Translational Research Symposium
Rigor in Translational Research: Issues, Experience and Solutions

Symposium Chair:

Andrew Cole, M.D.

Saturday, December 5, 2015
Convention Center – Room 204

5:30 – 7:30 p.m.

GENERAL INFORMATION

Accreditation

The American Epilepsy Society is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation

Physicians

The American Epilepsy Society designates this live activity for a maximum of 30.75 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Physician Assistant

AAPA accepts certificates of participation for educational activities certified for *AMA PRA Category 1 Credit*™ from organizations accredited by ACCME or a recognized state medical society. Physician assistants may receive a maximum of 30.75 hours of Category 1 credit for completing this program.

Jointly provided by AKH Inc., Advancing Knowledge in Healthcare and the American Epilepsy Society.

Nursing

AKH Inc., Advancing Knowledge in Healthcare is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is awarded 30.75 contact hours.

Nurse Practitioners

AKH Inc., Advancing Knowledge in Healthcare is accredited by the American Association of Nurse Practitioners as an approved provider of nurse practitioner continuing education. Provider Number: 030803. This program is accredited for 30.75 contact hours which includes 8 hours of pharmacology. Program ID #21547

This program was planned in accordance with AANP CE Standards and Policies and AANP Commercial Support Standards.

Pharmacy

AKH Inc., Advancing Knowledge in Healthcare is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Select portions of this Annual Meeting are approved for pharmacy CE credit. Specific hours of credit for approved presentations and Universal Activity Numbers assigned to those presentations are found in the educational schedules. Criteria for success: nursing and pharmacy credit is based on program attendance and online completion of a program evaluation/assessment.

If you have any questions about this CE activity, please contact AKH Inc. at service@akhcme.com.

International Credits

The American Medical Association has determined that non-U.S. licensed physicians who participate in this CME activity are eligible for *AMA PRA Category 1 Credits*™.

CME/CE Certificates

For those attendees who wish to claim CME or CE, there is an additional fee. Registrants can pay this fee as part of the registration process. Those who do not pre-purchase the credit will also have the ability to pay this fee at the time they attempt to claim credit. Fees for CME increase after January 16 and are a one-time charge per annual meeting.

The evaluation system will remain open through Friday, February 26, 2016. Evaluations must be completed by this date in order to record and receive your CME/CE certificate.

Member Fees:	$50 through January 15, 2016 $75 January 16 – February 26, 2016
Non-member Fees:	$75 through January 15, 2016 $100 January 16 – February 26, 2016

Attendance Certificate/International Attendees

A meeting attendance certificate will be available at the registration desk for international meeting attendees on Tuesday, December 8.

Policy on Commercial Support and Conflict of Interest

The AES maintains a policy on the use of commercial support, which assures that all educational activities sponsored by the AES provide in-depth presentations that are fair, balanced, independent and scientifically rigorous. All faculty, planning committee members, moderators, panel members, editors, and other individuals who are in a position to control content are required to disclose relevant relationships with commercial interests whose products relate to the content of the educational activity. All educational materials are reviewed for fair balance, scientific objectivity and levels of evidence. Disclosure of these relationships to the learners will be made through syllabus materials and the meeting app.

Disclosure of Unlabeled/Unapproved Uses

This educational program may include references to the use of products for indications not approved by the FDA. Faculty have been instructed to disclose to the learners when discussing the off-label, experimental or investigational use of a product. Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the AES.

OVERVIEW
Clinicians are knowledgeable about interpretation of clinical trials but have limited knowledge of pre-clinical discovery and development of therapeutic agents and devices. This symposium will address critical issues identified by AES and ILAE working groups that require solutions in order to facilitate and promote translational research in therapeutic development for epilepsy and related co-morbidities. Problems in reproducing pre-clinical research have increased the risk of embarking on programs for development of new therapies for venture and industrial sponsors. Multiple academic studies have documented the high rate of failure to reproduce critical preclinical studies. Criteria to increase the rigor, and therefore the reproducibility of preclinical work have been identified; initial efforts to implement these strategies have identified challenges and opportunities, as well as critical resources required to achieve the goal of increasing rigor. Finally, effective communication of positive and negative results, as well as reproducibility and validation studies requires novel publication models. This symposium states the problem, examines the components required to achieve rigor, reviews recent experience in designing and conducting studies designed to meet proposed criteria, and concludes with a discussion of the effects of publication bias and a description of a novel publication platform designed to serve the needs of the translational research community. In addition to addressing issues in research methodology for researchers, the information presented at this symposium will allow clinicians to better assess new therapeutic options.

LEARNING OBJECTIVES
Following participation in this symposium, learners should be able to:

- Articulate barriers to translation in the existing system and asses preclinical data for rigor and robustness
- Describe and discuss limitations in current publications of translational research
- Critically analyze the impact of inadequate pre-clinical data on the development of new therapeutics
- Recognize the limitations of available preclinical data when counseling patients regarding use of medications

TARGET AUDIENCE
Intermediate: Epilepsy fellows, epileptologists, epilepsy neurosurgeons, and other providers with experience in epilepsy care (e.g., advanced practice nurses, nurses, physician assistants), neuropsychologists, psychiatrists, basic and translational researchers.

Advanced: Address highly technical or complex topics (e.g., neurophysiology, advanced imaging techniques or advanced treatment modalities, including surgery.)

Agenda
Chair: Andrew Cole, M.D.

Introduction
Andrew Cole, M.D.

Crisis in Translation: Perspective from the NIH
Walter Koroshetz, M.D.

Rigor in Pre-Clinical Studies and Reproducibility of Published Research Findings
Shai Silberberg Ph.D.

Practical Experience in Achieving Pre-clinical Rigor
Kevin Staley, M.D., Ph.D.

Stuck in Translation: A Crisis of Commitment?
Annamaria Vezzani, Ph.D.

Shared Data Platforms: Efficiency, Integrity, Fairness and Utility
M. Brandon Westover, M.D., Ph.D.

Publication Bias: When Data Is AWOL
Michael Rogawski, M.D., Ph.D.

Conclusions
Andrew Cole, M.D.

Education Credit
2.0 CME Credits

Nurses may claim up to 2.0 contact hours for this session.

Pharmacy Credit
AKH Inc., Advancing Knowledge in Healthcare approves this knowledge-based activity for 2.0 contact hours (0.2 CEUs). UAN 0077-9999-15-038-L01-P. Initial Release Date: 12/5/2015.

The American Board of Psychiatry and Neurology has reviewed the Rigor in Translational Research: Issues, Experience and Solutions Symposium and has approved this program as part of a comprehensive program, which is mandated by the ABMS as a necessary component of maintenance of certification.

FACULTY/PLANNER DISCLOSURES
It is the policy of the AES to make disclosures of financial relationships of faculty, planners and staff involved in the development of educational content transparent to learners. All faculty participating in continuing medical education activities are expected to disclose to the program audience (1) any real or apparent conflict(s) of interest related to the content of their presentation and (2) discussions of unlabeled or unapproved uses of drugs or medical devices. AES carefully reviews reported conflicts of interest (COI) and resolves those conflicts by having an independent reviewer from the Council on Education validate the content of all presentations for fair balance, scientific objectivity, and the absence of commercial bias. The American Epilepsy Society adheres to the ACCME's Essential Areas and Elements regarding industry support of continuing medical education; disclosure by faculty of commercial relationships, if any, and discussions of unlabeled or unapproved uses will be made.

FACULTY / PLANNER BIO AND DISCLOSURES
Andrew Cole, M.D. (Chair)
Andrew J. Cole, MD, FRCP(C), is Professor of Neurology at Harvard Medical School and Director of the MGH Epilepsy Service and Chief of the Division of Clinical Neurophysiology Laboratory at Massachusetts General Hospital in Boston. Dr. Cole also directs Epilepsy and Clinical Neurophysiology Fellowship Program at MGH. Dr. Cole graduated magna cum laude from Dartmouth College in Hanover, New Hampshire, and obtained his medical degree from Dartmouth Medical School. He completed an internship in internal medicine at Case Western Reserve University in Cleveland, Ohio, and a residency and chief residency in neurology at the Montreal Neurological Institute, McGill University, Montreal, Quebec.

