OA research should focus on “mice”

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Disclosures and potential conflicts: *most (but not all) of my research and research funding is based on “mice”*.....

Definitions .....

I'm sure David does not advocate just supporting OA research in male humans.....

"man" = clinical research
"mice" = pre-clinical research

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"Focus" (Oxford dictionary):

- the act of concentrating interest or activity on something .... to pay particular attention to ....
- adapt to the prevailing level of light and become able to see clearly .....

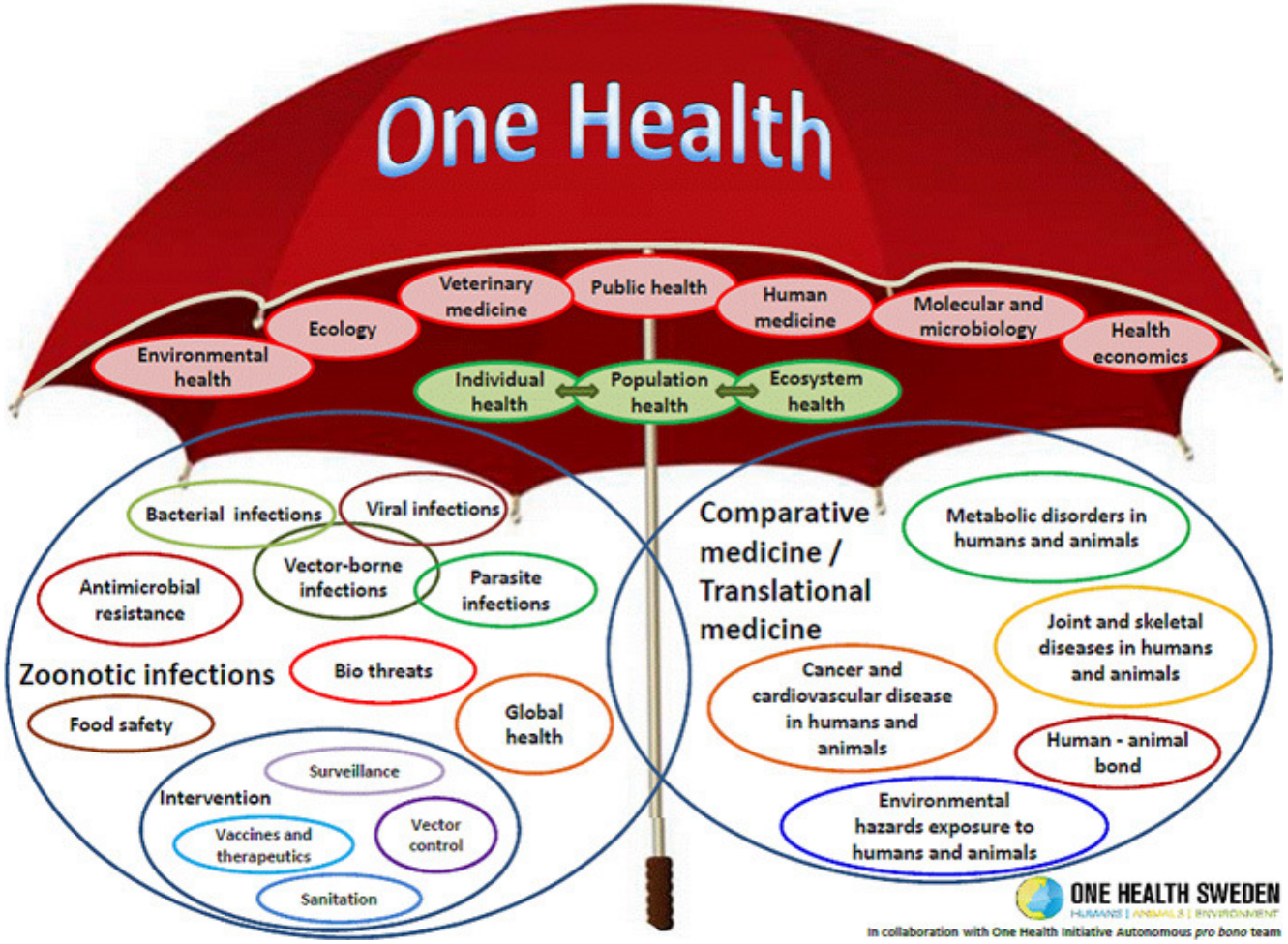
"... to understand..."

"So you can cure OA in mice ..... big deal!"

The "moral high ground"....

Its OA in people we care about, not mice!
Its human health that matters!
Its the niH, nHMrc, Mrc ..... human health pays the bills!

It IS a big deal: "One Health"

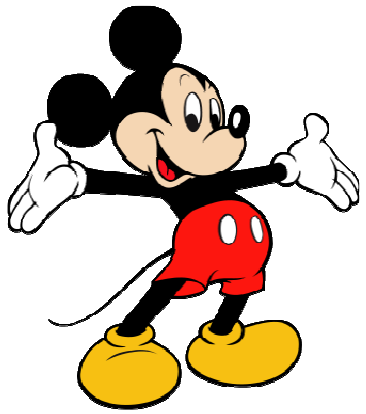


Synergism achieved will advance health care for the 21st century and beyond

It IS a big deal: "proof of principle"

In 2005 the first specific GM mouse with significant protection from induced OA was published

- now 43 with significant protection
  - constitutive and inducible
  - global and tissue specific
  - whole OA joint pathology and pain



This was and is the best proof of principle that:

- OA is a treatable condition
- it is possible to pharmacologically target OA
- there are multiple targetable pathways

Such discovery not possible in clinical research

"OK ..... but everything works in mice"

Successful therapies for Alzheimer's disease: why so many in animal models and none in humans?

Rafael Franco[1,2] * and Angel Cedazo-Minguez[3]

Frontiers in Pharmacology | Neuropharmacology
June 2014 | Volume 5 | Article 146 |

KOLLING
Institute of
Medical Research

Not everything works in mouse OA.....

