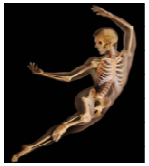

www.socrative.com Room No: 794352

Please vote: Should Osteoarthritis Research Focus on “Mice” or “Men”?

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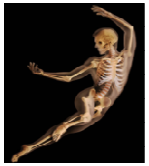
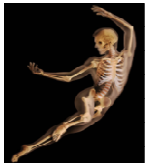


Great Debate 2015 – Should Osteoarthritis Research Focus on "Mice" or "Men"?

David Hunter
MBBS, PhD, FRACP
Florance and Cope Chair of Rheumatology, Professor of Medicine
University of Sydney and Royal North Shore Hospital
Consultant Rheumatologist, North Sydney Orthopedic and Sports Medicine

David.Hunter@sydney.edu.au
@ProfDavidHunter



Format

Vote	• Vote: Should Osteoarthritis Research Focus on “Mice” or “Men”?
Speaker 1	• Speaker 1 (DJH) content
Speaker 2	• Speaker 2 (CL) content and rebuttal
Speaker 1	• Speaker 1 rebuttal
Vote	• Vote: Should Osteoarthritis Research Focus on “Mice” or “Men”?
Questions and discussion	• Questions and discussion
Party time	• What happens in Vegas stays in Vegas

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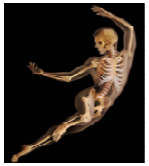

Outline

Definition

- Mice, Men, Research Focus

Conflicts of Interest

The cons of animal research and reasons for translational failure

- Humans are different to animals
- Animals do not reliably predict results in humans
- Animal tests may mislead researchers into ignoring potential cures and treatments
- Poor quality and lack of reproducibility

The best and worst of times

- Challenges of research funding and their allocation
- Failure to translate

Focus on translational research

Rebuttal

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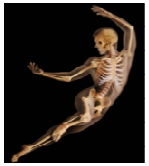
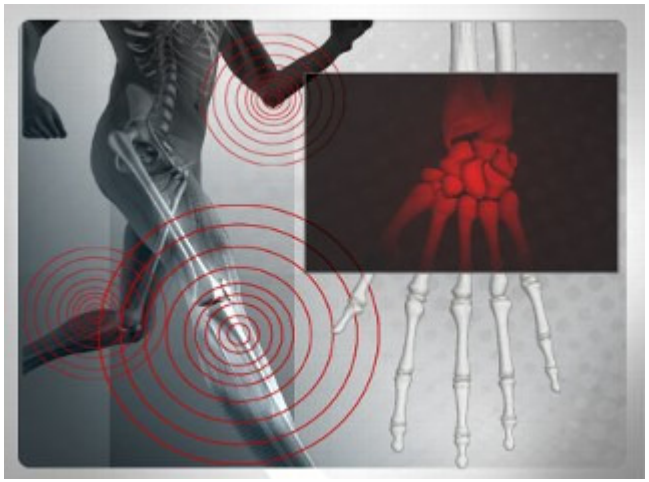


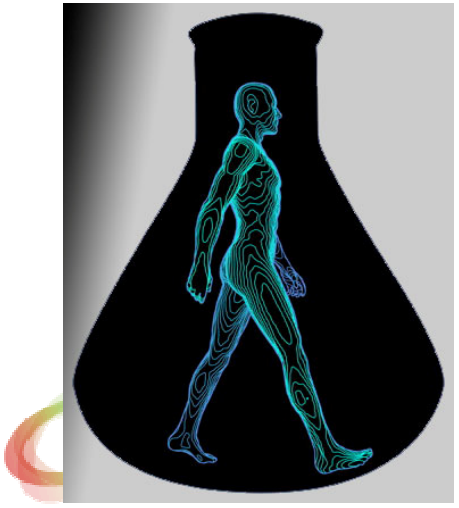
Declaration of interest

I declare that in the past three years I have:

- received royalties from: DJO for a patellofemoral brace patent
- Consulted for Flexion, Nestle
- Supported by an NHMRC Health Practitioner Fellowship.

Australian Government
National Health and Medical Research Council
N H M R C





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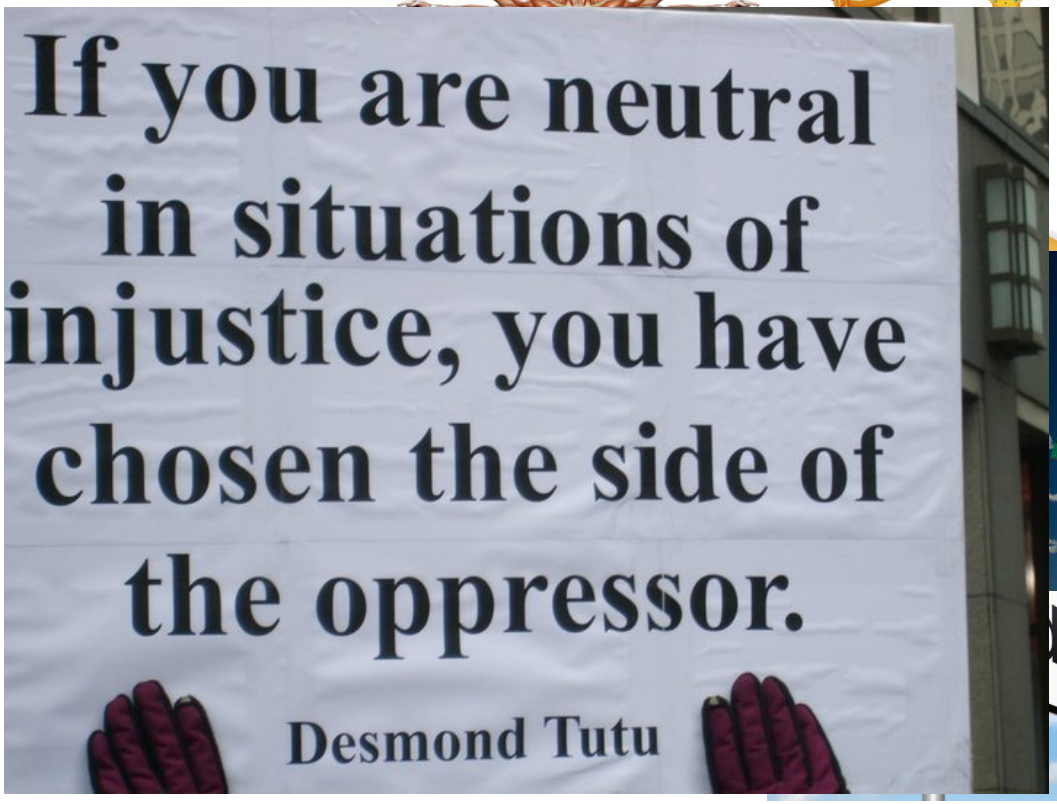

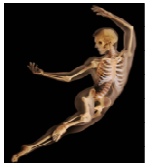

Animal Testing Cons

- **Many Animals Not Protected-**95% of animals used in experiments are not protected by Animal Welfare Act
- **Some Tests Have No Purpose in the End-**A 2009 study found serious flaws in the majority of publicly funded US and UK animal studies.
- **There are other methods than using animals available**
- **Drugs that pass animal tests are not necessarily safe**
    - Physicians Committee for Responsible Medicine (PCRM), "Vioxx Tragedy Spotlights Failure of Animal Research," pcrm.org, Mar. 2005

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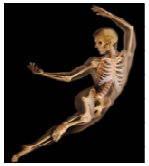
https://blog.udemy.com/animal-testing-cons/

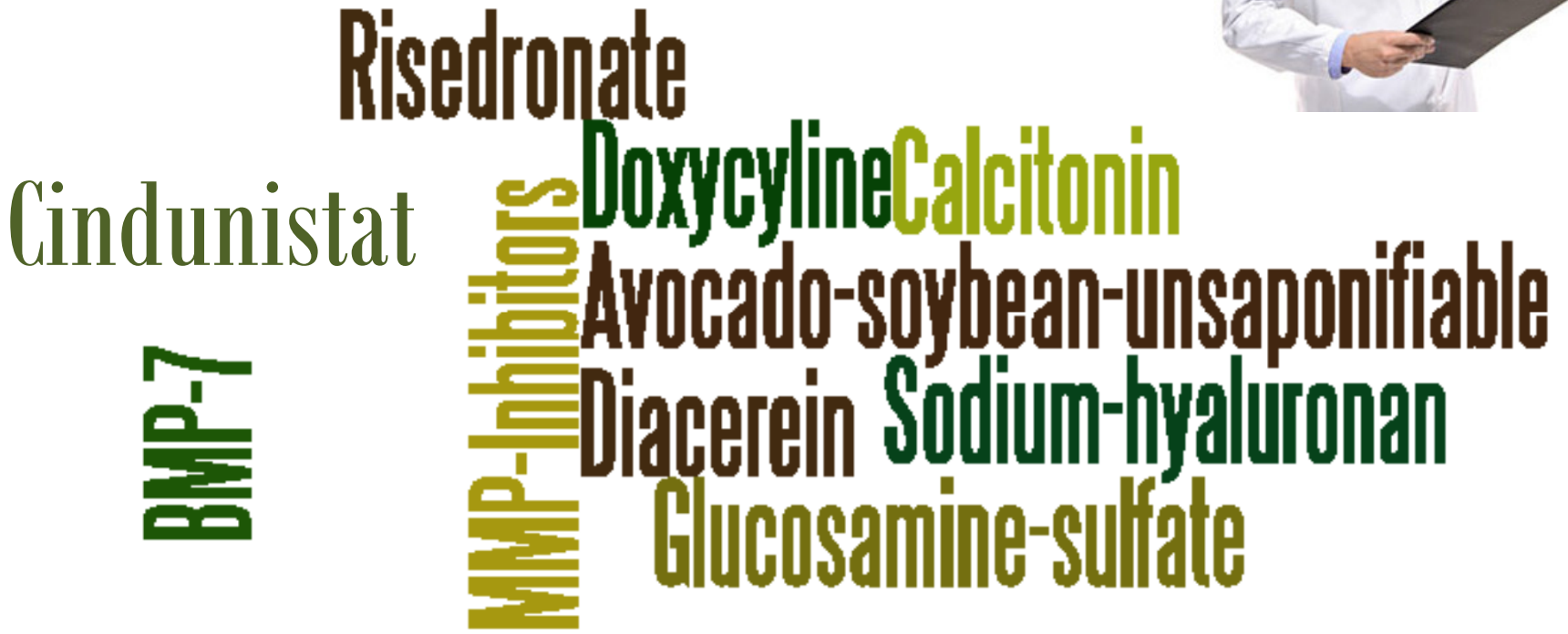


Animal tests may mislead researchers into ignoring potential cures and treatments.

- Aspirin, is dangerous for some animal species, and Fk-506 (tacrolimus), used to lower the risk of organ transplant rejection, was "almost shelved“ because of animal test results.

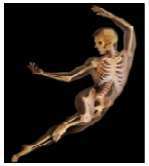
Animal tests do not reliably predict results in human beings

"The low predictivity of animal experiments in research areas allowing direct comparisons of mouse versus human data puts strong doubt on the usefulness of animal data as key technology to predict human safety." 2013 (*Archives of Toxicology)*

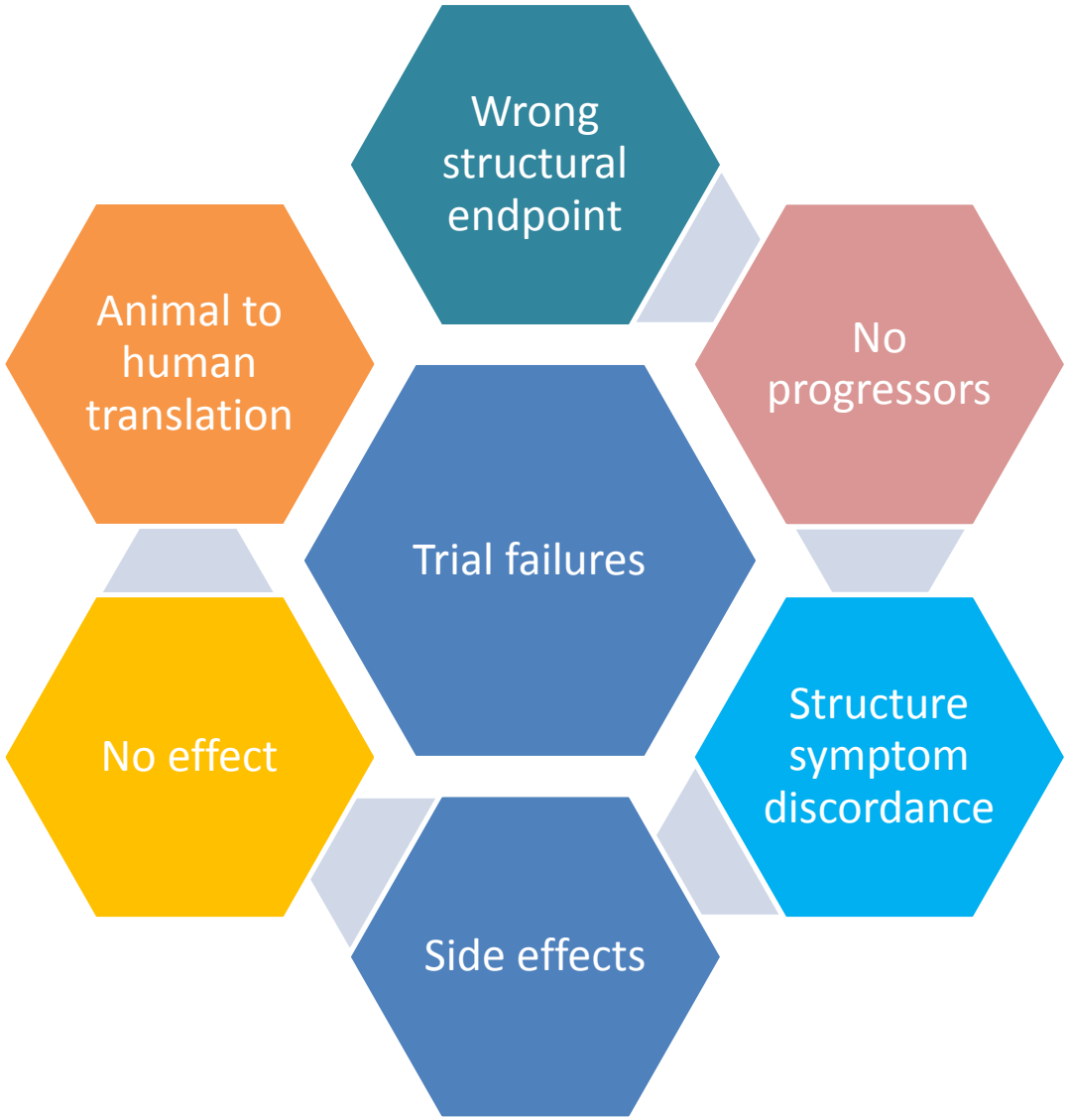


Hunter DJ. 2011. Pharmacologic therapy for osteoarthritis–the era of disease modification. Nat. Rev. Rheumatol. 7: 13–22.

