Brain cooling in acute stroke

SSNF Perth 2015
Developing new treatments for old diseases

**Understand**
- Understand what causes the disease
- Understand which biological processes are pivotal and which are not

**Influence in models**
- Be able to change these processes in experiments
- Be able to change outcome in disease models
- Know your treatment is probably safe

**Prevent in real life**
- Show, in clinical trials, that the treatment changes outcome
- Show that the treatment works in the real world
1026 interventions in experimental stroke

- 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
High blood pressure in animal stroke studies – NXY-059

Hypertension:

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

![Graph showing % Reduction in Infarct Volume for Hypertensive and Normotensive groups, with p < 0.001 significance.]
High blood pressure in animal stroke studies – tPA

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

Hypertension:
- 9% of animal studies
- Specifically exclusion criterion in (positive) NINDS study
Time to treatment in animal stroke studies

• Both tPA and tirilazad 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
Animal Studies

% Reduction in Infarct Volume

Delay to treatment

Clinical Studies

Odds of a good outcome

Delay to treatment
Cooling for stroke

- Cooling seems to work in patients who have brain injury due to cardiac arrest
- There’s lots of stories about individual patients who should have extensive brain damage but don’t
- Many labs use cooling as a positive control in their animal studies
- Preliminary evidence from clinical trials in stroke is encouraging
How to become cool
Evidence based trial design

Experimental Studies

- Systematic review and meta-analysis
  - 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?

Clinical Trial
How powerful is the treatment in animals?

101 publications
222 experiments
3256 animals

43.5% protection (40.1-47.0)
What is the quality of evidence?
What is the quality of evidence?
What is the range of evidence?

sex

Summary

favours hypothermia  favours control

Reduction in Infarct Volume

Mixed  Female  Male  Unknown
What is the range of evidence?

duration of ischaemia
What is the range of evidence?

presence of hypertension
Is there evidence of a publication bias?

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Reported Effect Size (95%CI)</th>
<th>Bias with Egger Regression</th>
<th>Bias with METATRIM</th>
<th>Additional % Studies Considered “Missing”</th>
<th>METATRIM Adjusted Effect Size (95%CI)</th>
<th>Absolute Overstatement of Efficacy</th>
<th>Relative Overstatement of Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogens</td>
<td>26.7% (20.4%–33.0%)</td>
<td>+</td>
<td>+</td>
<td>24</td>
<td>11.9% (4.6%–19.2%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14.8% (8.0%–21.6%)</td>
<td>124.4%</td>
</tr>
<tr>
<td>FK506</td>
<td>32.0% (27.8%–36.3%)</td>
<td>+</td>
<td>+</td>
<td>30</td>
<td>21.9% (17.5%–26.3%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.1% (5.8%–14.4%)</td>
<td>46.1%</td>
</tr>
<tr>
<td>Growth factors</td>
<td>29.7% (25.9%–33.4%)</td>
<td>+</td>
<td>+</td>
<td>14</td>
<td>25.1% (21.2%–28.9%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.6% (0.9%–8.3%)</td>
<td>18.3%</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>43.5% (40.1%–47.0%)</td>
<td>+</td>
<td>+</td>
<td>20</td>
<td>35.4% (31.7%–39.1%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.1% (4.5%–11.6%)</td>
<td>22.9%</td>
</tr>
<tr>
<td>IL1-RA</td>
<td>38.2% (31.2%–45.1%)</td>
<td>+</td>
<td>+</td>
<td>36</td>
<td>25.4% (18.4%–32.4%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.8% (5.9%–19.7%)</td>
<td>50.4%</td>
</tr>
<tr>
<td>Melatonin</td>
<td>42.1% (35.7%–48.5%)</td>
<td>+</td>
<td>+</td>
<td>14</td>
<td>41.0% (34.8%–47.3%)</td>
<td>1.1% (–5.1% to 7.4%)</td>
<td>2.7%</td>
</tr>
<tr>
<td>Minocycline</td>
<td>30.9% (24.1%–37.6%)</td>
<td>+</td>
<td>−</td>
<td>0</td>
<td>No adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>29.2% (23.0%–35.5%)</td>
<td>+</td>
<td>+</td>
<td>24</td>
<td>21.8% (14.9%–28.6%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.4% (0.8%–13.9%)</td>
<td>33.9%</td>
</tr>
<tr>
<td>NOS donors</td>
<td>21.4% (13.7%–29.1%)</td>
<td>+</td>
<td>+</td>
<td>25</td>
<td>14.0% (6.4%–21.6%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.4% (–0.1% to 14.9%)</td>
<td>52.9%</td>
</tr>
<tr>
<td>NOS inhibitors</td>
<td>22.2% (17.1%–27.3%)</td>
<td>+</td>
<td>+</td>
<td>13</td>
<td>14.7% (8.9%–20.6%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.5% (2.0%–13.0%)</td>
<td>51.0%</td>
</tr>
<tr>
<td>NXY-059</td>
<td>43.8% (34.7%–52.8%)</td>
<td>+</td>
<td>−</td>
<td>0</td>
<td>No adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piracetam and related</td>
<td>29.6% (16.1%–44.4%)</td>
<td>+</td>
<td>−</td>
<td>0</td>
<td>No adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>compounds</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stem cells</td>
<td>29.6% (23.7%–35.4%)</td>
<td>+</td>
<td>−</td>
<td>0</td>
<td>No adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tirilazad</td>
<td>31.9% (23.1%–40.7%)</td>
<td>+</td>
<td>−</td>
<td>0</td>
<td>No adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tPA</td>
<td>22.5% (19.2%–25.9%)</td>
<td>+</td>
<td>+</td>
<td>5</td>
<td>19.9% (16.4%–23.3%)</td>
<td>2.6% (–0.7% to 6.0%)</td>
<td>13.1%</td>
</tr>
<tr>
<td>Other Thrombolytics</td>
<td>46.6% (35.7%–57.5%)</td>
<td>+</td>
<td>−</td>
<td>0</td>
<td>No adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pooled analysis</strong></td>
<td><strong>31.3% (29.7%–32.8%)</strong></td>
<td><strong>+</strong></td>
<td><strong>+</strong></td>
<td><strong>214&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td><strong>23.8% (22.2%–25.5%)&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td><strong>7.5% (5.9%–9.1%)</strong></td>
<td><strong>31.1%</strong></td>
</tr>
</tbody>
</table>
What are the conditions of maximum efficacy?