GM mice and outcome in OA (as of Apr 2015)

- 165 GM mice where OA has been studied
  - 43 reduce disease
  - 86 worsen the disease
  - 28 have no effect
  - 8 have mixed results

Therapeutic trials in mouse OA

- 30 separate agents
  - 25% no cartilage protection
  - ± effects on osteophytes, SC-bone

"OK ..... but a mouse is not a man"

Genomic responses in mouse models poorly mimic human inflammatory diseases PNAS | February 26, 2013 | vol. 110 | no. 9 | 3507–3512

"... our study supports higher priority for translational medical research to focus on the more complex human conditions rather than relying on mouse models to study human inflammatory diseases"

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Small Jurassic Dinosaur May Have Flown Without Feathers | Russian Space Station Cargo Ship Is Said to Be Out of Control | California Governor Orders New Target for Emissions Cuts | PAID POST: Costa Ricans Share The Secret to Finding Work-Life Balance BY SAVE THE AMERICANS | New Study Li... Extremes to ... Warming

SEE HOW FORD OWNER IZZY PASKOWITZ GOES FURTHER FOR KIDS WITH AUTISM. Ford EXPAND

SCIENCE 285 COMMENTS

Mice Fall Short as Test Subjects for Some of Humans' Deadly Ills

By GINA KOLATA FEB. 11, 2013

Email Share Tweet Save More

FAR FROM THE MADDING CROWD FRIDAY

For decades, mice have been the species of choice in the study of human diseases. But now, researchers report evidence that the mouse model has been totally misleading for at least three major killers — sepsis, burns and trauma. As a result, years and billions of dollars have been wasted following false leads, they say.

The study's findings do not mean that mice are useless models for all human diseases. But, its authors said, they do raise troubling questions about diseases like the ones in the study that involve the immune system, including cancer and heart disease.

"Our article raises at least the possibility that a

Perspective & focus

Genomic responses in mouse models greatly mimic human inflammatory diseases

Keizo Takao[a,b] and Tsuyoshi Miyakawa[a,b,c,1]

PNAS January 27, 2015 112:1167–1172

"... demonstrate that gene expression patterns in mouse models closely recapitulate those in human inflammatory conditions and strongly argue for the utility of mice as animal models of human disorders"

Perspective & focus : we're closer than you think

Genomic responses in mouse models greatly mimic human inflammatory diseases

Keizo Takao[a,b] and Tsuyoshi Miyakawa[a,b,c,1]

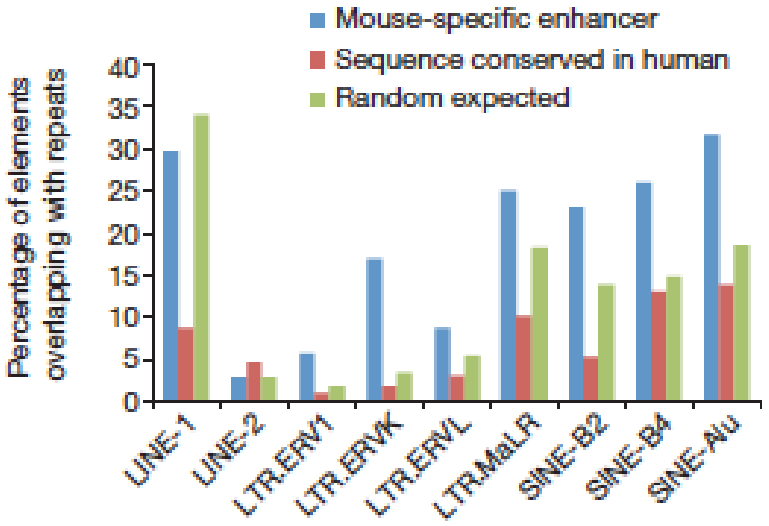
PNAS January 27, 2015 112:1167–1172

"OK ... but there really ARE some differences"

A comparative encyclopedia of DNA elements in the mouse genome

20 NOVEMBER 2014 | VOL 515 | NATURE | 355

"... we not only confirm substantial conservation in the newly annotated potential functional sequences, but also find a large degree of divergence of sequences involved in transcriptional regulation, chromatin state and higher order chromatin organization....."

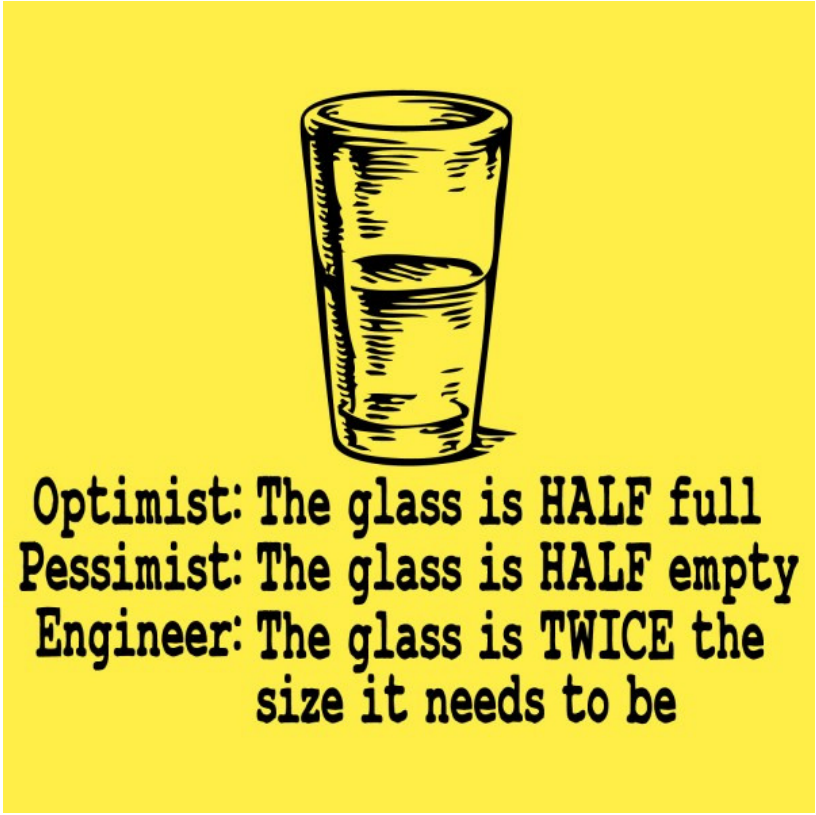


Species differences = opportunities

A comparative encyclopedia of DNA elements in the mouse genome

20 NOVEMBER 2014 | VOL 515 | NATURE | 355

"... provide a valuable reference to guide researchers to formulate new hypotheses .... a general resource for research into mammalian biology and mechanisms of human diseases...."



