

# Debunking common myths about translation

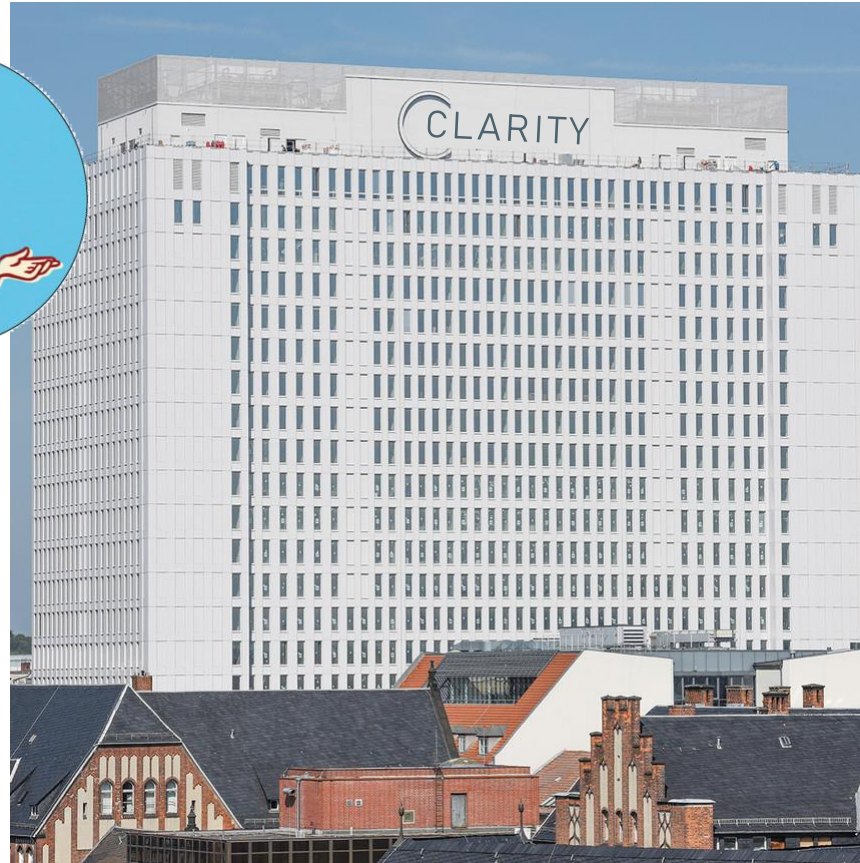
## Notes on the structure of translation

Berlin, 22.11.2019

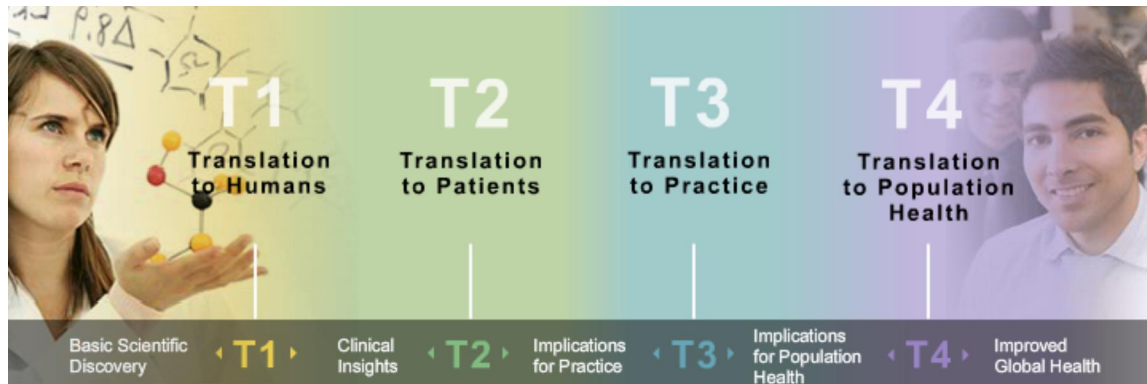
Slide download: <http://bit.ly/commonmythstranslation>



# Ask the Wissenschaftsnarr: Fostering 'Translation' at the imaginary university hospital, 'CLARITY'

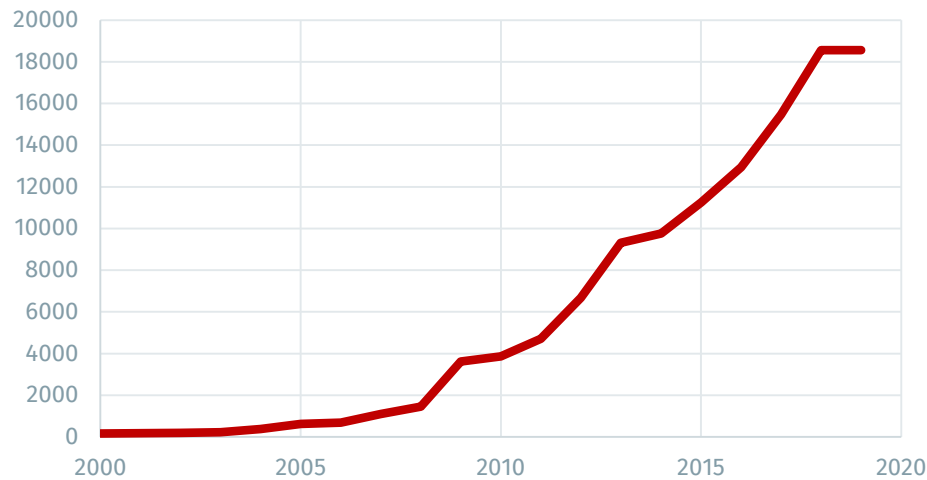


# A common narrative („generic model“)



# "Translational medicine"

Publications (total)



## Empfehlungen zur Förderung translationaler Forschung in der Universitätsmedizin

Stellungnahme der Arbeitsgruppe „Translation“ der Ständigen Senatskommission für Grundsatzfragen in der Klinischen Forschung der Deutschen Forschungsgemeinschaft

DFG

WR

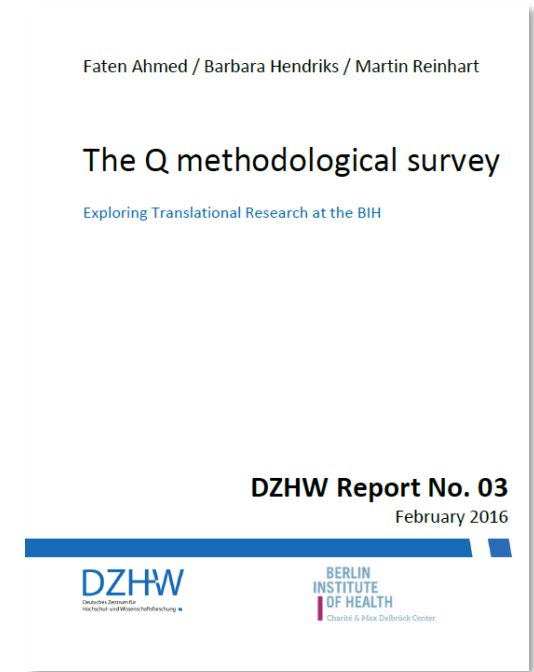
WISSENSCHAFTSRAT

Drs. 5663-16  
Weimar 21. 10. 2016

Perspektiven der  
Universitätsmedizin

**BIH QUEST**  
Transforming Biomedical Research

# BIH / DZHW white papers on translation (Cleverly hidden on the BIH website)



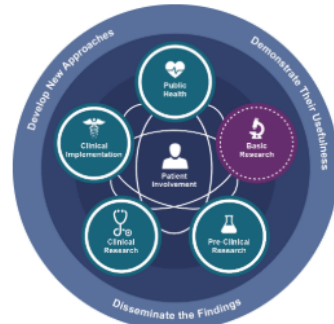
# NCATS and CSTA: 1.2 billion USD



Translational Science Education & Training  
 Translational Science Spectrum  
 Issues in Translation  
 Drug Discovery, Development and Deployment Maps  
 Translational Science Skills

## Translational Science Spectrum

The translational science spectrum represents each stage of research along the path from the biological basis of health and disease to interventions that improve the health of individuals and the public. The spectrum is not linear or unidirectional, each stage builds upon and informs the others. At all stages of the spectrum, NCATS develops new approaches, demonstrates their usefulness and disseminates the findings. Patient involvement is a critical feature of all stages in translation.



### Basic Research

Basic research involves scientific exploration that can reveal fundamental mechanisms of biology, disease or behavior. Every stage of the translational research spectrum builds upon and informs basic research. NCATS scientists typically do not conduct basic research; however, insights gained from the Center's studies along the translational spectrum can inform basic research.

### Pre-Clinical Research

Pre-clinical research connects the basic science of disease with human medicine. During this stage, scientists develop model interventions to further understand the basis of a disease or disorder and find ways to treat it. Testing is carried out using cell or animal models of disease, samples of human or animal tissues, or computer-assisted simulations of drug, device or diagnostic interactions within living systems.

### Clinical Research

Clinical research includes studies to better understand a disease in humans and relate this knowledge to findings in cell or animal models; testing and refinement of new technologies in people; testing of interventions for safety and effectiveness in those with or without disease; behavioral and observational studies; and outcomes and health services research. The goal of many clinical trials is to obtain data to support regulatory approval for an intervention.

### Clinical Implementation

The clinical implementation stage of translation involves the adoption of interventions that have been demonstrated to be useful in a research environment into routine clinical care for the general population. This stage also includes implementation research to evaluate the results of clinical trials and to identify new clinical questions and gaps in care.

### Public Health

In this stage of translation, researchers study health outcomes at the population level to determine the effects of diseases and efforts to prevent, diagnose and treat them. Findings help guide scientists working to assess the effects of current interventions and to develop new ones.

### Translation

The process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public — from diagnostics and therapeutics to medical procedures and behavioral changes.