Dr. Cole discloses receiving support for Consulting from Sage Therapeutics, Consulting Precsis AG Consulting; as Ownership Sage Therapeutics, Precisis Consulting

Walter Koroshetz, M.D.

Dr. Koroshetz has indicated he has no financial relationships with commercial interests to disclose.

Michael Rogawski, M.D., Ph.D.
Michael A. Rogawski is professor of neurology at the University of California, Davis. Until 2006, he was senior investigator and chief of the Epilepsy Research Section at NINDS. He received his B.A. from Amherst, and M.D. and Ph.D. (pharmacology) from Yale. After serving as a postdoctoral fellow in the Laboratory of Neurophysiology, NINDS, he completed residency training in neurology at Johns Hopkins. Dr. Rogawski's research encompasses cellular neurophysiological studies of ion channels with a focus on the mechanisms of action of antiepileptic drugs and new treatments for seizures and epilepsy. He served on the AES Board of Directors and is a founder and was co-chief editor of Epilepsy Currents. In 2011, he received the AES Service Award.

Dr. Rogawski discloses receiving support For Royalties the University of California, Davis; for Receipt Of Intellectual Property Rights/Patent Holder from University of California, Davis; for Consulting Fee (15) from Eisai, Upsher-Smith, Sage Therapeutics; as Contract Research from Acorda Therapeutics (indirectly to University of California, Davis); for Other Service from Past President, American Society for Experimental NeuroTherapeutics.

Shai Silberberg, Ph.D.
Dr. Shai D. Silberberg is a Program Director at NINDS leading the Institute efforts to increase the excellence of science and the completeness of research reporting. In addition, Dr. Silberberg is an Adjunct Investigator in the Intramural Research Program of NINDS studying the molecular mechanism of action of ATP-gated receptor channels (P2X receptors). Prior to joining NINDS, Dr. Silberberg was an Associate Professor at Ben-Gurion University of the Negev in Israel, investigating the biophysical functions and physiological roles of various ion channels. Dr. Silberberg obtained a Ph.D. in Neurophysiology from the Hebrew University in Jerusalem.

Dr. Silbergberg has indicated he has no financial relationships with commercial interests to disclose.

Kevin Staley, M.D.
Kevin Staley trained in physics at Loyola Marymount University; in medicine and pediatric neurology at the University of California, San Diego; and in cellular electrophysiology at Stanford University School of Medicine. He is the Joseph P. and Rose F. Kennedy Professor of Child Neurology and Mental Retardation at Harvard Medical School and the chief of the section of child neurology at Massachusetts General Hospital, where he studies mechanisms of neuronal ion transport. His lab studies the cellular and network processes by which seizures are initiated and spread in order to develop better treatments for epilepsy.

Dr. Staley has indicated he has no financial relationships with commercial interests to disclose.

Dr. Staley does intend to reference unlabeled/unapproved uses of drugs or products – bumetanide trial for adjunctive treatment of neonatal seizures clinical trials

Annamaria Vezzani, Ph.D.
PhD in neuropharmacology at the Mario Negri Inst, Milano. Post-doc at the Univ of Maryland working on the mechanisms of epileptogenesis. On sabbatical at the Albert Einstein College of Medicine in the laboratory of Developmental Epilepsy. Research interest related to mechanisms of seizures and epileptogenesis in experimental models with a focus on inflammatory mediators.

Currently, Head of the Laboratory of Experimental Neurology, Department of Neuroscience, Mario Negri Institute. Past Associate Editor of Basic Science for Epilepsia. Past Chair of the Commission on Neurobiology of ILAE and currently a member of the ILAE Commission of European Affairs. Recipient of the AES Research Recognition Award for translational research in 2009.

Dr. Vezzani discloses receiving support for Contract Research from UCB Pharma Pfizer (contract with my Institute for a collaborative research project related to basic science with UCB Pharma and Pfizer); for Honoraria from UCB Pharma symposium as a speaker.

M. Brandon Westover, M.D., Ph.D.
Dr. M. Brandon Westover completed a PhD degree in physics and an MD at Washington University School of Medicine in St. Louis. He directs the Critical Care EEG Monitoring Service at Harvard Medical School / Massachusetts General Hospital. His research focuses on automating interpretation of clinical EEG data, closed-loop control of sedation, biomedical informatics, medical decision modeling, and the neurophysiology of critical illness. Dr. Westover's research seeks to develop applications of engineering and computation to improve medical care for patients with acute neurological illnesses.

Dr. Westover, M.D., Ph.D. has indicated he has no financial relationships with commercial interests to disclose.

CME Reviewers
Ignacio Valencia, M.D.
Ignacio Valencia, MD is an Associate Professor of Pediatrics and Neurology at St. Christopher's Hospital for Children, Philadelphia, PA. He received his MD from Rosario University in Bogota, Colombia and residencies in adult and pediatric neurology at Rosario University and St. Christopher's Hospital for Children respectively. Dr. Valencia completed a Fellowship in Epilepsy and Clinical Neurophysiology at Children's Hospital in Boston. He is now pediatric neurology fellowship program director.

Dr. Valencia has indicated he has no financial relationships with commercial interests to disclose.

David Wheeler, M.D., Ph.D.
After completing undergraduate training at the University of Montana, Dr Wheeler attended Oxford University on a Rhodes Scholarship where he received a Masters degree in physiology. He then went on to Stanford University completing an MD and PhD in Neurosciences with research focused on the role of calcium channels in neurotransmitter release in the hippocampus. He received Neurology training and fellowship in Clinical Neurophysiology through the Partners Program at Mass General and the Brigham in Boston. Dr Wheeler is in private practice in Casper, WY. His practice covers general neurology with emphasis on epilepsy as well as acute stroke care. He is active in numerous organizations for both clinical medicine and health care administration.

Dr. Wheeler discloses receiving support for Contracted Research from Novartis; for Other Service from AHA SouthWest Affiliate Stroke Advisory Committee. Chairman Wyoming Dementia Care. Vice Chairman, Wyoming Medical Center Board of Directors.

Paul Levisohn, M.D. (Medical Content Specialist, AES)
Dr. Levisohn is a member of the faculty of the section of Pediatric Neurology at The University of Colorado School of Medicine and Children's Hospital Colorado Neuroscience Institute, having joined the faculty over 15 years ago following a similar period of time in the private practice of pediatric neurology. His academic career has focused on clinical care for children with epilepsy with particular interest in clinical trials and on the psychosocial impact of epilepsy. Dr. Levisohn is currently a

consultant on medical content for CME activities to staff of AES. He is a member of the national Advisory Board of EF and has been chair of the advisory committee for the National Center of Project Access through EF.

Dr. Levisohn has indicated he has no financial relationships with commercial interests to disclose.

AKH STAFF / REVIEWERS

Dorothy Caputo, MA, BSN, RN (Lead Nurse Planner) has indicated she has no financial relationships with commercial interests to disclose.

Bernadette Marie Makar, MSN, NP-C, APRN-C (Nurse Planner) has indicated she has no financial relationships with commercial interests to disclose.

John P. Duffy, RPh, B.S. Pharmacy (Pharmacy Reviewer) has indicated he has no financial relationships with commercial interests to disclose.

AKH staff and planners have nothing to disclose.

CLAIMING CREDIT:

PHYSICIANS

Physicians can claim CME credit online at **https://cme.experientevent.com/AES151/**

This Link is NOT Mobile-friendly! You must access it from a laptop, desktop or tablet.

How to Claim CME Credit

To claim CME credits online, please follow the on-screen instructions at the above url. Log in using your last name and zip code, OR your last name and country if you're not from the United States. All CME credits must be claimed **by February 26, 2106**.

Questions?

Contact Experient Customer Service at: 800-974-9769 or **AES@experient-inc.com**

NURSING & PHARMACY

PLEASE NOTE: Providing your NABP e-profile # is required.

The National Association of Boards of Pharmacy (NABP) requires that all pharmacists and pharmacy technicians seeking CE credit have an ID number issued by NABP. Pharmacy CE providers, such as AKH Inc., Advancing Knowledge in Healthcare, are required to submit participant completion information directly to NABP with your ID number and birth information to include month and date (not year) as a validation to this ID number. If you do not have an ID number (this is not your license #), go to: www.MyCPEmonitor.net

Nursing and Pharmacy credit (per session) is based on attendance as well as completion of an online evaluation form available at:

WWW.AKHCME.COM/2015AES

THIS MUST BE DONE BY JANUARY 15, 2016 TO RECEIVE YOUR CE CREDIT.
We cannot submit credit to NABP after this date.
If you have any questions, please contact AKH at service@akhcme.com.

