Basic-Science Research in MSK Disease

what, why, when, where, ….?

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KOLLING INSTITUTE
Bridging Medical Research and Health

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

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Disclosures & COI

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

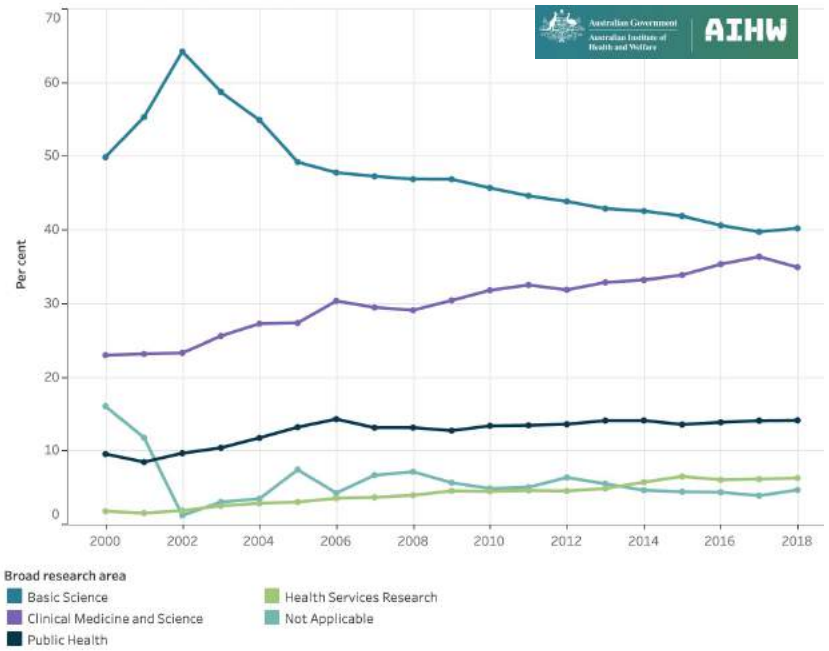
Basic Science research … "what?"

NHMRC Australian standard research classifications
Broad Research Area

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

NHMRC BUILDING A HEALTHY AUSTRALIA

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	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%

Basic Science research … "what?"

NHMRC Australian standard research classifications Broad Research Area

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

ABS R&D research classifications

- Pure Basic
- Strategic Basic
- Applied
- Experimental development

Pure basic: expeimental 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.

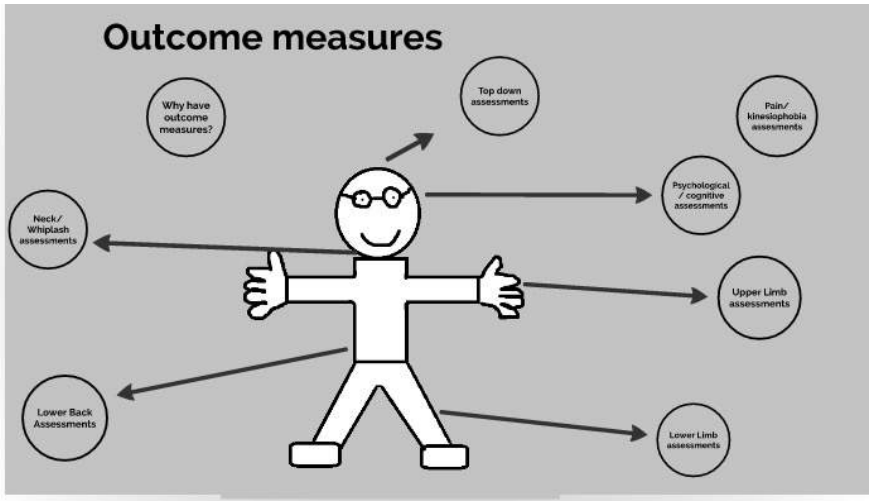
Basic Science research … "what?"