### Translational Science

The field of investigation focused on understanding the scientific and operational principles underlying each step of the translational process.

### Translation at NCATS

[Download the translational science fact sheet](#) (a PDF - 316KB).

### Translating Translation



NCATS Director Christopher P. Austin, M.D., [defines, distinguishes and explores the virtues of translation, translational research and translational science.](#)

## NCATS

Improving Health Through Smarter Science

## Clinical and Translational Science Awards Program

NCATS' Clinical and Translational Science Awards (CTSA) Program provides critical resources and support needed to strengthen the entire spectrum of our nation's clinical and translational research enterprise. CTSA Program biomedical research institutions — called "hubs" — provide core resources, essential mentoring and training, and opportunities to develop innovative approaches and technologies designed to re-engineer existing capabilities. Program support and collaborative initiatives harmonize efforts, foster collaboration and strengthen this network to improve the quality, safety, efficiency and speed of clinical and translational research nationally.

### CTSA Program Goals

- Train and cultivate the translational science workforce;
- Engage patients and communities in every phase of the translational process;
- Promote the integration of special and underserved populations in translational research across the human lifespan;
- Innovate processes to increase the quality and efficiency of translational research, particularly of multisite trials; and
- Advance the use of cutting-edge informatics.

### CTSA Program Activity Highlights

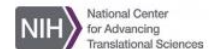
NCATS supports program activities to test and develop innovative approaches to barriers in clinical research. Examples include:

- The **Trial Innovation Network**, which brings together diverse medical research institutions from across the country to address roadblocks in clinical translation and to develop and test innovations that will effectively turn potential new interventions into therapies. The goal is not only to execute trials better, faster and more cost-efficiently, but also to be a national laboratory to study, understand and innovate the processes for conducting multisite studies. Composed of Trial Innovation Centers, a Recruitment Innovation Center and the CTSA Program hubs, the network soon will launch its first collaborative clinical trials with NIH Institutes and Centers and other partners.

[ncats.nih.gov/ctsa](http://ncats.nih.gov/ctsa)



U.S. Department of Health and Human Services  
 National Institutes of Health  
 NIH...Turning Discovery Into Health



**BIH QUEST**  
 Transforming Biomedical Research

# Best practice



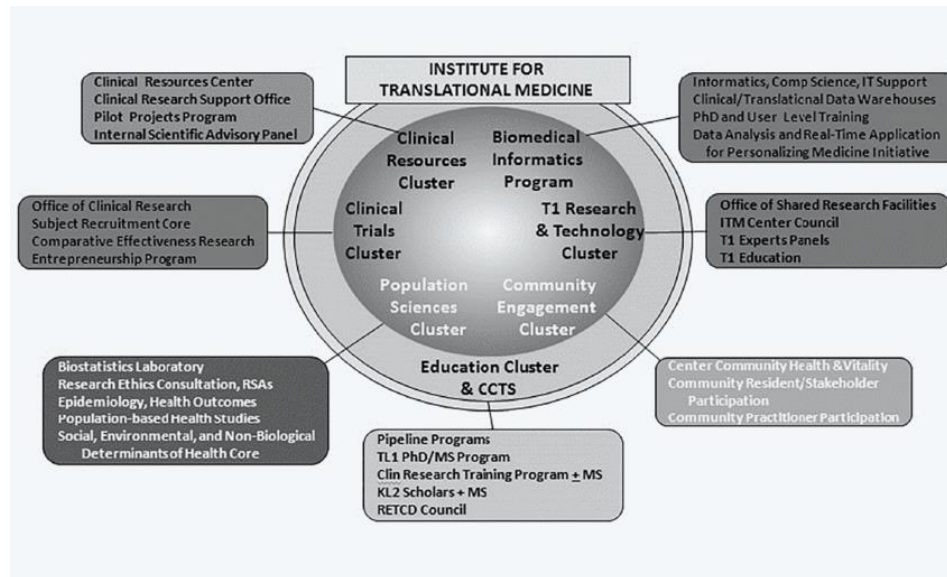


# Many figures, one standard model

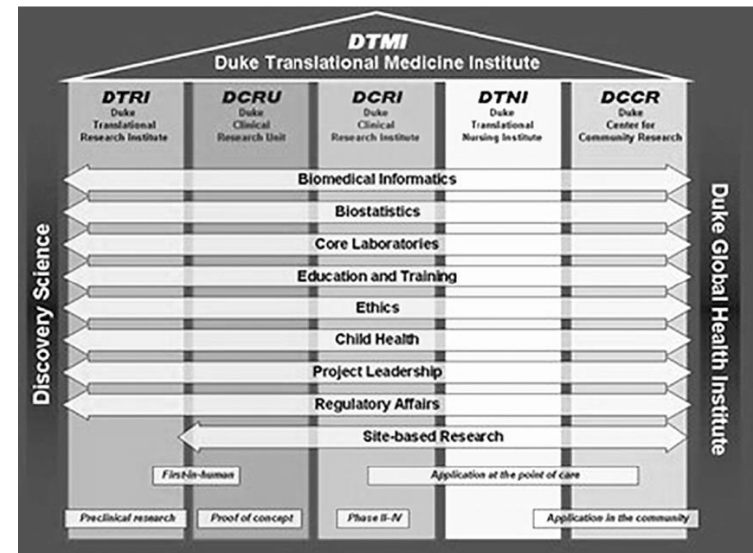
## Harvard Catalyst



## ITM Chicago



## Duke CTSI

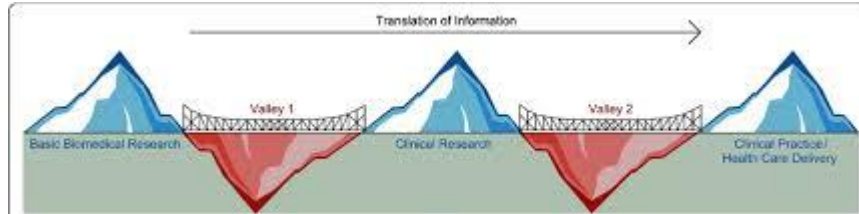
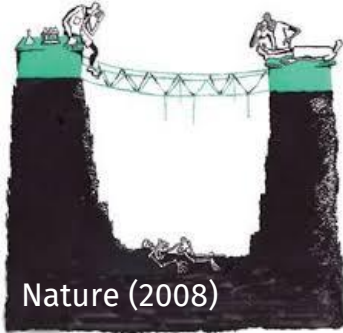




## A common narrative

- A valley of death must be crossed
- Translational attrition can (must!) be avoided
- Translational breakthroughs can be engineered

# Myth 1: The valley of death

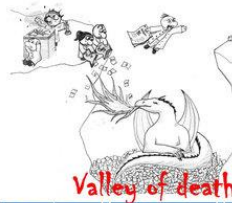
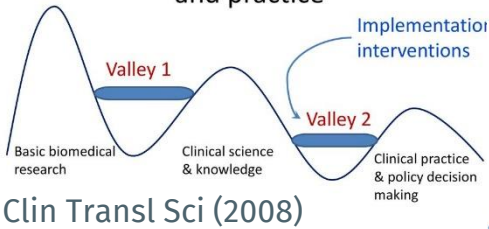


Canadian journal of kidney health and disease 2015



HaloCures (2008)

The 'death valleys' between research and practice



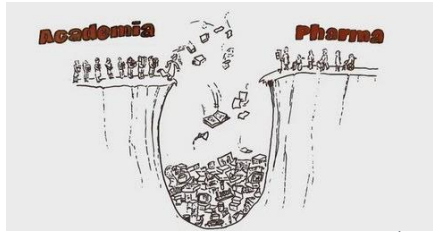
Gesundheitsindustrie-BW (2018)



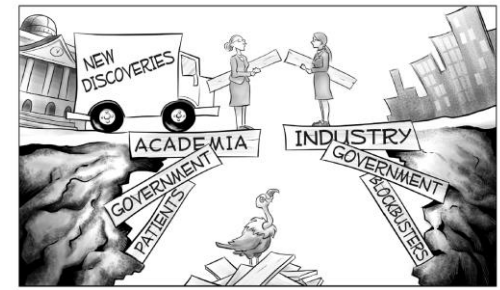
USF Health News (2008)

Drug Discovery	Pre-Clinical	Clinical trials	FDA Review	Manufacturing (Phase III)
10,000 compounds	250 compounds	5 compounds	1 FDA approved drug	
5 years	1.5 years	6 years	2 years	2 years

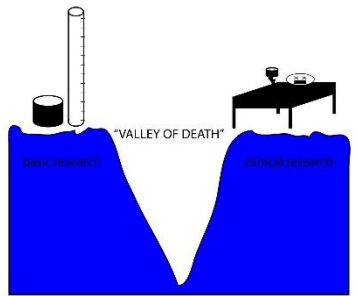
Juliane Gottwald (2013)



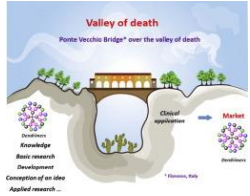
Myelin Repair Foundation (2011)



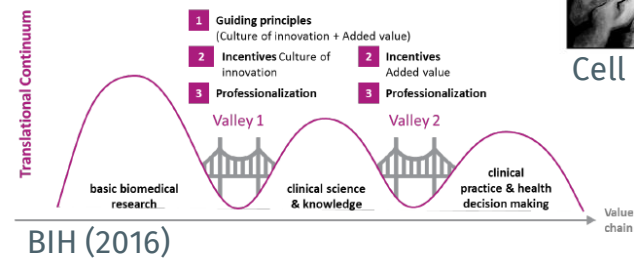
Cell (2016)



Genomic Enterprise (2011)



Advanced Drug Delivery Reviews 2018



BIH (2016)

