

# Basic-Science Research in MSK Disease

*what, why, when, where, ....?*

## Christopher Little

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School of Medical Sciences  
Northern Sydney Local Health District*



# Basic/Fundamental/Discovery-Science or Biomedical Research in MSK Disease

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Investigator- and company-initiated research for commercial entities:  
*contracts negotiated with and finances paid to and controlled by Sydney University or Northern Sydney Local Health District (past 24 months)*

- *IMCRC - Allegra Orthopaedics & Bone, Ligament Tendon*
- *Fidia Farmaceutici*
- *Cynata Therapeutics*
- *CEVA Animal Health*
- *Regeneus Pty Ltd*

Consultant: Galapagos Pharmaceuticals

Board of Directors: ORS(US), IBJR, SpineCare Australia

Editorial Board: OA&C, OACOpen, A&R, JOR, BJR

*My presentation does not include discussion of off-label or investigational drug use*

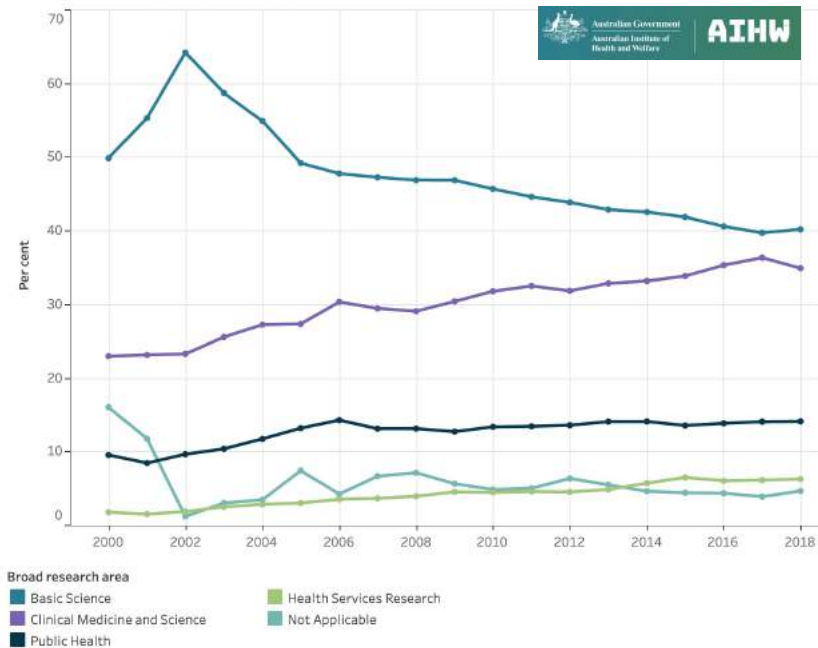


## NHMRC Australian standard research classifications Broad Research Area

- Basic Science
- Clinical Medicine and Science
- Health Services Research
- Public Health



Figure 2: NHMRC grant spending by broad research area, 2000 to 2018



Broad Research Area	Year	Applications	Grants awarded	Funded rate	Proportion of grants awarded	Total value
Basic Science	2019	1821	221*	12.1%	75.2%	\$173,947,106
	2020	1899	191	10.1%	67.5%	\$169,807,794
Clinical Medicine and Science	2019	566	45	8.0%	15.3%	\$40,231,653
	2020	675	59	8.7%	20.8%	\$57,272,149
Health Services Research	2019	117	12	10.3%	4.1%	\$8,263,881
	2020	125	10	8.0%	3.5%	\$10,869,947
Public Health	2019	147	16	10.9%	5.4%	\$19,301,455
	2020	190	23	12.1%	8.1%	\$21,772,673

\*Includes one application that was funded by the Australian Communications and Media Authority for research on the health effects of Electromagnetic Energy.

Broad Research Area	Year	Applications	Grants awarded	Funded rate	Proportion of grants awarded	Total value	Mean budget	Proportion of \$ awarded
Basic Science	2019	805	95	11.8%	38.6%	\$137,175,847	\$1,443,956	37.5%
	2020	690	71	10.3%	30.0%	\$124,347,696	\$1,751,376	33.8%
	2021	630	87	13.8%	34.3%	\$155,915,598	\$1,792,133	39.0%
Clinical Medicine and Science	2019	593	89	15.0%	36.2%	\$149,136,432	\$1,675,690	40.8%
	2020	600	100	16.7%	42.2%	\$154,395,383	\$1,543,954	42.0%
	2021	577	98	17.0%	38.6%	\$157,838,020	\$1,610,592	39.5%
Health Services Research	2019	194	20	10.3%	8.1%	\$23,962,685	\$1,198,134	6.5%
	2020	189	20	10.6%	8.4%	\$27,076,237	\$1,353,812	7.4%
	2021	196	16	8.2%	6.3%	\$16,684,710	\$1,042,794	4.2%
Public Health	2019	265	42	15.8%	17.1%	\$55,598,493	\$1,323,774	15.2%
	2020	301	46	15.3%	19.4%	\$61,655,829	\$1,340,344	16.8%
	2021	319	53	16.6%	20.9%	\$69,194,209	\$1,305,551	17.3%
Total	2019	1857	246	13.2%	100.0%	\$365,873,457	\$1,487,290	100.0%
	2020	1780	237	13.3%	100.0%	\$367,475,145	\$1,550,528	100.0%
	2021	1722	254	14.8%	100.0%	\$399,632,537	\$1,573,356	100.0%



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## ABS R&D research classifications

- Pure Basic
- Strategic Basic
- Applied
- Experimental development



**Pure basic:** experimental and theoretical work; acquire new knowledge without looking for long term benefits other than the advancement of knowledge.