PT, Pharma, Surgery …

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

MSK condition, patient pop^{n}…

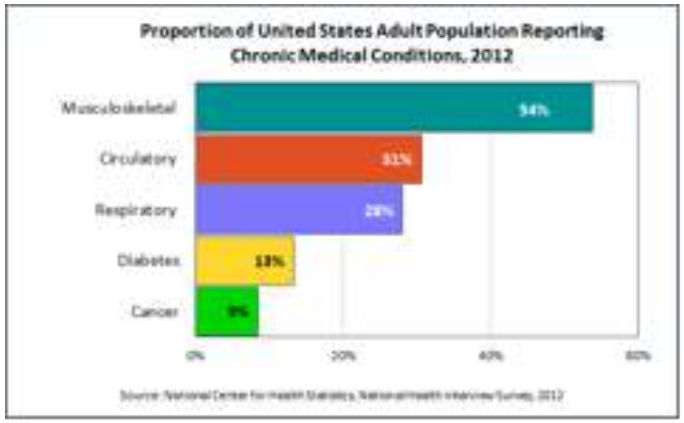


Clinical, Health Services, Public Health

Basic Science MSK research …. "why?"

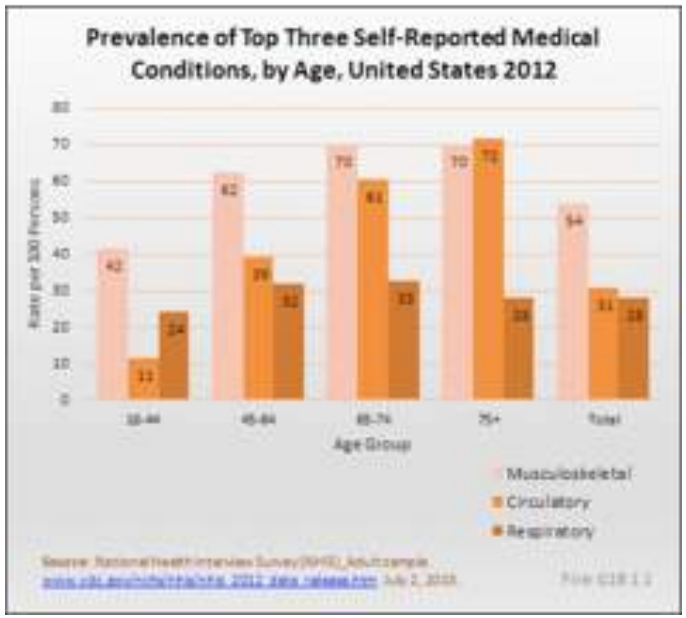
WHO Global Burden of Disease (2012) found that MSK diseases:

- affect >1.7 billion people worldwide
- 2nd greatest cause of disability
- have the 4th 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

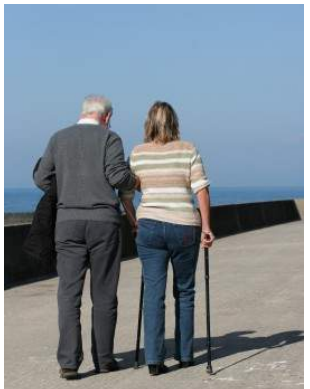


1 in 8 persons of prime working age reported lost work-days due to a MSK condition - a total of 216 million days in 2012!

Basic Science MSK research …. "why?"

Affecting >7 million Australians

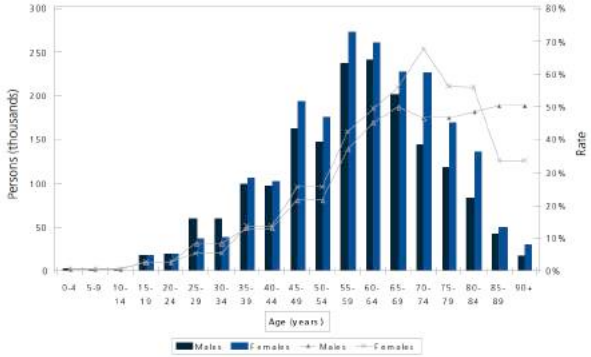
- 14% of the total burden of disease in Australia
- 2nd leading cause of non-fatal burden (23%) after mental health and substance abuse (24%), but the leading cause in women
- leading single cause by far of disability: 31% of all persons with a disability (1.2 million) report it is due due to a MSK condition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



Fourth most costly disease group in the health system

- $5.7 billion in direct costs (2008-09)
- nearly 1/3rd 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
- 2nd 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.