## Failure to connect two worlds, or rather multiple reasons for translational attrition?

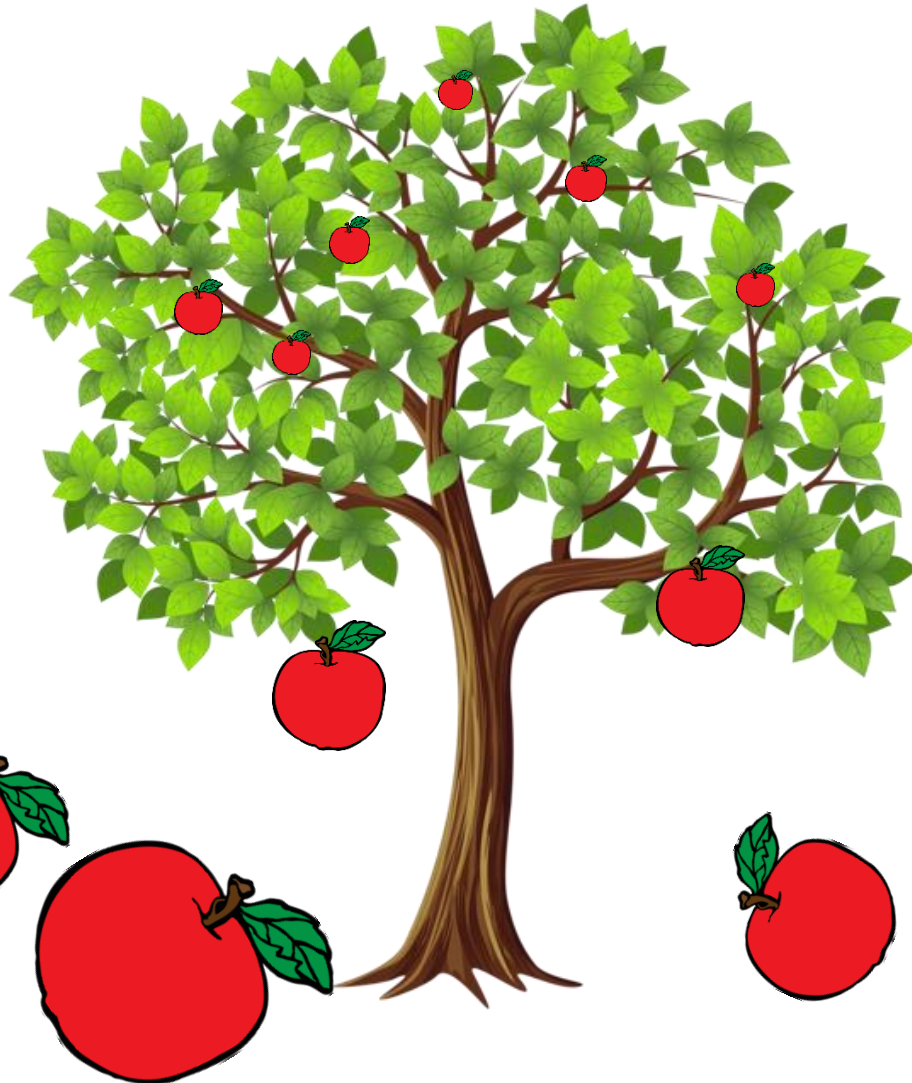
- It's damn hard: Complexity
- Someone else was there already: Low hanging fruits have been picked
- Lack of robustness and transparency of preclinical research results
- Lack of robustness and transparency of clinical study results
- Clinicians and scientists lacking resources (time!)
- ...

# Complexity





# Low hanging fruits have been picked?

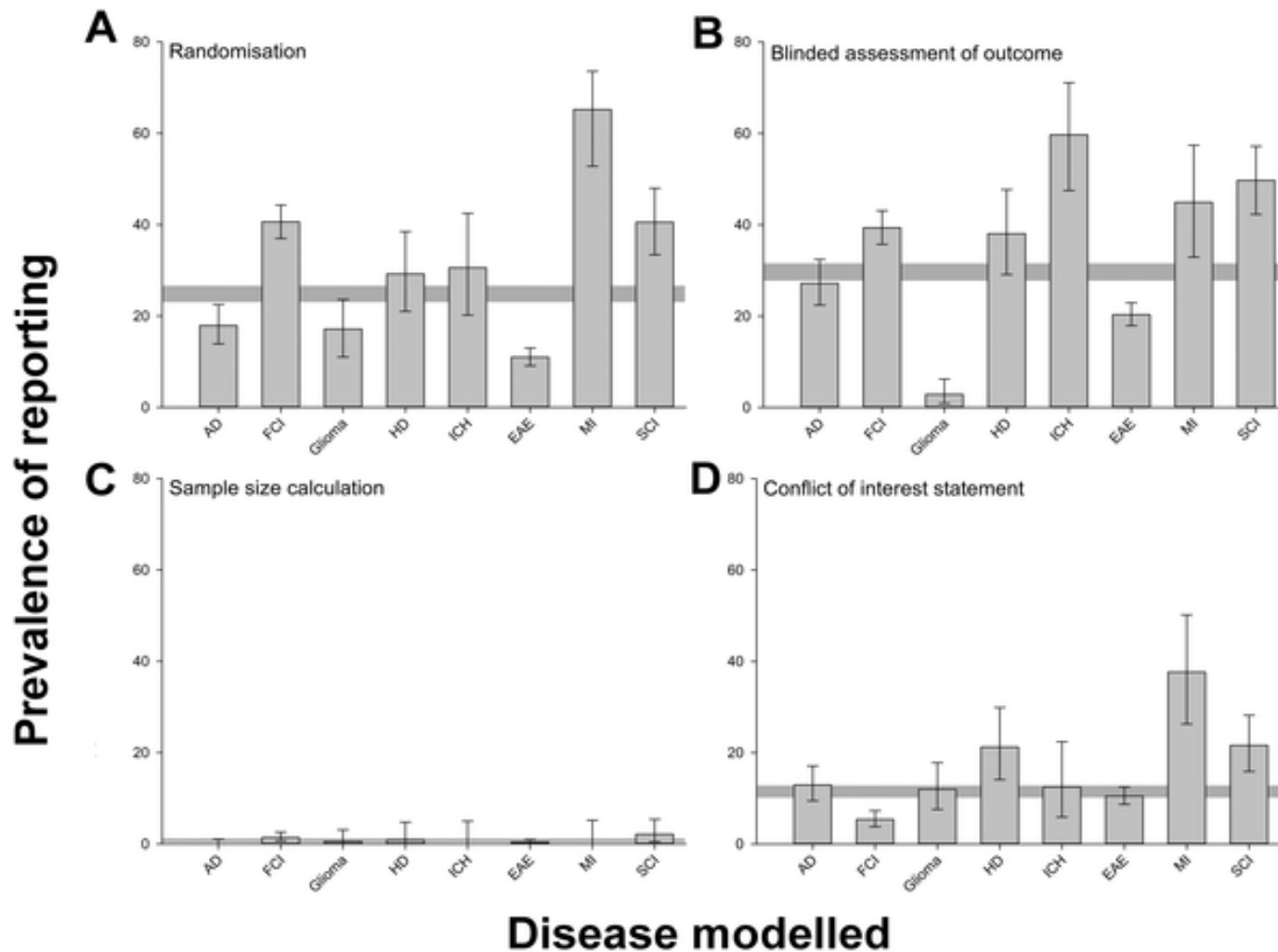


Bulk of novel opportunities  
(small effects, subgroups, side effects)

Low hanging fruits  
(tpa, stroke units)

Blindingly obvious  
(hospitals)

# Internal validity (preclinical)

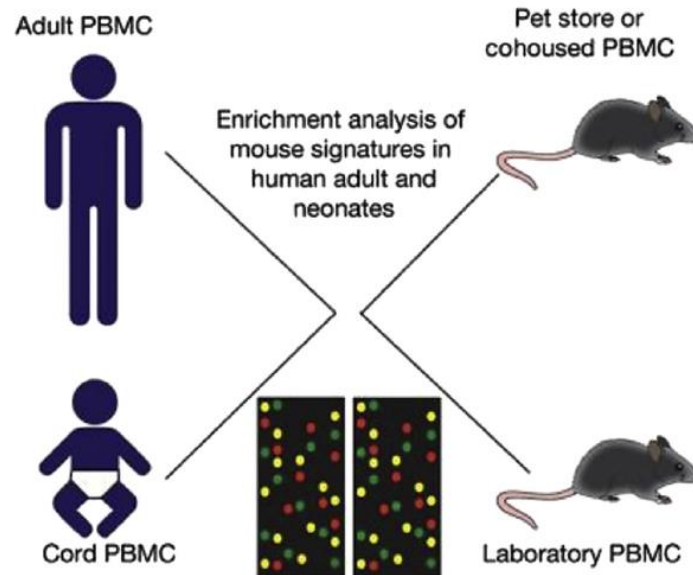


Macleod MR, et al. (2015) Risk of Bias in Reports of In Vivo Research: A Focus for Improvement. PLoS Biol 13: e1002273.