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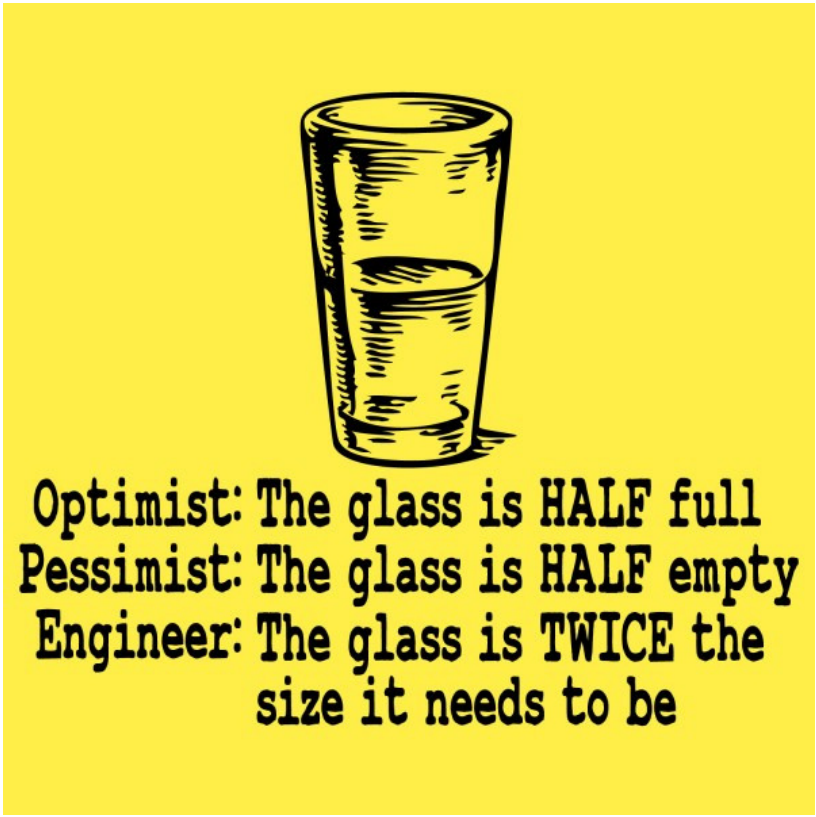


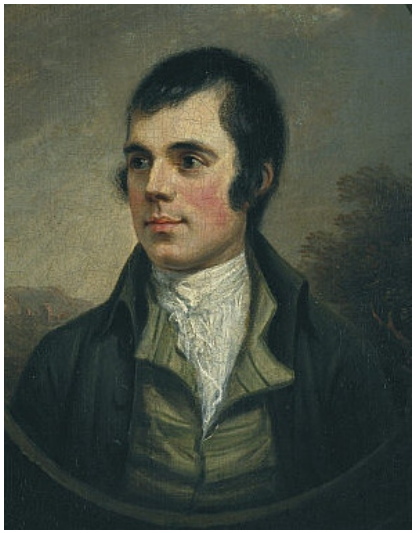
"Then why doesn't "mouse" research translate?"

- ~1/3rd of pre-clinical studies translated to RCTs and only ~10% through to approval for use in patients *JAMA 2006:296;1731–1732*
- Poor disease modelling (*"apples & oranges"*)
  - *age, gender, OA phenotype, outcome measures…* *Nat.Rev.Rheumatol. 2013*:9;485
- Poor reproducibility
  - *25% cardiovascular research corroborated* *Nat.Rev.Drug Discov. 2011*:10;712
  - *11% of clinical oncology findings reproduced* *Nature 2012*:483;531
- Poor reporting
  - *design, blinding, randomization, analysis*
    PLos ONE 2009:4;e7824
  - *up to 30% over-estimate of effect size*
    PLos Biology 2010:8;e1000344

Survey Finding	% of studies
Purpose NOT stated in Introduction	5
# of separate experiments NOT indicated	6
Experimental unit NOT identified	13
Sex of animal NOT identified	26
Age or weight NOT reported	24
Exact animal number NOT reported	36
Sample size NOT justified	100
Statistical methods NOT reported	4
Statistical methods INCORRECT	12
Measure of variability NOT presented	17
Random allocation reported	12
Blinding for quantitation reported	14

Research in neither "mouse" nor "man" has a good track record .....

But Mousie, thou art no thy lane,
In proving foresight may be vain:
The best-laid schemes o' mice an' men
Gang aft agley,
An' lea'e us nought but grief an' pain,
For promis'd joy!



How good is discovery research in "man"?

Assessment of Osteoarthritis Candidate Genes in a Meta-Analysis of Nine Genome-Wide Association Studies

ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 4, April 2014, pp 940–949

- Study optimised to find associations
  - meta-analysis of 9 GWAS
  - focus on 199 genes with previous associations
- 0/199 significant associations in knee OA
- 2/199 significant association with hip OA
- *"... a general lack of reproducibility of OA candidate genes"*
- *"..clear that the effect sizes and ORs [previously] reported were widely overestimated"*

RCT: the research "gold standard".....?