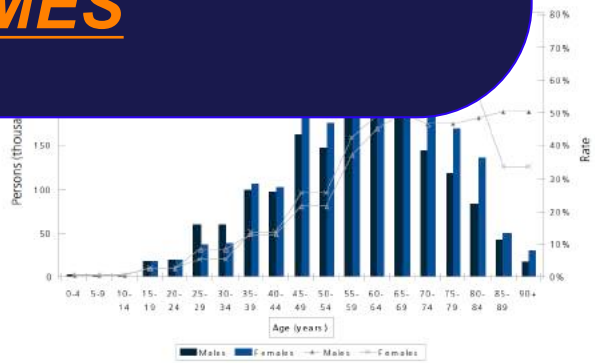
Back pain

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

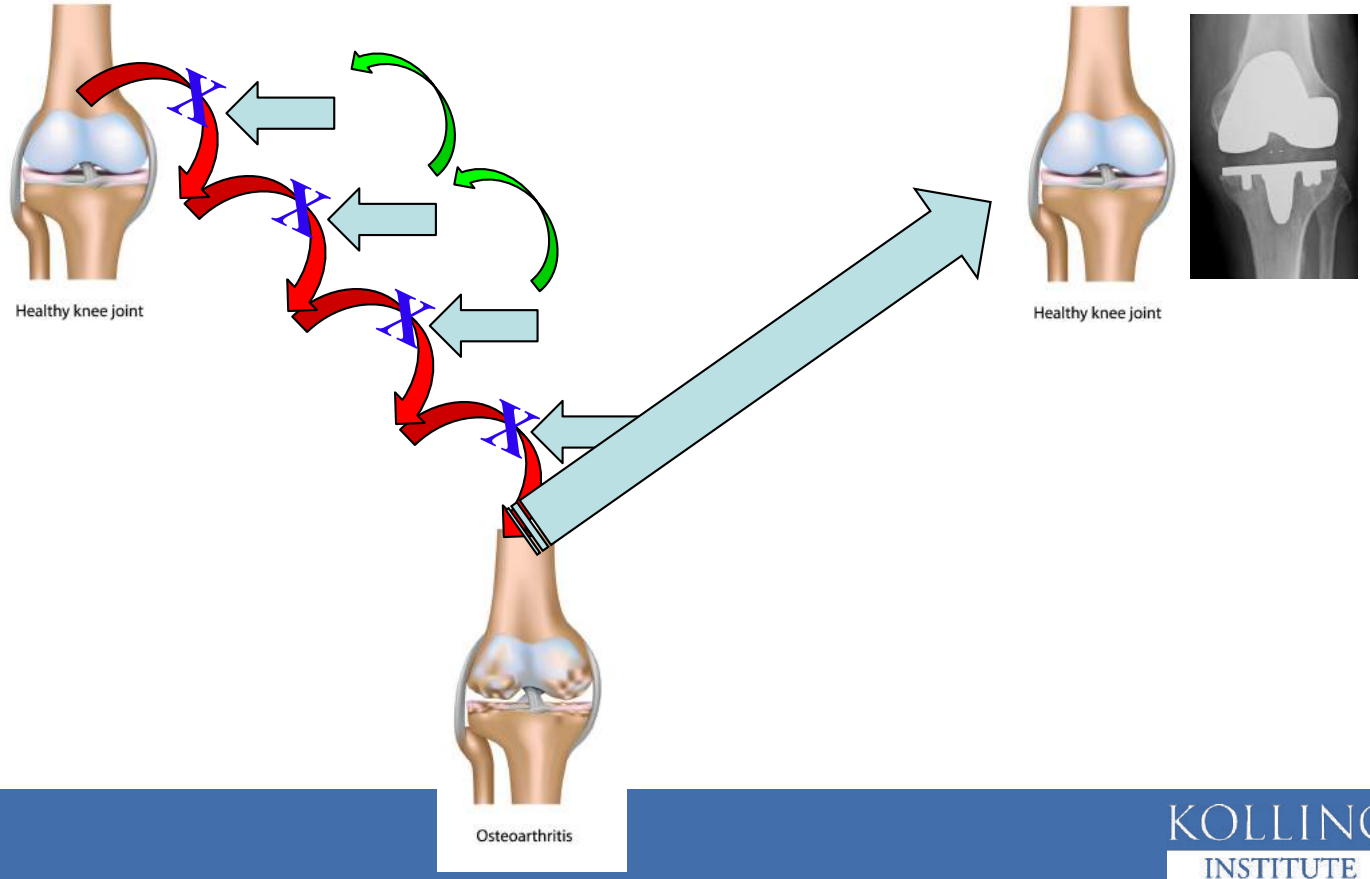


Basic Science MSK research …. "why?"

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%)[1];

T1

50-65% proceed to Phase II[1,2] with failure due to safety (62%) & efficacy (15%)

Development: Clinical trials (Phase II and III)
*~30% successfully transition from Phase II to Phase III;[1,2] greater success if existing human genetic linkage, efficacy biomarkers and confidence in patient selection; failure due to efficacy (65%)** & safety (30%)[1]*

