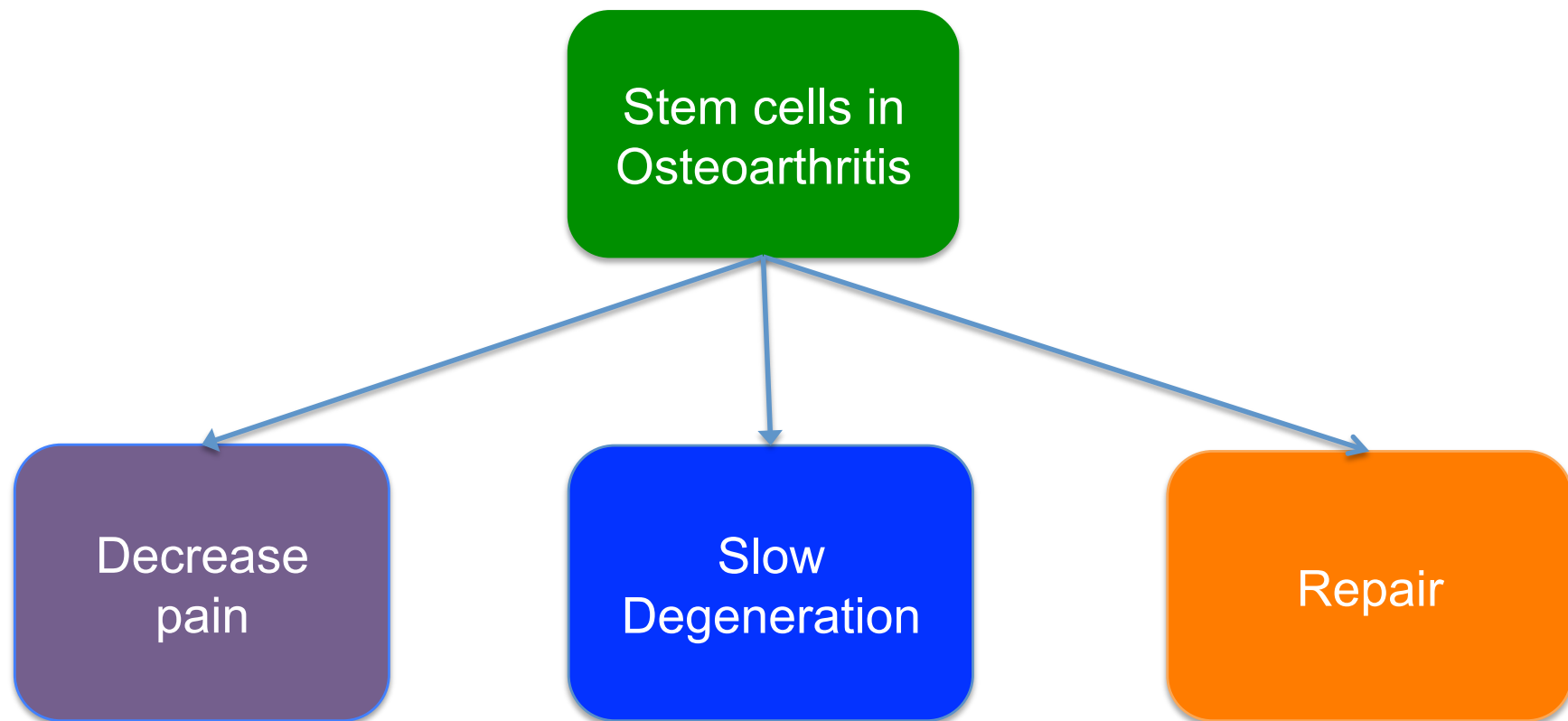
Stem cells in Osteoarthritis



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LAKE SIDE
SPORTS MEDICINE CENTRE



Which cells?

How do they
work?

Are they safe?

Which cells?

How do they
work?

Are they safe?

How do you develop
a novel, experimental
therapy?



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Which cells?

Source of cells?

- Mesenchymal stem cells
- Adipose derived
 - Lots going around for adequate cell numbers
 - Differentiate into cartilage
 - Cytokine mediate anti-inflammatory
 - Animal and human data available

Adipose derived stromal vascular fraction?

- Heterogeneous cell population
 - Endothelial cells
 - Pre-adipocytes
 - Smooth muscle
 - Fibroblasts
 - Pericytes
 - **Macrophages**
 - **T- Lymphocytes**
 - **Mesenchymal stem cells**

(Faustini et al, Tissue Engineering, 2010, Aron-Wisniewsky, J Endocrinol Metab, 2009, Bouloumie et al, Athro, Throm and Vasc biol, 2009, Zuk et al, Am Soc Cell Biol, 2002, Mizuno et al, J Nippon Med Sci, 2003,)

How do they
work?



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Are they safe?

Safety:

- Is the injection of Mesenchymal stem cells safe?

Table 1. Representative preclinical animal studies using adipose-derived stromal/stem cells and stromal vascular fraction cells

Tissue type	Defect	Species	References
Adipose/soft tissue	Fat pad generation	Murine, rat, ovine	[51-60]
	Lipodystrophy	Murine	[48,61]
	Burn/radiation trauma	Murine	[62-64]
Bone	Critical sized defect		
	Craniofacial	Murine, rat	[65,66]
	Long bone	Murine	[67]
	Spinal fusion	Rat	[68,69]
Cardiac	Myocardial infarction	Murine, rat	[42,43,70,71]
Central nervous system	Vascular injury/stroke	Murine, rat	[44,46,72]
	Spinal cord trauma	Rat	[47]
	Multiple sclerosis	Murine	[33]
Gastrointestinal tract	Crohn's disease/inflammatory bowel syndrome	Murine	[73]
Hematopoiesis	Bone marrow transplantation	Murine	[74,75]
Joint	Osteoarthritis	Canine, caprine, equine	[76-79]
Liver	Acute toxicity/regeneration	Murine	[80-88]
Pancreas	Type 1 diabetes mellitus	Murine, rat	[48,89,90]
Renal	Acute ischemia	Rat	(JMG, unpublished)
Skin	Wounds, burns	Murine, porcine	[62,64,91]
Tendon	Tendonitis	Equine	[92]
Urinary bladder	Incontinence	Rat	[93]
Vascular	Hind limb ischemia	Murine, rat	[36,41,45]

Animal evidence:

- Commercially available - VetStem
- 2500 horses intra-articular injection
- 0.5% local adverse events
- No systemic adverse events

(Reported in Black et al, Vet Therapies 2007)

Safety:

Author	Patients	Disease	Injection	Follow-up	Complication
Lendekel 2004	1	Carvarium defect	Fibrous glue bone	2 years	No reported
Yoshimura 2007	40	Cell Assisted breast augmentation	Subcut	2 years	2 microcalcification, 2 fibrosis, 1 Cyst formation <12mm
Rigotti 2007	20	Radiation burns	Subcut	31 months	No infections, no tissue necrosis, no treatment ceased due to complication
Yoshimura 2008	6	Fascial lipoatrophy	Subcut	12 months	Nil

Safety:

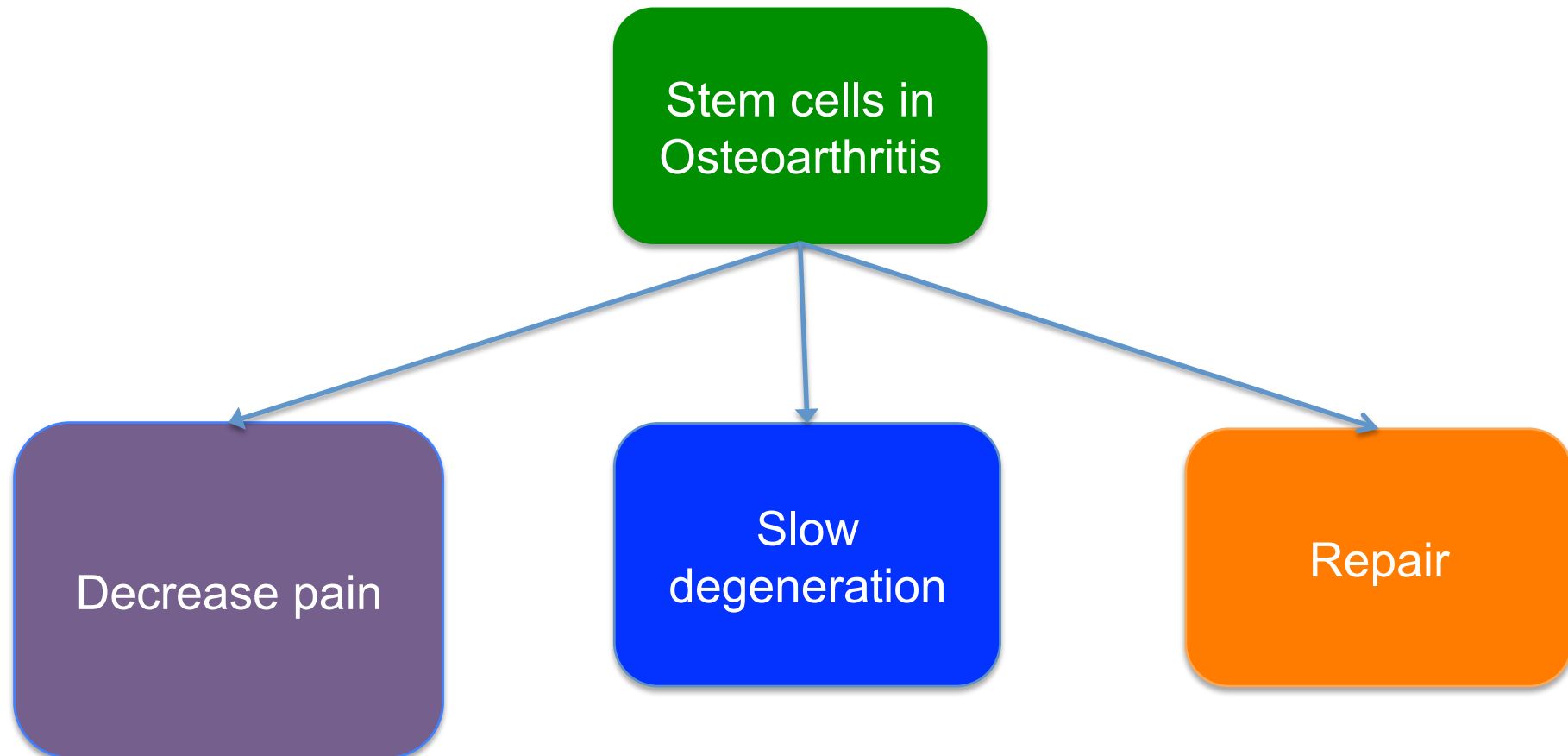
Author	Patients	Disease	Injection	Follow-up	Complication
Yoshimura et al 2010	15	Cell Assisted breast augmentation	Subcut	12 months	No abnormalities on MRI at 12 months
Riodan 2009	3	Multiple sclerosis	IV, intrathecal	7 months	Non-reported
Mesimaki 2009	1	Maxillary defect	Ectopic bone formation	36 months	Non reported
Garcia olmo, 2009 Guadalajada 2012	24	Peianal fistula	Perianal	3 years	2 abscess one in control and 1 in treatment group

Safety: MSK studies

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
Rodriguez 2012	13	Rheumatoid Arthritis	IV and IA	13 months	Safety study	One episode of fever & myalgia

Summary

- Animal data
 - 2500 animals (Now 11687)
 - AE 1.28% (unpublished data)
 - 50+ animal studies
- Small number of human case series
 - Small total numbers 378 (Now 503)
 - Mostly short follow-up in most up to 11 years
 - Multiple diseases and sites injected
 - All studies had concluded safe
- No randomised control trials



Animal evidence:

Author	Animals	Study	Number	Disease	Follow-up	Symptom Improvement
Black et al, 2007	Dogs	RCT	21	Hip Osteoarthritis	3 months	Improved lameness, Pain and ROM
Black et al, 2008	Dogs	RCT	14	Elbow Osteoarthritis	6 months	Improved lameness, Pain and ROM

Human evidence:

Author	Patients	Disease	Follow-up	Cartilage regeneration	Symptom Improvement
Centeno 2006	1	Hip Osteoarthritis	3 months	Yes – MRI	FRI – 1 pt improvement
Centeno 2008	1	Knee Osteoarthritis	6 months	Yes – MRI	VAS 4/10 to 0.3/10
Pak 2011	4	Hip and Knee Osteoarthritis	3 months	Yes – MRI	VAS 7/10 to 2/10
Davachi et al, 2011	4	Knee Osteoarthritis	12 months	No	VAS 86mm to 52.5mm
Emaddin 2012	6	Knee Osteoarthritis	12 months	Yes – MRI in 3 patients	VAS 57mm to 11mm.