EFFECTIVENESS OF EXERCISE THERAPY IN PATIENTS WITH OSTEOARTHRITIS OF THE HIP OR KNEE

ARTHRITIS & RHEUMATISM
Vol. 42, No. 7, July 1999, pp 1361–1369

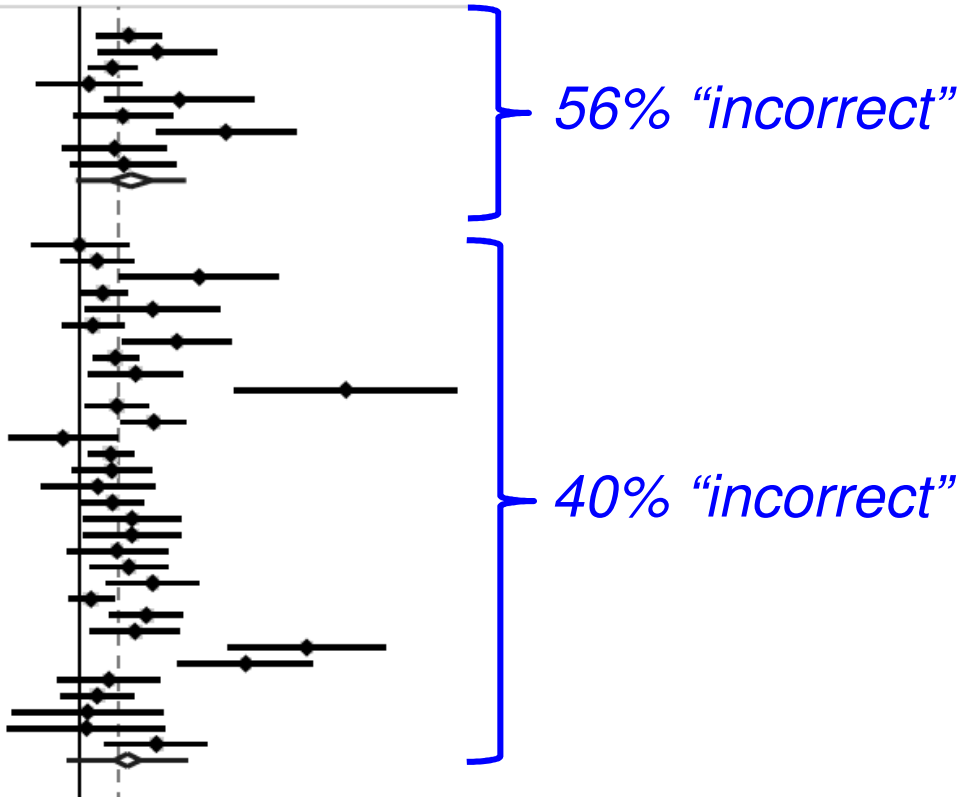
A Systematic Review of Randomized Clinical Trials

- 2/11(19) - acceptable validity score and sufficient power
- methodologic assessment revealed some major threats to validity:
  - blinding of providers and patients absent in all studies
  - half reported blinded outcome assessment
  - absence of information on adherence to the intervention
- *"..lack of information concerning long-term effects is a remarkable omission, since the clinical impression is that effects disappear over time"*
- *"..limited insight into the effectiveness of exercise therapy in OA of the hip"*

How "translatable" is OA research in "man"?

- systematic review and meta-analysis – exercise and OA
  - 48/94 RCTs included (35 no control, 10 insufficient data)
- *assume the standardised mean difference is "true effect"*

Author	Year	nE	mE	sdE	nC	mC	sdC
Aerobic exercise							
Kovar	1992	47	1.38	2	44	.1	2
Bautch	1997	15	1.3	2.05	15	−.62	1.67
Ettinger – aerobic	1997	117	.26	.61	64	0	.61
Talbot	2003	17	.12	.72	17	0	1.13
An	2008	11	78.9	74.7	10	−21.4	74.7
Lee	2009	29	2.2	4.1	15	.2	1.8
Ni	2010	14	1.36	.22	15	−.07	1
Wang – aquatic	2011	26	11	20	13	2	18
Wang – landbased	2011	26	11	14	13	2	18
Subtotal (I−squared = 44.3%, p = 0.073) with estimated predictive interval							
Resistance exercise							
Weidenhielm	1993	19	.1	2.3	20	.1	1
Børjesson	1996	34	.4	2	34	0	1.4
Schilke	1996	10	6.1	4.03	10	−.4	4.03
Ettinger – resistance	1997	120	.19	.66	64	0	.56
Røgind	1998	11	3	5.24	12	−1	2.62
Maurer	1999	49	43.54	86.95	49	28.49	86.95
Horstmann	2000	19	1.79	1.2	19	.53	.7
Petrella	2000	91	.51	.15	88	.44	.15
Baker	2001	22	79	87.96	22	20	71.05
Gür	2002	17	13.7	5	6	−2.5	2.6
Topp	2002	67	1.54	3.21	35	−.02	3.19
Huang – strength	2003	91	1.6	1.5	33	.2	1.3
Cheing	2004	15	37.8	64	16	49.6	42.4
McCarthy	2004	104	2.13	2.91	86	.95	2.91
Huang – isokinetic	2005	30	1.2	1.6	32	.5	1.7
Rooks	2006	14	.1	2.3	15	−.7	4
Lim	2008	50	9	16.62	47	1.81	16.8
Jan – high intensity	2008	34	3.7	3.64	15	1.2	3.64
Jan – low intensity	2008	34	3	2.62	15	1.2	2.62
Evgeniadis	2008	18	.46	1.6	20	−.5	2.2
Weng	2009	31	1.1	1.6	33	.1	1.5
Lin – strength	2009	36	4.6	3.31	18	1.2	4
McKnight	2010	95	1.35	9	87	0	9
Bennell	2010	39	2.6	2.44	37	.48	2.43
Bezalel	2010	25	3	4.13	25	0	4.13
Salli – isokinetic	2010	23	4.3	1.2	12	.6	1.3
Salli – isometric	2010	24	3.6	1.4	12	.6	1.3
Foroughi	2011	18	1.87	1.73	19	1.2	1.73
Swank	2011	36	.9	7.3	35	−.8	7.3
Sayers – high speed	2012	12	1.8	2.8	6	1.5	2.6
Sayers – low speed	2012	10	1.8	3.4	6	1.5	2.6
Chang	2012	24	2.3	1.3	17	.9	1.5
Subtotal (I−squared = 67.7%, p = 0.000) with estimated predictive interval							



C. Juhl,[1] R. Christensen,[2] E. M. Roos,[3] W. Zhang,[4] and H. Lund[3]

ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 3, March 2014, pp 622–636

... assuming the reported result is real ...

