Evidence-based translational medicine: connecting basic and clinical research

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University of Edinburgh
Disclosures

• **PCI Registered Reports** (co-founder/managing board)

  - [Peer Community In](#) Free and transparent pre- and post-study recommendations across research fields

• CZI Open Science Advisory Board (receive honorarium)

• I applied (& will continue to) and have received grant funding for this research
My perspective
The challenge of finding a path
Hypotheses

• In the life sciences there are perverse incentives (publication, funding, promotion) to produce positive results with little attention paid to their validity

• In the use of animal disease models, pressure to reduce the number of animals (cost, time, ethics, feasibility) results in studies either being underpowered or of unknown power

• These factors combine to compromise the utility of animal models and contribute to translational failure
What is translational failure?

In vitro and in vivo - 1026
Tested in vivo - 603
Effective in vivo - 374
Tested in clinical trial - 97
Effective in clinical trial - 1

O’ Collins et al, 2006
CAMARADES: Bringing evidence to translational medicine

Why do we do meta-analysis of animal studies?

• Preclinical studies are often performed with the purpose of improving human health

• Used in preclinical research to:
  – assess the quality and range of evidence
  – identify gaps in the field
  – assess for publication bias
  – try to explain discrepancies between preclinical and clinical trial results
  – inform clinical trial design

• Fundamental differences:
  – Many small (10s) animal studies
  – Fewer large (100s/1000s) clinical trials
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
- Investigating the sources behind this variation may be helpful in translation

Hypothermia: a systematic search identified 222 experiments in 3353 animals

Van der Worp et al. Brain 2007
Some potential sources of bias
You can usually find what you’re looking for ...

- 12 graduate psychology students
- 5 day experiment: rats in T maze with dark arm alternating at random, and the dark arm always reinforced
- 2 groups – “Maze Bright” and “Maze dull”

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Maze bright”</td>
<td>1.33</td>
<td>1.60</td>
<td>2.60</td>
<td>2.83</td>
<td>3.26</td>
</tr>
<tr>
<td>“Maze dull”</td>
<td>0.72</td>
<td>1.10</td>
<td>2.23</td>
<td>1.83</td>
<td>1.83</td>
</tr>
<tr>
<td>Δ</td>
<td>+0.60</td>
<td>+0.50</td>
<td>+0.37</td>
<td>+1.00</td>
<td>+1.43</td>
</tr>
</tbody>
</table>

Rosenthal and Fode (1963), Behav Sci 8, 183-9
Bias is prevalent and important

<table>
<thead>
<tr>
<th>Disease</th>
<th>Randomisation</th>
<th>Blinded Outcome Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>36%</td>
<td>29%</td>
</tr>
<tr>
<td>MND</td>
<td>31%</td>
<td>20%</td>
</tr>
<tr>
<td>AD</td>
<td>15%</td>
<td>25%</td>
</tr>
<tr>
<td>PD</td>
<td>12%</td>
<td>15%</td>
</tr>
<tr>
<td>EAE</td>
<td>8%</td>
<td>15%</td>
</tr>
<tr>
<td>Glioma</td>
<td>14%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Sena et al TiNS 2007
Things are improving


CAMARADES: Bringing evidence to translational medicine
The standardisation fallacy

• Efforts to increase reproducibility by reducing variation by standardisation of:
  – lab environment
  – tests used
  – genetics of the animals

• Increases the risk of detecting effects with **low external validity** (or of missing effects with high external validity)

Voekl (2016) PLOS Biology

“Nuisance” variable
Reproducibility of preclinical animal research improves with heterogeneity of study samples

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² Centre for Clinical Brain Sciences, Chancellor Building, University of Edinburgh, Edinburgh, United Kingdom
Time to Treatment in EAE

- Median: 0 days (IQR -11 to 4)
- 1% did not report time of administration

<p>| | |</p>
<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Before EAE</td>
<td>48%</td>
</tr>
<tr>
<td>Day of Induction</td>
<td>22%</td>
</tr>
<tr>
<td>After EAE</td>
<td>30%</td>
</tr>
<tr>
<td>Day of Symptom Onset</td>
<td>2%</td>
</tr>
</tbody>
</table>
The umbrella of reporting bias