### Normalizing the environment recapitulates adult human immune traits in laboratory mice

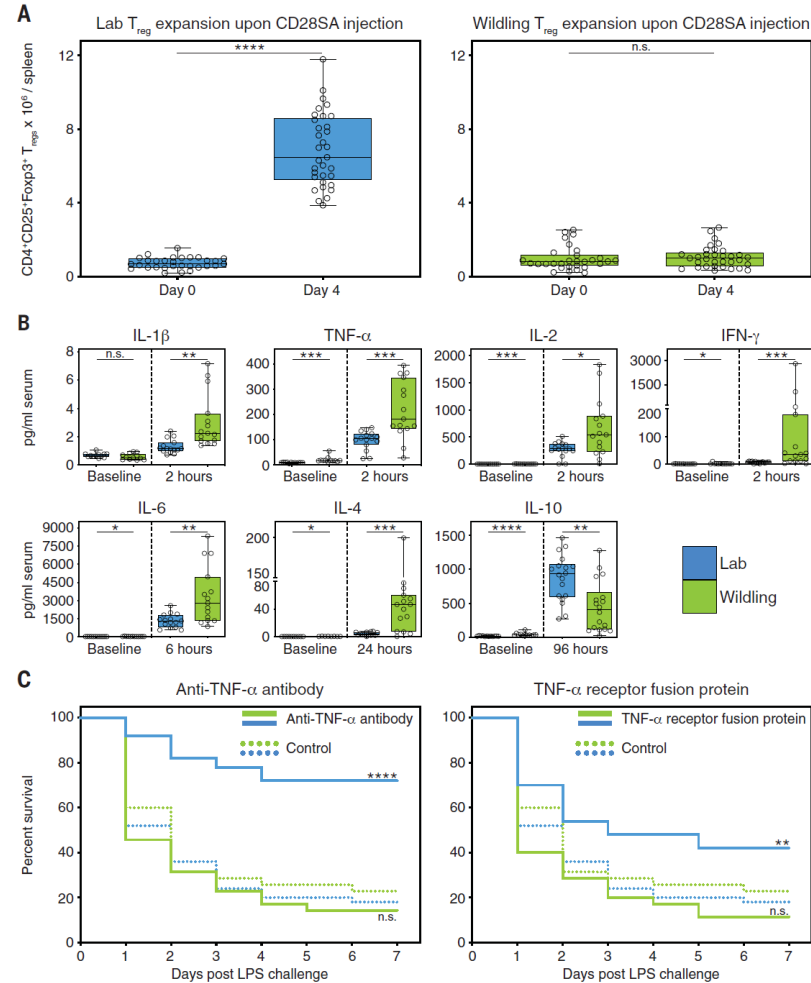
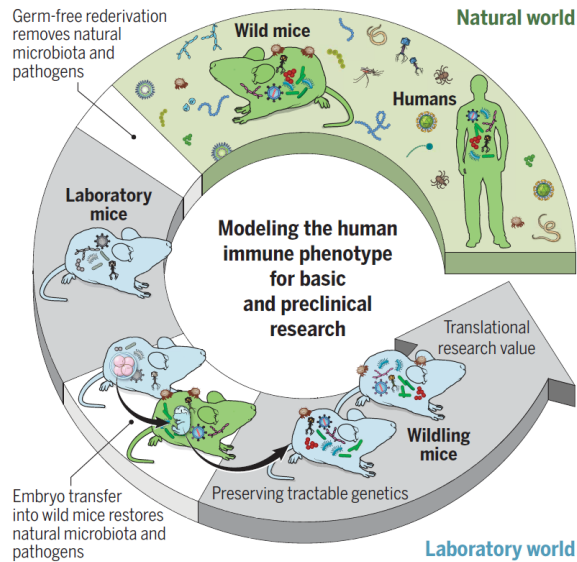
Lalit K. Beura<sup>1</sup>, Sara E. Hamilton<sup>2</sup>, Kevin Bi<sup>3</sup>, Jason M. Schenkel<sup>1</sup>, Oludare A. Odumade<sup>2†</sup>, Kerry A. Casey<sup>1†</sup>, Emily A. Thompson<sup>1</sup>, Kathryn A. Fraser<sup>1</sup>, Pamela C. Rosato<sup>1</sup>, Ali Filali-Mouhim<sup>4</sup>, Rafick P. Sekaly<sup>4</sup>, Marc K. Jenkins<sup>1</sup>, Vaiva Vezys<sup>1</sup>, W. Nicholas Haining<sup>3</sup>, Stephen C. Jameson<sup>2</sup> & David Masopust<sup>1</sup>

512 | NATURE | VOL 532 | 28 APRIL 2016





# External validity (e.g. micro/viro/fungobiome)

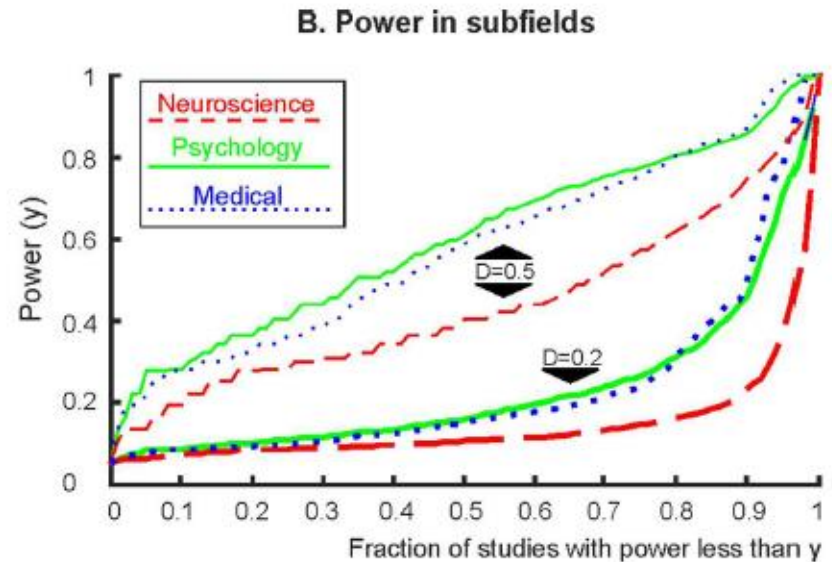
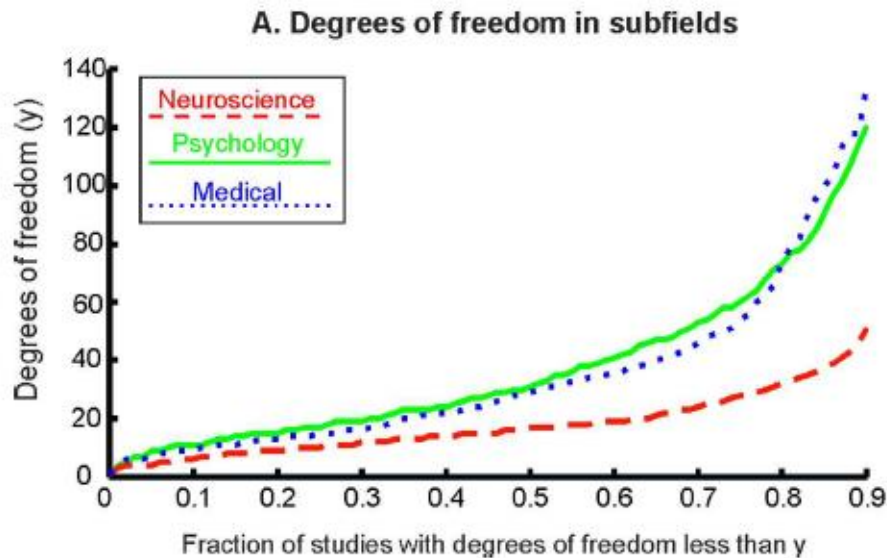


# Power failure

META-RESEARCH ARTICLE

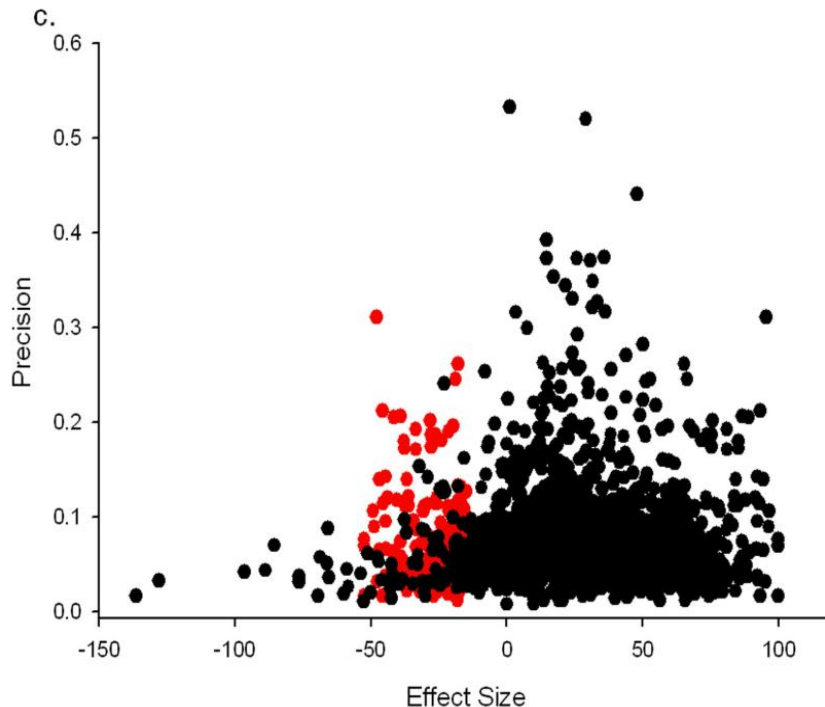
## Empirical assessment of published effect sizes and power in the recent cognitive neuroscience and psychology literature

Denes Szucs<sup>1\*</sup>, John P. A. Ioannidis<sup>2</sup>



## Publication Bias in Reports of Animal Stroke Studies Leads to Major Overstatement of Efficacy

Emily S. Sena<sup>1,2,3</sup>, H. Bart van der Worp<sup>4</sup>, Philip M. W. Bath<sup>5</sup>, David W. Howells<sup>2,3</sup>, Malcolm R. Macleod<sup>1,6\*</sup>



"Only ten publications (2%) [of 525] reported no significant effects on infarct volume and only six (1.2%) did not report at least one significant finding."

# Exploration vs confirmation

OPEN ACCESS Freely available online

PLoS Biol. (2014) 12:e1001863.