**Strategic basic:** experimental and theoretical work; acquire new knowledge directed into specified broad areas; expectation of useful discoveries; provides the broad base of knowledge necessary for the solution of recognised practical problems.

**Applied:** original work to acquire new knowledge with a specific application in view; determine possible uses for the findings of basic research or new ways of achieving some specific and predetermined objectives.

**Experimental development:** systematic work, using existing knowledge directed to producing new materials, products or devices, to installing new processes, systems and services, or to improving substantially those already produced or installed.





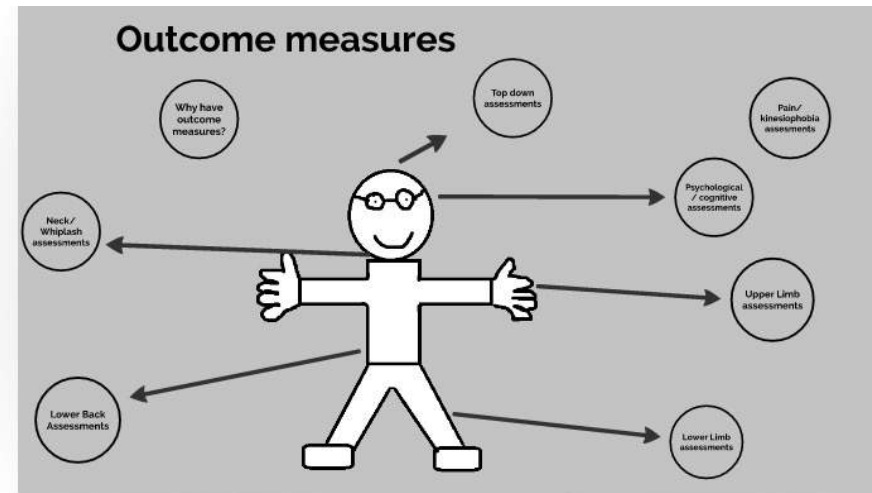
## Serial bio-samples

- Monitor response, Tx engagement – **Clinical/Exp Devel**
- Define responders/non-responders – **Applied**
- Identify pathways modulated – **Applied/Strategic Basic**
- RNA-Seq, MS proteomics ... – **Pure/Strategic Basic**

PT, Pharma, Surgery ...



MSK condition, patient pop<sup>n</sup>...



Clinical, Health Services, Public Health

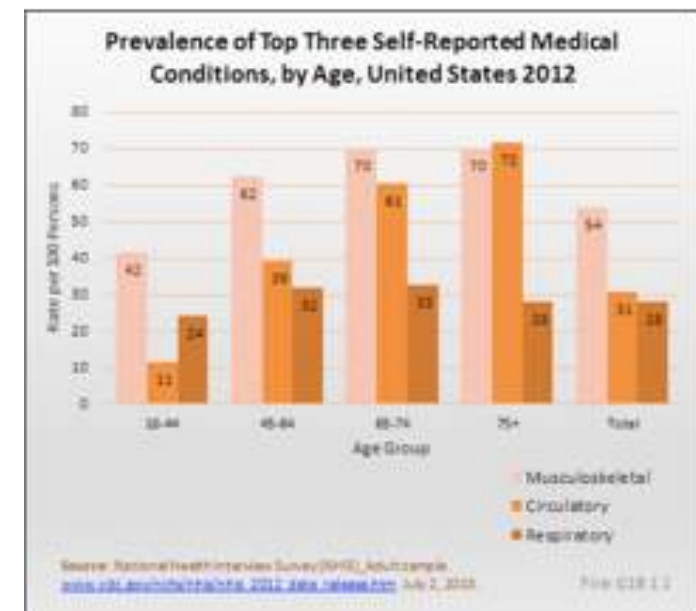
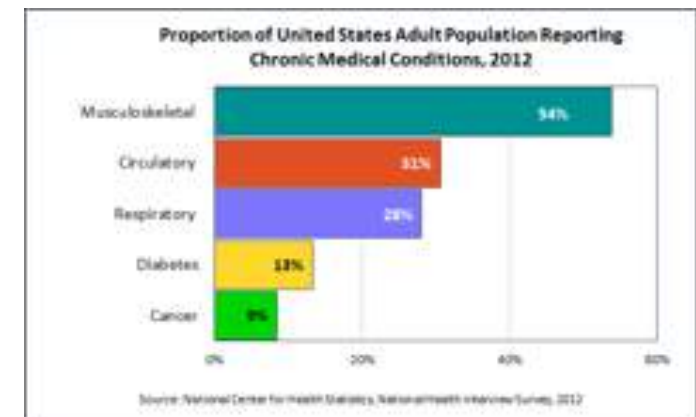
WHO Global Burden of Disease (2012) found that MSK diseases:

- affect >1.7 billion people worldwide
- 2<sup>nd</sup> greatest cause of disability
- have the 4<sup>th</sup> greatest impact on overall health of the world population when considering both death and disability

MSK disease in USA:

- affect >one of every two age 18 and over
- affect ~three out of four age 65 and over
- cost ~6% of the annual GDP

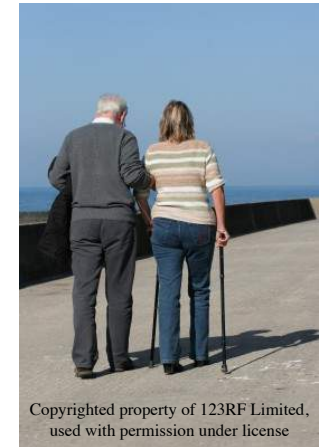
1 in 8 persons of prime working age reported lost work-days due to a MSK condition - a total of 216 million days in 2012!



