The failure to translate the basic science into therapy is due primarily to inadequacies in the preclinical (animal) data
...or
The quality of most animal studies is so shockingly poor that their results are an unreliable indicator of what happens in animals let alone what might happen in humans.
1026 interventions in experimental stroke
1026 interventions in experimental stroke

Tested in focal ischaemia
1026 interventions in experimental stroke

Effective in focal ischaemia
1026 interventions in experimental stroke

Tested in clinical trial

CAMARADES: Bringing evidence to translational medicine
1026 interventions in experimental stroke

Effective in clinical trial

CAMARADES: Bringing evidence to translational medicine
Where are we going wrong?

• Are animal experiments falsely positive?
• Have clinical trials tested the conditions of maximum efficacy?

... and what, if anything, does this mean for models of other diseases?
Treatment of experimental stroke with low-dose glutamate and homeopathic Arnica montana*

W. Jonas¹, Y. Lin², A. Williams², F. Tortella², R. Tuma³
¹ Uniformed Services University of the Health Sciences, Bethesda, Maryland
² Walter Reed Army Institute of Research, Washington, D.C.
³ Temple University, Philadelphia, PA

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Graph showing the effect of different doses of glutamate on infarct volume.
Animal data in stroke

- There are huge amounts of often confusing data
- Systematic review can help to make sense of it
- If you select extreme bits of the evidence you can “prove” either harm or substantial benefit
- However, if you have a precise and highly significant overall effect, then it is probably real

Hypothermia: a systematic search identified 277 experiments in 3353 animals
<table>
<thead>
<tr>
<th>LIST</th>
<th>STATE</th>
<th>AVERAGE POPULATION IQ</th>
<th>PRESIDENT ELECT</th>
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<tr>
<td>50</td>
<td>Mississippi</td>
<td>35</td>
<td>George Bush</td>
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</tbody>
</table>
Where are we going wrong?

• Are animal experiments falsely positive?
• Are clinical trials falsely negative?
• Do animal studies not model human disease with sufficient fidelity to be useful?
Potential sources of bias in animal studies

• Internal validity

<table>
<thead>
<tr>
<th>Problem</th>
<th>Solution</th>
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<tbody>
<tr>
<td>Selection Bias</td>
<td>Randomisation</td>
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<tr>
<td>Performance Bias</td>
<td>Allocation Concealment</td>
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<tr>
<td>Detection Bias</td>
<td>Blinded outcome assessment</td>
</tr>
<tr>
<td>Attrition bias</td>
<td>Reporting drop-outs/ ITT analysis</td>
</tr>
</tbody>
</table>

• External validity
  – Publication bias
  – Are the models we use good models?
    • Co-morbidities
Internal Validity
Hypothermia in experimental stroke

- Infarct Volume
  - 101 publications
  - 222 experiments
  - 3256 animals
  - Improved outcome by 43.5% (40.1-47.0)
Internal Validity
Randomisation and blinding in studies of hypothermia in experimental stroke

Randomisation

<table>
<thead>
<tr>
<th>Randomisation</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>37%</td>
</tr>
<tr>
<td>No</td>
<td>47%</td>
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</table>

Blinded outcome assessment

<table>
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<th>Efficacy</th>
</tr>
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<tbody>
<tr>
<td>Yes</td>
<td>39%</td>
</tr>
<tr>
<td>No</td>
<td>47%</td>
</tr>
</tbody>
</table>
Internal Validity
Stem Cell based therapies

• Infarct Volume
  – 54 publications
  – 127 experiments
  – 2012 animals
  – Improved outcome by 28.9% (24.8-33.0)

• Neurobehavioural score:
  – 72 publications
  – 111 experiments
  – 1876 animals
  – Improved outcome by 34.4% (29.5-39.2)
Randomisation
Stem Cell based therapies

Infarct volume
TRUE: 16.18 (10.01, 22.35)
FALSE: 36.01 (30.85, 41.16)

Neurological score
TRUE: 32.87 (25.83, 39.91)
FALSE: 35.53 (29.30, 41.76)
Blinded outcome assessment
Stem Cell based therapies

Infarct volume
- True: 21.60 (13.89, 29.32)
- False: 31.58 (26.71, 36.44)

Neurological score
- True: 27.88 (21.96, 33.81)
- False: 39.10 (32.60, 45.60)
Internal Validity
NXY-059

• Candidate neuroprotective drug unsuccessful in clinical trial

• Infarct Volume
  – 11 publications
  – 29 experiments
  – 408 animals
  – Improved outcome by 44% (35-53%)
Internal Validity
NXY-059
Treatment of experimental stroke with low-dose glutamate and homeopathic Arnica montana*

