What is 'bench to bedside translation'? What is 'translational medicine'? How is 'translation' done?
What is translational medicine?
From drug discovery to implementation into routine treatment
Do we have problem?
Let's get this out of the way: Translation does work!
The Göttingen EPO trial as case study
Quality in experimental research
The phases of the drug R&D process
After Type I translation comes Type II translation!
Monetization of intelectual property as key to translation?
From drug discovery to routine treatment
Phases of the drug R&D process

- Discovery
- Pre-clinical
- Phase I
- Phase II
- Phase III
- Approval
- Implementation
Life cycle of translational research for medical interventions

<table>
<thead>
<tr>
<th>ID</th>
<th>Intervention (earliest intervention in same class)</th>
<th>1990</th>
<th>1995</th>
<th>2000</th>
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<tbody>
<tr>
<td></td>
<td>Refuted, nonrandomized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Inhaled nitric oxide</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>29</td>
<td>Flavonoids</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>6</td>
<td>Postmenopausal HRT</td>
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<tr>
<td>14</td>
<td>Vitamin E</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Refuted, randomized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Vitamin E</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Endarterectomy-carotid</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>9</td>
<td>Angioplasty-coronary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Zidovudine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Stem-coronary</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>10</td>
<td>rt-PA (Streptokinase)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>26</td>
<td>Ramipril (Captopril)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>HA-1A (Abs to endotoxin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonrefuted, nonrandomized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Oral retinoic acid</td>
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<td>Spironolactone</td>
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<td>Zidovudine</td>
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<td>32</td>
<td>Tamoxifen</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>Levamisole with fluorouracil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Ribavirin with interferon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Captopril</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Captopril</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Enalapril (Captopril)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Bisoprolol (Metoprolol)</td>
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<tr>
<td>21</td>
<td>Carvedilol (Metoprolol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Lovastatin (Mevastatin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Piexavastatin (Mevastatin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Piexavastatin (Mevastatin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Simvastatin (Mevastatin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Clopidogrel (ticlopidine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Abciximab (murine GPIIb/IIIa Mo Ab)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Indinavir in triple therapy (Saquinavir)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **First description of intervention class**
- **First description of intervention**
- **First article about human use**
- **First article on specific human use**
- **Highly cited article**
- **Partially or fully refuted**
The regulators:
Approval (FDA; EMEA)
Evidence based medicine (EBM)

- Level I: Evidence obtained from at least one properly designed randomized controlled trial.
- Level II-1: Evidence obtained from well-designed controlled trials without randomization.
- Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
- Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
The problem
(Translation type I)
Not your problem, but there is a roadblock even further down the road....

Discovery → Pre-clinical → Phase I → Phase II → Phase III → Approval → Implementation

Type-2 Translation (Implementation)
A typical intervention in exp. stroke studies reduces infarct sizes by 30-50%.

Neuroregenerative strategies (eg. ‘stem cells’) improve functional outcome even after infarct maturation.
1026 interventions in experimental stroke

Developed in *in vitro* and *in vivo* experiments

O’ Collins et al, 2006
1026 interventions in experimental stroke

Tested in focal ischaemia

O’ Collins et al, 2006
Effective in focal ischaemia

O’Collins et al, 2006
1026 interventions in experimental stroke

Tested in clinical trial

97

O’ Collins et al, 2006
1026 interventions in experimental stroke

Effective in clinical trial

O’ Collins et al, 2006
I.v. thrombolysis is the only clinically proven pharmacological therapy of acute ischemic stroke. Benefit only to a small percentage of stroke victims. There is no therapeutic 'neuroregeneration' in human stroke.
A 'nuclear winter' for translational (stroke) research?
The stock market as indicator of the success of translational stroke research

SAINT II (Astra Zeneca)

DIAS-2 (PAION)
Comments and Opinions

Found in Translation
Preclinical Stroke Research Predicts Human Pathophysiology, Clinical Phenotypes, and Therapeutic Outcomes

Ulrich Dirnagl, MD; Matthias Endres, MD

Stroke. 2014;45:1510-1518
Tissue Plasminogen Activator Reduces Neurological Damage After Cerebral Embolism

