Multi-PART
(Multicentre Preclinical Animal Research Team)

Emily S Sena
Multi-PART

An international collaborative approach to overcoming the translational roadblock in neuroprotection and neuroregeneration research
1,026 Experimental Treatments in Acute Stroke

Victoria E. O’Collins, B.Sci,¹ Malcolm R. Macleod, MRCP, PhD,³ Geoffrey A. Donnan, MD, FRACP,² Laura L. Horky, MD, PhD,² Bart H. van der Worp, MD, PhD,⁴ and David W. Howells, PhD¹

Ann Neurol 2006;59:467-477

Tested in experiments

CAMARADES: Bringing evidence to translational medicine
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Effective in focal ischaemia

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Effective in clinical trial

CAMARADES: Bringing evidence to translational medicine
Hypotheses

• That potential compromises in animal models contributes to translational failure
  – In the life sciences there are perverse incentives (publication, funding, promotion) to produce positive results with little attention paid to their validity
  – Leads to a body of evidence with an inflated proportion of published studies with statistically significant results
Potential sources of bias in animal studies

• Internal validity

<table>
<thead>
<tr>
<th>Problem</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection Bias</td>
<td>Randomisation</td>
</tr>
<tr>
<td>Performance Bias</td>
<td>Allocation Concealment</td>
</tr>
<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
  – Are the models we use good models?
  – Publication bias
CAMARADES

• **Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies**

• Look systematically across the modelling of a range of conditions

• Data Repository
  – 7 Neurological Diseases
  – 2500 studies
  – 4700 *in vivo* experiments
  – from over 60,000 animals
## Internal Validity

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Number of Publications</th>
<th>Sample Size Calculation (%)</th>
<th>Random Allocation to Group (%)</th>
<th>Blinded conduct of experiment (%)</th>
<th>Blinded Assessment of Outcome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NXY-059</td>
<td>9</td>
<td>22</td>
<td>33</td>
<td>56</td>
<td>44</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>101</td>
<td>0</td>
<td>36</td>
<td>4</td>
<td>38</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>19</td>
<td>0</td>
<td>37</td>
<td>21</td>
<td>42</td>
</tr>
<tr>
<td>Tirilazad</td>
<td>18</td>
<td>0</td>
<td>67</td>
<td>6</td>
<td>72</td>
</tr>
<tr>
<td>tPA</td>
<td>113</td>
<td>7</td>
<td>37</td>
<td>20</td>
<td>21</td>
</tr>
</tbody>
</table>
Internal Validity: Lessons from NXY-059

- Infarct Volume
  - 11 publications, 29 experiments, 408 animals
  - Improved outcome by 44% (35-53%)

Efficacy

Randomisation

Blinded conduct of experiment

Blinded assessment of outcome
Sample Size:
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>
</thead>
<tbody>
<tr>
<td>4</td>
<td>18.6%</td>
<td>81.4%</td>
</tr>
<tr>
<td>8</td>
<td>32.3%</td>
<td>67.7%</td>
</tr>
<tr>
<td>16</td>
<td>56.4%</td>
<td>43.6%</td>
</tr>
<tr>
<td>32</td>
<td>85.1%</td>
<td>14.9%</td>
</tr>
</tbody>
</table>
Chances of wasting an animal

![Graph showing the relationship between the number of animals per group and the percentage of animals wasted. The graph indicates a decrease in the percentage of animals wasted as the number of animals per group increases.]
External Validity
Hypertension in studies of tPA in experimental stroke

- High prevalence of hypertension in patients with stroke
- tPA is substantially less effective in hypertensive animals
External Validity

Hypertension in studies of NXY-059 in experimental stroke

Hypertension:
- 7% of animal studies
- 77% of patients in the (neutral) SAINT II study

Macleod et al Stroke 2008
External Validity
Time to treatment: a tale of two drugs