# Basic Science MSK research .... “why?”

## Affecting >7 million Australians

- 14% of the total burden of disease in Australia
- 2<sup>nd</sup> leading cause of non-fatal burden (23%) after mental health and substance abuse (24%), but the leading cause in women
- leading single cause by far of disability: 31% of all persons with a disability (1.2 million) report it is due due to a MSK condition
- >80% of chronic pain

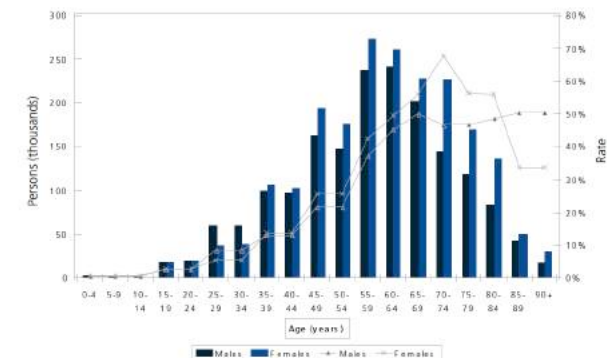


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## Fourth most costly disease group in the health system

- \$5.7 billion in direct costs (2008-09)
- nearly 1/3<sup>rd</sup> of all presentations to health professionals
- 12% of hospitalizations
- 13% of persons who took medication did so for a MSK disorder
- 41% of early retirements due to ill-health in 45-64 yo, at an annual cost of >\$16 billion in lost GDP

*Arthritis and Musculoskeletal Diseases was added as an Australian National Health Priority in 2002*





# Basic Science MSK research .... “why?”

Affecting >7 million Australians

- 14% of the total burden of disease in Australia
- 2<sup>nd</sup> leading cause of non-fatal burden (23%) after mental health and substance abuse (24%), but the leading cause in women



For the most common chronic painful MSK conditions e.g.

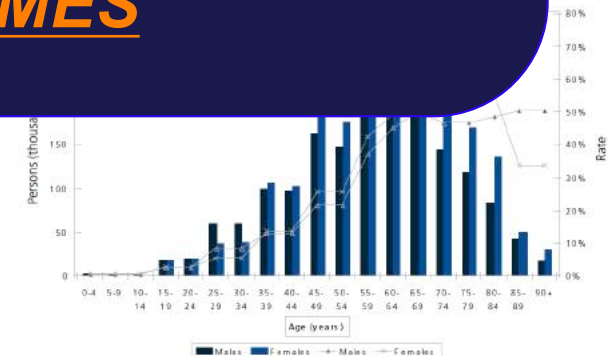
Back pain

Osteoarthritis (OA)