Abstract. Intravenous administration of tissue plasminogen activator immediately after the injection of numerous small blood clots into the carotid circulation embolic stroke model animals caused a significant reduction in neurological damage. In vitro studies indicate that tissue plasminogen activator produced by the initial clot thrombosis and embolism is treatable by thrombolytic therapy. Thus, it is reasonable to consider that intravenous injection of thrombolytic activator may be a feasible treatment of embolic stroke induced by intravenous injection of clot material. It demonstrates that 50 percent of the animals injected with 45.5 mg of clot will be normal or dead at 24 hours after the injection of clot. The curves on the left shows the fraction of control animals damaged by varying doses of clot material. It demonstrates that 50 percent of the animals injected with 45.5 mg of clot will be normal or dead at 24 hours after the injection of clot. The curves on the right indicates that, if FTA is injected intravenously after the injection of clot by the schedule indicated in the text, the weight of clot can be increased to 75.7 mg before 50 percent of the treated animals suffer neurological damage or death. The horizontal bar on each curve indicates the standard error of the ED50. The data plotted here are presented in Table 1.

Fig. 1. Percentage of animals dead or severely damaged neurologically as a function of the weight of clots injected into the carotid artery system. The curve on the left shows the fraction of control animals damaged by varying doses of clot material. It demonstrates that 50 percent of the animals injected with 45.5 mg of clot will be normal or dead at 24 hours after the injection of clot. The curves on the right indicates that, if FTA is injected intravenously after the injection of clot by the schedule indicated in the text, the weight of clot can be increased to 75.7 mg before 50 percent of the treated animals suffer neurological damage or death. The horizontal bar on each curve indicates the standard error of the ED50. The data plotted here are presented in Table 1.
Time window for rt-PA thrombolysis

**Rodent**

Metaanalysis, > 3000 animals

**Man**

Immunodepression after stroke

**Lymphocytes**

<table>
<thead>
<tr>
<th>Time after MCAO</th>
<th>Cell count (Mpt/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham 14h</td>
<td>2.5</td>
</tr>
<tr>
<td>14h</td>
<td>0</td>
</tr>
<tr>
<td>2d</td>
<td>0.8</td>
</tr>
<tr>
<td>5d</td>
<td>1.2</td>
</tr>
<tr>
<td>14d</td>
<td>2.5</td>
</tr>
<tr>
<td>42d</td>
<td>7.5</td>
</tr>
</tbody>
</table>

**Monocytes**

<table>
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<tr>
<th>Time after MCAO</th>
<th>Cell count (Mpt/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham 14h</td>
<td>0</td>
</tr>
<tr>
<td>14h</td>
<td>0.4</td>
</tr>
<tr>
<td>2d</td>
<td>0.8</td>
</tr>
<tr>
<td>5d</td>
<td>1.2</td>
</tr>
<tr>
<td>14d</td>
<td>2.5</td>
</tr>
<tr>
<td>42d</td>
<td>7.5</td>
</tr>
</tbody>
</table>

**Figures**

- **e**: CD4+ T cells gpt/l
  - control: 1.0
  - d0: 0.5
  - d1: 1.0
  - d7: 1.5
  - d14: 2.0

- **g**: monocytes mpt/l
  - control: 500
  - d0: 1000
  - d1: 1500
  - d7: 2000
  - d14: 1500

References:

- Vogelgesang et al. Stroke 2007
Infection (and mortality) after stroke

**Mouse**


![Graph showing number of animals over days post MCAO](graph.png)

**Table 2. Incidence of infections in ITT and PP population**

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>No infection n [%]</th>
<th>Infection n [%]</th>
<th>Sum n</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>27 [67.5]</td>
<td>13 [32.5]</td>
<td>40</td>
</tr>
<tr>
<td>Verum</td>
<td>33 [84.6]</td>
<td>6 [15.4]</td>
<td>39</td>
</tr>
<tr>
<td>Sum</td>
<td>60 [75.9]</td>
<td>19 [24.1]</td>
<td>79</td>
</tr>
<tr>
<td>PP population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>18 [58.1]</td>
<td>13 [41.9]</td>
<td>31</td>
</tr>
<tr>
<td>Verum</td>
<td>29 [43.9]</td>
<td>6 [17.1]</td>
<td>35</td>
</tr>
<tr>
<td>Sum</td>
<td>47 [71.2]</td>
<td>19 [28.8]</td>
<td>66</td>
</tr>
</tbody>
</table>

