STAIR
A starting point for evidence-based translational medicine in stroke

David Howells
For the CAMARADES Collaboration
**FDA drug approvals per year**

**Success by class for compounds first tested in man from 1992-04 through to 2009**

<table>
<thead>
<tr>
<th>Therapeutic class</th>
<th>$n$</th>
<th>Approved molecules</th>
<th>Current success rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antineoplastic/immunologic</td>
<td>254</td>
<td>18</td>
<td>7.1</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>134</td>
<td>4</td>
<td>3.0</td>
</tr>
<tr>
<td>CNS</td>
<td>235</td>
<td>9</td>
<td>3.8</td>
</tr>
<tr>
<td>GI/metabolism</td>
<td>120</td>
<td>4</td>
<td>3.3</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>88</td>
<td>8</td>
<td>9.1</td>
</tr>
<tr>
<td>Respiratory</td>
<td>83</td>
<td>4</td>
<td>4.8</td>
</tr>
<tr>
<td>Systemic anti-infective</td>
<td>122</td>
<td>19</td>
<td>15.6</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>189</td>
<td>21</td>
<td>11.1</td>
</tr>
</tbody>
</table>

**Estimates of the cash and capitalized cost of drug development**
From: Morgan et al, Health Policy 100 (2011) 4-17.

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Cash</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-clinical</td>
<td>$46</td>
<td>$111.0</td>
<td>$149.8</td>
<td>$164.7</td>
</tr>
<tr>
<td>Clinical</td>
<td>$46</td>
<td>$81.5</td>
<td>$349.0</td>
<td>$573.0</td>
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<tr>
<td>Total</td>
<td>$92</td>
<td>$192.5</td>
<td>$498.8</td>
<td>$737.7</td>
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<tr>
<td>Capitalized</td>
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<td></td>
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<tr>
<td>Pre-clinical</td>
<td>$89</td>
<td>$263.7</td>
<td>$414.6</td>
<td>$481.9</td>
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<tr>
<td>Clinical</td>
<td>$73</td>
<td>$127.5</td>
<td>$578.0</td>
<td>$964.9</td>
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<tr>
<td>Total</td>
<td>$161</td>
<td>$391.2</td>
<td>$992.6</td>
<td>$1446.8</td>
</tr>
</tbody>
</table>

| Assumptions               |                                 |                     |                           |                                    |
| Success rate              | 12.0%                           | 23.0%               | 21.5%                     | 21.5%                              |
| Cost of capital           | 8.0%                            | 9.0%                | 11.0%                     | 11.5%                              |
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

“STAIR” Scope of testing

1. Laboratory setting: 2+ labs
2. Animal species: 2+ species
3. Health of animals: comorbidities
4. Sex of animals: Male and female
5. Reperfusion: tMCAo and pMCAo models
6. Time window: 1 hour post occlusion +
7. Dose response: 2+ doses
8. Route of delivery: Realistic
9. Functional and histological outcome
10. Long term effect: 4+ weeks
NXY-059 for Acute Ischemic Stroke

Kennedy R. Lees, M.D., Justin A. Zivin, M.D., Tim Ashwood, Ph.D., Antonio Davalos, M.D., Stephen M. Davis, M.D., Hans-Christoph Diener, M.D., James Grotta, M.D., Patrick Lyden, M.D., Ashfaq Shuaib, M.D., Hans-Göran Härdemark, M.D., and Warren W. Wasienski, M.D., for the Stroke–Acute Ischemic NXY Treatment (SAINT I) Trial Investigators*

BACKGROUND

NXY-059 is a free-radical–trapping agent that is neuroprotective in animal models of stroke. We tested whether it would reduce disability in humans after acute ischemic stroke.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial involving 1722 patients with acute ischemic stroke who were randomly assigned to receive a 72-hour infusion of placebo or intravenous NXY-059 within 6 hours after the onset of the stroke. The primary outcome was disability at 90 days, as measured according to scores on the modified Rankin scale for disability (range, 0 to 5, with 0 indicating no residual symptoms and 5 indicating bedbound, requiring constant care).

RESULTS

Among the 1699 subjects included in the efficacy analysis, NXY-059 significantly improved the overall distribution of scores on the modified Rankin scale, as compared with placebo (P = 0.038 by the Cochran–Mantel–Haenszel test). The common odds ratio for improvement across all categories of the scale was 1.20 (95 percent confidence interval, 1.01 to 1.42). Mortality and rates of serious and nonserious adverse events were similar in the two groups. NXY-059 did not improve neurologic functioning as measured according to the National Institutes of Health Stroke Scale (NIHSS): the difference between the two groups in the change from baseline scores was 0.1 point (95 percent confidence interval, −1.4 to 1.1; P = 0.86). Likewise, no improvement was observed according to the Barthel index (P = 0.14). In a post hoc analysis of patients who also received alteplase, NXY-059 was associated with a lower incidence of any hemorrhagic transformation (P = 0.001) and symptomatic intracranial hemorrhage (P = 0.036).