Tendinopathy

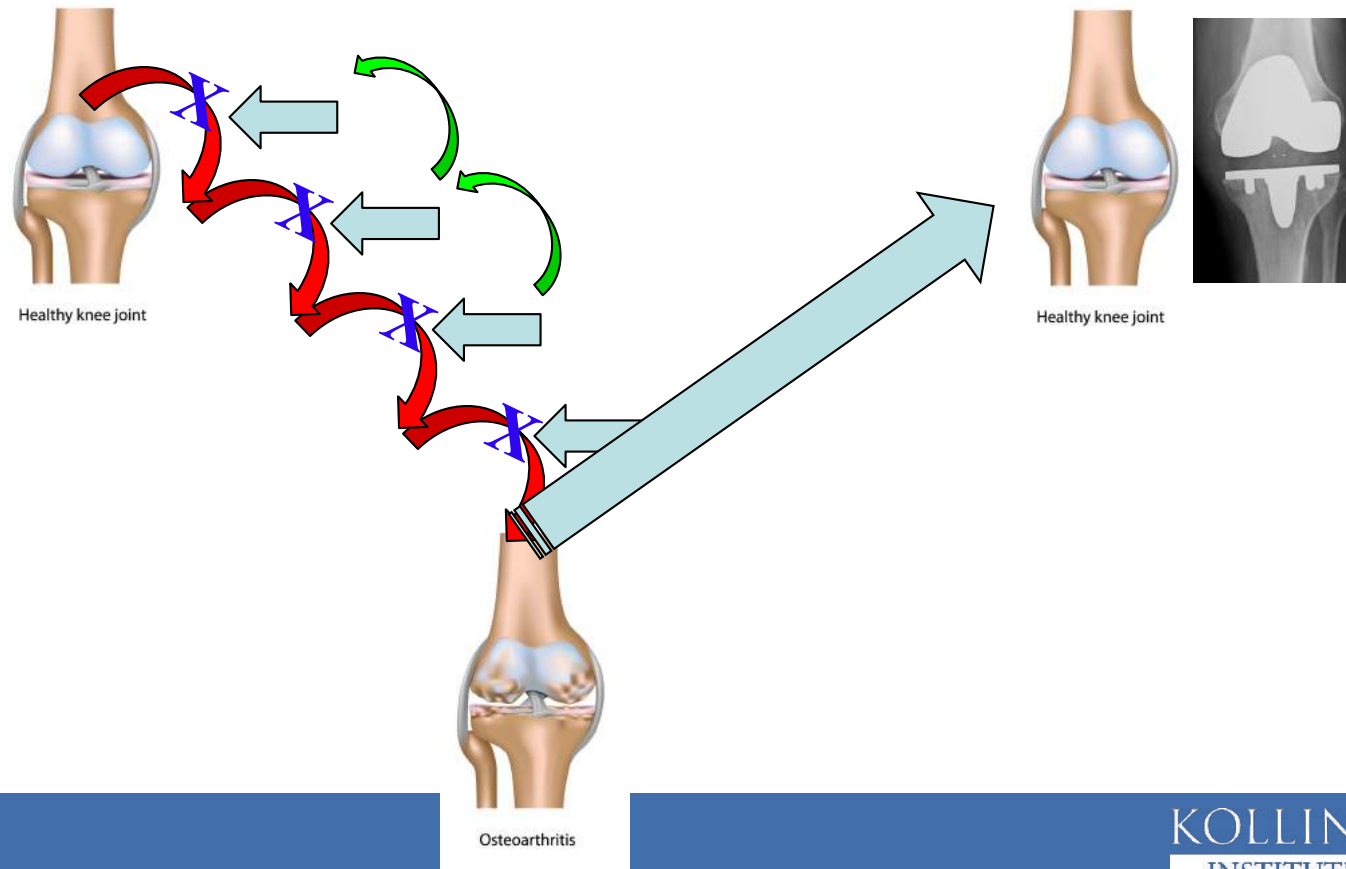
**THERE IS NO CURE & CURRENT TREATMENTS HAVE POOR LONG-TERM OUTCOMES**

*Arthritis and Musculoskeletal Diseases was added as an Australian National Health Priority in 2002*



## Define pathophysiologic disease mechanisms Structural AND Symptomatic

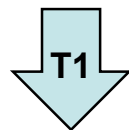
- ***OA, tendon & ligament injury/disease, IVDD .....***
- ***Cell biology, molecular biology, biochemistry, biomechanics, genetics .....***



# Basic Science MSK research .... "when?"

**Discovery: Pre-clinical models**  
**(*in vitro* and animal models)**

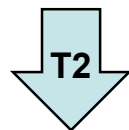
63% proceed to Phase I with failure primarily due to safety (82%)<sup>1</sup>;



50-65% proceed to Phase II<sup>1,2</sup> with failure due to safety (62%) & efficacy (15%)

**Development: Clinical trials (Phase II and III)**

~30% successfully transition from Phase II to Phase III;<sup>1,2</sup>  
greater success if existing human genetic linkage, efficacy biomarkers and confidence in patient selection;  
failure due to efficacy (65%)<sup>\*\*</sup> & safety (30%)<sup>1</sup>



60-67% of Phase III progress to approval (~10% of all drugs entering Phase 1);<sup>1,2</sup>  
failure primarily due to efficacy<sup>\*\*</sup>