T2

60-67% of Phase III progress to approval (~10% of all drugs entering Phase 1);[1,2] failure primarily due to efficacy**

Delivery: Evidence based guidelines, post-market surveillance
~21% have post-market safety warnings added and ~4% are withdrawn[3,4]

T3

Dissemination: Health policy & practice implementation

T4

Population Health Impact

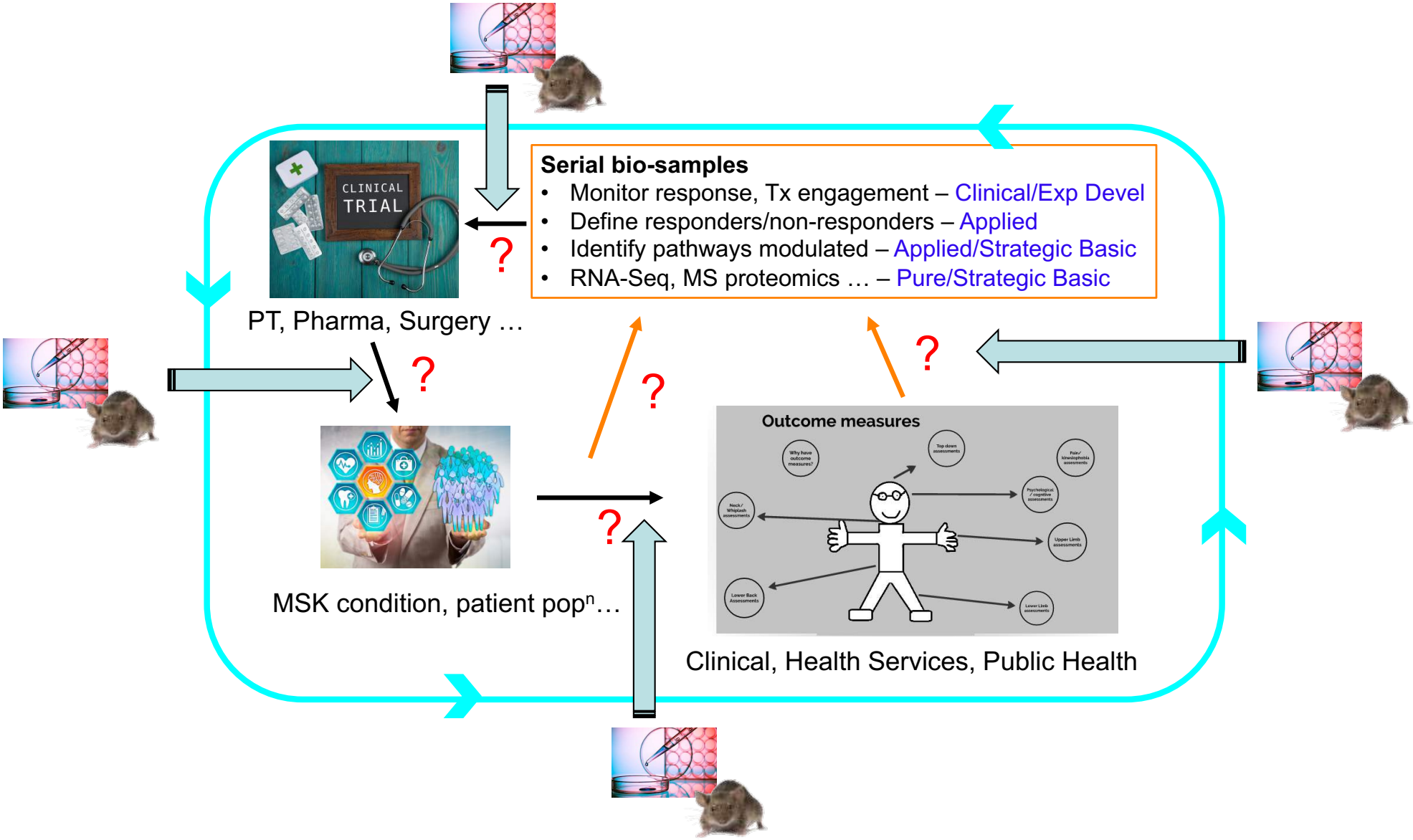
On the predictive utility of animal models of osteoarthritis