Summary

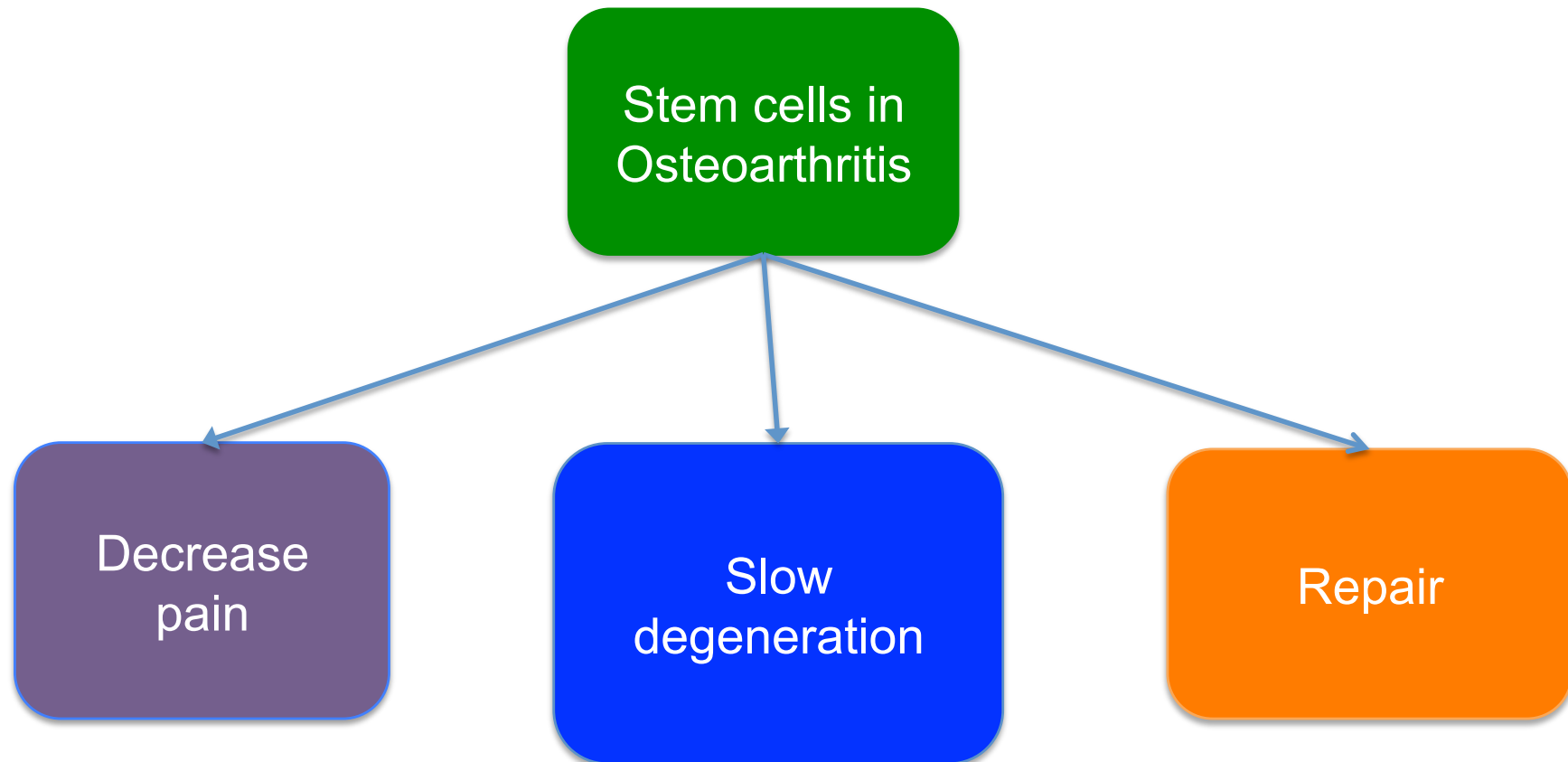
- Animal data
 - Limited but symptoms relief difficult to assess
- Small number of human case series
 - Very small numbers (16)
 - Promising but unable to assess
- No randomised control trials



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Why slow degeneration?

Meniscal tear

- 10 year follow up (Stein et al, AJSM, 2010)
 - Repair meniscus 20% develop OA
 - Partial Menisectomy 60% develop OA

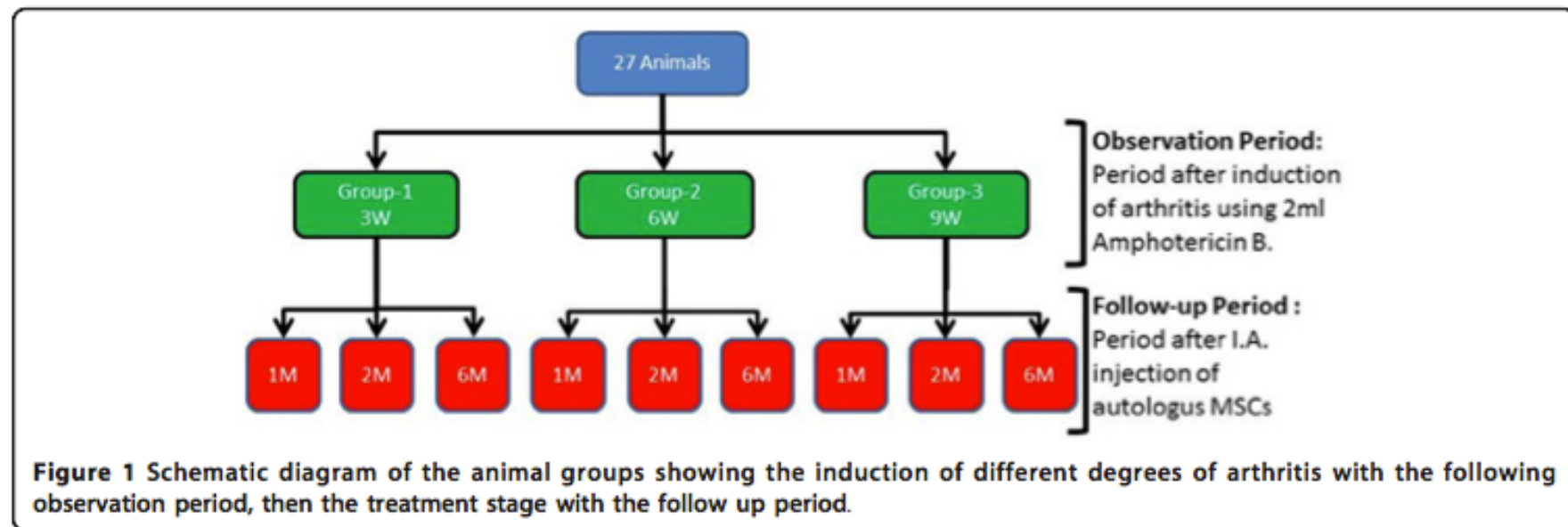
ACL injury

- ACL - repair – 42% OA (Keesler et al, Knee Sport, traum, 2008)
- ACL – repair – 26% PFJ OA by 12 years (Olstad et al, Knee Sport traum, 2012)

Animal evidence:

- Prevent cartilage degeneration
 - Goats: Meniscectomy and ACL resection (Murphy et al, Arth & Rheum, 2003)
 - Mice: post traumatic (Deikman et al, Cell Transplant, 2012)
 - Rabbits: ACL resection (Tograhie et al, Knee, 2012)
 - Guinea Pigs: Spontaneous OA (Sato et al, Arth Resear & Ther, 2012)
 - Donkeys: Chemically induced (Mokbel et al, MSK Disorders, 2011)

Mokbel et al, 2011:



Mokbel et al, 2011:

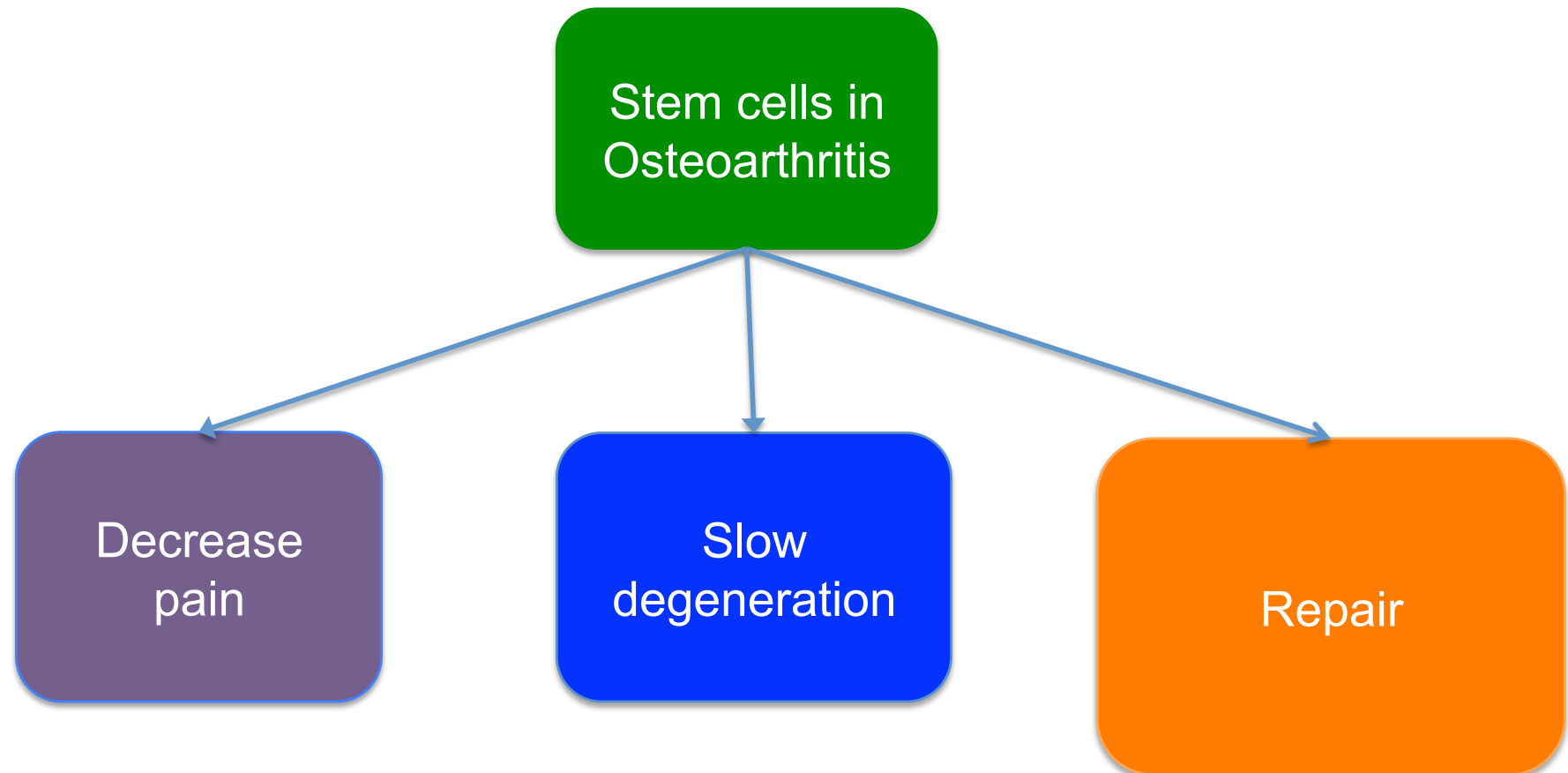
Table 4 Mean value of the radiographic scoring of osteophytes formation and cartilage loss of different groups; before and at 1, 2, 6 months from the treatment

Assessment time	Group-I		Group-II		Group-III	
Before Treatment	0(2)		2(3)		4(4)	
	R	L	R	L	R	L
1 month After Treatment	0	0	2	3	4	4
2 month After Treatment	0	0	1	3	4	4
6 month After Treatment	0	0	1	2	3	4

R: right joint; L: left joint; (Values between brackets) indicate score of cartilage loss.

Human evidence:

- No human studies looking at the prevention of progression of disease
- Mesoblast study underway in Melbourne looking at prevention of osteoarthritis post ACL



Why treat Chondral Defects and OA?