**Delivery: Evidence based guidelines, post-market surveillance**

~21% have post-market safety warnings added and ~4% are withdrawn<sup>3,4</sup>



**Dissemination: Health policy & practice implementation**

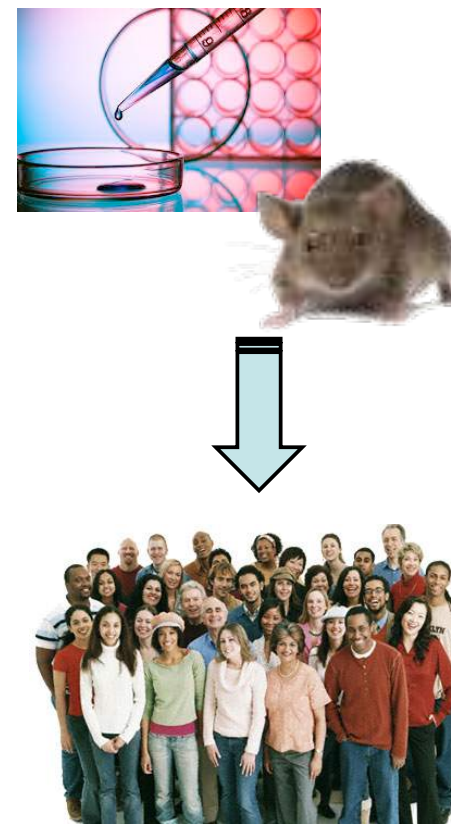


**Population Health Impact**

On the predictive utility of animal models of osteoarthritis

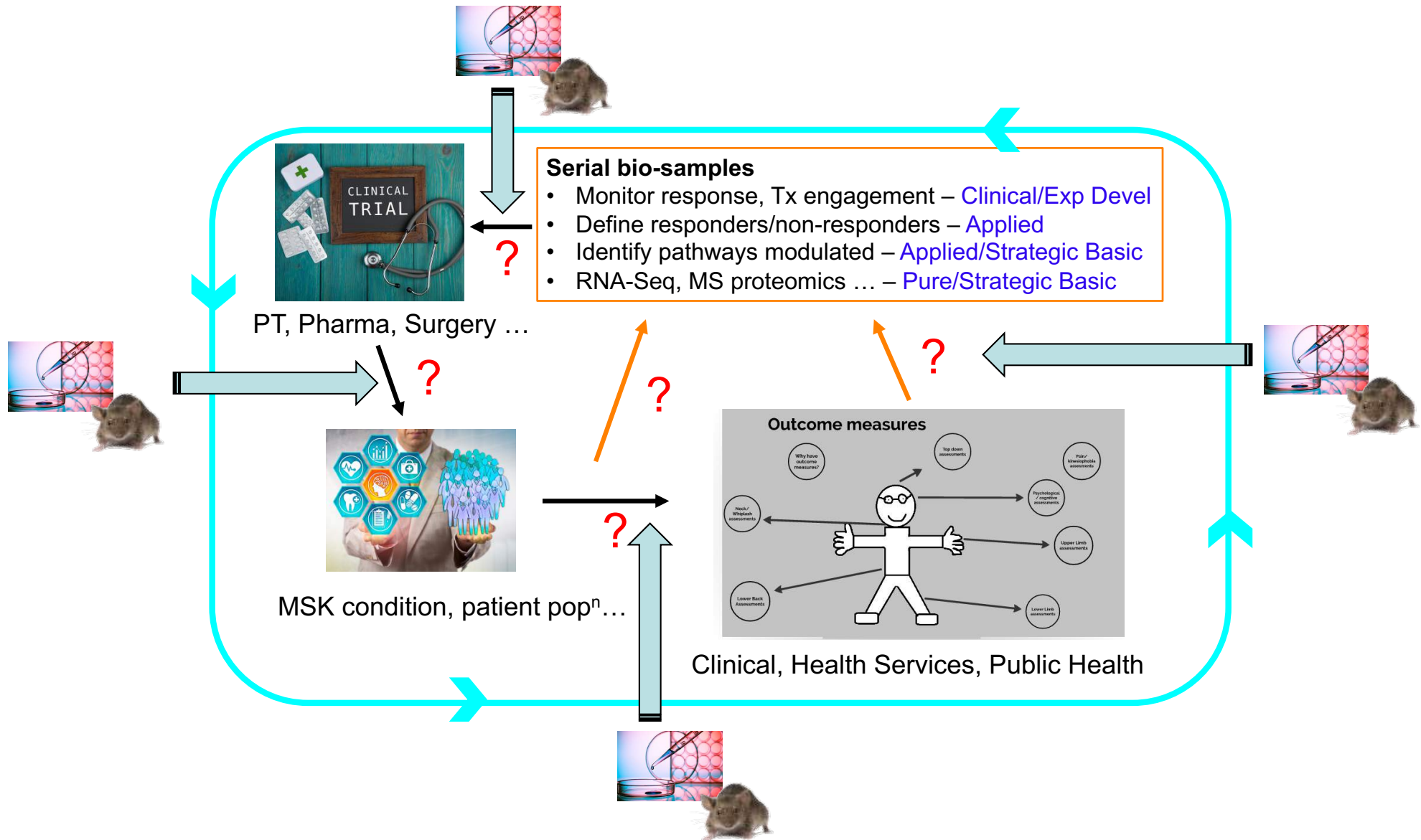
*Arthritis Research & Therapy* (2015) 17:225

Anne-Marie Malfait<sup>1\*</sup> and Christopher B. Little<sup>2</sup>



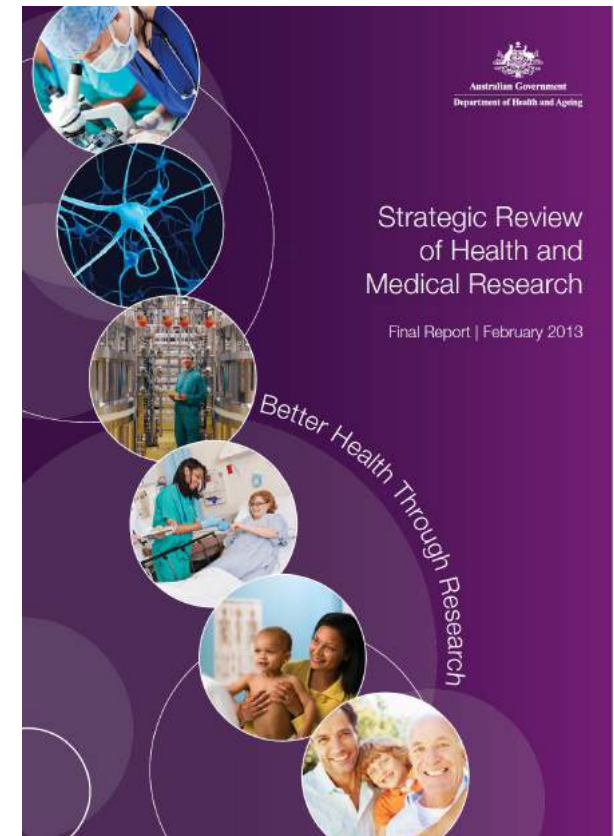
<sup>1</sup>Cook et al. *Nat Rev Drug Discovery* 2014;13:419-431.  
<sup>2</sup>Hay et al. *Nat Biotechnol.* 2014;32:40-51. <sup>3</sup>Lexchin J. *Br J Clin Pharmacol.* 2015;79:847-59. <sup>4</sup>Lexchin J. *Open Med.* 2014;28:e14-9