W. Jonas¹, Y. Lin², A. Williams², F. Tortella², R. Tuma³

¹ Uniformed Services University of the Health Sciences, Bethesda, Maryland
² Walter Reed Army Institute of Research, Washington, D.C.
³ Temple University, Philadelphia, PA

Reported Efficacy 36%
Corrected Efficacy <0%
The File Drawer problem
Publication bias
External Validity
Publication Bias for FK506

• All outcomes
  – 29 publications
  – 109 experiments
  – 1596 animals
  – Improved outcome by 31% (27-35%)
Publication bias - gCSF

England T et al 2009
Publication bias in experimental stroke

• Only 11/525 publications (2.2%) reported no significant treatment effects
• Trim and Fill suggested ~16% (214/1573) of experiments remain unpublished
• Best estimate of magnitude of problem
  – Observed efficacy 31.3% (29.7-32.8)
  – Adjusted efficacy 23.8% (22.2-25.5)
External Validity
Hypertension in studies of tPA in experimental stroke

• Infarct Volume
  – 113 publications
  – 212 experiments
  – 3301 animals
  – Improved outcome by 24% (20-28)

Comorbidity

Infarct Volume

Efficacy

25%  -2%

“Normal”  ↑BP

Comorbidity
External Validity
Hypertension in studies of NXY-059

• 7% of studies used animals with hypertension
• 77% of patients in SAINT II had a history of hypertension at study entry
Summary

• Certain aspects of the design of animal experiments probably do lead to the overstatement of neuroprotective efficacy

• A substantial publication bias is present

• Neuroprotective efficacy may be substantially lower in animals with relevant co-morbidities
How much efficacy is left?

Publication bias

Randomisation

Comorbidity bias

CAMARADES: Bringing evidence to translational medicine
“...you will meet with several observations and experiments which, though communicated for true by candid authors or undistrusted eye-witnesses, or perhaps recommended by your own experience, may, upon further trial, disappoint your expectation, either not at all succeeding, or at least varying much from what you expected”

Robert Boyle (1693), Concerning the Unsuccessfulness of Experiments
A toolkit for effective translation

- Clear, rigorous SOPs for all aspects of experimental design
- On-line tools for
  - Sample size calculation
  - Random allocation to group
- Development of experimental methods and funding streams to support multi-centre animal studies
- Adoption of CONSORT statement for animal stroke studies
Review Article
Reprint: Good laboratory practice: preventing introduction of bias at the bench

Malcolm R Macleod¹, Marc Fisher², Victoria O’Collins³⁴, Emily S Sena¹³⁴, Ulrich Dirnagl⁵,
Philip MW Bath⁶⁺, Alistair Buchan⁷, H Bart van der Worp⁸, Richard J Traysman⁹,
Kazuo Minematsu¹⁰, Geoffrey A Donnan³⁴ and David W Howells³⁴

(1) Animals: The precise species, strain, substrain, and source of animals used should be stated. Where applicable (for instance in studies with genetically modified animals) the generation should also be given, as well as the details of the wild-type control group (for instance littermate, back cross, etc.).

(2) Sample size calculation: The manuscript should describe how the size of the experiment was planned. If a sample size calculation was performed this should be reported in detail, including the expected difference between groups, the expected variance, the planned analysis method, the desired statistical power, and the sample size thus calculated. For parametric data, variance should be reported as 95% confidence limits or standard deviations rather than as the standard error of the mean.

(3) Inclusion and exclusion criteria: Where the severity of ischemia has to reach a certain threshold for inclusion (for instance a prespecified decrease in perfusion detected with laser-Doppler flowmetry, or the development of neurologic impairment of a given severity) this should be stated clearly. Usually, these criteria should be applied before the allocation to experimental groups. If a prespecified lesion size is required for inclusion this should be detailed, as well as the corresponding exclusion criteria.

(4) Randomization: The manuscript should describe the method by which animals were allocated to experimental groups. If this allocation was by randomization, the method of randomization (coin toss, computer-generated randomization schedules) should be stated. Picking animals ‘at random’ from a cage is unlikely to provide adequate randomization. For comparisons between groups of genetically modified animals (transgenic, knockout), the method of allocation to for instance sham operation or focal ischemia should be described.

(5) Allocation concealment: The method of allocation concealment should be described. Allocation is concealed if the investigator responsible for the induction, maintenance, and reversal of ischemia and for decisions regarding the care of (including the early killing of) experimental animals, has no knowledge of the experimental group to which an animal belongs. Allocation concealment might be achieved by having the experimental intervention administered by an independent investigator, or by having an independent investigator prepare drug individually and label it for each animal according to the randomization schedule as outlined above. These considerations also apply to comparisons between groups of genetically modified animals, and if phenotypic differences (e.g., coat coloring) prevent allocation concealment this should be stated.