DISCLAIMER

Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the American Epilepsy Society or any manufacturers of pharmaceuticals.

Translational Research Symposium

Crisis in Translation: Perspective from the NIH

Walter Koroshetz, M.D.

Slides not available

Rigor in Pre-Clinical Studies and Reproducibility of Published Research Findings

Disclosure
Opinions I will voice are not official opinions of NIH

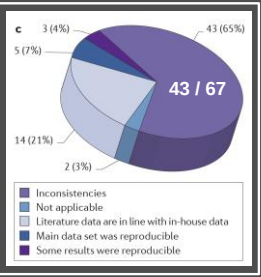
Shai D. Silberberg
National Institute of Neurological Disorders and Stroke National Institutes of Health

Believe it or not: how much can we rely on published data on potential drug targets?

Prinz, Schlange and Asadullah

Bayer HealthCare

Nature Reviews Drug Discovery 2011; 10:712-713



Objectives

To increase awareness on:

- Causes for low reproducibility
- The magnitude of the problem
- What can be done to improve reproducibility

7:00 p.m. – 10:00 p.m.
Fourth Annual Wine Tasting and Silent Auction
Additional fee applies.

Enjoy an evening of fine wines, food pairing and camaraderie at the Philadelphia Center for Architecture, directly across from the Convention Center. In addition to the fun, a silent auction of exceptional wines will be held, benefiting basic science and clinical fellowships in epilepsy.

What are the causes for low reproducibility?

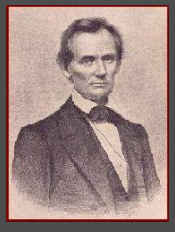
Complex innovative techniques

Confounding variables

Problems with resources

- Human nature: unconscious bias
- Lack of transparency in reporting
- Deficient experimental procedures
- Chance & Publication bias

Human Nature



"Human action can be modified to some extent, but human nature cannot be changed."

Abraham Lincoln

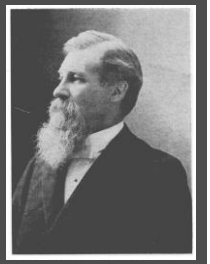
Cooper Union Address
New York, New York
February 27, 1860

The Method of Multiple Working Hypotheses

"The moment one has offered an original explanation for a phenomenon which seems satisfactory, that moment affection for his intellectual child springs into existence...

....There is an unconscious selection and magnifying of the phenomena that fall into harmony with the theory and support it, and an unconscious neglect of those that fail of coincidence."

Journal of Geology, 1897



Thomas Chamberlin

"I used to think that the brain was the most wonderful organ in my body. Then I realized who was telling me this."

Emo Phillips

The definition of experimental bias

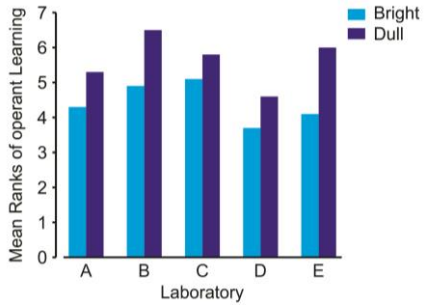
"The reliability of a study is determined by the investigator's choices about critical details of research design and conduct"

"Bias is unintentional and unconscious. It is defined broadly as the systematic erroneous association of some characteristic with a group in a way that distorts a comparison with another group….."

"…..The process of addressing bias involves making everything equal during the design, conduct and interpretation of a study, and reporting those steps in an explicit and transparent way."

David F. Ransohoff, 2010. *J Clin Oncol* 28: 698-704

Evidence for expectation bias



Rosenthal and Lawson, *J. Psychiat. Res.*1964; 2: 61-72

BIAS IN TREATMENT ASSIGNMENT IN CONTROLLED CLINICAL TRIALS

THOMAS C. CHALMERS, M.D., PAUL CELANO, M.D., HENRY S. SACKS, PH.D., M.D., AND HARRY SMITH, JR., PH.D.

Table 6. Conclusions of Authors about Efficacy of Treatment (Based on Clinical-Response Data in Addition to Case-Fatality Rate).

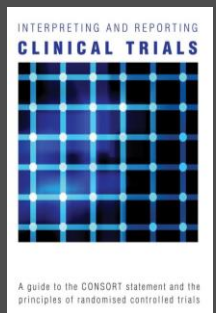
Type of Study	Total No. of Studies	Authors' Conclusions				
		Strongly Favor Treatment	Slightly Favor Treatment	No Preference	Slightly Favor Control	Strongly Favor Control
		per cent				
Blinded randomization	57	29.8	21.1	45.6	3.5	0
Unblinded randomization	45	31.1	15.6	48.9	4.4	0
Nonrandom assignment	43	55.8	16.3	20.9	4.7	2.3

Chalmers *et al., N Engl J Med* 1983; 309: 1358-1361

The CONSORT statement provides guidelines for reporting clinical trials

"Randomized trials can yield biased results if they lack methodological rigour.

To assess a trial accurately, readers of a published report need complete, clear, and **transparent** information on its methodology and findings."



Schulz *et al., PLOS Medicine* 2010; 7: 1–7

Among the 35 items included in the CONSORT guidelines are:

- How sample size was determined
- Method used to generate the random allocation sequence
- Mechanism used to implement the random allocation sequence
- Who was blinded after assignment to interventions and how
- Losses and exclusions after randomisation, together with reasons

Ignoring any one of these items can lead to bias

What about pre-clinical studies?

in vivo

in vitro

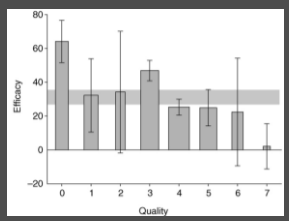
Do animal studies transparently report key aspects of experimental design and conduct and if not, is the lack of reporting associated with bias?

Insufficient reporting of methodological approaches is evident for pre-clinical studies

	Number of publications	Masked assessment of outcome (%)	Random allocation to group (%)	Sample size calculation (%)
Alzheimer's disease[30]	428	95 (22)	67 (16)	0 (0)
Multiple sclerosis[11]	1,117	178 (16)	106 (9)	2 (<1)
Parkinson's disease[31]	252	38 (15)	40 (16)	1 (<1)
Intracerebral hemorrhage[32]	88	43 (49)	27 (31)	0 (0)

Sena *et al*., *JCBFM.* 2014; 34: 737-742

The fewer methodological parameters are reported, the greater the apparent efficacy!



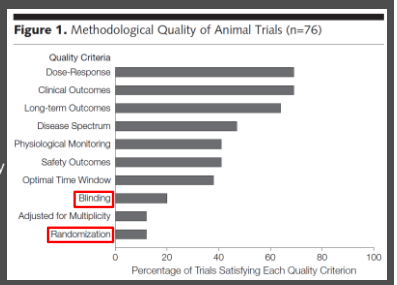
Effect size for studies of **FK506** (Tacrolimus) in experimental stroke.

Sena *et al., Trends Neurosci* 2007; 30: 433-439

Inadequate reporting is widespread

Journals:
- Cell
- Nature
- Science
- Nature Medicine
- Nature Genetics
- Nature Immunology
- Nature Biotechnology

>500 citations



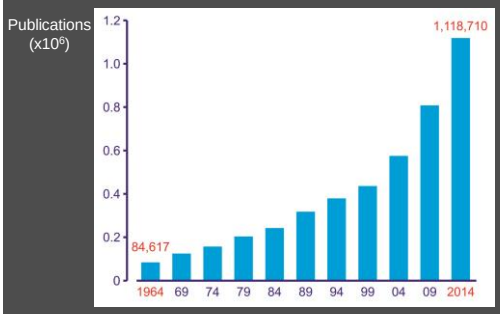
Hackam and Redelmeier, *JAMA* 2006; 14: 1731-1732

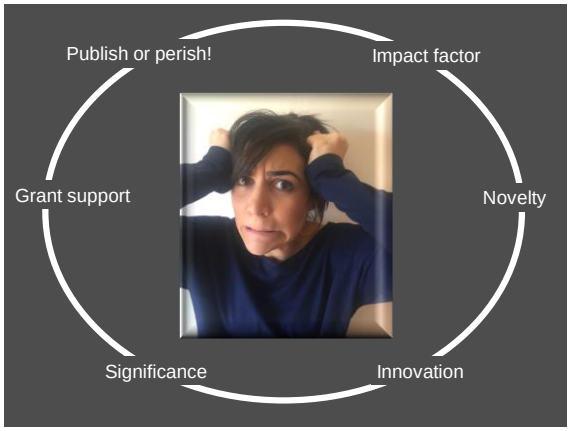
Peer Review

"Peer review is the evaluation of work by one or more people of similar competence to the producers of the work."