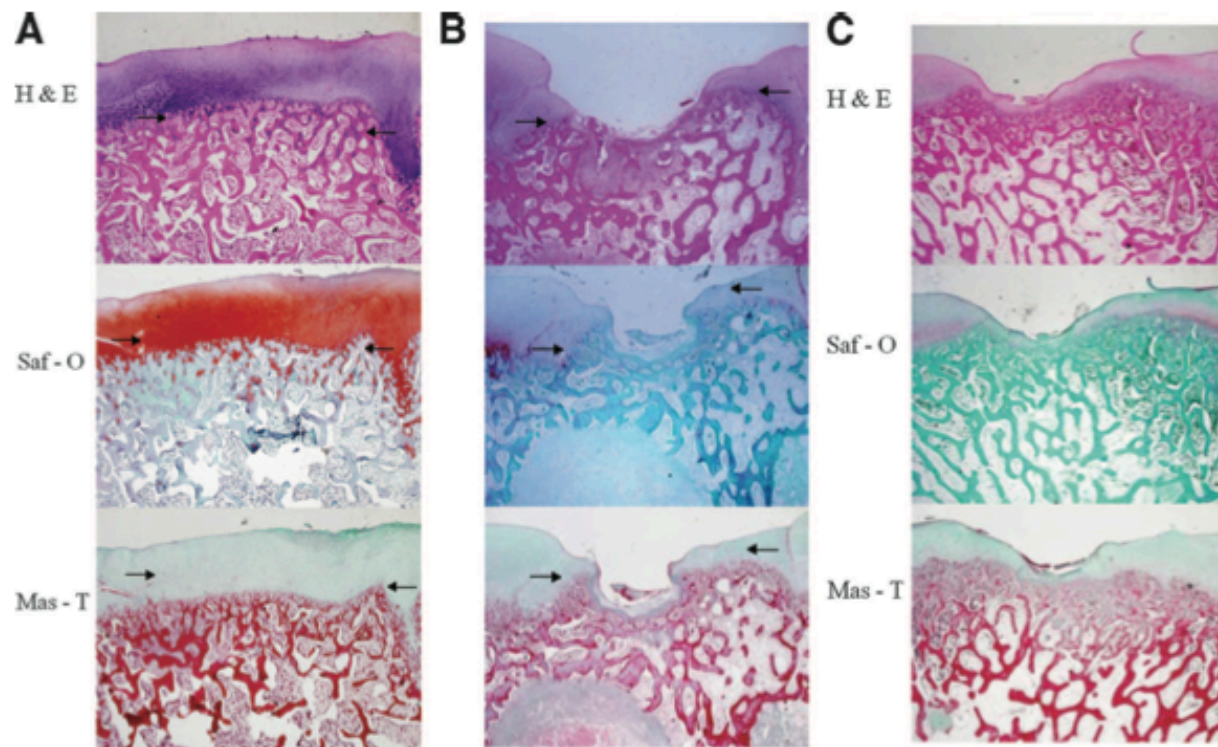
- 12% of the population will suffer chondral lesions
- These are accepted to progress to osteoarthritis

Animal evidence:

MSC's – chondral defects

- Been shown to regenerate cartilage in
 - Rabbits (Wakitani et al, JBJS, 1994)
 - Rabbits (Im et al, JBJS, 2001)
 - Pigs (Lee et al, Stem Cells, 2007)
 - Dogs (Mokbel et al, Clin Ex Rheum, 2011)

12 weeks post injection of MSC's in a pig:



MSC +
HA
injection

HA injection

Control

(Lee et al, Stem Cells, 2007)

Animal evidence:

MDSC's – Regeneration in OA

- Been shown to regenerate cartilage in
 - Rats (Matsumoto et al, Arth Rheum, 2009)
 - Rats (Mifune et al, Osteo Cart, 2012)

Bone marrow derived - Japan

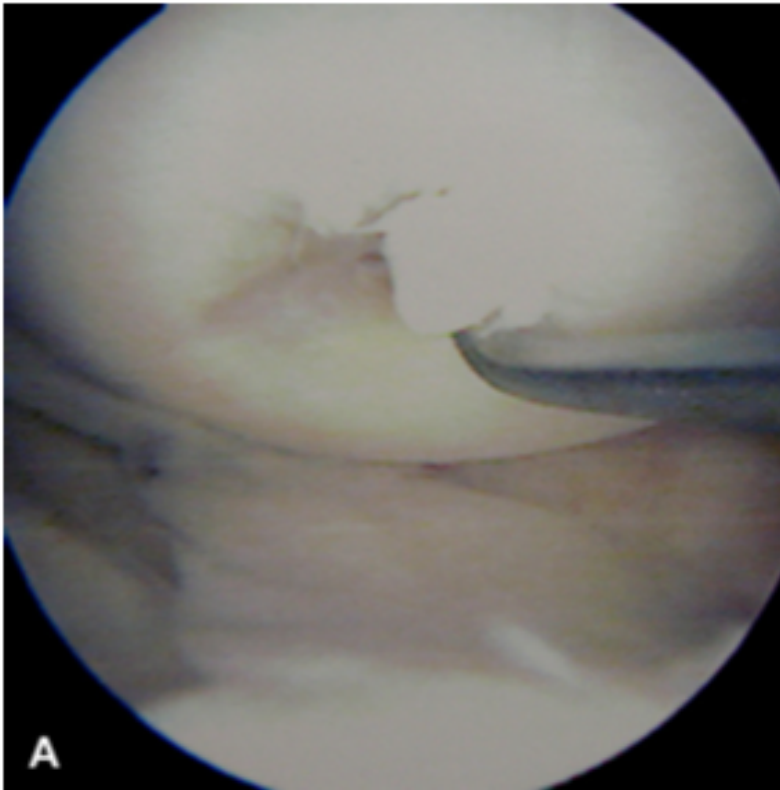
Author	Patients	Disease	Follow-up	Cartilage regeneration	Symptom Improvement
Wakitani 2002	24	HTO Vs HTO and cells	3.5 years	Yes – 2 nd look	Wilcox signed rank test * HTO vs HTO + SC ^
Wakitani 2004	2	PFJ cartilage defect	5 years	Yes – 2 nd look	Improved pain and walking
Wakitani 2007	3	PFJ Cartilage defect	2 years	Yes – MRI	Improved pain and walking
Koruda 2007	1	Medial Femoral cartilage defect	1 year	Yes – 2 nd look	Pain free Returned to sport



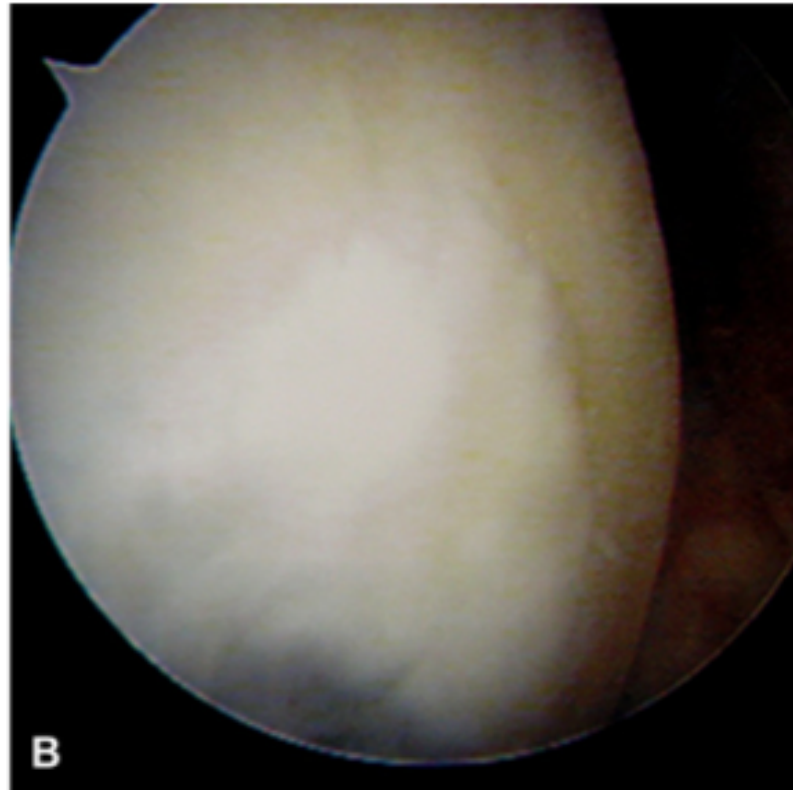
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20 X 30mm Cartilage defect



2nd look at 7 months

Koruda et al, Osteo & Cart, 2007,

Bone marrow derived - USA

Author	Patients	Disease	Follow-up	Cartilage regeneration	Symptom Improvement
Centeno 2008	1	Lateral condyle defect	6 months	Yes - MRI	Modified VAS 0.67-0* FRI 17-3 *