**Man**

*Nat Neurosci Rev 2005 Plos One 2008*

*Escherichia coli Pneumonia*

preventive antibacterial therapy in stroke
Posthoc 'prediction' of failed trials

Use of anti-ICAM-1 therapy in ischemic stroke
Results of the Enlimomab Acute Stroke Trial

Enlimomab Acute Stroke Trial Investigators*

Examination of Several Potential Mechanisms for the Negative Outcome in a Clinical Stroke Trial of Enlimomab, a Murine Anti-Human Intercellular Adhesion Molecule-1 Antibody
A Bedside-to-Bench Study

Kazuhide Funuya, MD; Hidetaka Takeda, MD, PhD; Salman Azhar, MD; Richard M. McCarron, PhD; Yong Chen, MD, PhD; Christl A. Ruetzler, BA; Karen M. Wolcott, BS; Thomas J. DeGraba, MD; Robert Rothlein, PhD; Tony E. Hugli, PhD; Gregory J. del Zoppo, MD; John M. Hallenbeck, MD

Figure 2. Patient survival in the first 90 days.

Neurology. 2001; 57:1428-34
If translation is possible in principle, why have we not succeeded in neuroprotection?
Effect size inversely correlates with study quality

- Treatment with NXY-059. Outcome: Infarct Volume
  - 11 publications, 29 experiments, 408 animals
  - Improved outcome by 44% (35-53%)

(Stroke 2008; 39:2824-9.)
Lessons from other neuroscience domains

**Multiple Sclerosis**

- **A**
  - Y-axis: Effect Size (% Improvement in Neurobehavioural Score)
  - X-axis: Random Allocation to Group
  - Comparison between No and Yes conditions.

- **B**
  - Y-axis: Effect Size (% Improvement in Neurobehavioural Score)
  - X-axis: Blinded Assessment of Outcome
  - Comparison between No and Yes conditions.

**Alzheimer’s disease**

- **A**
  - Y-axis: Improvement in behavioural outcome (Standardised Effect Size)
  - X-axis: Blinded assessment of behavioural outcome
  - Comparison between No and Yes conditions.

**Parkinson’s disease**

- **A**
  - Y-axis: Improvement in Neurobehavioural Score (SD)
  - X-axis: Various assessments (e.g., Spontaneous Activity, Skilled Motor Activity, Limb Asymmetry, Parkinson’s Disability Rating, Balance and Gait)
  - Comparison of improvement in different conditions (Yes vs. No)
Risk of bias in in vivo research

<table>
<thead>
<tr>
<th>Disease modelled</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>Alzheimer's Disease</td>
<td>428</td>
<td>0</td>
<td>16</td>
<td>n/a</td>
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<td>Multiple Sclerosis</td>
<td>1117</td>
<td>&lt;1</td>
<td>9</td>
<td>n/a</td>
<td>16</td>
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<td>Parkinson's Disease</td>
<td>252</td>
<td>&lt;1</td>
<td>16</td>
<td>n/a</td>
<td>15</td>
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<tr>
<td>Intracerebral Haemorrhage</td>
<td>88</td>
<td>0</td>
<td>31</td>
<td>8</td>
<td>49</td>
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<tr>
<td>Pain</td>
<td>160</td>
<td>0</td>
<td>12</td>
<td>n/a</td>
<td>26</td>
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<tr>
<td>NXY 059</td>
<td>9</td>
<td>22</td>
<td>33</td>
<td>56</td>
<td>44</td>
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<tr>
<td>Hypothermia</td>
<td>101</td>
<td>0</td>
<td>36</td>
<td>4</td>
<td>38</td>
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<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>
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<tr>
<td>Alteplase</td>
<td>113</td>
<td>7</td>
<td>37</td>
<td>20</td>
<td>21</td>
</tr>
</tbody>
</table>
Internal validity of preclinical studies is low

- Selection bias (creating groups with different confounders; solved by randomization)
- Performance bias and detection bias (investigators respectively treating or assessing more positively those subjects on the treatment arm; controlled by blinding interventions and outcome assessments)
- Attrition bias (dropouts of subjects with a negative outcome not included in the final result, controlled by predefined in- and exclusion criteria)

Dirnagl and Endres (2014) Stroke, 2014;45:1510-1518
External validity of experimental (stroke) studies is low

Healthy, pubertal male twins raised in 6 m² isolator tents on an enriched granola diet

vs.