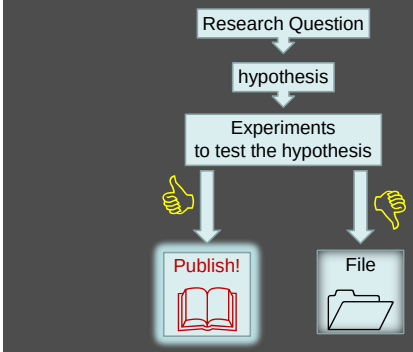
Wikipedia

The Escalation in Scientific Reporting (Annual PubMed Publications in English)





Publication Bias



"Publication bias in reports of animal stroke studies leads to overstatement of efficacy"

"We identified 16 systematic reviews of interventions tested in animal studies of acute ischaemic stroke involving **525** unique publications.

Only ten publications (2%) reported no significant effects on infarct volume."

Sena *et al., PLOS Biol* 2010; Vol 8 Issue 3

Amyotrophic lateral sclerosis (ALS)

- Death within 5 years of diagnosis
- Central pathological finding is motor neuron death
- 3% of cases from gain of function mutations in SOD1
- Rodents over-expressing SOD1 recapitulate ALS

2002: Minocycline reported by a number of groups to extend survival of SOD1 mice

2003: Randomized placebo controlled trial (412 patients treated for 9 months)

2007: Results of the trial are published - minocycline found to have a harmful effect on patients with ALS

Design, power, and interpretation of studies in the standard murine model of ALS

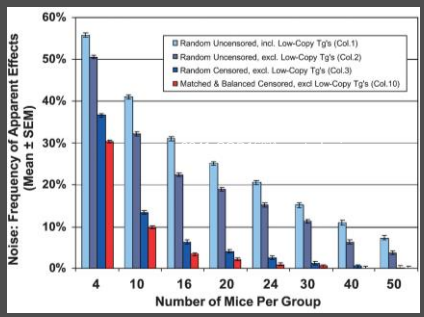
ALS Therapy Development Institute (ALS TDI)

"In the past five years we have screened more than 70 drugs in 18000 mice across 221 studies, using rigorous and appropriate statistical methodologies. While we were able to measure a significant difference in survival between males and females with great sensitivity, we observed no statistically significant positive (or negative) effects for any of the 70 compounds tested, including several previously reported as efficacious. "

"…the majority of published effects are most likely measurements of noise in the distribution of survival means as opposed to actual drug effect."

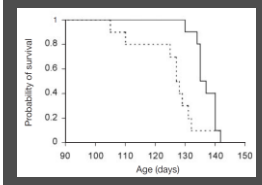
Scott *et al., Amyotroph Lateral Scler* 2008; 9: 4-15

The probability of seeing an effect by chance alone is significant even with 10 animals per group

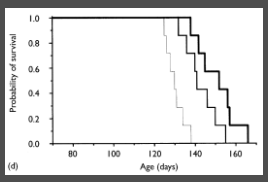


Scott *et al., Amyotroph Lateral Scler* 2008; 9: 4-15

The survival benefit of minocycline in the SOD1^{G93A} mouse model of ALS might be due to small sample size and/or Bias



- SOD1^{G93A} transgenic mice
- Started at 5 weeks of age
- i.p. 10mg/kg/day
- **10** animals / group (sex?)
- Not randomized
- Not blinded

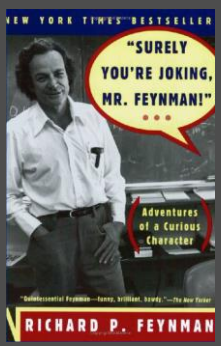


- SOD1^{G93A} transgenic mice
- Started at 10 weeks of age
- i.p. 25 and 50 mg/kg/day
- **7** animals / group (females)
- Not randomized
- "The experimenter was blinded to the treatment protocol."

How to improve reproducibility?

Lack of transparency in reporting	Review	Transparency in reporting
Unconscious bias; Deficient experimental procedures	Education	Attentiveness to bias; Good experimental design
Chance and Publication bias	Culture	Focus on rigor not glitter

Utopia



"If you're doing an experiment, you should report everything that you think might make it invalid – not only what you think is right about it.…

American Epilepsy Society Translational Research Symposium

Rigor in Translational Research: Issues, Experience and Solutions

Practical Experience in Achieving Pre-Clinical Rigor

Kevin Staley MD
Harvard Medical School
Massachusetts General Hospital

1

Disclosures:

- No financial disclosures

2

How do studies become preclinical?

- Exploratory research:
  - Many hypotheses tested and rejected
  - Minimal number of experiments to test each hypothesis
  - Only rarely is a hypothesis is validated
- Preclinical research
  - Research that has an immediate clinical implication
  - Exploratory labs tend to stumble onto findings with preclinical implications
  - The path to preclinical findings is filled with rejected hypotheses and small numbers of experiments
- Most exploratory labs do not drop their method of exploration to switch to preclinical research mode

3

Preclinical checklist

- Randomization
  - Allocation
  - Execution
  - Analysis
- Blinding
  - Treatment arms
  - Data analysis
- Number of experiments
  - Sample size pre-estimation
  - Stopping rules
  - vs increasing N until $p < 0.05$
- Predefined data handling
  - Endpoint(s)
  - outliers

Landis et al. *Nature* (2012) 490:189-91
Steward et al. *Exp Neurol* (2012) 233: 597-605

4

Preclinical rigor: Case study 1

- Bumetanide for neonatal seizures
- 2005: submitted to *Nature Medicine*
- Editor: add molecular and in vivo experiments
- Speed dictated the in vivo trial
  - not blinded or randomized
  - Smallest possible N (5)
  - No analysis of toxicity
- Preclinical:
  - ☹ The small positive in vivo trial undermined the novelty of a larger in vivo trial.
  - Replications have not been direct: different protocols to enhance novelty
    - Other injuries
    - Combination with hypothermia
- Clinical translation:
  - 2 clinical trials (50 neonates, $8M) based on N = 6 rats (and a lot of in vitro)
  - 1 trial halted:
    - ? ototoxicity
    - ? Efficacy (when non-seizing subjects included in analysis)

Dzhala et al. *Nat Med* (2005) 11: 1205-13
Pressler et al. *Lancet Neurol* (2015) 14: 469-77
Thoresen and Sabir *Nat Rev Neurol* (2015) 11:1-2

5

Preclinical rigor: case study 2

- Do interictal spikes predict epilepsy after brain injury?
- Collaboration with Ed Dudek
- Exploratory studies: Yes (in severe models of epilepsy)
  - Positive predictive value proportional to prevalence of disease
  - Epilepsy prevalence of model should match human incidence
- Proposed study:
  - Clinically relevant injury: trauma, stroke
  - Randomized, blinded execution
  - Blinded, quantifiable analysis (EEG seizure detection)
  - Large N (150)
- First flight of 50 subjects:
  - Incidence of stroke and post-stroke epilepsy too low
  - Electrode injuries
- Blinded execution and analysis
  - ☹ Retarded protocol optimization
  - ☺ Separated recognition of protocol problems from responsibility for problems
  - ☹ Less sense of ownership of the project
  - ☹ 100% rate of personnel turnover

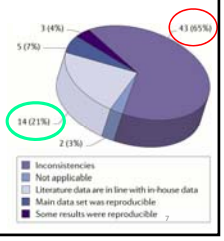
White A et al. *Epilepsia* (2010) 51:371-83
Kadam et al. *J Neurosci* (2010) 30:404-15

6

Preclinical rigor: do the priorities of exploratory research create perverse incentives?