duration of hypothermia

<table>
<thead>
<tr>
<th>0 to 105 mins</th>
<th>Favours hypothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td>110 to 130 mins</td>
<td></td>
</tr>
<tr>
<td>135 to 180 mins</td>
<td></td>
</tr>
<tr>
<td>195 to 480 mins</td>
<td></td>
</tr>
<tr>
<td>960 to 4470 mins</td>
<td>Favours control</td>
</tr>
</tbody>
</table>

Summary

Reduction in Infarct Volume
What are the conditions of maximum efficacy?

delay to treatment

Pretreatment
  0 - 29 min
  30 - 59 min
  60 - 89 min
  90 - 179 min
  180 - 359 min
  360 min

Summary
What are the conditions of maximum efficacy?

depth of hypothermia

24 to 29°C
30°C
31°C
32°C
33°C
34°C
35°C

Summary

Reduction in Infarct Volume
## EuroHYP-1

### Knowledge translation table

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Animal data</th>
<th>EuroHYP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>How powerful is the treatment?</td>
<td>&gt;40% improvement in outcome</td>
<td>Powered to detect 7% improvement in outcome</td>
</tr>
<tr>
<td>What is the quality of evidence?</td>
<td>Efficacy maintained in high quality studies</td>
<td>Randomised, blinded outcome assessment, intensely monitored</td>
</tr>
<tr>
<td>Is there evidence of a publication bias?</td>
<td>Yes, but &gt;35% improvement in adjusted outcome</td>
<td>Registered</td>
</tr>
<tr>
<td>What is the range of evidence?</td>
<td>Good: sex, duration, delay to treatment, intensity, hypertension, reperfusion</td>
<td>Patients &gt;18yo with acute ischaemic stroke, NIHSS 6 to 20, treated within 6hrs</td>
</tr>
<tr>
<td>What are the conditions of maximum efficacy?</td>
<td>Temperature dependent: otherwise robust across dimensions</td>
<td>Target 34-35°C</td>
</tr>
</tbody>
</table>
EuroHYP-1

• International randomised controlled clinical trial of modest cooling in patients with stroke

• Evidence based trial design
  – entry within 6 hours of stroke onset
  – Cooling to 34 to 35°C
  – Patients with hypertension allowed
  – Cooling for 24 hours
EuroHYP-1

- FP7 funding of €11m awarded from 01/02/12
- Target 50 – 70 centres in more than 15 countries
- First patient recruited November 2013
- 1500 patient target over 4 years
- Results late 2017
Recruitment
Performance by country

<table>
<thead>
<tr>
<th></th>
<th>Germany</th>
<th>UK</th>
<th>Denmark</th>
<th>France</th>
<th>Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centre months open</td>
<td>277.77</td>
<td>70.33</td>
<td>16.10</td>
<td>7.63</td>
<td>8.60</td>
</tr>
<tr>
<td>Patients Randomised</td>
<td>20</td>
<td>14</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Patients per centre Month</td>
<td>0.072</td>
<td>0.199</td>
<td>0.186</td>
<td>0.131</td>
<td>0.349</td>
</tr>
</tbody>
</table>
Protocol amendments

• Reduced duration of cooling
• Reduced target sample size
  – Improved ascertainment of mRS
  – mRS shift analysis
  – Covariate adjustment
Thank you

• If you are interested in joining the trial, contact Bridget.Colam@ed.ac.uk