# Basic Science MSK research .... "when?"



*“... lack of a sufficiently strong connection between Health and Medical Research and the delivery of healthcare services ...”*

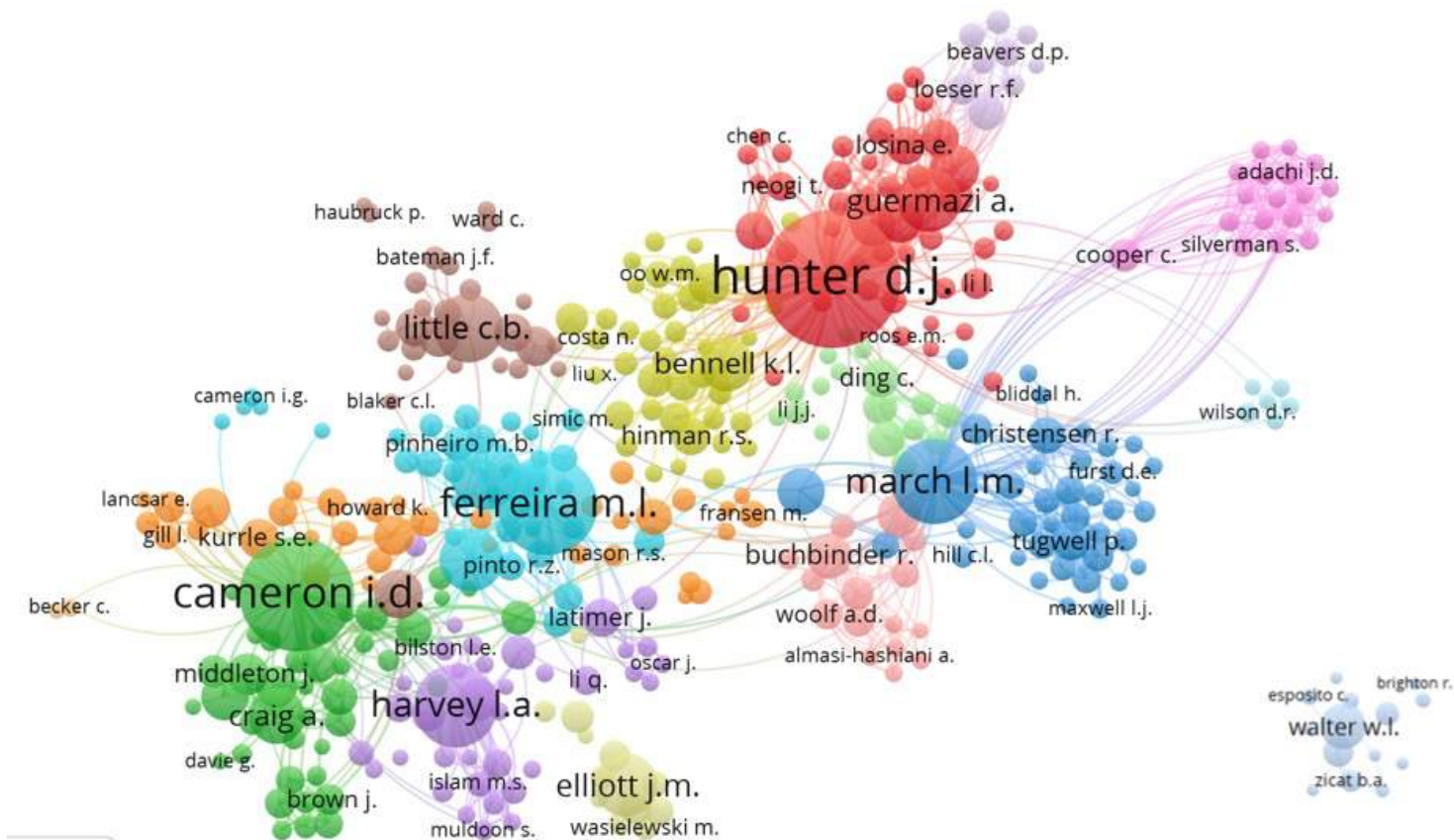
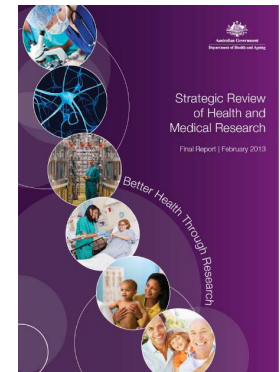
*“... overarching vision for Health and Medical Research is one where research is fully embedded in all aspects of healthcare to deliver ‘Better Health Through Research’ ...”*