## Perspective

# Distinguishing between Exploratory and Confirmatory Preclinical Research Will Improve Translation

Jonathan Kimmelman<sup>1\*</sup>, Jeffrey S. Mogil<sup>2</sup>, Ulrich Dirnagl<sup>3,4,5</sup>

	Exploratory	Confirmatory
Hypothesis	(+)	+++
Establish pathophysiology	+++	(+)
Sequence and details of experiments established at onset	(+)	+++
Primary endpoint	-	++
Sample size calculation	(+)	+++
Blinding	+++	+++
Randomization	+++	+++
External validity (aging, comorbidities, etc.)	-	++
In/Exclusion criteria	++	+++
Test statistics	+	+++
Preregistration	(-)	+++
Sensitivity (Type II error) Find what might work	++	+
Specificity (Type I error) Weed out false positives	+	+++

Dirnagl (2016) Stroke 47:2148-2153

# Insufficient vetting of preclinical evidence by IRBs and regulators



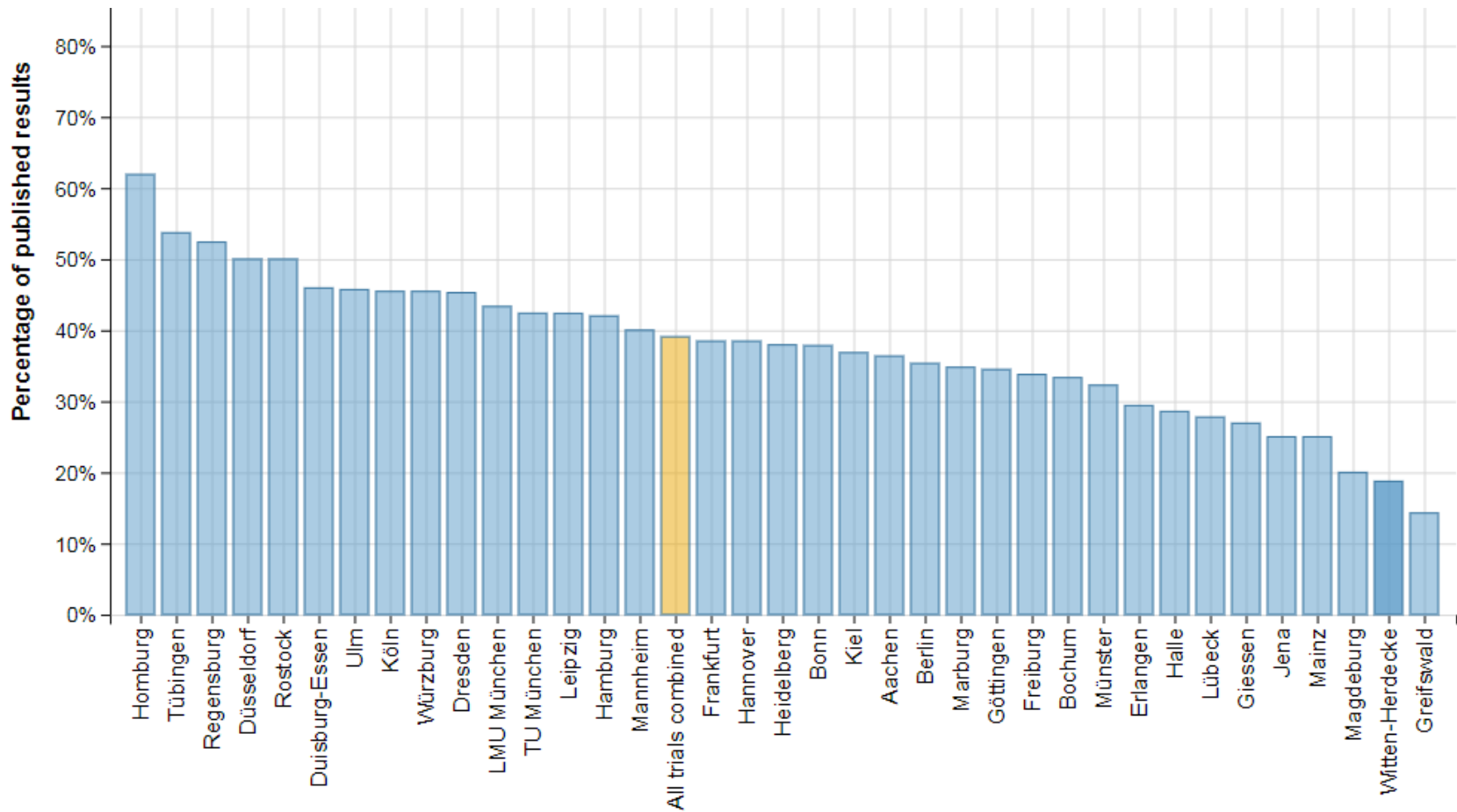
16(4): e2004879.

META-RESEARCH ARTICLE

## Preclinical efficacy studies in investigator brochures: Do they enable risk–benefit assessment?

Susanne Wieschowski<sup>1</sup>, William Wei Lim Chin<sup>1</sup>, Carole Federico<sup>2</sup>, Sören Sievers<sup>1</sup>, Jonathan Kimmelman<sup>2</sup>, Daniel Strech<sup>1\*</sup>

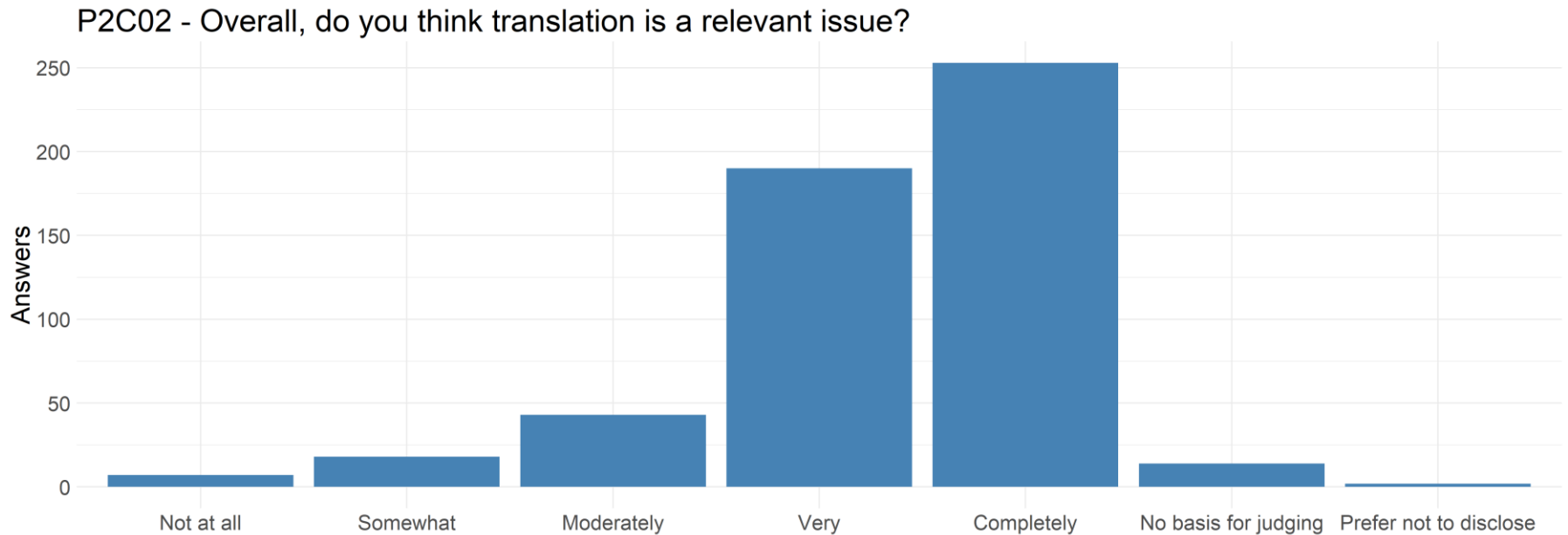
# Delayed or non-publication of clinical trial results by German university medical centers (incl. Charité)



Journal of Clinical Epidemiology 115 (2019) 37-45

<http://s-quest.bihealth.org/intovalue/>

# Importance of translation highly valued by Charité and MDC researchers

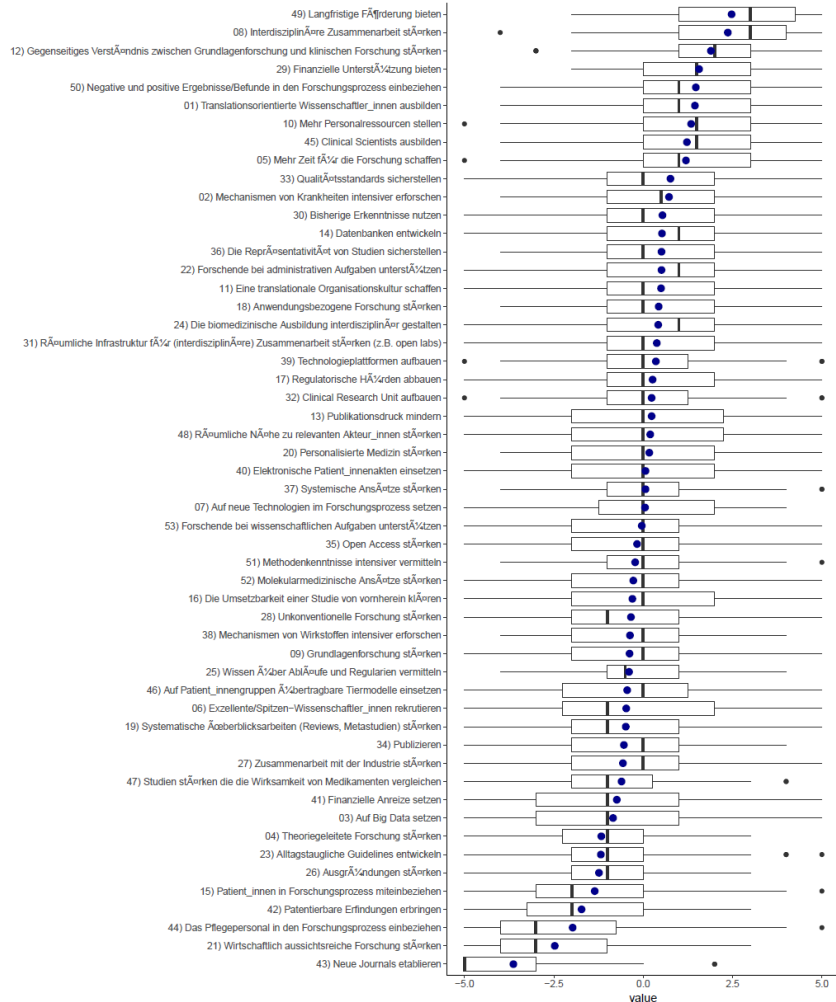


DZHW survey among clinicians and researchers (includes employed =PhD students) on translational climate at Charité and MDC (2018)