- Both appear to work in animals
- tPA works in humans but tirilazad doesn’t

Time to treatment in animal studies:
- Tirilazad – median 10 minutes
- tPA – median 90 minutes

Time to treatment in clinical trials:
- Tirilazad – >3 hrs for >75% of patients
- tPA – median 90 minutes

Perel et al BMJ 2007

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Publication Bias

• Neutral and negative studies
  – remain unpublished
  – less likely to be identified in systematic review
  – leads to the overstatement of efficacy in meta-analysis.
Publication Bias in Reports of Animal Stroke Studies Leads to Major Overstatement of Efficacy

Emily S. Sena\textsuperscript{1,2,3}, H. Bart van der Worp\textsuperscript{4}, Philip M. W. Bath\textsuperscript{5}, David W. Howells\textsuperscript{2,3}, Malcolm R. Macleod\textsuperscript{1,6*}
Publication bias in experimental stroke

- Trim and Fill suggested 16% of experiments remain unpublished
- Best estimate of magnitude of problem
  - Overstatement of efficacy 31%
- Only 2% publications reported no significant treatment effects
How do models of neurological disorders compare?

<table>
<thead>
<tr>
<th></th>
<th>Randomisation</th>
<th>Blinded Outcome Assessment</th>
<th>Sample Size calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>36%</td>
<td>29%</td>
<td>3%</td>
</tr>
<tr>
<td>MND</td>
<td>31%</td>
<td>20%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>AD</td>
<td>15%</td>
<td>25%</td>
<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>

Sena et al TiNS 2007

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Hypotheses

• That potential compromises in animal models contributes to translational failure
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What happens …

• Small (underpowered), poorly conducted (randomisation, blinding) studies reach spurious (falsely positive) conclusions but are published because they are seen to be “interesting”.

• Small (perhaps) poorly conducted (sometimes) studies not reaching the same conclusions are not published.

• Some investigators become conditioned by the apparent success that comes from conducting small underpowered studies.
What should we do?

• Be rigorous in demanding the highest quality standards in the conduct and reporting of studies
• Develop model specific GLP guidelines
• Develop a registry of animal studies to prevent unnecessary replication
• Where effect sizes are small (preclinical testing), develop tools for multicentre animal studies
## Differences between animal and human studies

<table>
<thead>
<tr>
<th>Centres</th>
<th>Animal/ pre-clinical studies</th>
<th>Clinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Centres</strong></td>
<td>Many single-centre studies</td>
<td>1 or 2 large multicentre trials</td>
</tr>
<tr>
<td><strong>Staff</strong></td>
<td>Academic/laboratory</td>
<td>Academic/clinical</td>
</tr>
<tr>
<td><strong>Dose response</strong></td>
<td>Variable</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Time response</strong></td>
<td>Variable – most look early</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Functional outcome</strong></td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>Sacrificed but deaths not reported</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>Small (10s)</td>
<td>Large (100s, 1000s)</td>
</tr>
<tr>
<td><strong>Publication bias</strong></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Data sharing</strong></td>
<td>Limited</td>
<td>Moderately Common</td>
</tr>
<tr>
<td><strong>Regulatory involvement</strong></td>
<td>Minimal</td>
<td>Considerable</td>
</tr>
<tr>
<td><strong>Ethics</strong></td>
<td>Common (often institutional)</td>
<td>Common (often external)</td>
</tr>
</tbody>
</table>
The place of multicentre studies in the pipeline

• It is neither appropriate nor desirable that every *in vivo* study be conducted as part of a multicentre programme

• Hypothesis-generating/testing experiments can and should remain as single-centre studies

• For confirming efficacy in robust and intensively monitored experiments with transparent analysis and reporting.
Potential Financial Impact

- Current cost to develop a successful stroke drug is around €11bn
- A more robust estimate of efficacy in *in vivo* studies are likely to lead to a reduction in the number of compounds taken to clinical trial.
- Economic modelling suggests that the impact of multicentre animal studies in stroke is likely to be a reduction in the total costs of developing an effective new treatment of around 20%
Has this been done before?