Centeno et al, 2008

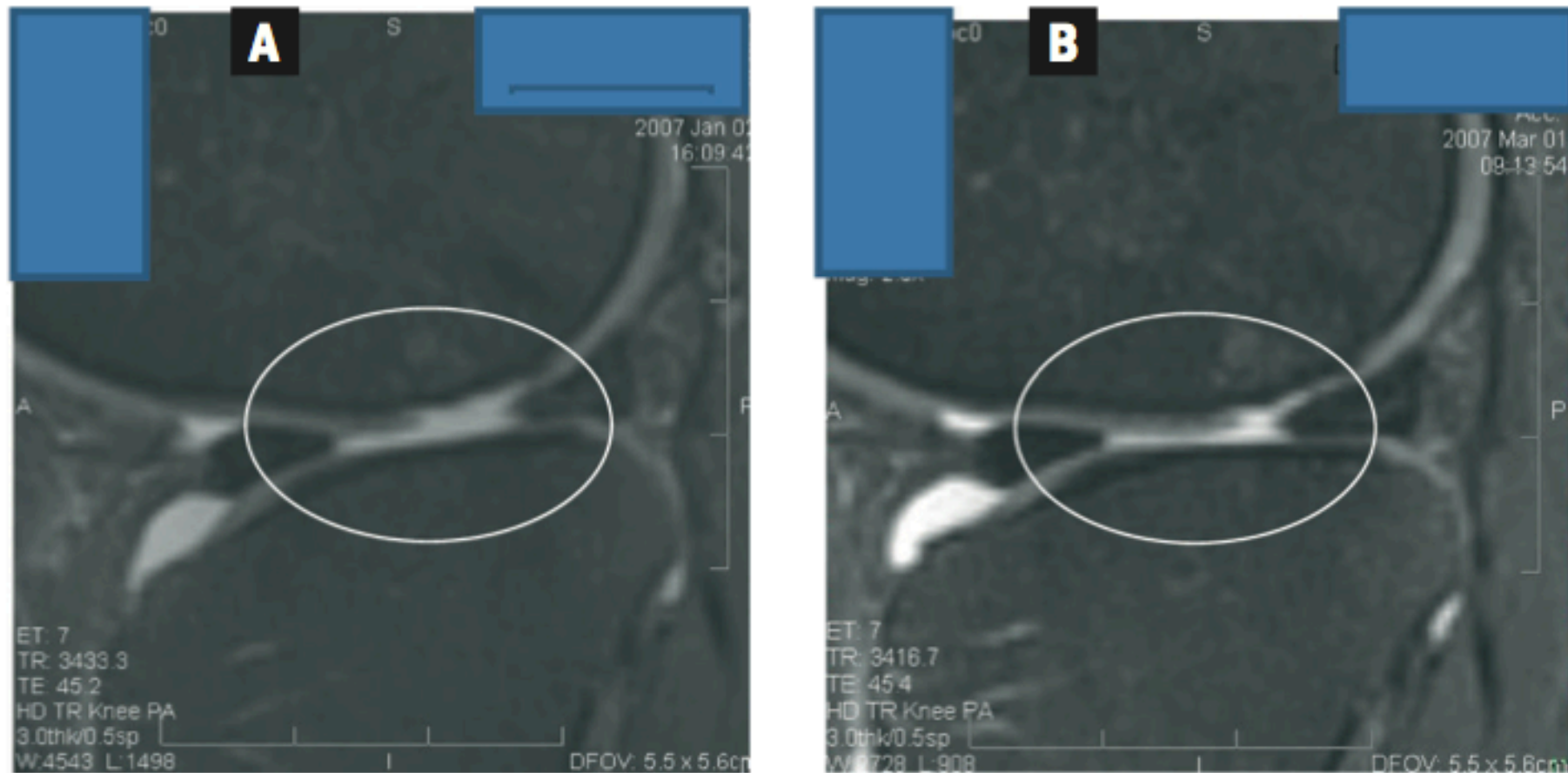


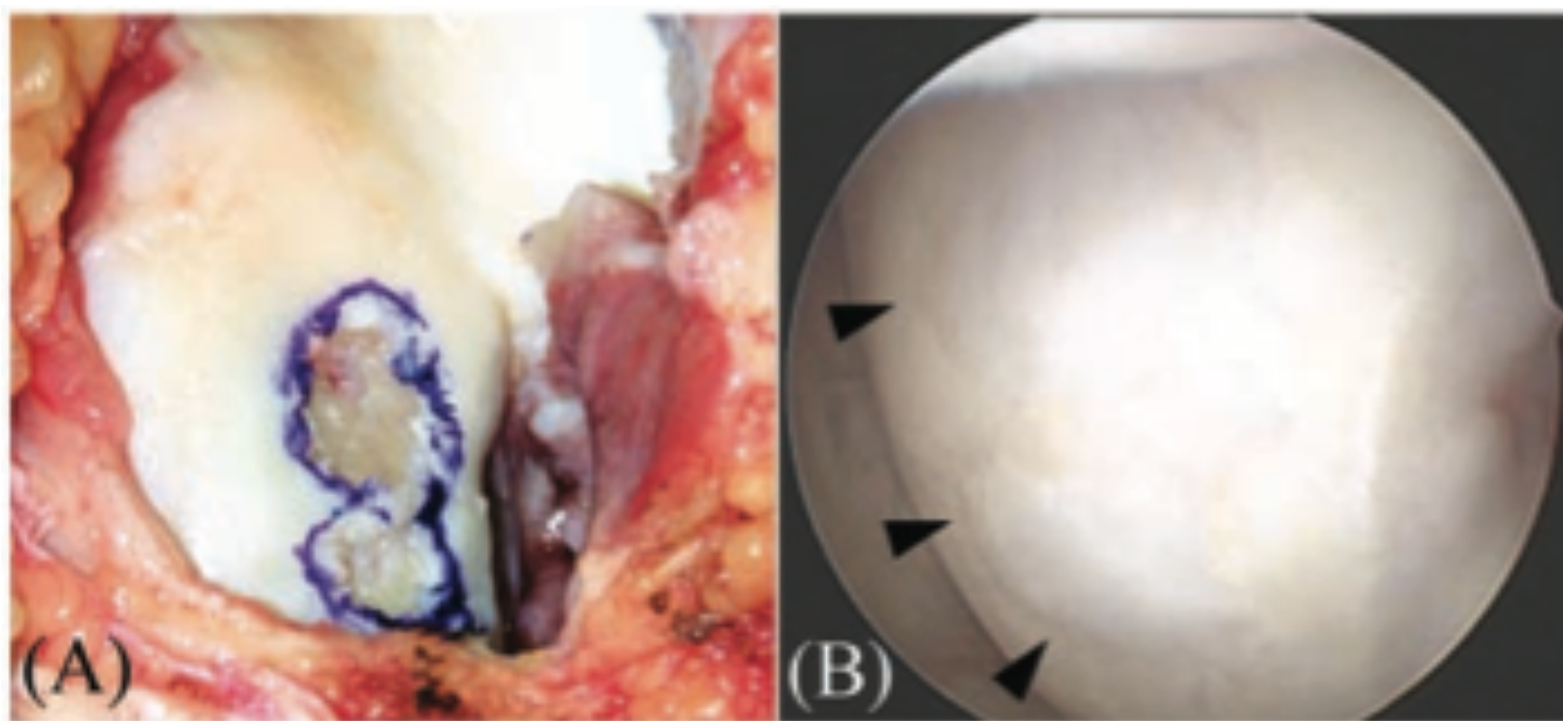
Figure 1. A. Pre Treatment. B. 2 Months Post Treatment.

Bone marrow derived - Others

Author	Patients	Disease	Follow-up	Cartilage regeneration	Symptom Improvement
Amgad 2010	5	Femoral Cartilage defects	1 year	Yes – MRI and 2 nd look	RHSSK *
Kasemkijwattana 2010	2	Femoral Cartilage defects	2.5 years	Yes – 2 nd look	IKDC * KOOS *
Nadiadnik 2010	72	MACI vs BMSC Cartilage defects	1 year	Yes – 2 nd look	Lysholm * Tegner * IKDC * BMSC vs MACI ^



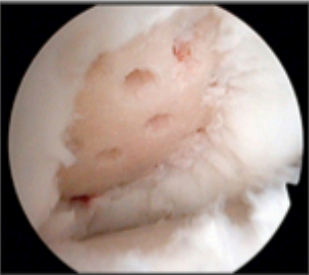
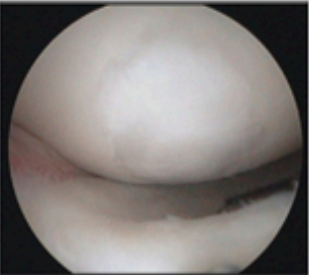
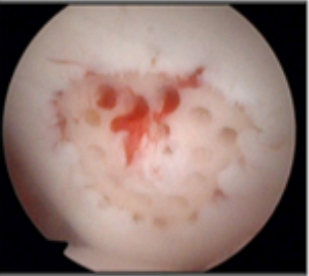
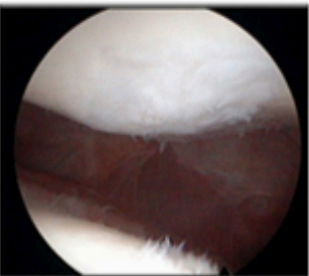
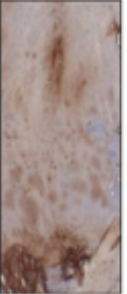
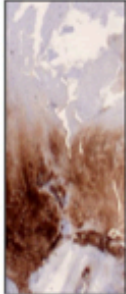
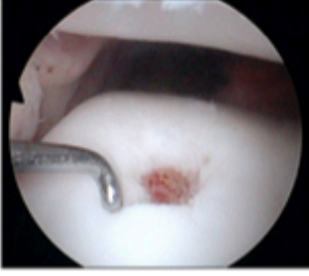
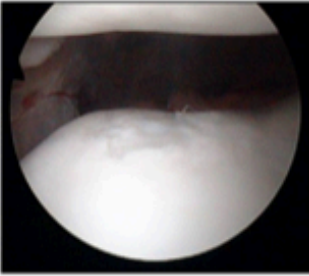
CELL MEDICINE
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Nejadnik et al, AJSM 2011. BMSC

Blood derived - Malaysia

Author	Patients	Disease	Follow-up	Cartilage regeneration	Symptom Improvement
Saw 2011	180	Cartilage defects and OA	2 years	Yes – 2 nd look	Unclear

	Intra-Op	2 nd look arthroscopy	H&E	Safarin-O	Collagen I	Collagen II
Case 3 Lateral Femoral Condyle						
Case 4 Lateral Patella Facet						
Case 5 Lateral Trochlear						

Saw et al, Arthroscopy, 2011

Summary

- Animal data
 - Macroscopic and histological evidence of cartilage regeneration – in chondral defects
 - One Group successful in OA
- Small number of human case series - 9
 - Total number patients - 286
 - Small Numbers
 - Promising evidence of cartilage regeneration
- No randomised control trials

Summary

- Safety
 - Animal and human data indicating initial safety
 - Requires RCT' s
- Efficacy
 - Animal data supports decreasing degeneration
 - Animal and human data promising for regeneration in defects
 - Limited animal and human evidence for improved pain and function in OA
- No randomised control trials

How do you develop
a novel, experimental
therapy?

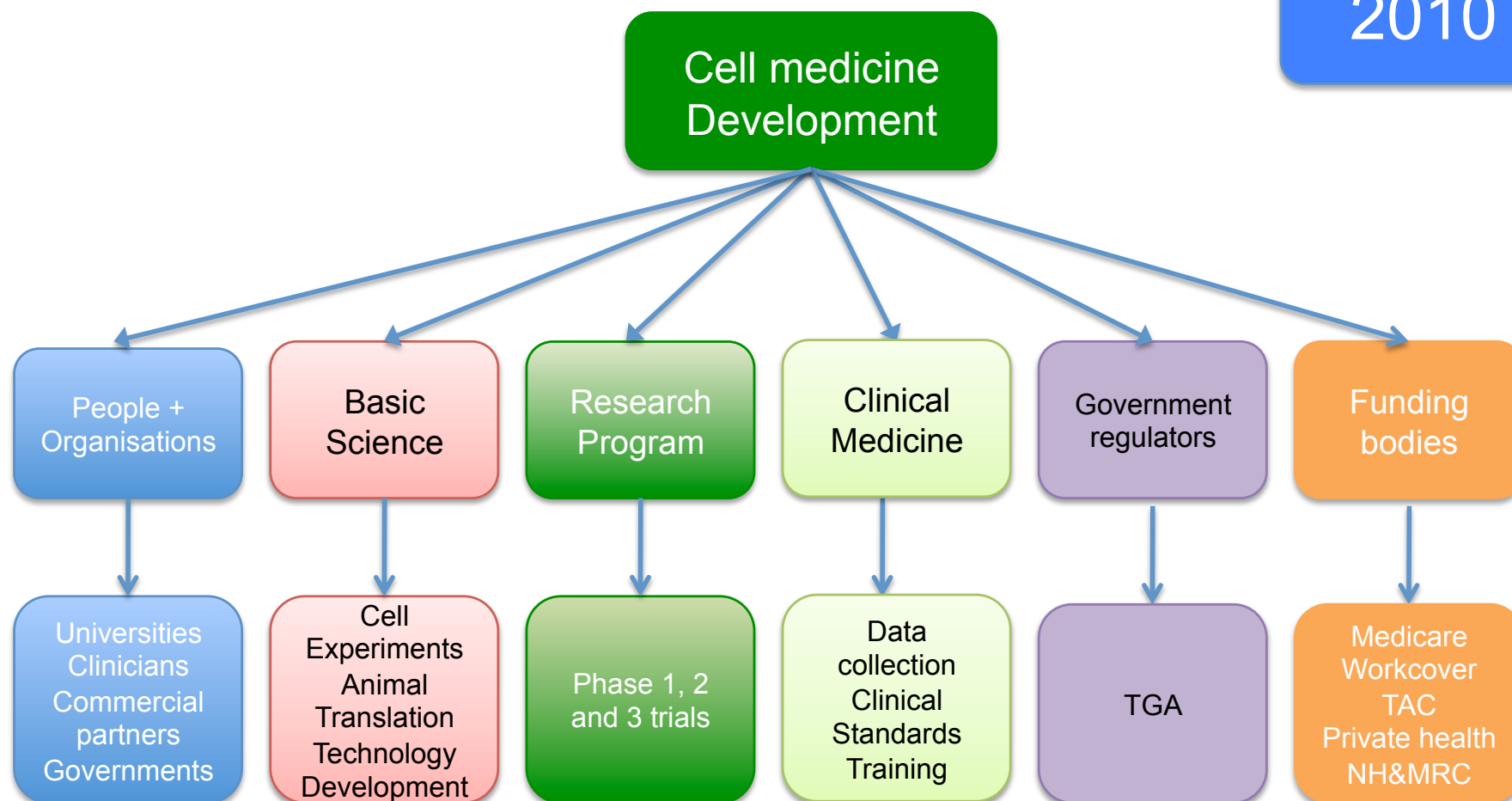
Response to the environment

- Poor scientific rationale
- Poor cell characterisation
- Poor diagnosis
- Poor follow up
- Poor consenting
- Poor clinician accountability
- Clinicians treating outside clinical expertise
- Undertaking non-ethics approved procedures
- No ongoing research program
- No peer review or publishing

My aim:

- Aim is to develop cell medicine to be
 - Safe
 - Reliable
 - Effective
 - Affordable

2010



That's great – but there is just me!