- Publication
  - Journals with high impact factor → jobs, grants, influence
  - Positive findings have higher impact than negative
    - Who cares about the day Little Red Riding Hood did NOT visit grandma?
  - Authorship: 1st or last; not middle of a collaborative (multi-author) effort
  - Impact factor = average # citations *in 1st 2 years after publication*
    - False positives very unlikely to be clarified in 2 years
    - 65% false positive rate

Prinz F et al. *Nat Rev Drug Discov* 2011 10:712



7

Preclinical rigor: do the priorities of exploratory research create perverse incentives?

- Speed of investigation
  - Maximize the number of tested hypotheses
  - Be the first to publish a new result
  - Increases chance of a false positive
    - Don't repeat a positive experiment
    - Historical controls increase speed
  - No time to follow up negative experiments
    - Unlikely to pursue a failure to replicate to the point of publishing
    - This creates a "wake of silence" behind false positive reports
    - Many labs and trainees attempt replication, unaware that others have tried & failed
    - This ultimately slows research (and demoralizes trainees)

8

Preclinical rigor: do the priorities of exploratory research create perverse incentives?

- Funding
  - Investigator-initiated grants (R01s) reward
    - High impact factor of publications
    - Positive findings
    - N = 1 preliminary data
      - False positives not tested or detectable at this stage
      - No penalty for false positives
  - Negative findings considered a red flag regarding competency
    - "failed to discover…"
  - Large numbers of experiments are often considered
    - Wasteful (padding)
    - Expensive
    - Unethical

9

Preclinical rigor: do the priorities of exploratory research create perverse incentives?

- Institutional animal care and use committees
  - Applications are labor-intensive
    - Reviewed by inexperienced committee members
    - Multiple revisions often requested
  - PI is required to estimate the number of animals
  - This estimate becomes the maximum number of experiments that can be run
    - Can't order more animals without submitting an amended application
  - But N cannot be estimated for truly exploratory experiments
    - No way to estimate the effect size or variance in proposed experimental groups
    - ☹ Encourages a "statistics are arbitrary" attitude
- Vertebrate animals section of NIH grant applications
  - Often replicate many IACUC requests
  - 2015: recognize that N may not be possible to estimate

10

Preclinical rigor: do the priorities of exploratory research create perverse incentives?

- Blinding
  - Expensive
    - requires 2 persons: 1 to blind, 1 to do the experiment
    - Expense reduces the number of hypotheses that can be tested
  - Increases probability of error
    - Mis-identification of blinded subjects
  - Reduces the opportunity for serendipitous discovery
    - This is the nature of exploration
  - Reduces the opportunity to optimize protocols
    - Increases chance that the experiment will need to be repeated after unblinding

11

Preclinical rigor: do the priorities of exploratory research create perverse incentives?

- Number of experiments
  - Small N maximizes the number of hypotheses that can be tested
  - Smal N maximizes speed – first to publish – higher impact
  - There are multiple experiments / publication
    - Cumulative N may be very high
    - But the critical translational N is often small e.g. case study #1
- Homogeneity of subjects
  - Minimize untested variables
  - Age, sex, strain variance purposely avoided
- Small, homogenous pool of subjects reduces predictive power re: human responses

12

Preclinical rigor: do the priorities of exploratory research create perverse incentives?

- Manuscript review
  - Free service by PI
    - Only reward for careful, timely review = more reviews
    - Pressure to complete as rapidly as possible
  - No statistical support
  - Checklist (statistics, blinding) required, but not provided to potential referees
    - No easy way to ask for this information prior to accepting review
    - Author response: "we forgot to say this was blinded"
      - 8 / 8 requests 2012 - 15
      - Vs blinded re-analysis of data
  - Not designed to assess false positives i.e. say "I doubt it"

13

Preclinical rigor: do the priorities of exploratory research create perverse incentives?

- Replication studies
  - Impact of negative studies: very low
  - Impact of positive replications: even lower
  - Most labs will attempt to replicate a key published result once
    - If that replication fails at a small N, the attempt is abandoned
    - A new project is formulated
    - This is the nature of exploration
  - Effort to negate a false positive >> effort to create a false positive.
    - Hypotheses aren't disproven, just demonstrated to be improbable
    - This requires many "failures to replicate", each of which makes the original report slightly less likely
    - Not feasible to increase N until the probability of a false positive > 95%

14

Preclinical rigor: barriers
Exploratory labs: are they suited for translational research?

- Funding: R01s not a good match
  - Innovation
  - Required N: expensive, nonmodular grants
- Personnel:
  - Insufficient for blinding, random allocation, number of subjects
- Opportunity costs
  - Tying up resources in validation or translational trials does not get the next R01
- What happens to lab personnel when a large trial is over?
  - Training vs. service
  - Anticonvulsant Screening Program = early Contract Research Organization

Galanopoulou AS, *Epilepsia* (2012) 53:571-8

15

Preclinical rigor: barriers
Consortia of exploratory labs: suited for translational research?

- Advantages
  - Heterogeneity of personnel, approaches, strains
  - Large N possible
- Funding:
  - Multicenter studies are very expensive
  - Grant mechanisms not well established
- Academic credit
  - Effort vs authorship in multi-investigator trials closer to clinical trials than exploratory research
- Opportunity costs
  - Smaller fraction of lab resources devoted to validation & translational trials
  - When a large trial is over – retain personnel until next trial?

O'Brien et al. *Epilepsia* (2013) 54 Suppl 4:70-4

16

Barriers to preclinical rigor Proposals

- Exploratory research:
  - Animal care and use: exploratory studies do not require pre-estimation of N
  - Journals: send checklist with request to review
  - Pay or academic credit for reviews?
  - Authors: Don't discuss pre-clinical implications if preclinical guidelines not addressed
  - False positives
    - Recognize: Pools of replication studies
    - Publish pooled failed replications
- Pre-clinical translational:
  - Adhere to all 2012 guidelines
  - NIH: Separate study sections
    - Weight of exploratory evidence
    - Larger N OK
    - Heterogeneity:
      - Multiple sexes, ages, strains
      - Collaborations between labs

17

CME question

- What is a current barrier to rigorous preclinical studies?
- a. Financial costs
- b. Opportunity costs
- c. Limited novelty
- d. All of the above

18

Stuck in Translation: A Crisis of Commitment?

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December 5, 2015

AMERICAN EPILEPSY SOCIETY 69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Disclosure

UCB Pharma

Pfizer Inc

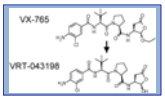
Takeda Pharmaceutical Company

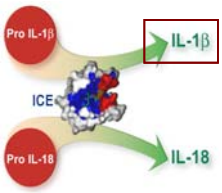
Learning Objectives

- To learn about the preclinical to clinical development path and the difficulties related to bench-to-bedside translation
- To learn about the role of neuroinflammation in epilepsy
- To describe preclinical data on candidate new targets for novel therapies

VX-765

- Orally active small molecule prodrug of VRT-43198, a potent and selective competitive inhibitor of ICE/caspase-1 (Ki=0.8 nM)
- Developed by Vertex Pharmaceuticals, Inc. (Cambridge, MA) for the treatment of peripheral inflammatory diseases
- Phase I & II studies showed good safety & tolerability





- IL-1β is induced in glia and neurons in epileptic foci in human pharmacoresistant focal epilepsies
- Signal transduction molecules are also induced in human epilepsy in glia, neurons and BBB (IL-1R1 and IRAK1)

ICE is activated in human epilepsy

IL-1β is implicated in ictogenesis and epileptogenesis in experimental models

Activation of the IL-1β system in epilepsy

Temporal Lobe Epilepsy with/without HS
(Ravizza et al, Neurobiol Dis, 2008; Roseti et al, Neurobiol Dis, 2015; Tan et al, J Neuroinflamm, 2015)

Malformations of Cortical Development:
FCD type 2, Tuberous Sclerosis, Glioneuronal tumors
(Aronica & Crino, Glia, 2013)

Rasmussen's encephalitis
(Ramaswamy et al, J Neuroinflamm, 2013)