Kraus VB, et al. 2012. Effects of intraarticular IL1-Ra for acute anterior cruciate ligament knee injury: a randomized controlled pilot trial (NCT00332254). Osteoarthr. Cartil. OARS Osteoarthr. Res. Soc. 20: 271–278.



Reasons for trial failures



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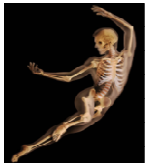

Reasons for failure

- Most animal models of OA induce disease via mechanical disruption of joint biomechanics in young individuals rather than the spontaneous development of age-associated disease.
- Studies in mice suggest that PTOA has a distinct molecular pathophysiology compared with that of spontaneous OA.

Nat Rev Rheumatol. 2013 Aug;9(8):485-97.
Post-traumatic osteoarthritis: from mouse models to clinical trials. Little CB[1], Hunter DJ.

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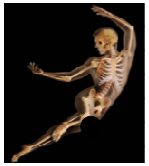
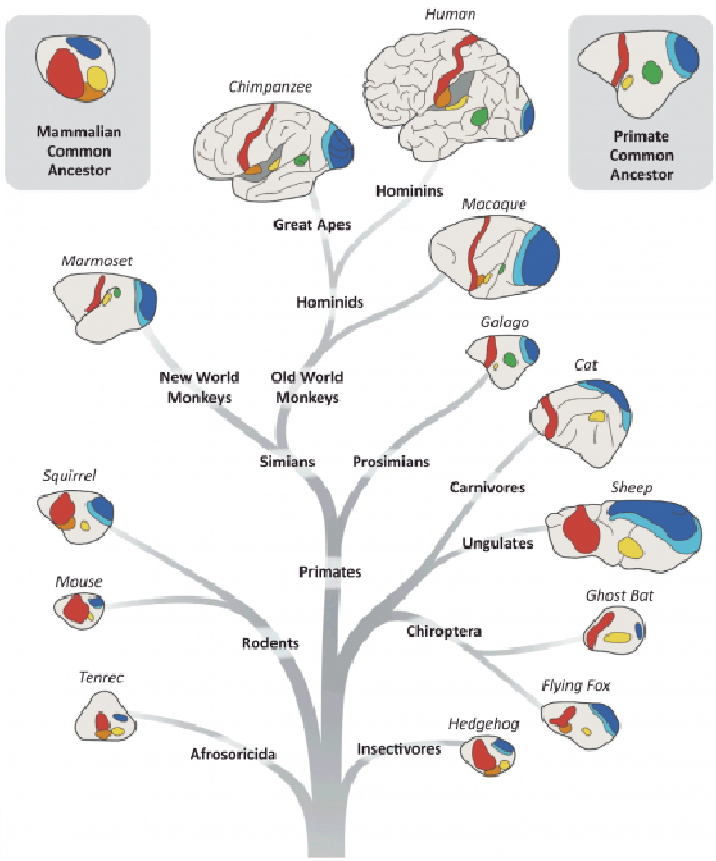


80 to 85 million years ago, we took a different evolutionary path



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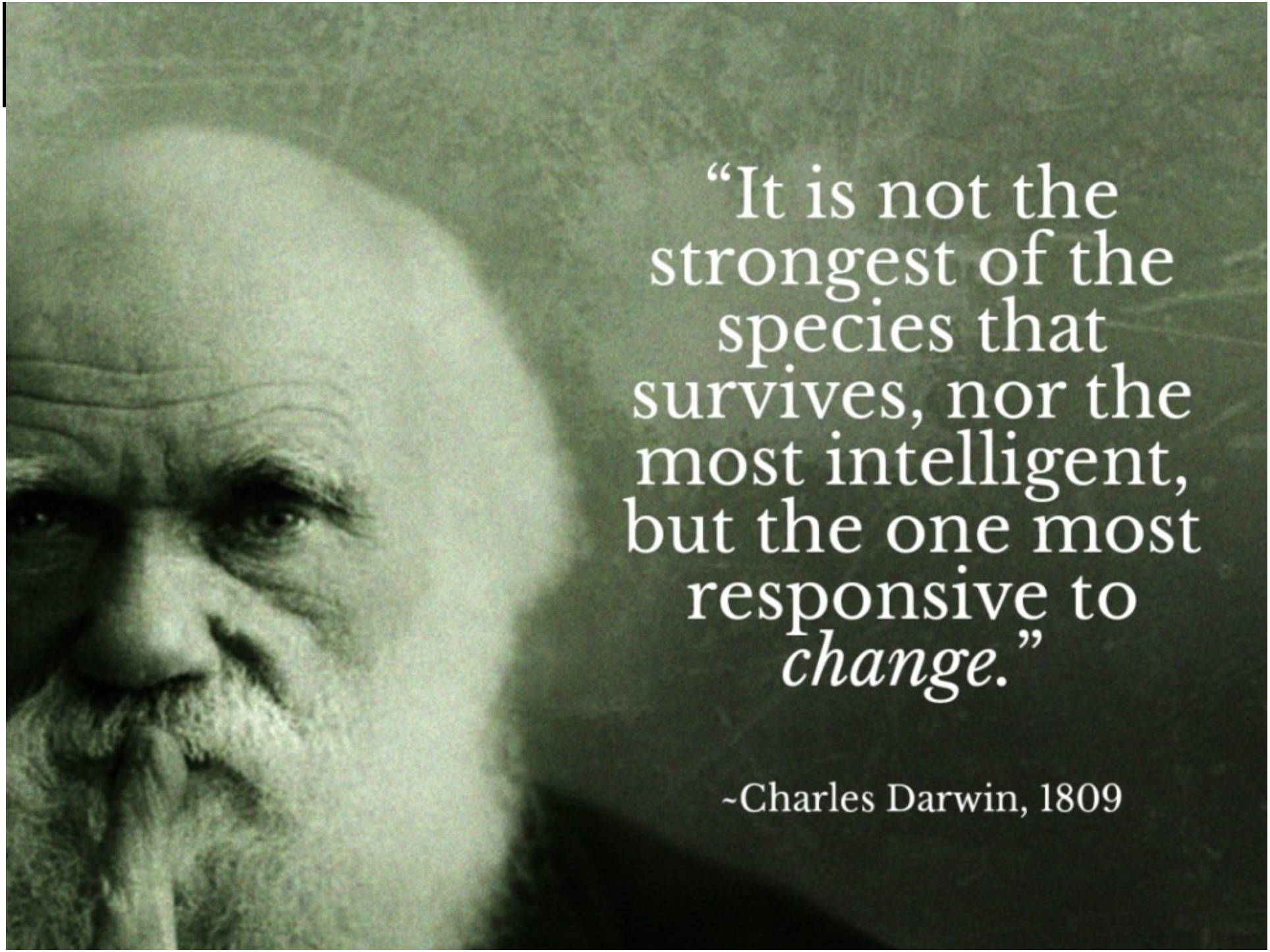
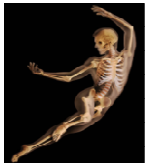
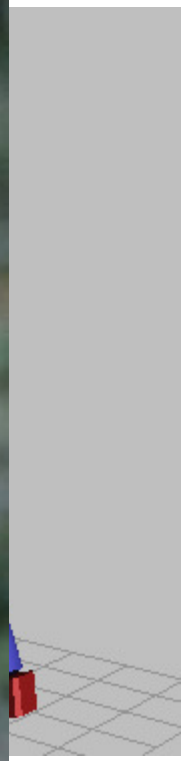
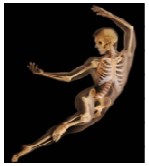

"It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to *change*."
~Charles Darwin, 1809



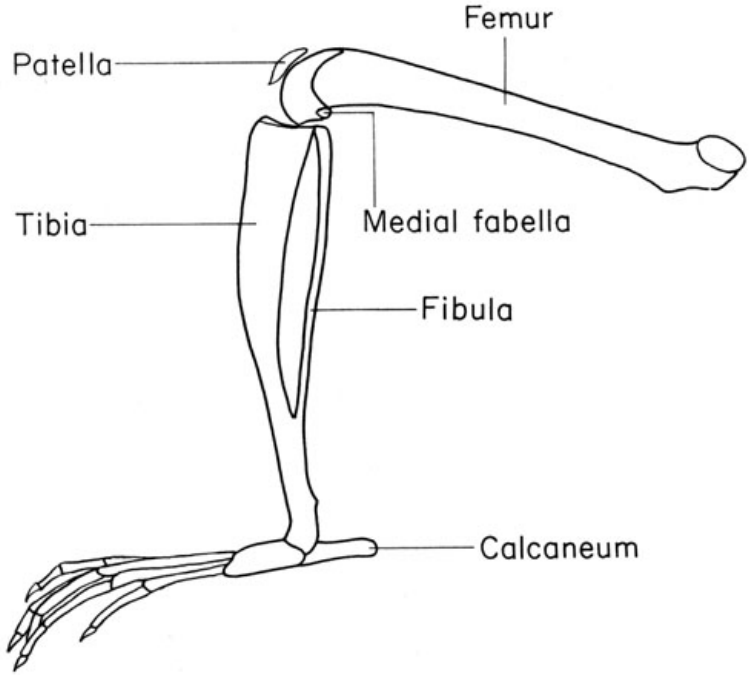
quadruped vs biped

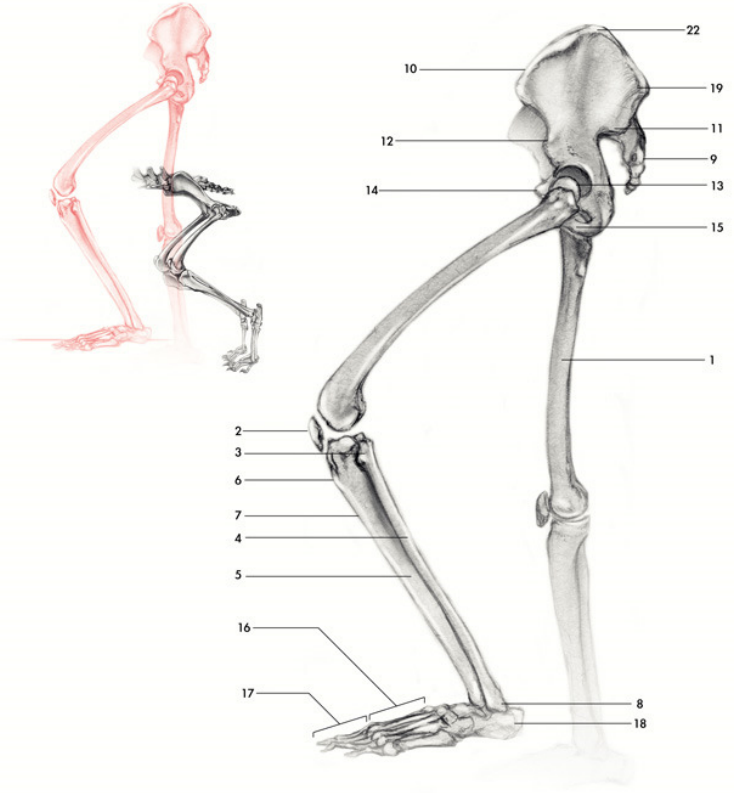
"we are not 70 kg rats”