Arthritis Research & Therapy (2015) 17:225

Anne-Marie Malfait[1*] and Christopher B. Little[2]

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

Basic Science MSK research …. "when?"



Basic Science MSK research …. "where?"

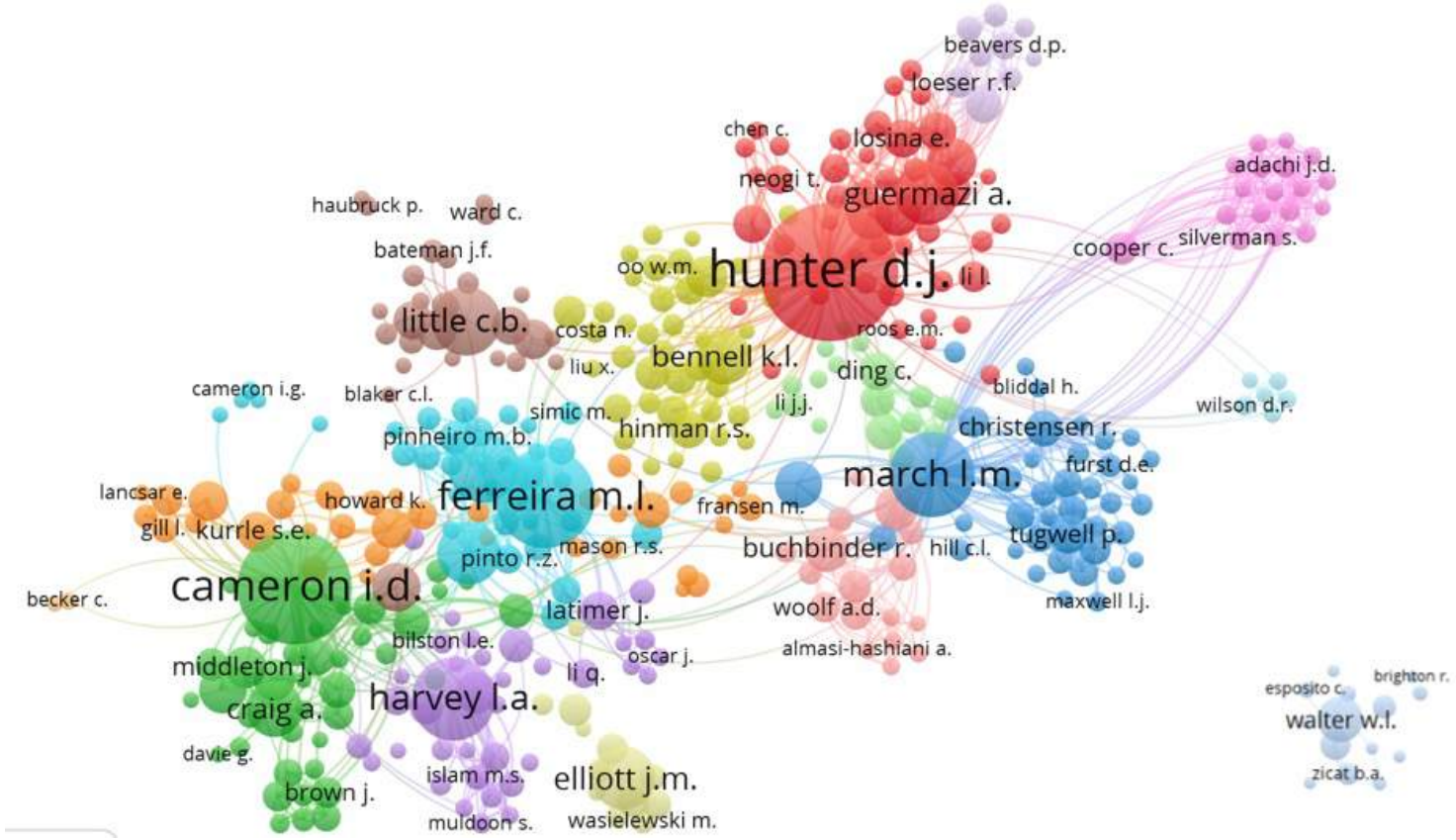
"… lack of a sufficiently strong connection between Health and Medical Research and the delivery of healthcare services …"