Table 2. Differences in Methods Used in the Reanalysis

Differences Cited in the Reanalysis	No. (%)				
		Did the Reanalysis Modify Inferences of the Original Trial?			
	Reanalyses (n = 37)[a]	No (n = 29)	Treat Different Patients (n = 3)	Treat More Patients (n = 13)[b]	Treat Fewer Patients (n = 1)
Differences in statistical or other analytical methods	18 (48.6)	11 (61)	3 (17)	3 (17)	1 (5.5)
Nonparametric statistical technique	1	1			
Separation of composite end points for analysis	1				1
Measure of clinical significance to confirm original findings	2	2			
Informative censoring approach	3	3			
Competing risks model	1		1		
Nonlinear model	2	1	1		
Triangular and restricted sequential design	1	1			
Multivariate techniques	1	1			
Matched site-to-site image analysis between trial centers	1			1	
Linear transformation of scores	1	1			
Adjustment for confounders[c]	1	1			
Bayesian methods	1			1	
Additional Poisson models	1		1		
Wilcoxon and Mann-Whitney *U* tests to compare treatment groups	1			1	
Differences in the definition or measurement of same outcome	12 (32.4)	6 (50)		6 (50)	
Computer-assisted method for measurement of outcome	1			1	
New criteria for the assessment of outcome[d]	7	4		3	
Use of rate of change of the outcome as end point	1			1	
Different measurement to assess the same construct	3	2		1	
Differences in the handling of missing data	8 (21.6)	5 (63)		3 (37)	
Single imputation (baseline or last observation carried forward)[e]	3	3			
Multiple imputation[d]	2	1		1	
Use of associations between predictor and outcome for imputations[c]	1	1			
Excluded patients in reanalysis[c]	2			2	
Differences in the intention-to-treat or on-treatment principle	2 (5.4)	2 (100)			
Original without ITT; reanalysis with ITT[c]	1	1			
Original with modified ITT; reanalysis with standard ITT	1	1			
Differences in any other aspect of the analysis or methods	6 (16.2)	5 (83.3)	0	1 (16.7)	
Correction of errors—exclusion of patients	2	2			
Testing sensitivity of excluding 1 or more sites	1			1	
Testing differences in study design	1	1			
Central site reanalysis	1	1			
Exclusion of 1 site because of protocol inconsistencies	1	1			

Reanalyses of Randomized Clinical Trial Data

JAMA. 2014;312(10):1024-1032.

Shanil Ebrahim, PhD; Zahra N. Sohani, MSc; Luis Montoya, DDS; Arnav Agarwal, BSc; Kristian Thorlund, PhD; Edward J. Mills, PhD; John P. A. Ioannidis, MD, DSc

35% of published re-analyses led to interpretations different from that of the original article

- 22% changed direction or gain/loss of effect
- 8% showing that different patients should be treated
- 3% that fewer patients should be treated

Research methodology in “mice” vs “man”.....

OK, we both have issues - why focus on "mice"?

- Both sides can do "better" research & reporting
- Both sides care about the human disease
  - "mice" have added "one health" outcomes
- While there are species differences:
  - any differences = therapeutic opportunities
  - "mice" can and do model "man"
  - need to match the model and disease

Difference in the potential outcomes of the research

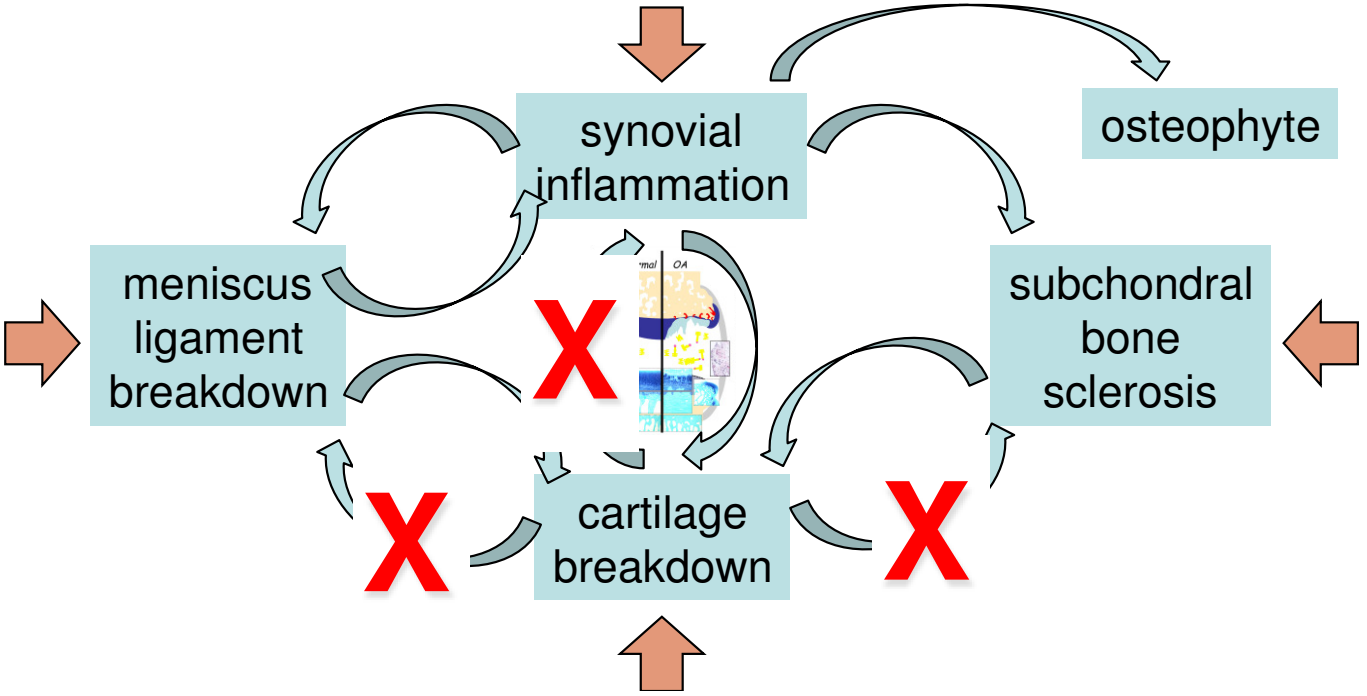
It comes down to philosophy – what do you believe in – what do you think will ultimately make a difference?