Models of acute symptomatic seizures & status epilepticus (SE)
(reviewed by Vezzani et al, BBI, 2011)

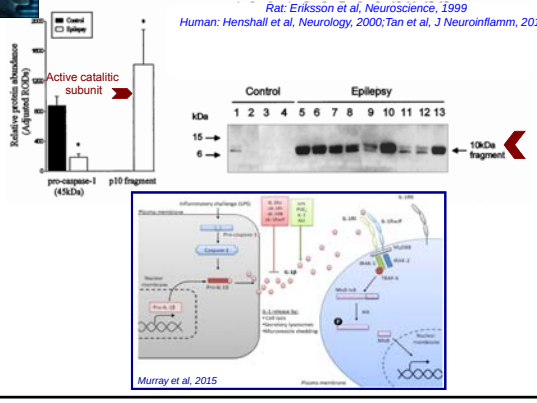
Models of febrile seizures and febrile SE
(Dube ' et al, Ann Neurol, 2005; J Neurosci, 2010)

Models of symptomatic epilepsies
(prodromal and chronic phases, *reviewed by Vezzani et al, BBI, 2011*)

Models of absence seizures
(Akin et al, 2011; Kovács et al, 2011)

Activation of ICE in mTLE

Rat: Eriksson et al, Neuroscience, 1999
Human: Henshall et al, Neurology, 2000;Tan et al, J Neuroinflamm, 2015



The IL-1β system is involved in seizure mechanisms

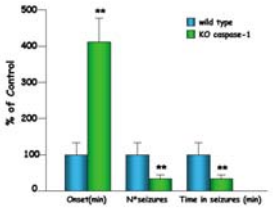
Vezzani et al, J Neurosci 1999; Vezzani et al, Epilepsia 2002; Ravizza et al., Epilepsia, 2006

	Control	Kainic acid 24 h
IL-1β	1.5 ± 0.15 pg/mg	**24.2 ± 8.4** pg/mg

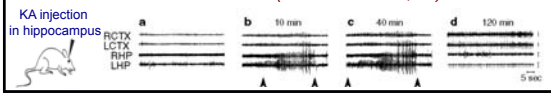
- IL-1β aggravates seizures
- IL-1Ra inhibit seizures

Treatment	Time in seizures
Vehicle	26.3 ± 1.8
IL-1β 1ng, i.h.	52.3 ± 4.9**
IL-1Ra 6μg, icv	13.4 ± 2.6**

- Caspase-1 (ICE) KO mice are seizure resistant



In coll with S.Allan (Univ of Manchester, UK)



The Journal of Neuroscience, June 15, 1999, 19(12):5054–5065

Interleukin-1β Immunoreactivity and Microglia Are Enhanced in the Rat Hippocampus by Focal Kainate Application: Functional Evidence for Enhancement of Electrographic Seizures

Annamaria Vezzani,[1] Mirko Conti,[1] Ada De Luigi,[2] Teresa Ravizza,[1] Daniela Moneta,[1] Francesco Marchesi,[1] and Maria Grazia De Simoni[2]

[1]Laboratory of Experimental Neurology and [2]Laboratory of Inflammation and Nervous System Diseases, Department of Neuroscience, Istituto di Ricerche Farmacologiche "Mario Negri," 20157 Milan, Italy

Powerful anticonvulsant action of IL-1 receptor antagonist on intracerebral injection and astrocytic overexpression in mice

A. Vezzani*†, D. Moneta*, M. Conti*, C. Richichi*, T. Ravizza*, A. De Luigi‡, M. G. De Simoni‡, G. Sperk§, S. Andell-Jonsson¶, J. Lundkvist¶, K. Iverfeldt¶, and T. Bartfai‖

Laboratories of *Experimental Neurology and ‡Inflammation and Central Nervous System Diseases, Department of Neuroscience, Mario Negri Institute for Pharmacological Research, via Eritrea 62, 20157 Milano, Italy; §Department of Pharmacology, University of Innsbruck, Peter-Mayr Strasse 1A, 40028 Innsbruck, Austria; ¶Department of Neurochemistry and Neurotoxicology, University of Stockholm, S-106 91 Stockholm, Sweden; and ‖Harold L. Dorris Neurological Center, Department of Biopsychology, Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, CA 92037

11534–11539 | PNAS | October 10, 2000 | vol. 97 | no. 21

Vertex in 2004 proposed to study whether selective ICE inhibitors have anticonvulsive effects in animal models

Epilepsia, 47(7):1160–1168, 2006
Blackwell Publishing, Inc.

Inactivation of Caspase-1 in Rodent Brain: A Novel Anticonvulsive Strategy

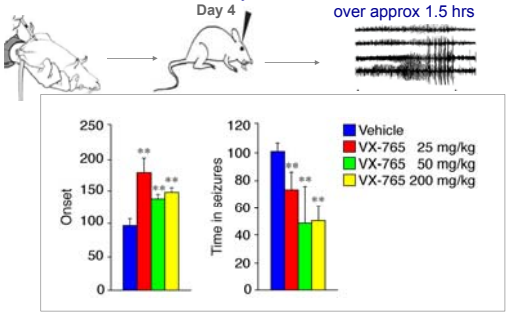
*Teresa Ravizza, †Sian-Marie Lucas, *Silvia Balosso, ‡Liliana Bernardino, §George Ku, *Francesco Noé, ‡Joao Malva, §John C. R. Randle, †Stuart Allan, and *Annamaria Vezzani

*Department of Neuroscience, Mario Negri Institute for Pharmacological Research, Milan, Italy; †Faculty of Life Sciences, University of Manchester, Manchester, United Kingdom; ‡Center for Neuroscience and Cell Biology, Institute of Biochemistry, University of Coimbra, Portugal; and §Vertex Pharmaceuticals, Inc., Cambridge, Massachusetts, U.S.A.

Leading group: Lab Exp Neurology, Mario Negri Inst
Collaborators: University of Manchester, UK; University of Coimbra, Portugal

VX-765 anticonvulsive effect in acute models

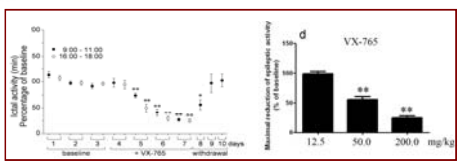
VX-765 days 1-4 Kainate i.h. Injection Day 4 Monitor & record seizures over approx 1.5 hrs



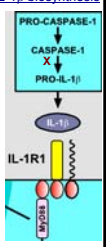
- Pralnacasan shows similar effects
- ICE inhibitors blocked the IL-1β increase measured in brain during seizures

Ravizza et al, Epilepsia, 2006

VX-765 reduced AEDs resistant seizures



VX-765 x 4 d inhibits IL-1β biosynthesis



Maroso, French et al, Neurotherapeutics, 2011

- Reduction of epileptic activity is associated with reduction of inflammation
- Drug exposures (Cmax, AUC) are within the range of those observed with human dosing

Anticonvulsive effects in various models

IL-1β/IL-1R1signaling

1. Seizures induced by kainic acid (lesional) or bicuculline and FS (non lesional)
   (Vezzani et al, 1999; 2000; Dube ' et al, 2005; 2011; Ravizza et al, 2006)
2. Status epilepticus in rats is reduced by anakinra *(De Simoni et al, 2000; Marchi et al, 2009)*
3. Electrical kindling in rats: delayed + no seizure generalization
   (Ravizza et al, 2008; Auvin et al, 2010; 2011)
4. Chronic recurrent seizures in epileptic mice (mTLE model) *(Maroso et al, 2009; 2010)*
5. SWD in GAERS & WAG/Rij (absence seizures) *(Akin et al, 2011; Kovács et al, 2011)*

↓

50-70% decrease in seizure recurrence, delayed seizure onset, reduced generalization
Resolution of inflammation in areas involved in seizures

VX09-765-401

A phase 2 randomized, double-blind placebo controlled study of VX-765 in subjects with treatment resistant partial epilepsy.