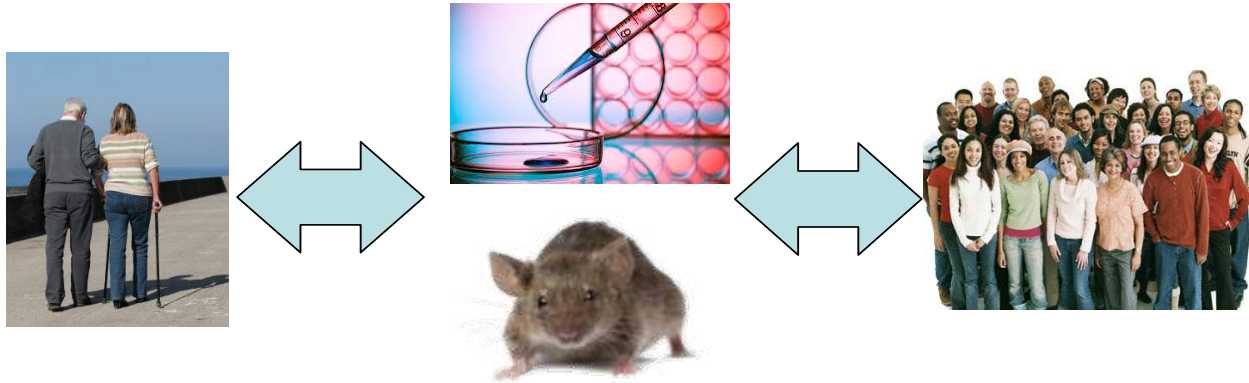


## "Embedded" in Healthcare ...

- *± physically embedded on a Health campus*
- Network and Connectivity with Health Research/ers



*“Bedside-bench-bedside-bench.....”*



## Basic Science Research: defining and targeting pathophysiology

### *Successes*

- Biologic therapies for RA
- New treatments and biologics for osteoporosis

### *Maybe.....?*

- OA: Lorecivivint (Wnt-pathway), Sprifermin (FGF18), Canakinumab (IL1), stem cells, joint distraction, .....

### *Maybe not .....?*

- Chronic pain: Tanezumab vs Fasinumab (anti-NGF)



# Gaps & Opportunities .....

**CLINICIAN**  
*Anita Mudge*



Software based on the conventional gait model is used in most clinical gait laboratories. However, known limitations in the model can affect data output and influence surgical decision-making.

**CLINICAL RESEARCHER**  
*Michelle Hall*




The majority of OA research has investigated the influence of gait parameters in isolation. However, it is likely that multiple biomechanical variables interplay with each other to characterise movement strategies.

**BASIC SCIENTIST**  
*Farshid Guilak*




The magnitudes and modes of joint loading which result in pathological changes and disease progression are poorly understood. The mechanisms by which cellular-level signals influence tissue homeostasis, and their interaction with systemic factors needs to be determined.

**CLINICIAN**  
*Shirley Yu*



Successful clinical outcome measures do not reach widespread use in the clinical context. This is in part due to differing values, goals and assumptions between efficacy and effectiveness research, and the application of outcome measures in a real-world context and its feasibility.

**CLINICAL RESEARCHER**  
*Michele Sterling*



Pain is what the person says it is. The construct is difficult to measure. Besides clinical assessment of pain mechanisms is blunt and confounded by many factors – psychological, general health, time of measurement, etc.

**BASIC SCIENTIST**  
*Sanaa Zaki*



Minimum symptomatic relief targets that are translationally relevant have not been established for pain outcomes or animal models used in pre-clinical OA research. There is a gap between how pain is measured and defined in pre-clinical studies and how it is reported through patient-reported outcomes.

**CLINICIAN**  
*Rory Clifton-Bligh*




Lack of gold standard measurement to assess a new test against, unacceptable assay variation, over-estimation of diagnostic accuracy through inappropriate study design, lack of clinical outcome studies, lack of cost constraint that allows testing with low clinical utility.

**CLINICAL RESEARCHER**  
*Brian Johnstone*



Basic scientific discovery, validation, qualification and reporting standards in the field of biomarkers have lagged behind. The most promising molecular targets and assays still rest largely on face validity and lack both proof of origin and clinical relevance.

**BASIC SCIENTIST**  
*Brian Johnstone*



Biomarker science has been too focused on cartilage matrix protein degradation products as biomarkers without success. Poor in vitro OA model systems, which do not recapitulate the whole joint disease process. Degradation biomarkers may not be good for all facets of OA, biomarkers not matched to disease activity and status.

**BIOMECHANICS SOLUTIONS**

- Any solutions to enhance repeatability of gait lab output need to be applicable to those of all abilities and limitations referred for gait analysis. Minimising additional demands on the patient is important to translate a new tool into clinical practice.
- Hypothesis-generating analyses of existing OA biomechanical datasets to explore complex movement strategies in people with OA and subsequently examine the relevance of distinct movement strategies with clinical outcomes. Robust longitudinal studies to evaluate the association between biomechanical outputs from gait models informed with patient-specific parameters and clinical outcomes. Machine learning techniques may provide a novel way to capture information of equivalent quality as can be generated from laboratory data through wearable sensors in a real-world setting.
- A fundamental understanding of biomechanics in normal and pathological conditions from the whole body to subcellular levels is required. With this knowledge, identification of the cellular mechanotransduction pathways may provide new therapeutic targets to enhance tissue regeneration or alter the course of OA.

**MEASUREMENT OF PAIN SOLUTIONS**

- Use advances in technology and statistics to develop novel chronic pain measurement tools. Identification of truly meaningful outcomes measures that clinicians can prioritise and act upon.
- Pilot and phased implementation of outcome measures to ensure feasibility and uptake.
- Standardised language about pain and pain mechanisms.
- Better alignment of pain measurements in the animal models and the pain experience in human patients.
- Reconsider how we design and conduct human pain trials - match model phenotype to disease phenotype, match clinical trial cohort with pre-clinical study cohort and the timing of the intervention.