"risk-factor-reduction" vs "cause-and-cure"

Association vs Cause

Observing two things changing in parallel (no matter how small the “p-value”) = association

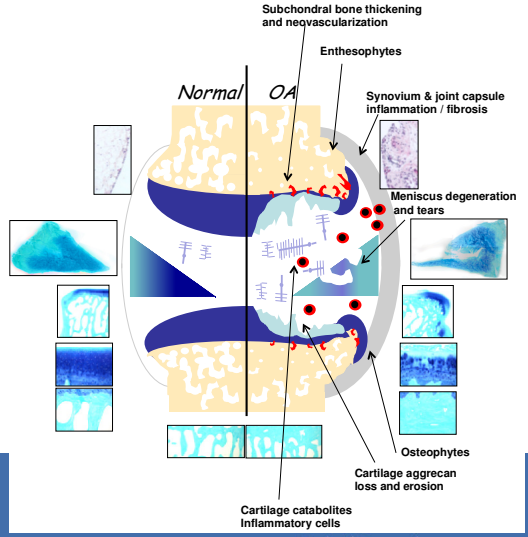
Intervention to specifically target one thing and see what happens to the other = mechanism (cause)



Not everything works in mouse OA ..... but everything informs ....

GM mice and outcome in OA (as of Apr 2015)

- 165 GM mice where OA has been studied
  - 43 reduce disease *= mechanisms = target*
  - 86 worsen the disease *= mechanisms ± target*
  - 28 have no effect *= not mechanisms*
  - 8 have mixed results *= OA phenotypes*
  - *only 60-70% coordinate joint tissue/pain effects*



Clinical research = association and risk factors

"Great you've calculated my OA risk, now what?"

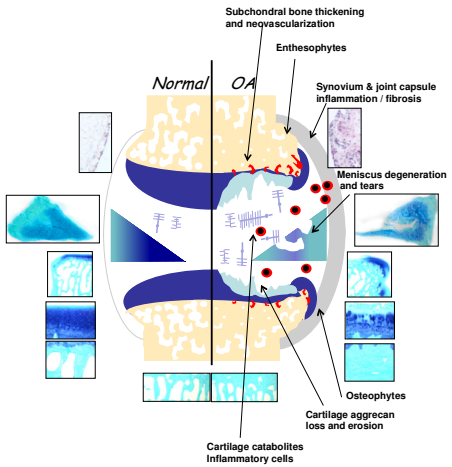
"make sure your get enough exercise BUT don't do anything that might injure your joint!"

"don't eat too much!!".....".....don't get old!!!"

"don't be a post-menopausal woman!!!"

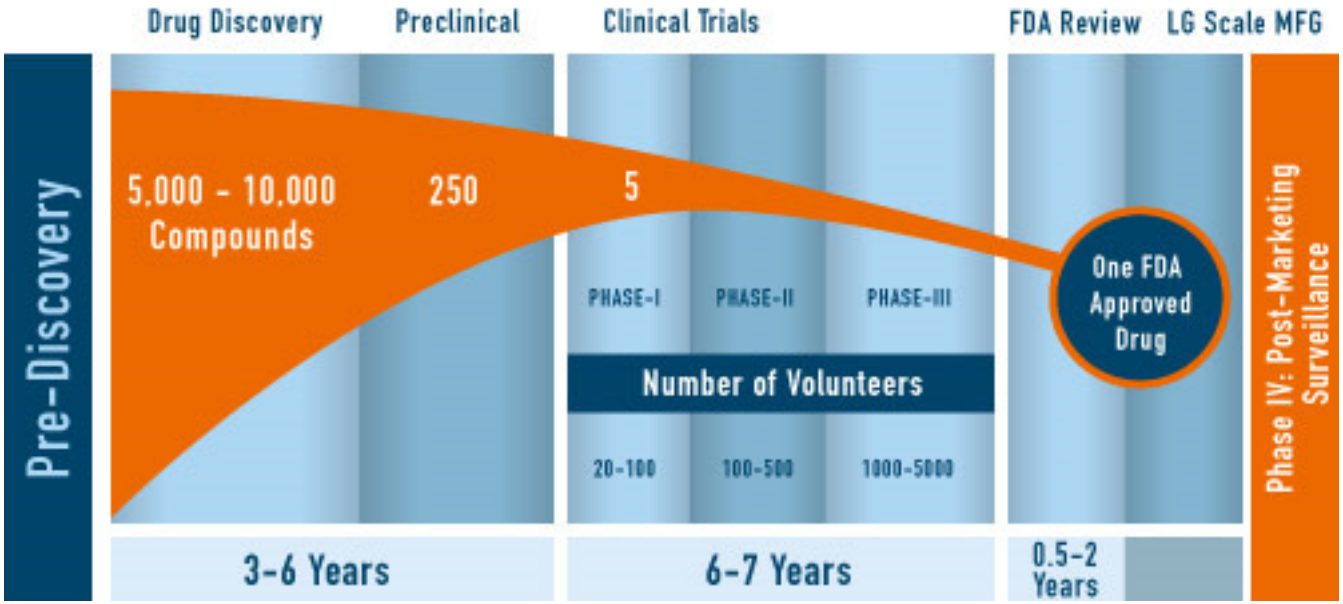
"for goodness sake - don't be an overweight, older, post-menopausal woman with a joint injury!!!!!!"