(6) Reporting of animals excluded from analysis: All randomized animals (both overall and by treatment group) should be accounted for in the data presented. Some animals may, for very good reasons, be excluded from analysis, but the circumstances under which this exclusion will occur should be determined in advance, and any exclusion should occur without knowledge of the experimental group to which the animal belongs. The criteria for exclusion and the number of animals excluded should be reported.

(7) Masked assessment of outcome: The assessment of outcome is masked if the investigator responsible for measuring infarct volume, for scoring neurobehavioral outcome or for determining any other outcome measure has no knowledge of the experimental group to which an animal belongs. The method of blinding the assessment of outcome should be described. Where phenotypic differences prevent the masked assessment of for instance neurobehavioral outcome, this should be stated.

(8) Reporting potential conflicts of interest and study funding: Any relationship which could be perceived to introduce a potential conflict of interest, or the absence of such a relationship, should be disclosed in an acknowledgements section, along with information on study funding and for instance supply of drugs or of equipment.
Chances that data from any given animal will be non-contributory

assume simple two group experiment seeking 30% reduction in infarct volume, observed SD 40% of control infarct volume

<table>
<thead>
<tr>
<th>Number of animals</th>
<th>Power</th>
<th>% animals wasted</th>
</tr>
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<tbody>
<tr>
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<td>18.6%</td>
<td>81.4%</td>
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<tr>
<td>8</td>
<td>32.3%</td>
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<td>16</td>
<td>56.4%</td>
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<tr>
<td>32</td>
<td>85.1%</td>
<td>14.9%</td>
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</table>
Systematic survey of the design, statistical analysis, and reporting of studies published in the 2008 volume of the *Journal of Cerebral Blood Flow and Metabolism*

**Discussion**

Systematic assessment of all 156 original articles published in JCBFM in 2008 revealed a surprisingly high prevalence of deficiencies in the reporting of key components of scientific quality: design, reporting, and statistics. This is the first systematic study of this type in research on physiology and pathophysiology of brain metabolism and blood flow, but several studies and commentaries have already hinted that methodological and reporting problems are prevalent, and that this might be an important contributor to the ‘translational roadblock’ that exists in the field (Dirmagl, 2006; Sena et al., 2007; Phillips et al., 2009; Fisher et al., 2009; Courbier et al., 2009; Joubert et al.,...
Current performance against key quality items

<table>
<thead>
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<th>Stroke</th>
<th>Randomisation</th>
<th>Blinded Outcome Assessment</th>
<th>Sample Size calculation</th>
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<tr>
<td></td>
<td>36%</td>
<td>29%</td>
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How does stroke compare?

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<td>36%</td>
<td>29%</td>
<td>3%</td>
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<tr>
<td>MND</td>
<td>31%</td>
<td>20%</td>
<td>&lt;1%</td>
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<tr>
<td>AD</td>
<td>15%</td>
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<td>0%</td>
</tr>
<tr>
<td>PD</td>
<td>12%</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>EAE</td>
<td>8%</td>
<td>15%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Glioma</td>
<td>14%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Systematic review - PD

11604 publications identified from three online databases and one unpublished thesis

253 reporting the use of 74 dopamine agonists tested in an animal model of PD with a neurobehavioural outcome (appendix 1)

13 publications used Apomorphine for screening purposes only

37 Abstracts with no extractable data; of these 3 papers identified as being an abstract from a full publication included in the meta-analysis

83 Excluded from the analysis: no control (59 publications); dichotomous data only (1); no variance (7); number of animals per group missing (1); median or range (3); uninterpretable data (1); qualitative data (2); a sample size of one per group (1); no relevant neurobehavioural outcome (1); one or more of the above reasons (7)

121 Publications with at least one valid neurobehavioural outcome

24 individual outcomes from 10 publications excluded from analysis due to: a variance of zero or too few animals per group

Standardised mean difference meta-analysis on 601 individual, valid outcomes

47 dopamine agonists tested (Table 2 / Figure 2)

6 neurobehavioural outcomes reported (Table 1 / Figure 4)

83 Excluded from the analysis: no control (59 publications); dichotomous data only (1); no variance (7); number of animals per group missing (1); median or range (3); uninterpretable data (1); qualitative data (2); a sample size of one per group (1); no relevant neurobehavioural outcome (1); one or more of the above reasons (7)
Internal validity in PD models

Blinded outcome assessment

Composite quality
Modelling MS

Pubmed Search: 9726 Publications

1174 Publications Testing A Drug

1111 Drugs

Pick Drugs Which Have Been Tested at Least 5 Times

401 Publications

39 Drugs

Weighted Means Meta-Analysis

Animal Model Of MS Used:

- Direct EAE: 1015
- Passive EAE: 171
- Other*: 83

Missing Data**: 191

Did Not State Number of Animals Used

29

13

1

5

105

1

6

32

Did Not State Whether SEM or SD Used

No Variance
External validity - MS

A

Effect Size (% improvement in Neurobehavioural Score)

Before EAE  |  Day of EAE  |  Days 1 to 7  |  Days 8 to 14  |  Beyond 14  |  Unknown

Time to Treatment

B

Effect Size (% improvement in Neurobehavioural Score)

1-4  |  5 & 6  |  7-9  |  10+

Mean Number of Animals Per Group

CAMARADES: Bringing evidence to translational medicine
Summarising data from animal experiments

- how powerful is the treatment?
- what is the quality of evidence?
- what is the range of evidence?
- is there evidence of a publication bias?
- What are the conditions of maximum efficacy?
<table>
<thead>
<tr>
<th>Disease model</th>
<th>Interventions</th>
<th>Publications</th>
<th>Experiments</th>
<th>Animals</th>
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<tbody>
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<td>Focal cerebral ischaemia</td>
<td>17</td>
<td>556</td>
<td>1439</td>
<td>20690</td>
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<tr>
<td>Intracerebral Haemorrhage</td>
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<td>97</td>
<td>407</td>
<td>3647</td>
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<tr>
<td>Experimental Allergic Encephalomyelitis</td>
<td>36 (1717)</td>
<td>123 (1152)</td>
<td>438</td>
<td>7224</td>
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<td>Transgenic models of AD</td>
<td>207</td>
<td>612</td>
<td>1794</td>
<td>22000</td>
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<td>Parkinson’s Disease</td>
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<td>Spinal Cord Injury</td>
<td>34</td>
<td>69</td>
<td>331</td>
<td>3596</td>
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<tr>
<td>Total</td>
<td>2543</td>
<td>4712</td>
<td>59402</td>
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</table>
Estimates of affinity at cannabinoid receptors

McPartland et al. 2007
What causes EAE?

<table>
<thead>
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<tr>
<td>+</td>
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<tr>
<td></td>
<td>+</td>
<td>2</td>
<td>+</td>
<td>2</td>
</tr>
</tbody>
</table>
• Metrics of Research Quality
  – Does Journal Impact Factor reflect study quality?

\[
JIF = 3.7 + 2.4 \text{ (Conflict of Interest statement)} + 1.2 \text{ (Blinded Induction of ischaemia)}
\]

465 publications: adjusted \( r^2 = 0.06 \)
CAMARADES
Bringing evidence to translational medicine

• Most animal studies can’t even tell you what happened in the animals
  – Underpowered
  – Poor internal validity
  – Publication bias

• Functional (Neurobehavioural) outcome is not so different from structural (infarct size) outcome

• Judging from journal impact factors, scientists can’t tell the difference between high quality studies and low quality studies
Un Canard
CAMARADES: Bringing evidence to translational medicine
Un canard mort
CAMARADES: Bringing evidence to translational medicine
Quality of Translation

**tPA and tirilazad**

- Both appear to work in animals
- tPA works in humans but tirilazad doesn’t
- Time to treatment: tPA:
  - Animals – median 90 minutes
  - Clinical trial – median 90 minutes
- Time to treatment: tirilazad
  - Animals – median 10 minutes
  - Clinical trial - >3 hrs for >75% of patients
tPA: Effect of time to treatment on efficacy

Animal Studies

Clinical Studies

% Reduction in Infarct Volume

Odds of a good outcome

Delay to treatment

CAMARADES: Bringing evidence to translational medicine
AstraZeneca Announces SAINT II Trial Results Showed No Efficacy in Acute Ischaemic Stroke

Results from the SAINT II (Stroke Acute Ischemic NXY-059 Treatment) trial, announced today by AstraZeneca, showed that the investigational drug NXY-059 did not meet its primary outcome of a statistically significant reduction in stroke-related disability, as assessed by the modified Rankin Scale (mRS) (p=0.33, odds ratio 0.94) compared to placebo.

Subgroup analyses, including time to treatment, did not demonstrate a treatment benefit.

In addition, NXY-059 did not cause a statistically significant improvement in neurological status versus placebo on the National Institutes of Health Stroke Scale (NIHSS) (p=0.70).
What is a neuroprotective drug worth?

• Current market capitalisation
  – £31.98bn

• Current Market Price
  – £21.95
  ❄️ ❄️ approx 15 million shares

• Price fell from £35.29 to £31.52 in first week
  ❄️ ❄️ Market valuation of neuroprotective efficacy is approximately £5.5bn
What forces drive bias?