Joint Anatomy





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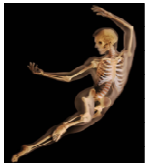
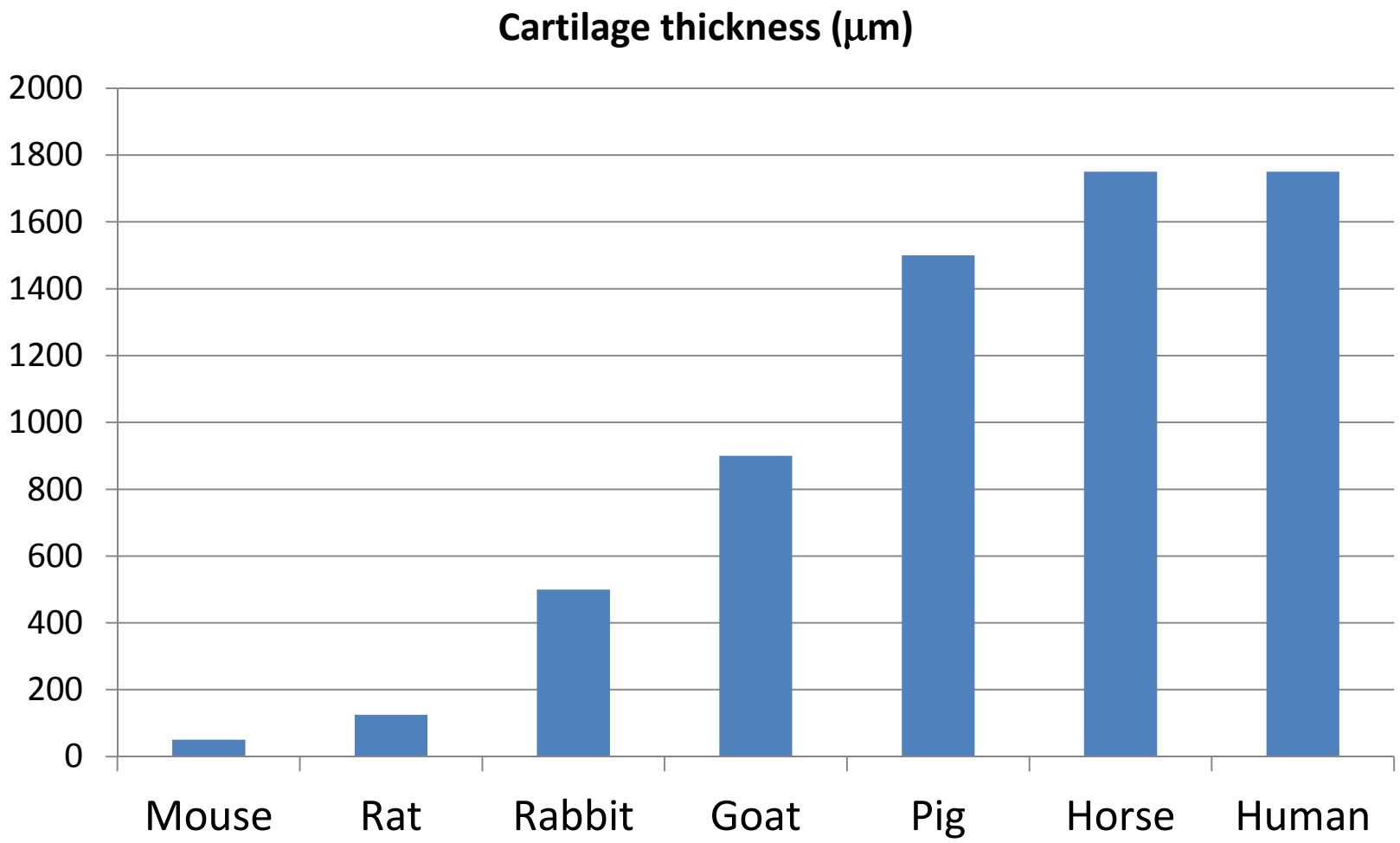
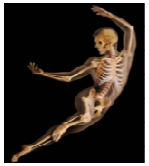


Cartilage thickness



A Rabbit Model Demonstrates the Influence of Cartilage Thickness on Intra-Articular Drug Delivery and Retention Within Cartilage. Bajpayee AG, et al. JOR (in press)



Why not mice?

- Small animals have commonly been used in OA research due to their lower costs and ease of manipulation relative to larger species; more recently, the development of transgenic mouse models have broadened their utility.
- Data from larger animal models are clinically more relevant and generally preferred by the FDA.

A Rabbit Model Demonstrates the Influence of Cartilage Thickness on Intra-Articular Drug Delivery and Retention Within Cartilage. Bajpayee AG, et al. JOR (in press)

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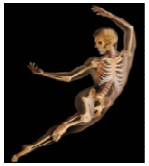
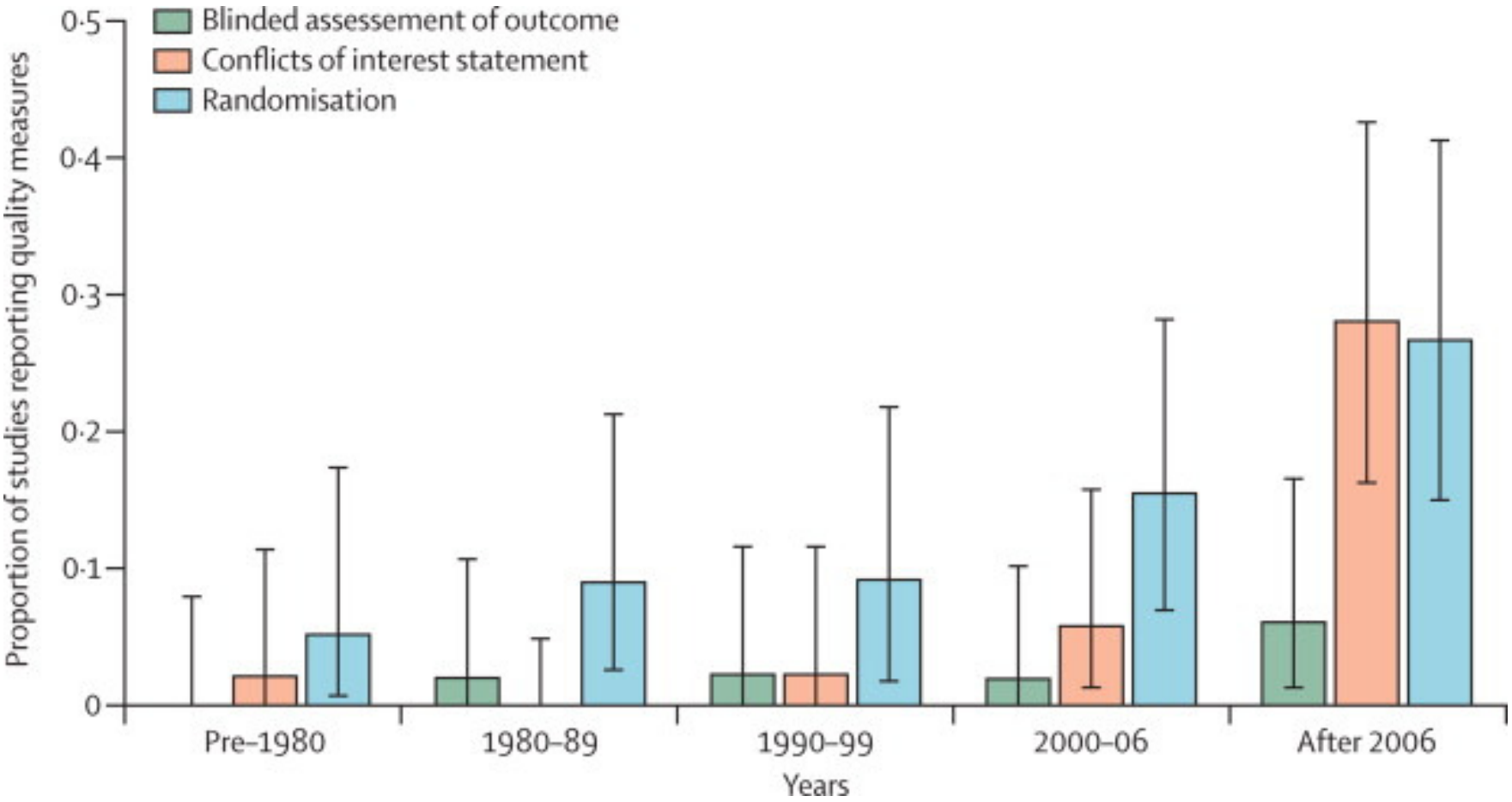


Quality of reported research is woeful



Trends in three methodological quality indicators for reports of in-vivo studies

Ioannidis et al. Increasing value and reducing waste… The Lancet, Volume 383, Issue 9912, 2014, 166 - 175

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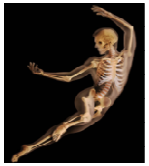
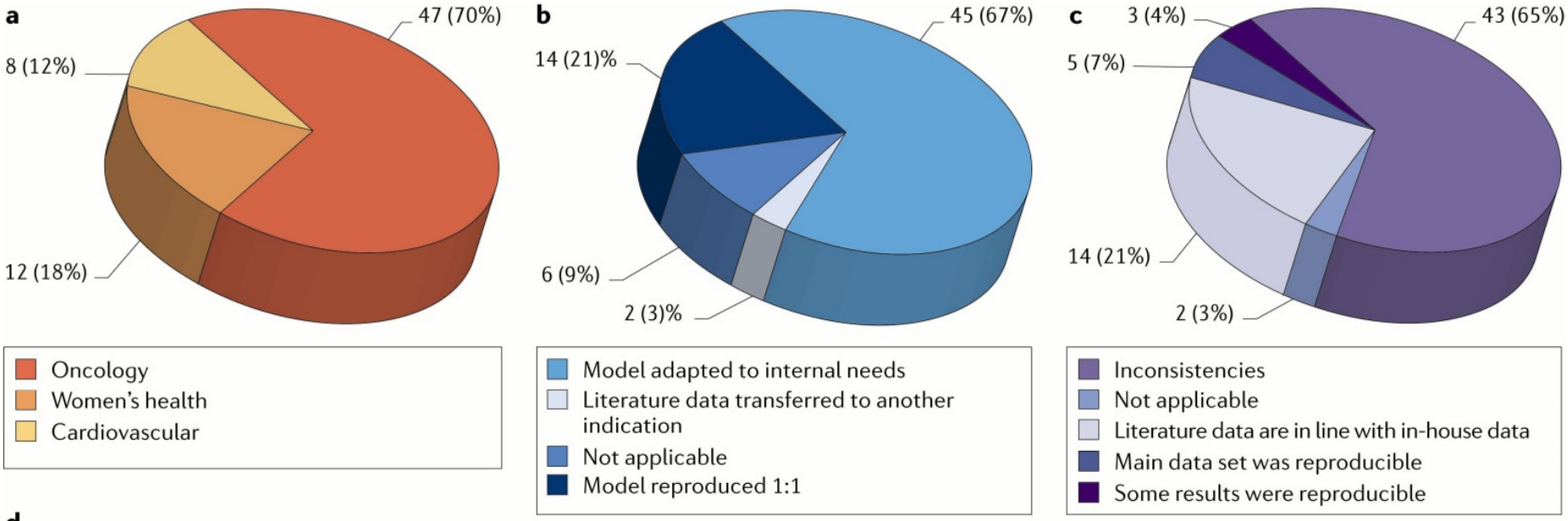


Lack of reproducibility

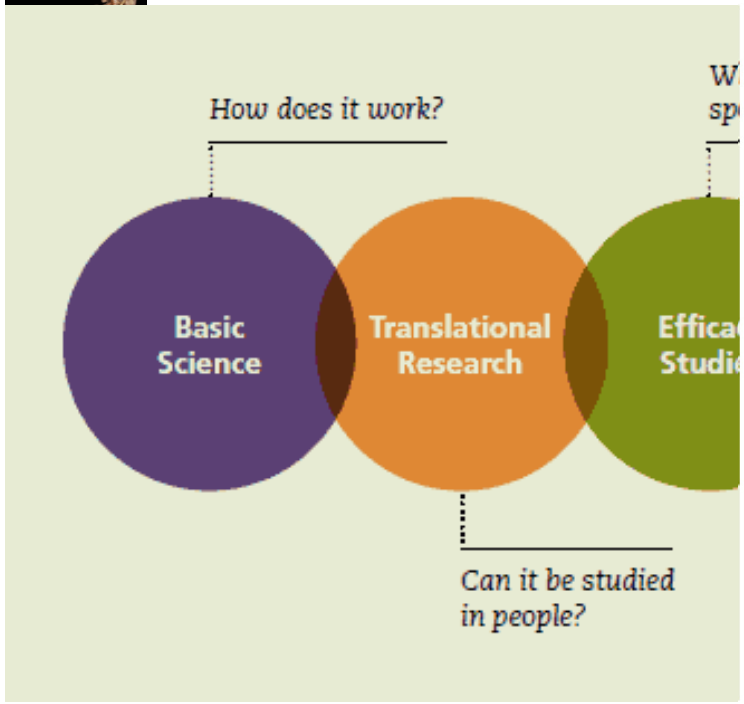


d

	Model reproduced 1:1	Model adapted to internal needs (cell line, assays)	Literature data transferred to another indication	Not applicable
In-house data in line with published results	1 (7%)	12 (86%)	0	1 (7%)
Inconsistencies that led to project termination	11 (26%)	26 (60%)	2 (5%)	4 (9%)

Nature Reviews | Drug Discovery

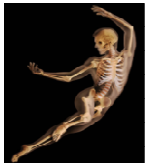
Nature Reviews Drug Discovery 10, 712 (September 2011)



"What do you mean 'Don't expect miracles'? why <u>shouldn't</u> I expect miracles?"