<https://osf.io/preprints/socarxiv/mjg7t/>



# Top priorities of Charité and MDC researchers regarding translation



1. Provide sustainable funding
2. Foster interdisciplinary collaboration
3. Strengthen basic and clinical research interaction
4. Publish / value negative results
5. Education in translational orientation
6. More resources (personel)
7. More time for research

Assessing the organizational climate for translational research with a new survey tool

<https://osf.io/preprints/socarxiv/mjg7t/>

# Myth 2: Translational attrition can (must) be avoided

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## Another Voice

Translational Research May Be Most Successful When It Fails

by JOHN P. A. IOANNIDIS

*Hastings Center Report* 45, no. 2 (2015)

## The S·T·R·U·C·T·U·R·E of Clinical Translation: *Efficiency, Information, and Ethics*

BY JONATHAN KIMMELMAN AND ALEX JOHN LONDON

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The so-called drug pipeline is not really about drugs and is not much like a pipeline. It is really about the production and dissemination of information, and it is much more like a web. The misunderstanding leads to a poor understanding of what's wrong with clinical translation and how it can be improved.

Hastings Center Report (2015) 45:27-39



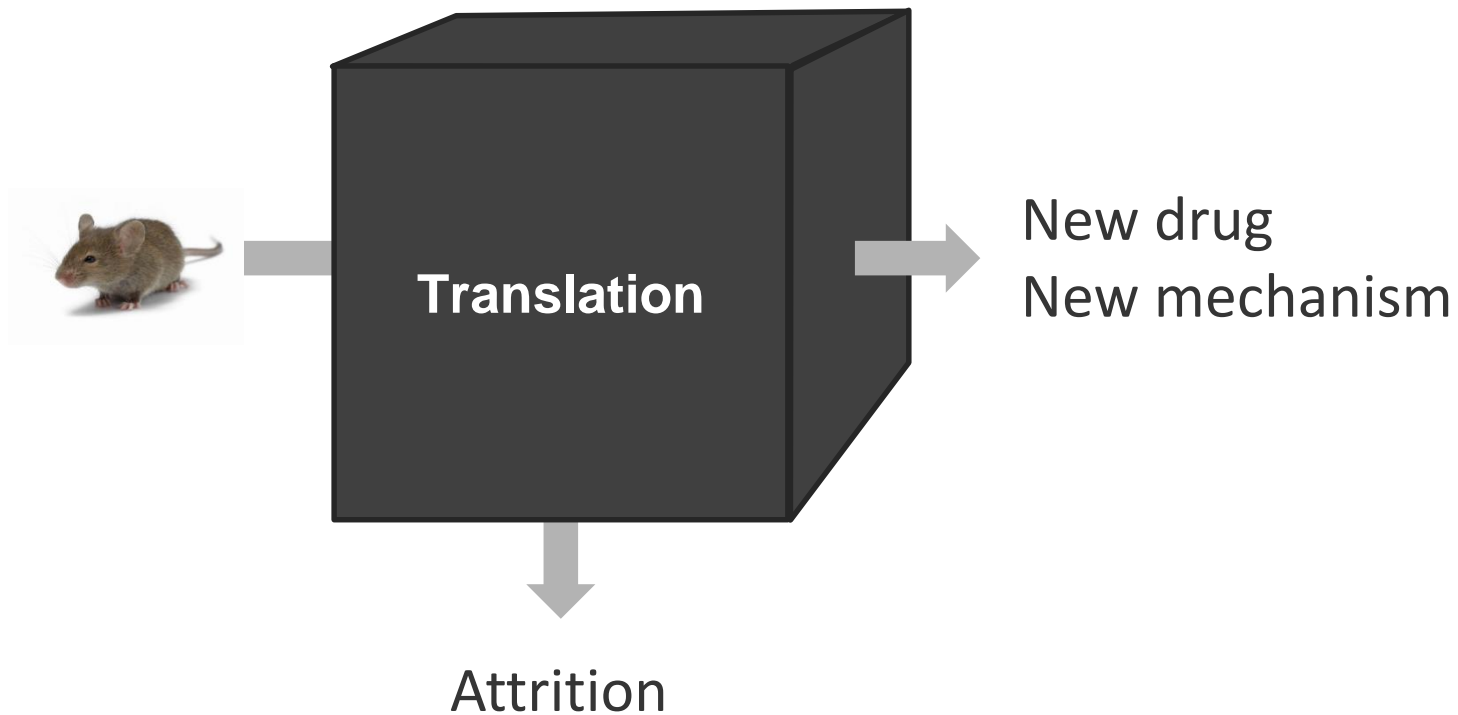
## Why clinical translation cannot succeed without failure

The high rates of attrition that occur in drug development are widely regarded as problematic, but the failure of well-designed studies benefits both researchers and healthcare systems by, for example, generating evidence about disease theories and demonstrating the limits of proven drugs. A wider recognition of these benefits will help the biomedical research enterprise to take full advantage of all the information generated during the drug development process.

ALEX JOHN LONDON AND JONATHAN KIMMELMAN

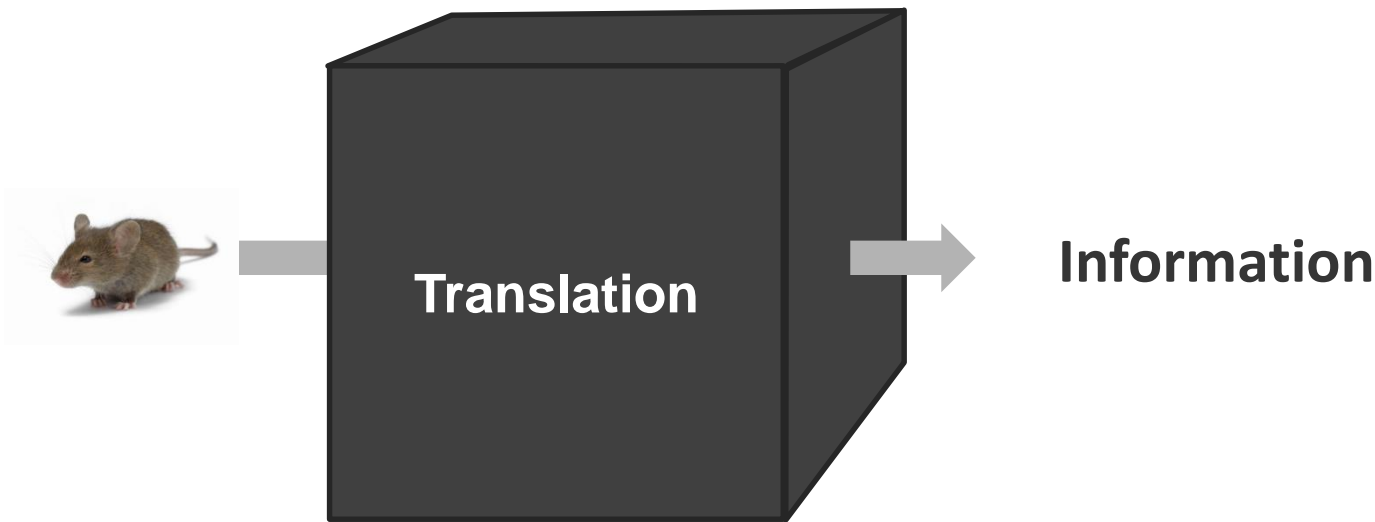
eLife 2015;4:e12844. |

# The canonical black box model of translation



## An alternative model

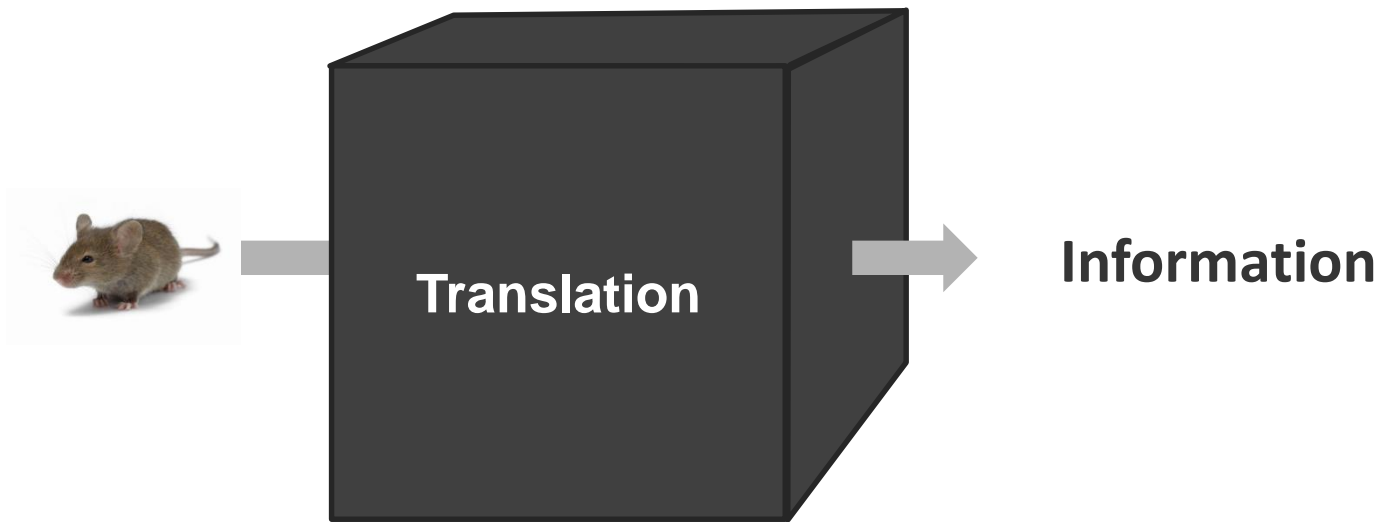
Negative results in well designed studies providing good quality evidence result in *information* which can,



among other benefits, correct mechanistic concepts, define dosing and timing of treatments, and free up resources for other avenues of investigation.