"… 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' …"

Basic Science MSK research …. "Where/Who?"

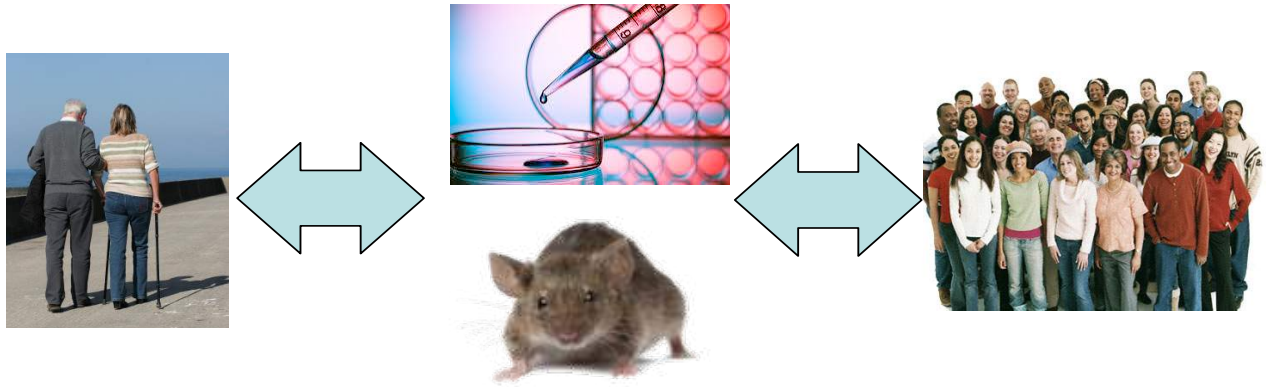
"Embedded" in Healthcare …

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



Translational MSK research

"Bedside-bench-bedside-bench....."