Discover and treat the cause: “a pill for your ills”

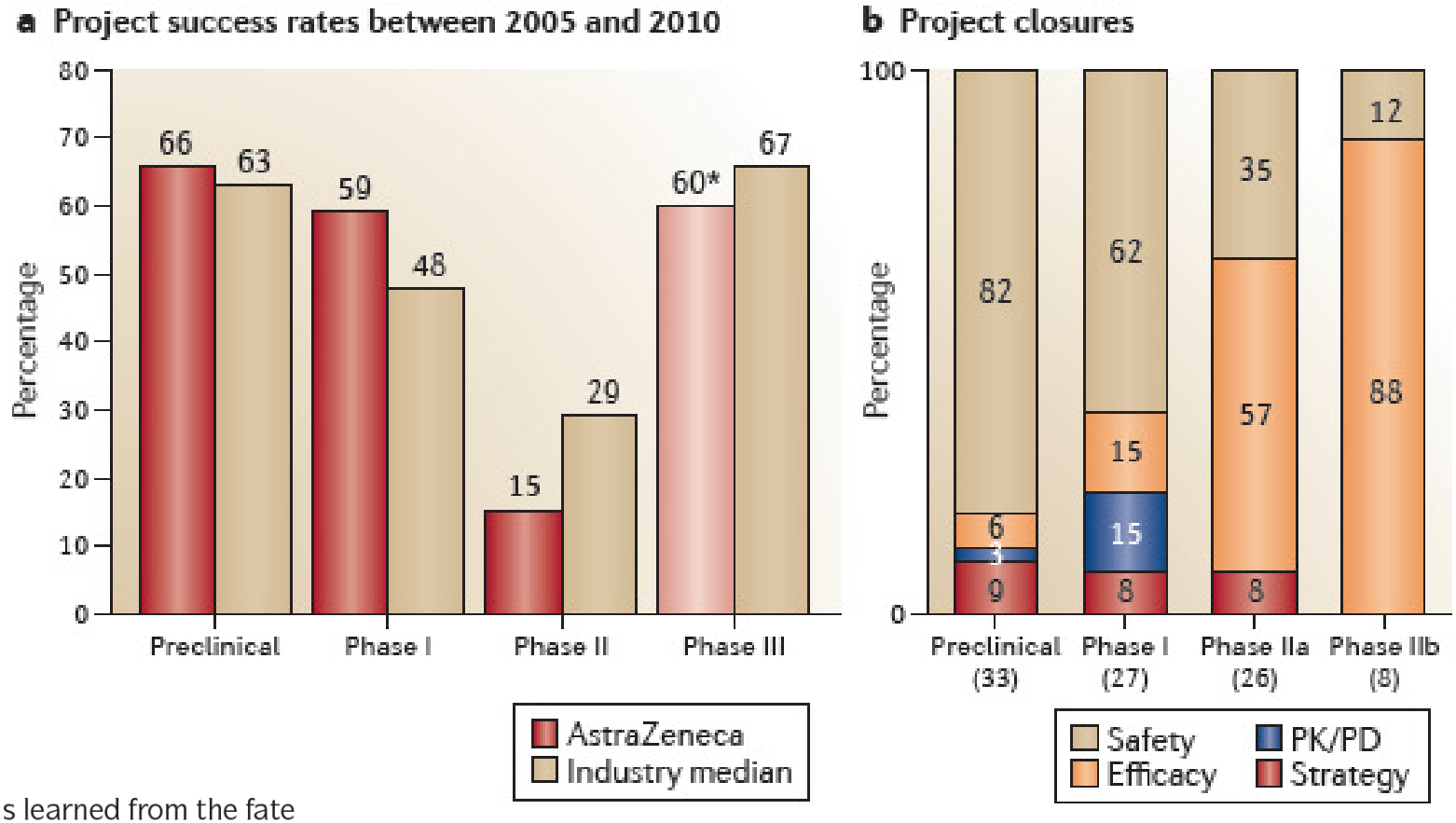


TREATMENT

CURE



Why do drug development programs fail?



Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework

David Cook, Dearg Brown, Robert Alexander, Ruth March, Paul Morgan, Gemma Satterthwaite and Menelas N. Pangalos