Summary

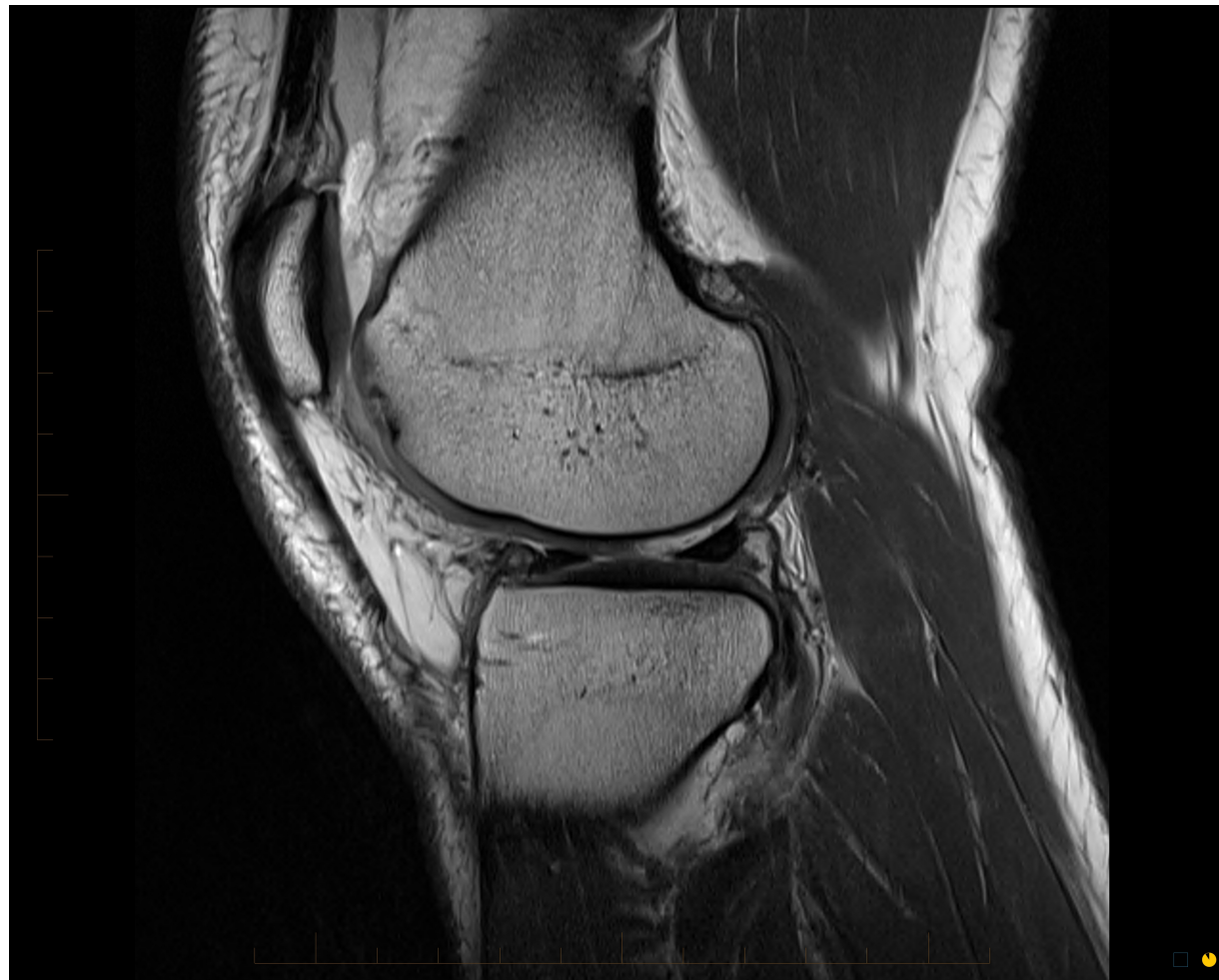
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What have we done in knees?

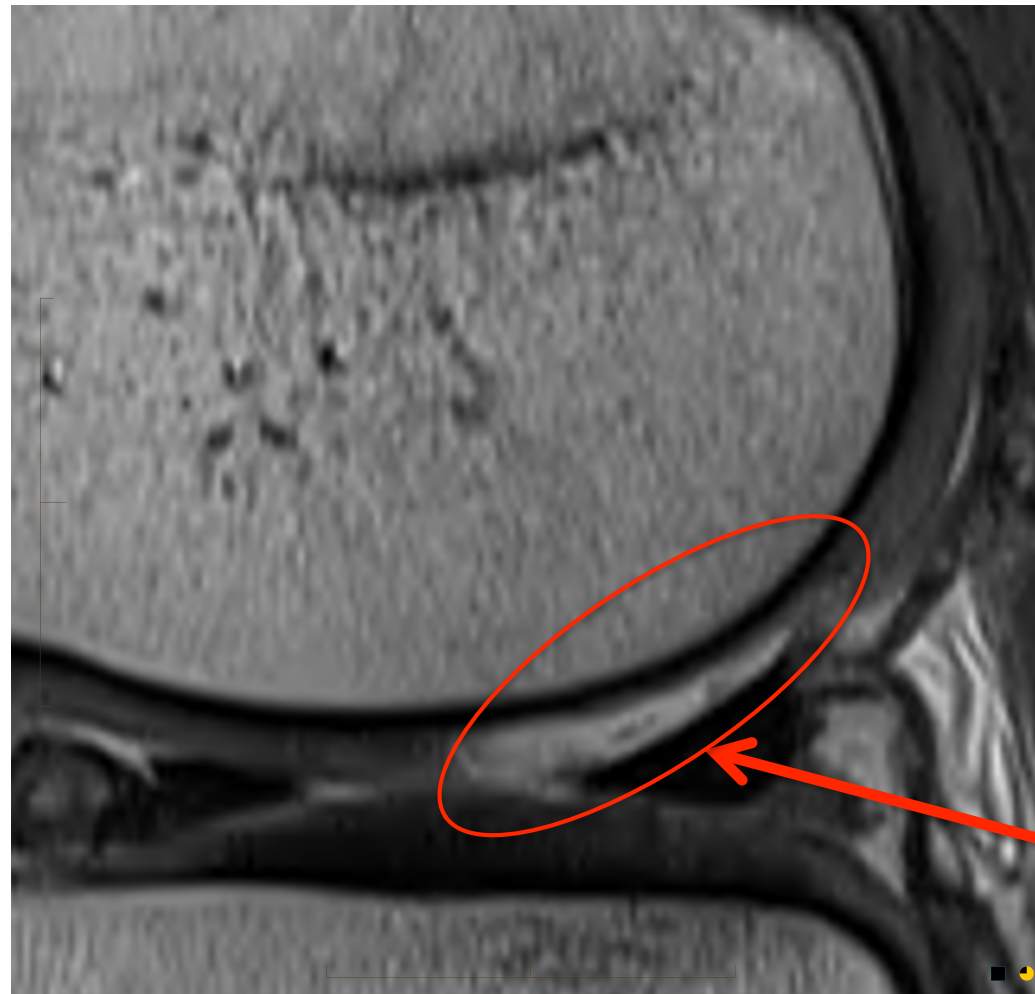
- Adipose derived stromal vascular fraction
 - 1 patient with cartilage defect
 - 4 years of pain
 - Refused surgery
 - Healthy
 - Competent
 - Fully informed and consented
 - 12 months follow up

2010

MRI – Left Knee 43 yo male

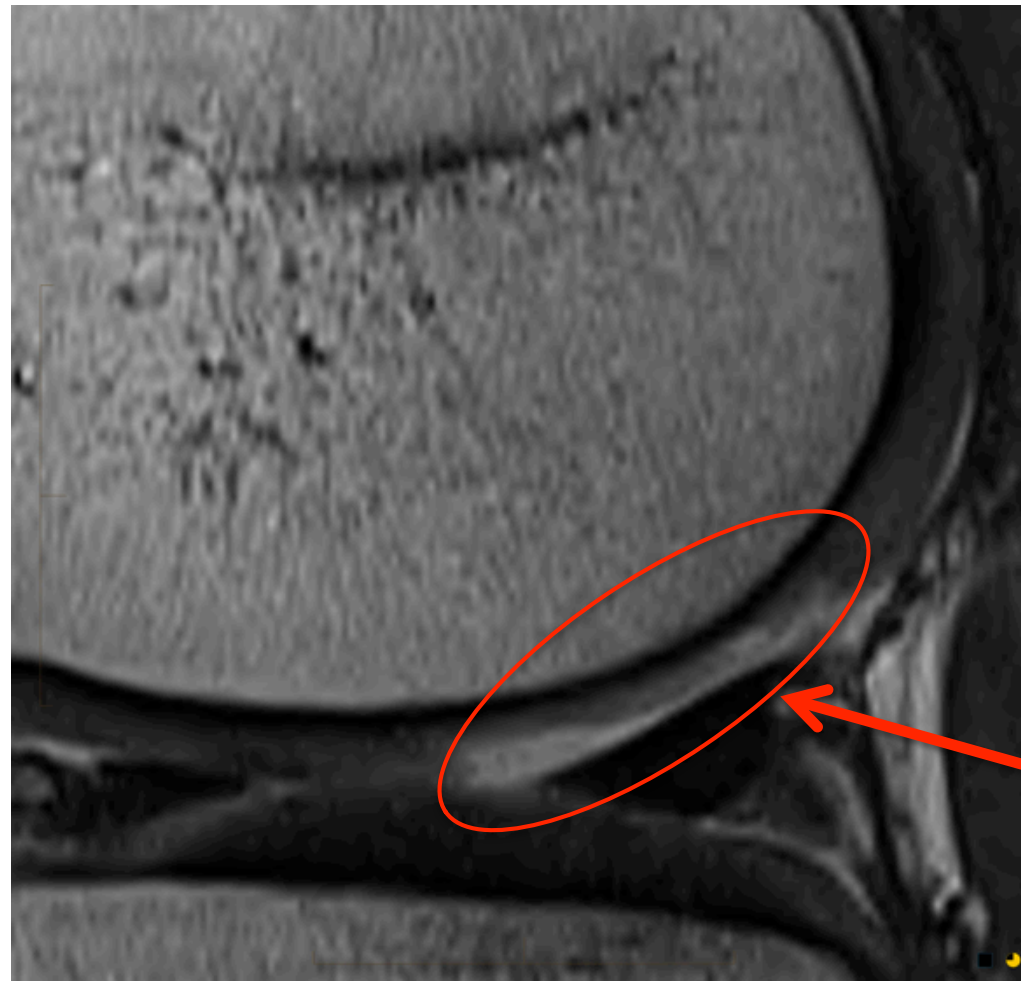


Left Lateral Femoral Condyle – Pre-treatment



Chondral
Defect

5 Months post treatment



Complete
Coverage of
defect with
30-50% thick
cartilage
(Grey Line)

12 Months post treatment



Defect
Coverage at
12 months
(Grey Line)

While we waited

2010/11



RCT - PRP



Ethics - SVF

Ethics PRP



Our work to date: Knees

2011

- Single injection of adipose derived stromal vascular fraction
- Three patients - 4 Knees osteoarthritis
 - One Grade 4
 - One Grade 3
 - Two patellofemoral joint arthritis – same patient

The this happened

Treatment trial for top agent

Kelly Ryan | Herald Sun | June 30, 2011 12:00AM



TIM Fletcher became a "human guinea pig" last week when he had stem cell therapy to try to repair a painful old knee injury.

The top real estate agent is one of only five Victorians to have had the treatment.

Mr Fletcher suffered years of pain caused by bone grinding on bone.

It was the success of stem cell therapy on animals that gave him the confidence to proceed with a medical technique still in its infancy.

"I had nothing to lose and I was very prepared to take the risks," Mr Fletcher said.

"No one really knows what the downsides are, but the upsides are out there and well known."

It was his family vet who tipped him off to the success of stem cell trials on animals.

"Given all the positive feedback I had heard about stem cell therapy in animals I was perfectly comfortable to proceed," he said.