## An alternative model

Practical consequences?



- Design experiments that lead to useful information even when the NULL is rejected
- Do not stop experiments as soon as first signs of NULL results appear
- Publish NULL results, etc.

# „Translation may be most successful when it fails...‘

„Essential attrition“



To boldly go where no man...  
Exploration at low base rate  
Innovation  
,Paradigm shift‘ (,Disruption‘)  
Defines boundaries of evidence  
etc.

„Detrimental attrition“



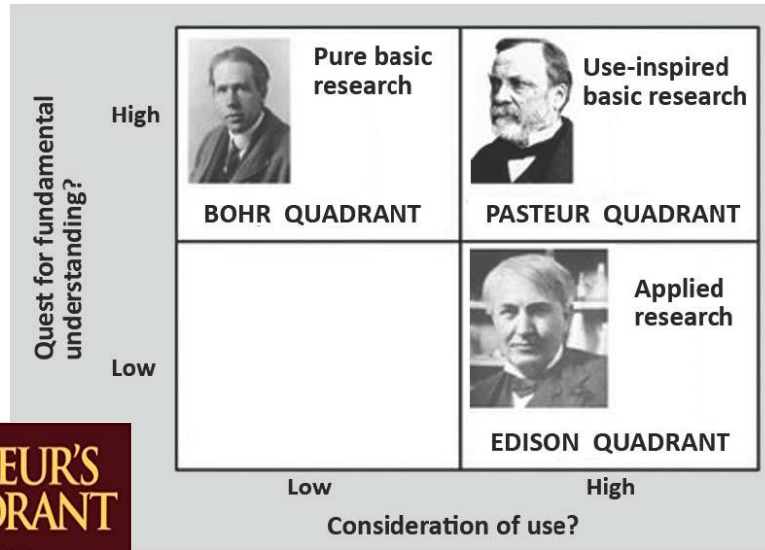
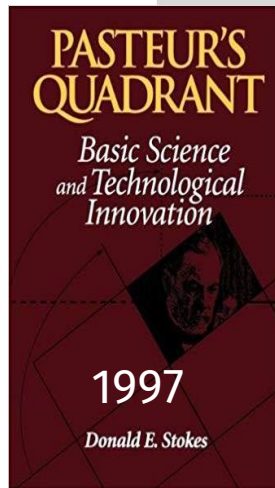
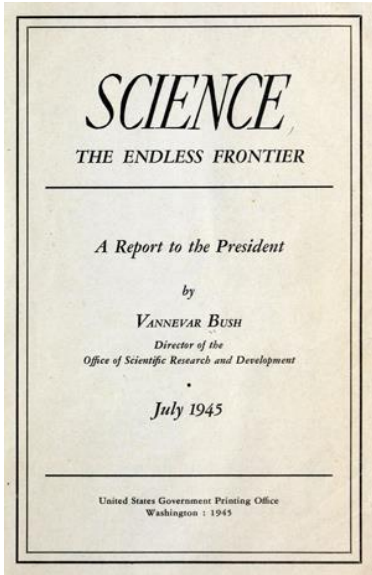
Incompetence  
Intransparence  
Bad designs  
Tacit knowledge (bad reporting)  
Low validity (bias)  
Misconduct  
etc.

## Myth 3: Translational breakthroughs can be engineered





# From Vannevar Bush via Pasteur's quadrant to strong focus on applied research



postwar

today



# Where do medical breakthroughs come from?

## Scientific Basis for the Support of Biomedical Science

Julius H. Comroe, Jr., and Robert D. Dripps



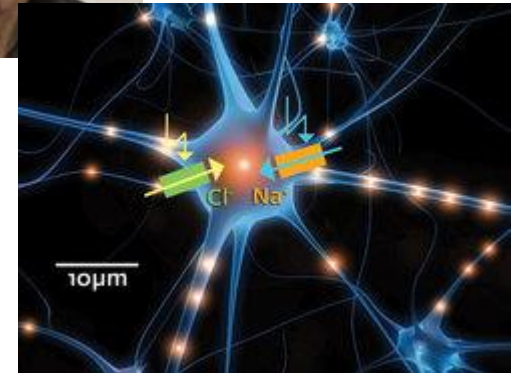
Table 5. Goal of authors of 529 key articles that later were judged to be essential for a clinical advance.

Clinical advance	Clinically oriented	Not clinically oriented	Total	Percent of total not clinically oriented
Cardiac surgery	53	35	88	39.8
Vascular surgery	40	8	48	16.7
Hypertension	35	44	79	55.7
Coronary insufficiency	44	21	65	32.3
Cardiac resuscitation	24	16	40	40.0
Oral diuretics	19	24	43	55.8
Intensive care	*	*	*	*
Antibiotics	40	13	53	24.5
New diagnostic methods	41	53	94	56.4
Poliomyelitis	16	3	19	15.8
Total	312	217	529	41.0

# Berlin's poster childs regarding 'transformative therapies' entirely based on basic research

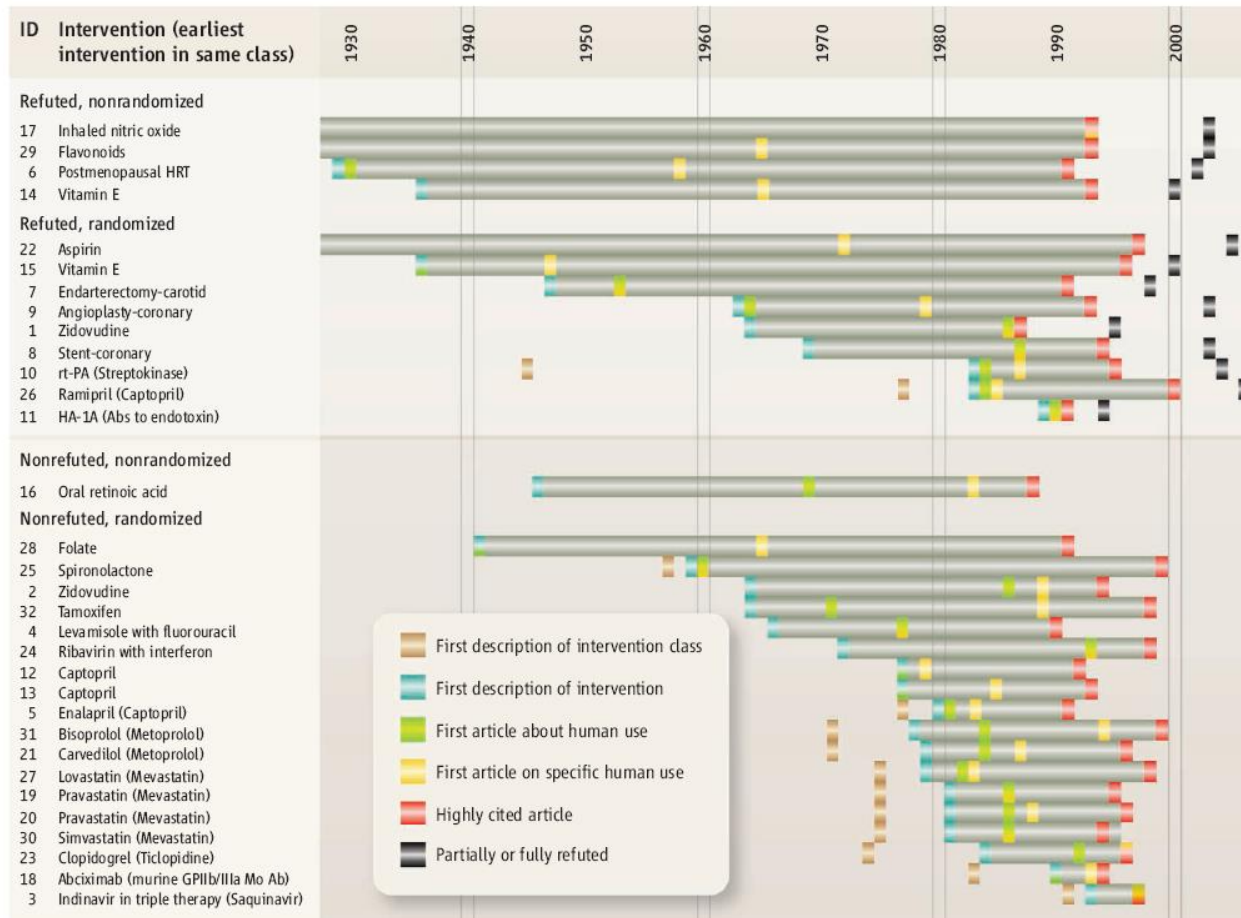


Bacterial immune systems



Algal biology

# Life cycle of translational research for medical interventions



If you don't know which ticket is a winner, buy many!