IDEA

Messier S et al. JAMA 2013 Sep 25;310(12):1263-73.



IT WAS THE BEST OF TIMES, IT WAS THE WORST OF TIMES.

Charles Dickens
English writer
1812 - 1870

QuoteHD.com

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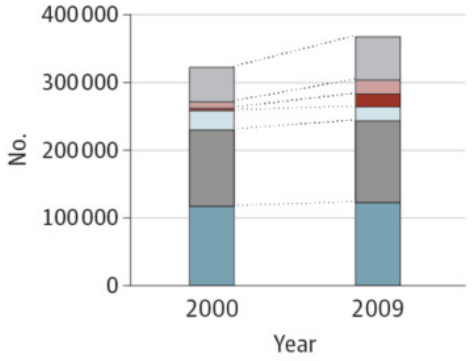
.org.au

From: **The Anatomy of Medical Research: US and International Comparisons**

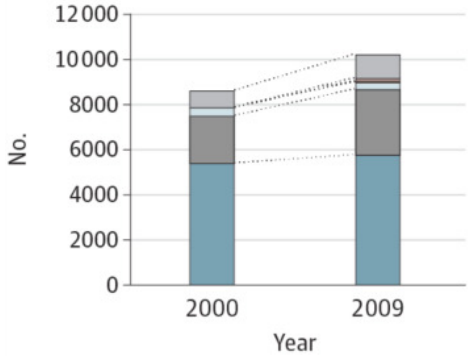
JAMA. 2015;313(2):174-189. doi:10.1001/jama.2014.15939

A No. of medical research articles



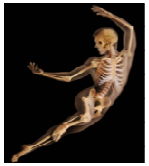
	No. of Medical Research Articles		Annual Growth Rate, %[a]
	2000	2009	2000-2009
Other[b]	49 946	63 483	2.7
Other Asia[c]	10 029	20 790	8.4
China	3937	18 399	18.7
Japan	26 755	21 477	-2.4
European Union[d]	114 970	120 421	0.5
United States	116 156	122 659	0.6
Overall	321 795	367 229	1.5

B No. of highly cited medical research articles



	No. of Highly Cited Medical Research Articles		Citation Index of Highly Cited Articles		Compound Annual Growth Rate (Citation Index), %[a]
	2000	2010	2000	2010	2000-2009
Other[b]	763	1034	0.57	0.59	0.4
Other Asia[c]	20	113	0.1	0.22	8.6
China	16	82	0.22	0.22	0.3
Japan	345	294	0.5	0.45	-1.0
European Union[d]	2079	2936	0.68	0.86	2.5
United States	5402	5729	1.67	1.63	-0.2
Overall	8626	10 189	NA	NA	NA

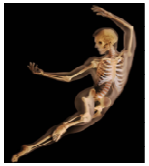
Figure Legend: Medical Research Articles and Citations by Selected Countries/Regions, 2000-2010NA indicates not available



Delayed translation

- Today, it takes a minimum of 6.3 years for evidence to reach reviews, papers and textbooks.
- On average it *then* takes an additional 9.3 years to implement evidence from reviews, papers and textbooks into clinical practice.
- But to expect to do research 'just because' with no questions asked, is unacceptable in a climate where competition for funding is fierce.

Balas and Boren, Yearbook of Medical Informatics

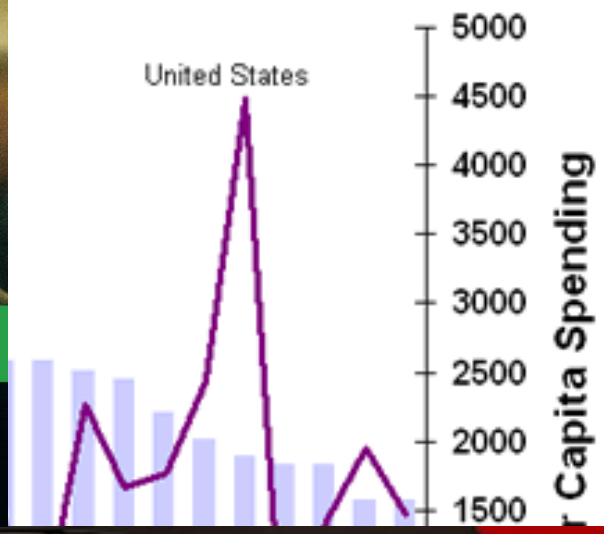


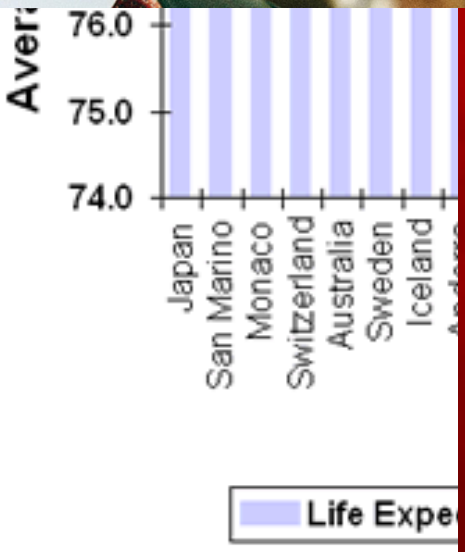
Share the love proportionately

- Since the mid 1990s industry has invested 14% to 21% of their revenue R&D.
- In 2004 spending on biomedical research was 5.6% of the amount spent on health care services and products.
- In contrast, US spending on research on best practices, effectiveness, quality, cost, and outcomes was only 0.2% of spending on physicians and hospitals and 0.1% of spending overall.

Moses H III, Dorsey R, Matheson DHM, Thier SO. Financial anatomy of biomedical research. *JAMA*. 2005;294(11):1333-1342.

Editorial: reforming heath care: this is going to hurt. *Economist*. 2009; 27:13.





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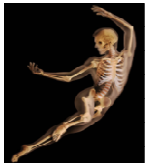
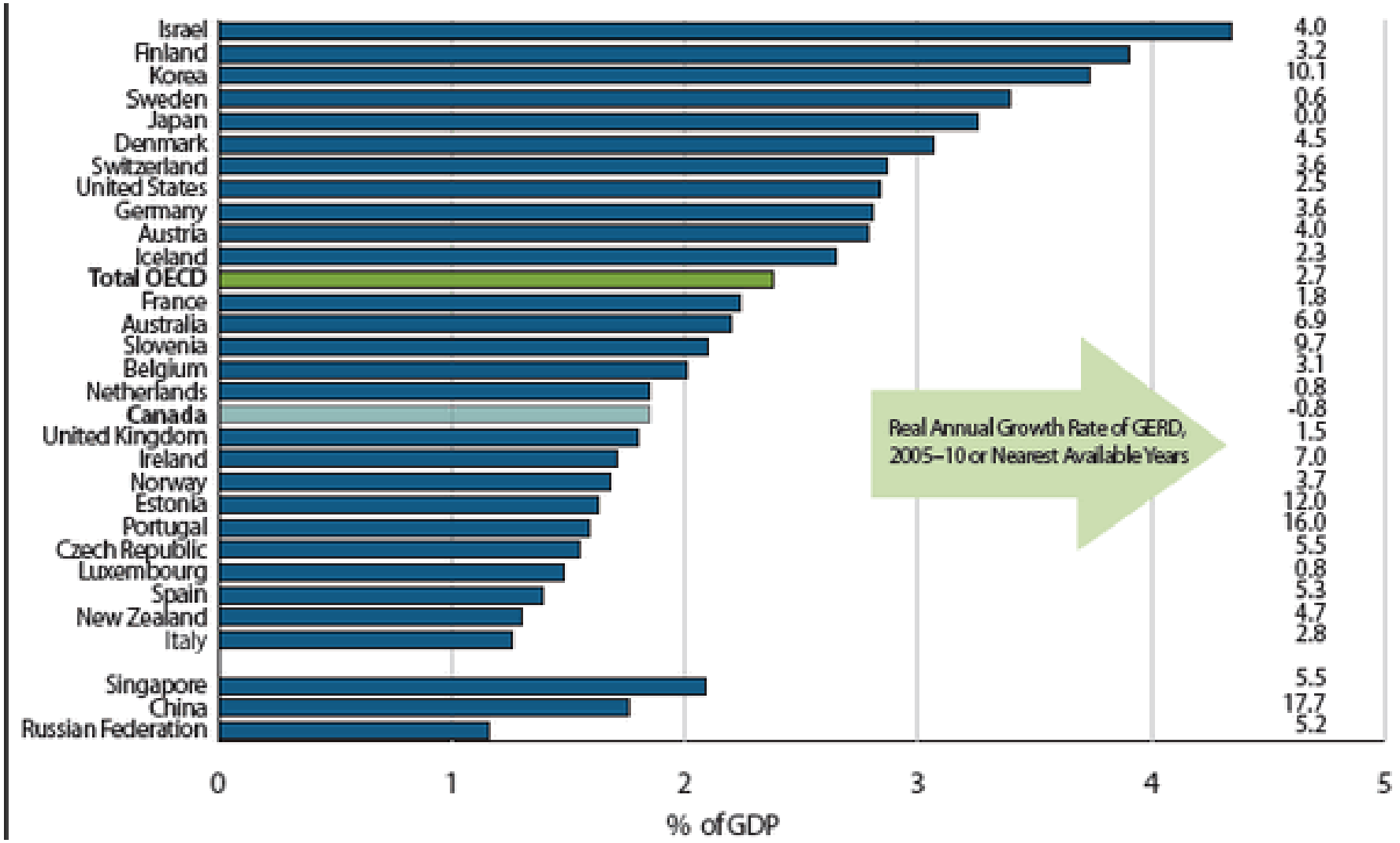
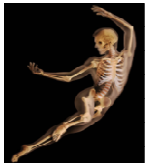
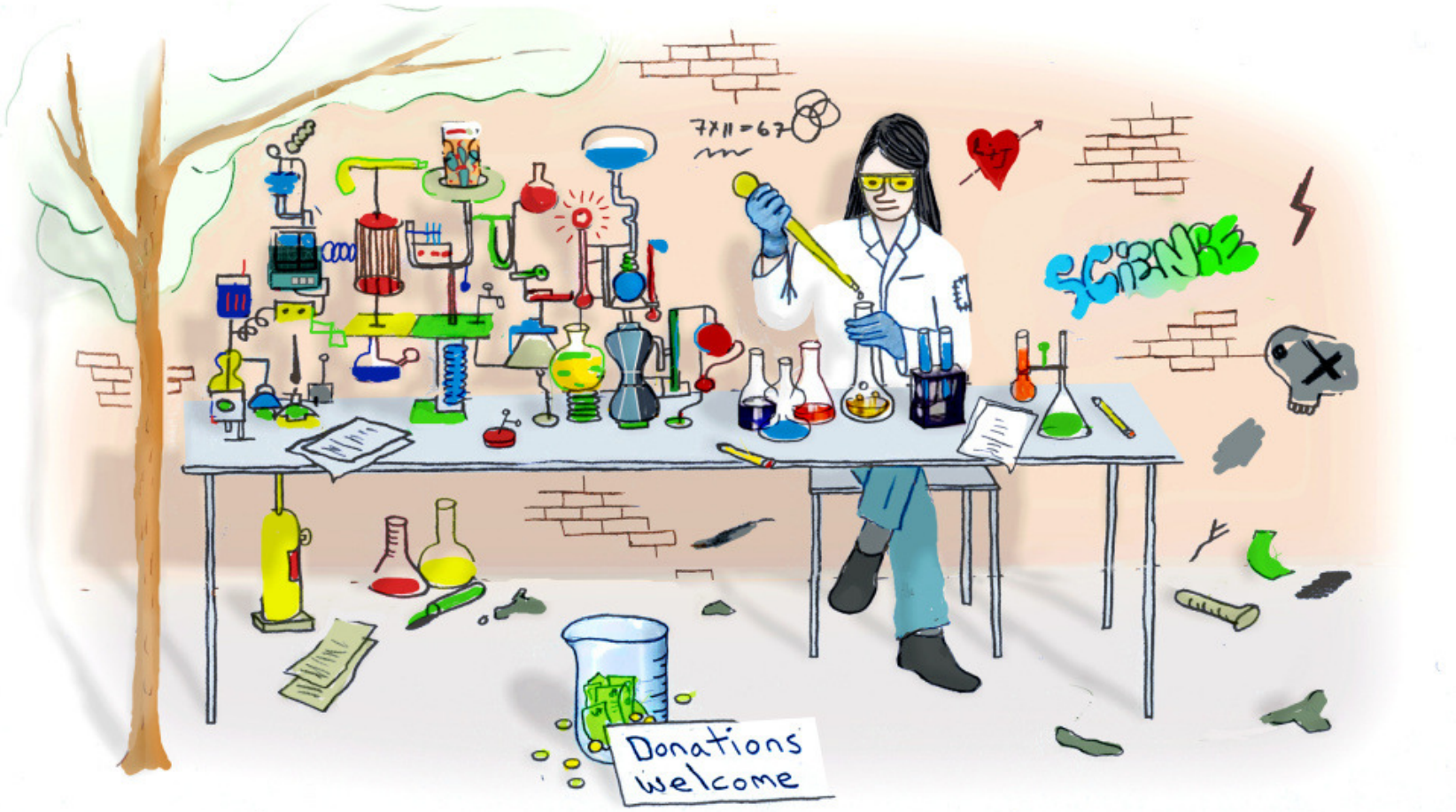
- http://uca