Patients of both sexes, elderly, comorbid, multiple medications, exposed to multiple pathogens and antigens throughout life
Publication bias is highly prevalent (present in the literature describing the efficacy of at least 16 of 18 interventions) and accounts for around 30% of the reported efficacy of candidate neuroprotective interventions."
Preclinical stroke research: A game of *chance*!

The typical stroke study reports infarct reductions of approx. 30 % and SDs of 30 % of the mean (standardized effect size =1). Results are obtained from 5-10 animals per group.

Power: 0.28 - 0.56

Power of throwing a coin: 0.5

Exceedingly low power / positive predictive value!
Power failure: Sample sizes in neuroscience (and exp. stroke research) are exceedingly low

Figure 4 | Positive predictive value as a function of the pre-study odds of association for different levels of statistical power.
Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies factors that influence this problem and some corollaries thereof.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the
<table>
<thead>
<tr>
<th>Disease</th>
<th>n</th>
<th>Observed positive</th>
<th>Expected positive</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>All</td>
<td>4445</td>
<td>1719</td>
<td>919</td>
<td>&lt;1 \cdot 10^{-9}</td>
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<tr>
<td>Alzheimer’s</td>
<td>1054</td>
<td>418</td>
<td>86·4</td>
<td>&lt;1 \cdot 10^{-9}</td>
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<tr>
<td>EAE</td>
<td>483</td>
<td>212</td>
<td>131</td>
<td>&lt;1 \cdot 10^{-9}</td>
</tr>
<tr>
<td>Focal ischemia</td>
<td>1403</td>
<td>626</td>
<td>370</td>
<td>&lt;1 \cdot 10^{-9}</td>
</tr>
<tr>
<td>ICH</td>
<td>424</td>
<td>145</td>
<td>108</td>
<td>5·6•10^{-5}</td>
</tr>
<tr>
<td>Parkinson’s</td>
<td>873</td>
<td>228</td>
<td>202</td>
<td>0·04</td>
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<tr>
<td>SCI</td>
<td>208</td>
<td>90</td>
<td>21·6</td>
<td>&lt;1 \cdot 10^{-9}</td>
</tr>
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</table>

Tsilidis et al, PLoS Biology, 2014
Facilities of Research Excellence (FORE) in Spinal Cord Injury (SCI) Replication Studies - Request for Information (RFI NS-08-003)

Notice Number: NOT-NS-08-003

Key Dates
Release Date: October 15, 2007

Issued by
National Institute of Neurological Disorders and Stroke (NINDS) (http://www.ninds.nih.gov)

Prinz (Nat Drug Discov Rev´), Begley (Nature), FORE-SCI (Exp. Neurol.) etc.

Table 1: Reproducibility of research findings
Preclinical research generates many secondary publications, even when results cannot be reproduced.

<table>
<thead>
<tr>
<th>Journal impact factor</th>
<th>Number of articles</th>
<th>Mean number of citations of non-reproduced articles</th>
<th>Mean number of citations of reproduced articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20</td>
<td>21</td>
<td>248 (range 3–800)</td>
<td>231 (range 82–519)</td>
</tr>
<tr>
<td>5–19</td>
<td>32</td>
<td>169 (range 6–1,909)</td>
<td>13 (range 3–24)</td>
</tr>
</tbody>
</table>
A Concerted Appeal for International Cooperation in Preclinical Stroke Research

Ulrich Dirnagl, MD; Antoine Hakim, MD; Malcolm Macleod, PhD, FRCP; Marc Fisher, MD; David Howells, BSc, PhD; Stuart M. Alan, PhD; Gary Steinberg, MD, PhD; Anna Planas, PhD; Johannes Boltze, MD, PhD; Sean Savitz, MD; Costantino Iadecola, MD; Stephen Meairs, MD, PhD

Despite dramatic advances in the molecular pathogenesis of disease, translation of basic biomedical research into safe and effective clinical applications remains a slow, expensive, and failure-prone endeavor.

Despite dramatic advances in the molecular pathogenesis of disease, translation of basic biomedical research into safe and effective clinical applications remains a slow, expensive, and failure-prone endeavor.

to recover lost function. Treatment approaches based on this understanding have demonstrated efficacy in a variety of preclinical models of the disease.