**BIOLOGICAL MEASUREMENTS SOLUTIONS**

- Methodological standards for designing and reporting studies of diagnostic accuracy, including standardised expression of association between biomarker and disease outcome and assessing dependence of biomarker associations on other clinical factors.
- Improve systematic evaluation of the evidence which requires a coordination of the wider biomarker research agenda – which requires international multi-team collaborations. Such collaborations will enable the use of case definitions with standardised and transparent criteria, gold standard clinical end points, standardised and transparent sample collection and assay methodologies, standardised and transparent reporting.
- Going beyond protein degradation biomarkers into use of techniques of the many omics fields. 'Joint on a chip' and other multi-tissue 3D in vitro systems. Wider range of OA animal models involving different joints, naturally occurring OA in older animals particularly useful if different causative factors were identified, better matching the newer thinking of multiple OA phenotypes.

**CLINICIAN**  
*Shaun O'Leary*



Predicting response to management based on patient characteristics alone is challenging and often influenced by many patient characteristics. Clinical decision making regarding different management approaches can be especially difficult for those with a higher severity of disease.

**CLINICAL RESEARCHER**  
*Leticia A. Deveza*




Identifying phenotypes in clinical practice and research is not well established. Phenotypes need to be recognisable using easy to obtain patient data (either clinical, imaging or laboratory).

**BASIC SCIENTIST**  
*Chris Little*



Poor alignment of discovery/pre-clinical research to patients to define relevant pathophysiological stratification. Focus on patient phenotypes (observable characteristics) rather than endotypes (pathophysiological mechanism).

**CLINICIAN**  
*James Linklater*




Significant discordance between the use of imaging in clinical practice and the findings of studies looking at the utility of imaging in various musculoskeletal conditions. Imaging techniques in basic science and clinical research require technology and data processing which are not always available in routine clinical imaging.

**CLINICAL RESEARCHER**  
*Jim Elliott*



The prediction of recovery following trauma involves a complex interplay between biological, psychological and environmental processes. Biopsychosocial data and imaging (CT and MRI) data can be compared.

**BASIC SCIENTIST**  
*Luke Henderson*



Detailed knowledge of the interactions between neural and glial cells during the transition from acute to chronic pain following injury in preclinical models and humans. Limited patient population that can be accessed prior to developing chronic neuropathic pain.

**PHENOTYPE SOLUTIONS**

- A clinical decision tree incorporating measures of progressively increasing sophistication (and expense) as required may assist stratified care, matching appropriate care to patients.
- Further validation of proposed phenotypes is needed, providing prognostic information and/or likelihood of treatment response, ultimately allowing more precise therapeutic approaches.
- Use multiple pheno-/endo-type pre-clinical models in discovery and therapeutic-testing studies to define appropriate human target patient population.
- Develop biomarkers (clinical, imaging, wet biomarkers, structural progression, symptoms – pain and disability) that identify endotypes, which will enable disease-specific intervention and define who will respond to nonpharmacological, specific drug, and surgery approaches.

**NEUROMUSCULOSKELETAL IMAGING SOLUTIONS**

- Diagnostic imaging should be reserved for specific or serious pathology. Imaging should be clinically relevant and have the potential to influence management.
- Be mindful of the high prevalence of asymptomatic pathology in the musculoskeletal system with increasing age.
- Imaging based methods to quantify alterations in brain, spinal cord anatomy and whole-body skeletal muscles as potential markers of poor recovery.
- Normative datasets are required across the lifespan and considering sex-as-a-biological variable.
- Longitudinal studies are required to determine the sequence of events that underpin the development of chronic pain following injury and why seemingly identical injuries result in some, but not all, patients developing chronic pain.

Exploring translational gaps between basic scientists, clinical researchers, clinicians, and consumers: Proceedings and recommendations arising from the 2020 mine the gap online workshop [Osteoarthritis and Cartilage Open 3 \(2021\) 100163](#)

Vicky Duong<sup>a,\*</sup>, Kim L. Bennell<sup>b</sup>, Roderick Clifton-Bligh<sup>c</sup>, Leticia A. Deveza<sup>a</sup>, James M. Elliott<sup>d,e</sup>, Farshid Guilak<sup>f,g</sup>, Michelle Hall<sup>b</sup>, Luke A. Henderson<sup>h</sup>, Paul Hodges<sup>i</sup>, Brian Johnstone<sup>j</sup>, James Linklater<sup>k,l</sup>, Christopher B. Little<sup>m</sup>, L. Stefan Lohmander<sup>n</sup>, Liam Maclachlan<sup>i</sup>, Anita Mudge<sup>o</sup>, Shaun O'Leary<sup>p,q</sup>, Varshini Ravi<sup>a</sup>, Michele Sterling<sup>r</sup>, Bill Vicenzino<sup>i</sup>, Shirley P. Yu<sup>a</sup>, Sanaa Zaki<sup>s</sup>, David J. Hunter<sup>a</sup>

## Basic Science SIG – bidirectional benefit

- **Networking and Connectivity**
  - *what are the key clinical issues/questions?*
  - *resources/approaches to ask about disease mechanism, biomarkers etc?*
  - *share research resources/samples/expertise*
- **Improve research rigour**
  - *apply clinical methods/approaches to pre-clinical research*
  - *better use pre-clinical research to guide clinical studies*
- **Increased funding/research opportunities**
  - *expand research classification outcomes*
  - *recognise other opportunities with existing partners*