The Herald Sun previously reported that stem cell trials on dogs in Melbourne had shown stunning



Then this

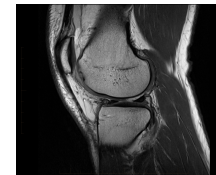


Then this



Ethics

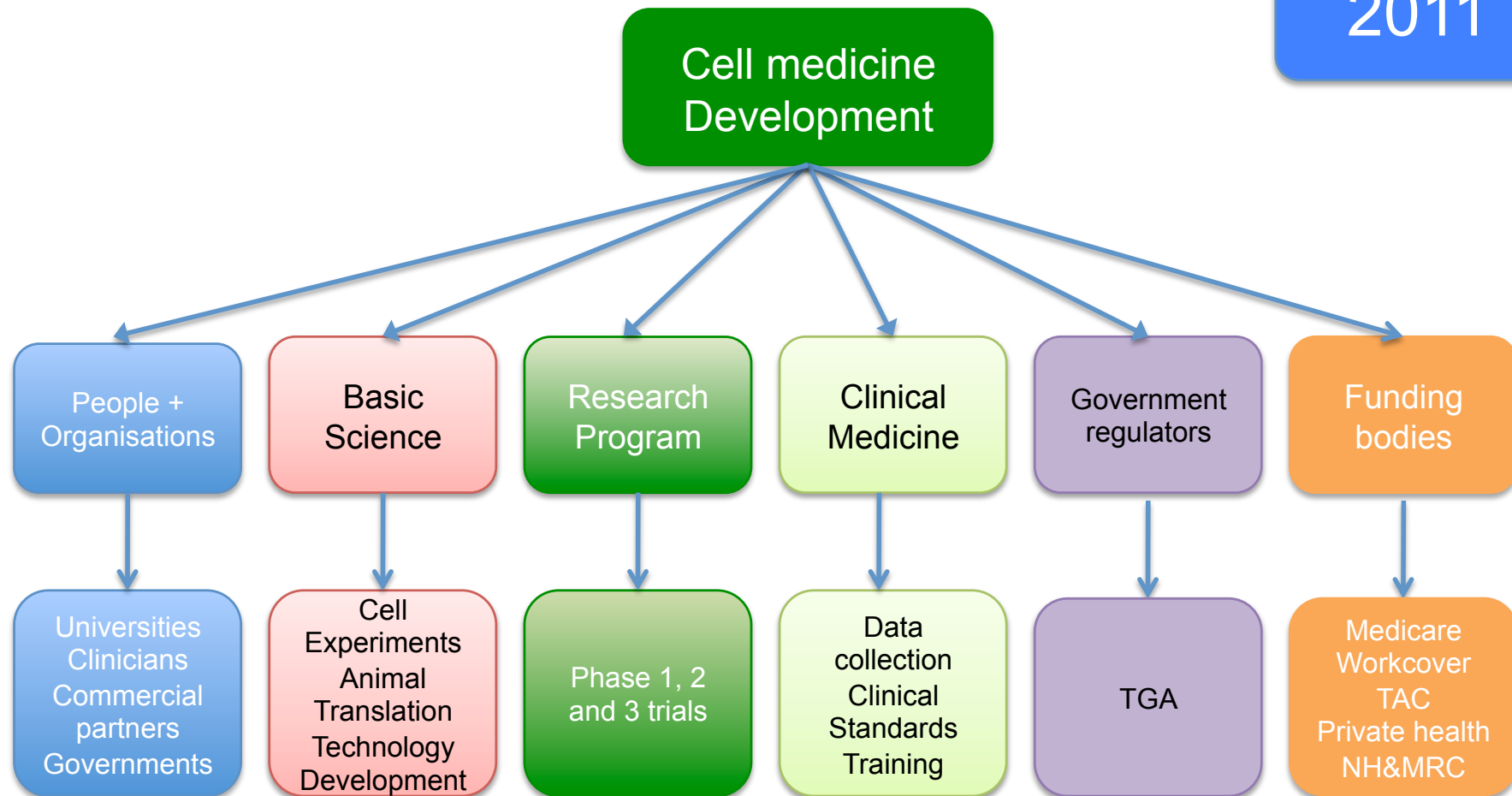
PRP RCT



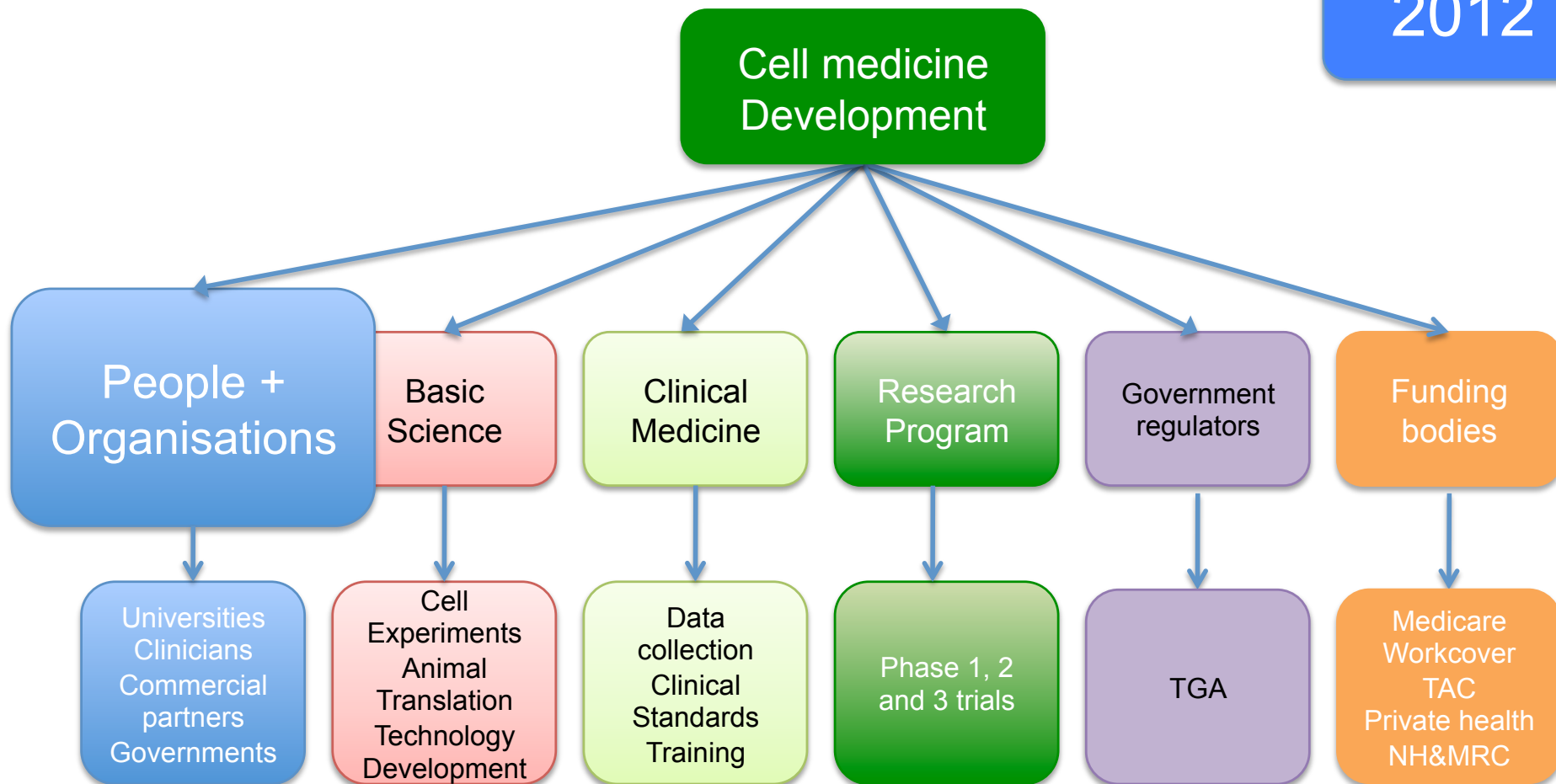
The big fish – Prof Richard Boyd (MISCL)



2011



2012

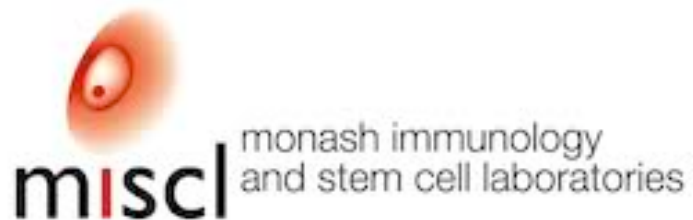
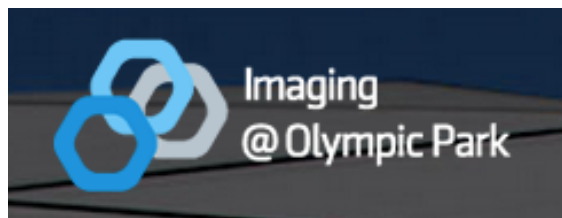


People and organisations

2011



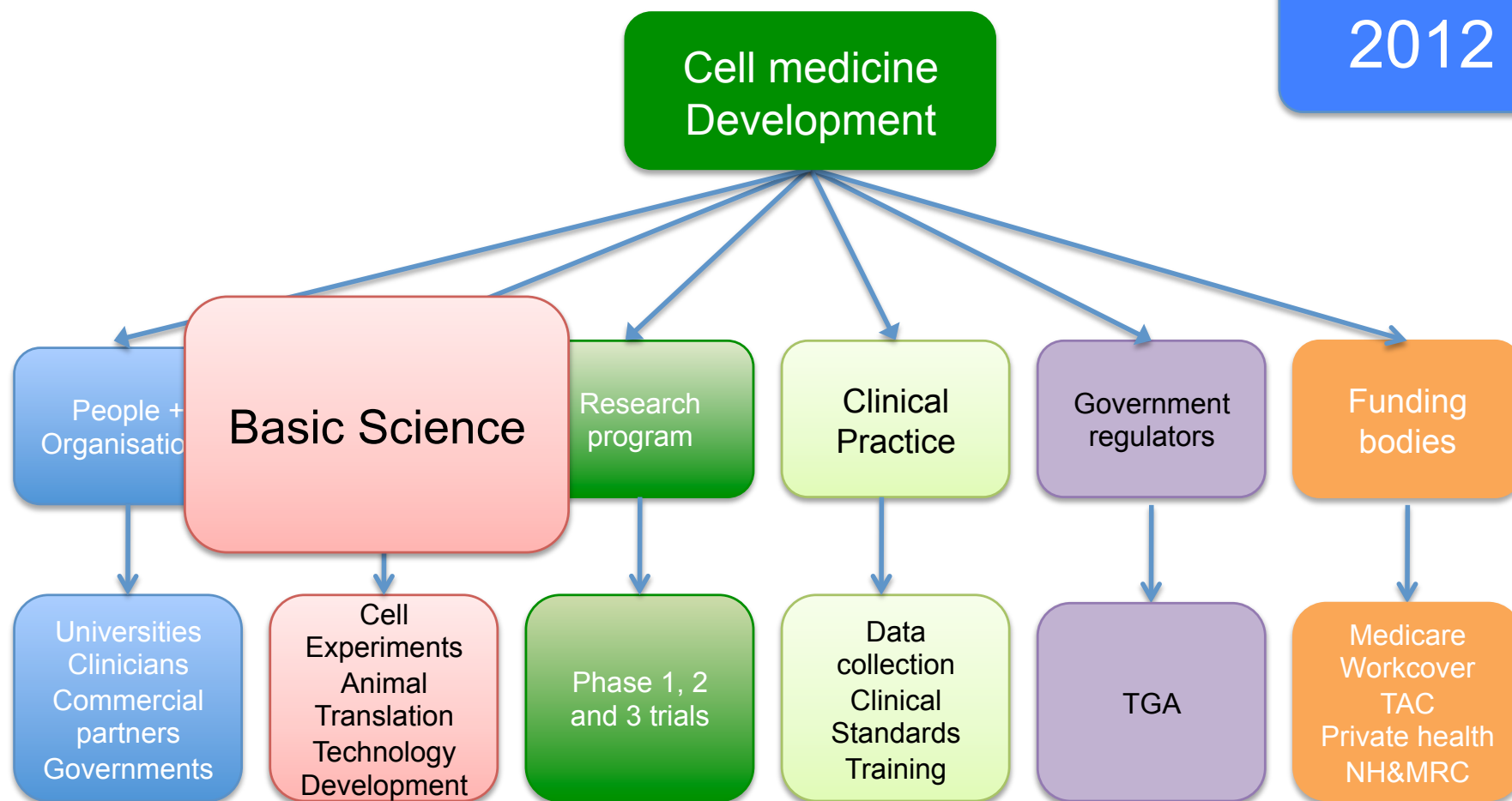
People and organisation



People

- Professor Richard Boyd (MISCL)
- A/Prof David Connell (IOP)
- Professor Flavia Cicutini (Alfred Hospital)
- Dr Kade Paterson (ACU)
- Dr Andrew Rotstein (Vic house Imaging)
- Dr John Flynn (Cosmetic surgeon)