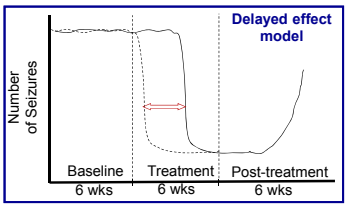
20 Nov 2009

VERTEX

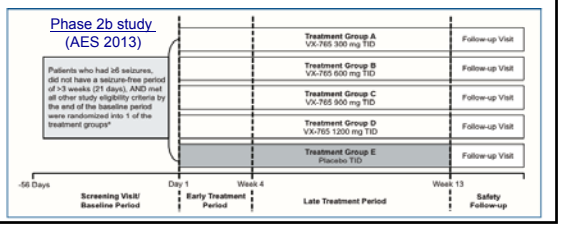
Phase 2a study (AES 2011):
treatment resistant
partial onset epilepsy

Primary endpoint:
safety and tolerability

Secondary endpoint:
% Reduction in seizure rate
Responder rate
% of patients seizure-free



Phase 2b study
(AES 2013)

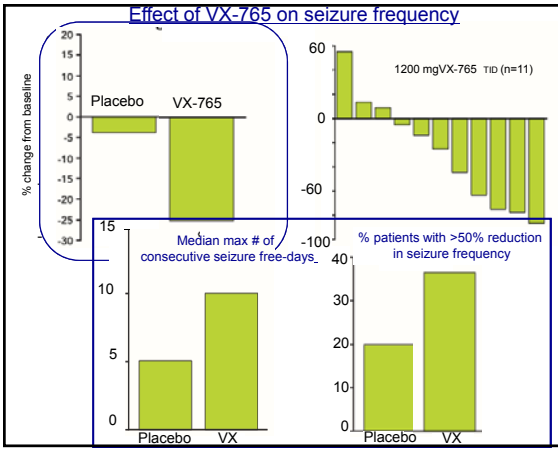


Stuck in translation

Although the study was originally designed and powered
to enroll 500 patients
it was terminated early for administrative (business) reasons

A total of 55 patients were enrolled and randomized
prior to study termination
49 were included in the final analysis

Effect of VX-765 on seizure frequency



Stuck in translation

But……

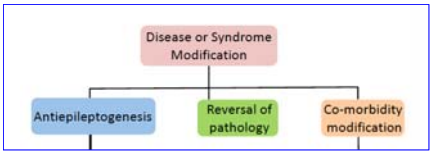
• New preclinical evidence of target validation
(e.g. HMGB1 is an ictogenic molecule found to be released following ICE activation; antiinflammatory drugs provide disease modifications)

•Novel clinical trial designs are discussed to reveal disease-modifications

•Biomarkers for patients stratification are becoming available

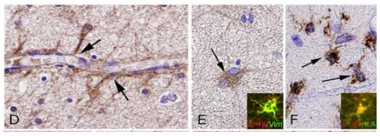
Antiinflammatory treatments and disease modifications

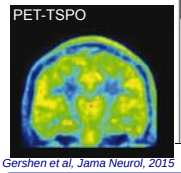
Celecobix, Parecobix	COX-2 inhibition	SE	*Jung et al., 2006; Polascheck*
Aspirin	COX1&2 inhibition	SE	*et al., 2010; Ma et al, 2012*
α4-integrin-specific Ab	Adhesion molecules	SE	*Fabene et al., 2008*
Erythropoietin	Broad spectrum	SE	*Chu et al., 2008*
Fingolimod	SP1/ Astrocytes	SE	*Gao et al, 2012*
Minocyclin	⇩Cytokines/Microglia	SE	*Wang et al, 2015*
Minozac	⇩Cytokines/Glia	TBI	*Chrzaszcz et al., 2010*
Anakinra+COX-2 antagonist	IL-1R1/COX-2 inhibition	SE	*Kwon et al, 2013*
VX-765+TLR antagonist	IL-1R1/HMGB1 inhibition	SE	*Vezzani et al, unpublished*
Nrf2 gene therapy	Oxidative stress	SE	*Mazzuferi et al, 2013*
miRNA146a	IL-1R1/TLR4	SE	*Vezzani & Aronica, submitted*
EP2 antagonists	Neuroinflammation/EP2R	SE	*Jiang & Dingledine, 2013*
Ketogenic diet	⇩IL-1β biosynthesis		*Youm et al, 2014*



Patients stratification IL-1β (astrocytes & microglia): TLE; MCD; RE

Butler et al, J Neuroimaging, 2010
Hirvonen et al, J Nucleic Med, 2012





Gershen et al, Jama Neurol, 2015

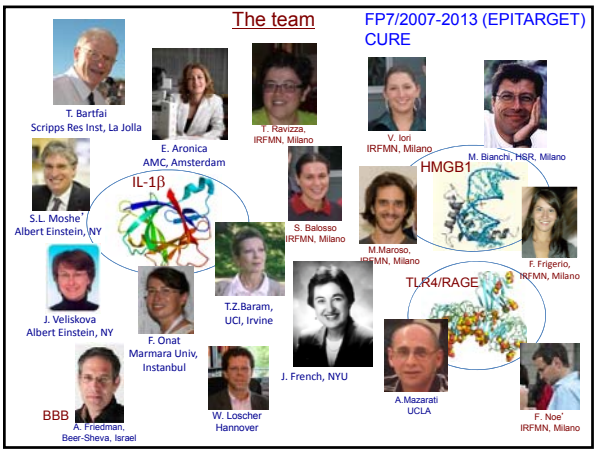
Box 1. Potential biomarkers of brain inflammation in epilepsy.

- Brain imaging (cell types or macromolecules)
  - PET (microglia/macrophages, endothelial cell adhesion molecules)
  - Magnetic resonance spectroscopy (astrocytes)
  - Molecular MRI (endothelial dysfunction; VCAM)
  - Contrast-enhanced MRI (endothelial dysfunction; increased permeability)
- Soluble inflammatory mediators in cerebrospinal fluid/blood
  - Citokines/chemokines/danger signals[1]
  - Cell adhesion molecules
  - Auto-antibodies

Vezzani and Friedman, Biomark Med, 2011

Astrocytes:
PET-Deprenyl *(Kumlien et al, 2001)*
MRS-mIns *(Hammen et al, 2008; Wellard et al, 2003; Ravizza et al, 2012)*

Human TBI:
Higher CSF/Serum IL-1β ratio & CT functional phenotype associated with increased risk of PTE
(Diamond et al, Epilepsy, 2014)



Shared Data Platforms: Efficiency, Integrity, Fairness, and Utility

M. Brandon Westover, MD, PhD
Massachusetts General Hospital

December 5, 2015

Disclosure

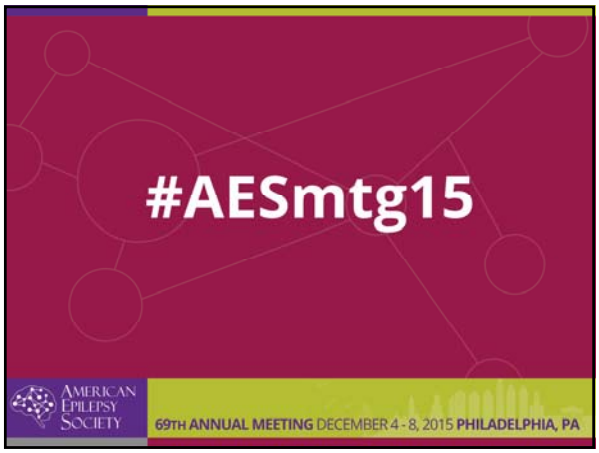
None

Learning Objectives

- First objective for your presentation
- Second objective for your presentation
- Third objective for your presentation

Impact on Clinical Care and Practice

- First point
  - Sub-point 1
  - Sub-point 2
- Second point
  - Sub-point 1
  - Sub-point 2


#AESmtg15
American Epilepsy Society
69TH ANNUAL MEETING DECEMBER 4 - 8, 2015 PHILADELPHIA, PA

Publication Bias: When Data Is AWOL

Michael A. Rogawski, M.D., Ph.D.
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December 5, 2015

Disclosure

None relevant

Learning Objectives

- Causes of translational failure
- File drawer problem
- Adequate reporting of methods
- Data sharing
- Is a new journal necessary?