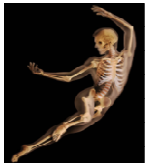




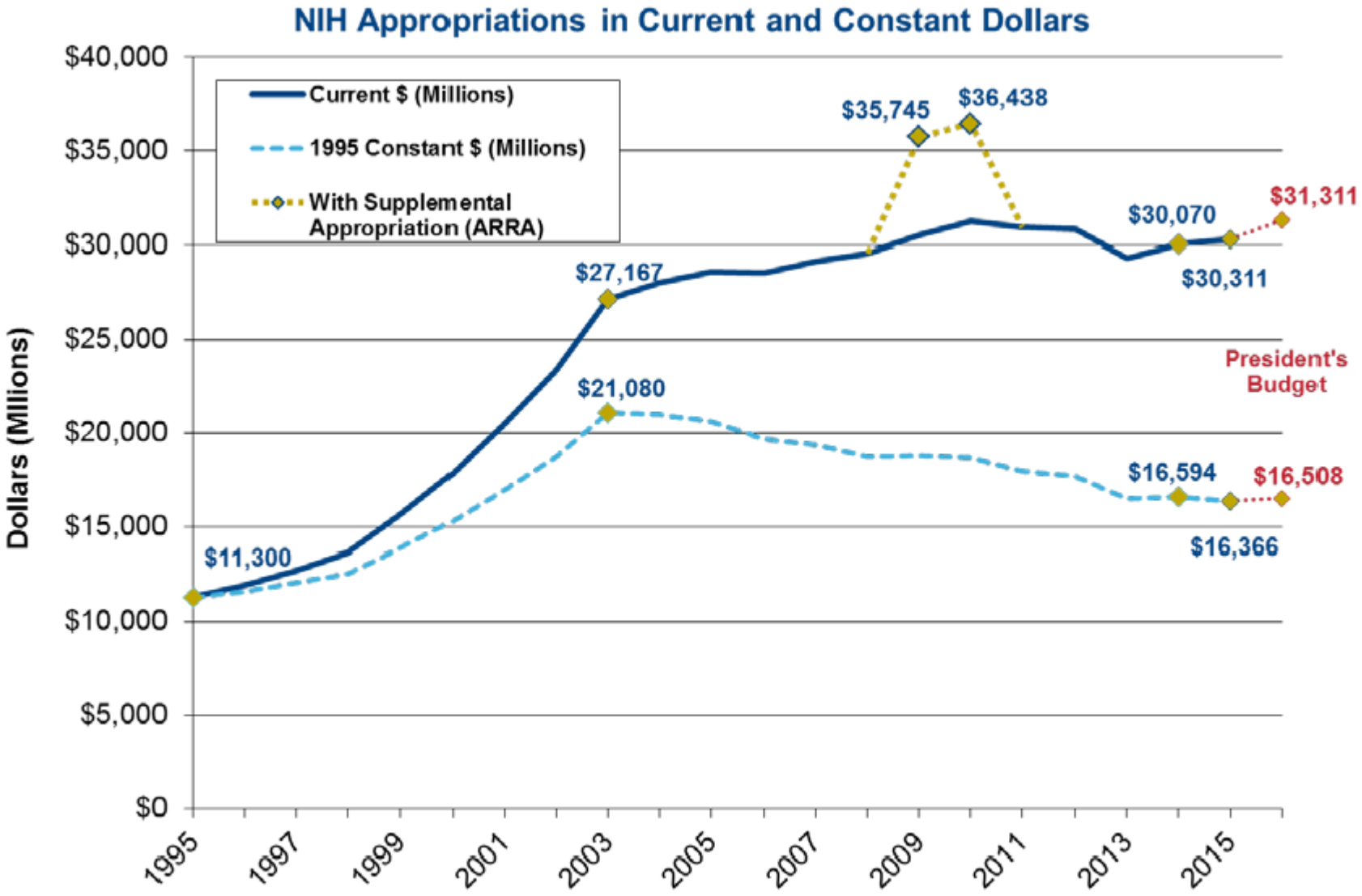
OECD, *Main Science and Technology Indicators*: 2012/2




7x11=67
SCIENCE
Donations welcome



Funding for NIH



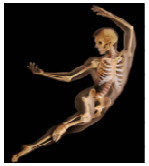
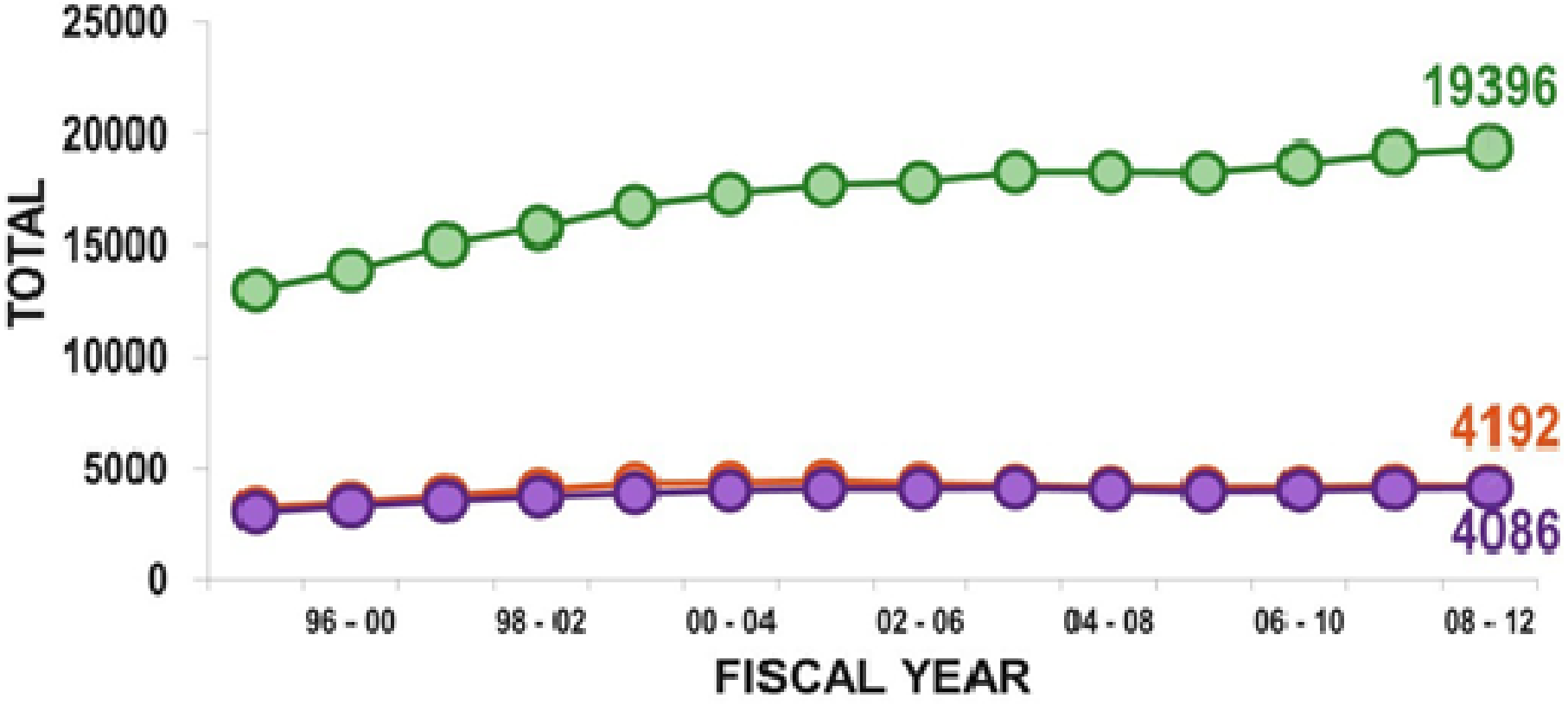


Figure 3.3. Individual NIH Research Project Grant Awardees, PhD, MD, and MD/PhD Degree (FY1995-2012)



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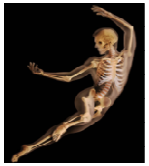
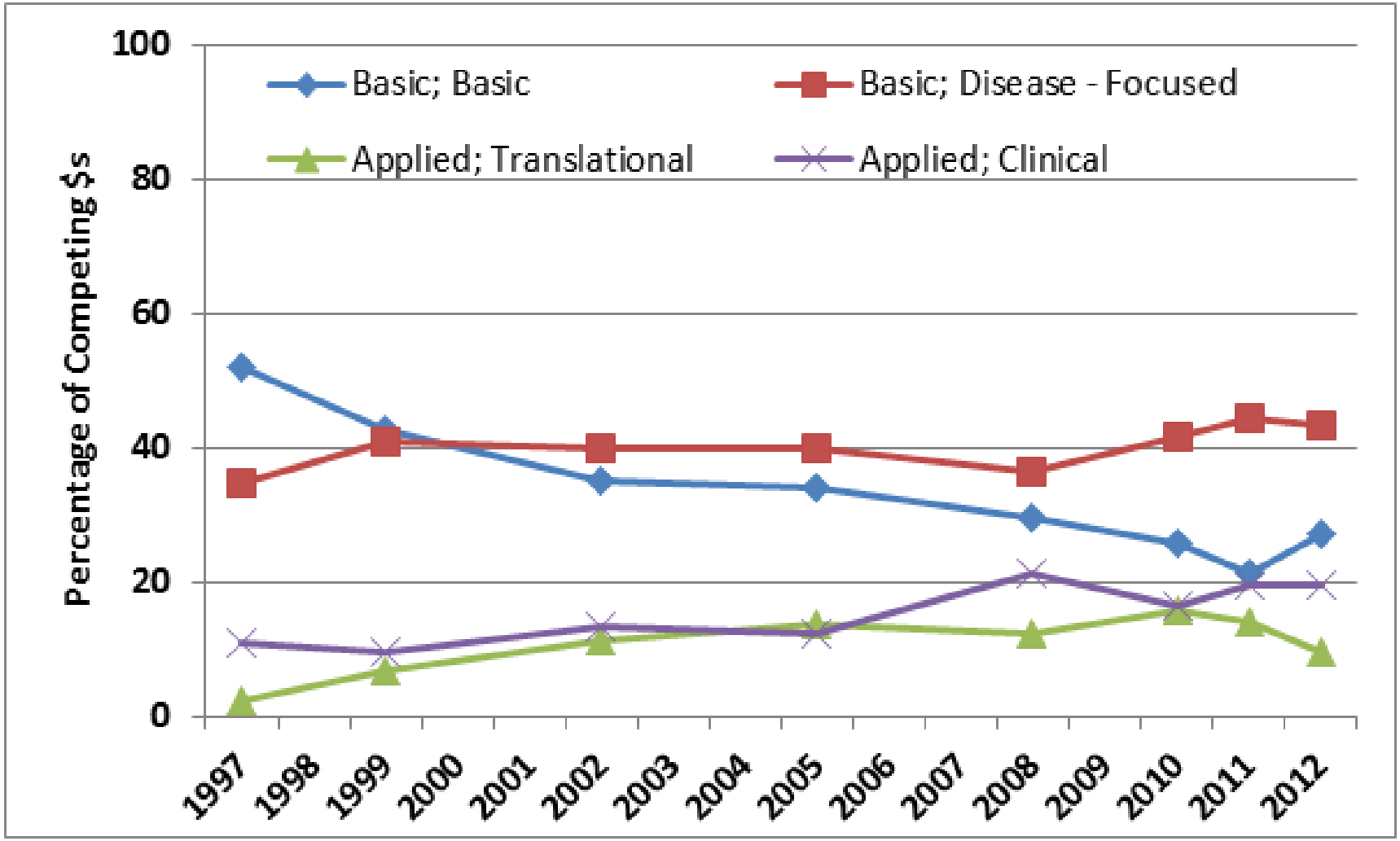


Disproportionate funding to basic science research



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http://blog.ninds.nih.gov/2014/03/27/back-to-basics/

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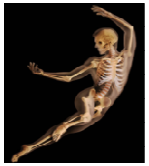