However, associated clinical trials have been unable to translate most of these advances into drugs with a clear benefit for patients, leading to the number of new drugs approved for clinical use to be very limited. Although large numbers of drugs have been developed in laboratories and proved to be effective in animal models, very few have translated to effective in patients. The reasons for this failure are still debated, in part affected by the failure to translate from animal studies to clinical practice.

The Editorial in Stroke (2013; 44:1754-60) calls for an increase in cooperation in translational research, specifically suggesting that international, multicenter randomized preclinical trials are needed along with well-designed clinical trials. The authors argue that such approaches are essential for accelerating the translation of basic science to clinical practice, and that international collaboration is crucial for achieving these goals. The editorial is a call to action for the global research community to work together to improve the translation of stroke research from bench to bedside.
Multi-PART
Multicenter Preclinical Animal Research Team

David Howells
University of Melbourne

Malcolm Mackay
University of Edinburgh

L. Mhara Macrae
University of Glasgow

Nathalie Pericel du Sert
UK NC3Rs

Philip Bath
University of Nottingham

Stuart Allan
University of Manchester

Emily Sena
University of Edinburgh

Denis Vivien
University of Caen

Patrick Presl
Sanisys

Uli Dimagli
Charite, Berlin

Anna Planas
Institute for Biomedical Research, Barcelona

Hanno Wuerbel
University of Bern

Joan Montaner
Vall d’Hebron Research Institute, Barcelona

Bart van der Worp
University Medical Centre, Utrecht

www.multi-part.org
A case study: The Göttingen EPO trial
Endogenous neuroprotection: Erythropoietin

\[ \downarrow \text{O}_2 \]

HIF-1\( \alpha \)

EPO-R

PI3K

JAK2

PkB/Akt

BAD

P

Neuron

Astrocyte

Nucleus

mRNA

EPO

Clinical Trial

Erythropoietin Therapy for Acute Stroke Is Both Safe and Beneficial

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rhEPO n=21, Placebo n=19

Fig. 3. Clinical outcome of patients in the efficacy trial. (A) DWI. (B) FLAIR. Data represent mean ± SEM. p-Value according to multiple regression analysis. Dead patients have been censored.
Recombinant Human Erythropoietin in the Treatment of Acute Ischemic Stroke

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Background and Purpose—Numerous preclinical findings and a clinical pilot study suggest that recombinant human erythropoietin (EPO) provides neuroprotection that may be beneficial for the treatment of patients with ischemic stroke. Although EPO has been considered to be a safe and well-tolerated drug over 2 decades, recent studies have identified increased thromboembolic complications and/or mortality risks on EPO administration to patients with cancer or chronic kidney disease. Accordingly, the double-blind, placebo-controlled, randomized German Multicenter EPO Stroke Trial (Phase II/III; ClinicalTrials.gov Identifier: NCT00604630) was designed to evaluate efficacy and safety of EPO in stroke.

Methods—This clinical trial enrolled 522 patients with acute ischemic stroke in the middle cerebral artery territory (intent-to-treat population) with 460 patients treated as planned (per-protocol population). Within 6 hours of symptom onset, at 24 and 48 hours, EPO was infused intravenously (40 000 IU each). Systemic thrombolysis with recombinant tissue plasminogen activator was allowed and stratified for.

Results—Unexpectedly, a very high number of patients received recombinant tissue plasminogen activator (63.4%). On analysis of total intent-to-treat and per-protocol populations, neither primary outcome Barthel Index on Day 90 (P=0.45) nor any of the other outcome parameters showed favorable effects of EPO. There was an overall death rate of 16.4% (n=42 of 256) in the EPO and 9.0% (n=24 of 266) in the placebo group (OR, 1.98; 95% CI, 1.16 to 3.38; P=0.01) without any particular mechanism of death unexpected after stroke.

Conclusions—Based on analysis of total intent-to-treat and per-protocol populations only, this is a negative trial that also raises safety concerns, particularly in patients receiving systemic thrombolysis. (Stroke. 2009;40:e647-e656.)