Translational Failure Has Many Causes

- Fraud is rare
- System overlooks/ignores lack of scientific rigor and instead rewards flashy results that generate buzz or excitement
- Rush to publish: unexpected, unexplained observations should be tested rigorously – repeated and confirmed – before announce to world
- Poor experimental design and analysis leads to overstatement of treatment effects

Begley and Ioannidis, *Circ Res* 2015

Francis Bacon (1605)

Human tendency to ignore negative results.

It is human nature for "the affirmative or active to effect more than the negative or privative. So that a few times hitting, or presence, countervails oft-times failing or absence"

False Conclusions from Publications Decisions

Type 1 error: rejecting null hypothesis when it is in fact true.

PUBLICATION DECISIONS AND THEIR POSSIBLE EFFECTS ON INFERENCES DRAWN FROM TESTS OF SIGNIFICANCE —OR VICE VERSA*

J Am Stat Assoc 1959

. . . Research which yields nonsignificant results is not published. Such research being unknown to other investigators may be repeated independently until eventually by chance a significant result occurs . . . and is published . . .

The File Drawer Problem

1979

Psychological Bulletin
1979, Vol. 86, No. 3, 638-641

The "File Drawer Problem" and Tolerance for Null Results

Robert Rosenthal
Harvard University

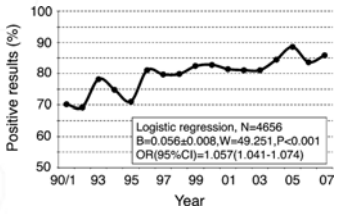
For any given research area, one cannot tell how many studies have been conducted but never reported. The extreme view of the "file drawer problem" is that journals are filled with the 5% of the studies that show Type I errors, while the file drawers are filled with the 95% of the studies that show nonsignificant results. Quantitative procedures for computing the tolerance for filed and future null results are reported and illustrated, and the implications are discussed.

Both behavioral researchers and statisticians have long suspected that the studies published in the behavioral sciences are a biased sample of the studies that are actually carried out (Bakan, 1967; McNemar, 1960; Smart, 1964; Sterling, 1959). The extreme view of this problem, the "file drawer problem," is that the journals are filled with the 5% of the studies that show Type I errors, while the file drawers back at the lab are filled with the 95% of the studies that show nonsignificant (e.g., $p > .05$) results.

In the past there was very little one could do to assess the net effect of studies, tucked away in file drawers, that did not make the magic .05 level (Rosenthal & Gaito, 1963, 1964). Now, however, although no definitive tematically and quantitatively, both with respect to significance levels (Rosenthal, 1969, 1976, 1978) and with respect to effect-size estimation (Hall, 1978; Rosenthal, 1969, 1976; Rosenthal & Rosnow, 1975; Smith & Glass, 1977; Glass, Note 1). One hopes that this interest in summarizing entire research domains will lead to an improvement in bookkeeping so that eventually all results will be recorded both with an estimate of effect size (e.g., r or d; Cohen, 1977) and with the level of significance obtained, or more practically, with the standard normal deviate (Z) that corresponds to the obtained p (Rosenthal, 1978).[1] Future appraisals of research domains of the type found in *Psychological Bulletin* should give estimates of overall

The File-Drawer Problem: Tendency of Journals to Preferentially Publish Statistically Significant Results

Percentage of papers reporting support for tested hypothesis; 4,600 papers published between 1990 and 2007.



D. Fanelli, *Scientometrics* 2012

Why Is There a Failure to Publish Negative Results?

- Erroneous belief that progress in science means continual production of positive findings
- Negative results carry a stigma: a sense that the study is basically a failure
- Concern that career won't advance, may not get grants, may not get published
- No incentives to report negative results, replicate experiments or recognize inconsistencies, ambiguities and uncertainties

Consequences of Failure to Report Negative Results

- Effects that are not real may appear to be supported by research
- Wasted human effort as futile research is conducted over and over again
- Resources diverted from promising research directions

Other Key Practices to Enhance Translational Success

- More detailed reporting of experimental methods
- Data sharing

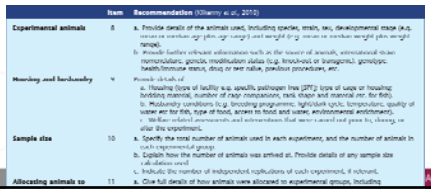
More Detailed Reporting of Experimental Methods

- Encourages better experimental design
- Allows reviewers, editors and readers to assess quality of work
- Enables replication studies
- Makes quantitative review/meta-analyses feasible

Guidelines for Reporting Experimental Methods in Animal Translational Studies

- NINDS guidelines (Landis et al., Nature 2012)
- Gold standard publication checklist to improve quality of animal studies (Hooijmans et al., 2010)
- ARRIVE (Animals in Research: Reporting In Vivo Experiments) guidelines (Kilkenny et al., 2010)

ARRIVE



Item		Recommendation (Kilkenny et al., 2010)
Experimental animals	8	a. Provide details of the animals used, including species, strain, sex, developmental stage (e.g. neonate or mature adult, age range) and weight (e.g. means or median weight plus weight range).
		b. Provide further relevant information such as the source of animals, international strain nomenclature, genetic modification status (e.g. knockout or transgenic), genotype, health/immune status, drug or test naive, previous procedures, etc.
Housing and husbandry	9	Provide details of:
		a. Housing (type of facility e.g. specific pathogen free (SPF); type of cage or housing; bedding material; number of cage companions; cage size and material etc. for fish).
		b. Husbandry conditions (e.g. breeding programme; light/dark cycle; temperature; quality of water etc for fish; type of food; access to food and water; environmental enrichment).
		c. Welfare-related assessments and interventions that were carried out prior to, during, or after the experiment.
Sample size	10	a. Specify the total number of animals used in each experiment, and the number of animals in each experimental group.
		b. Explain how the number of animals was arrived at. Provide details of any sample size calculations used.
		c. Indicate the number of independent replications of each experiment, if relevant.
Allocating animals to	11	a. Give full details of how animals were allocated to experimental groups, including

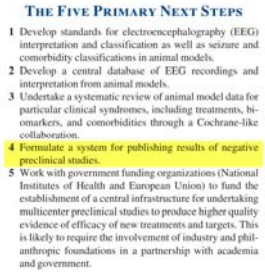
Make Raw Data Available

- Not "if someone asks for it" but as supplementary material
- Data set from animals studies are typically small
- No confidentiality issues
- Allows claims to be verified and data to be reanalyzed
- Helps prevent selective reporting
- Simplifies meta-analysis

AES/ILAE Joint Workshop to Optimize Preclinical Epilepsy Therapy Discovery, London, September 2012

INTRODUCTION

Joint AES/ILAE translational workshop to optimize preclinical epilepsy research



THE FIVE PRIMARY NEXT STEPS

1 Develop standards for electroencephalography (EEG) interpretation and classification as well as seizure and comorbidity classifications in animal models.
2 Develop a central database of EEG recordings and interpretation from animal models.
3 Undertake a systematic review of animal model data for particular clinical syndromes, including treatments, biomarkers, and comorbidities through a Cochrane-like collaboration.
4 Formulate a system for publishing results of negative preclinical studies.
5 Work with government funding organizations (National Institutes of Health and European Union) to fund the establishment of a central infrastructure for undertaking multicenter preclinical studies to produce higher quality evidence of efficacy of new treatments and targets. This is likely to require the involvement of industry and philanthropic foundations in a partnership with academia and government.

Is A New Journal Necessary?

- Statistically-valid studies with negative results (null hypothesis accepted)
- Replication/corroboration studies
- Fragmentary studies insufficient to fully resolve a hypothesis
- Elaboration of specific methodological advances
- Proceedings of meetings, case reports, meta-analyses, and systematic reviews

Some Concepts for Discussion

- The sole standard for acceptance is scientific rigor of the methods, experimental design and execution, analysis and interpretation; detailed methods reporting; data sharing.
- Not considered: impact, novelty, originality, significance, likelihood of moving the field forward, or conceptual importance.
- Open access (online only)
- Peer-reviewed; peer reviewers compensated to encourage high quality, rapid reviews
- Indexed in PubMed (hosted on PubMed Central)
- Submission-fee (article processing charge) business model (reasonable fee: $625); nonprofit business structure
- Rapid review, decision, and publication, rolling on-line publication
- Broad, diverse international Editorial Board

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