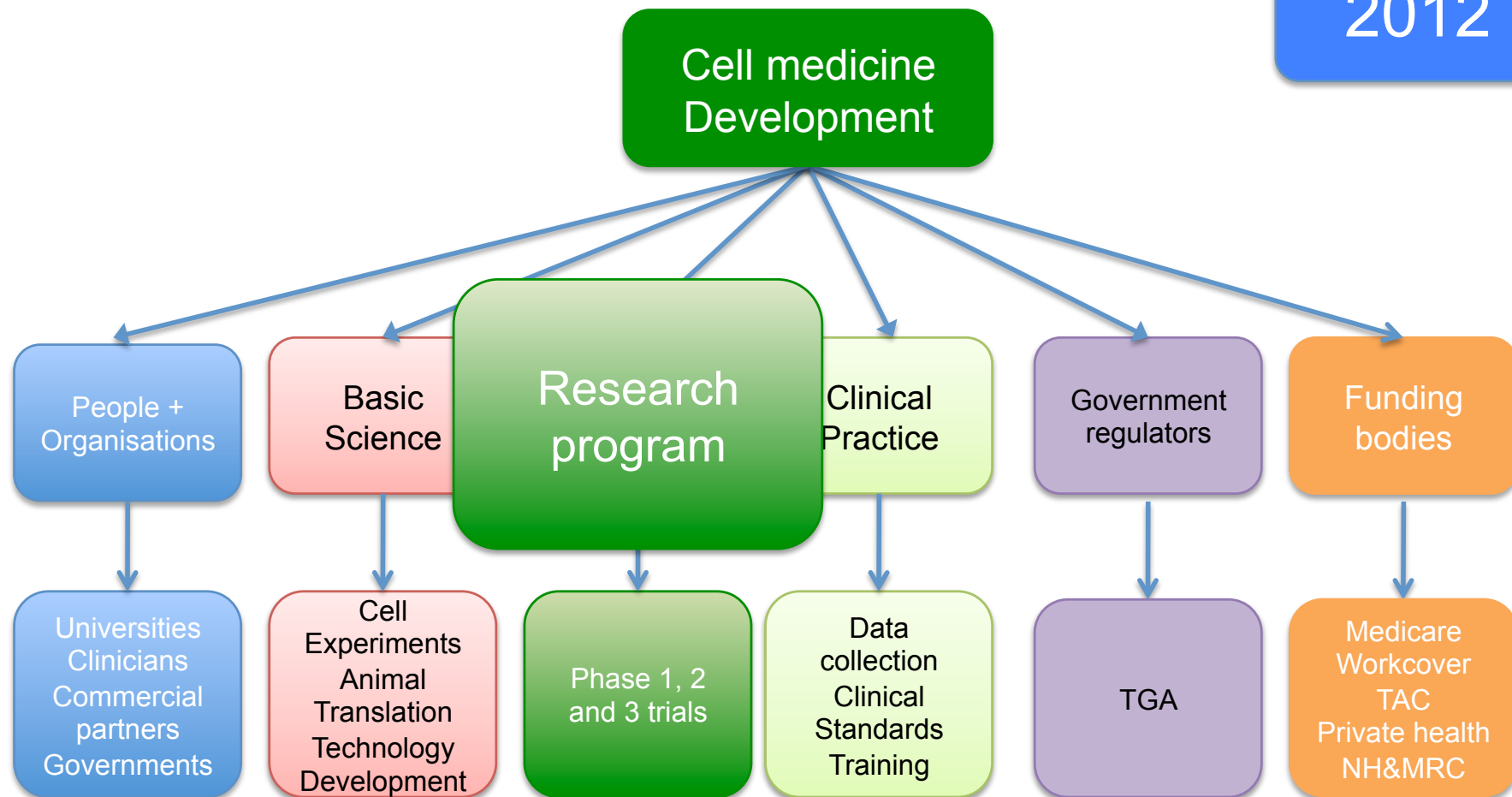
2012



Basic Science

- MISCL
 - Cell processing and storage protocols
 - Cell typing
 - Cell cytokine profiling
 - Basic cell research
 - Development of new technology
 - Translation to small animal models
- St George Veterinary Hospital
 - Large animal translation

2012



Research program

- Autologous adipose derived SVF for the treatment of Chondral defects and osteoarthritis
 - Collaboration between ACU MISCL Lakeside Sports Medicine, Imaging at Olympic Park
 - Ethics approval from ACU
 - Registered with the ANZTR
 - 3 injections of SVF 1 month apart
 - Cell counting and typing
 - Cytokine profiling of cells
 - Pain scales
 - Functional outcome measures
 - MRI follow up

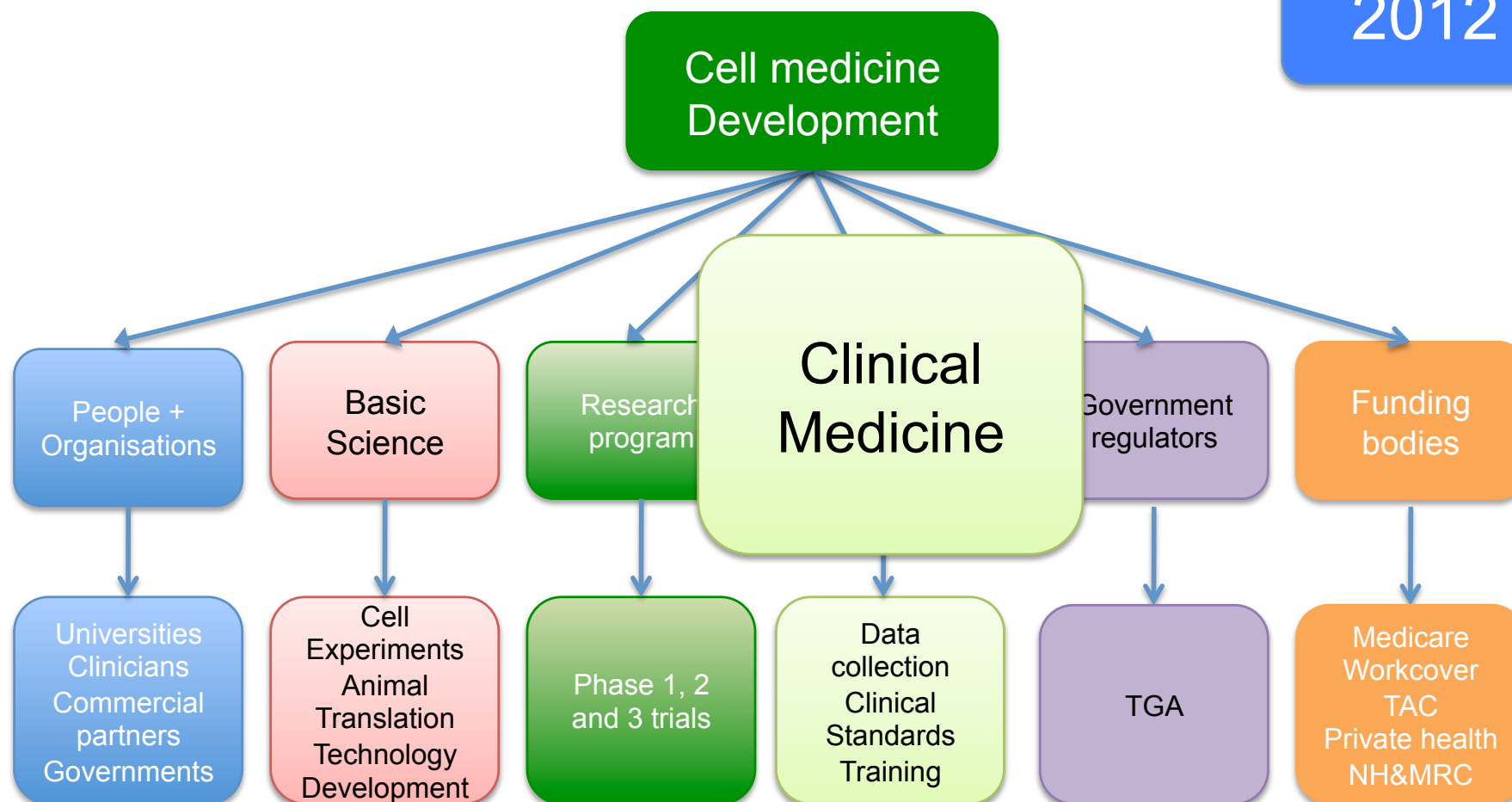
Research program

- SVF vs PLACEBO
 - Collaboration between MISCL, ACU, ProStem Cell
 - Ethics submitted
 - 3 injections of 1 month apart
 - Cell counting and typing
 - Cytokine profiling of cells
 - Pain scales
 - Functional outcome measures
 - MRI follow up

Research program

- Microfracture + HA, or PRP, or SVF
 - Dr Julien Frietag, La Trobe Uni, ACU and MISCL
 - Ethics approval from Latrobe University
 - Microfracture + 3 injections of test agent
 - Cell counting and typing
 - Cytokine profiling of cells
 - Pain scales
 - Functional outcome measures
 - MRI follow up

2012



Clinical Medicine

- All patients will be offered to enter a trial if eligible
- If ineligible or refuse entry they will be offered treatment if appropriate

Clinical Medicine

- MSC Clinic development
 - Benchmarking to IVF clinics
 - Clinic structure
 - Personnel
 - Quality control
 - Adverse event reporting
 - Work in progress

Clinical Medicine - Standardisation

- Standardised clinical practice
 - Ethical practice
 - Ethics approved treatment protocols only
 - Treatment by expert in their areas
 - Standardise patient selection and treatment
 - Standard patient diagnosis and classification
 - Exclusion and inclusion criteria
 - Treatment protocols
 - Standardise cell harvest and processing protocols (MISCL)
 - Standardised cell profiling (MISCL)
 - Standardised Patient follow up
 - Pain scales
 - Functional outcome measures
 - MRI follow-up
 - All outcomes will be published

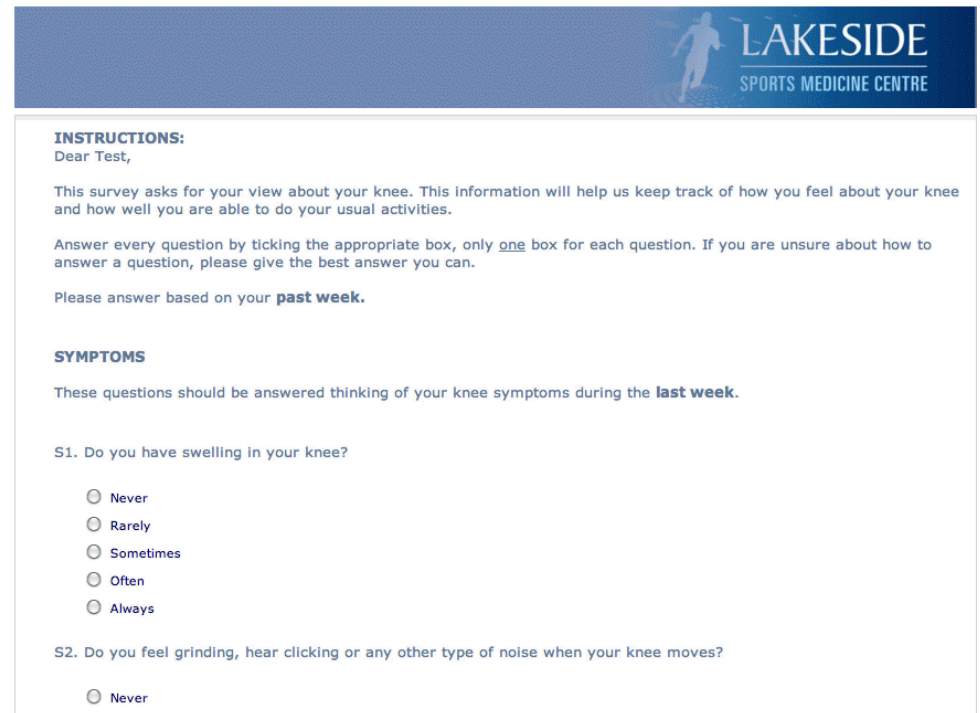
Patient follow-up



- Online data collection

Patient follow-up

- Tracking of pain and function
- Online outcome measures
 - WOMAC
 - KOOS
 - VAS

A screenshot of a patient follow-up survey form from Lakeside Sports Medicine Centre. The form has a blue header with the center's logo. The main content area is white with black text. It includes instructions for the patient, a section for symptoms, and two questions with radio button options.

INSTRUCTIONS:
Dear Test,

This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to do your usual activities.

Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Please answer based on your **past week**.

SYMPTOMS

These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?