Key Words: clinical trial ■ hematopoietic growth factor ■ neuroprotection ■ NIHSS ■ rtPA
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To do list

- Improve internal validity (blinding, randomization, ...)
- Improve external validity (aged animals, mixed gender, comorbidities, ...)
- Improve positive predictive value (Power!)
- Replicate
- Use meta-analysis of preclinical studies
- Publish negative findings
- Establish international multicenter 'phase III' type preclinical trials
Monetization and intellectual property: key to the translational process?
Monetary bottlenecks

Discovery ➔ Pre-clinical ➔ Phase I ➔ Phase II ➔ Phase III ➔ Approval ➔ Implementation

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Big pharma  Public funding, foundations...  VC, Pharma  Big pharma  Big pharma, Public funding
- In most fields, without IP an idea, treatment principle, or therapeutic compound is 'lost in translation'. If there is no way to recover the costs incurred in clinical testing, no one will pay for it.

- A large fraction of the results of basic research in the life sciences of Universities enters the public domain via publication (without claiming IP) and is thus lost for translation.

- Paradox: Not claiming IP in many instances may be unethical!
Bayh Dole Act (1980). Permits a university, small business, or non-profit institution to elect to pursue ownership of an invention in preference to the government.

Arbeitnehmer-Erfindergesetz (1957) with Hochschullehrerprivileg (§42) = 'Faculty privilege'. Allowed university employed scientists to act as free inventors. Revoked in 2002.
Why we should stay away from claiming IP

- IP and TT- issues are time consuming and distract from research or patient care.
- IP generates bias towards results that favor monetization, and bias against those that may harm a commercial interest.
- It generates conflicts of interest.
- Disclosure of IP may have negative effects on the review process of papers or grants.
- Risk of publication delay, potential change in publication strategy.
- Society pays for research (via University, DFG, etc.), but by claiming IP (and exclusive licensing) society is excluded.
Stroke mortality rates
(age & sex-adjusted)
Who is UAEM?

Many important medicines and public health technologies are developed in academic laboratories. Their accessibility in poor nations is profoundly affected by the research, patenting and licensing decisions made by universities.

We are a group of university students who believe that our universities have an opportunity and a responsibility to improve global access to public health goods.

Technology transfer metrics

Developing new ways to measure the success of university technology transfer, emphasizing social impact. [Read More]

More UAEM projects

Urgent action needed:

Help us make sure the Canadian government reforms its law to allow export of generic medicines to poor countries! Rachel Kiddell-Monroe to address government committee on October 26—we want the government to hear from you too!

For deutschsprachige Interessierte besuchen Sie gerne auch die Website von UAEM Deutschland unter: http://www.uaem-germany.de

Remembering Our Dear Friend, Sujal Parikh

Share your memories here
Equitable licensing of university (public) IP

“In the Public Interest: Nine Points to Consider in Licensing University Technology”

- Universities should reserve the right to practice licensed inventions, and to allow other nonprofit and governmental organizations to do so.
- Exclusive licenses should be structured in a manner that encourages technology development and use.
- Strive to minimize the licensing of “future improvements.”
- Universities should anticipate and help to manage technology transfer related conflicts of interest.
- Ensure broad access to research tools.
- Enforcement action should be carefully considered.
- Be mindful of export regulations.
- Be mindful of the implications of working with patent aggregators.
- Consider including provisions that address unmet needs, such as those of neglected patient populations or geographic areas, giving particular attention to improved therapeutics, diagnostics, and agricultural technologies for the developing world.

Tackle the problem at its root!

- Public funding of clinical trials on a grand scale. Collect money from stakeholders in the health industry (in particular health insurers). They will be rewarded by less expensive medicines.
- The public should hold the IP, and grant equitable licences (not only to third world countries).
- As a spin off, this may also solve the problem of an overwhelming of the health system by exploding costs.
Bench to beside translation

Reflow of funds for further academic R&D

Biased research
Conflict of interest
Distraction of the researcher and clinican
Un-affordable treatment for many (in particular develop. countries)
Misappropriation of public funding

IP and monetization in academic medicine
Conclusions

• IP is key to translation

• Universities have the responsibility to foster global access to public health goods

• Universities should provide professional IP and TT services

• The public should fund clinical trials and hold IP
- Translational roadblock
- Clinical trial phases I, II, III, regulatory approval
- Translation works in principle
- External and internal validity, bias
- Intellectual property, monetization
- Global perspective

Take home