In the 80s US National Heart, Lung and Blood
• 5 study sites
• Verapamil & Ibuprofen in myocardial infarction
• One site found large and significant results
• Statistical analysis found inconsistencies
  • between left ventricular weight and body weight
  • Collateral blood flow and infarct size
• Data fabrication/fraud

Figure 1A  Ventricle weight versus dog weight, sites A and B.

Figure 1B  Ventricle weight versus dog weight, sites C and D.
Funding

Support Action

€497,781
24 months
1st Sept 2013

12 Participants, 7 countries, 11 Academic Institutions and 1 SME

- Edinburgh
- Florey
- Manchester
- Berlin
- Utrecht
- Barcelona x2
- Caen
- Bern
- Glasgow
- Nottingham
- SANISYS

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Purpose

Through a “worked example” of animal modelling of ischaemic stroke, we will define the elements of a successful multicentre animal trial and describe the tools (technical, regulatory, organisational) that will allow such studies to be conducted.

This will inform the design and conduct of adequately powered multicentre animal studies with improved internal and external validity, not just in stroke but also for other disease models.
Each work package will be jointly led by an individual with expertise in the theme and an *in vivo* practitioner who can ensure the practicality of solutions developed.
WP1

- Defining the requirements for study sites
- Establishing a framework for recruiting and approving new sites
- Development of training materials to support the accession of new sites
- Develop a framework for financial management of multicentre studies.
- Development of a framework to attribute intellectual property arising from multicentre studies
- Development of a data dissemination strategy
- Establishment of a Consortium agreement
WP2

• Establish
  • a core set of rodent stroke models
  • a standard operating procedure for designing the structure of a study protocol
  • a system for monitoring standards of laboratory practice and compliance with the protocol and quality control
  • the structure, remit, membership and powers for a study “Data monitoring committee”
  • the structure, membership, remit and powers for a preclinical trial Steering Committee and the mechanism for initiating and approving preclinical stroke studies
  • a process for information and knowledge exchange relating to each therapy to be investigated
WP3

- Protocols for:
  - Centralised randomisation
  - Restricted randomisation strategies – blocking, stratification, and factorial designs
  - Blinding – treatment and outcome assessment
  - Sample size calculations
  - Systematic variation and external validity
WP4  Regulation and ethics

- Identify relevant regulatory authorities across countries
- Examine existing ethical approval processes across participating countries
- Establish ethical review process for Multi-PART studies
- Explore the potential to establish a single point of contact and approval for preclinical studies
- Explore the role of other regulatory bodies
WP5

- Specification of web based trial management system
- Specification of information resource for tracking site management and approvals
- Specification for central randomisation service
- Specification for data management system
- Development of web based pilot data management system
- Testing of outcome adjudication system with real data
WP6

- Establishment of data sets for statistical development
- Adjustment of primary analysis for baseline covariates
- Influence of considering death in assessment of outcome
- Interim analyses
- Sample size calculations
- Central statistical monitoring
- Development of protocol for multi-rater assessment of structural and functional outcomes
- Creation of statistical analysis guide
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WP1
Project management, training and dissemination

WP2
Scientific Coordination

WP3
Experimental design

WP4
Regulation & ethics

WP5
Data management

WP6
Statistical analyses
Meetings

Across the two years:

• an initial start-up meeting,
• a series of WP themed meetings
• and a final consolidation meeting.

• Themed meetings will be open to all participants and attended by other relevant stakeholders depending on subject and expertise.
• WP meetings will consist of three face-to-face meetings (every 6 months) and eight teleconferences (every 2 months).
• Each WP lead will be supported by a postdoctoral researcher to support work in pursuit of deliverables
Thanks to.........

• The Multi-PART Team
• CAMARADES

www.multi-part.org