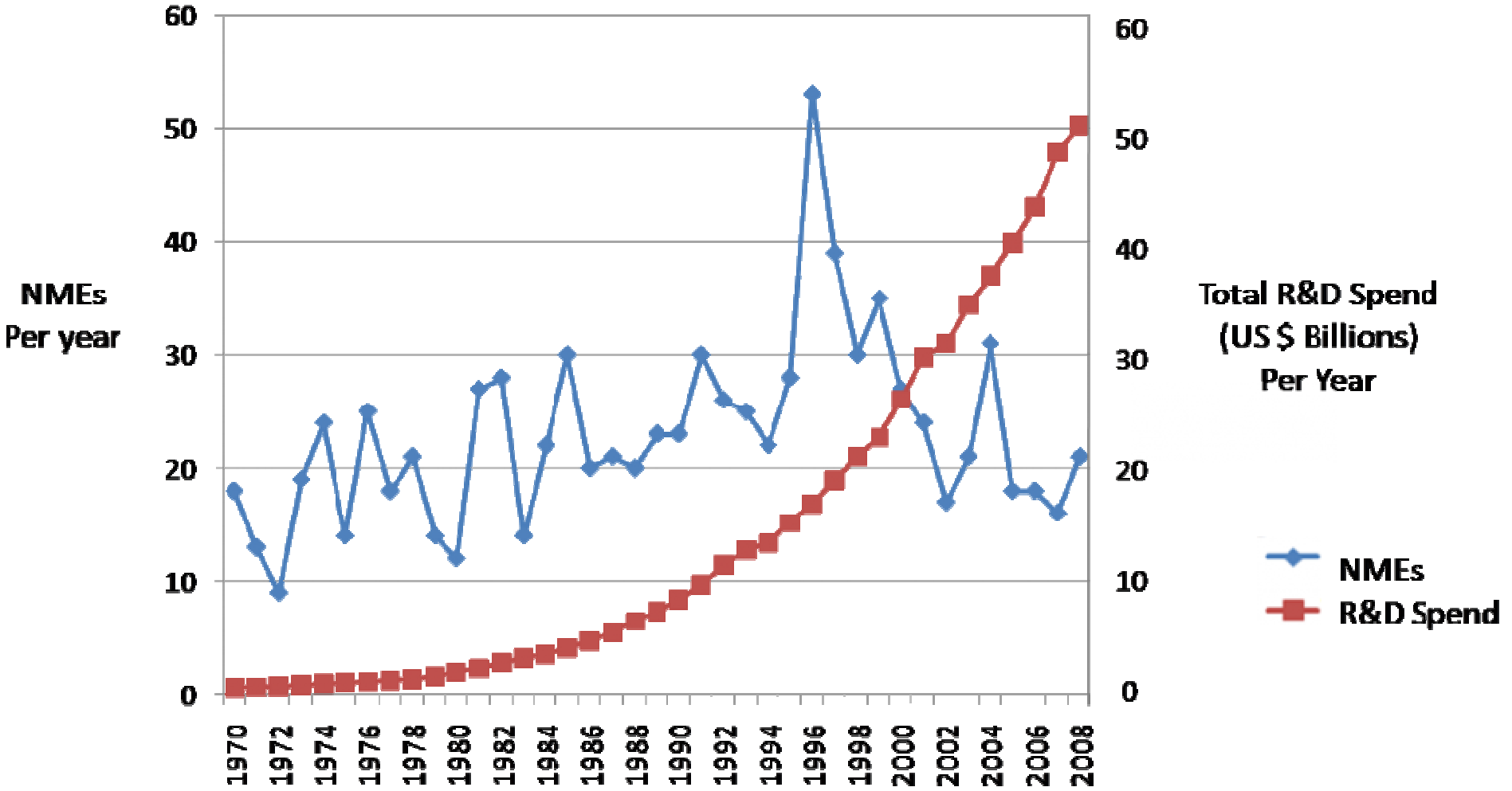

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From: **The Anatomy of Medical Research: US and International Comparisons**
JAMA. 2015;313(2):174-189. doi:10.1001/jama.2014.15939

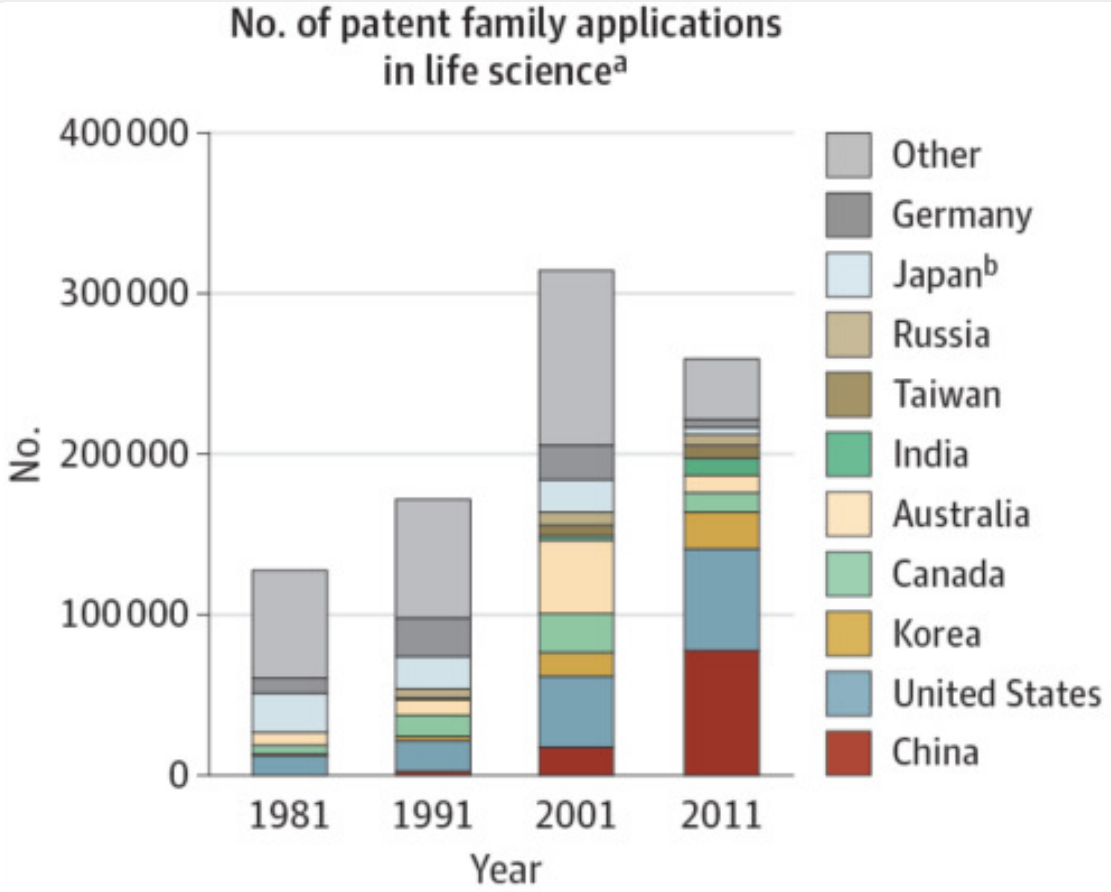
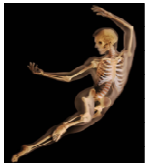


Figure Legend: Global Life Science Patent Applications by Country of Origin, 1981-2011



Movements in the right direction

- US and Europe have invested heavily in translational research. In the US, the NIH have invested $480 million in its Clinical and Translation Science Awards, and another $500 million in a National Centres for Advancing Translational Sciences.
- In the UK they have recently invested 900 million pounds setting up a system similar to the US.

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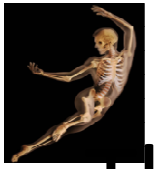

The way forward-can OARSI play a role?

- There will never be enough funding and it is a matter of prioritizing.
- For translational research to be fully effective, we need more than funding, we need cultural change.

1. Removing silos
2. Developing new ways to evaluate translational researchers and institutions
3. Rethinking the relationship between academia and industry.
4. Developing new training programs for budding translational researchers
5. More dollars are spent in meeting research regulations while direct programmatic dollars are declining.

Nat Med. 2011 Dec 6;17(12):1567-9.

Improving the efficacy of translational medicine by optimally integrating health care, academia and industry. Bornstein SR[1], Licinio J.

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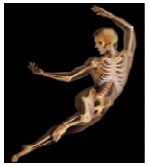

Summary

- I am not suggesting don't fund mice research but make it relevant and improve its quality.
- Disproportionate support to mouse research.
- Trial failures and translation will not be improved by more mouse research.
- More focus towards the clinical impact of our research and its translation.

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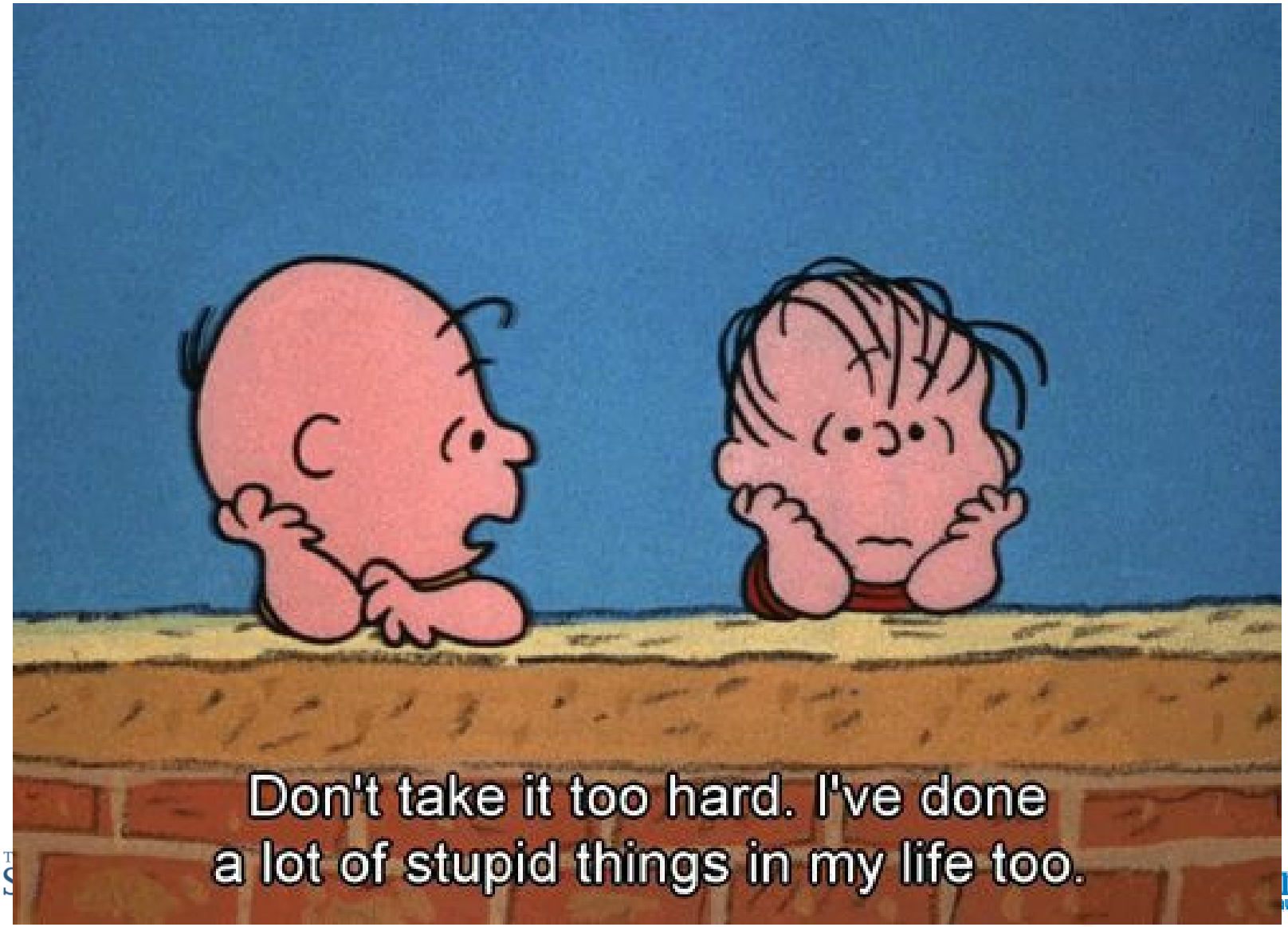
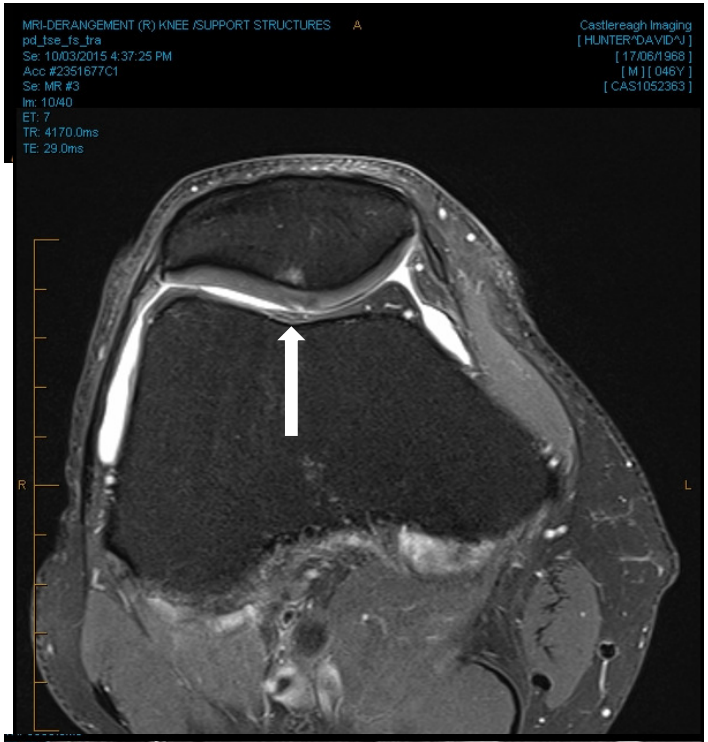
Rebuttal


Don't take it too hard. I've done
a lot of stupid things in my life too.