Not all outcomes and *a priori* analyses are reported

- **Publication bias**
  - Neutral and *negative* studies
  - Time lag/remain unpublished
  - Less likely to be identified

- **p-hacking**
  - Selective analysis
  - Selective outcome reporting
• Overall efficacy was reduced from;
  – 32% (95% CI 30 to 34%) to 26% (95% CI 24 to 28%)
• 16% of experiments remain unpublished
The problem.....

- The reproducibility, replicability, and reliability of biomedical research is under threat.
- If research results are non-replicable, then:
  - scientific progress is stalled
  - research cannot be translated into clinical applications
  - time and money are wasted
  - the public loses trust in scientific findings
  - capable and talented early career researchers are disillusioned and leave the field.
Ideally............

• Studies will benefit from strategies that facilitate:
  – Robust design
    • Internal validity/robustness
  – Collaborative studies
    • External validity
  – Clarity of how studies were performed
    • Robustness/replication
  – Confirmation that studies report what they set out to do
    • Reporting biases
  – Access to data that can be used and compared efficiently
    • Robustness/replication
Improvement strategies

- Design
  - EDA
  - Multi-centre studies
  - Statistical input
- Conduct

The Experimental Design Assistant - EDA

Click here to access the EDA
Improvement strategies

PRECLINICALTRIALS.EU
International register of preclinical trial protocols

About Animal Study Registry

Animal Study Registry is an online registry for scientific studies involving animals conducted around the world. It is operated by the German Centre for the Protection of Laboratory Animals (BfAL) at the German Federal Institute for Risk Assessment (BfR). All registrations are voluntary and free of charge. We strongly believe that our Animal Study Registry will enhance the reproducibility of in vivo biomedical studies and improve the quality of biomedical research by:

Open Science Framework
A scholarly commons to connect the entire research cycle
Improvement strategies

- Reporting
  - Guidelines (ARRIVE, CONSORT etc)
  - Publication policies

- Publication
  - Support new models (data, registered reports)
  - Encourage rapid publication anywhere, not vanity publishing in journals of the highest “impact” .... preprints
Allow others to check your work

- Data should be available

- Undocumented data dumps
  - No quality control
  - Often not linked to original study
  - How to re-analyse?
Who did what?

<table>
<thead>
<tr>
<th>Contributor Role</th>
<th>Resources</th>
</tr>
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<tbody>
<tr>
<td>Conceptualization</td>
<td>Resources</td>
</tr>
<tr>
<td>Data Curation</td>
<td>Software</td>
</tr>
<tr>
<td>Formal Analysis</td>
<td>Supervision</td>
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<tr>
<td>Funding Acquisition</td>
<td>Validation</td>
</tr>
<tr>
<td>Investigation</td>
<td>Visualization</td>
</tr>
<tr>
<td>Methodology</td>
<td>Writing – Original Draft Preparation</td>
</tr>
<tr>
<td>Project Administration</td>
<td>Writing – Review &amp; Editing</td>
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</table>
To bring evidence to translational medicine

• Primary research reports include
  – Information that allows the reliability of the findings to be assessed
  – Methodological details that describe how the study was done, and allow the methods to be reproduced
  – Research context and relevance that helps with the interpretation of the findings
  – Meta-data information that allows studies to be identified, and be used to their full potential in retrospective studies
  – Clarity on what the researchers set out to do
What we know

• *In vivo* studies which do not report simple measures to avoid bias give larger estimates of treatment effects
• Most do not report simple measures to reduce bias
• Reporting biases are important and prevalent
• Most *in vivo* research is underpowered (or of unknown power)
• All stakeholders have a role to play
• You can only find these things out by studying large numbers of studies
• Help is at hand but improvement strategies must be tested
• Any experimental design can be subverted; what’s important is knowing how to recognise when this has happened
Thanks to...........