Basic Science Research: defining and targeting pathophysiology

Successes

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

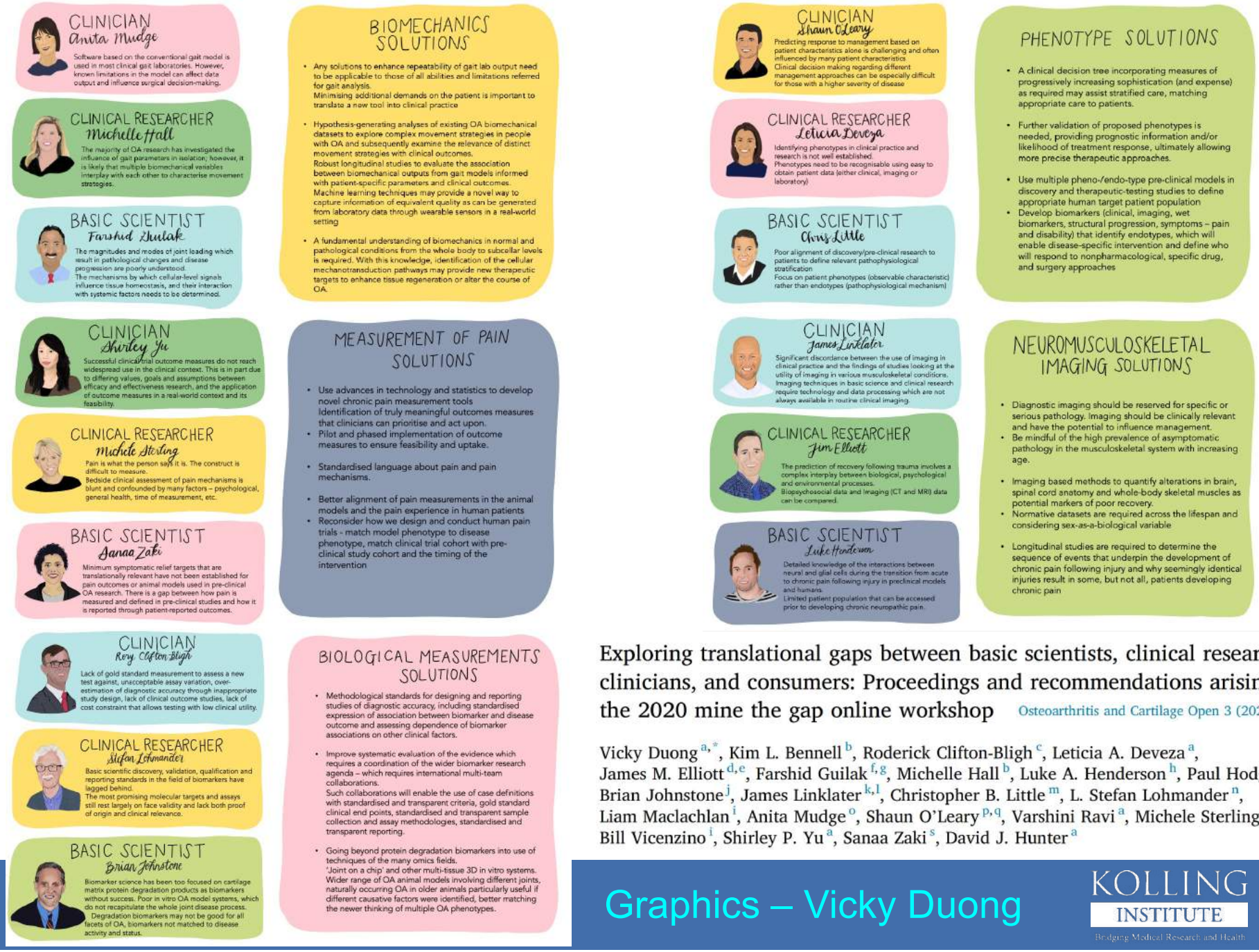
Maybe…..?

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

Maybe not …..?

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

Gaps & Opportunities …..



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

Graphics – Vicky Duong

Gaps & Opportunities …..

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*