Conflicts of Interest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Castlereagh Imaging
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[M] [046Y]
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TE: 38.0ms
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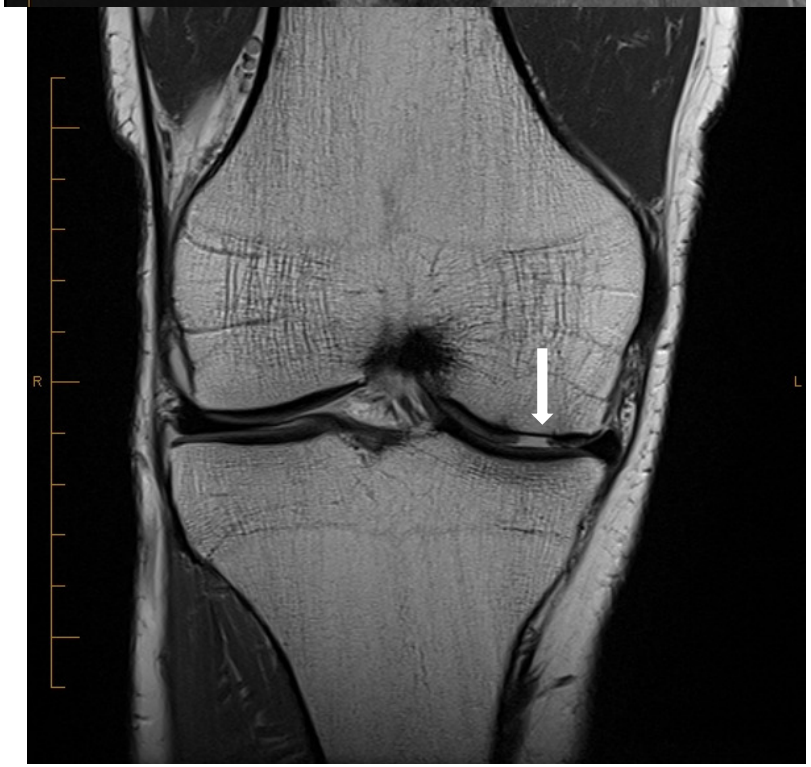
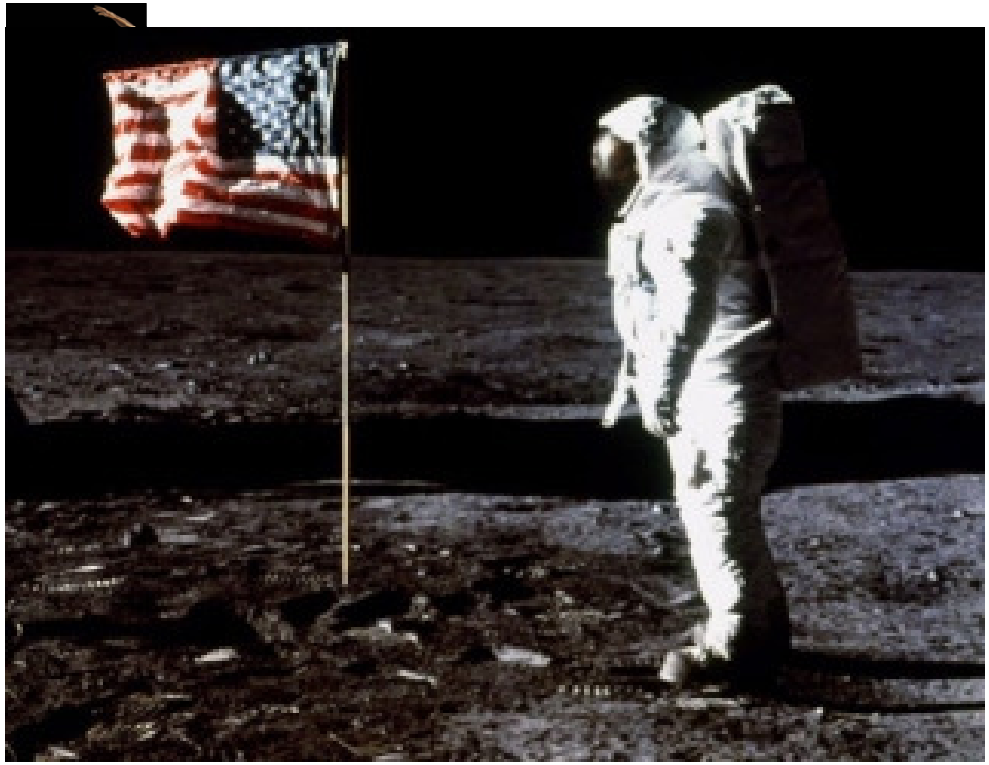
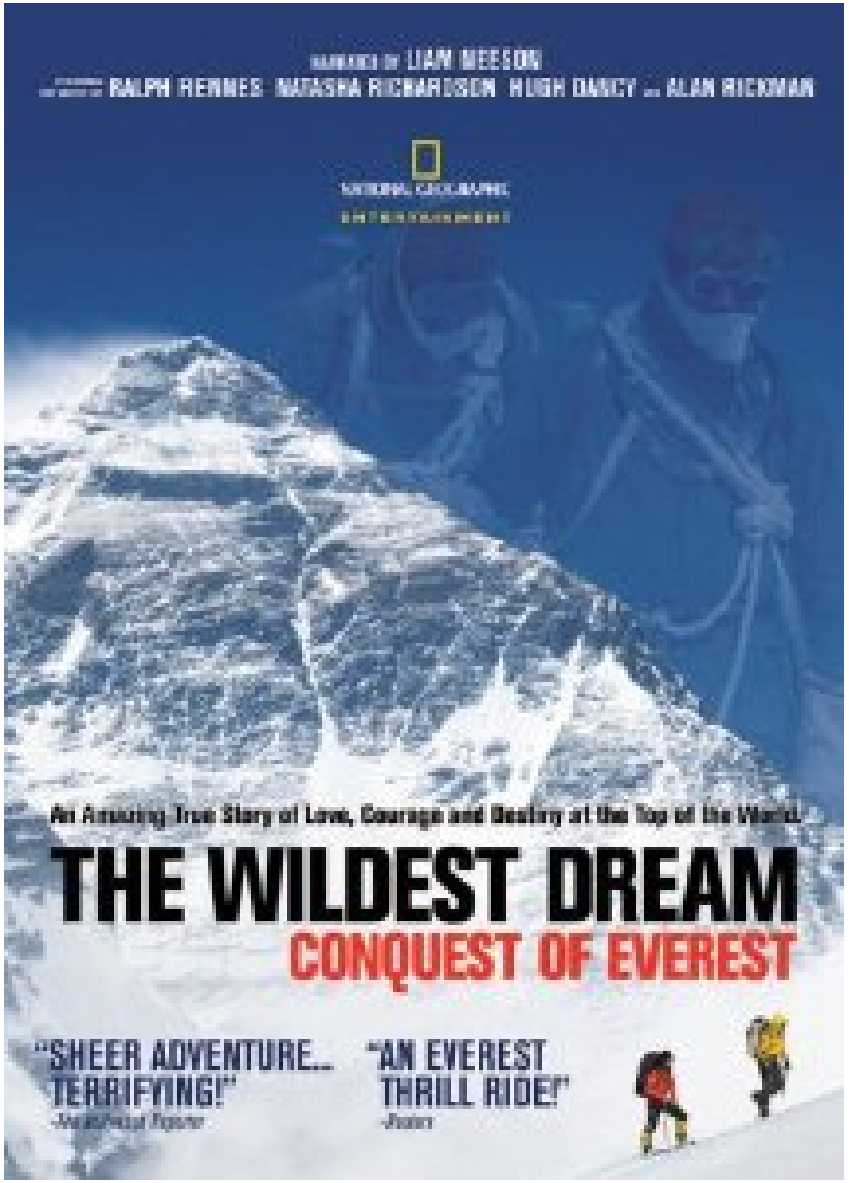
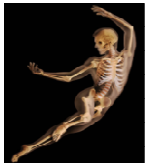

R
L




I don't give a


LIAM NEESON
RALPH FIENNES NATASHA RICHARDSON HUGH DANCY ALAN RICKMAN
An Amazing True Story of Love, Courage and Destiny at the Top of the World
THE WILDEST DREAM
CONQUEST OF EVEREST
"SHEER ADVENTURE... TERRIFYING!"
"AN EVEREST THRILL RIDE!"



Why are you here?
To serve mice or men

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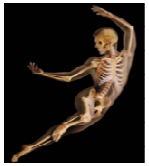

Final Word

- Disproportionate support to mouse research.
- Trial failures and translation will not be improved by more mouse research.
- More focus towards the clinical impact of our research and its translation.

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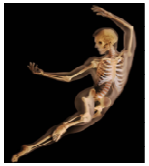

Acknowledgements

Australian Government
Australian Research Council

U.S. Department of Health and Human Services

Supported by the National Institutes of Health
NIAMS National Institute of Arthritis and Musculoskeletal and Skin Diseases