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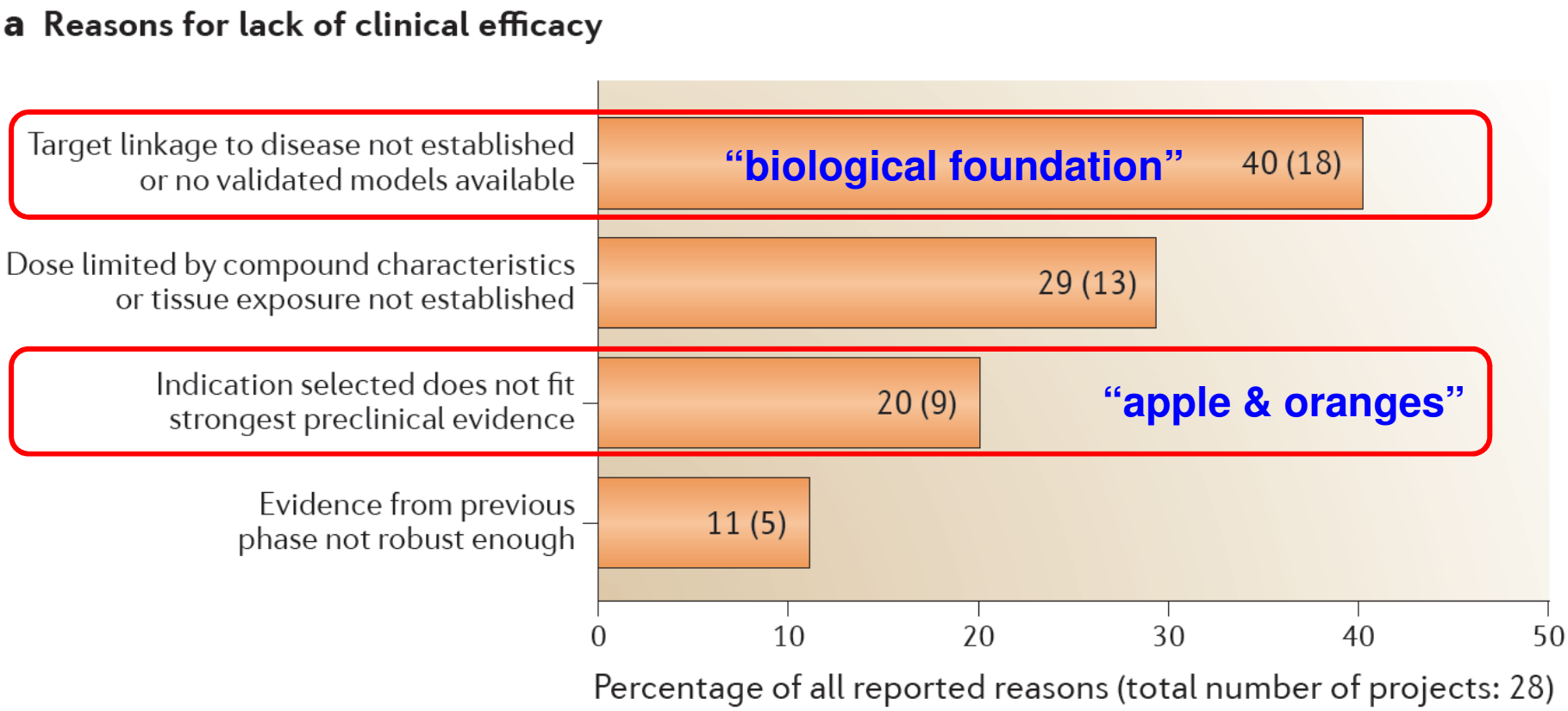

Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework

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Solid biological foundation is critical

"... clinical research follows on from animal research. If the foundations of the biomedical research enterprise are unsound, then whatever is built on these foundations will be similarly precarious"

Is animal research sufficiently evidence based to be a cornerstone of biomedical research?

BMJ 2014;348:g3387 doi: 10.1136/bmj.g3387 (Published 30 May 2014)

We MUST focus OA research on "mice"!

Defining OA pathophysiology, mechanisms, causes

- is the only way to define optimal targets
- is the only way to develop treatments, cures
- can only be done in pre-clinical research
- provides the foundation for clinical trials

Improve the practice of pre-clinical research

- rigour, reproducibility, repeatabilty
- more not less

Align the model and the human disease

- repeat all findings from ptOA in young, healthy....
- more not less

OA "therapeutic recession"

Roaring Out of Recession

March 2010 Harvard Business Review

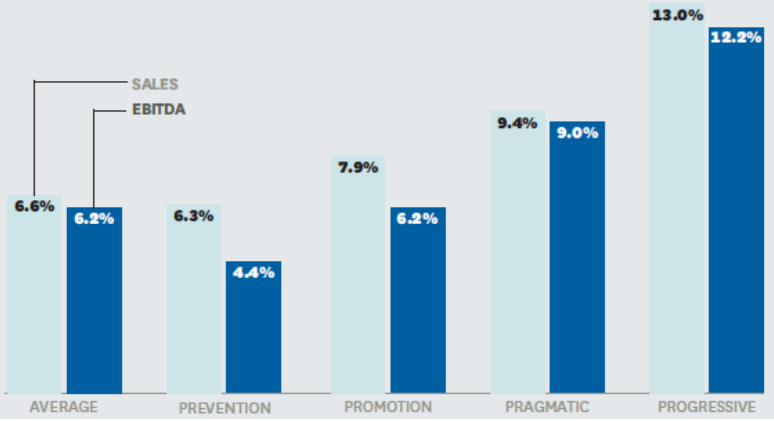
Ranjay Gulati (rgulati@hbs.edu) is the Jaime and Josefina Chua Tiampo Professor at Harvard Business School and the author of *Reorganize for Resilience* (Harvard Business Press, 2010).

Nitin Nohria (nnohria@hbs.edu) is the Richard P. Chapman Professor at Harvard Business School and the author, with Rakesh Khurana, of *Handbook of Leadership Theory and Practice* (Harvard Business Press, 2010).

Franz Wohlgezogen (f-wohlgezogen@kellogg.northwestern.edu) is a doctoral student at Northwestern University's Kellogg School of Management.

POSTRECESSION LEADERS IN SALES AND PROFITS GROWTH

After a recession, progressive companies outperform pragmatic companies by almost four percentage points in sales and more than three percentage points in earnings before interest, taxes, depreciation, and amortization (EBITDA)—and do about twice as well as companies in general. (Percentages, which are adjusted for industry averages, refer to the three-year compound annual growth rate.)



The companies that did best, that not only survived but thrived after GFC, were those that invested in R&D

Remember what your voting for.....

"... the compelling urge of man to explore and to discover, the thrust of curiosity that leads men to try to go where no one has gone before...."
(USA Space Program)

"cause-and-cure-research" or *"risk-factor-reduction-research"*

explorer *accountant*

Finding the right path.....