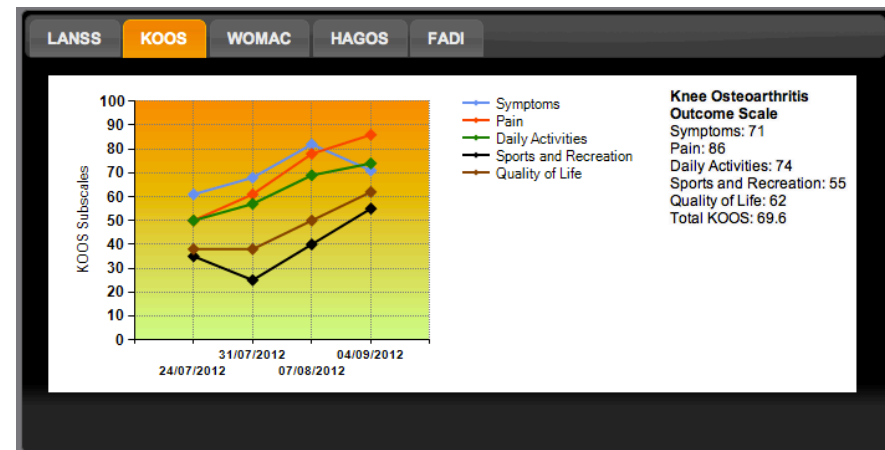
☐ Never
☐ Rarely
☐ Sometimes
☐ Often
☐ Always

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

☐ Never

Patient follow-up

- Individualised patient reporting
- Graph based system for reporting patient outcomes



Patient follow-up

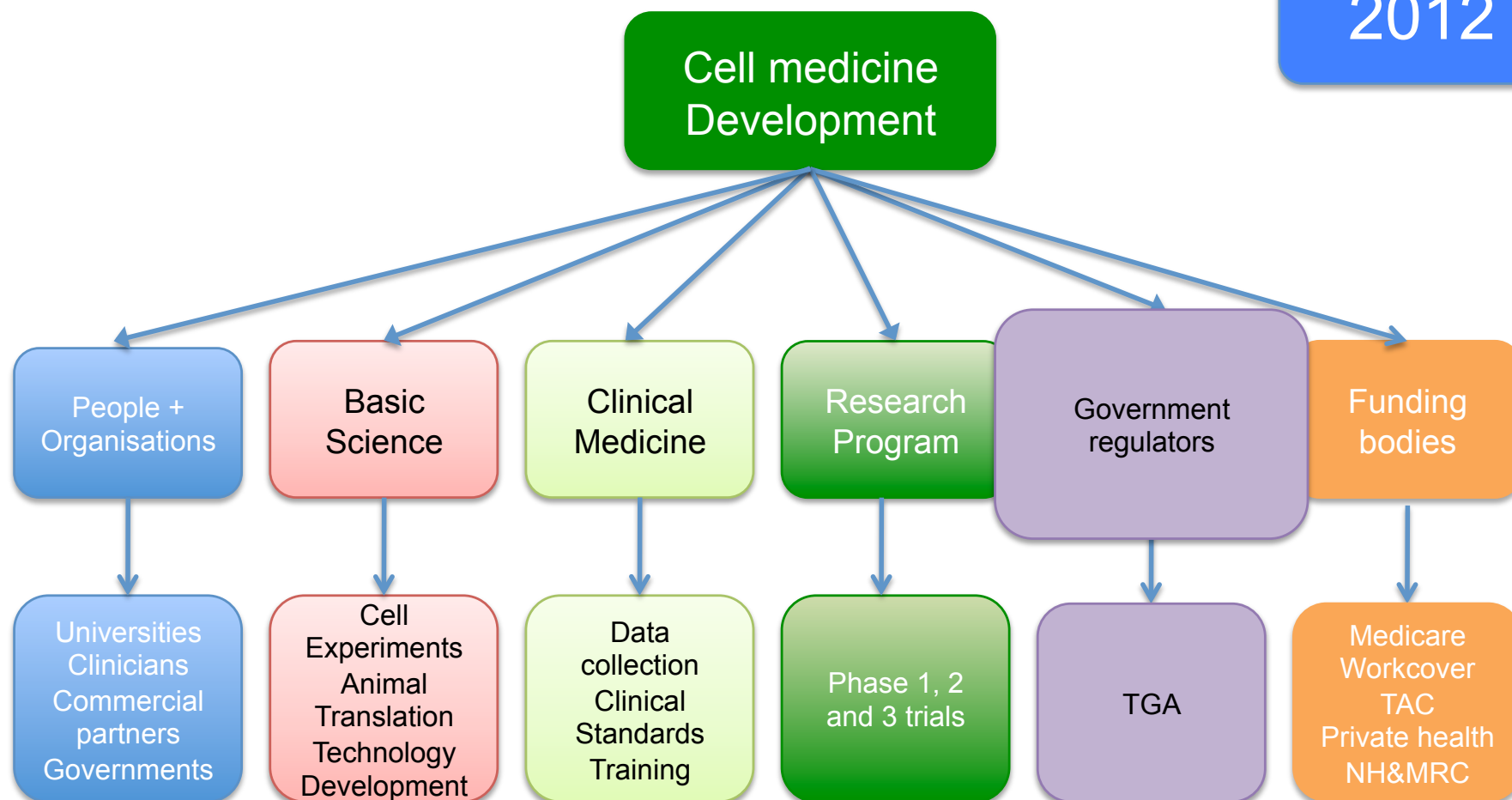
- Pooled data
- Long term data analysis
- Improved patient expectation and knowledge



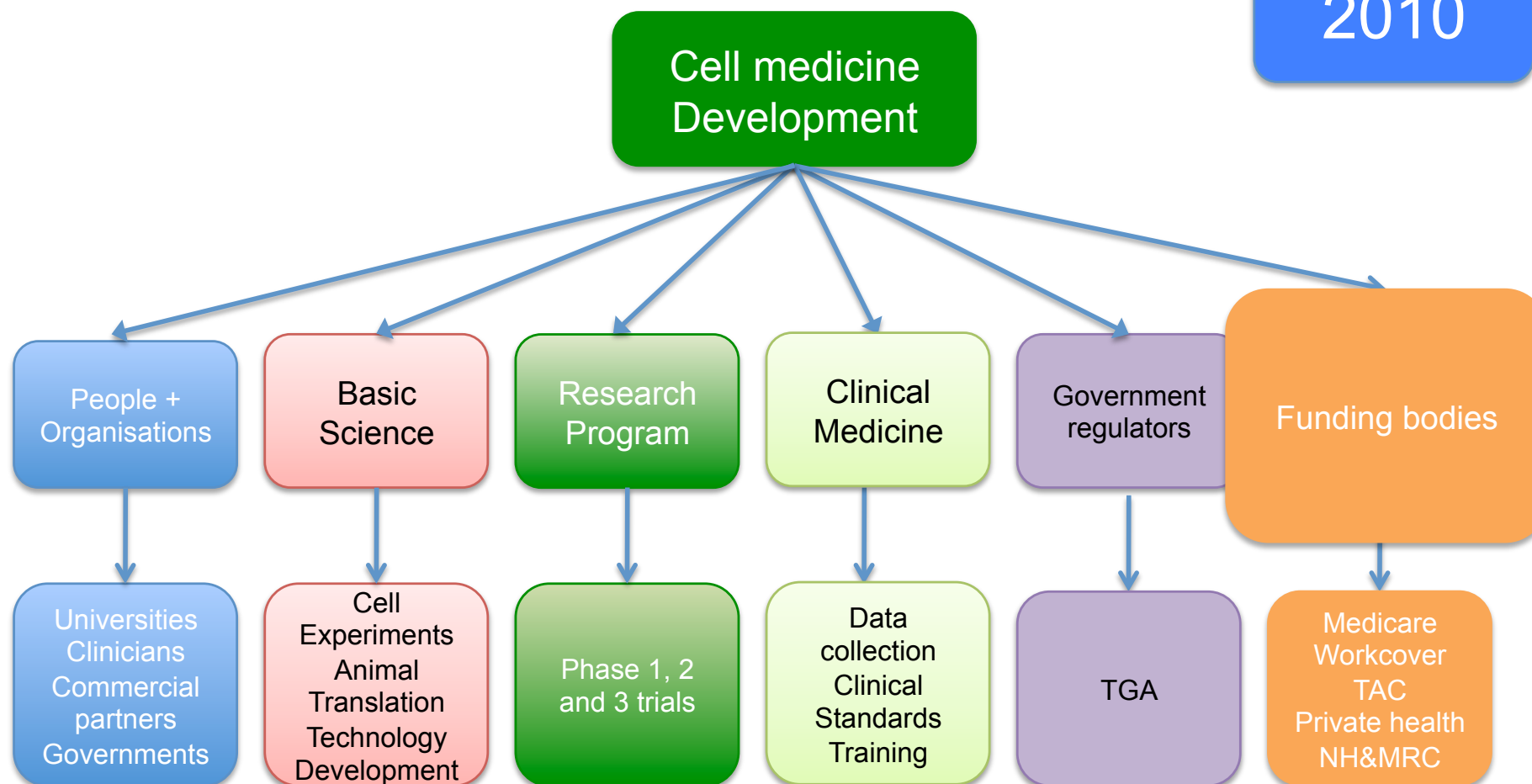
Patient follow-up

- Single database for
 - Patient demographics
 - Patient diagnosis and classification
 - Treatment protocol
 - Cell profiling
 - Patient outcomes
 - Pain
 - Function
 - Imaging

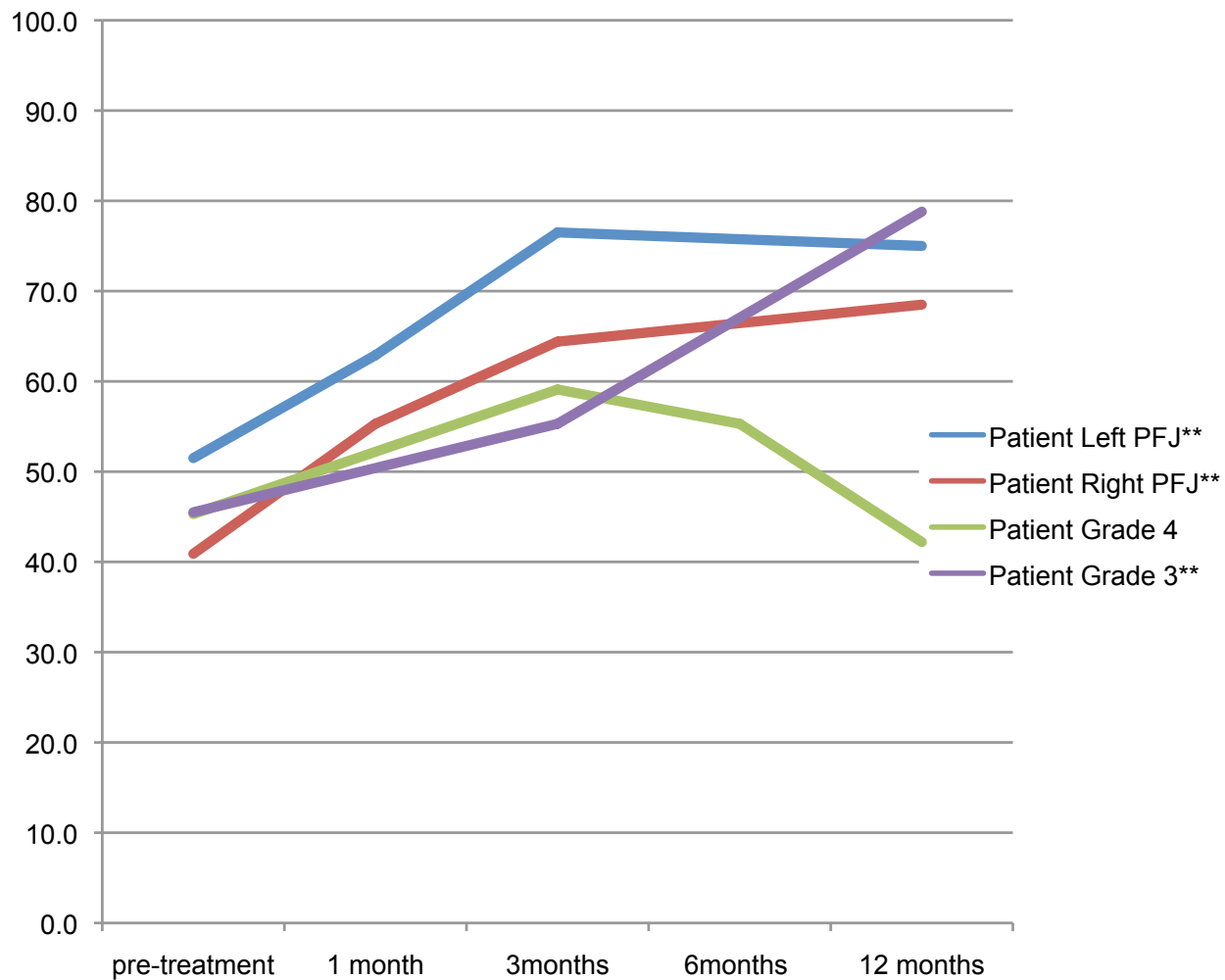
2012



2010



Osteoarthritis Knee– WOMAC



2012

Clinical thoughts for Cells + OA

- Will need multiple injections
- We will decrease pain and improve function in OA and cartilage defects
- Likely regenerate cartilage in some defects
- Possibly slow the degenerative process of OA
- With lots on technology and money will regenerate cartilage in OA.

Response to the environment

- Poor scientific rationale
- Poor cell characterisation
- Poor diagnosis
- Poor follow up
- Poor consenting
- Poor clinician accountability
- Clinicians treating outside clinical expertise
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Review aim:

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 - Safe
 - Reliable
 - Effective
 - Affordable

Review aim:

- Aim is to develop cell medicine to be
 - Safe
 - Reliable
 - Effective
 - Affordable
- On the way

Many thanks