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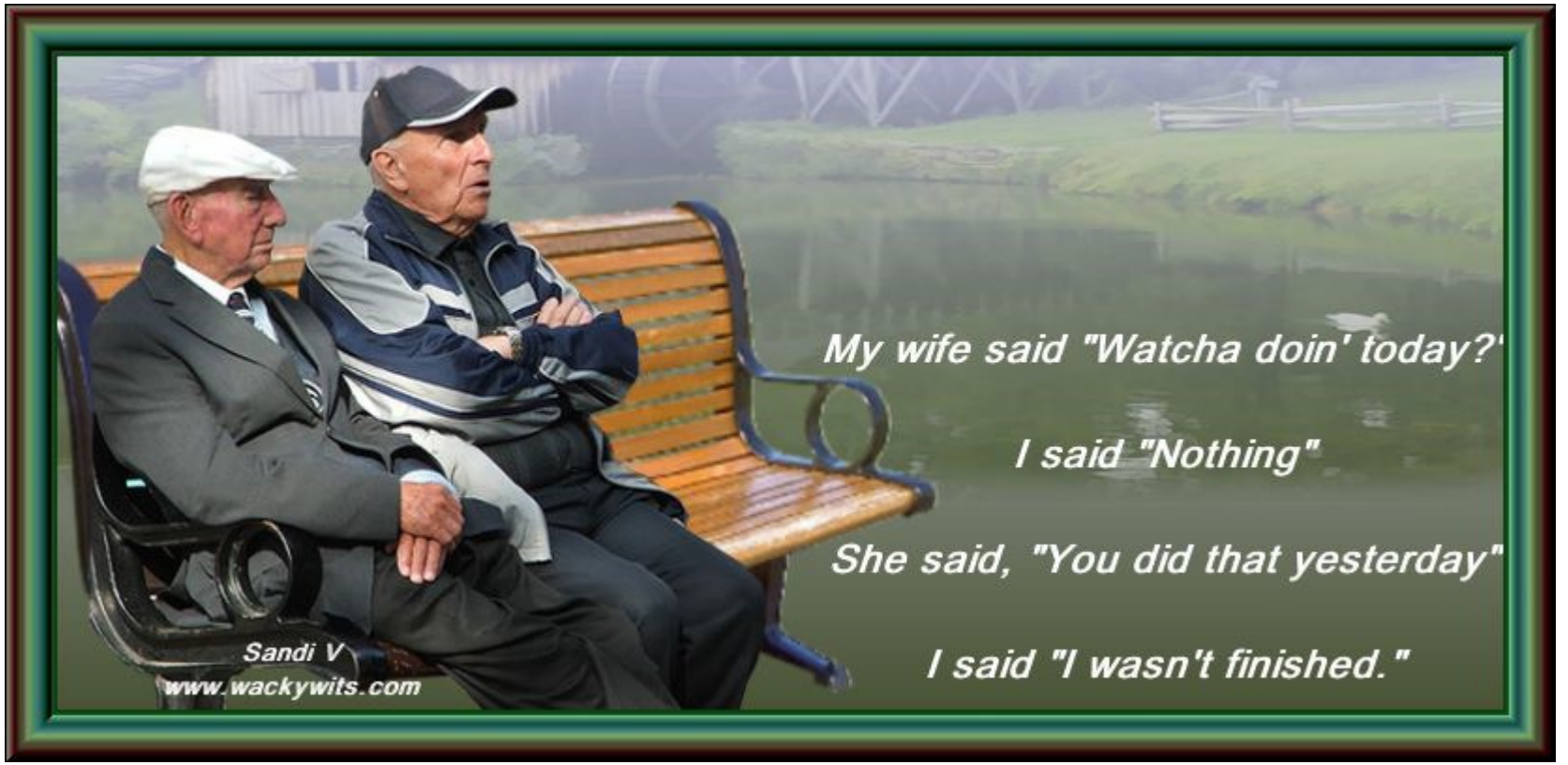
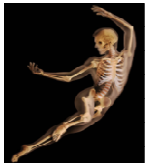
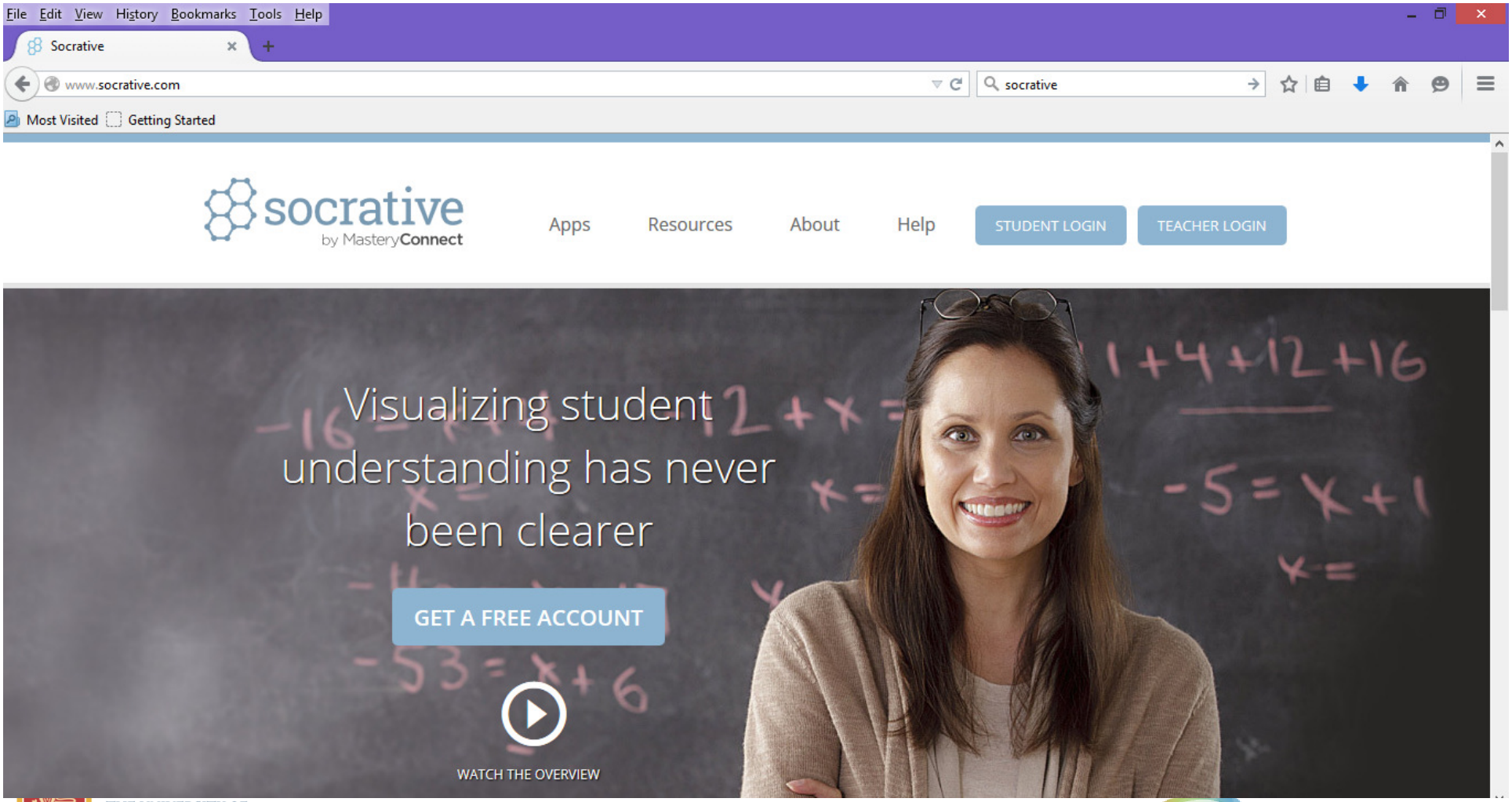
Australian Government
National Health and Medical Research Council
NHMRC


My wife said "Watcha doin' today?"
I said "Nothing"
She said, "You did that yesterday"
I said "I wasn't finished."
Sandi V
www.wackywits.com



www.socrative.com Room No: 794352

Please vote: Should Osteoarthritis Research Focus on “Mice” or “Men”?



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MAGNETIC RESONANCE IN MEDICINE

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Imaging Based Measures of Osteoarthritis

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David.Hunter@sydney.edu.au
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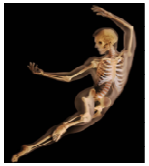
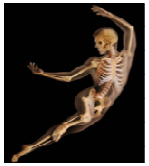


"NIH stands for the National Institutes of Health, not the National Institutes of Biomedical Research, or the National Institutes of Basic Biomedical Research".

- Alan Schechter

- Despite massive investment in translational research clinical and basic scientists don't really communicate.



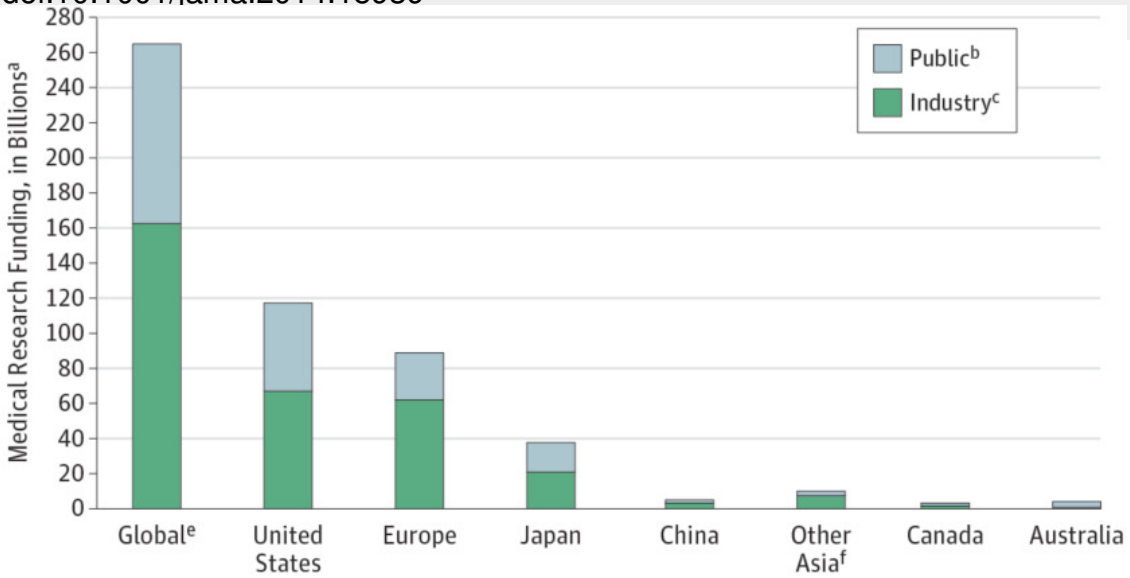
Return on investment

- Funding research is all about return on investment. By funding basic research, we have seen that there is usually little return, certainly very little *immediate* return.
- Basic research is rarely developed in a practical way for doctors, hospitals or pharmaceutical companies.
- But if we invest in translational research, the wealth of knowledge available will be amplified since it all of a sudden has clinical applications

Moses H III, Dorsey R, Matheson DHM, Thier SO. Financial anatomy of biomedical research. *JAMA*. 2005;294(11):1333-1342.

From: **The Anatomy of Medical Research: US and International Comparisons**

JAMA. 2015;313(2):174-189. doi:10.1001/jama.2014.15939

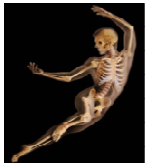


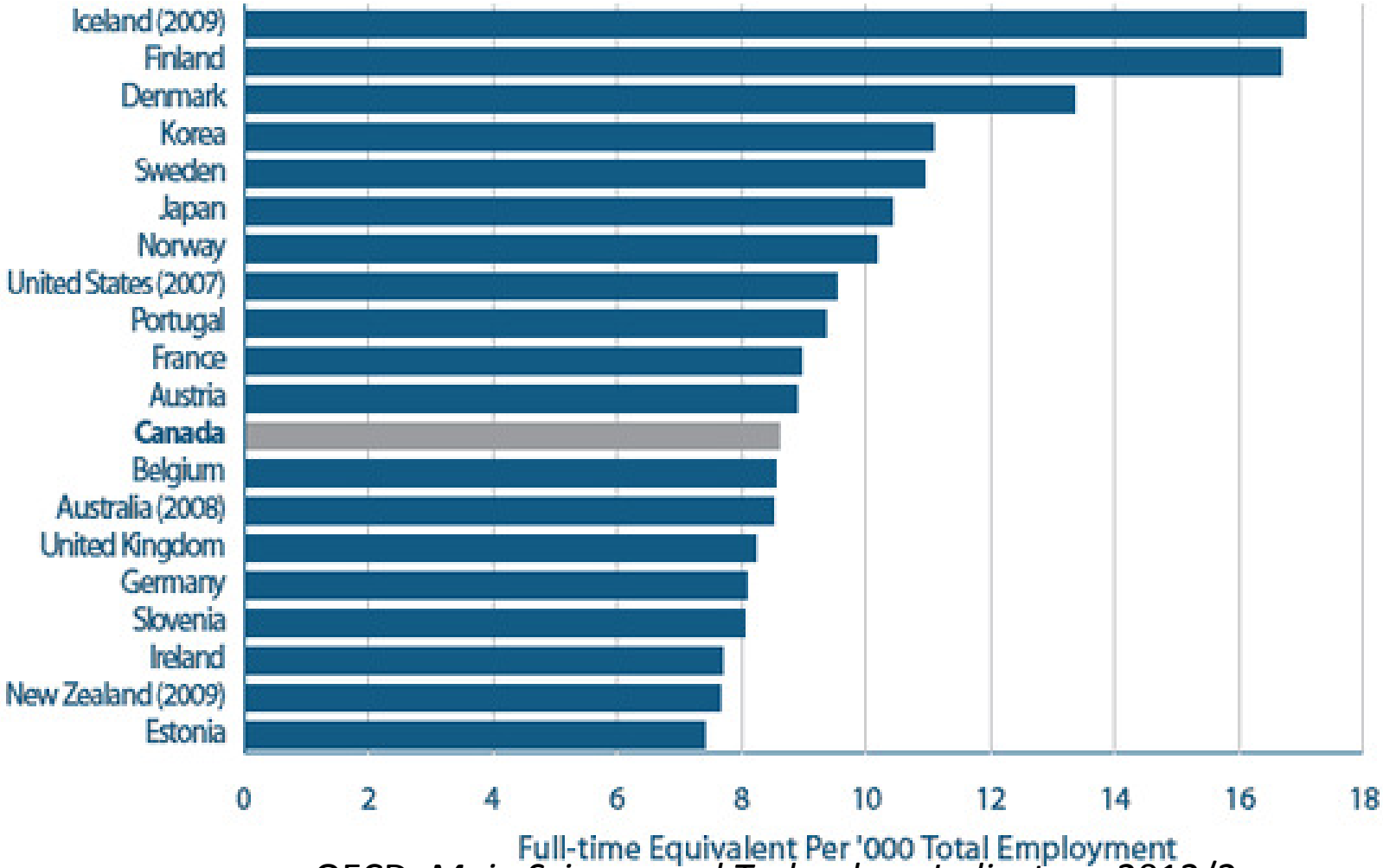
Medical research funding, $, in billions (%)[a]								
Overall	265.0 (100)	117.2 (44)	88.6 (33)	37.8 (14)	4.9 (1.2)	9.7 (4)	3.1 (1.2)	3.8 (1.4)
Public[b]	102.8 (100)	50.5 (49)	26.9 (26)	17.0 (17)	1.3 (2)	2.4 (2)	1.8 (2)	2.8 (3)
Industry[c]	162.2 (100)	66.6 (41)	61.6 (38)	20.8 (13)	3.6 (0.8)	7.3 (4)	1.3 (0.8)	1.0 (0.6)
Compound annual growth rate, % (2004-2011)[d]	3.5	1.0	4.1	6.8	16.9	20.8	4.5	9.3

Figure Legend:

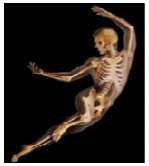
Global Medical Research Funding in Select Countries/Regions, 2011The regions/countries/economies in the analysis include the major countries of North America (United States, Canada), Europe (including the 10 largest European countries in the Organisation for Economic Co-operation and Development), and Asia-Oceania (Australia, China, India, Japan, Singapore, and South Korea). Data for African and South American countries and Russia were not available. Data were calculated according to methods outlined in eTable 6 in the Supplement.

Data were converted to US currency using an average annual exchange rate for the respective year and adjusted to 2012 dollars using the Biomedical Research and Development Price Index.





OECD, *Main Science and Technology Indicators*: 2012/2



Number of competing RPGs and R01 equivalent awards