CONCLUSIONS

The administration of NXY-059 within six hours after the onset of acute ischemic stroke significantly improved the primary outcome (reduced disability at 90 days), but it did not significantly improve other outcome measures, including neurologic functioning as measured by the NIHSS score. Additional research is needed to confirm whether NXY-059 is beneficial in ischemic stroke. (ClinicalTrials.gov number, NCT00119626.)

Shuaib et al, NEJM (2007) 357, 562-571

NXY-059 is ineffective for the treatment of acute ischemic stroke within 6 hours after the onset of symptoms. (ClinicalTrials.gov number, NCT00061022.)
Bias & NXY-059

Systematic review and meta-analysis
- 11 publications, 29 experiments, 408 animals
- Improved outcome by 44% (35-53%)

Randomisation
- YES
- NO

Allocation concealment
- YES
- NO

Blinded assessment
- YES
- NO

62% reduction of effect size

Effect size (% improvement over control)

Co-morbidity
- 7% of studies used animals with hypertension
- 77% of patients in SAINT II had a history of hypertension at study entry

446 Neuroprotection Experiments in Sprague Dawley rats

Number of Sprague Dawley rats/cohort

Infarct Volume (mm³)

Experiment Number

Control cohorts

Treatment cohorts

Sprague Dawley
WKY
SHR

Power = 0.8, Alpha = 0.05

Sample size

SD

50% Effect size: 29
30% Effect size: 80
10% Effect size: 715

WKY: 12
SHR: 4

WKY: 33
SHR: 8

WKY: 295
SHR: 80
Selection from 1026 candidates:
- Key target mechanisms;
- Reported efficacy in animal stroke;
- Cost and availability;
- Stability;
- Mode of delivery;
- Safety.

Meta-analysis
Magnesium (Excitotoxicity)
(M=25.9%, 95%CI=23.6-28.1%)

Melatonin (Anti-oxidant)
(M=40.0%, 95%CI=38.0-42.1%)

Minocycline (Anti-inflammatory)
(M=30.6%, 95%CI=28.9-32.3%)

1000 papers randomly retrieved from PubMed

- 55% of articles identified as primary research,
- 32% as reviews,
- 5% as opinion/editorial articles,
- 1% as systematic reviews,
- 7% as other publications.
Good Laboratory Practice
Preventing Introduction of Bias at the Bench
Malcolm M. Macleod; Marc Fisher; Victoria O’Collins; Emily S. Sena; Ulrich Dirnagl; Philip M.W. Bath; Alistair Buchan; H. Bart van der Worp; Richard Traystman; Kazuo Minematsu; Geoffrey A. Donnan; David W. Howells
Scope of pre-clinical evaluation

- Adequate dose-response curve
- Define the time window in a well-characterized model
- Blinded, physiologically controlled reproducible studies
- Histological and functional outcomes assessed acutely and long-term
- Initial rodent studies, then consider gyrencephalic species
- Permanent occlusion then transient in most cases

Recommendations for ensuring good scientific inquiry

- Sample size calculation
- Inclusion and exclusion criteria
- Randomisation
- Allocation concealment
- Reporting of animals excluded from analysis
- Blinded assessment of outcome
- Reporting potential conflicts of interest and study funding
Camarades Collaborators

- Malcolm MacLeod
- Emily Sena
- Gillian Currie
- Hanna Vesterinen
- Peter Sandercock
- Ulrich Dirnagl
- Ana Antonic
- Jennifer Lees
- Kieren Egan
- Simon Koblar
- Verna Aykanat
- Mikael Jerndal
- Kalle Fosberg
- Thomas Linden
- Michael Nilsson
- Philip Bath
- Geoffrey Donnan
Cost of Stroke

Stroke incidence
- Developed world population ~ 1.2bn
- Estimated stroke incidence 300-500 per 100,000
- Conservative estimate = 360,000-600,000/year

Lifetime cost
- 1990 US data suggest ~$100,000
- 2004 Australian data suggest ~$60,000
- 2009 UK data suggest ~$95,000

Annual cost to developed world
- Conservative estimate = $21.6 – $60.0 bn/year

tPA currently helps ~10% of ischemic stroke patients