# Translation in the academic setting

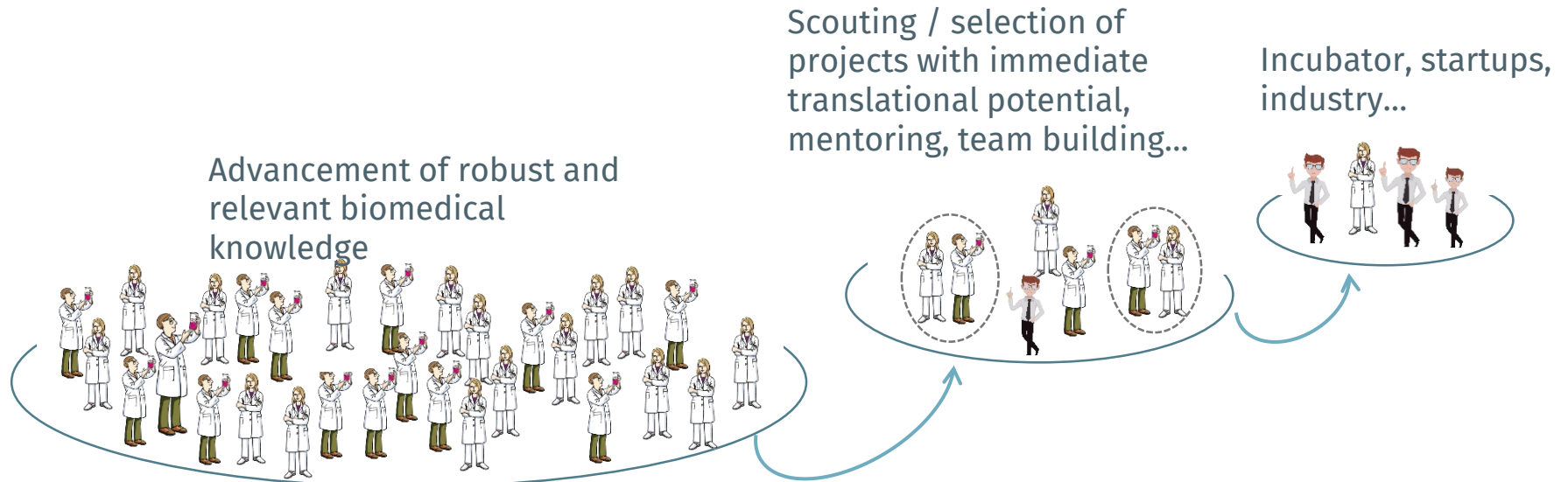
(Harvard Catalyst, Duke Clinical and Translational Science Institute, Chicago Institute for Translational Medicine, etc.)



- A host of relevant roadblocks to successful translation are not addressed
- Hyperfocus on linking academic and industry research
- Fear and loathing of attrition
- Preference of engineering success over discovery and serendipity

# Translation in the academic setting

(Harvard Catalyst, Duke Clinical and Translational Science Institute, Chicago Institute for Translational Medicine, Charité/BIH etc.)



Tools: ELN, Clinical study registry...

Services & Infrastructure: Cores, Platforms, TT/BIH...

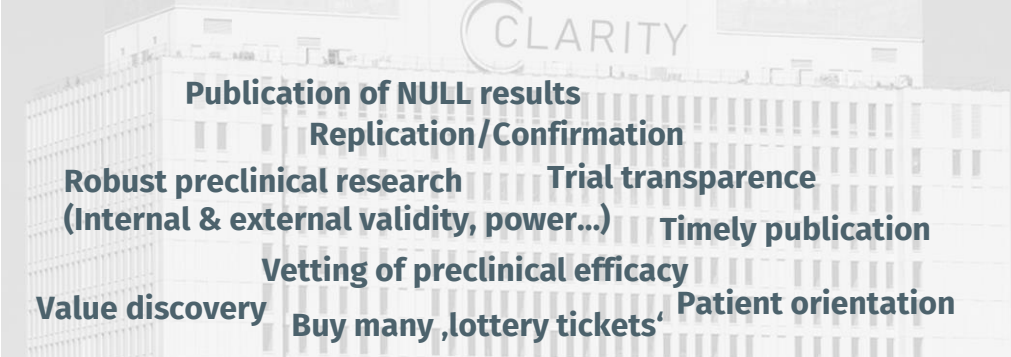
Programs: C(J)SP, SPARK....

Partnering: Fraunhofer, Industry

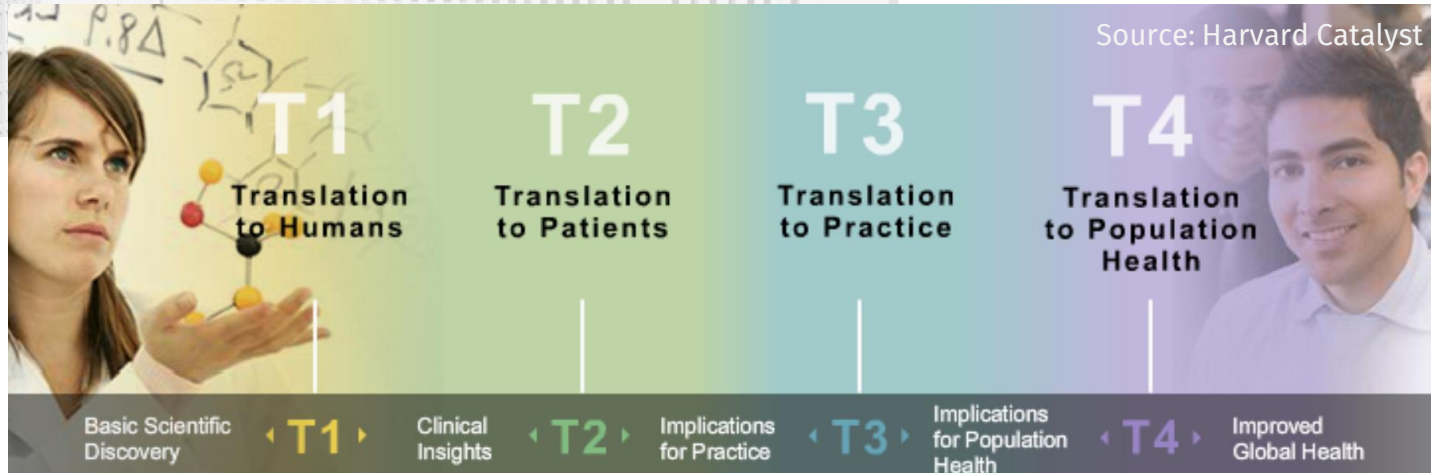


# Ask the Wissenschaftsnarr: Fostering 'Translation' at the imaginary university hospital CLARITY

USPs (=,proprietary translational framework'):



**Publication of NULL results**  
**Replication/Confirmation**  
**Robust preclinical research**      **Trial transparency**  
 (Internal & external validity, power...)      **Timely publication**  
**Vetting of preclinical efficacy**  
**Value discovery**      **Buy many ,lottery tickets'**      **Patient orientation**



,Canonical (generic) framework of translation':  
 Services & Infrastructure; Education;  
 Partnering



Slide download: <http://bit.ly/commonmythstranslation>



# Laborjournal

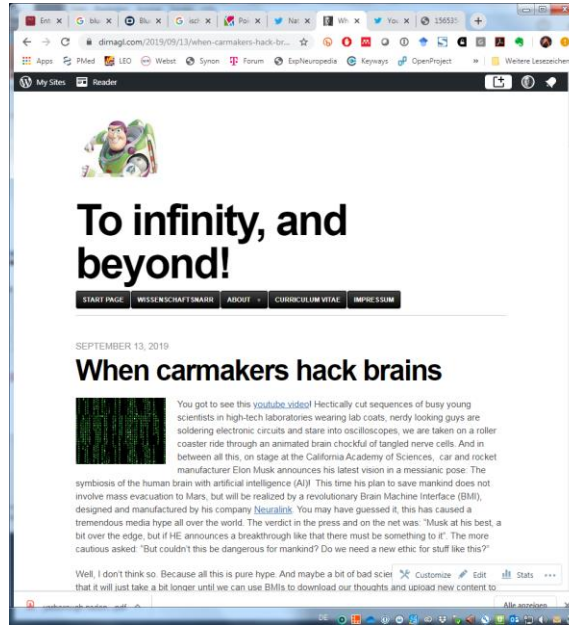
SERIE



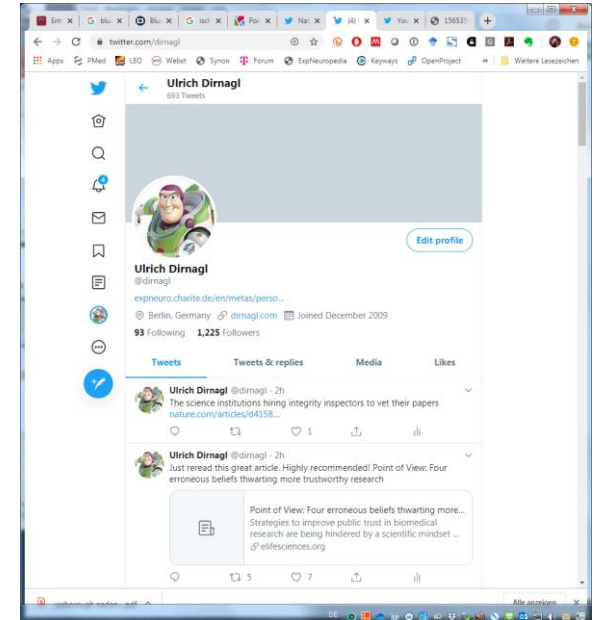
Einsichten eines Wissenschaftsnarren (24)

**Warum trauen WIR dem Weltklimarat, die Klimaskeptiker aber nicht?**

Monthly column  
[laborjournal.de](http://laborjournal.de)



Blog  
[dirnagl.com](http://dirnagl.com)



 @dirnagl